The MARS Pilot Project:

Implementing real-time measles and rubella surveillance during elimination phase in Canada

By

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ABSTRACT

OBJECTIVES

Measles and rubella are nationally notifiable, vaccine-preventable diseases targeted for elimination by the Pan American Health Organization (PAHO). To support national and international elimination efforts, surveillance optimization is important to ensure rapid case detection, document endemic transmission interruption, identify susceptible populations and inform immunization strategies. While current national surveillance captures confirmed-case data, its performance cannot be assessed using PAHO-recommended surveillance indicators as suspect-case investigation data are required for their estimation. In Canada, the investigation of clinically-suspect measles-like illness (MLI) is highly dependent on laboratory evidence, providing an opportunity to use laboratory data to estimate MLI investigation rates. The Measles and Rubella Surveillance (MARS) pilot project was developed to address existing surveillance challenges with the central hypothesis that (I) 'it is feasible to develop and implement a real-time, web-based measles and rubella surveillance system in the Canadian setting', and the following sub-hypotheses: (II) 'implementation of real-time surveillance in MARS pilot provinces will result in increased timeliness of national measles and rubella surveillance when compared with established confirmed-case surveillance', and (III) 'it is possible to use augmented laboratory data to estimate the performance of national measles and rubella surveillance using adapted PAHO indicators'.

METHODS

A MARS application was designed to support centralized real-time measles/ rubella investigation reporting and alerting with integration of non-nominal laboratory and epidemiological data, then developed and piloted using the web-based Canadian Network for Public Health Intelligence platform in British Columbia, Alberta and Newfoundland from June/2011-May/2012. Pre- and post-pilot

laboratory surveys were conducted to retrospectively assess national surveillance performance in 'outbreak' and 'non-outbreak' settings during the 2005-2011 and pilot years using various surveillance indicators and attributes. Measles IgM serology testing was used as a laboratory-based proxy for MLI investigation to support indicator estimation.

RESULTS

Real-time, integrated surveillance was successfully implemented in MARS pilot provinces as modeled within the context of established reporting roles, and surveillance indicators and attributes were estimated using augmented laboratory data. MARS surveillance was more timely than confirmed-case surveillance, and real-time MARS reports exceeded all laboratory-related PAHO targets evaluated: 100% met 'sample collection' and 'receipt' timelines, and 91.7% met 'result' timelines (Targets:≥80%); 99.8% of all MLI investigations were discarded (Target:≥95%). A national 'non-outbreak' baseline rate of 14 MLI investigations/100 000 population was estimated, whereas MARS pilot sites averaged 22 MLI investigations/100 000 population during the pilot year. While 'non-outbreak' investigation rates varied between provinces, all annual provincial and national rates estimated for the 2005-2011 and MARS pilot years exceeded the PAHO investigation target of ≥2 suspected cases/100 000 population in settings attempting elimination.

CONCLUSIONS

The MARS model supported more timely and integrated national measles and rubella surveillance, and enabled indicator-based performance assessment. Results underscore the importance of laboratory data when evaluating and documenting surveillance performance to support elimination efforts. Consideration should be given to national MARS implementation and its use as a model adaptable to the case-based surveillance of other nationally notifiable diseases.

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CHAPTER 1: INTRODUCTION

BACKGROUND

Pathogen Characteristics

Measles Virus

Measles is caused by infection with the measles virus (MV), an enveloped, non-segmented single-stranded negative sense RNA virus belonging to the genus *Morbillivirus* in the family *Paramyxoviridae*. The measles virus genome is 15,894 nucleotides in length and contains 6 structural genes (3' - N, P, M, F, H, F – 5') which encode 8 viral proteins. The nucleoprotein (N), phosphoprotein (P) and large protein (L) together form the nucleocapsid which encloses the viral RNA. The viral envelope is comprised of the haemagglutinin (H), fusion (F) and matrix (M) proteins, along with lipids acquired when the virus buds from the host cell membrane (1). The functions of 2 non-structural proteins, V and C, have yet to be clearly defined (2). The H protein binds with host cellular MV receptors SLAM (CD150) and CD46 (1)(3)(4) and interacts with F to mediate viral attachment and fusion with the host cell membrane (2). More recently, the adherens junction protein nectin-4 has been identified as the epithelial receptor mediating measles virus entry and dissemination in human airway epithelial cells through interaction with the H surface antigen (5-7).

Measles virus is considered to be serologically monotypic, such that immunity against one measles strain is expected to confer lasting immunity against other circulating strains. Although only one serotype is recognized, some antigenic and genetic variability is present both between and among circulating wild-type and vaccine virus strains. The greatest sequence variability (7-10%) is observed in genes encoding the N and H proteins in wild-type measles viruses. A maximum variability of 12% is

observed in the last 450 nucleotides (nt) of the N gene, and the standard measles genotyping nomenclature used to support molecular epidemiological efforts is therefore based on the sequence of this region. At present, 8 taxonomically distinct clades (A, B, C, D, E, F, G, and H) are recognized by the World Health Organization (WHO), and these clades currently encompass 24 distinct genotypes (1)(8)(9).

Rubella Virus

Rubella virus, the causative agent of rubella (also known as German measles) is the sole member of the *Rubivirus* genus in the family *Togaviridae.* It is an enveloped virus with a positive-sense single-stranded RNA genome approximately 9760 nt in length. The rubella genome encodes 2 non-structural proteins (p150 and p90) and 3 structural proteins, the C (capsid) protein and E1 and E2 glycoproteins. E1 and E2 form heterodimeric spikes on the membrane surface, and are primary targets of the host immune response to rubella infection (1) As with measles, the immune response to infection with any given rubella virus is considered protective against clinical disease caused by other known rubella strains (10)(1). Rubella viruses that are currently circulating fall into two phylogenetically distinct clades, 1 and 2, which differ in genetic sequence by approximately 8-10% (11). Within the 2 clades are 9 recognized genotypes and 4 provisional genotypes (12). In accordance with WHO recommendations, rubella genotype is determined by sequencing a minimum recommended 739 nt window within the E1 coding region of the genome to support molecular epidemiology and strain surveillance (11).

Pathogenesis, Immune Response and Clinical Illness

Measles Pathogenesis and Immune Response

Measles infection is acquired by susceptible hosts primarily through the inhalation of infectious aerosols and droplets which deliver virus to alveolar macrophages and/or dendritic cells (DC) present in the upper respiratory tract, and through contact with infected fomites. Infected DC then migrate to regional draining lymph nodes, initiating measles infection through the transmission of virus to $CD150^{+}$ lymphocytes (1,2)(6). Initial measles infection is followed by a 10-14 day incubation period during which lymphoid organs and tissues serve as the major sites of viral replication. This is followed by viraemia and dissemination of virus to multiple organs including the lymph nodes, skin, kidney, gastrointestinal tract, liver, lymphocytes, monocytes and macrophages (2)(6).

Both humoral and cell-mediated immune responses are elicited by measles virus infection. The primary humoral response involves the production of both anti-measles immunoglobulin (Ig)M and IgG antibodies, the detection of which are useful for diagnostic purposes. In a majority of measles cases, IgM antibodies are detectable in serum at 3 days post-rash onset using a sensitive enzyme-linked immunoassay (13,14). IgM antibody levels peak approximately 7-10 days after rash onset before rapidly declining, and are rarely detectable after 6-8 weeks. IgG antibody levels in serum peak within 4 weeks of rash onset and persist long after the primary infection has cleared, conferring lifelong immunity following natural infection. Diagnostically, the demonstration of a qualitatively significant rise in IgG antibody titre between acute and convalescent sera obtained at least 10-14 days apart can aid in confirming acute measles infection (14,15). Serum and secretory IgA antibodies are also produced in response to infection, but are not assessed for diagnostic purposes (14). Antibodies produced during the humoral response primarily target the N protein, however

antibodies against the H and F proteins are also protective (2). The cellular immune response is crucial to viral clearance and recovery, as individuals with defects in cell-mediated immunity frequently experience severe progressive infection and have a significantly increased risk of death (14). Cellular immunity to measles is characterized by a Th1 response with cytotoxic T-lymphocyte cellular immunity and increased IFN-γ in early acute infection, followed by a Th2 – type response during convalescence with increased levels of IL-4, IL-10 and IgG antibodies. Significantly, the immune response to measles is associated with depressed cellular and humoral immune responses to non-measles virus antigens following the resolution of acute illness. This state of measles-induced immunosuppression can persist for months, and is responsible for measles associated morbidity and mortality due to increased susceptibility to secondary bacterial and viral infections which can cause pneumonia and diarrhoeal illness (2).

Measles Clinical Illness

Clinical symptoms typically appear 7-10 days after initial exposure, and are characterized by a prodrome including fever, cough, coryza (runny nose) and conjunctivitis. In approximately 50 – 90% of cases, Koplik's spots may also be observed on the buccal mucosa during the prodrome phase 2-3 days prior to rash onset, and are considered clinically diagnostic when present. Onset of the erythematous maculopapular measles rash occurs approximately 2 weeks post-exposure, appearing first on the face and behind the ears before spreading to the trunk and extremities. The rash persists for approximately 3-4 days before it begins to resolve in the order of its appearance, disappearing first from the face and neck. In uncomplicated measles cases, recovery begins shortly after rash onset (2)(1).

Measles Complications

Measles complications can potentially affect nearly every organ system. Frequent complications include otitis media (7-9%), diarrhoea (6%), and pneumonia (1-6%); the latter accounting for the majority of measles-related deaths annually. Pneumonia can take the form of primary measles virus pneumonia, or be caused by secondary viral infection or bacterial super-infection (1)(2). Keratoconjunctivitis is a common sequela of measles infection in children with Vitamin A deficiency, and can lead to blindness (2). The central nervous system is also frequently involved in measles infection, with electroencephalographic abnormalities reported in up to 50% of cases. While infection during pregnancy is associated with an elevated risk of prematurity and miscarriage, and possibly neonatal infection, prenatal infection is not associated with congenital malformations (1)(16).

Rare but severe complications of measles infection involve the CNS, and include acute post-infectious encephalomyelitis (APIE), measles inclusion body encephalitis (MIBE) and subacute sclerosing panencephalitis (SSPE). APIE is considered an autoimmune disorder triggered by MV infection, and typically occurs within 2 weeks of rash onset. Clinical illness is characterized by fever, seizures, and various neurological abnormalities including coma (2)(1). While the incidence of APIE is approximately 1 in 1000 measles cases, as many as 30% of APIE cases result in death, and long term sequelae are observed in approximately 30% of survivors(1). MIBE and SSPE are rare, fatal complications resulting from persistent measles virus infection of the CNS. MIBE typically occurs months after initial infection in immunocompromised individuals with defective cellular immunity (2)(1). SSPE is a late onset fatal neurological complication which typically manifests several years (5-15 years) after primary infection with wild-type measles virus. SSPE is most frequently observed in those aged 2 and under when first infected, with disease characterized by progressive deterioration

of motor and cognitive functions, involuntary myoclonic movement, muscular rigidity and death(1,2). SSPE has a reported incidence of 1 in 100 000 measles cases (1,2), however the incidence has been estimated to be as frequent as 1 in 11 000 measles cases (17).

Rubella Pathogenesis and Immune Response

Rubella, like measles, is transmitted through the inhalation of infectious droplets and aerosols. Targeting the cells of the upper respiratory tract, rubella virus gains entry to host cells through receptor-mediated endocytosis. Further spread and replication occur in upper respiratory and nasopharyngeal lymphoid tissues, with subsequent viraemia leading to systemic infection. Multiple organ systems may be affected, including the placenta (18).

Primary rubella virus infection results in both humoral and cellular immune responses. IgM and IgG antibodies are observed 14-18 days post-infection, their appearance coincident with the development of rash. Diagnostically, IgM antibodies are detectable in serum 5 days post-rash onset. IgM antibody levels wane quickly, becoming undetectable after 2 months, whereas IgG peaks approximately 5-6 weeks post-rash and persists in serum indefinitely (14,15). As with measles, demonstration of a significant (4-fold) rise in IgG titre between acute and convalescent sera taken 10-14 days apart can be used to confirm primary rubella infection (15). A cell-mediated lymphocytic response specific for rubella emerges 1 week after the humoral response, and provides lifelong protection against reinfection (14).

Rubella Clinical Illness

Clinically apparent rubella is characterized by the appearance of a non-confluent maculopapular rash approximately 12 – 23 days post-infection. While rubella infection is typically mild in children, adults

more frequently experience a prodrome phase of malaise and low grade fever which may include headache, sore throat, cough and conjunctivitis. Lymphadenopathy may also be present prior to rash onset, and persist for up to 14 days after the rash disappears (19). Whereas measles infection is invariably symptomatic, as many as 20 – 50% of rubella infections are subclinical, thereby enabling asymptomatic spread (19). Post-natal rubella infection is most frequently complicated by arthralgia and arthritis, occurring in up to 70% of post-pubertal females. Rarer complications include thrombocytopaenic bleeding disorders (1 in 3000 cases) and post-infectious encephalopathy (1 in 6000 cases).

Congenital Rubella Syndrome (CRS)

In contrast with the generally mild course associated with post-natal infection, rubella virus can act as a potent teratogen when infection occurs during early pregnancy. Rubella infection during the first 11 weeks of gestation is associated with a high likelihood (up to 90%) of congenital rubella syndrome (CRS) in the newborn, which encompasses a constellation of transient manifestations and permanent abnormalities (20). Manifestations including low birth weight, hepatosplenomegaly, meningoencephalitis, thrombocytopaenia, and bony radiolucency usually resolve spontaneously within weeks after birth. Permanent abnormalities include cardiovascular defects, eye abnormalities, sensorineural deafness and other CNS issues including microcephaly, and cognitive and psychomotor delay (19).While the pathogenesis of congenital rubella infection (CRI) is not well understood, rubella infection in early pregnancy is known to result in an altered, tolerant immune response to rubella infection and altered organogenesis(1). Infection after 20 weeks of gestation is unlikely to result in CRS-associated abnormalities (18); however, congenitally infected infants continue to be infected at birth and persistently shed rubella virus through urine and nasopharyngeal secretions for prolonged periods of time, serving as a potential long-term source of transmission (1,14). Persistent elevation of

anti-rubella IgG is also seen in congenitally infected infants beyond 6-months when maternally acquired immunity is expected to wane, and can be used diagnostically (15).

Measles and Rubella Vaccines

Measles and rubella are vaccine-preventable diseases for which highly effective live-attenuated vaccines are available globally. Depending on the setting, vaccine may be available in monovalent form or in combination with other vaccine viruses as with the widely administered measles–mumps–rubella (MMR) vaccine. Measles and rubella vaccines were first licensed for use in 1963 and 1969-70 respectively (2,18)(21).

Measles Vaccine

Live measles vaccine is produced in chick embryo culture, while live rubella vaccine is grown in human diploid cell culture (22). The majority of measles vaccines are derived from the Edmonston strain of measles virus first isolated in 1954. While the various attenuated vaccine strains have differing passage histories in cell culture, most demonstrate nucleotide sequence differences of less than 0.6% (2)(23). Measles immunization is associated with a mild, non-communicable infection which results in anti-measles antibody production in approximately 95% of children vaccinated at 12 months of age, yielding a primary vaccine failure rate of approximately 5%. The CDC reports that over 99% of individuals receiving two doses of measles-containing vaccine develop serological evidence of immunity provided the first dose was administered on or after the first birthday (22). The timing of the first vaccine dose may play a role in vaccine efficacy; during the 2011 Québec outbreak, the risk of measles among 2-dose recipients was reported to be significantly higher in individuals whose first dose was administered at 12 months of age versus ≥ 15 months (24).

Rubella Vaccine

The rubella vaccine used in most countries including Canada is the RA27/3 strain, with China and Japan using similar locally developed live-attenuated vaccines (18,25). Immunization with rubella vaccine results in serologic evidence of immunity in ≥95% of susceptible individuals 12 months and older, with immune challenge studies demonstrating that > 90% of immunized individuals are protected against clinical rubella and viraemia for a minimum of 15 years post-vaccine(22)(26) (27). Although both measles and rubella vaccines elicit lower IgG antibody levels relative to those produced in response to natural infection, available serological and epidemiological evidence suggest that these vaccines induce lasting and probably life-long protective immunity (28)(29,30).

Infectivity and Transmission of Measles and Rubella

While measles and rubella are both transmitted through the respiratory route, they differ in their infectivity. Measles is one of the most infectious diseases known, with a reproductive number (R_o) of 12-18. That is, the introduction of a single case into a fully susceptible population would be expected to result in 12-18 secondary cases, although R_o values as high as 200 are known (2). Susceptible individuals having close contact with a measles case have a 99% probability of acquiring the disease, and in the pre-vaccine era over 90% of individuals contracted measles prior to 10 years of age (1). Rubella is less infectious relative to other respiratory illnesses including measles and influenza, and close contact with infectious secretions is usually needed for effective transmission. Sustained transmission of both measles and rubella depends on the availability of susceptible individuals. In unvaccinated populations, measles and rubella cause periodic large epidemics with inter-epidemic periods of 2-5 years for measles, and 4-7 years for rubella (1)(19).

Possibility of Reinfection

Measles Reinfection

Re-exposure to measles virus after natural infection results in a potent anamnestic immune response with rapid elevation of IgG antibody levels, thereby preventing clinical disease (14). While symptomatic measles reinfection is expected to be a relatively rare occurrence, asymptomatic reinfection with virus isolation has been documented in a naturally immune case contact (31). The possibility has also been raised that measles virus may circulate in vaccinated populations causing asymptomatic or mild disease in individuals with pre-existing immunity, although the frequency, efficiency and epidemiological significance of transmission by asymptomatically infected individuals with respect to elimination efforts remain unclear (31,32).

Rubella Reinfection

While natural rubella infection is generally associated with lifelong immunity, rubella reinfection following previous infection is known to occur (14). Reinfections are generally asymptomatic, and have been identified through serological testing of expectant mothers following close contact with a rubella case. The estimated risk of foetal damage associated with rubella re-infection during the first trimester is considerably reduced when compared with primary rubella, and is likely less than 5%. For clinical management purposes, the ability to distinguish between primary rubella infection and secondary or reinfection using laboratory testing is critical (19) (14).

Non-human reservoirs

Humans are the sole reservoir for measles and rubella viruses (2). There is no known animal reservoir for rubella virus, and while measles virus can infect and cause measles-like disease in non-human

primates, primate populations are not sufficiently large to sustain measles transmission (2,19,33).

Global Burden and Significance

Measles: Global Significance

Measles is considered one of the most important infectious diseases of humans due to its extreme infectivity which can result in explosive epidemics, and the high global burden of measles-associated morbidity and mortality. Before measles vaccines were first introduced in the 1960s, global measles transmission resulted in an estimated 130 million cases, and 2.5 million deaths annually, mainly in children (14). While measles has remained a leading vaccine-preventable cause of death in children for over 40 years, significant mortality reductions have been realized following the implementation of global immunization strategies. In 2001, WHO/UNICEF announced a joint strategy to deliver 2 doses of measles-containing vaccine to all children through routine immunization services and supplementary immunization activities (SIAs) (14)(34). By 2008, WHO estimated a 74% decrease in global measles-attributed mortality from an estimated 750 000 deaths in 2000 to 197 000 deaths in 2007, with approximately 90% of deaths occurring in children <5 years of age (35).

Rubella: Global Significance

The public health importance of rubella lies in the teratogenic effects of rubella virus infection on foetal development during early pregnancy, which can lead to miscarriage, still birth, congenital birth defects and delayed onset chronic conditions requiring long-term management and care. The risk of congenital defects was underestimated until the late 1960s, but it is now recognized that primary rubella infection during the first 12 weeks of pregnancy carries a >80% risk of congenital defects (19,22). Notably, the last U.S. rubella epidemic prior to the availability of rubella vaccine resulted in

an estimated 11 000 foetal deaths and 20 000 CRS cases between 1964-65(21,22). The primary objective of rubella immunization is to prevent the occurrence of CRS by achieving and maintaining high immunization levels in children and adults, particularly women of childbearing age (22). By 2002, 124 countries (58%) were including rubella vaccine in their national immunization system. Even so, a high global burden of CRS remained, with an estimated 100 000 infants affected annually in 2003(21).

Worldwide, the greatest burdens of morbidity and mortality are observed in developing countries with limited access to measles and rubella containing vaccines, whereas infection and associated complications are relatively rare in low incidence countries with high levels of vaccine coverage (14) (18).

Measles and Rubella Elimination

Elimination and eradication programs are considered to be distinct from ongoing disease control programs in their requirement for targeted surveillance, rapid response capability, high standards of performance and a dedicated national focal point (36).

Eradication Definition

Eradication of an infectious disease has been defined as the permanent reduction to zero of the global incidence of infection caused by a specific agent as a result of deliberate efforts with the result that intervention measures are no longer needed. To assess the potential for eradicability of an agent, the 1997 Dahlem Workshop identified three indicators of primary importance: availability of effective interventions capable of interrupting transmission; sensitive and specific diagnostic tools; and humans serving an essential role in the agent life-cycle which has no vertebrate or

environmental reservoir (36). While both measles and rubella meet these eradication criteria, global efforts are currently focused on achieving and maintaining the elimination of measles and rubella from WHO-defined geographical regions.

Regional Elimination: PAHO Definition

Recently published PAHO guidelines define elimination in the WHO Region of the Americas as the interruption of endemic measles/rubella virus transmission in all the countries of the Americas for a period ≥ 12 months (without the occurrence of CRS cases associated with endemic rubella transmission), in the presence of high-quality surveillance (see Table 1.1) (37).

Table 1.1 PAHO definitions - Measles and rubella elimination in the Region of the Americas (37)**.**

Measles Elimination in the Americas	Rubella Elimination in the Americas
Measles elimination is defined as interruption of endemic measles virus transmission in all the countries of the Americas for a period ≥ 12 months in the presence of high quality* surveillance.	Rubella and CRS elimination is defined as interruption of endemic rubella virus transmission in all the countries of the Americas for a period ≥ 12 months without the occurrence of CRS cases associated with endemic transmission, in the presence of high quality* surveillance.
**High quality surveillance system sensitive enough to detect imported and import-related cases.*	

Measles and Rubella Elimination: National and International Targets

At the XXIV Pan American Sanitary Conference in 1994, Canada and other nations committed to the elimination of measles from the WHO region of the Americas by 2000 (38). In 2003, PAHO set the international goal of eliminating rubella and CRS from the region of the Americas by 2010; a goal that

Canada went on to adopt in 2005 at the National Goals and Consensus Conference on vaccine-preventable diseases(39).

Measles and Rubella Elimination in Canada

To assess national progress towards measles elimination in Canada, elimination has been defined as the 'interruption of endemic measles transmission and failure to re-establish endemic transmission after importation.'(40) More recently, rubella elimination in the Canadian setting was similarly defined as 'the interruption of endemic transmission and failure to re-establish endemic transmission within 12 months following importation (39). The latter definition correlates with current PAHO guidelines by including a criterion for the re-establishment of endemic transmission, which PAHO defines as occurring 'when epidemiological and laboratory evidence indicates the presence of a chain of transmission of a virus strain that continues uninterrupted for >12 months in a defined geographical area' (37)

Measles and Rubella Immunization Programs in Canada

In Canada, measles immunization programs using live measles vaccine were first introduced by provinces and territories in 1967(41). A killed measles vaccine was also used in 2 provinces before its discontinuation in 1970 due to the occurrence of atypical measles syndrome in recipients (42). By 1983, every province and territory had implemented routine infant immunization with the combined live measles-mumps-rubella (MMR) vaccine at 12 months of age (41). To support the PAHO goal of eliminating indigenous measles from the Region of the Americas by the year 2000, the National Advisory Committee on Immunization (NACI) published recommendations in 1996 for the national introduction of a two-dose MMR vaccine schedule(43). Between 1996 and 1997, all provinces and territories introduced a routine second dose of MMR or combined measles-rubella (MR) vaccine

given at either 18 months of age, or between 4 and 6 years of age to coincide with school entry. Nine P/T jurisdictions currently administer the second dose of measles-mumps-rubella containing vaccine in the form of MMR or MMRV (varicella) at 18 months of age, while the remaining jurisdictions provide a second dose between 4 and 6 years of age (41).

Measles and Rubella Epidemiology in Canada

Measles, Pre-elimination: 1924 - 1997

Prior to the advent of measles immunization in Canada, measles epidemics were cyclical with increased incidence every 2 to 3 years. Between 300 000 and 400 000 cases were estimated to occur annually, with a peak of over 83 000 cases (770/100 000 population) reported nationally in 1935 (Figure 1.1). Measles-associated mortality was also common in the early 1900s, with an all-time high of 892 measles-associated deaths reported in 1926 just two years after measles first became nationally notifiable (40,44,45).

Between early vaccine introduction and recommencement of national reporting in 1969, and the first implementation of national routine 1-dose MMR in 1983, an average of 9 863 measles cases were reported annually with a range of 934 to 25 137 reported cases/year. Following the establishment of routine national 1-dose MMR, this average declined further to 3, 571 cases/year with a range of 187 – 14 941 cases (46)(40,47). Although reliable vaccine coverage estimates are not available for this period, national coverage was assumed to exceed 85% by the late 1970s (46). National introduction of MMR at 12 months of age began in 1983, and by the late 1980s school entry 'catch-up' campaigns were estimated to result in immunization coverage rates of 95 – 100% (40, 47, 48). Even with very high level 1-dose coverage, large measles outbreaks primarily involving vaccinated children continued to occur between 1989 and 1995(40, 45).

The number of measles cases reported annually between 1990 and 1997 ranged from 204 to 6178, with an average of 1745 cases per year and an average incidence of 6.1/100 000 population. Single-dose immunization at 12 months was associated with an estimated primary vaccine failure rate of 10-15%, resulting in a sufficiently large susceptible population to allow endemic circulation of the virus to continue (45). In 1995, Canada was the sole country in WHO region of the Americas that had yet to implement a two-dose or catch-up program, and represented 40% of all reported cases with only 3.6% of the population of the region (40) (49).

FIGURE 1.1 Measles in Canada: Annual number of reported cases and incidence rate per 1,000,000 population; 1924-2011. Public Health Agency of Canada. Measles first became a nationally notifiable disease in 1924. Since then, confirmed measles case data have been collected on an ongoing basis with the exception of the 1959-1968 period, during which neither measles nor rubella case data were captured at the national level (45).

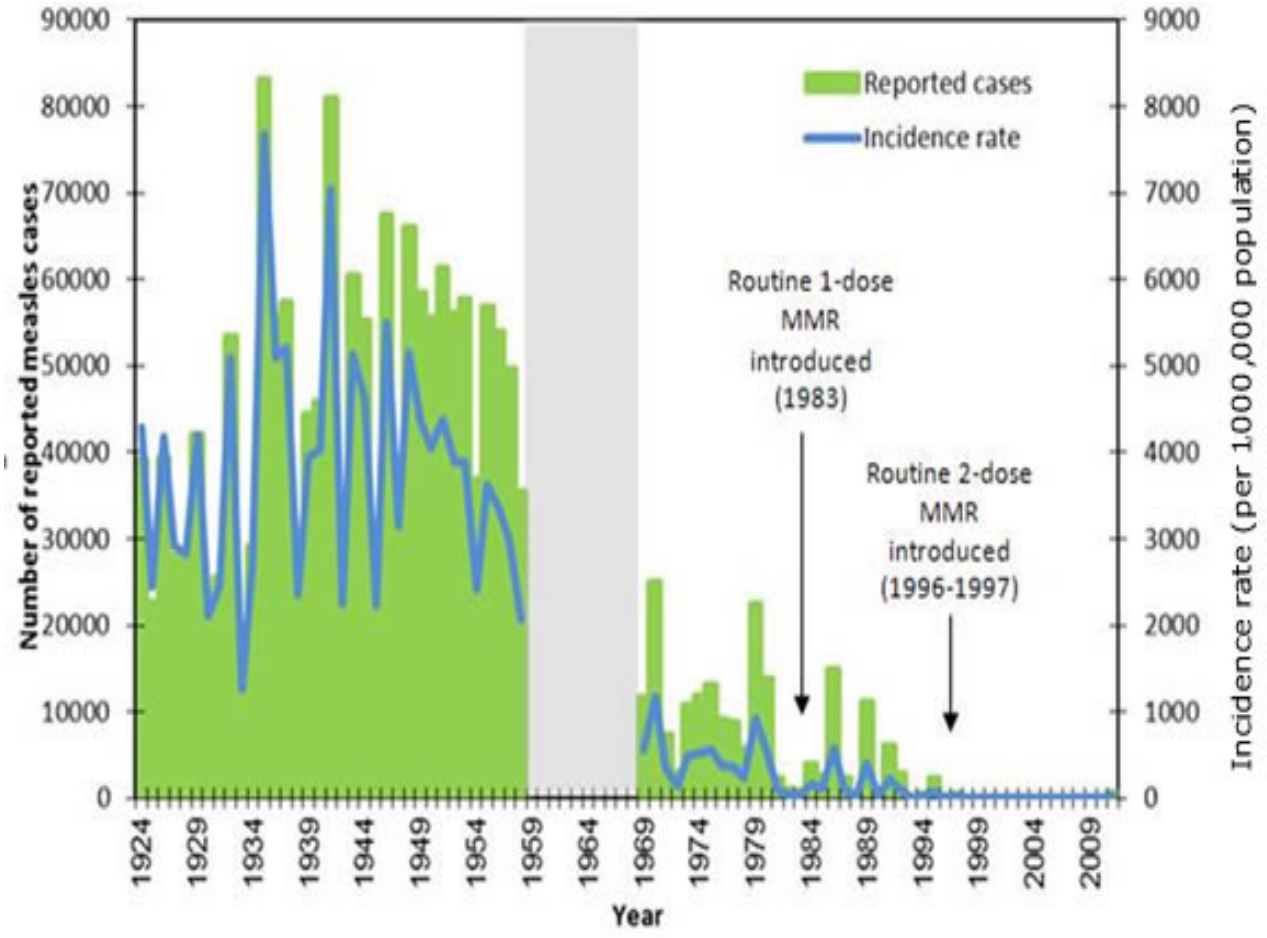


FIGURE 1.1 Measles in Canada: Annual number of reported cases and incidence rate per 1,000,000 population; 1924-2011. Public Health Agency of Canada (45)

Measles - Elimination Phase: 1997 - 2008

Following the 1996-7 introduction of 2-dose MMR, an average of 36 measles cases were reported annually from 1998-2005. This includes data for the year 2000 during which a large Alberta outbreak resulted in 123 cases. The corresponding average incidence of 0.12 measles cases/100 000 population represents a 98% decrease in incidence when compared with the 1990 -97 reporting period (47). The 2006 – 2008 reporting period saw a slight increase in average incidence to 0.18 /100 000 (range: 0.04- 0.31) due to outbreaks in 2007 (Québec) and 2008 (Ontario) (47). While import-related cases have continued to occur, indigenous cases have not been reported in Canada since 1997. The largest outbreaks have occurred in isolated populations philosophically opposed to immunization, with limited secondary transmission within the general population (45).

In 2004, Canada reported with some caution that it had achieved measles elimination based on epidemiological evidence from the 1997-2001 reporting period coupled with molecular evidence obtained through genotypic analysis of circulating measles strains (40).

Molecular Evidence of Measles Elimination

Limited genotypic information is available on endemic measles strains circulating in Canada during the pre-1989 and 1990-96 periods. In 1988-89, a province–wide measles outbreak in Québec resulted in 10,184 cases and accounted for 91% of all cases in 1989. All isolates were found to be identical strains of genotype D4, which was consequently considered to be the predominant circulating genotype in Canada at the time. Routine collection of measles genotyping data commenced as part of enhanced measles surveillance efforts in 1997, resulting in the identification of a D6 measles strain as the endemic strain responsible for >90% of reported cases that year(50). Since 1997, there has not been a recurrence of a predominant genotype as would be expected with continued endemic spread.

Rather, a variety of different genotypes has been detected, reflecting the importation of measles virus from various regions worldwide as would be expected once a region enters elimination phase. Additionally, the use of molecular epidemiological data allows the differentiation of independent outbreaks and/or importation events which would otherwise be linked using traditional epidemiological methods due to close spatiotemporal association (47,50).

Rubella and CRS Pre-elimination: 1924 - 1997

Prior to the availability of rubella vaccines, rubella was endemic in Canada. While reliable Canadian data are not available for the pre-vaccine period, the 1962-1965 worldwide rubella epidemic resulted in an estimated 12.5 million cases in the United States and the birth of 20, 000 infants with CRS. The health burden and economic impact of this global epidemic spurred the development of rubella vaccines and implementation strategies (51).

Following the licensing of rubella vaccine in 1969-70, Canadian provinces introduced rubella immunization programs during the 1970s in accordance with NACI recommended strategic options. Of the 10 provinces, 7 implemented mass immunization of 1-year-old children, and 4 of the 7 provinces supplemented their routine immunization with selective immunization of pre-pubertal girls. The 3 provinces of Manitoba, Saskatchewan and Alberta implemented only selective immunization of pre-pubertal girls and women of child-bearing age (39). From 1971-1982, an average of 5300 rubella cases were reported on an annual basis (25).

With the implementation of routine 1-dose MMR for all infants in 1983, the average number of rubella cases reported decreased to 1800 per year from 1983 - 1997(52). During this period, rubella epidemics continued to occur every 3 to 10 years with peak incidences in the spring and winter months. These outbreaks, including the 1997 Manitoba outbreak, were found to affect 15-24 year

old males disproportionately due to pre-1983 selective immunization practices (25). Although endemic transmission continued to occur, the implementation of 1-dose programs reduced rubella annual incidence by an estimated 74% from an average of 18.9 rubella cases/100 000 population for the preceding period to 5.0 /100 000(39).

CRS first became nationally reportable in 1979(53). From 1980 – 1997, its incidence decreased in parallel with that of rubella. Having a pre-routine MMR annual incidence of 3 cases per 100 000 live births with an average of 11.2 cases reported per year, CRS incidence decreased 73.7% to 0.8/100 000 with the introduction of 1-dose MMR (39).

FIGURE 1.1 Rubella in Canada: Annual number of reported cases and incidence rate per 1,000,000 population; 1979-2011. Public Health Agency of Canada. National collection of rubella confirmed case data began in 1924, and has continued to the present with the exception of the 1959-1968 period. This figure displays the incidence and total numbers confirmed rubella cases reported at the national level in keeping with national confirmed case definitions during the 1979-2011 reporting period (52).

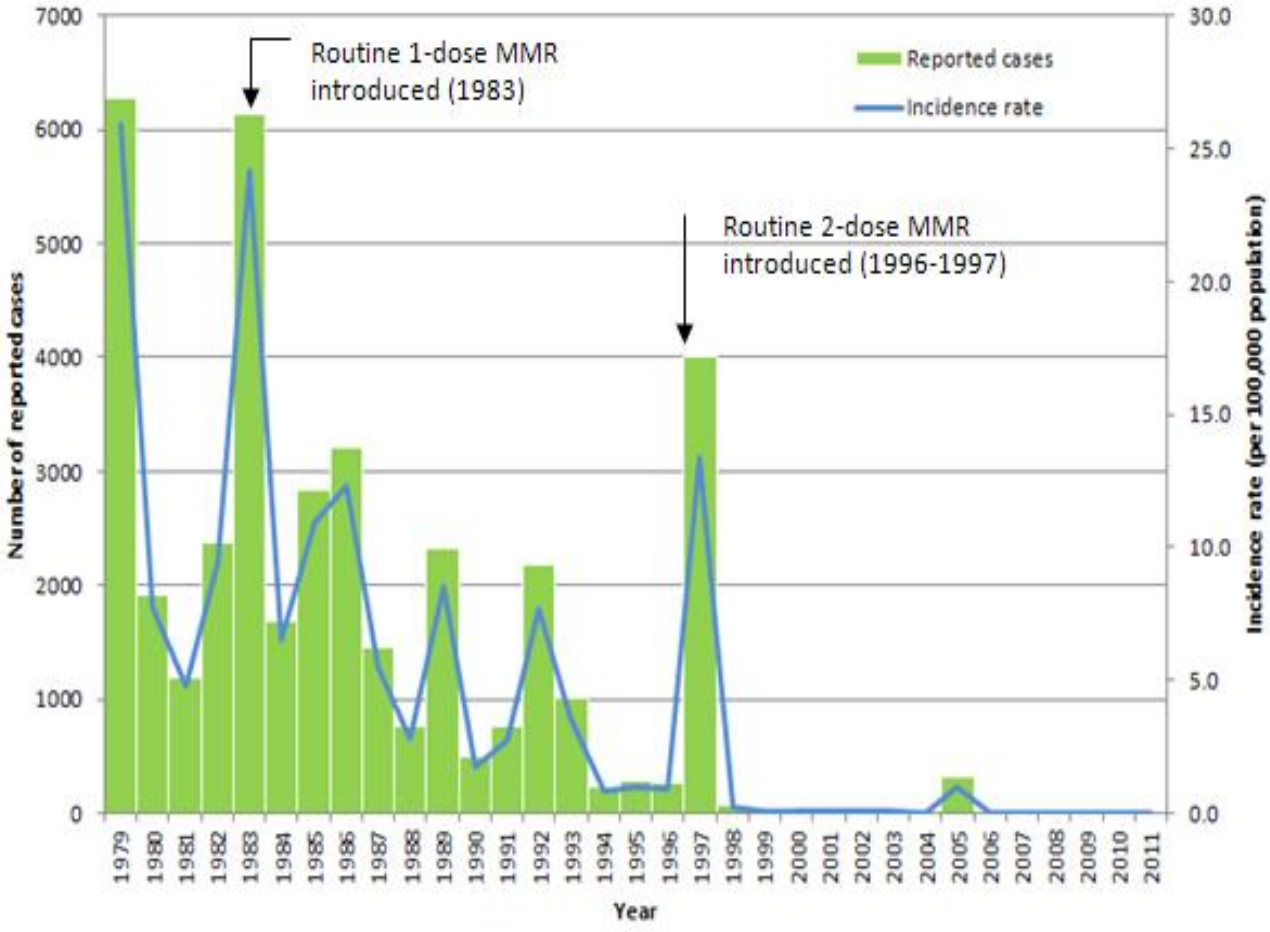


FIGURE 1.2 Rubella in Canada: Annual number of reported cases and incidence rate per 1,000,000 population; 1979-2011. Public Health Agency of Canada (52)

Rubella and CRS – Elimination Phase: 1997-2008

Following the national introduction of routine 2-dose MMR, the average number of rubella cases reported annually decreased from 1800 to <50 per year from 1998-2008. If the 2005 outbreak year is excluded, this average decreases further to <20 cases per year. Overall, annual incidence declined 99.5% when compared with the pre-MMR period. Peaks in incidence are no longer observed, and seasonality has been absent since 1997 (39). Since 1998, rubella cases have been predominately import-related, with larger outbreaks affecting under-vaccinated individuals and groups without sustained transmission in the general population (52).

Further reductions in CRS incidence to 0.2 cases/100 000 live births were observed with 2-dose MMR implementation for a 92.8 % reduction in incidence. CRS incidence has since remained consistently low, with 12 cases reported between 1996 and 2005. Most reported cases had an exposure history outside Canada in a country or region with endemic rubella transmission (39). To support national CRS elimination efforts, existing policies support screening of 100% of pregnant women for rubella, and providing an opportunity for post-partum immunization to all susceptible women (39,54).

Molecular Evidence of Rubella Elimination

Genotypic analysis of Canadian rubella virus strains isolated from 1984 – 2008 substantiates the interruption of endemic transmission following 2 –dose MMR implementation in 1996-1997. The 1997 Manitoba rubella outbreak was associated with a known endemic 1E genotype, while the 2005 Ontario outbreak in an under-vaccinated religious community was associated with an imported 1G genotype strain related to rubella viruses known to be circulating in Romania in 2003 (55); neither strain has been detected again in Canada post-outbreak. Rather, a variety of different genotypes associated with importation have been documented by the laboratory, evidence which supports the

elimination status of rubella in Canada (39).

Immunization Coverage in Canada

Due to the absence of immunization registries in a number of provincial jurisdictions, reliable vaccine coverage data are not available for the decades preceding or immediately following implementation of measles and rubella vaccine programs. In the early 1990s, coverage estimates became available through the National Immunization Coverage Surveys (NICS) which went on to be administered in 2 year cycles from 1991-97, and from 2002 – 2009. Childhood NICS data consistently yield national measles and rubella 1-dose coverage estimates ≥92% in 2 year olds for the 1997 – 2009 survey years, One-dose measles and rubella coverage are estimated at ≥ 89% in 7 and 17 year olds for the 2004 – 2009 survey years. By contrast, available 2-dose measles coverage estimates range from 69 – 79% at 7 years, and from 52 – 64% at 17 years of age for the 1997 - 2009 period (47). While the coverage surveys are expected to underestimate the true coverage rate, the 2-dose coverage estimates fall notably short of Canadian immunization coverage targets established at the 2005 national consensus conference. The national targets for measles are 97% coverage for 1-dose measles containing vaccine by the 2nd birthday, and 99% coverage for a second dose by the 7th birthday. Rubella coverage targets are 97% coverage with 1-dose of rubella-containing vaccine by the 2nd birthday, 97% age-appropriate (2-dose) rubella immunization for adolescents 14 – 16 years of age, and postpartum immunization coverage in 99% of susceptible women prior to hospital discharge (54).

Measles and Rubella Surveillance in Canada – A Brief History

Passive Measles/Rubella Surveillance: 1924 - Present

In Canada, measles, rubella and CRS are provincially reportable, nationally notifiable diseases for

which outbreak control measures are initiated upon detection of a single clinically compatible case (56). Provincial and territorial (P/T) legislation mandate the timely reporting of these diseases to P/T public health; at the national level, P/T notification of federal public health counterparts within the Public Health Agency of Canada (PHAC) is done on a voluntary basis. (41) (57).

Measles and rubella have been nationally notifiable since 1924, with the exception of the 1959-1968 period during which case data for these diseases were not collected at the federal level (53,58,59). Coincident with the introduction of a single-dose measles vaccine schedule into all P/T routine immunization programs in the early 1970s, national measles and rubella surveillance through the Canadian notifiable diseases surveillance system (CNDSS) was reintroduced in 1970. CRS was added to the list of notifiable diseases captured by CNDSS in 1979. CNDSS is a passive national surveillance system which depends on voluntary P/T reporting to monitor over 50 nationally notifiable infectious diseases, and captures very limited epidemiological data provided with confirmed cases reported to PHAC (i.e. region, age, sex)(47). CNDSS data support the national estimation of annual case numbers; however the system is not suited to timely case-based surveillance as required for diseases with regional elimination targets such as measles and rubella. Annual summaries of CNDSS data including aggregate measles and rubella case counts are published on the PHAC website, however these data were only publically available for the 1989 – 2004 reporting years as of July 2012 (60).

Enhanced CRS Surveillance: 1992 – 2004

To supplement passive CNDSS surveillance, active surveillance of CRS was initiated in 1992 through the Immunization Monitoring Program ACTive (IMPACT) which consists of a network of tertiary care paediatric hospitals representing over 90% of Canadian paediatric tertiary care beds. To increase CRS case finding and to introduce surveillance for congenital rubella infection (CRI), surveillance was

expanded in 1996 to the Canadian Paediatric Surveillance Program (CPSP) which employs mail-based surveillance targeting all practicing paediatricians across the country to report on rare events and diseases. Notably, active case finding via CPSP from 1996 – 2004 resulted in the detection of only 11 CRS cases and zero cases of CRI, the majority of which were also reported in parallel to CNDSS. Given the concordance in reporting between the passive CNDSS and active CPSP systems, parallel CRS/I reporting via CPSP was discontinued in 2004 (47,61,62). In 2007, CRS and congenital rubella infection (CRI) were incorporated into national active surveillance of measles and rubella (63).

Canadian Measles and Rubella Surveillance System: 1998 - Present

National enhanced surveillance of measles, rubella, CRS and CRI is currently conducted through the Canadian Measles and Rubella Surveillance System (CMRSS), with data collection coordinated by epidemiologists with the Centre for Immunization and Respiratory Infectious Diseases within PHAC. CMRSS was first implemented in 1998 as the Enhanced Measles Surveillance System (EMSS) to support timely national confirmed-case surveillance of measles, ensure the thorough epidemiological and laboratory investigation of confirmed measles cases, and to document national progress towards the elimination of measles in Canada(40)(64). Joint national surveillance of measles and rubella via CMRSS commenced with the addition of rubella and CRS/I to the existing enhanced measles surveillance system in 2006 and 2007 respectively, in the wake of confirmed national consensus on the goal of rubella elimination(54)(65). The rationale for integrating measles and rubella surveillance stems from their similar febrile rash clinical presentation which requires lab confirmation for differential diagnosis, as well as their linked immunization schedules (40,66).

CMRSS is used to monitor progress towards the elimination of measles and rubella at the national level through the weekly electronic solicitation of confirmed-case reports from all provinces and

territories, including zero reporting, with submission to PHAC via email or fax. PHAC in turn reports all nationally confirmed cases to PAHO on a weekly basis in keeping with PAHO elimination targets (53). All reported cases are reviewed by CIRID to ensure that they meet the national confirmed case definitions prior to their addition to the national database. Measles and rubella surveillance data are used to support routine national and international reporting obligations, to identify gaps in national surveillance, and to inform national immunization strategies (47).

Measles and Rubella Case Definitions

Standardized case definitions for communicable diseases under national surveillance were first published in 1991. Prior to their publication, Canadian provinces and territories relied upon existing jurisdiction-specific reportable disease case definitions when reporting to the national level (67). Since 1991, two revisions to the national case definitions have been published in 2000 and 2009 respectively. Confirmed measles, rubella and CRS/I definitions for the most recent revisions are provided in Tables 1.2 – 1.4 below. It should be noted that the case definitions published in 2000 were in effect during the initial development of the MARS pilot project, while the 2009 definitions were in effect during the implementation and piloting phase. The 2000 and 2009 national case definitions include both confirmed and probable case definitions for measles and rubella, however only confirmed measles and rubella cases have been reportable at the national level throughout this period (53,67). Any information pertaining to suspected or probable measles/rubella cases which are either discarded or not able to be confirmed upon further provincial investigation is maintained at the provincial and possibly regional level.

Table 1.2 Measles: National Confirmed Case Definitions; 2009, 2000.

2009	2000
Laboratory confirmation of infection in the absence of recent immunization with measles-containing vaccine: • isolation of measles virus from an appropriate clinical specimen OR • detection of measles virus RNA OR • seroconversion or a significant (e.g. fourfold or greater) rise in measles IgG titre by any standard serologic assay between acute and convalescent sera OR • positive serologic test for measles IgM antibody using a recommended assay in a person who is either epidemiologically linked to a laboratory-confirmed case or has recently travelled to an area of known measles activity OR Clinical illness* in a person with an epidemiologic link to a laboratory-confirmed case	Laboratory confirmation of infection in the absence of recent immunization with measles-containing vaccine: 1. isolation of measles virus from an appropriate clinical specimen OR 2. significant rise in measles specific antibody titre between acute and convalescent sera OR 3. positive serologic test for measles IgM antibody using a recommended assay. If the clinical and epidemiologic presentations are inconsistent with a diagnosis of measles, IgM result must be confirmed by additional testing (e.g. 1 or 2 above) OR Clinical illness* in a person who is epidemiologically linked to a laboratory confirmed case

*Measles Clinical Illness - 2009, 2000**:**

Clinical illness is characterized by all of the following features:

- fever of 38.3 ^{o}C or greater
- cough, coryza or conjunctivitis
- generalized maculopapular rash for at least 3 days

Table 1.3 Rubella: National Confirmed Case Definitions; 2009, 2000.

2009	2000
Laboratory confirmation of infection in the absence of recent immunization with rubella containing vaccine: • isolation of rubella virus from an appropriate clinical specimen OR • detection of rubella virus RNA OR • seroconversion or a significant (e.g. fourfold or greater) rise in rubella IgG titre by any standard serologic assay between acute and convalescent sera OR • positive serologic test for rubella IgM antibody using a recommended assay in a person with an epidemiologic link to a laboratory-confirmed case or who has recently travelled to an area of known rubella activity OR Clinical illness** in a person with an epidemiologic link to a laboratory-confirmed case	Laboratory confirmation of infection in the absence of recent immunization with rubella-containing vaccine • isolation of rubella virus from an appropriate clinical specimen OR • significant rise in serum rubella IgG antibody level by any standard serologic assay OR • positive serologic test for rubella-specific IgM OR clinical illness** in a person who is epidemiologically linked to a laboratory-confirmed case

** Rubella Clinical Illness - 2009, 2000

Clinical illness is characterized by fever and rash, and at least one of the following:

- arthralgia/arthritis
- lymphadenopathy
- conjunctivitis

Table 1.4 Congenital Rubella Syndrome/Infection: National Confirmed Case Definitions; 2009, 2000.

2009	2000
CRS *Live Birth*: two clinically compatible manifestations (any combination from Table I, Columns A and B) with laboratory confirmation of infection: • isolation of rubella virus from an appropriate clinical specimen OR • detection of rubella virus RNA OR • positive serologic test for IgM antibody in the absence of recent immunization with rubella-containing vaccine OR • rubella IgG persisting for longer than would be expected (~ six months after birth) from passive transfer of maternal antibody, or in the absence of recent immunization *Still Birth:* two clinically compatible manifestations with isolation of rubella virus from an appropriate clinical specimen *CRI* Laboratory confirmation of infection but with no clinically compatible manifestations: • isolation of rubella virus from an appropriate clinical specimen OR • detection of rubella virus RNA OR • positive serologic test for rubella IgM antibody in the absence of recent immunization with rubella-containing vaccine OR • rubella IgG persisting for longer than would be expected (approximately six months after birth) from passive transfer of maternal antibody, or in the absence of recent immunization	*CRS* *Live Birth*: two clinically compatible manifestations (any combination from Table I, Columns A and B) with laboratory confirmation of infection: • isolation of rubella virus from an appropriate clinical specimen OR • detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine OR • rubella-specific IgG persisting at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization *Still Birth:* two clinically compatible manifestations with isolation of rubella virus from an appropriate clinical specimen *CRI* A case with laboratory confirmation of infection but with no clinically compatible manifestations: • isolation of rubella virus from an appropriate clinical specimen OR • detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine OR • persistence of rubella-specific IgG at elevated levels for longer than would be expected from passive transfer of maternal antibody, or in the absence of recent immunization

TABLE I: Congenital Rubella Syndrome: Clinically Compatible Manifestations (2009, 2001)

Column A	Column B	
1. Cataracts or congenital glaucoma (either one or both count as one)	1. Purpura	7. Radiolucent bone disease
2. Congenital heart defect	2. Hepatosplenomegaly	8. Developmental or late onset conditions such as diabetes and progressive panencephalitis and any other conditions possibly caused by rubella virus
3. Sensorineural hearing loss	3. Microcephaly	
4. Pigmentary retinopathy	4. Micro ophthalmia	
	5. Mental retardation	
	6. Meningoencephalitis	

Laboratory Role: Case detection, confirmation and surveillance

In Canada, public health laboratories have a central role in measles and rubella case detection, confirmation and surveillance. The correct interpretation of laboratory results is critical to the timely investigation and confirmation of measles and rubella cases, and to inform evidence-based public health action.. Provincial public health laboratories (PHLs) are expected to be the first point of detection for clinically suspect measles/rubella cases, and additional laboratory evidence is required to confirm measles and rubella cases at the national level, either directly through laboratory testing of a case, or by demonstrating an epidemiological link to another lab-confirmed case (53).

Front-line Testing: IgM Serology

Internationally, the standard front-line test used to diagnose acute measles and rubella infection is the detection of measles- or rubella-specific IgM antibodies in serum (68) (14). Acute IgM serology is most commonly performed using commercially available enzyme immunoassay (EIA) test kits, and may employ indirect or capture methods of antibody detection (14). Comparative evaluations of commercially available measles and rubella IgM assays have been performed, and have found a number of measles and rubella IgM assays to be both sensitive and specific.

It is expected that in WHO Regions with adopted measles and rubella elimination targets, laboratories will test all samples from suspected cases for both measles and rubella-specific IgM. Where testing of all samples for both agents is not feasible, it is recommended that all suspected cases be tested for measles IgM, and if negative, tested in turn for rubella IgM. A suspected measles/rubella case is considered laboratory confirmed by a positive measles or rubella IgM serology result (14).

IgM Serology – Interpretation Issues

While IgM serology is the standard primary diagnostic test for measles and rubella, a number of circumstances may lead to challenges in interpreting a positive IgM result. These include history of recent immunization, cross-reactivity, sample timing, assay sensitivity and specificity, and the incidence of disease at a population level.

Recent Immunization

An important consideration is that immunization with MMR is known to result in fever/rash illness typically within 9-10 days, but up to 6 weeks post-vaccine (14,69). Measles and rubella IgM serology testing is not able to differentiate between the host immune response to natural infection and immunization, this can only be determined through genotypic analysis. In the absence of an epidemiological link, the WHO recommends that IgM positive cases with a history of recent immunization (i.e.1-6 weeks prior to rash onset) be discarded (14). For measles and rubella, the national case definition defines recent MMR immunization as 7-12 days prior to rash onset, but notes that a case-based evaluation is needed as reactions and time frame may vary (53).

False-positive results

Even with the use of highly specific IgM assays (≥ 95%) for measles and rubella, it is possible for a number other agents responsible for fever/rash illness to produce false positive measles and rubella IgM test results. Test sera may yield IgM positive results for more than one agent, including measles, rubella, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and human parvovirus B19. More broadly, the presence of rheumatoid factor, cross-reactive non-specific IgM, persistently elevated IgM (post-acute), and specific IgG may all contribute to false positive IgM results (14,70,71).

False Negative Results- Timing of serological samples

Measles IgM

In measles cases, false negative results may occur when patient serum samples are obtained too soon following the onset of rash, before detectable levels of IgM antibodies are present. While measles IgM tests are generally expected to have a sensitivity exceeding 95%, the sensitivity of measles IgM capture EIAs have been shown to drop to 77% for samples tested within the first 72 hours after rash onset. For measles, the optimal sampling window is between 4 and 11 days post-rash onset (100% sensitivity), however samples obtained up to 4 weeks post-rash are still associated with high assay sensitivity (94%) (14,72).

Rubella IgM

For post-natal rubella cases, approximately 50% of cases are IgM-negative on the day of rash-onset, and IgM may not be present in serum at detectable levels until 4-5 days post-rash. This can lead to false negative IgM serology results for samples obtained during the early post-rash period. Most post-natal rubella cases are strongly positive between 5 and 7 days post-rash onset, and special

efforts may be required to obtain a second serum sample in such cases. In the case of CRS, patients remain IgM-positive for months after birth, and the timing of sample collection is less critical (1).

Low Incidence and Decreased PPV

In settings attempting measles and rubella elimination, another key consideration when interpreting the results of IgM serology testing is the effect of very low disease incidence in the population on the positive predictive value (PPV) of the assay being performed. PPV is defined as the proportion of cases diagnosed as a given disease that are in fact true cases. Even when the sensitivity and specificity of a diagnostic test remain unchanged, decreasing incidence in a population can dramatically decrease the PPV of the test. As previously demonstrated for measles, a diagnostic test that is 95% sensitive and 90% specific would yield a PPV of 70% when measles incidence is 20% in a given population. If the population incidence were to decrease to 2%, the PPV of the same test would drop precipitously to only 16%, with the result that approximately 5 out of 6 positive test results would be expected to be false positives (73).

Given existing challenges with the correct interpretation of IgM serology results, particularly in elimination settings, an IgM result alone is not considered adequate to confirm a measles or rubella case without a confirmatory test result or a confirmed epidemiological link. Conversely, PPV would be expected to improve in outbreak settings where population-based incidence is increased.

Measles and Rubella Confirmatory Testing

At the national level, a positive result using one of the following tests is required to confirm measles and rubella infection in the absence of recent immunization and where there is neither history of travel to an endemic region, nor an epidemiological link to another laboratory-confirmed case: a 4-

fold or greater rise in measles/rubella IgG titre between acute and convalescent serum samples, RT-PCR detection of viral RNA or virus isolation; rubella IgG avidity testing may also be performed to support diagnostic efforts (53,67,74)

IgG Serology

IgG serology testing can be used to confirm recent acute infection with measles or rubella by demonstrating evidence of seroconversion through a significant (4-fold) rise in IgG titre between paired acute and convalescent sera using an enzyme-linked immunoassay (EIA). To do this, a second convalescent serum sample must be obtained 10-30 days after procurement of the first acute serum sample, and the samples tested in parallel at the same time using the same assay method. Indirect IgG EIA assays are most widely used for measles and rubella testing. In this method, purified viral antigen is adsorbed to a solid substrate, and patient test serum is added. Virus-specific IgG antibody present in the test serum will bind to the adsorbed viral antigen. The bound serum IgG is then in turn detected using anti-human IgG coupled with an indirect or direct chromogenic detector system. The result is positive if a 4-fold or greater rise in IgG antibody to measles or rubella is observed between the acute and convalescent serum samples. Criteria for documenting the increase in titre are assay-dependent, and for interpretation purposes it should be noted EIA optical density (OD) values are not titres and OD increases cannot be directly correlated to increases in titre (14).

Rubella IgG Avidity

IgG avidity testing can be used to differentiate between primary and secondary rubella infections, and to exclude the possibility of persistent IgM months and years after primary infection. This is of particular importance to clinical decision making when an IgM-positive serology result is obtained during pregnancy. Avidity refers to the strength of interaction between an antibody and a multi-

valent antigen. Low avidity antibodies are produced in response to a primary infection, and are replaced over time with high-avidity antibodies as the immune response matures (14). In avidity testing, protein denaturants are used to differentiate between high and low-avidity IgG antibodies based on the relative resistance of the antibody/antigen complex to dissociation following a series of wash steps. An avidity index is then calculated by comparing the OD values obtained in the presence and absence of the protein denaturant (1). Performance of in-house avidity assays has been largely limited to experienced WHO reference laboratories due to challenges in their development, standardization and interpretation, however kit-based assays have been evaluated for commercial use and show high correlation with established in-house methods(75) (14).

Virus Isolation, Detection and Genotyping

Measles and rubella viruses can be detected through virus isolation or by directly detecting viral RNA using reverse-transcription (RT) polymerase chain reaction (PCR). Both methods are confirmatory of acute measles and rubella infection. Appropriate samples for measles and rubella virus isolation and RT-PCR are throat/nasopharyngeal or urine specimens collected as soon as possible after rash onset, ideally within 4- 5 days; measles virus can also be detected in blood samples but with much poorer sensitivity (15).

Molecular Detection: RT-PCR

Although not routinely used as a front-line diagnostic tool, RT-PCR is increasingly used as a relatively rapid confirmatory test method which directly detects amplified measles and rubella viral RNA in clinical samples. An advantage of RT-PCR is that it can detect inactivated virus particles, thereby extending the post-rash detection window by 3-4 days, and possibly weeks, beyond that of viral isolation (14). Most significantly, RT- PCR amplification of WHO target sequences (measles N gene,

rubella E1 gene) combined with nucleotide sequencing permits more timely genetic characterization of measles and rubella viruses. This supports both strain surveillance and diagnostic efforts including linking of cases and outbreaks, and differentiating illness caused by vaccine versus wild-type strains (47).

Virus Isolation

Virus isolation in culture is confirmatory for measles and rubella infection, but is infrequently used for diagnostic purposes as direct molecular detection is more timely and practical. Even so, virus isolation is important for the acquisition of representative virus isolates to support national and international measles and rubella strain characterization and surveillance efforts. Measles and rubella viruses can be isolated through culture in the Vero/SLAM cell line, which consists of Vero cells transfected with a plasmid encoding the gene for human SLAM (signalling lymphocyte activation molecule) which is known to be a cellular glycoprotein receptor for measles virus on certain T and B cells (14)(4). While measles virus can be isolated from urine and nasopharyngeal samples as late as 4-7 days after rash onset, viraemia typically concludes 2-3 days after rash onset with the appearance of IgM antibody. The optimal sampling window for measles virus isolation is therefore 2-4 days prior to rash onset up to approximately 4-5 days after rash. Rubella virus can be isolated from blood, urine, cerebrospinal fluid (CSF), throat and nasopharyngeal sample (T/NP) from rubella and CRS cases; the detection of rubella virus in samples collected during the first few months of life is confirmatory for congenitally-acquired rubella (1,14,15,40,53).

Genotyping

Genotype information is determined by sequencing RT-PCR products that have been directly amplified from either a clinical specimen, or from a viral isolate. While the former process yields

more timely results, the availability of measles and rubella isolates representative of circulating strains is of particular importance when more complete genotypic characterization is required to classify novel strains. Viral genotyping is an important molecular epidemiological tool used for a variety of surveillance related purposes. Comparative analysis of genotypic information can be used to differentiate vaccine and wild-type virus strains, identify the source of imported cases, establish links between cases and outbreaks lacking a conventional epidemiological link, and document progress towards measles and rubella regional elimination through ongoing strain surveillance efforts (15,50).

Measles and Rubella Testing: Provincial and National Roles

Provincial/Territorial Laboratories

In Canada, front-line measles and rubella IgM serology testing is performed by provincial public health laboratories in a majority of provinces, and by regional hospital laboratories in a sub-set of provinces including Ontario, Québec and New Brunswick. A number of provincial laboratories also have the capacity to perform confirmatory testing, including acute and convalescent IgG serology for measles and rubella, and molecular detection of measles using RT-PCR. Rubella RT-PCR and measles and rubella genotyping are performed exclusively at the national level. The Canadian territories do not have the capacity for front-line serology testing, and refer any test requests to neighbouring provincial public health laboratories.

National Microbiology Laboratory

The National Microbiology Laboratory (NML) performs measles and rubella diagnostic and confirmatory testing as required to support measles and rubella laboratory investigations. This

includes measles and rubella IgM and IgG (acute and convalescent) serology; molecular detection of measles and rubella using RT-PCR; measles SSPE diagnostic testing; rubella avidity testing to support rubella case confirmation during pregnancy; CRS/I confirmatory testing; and genotyping to support vaccine/wild-type strain differentiation. The NML also supports national maintenance of laboratory proficiency by distributing proficiency panels for RT-PCR, IgM and IgG serology to measles and rubella testing laboratories on an annual basis.

At an international level, the NML is a certified PAHO/WHO Measles and Rubella Regional Reference Laboratory, and has received WHO Measles and Rubella LabNet Accreditation. To support measles and rubella surveillance, the NML has sole responsibility for virus isolation and genotyping of representative viral strains to support molecular epidemiological analysis. As such, the NML encourages all provincial laboratories to provide appropriate samples for molecular detection and genotyping in all suspect measles and rubella cases. Additionally, the NML seeks to isolate representative measles and rubella viral strains from each chain of transmission occurring in Canada. Measles and rubella sequencing data are submitted by the NML to the WHO database, GenBank, and the genotype is reported to PAHO (47,76).

CHALLENGES OF ELIMINATION-PHASE SURVEILLANCE

Available epidemiological and laboratory evidence supports the regional elimination status of measles and rubella in Canada. However, until global eradication of measles and rubella occurs, there will be an ongoing risk of importation due to travel to and immigration from endemic regions, as well as travel to non-endemic regions with high levels of foreign travel and immigration (39,40). The optimization of surveillance during elimination phase becomes particularly important to detect cases in a timely fashion, ensure that the interruption of endemic transmission is retained, detect

susceptible populations, and identify the need to modify immunization strategies (40, 66).

Surveillance Performance

When considering the quality of measles and rubella surveillance in Canada with the objective of elimination-phase optimization, it is important to emphasize that national CMRSS surveillance is 'confirmed case' surveillance, with provinces and territories submitting zero and confirmed case reports for measles, rubella, CRS and CRI on a weekly basis via email or fax (63) (Appendix I). Suspected case data are not collected at the national level via CMRSS (67)(53). While the ability of CMRSS to detect sporadic cases suggests adequate surveillance performance(39,40), this is not able to be substantiated as existing data limitations prevent the routine assessment of surveillance quality using PAHO-recommended indicators which are largely based on the detection and reporting of 'suspected case' investigations. For surveillance purposes, PAHO defines a 'suspected case' as a patient in whom a health care provider suspects measles or rubella virus infection, or a patient with fever and rash (77). However, the ability to clinically diagnose fever-rash illness caused by measles and rubella is an increasing challenge in Canada and in other low incidence settings as physicians and other health care workers rarely encounter cases (1)(65, 105). During elimination phase, laboratory testing is particularly critical to measles and rubella detection and confirmation given the number of other pathogens having a similar fever-rash clinical presentation, including parvovirus B19, human herpes virus 6 (HHV-6) and dengue virus (2) .

Measles and rubella cases meeting the national 'confirmed case' definitions are reported internationally to PAHO by the Centre for Immunization and Respiratory Infectious Diseases (CIRID), PHAC. From the outset of this project in 2006, Canada has remained one of a minority of countries in the World Health Organization (WHO) Region of the Americas that do not report established 'suspect

case'-based surveillance indicators to PAHO (Tables 1.5, 1.6, 1.7) (78). While it has not been feasible to estimate the performance of surveillance in Canada using PAHO indicators due to national data limitations, a separate question is whether the estimation of established PAHO indicators is appropriate as a measure of the quality of surveillance in the Canadian setting. PAHO indicators are designed to assess quality of surveillance in all countries in the region of the Americas, including countries that rely more heavily on the detection of clinically suspect cases and which do not have the laboratory infrastructure and capacity for rapid confirmatory testing present in Canada and other more industrialized countries.

Table 1.5 PAHO Integrated Measles/Rubella Indicators and Targets, 2005(77,78)

Indicator	Target/Threshold
Proportion of reporting sites that report weekly	≥80% of surveillance sites should report each week on the presence or absence of suspected cases
Proportion of suspected cases with adequate investigation	≥80% of all suspected cases should have had an adequate investigation
Proportion of suspected cases with adequate sample	≥80% of suspected cases must have a blood specimen collected within 30 days of rash onset or be linked epidemiologically to a lab-confirmed case
Proportion of suspected cases with a blood specimen received at the laboratory within 5 days of collection	≥80% of all laboratory specimens collected from suspected cases must arrive at the laboratory within 5 days of collection.
Proportion of suspected cases with a blood specimen processed within 4 days of laboratory reception	≥80% of specimens must be tested and the results reported back to the surveillance unit within 4 days of specimen reception at the laboratory.
Proportion of suspected cases that were laboratory discarded	≥95% of all suspected cases should be discarded due to serological results ruling out measles/rubella, or ruling in another cause.
Proportion of chains of transmission with representative samples for viral isolation	≥90% of transmission chains should have representative samples for viral isolation

PAHO Definitions:

Suspected case: a patient in whom a health care provider suspects measles or rubella virus infection, or a patient with fever and rash is, for surveillance purposes, considered to be a suspected measles/rubella case.

Adequate sample: blood specimen collected within 30 days of rash onset or epidemiologic link to a laboratory-confirmed case

Adequate investigation: home visit within 48 hours of notification (clinical and epidemiologic investigation of the suspected case as well as of contacts of the suspected case); completeness of relevant data (i.e. date of notification, date of investigation, date of rash onset, date sample taken, type of rash, presence of fever, dates of previous measles/rubella vaccinations); and active case-searches.

[4]

Chain of transmission: Two or more confirmed cases that are linked epidemiologically

Table 1.6 PAHO Integrated Measles/Rubella Indicators and Targets, 2011-2012(37,79)

Criterion	Indicator	Target
Reporting Rate	Annual rate of suspected measles and rubella cases	≥2 suspected measles and rubella cases/100 000 pop.
Adequate Investigation	% suspected cases with household visit within 48 hours following reporting	≥80%
	% suspected cases with household visit with the following 11 data points completed: name and/or identifier, place of residence, sex, age or date of birth, date of reporting, date of investigation, date of rash onset, date of specimen collection, presence of fever, date of prior MR vaccination, travel history	≥80%
	% confirmed cases with follow-up of contacts for 30 days	≥80%
	Proportion of reporting sites that report weekly*	≥80% of surveillance sites should report each week on the presence or absence of suspected cases
Laboratory Confirmation	% suspected cases with adequate blood specimen	≥80%
	% suspected cases with a blood specimen processed within 4 days of laboratory reception*	≥80%**
Viral detection	% outbreaks with adequate specimens and genotype information available from at least 1 viral specimen	≥80%

**Signifies indicators which are not key elimination verification criteria, but are requested weekly by PAHO and published in M/R bulletin tables.*
***≥80% of specimens must be tested and the results reported back to the surveillance unit within 4 days of specimen reception at the laboratory.*

PAHO Definitions:

Suspected case: a patient in whom a health care provider suspects measles or rubella virus infection, or a patient with fever and rash is, for surveillance purposes, considered to be a suspected measles/rubella case.

Adequate sample: blood specimen collected within 30 days of rash onset or epidemiologic link to a laboratory-confirmed case

Outbreak: two or more confirmed cases of measles, or two or more confirmed cases of rubella, determined to be related as supported by epidemiological or virological evidence.

Table 1.7 PAHO CRS Surveillance Indicators: 2011-2012 (37,79)

Criterion	Indicator	Target
Reporting Rate	Annual rate of suspected CRS cases	≥1 suspected CRS case/10 000 live births
Adequate Investigation	% suspected CRS cases with the following 8 data points completed: name and/or identifier, place of residence, sex, date of birth, date of reporting, date of investigation, date of specimen collection, and vaccination history of mother; also clinical examinations for deafness, blindness, and congenital cardiopathy	≥80%
Laboratory Confirmation	Proportion of suspected cases with adequate blood specimen	≥80%
Viral detection	% confirmed cases with adequate specimen analyzed for virus detection/isolation	≥80%
Monitoring of virus excretion	% confirmed cases with at least 2 negative tests for virus detection/isolation, after 3 months of age, with 1-month lapse between tests	≥80%

PAHO Definitions:

Suspected CRS: An infant aged ≤1 year in whom a health-care worker suspects CRS due to:

1. One or more of the following birth outcomes detected: congenital cataracts, congenital heart defects, purpura at birth, or hearing impairment, and/or

2. History of confirmed or suspected maternal rubella infection during pregnancy.

Adequate specimen: blood specimen collected within 30 days of rash onset or epidemiologic link to a laboratory-confirmed case

Integration of Laboratory and Epidemiological Data

When this project was first considered in 2005, rubella and CRS/CRI surveillance had not yet been integrated with enhanced measles surveillance at the national level, and detailed laboratory results to support case review and confirmation efforts were not captured; rather, case reports would simply include the status of a reported case as laboratory-confirmed or epidemiologically-confirmed (80). With the implementation of CMRSS and the integration of measles and rubella reporting, the national case report form was updated to incorporate whether positive test results had been obtained for measles/rubella IgM serology, IgG seroconversion, virus isolation and virus detection (i.e. yes, no, not done)(63).

During the present elimination phase, measles and rubella investigations are performed on a case-by-case basis (53,67). Most cases are expected to be import-related or sporadic (i.e. having neither a known travel history nor an epidemiologic (epi) link to a lab-confirmed case), thereby requiring laboratory confirmation. IgM serology is the first laboratory test performed during measles and rubella investigations, and given the unreliability of differential clinical diagnosis of fever/rash illness, the detection of an IgM-positive result by a provincial public health lab is expected to be the earliest point of detection for suspect case surveillance purposes. However, the decreased positive predictive value (PPV) of IgM serology under low incidence elimination circumstances requires that all sporadic cases be confirmed through additional lab testing including IgG serology, virus isolation or molecular detection (RT-PCR)(74,81)(73)(53,67). Genotypic characterization is also recommended to support molecular epidemiological efforts to differentiate vaccine and wild-type strains, determine the source of sporadic and imported cases, and to document and verify the status of measles and rubella elimination in Canada (53)(40)(39)(74).

Timely communication and integration of data held by laboratory and epidemiology public health counterparts at the provincial and federal level are needed to ensure that appropriate samples are obtained to support confirmatory testing and molecular epidemiology efforts. This is particularly important given the narrow window of opportunity after rash onset to obtain samples for molecular detection and virus isolation (14). The discarding of a provincially suspected measles or rubella case at the national level due to a missed opportunity for confirmatory testing constitutes a failure of surveillance.

Integration of laboratory and epidemiology data is a significant challenge in the Canadian setting. Provincial and national laboratory and epidemiology counterparts involved in suspect measles and rubella investigations have specific areas of responsibility, and often do not have all relevant information available to them due to the compartmentalization of data during the early stages of a given investigation. At the provincial and national laboratory levels, epidemiological data necessary to the appropriate interpretation of test results may not be provided on test requisition forms (e.g. rash onset date, travel and immunization history). In particular, the confirmation of sporadic cases by provincial and national public health frequently depends on the correct interpretation of confirmatory test results by laboratory experts. This analysis in turn depends upon the timely linking of lab and epi data for the investigation in question. Existing provincial legislation related to the communication of public health information further complicates data linkage between provincial and national investigators as PHAC is not, under routine circumstances, able to receive data elements used for case identification and tracking at the provincial level if they are considered 'personally identifiable'; these include 'name', 'public health identification number', and possibly 'date of birth'(57,82). An additional consideration is that disease reporting at the provincial/territorial level is mandated by P/T legislation, whereas nationally notifiable diseases including measles, rubella and

CRS are so designated through a provincial/territorial consensus process. Case notification to the national level is voluntary and by mutual agreement as there is no existing legislative basis to compel the provision of data (53,67).

Information Technology Initiatives: 2005-2006

A primary consideration in the development of timely and integrated interjurisdictional surveillance systems is the availability of information technology (IT) tools and platforms capable of their support, and the ability to secure associated resource requirements both human and financial. At the time this investigation was first considered in 2005 - 2006, there were no known models of real-time, integrated measles, rubella and CRS/I surveillance systems in the PAHO region of the Americas or in other regions that could be adapted or adopted to address the surveillance challenges identified in the Canadian setting. If a measles and rubella surveillance (MARS) system were to be piloted in Canada to explore the feasibility of addressing existing challenges, it would first need to be modeled and developed to support elimination-phase surveillance requirements within the context of existing jurisdictional surveillance roles and personal health information sharing policies and legislation.

Canadian Network for Public Health Intelligence (CNPHI)

As a national PHAC initiative within the NML, the Canadian Network for Public Health Intelligence (CNPHI) developed an innovative web-based IT platform to support interjurisdictional collaboration and sharing of disparately sourced P/T and national data, and to facilitate expert interpretation and analysis to inform public health action. In 2005, the CNPHI platform was already being used to support the national electronic distribution of public health alerts by national and provincial infectious disease epidemiologists, as well as laboratory-based surveillance efforts such as the National Enteric Surveillance Program (NESP) (83). NESP employs a custom designed CNPHI

application to facilitate weekly centralized reporting of the total numbers of enteric pathogens detected by public health laboratories, and incorporates an algorithm which flags higher than average detection levels by pathogen to support national public health outbreak investigation efforts(83)(84). The development of custom CNPHI applications is dependent on a grassroots, program expert-driven approach whereby disease-specific surveillance requirements and data elements are agreed upon by the public health experts responsible for infectious disease surveillance, and communicated to CNPHI to inform IT development efforts.

Canada Health Infoway

At the inception of the MARS pilot project, Canada Health Infoway (CHI) led the development of another national IT-based initiative seeking to support interjurisdictional electronic sharing of public health-related data and information. CHI was created as an independent, not-for-profit corporation in 2001 by the First Ministers of Canada, with funding provided by the Government of Canada (85). The role of CHI is to co-invest with the provinces and territories to develop and monitor projects that support the CHI mandate, i.e. to foster the development and adoption of a pan-Canadian Electronic Health Record (EHR)(85,86). In March of 2004, the Government of Canada provided $100 million in funding (increased to $135 million in 2007) to support the development of a pan-Canadian Public Health Surveillance (PHS) system. The Addendum Funding Agreement defined the PHS system as 'an electronic information system that supports the collection, collation, analysis, interpretation and dissemination of routinely collected health surveillance data through the integration of business processes, standards, information and communications technologies to guide public health action generally and to manage infectious diseases specifically'(87)(88). To support the pan-Canadian PHS system, a set of IT applications and tools known collectively as Panorama© was developed around 6 functional areas to support the management of 'communicable disease cases, outbreaks,

immunization programs, public health materials and vaccines, notifications regarding critical events and public health work tasks'. Panorama was initially scheduled for completion in 2007, approximately 12 months after selection of IBM as the IT vendor (87). Notably, CHI funding support for jurisdictional EHR-interoperable solutions was available solely to regional and P/T level stakeholders; the funding of national surveillance initiatives was outside the scope of Panorama. Independently of project funding, it was also unclear at the national level whether Panorama solutions implemented by participating P/T stakeholders would ultimately meet national disease-specific notifiable disease surveillance requirements, whether Panorama would be significantly adopted by all P/T jurisdictions, and whether PHAC would have a role in Panorama. In 2006, Canada Health Infoway was in the early stages of public health stakeholder consultation to discuss existing public health information terminology and messaging standards (i.e. HL7v3, LOINC, and SNOMED) that could be adapted or adopted to support Panorama implementation. Notably, CHI funding support for EHR-interoperable solutions was available solely at the P/T level. The incorporation of disease-specific data and messaging requirements to support notifiable disease surveillance efforts at the national level were not included in the scope of the initiative.

PURPOSE

The purpose of the measles and rubella surveillance (MARS) pilot project is to explore methods by which surveillance can be optimized to support elimination efforts at the provincial, national and international levels, and to address existing challenges associated with elimination-phase surveillance in Canada. In particular it seeks to investigate the feasibility of implementing real-time measles and rubella surveillance using a model that is capable of capturing suspect cases at the earliest point of detection, and that integrates provincial and federal laboratory and epidemiology data in a manner that supports centralized access to non-nominal data at the outset of each suspect case

investigation. The intent is then to use suspected measles and rubella investigation data captured through this initiative to estimate the performance of measles and rubella surveillance using indicators, and to investigate the usefulness of various recommended and adapted surveillance indicators in the Canadian setting.

HYPOTHESIS

Central Hypothesis

I. It is feasible to develop and implement a real-time, web-based measles and rubella surveillance system in the Canadian setting that incorporates the following features:

a. Real-time automated alerting of provincial and federal stakeholders upon the initiation of a laboratory investigation (e.g. lab-based entry of an IgM-positive result), or initiation of a novel epidemiological investigation
b. Real-time, centralized contribution of case investigation data via a common report form accessible by provincial and national laboratory and public health counterparts
c. Collection of augmented laboratory data to support measles/rubella investigation efforts and the estimation of surveillance performance using indicators
d. Integration of non-nominal provincial and federal laboratory, epidemiological and clinical data fields to support case investigation and national case confirmation
e. Monthly collection of aggregate laboratory test data to estimate the ongoing level of investigation into MLI, and to provide denominator data for surveillance indicator estimation

Sub-Hypotheses

II. Implementation of real-time surveillance in MARS pilot provinces will result in increased timeliness of national measles and rubella surveillance when compared with established confirmed-case surveillance conducted via CMRSS.

III. It is possible to use laboratory data to estimate the performance of national measles and rubella surveillance using adapted PAHO surveillance indicators*.

   a. **using the performance of measles IgM serology testing as a lab based proxy for an MLI or 'suspected case' investigation as defined by PAHO.*

OBJECTIVES

I. To investigate the feasibility of optimizing and evaluating the performance of national elimination-phase surveillance as described in the central hypothesis, the specific objectives of the MARS pilot project are as follows:

   a. To design a real-time, integrated measles and rubella surveillance model for custom IT application development using the CNPHI platform.
   b. To implement real-time, integrated measles and rubella surveillance at participating national and provincial laboratory and public health pilot sites in BC, AB and NL over a 1 –year period using a web-based MARS application, including the collection of augmented laboratory data.
   c. To use the augmented laboratory data collected to estimate measles and rubella surveillance performance in MARS pilot provinces using various surveillance indicators, with comparison to PAHO/WHO surveillance targets and other suggested literature values.

d. To compare the timeliness and completeness of real-time measles/rubella investigation surveillance at MARS pilot sites with established confirmed-case surveillance conducted via CMRSS using surveillance indicators.

e. To conduct a post-pilot national survey of all known measles and rubella testing labs in Canada, and use aggregate provincial measles and rubella IgM serology testing data for the 2007 – 2011 and MARS pilot years to assess the level of investigation into MLI* using surveillance indicators.

f. To conduct a post-pilot survey of MARS pilot participants to support the descriptive assessment of MARS real-time surveillance attributes, and the overall success of pilot implementation.

CHAPTER 2: MATERIALS AND METHODS

STUDY DESIGN - OVERVIEW

The MARS pilot project has an observational, primarily cross-sectional study design that includes both descriptive and analytical elements. To assess the feasibility of implementing real-time surveillance in the Canadian setting, key elements of the study design included the creation of a real-time, integrated measles and rubella surveillance (MARS) model capable of addressing existing surveillance challenges, and the subsequent implementation and piloting of the CNPHI-developed MARS web-based application at national and provincial pilot sites for a 1-year data collection period. An expanded set of laboratory-based data was requested via pilot sites to enable the performance of MARS real-time surveillance to be assessed using surveillance indicators, and compared with national CMRSS confirmed-case surveillance wherever feasible. The study design also includes the retrospective collection of measles and rubella laboratory testing data via survey both prior to MARS application development to support preliminary surveillance indicator estimation using 2005-2006 laboratory data, and immediately following the pilot to support national surveillance indicator estimation and evaluation for the 2007-2011 reporting years in addition to the MARS pilot period. This information was gathered to allow the performance of surveillance via MARS to be compared with national surveillance performance during the pilot year, and to allow evaluation and comparison of national measles and rubella surveillance performance during outbreak and non-outbreak years at the national and provincial levels during the previous 5-year period (2007-2011). A separate, post-pilot study of MARS pilot participants was also conducted to contribute to the descriptive assessment of MARS surveillance attributes, including simplicity/ease of use, stability, acceptability, and usefulness of the MARS real-time surveillance model.

MARS PILOT SITE RECRUITMENT

Rationale for selection

MARS pilot sites were selectively recruited based on a number of considerations. To ensure that the measles and rubella investigation data captured by provincial pilot sites would be representative of the entire provincial population, it was considered necessary to enlist the participation of both the laboratory and epidemiology counterparts of provincial public health. This would also be needed to support full integration of laboratory, epidemiological and clinical data to achieve the objectives of real-time investigation-based surveillance. Other important considerations included: the complexity of provincial public health laboratory structures (i.e. central provincial PHL versus a decentralized laboratory model) and the concomitant practicality of timely pilot implementation and coordination; the inclusion of provinces representative of geographically distinct regions with varying population densities, and the objective that all pilot sites combined represent a significant proportion of the Canadian population. It should be noted that Canadian territories were not considered in the recruitment process as measles and rubella testing capacity exists solely within the provinces.

Approach

Given the voluntary nature of national infectious disease notification in the Canadian setting, the ability to pilot an integrated real-time surveillance model would depend on the successful enlistment of laboratory and epidemiology counterparts within a province as data contributors. To have provincial support, the surveillance model would have to address not only national surveillance challenges, but also provincial stakeholder needs while at the same time minimizing any additional efforts required to participate. To respect jurisdictional roles and ensure a collaborative national/provincial approach to pilot development and implementation, the considered approach

was to first ensure that the pilot concept had the support of the federal epidemiologists within CIRID responsible for national CMRSS surveillance, and then present the draft pilot concept to both laboratory and epidemiology stakeholders within potential pilot provinces for review.

Stakeholder Consultation

Prior to commencing the development of a detailed model for the MARS surveillance application, a preliminary MARS project proposal was developed for review and discussion with epidemiologists within the Immunization and Respiratory Infections Division, PHAC (now CIRID) to ensure an integrated approach at the national level. The proposal was subsequently presented to provincial public health laboratory and epidemiology stakeholders in British Columbia (BC), Alberta, Manitoba and Newfoundland during the summer and fall of 2006 to gauge provincial interest in participating in a real-time surveillance pilot, and to capture preliminary input regarding the draft model. Participation was ultimately confirmed by provincial laboratory and epidemiology counterparts in BC, Alberta, and Newfoundland, which at the time of enlistment collectively represented 25% of the Canadian population by 2006 census (89). An overview of participating provincial pilot sites and the populations represented is given by Table 2.1.

MARS Pilot Application – Development of the Surveillance Model

Surveillance Data Flow Mapping

To develop an integrated measles and rubella surveillance model supportive of real-time elimination phase surveillance, the first step was to map the current flow of data between provincial and national public health laboratory and epidemiology stakeholders. The resulting data flow map provided a high level overview of national 'confirmed case' surveillance as conducted via CMRSS, and

was validated through review and discussion with national and provincial public health stakeholders involved in measles and rubella surveillance (Figure 2.1). The CMRSS data flow map was then used to model an alternate approach to surveillance through the implementation of real-time, centralized data entry by provincial and national stakeholders via a web-based MARS pilot application (Figure 2.2).

Table 2.1 MARS Provincial Pilot Sites

Province	Provincial Pilot Sites	Provincial Population *(census year)*		% Canadian Population***	
British Columbia	BC Centre for Disease Control	4 113 487	*(2006)*	13.0%	*(2006)*
	BC Public Health Microbiology and Reference Laboratory (PHMRL)*	4 400 057	*(2011)*	13.1%	*(2011)*
Alberta	Alberta Health	3,290,350	*(2006)*	10.4%	*(2006)*
	Alberta Provincial Laboratory for Public Health **	3,645,257	*(2011)*	10.9%	*(2011)*
Newfoundland and Labrador	Newfoundland and Labrador Public Health Laboratory	505,469	*(2006)*	1.6%	*(2006)*
	Newfoundland and Labrador Department of Health and Community Services	514,536	*(2011)*	1.5%	*(2011)*
All Pilot Provinces = 3	Participating Sites = 6	7 909 306	*(2006)*	25.0%	*(2006)*
		8 559 850	*(2011)*	25.6%	*(2011)*

**At the time of MARS pilot development, BC PHMRL was a part of BCCDC.*
***The AB provincial public health laboratory is located across 2 sites: Calgary and Edmonton*
****Canada census population: 31 612 897 (2006); 33 476 688 (2011)*

FIGURE 2.1 CMRSS Data Flow Map: 'Confirmed case' Measles and Rubella Surveillance. The surveillance process begins when a Physician sees a patient with clinically suspect MLI, and submits a test request for measles/rubella IgM serology testing to the Provincial Laboratory (PL). If positive, the PL has a central role in reporting the positive result to the Physician, Regional and Provincial Epidemiology (PE) counterparts during the course of the MLI investigation. Regional Epidemiologists gather case information and perform contact tracing, and report their results to the PE unit. At the conclusion of the provincial case investigation process, PE completes a National Confirmed Case Report which is submitted via CMRSS to National Epidemiology counterparts in CIRID. Following case review, CIRID reports confirmed cases to PAHO on a weekly basis. The National Microbiology Laboratory performs confirmatory diagnostic reference testing and is solely responsible for all genotyping, the results of which are reported to PAHO to support international strain surveillance efforts. However, there is no formalized mechanism by which the NML or the PL are integrated into national measles and rubella surveillance and reporting using the CMRSS surveillance model.

FIGURE 2.2 MARS Data Flow Map: 'Real-time' Measles and Rubella Surveillance Model. The MARS surveillance model seeks to support real-time, integrated measles/rubella surveillance at the earliest point of detection by enabling the PL to report positive IgM serology results into Measles/Rubella Investigation Reports via the MARS surveillance application. While PE can also initiate investigation reporting, the majority of investigations are expected to be detected by the PL under elimination circumstances. Once a report is initiated, all provincial and national laboratory and epidemiology counterparts are simultaneously notified that an investigation is underway to support timely public health action. Investigators are then able to contribute data to the common report form to support case classification efforts in keeping with established surveillance roles.

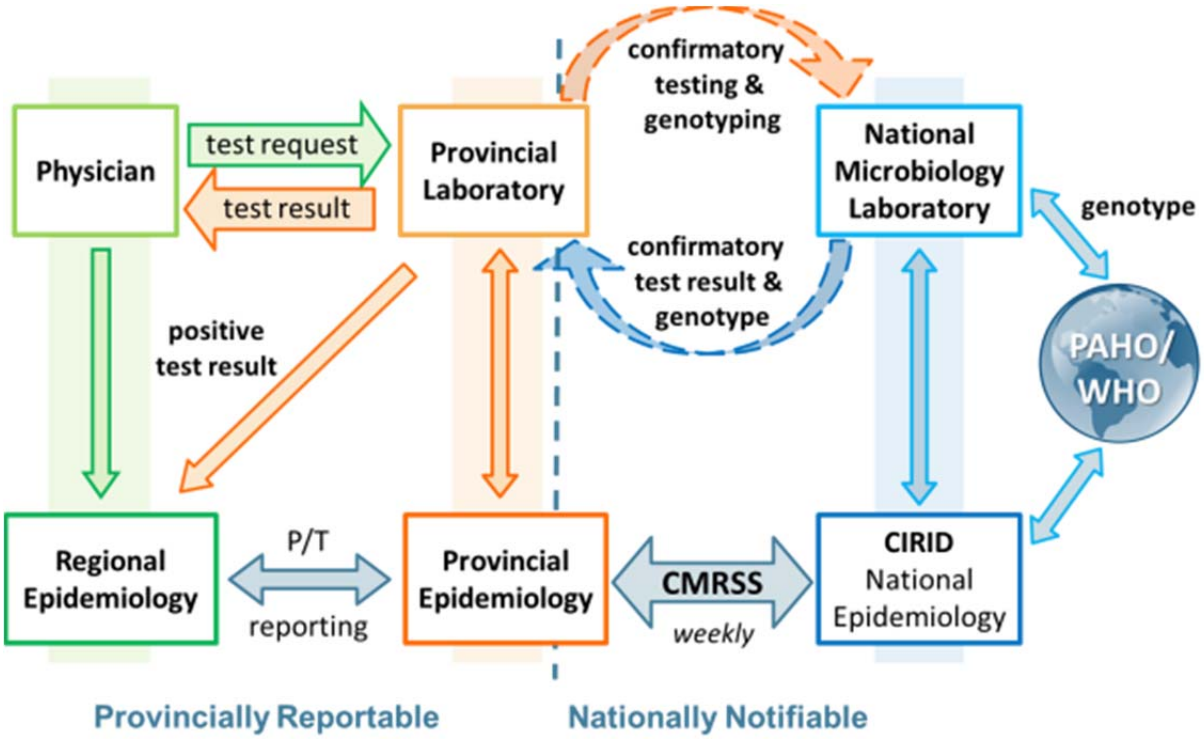


FIGURE 2.1 CMRSS Data Flow Map: 'Confirmed Case' Measles and Rubella Surveillance

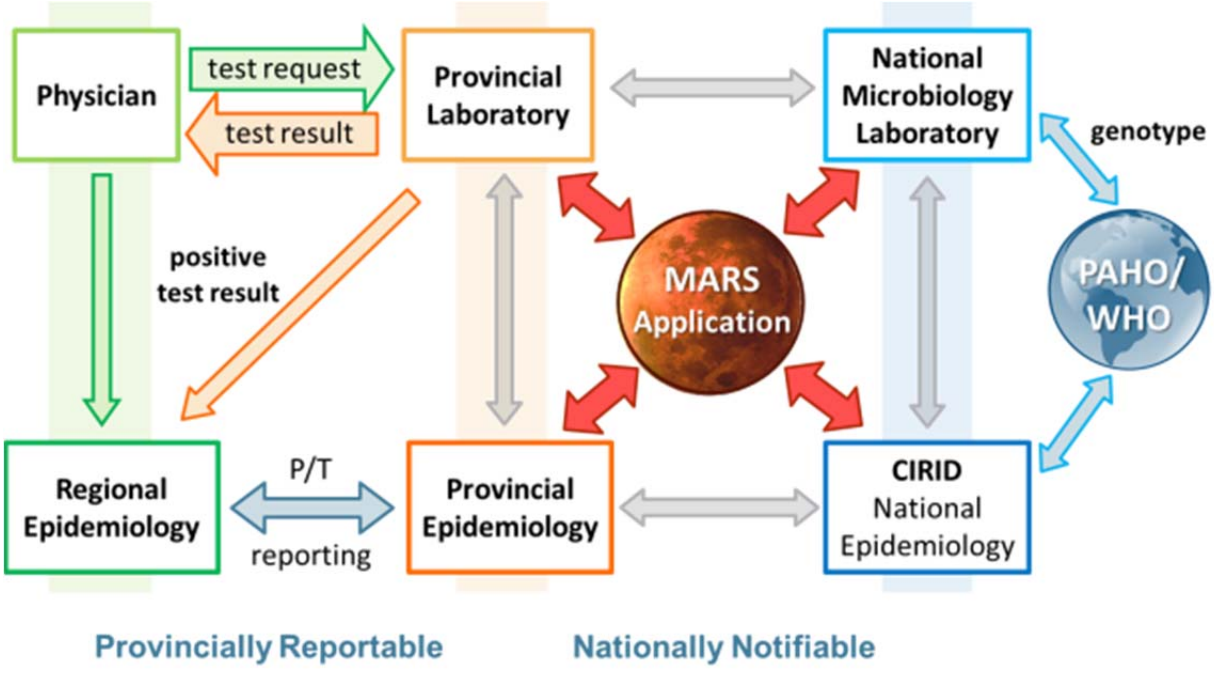


FIGURE 2.2 MARS Data Flow Map: 'Real-time' Measles and Rubella Surveillance Model

Scope

The MARS pilot application was designed to collect non-nominal laboratory, epidemiologic and clinical data to support real-time measles, rubella, CRS and CRI surveillance, and to enable the estimation of various surveillance indicators and attributes. Key application features incorporated into the data flow model for the MARS pilot application are described in the following sections.

Access/User Roles

The CNPHI platform chosen for IT development of the MARS application provides flexible web-based user access from any location with internet connectivity. A user name and password are required to enter the secure CNPHI website hosting the MARS application, and the corresponding level of MARS access granted to the user is dependent upon the assigned user role. Draft national and provincial user access roles were developed based on preliminary consultation with provincial and national MARS pilot sites (Table 2.1), then reviewed and confirmed prior to finalizing the MARS data flow model (Appendices II – XI).

To register MARS application users, participating provincial and federal pilot site leads provide contact information for all MARS participants at their site, and specify the appropriate user roles in accordance with their business rules. Prior to gaining access to the CNPHI site, each user is required to complete the online CNPHI registration process and specify the type of MARS access requested, then submit a CNPHI User Agreement via fax which describes general user responsibilities (90). CNPHI then verifies the access request details with the MARS pilot coordinator prior to granting access.

Table 2.2 MARS User Roles and Data Access

User Role*	Data Access
Provincial Reader/Writer	▪ Can access all provincial reports, and enter lab, epi and clinical data ▪ Can view and query aggregate level data for all provinces and nationally ▪ Can query report level data for their province only by any combination of data fields
National Reader/Writer	▪ Can access all provincial reports, and enter lab, epi and clinical data ▪ Can view and query aggregate level data for all provinces and nationally ▪ Can query report level data for all contributing provincial sites by any combination of data fields

**Provincial and national MARS user roles are defined at the site level, and MARS data entry is expected to reflect the established surveillance roles of laboratory and public health sites* (Table 2.3).

Centralized Reporting and Data Linkage

To address data linkage challenges associated with the inability to receive personally identifiable information at the national level, the MARS application was designed to assign a unique, auto-generated 'MARS Identifier' to each non-nominal report upon submission by the participating pilot site. The MARS identifier format incorporates information regarding the report type, submitting province, and date of submission (Appendices VIII - XI). Additional 'identifier' fields were included to allow provincial and federal laboratory and epidemiology stakeholders to enter site-based identifiers which in combination with the MARS identifier could be used to link MARS reports with their site-based data. This approach was taken to support seamless interjurisdictional communication regarding non-nominal measles and rubella investigation data entered centrally into MARS investigation reports. In keeping with established national/provincial surveillance roles, the decision to share provincial data via MARS remains at the discretion of the province.

Stakeholder Alerting and Notification

To support stakeholder notification and communication from the outset of a suspect measles/rubella case investigation, an automated notification function was included in the MARS model. The MARS application was designed to distribute an automated notification email under the following circumstances (i) a new MARS report is created and submitted by provincial laboratory or epidemiology stakeholders, or (ii) information in an investigation report is updated. The electronic alert notification is then distributed via email to all laboratory and epidemiology stakeholders within the reporting province, and to national stakeholders at the NML and CIRID. Notification emails were designed to include the following basic information: the unique MARS identifier, the report type (Measles/Rubella, CRS/I, Weekly Zero, Monthly Test), the intent of the notification (new report, measles/rubella IgM+ result entry , report update), and a direct link to the report form on CNPHI, which is username/password accessible by the recipient.

Scenario: A MARS user at the provincial laboratory having a 'Provincial Reader/Writer' role opens a new 'Measles/Rubella Investigation Report', enters a measles/rubella IgM+ test result and any other non-nominal information provided with the test requisition, and submits the report. The MARS application automatically assigns a unique 'MARS Identifier' to the report, and distributes an automated email to notify relevant stakeholders that a new report with an IgM+ result had been submitted (i.e.: provincial public health laboratory and epidemiology stakeholders in the reporting province, and national stakeholders within the NML and CIRID). The alert notification email provides a link to the investigation report on the MARS site including the unique 'MARS Identifier' to ensure that stakeholders have central access to the same report from the outset of the investigation. Provincial and national stakeholders then contribute data elements for which they are responsible to the central report form as the investigation progresses.

It should be noted that MARS was not designed to support the sharing of provincial information regarding measles and rubella investigations, cases and outbreaks with other provinces and territories as this particular functionality is already provided by the national web-based Public Health Alerts system for all infectious diseases of interest.

MARS Reporting

The MARS application was designed to support both real-time and periodic reporting through the development of four distinct report types: real-time 'measles/rubella' and 'CRS/CRI' investigation reports, and periodically submitted 'weekly zero' reports and 'monthly test' reports. As part of the MARS development process, detailed mock-ups of the four report types were designed to support stakeholder review (Appendices II-V).

Periodic Reporting: 'Weekly Zero' and' Monthly Test' Reports

A Weekly Zero Report form was incorporated into the MARS application to allow participating pilot sites to fulfill their routine CMRSS reporting requirements by contributing this data via the MARS system. The MARS Weekly Zero Report data fields were designed to mirror the CMRSS weekly zero report request, with the difference that reporting the confirmation of a case in the MARS Weekly Report prompts the MARS application to provide a summary of the number of measles, rubella, CRS and CRI cases classified as confirmed within the MARS application for user verification (Appendix IX).

The MARS Monthly Test Report was developed to support the routine monthly contribution of aggregate measles and rubella IgM test data (i.e. total tests performed, total positive test results) by provincial public health laboratories, and to document the test kit employed. This report type is unique to MARS, and was included both to support estimation of the level of investigation into

measles and rubella, and to provide denominator data for the estimation of other lab-based surveillance indicators (Appendix VIII).

Real-time Reporting: 'Measles/Rubella' and 'CRS/I' Investigation Reports

In contrast with CMRSS which involves the national reporting of 'confirmed cases' once the provincial investigative process has concluded, MARS was designed to support the real-time submission of 'investigation reports' at the outset of suspect case investigations. 'Measles/rubella' and 'CRS/CRI' investigation report templates were modelled in accordance with current data requirements for national case classification (53) with the incorporation of additional MARS-specific data fields to facilitate data linkage, integration of laboratory data, and surveillance indicator estimation (Appendix II, III, X, XI). Additional measles and rubella clinical data fields were also incorporated to allow MARS to capture the full scope of data that might be collected at the provincial level (91). Measles/rubella and CRS/CRI investigation reports were designed to be initiated by either the provincial laboratory when a test result is detected that requires either further testing or additional epidemiological information to confirm or discard (e.g. measles/rubella IgM+ results), or by provincial public health should this be the first point of detection (e.g. identification of a clinical case with a link to a lab-confirmed case). Once created, the common report form can then be viewed and updated centrally in real-time by both national and provincial public health laboratory and epidemiology stakeholders as additional data become available. At the conclusion of each investigation, the case investigation is classified as either 'confirmed' (i.e.: laboratory confirmed, or epidemiologically confirmed) or 'discarded' (Appendix II, III) (53).

Real-time Reporting: MARS-Specific Data Fields

To ensure the ability to integrate and compare surveillance conducted at MARS pilot sites with

routine surveillance via CMRSS, the MARS real-time investigation report forms and were designed to capture all data elements included in current CMRSS reporting. This was done with reference to the current national case report forms for measles/rubella and CRS/CRI and national case definitions (63) (53)(Appendix II, III). In addition to CMRSS data fields, MARS measles/rubella and CRS/CRI investigation reports were designed to incorporate a number of MARS-specific data fields.

To support data linkage, 'MARS identifier', 'Laboratory Sample Identifier' and 'Public Health Identifier' fields were added. Augmented laboratory data fields were incorporated to enable more complete integration of laboratory and epidemiological data, to inform case classification efforts, and to support the estimation of surveillance indicators. For both 'Measles/Rubella' and 'CRS/CRI' investigation reports, the entry of laboratory data was structured to link test results to the sample tested using the 'Laboratory Sample ID' field, with the ability to enter multiple samples per investigation, and link multiple test results to each sample. Sample-associated data fields included the 'Sample Type', 'Sample Collection Date' and 'Lab Receipt Date', and whether a 'virus isolation/genotyping sample' was provided. Laboratory data fields included primary diagnostic (measles, rubella and parvovirus B19 IgM serology) and confirmatory/supplementary testing results (measles/rubella acute and convalescent IgG serology, RT-PCR virus detection, virus isolation, genotype, and rubella avidity) (Appendix X, XI). For each test type, the following result status options (i.e. positive, negative, indeterminate, not detected, inconclusive, not done), and associated 'Result Date', 'Testing Lab', "Test Kit' and 'History of repeat testing' fields were included as appropriate. Data fields were also included to capture the results of other IgM serology testing that might be performed in the course of a measles/rubella laboratory investigation, including HHV-6, dengue, Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus, and 'other' IgM serology results (Supplemental data field info provided to CNPHI). Any MARS data fields that were not visually

illustrated in version 4.4 of the data flow mock-ups due to space and time considerations were documented separately and provided to CNPHI for incorporation into the MARS IT build.

Data Entry Roles

The data entry roles of participating federal and provincial MARS pilot sites were designed in accordance with their established roles in national surveillance (Fig. 2.1, 2.2). A summary of anticipated site-based roles in contributing data to the four MARS reporting forms is provided in Table 2.3.

Note: During both the MARS model development and application launch process, it was emphasized to stakeholders that MARS data collection is intended to reflect current lab/epi investigative processes. While MARS was designed to capture all epidemiological, clinical and laboratory data that might be relevant to a given measles/rubella investigation, there was no expectation that either the lab or public health gather data beyond what is normally collected as part of a routine investigation.

Data Entry Methods

The MARS application was designed to support manual data entry during the pilot period. Outside of the routine periodic data entry requirements (weekly zero reporting, monthly aggregate test reporting), it was anticipated that the actual time requirement for real-time data entry on the part of provincial lab and epidemiology counterparts would be minimal as measles/rubella and CRS/CRI investigations were expected to be infrequent under elimination circumstances. Inclusion of the capacity for standardized batch uploading of line-listed case data was considered, but was ultimately deemed out of scope for the pilot as significant additional stakeholder consultation and IT development efforts would have been required.

Table 2.3 MARS Pilot Reporting Model: Site-based Data Entry Roles

MARS User	Measles/Rubella & CRS/CRI Reports	Weekly Zero Reports	Monthly Test Reports
Provincial Lab	**Real-time** data entry Create and submit **Measles/ Rubella** and **CRS/CRI Investigation Reports** when a positive/ indeterminate test result is detected that requires further lab and/or epi investigation to confirm or discard, including all lab data Update MARS investigation reports as lab test data become available Contribute to provincial review and classification of case investigations	NA	**Monthly** data entry Enter aggregate measles/ rubella IgM serology test numbers into the **Monthly Test Report**
Provincial Public Health	**Real-time** data entry Create and submit **Measles/Rubella** and **CRS/I Investigation Reports** for epi-initiated case investigations Update existing MARS investigation reports as new epi data become available Contribute to provincial review and classification of case investigations	**Weekly** data entry If there are **no confirmed cases** a 'zero' **Weekly Report** is submitted If there are **confirmed cases**[*], the total number is entered in the Weekly Report	NA
National Microbiology Laboratory	**Real-time** data entry Contribute NML test data to provincially submitted MARS investigation reports	NA	NA
Centre for Immunization and Respiratory Infectious Diseases	**Real-time** data entry Contribute epi data as required Responsible for national review and classification of case investigations	NA	NA

[*] *All confirmed cases entered into weekly confirmed case reports should have a corresponding MARS investigation report*

Prior to application development, it was confirmed with CNPHI that the MARS application would have the future flexibility to incorporate batch uploading of line-listed measles and rubella investigation data from provincial databases upon provincial request. This was flagged as a feature that would need to be explored and supported if broader adoption of the MARS application were to be sought beyond the initial pilot period. In particular, the need to support batch uploading would become particularly important to support timely national reporting in the event of a large outbreak. In future, the ability to support monthly uploading of aggregate measles/rubella test data might also facilitate the participation of provincial laboratories in providing data to support indicator estimation on an ongoing basis.

Query and Data Extraction Functions

A need identified in the MARS data flow model was the inclusion of full query functionality to allow users to search for and locate report-level data using any combination of data fields captured by the MARS application, and to specify the output fields required. Line listed query results would need to be exportable to Excel for further manipulation and analysis using statistical software applications. Through CNPHI consultation, it was confirmed that this capacity would be provided by appending the standard Query Console previously developed as part of the CNPHI platform to the MARS custom application.

Another requirement specified was the ability to generate, extract and print 'Measles/Rubella' and 'CRS/CRI' reports which capture all information (epidemiology, laboratory and clinical) associated with a particular episode, including clear reporting of complex fields. Examples of complex reporting fields documented in the data flow model included: laboratory test reporting for a given investigation which may include multiple tests performed on different samples/sample types, with

the possibility that a given test may be performed more than once with different results; and the need to link each test result to information regarding the sample tested (i.e.: 'Sample ID' 'Sample Type' and 'Date of Sample Collection') as well as detailed travel history information including locations, arrival and departure dates, and associated comments. To support document control, traceability and user accountability, the ability to export investigation reports as pdf documents with a time/date/username stamp was also requested.

Summary Charts

A series of draft summary charts was developed to provide MARS users with the ability to rapidly generate an aggregate-level overview of specific data elements of interest. Each chart format was designed to support the display of aggregate report-level data at either the national or provincial-level over a time period specified by the user (Table 2.4). The frequency of data aggregation into summary charts was specified in accordance with reporting periodicity, i.e.: aggregation of real-time report data on a weekly basis, and IgM test result data on a monthly basis. Illustrated descriptions of the proposed summary charts were provided for review and comment by provincial and federal stakeholders as part of the MARS data flow model (Appendix VII). To support CNPHI IT development requirements, summary charts were designed for review and approval prior to the initiation of MARS application development to ensure that the elements captured met the specific needs of provincial and national users.

MARS Data Flow Model: Review Process

Once development of the MARS data flow model was completed, it was presented first to national stakeholders at CIRID for review and discussion to ensure consensus at the federal level. The model was then distributed to provincial pilot sites via email for review and comment.

Table 2.4 MARS Data Flow Model: Summary Charts*

Chart Type	Case Data Aggregated	Display Output
Epidemic Curve	Measles, rubella	Number of confirmed cases by week of onset for the selected time period; includes confirmation method (i.e. lab/epi-confirmed)
Cases by Week of Onset	Measles, rubella, CRS, CRI, and for all episode types combined	Number of confirmed cases by week of onset for a selected time period
Investigation Overview Chart	Measles, rubella	Number of 'Confirmed Cases', 'Discarded IgM+ Investigations', 'IgM+ Investigations' and 'IgM Tests Performed' at 1-month intervals over a selected time period
Confirmed Case Summary Chart	All episode types combined (measles, rubella, CRS, CRI)	Number of confirmed cases reported at 1-month intervals for a specified time period, including method of classification (i.e. lab/epi confirmed)
Age Distribution Chart	Measles, rubella, CRS, CRI	Confirmed cases by age range for a specified time period
Immunization Status Chart	Measles, rubella, CRS, CRI	Confirmed cases by immunization status for a specified time period
Source Chart	Measles, rubella	Number of confirmed cases reported over the selected time period according to 'Source' of infection, i.e.: 'Outside Canada', 'In Canada, linked to an imported case/chain', 'In Canada, linked to an unknown case/chain', or 'Unknown Source'
Weekly Zero Report Chart	All episode types combined (measles, rubella, CRS, CRI)	Total confirmed cases reported by 'week of onset', and P/T reporting status by epi week including zero reporting.

* *Summary chart mock-ups included in the MARS data flow model are provided in Appendix VII*

The draft data flow model included mock-ups illustrating MARS-based measles/rubella and CRS/CRI reporting, a summary of the augmented data fields to be collected, and a description of site-based data entry roles. Prior to finalizing the data flow model, a series of teleconferences was convened with attendance by national and provincial laboratory and epidemiology pilot site stakeholders to provide an opportunity to review the MARS model in detail, answer questions and capture any additional provincial input. Upon completion of the review and approval process, a final version of the MARS data flow model was provided to CNPHI to support custom application development using the CNPHI IT platform (Appendices II - XI).

MARS Application Development: CNPHI Platform

The web-based MARS application was developed by CNPHI as a custom-built application using the proprietary CNPHI IT platform. The CNPHI platform includes a scalable suite of secure web-based tools which enable the strategic integration of disparate data sources and dissemination of public health intelligence to support a coordinated interjurisdictional public health response (92,93). Upon the completion of custom application development, MARS was launched on the CNPHI website (83) which hosts a collection of secure web-based public health applications developed by PHAC and accessible through the secure user registration process.

MARS Pilot Application – Implementation Phase

Once CNPHI announced the completion of MARS custom application development, live-user testing of the first MARS release version was arranged with laboratory and epidemiology participants at MARS provincial and federal pilot sites. The purpose of the test phase was two-fold; to provide MARS pilot users with the opportunity to become familiar with the application prior to launch, and to identify any functionality issues that would need to be addressed prior to commencing the pilot. User

input was documented and all user comments and any associated action items were provided to CNPHI. A single pre-launch development phase was conducted to address outstanding issues identified during the live testing phase.

Following CNPHI completion of a launch-ready version of the MARS application in Spring of 2011, the launch week was confirmed with epidemiologists at CIRID to ensure national coordination. To fully integrate MARS reporting with CMRSS reporting during the pilot period, the weekly zero reporting email distributed by CIRID to provincial public health epidemiologists was revised to include instructions asking that pilot sites submit their weekly zero reports and real-time measles/rubella investigation reports via the MARS application. The intent was to allow pilot sites to fulfill their national reporting requirements by reporting once via MARS. The confirmed pilot week and more detailed information regarding site-based reporting roles were also separately communicated to all public health laboratory and epidemiology pilot sites via email (Table 2.3).

National 'Measles and Rubella Laboratory Investigation' Surveys: 2007, 2012

To estimate the level of investigation into measles-like illness in the Canadian setting at the outset of the project, a national 'Measles and Rubella Laboratory Investigation ' survey was distributed in 2007 to all measles and rubella testing laboratories known to perform front-line measles and rubella diagnostic testing. The purpose of the survey was to investigate measles and rubella testing algorithms used, and to obtain aggregate measles and rubella IgM test numbers and positive results for the 2005 and 2006 calendar years to estimate the level of investigation into measles and rubella-like illness in Canada (Appendix XII).

Upon completion of the 1-year pilot period, a follow-up survey was distributed in July 2012 to all Canadian laboratories known to perform measles and rubella IgM serology testing. Total measles and

rubella IgM test numbers and positive results were requested for the pilot period (i.e. June1, 2011 – May 31, 2012) and for the 2007 – 2011 calendar years to support the national estimation of surveillance indicators in both outbreak and non-outbreak settings. The 2012 survey differed from the 2007 survey as follows: the wording of the testing algorithm question was updated for clarity, and a question was added to investigate the capacity of measles and rubella diagnostic laboratories to perform confirmatory testing (Appendix XIII).

MARS Pilot: User Survey, 2013

The MARS Pilot User Survey was conducted in March 2013 to gather input from both national and provincial pilot participants regarding their experience in using the MARS application to support national measles and rubella reporting. The purpose of the survey was to contribute to the assessment of MARS application surveillance attributes including simplicity/ease of use, stability, acceptability and overall usefulness; and to inform next steps regarding the potential broader implementation of the MARS real-time surveillance model at the national level. A composite approach was used to assess acceptability and usefulness attributes by including questions addressing both 'report-form specific' and 'overall' ease of use, intuitiveness, and perceived effectiveness in supporting measles/rubella surveillance. This was done to obtain more specific feedback regarding potential areas for improvement. The 55 question multiple choice survey was conducted using a web-form for ease of response, with an estimated completion time of 20-30 minutes based on the longest survey path. All multiple choice questions were presented as 5-value Likert items with an additional 'not applicable' option (Appendix XIV). The survey form included a hyperlink to the MARS application on CNPHI to allow users to easily access the live application for reference if/as needed while proceeding through the survey.

Data Analysis

The MARS pilot period was defined as June 1, 2011 – May 31, 2012. All MARS report types submitted during this period, or having an epidemiological date (e.g. rash onset) falling within the pilot period were included in the results analysis. Data were exported from the web-based MARS database application on CNPHI to Excel in preparation for analysis.

In order to estimate established PAHO surveillance indicators based on measles/rubella clinically 'suspected case' investigations rather than measles and rubella 'confirmed case' surveillance, it was necessary to employ a lab-based proxy for 'suspected case'. For this purpose, the performance of a measles IgM serology test was considered to represent a single investigation into measles-like (i.e. clinical/febrile-rash) illness; this 'MLI investigation' definition was then used for surveillance indicator estimation.

Using augmented laboratory data collected through the MARS application, the performance of measles and rubella surveillance was evaluated at MARS pilot sites by estimating various surveillance indicators representative of the timeliness and level of investigation into measles and rubella. Augmented laboratory data requested included enhanced timeliness data, including 'sample collection', 'laboratory receipt' and 'laboratory result' dates for all tests performed in association with each real-time measles/rubella investigation; the sample type information associated with each test type, e.g. serum, T/NP, urine, CSF; and the total number of measles and rubella IgM serology tests performed on a monthly basis (Appendix II, X).

Surveillance indicator estimates were compared with existing targets set by PAHO/WHO, and with other suggested literature values where available. Surveillance system attributes were also quantitatively and qualitatively evaluated where feasible for the MARS Pilot, including data

quality/completeness, simplicity/ease of use, flexibility, acceptability, stability, sensitivity and positive predictive value (PPV). MARS and CMRSS surveillance system performances were compared where possible using indicators and attributes estimable for both systems, including timeliness of reporting and data quality.

A variety of statistical techniques were used to assess the significance of differences in surveillance indicator values estimated at the national and provincial levels, between MARS pilot and non-pilot sites, and in outbreak and non-outbreak settings during the 2005-2012 period. Statistical methods employed include the calculation of average, median, minimum and maximum values observed, Chi-Squared analysis for the comparison of categorical data and proportion-based indicators, rate ratio (*RR*) estimation to quantify the magnitude of observed differences for indicators with large population-based denominators, determination of 95% confidence intervals, and use of Student's t-test to assess the significance of differences (*P=0.05*).

When analyzing MARS User Survey results, Likert item data were treated as ordinal rather than interval. For questions employing the response variables 'Strongly Disagree (SD), Disagree (D), Undecided (U), Agree (A), Strongly Agree (SA)', responses were grouped into two categories as follows: 'A and SA' were grouped into 'Agree', and 'SD and D' grouped into 'Disagree', and 'U' responses were grouped with 'Not applicable/Did not use' responses into a third 'Undecided/Not Applicable' response category; the proportions of responses falling into each category were then assessed. For all other Likert items, proportions were calculated directly without grouping of response variables.

MARS PILOT PERIOD

The MARS application was launched to support live data entry by provincial laboratory and epidemiology stakeholders in British Columbia, Alberta and Newfoundland from June 1, 2011 to May 31, 2012 using the web-based CNPHI platform. Measles and rubella investigation data were reported nationally via the MARS application for the duration of the 1-year pilot period using the web-based Measles/Rubella and CRS/I investigation forms, Monthly Reports and Weekly Zero Reports. All confirmed measles and rubella cases reported via MARS pilot sites were integrated with national confirmed case reports submitted via CMRSS in the national PHAC database. Discarded investigation data were housed solely on the MARS application database.

MARS Pilot Provinces: Measles and Rubella Investigation Levels

During the pilot, a total of 2005 measles-like illness (MLI) investigations and 2758 rubella IgM serology tests were reported by MARS pilot provinces, using measles IgM serology testing as a proxy for the investigation of MLI to support surveillance indicator estimation. Annual levels of laboratory-based measles and rubella investigation activity including %positive values for measles and rubella IgM serology testing are summarized in Table 3.1.

Total measles and rubella IgM serology test numbers and positives were collected through the MARS Monthly Test Report forms; monthly totals are displayed in Figure 3.1. Annual measles and rubella IgM serology test data reported via MARS were subsequently verified using data reported through the 2012 national survey of measles and rubella testing laboratories.

Table 3.1. Measles/Rubella IgM Serology Test Summary: MARS Pilot Period, All Sites[*]

Province	Measles IgM Serology	MLI investigations/ 100 000 pop. [†]	Measles IgM+ *N (%)*	Rubella IgM Serology	Rubella IgM serology/ 100 000 pop. [†]	Rubella IgM+ *N (%)*
BC	820	17.8	4 (0.5%)	952	20.7	14 (1.5%)
AB	1141	29.9	13 (1.1%)	1785	46.7	21 (1.2%)
NL	44	8.6	1 (2.3%)	43	8.4	1 (2.3%)
All Sites*	2005	22	18 (0.9%)	2758	31	36 (1.3%)

[*]*Total annual measles and rubella IgM serology test numbers, positives (+), and IgM testing rates/100 000 population as reported by all pilot sites through MARS Monthly Test Reports. Aggregate annual totals reported through MARS were verified through the 2012 national survey conducted following the pilot; total test numbers included in the chart reflect the verified annual numbers obtained via survey.*

[†]*MLI investigation and rubella IgM serology rates were calculated using the following census-based provincial population estimates for the MARS pilot period: BC: 4593853, AB: 3818664, NL: 511462*

FIGURE 3.1 Measles and Rubella IgM Serology Testing Summary: Monthly Test Reporting via MARS Pilot Provinces, June 2011 – May 2012. Total monthly measles and rubella IgM serology test numbers and positives collected through the MARS Monthly Test Reports submitted by public health laboratory sites in BC, AB and NL. Rubella/measles IgM serology testing rate ratios (*RR*) were estimated for each reporting month to assess the magnitude of rate differences observed for rubella versus measles investigation.

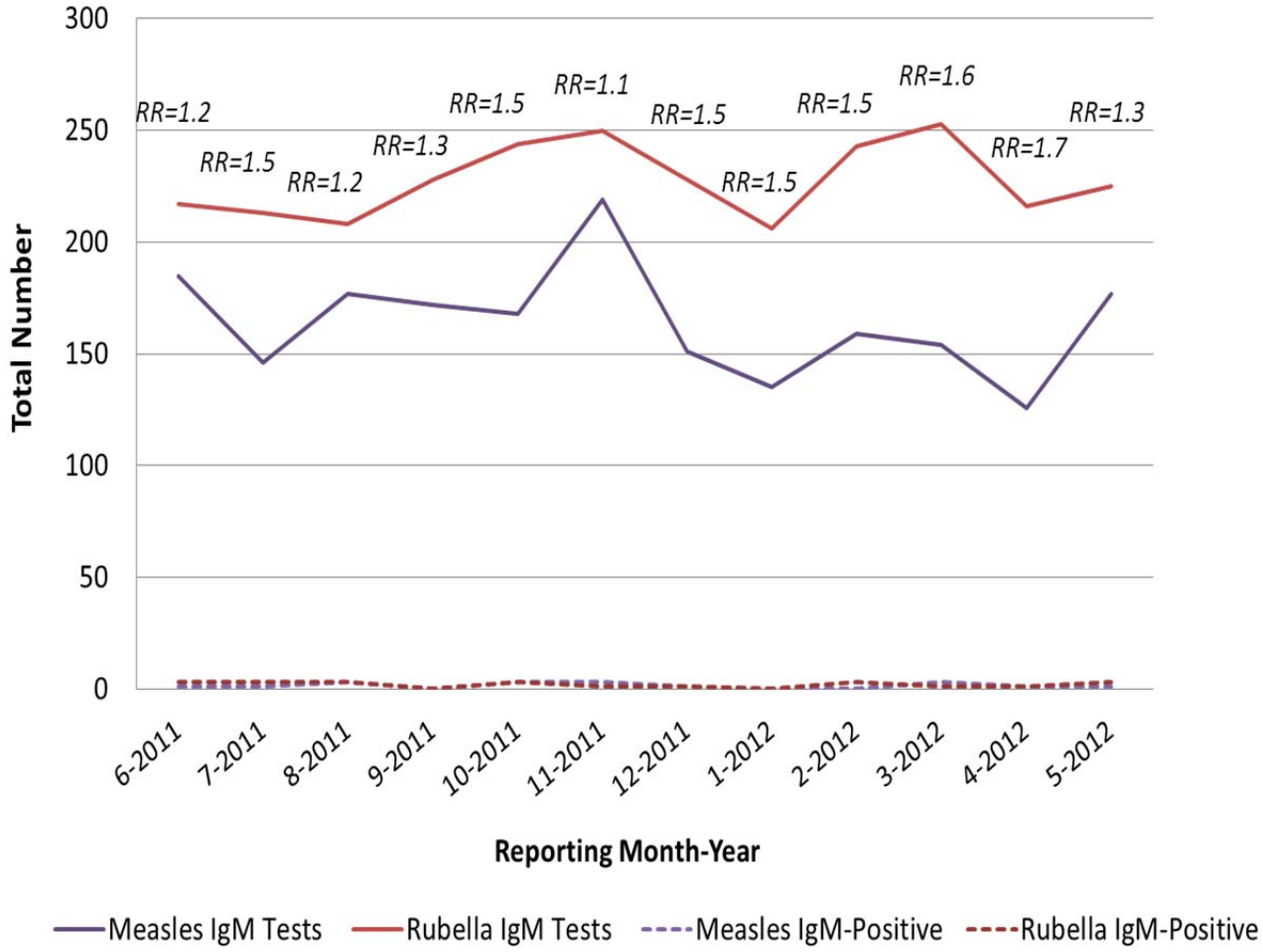


FIGURE 3.1 Measles and Rubella IgM Serology Testing Summary: Monthly Test Reporting via MARS Pilot Provinces, June 2011 – May 2012.

MARS Pilot Provinces: Real-time Measles/Rubella Investigations (RTMRI)

MARS pilot provinces reported a total of 24 measles/rubella investigations in real-time through the MARS application using the centralized MARS measles/rubella investigation report form. Of these investigations, 4 were confirmed as measles cases, 1 was confirmed as a rubella case, and 19 were ultimately discarded. All cases were laboratory – confirmed in keeping with the national notifiable disease case definitions (53). Additionally, 1 CRS/I investigation was reported during the pilot period and ultimately discarded due to a clinical picture inconsistent with CRS. RTMRI totals and proportions by MARS reporting province, including classification status, are summarized in Table 3.2.

Table 3.2 MARS Pilot: Real-time Measles/Rubella Investigation (RTMRI) Summary

Province	RTMRI* *N*	Confirmed Measles *N (%)*	Confirmed Rubella *N (%)*	Discarded *N (%)*
BC	6	1 (16.7%)	1 (16.7%)	4 (66.7%)
AB	17	3 (17.7%)	0 (0%)	14 (82.4%)
NL	1	0 (0%)	0 (0%)	1 (100%)
All Pilot Provinces	24	4 (16.7%)	1 (4.2%)	19 (79.2%)

**For analysis purposes, only measles and rubella investigation reports submitted in real-time through the MARS application at participating pilot sites, and having an epi-date falling within the MARS 1-year pilot period of June1, 2011 – May 31, 2012 were included.*
N= Total number, % = Proportion of all RTMRIs reported by geographic region

MARS Pilot Provinces: Confirmed Case Summary

A summary of key laboratory, epidemiological and clinical data associated with all confirmed measles and rubella cases reported by MARS pilot provinces during the pilot is provided by Table 3.3.

Table 3.3 Measles and Rubella Confirmed Case Summary: MARS Pilot Provinces

	Case 1	Case 2	Case 3	Case 4	Case 5
Province	BC	AB	AB	AB	BC
Age	39	13	35	20	5
Sex	Female	Male	Male	Female	Female
Immunization History	Unknown	No	Yes (childhood recall, no doc.)	Unknown	No (Parents chose not to vaccinate)
Travel History					
Within Canada	Unknown	-	No	No	No
Outside Canada	Yes	Thailand	New Zealand	India	Uganda lab-confirmed case contact
Fever	Yes	No	Yes	Yes	Yes
Rash Onset Date	22-Jun-11	15-Aug-11	07-Nov-11	04-Mar-12	16-Apr-12
Sample Collection Date[†]	24-Jun-11	16-Aug-11	09-Nov-11	11-Mar-12	16-Apr-12
IgM Serology					
Measles	Negative	Positive	Positive	Positive	Positive[**]
Rubella	1. Equivocal[*] 2. Positive	-	-	-	Positive[**]
IgG Serology	Rubella				
Acute:	<0.2 IU/ml	Not done	-	-	-
Convalescent:	133.1 IU/ml				
RT-PCR					
Measles	ND[***]	Positive	Positive	Positive	Positive
Rubella	Positive	-	-	-	-
Case Classification	Rubella	Measles	Measles	Measles	Measles
Confirmation	Lab-confirmed	Lab-confirmed	Lab-Confirmed	Lab-Confirmed	Lab-Confirmed
Genotype	1j	D8	D4	D4	B3

[†]*Sample Collection Date represents the earliest sampling date (i.e. serum procurement) in the event that multiple samples were procured for testing; equivalent to public health 'Date of Investigation' for measles/rubella laboratory investigations.*

[*]*Reported as equivocal; the first serum sample was tested twice with 2 different kits in keeping with the laboratory testing algorithm; first result was positive, second was equivocal; result was reported as equivocal/indeterminate. A second serum sample taken ~1 week later was IgM-positive.*

[**]*Serum samples tested twice each for measles and rubella IgM serology using different kits; all test results were positive.*

[***]*ND = Not detected*

MARS Pilot Provinces: Sample Collection Data

The sample types (e.g. serum, throat/nasopharyngeal, urine) associated with all RTMRI reports submitted through MARS were assessed, and summarized in Table 3.4. Sample data associated with confirmed case investigations are included as a subset of RTMRIs for comparison purposes. Of the 5 confirmed measles/rubella investigations, 4 had virus isolation samples (both urine and T/NP) collected in addition to serum. The fifth investigation had a serum sample collected on the rash onset date, which was successfully genotyped. Of the 4 investigations with VI samples, 3 had all VI samples collected within 1-3 days of rash onset; the fourth had samples collected at 7 days (serum) and 11 days (urine, T/NP) after rash onset.

Real-time Measles/Rubella Investigation (RTMRI): Summary of Laboratory Testing Performed

Laboratory investigation methods associated with the 24 RTMRI reports submitted during the pilot period were assessed by determining the number and proportion of RTMRIs for which specific laboratory tests were performed. Test type and result information was assessed for all 24 RTMRIs, and for the 5 confirmed measles/rubella cases and 19 discarded investigations as RTMRI subsets. Measles and rubella IgM serology testing results are summarized in Table 3.5, acute, paired acute/convalescent, and avidity IgG serology test results are provided in Table 3.6, and an overview of RT-PCR, virus isolation and genotyping results is given in Table 3.7.

Table 3.4 MARS Real-time Investigations: Sample Type Data

Sample Type	Real-time Measles/Rubella Investigations, n=24[*†] N (%)[*]	Confirmed Measles/Rubella Investigations, n=5[**] N (%)[*]
Serum	22 (91.7%)	5 (100%)
Throat/ Nasopharyngeal (T/NP)	6 (25.0%)[†]	4 (80.0%)
Urine	5 (20.8%)[†]	4 (80.0%)
Serum + urine + T/NP	4 (16.7%)[†]	4 (80.0%)
Serum only	18 (75.0%)[†]	1 (20.0%)
Urine and/or T/NP only	2 (8.3%)	0 (0 %)
Virus Isolation (VI) sample collected	6 (25.0 %)[****]	4 (80.0 %)[***]
VI sample meets WHO recommendations	4 (66.7%)[*††]	3 (75.0%)
Same day collection of serum and VI samples	0 (0%)[*†††]	0 (0%)[*†††]

[*]N = Total number of reports for which the specified data field was completed; % = Proportion of reports for which the specified data field was completed.

[†]These summary data capture sample types tested as part of each investigation process, and do not include the number of investigations for which urine and/or T/NP samples were collected but not tested.

[†]Of the 24 RTMRI reports entered during the pilot period, 23 reports included information related to sample type. The sole report for which the sample type field was not populated is presumed to have had a serum sample collected as the report included the sample collection date and included test results for measles and rubella IgM serology.*

[**]A total of 5 RTMRI reports were subsequently confirmed as measles (n=4) or rubella (n=1).

[***]Four of five confirmed cases had an appropriate VI sample collected; the fifth had only a serum sample collected, which was successfully genotyped.

[****]This number may underestimate the proportion of RTMRI for which VI samples were collected. It was not possible to assess the status of VI sample collection for all RTMRIs as the 'Virus Isolation Sample Provided' field was not captured as an exportable field in the launch version of MARS, and is not viewable at the report summary level. As such, the number of investigations for which virus isolation samples were collected but not tested as part of the investigation process was not able to be assessed.

[††]Of the 6 RTMRI with a VI sample, 4 investigations had VI samples meeting WHO recommendations, one investigation report (discarded) did not include the sample collection date and timeliness could not be assessed, and another (confirmed measles) had serum and VI samples collected at 7 and 11 days post-rash onset respectively.*

[†††]Assessed for the 4 RTMRI (all confirmed cases) with serum and VI samples collected, based on the WHO recommendation that virus isolation samples be collected at the same time as serum*(14)*.*

Table 3.5 Real-time Measles/Rubella Investigation (RTMRI) Reports: IgM Serology Testing

Test Performed	RTMRI Reports *N (%)*	Confirmed Measles/Rubella *N (%)*	Discarded RTMRI *N (%)*
Measles/Rubella IgM Serology	**22 (91.7%)**	5 (100%)	17 (89.5%)
Positive, measles/ rubella	22 (91.7%)	5 (100%)	17 (89.5%)
Measles IgM Serology	14 (60.7%)	5 (100%)	9 (47.4%)
Positive	11 (45.8%)	4 (80.0%)	7 (36.8%)
Negative/ Indeterminate	3 (12.5%)	1 (20.0%)	2 (10.5%)
Rubella IgM Serology	14 (60.7%)	2 (40.0%)	12 (63.2%)
Positive	13 (54.2%)	1 (20.0%)	12 (63.2%)
Negative/ Indeterminate	1 (4.2%)	1 (20.0%)	0 (0%)
Measles + Rubella IgM Serology	**7 (29.2%)**	2 (40.0%)	5 (26.3%)
Positive, measles and rubella	**2 (8.3%)**	0 (0%)	2 (10.5%)
Measles IgM Serology: Repeat Testing	5 (20.8%)	1 (20.0%)	4 (21.1%)
Rubella IgM Serology: Repeat Testing	3 (12.5%)	1 (20.0%)	2 (10.5%)

N= Total reports for which the testing was performed

% = Proportion of all reports according to investigation status (RTMRI, confirmed, discarded)

Table 3.6 Real-time Measles/Rubella Investigation (RTMRI) Reports: IgG Serology Testing

Test Performed	RTMRI Reports *N (%)*	Confirmed Measles/Rubella *N (%)*	Discarded RTMRI *N (%)*
Measles/Rubella IgG Acute/Convalescent Serology[†]	2 (8.3%)	1 (20.0%)	1 (5.3%)
Measles IgG Acute/Convalescent Serology[†]	1 (4.2%)	0 (0%)	1 (5.3%)
Positive (i.e. seroconversion)	0 (0%)	0 (0%)	0 (0%)
Negative/Indeterminate (i.e. no seroconversion)	1 (4.2%)	0 (0%)	1 (5.3%)
Rubella IgG Acute/Convalescent Serology[†]	1 (4.2%)	1 (20.0%)	0 (0%)
Positive (seroconversion)	1 (4.2%)	1 (20.0%)	0 (0%)
Negative/Indeterminate (i.e. no seroconversion)	0 (0%)	0 (0%)	0 (0%)
Rubella IgG Avidity[†]	0 (0%)	0 (0%)	0 (0%)
Measles/Rubella IgG Serology, Acute[†*]	20 (83.3%)[*]	4 (80.0%)	16 (84.2%)
Positive, measles/rubella	16 (66.7%)[*]	2 (40.0%)	14 (73.7%)
Measles IgG Serology, Acute[†*]	12 (50.0%)	4 (80.0%)	8 (42.1%)
Positive	6 (25.0%)	2 (40.0%)	4 (21.1%)
Negative/Indeterminate	6 (25.0%)	2 (40.0%)	4 (21.1%)
Rubella IgG Serology, Acute[†*]	14 (58.3%)	1 (20.0%)	13 (68.4%)
Positive	12 (50.0%)	0 (0%)	12 (63.2%)
Negative/Indeterminate	2 (8.3%)	1 (20.0%)	1 (5.3%)
Measles and Rubella IgG Serology, Acute[†*]	6 (25.0%)	1 (20.0%)	5 (26.3%)
Positive, measles and rubella	2 (8.3%)	0 (0%)	2 (10.5%)

N= Total reports for which the testing was performed

% = Proportion of all reports according to investigation status (RTMRI, confirmed, discarded)

[†] *Paired acute/convalescent IgG serology and rubella IgG avidity are confirmatory methods.*

[†*] *IgG serology testing of acute sera is not used in a confirmatory capacity, but to assess history of exposure through the detection of anti-measles/rubella IgG antibodies*

[*] *Acute IgG serology results do not include paired acute/convalescent serology test data.*

Table 3.7 Real-time Measles/Rubella Investigations: RT-PCR, Virus Isolation and Genotyping

Test Performed	RTMRI Reports *N (%)*[*]	Confirmed Measles/Rubella *N (%)*[*]	Discarded RTMRI *N (%)*[*]
Measles/Rubella RT-PCR	**7 (29.2%)**	**5 (100%)**	**2 (10.5%)**
Positive, measles/rubella	7 (29.2%)	5 (100%)	2 (10.5%)
Measles RT-PCR	**7 (29.2%)**	**5 (100%)**	**2 (10.5%)**
Positive	6 (25.0%)	4 (80.0%)	2 (10.5%)
Not detected /inconclusive	1 (4.2%)	0 (0%)	1 (5.3%)
Rubella RT-PCR	**1 (4.2%)**	**1 (20.0%)**	**0 (0%)**
Positive	1 (4.2%)	1 (20.0%)	0 (0%)
Not detected/ inconclusive	0 (0%)	0 (0%)	0 (0%)
Measles + Rubella RT-PCR	1 (4.2%)	1 (20.0%)	0 (0%)
Measles/Rubella Genotyping	**7 (29.2%)**	**5 (100%)**	**2 (10.5%)**
Genotype determined	6 (25.0%)	5 (100%)	1 (5.3%)
Unable to type	1 (4.2%)	0 (0%)	1 (5.3%)
Measles Genotyping	**6 (25.0%)**	**4 (80.0%)**	**2 (10.5%)**
Genotype determined	5 (20.8%)	4 (80.0%)	1 (5.3%)
Unable to type	1 (4.2%)	0 (0%)	1 (5.3%)
Rubella Genotyping	**1 (4.2%)**	**1 (20.0%)**	**0 (0%)**
Genotype determined	1 (4.2%)	1 (20.0%)	0 (0%)
Unable to type	0 (0%)	0 (0%)	0 (0%)
Total	**7 (29.2%)**	**5 (100%)**	**2 (10.5%)**
Measles/Rubella Virus Isolation	**0 (0%)**	**0 (0%)**	**0 (0%)**

[*] *N= Total reports for which the testing was performed*

% = Proportion of all reports according to status (24 RTMRIs total; 5 confirmed, 19 discarded)

2007 National Survey Results - Summary

The 2007 'Measles and Rubella Laboratory Investigation Survey' was distributed in October 2007 to assess the testing protocols used by all Canadian laboratories known to perform measles and/or rubella IgM serology, and to estimate the level of investigation into measles/rubella-like illness (MRLI) in Canada by requesting aggregate test data for the 2005 and 2006 reporting years (Appendix XII). By December 2007, responses had been provided by 16/18 (88.9%) of laboratories for a final survey period of 3 months. It should be noted that while the term MRLI was used in the 2007 survey to refer to a clinically suspect case of measles or rubella, it is synonymous with MLI for analysis purposes. The testing roles and screening protocols used by responding laboratories in 2005-2006 are summarized in Tables 3.8 and 3.9. The total numbers of measles and rubella IgM serology tests performed by responding laboratories are provided in Table 3.10. Although measles and rubella IgM-positive data were requested in addition to total test numbers, these were not consistently available from laboratories for this survey period and are not included in the results.

Table 3.8 Measles/Rubella Testing Laboratories: IgM Serology Testing Performed, 2005-2006

Testing Performed*	**Testing Laboratories (Total)**	**% Laboratories Surveyed** *(n=16)*
Measles and Rubella IgM Serology	10	62.5%
Measles IgM Serology (only)	4	25.0%
Rubella IgM Serology (only)	2	12.5%

**Note: The 2007 survey looked solely at measles and rubella IgM serology testing; laboratory capacity to perform confirmatory testing was not included.*

Table 3.9. Measles/Rubella Testing Laboratories: MRLI* Screening Protocols, 2005-2006

Q: What IgM testing protocol is used by the laboratory when screening clinically suspect MRLI cases?	**Total Laboratories**	**%Laboratories**** *(n=16)*
All MRLI cases are screened for measles, rubella and pB19	9	56.3%
Only MRLI cases negative for measles IgM are screened for rubella and pB19 IgM	2	12.5%
Rubella and pB19 IgM testing performed only when specifically requested	2	12.5%
Other screening protocol used	2	12.5%
No response	1	6.3%
Total	16	100%

**The term measles/rubella-like illness (MRLI) was used in the 2007 survey to refer to a clinically suspect case of measles/rubella; it is synonymous with MLI for analysis purposes.*
***The proportion of responding laboratories (n=16); a total of 18 laboratories were surveyed.*

Table 3.10 Level of Investigation: National Measles/Rubella IgM Serology Testing : 2005-2006

Year	**Measles IgM Serology Tests**	**Rubella IgM Serology Tests**
2006	3829	7719
2005	4635	8201

Note: The 2007 survey requested measles and rubella IgM-positive data in addition to total test numbers; however, these data were not consistently available from laboratory sites surveyed. There have been minor updates made to these survey numbers since their original publication in the article by Macey et al (39). *The differences in reported test numbers are small, and do not significantly influence the overall rates estimated here, which are based on the most current numbers available.*

2012 National Survey Results

Response Rate

Following the conclusion of the MARS pilot period in May 2012, the national 'Measles and Rubella Laboratory Investigation Survey' was distributed in July 2012 to all provincial laboratories known to perform measles and rubella IgM serology testing across Canada (Appendix XIII). The final survey responses were received in March 2013, for an 8 month survey period. A total of 16 laboratories in 10 provinces provided survey responses, with participation by the provincial public health laboratory in all nine provinces having a centralized PHL. It should be noted that while all Québec laboratories performing measles IgM serology were surveyed directly, this approach was not feasible for rubella IgM data procurement as rubella serology testing in Québec is highly decentralized across 42 testing laboratories. The provision of province-wide rubella IgM test data for the pilot period was therefore centrally coordinated through the provincial PHL via the Ministry of Health.

Testing Protocols: 2007-2011

A summary of the MLI screening protocols employed by measles and rubella testing laboratories surveyed during the 2007-2011 period is provided in Table 3.8. It should be noted that as the response categories for the testing protocol question included in the 2012 survey were updated for clarity, responses obtained via the 2007 survey for the 2005 and 2006 reporting years are not directly comparable to the 2007-2011 responses.

Table 3.11 MLI Screening Protocols Used by Measles/Rubella Testing Laboratories: 2007-2011

Q: What IgM testing protocol is used by the laboratory when screening clinically suspect MLI cases?	Number of Laboratories	%Laboratories *(n=16)*
All MLI cases are screened for measles, rubella and parvovirus B19 IgM	3	18.8%
All MLI cases are screened for measles and rubella IgM	0	0.0%
Only the specific IgM test(s) requested will be performed initially; if negative, additional measles/rubella and parvovirus B19 IgM testing will be performed	2	12.5%
The lab will perform only the specific IgM screening test(s) requested	9	56.3%
*Other screening protocol used (please provide details below)	2	12.5%
Total	16	100%

**Note: The 2 laboratories that reported using an 'other' screening protocol currently refer their measles and/or rubella IgM serology testing to other laboratories.*

Testing Capacity: Measles/Rubella IgM Serology and Confirmatory Testing

Testing laboratories were asked to confirm whether they perform measles or rubella IgM serology testing or both, and which confirmatory tests they have the capacity to perform. A summary of the front-line diagnostic and confirmatory testing performed by measles and rubella testing laboratories during the 2007-2011 survey period is provided in Table 3.12.

Table 3.12 Provincial Measles/Rubella Laboratory Testing Capacity: IgM Serology and Confirmatory Testing, 2007-2011

Test Type	Testing Laboratories (Total)	% Laboratories Surveyed *(n=16[*])*
Measles IgM Serology	13	81.3
Rubella IgM Serology	13	81.3
Measles and Rubella IgM Serology	11	68.8
All Measles/Rubella IgM Serology Referred	1	6.3
Measles RT-PCR	4	25.0
Measles Paired Acute/Convalescent IgG	8	50.0
Measles Virus Isolation	3	18.8
Rubella RT-PCR	1	6.3
Rubella Paired Acute/Convalescent IgG	5	31.3
Rubella Virus Isolation	3	18.8
Other Confirmatory Testing	1	6.3
Confirmatory Testing Referred	12	75.0

[*]% Laboratories Surveyed is expressed as a proportion of all responding laboratories, n=16.

Note: The survey was distributed to provincial laboratories only; this data does not include testing performed at the National Microbiology Laboratory

MEASLES AND RUBELLA SURVEILLANCE (MARS) PILOT USER SURVEY: MARCH 2013

The MARS Pilot User Survey gathered input from MARS pilot participants regarding their experience in using the MARS application to support real-time national measles and rubella surveillance during the June 2011 - May 2012 pilot period. The survey was designed to support the quantitative and descriptive assessment of various surveillance attributes used to inform overall analysis of MARS pilot performance.

An overview of survey participation by user role including representation by jurisdiction is provided by Figure 3.2 and Table 3.13. Survey response data are summarized in Tables 3.14 – 3.20 and grouped according to the surveillance attribute or function under assessment, i.e. simplicity/ease of use, data quality/completeness, stability, reporting requirements (time, personnel, frequency), acceptability, usefulness, and other implementation factors.

FIGURE 3.2 MARS User Survey 2013: Response Summary by National/Provincial User Role. Representativeness of the survey was assessed by determining the proportion of survey responses provided by MARS users within public health epidemiology and laboratory organizations at the provincial and national levels.

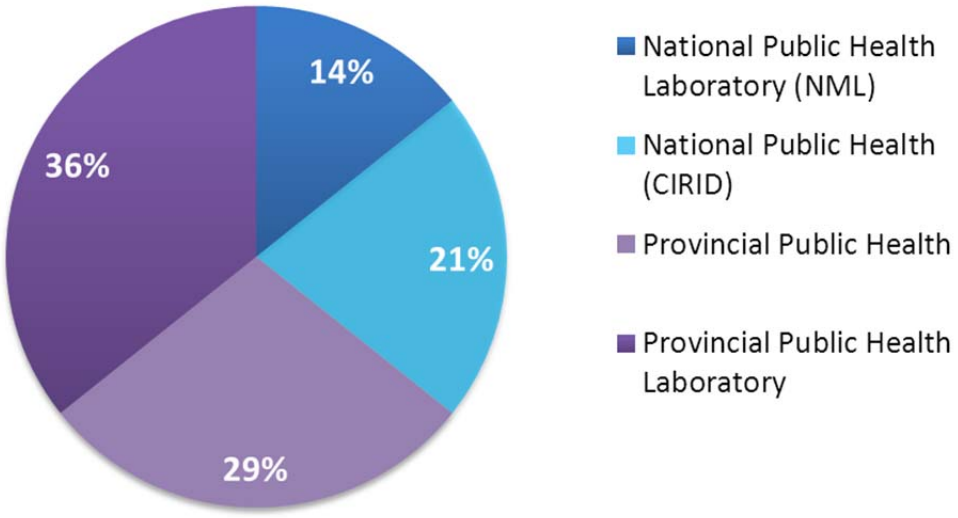


FIGURE 3.2 MARS User Survey 2013: Response Summary by National/Provincial User Role.

Table 3.13 MARS User Survey, 2013: Participation by Jurisdiction and User Role

Jurisdiction	Public Health Laboratory *N** (%)	Public Health *N* (%)	Total Responses *N* (%)
National	2 (14.3%)	3 (21.4%)	5 (35.7%)
Provincial	5 (35.7%)	4 (28.6%)	9 (64.3%)
BC	*2 (14.3%)*	*2 (14.3%)*	*4 (28.6%)*
AB	*2 (14.3%)*	*1 (7.1%)*	*3 (21.4%)*
NL	*1 (7.1%)*	*1 (7.1%)*	*2 (14.3%)*
Total *N* (%)	7 (50%)	7 (50%)	14 (100%)

* *N=Total survey respondents in each category; denominator value for all proportions is total responses = 14.*

Surveillance Attributes

Simplicity/Ease of Use

Simplicity and ease of use were assessed for the four MARS report form types (Table 3.14) and for the MARS application overall (Table 3.15). Only MARS users having previous experience in the use of each respective reporting form were prompted to complete survey items related to the specific form. All respondents were required to respond to items relating to overall simplicity/ease of use of the MARS application.

Table 3.14 Simplicity/Ease of Use: MARS Reporting Forms

	%Agree*	%Disagree†	%Undecided/NA†*	Users *(N)*††
The *report form* is well structured and easy to follow.				
Measles/Rubella Report	100%	0%	0%	12
CRS/I Report	100%	0%	0%	2
Monthly Test Report	100%	0%	0%	4
Weekly Zero Report	100%	0%	0%	9
The *report form* is intuitive, requiring minimal training to use.				
Measles/Rubella Report	100%	0%	0%	12
CRS/I Report	100%	0%	0%	2
Monthly Test Report	100%	0%	0%	4
Weekly Zero Report	100%	0%	0%	9
Data field names are clearly described and easy to understand.				
Measles/Rubella Report	100%	0%	0%	12
CRS/I Report	50.0%	0%	50.0%	2
Monthly Test Report	100%	0%	0%	4
Weekly Zero Report	100%	0%	0%	9

** %Agree represents the proportion of users choosing 'Strongly Agree' or 'Agree' as their response.*
† %Disagree represents the proportion of users choosing 'Strongly Disagree' or 'Disagree' as their response.
† %Undecided/NA represents the proportion of users selecting 'Undecided' or 'Not Applicable' as their response.*
†† The total number of MARS Users indicating that they had used the report form in question (i.e. Measles/Rubella, CRS/I, Monthly Test, Weekly Zero) during the pilot period.

Table 3.15 Simplicity/Ease of Use: MARS Application, Overall

	%Agree*	%Disagree†	%Undecided/NA†*	Users *(N)* ††
Overall, the MARS application is easy to use.	100%	0%	0%	14
It was easy to access newly submitted and updated reports through automated MARS email notifications.	100%	0%	0%	14
Using the MARS 'Summary Reports' function, it is easy to view aggregate measles/rubella report data of interest for a specified time period.	57.1%	0%	42.9%	14
Using the MARS 'Query Builder', it is easy to perform custom data queries for export into Excel.	21.4%	0%	78.6%	14

** %Agree represents the proportion of users choosing 'Strongly Agree' or 'Agree' as their response.*
† %Disagree represents the proportion of users choosing 'Strongly Disagree' or 'Disagree' as their response.
† %Undecided/NA represents the proportion of users selecting 'Undecided' or 'Not Applicable/Did Not Use' as their response.*
†† The total number of respondents having used the MARS application during the pilot period.

Data Quality/Completeness

Users were asked to assess the quality and completeness of MARS data fields for Measles/Rubella and CRS/I report forms respectively, as well as the review section of Measles/Rubella investigation reports which summarizes key data fields used to support final investigation review and classification efforts. Only those users having previous experience in the use of the specific form were prompted to complete form-related survey items (Table 3.16).

Table 3.16 Data Quality/Completeness: MARS Measles/Rubella and CRS/I Report Forms

	%Agree*	%Disagree†	%Undecided/NA†*	Users *(N)* ††
The *report form* includes all laboratory data fields required to investigate and confirm measles/rubella.				
Measles/Rubella Report	100%	0%	0%	12
CRS/I Report	50.0%	0%	50.0%	2
The *report form* includes all epidemiological and clinical data fields required to investigate and confirm measles/rubella.				
Measles/Rubella Report	83.3%	0%	16.7%	12
CRS/I Report	50.0%	0%	50.0%	2
The 'Review' page…includes all measles/rubella data fields needed for review and classification purposes.				
Measles/Rubella Report	83.3%	0%	16.7%	12

** %Agree represents the proportion of users choosing 'Strongly Agree' or 'Agree'.*
† %Disagree represents the proportion of users choosing 'Strongly Disagree' or 'Disagree'.
† %Undecided/NA represents the proportion of users selecting 'Undecided' or 'Not Applicable'.*
†† The total number of MARS Users indicating that they had used the report form/application function in question (i.e. Measles/Rubella or CRS/I reports) during the MARS pilot period.

Stability

The stability of the MARS application was assessed by looking at the consistency with which it was available for reporting purposes, the frequency of application use, and levels of site-based personnel support for data entry and review respectively (Table 3.17). All respondents were required to complete stability-related survey items.

Table 3.17 MARS Reporting: Stability, Frequency of Use, Personnel Support

Application Stability	**%Agree***	**%Disagree†**	**%Undecided/NA†***		**Users *(N)*** ††
The web-based MARS application on CNPHI was consistently available for use as needed for reporting purposes	92.9%	0%	7.1%		14
Frequency of Use:	**Rarely** *<1 time/ month*	**Infrequently** *~ 1 time/ month*	**Occasionally** *~1 time/ 2 week period*	**Frequently** *~1 time/ week*	**V. Frequently** *≥ 2 times/ Week*
How often did you access the MARS application to create, update or review MARS reports for your site?	21.4%	21.4%	14.3%	21.4%	21.4%
MARS Users per Site:	**1**	**2**	**3**	**4**	**≥5**
At my site, the number of users concurrently responsible for MARS data entry was:	35.7%	28.6%	35.7%	0%	0%
At my site, the number of users involved in the routine review of MARS report data was approximately:	35.7%	28.6%	28.6%	0%	7.1%

** %Agree represents the proportion of users choosing 'Strongly Agree' or 'Agree'.*
† %Disagree represents the proportion of users choosing 'Strongly Disagree' or 'Disagree'.
† %Undecided/NA represents the proportion of users selecting 'Undecided' or 'Not Applicable'.*
†† The total number of MARS users having submitted a survey response; all results above are presented as a proportion of this denominator.

MARS Data Entry - Time Requirements

Users were asked to estimate the time required to contribute data via each MARS report type, and via CMRSS Weekly Zero and National Case Reports to facilitate comparative assessment (Table 3.18).

Table 3.18 MARS and CMRSS Reporting: Data Entry Time Requirements

Reporting Time	<30 minutes	30 - <60 minutes	1 – <1.5 hours	1.5 - <2 hours	≥2 hours	NA*†
The time required to create and submit a new *report form* is approximately:						
*Measles/Rubella Report**	25.0%	16.7%	8.3%	0%	0%	50.0%
*CRS/I Report***	0%	0%	0%	0%	0%	100%
Monthly Test Report†	50.0%	0%	0%	0%	0%	50.0%
Weekly Zero Report††	55.6%	0%	0%	0%	0%	44.4%
The time required to complete a single update to an existing *report form* is approximately:						
*Measles/Rubella Report**	66.7%	0%	0%	0%	0%	33.3%
*CRS/I Report***	50.0%	0%	0%	0%	0%	50.0%
The time required to complete and submit a measles/ rubella 'National Case Report' form via CMRSS is approximately*:	16.7%	0%	8.3%	0%	0%	75.0%
The time required to complete and submit a 'Weekly Zero Report' form via CMRSS is approximately††:	44.4%	0%	0%	0%	11.1%	44.4%

Reporting Time	<30 minutes	30 - <60 minutes	1 – <2 hours	2 - <3 hours	≥3 hours	NA
The time required by the PHL*† to contribute aggregate measles and rubella IgM serology test data on a monthly basis is approximately†:	25.0%	25.0%	0%	0%	0%	50.0%

** Respondents having used Measles/Rubella Reports = 12; results are a proportion of this denominator.*

*** Respondents having used CRS/I Reports = 2; results are presented as a proportion of this denominator.*

† Respondents having used Monthly Test Reports = 4; results are a proportion of this denominator.

†† Respondents having used Monthly Test Reports = 9; results are a proportion of this denominator.

**† NA = Not Applicable, PHL = Public Health Laboratory*

Usefulness and Acceptability

All users were required to indicate their level of agreement with survey items related to the overall acceptability and usefulness of key functions of the MARS real-time surveillance application.

Table 3.19 Usefulness and Acceptability: MARS Real-time, Integrated Surveillance Model

	%Agree*	%Disagree†	%Undecided/NA†*	Users *(N)* ††
MARS automated email notifications effectively support interjurisdictional communication regarding measles/rubella reports.	92.9%	0%	7.1%	14
Centralized reporting of measles/rubella investigation data via MARS supports improved linkage of laboratory and epidemiological data.	85.7%	0%	14.3%	14
The ability to report measles/rubella investigation data in real-time via MARS enables more timely national surveillance.	100%	0%	0%	14
Overall, the MARS application successfully supports integrated national measles and rubella surveillance and reporting.	92.9%	0%	7.1%	14
Reporting forms effectively integrate laboratory, epidemiological and clinical measles/rubella data contributed by national and provincial public health and laboratory users.				
Measles/Rubella Report	100%	0%	0%	12
CRS/I Report	50.0%	0%	50.0%	2

** %Agree represents the proportion of users choosing 'Strongly Agree' or 'Agree' as their response.*
† %Disagree represents the proportion of users choosing 'Strongly Disagree' or 'Disagree' as their response.
† %Undecided/NA represents the proportion of users selecting 'Undecided' or 'Not Applicable'.*
†† The total number of MARS Users indicating that they had used the report form/application function in question (i.e. Measles/Rubella or CRS/I reports) during the MARS pilot period.

MARS Implementation Factors

Users were asked to provide input regarding the most important factors supporting implementation of the MARS real-time surveillance model, and to identify the most significant challenges related to implementation to inform pilot evaluation (Table 3.20).

Table 3.20 MARS User Survey: Implementation Factors

Question	User Comments
In your experience, what site-based factors were most important in facilitating the implementation of real-time surveillance using the MARS application?	1. Personal *[sic]* support for importing MARS case info into CMRSS 2. The ability to link in real time a lab specimen to the epidemiological data is invaluable. 3. In house (email) notification of measles/rubella cases to lab/epi. 4. communication of lab and the Zone MOH/designate to ensure all the details that were known about the case were filled out 5. The ability to create case report forms under 2 different titles (lab vs epi), which gave viewing access/alerts to 2 different audiences, as needed. 6. Defining role expectations: Lab, public health
In your experience, what were the most significant challenges in implementing real-time surveillance using the MARS application?	1. Clear understanding of federal/provincial roles in terms of final case classification i.e. not reporting to PAHO until province signed off. 2. No challenges compared to the status quo. Now let's make MARS national. 3. Establishing roles plus agreeing on notification for lab/epi 4. Communication between the lab/Zone MOH and provincial MOH 5. The issue of alerting needed to be clarified, and caused some concern (some members thought a public health alert was sent across Canada). Also the issue of entering data in real-time was an issue, but was resolved using the alerting strategy above. 6. (1) Knowledge/skill of the user (2) Reporting expectations change (shorten) 7. Unable to evaluate as there were no cases thus the surveillance piece is easy when there is nothing to report.

Level of Investigation into Measles and Rubella

National Case Numbers and Incidence: 2005 – 2011 and Pilot Years

National case numbers and the incidence of confirmed measles and rubella during the 2005-2011 reporting years and the MARS pilot period are summarized in Table 3.21. National confirmed case data were obtained through CMRSS.

Table 3.21 Measles and Rubella: National Case Numbers and Incidence Rates; 2005-2011, Pilot

Year	Confirmed Measles*	Confirmed Rubella*	Confirmed Measles/ 100 000 pop.	Confirmed Rubella/ 100 000 pop.
Pilot	727	7	2.10	0.02
2011	750	1	2.17	0.003
2010	99	12	0.29	0.03
2009†	14	7	0.04	0.02
2008	62	1	0.19	0.003
2007	102	1	0.31	0.003
2006†	13	4	0.04	0.01
2005	6	315	0.02	0.98

**National confirmed measles and rubella case data were sourced from CMRSS, and are summarized here to facilitate comparison with estimated MLI investigation and rubella IgM testing rates for the 2005-2011 and Pilot years (Table 3.22).*

†2006 and 2009 are 'non-outbreak' years, having combined national measles/rubella incidence rates of 0.05 and 0.06 per 100 000 population respectively.

To support comparative analysis of measles and rubella investigation rates in outbreak and non-outbreak settings, national case incidence data for the 2005-2011 years were reviewed and both 2006 and 2009 were classified as national non-outbreak years, having annual combined

measles/rubella case incidence rates of 0.05 and 0.06 per 100 000 population respectively. The 2005, 2007, 2008 , 2010, 2011 and MARS pilot reporting years were classified as national outbreak years, each being characterized by a national combined measles/rubella incidence ≥ 0.2 cases/100 000 population (range: 0.2 – 2.2/100 000 population), and the occurrence of at least one notable provincial outbreak during each annual reporting period. None of the provincial outbreaks occurring between 2005 and 2011 spanned multiple reporting years. There is, however, significant overlap between the MARS pilot period of June 2011 - May 2012, and the large 2011 Québec provincial outbreak which was responsible for most of the 727 confirmed cases reported nationally during the MARS pilot year (Table 3.21).

National Measles and Rubella IgM Serology Testing Levels and Rate Ratios: 2005-11 and Pilot Years

An overview of the national level of laboratory investigation into measles and rubella is given by Figure 3.3a, which displays measles and rubella IgM serology testing rates/100 000 population as well as rubella/measles rate ratios within the context of confirmed measles and rubella case numbers and incidence rates/100 000 population. The source data for Figure 3.3a are summarized in Tables 3.21 and 3.22.

FIGURE 3.3a National Measles and Rubella Investigation Rates: 2005-2011 and Pilot years. Annual rates of measles and rubella IgM serology testing per 100 000 population were assessed for the 2005-2006 and 2007-2011 and pilot years using aggregate pre- and post-pilot laboratory survey data (2007 and 2012 surveys). *RR* values were assessed to compare the magnitude of rubella/measles IgM serology testing rate differences. Measles and rubella test data are presented within the context of measles and rubella confirmed case numbers and incidence per 100 000 population using national confirmed case data obtained through CMRSS (94).

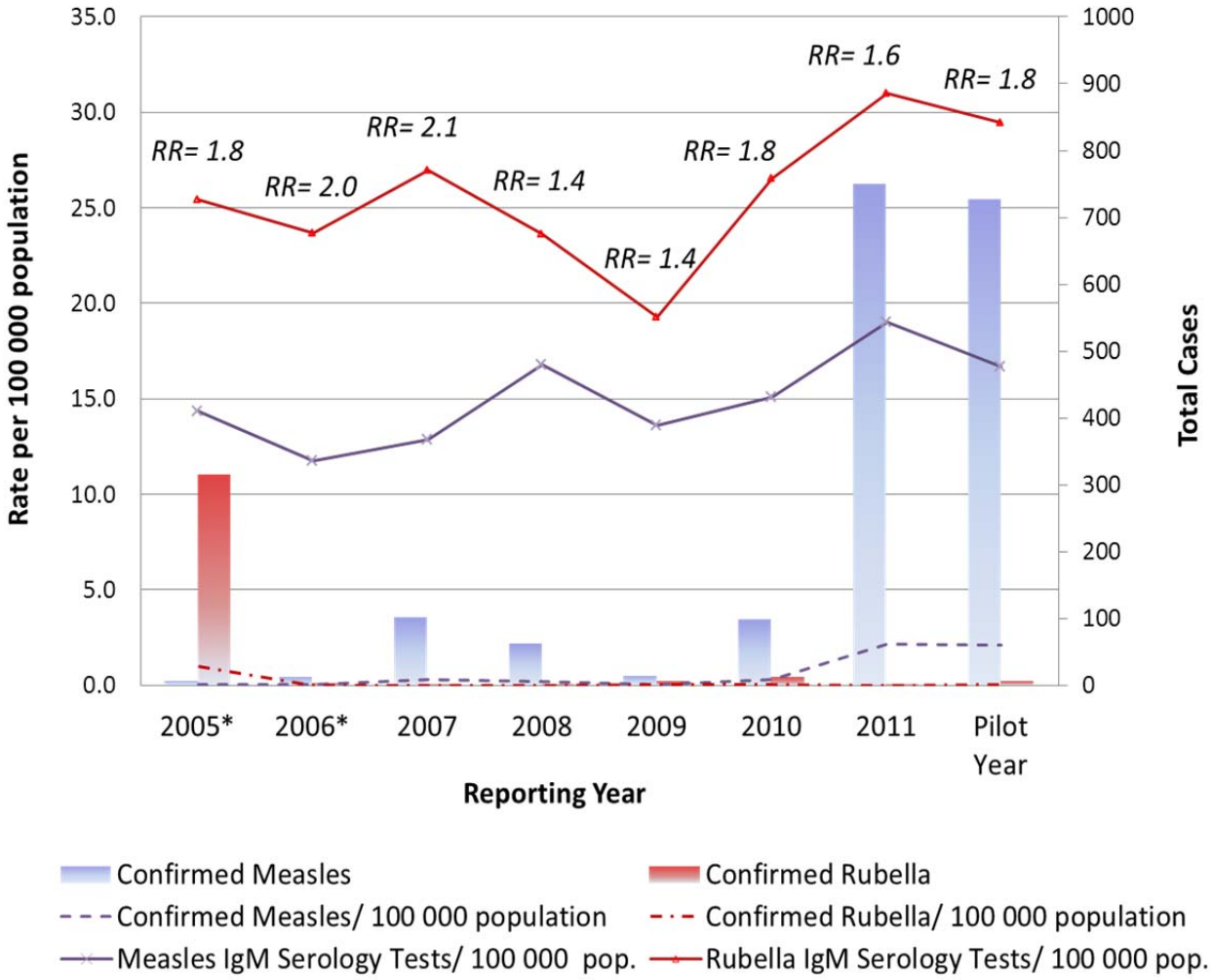


FIGURE 3.3a National Measles and Rubella Investigation Rates: 2005-2011 and Pilot Years

Table 3.22 National Measles and Rubella Investigation Rates: 2005-2011 and Pilot Years

Year	Measles IgM Serology	Rubella IgM Serology	Population[†*]	MLI Investigations /100 000 pop.	Rubella IgM Serology/ 100 000 pop.	Rate Ratio Rubella/ Measles
Pilot	5784	10212	34648537	17	29	1.8
2011	6558	8209	34482777	19	31	1.6
2010	5158	6960	34126181	15	27	1.8
2009	4594	4998	33729690	14[†]	19[†]	1.4
2008	5417	5783	33319098	17	24	1.4
2007	4096	6515	32929733	13	27	2.1
2006[*]	*3829*	*7719*	32576074	*12[†]*	*24*	*2.0*
2005[*]	*4635*	*8201*	32245209	*14*	*25*	*1.8*

[*] 2005 and 2006 data were taken from the 2007 national survey results and are not directly comparable to the 2012 survey results for the 2007-2011/Pilot periods due to differing survey response rates and responding labs
[†] Baseline, non-outbreak MLI investigation and rubella testing rates
[†] National census population data estimates used to calculate MLI investigation rates for the 2005-2011 and pilot years; pop.[†*] denominator was adapted to exclude NS/PEI populations when estimating 2007/8 MLI investigation rates as measles IgM serology data were unavailable* (95)
[††] Rubella IgM serology testing rates/100 000 pop. were estimated using adapted population[†] denominator data to exclude provinces for which rubella IgM data were unavailable (i.e. QC: 2007-11; NS/PEI 2007-8)*

National MLI Investigation versus Measles/Rubella Incidence Rates: 2007-2011

The association between observed national incidence of confirmed measles/rubella and MLI investigation rates estimated using measles IgM serology testing data was assessed (Figure 3.3b).

FIGURE 3.3b National MLI Investigation versus Measles/Rubella Incidence Rates per 100 000 population: 2007-2011. Linear regression analysis was used to quantify the association between annual MLI investigation rate/100 000 population and the observed measles/rubella confirmed case incidence/100 000 population per year for the 2007-2011 reporting years. The correlation coefficient (r=0.79) and the coefficient of determination measuring 'goodness of fit' (R^2= 0.62) were assessed. Source data are found in Tables 3.22 and 3.21 respectively. Note: 2005-2006 pre-pilot data were excluded from analysis as they are not directly comparable with 2007-2011 post-pilot survey data; pilot year data were also excluded due to overlap with the 2011 reporting year.

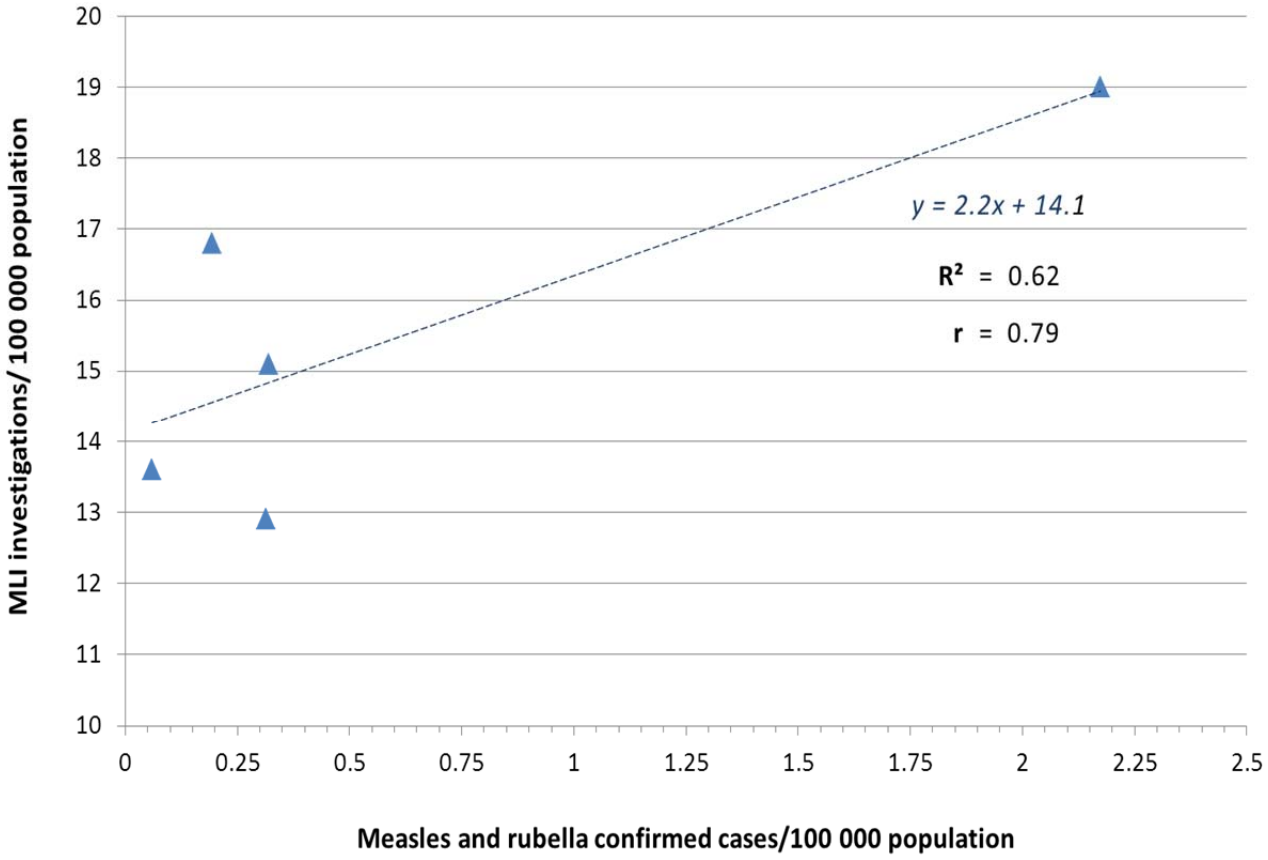


FIGURE 3.3b National MLI Investigation versus Measles/Rubella Incidence Rates per 100 000 population: 2007-2011.

Measles and Rubella Serology: %Positive in Non-Outbreak Settings, 2007-2011 and Pilot Years

Using national laboratory data obtained through the 2012 post-pilot Measles and Rubella Laboratory Investigation Survey, the proportions of measles and rubella IgM serology tests yielding positive results (%positive values) were estimated at the national level in both outbreak and non-outbreak settings. The %positive values obtained for measles and rubella IgM serology testing in non-outbreak settings during each of the 2007-2011 reporting years are summarized in Table 3.23. Baseline, non-outbreak measles and rubella IgM %positive values were then compared according to average, median and range, and associated confidence intervals (Figure 3.4, Table 3.4)

Table 3.23*:* National Measles and Rubella IgM Serology Testing: %Positive, Non-outbreak Settings*

Year	Measles IgM Serology	Measles IgM-Positive	% Measles IgM-Positive	Rubella IgM Serology	Rubella IgM-Positive	% Rubella IgM-Positive
Pilot	4622	143	3.1	8238	143	1.7
2011	4926	163	3.3	8192	135	1.6
2010	3697	80	2.2	6884	87	1.3
2009	4594	44	1.0	6256	52	0.8
2008**	3411	37	1.1	5393	94	1.7
2007**	3490	76	2.2	6515	98	1.5

**To estimate testing levels in non-outbreak settings, test data from provincial outbreak settings were excluded for the following years: QC: 2011, BC: 2010, ON: 2008, QC: 2007.*
***Provincial data for NS, PE were unavailable for the 2007 and 2008 reporting years*

FIGURE 3.4 %Positive Values: Measles and Rubella IgM Serology Testing in National Non-outbreak Settings, 2007-2011. Baseline %positive values were determined for measles and rubella IgM serology testing in non-outbreak settings using aggregate data provided by laboratories in non-outbreak provincial settings during the 2007 – 2011 years (Table 3.23). All laboratory test data submitted without corresponding positive results for a given year were excluded from analysis.

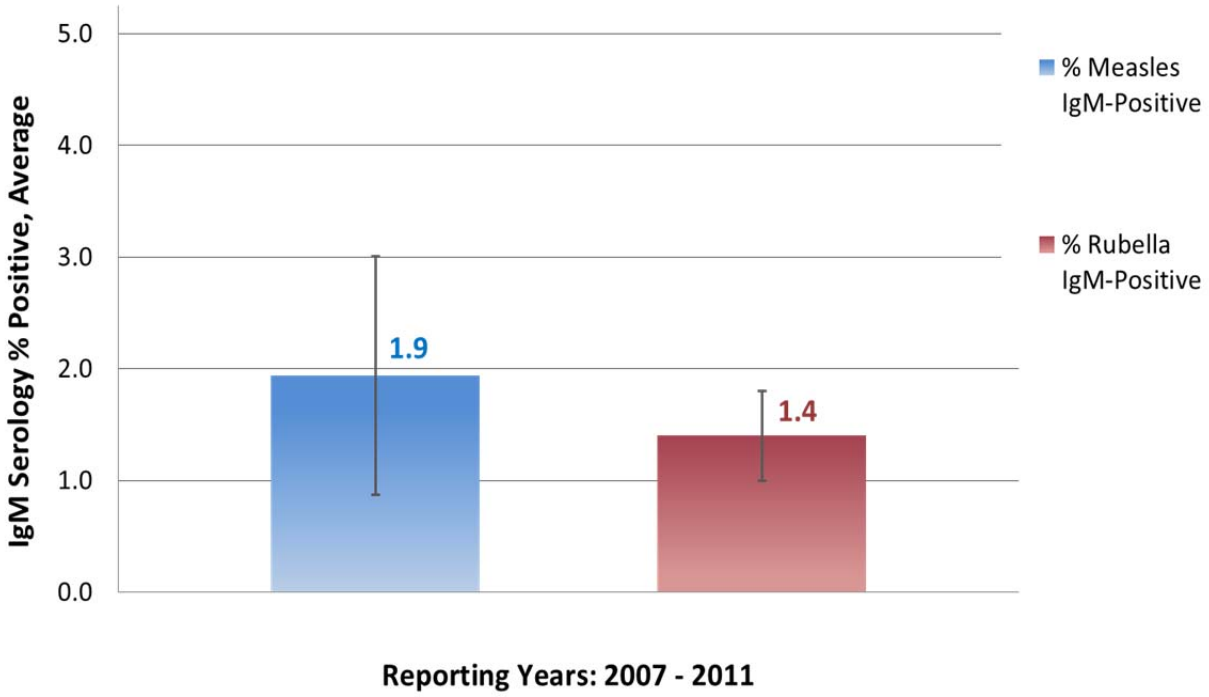


FIGURE 3.4 %Positive Values: Measles and Rubella IgM Serology Testing in National Non-outbreak Settings, 2007-2011

Table 3.24 %Positive: Measles/Rubella IgM Serology Testing in Non-outbreak Settings, 2007-11

	Measles IgM %Positive: Non-Outbreak, 2007-11	Rubella IgM %Positive: Non-Outbreak, 2007-11
Average	**1.9**	**1.4**
Median	2.2	1.5
Min	1.0	0.8
Max	3.3	1.7
95% CI*	0.9 – 3.0	1.0 – 1.8

**95% Confidence Intervals were determined for average %positive values.*

%Positive: Measles IgM Serology in Outbreak Settings, 2007-2011 and Pilot Years

Measles IgM serology %positive values were estimated in provincial outbreak settings (QC, 2007; ON, 2008; BC, 2009; QC, 2011) and compared with those observed in non-outbreak settings for the 2007-2011 reporting years as well as the MARS pilot year. Rate ratios (outbreak/non-outbreak) were estimated to assess the magnitude of differences in measles IgM %positive values, and ranged from 2.2 – 5.5 for the 2007, 2008, 2010 and 2011 outbreak years (Table 3.25, Figure 3.5). Results are summarized in Figure 3.5 with comparison to the baseline average %positive of 1.9% estimated for measles IgM serology in non-outbreak settings during the 2007-2011 reporting years.

Table 3.25 %Positive: Measles IgM Serology - Outbreak vs Non-Outbreak Settings; 2007-11, Pilot

Year	Non-Outbreak Settings %Measles IgM-Positive	Outbreak Settings %Measles IgM-Positive	Outbreak/ Non-Outbreak †Rate Ratio (RR)
Pilot	3.1%	16 %	5.0
2011	3.3%	18 %	5.5
2010	2.2%	4.7 %	2.2
2009	1.0%	*	*
2008	1.1%	3.9%	3.6
2007	2.2%	9.4%	4.3

*† Using Chi-squared analysis, **P <0.001** for all differences in %positive values observed between outbreak and non-outbreak settings during the 2007, 2008, survey period. 2010, 2011 and Pilot years.*
**2009 is a national non-outbreak year*

FIGURE 3.5 Measles IgM Serology: %Positive in National Outbreak versus Non-outbreak Settings during the 2007-2011 and Pilot Years. Measles IgM serology %positive values were estimated and *RR* values determined as a measure of the magnitude of differences in measles IgM %positive between outbreak/non-outbreak settings during each of the 2007-2011 and Pilot reporting years. All differences were significant by Chi-squared analysis (*†P <0.001).* The 2007-2011 average non-outbreak measles IgM %positive value of 1.9% is shown for comparison.

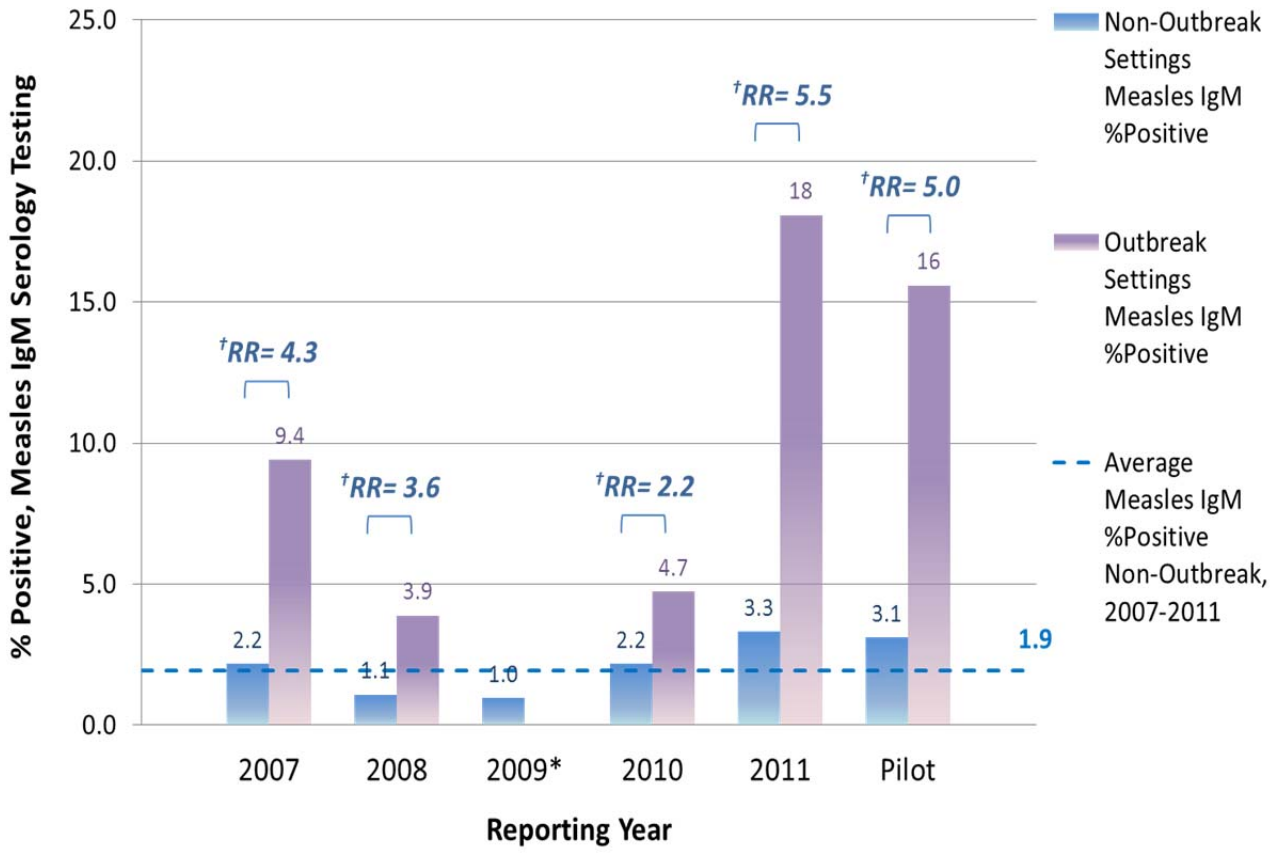


FIGURE 3.5 Measles IgM Serology: %Positive in National Outbreak versus Non-outbreak Settings during the 2007-2011 and Pilot Years.

National MLI Investigation Rates: MARS Pilot Year; June 2011 – May 2012

MLI rates of investigation during the MARS pilot period were estimated for participating MARS provinces (BC, AB, NL), CMRSS reporting provinces, CMRSS reporting provinces excluding Québec, and at the national level (Table 3.26).

Table 3.26 MLI Investigation Rates during the MARS Pilot Year: MARS Sites, CMRSS Sites, National

Pilot Year	MLI investigations/ 100 000 pop.[†]	Confirmed Measles	Confirmed Rubella	Confirmed Measles/ 100 000 pop.	Confirmed Rubella/ 100 000 pop.	Population (Pilot)[††]
MARS Sites (BC, AB, NL)	22	4	1	0.045	0.011	8923979
CMRSS Sites excl. QC*	15	11	6	0.062	0.034	17713587
CMRSS Sites	15	723	6	2.8	0.020	25724557
National, All Sites	17	727	7	2.1	0.023	34648537

[†]**PAHO Target =** ≥2 suspected cases/ 100 000 population **Target Status:** (Pilot Year) **Met at all MARS/CMRSS Provincial Sites** (Range: 15 – 22/100 000 population)

[†]Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash.'

[††]Rates per 100 000 population were determined using national and provincial census population data ((95)). MARS sites= BC, AB, NL. CMRSS sites = SK, MB, ON, QC, NB, NS, PE. Territorial data were excluded from rate estimation all laboratory investigations are referred to various provincial laboratories. Their exclusion will not significantly impact population level rate estimates given the small YT, NT and NU territorial populations and associated measles/rubella testing volumes.

**Québec provincial data were excluded In order to compare the level of MLI investigation observed for CMRSS reporting provinces in non-outbreak settings with MARS reporting provinces.*

As the MARS pilot period had significant overlap with the 2011 outbreak year, MLI investigation rates observed at MARS provincial sites during the pilot year were compared with baseline non-outbreak rates estimated for the same geographical jurisdictions during the 2009 national non-outbreak year. The statistical significance of rate differences was determined using Chi-squared analysis; outbreak/ non-outbreak rate ratios were calculated to compare the magnitude of differences observed, and results were summarized within the context of confirmed measles and rubella case rates observed in each geographical jurisdiction (Table 3.27, Figure 3.6).

Table 3.27 MARS Pilot MLI Investigation Rates: Comparison with Baseline Non-outbreak Rates

MLI Investigations/ 100 000 population	MARS Sites (BC, AB, NL)	CMRSS Sites excluding QC*	CMRSS Sites	National, All Sites
Outbreak Rate (MARS Pilot Period)	22	15	15	17
Non-Outbreak Baseline Rate* (2009)	16	16	13	14
Rate Ratio: Outbreak/ Non-Outbreak	1.4	0.95	1.1	1.2
P†	<0.001	<0.1	<0.001	<0.001

**Baseline 'non-outbreak' MLI investigation rates were estimated for each of the defined reporting regions using survey data for the 2009 national non-outbreak year.*

†Chi-squared analysis was used to assess the significance of differences between 'outbreak' and baseline 'non-outbreak' rates for geographically matched regions, with probability P<0.05 set as the significance threshold. All differences were highly significant with the exception of 'CMRSS Sites excluding QC'. Rate ratios were calculated to determine the relative magnitude of differences.

FIGURE 3.6 MLI Investigation Rates during the MARS Pilot Year at MARS sites, CMRSS sites (including and excluding QC) and all National sites. Baseline 'non-outbreak' MLI investigation rates were estimated for each of the defined reporting regions using survey data for the 2009 national non-outbreak year. Chi-squared analysis was used to assess the significance of differences between 'outbreak' and baseline 'non-outbreak' rates for geographically matched regions, with probability *P<0.05* set as the significance threshold. The *'CMRSS sites excluding QC' jurisdictional category was included to allow comparison of CMRSS and MARS investigation rates within a non-outbreak context. †*P <0.001* for all outbreak/non-outbreak rate differences with the exception of 'CMRSS Sites excluding QC'. Rate ratios were calculated to determine the relative magnitude of differences. MLI investigation rates were estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation. Rates are compared with the national baseline MLI investigation rate of 14/100 000 estimated for the 2009 non-outbreak year, and the PAHO Target: ≥2 suspected cases/100 000 population, where PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'.

National MLI Investigation and Measles and Rubella Incidence Rates: 2005-11, Pilot Year

MLI rates of investigation observed at the national level were estimated for the 2005-6 reporting years using pre-pilot 2007 national laboratory survey data, and for the 2007-2011 and Pilot years using data obtained through the post-pilot 2012 national laboratory survey (Table 3.26). The significance of MLI investigation rate differences observed during outbreak versus non-outbreak years was assessed using Chi-squared analysis. Outbreak/non-outbreak rate ratios were calculated using the baseline non-outbreak rates corresponding with the 2007 and 2012 survey periods, i.e. 2006 and 2009 non-outbreak year MLI investigation rates (Table 3.28a).

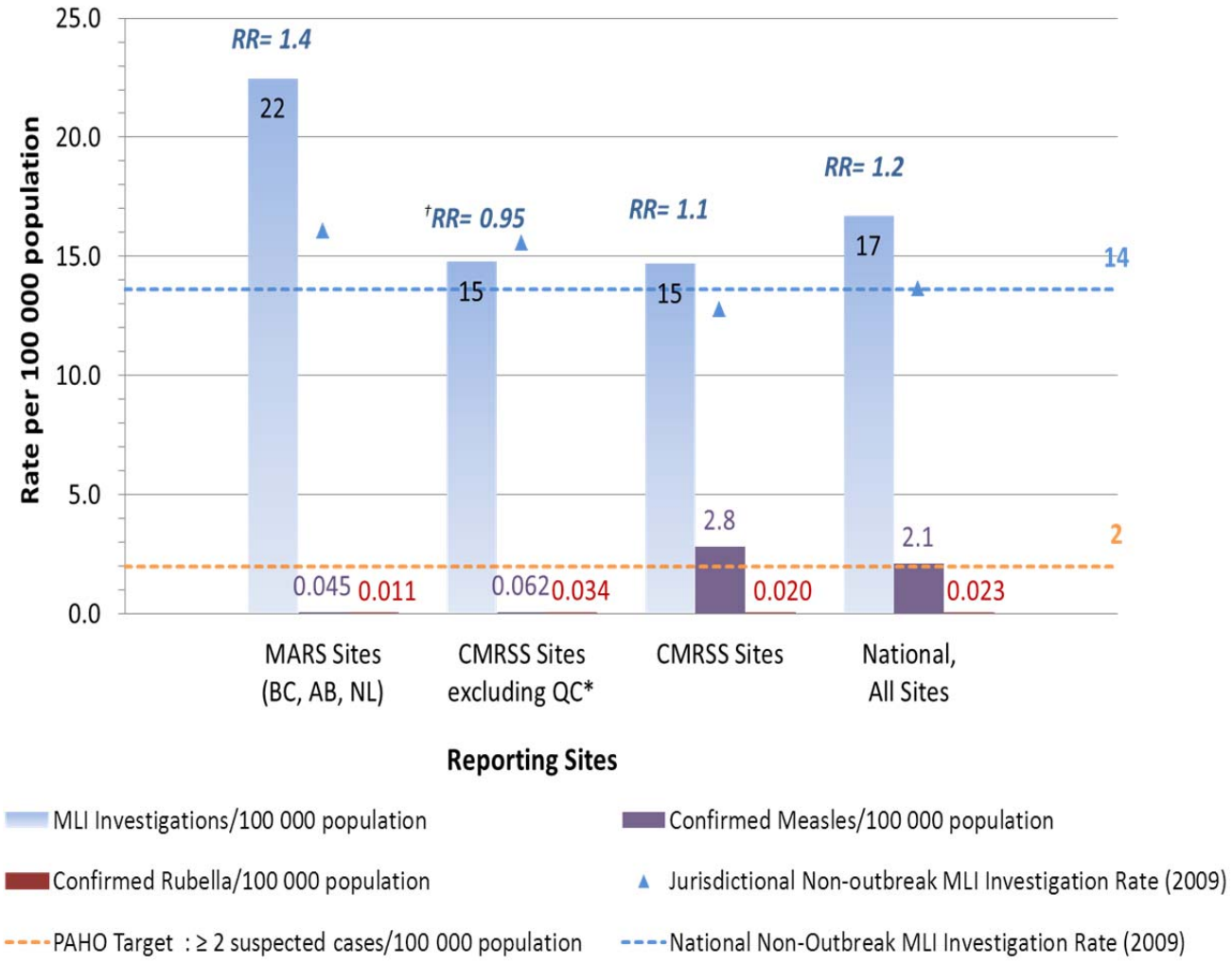


FIGURE 3.6 MLI Investigation Rates during the MARS Pilot Year at MARS sites, CMRSS sites (including and excluding QC) and all National sites.

Table 3.28a National MLI Investigation Rates and *RR*s - Outbreak vs Non-outbreak: 2005-11, Pilot

Year	MLI Investigations/ 100 000 pop.*	National Non-outbreak MLI Investigation Rate	Rate Ratio†* Outbreak/ Non-outbreak	*P*
Pilot	17	14	1.2	<0.001
2011	19	14	1.4	<0.001
2010	15	14	1.1	<0.001
2009	14†	14	-	-
2008	17	14	1.2	<0.001
2007	13	14	0.94	<0.1
2006	*12††*	*12*	-	-
2005	*14*	*12*	*1.2*	*<0.001*

*__PAHO Target =__ ≥2 suspected cases/ 100 000 population

Target Status: Met, all national reporting years (2005-11, Pilot) (Range: 12 – 19/100 000 population)

**Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'*

† Baseline 'non-outbreak' MLI investigation rate, estimated using data for the 2009 national non-outbreak year collected via the 2012 national survey.

†† National 'non-outbreak' MLI investigation rate estimated using data for the 2006 national non-outbreak year collected via the 2007 national survey.

† As data obtained through the 2007 and 2012 national survey are not directly comparable, outbreak/non-outbreak RRs were calculated using the baseline 'non-outbreak' rates falling within the respective survey periods.*

FIGURE 3.7 National MLI Investigation Rates and Rate Ratios during Outbreak and Non-outbreak Years: 2005-2011 and Pilot. National MLI investigations rates estimated for the 2005-11 and Pilot years using pre- and post-pilot national laboratory survey data are displayed within the context of national confirmed measles and rubella incidence rates for the same period, as well as the PAHO Target: ≥2 suspected cases/100 000 population. Annual outbreak/ non-outbreak rate ratios (RR) were estimated for the 2005-6 period using the baseline non-outbreak rate for the †2006 non-outbreak year, whereas RR values for the 2007-11 and Pilot years were calculated using the 2009 non-outbreak year baseline rate (Table 3.28a). Chi-squared analysis demonstrated significant rate differences during outbreak vs non-outbreak years (*P<0.001)* with the exception of the 2007 outbreak year.

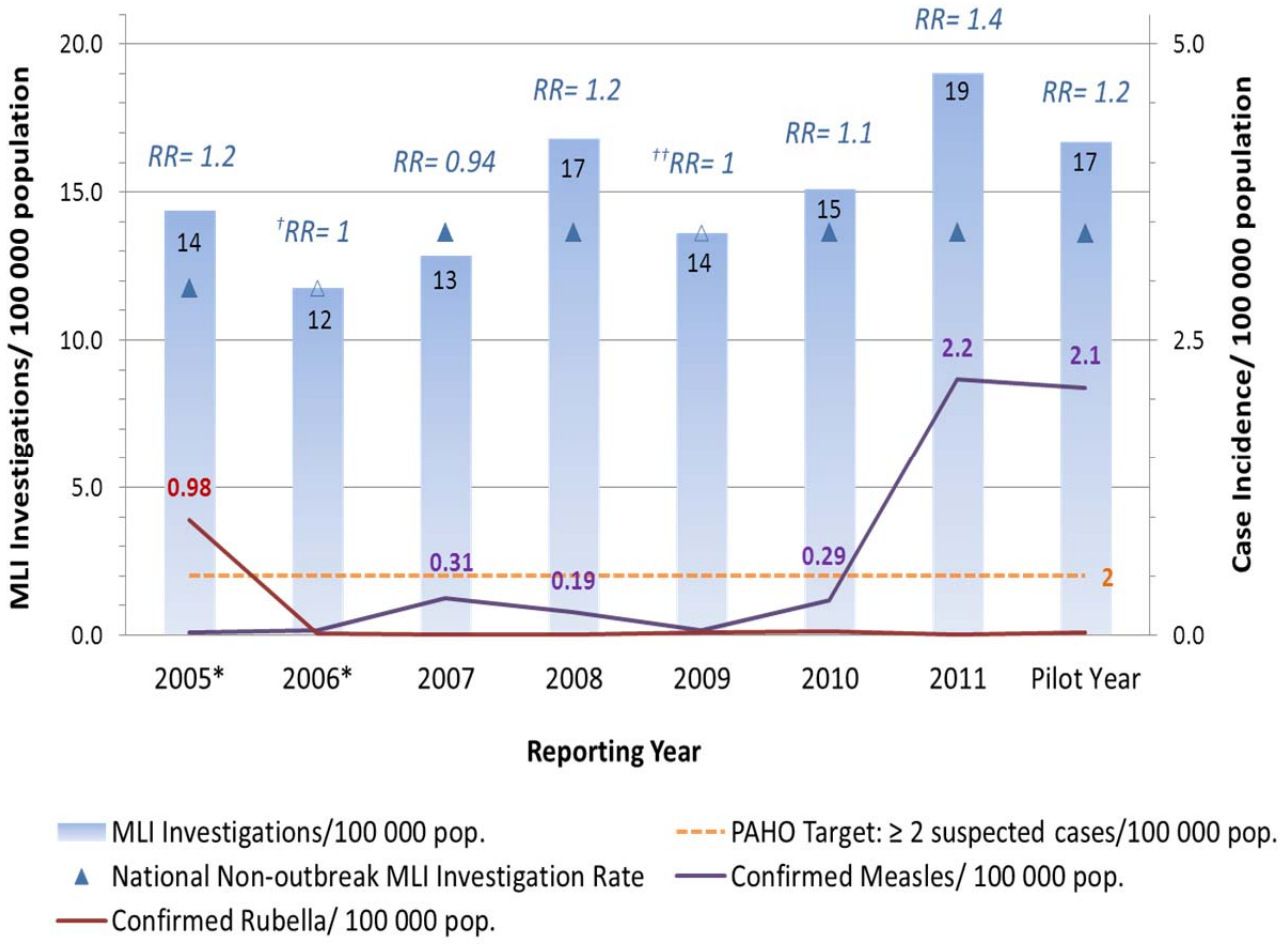


FIGURE 3.7 National MLI Investigation Rates and Rate Ratios during Outbreak and Non-outbreak Years: 2005-2011 and Pilot

National versus International MLI Investigation Rates: Canada, Mexico and Brazil; 2009

To assess the performance of national surveillance in an international context, the level of investigation into MLI in Canada was compared with other countries in the Region of the Americas that report their national rates of suspected case investigation to PAHO, i.e. Mexico and Brazil. Canadian data from the 2009 non-outbreak year were used to provide a conservative estimate based solely on the baseline rate of MLI investigation (Table 3.28b).

Table 3.28b MLI Investigation Rates in PAHO Countries: Canada, Mexico and Brazil; 2009

Country	MLI Investigations/ 100 000 pop.*	Total MLI investigations	Rate Ratio (National Rate/ PAHO Target*)	Population (2009) ††
Canada*	14	4594	6.8	33 729 690
Mexico	3.1	3426†*	1.6	111 211 800
Brazil	4.6	9134†*	2.3	198 739 300

***PAHO Target =** ≥2 suspected cases/ 100 000 population **Target Status:** Met: All countries (2009)

**Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'*

† Baseline 'non-outbreak' MLI investigation rate, estimated using data for the 2009 national non-outbreak year collected via the 2012 national survey.

†† 2009 population estimates for Mexico and Brazil were obtained from the CIA World Factbook,2009 (96)*; Canadian census-based population estimate source is Statistics Canada* (95)

† Total numbers of suspected cases reported by Mexico and Brazil to PAHO in 2009* (97)

Provincial MLI Investigation Rates in Outbreak Settings: 2007-2011 and Pilot Years

Annual provincial MLI investigation levels were assessed for Québec, Ontario and BC, each of which experienced at least one notable outbreak during the 2007-2011 and Pilot reporting years. Provincial

outbreak rates were compared with baseline rates estimated by averaging MLI investigation rates during provincial non-outbreak years, and *RR*s calculated to assess the magnitude of outbreak/non-outbreak rate differences (Tables 3.29, 3.30 and 3.31; Figures 3.8, 3.9, 3.10). Data sources used include the post-pilot 2012 national laboratory survey (Appendix XIV), national confirmed case data (45, 94), and national census population data (95).

Québec

Québec experienced measles outbreaks in 2007 and 2011, with significant overlap of the latter with the MARS pilot period. Provincial MLI investigation rate data are shown in Table 3.29 and Figures 3.8.

Table 3.29 Québec: MLI Investigation Rates, *RR*s: Outbreak vs Non-outbreak, 2007-11 and Pilot

Year	MLI Investigations[Δ] 100 000 pop.[†]	Confirmed Measles[*]/ 100 000 pop.[†]	Confirmed Rubella[*]/ 100 000 pop.[†]	Provincial Non-Outbreak MLI Rate (Avg.)[**]	*RR*[††] Outbreak/ Non-outbreak	*P*
Pilot	15	8.9	0.000	4.6	3.2	<0.001
2011	20	9.1	0.000	4.6	4.5	<0.001
2010	3.1	0.063	0.000	-	-	-
2009	6.7	0.077	0.000	-	-	-
2008	4.0	0.013	0.000	-	-	-
2007	7.9	1.2	0.013	4.6	1.7	<0.001

[Δ]**PAHO Target =** ≥2 suspected cases/ 100 000 population | **Target Status:** (2007-11, Pilot) | **Met, all QC provincial reporting years** (Range: 3.1 – 20 /100 000 population)

[Δ*] *Measles IgM serology was used as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'.*
[*] *Data source for confirmed measles and rubella case data is CMRSS*
[**] *The baseline 'non-outbreak' MLI investigation rate of 4.6/100 000 population was estimated for Québec by averaging provincial rates for the 2008-2010 non-outbreak years.*
[†] *Rates per100 000 population were determined using provincial census population data* (95)
[††] *RRs were calculated to assess the magnitude of differences between provincial MLI investigation rates during outbreak periods (2007, 2011 and Pilot years) and the baseline non-outbreak rate. Chi-squared analysis yielded P<0.001 for all outbreak vs non-outbreak rate differences assessed.*

FIGURE 3.8 Québec - MLI Investigation Rates and Rate Ratios: Outbreak vs Non-outbreak; 2007 – 11 and Pilot Years. QC MLI investigation rates and measles and rubella incidence rates are shown for the 2007 - 2011 and Pilot years. Outbreak-associated MLI investigation rates observed during the 2007, 2011 and Pilot years were compared with the baseline provincial 'non-outbreak' rate of 4.6 MLI investigations/100 000 population, estimated by averaging 2008-2010 non-outbreak rates. The PAHO Target: ≥2 suspected cases/100 000 population was included for comparison purposes. All 'outbreak' vs 'non-outbreak' rate differences were significant (*P <0.001)* using Chi-squared analysis. *RR* values were calculated to assess the magnitude of observed rate differences (Table 3.29)

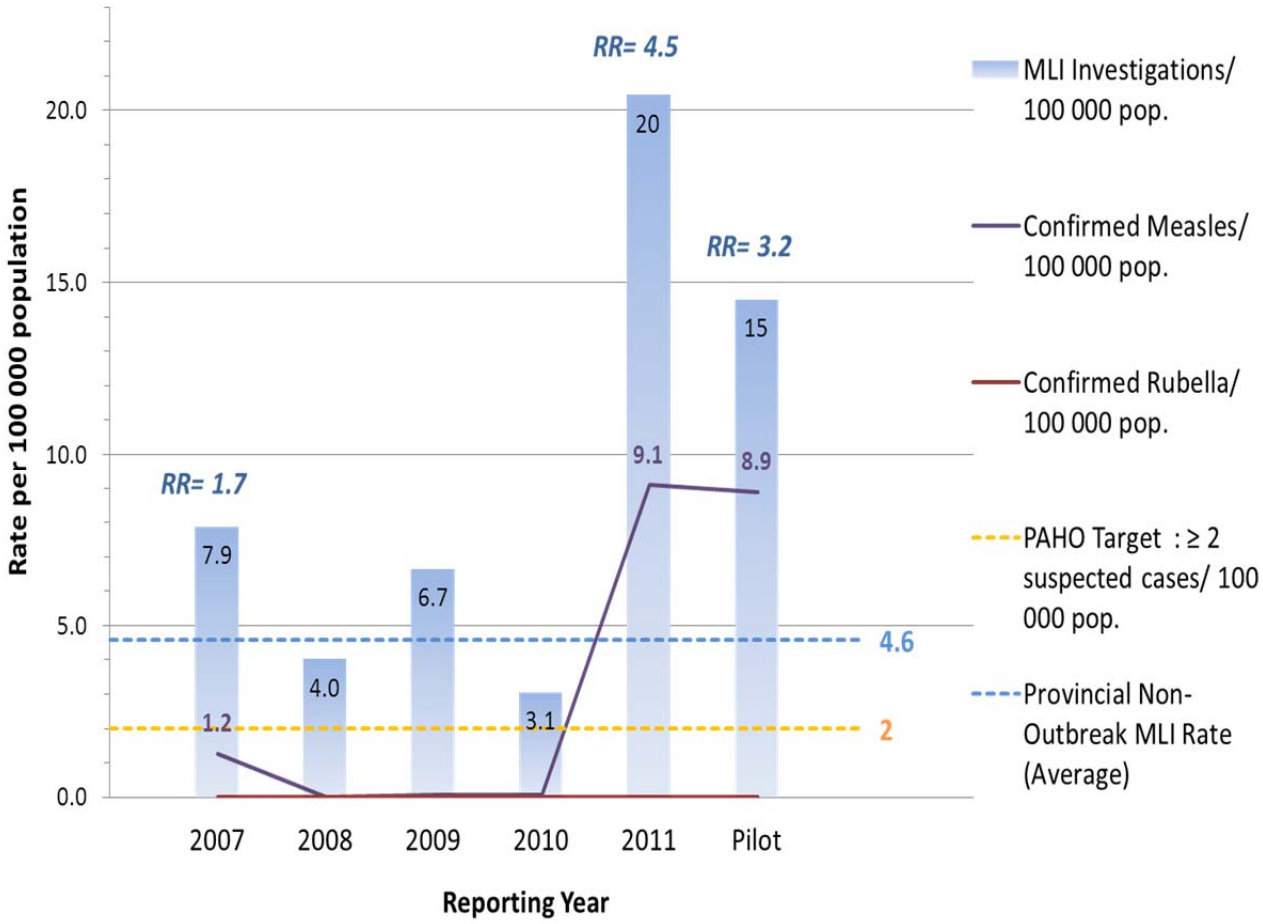


FIGURE 3.8 Québec: MLI Investigation Rates and Rate Ratios: Outbreak vs Non-outbreak; 2007 - 2011 and Pilot Years**.**

Ontario

Ontario experienced a measles outbreak in 2008. Provincial MLI investigation rate data for the 2007-2011 and Pilot years are displayed in Table 3.30, Figures 3.9.

Table 3.30 Ontario - MLI Investigation Rates, *RR*s: Outbreak vs Non-outbreak; 2007-11 and Pilot

Year	MLI Investigations$^{\Delta}$/ 100 000 pop.†	Confirmed Measles*/ 100 000 pop.†	Confirmed Rubella*/ 100 000 pop.†	Provincial Non-Outbreak MLI Rate (Avg.)**	*RR*†† Outbreak/ Non-outbreak	*P*
Pilot	7.9	0.000	0.000	-	-	
2011	9.3	0.060	0.000	-	-	
2010	6.9	0.068	0.008	-	-	
2009	14	0.054	0.023	-	-	
2008	16	0.45	0.000	11	1.6	<0.001
2007	7.9	0.000	0.000	-	-	

$^{\Delta}$**PAHO Target =** ≥2 suspected cases/ 100 000 population **Target Status:** (2007-11, Pilot) **Met, all ON provincial reporting years** (Range: 6.9 – 16/100 000 population)

$^{\Delta}$*Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'*
**Data source for confirmed measles and rubella case data is CMRSS*
***A baseline 'non-outbreak' MLI investigation rate of 11/100 000 population was estimated for Ontario by averaging provincial rates for the 2007 and 2009-2011 non-outbreak years.*
†*Rates per100 000 population were determined using provincial census population data* (95)
†† *RR was calculated to assess the magnitude of the difference between the provincial MLI investigation rate during the 2008 outbreak year and the baseline non-outbreak rate (P<0.001: Chi-squared analysis)*

FIGURE 3.9 Ontario: MLI Investigation Rates and Rate Ratios: Outbreak vs Non-outbreak; 2007 - 2011 and Pilot Years. ON MLI investigation and measles and rubella incidence rates are shown for the 2007 - 2011 and Pilot years. The 2008 outbreak rate was compared with the baseline provincial non-outbreak rate of 11 MLI investigations /100 000 population. The PAHO Target: ≥2 suspected cases/100 000 population is shown for comparison. The 2008 outbreak and non-outbreak rates differed significantly (*P <0.001,* Chi-squared analysis). *RR* was calculated to assess the magnitude of the rate difference (Table 3.29).

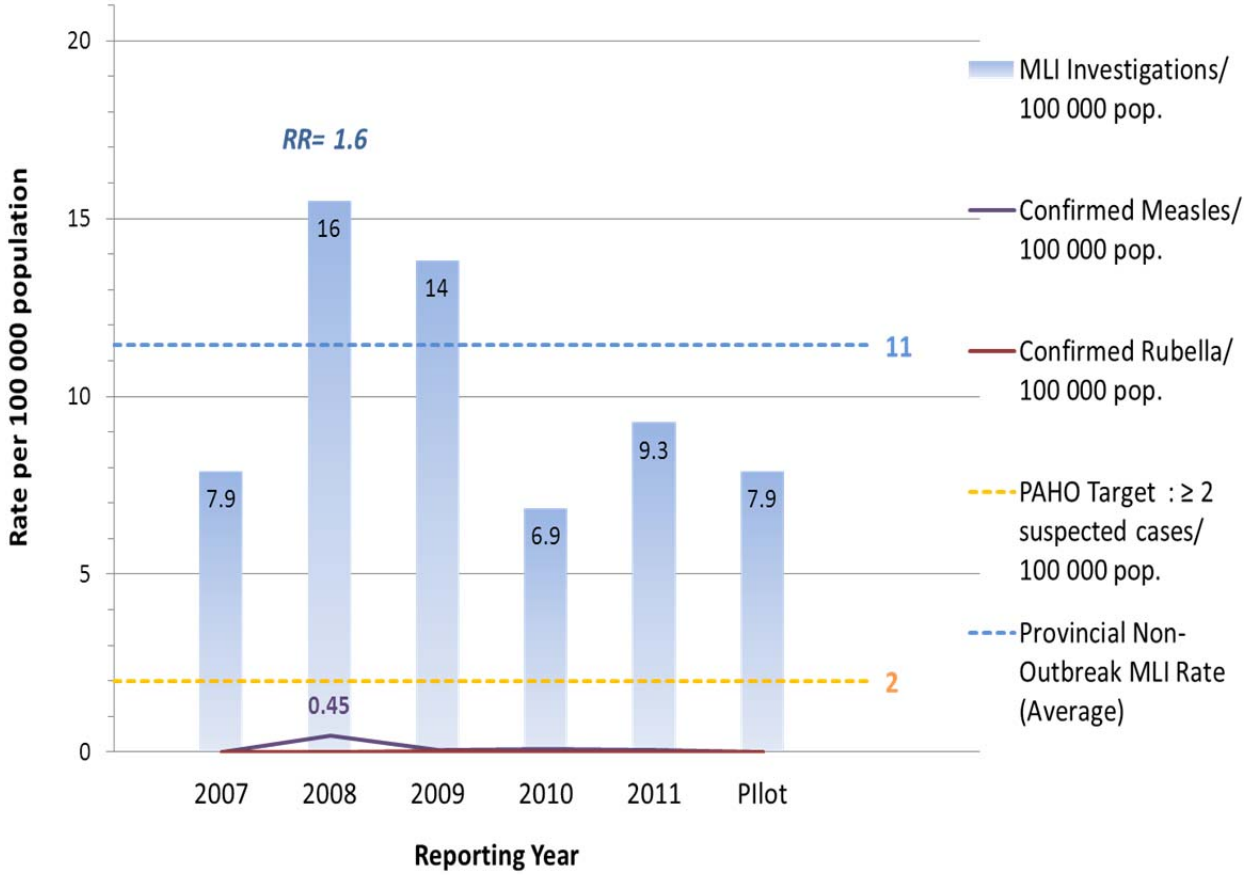


FIGURE 3.9 Ontario: MLI Investigation Rates and Rate Ratios: Outbreak vs Non-outbreak; 2007 - 2011 and Pilot Years.

British Columbia

BC experienced a measles outbreak in 2010. Provincial MLI investigation rate data for the 2007-2011 and Pilot years are displayed in Table 3.31, Figures 3.10.

Table 3.31 BC - MLI Investigation Rates, Rate Ratios: Outbreak vs Non-outbreak; 2007-11 and Pilot

Year	MLI Investigations$^{\Delta}$ /100 000 pop.†	Confirmed Measles*/ 100 000 pop.†	Confirmed Rubella*/ 100 000 pop.†	Provincial Non-Outbreak MLI Rate (Avg.)**	$RR^{\dagger\dagger}$ Outbreak/ Non-outbreak	*P*
Pilot	18	0.000	0.000	-	-	-
2011	19	0.22	0.022	-	-	-
2010	32	1.8	0.20	23	1.4	<0.001
2009	18	0.000	0.022	-	-	-
2008	36	0.000	0.023	-	-	-
2007	20	0.070	0.000	-	-	-

$^{\Delta}$**PAHO Target =** ≥2 suspected cases/ 100 000 population | **Target Status:** (2007-11, Pilot) | **Met, all BC provincial reporting years** (Range: 18 – 36/100 000 population)

$^{\Delta}$*Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'*
**Data source for confirmed measles and rubella case data is CMRSS*
***A baseline 'non-outbreak' MLI investigation rate of 23/100 000 population was estimated for British Columbia by averaging provincial rates for the 2007- 2009 and 2011 non-outbreak years.*
†*Rates per100 000 population were determined using provincial census population data* (95)
†† *RR was calculated to assess the magnitude of the difference between the 2010 provincial outbreak rate and the baseline non-outbreak MLI investigation rate (P<0.001, Chi-squared analysis)*

FIGURE 3.10 British Columbia: MLI Investigation Rates and Rate Ratios: Outbreak vs Non-outbreak; 2007 - 2011 and Pilot Years. BC MLI investigation and measles and rubella incidence rates are shown for the 2007 - 2011 and Pilot years. The 2010 outbreak rate was compared with the baseline provincial non-outbreak rate of 23 MLI investigations /100 000 population. The PAHO Target: ≥2 suspected cases/100 000 population is shown for comparison. The 2010 outbreak and non-outbreak rates differed significantly using Chi-squared analysis (*P <0.001).* The *o*utbreak/ non-outbreak *RR* was calculated to quantify the rate difference (Table 3.30).

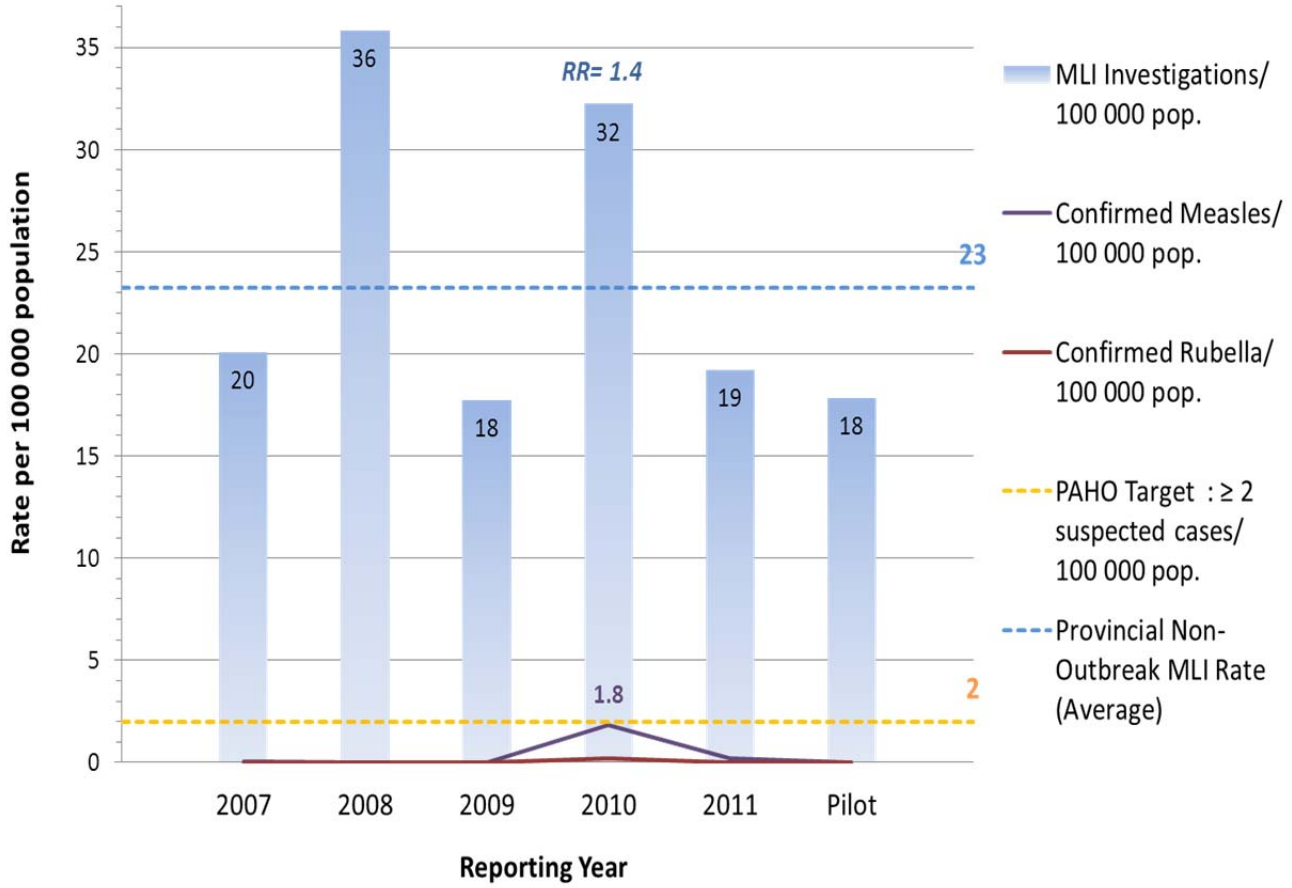


FIGURE 3.10 British Columbia: MLI Investigation Rates and Rate Ratios: Outbreak vs Non- outbreak; 2007 - 2011 and Pilot Years.

Provincial MLI Investigation Rates in Non-outbreak Settings: 2007 – 2011

A majority of 7 provinces did not experience a notable measles or rubella outbreak during the 2007-2011 reporting years: AB, SK, MB, NB, NS, PE and NL; none of the Canadian territories (YT, NT, NU) reported measles or rubella cases during this period(94).

To assess the potential contribution of extra-jurisdictional outbreak activity to MLI investigation rates observed within the 7 provincial non-outbreak settings, rates of investigation during the 2007, 2008, 2010 and 2011 national outbreak years were averaged for each province, and compared intra-provincially with 2009 baseline non-outbreak rates estimated for each province (Figure 3.11a, Table 3.32a). Data sources used include the post-pilot 2012 national laboratory survey (Appendix XIII), national confirmed case data (45, 94) and national census population data (95).

FIGURE 3.11a Provincial MLI Investigation Rates in Non-outbreak Settings: Extrajurisdictional Outbreak versus Non- outbreak Years; 2007 – 2011. The baseline MLI investigation rate estimated for each province during the 2009 national non-outbreak year was compared with the average provincial rate associated with the 2007, 2008, 2010 and 2011 extra-jurisdictional outbreak years. The PAHO Target: ≥2 suspected cases/100 000 population is shown for comparison. The significance of differences between extra-jurisdictional outbreak and non-outbreak rates were assessed using Chi-squared analysis, with a significance threshold of $P < 0.05$. *Indicates a significant rate difference. *RR* values were calculated to quantify the magnitude of intra-provincial rate differences (Table 3.32).

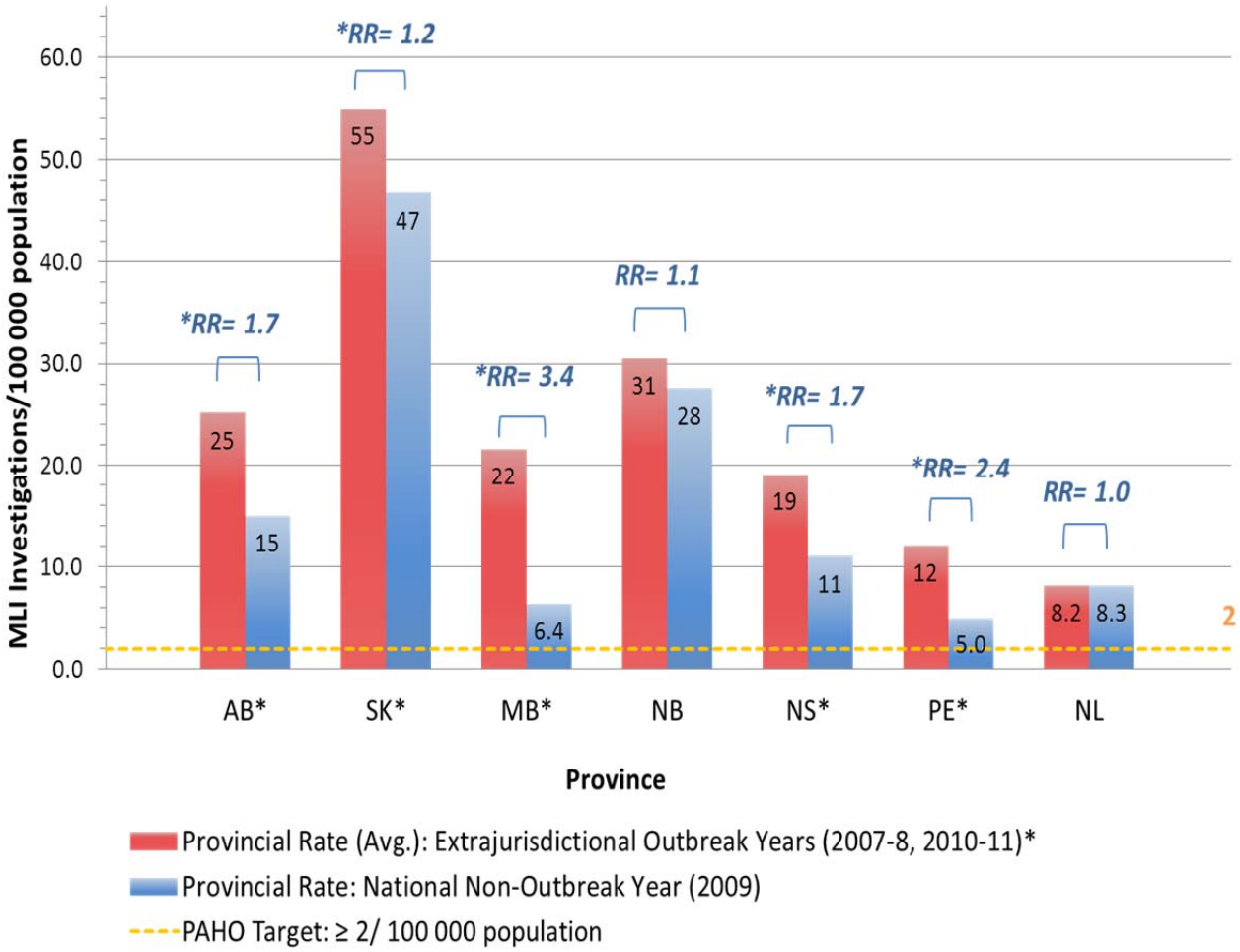


FIGURE 3.11a Provincial MLI Investigation Rates in Non-outbreak Settings:
Extra-jurisdictional Outbreak versus Non- outbreak Years; 2007 – 2011.

Table 3.32a Provincial MLI Investigation Rates in Non-outbreak Settings: 2007-2011

MLI Investigations/ 100 000 population[Δ]	AB	SK	MB	NB	NS	PE	NL
Provincial Rate (Avg.): Extra-Jurisdictional Outbreak Years (2007-8, 2010-11)	25	55	22	31	19	12	8.2
Provincial Baseline Rate[*]: National Non-outbreak Year (2009)	15	47	6.4	28	11	5.0	8.3
Provincial Rate (Avg.): Provincial Non-outbreak Years (2007-11) [**]	23	53	18	30	16[**]	10[**]	8.3
RR[***] Outbreak/Non-Outbreak (2009)	1.7	1.2	3.4	1.1	1.7	2.4	1.0
P[†]	<0.001	<0.01	<0.001	NSD	<0.001	<0.05	NSD

[Δ]**PAHO Target =** ≥2 suspected cases/ 100 000 pop. **Target Status:** (2007-11) **Met in all provincial 'non-outbreak' settings**

[Δ]*Estimated using measles IgM serology as a lab-based proxy for MLI or 'suspected case' investigation, whereas PAHO defines a 'suspected case' of measles/rubella as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash'*

[*]*Provincial baseline 'non-outbreak' rates were estimated using 2009 national non-outbreak year data.*

[**] *Provincial average 'non-outbreak' rates were estimated for all 2007-11 reporting years with the exception of NS (2009-11) and PE (2008-11) as data were unavailable for previous years.*

[***]*Rate ratios were calculated to determine the magnitude of extra-jurisdictional outbreak/non-outbreak differences; RR=1 indicates no difference.*

†*Chi-squared analysis was used to assess the significance of differences between intra-provincial MLI investigation rates observed during national 'outbreak' and 'non-outbreak' years, with a significance threshold of P<0.05; NSD = No significant difference.*

Provincial versus National Rate Ratios: Differential Impact of Provincial Outbreaks on MLI Investigation Rates at the Provincial and National Levels; 2007-2008, 2010 - 2011 and Pilot Year

To compare the relative magnitude of the impact a provincial measles outbreak has on MLI investigation rates per 100 000 population at the provincial versus the national level, outbreak/baseline *RRs* assessed in provincial outbreak settings were compared with national *RR* values for the 2007, 2008, 2010, 2011 and Pilot reporting years. Each of these reporting years saw a single, larger-scale measles outbreak at the provincial level, which was responsible for the majority of nationally reported cases (45). All provincial and national *RR* values were calculated using 2009 non-outbreak year data to estimate baseline MLI investigation rates (Table 3.32b, Figure 3.11b).

Table 3.32b: Provincial versus National Rate Ratios: Comparing the Impact of a Provincial Outbreak on Provincial versus National MLI Investigation Rates

Outbreak Province	Reporting Year	**Provincial *RR*$^{\Delta}$** *(outbreak/non-outbreak)*	**National *RR*$^{\Delta}$** *(outbreak/non-outbreak)*
QC	Pilot	3.2	1.2
QC	2011	4.5	1.4
BC	2010	1.4	1.1
ON	2008	1.6	1.2
QC	2007	1.7	0.94
Range (*RR*$^{\Delta}$ *outbreak/non-outbreak):*		1.4 – 4.5	0.94 – 1.4

$^{\Delta}$ *RR outbreak/non-outbreak represents the magnitude of the difference between the annual rate of MLI investigation/100 000 population observed during the outbreak year versus the baseline non-outbreak rate within the national or provincial setting; an RR=1 indicates no difference. Data presented in this table are a synthesis of RR values previously presented in Tables 3.28 – 3.31*

FIGURE 3.11b Provincial versus National Rate Ratios: Comparing the Impact of a Provincial Outbreak on Provincial versus National MLI Investigation Rates. Provincial outbreak/baseline *RRs* associated with provincial outbreak years (QC, 2007; ON, 2008; BC, 2010; QC, 2011; QC, Pilot) are compared with national *RR*s obtained for the same reporting year. An *RR*= 1 indicates no difference in MLI investigation rate between outbreak and baseline. All provincial and national *RR* values were calculated using 2009 non-outbreak year data to estimate baseline MLI investigation rates (Table 3.32b).

Level of Investigation: % MLI Investigations Discarded

MARS Pilot Year

As a measure of the level of investigation into MLI, the surveillance indicator '% MLI investigations discarded' was estimated as an adapted version of the PAHO surveillance indicator 'proportion of suspected cases that were laboratory discarded' having the PAHO Target: '≥95% of all suspected cases should be discarded due to serological results ruling out measles/rubella, or ruling in another cause' (77,78). The performance of this indicator was comparatively assessed at MARS provincial pilot sites, CMRSS reporting sites (including and excluding Québec) and nationally during the June 2011 – May 2012 pilot year (Table 3.33, Figure 3.12). Data sources used to estimate this indicator included MARS pilot data, CMRSS national confirmed case data (94), and MARS post-pilot national laboratory survey data (Appendix XIII).

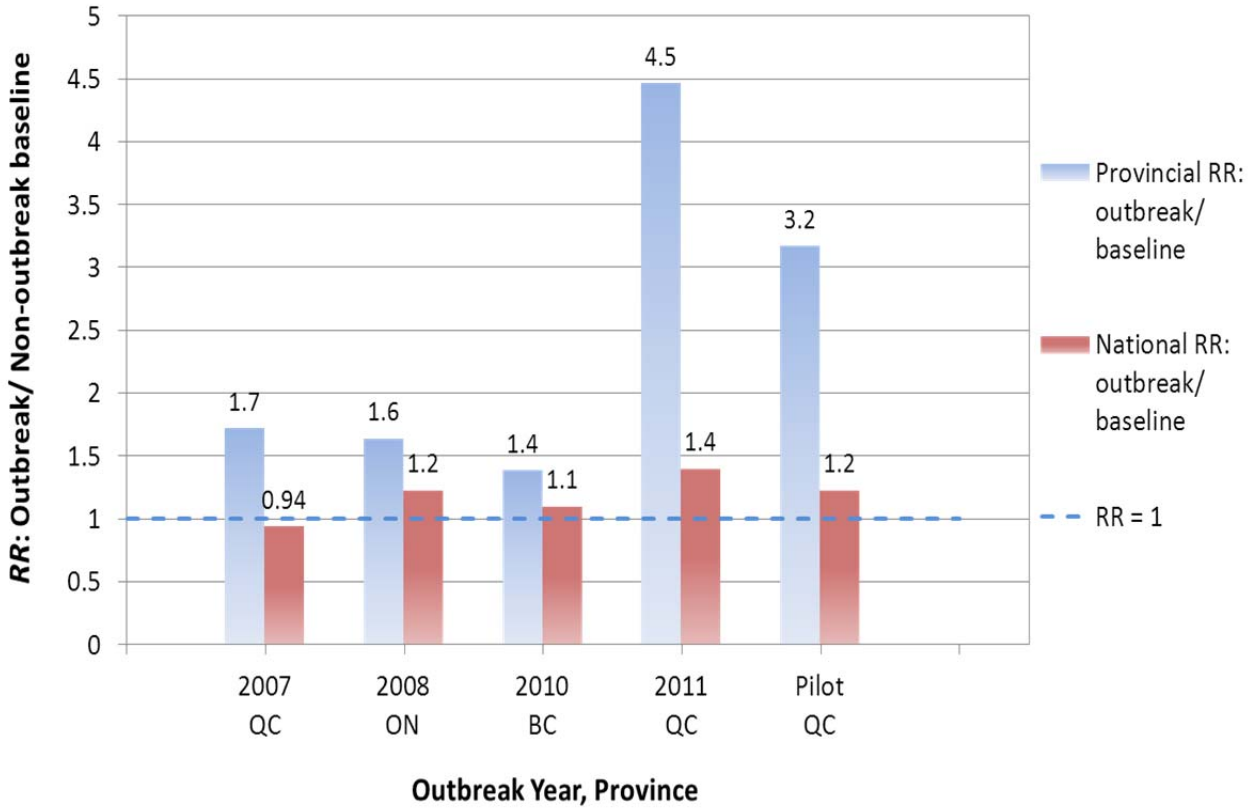


FIGURE 3.11b Provincial versus National Rate Ratios (*RR*): Comparing the Impact of a Provincial Outbreak on Provincial versus National MLI Investigation Rates

Table 3.33 %MLI Investigations Discarded: MARS Pilot Year - MARS Sites, CMRSS Sites, National

Pilot Year	%MLI Investigations Discarded**	PAHO Target: ≥95% Discarded	Confirmed Measles/ 100 000 population	Confirmed Rubella/ 100 000 population
MARS Sites (BC, AB, NL)	99.8	Met	0.045	0.011
CMRSS Sites, excl. QC*	99.6	Met	0.062	0.034
CMRSS Sites	80.7	Not met	2.8	0.023
National, All Sites	87.3	Not met	2.1	0.020

**Québec provincial data were excluded In order to compare the % MLI investigations discarded between MARS non-outbreak provinces and CMRSS non-outbreak provinces.*

** *The proportion of MLI investigations discarded through laboratory investigation was estimated for MARS and CMRSS reporting provinces and at the national level for the 2011-2012 Pilot year as '%MLI investigations discarded = (Total MLI investigations-Total confirmed measles/rubella cases)/Total MLI investigations*100.' The indicator was estimated using measles IgM serology as a proxy for MLI investigation; data sources include MARS pilot data, national data obtained through the post-pilot laboratory survey, and confirmed case data obtained through the national CMRSS database*(94)

FIGURE 3.12 %MLI Investigations Discarded during the MARS Pilot Year: MARS sites, CMRSS sites (including and excluding QC) and all National sites. The '% MLI investigations discarded' surveillance indicator was estimated for all 'MARS pilot sites', 'CMRSS sites excluding Québec', all 'CMRSS sites', and nationally using measles IgM serology as a proxy for MLI investigation. The 'CMRSS sites excluding QC' jurisdictional category was included to allow comparison of CMRSS and MARS investigation rates within a non-outbreak context, whereas indicator estimates for 'CMRSS sites' and 'National, All Sites' categories include the Québec outbreak setting (Table 3.33). Surveillance performance was assessed by comparing indicator estimates with the PAHO Target: '≥95% of all suspected cases should be discarded due to serological results ruling out measles/rubella, or ruling in another cause' (77, 78). At MARS pilot sites, the indicator incorporates MLI investigations discarded due to a negative serology result as well as those with a false-positive IgM serology result which are subsequently discarded through confirmatory testing. Confirmed measles and rubella incidence rates are displayed to provide context for the interpretation of indicator performance in outbreak and non-outbreak settings.

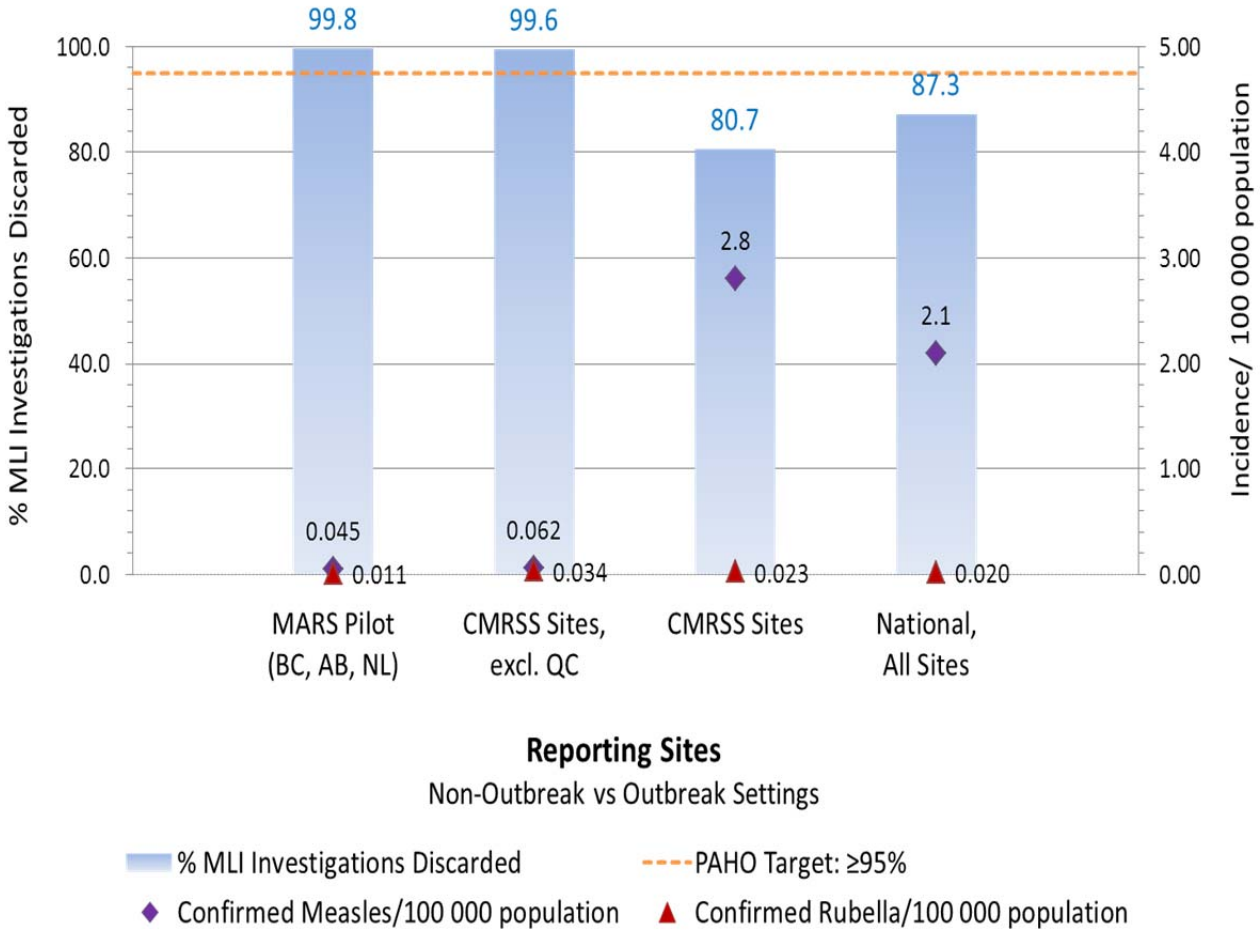


FIGURE 3.12 %MLI Investigations Discarded during the MARS Pilot Year: MARS Sites, CMRSS Sites (including and excluding Québec) and all National Sites

National, 2005-2011

The '% MLI investigations discarded' indicator was estimated nationally for each of the 2005-2011 reporting years within the context of measles and rubella incidence rates (Table 3.34, Figure 3.13). Data sources include the MARS pre- and post-pilot national laboratory surveys (Appendix XII, XIII) and CMRSS national incidence data (94).

Table 3.34 National Level of Investigation: %MLI Investigations Discarded, 2005 – 2011

Year	% MLI Investigations Discarded*	PAHO Target: ≥95% Discarded	Confirmed Measles/ 100 000 population	Confirmed Rubella/ 100 000 population
2011	93.1	Not met	2.2	0.003
2010	99.6	Met	0.29	0.035
2009	97.5	Met	0.042	0.021
2008	98.8	Met	0.19	0.003
2007	99.5	Met	0.31	0.003
2006	*97.8*	*Met*	*0.040*	*0.012*
2005	*88.5*	*Not met*	*0.019*	*0.98*

**The proportion of MLI investigations discarded through laboratory investigation was estimated at the national level for each of the 2005-2011 reporting years as '%MLI investigations discarded = (Total MLI investigations-Total confirmed measles/rubella cases)/Total MLI investigations*100'. The indicator was estimated using measles IgM serology as a proxy for MLI investigation. National data sources include the MARS pre-pilot and post-pilot laboratory surveys, with confirmed case data obtained through the national CMRSS database* (94).

FIGURE 3.13 National Level of Investigation: %MLI Investigations Discarded, 2005-2011. The '% MLI investigations discarded' indicator was estimated for each of the 2005-2011 reporting years, and results compared with the PAHO Target: '≥95% of all suspected cases should be discarded due to serological results ruling out measles/rubella, or ruling in another cause.' (77, 78). National measles and rubella incidence rates are displayed to provide context for the interpretation of indicator performance in outbreak vs non-outbreak settings (Table 3.34).

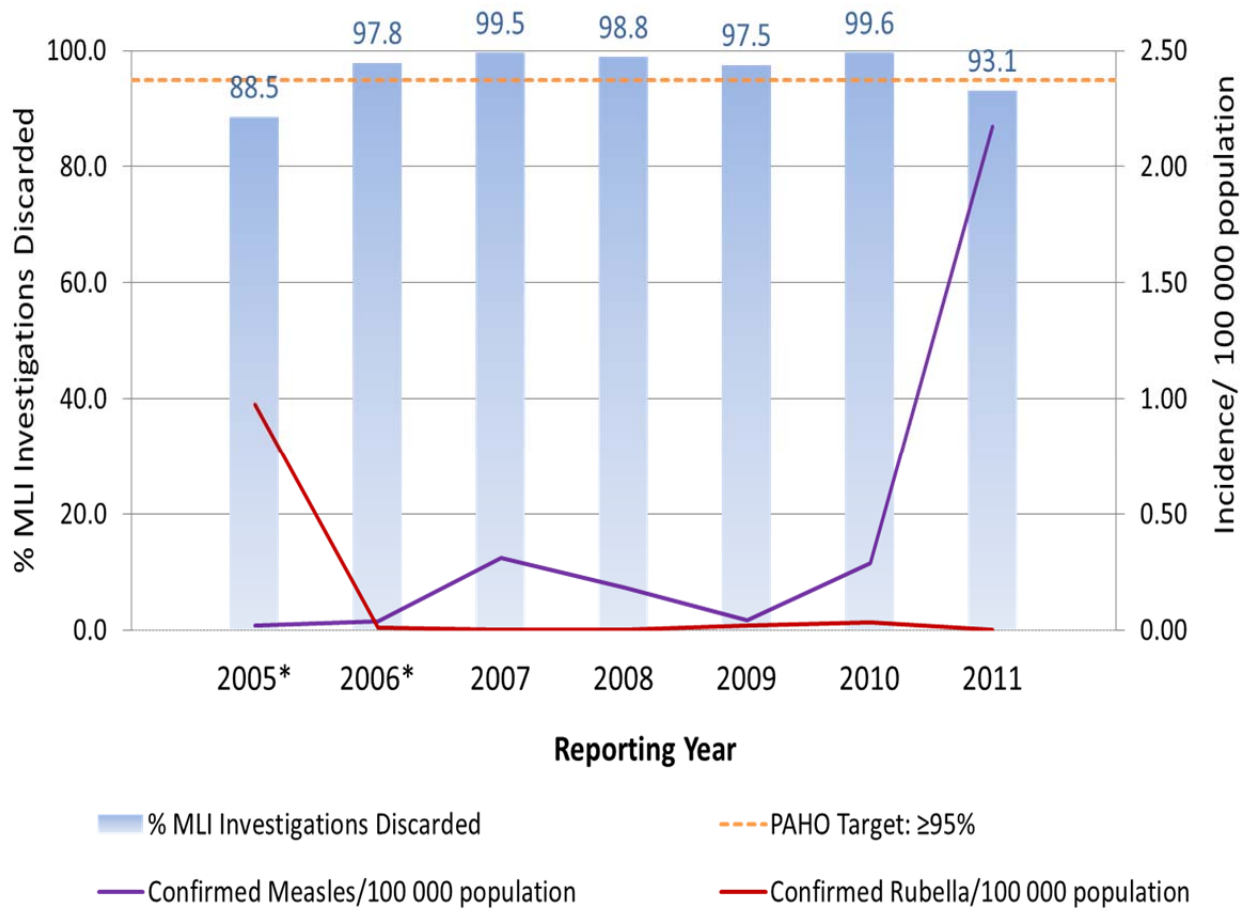


FIGURE 3.13 National Level of Investigation: %MLI Investigations Discarded, 2005 – 2011

Positive Predictive Value (PPV) and Sensitivity

PPV of MLI investigation

Using data collected via MARS sites and through the 2012 national post-pilot survey, the PPV of MLI investigation (i.e. likelihood that an MLI investigation will result in a confirmed measles or rubella case) was estimated for MARS pilot provinces (Table 3.35). MLI investigation at MARS pilot sites was found to have a PPV = 0.2%, with approximately 1 in 500 investigations resulting in a true positive.

Table 3.35 Positive Predictive Value (PPV) of MLI Investigation in MARS Pilot Provinces

	Confirmed Measles/Rubella Case		
MLI Investigation? (Measles IgM Serology)	Yes (Confirmed)	No (Discarded)	Total
Yes	5	2000	2005*

PPV = Confirmed Cases (MARS Provinces)/ Total MLI Investigations (MARS Provinces)* 100 = **0.2%**

**Total MLI investigations in MARS pilot provinces, estimated using measles IgM serology testing as a proxy. Data obtained through MARS reporting, and verified using post-pilot MARS survey data.*

The proportion of MLI investigations resulting in a MARS RTMRI report was estimated as 1.2% for all MARS pilot provinces (Table 3.36), approximating the likelihood that an MLI investigation will be investigated in real-time using the MARS surveillance model.

Table 3.36 %MLI Investigations Resulting in Real-time Measles/Rubella Investigation via MARS

	Real-time Measles/Rubella Investigation		
MLI Investigation (Measles IgM Serology)	Yes (RTMRI via MARS)	No (Discarded)	Total
Yes	24	1981	2005*

%MLI Investigations resulting in RTMRI reports = $\frac{\text{RTMRI Investigations}}{\text{Total MLI Investigations}} * 100 =$ **1.2%**

**Total MLI investigations in MARS pilot provinces, estimated using measles IgM serology testing as a proxy. Data obtained through MARS reporting, and verified using post-pilot MARS survey data.*

The PPV (20.8%) and sensitivity (100%) of real-time measles and rubella investigation reporting using the MARS surveillance model were assessed for the pilot period using data collected via MARS, national survey, and CMRSS (Table 3.37).

Table 3.37 PPV and Sensitivity of Surveillance Using the MARS Pilot Model

	Confirmed Measles/Rubella Case		
Reported via MARS (RTMRI Investigation)	Yes (Confirmed)	No (Discarded)	Total
Yes	5	19	24
No	0*	-	
Total	5		

Sensitivity = Confirmed Cases(MARS) / Total Cases (CMRSS)* 100 = **100%**

PPV = Confirmed Cases (MARS)/ Total RTMRI Investigations (MARS)* 100 = **20.8%**

**During the pilot period, all national confirmed measles/rubella cases in the CMRSS database reported by BC, AB and NL were captured through the MARS pilot application.*

Timeliness of Measles/Rubella Surveillance

MARS Pilot Sites vs CMRSS Reporting Sites

The timeliness of measles and rubella surveillance at MARS pilot sites was able to be assessed and compared with CMRSS surveillance using data fields common to both systems, i.e. 'Rash Onset Date' and 'National Reporting Date'. To allow the comparison of surveillance performance in outbreak and non-outbreak settings, timeliness was estimated at all CMRSS sites, and at CMRSS sites excluding the Québec outbreak setting during the June 2011 – May 2012 pilot period. (Table 3.38, Figure 3.18). Data sources used to estimate this indicator included MARS pilot data and CMRSS national confirmed case data.

Table 3.38 Timeliness of Measles/Rubella Surveillance: MARS vs CMRSS Sites, June 2011 - May 2012

Rash Onset/ National Report Interval	**MARS Pilot Provinces** *N=6*	**CMRSS Provinces** *N=706*	***CMRSS Provinces excluding Québec** *N=12*
Average	12.0[†]	36.0[†]	15.9
Median	8.5	28.0	14.5
95%CI	(2.8 - 21.2)	(33.5 - 38.5)	(11.1 - 20.7)

N=Total number of reports for which 'rash onset' and 'national report' dates were available.

[*] *Québec was excluded to allow comparison of CMRSS surveillance in non-outbreak settings.*

[†] *Student's t-test (one-tailed) used to assess whether MARS real-time surveillance resulted in a significant increase in the timeliness of national reporting when compared with CMRSS (P = 0.0417).*

FIGURE 3.14 Timeliness of National Measles/Rubella Surveillance: MARS Pilot versus CMRSS Non-pilot Provinces, June 2011 – May 2012. The average and median timeliness of surveillance (days) from `Rash Onset Date` to `National Reporting Date` was assessed for MARS Pilot Provinces and CMRSS Provinces including and excluding the Québec outbreak setting; 95% confidence intervals are shown for average timeliness values in each reporting jurisdiction, and '*n*' = total reports for which both 'Rash Onset' and 'National Reporting Date' were available. Average timeliness of MARS real-time surveillance was significantly greater than CMRSS national surveillance during the pilot year (Student's t-test, one-tailed: *P= 0.0417*) (Table 3.38).

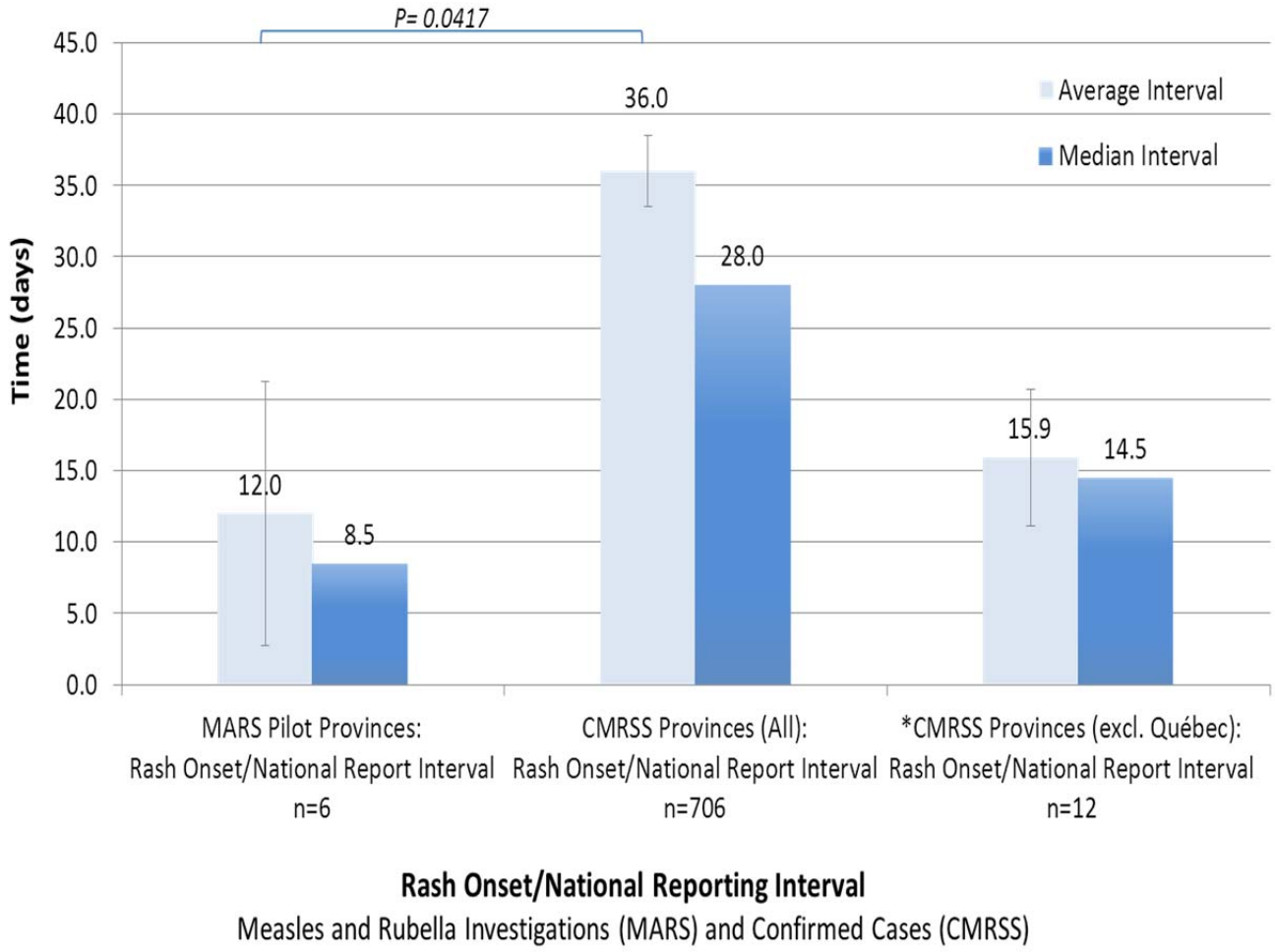


FIGURE 3.14 Timeliness of National Measles/Rubella surveillance: MARS Pilot versus CMRSS Non-pilot Provinces, June 2011 – May 2012.

Timeliness of Real-time Measles/Rubella Investigations (RTMRI) – MARS Pilot Sites

The timeliness of real-time measles/rubella investigation (RTMRI) at MARS pilot sites in BC, AB and NL was able to be assessed at defined surveillance intervals between 'Rash Onset Date' and 'National Reporting Date' during the June 2011 – May 2012 pilot period. (Table 3.39, Figure 3.15). All timeliness intervals were assessed using MARS RTMRI report data.

Table 3.39 Timeliness of Real-time Measles/Rubella Investigation in MARS Pilot Provinces

Surveillance Interval		**Average** (days)	**Median** (days)	**Minimum** (days)	**Maximum** (days)	**95% CI** (days)
Rash Onset/Sample Collection	*(N=6)*	2.3	2.0	0*	7	(0.0 – 4.7)
Sample Collection/Lab Receipt	*(N=23)*	0.9	1.0	0	4	(0.5 - 1.3)
Lab Receipt/Test Result	*(N=24)*	2.2	1.5	0	8	(1.4 – 2.9)
Test Result/MARS Notification	*(N=24)*	5.1	3.5	0	26	(2.2 - 8.0)
Test Result/MARS Notification Excluding 1^{o} Reports†	*(N=21)*	*3.1*	*3.0*	*0*	*14*	*(1.7 – 4.5)*
Sample Collection/MARS Report	*(N=23)*	8.8	7.0	7	3	(5.8 - 11.8)
Sample Collection/MARS Report Excluding 1^{o} Reports†	*(N=21)*	*6.9*	*6.5*	*1*	*19*	*(5.0 – 8.8)*

N=Total number of RTMRI reports for which both date values are available; total RTMRI reports = 24.
** An interval = 0.0 days indicates same-day surveillance events e.g. sample collection and receipt*
† Interval excludes the first RTMRI report submitted via the MARS application by each pilot province

FIGURE 3.15 Timeliness of Real-time Measles/Rubella Investigation in MARS Pilot Provinces: June 2011-May 2012. Average and median timeliness intervals associated with real-time measles/rubella investigation at MARS pilot sites are displayed, with 95% confidence intervals shown for average values. 'N' = indicates the number of RTMRI reports for which both interval data points were available; a total of 24 reports were received. All surveillance interval estimates include the first reports submitted by each provincial MARS pilot site (Table 3.39).

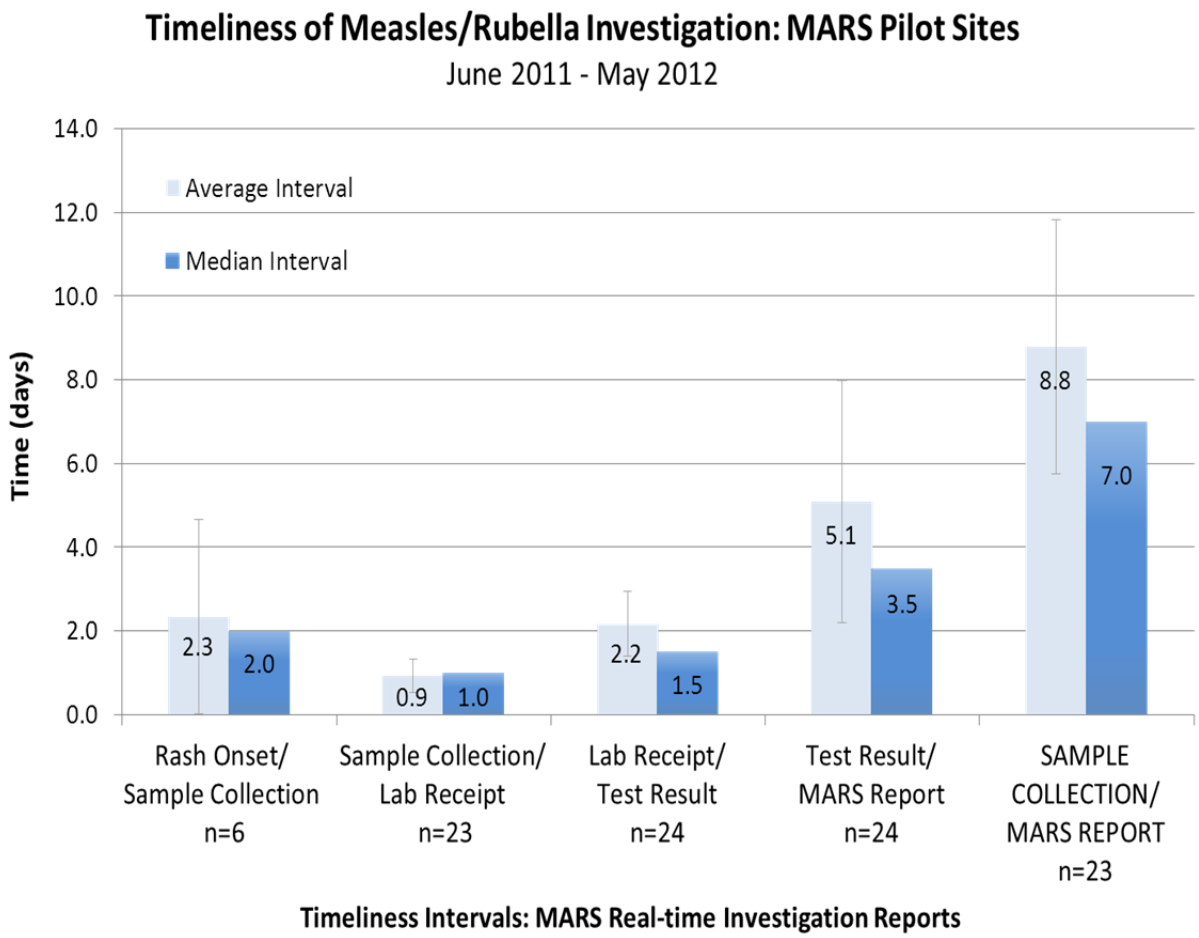


FIGURE 3.15 Timeliness of Real-time Measles/Rubella Investigation in MARS Pilot Provinces: June 2011-May 2012

Timeliness of Measles/Rubella Surveillance – PAHO Laboratory-based Indicators

The timeliness of national measles and rubella surveillance was estimated using adapted PAHO and WHO – recommended indicators, and assessed against PAHO and WHO performance targets specified in the literature. All timeliness indicators were assessed using augmented laboratory data associated with MARS RTMRI reports (Table 3.40).

Data Quality/Completeness

Completeness of Enhanced Laboratory Data Fields – MARS Pilot

Data quality was evaluated for the MARS application by assessing the completeness of augmented laboratory data fields collected during the pilot period with respect to all RTMRI reports, and according to their final classification as confirmed or discarded (Table 3.41). Additionally, the adequacy of investigation via MARS and CMRSS was assessed by comparing the proportion of measles/rubella investigations for which the key 11 PAHO-recommended data points were completed (Table 3.42).

Table 3.40 PAHO Surveillance Indicators: Timeliness of Laboratory Investigation, MARS Sites

Surveillance Indicator	MARS Estimate	Target	Source	Target Status
Proportion of real-time measles/rubella investigations with a serum sample collected within 30 days of rash onset[†]	**100%**	≥ 80%	PAHO (adapted)[*]	**Met**: Average interval between rash onset and sample collection[**] is 2.3 days
Proportion of real-time measles/rubella investigations for which samples are received by the laboratory within 5 days of collection	**100%**	≥ 80%	PAHO (adapted)[*]	**Met:** Average interval between sample collection and lab receipt[**] is 0.9 days
Proportion of real-time measles/rubella investigations with a laboratory result within 4 days of sample receipt	**91.7%**	≥ 80%	PAHO (adapted)[*]	**Met:** Average interval between lab receipt and test result[**] is 2.2 days
Proportion of virus isolation samples collected within 5 days of rash onset	**66.7%**	No target	WHO (adapted)[*]	NA
Proportion of virus isolation samples received by the lab within 3 days of sample collection	**100%**	No target	WHO (adapted)[*]	NA
Proportion of measles/rubella genotyping completed within 2 months of laboratory sample receipt[***]	**100%**	≥80%	WHO (adapted)[*]	**Met:** Average interval between lab receipt and genotyping result is 21.3 days[***]

†Adapted from PAHO indicator : Proportion of suspected cases with an adequate blood specimen collected within 30 days of rash onset; Target: ≥ 80% where 'adequate blood sample' is defined as a serum sample collected within 30 days of rash onset; estimated for all RTMRI for which 'Rash Onset Date' was available (n=6)

**Note: 'Adapted' PAHO*(77,78)(37,79) *and WHO*(14)(98) *indicators in this table use 'real-time measles/rubella investigations' captured via MARS as a proxy for a PAHO defined 'suspect case' investigation unless otherwise specified*

***Surveillance intervals (days) represent the timeliness of the first sample collected as part of the real-time measles/rubella investigation; this is most frequently serum with exception of 2 discarded investigations (8.3%) for which only urine and/or T/NP were collected*

****Estimated for all investigations with an appropriate sample was provided. Note: This interval was assessed as of PHL sample receipt, and includes sample transport to NML for genotyping.*

Table 3.41 MARS Reporting: Completeness of Enhanced Laboratory Data Fields

Laboratory Data Field	**Real-time Measles/Rubella Investigation** (RTMRI) **Reports** *N (%)*[*]	**Confirmed Measles/Rubella Investigations** *N (%)*[*]	**Discarded RTMRI** *N (%)*[*]
Sample Type	23 (95.8%)	5 (100%)	18 (94.7%)
Sample Collection Date	23 (95.8%)	5 (100%)	18 (94.7%)
Laboratory Receipt Date	24 (100%)	5 (100%)	19 (100%)
Test Result Date	24 (100%)	5 (100%)	19 (100%)
MARS Notification Date[**]	24 (100%)	5 (100%)	19 (100%)

Note: A total of 24 RTMRI reports were entered during the pilot period; all reports involved laboratory investigation with the performance of at least one laboratory test. 19 investigations were discarded following laboratory investigation; all 5 confirmed measles/rubella cases were classified as laboratory-confirmed.

[*]*N = Total number of reports for which the specified data field was completed; % = Proportion of reports for which the specified data field was completed.*

[**] *MARS Notification Date represents the alerting date and is automatically generated*

Data Completeness – MARS vs CMRSS National Reporting

The PAHO criterion for adequate investigation of suspected cases is the 'Proportion of suspected cases with the following 11 data points completed: name and/or identifier, place of residence, sex, age or date of birth, date of reporting, date of investigation, date of rash onset, date of specimen collection, presence of fever, date of prior measles-rubella vaccination, travel history', with a minimum threshold of ≥80% for the completion of all 11 points. Completion rates for the 11 data points were assessed for CMRSS confirmed case reports and for MARS RTMRI and confirmed case investigations both individually and combined (Table 3.42).

Table 3.42 Completeness of PAHO Data Elements: CMRSS vs MARS, June 2011 – May 2012

PAHO INDICATOR (adapted): **Proportion of real-time measles/rubella investigation reports with each of the following 11 data points completed†:**	**%CMRSS**	**%RTMRI (MARS)**	**%Confirmed (MARS)**	**%Discarded RTMRI (MARS)**	**PAHO Target: ≥80%†**
1. Name and/or identifier	99.9	100.0	100.0	100.0	Met
2. Place of residence	100.0	100.0	100.0	100.0	Met
3. Sex	100.0	95.8	100.0	94.7	Met
4. Age or Date of Birth	100.0	100.0	100.0	100.0	Met
5. Date of Reporting (national)	97.5	100.0	100.0	100.0	Met
6. Date of Investigation	96.4	33.3††	80.0	21.1	Not met
7. Date of Rash Onset	97.4	25.0	80.0	5.3	Not met
8. Date of Specimen Collection	*	95.8	100.0	94.7	Met
9. Presence of fever	*	29.2	100.0	10.5	Not met
10. Date of prior MR vaccination	22.2	20.8	60.0	10.5	Not met
11. Travel history	**	29.2	100.0	10.5	Not met
All 11 Data Points Complete	**0.0%**	**20.8%**	**60.0%**	**10.5%**	Not met

**Data field not captured by surveillance system*

***Travel history status (Yes/No, Within Canada/Outside of Canada) was not assessed as this is not a defined field in the national case report (NCR); it is requested in the NCR that this information be appended in a separate sheet if known.*

†Adapted from the PAHO suspect case based indicator: 'Proportion of suspected cases with the following 11 data points completed: name and/or identifier, place of residence, sex, age or date of birth, date of reporting, date of investigation, date of rash onset, date of specimen collection, presence of fever, date of prior measles-rubella vaccination, travel history'(37)*. As such, while completion rates of the 11 data fields are estimated individually and in total for both MARS and CMRSS confirmed case reports, the status of the PAHO Target (Met vs Not met) reflects the completion rate for MARS RTMRI reports only.*

††For RTMRI, Date of Specimen collection would be considered the appropriate Date of Investigation, and is complete in 95.8% of RTMRI reports.

CHAPTER 4: DISCUSSION

The MARS application was successfully piloted in BC, AB and NL from June 1, 2011 to May 31, 2012 to support national real-time investigation and reporting of measles and rubella. During the pilot period, provincial and national laboratory and public health stakeholders contributed measles and rubella investigation data through centrally accessible web-based Measles/Rubella and CRS/I investigation forms, Monthly Reports and Weekly Zero Reports. In non-pilot provinces and territories, national surveillance was conducted as usual through the national CMRSS confirmed-case reporting system. All real-time measles/rubella investigations (RTMRIs) reported by MARS pilot sites and subsequently confirmed as measles or rubella were imported into the national CMRSS confirmed-case database to ensure integrated national reporting for the duration of the pilot year.

MARS PILOT PERIOD

Measles and Rubella Investigation Summary

During the 1-year MARS pilot period, a total of 2005 measles IgM and 2758 rubella IgM serology tests were reported by MARS pilot provinces (BC, AB, NL), with 0.9% of measles IgM and 1.3% of rubella IgM serology tests yielding positive results. Using measles IgM serology testing as a proxy for the investigation of MLI, these data yielded investigation rates of 22 MLI investigations and 31 rubella IgM serology tests/100 000 population for all MARS pilot provinces combined (Table 3.1).

Rubella IgM serology testing rates exceeded those observed for measles in each monthly reporting period during the pilot year, with an average annual rubella/measles testing *RR* of 1.4 (range: 1.1 – 1.7) (Fig. 3.1). The higher rates of rubella IgM testing may be in part accounted for by physicians specifically investigating rubella particularly during pregnancy, whereas measles IgM testing is more

likely to be associated with the investigation of MLI. With respect to testing levels observed during the pilot period, combined measles/rubella testing levels were noted to be higher during late fall (October/November) and early spring (February/March), with measles IgM serology testing showing a separate increase during the early summer months (May/June) (Fig. 3.1). While not possible to substantiate using the limited pilot data, the assessment of monthly testing patterns over multiple reporting years may be used to verify the presence or absence of seasonal trends in testing.

Real-time Measles/Rubella Investigation Summary

Of the 2005 MLI investigations reported through pilot sites, 24 (1.2%) were reported via MARS as real-time measles/rubella investigations (RTMRIs) using the centralized Measles/Rubella Investigation Report form. Of all RTMRIs, 4 (16.7 %) were confirmed as measles, 1 (4.2%) was confirmed as rubella, and 19 (79.2%) were discarded (Table 3.2). Additionally, 1 CRS/I investigation was reported during the pilot and ultimately discarded due to a clinical picture inconsistent with CRS.

Confirmed Case Summary

A summary of confirmed measles/rubella case data is given in Table 3.3. Of the 5 confirmed cases reported by pilot provinces, 3 measles cases were reported by AB, with BC reporting 1 measles and 1 rubella case. There were no cases in NL. The age range for confirmed cases was 5-39 years. Sex distribution of measles cases was equivalent with 2 male and 2 female cases; the rubella case was female. All cases were import-related, having a recent history of travel outside of Canada during the incubation period. Two of the four measles cases had no history of immunization with measles/rubella vaccine (ages: 5, 13 years); the parents of the 5 year old chose not to vaccinate. One measles case had an unknown immunization history (20 year old), and one was undocumented with recollection of childhood immunization (35 year old).

All measles and rubella cases were laboratory-confirmed in keeping with national notifiable disease case definitions (53). The 4 measles cases had positive IgM serology results, with 1 measles case positive for both measles and rubella IgM. Such false-positive results are commonly associated with cross-reactivity of non-specific IgM, or the presence of rheumatoid factor or specific IgG, and underscore the importance of confirmatory testing when interpreting results (14). All 4 measles cases were confirmed through measles RT-PCR. The rubella case was IgM-positive, with positive confirmatory results obtained for rubella IgG acute/convalescent serology, and rubella RT-PCR. Genotyping was successfully performed in all cases. Two of the AB measles cases were genotype D4 (travel histories: India, New Zealand), and one was D8 (travel to Thailand). The D4 strains were identified as D4 strains circulating in New Zealand and India respectively in keeping with available travel histories; neither strain was identical to the Québec D4 outbreak strain. The BC measles case was genotype B3 (travel to Uganda), a genotype that has been associated with endemic transmission in Uganda and other countries in the African Region in recent years (99). The rubella case with unspecified travel history outside of Canada was genotype 1j, which has been associated with rubella cases in the United States, United Kingdom and the Philippines between 2006 and 2010 (100) (Table 3.3). These findings are consistent with recent molecular epidemiological data regarding the global distribution of measles and rubella genotypes. While 4 of the 5 cases also met clinical case definitions with both fever and rash present, the measles case caused by strain D8 was notable for the absence of reported fever.

RTMRI vs Confirmed Case Sample Data

The timely procurement of appropriate samples is an important consideration in the laboratory investigation of measles and rubella. A review of sample data entered in association with the 24 RTMRI reports demonstrated that 23 (95.8%) reports included information related to sample type;

the sole report for which the sample type field was not populated did include a sample collection date and test results for measles and rubella IgM serology. A serum sample was associated with the majority of RTMRI reports (22, 91.7%), and with all confirmed cases (5, 100%) (Table3.4). Rash onset date was available for 5 RTMRIs for which serum samples were collected, all 5 investigations were confirmed as measles/rubella. Of these, 4 had serum samples (80%) collected within 2 days of the recorded rash onset date, with 1 (20%) collected 7 days after rash onset. All cases had IgM-positive serology results, however the rubella case was retested using a second serum sample obtained 12 days post-rash after the first serum sample collected 2 days post-rash onset yielded equivocal results (Table 3.3). Ideally, it is desirable to obtain serum and virus isolation samples at the same time, within approximately 4-5 days of rash onset. If serum samples are obtained too soon after rash onset, the likelihood of a false-negative IgM serology result increases as anti-measles or anti-rubella IgM may not yet be present in serum at detectable levels. For measles, sera collected within the first 3 days of rash onset correlate with decreased sensitivity of IgM capture EIAs (14, 72); for rubella, 50% of cases are IgM-negative the day of rash onset, and IgM antibodies may not develop to detectable levels until 4-5 days after rash onset (1). While the serum sampling window was only able to be assessed for a small subset of RTMRIs, it is notable that the majority (80%) were obtained at a time associated with an increased risk of false-negative results. Challenges associated with the timing of serum sample procurement raise the possibility that MLI investigations may be discarded due to false-negative IgM serology results, and it is recommended that clinically-suspect MLI cases for which an IgM-negative serology result is obtained using serum collected ≤3 days after rash have a second serum sample obtained >3 days post-rash for re-testing (53). The ability to assess the timing of sample procurement for clinically suspect MLI via the MARS pilot was limited as only MLI investigations with a positive test result were reported in real-time and accompanied by the necessary augmented laboratory data.

Virus isolation (VI) samples (i.e. throat/nasopharyngeal, urine) were collected and tested for 6 RTMRIs (25.0%). Of the 5 RTMRIs ultimately confirmed as measles or rubella, 4 (80%) had an appropriate VI sample collected; the fifth had only a serum sample collected, which was successfully genotyped. Of the 6 real-time investigations with a VI sample collected, 4 (66.7%) had VI samples meeting WHO recommendations, 1 (discarded investigation) did not include the sample collection date and timeliness could not be assessed, and 1 (confirmed measles) had serum and VI samples collected at 7 and 11 days post-rash onset respectively. None of the VI samples were obtained on the same date as serum collection, as is recommended by the WHO for ease of follow-up with respect to confirmatory testing, virus isolation and genotyping efforts. It should be noted that the proportion of all RTMRIs for which VI samples were collected may be underestimated as it was not possible to assess the number of investigations for which virus isolation samples were collected but not tested as part of the investigation process (Table 3.4). (14,15,53) To support measles and rubella virus isolation and characterization efforts, the WHO recommends the collection of an appropriate virus isolation sample as soon as possible after rash onset. The ideal sample for measles virus isolation is a T/NP or urine sample collected within 3 days of rash onset, although virus may still be present up to 5 days. Isolation of rubella virus from a T/NP sample is preferred, with virus detectable from a few days prior to rash onset to several days after (15,101)(14).

Summary of Testing Methods

IgM serology testing is the standard front-line method used to screen for measles and rubella in the event of clinically suspect MLI (14) (68). A majority of real-time investigations reported via MARS involved either measles or rubella IgM serology testing (22, 91.7%); 14 (60.7%) had only measles IgM serology testing performed and another 14 (60.7%) involved only rubella IgM serology testing. Only 7

investigations (29.2%) had both measles and rubella IgM serology testing performed as part of the testing algorithm, whereas PAHO recommends that all serum samples from clinically suspect cases be tested for both measles and rubella-specific IgM except in outbreak settings (77). A total of 5 investigations (20.8%) involved a history of repeat measles IgM serology testing, and 3 (12.5%) involved repeat rubella IgM serology testing on the same serum sample, using a different test kit (Table 3.5).

Measles and rubella confirmatory testing methods include paired acute/convalescent IgG serology, virus detection using RT-PCR, and virus isolation; rubella IgG avidity testing may also be used to support confirmatory efforts in the event of pregnancy; genotyping is performed to support molecular epidemiology and strain surveillance of measles and rubella (14,53). Of the 24 RTMRIs reported via MARS, only 2 (8.3%) involved acute/convalescent IgG serology testing: 1 discarded measles investigation, and 1 confirmed rubella case (Table 3.6). RT-PCR was the most frequently used confirmatory method. Either measles or rubella RT-PCR was performed as a part of 7 RTMRIs (29.2%), and all 5 measles/rubella cases (100%) were confirmed using RT-PCR. Genotyping was attempted for 7 RTMRIs (29.2%), and was successfully determined for 6 investigations (25.0%); 5 were confirmed measles/rubella cases, 1 was discarded as vaccine-associated (measles genotype A) (Table 3.7). Neither virus isolation nor rubella avidity testing were performed in the course of RTMRI investigation during the pilot period.

Measles and rubella IgG serology testing of acute sera is not used in a confirmatory capacity as per the national case definitions, but may be used to assess serostatus by demonstrating the presence of circulating anti-measles or anti-rubella IgG antibodies thereby providing evidence of pre-existing immunity to measles or rubella in response to immunization or infection (14). A total of 20 RTMRIs (83.3%) had measles or rubella IgG serology testing performed as part of the laboratory investigation

process; of the 19 RTMRIs discarded, 14 (73.7%) had a positive acute rubella IgG serology result (Table 3.6).

MEASLES/RUBELLA TESTING ALGORITHMS, CAPACITY: 2005-2006, 2007-2011 and PILOT YEARS

National pre-pilot and post-pilot surveys were conducted to assess the testing algorithms used by measles and rubella testing laboratories performing IgM serology in Canada during the 2005-2006 and 2007-2011 and Pilot periods respectively. The 2007 pre-pilot survey had a response rate of 16/18 (88.9%) over a 3-month survey period; 10 (62.5%) of responding laboratories performed both measles and rubella IgM serology, 4 (25.0%) performed measles IgM serology only, and 2 (12.5%) performed only rubella IgM serology (Table 3.8). A variety of testing algorithms were reportedly used by responding laboratories when screening MLI cases. During the 2005-2006 reporting period, a majority of 9 laboratories (56.3%) reported screening all MLI cases for measles, rubella and parvovirus B19 (pB19). Of the 6 other labs for which testing algorithm data were provided, 2 (12.5%) performed rubella and pB19 IgM testing only if the MLI investigation was measles IgM-negative, 2 (12.5%) would perform rubella and pB19 testing only if specifically requested, and 2 (12.5%) reported using another screening protocol (Table 3.9).

The 2012 post-pilot survey had a 100% response rate over an 8 month survey period, with 16 responding laboratories in 10 provinces, and participation of the provincial public health laboratories in all nine provinces having a centralized PHL. All Québec laboratories performing measles IgM serology were surveyed directly, however this approach was not feasible for rubella IgM data procurement as rubella serology testing in Québec is highly decentralized across 42 testing laboratories. As an alternative, the provision of province-wide rubella IgM serology test data for the MARS 2011-12 pilot period was centrally coordinated through the Québec PHL via the Ministry of

Health.

Various front-line testing capacities were reported by the 16 laboratories surveyed; 11 (68.8%) performed both measles and rubella IgM serology, with 13 (81.3%) performing measles IgM serology and 13 (81.3%) performing rubella IgM serology (Table 3.12). One provincial public health laboratory referred all measles and rubella IgM serology testing to another regional PHL, and one laboratory ceased to perform measles IgM testing in 2009.

The 2012 survey added a question to assess the current confirmatory testing capacities of measles and rubella testing laboratories. The confirmatory test method for which provincial capacity was highest was paired acute/convalescent IgG serology testing, which was available for measles at 8 laboratories (50.0%) and for rubella at 5 laboratories (31.3%) (Table 3.12). The capacity for molecular detection is largely restricted to public health laboratories in the most populous provinces, with measles RT-PCR performed by 4 laboratories (25.0%); only 1 provincial laboratory reported performing rubella RT-PCR (6.3%). While 3 provincial laboratories (18.8%) also reported the capacity to perform measles and rubella virus isolation respectively, the NML has sole national responsibility for virus isolation and genotyping in support of international surveillance efforts as a certified PAHO/WHO Measles and Rubella Regional Reference Laboratory with WHO Measles and Rubella LabNet Accreditation (102). Overall, provincial capacity to perform measles and rubella confirmatory testing varies jurisdictionally across Canada, with the highest relative capacity existing in the more populous provinces (i.e. Ontario, BC, QC) whereas less populous provinces may refer all of their confirmatory testing to the NML. A majority of laboratories (75%) reported referring either some or all of their confirmatory testing, primarily to the NML.

The 2012 post-pilot survey results demonstrate that the laboratory testing algorithms used to

investigate clinically suspect MLI continued to vary during the 2007-2011 and Pilot years (Table 3.11). A majority of 9 laboratories reported performing only the specific IgM screening test(s) requested (56.3%). Another 2 laboratories (12.5%) reported initially performing only the specific IgM serology test(s) requested, with subsequent performance of additional measles/rubella and pB19 testing if the initial test result is negative. Only 3 laboratories (18.8%) used IgM serology testing to screen all MLI for measles, rubella and parvovirus B19, whereas this represented the approach taken by a majority (56.3%) of laboratories during the 2005-2006 survey period. Both laboratories that reported using an 'other' testing protocol (12.5%) currently refer their measles and rubella testing to other laboratories. It should be noted that the response categories for the testing protocol question included in the 2012 survey were updated for clarity; as such, data for the 2005-2006 and 2007-2011/Pilot reporting periods are not directly comparable.

SURVEILLANCE INDICATORS AND ATTRIBUTES

Measles IgM serology testing: Use as a lab-based proxy for MLI investigation

In Canada, established national measles and rubella surveillance conducted via the Canadian Measles Rubella Surveillance System (CMRSS) consists of confirmed-case surveillance, and does not capture the number of clinical or suspect (i.e. febrile-rash) measles-like illness (MLI) cases investigated. International PAHO-recommended surveillance indicators are based on the investigation of suspected measles/rubella cases, where a 'suspected case' is defined as 'a patient in whom a health-care worker suspects measles or rubella infection or a patient with fever and maculopapular rash' i.e. clinically-suspect MLI (77). During the current elimination phase In Canada, adequate laboratory investigation of MLI is critical to the detection and confirmation of sporadic and import-related measles and rubella cases in keeping with national case definitions, and IgM serology is the test most

universally performed at the initiation of an MLI investigation (53,102).

To support surveillance indicator estimation, measles IgM serology testing was considered the best proxy for the investigation of MLI in Canada. This was suggested by the pre-pilot 2007 measles and rubella laboratory investigation survey results, and substantiated by the results of the 2012 post-pilot survey. Both surveys demonstrated that measles and rubella IgM serology testing laboratories vary in the testing algorithms used for the investigation of suspect MLI (Tables 3.9, 3.11), which may involve testing for measles only, rubella only, or both measles and rubella. As it is not possible to link the specific tests performed with a given MLI investigation, meaningful integration of rubella and measles IgM serology testing rates is not feasible. Also, while an integrated measles/rubella-like illness indicator was initially considered, the 2007 pre-pilot survey data provided evidence that national rubella IgM serology testing levels may significantly exceed those observed for measles as a rubella/measles testing ratio of approximately 2:1 was estimated for the 2006 non-outbreak year (Table 3.22; 2006 survey data were previously published (39)). The use of measles IgM serology test performance as a proxy for MLI investigation was therefore considered to provide a more conservative laboratory-based estimate of MLI investigation rates.

Correlation between MLI investigation rate and measles/rubella Incidence

Linear regression analysis was performed to quantify the degree of association between annual estimated MLI investigation rates and combined measles/rubella case incidence rates per 100 000 population observed during the 2007-2011 reporting years. As would intuitively be expected, a positive correlation was observed such that MLI investigation rates increased with measles/rubella incidence rate, with a correlation coefficient of $r = 0.79$ and $R^2 = 0.62$ (Figure 3.3b). Data for 2005 and 2006 were collected through a separate survey process and excluded from the analysis, as were

MARS pilot data due to significant overlap with the 2011 reporting year.

National Outbreak vs Non-outbreak Years: 2005 – 2011 and MARS Pilot period

To support the comparative analysis of national surveillance performance, the 2005-2011 and MARS pilot years were classified as either 'outbreak' or 'non-outbreak' years. The 2006 and 2009 reporting years were identified as national non-outbreak years, having annual combined measles/rubella case incidences of only 0.05 and 0.06 per 100 000 population respectively. The 2005, 2007, 2008 , 2010, 2011 and MARS pilot reporting years were classified as national outbreak years, each being characterized by a national combined measles/rubella incidence ≥ 0.2 cases/100 000 population (range: 0.2 – 2.2/100 000 population), and the occurrence of at least one large provincial outbreak during the annual reporting period. None of the provincial outbreaks occurring between 2005 and 2011 spanned multiple reporting years. There was, however, significant overlap between the MARS pilot period of June 2011 and May 2012, and the large 2011 Québec provincial outbreak (Table 3.21); of the 725 confirmed cases reported between January 8 and December 22, 2011, 712 were reported during the MARS pilot (45,94). As such, the MARS pilot period was considered an outbreak period for national data analysis purposes.

Provincial Outbreak vs Non-outbreak Years: 2005 – 2011 and MARS Pilot period

To facilitate the provincial level comparison of surveillance performance in 'outbreak' versus 'non-outbreak' settings during the 2005-2011 and pilot years, the following province-specific outbreak periods were identified using national CMRSS confirmed case incidence data where n=confirmed cases: Ontario, 2005 (rubella outbreak, n=309)(52); Québec, 2007 (measles outbreak, n=96); Ontario, 2008 (measles outbreak, n=53); British Columbia, 2010 (measles outbreak, n=82); Québec, 2011 (measles outbreak, n=725)(45); Québec, MARS 2011-12 Pilot period (measles outbreak, n=712)(94)

(Table 3.26).

Level of Investigation

PAHO Target: ≥2 suspected case investigations per 100 000 population

To assess the level of investigation into MLI in the Canadian setting, the surveillance indicator 'Annual rate of MLI investigation per 100 000 population' was evaluated at the national and provincial level during outbreak and non-outbreak years between 2005 and 2011, and in MARS pilot provinces and CMRSS reporting provinces during the MARS pilot year. This indicator was adapted from the PAHO surveillance indicator 'Annual rate of suspected measles and rubella cases' which is used as a measure of the level of investigation into suspected measles/rubella (MLI) with the minimum annual performance target of '≥2 suspected measles and rubella cases/100 000 population' (37,79)

National – Outbreak, Non-outbreak

National MLI investigation rates per 100 000 population per year were estimated for the 2005-2011 and MARS Pilot years. Rates observed during national outbreak years were then compared with the baseline, national non-outbreak investigation rates estimated for the 2005-6 and 2007-2011/Pilot survey periods respectively, and rate ratios (RR) estimated to assess the magnitude of rate differences (Figure 3.7, Table 3.28).

Using data gathered through the pre-pilot survey, a national baseline rate of 12 MLI investigations/ 100 000 population was estimated for the 2006 non-outbreak year. By comparison, the 2005 rubella outbreak year yielded a significantly higher national MLI investigation rate of 14/100 000 population, *RR* = 1.2 (*P<0.001)* during the same survey period.

For the 2007-2011 and Pilot survey period, a baseline annual rate of 14 MLI investigations/100 000 population was estimated using 2009 data as this was the sole national non-outbreak year. MLI investigation rates estimated for the 2007-8 and 2010-11 national outbreak years ranged from 13 – 19 MLI investigations/100 000 population. MLI investigation rates for the 2008, 2010, 2011 and MARS pilot years were found to differ significantly (P<0.001) from the 2009 baseline non-outbreak rate. National outbreak/non-outbreak *RR* values ranged from 1.1 – 1.4 for the 2008, 2010, 2011 and Pilot years for which significant differences were assessed. There was there was no significant difference observed between the 2007 national investigation rate and the 2009 non-outbreak rate (*RR*= 0.94, P<0.1).

All national MLI investigation rates observed during the 2005 – 2011 and MARS Pilot years successfully met the recommended PAHO surveillance target of ≥2 suspected case investigations/100 000 population per year (Figure 3.7, Table 3.28)(37).

International MLI Investigation Rates in PAHO Countries: Canada, Mexico and Brazil – 2006, 2009

At an international level, the 2009 baseline MLI investigation rate of 14/100 000 population observed in Canada exceeded the PAHO Target with an *RR*=6.8 and compared favourably with combined measles/rubella suspected case (MLI) investigation rates reported by other PAHO reporting countries including Brazil (4.6/100 000 population, *RR*=2.3) and Mexico (3.1/100 000 population, *RR*=1.6) (Table 3.28b). Internationally, these findings are consistent with those for the 2006 non-outbreak year which yielded a baseline rate of 12 MLI investigations/100 000 population and exceeded the PAHO target rate with *RR* = 5.9. The national 2006 investigation rate also compared well with international rates estimated for Brazil (9.55 suspected cases/100 000 population, *RR*= 4.8) and Mexico (3.93 suspected cases/100 000 population, *RR*= 2.0); the 2006 results were previously

published in Macey et.al.(39)

Provincial Outbreak and Non-outbreak Settings

In addition to estimating the annual rate of suspected measles and rubella cases at the national level, 2011 PAHO elimination guidelines recommend estimating these rates at subnational levels (i.e. state, provincial or equivalent level)(37). In Canada, provincial MLI investigation rates per 100 000 population per year were estimated for the 2007-2011 and MARS Pilot years. For those provinces experiencing one or more provincial outbreaks during this time period (i.e. QC, ON, BC), rates observed during provincial outbreak years were compared with the baseline average provincial non-outbreak MLI investigation rates to look at the impact of an outbreak on intra-provincial investigation rates.

Québec

Québec experienced 2 outbreaks during the 2007-2011 and Pilot years. The 2007 measles outbreak (96 confirmed cases) was associated with an MLI investigation rate of 7.9/100 000 population, whereas the second large measles outbreak in 2011 (725 confirmed cases) saw a rate of 20 MLI investigations /100 000 population (Fig.3.8, Table 3.29) (45). A rate of 15 MLI investigations/100 000 population was estimated for the MARS pilot year, which significantly overlapped the 2011 outbreak year. A baseline, non-outbreak provincial MLI investigation rate of 4.6/100 000 population was estimated by averaging provincial rates observed during the 2008-2010 non-outbreak years which ranged from 3.1 – 6.7/100 000 population. Outbreak/non-outbreak MLI investigation rate ratios were calculated for 2007 (*RR*=1.7), 2011 (*RR*=4.5) and the MARS pilot year (*RR*=3.2). Provincial MLI investigation rates observed during all outbreak periods differed significantly from the baseline non-outbreak rate (*P<0.001*).

The PAHO surveillance target of ≥2 suspected cases/100 000 population was exceeded by Québec in each of the 2007-2011 and Pilot reporting years, with outbreak and non-outbreak MLI investigation rates ranging from 3.1 – 20/100 000 population.

Ontario

Ontario experienced a measles outbreak in 2008 (53 confirmed cases) (45), which was associated with an annual MLI investigation rate of 16/100 000 population (Fig. 3.9, Table 3.30). A baseline, non-outbreak provincial MLI investigation rate of 11/100 000 population was estimated by averaging provincial MLI investigation rates observed during the 2007 and 2009-2011 non-outbreak years; these ranged from 6.9 – 14/100 000 population. The MLI investigation rate estimated for the 2008 outbreak year was significantly higher than the provincial baseline rate, having an *RR* = 1.6 (*P<0.001*). It was interesting to note that the MLI investigation rate of 14/100 000 observed directly following the outbreak year more closely approximated the 2008 outbreak rate than the rates observed during other non-outbreak years (range: 6.9 - 9.3)(Fig. 3.9). Given that 2009 was a national non-outbreak year, it is speculated that this sustained elevation in the provincial investigation level may be a 'hangover' effect, possibly reflecting an increased index of suspicion among physicians in the aftermath of the outbreak during the previous year.

The PAHO surveillance target of ≥2 suspected cases/100 000 population was exceeded by Ontario in each of the 2007-2011 and Pilot reporting years, with provincial outbreak and non-outbreak MLI investigation rates ranging from 6.9 – 16/100 000 population.

British Columbia

The 2010 BC measles outbreak involved 82 confirmed cases (45), and was associated with an annual

MLI investigation rate of 32/100 000 population (Fig. 3.10, Table 3.31). A baseline, non-outbreak provincial MLI investigation rate of 23/100 000 population was estimated for BC by averaging provincial MLI investigation rates observed during the 2007-2009 and 2011 non-outbreak years which ranged from 18 – 36/100 000 population. The 2010 MLI investigation rate was found to significantly exceeded the provincial baseline rate, having an *RR* = 1.4 (*P<0.001*).

The level of investigation in BC exceeded the PAHO surveillance target of ≥2 suspected cases/100 000 population in each of the 2007-2011 and Pilot reporting years, with provincial outbreak and non-outbreak MLI investigation rates ranging from 18 – 36/100 000 population.

Provincial Non-outbreak Settings

A majority of provinces did not experience measles or rubella outbreaks during the 2007-2011 and Pilot years, having either zero confirmed cases reported, or the occasional detection of sporadic, import-related cases with limited, if any, secondary transmission as would be expected under elimination circumstances (94). The 7 provinces classified as 'non-outbreak' settings for the full 5-year survey period include Alberta (AB), Saskatchewan (SK), Manitoba (MB), New Brunswick (NB), Nova Scotia (NS), Prince Edward Island (PE) and Newfoundland and Labrador (NL). Average provincial MLI investigation rates/100 000 population estimated for the 2007-2011 survey years are as follows: 23 (AB), 53 (SK), 18 (MB), 30 (NB), 16 (NS; 2009-11 years) and 10 (PE; 2008-11 years). No measles or rubella cases were reported by the territories. It was not possible to separately estimate MLI investigation rates for the territories as all laboratory investigation requests are referred to provincial laboratories and would be captured in their test data. Given the very small territorial population base, provincial rate estimates would not be impacted.

To look at the potential contribution of extra-jurisdictional outbreak activity to MLI investigation

levels within non-outbreak provincial settings, baseline provincial MLI investigation rates were estimated for the 2009 non-outbreak year, then compared intra-provincially with average provincial MLI investigation rates estimated during years in which extra-jurisdictional outbreaks were observed, i.e. 2007-8, 2010-11 and Pilot reporting years. (Fig. 3.11, Table 3.32)

Non-outbreak MLI investigation rates observed in 2009 varied widely between provinces, with values ranging from 5.0 – 47/100 000 population. Average provincial rates estimated for the 2007-8 and 2010-11 extra-jurisdictional outbreak years ranged from 8.2 – 55 MLI investigations/100 000 population, and were found to be significantly higher than baseline non-outbreak rates observed intra-provincially in AB (*RR* = 1.7, *P<0.001*), SK (*RR* = 1.2, *P<0.01*), MB (*RR* = 3.4, *P<0.001*), NS (*RR* = 1.7, *P<0.001*) and PE (*RR* = 1.2, *P<0.05*). There was no significant difference observed for NB (*RR* = 1.1) or NL (*RR* = 1.0). In all cases, the average rate of MLI investigation observed during extra-jurisdictional outbreak years was either equivalent to or greater than the baseline non-outbreak rate. This evidence further supports the use of the 2009 national non-outbreak year to estimate baseline levels of investigation when assessing provincial and national MLI investigation rates. While these findings suggest that extra-jurisdictional outbreak activity may influence testing levels within provincial 'non-outbreak' settings, potentially through increased vigilance on the part of physicians, the sporadic detection of even a single imported case in a 'non-outbreak' setting could potentially contribute to increased provincial levels of investigation depending on the epidemiology of the case. Sporadic detections would not, however, be expected to influence overall levels of investigation at the national level.

In terms of surveillance performance, the levels of investigation observed in all 7 provincial non-outbreak settings exceeded the PAHO minimum surveillance target of ≥2 suspected cases/100 000 population during each of the 2007-2011 and Pilot years, with baseline non-outbreak and average

extra-jurisdictional outbreak rates ranging from approximately 5 – 55 MLI investigations/100 000 population.

MARS Pilot Year: Outbreak vs Non-outbreak Settings

During the MARS pilot period (June 2011-May 2012), the national MLI investigation rate of 17/100 000 population was significantly higher than the baseline non-outbreak rate of 14/100 000 population *(RR* = 1.2, *P<0.001*). This would be expected, given the large 2011 Québec outbreak which saw most of its cases during the MARS pilot period.

When looking at all CMRSS reporting sites excluding the Québec outbreak setting, a rate of 15 MLI investigations/100 000 population was observed during the pilot year. This rate did not differ significantly from the slightly higher 2009 non-outbreak rate of 16 MLI investigations/100 000 population estimated for the same reporting provinces (*RR* = 0.95, *P<0.1*), which suggests that overall MLI investigation levels in CMRSS non-outbreak provinces remained consistent with rates that would be expected during non-outbreak circumstances (Table 3.27).

The rate of investigation at all CMRSS reporting sites including the Québec outbreak setting during the pilot year was 15 MLI investigations/100 000 population. This rate was significantly higher than the baseline 2009 non-outbreak rate of 13 MLI investigations/100 000 population estimated for the same reporting provinces (*RR* = 1.2, *P<0.001*) (Table 3.27). As no significant rate difference from baseline was observed when Québec was excluded from CMRSS reporting provinces, and given the significantly increased investigation level observed in the Québec provincial data when compared with baseline provincial rates (Fig. 3.8), this increased rate is expected to be largely attributable to increased rates of investigation in Québec.

As provincial baseline MLI investigation rates have been demonstrated to vary widely, the direct comparison of inter-provincial investigation rates observed during the pilot period could easily lead to misinterpretation as there was no significant difference in MLI investigation rate between all CMRSS sites including Québec (15/100 000 population) and excluding Québec (15/100 000 population).

The MLI investigation rate of 22/100 000 population observed in MARS provinces (BC, AB, NL) during the pilot year was significantly higher than their baseline non-outbreak rate of 16/100 000 population (*RR*=1.4, *P<0.001*), although MARS provinces were considered non-outbreak settings as they collectively experienced very low measles/rubella incidence rates with activity limited to 5 sporadic, import-related cases detected in BC and AB without secondary transmission. It is expected that the elevated MLI investigation levels observed during the pilot may have been partially influenced by the large 2011 extra-jurisdictional outbreak in Québec. The MLI investigation rate of 22/100 000 population in MARS pilot provinces also exceeded the rate of 15/100 000 population observed at CMRSS sites including and excluding the Québec outbreak setting, and the national rate of 17/100 000 population (Figure 3.6, Table 3.26, Table 3.27).

In summary, measles IgM serology testing was effectively used as a proxy to estimate levels of investigation into MLI at both the national and provincial levels as recommended by PAHO. National non-outbreak MLI investigation rates compared favourably with rates reported internationally by other countries in the PAHO Region of the Americas. The PAHO Target of ≥2 suspected cases/100 000 population was consistently exceeded at both the provincial and national levels in outbreak and non-outbreak settings for all years assessed (i.e. 2005-2011 and Pilot years)(37). As would be expected intuitively, MLI investigation rates were seen to increase with measles and rubella incidence rates. Also, larger provincial outbreaks were observed to result in higher MLI investigation rates (relative to

baseline) within the provincial outbreak setting when compared with the national level, as reflected by provincial (RR_p) and national (RR_n) rate ratios for the following outbreak years: 2007 (RR_p = 1.7, RR_n = 0.94), 2008 (RR_p = 1.6, RR_n = 1.2), 2010 (RR_p = 1.4, RR_n = 1.1), 2011 (RR_p = 4.5, RR_n = 1.4) Pilot (RR_p = 3.2, RR_n = 1.2) (Table 3.32b, Figure 3.11b). At the national level, the only outbreak year for which the MLI investigation rate did not differ significantly from baseline was 2007 (RR_n = 0.94); this may be partially explained by the lower average 'non-outbreak' MLI investigation level (4.6/100 000 population) observed in Québec relative to other provinces for the 2005-11 reporting period (provincial range: 4.6 – 53/100 000), increases in which would have a proportionately lesser impact on overall national rates

Limitations, Considerations

One consideration when assessing MLI investigation rate differences between 'outbreak' and 'non-outbreak' settings as defined in this study is that in 'non-outbreak' settings, sporadic import-related cases with or without limited secondary transmission may still be detected , although it is expected that such events would not significantly impact overall national rates. With respect to limitations, laboratory-level differences in MLI testing algorithms coupled with the wide variation in average provincial MLI investigation rates estimated during provincial non-outbreak years (Range: 4.6 - 53/100 000 population per year) make the comparison of interprovincial rate differences problematic. Any interprovincial or interjurisdictional comparisons of MLI investigation rates must be made with caution, and interpreted within the context of known provincial baseline non-outbreak investigation rates as well as provincial and national measles and rubella outbreak activity levels for the period under investigation.

While the estimation of national and provincial MLI investigation rates using measles IgM serology

testing data is feasible and provides a reliable, consistent proxy measure across jurisdictions, a limitation associated with these rate estimates is that no data are available regarding the proportion of measles IgM serology testing that may be requested in error (e.g., an IgM serology test is requested by the physician rather than IgG serology when the intent is to obtain evidence of prior immune response as opposed to acute infection), or in association with the investigation of non-MLI clinical presentation. It has been suggested that these occurrences may inflate MLI investigation rate estimates relative to the PAHO performance targets which are based on investigation of clinically-suspect measles/rubella and against which these rate estimates are assessed. Even if a relatively high proportion of measles IgM testing was performed for reasons other than acute MLI investigation, this would not be expected to impact the assessment of national surveillance performance as all national MLI investigation rates observed from 2005-2011 exceeded the PAHO investigation target of ≥ 2 suspected cases/100 000 population by a minimum factor of 6. While more significant variation is observed at the provincial level, even the lowest annual MLI investigation rate observed provincially (3.1/100 000 population) would still exceed the PAHO target if one-third of all requests were associated with non-MLI testing, and would continue to meet the minimum criterion if half of all measles IgM serology tests were performed for reasons unrelated to the investigation of acute MLI.

%MLI investigations discarded: PAHO Target: ≥ 95%

The surveillance indicator '% MLI investigations discarded' was estimated at the national and provincial levels during outbreak and non-outbreak years. This indicator was adapted from the PAHO surveillance indicator 'proportion of suspected cases that were laboratory discarded' which is used as a measure of the level of investigation into suspected measles/rubella (MLI) with the performance target '≥95% of all suspected cases should be discarded due to serological results ruling out measles/rubella, or ruling in another cause.' (77,78) In estimating the %MLI investigations discarded

indicator, it should be noted that this proportion includes laboratory investigations discarded due to a negative IgM serology result as well as those having a false-positive IgM serology result which are subsequently discarded through confirmatory testing.

National – Outbreak, Non-outbreak

The surveillance indicator '%MLI investigations discarded following laboratory investigation' was estimated at the national level for each of the 2005 – 2011 years (Figure 3.13, Table 3.34). The PAHO minimum target of ≥95% was met during each of the 2006-2011 reporting years, with the %MLI investigations discarded ranging from 97.5 – 99.5%. The PAHO target was not met in 2005 (88.5% discarded) or 2011 (93.1% discarded). The 2005 and 2011 national reporting years were notable for large rubella and measles outbreaks respectively, and were the only years for which combined measles/rubella incidence rates were ≥ 1.0 case/100 000 population.

MARS Pilot Year vs Non-Pilot Provinces

The proportion of MLI investigations discarded during the MARS pilot period was assessed for MARS pilot provinces, CMRSS reporting provinces excluding Québec, all CMRSS provinces, and at the national level in order to facilitate comparison between outbreak and non-outbreak settings irrespective of reporting method (i.e. via MARS versus CMRSS). (Figure 3.12, Table 3.33) Both the MARS pilot provinces and CMRSS reporting provinces excluding Québec met the PAHO target with 99.8% and 99.6% of MLI investigations discarded; combined measles/rubella incidence rates were 0.05 and 0.09 confirmed cases/100 000 population respectively . By comparison, the target was not met when looking at all CMRSS provinces including Québec (80.7% MLI investigations discarded), nor was it met at the national level (87.3% MLI investigations discarded). Combined measles/rubella incidence rates in these outbreak settings were 2.8 and 2.1 confirmed cases/100 000 population

respectively due to measles outbreak activity in Québec during the pilot period.

Indicator Performance

The PAHO surveillance target of ≥95% MLI investigations discarded following laboratory investigation was successfully met in all settings except those having an annual combined measles/rubella incidence rate ≥ 1.0 confirmed case/100 000 population. The performance of this indicator within the context of observed national MLI investigation rates supports the adequacy of MLI investigation levels under elimination circumstances, during which measles and rubella incidence would be expected to be very low with the infrequent occurrence of sporadic, import-related cases and limited secondary transmission if any. However, in the event of a larger outbreak in a defined geographical area, the proportion of investigations that are lab-discarded would be expected to decrease with increased case incidence. Also, the process by which cases are investigated is expected to shift from the laboratory confirmation of all suspected cases to the confirmation of cases through identification of an epidemiological link to a lab-confirmed case. In provincial and national outbreak settings where routine levels of investigation are already high relative to the PAHO target rate of ≥ 2 suspected case investigations/100 000 population, the sub-target performance of the '%MLI investigations discarded' indicator does not speak to the adequacy of surveillance, but to the scale of the outbreak. While this particular indicator is suitable for use in elimination settings as means of monitoring the adequacy of laboratory investigation into MLI, its performance in the Canadian setting suggests that other measures are more appropriate for the assessment of adequacy of investigation during larger outbreaks with incidence rates ≥ 1.0 confirmed case/100 000 population.

Measles and Rubella IgM Serology Testing Levels, Rate Ratios

Rubella versus Measles IgM Serology Testing Rates

To quantitatively evaluate differences in rubella/measles testing rates observed during each of the 2005-2011 and MARS pilot years, annual rubella IgM serology testing rates were compared with MLI investigation rates estimated using measles IgM serology test data, and *RR* values determined (Fig.3.3a, Table 3.22). MLI investigation rates ranged from 12 – 19/100 000 population, whereas rubella IgM serology testing rates ranged from 19 – 31/100 000 population for the 2005-2011 and pilot years. Annual rubella IgM serology testing rates consistently exceeded those for measles in all across all reporting years, with rubella/measles *RR* values ranging from 1.4 – 2.1.

Using pre-pilot survey data, baseline measles and rubella investigation rates of 12 MLI investigations/100 000 population and 24 rubella IgM serology tests/100 000 population were assessed for the 2006 non-outbreak year, yielding a rubella/measles IgM serology testing *RR* = 2.0 (data previously published (39)). During the 2009 national non-outbreak year a *RR*= 1.4 was observed, with measles and rubella investigation rates of 14 MLI investigations and 19 rubella IgM serology tests/100 000 population. Within the context of observed MLI investigation rates in Ontario during the 6 years following the 2005 rubella outbreak (Fig.3.9), the relatively high national *RR* of 2.0 observed during the 2006 non-outbreak year may be partially attributable to the post-outbreak elevation in MLI investigation levels observed in Ontario. The more conservative baseline *RR* of 1.4 estimated during the 2009 non-outbreak year is therefore expected to provide a more reliable benchmark for future comparison purposes.

At MARS pilot sites, monthly rubella/measles IgM serology *RR* values ranged from 1.1 – 1.7 with an average annual *RR*= 1.4 observed over the course of the pilot year (Figure 3.1). That the *RR* observed

in non-outbreak MARS pilot provinces matches the baseline, non-outbreak *RR* = 1.4 estimated for the 2009 reporting year lends additional weight to its use as a reasonable baseline value within the Canadian setting for planning purposes.

During non-outbreak years (i.e. 2006, 2009), it would be expected that a majority of clinically suspect MLI cases would be tested for both measles and rubella IgM as part of the differential diagnosis given their similar clinical presentation. If rubella IgM serology testing were to be performed solely on the basis of a clinical presentation consistent with MLI, an *RR* more closely approaching 1.0 would be expected. This suggests that the consistently higher levels of rubella testing may be associated with physicians looking to specifically investigate rubella infection. Given that rubella infection is expected to be asymptomatic in 20% to 50% of cases (19), it is speculated that the consistent disparity between rubella and measles IgM serology testing rates in the Canadian setting may be attributable in part to physician-level pre-natal screening practices in response to non-MLI illness. Another contributor to rubella IgM testing rates may be the serological investigation of CRS and other suspected congenital infections via (S)TORCH screening (i.e., (syphilis), toxoplasmosis, other infections, rubella, cytomegalovirus and herpes simplex virus) (103)(39,104)(105).

Measles and Rubella IgM Serology - %Positive: Outbreak vs Non-Outbreak

%Positive, Measles and Rubella IgM Serology: Non-Outbreak Settings

In order to characterize the observed elimination-phase performance of national measles and rubella IgM serology testing in the Canadian setting, annual %positive values were estimated for all non-outbreak provincial settings during the 2007-2011 survey period (Figure 3.4, Table 3.24). In non-outbreak settings, measles IgM serology testing yielded an average %positive value of 1.9% (CI: 0.9 – 3.0%), whereas the average %positive estimated for rubella IgM serology was 1.4% (CI: 1.0–1.8%).

%Positive, Measles IgM Serology: Outbreak versus Non-Outbreak Settings

In light of provincial measles outbreak activity during the 2007-2011 and pilot period, it was also possible to assess measles IgM serology %positive values in provincial outbreak settings (QC, 2007; ON, 2008; BC, 2009; QC, 2011; Pilot) and compare these with the %positive values observed in non-outbreak provincial settings during the same reporting years(Figure 3.5, Table 3.25). As would be expected, measles IgM serology %positive values were higher in outbreak settings and ranged from 3.9% – 18.1%, whereas the %positive values observed in non-outbreak provincial settings ranged from 1.0% – 3.3%. All differences in %positive values observed between outbreak and non-outbreak settings in a given year were found to be significant (*P <0.001)*, with *RR* values ranging from 2.2 – 5.5%. All %positive values observed in outbreak settings exceeded the baseline average of 1.9% positive estimated in non-outbreak settings. During the present elimination phase and in the absence of jurisdictional outbreak activity, %positive values would be expected to closely approximate the proportion of measles and rubella tests yielding false positive results (%false positive).

Average %positive values may be used in combination with jurisdiction-specific 'non-outbreak' measles and rubella IgM serology testing rates and jurisdictional population data to predict the annual number of measles and rubella investigations likely to require further laboratory investigation to confirm or discard. From a national surveillance perspective, this information may be used to predict the annual number of measles/rubella investigation reports likely to be received under routine elimination circumstances should the MARS real-time surveillance model be more broadly implemented at the national level.

Limitations and Considerations

While all laboratories were able to provide test numbers, not all laboratories were able to provide

measles and rubella IgM-positive result data for the time period assessed. Laboratories for which IgM-positive data were unavailable had their total test numbers excluded from the denominator for estimation purposes. As aggregate IgM-positive data were available for only a subset of the laboratories surveyed, and as these data cannot be associated with specific measles and rubella investigations and outcomes, it was not possible to directly assess PPVs for measles and rubella IgM serology testing at the national level. The PPV of MLI investigation was, however, able to be assessed for participating pilot provinces.

It should also be noted that non-outbreak %positive values were estimated to characterize the actual performance of IgM serology testing in an elimination setting. While these data do not take into account the use of different measles and rubella IgM serology testing kits by different laboratory sites, it is expected that all Canadian measles and rubella testing laboratories are using standardized test kits with similarly high sensitivities and specificities.

Timeliness of Investigation

MARS Pilot Sites

Using augmented laboratory data collected as a part of MARS real-time measles and rubella investigation reporting, it was possible to estimate the timeliness of measles and rubella investigation at key surveillance intervals spanning rash onset in clinically suspect MLI cases to the date the MLI investigation is reported via the MARS real-time surveillance system (Figure 3.15 Table 3.39). An interval of 0 days signifies surveillance events occurring on the same day

The average interval between rash onset and sample collection was estimated as 2.3 days (median = 2.0 days, CI = 0.0 – 4.7 days) based on all RTMRI reports for which ‘rash onset date’ was available

(n=6). Only 25% of all RTMRI reports and only 10.5% of discarded RTMRIs included a reliable rash onset date, reflecting its frequent unavailability to the laboratory at the outset of the MLI investigation process. This is a significant observation given the importance of rash onset date to the timing of sample collection and the correct interpretation of serological and confirmatory test results.

An average interval of 0.9 days (median = 1.0, CI = 0.5 – 1.3 days) was observed between sample collection and laboratory sample receipt, assessed for the first sample obtained in association with each RTMRI (n=23). There was only one RTMRI report for which sample collection date was not available. The average interval between laboratory sample receipt and the earliest test result associated with each RTMRI was 2.2 days (median = 1.5, CI = 1.4 – 2.9 days). This interval was assessed for all 24 RTMRI reports received via MARS.

The average interval between the first laboratory test result and the submission of a Measles/Rubella Investigation Report in real-time via MARS was 5.1 days (median = 3.5 days, CI = 2.2 – 8.0 days), with a difference of 1.6 days between the average and median results. This estimate includes all 24 RTMRI reports submitted via MARS, including the very first reports submitted by MARS pilot provinces. These 'first reports' were delayed relative to subsequent reports as might be expected when a new reporting system is first implemented. When the 3 first reports are excluded from the data, the average time interval between 'Test Result' and 'MARS Report' decreases by 2 days from an average of 5.1 days to 3.1 days (median = 3.0 days, CI = 1.7 – 4.5 days). This estimate is considered to more accurately represent the timeliness of MARS real-time surveillance performance following site-based implementation. It should be noted that between sample collection and MARS national reporting, this is the longest of the surveillance intervals, and is very dependent on the availability of personnel to complete data entry into the MARS application. This interval also incorporates the time needed for

any internal review of the result data and sample-associated information prior to creating a MARS real-time investigation.

The overall timeliness of surveillance between sample collection and MARS report submission was assessed for all reports (n=23) as a measure of the timeliness of public health response from the initiation of an MLI investigation. In most cases, the investigation process begins when a clinically suspect MLI case first comes into contact with health care, and a sample is collected for laboratory testing. When all reports (including first reports) were assessed, the average timeliness of investigation was 8.8 days (median = 7.0, CI = 5.8 – 11.8). Post-implementation (excluding first reports), the average timeliness of public health investigation via MARS was determined to be 6.9 days (median = 6.5, CI = 5.0 – 8.8) from sample collection to MARS report submission.

MARS vs CMRSS

The timeliness of real-time, investigation-based surveillance as conducted at MARS pilot provinces (BC, AB, NL) was compared with the timeliness of established confirmed-case surveillance in CMRSS reporting provinces (SK, MB, ON, QC, NB, NS, PE) during the June 2011- May 2012 pilot period. Timeliness of surveillance was comparatively assessed using the interval between 'Rash Onset Date' and 'National Report Date' as this was the sole surveillance interval estimable for both MARS and CMRSS (Figure 3.14, Table 3.38).

In MARS pilot provinces, real-time national reporting via MARS took place an average of 12.0 days after rash onset (median = 8.5 days, CI = 2.8 – 21.2), and was significantly more timely than the CMRSS confirmed-case reporting interval which averaged 36.0 days (median = 28 days, CI = 33.5 – 38.5), *P = 0.042*.

The vast majority of confirmed cases reported to CMRSS during the pilot period were associated with the large Québec outbreak. As MARS pilot provinces did not experience outbreak activity during the pilot period, the timelines of MARS surveillance was also compared with reporting in CMRSS non-outbreak provinces (i.e. excluding QC). MARS surveillance was found to be more timely than CMRSS surveillance in non-outbreak provinces as well, which had average timeliness of 15.9 days (median = 14.5 days, CI = 11.1 – 20.7). With respect to the timelines of surveillance in CMRSS provinces including and excluding the QC outbreak setting, the differences observed clearly demonstrate the impact of a large outbreak on the timeliness of national reporting.

Limitations associated with comparison of the timeliness of MARS versus CMRSS reporting included the limited date information associated with CMRSS case reports, and the low confirmed case incidence at MARS pilot sites which resulted in a relatively low number of reports for which 'rash onset' date was available. Even so, the timeliness of MARS real-time reporting was found to exceed the timeliness of CMRSS reporting as observed in outbreak and non-outbreak settings. It should also be considered that when a MARS real-time report is submitted, it is simultaneously received by all provincial and national laboratory and epidemiology public health stakeholders having a role in measles/rubella investigation, supporting early and efficient collaboration while an investigation is ongoing until it is classified as confirmed or discarded.

By contrast, the CMRSS national reporting date represents the date that a final confirmed-case report is received by national epidemiologists within PHAC upon submission by provincial public health. On a weekly basis, the total aggregate number of confirmed cases is in turn reported internationally to PAHO, nationally to PHAC laboratory and epidemiology counterparts, and provincially to public health epidemiology stakeholders. There is therefore the possibility that national and international reporting of measles/rubella cases received at the beginning of the weekly

reporting cycle would be delayed by up to 7 days in addition to the average timeliness of reporting previously estimated for confirmed case report submission. While informal communications do occur prior to CMRSS case report submission, the lack of formalized integration and data sharing among laboratory and epidemiology stakeholders from the outset creates a vulnerability whereby it is possible that the need for additional case information (e.g. additional sample procurement to support confirmatory testing and/or genotyping efforts or other necessary public health investigation) is not identified in a timely manner, or can no longer be accomplished given the narrow windows available for laboratory investigation (14). This particular surveillance challenge was a key motivator in the development of the MARS project. Prior to MARS development, it routinely transpired that the NML would be notified through informal channels that a suspected measles case had been detected weeks after the fact, precluding the possibility of collecting supplementary samples for confirmatory testing (106). Notably, the CMRSS confirmed case reporting process does not close the reporting loop by including provincial laboratory stakeholders with whom the majority of investigations are expected to originate.

Using Laboratory Data to Estimate Surveillance Performance

Using augmented laboratory data collected via MARS, it was possible for the first time to estimate the timeliness of measles and rubella surveillance performance in the Canadian setting at each interval in the investigative process, including the estimation of a number of adapted PAHO-recommended indicators (Table 3.40).

The timeliness of surveillance in MARS pilot provinces successfully met all laboratory-based PAHO targets evaluated: 100% of RTMRIs had a serum sample collected within 30 days of rash onset (PAHO Target ≥80%), with an average interval of 2.3 days observed between rash onset and first sample

collection; 100% of RTMRIs had samples received by the laboratory within 5 days of collection (PAHO Target ≥80%) with an average interval of 0.9 days between sample collection and laboratory receipt; 91.7% of RTMRIs had a laboratory result within 4 days of receipt (PAHO Target ≥80%) with an average interval of 2.2 days (77,78)(37,79). With respect to molecular epidemiological investigation, 100% of confirmed measles/rubella cases reported via MARS were successfully genotyped, 80% of which had a virus isolation sample collected for analysis (i.e. T/NP, urine) thereby meeting the PAHO recommendation that ≥80% of outbreaks have adequate specimens and genotype information available from at least 1 viral specimen (37,79).

Additionally, surveillance performance was assessed using laboratory-based indicators recommended by the WHO. Of the RTMRIs for which genotyping was performed, 100% of measles/rubella genotyping was completed within 2 months of sample receipt (WHO Target ≥80%), with an average of 21.3 days between lab receipt and genotyping result (range: 5 – 44 days); all genotyping was performed at the NML. This represents the timeliness of genotyping from the date an appropriate sample is received at the provincial PHL, and includes the time required for the sample to be received by and tested at the NML which is responsible for national genotyping efforts. While all testing did meet the WHO Target, genotyping should ideally be performed in as timely a manner as possible (i.e. within several days) to ensure its relevance to case and outbreak investigation efforts both at the national and international levels, in addition to supporting ongoing efforts to document and monitor the global distribution of measles and rubella in support of elimination efforts. With respect to virus isolation efforts, 66.7% of virus isolation samples were collected within 5 days of rash onset (14), and 100% of virus isolation samples were received by the laboratory within 3 days of sample collection (14,98). As there is no stated WHO Target for the latter two recommended indicators, they were assessed to estimate baseline surveillance performance in

the Canadian setting.

PAHO-recommended CRS Surveillance Indicators

During the MARS pilot period, only one suspected CRS/I investigation was reported by MARS pilot provinces, and was subsequently discarded. While the CRS/I Investigation Report form on the MARS application has been designed to capture all data fields required to estimate PAHO-recommended CRS surveillance indicators (Table 1.7) (37,79), it was not possible to estimate these indicators during the pilot period due to data limitations. With the very low incidence of CRS in Canada, i.e. only 2 confirmed CRS cases reported since the inception of the MARS pilot project in 2006 (52), data would likely need to be collected over a prolonged time period at the national level to estimate surveillance performance as per PAHO recommendations.

MARS Surveillance Attributes

MARS User Survey

In order to assess the performance of measles and rubella surveillance as conducted via the MARS application at participating provincial pilot sites, a post-pilot MARS User Survey was distributed to all registered MARS users. A total of 14 survey responses were received; 5 respondents (35%) were national PHAC (CIRID/NML) participants, and 9 (65%) were provincial participants. Survey responses represented all three pilot provinces (BC, AB, NL), and included laboratory and epidemiology counterparts at all national and provincial pilot sites. Equivalent representation was observed for public health laboratory (50%) and public health (50%) stakeholders (Figure 3.2, Table 3.13). While the total number of potential respondents is by nature limited by the scale of the pilot project and by organizational changes in personnel over its duration, the distribution of responses among

stakeholder groups is considered ideal to ensure well-balanced user representation when descriptively assessing MARS surveillance attributes.

Information obtained through the MARS User Survey was used to inform the assessment of a number of surveillance attributes, including the simplicity, sensitivity, data quality/completeness, stability, acceptability and overall usefulness of the MARS surveillance model, with comparisons made with CMRSS surveillance where applicable.

Simplicity/Ease of Use

Simplicity and ease of use were assessed through the MARS User Survey as they related to the four MARS report form types and to the use of the MARS application overall. Only those users identifying prior experience in using specific report forms were prompted to answer form-related questions, while questions regarding overall simplicity and ease of use were asked of all survey participants.

With respect to MARS reporting forms, 100% either agreed or strongly agreed that the Measles/Rubella (12 users), CRS/I (2 users), Monthly Test (4 users) and Weekly Zero (9 users) report forms on MARS were 'well-structured and easy to follow'; and 'intuitive, requiring minimal training to use'. 100% of respondents also agreed or strongly agreed that 'data field names are clearly described and easy to understand' for Measles/Rubella, Monthly Test, and Weekly Zero report forms; of the 2 respondents having used the CRS/I report form, 1 (50%) agreed and 1 (50%) selected not applicable as their response (Table 3.14). As anticipated, lower user response levels were associated with role-specific report forms (e.g. Monthly Test and Weekly reports), and with the CRS/I form which was used by 1 site during the pilot period.

With respect to the application as a whole, 100% (14 users) agreed or strongly agreed that 'overall,

the MARS application is easy to use' and that 'it was easy to access newly submitted and updated reports through automated MARS email notifications'. When asked questions related to user experience in viewing, querying and exporting data, 57.1% agreed that 'it is easy to view aggregate measles/rubella report data of interest for a specified time period' using the MARS 'Summary Reports' functionality, while 42.9% selected 'not applicable/did not use' as their response. When asked about their experience in using the MARS Query Builder, 21.4% (3 users) agreed or strongly agreed that it was 'easy to perform custom data queries for export into Excel', whereas a majority 78.6% selected either not applicable/did not use (10 users) or undecided (1 user) as their response.

Overall, the MARS application and alert notification functions were considered easy to use by all respondents. Specific MARS report forms were also universally rated as easy to use by those having experience in their use.

Flexibility of MARS Surveillance

The flexibility of a surveillance system represents the ease with which it adapts to changing information needs and operating conditions over time; these can include changes in reporting source, data fields, technology and the ability to integrate with other systems (107). During the pre-launch development period, the MARS application on the CNPHI platform was sufficiently flexible to permit a number of changes to be made to the centralized reporting forms: changes included data fields additions and changes to report form structures, as well as the post-CNPHI development updating of national measles and rubella confirmed case definitions within the report forms to match those published in November 2009 (53). The application also successfully adapted to a change in provincial reporting sources by allowing user roles to be redefined when structural reorganization at the provincial level resulted in the separation of the BC Public Health Microbiology and Reference

Services (BC PHMRL) from the BC Centre for Disease Control (BCCDC) which is responsible for provincial public health epidemiological services.

To manage fiscal and human resource requirements associated with internal IT development of the MARS application by CNPHI, the CNPHI launch version of the MARS application was considered to be final pending post-pilot evaluation. No additional modifications were considered unless required to address major functionality issues not identified through the pre-launch testing process. As such, there were limited opportunities to assess the flexibility of the MARS application on the CNPHI platform during the live pilot period. The MARS application was, however, successfully adapted during the pilot period to meet a province-specific request that the structure of alert notifications be selectively adapted to exclude provincial epidemiology stakeholders from simultaneous MARS alerting. This was requested to respect the pre-existing provincial reporting structure whereby regional public health authorities are traditionally the first to notify provincial public health that a measles or rubella investigation is underway once they have received regional notification of a positive measles or rubella result by the provincial public health laboratory. While this need was not identified by the province during the design and development process, the CNPHI platform was sufficiently flexible that this change request was successfully completed within days of its identification. Over the course of the MARS pilot period, personnel changes at pilot sites resulted in multiple requests for new user registration, as well as changes to MARS user access roles. These were completed seamlessly through CNPHI registration support services. It must be noted that while the CNPHI platform has to date been sufficiently flexible to address key changes to MARS application reporting requirements, the ability to flexibly address change requests in a timely manner is in turn dependent on the stability of ongoing public health infrastructure funding and availability of CNPHI IT expertise as an internal PHAC resource.

During the design process, it was confirmed that the MARS application on the CNPHI platform would have the future flexibility to incorporate the bulk uploading of line listed data to support national reporting in the event of a large outbreak; this feature will be developed should MARS be implemented more broadly following evaluation of the pilot. Additionally, CNPHI seeks to flexibly accommodate the receipt of surveillance data from provincial systems in whatever form it is available in order to meet public health surveillance requirements and maximize interoperability between systems. As flexibility is considered to be best evaluated retrospectively by observing system responsiveness to new demands (107), a more thorough descriptive assessment of MARS system flexibility will be possible should the MARS model be more broadly implemented following the pilot period.

Stability

The stability, or resilience of the MARS application to change, was assessed over the course of the pilot period based on its consistent availability to users to support national surveillance and alerting, its frequency of use, the level of personnel support for measles/rubella data entry and review, person-time required to support MARS data entry, along with implementation-associated budget considerations.

Based on responses received through the MARS User Survey (Table 3.17), 92.9% of MARS users agreed that the MARS application on CNPHI was consistently available for use as needed for reporting purposes, with 7.1% choosing 'not applicable' as their response. No system outages were reported by users during the 1-year pilot period. MARS users accessed the MARS application with varying frequencies to create, update or review reports for their sites: 21.4% were 'very frequent' users, accessing the application ≥2 times/week, 21.4% were 'frequent' users, accessing MARS

approximately 1 time/week, 14.3% reported 'occasionally' using MARS approximately 1 time every 2 weeks, 21.4% used the application 'infrequently' or approximately 1 time/month, and 21.4% used it 'rarely', or less than 1 time/month. With approximately 21.4% of users accessing the application less than once a month, the 'user friendliness' of the MARS application becomes very important to ensure ongoing user acceptability as well as data quality (see Table 3.17). The wide variation in frequency of use is to be expected given the differing roles of national and provincial MARS users, and the infrequency of measles/rubella investigations at the provincial level. Provincial laboratory users were involved in data entry at least 1 time/month in association with Monthly Test Reporting, and were responsible for the initiation of 96% of RTMRIs. Only a subset of RTMRIs involved both laboratory and public health investigation at the provincial level prior to being discarded through laboratory investigation. National level participation involves more frequent access to review reports submitted by all provincial sites, and to follow up with confirmatory laboratory testing and interjurisdictional/international information gathering and notification as required. In terms of site-based personnel support for MARS data entry, 64.3% of users reported having 2-3 users concurrently responsible for data entry at their site, with 35.7% of users reported having 1 person responsible. With respect to the number of persons responsible for routine review of MARS data, 7.1% of users reported having ≥5 persons on site responsible for routine data review; 57.2% reported having 2-3 persons, and 35.7% had 1 person on-site. It is important that data contribution and review functions be supported by more than one position per site to ensure continuity and timeliness of surveillance. Notably, all MARS pilot sites had more than ≥2 registered users per site during the pilot period.

In terms of information technology infrastructure and budgetary considerations, implementation of the MARS application system was at no cost to participating provincial/territorial jurisdictions as the MARS surveillance model and CNPHI application were entirely developed using PHAC/NML internal

resources to support national notifiable disease surveillance of measles and rubella. To access the MARS application, all that was required of the participating site was the availability of a computer with internet access and a CNPHI-compatible web-browser (Internet Explorer versions 6, 7, or 8; FireFox, Google Chrome, or Safari).

In order to estimate the person-time required to participate in MARS data entry, users were asked to estimate the time required to complete data entry via MARS based on the investigation report type, i.e. Measles/Rubella, CRS/I, Monthly Test and Weekly Zero reports (Table 3.18). It should be noted that unless otherwise stated, all proportions discussed here exclude from their respective denominators those users who selected 'not applicable' when asked about their use of specific report forms.

The time required to create and submit a new Measles/Rubella Investigation Report was estimated as <30 minutes by 50% of users, 30-<60 minutes by 33.4% of users, and as 1-<1.5 hours by 16.6% of users. All respondents estimated that a single update to an existing Measles/Rubella Investigation Report form could be completed in <30 minutes. No input was provided regarding the time required to create and submit a CRS/I investigation Report form; completion of a single update to an existing CRS/I report form was estimated to take <30 minutes. Monthly Test Reports and Weekly Zero Reports were estimated to take <30 minutes to complete and submit by 100% of responding users. The time required by provincial laboratory participants to contribute aggregate measles and rubella IgM serology test data on a monthly basis was estimated as <30 minutes by 50% of respondents, and as 30 - <60 minutes by the remaining 50%.

For comparison purposes, users were asked to estimate the time required to complete comparable forms via established CMRSS reporting. The submission and completion of a CMRSS National

Measles/Rubella Case Report was estimated to require <30 minutes by 66.8% of respondents, with 33.2% estimating 1 – <1.5 hours for completion. For CMRSS Weekly Zero Reports, 80% of respondents estimated a completion time of <30 minutes, and 20% estimated ≥2 hours to complete. Overall, the estimated time required for data entry via MARS Measles/Rubella Investigation and Weekly Zero reporting forms was very comparable with CMRSS data entry estimates.

Established CMRSS confirmed case reporting is conducted by provincial public health epidemiology stakeholders. Based on responses provided via the user survey, the person-time required by epidemiologists to report via the MARS application rather than CMRSS is not expected to increase. Rather, when the MARS model is implemented, most real-time investigation reports are created and populated with test result data by the provincial laboratory prior to the contribution of epidemiology data to the same report (i.e. 96% of MARS real-time reports were initiated by the PHL), thereby streamlining the data entry and reporting process for public health epidemiologists, and mitigating the requirement for ad hoc communication and linkage of measles/rubella investigation data among laboratory and epidemiology stakeholders at the provincial and national level.

By contrast, while the provincial public health laboratory has a central role in MLI investigation and the detection of suspected measles/rubella cases, their central involvement in real-time, centralized reporting of measles/rubella investigations as the first point of detection in non-outbreak settings is new to the MARS model. As such, it is worthwhile to provide a rough estimate of the time required by the PHL to participate in MARS surveillance. Based on all responses received, and assuming that RTMRI reporting by the laboratory involves both (i) report creation with entry of preliminary test results and (ii) 1 subsequent update, this would involve <60 minutes of person-time per RTMRI report. In addition, monthly test data entry (including aggregate test data procurement) is conservatively estimated to require <90 minutes/month. These data can be used to roughly estimate

the amount of person-time required by an implementing PHL based on the non-outbreak provincial MLI investigation rate and the observation that 1.2% of MLI investigations were ultimately reported as RTMRIs during the pilot period by all sites combined. Notably, this proportion falls within the measles IgM serology %positive confidence intervals estimated for non-outbreak years (1.9%, CI: 0.9-3.0%). In MARS pilot provinces, the reporting time requirement at provincial laboratories is estimated to have ranged from <95 minutes - <180 minutes/month for both RTMRI and Monthly Test reporting, or <5 minutes - <90 minutes/month for RTMRI reporting only based on observed site-based reporting activity.

The overall time requirements associated with MARS reporting are expected to be more than offset by the benefit of centralized reporting using the MARS model. By reporting measles/rubella investigations via MARS at the earliest point of detection, all national and provincial stakeholders involved in investigation and reporting are simultaneously notified, which is expected to save considerable time that would formerly have been required to communicate results and link together investigation data held by the various surveillance partners. Prior to implementation of the MARS model, case confirmation efforts within MARS pilot provinces in some instances involved multiple emails and phone calls to communicate results and link data held by separate surveillance partners (106).

In addition to the person-time required to participate, other personnel issues which contribute to the stability of the surveillance model include the identification of site-based personnel to participate in and coordinate data entry at the implementation phase, and ongoing continuity of trained personnel at the national and provincial levels to support data entry on a real-time basis.

Availability of personnel is a significant challenge to the ongoing stability of national infectious

disease surveillance activities including integrated interjurisdictional surveillance initiatives such as the MARS pilot. With respect to personnel turn-over at the national level, development and implementation of the MARS pilot project was led by the NML in close collaboration with federal epidemiologists at CIRID. Between the inception of the MARS pilot project in 2006 and completion of the final data collection phase in Spring 2013, the lead project contact within CIRID changed 9 times. During the brief 1-year pilot period, changes in registered MARS participants involved in data contribution were noted for the majority of participating pilot sites. Personnel availability and continuity is not solely an issue for MARS surveillance, but one which needs to be addressed to ensure ongoing national capacity for infectious disease surveillance and outbreak response. A benefit of the MARS system is that it provides a more formalized surveillance structure that reduces the dependence on maintaining current intra-jurisdictional working relationships with specific site-based contacts to be able to effectively coordinate surveillance. When sites participating in MARS surveillance register new users, they are required to provide user profile and contact information as well as defined access roles as part of the registration process. This in turn supports a strengthened surveillance network in which user roles are clearly defined, and all users receive up to date information regarding investigations in keeping with their defined user roles. There is also the ability for MARS notifications/alerts to be sent to a centralized email account that is accessible to all staff in a laboratory or surveillance unit responsible for measles/rubella surveillance; the user accessing the notification then follows the link which provides access to the MARS investigation report on CNPHI following username and password verification. While turn-over and changing responsibilities of personnel within national and provincial public health require ongoing registration and training of new participants in use of the MARS application, the application was found to rank highly with respect to ease of use (Table 3.14, 3.15), and the training component is expected to be minimal based on pilot experience (approximately 1 hour).

Sensitivity, Positive Predictive Value (PPV)

The sensitivity of a surveillance system has previously been defined at the case reporting level as the proportion of cases of a disease or other health-related event detected by the surveillance system (107). As it is not feasible to determine the true incidence of measles or rubella in Canada, the only way in which sensitivity has previously been estimable at the national level has been through periodic assessment of the level of investigation into measles and rubella using laboratory test data (39, 40). While CMRSS confirmed-case surveillance is sufficiently sensitive to detect sporadic, import-related measles and rubella cases during the current elimination-phase (45, 52) (39, 40), the routine indicator-based estimation of surveillance sensitivity is precluded by CMRSS data limitations.

The MARS system has demonstrated the sensitivity to monitor the performance of measles and rubella surveillance at three levels. Through the capture of augmented laboratory data, MARS is capable of estimating the number of clinically suspect MLI cases investigated diagnostically through IgM serology testing on a monthly/annual basis (Figure 3.1); the proportion of MLI investigations that go on to be investigated as suspected measles/rubella cases (i.e. RTMRI reports), and the proportion of RTMRI reports that are ultimately confirmed as measles or rubella cases at the provincial and national level. As MARS surveillance was integrated with CMRSS during the pilot year to ensure that all confirmed measles/rubella investigations reported via MARS were captured in the national CMRSS database, the sensitivity of MARS surveillance was further verified by determining that confirmed cases reported via MARS represented 100% of the confirmed cases attributed to pilot provinces in the CMRSS database for the period under review (Table 3.37).

The PPV of MLI investigation was estimated as 0.2% In MARS pilot provinces; that is, the likelihood of an MLI investigation resulting in a confirmed measles or rubella case was approximately 1 in 500 in

the absence of provincial outbreak activity (Table 3.35). Based on MARS data, only 1.2% of all MLI investigations were ultimately reported as RTMRIs via MARS, where RTMRIs are MLI investigations for which a positive measles/rubella laboratory test result was obtained and additional investigation was conducted by the reporting site in order to confirm or discard (Table 3.36).

From a surveillance perspective, the submission of an RTMRI report via MARS triggers simultaneous alerting of provincial and national stakeholders. The associated PPV of real-time MARS system alerting, i.e. the probability that an RTMRI report submitted via MARS represents a true measles/rubella case, was found to be 20.8%, or approximately 1 in 5 (Table 3.37). This represents a 100-fold increase in PPV when compared with that of MLI investigation. At first glance, a PPV of 20.8% represents a significant number of false-positives reported via MARS surveillance, with the majority of RTMRIs ultimately discarded. It is, however, the ability to capture both confirmed and discarded case data at the 'suspected case investigation' level that supports timely, integrated investigation efforts and enables surveillance performance to be monitored and evaluated using the MARS model. It should also be noted that all suspect-level investigation data (i.e. MLI, RTMRI-associated data) captured by MARS are generated through routine surveillance practices, but are not normally captured at the national level or in an integrated fashion. MARS pilot sites were not asked to collect any data in addition to that which would normally be gathered In support of routine measles and rubella investigation.

One of the challenges associated with optimizing surveillance is ensuring that changes made to improve the sensitivity of the system do not detract from other important surveillance attributes, in particular the timeliness and simplicity of the system (107). The improved timeliness of MARS real-time surveillance when compared with the existing confirmed-case model has been demonstrated. While MARS surveillance does require that augmented laboratory data be contributed on a routine

basis to support real-time investigation and the ongoing monitoring of surveillance performance, the use of a centralized integrated model was implemented to simplify (Appendix XIV) the overall investigation process. By simultaneously alerting all provincial and national stakeholders at the outset of an investigation, the MARS model ensures common access to all relevant data at the same time through centralized reports which can be updated in real-time over the course of an active investigation in keeping with established surveillance roles.

Data Quality/Completeness

MARS and CMRSS: PAHO Criterion – Adequacy of Investigation

To evaluate the quality and completeness of data collected through MARS, key data fields in Measles/Rubella Investigation Reports were assessed for completeness and the results compared with those observed for comparable data fields captured by CMRSS surveillance.

The PAHO criterion for adequate investigation of suspected cases is the 'Proportion of suspected cases with the following 11 data points completed: Name and/or Identifier, Place of Residence, Sex, Age or Date of Birth, Date of Reporting, Date of Investigation, Date of Rash Onset, Date of Specimen Collection, Presence of Fever, Date of Prior Measles-Rubella Vaccination, Travel History', with a minimum threshold of ≥80% for the completion of all 11 points (37).

To assess the adequacy of MARS and CMRSS surveillance using this PAHO criterion, completeness of the 11 data points was assessed for CMRSS confirmed case reports, and for MARS RTMRI and confirmed case investigations both separately and in total (Table 3.42). The following 5 data fields captured by all MARS and CMRSS reports were completed in 95.8% – 100% reports: 'Name and or Identifier', 'Place of Residence', 'Sex', 'Age or Date of Birth' and 'Date of Reporting'. While the 'Date

of Rash Onset' was available for 4 of the 5 confirmed cases reported via MARS (80.0%), this field was complete for only 6 of the 24 RTMRI reported (25.0%). This result is not unexpected using a real-time investigation model. In instances when the 'Date of Rash Onset' is not included with the initial testing requisition form submitted to the public health laboratory, and confirmatory testing results in the investigation being rapidly discarded following a positive IgM serology result, there would be no reason for the laboratory to request this information from provincial public health. Similarly, the completeness of other epidemiological data fields is considerably lower for MARS RTMRI versus confirmed case reports respectively, i.e. 'Date of Investigation' (33.3% vs 80.0%), 'Presence of Fever' (29.2% vs 100%), 'Date of prior MR vaccination' (20.8% vs 60.0%) and 'Travel History' (29.2% vs 100%).

As the majority of RTMRI were initiated by the provincial public health laboratory (95.8%), the most reliable epidemiological date for MARS reporting was the 'Date of Specimen Collection', which was completed in 95.8% of RTMRI and 100% of confirmed case reports in MARS (Table 3.42). CMRSS does not capture 'Date of Specimen Collection' as a data field. Similarly, the completeness of other epidemiological data fields is considerably lower for MARS RTMRI versus MARS confirmed case reports respectively, i.e. 'Date of Investigation' (33.3% vs 80.0%).

The lowest completeness value observed for a data field common to CMRSS and MARS was the 'Date of prior MR vaccination' field, which was complete for 20.8% of RTMRI and 60.0% of confirmed cases reported through MARS, and only 22.2% of CMRSS confirmed case reports. This highlights the ongoing challenge of obtaining reliable, up to date immunization history information in the Canadian setting in the absence of a national immunization registry.

In summary, CMRSS confirmed case reporting met the PAHO target for 7 of the 11 data points, but

had an overall completeness of 0.0% for all 11 data points as 'Date of Specimen Collection' and 'Presence of Fever' are not captured by CMRSS. While 'Travel history' is captured by CMRSS, its completion rate was not able to be fully assessed as the information is not included as a defined field in the national CMRSS database. Of the 8 data points able to be assessed, only 'Date of prior MR vaccination' fell short of the PAHO Target, with a completion rate of 22.2%.

By comparison, MARS RTMRI reports confirmed as measles or rubella met the PAHO Target of ≥80% completion for 10 of the 11 data points on an individual basis, with the exception of 'Date of prior MR vaccination' (60.0%). This resulted in a corresponding 60.0% rate of completion for all 11 PAHO data points. MARS RTMRI reports as a whole (confirmed and discarded) met the target for 6 of the 11 data fields, but had low completion rates for the 5 epidemiological data fields 'Date of Rash Onset', 'Date of Investigation', 'Presence of Fever', 'Date of prior MR vaccination' and 'Travel History' for a total completion rate of 20.8% for all 11 PAHO data points.

When only confirmed measles/rubella case reports are considered, the completeness of MARS surveillance (≥80% completeness of 10/11 data points) exceeds that of CMRSS (≥80% completeness of 7/11 data points) as assessed using the PAHO criterion. Given the very laboratory-centric nature of suspected case investigation in non-outbreak settings, the lower completeness of RTMRI reports (≥80% completeness of 6/11 data points) suggests the need to improve the provision of key epidemiological data points to the laboratory at the time measles or rubella IgM serology testing is requested.

MARS: Completeness of Augmented Laboratory Data Fields

To support the estimation of surveillance indicators, PHL participants were asked to complete a number of laboratory-specific data fields when reporting via MARS in addition to providing

laboratory test results. These included 'Sample Type', 'Sample Collection Date' and 'Laboratory Receipt Date' information associated with all samples collected in the course of each investigation, and the 'Test Result Date' for each test performed on a given sample (Table 3.41). These data fields were all observed to have high completeness values: 'Laboratory Receipt Date' and 'Test Result Date' were 100% complete for all confirmed and discarded RTMRI reports, and 'Sample Type' and 'Sample Collection Date' information were provided for 95.8% of all RTMRI reports and 100% of confirmed case measles/rubella investigations.

MARS: User Assessment of Data Quality/Completeness

Results of the MARS User Survey demonstrated that Measles/Rubella Investigation Reports were highly rated by users with respect to data field quality and completeness (Table 3.16). Of the 12 respondents having used the Measles/Rubella Investigation Report form, 100% agreed or strongly agreed that it 'includes all laboratory data fields required to investigate and confirm measles/rubella'; 83.3% (10 users) agreed or strongly agreed that the report 'includes all epidemiological and clinical data fields required to investigate and confirm measles/rubella' and that the 'review page includes all data fields needed for review and classification purposes' with 16.7% (2 users) submitting undecided/not applicable responses. Responses related to use of the CRS/I Investigation report were very limited, with only 2 users providing review responses for this survey section; of these, 1 user agreed that the report included 'all laboratory' and 'all epidemiological and clinical data fields required to investigate and confirm CRS/I', and 1 provided 'not applicable' as their response. As with the Measles/Rubella Investigation report form, the CRS/I report form captures all data fields required to support national confirmed case surveillance, as well as augmented laboratory data fields to support surveillance indicator estimation (53).

Acceptability

Acceptability is considered a measure of the willingness of persons and organizations to participate in a surveillance system. Given the subjective nature of acceptability, it may be expected to be influenced by a number of factors including the public health importance of the health-related event, time requirements associated with reporting, timeliness of data dissemination, cost of reporting, confidentiality, and the legislative and regulatory requirements for data collection and reporting (107). The acceptability of the MARS application was therefore descriptively and quantitatively assessed as a composite of other indicators and attributes which contribute to the timeliness of surveillance and the quality and completeness of data.

The acceptability of the MARS surveillance model is supported by its successful implementation and use at provincial and national pilot sites by both laboratory and public health stakeholders throughout the pilot period, with provincial pilot sites collectively representing 25% of the Canadian population. Quantitatively, its acceptability is further supported by the demonstrated increase in timeliness of reporting using the real-time model, and by the high level of completeness observed for both augmented MARS laboratory data fields, and for key PAHO-recommended data points when compared with CMRSS.

At a subjective level, the usefulness and acceptability of the MARS model were highly rated by application users as assessed through the MARS User Survey (Table 3.19). Of all 14 survey respondents, 92.9% agreed or strongly agreed that 'MARS automated email notifications effectively support interjurisdictional communication regarding measles/rubella reports' and that 'overall, the MARS application successfully supports integrated national measles and rubella surveillance and reporting' with 7.1% selecting 'undecided/not applicable' as their response. With respect to data

linkage, 85.7% agreed or strongly agreed that 'centralized reporting of measles/rubella investigation data via MARS reports improved linkage of laboratory and epidemiological data' with 14.3% providing an 'undecided/not applicable' response. Of survey respondents, 100% (14 users) agreed or strongly agreed that 'the ability to report measles/rubella investigation data in real-time via MARS enables more timely national surveillance', and that MARS Measles/Rubella Investigation Report forms 'effectively integrate laboratory, epidemiological and clinical measles/rubella data contributed by national and provincial public health and laboratory users'.

Factors that support the acceptability of national surveillance optimization efforts via MARS include the recognized public health importance of measles and rubella within the public health community. Both diseases are provincially reportable and nationally notifiable, and have established PAHO regional elimination targets with the concomitant international responsibility to document and verify national progress towards elimination (53)(38)(39)(37). As assessed through the MARS project, levels of measles and rubella IgM testing at the provincial and national level have consistently exceeded the established PAHO target for suspected case investigation throughout the 2005-2011 and Pilot reporting years, reflecting the continued consideration of these diseases by physicians in the differential diagnosis of MLI despite their very low incidence rates in the Canadian setting.

The timeliness of real-time reporting also supports user acceptability; in addition to demonstrated increases in the timeliness of national surveillance via MARS, there was a high level of agreement among MARS users that centralized, integrated national reporting via MARS effectively supports timely data linkage and information sharing among all stakeholders involved in measles/rubella investigation. From a user perspective, the time requirement associated with MARS data entry and reporting was found to be comparable with that of established CMRSS reporting suggesting that there was no additional time requirement associated with public health reporting via MARS (Table

3.19). The timeliness of person-dependent surveillance intervals may also be considered in the assessment of acceptability. During the MARS pilot the time interval between rash onset date and the date of sample collection, which represents the timeliness with which individuals with MLI seek physician care, ranged from 0 – 7 days (mean = 2.3 days, SD ± 2.2 days). While this interval may be influenced by a number of factors outside the scope of the project (health care access, education, public health awareness), it is essential both to the timely investigation and testing of clinically suspect measles and rubella and to the initiation of public health action. Of the timeliness intervals dependent upon public health response, the longest interval observed was that between the first test result and national reporting; this step is highly dependent on the availability of personnel at the public health laboratory to enter data as required to initiate a MARS report. While a majority of MARS users (83.4%) reported that the time required to create and submit a new Measles/Rubella Investigation Report was <60 minutes, the mean post-implementation time interval between the first test result and MARS notification was 3.1 days, SD ± 3.2 days. Although this assessment does not account for the time required for internal site-based review of preliminary results prior to reporting, these data suggest that there may be an opportunity to improve on the timeliness of this particular reporting interval by ensuring adequate site-based personnel support for laboratory-based participation in national surveillance.

Acceptability was also supported by the ability to design and develop the custom MARS application using PHAC in-house resources, and to provide access to the application on the CNPHI IT platform at no direct implementation cost to provincial stakeholders. To further ensure the acceptability of the model, provincial and national laboratory stakeholders were engaged in review of the data flow model prior to CNPHI development, and in live-testing of the MARS application in preparation for launch to ensure that the MARS application design met key surveillance requirements. As national

MARS data are located on CNPHI servers within PHAC, all case-based investigation data captured by MARS are strictly non-nominal in nature to support and respect provincial legislative and regulatory requirements regarding the communication of personal health information at the national level.

Usefulness

The usefulness of a surveillance system can be descriptively assessed as a composite of the performance of all attributes of the surveillance system within the context of key surveillance system objectives (107). Using this approach, the usefulness of the MARS surveillance model has been demonstrated in a number of ways.

The primary objective of the MARS pilot project was to address existing surveillance challenges by investigating the feasibility of optimizing the performance of national measles and rubella surveillance, and its evaluation using surveillance indicators. As stated in the central hypothesis, the real-time, web-based measles and rubella surveillance (MARS) model was able to be successfully developed, implemented and piloted in the Canadian setting (I) while incorporating all key features identified as important to the optimization of elimination-phase surveillance (Ia-e). These included support for real-time automated stakeholder alerting from the outset of each investigation (Ia); real-time centralized contribution of investigation-related data through a common report form accessible to all stakeholders (Ib); collection of augmented laboratory data to support measles/rubella investigation efforts and the estimation of surveillance performance using indicators (Ic); integration of non-nominal provincial and federal laboratory, epidemiological and clinical data (Id); and the routine monthly collection of aggregate laboratory test data (i.e. IgM serology test numbers and total positives) to support surveillance indicator estimation (Ie). Increased timeliness of national surveillance was observed at pilot sites implementing the MARS real-time surveillance model when

compared with CMRSS confirmed-case surveillance in non-pilot provinces, providing an opportunity for more timely and coordinated public health investigation and response activities at all levels (II). Augmented laboratory data were successfully collected through MARS pilot sites and via post-pilot survey of national testing laboratories, enabling national surveillance performance (i.e. timeliness, level of investigation) to be estimated using adapted PAHO surveillance indicators, a majority of which were able to be assessed for the first time in the Canadian setting (III). Verification of both the central (I) and sub-hypotheses (II, III) through evidence gathered during the pilot period demonstrated the usefulness of the MARS surveillance model in optimizing measles and rubella surveillance performance and supporting indicator-based evaluation during elimination-phase. Overall usefulness of the MARS surveillance model was further reinforced by very positive user-based performance assessment of various surveillance attributes, including the acceptability and usefulness of the model, simplicity and ease of use, stability, data quality/completeness and timeliness; and by the ability to quantitatively and descriptively analyze these and other surveillance attributes including sensitivity and positive predictive value using MARS pilot data.

MARS Implementation: Advantages, Considerations

Overall, the results of MARS pilot project evaluation support broader national implementation of the MARS model as a means of optimizing the performance of elimination-phase measles and rubella surveillance in the Canadian setting. Experiences gained during MARS pilot development and implementation highlight a number of factors that should be considered and which may impact broader implementation efforts.

At the inception of the MARS pilot project in 2006, very low national measles and rubella incidences had been consistently observed following the implementation of 2-dose MMR in 1997-1998 with an

average of 36 measles cases reported annually between 1998-2005, and <20 rubella cases per year from 1998-2008 (excluding the 2005 Ontario rubella outbreak) (47). At the time of MARS pilot implementation in June 2011 however, the context for elimination-phase surveillance had changed significantly. Large measles outbreaks were observed in multiple European countries in the spring of 2011, increasing the probability of importation from countries which were formerly in elimination status. The scale of the international resurgence of measles activity resulted in significant concerns regarding the feasibility of achieving the WHO measles elimination target of 2015 In the European Region (108). The 2011 Québec outbreak which coincided with the MARS pilot year was associated with a measles importation from Europe, and was the largest measles outbreak to occur in North America in a decade with over 725 cases confirmed (109). This, coupled with the observation of at least one provincial measles outbreak in Canada annually from 2007-2011 with the exception of 2009(45), serves to emphasize the importance of sustained public health vigilance in meeting the challenges associated with maintaining elimination status, including the need to strengthen and optimize surveillance efforts to ensure rapid case detection and public health action.

To meet elimination-phase surveillance challenges, highly effective measles/rubella surveillance requires the ability to sensitively detect, investigate and confirm or discard suspected cases in a timely, coordinated and integrated manner to support appropriate decision-making and public health action at all levels. From a public health surveillance perspective, the most significant advantage associated with implementing the MARS model is its demonstrated ability to simultaneously notify and engage all national and provincial investigators in the investigation of suspected measles and rubella at the earliest feasible point of detection with full integration of laboratory, epidemiological and clinical data while respecting established surveillance roles.

During the pilot period, one of the questions raised during stakeholder discussion was whether the

MARS model actually represented real-time surveillance, with the suggestion that real-time surveillance would involve physician-level detection of clinically suspect MLI. This raises the interesting question, 'how 'real-time' is it possible for measles and rubella surveillance to be?' One of the issues associated with optimizing measles and rubella surveillance in the Canadian setting is that the differential diagnosis of fever-rash illness includes a number of infectious agents other than measles and rubella (e.g. parvovirus B19, human herpesvirus-6 (HHV-6), Epstein-Barr virus, adenovirus, enterovirus and dengue virus), most of which would be expected to have higher annual incidences in the population (110)(111). Looking at MLI investigation data for the 2007-11 and pilot years, the annual proportion of MLI investigations discarded exceeded the PAHO minimum target of ≥95% in all non-outbreak settings, confirming that most clinically suspect MLI is associated with other causes. Furthermore, given the very low incidence of these diseases, few physicians practicing in the Canadian setting will have seen a measles or rubella case during their history of practice, with the recent exception of Québec which saw a large outbreak in 2011 (1)(18)(45). As laboratory evidence is necessary to the confirmation of measles and rubella, the point at which a health-care worker collects a serum sample for measles/rubella IgM serology testing by a public health laboratory arguably represents the earliest date of public health investigation into MLI in an elimination setting. The earliest point at which an MLI investigation would be deemed to more specifically represent a measles/rubella investigation is when the front-line measles or rubella IgM serology test yields a positive result. For real-time surveillance purposes, this would represent the earliest point of detection of suspected measles/rubella (as opposed to clinically suspect MLI) by public health in an elimination setting. It is at this point that the MARS surveillance model is able to detect the measles/rubella investigation, and further confirmatory testing and epidemiological investigation would be conducted to confirm or discard. While MARS is also able to routinely monitor the levels of investigation into clinically suspect MLI (PPV = 0.2%), stakeholder notification of measles/rubella

investigations following the detection of a positive laboratory test result arguably represents the most timely and sensitive real-time model (PPV = 20.8%) feasible in the Canadian setting.

Another important advantage of implementing the MARS surveillance model is its ability to routinely assess the performance of measles and rubella surveillance using various adapted PAHO indicators. The availability of indicator-based evidence is critical to substantiate the performance of national surveillance and to document and verify progress towards national and international measles and rubella elimination goals (37)(77). Preliminary results obtained through the 2007 MARS pre-pilot survey of measles and rubella testing laboratories have already been used effectively for this purpose, i.e. to estimate national levels of investigation into suspected measles and rubella (39,47,102). PAHO uses a number of criteria to assess progress towards regional elimination, including 'reporting rate', 'adequate investigation', 'laboratory confirmation' and 'viral detection'. The PAHO integrated measles and rubella surveillance indicator used to evaluate the 'reporting rate' criterion is the 'Annual rate of suspected measles and rubella cases at the national and subnational levels (state, province, or equivalent level)' (37). The MARS model enables routine estimation of this indicator at both the national and provincial levels by implementing provinces. As previously demonstrated, MARS also supports the estimation of indicators representing the 'adequate investigation', 'laboratory confirmation' and 'viral detection' PAHO criteria, i.e. '% of suspected cases with the following 11 data points completed: name and/or identifier, place of residence, sex, age or date of birth, date of reporting, date of investigation, date of rash onset, date of specimen collection, presence of fever, date of prior measles-rubella vaccination, travel history'; '% suspected cases with adequate blood specimen', and '% outbreaks with adequate specimens and genotype available from at least 1 viral specimen'. The only PAHO indicators that are not able to be estimated at the national level via MARS or CMRSS are '% suspected cases with household visit within 48 hours following

reporting' and '% confirmed cases with follow-up of contacts for 30 days' which support evaluation of the 'adequate investigation' criterion (37). While data fields which support the collection of these data can easily be incorporated into MARS reporting forms, follow-up and contact tracing of this nature is conducted at the regional public health level rather than at the provincial level, and these data are not routinely captured at the provincial or national levels through existing surveillance structures.

An important implementation consideration is the jurisdiction-specific identification of key public health surveillance partners and their respective surveillance roles. To support implementation, the MARS application model allows provinces to customize access to MARS reports based on reporting site and the role of the user in reporting. On a user-specific basis, access can be configured as 'read-only' to allow the review of jurisdiction-specific investigation reports, or to allow the user to create new reports and enter and update data as needed on behalf of their contributing site. Provincial user role designation and access is strictly at the discretion of the provincial reporting site. As such, while the MARS application is capable of supporting expanded provincial reporting with participation by regional health authorities and the provincial Ministry of Health if needed, the decision to do so would remain at the discretion of the province in keeping with established surveillance roles. To achieve full implementation of the MARS application, participation of both provincial public health and laboratory counterparts is required.

Implementation of MARS in smaller provinces having a central PHL and less complex public health structures (e.g., Saskatchewan, Nova Scotia) is expected to be relatively straightforward from a technical and logistical perspective. In larger provinces, the existence of more complex intra-provincial public health reporting structures as well as the decentralization of front-line measles and rubella IgM serological testing among regional laboratories (e.g., Ontario, Québec) may present a

greater implementation challenge. A factor supporting MARS implementation in these settings is the flexibility to use a staged implementation strategy. An important advantage of the MARS application design is that while it fully supports real-time surveillance when used as designed, it can also be used to support established CMRSS confirmed case reporting during the early stages of jurisdictional implementation without significantly changing the established provincial reporting structure. Using this alternate implementation model, provincial public health epidemiologists would begin submitting their routine Weekly Zero reports and any Measles/Rubella and CRS/I case reports via the MARS web-based application using the 'real-time' web-based forms as per usual. Measles/rubella and CRS/I case reports would be entered at the conclusion of the provincial investigation process, and automated MARS notification of all provincial/national stakeholders would occur at this point. This would allow public health epidemiologists to become familiar with use of the system without interrupting or substantially changing routine national reporting while public health user roles for MARS data entry and suspect case notification at the provincial and regional levels are defined as appropriate. Provincial laboratories involved in measles and rubella testing could be either simultaneously or subsequently incorporated as participating sites; once laboratories are registered, the reporting model would then be able to transition to a real-time model whereby investigations are able to be initiated either by PPH or by the PHL upon detection of a positive result. Based on MARS data, the earliest point of detection for reporting of sporadic/import-related cases is in most cases the PHL (i.e. 96% of MARS RTMRI reports). This proportion would be expected to decrease in outbreak circumstances during which public health may more routinely detect clinical cases having an epidemiological link with a laboratory-confirmed case through contact-tracing efforts. Irrespective of whether a given provincial laboratory site contributes data directly to MARS investigation reports in real-time at the outset of a staged implementation process, they would still have a distinct role in contributing aggregate test data to Monthly Test Reports to enable surveillance indicator estimation

and performance evaluation at the provincial and national level.

The MARS application supported manual data entry only during the initial MARS pilot period. This was considered a reasonable piloting strategy at the time of development given the very low national measles and rubella incidence rates observed in prior years, however the addition of support for batch uploading of line-listed data is considered a necessary requirement should MARS be more broadly implemented to support ease of reporting by provincial public health in the event of an outbreak. This need is underscored by the occurrence of importation-associated provincial outbreak activity during each of the 2007-2011 reporting years with the exception of 2009 (45); and by the decreased timeliness of national CMRSS reporting observed during the large 2011 Québec outbreak when compared with the timeliness of CMRSS reporting in non-outbreak provinces.

One of the most critical implementation factors is the capacity of participating sites to enter data. National reporting of measles/rubella case data is routinely required of provincial public health epidemiologists, and transition to the MARS model is not expected to require additional personnel time beyond what is routinely required for reporting on an ongoing basis. The success of the MARS real-time model does, however, depend on the timeliness and consistency with which positive test result data are entered into the MARS application by the PHL. Provincial laboratories are routinely responsible for timely intra-provincial reporting of test results through established mechanisms to support diagnostic and surveillance efforts. However, having the PHL initiate and update national suspect case-based investigation reports through direct contribution of test data constitutes a new role with respect to national notifiable disease surveillance even though it mirrors the functional role of the PHL in the investigation process. Given the central role of the laboratory in case-based detection and confirmation of most nationally notifiable diseases, and the availability of technology to support centralized real-time reporting (53), the role of provincial laboratories in national

surveillance may be expected to expand in the future to encompass other notifiable diseases that require laboratory evidence to support rapid case-based investigation and public health action (e.g., mumps, laboratory-confirmed influenza and severe acute respiratory infection surveillance, hepatitis B).

The availability of provincial laboratory personnel to support timely data contribution presents a significant logistical challenge for broader implementation of the MARS real-time model, and for the optimization of national infectious disease surveillance as a whole. This is particularly the case as provincial participation in national notifiable disease surveillance is voluntary and by mutual agreement as there is no existing legislative basis to compel the provision of data (53,67).

During implementation of the MARS pilot, the availability of site-based personnel to support data entry was raised by prospective pilot sites as a key consideration with respect to participation. The issue of personnel availability was successfully addressed in BC by the ability to assign responsibility for site-based coordination of MARS data entry to a nationally-funded PHAC Laboratory Liaison Technical Officer (LLTO) position located at the provincial public health laboratory. At the time of the pilot, neither AB nor NL had site-based LLTO position support due to fiscal constraints at the national level; however participation in AB was facilitated in part by existing PHAC field position support. NL, which did not have the benefit of site-based PHAC personnel support, was delayed in their ability to contribute aggregate data via MARS Monthly Test Reports due to PHL staff turnover at the outset of the pilot period. Personnel-associated limitations in provincial surveillance capacity may be addressed at a national level through field programs such as the NML-based LLTO Program, which places laboratory technical positions within provincial public health laboratories across Canada to enhance national capacity for laboratory-based infectious disease surveillance, outbreak preparedness and response. As LLTO positions are PHAC-funded, they can be called upon to provide

targeted, site-based data entry, liaison and laboratory technical support for national surveillance and outbreak response activities. While this enhanced personnel capacity was a key determinant in MARS pilot project implementation specifically, this experience suggests that the presence of LLTO support in each province would greatly support the implementation, ongoing stability and optimization of national infectious disease surveillance activities having a significant laboratory component (e.g., surveillance of vaccine-preventable diseases including measles, rubella, mumps; influenza and emerging respiratory infectious diseases; enteric disease and sexually transmitted and blood-borne infections).

MARS users identified a number of factors important in facilitating the implementation process, and highlighted challenges for consideration with respect to future implementation efforts. The ability of MARS to link laboratory specimens with epidemiological data in a timely manner, and the receipt of real-time alert notifications by both laboratory and epidemiology stakeholders including all known case data were seen as important factors supporting implementation. Also highlighted were the ability of MARS to support user role customization, and the fundamental importance of clearly defined user roles and reporting expectations when implementing (Table 3.20). While MARS supports clear definition of user roles based on organization and position as needed, provincial user roles must be defined by the implementing province.

The implementation of national surveillance programs in provinces with differing organizational models for the delivery of public health presents a challenge which is expected to require jurisdictionally tailored approaches based on experiences from the pilot period. In BC, one of the issues that was encountered during early implementation was the request to adapt the MARS alert notification process to respect historically established reporting roles between provincial public health epidemiologists (BCCDC) who are responsible for national reporting, and regional public

health stakeholders who are integrally involved in gathering epidemiological and clinical evidence to support case investigation and contact tracing efforts upon PHL notification of a positive laboratory result. In BC, regional public health is traditionally responsible for notifying provincial public health upon completion of their case investigation process (as opposed to the PHL), and there was concern expressed regarding the prior receipt of a MARS alert notification by provincial public health irrespective of informal notification and communication processes in place. As such, the MARS alert notification structure was altered during the pilot to exclude provincial (BCCDC) and national (CIRID) epidemiologists from alert receipt when a case was entered by the PHL, although all stakeholders were still able to access MARS reports entered in real-time by directly accessing the application. BC continued to use the MARS application to support national reporting following the initial 1-year pilot period; importantly, BCCDC requested in 2013 that the alert notification process revert to its original design to include epidemiology stakeholders at the national and provincial level to support timely stakeholder notification and response.

In AB, the investigation and surveillance of measles and rubella also involves significant coordination between provincial and regional public health. Infectious disease surveillance and public health activities including immunization, case investigations and laboratory testing for suspected measles and rubella cases fall within Alberta Health Services (AHS) which is responsible for the regional delivery of health care and public health in Alberta. The provincial Ministry of Health, Alberta Health (AH), includes the Office of the Chief Medical Officer of Health and the provincial epidemiologists responsible for gathering data on provincially reportable diseases, and the reporting of nationally notifiable diseases to PHAC (106).

While the ability to simultaneously alert all stakeholders via MARS from the outset of a measles/rubella investigation provides the significant advantage of increased timeliness and

integration of case investigation data, it also presents a challenge to established reporting structures at the regional, provincial and national levels. There are significant political sensitivities associated with the timeliness and order in which public health stakeholders are notified regarding measles and rubella cases, and clearly defining how and when users at all levels will have access to data using a real-time model is essential prior to initiation of a site-based implementation process. The implementation of the MARS model in more complex public health environments may be expected to require significant coordination and cooperation to accomplish; however once implemented in keeping with established roles, it is expected to diminish the communication-based challenges as previously discussed. Significantly, user input provided by both provincial and federal sites has highlighted that while there are a number of factors that should be considered to ensure effective implementation, the MARS model does successfully address the main surveillance challenges associated with the established confirmed case surveillance system particularly with respect to timely alerting and integration of investigation data. This is important from both an acceptability and usefulness perspective, particularly as one of the pre-implementation challenges raised by provincial public health at one pilot site was the perception that while the MARS model might improve national surveillance, it was not expected to improve surveillance at the provincial level.

It is useful to consider the development and implementation of the MARS application within the context of other electronic public health information-sharing initiatives proposed at approximately the same time the MARS pilot was conceptualized, particularly the Canada Health Infoway initiative. To support electronic public health information sharing, Infoway sought to accelerate the development and adoption of electronic health information systems that employ standards and communications technologies interoperable with the planned implementation of a pan-Canadian Electronic Health Record (EHR). To this end, Infoway engaged with public sector partners on various

projects in nine targeted program areas: Registries, Diagnostic Imaging Systems, Drug Information Systems, Telehealth, Public Health Surveillance (PHS), Laboratory Information Systems (LIS), Interoperable EHR, Innovation and Adoption, and Infostructure (86). The LIS program was aimed at implementing solutions that would allow clinicians to view EHR – linked lab results and reports from all hospital, community and public health laboratories. Development of the Infoway PHS program began in 2004, with the goal of enabling communicable disease case tracking and outbreak management (112)(113). Based upon the information available during MARS development and implementation, it was difficult to predict how the planned Infoway LIS and PHS applications under development would permit the customized integration of laboratory and epidemiology data in a disease-specific manner as required for enhanced national surveillance. Other unknowns associated with the Infoway initiative with implications for national surveillance included the extent to which various jurisdictions would invest in the nine Infoway program areas given the substantial costs associated with implementation, how jurisdiction-specific levels of uptake would vary for particular solutions (e.g. LIS and PHS solutions), and changing implementation timelines and statuses. The specific target of the Infoway initiative was to provide an interoperable EHR to 50% of the Canadian population by the end of its mandate in 2009 (86). For the PHS program specifically, the target outcome was to 'implement an integrated public health surveillance system in all jurisdictions by December 31, 2009'. In 2009, Panorama jurisdictional phase 1 (planning) and phase 2 (implementation) projects were reported to be underway in 9 out of 10 provinces and 1 territory with anticipated end dates ranging from 2010 – 2012. However, given that AB has opted not to implement Panorama, and considering the highly selective manner in which the health regions within provinces and territories have opted to implement only specific Panorama solutions (e.g., immunization registries, outbreak management applications), the extent to which the Panorama target of implementing an integrated interoperable public health surveillance system in all P/T

jurisdictions has been achieved remains questionable (87). At the national level, regardless of whether a P/T jurisdiction has implemented Panorama or another solution, the need remains the same: to be able to receive laboratory and epidemiological surveillance data from disparate provincial sources in whatever form they are able to provide it, and to integrate the data received in a disease-specific manner to support national surveillance requirements.

The premise behind the CNPHI platform is conceptually distinct from the Panorama standards-based approach to electronic public health information sharing. Panorama efforts have focused on ensuring that jurisdictions implementing Panorama modules commit to adopting prescribed messaging and nomenclature standards. By contrast, the CNPHI approach to the electronic sharing of information and data is to work with jurisdictional stakeholders to identify flexible solutions for the importing of public health data in whatever format they are available jurisdictionally into web-based CNPHI disease surveillance platforms. In this model, public health stakeholders have the role of arriving at a consensus with respect to the appropriate nomenclature, case definitions and data fields that will be used and shared to support national surveillance, which in turn are communicated as part of the data model provided to CNPHI for development.

The MARS project was developed with an awareness that various provincial and territorial jurisdictions will be in the process of implementing Infoway modules which employ specific messaging and terminology standards (e.g., HL7 v3, LOINC, and SNOMED-CT) to enable communication with the planned pan-Canadian EHR (112,113)(86,112). As such, the intent was to ensure that the MARS surveillance platform is interoperable and able to seamlessly receive data from jurisdictions that have implemented Infoway solutions as well as those which have elected to implement other systems as needed to support P/T surveillance partners.

At the stakeholder level, one of the challenges associated with developing and piloting MARS concurrently with Panorama development was the level of uncertainty and lack of clarity regarding the functionality that Panorama would offer; whether PHAC would commit to the purchase of a Panorama 'instance' to support information sharing with P/T stakeholders, and ultimately the delivery timelines for Panorama modules. Both during MARS development and immediately prior to the commencement of MARS pilot implementation in 2011, a number of provincial stakeholders expressed the perception that the proposed MARS functionality would be provided by Panorama for all notifiable diseases following its implementation at the provincial level. When first proposing the development of the MARS application to address existing surveillance challenges, it was communicated to provincial partners that from the national perspective the receipt of provincial data from Panorama would not be considered qualitatively different from the provision of data collected through other provincial information-sharing solutions or systems. The approach taken with respect to MARS design was to customize the surveillance application to meet disease-specific requirements and address challenges associated with measles and rubella surveillance within the Canadian context, whereas there was no evidence that a similar consultative disease-specific approach had been incorporated into Panorama PHS and LIS module development. A further consideration was that, if successful, the MARS pilot would provide a useful model for the optimization of other infectious diseases under case-based national surveillance, particularly other vaccine-preventable diseases for which fully integrated surveillance systems do not exist. Since the successful implementation and evaluation of the MARS pilot application, no comparable solution has been made available to address the disease-specific national surveillance requirements of measles and rubella, nor have any participating provincial jurisdictions identified the need for MARS surveillance to support interoperability with a Panorama or other jurisdictional electronic health information solution. At the current time, Panorama has not been adopted as a pan-Canadian solution; nor does PHAC currently

have an instance of the Panorama module.

Development and implementation of the MARS web-based application would not have been possible without the availability of PHAC-funded CNPHI tools and development support. The CNPHI platform provides a single portal through which all CNPHI surveillance applications are accessible by public health stakeholders at the provincial and federal level. As of May 2013, over 4200 CNPHI users were registered with representation in all provinces and territories. The scope of CNPHI activities and the level of national interest in use of the CNPHI platform to address surveillance integration challenges have only expanded since the inception of the MARS pilot project; however CNPHI capacity remains dependent upon sustained national funding and the retention of highly skilled IT personnel for ongoing support of its activities and initiatives. From a program perspective, this can affect deliverable timelines during times of fiscal constraint, and when shifting priorities require the redirection of CNPHI development resources to meet immediate needs. Deliverable timelines may also be impacted by limitations in the capacity of CNPHI to engage in a more iterative development process whereby periodic updating and communication during the course of custom IT application development is supported. The ability to support a more routine consultative process may provide the opportunity to identify and discuss key IT development decision-points in advance which have the potential to impact application functionality from a program perspective, thereby minimizing the need for significant modifications following the initial development process. Additionally, continued support is required within PHAC to retain the program-specific infectious disease laboratory and public health surveillance expertise upon which the capacity for timely surveillance and outbreak response depend.

In 2009, the need to employ available CNPHI resources to address H1N1 pandemic surveillance and response issues did impact projected timelines associated with custom surveillance application

development for other program areas. From a MARS development perspective, the timing of the H1N1 pandemic response was also associated with delays in national/provincial stakeholder meetings to discuss and review the final MARS design as many of the same stakeholders involved in the MARS review process were also involved in H1N1 outbreak response. While this is only one example of the impact a large scale interjurisdictional public health outbreak response can have on an individual surveillance initiative, it does underscore the importance of maintaining public health capacities to ensure that infectious disease laboratory and epidemiology programs have sufficient flexibility to maintain routine program activities without significant or prolonged interruption during a large outbreak or pandemic response. The availability of a network of PHL-located, nationally funded field positions mandated to support national surveillance activities and initiatives (e.g. LLTO positions) would significantly address the challenges associated with sustaining national capacity for infectious disease surveillance during routine and outbreak circumstances, and is a factor that would considerably favour implementation and optimization of MARS and other national surveillance activities.

Ultimately, the decision to support implementation of the MARS model at a national level to optimize measles and rubella surveillance will be decided through an evidence-based review of MARS performance by members of the national Measles and Rubella Elimination Working Group in consultation with national laboratory and public health experts. While MARS has demonstrated the ability to address key elimination-phase surveillance challenges in the Canadian setting, the success of national implementation efforts will depend on close collaboration with national and provincial laboratory and epidemiology stakeholders to ensure that stakeholder roles are clearly defined and respected, and that province-specific surveillance needs are identified and met.

APPENDIX I: National Measles, Rubella CRS/I Case Report Form, 2007

Check one: MEASLES RUBELLA CONGENITAL RUBELLA SYNDROME/ INFECTION

IDENTIFICATION

Case Number
assigned by province/territory

Health Unit, City & 1st Three Postal Code Digits

Date of Birth YYYY-MM-DD
If not available, specify AGE in years

Date Reported to Health Unit
YYYY-MM-DD

Sex FEMALE MALE
If FEMALE, pregnant? Yes No Unknown

Date Investigation Initiated YYYY-MM-DD

BACKGROUND, EXPOSURE & CLINICAL INFORMATION

MEASLES incubation period is 7-21d prior to onset of rash; communicable 4d before to 4d after rash onset

Date of Rash Onset YYYY-MM-DD

Clinical illness and epidemiologic link to a lab-confirmed case Yes No

Hospitalized Yes No
Unknown
Due to measles/rubella or due to disease complications

RUBELLA incubation period is 14-21d prior to onset of rash; communicable 7d before to min. 4d after rash onset

Vaccination History Yes No
Unknown
Date dose 1 YYYY-MM-DD
Date dose 2 YYYY-MM-DD
Date dose 3 YYYY-MM-DD

Outbreak associated Yes No
Unknown

Source: outside Canada
OR in Canada, linked to an imported case/chain
OR in Canada, linked to case/chain of unknown source
OR unknown source

In the space provided or attach a sheet:
- list all countries, dates of travel and setting(s) of exposure during incubation and communicable periods
- if new to Canada, note country of birth and/or year of immigration
- any other lab or exposure information

LABORATORY INFORMATION

measles virus isolated	Yes	No	Not Done	rubella virus isolated	Yes	No	Not Done
measles virus detected	Yes	No	Not Done	rubella virus detected	Yes	No	Not Done
significant rise/change in measles-specific antibody	Yes	No	Not Done	significant rise/change in rubella-specific antibody	Yes	No	Not Done
positive measles-specific IgM serology*	Yes	No	Not Done	positive rubella-specific IgM serology*	Yes	No	Not Done

* Cases with no epidemiologic link to a lab-confirmed case nor with recent travel history to an area with known disease activity must
be lab-confirmed by virus isolation or convalescent serology

All cases diagnosed within Canada, regardless of citizenship, should be reported to the Public Health Agency of Canada.

PLEASE SEND YOUR DETAILED PROVINCIAL/TERRITORIAL FORM FOR CONGENITAL RUBELLA SYNDROME/INFECTION

PHAC USE : RecDATE PROV WK STRAIN AdjDATE
CASE: Y N SEP2007

REAL-TIME DATA ENTRY

MEASLES/RUBELLA REPORTING

CREATING A 'MEASLES/RUBELLA REPORT':

- A new 'Measles/Rubella Report' may be created by either the provincial laboratory when an IgM-positive measles/rubella test result is generated, or by provincial public health upon investigation of a suspect case
- The 'Contributing Site' is specified, and 'Measles/Rubella' is selected as the 'Report Type'; a new report is then created, or an existing report is viewed or edited

'MEASLES/RUBELLA REPORT' DATA FIELDS:

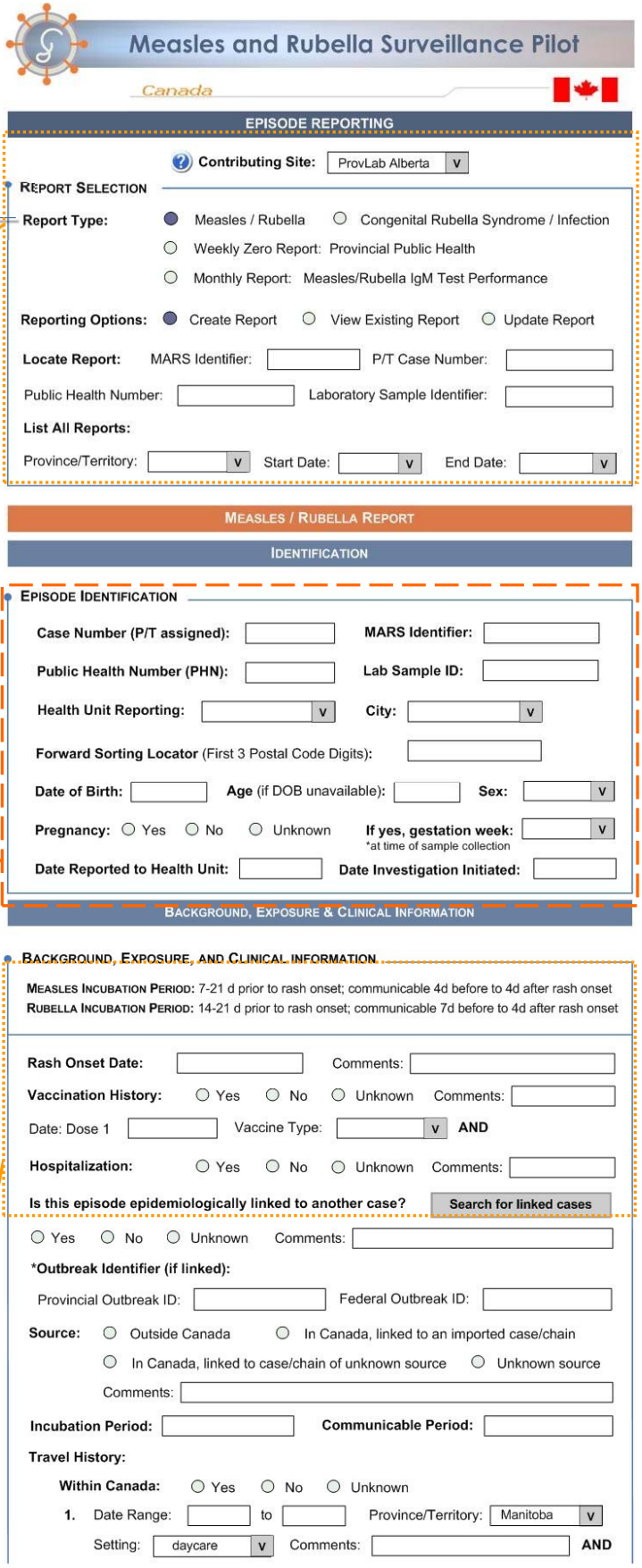
NOTE: Each Measles/Rubella Report will capture all data fields required by CMRSS [1] for national reporting, plus enhanced lab data to support alerting, case classification and estimation of surveillance indicators

The **IDENTIFICATION** section captures:

- The system-generated 'MARS Identifier', P/T assigned 'Case Number', 'Public Health Number', and 'Lab Sample ID(s)'
- Various epidemiology fields, including 'Health Unit Reporting', 'City', 'Forward Sorting Locator', 'Date of Birth', 'Age' (if DOB unavailable), 'Sex', 'Pregnancy' and 'Gestation Week', 'Date Reported to Health Unit' and 'Date Investigation Initiated'

The **BACKGROUND, EXPOSURE AND CLINICAL INFORMATION** section captures various epidemiology and clinical data fields, including:

- 'Rash Onset Date'
- 'Vaccination History' including the 'Vaccine Type(s)' received, dose number, and administration dates for each
- Hospitalization



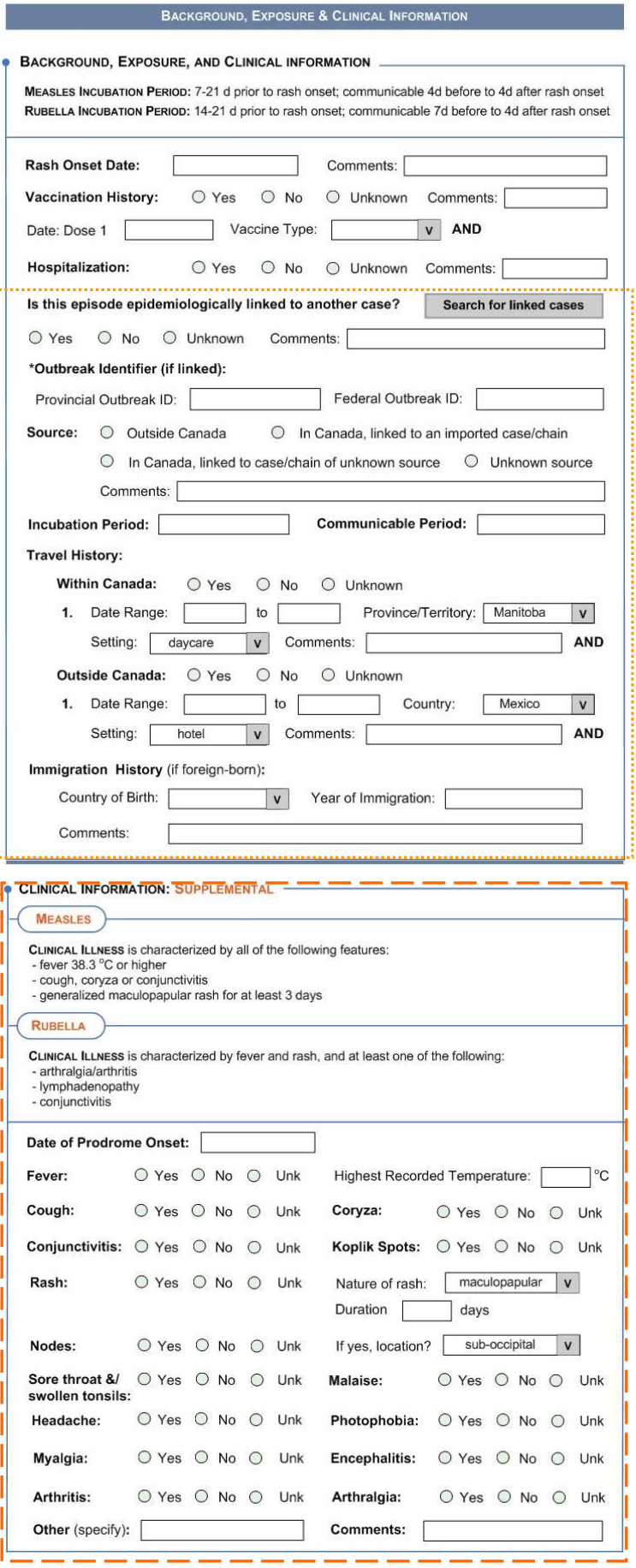
BACKGROUND, EXPOSURE AND CLINICAL INFORMATION (continued)

- Whether the episode is 'epi-linked' to another case, and the 'Outbreak Identifier'
- 'Source', identified as 'Outside Canada', 'In Canada, linked to an imported case/ chain', 'In Canada, linked to a case/chain of unknown Source' or 'Unknown source'
- 'Incubation Period' and 'Communicable Period' fields, which are automatically estimated by MARS based on the 'Rash Onset Date' provided and the known 'Incubation' and 'Communicable' periods for measles and rubella respectively
- 'Travel History', which may be specified as 'Within Canada' and/or 'Outside Canada', along with the associated travel 'Date Range(s)', 'P/T', 'Country', 'Setting(s)', and additional 'Comments'
- 'Immigration History', including 'Country of Birth', and 'Year of Immigration'

The **ADDITIONAL CLINICAL INFORMATION** section includes various clinical data fields which may be captured at the provincial level by public health, but which are not included in CMRSS national measles/rubella notification

- Current definitions for measles and rubella clinical illness are provided for reference
- Clinical data fields captured here include 'Date of Prodrome Onset', 'Fever (°C)', 'Cough', 'Coryza', 'Conjunctivitis', 'Koplik Spots', 'Rash (Nature of Rash, Duration)', 'Lymphadenopathy', 'Sore throat and/ swollen tonsils', 'Malaise, 'Headache', 'Myalgia', 'Photophobia', 'Arthritis', 'Arthralgia', 'Encephalitis', 'Other', and 'Comments'

NOTE: Suggested value sets for all data fields are described in Appendix III, e.g.: 'Sample Type' may be selected from the value set: 'serum, CSF, urine, T/NP, amniotic fluid, chorionic villi, etc.'



BACKGROUND, EXPOSURE & CLINICAL INFORMATION

BACKGROUND, EXPOSURE, AND CLINICAL INFORMATION

MEASLES INCUBATION PERIOD: 7-21 d prior to rash onset; communicable 4d before to 4d after rash onset
RUBELLA INCUBATION PERIOD: 14-21 d prior to rash onset; communicable 7d before to 4d after rash onset

Rash Onset Date: Comments:
Vaccination History: Yes No Unknown Comments:
Date: Dose 1 Vaccine Type: AND
Hospitalization: Yes No Unknown Comments:
Is this episode epidemiologically linked to another case? Search for linked cases
Yes No Unknown Comments:
*Outbreak Identifier (if linked):
Provincial Outbreak ID: Federal Outbreak ID:
Source: Outside Canada In Canada, linked to an imported case/chain
In Canada, linked to case/chain of unknown source Unknown source
Comments:
Incubation Period: Communicable Period:
Travel History:
Within Canada: Yes No Unknown
1. Date Range: to Province/Territory: Manitoba
Setting: daycare Comments: AND
Outside Canada: Yes No Unknown
1. Date Range: to Country: Mexico
Setting: hotel Comments: AND
Immigration History (if foreign-born):
Country of Birth: Year of Immigration:
Comments:

CLINICAL INFORMATION: SUPPLEMENTAL

MEASLES

CLINICAL ILLNESS is characterized by all of the following features:
- fever 38.3 °C or higher
- cough, coryza or conjunctivitis
- generalized maculopapular rash for at least 3 days

RUBELLA

CLINICAL ILLNESS is characterized by fever and rash, and at least one of the following:
- arthralgia/arthritis
- lymphadenopathy
- conjunctivitis

Date of Prodrome Onset:
Fever: Yes No Unk Highest Recorded Temperature: °C
Cough: Yes No Unk Coryza: Yes No Unk
Conjunctivitis: Yes No Unk Koplik Spots: Yes No Unk
Rash: Yes No Unk Nature of rash: maculopapular
Duration days
Nodes: Yes No Unk If yes, location? sub-occipital
Sore throat &/ swollen tonsils: Yes No Unk Malaise: Yes No Unk
Headache: Yes No Unk Photophobia: Yes No Unk
Myalgia: Yes No Unk Encephalitis: Yes No Unk
Arthritis: Yes No Unk Arthralgia: Yes No Unk
Other (specify): Comments:

The **LABORATORY INFORMATION** section captures both required CMRSS data fields, and enhanced laboratory data fields to enable estimation of various surveillance indicators

- The user may enter lab data for either a 'New Sample', or update results for a previously recorded sample, located by 'Sample ID'
- **SAMPLE INFORMATION** required includes the 'Lab Sample ID', 'Sample Type' (see Appendix III for drop-down lists), 'Sample Collection Date', and 'Lab Receipt Date'
- 'Rash Onset Date' (if provided with the lab test requisition) may be entered here with sample information, and will auto-populate the same field in 'Background'
- The user is also asked to specify whether a 'Viral Culture/Detection Sample' was provided with the initial test request

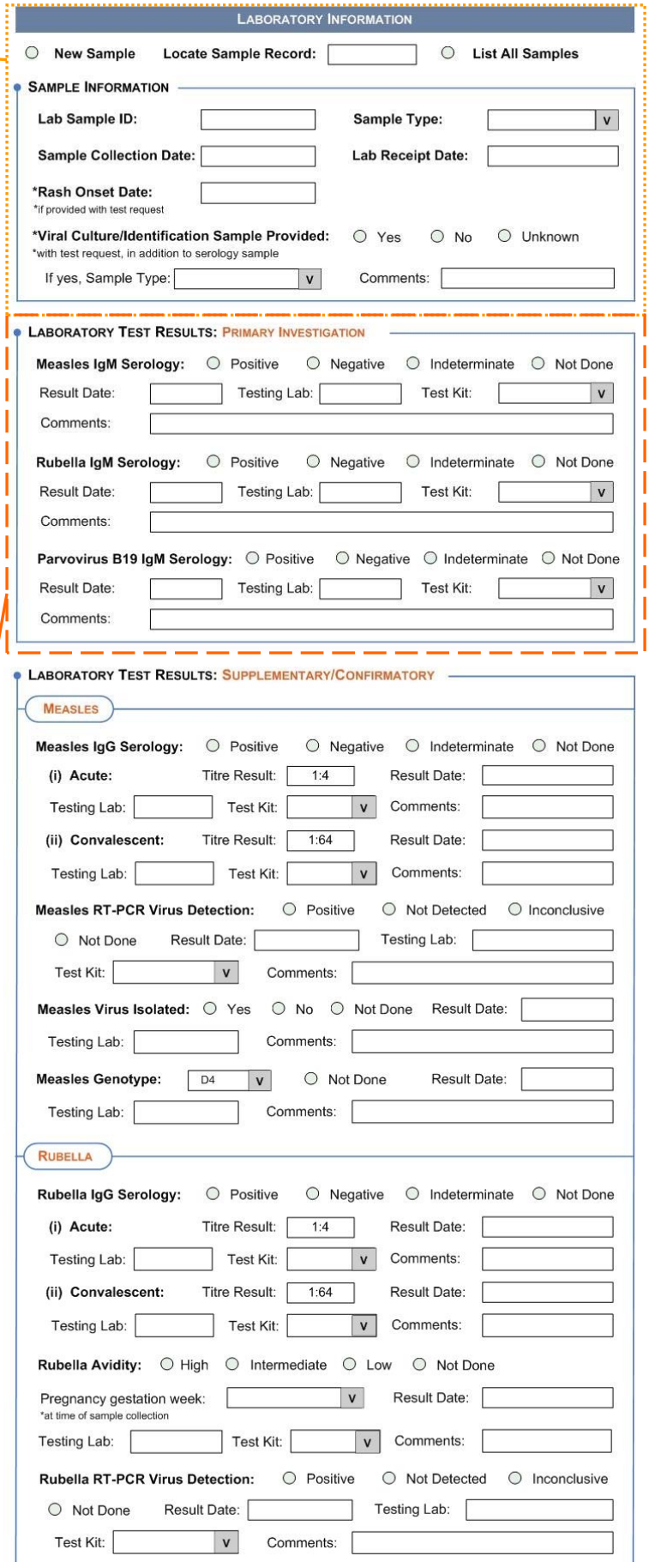
The **LABORATORY TEST RESULTS** section may be completed once the appropriate sample information has been captured

NOTE: Multiple test results may be captured for all measles/rubella lab test fields, such that each result entered in the report is linked to the sample that produced the test result

- **PRIMARY INVESTIGATION** associated lab tests include 'Measles, Rubella and Parvovirus B19 IgM Serology'; results for these tests may be specified as 'Positive', 'Negative', 'Indeterminate', or 'Not Done'; 'Result Date', 'Testing Lab', and 'Test Kit' are captured

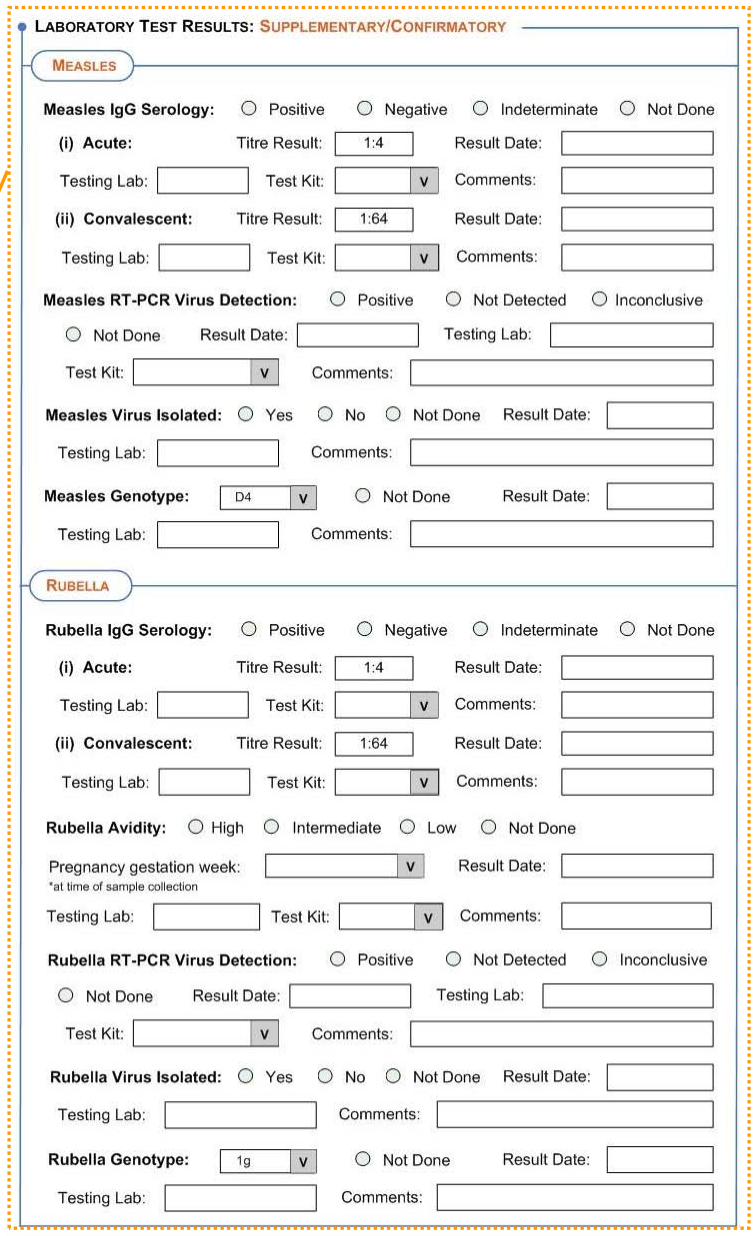
ALERTING: Entry of a measles/rubella IgM+ test result in this section will trigger:

- Real-time **alerting** of stakeholders via email to support timely communication and response regarding the investigation
- An in-system **reminder** to obtain an appropriate 'Viral Culture/ Detection' sample if not provided with test request



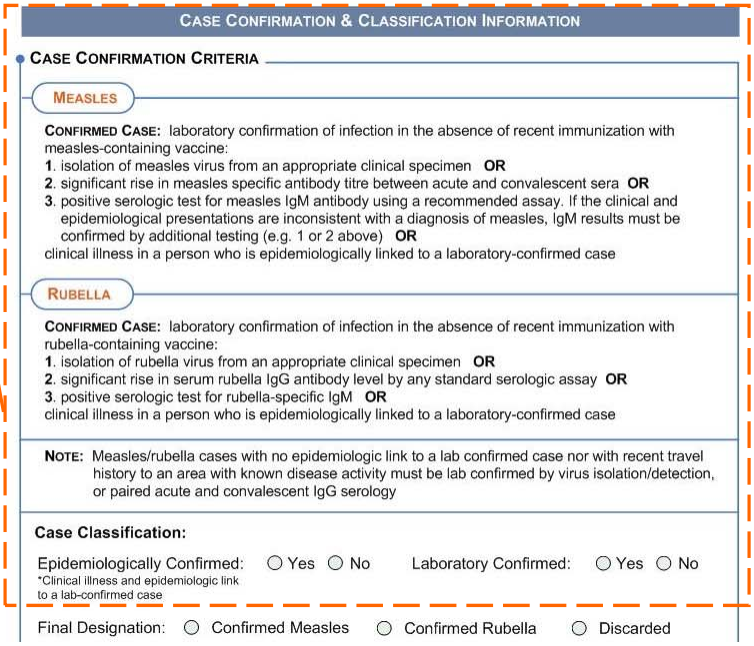
LABORATORY INFORMATION (continued)

- If an IgM+ result is generated for measles or rubella, subsequent supplementary/ confirmatory testing may be performed by the provincial laboratory or NML in the absence of an epi-link for the case
- **SUPPLEMENTARY/CONFIRMATORY** test results which may be captured for measles/ rubella include acute and convalescent paired 'IgG Serology' (including 'titre result' or 'signal' value in IU), 'RT-PCR Virus Detection', and 'Virus Isolation'
- Measles/rubella 'Genotype' data may be entered to support case characterization using molecular epidemiology methods
- To support the investigation of suspect rubella in pregnant women, 'Rubella Avidity' test results may be reported, along with 'Pregnancy gestation week' at the time of sample collection
- 'Result Date', 'Testing Lab' and 'Test Kit' data fields are associated with each test as appropriate
- Both the 'Testing Lab' and 'Test Kit' data fields will have drop-down selection menus, including an 'Other' option



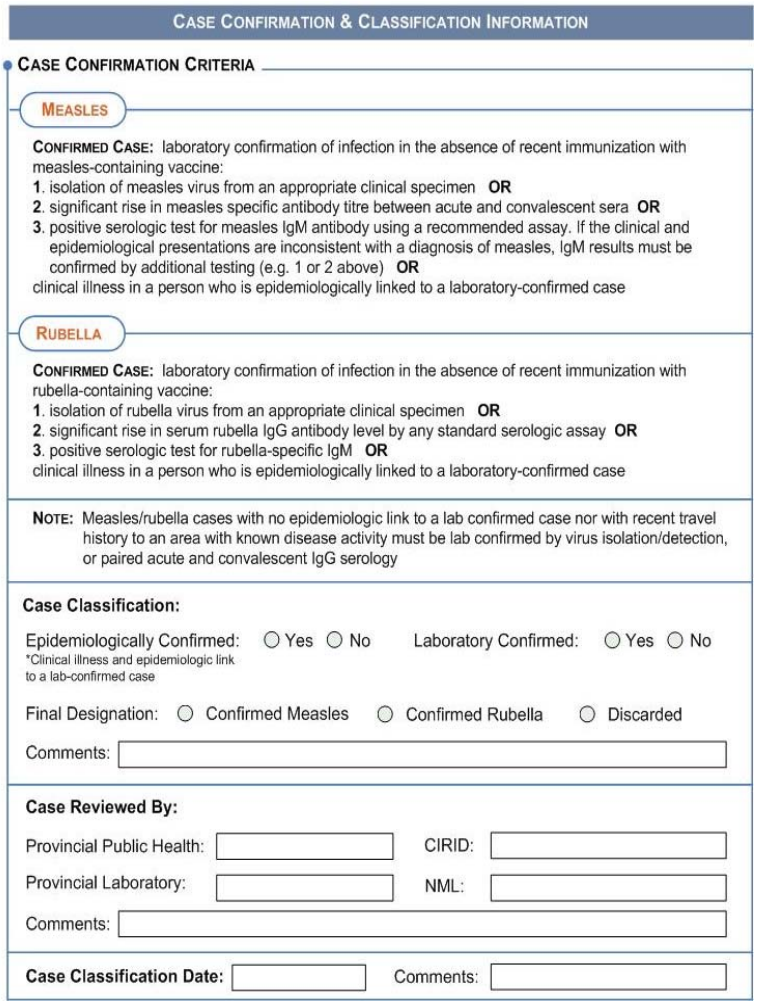
The **CASE CONFIRMATION & CLASSIFICATION** section will capture the following:

- Information regarding the current 'Case Confirmation Criteria' for measles and rubella; this information may either be incorporated into the page design of this section as a permanent reference, or made available as 'mouse-over' help text for the classification fields
- 'Case Classification' data, including whether the episode under investigation is 'Lab Confirmed' or 'Epidemiologically Confirmed' (i.e. clinical illness and epi-linked to lab-confirmed case)



CASE CONFIRMATION & CLASSIFICATION
(contd.)

- Based upon case confirmation criteria, the episode is finally designated as either 'Confirmed Measles', 'Confirmed Rubella', or 'Discarded'
- As with current national reporting via CMRSS, final responsibility for the national 'Case Classification' will rest with CIRID.
- The 'Case Reviewed By' field will capture the names of the provincial and federal lab and epidemiology stakeholders responsible for the review and classification of the episode; this may be through an 'approval' checkbox system which auto-populates the stakeholder signature based on secure login user ID
- The 'Case Classification Date' will be captured by the application once the 'Case Classification' fields have been completed, and all four reviewers have signed off on the final designation of the episode



CASE CONFIRMATION & CLASSIFICATION INFORMATION

CASE CONFIRMATION CRITERIA

MEASLES

CONFIRMED CASE: laboratory confirmation of infection in the absence of recent immunization with measles-containing vaccine:
1. isolation of measles virus from an appropriate clinical specimen **OR**
2. significant rise in measles specific antibody titre between acute and convalescent sera **OR**
3. positive serologic test for measles IgM antibody using a recommended assay. If the clinical and epidemiological presentations are inconsistent with a diagnosis of measles, IgM results must be confirmed by additional testing (e.g. 1 or 2 above) **OR**

clinical illness in a person who is epidemiologically linked to a laboratory-confirmed case

RUBELLA

CONFIRMED CASE: laboratory confirmation of infection in the absence of recent immunization with rubella-containing vaccine:
1. isolation of rubella virus from an appropriate clinical specimen **OR**
2. significant rise in serum rubella IgG antibody level by any standard serologic assay **OR**
3. positive serologic test for rubella-specific IgM **OR**

clinical illness in a person who is epidemiologically linked to a laboratory-confirmed case

NOTE: Measles/rubella cases with no epidemiologic link to a lab confirmed case nor with recent travel history to an area with known disease activity must be lab confirmed by virus isolation/detection, or paired acute and convalescent IgG serology

Case Classification:

Epidemiologically Confirmed: ○ Yes ○ No (*Clinical illness and epidemiologic link to a lab-confirmed case) Laboratory Confirmed: ○ Yes ○ No

Final Designation: ○ Confirmed Measles ○ Confirmed Rubella ○ Discarded

Comments:

Case Reviewed By:

Provincial Public Health: CIRID:

Provincial Laboratory: NML:

Comments:

Case Classification Date: Comments:

NOTE: The process of arriving at a final 'Case Classification' status involves collaboration, review and discussion between epidemiology and laboratory stakeholders at the provincial and federal level. While the intent of the MARS pilot is to support this communication by ensuring real-time access to all relevant episode data, the 'Case Reviewed By' section seeks to formally incorporate this review mechanism into the application. Finalization of each classified case is achieved when signed off by the appropriate provincial and federal public health and laboratory representatives.

REAL-TIME DATA ENTRY

CRS/CRI REPORTING

CREATING A 'CRS/CRI REPORT':

- A new 'CRS/CRI Report' may be created by either provincial public health upon investigation of a suspect CRS/CRI case, or by the laboratory when an IgM-positive rubella test result is generated
- The 'Contributing Site' is specified, and 'Congenital Rubella Syndrome/Infection' is selected as the 'Report Type'; a new report is then created, or an existing report is viewed or edited

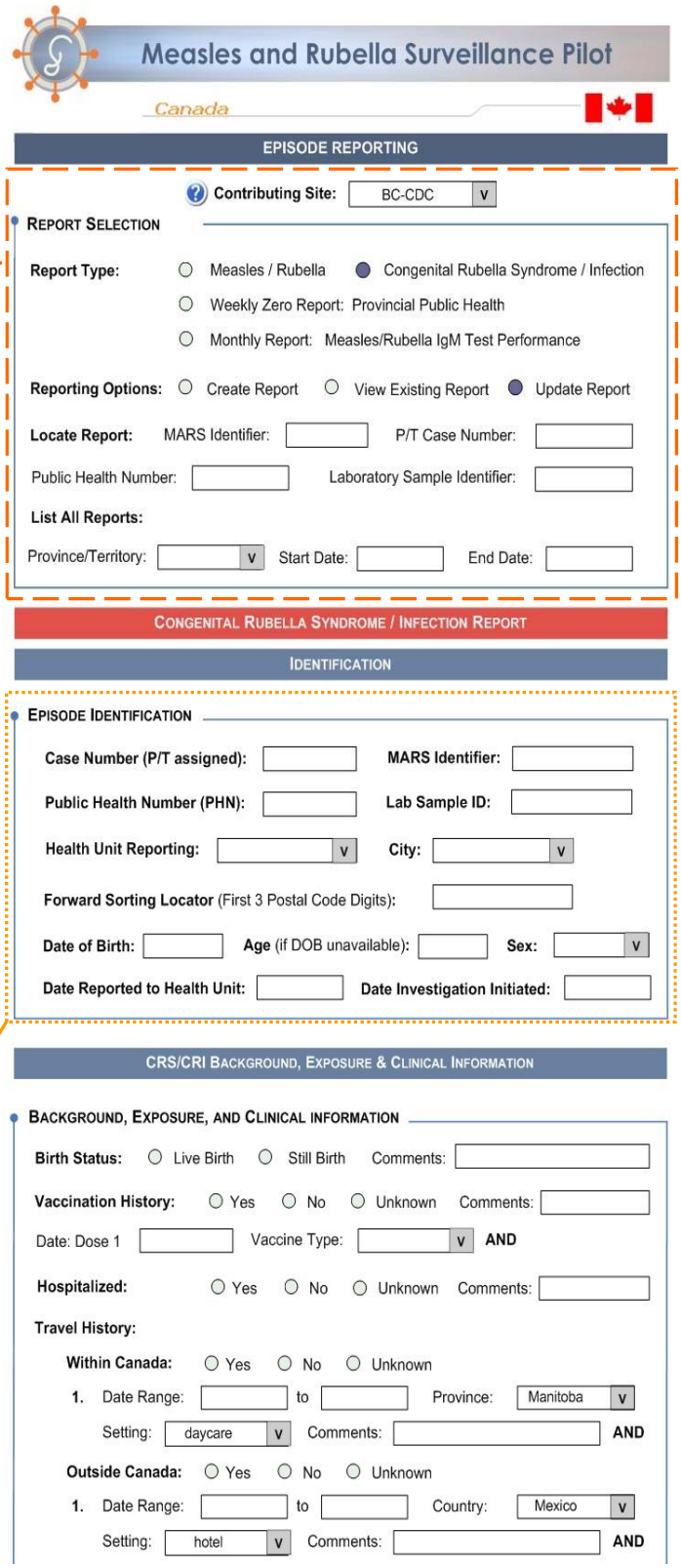
'CRS/CRI REPORT' DATA FIELDS:

NOTE: Each CRS/CRI Report will capture all data fields required by CMRSS for national reporting, plus enhanced lab data to support alerting, case classification and estimation of surveillance indicators

The **EPISODE IDENTIFICATION** section captures:

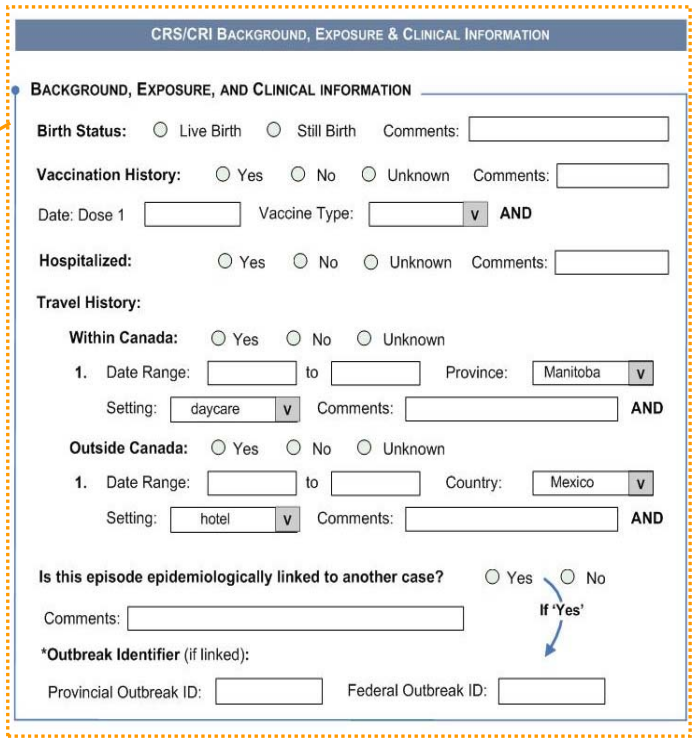
- The system-generated 'MARS Identifier', P/T assigned 'Case Number', 'Public Health Number', and 'Lab Sample ID(s)'
- Various epidemiology fields, including 'Health Unit Reporting', 'City', 'Forward Sorting Locator', 'Date of Birth', 'Age' (if DOB unavailable), 'Sex', 'Date Reported to Health Unit' and 'Date Investigation Initiated'

NOTE: For CRS/CRI episodes, data will be aggregated into charts according to 'Week of Onset' based on 'Date of Birth': DOB will be considered synonymous with 'Date of Onset'



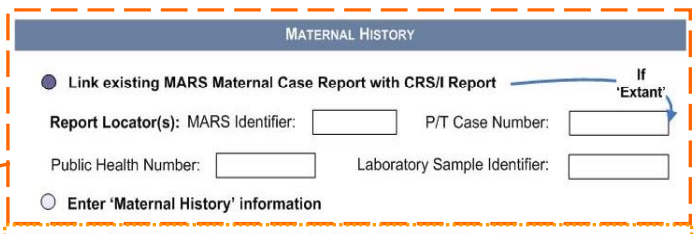
The **CRS/CRI BACKGROUND, EXPOSURE AND CLINICAL INFORMATION** section captures both epidemiology and clinical data fields, including:

- 'Birth Status' (i.e. 'Live Birth' or 'Still Birth'); this field will determine the case confirmation criteria to be used
- 'Vaccination History' including the 'Vaccine Type(s)' received, dose number, and administration dates for each
- Hospitalization information for the episode, along with related 'Comments'
- 'Travel History', which may be specified as 'Within Canada' and/or 'Outside Canada', along with the associated travel 'Date Range(s)', 'P/T', 'Country', 'Setting(s)', and additional 'Comments'
- Whether the episode is 'Epidemiologically Linked' to another case (i.e. mother); if 'Yes', the relevant 'Outbreak Identifier(s)' may be entered

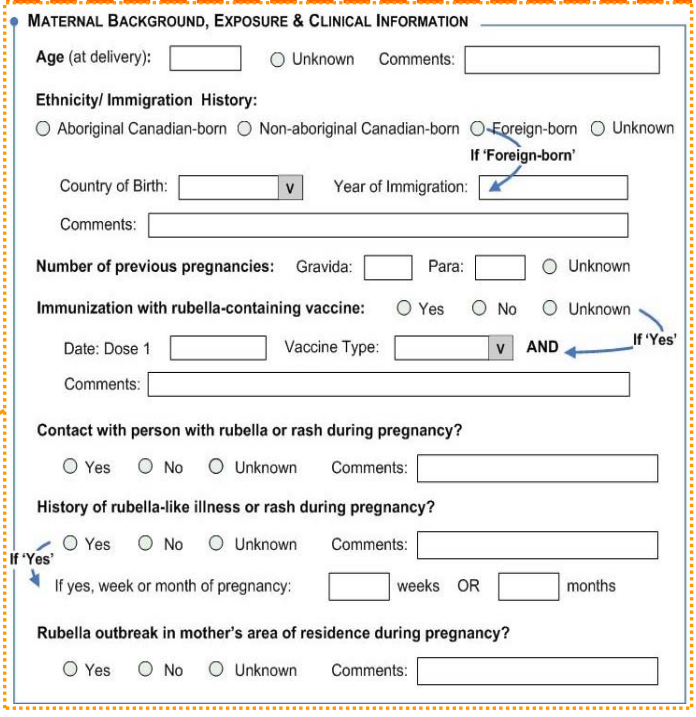


The **MATERNAL HISTORY** section captures background, exposure , clinical and laboratory information associated with the mother, and is modelled on the national CRS case report form (CIRID[15])

- If a maternal rubella case report is known to exist in MARS, the CRS/I report can be linked by entering a 'Report Locator', e.g.: MARS Identifier, PHN, etc.
- 'Enter Maternal History Information' may be selected to enter available maternal data



The **MATERNAL BACKGROUND, EXPOSURE & CLINICAL INFORMATION** section includes:



- 'Age'(at delivery)
- 'Ethnicity/Immigration History'
- 'Number of previous pregnancies'(G/P)
- 'Immunization with rubella-containing vaccine'(may capture multiple instances)
- 'Contact with person with rubella/rash during pregnancy'
- 'History of rubella-like illness or rash during pregnancy', and 'if yes, week or month of pregnancy'
- 'Rubella outbreak in mother's area of residence during pregnancy'

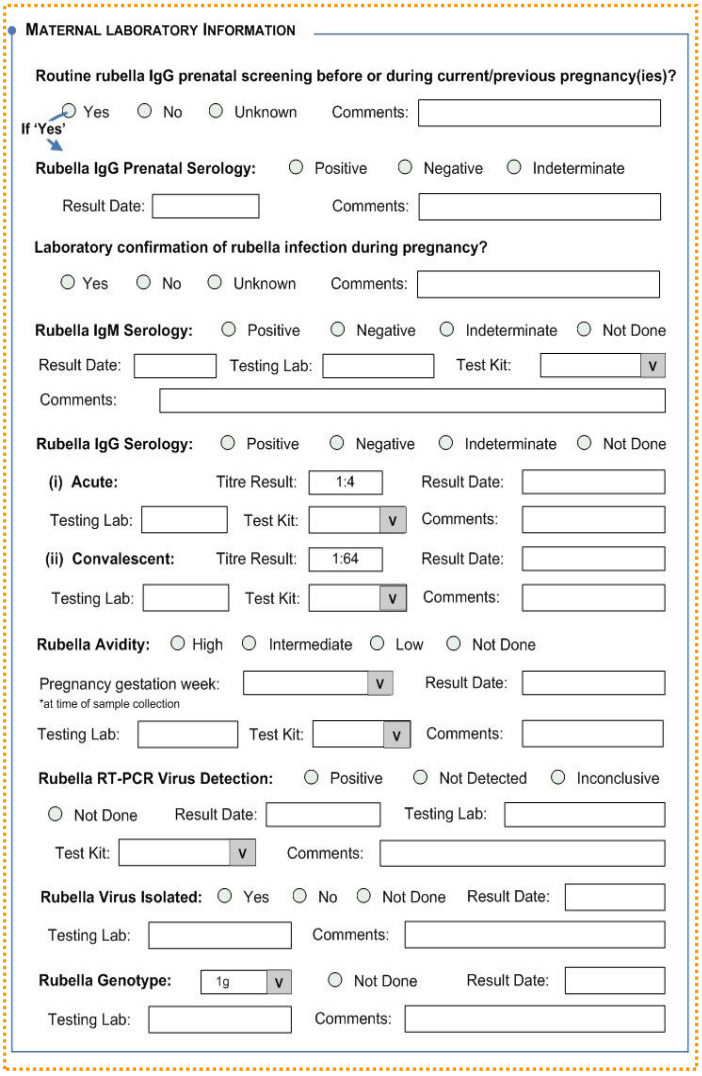
The **MATERNAL LABORATORY INFORMATION** section includes the following data fields:

- 'Routine rubella IgG prenatal screening before or during current/previous pregnancies?', and if yes; 'Rubella IgG Prenatal Serology' screening result
- 'Laboratory confirmation of rubella infection during pregnancy?': Yes, No, or Unknown

The following rubella test results may then be specified if applicable:

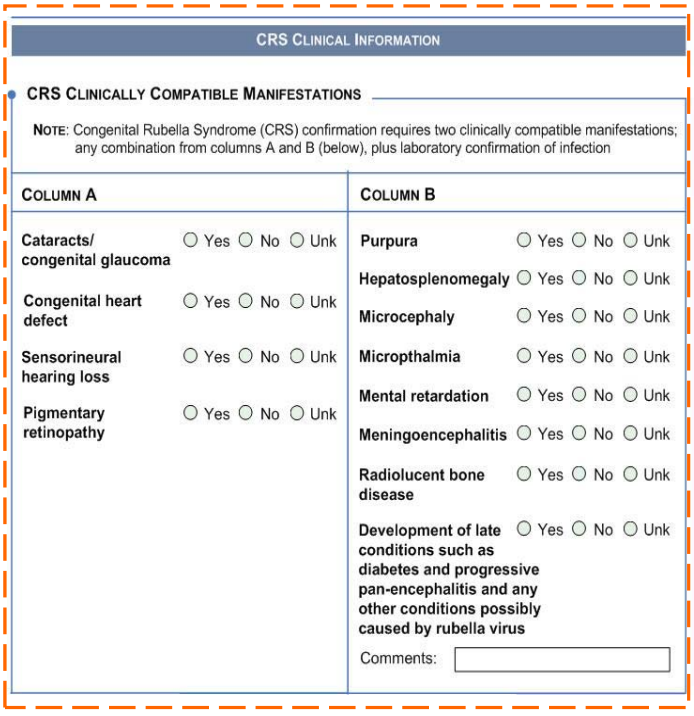
- 'Rubella IgM Serology'
- 'Rubella IgG Serology'(acute/convalescent)
- 'Rubella Avidity' at a specified 'pregnancy gestation week'
- 'Rubella RT-PCR Virus Detection'
- 'Rubella Virus Isolation'
- 'Rubella Genotype'

NOTE: Multiple test results may be captured for all rubella lab test fields



The **CRS CLINICAL INFORMATION** section captures data regarding the specific clinical manifestations used to support CRS case classification, which requires the presence of any combination of 2 clinical manifestations from Columns A and B, plus laboratory confirmation of rubella infection:

- **Column A**: 'Cataracts/congenital glaucoma', 'Congenital heart defect', 'Sensorineural hearing loss', and 'Pigmentary Retinopathy'
- **Column B**: 'Purpura', 'Hepatospleno-megaly', 'Microcephaly', 'Microopthalmia', 'Mental Retardation', 'Meningoencephalitis', 'Radiolucent bone disease', and 'Development of late conditions such as diabetes and progressive pan-encephalitis and any other conditions possibly caused by rubella virus'



The **CRS/CRI LABORATORY INFORMATION** section captures enhanced laboratory data to support case investigation/confirmation

- The user may enter lab data for a 'New Sample', or update an existing sample record, located by 'Sample ID'
- **SAMPLE INFORMATION** required includes the 'Lab Sample ID', 'Sample Type', 'Sample Collection Date', and 'Lab Receipt Date'
- The user is also asked to specify whether a 'Viral Culture/Identification Sample' was provided with the initial test request

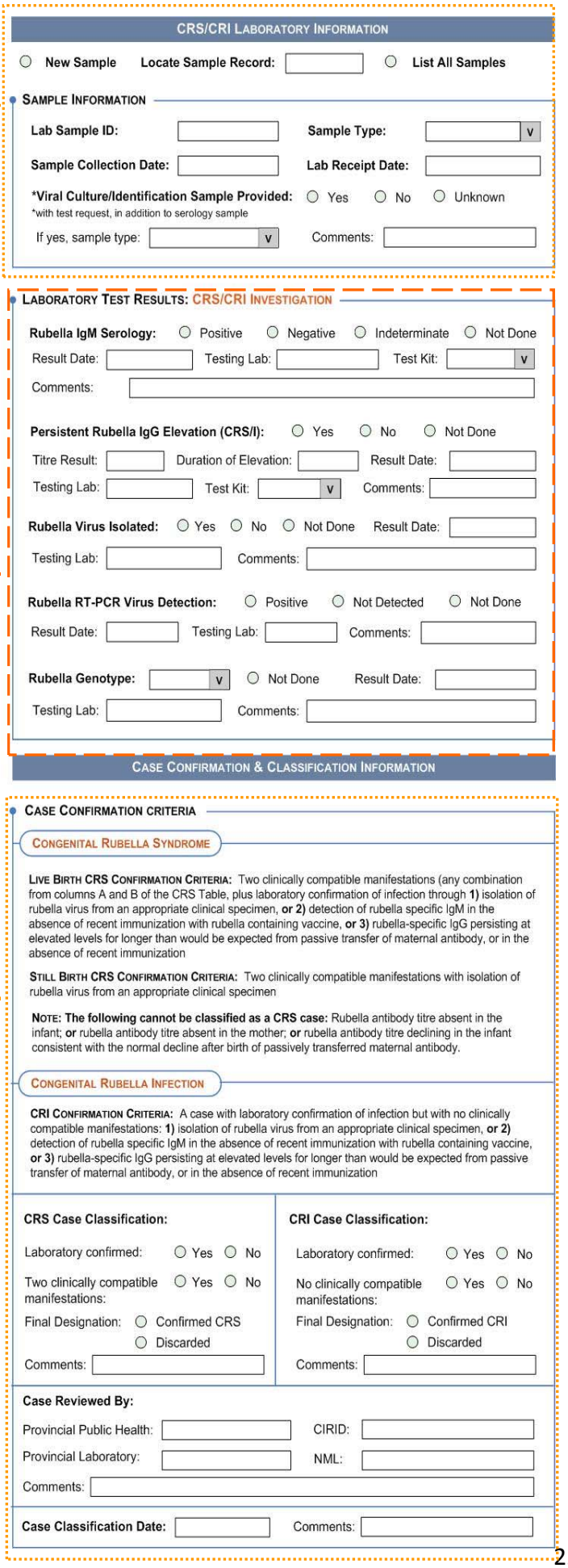
NOTE: Each CRS/CRI laboratory test result entered is linked with the sample tested

LABORATORY TEST RESULTS are specified following sample data entry; lab test fields associated with CRS/I investigation include:

- 'Rubella IgM Serology'
- 'Persistent Rubella Elevation (CRS/I)': 'Yes', 'No' or 'Not Done'; if yes, the 'Titre Result' and 'Duration of Elevation' may be specified
- 'Rubella Virus Isolated'
- 'Rubella RT-PCR Virus Detection': 'Positive', 'Not Detected', or 'Not Done'
- 'Rubella Genotype'

The **CRS/CRI CASE CONFIRMATION & CLASSIFICATION** section will capture:

- Current CRS/I 'Case Confirmation Criteria', including live and still-birth criteria for CRS
- CRS/I 'Case Classification' data, including whether the episode is 'Lab Confirmed' and has either 'Two clinically compatible manifestations' (CRS) or 'No clinically compatible manifestations' (CRI); plus 'Final Designation' of the episode as 'Confirmed CRS', 'Confirmed CRI' or 'Discarded'
- 'Case Review' approval signatures by the provincial/federal lab/epi reviewers, and the 'Case Classification Date'



PERIODIC DATA ENTRY

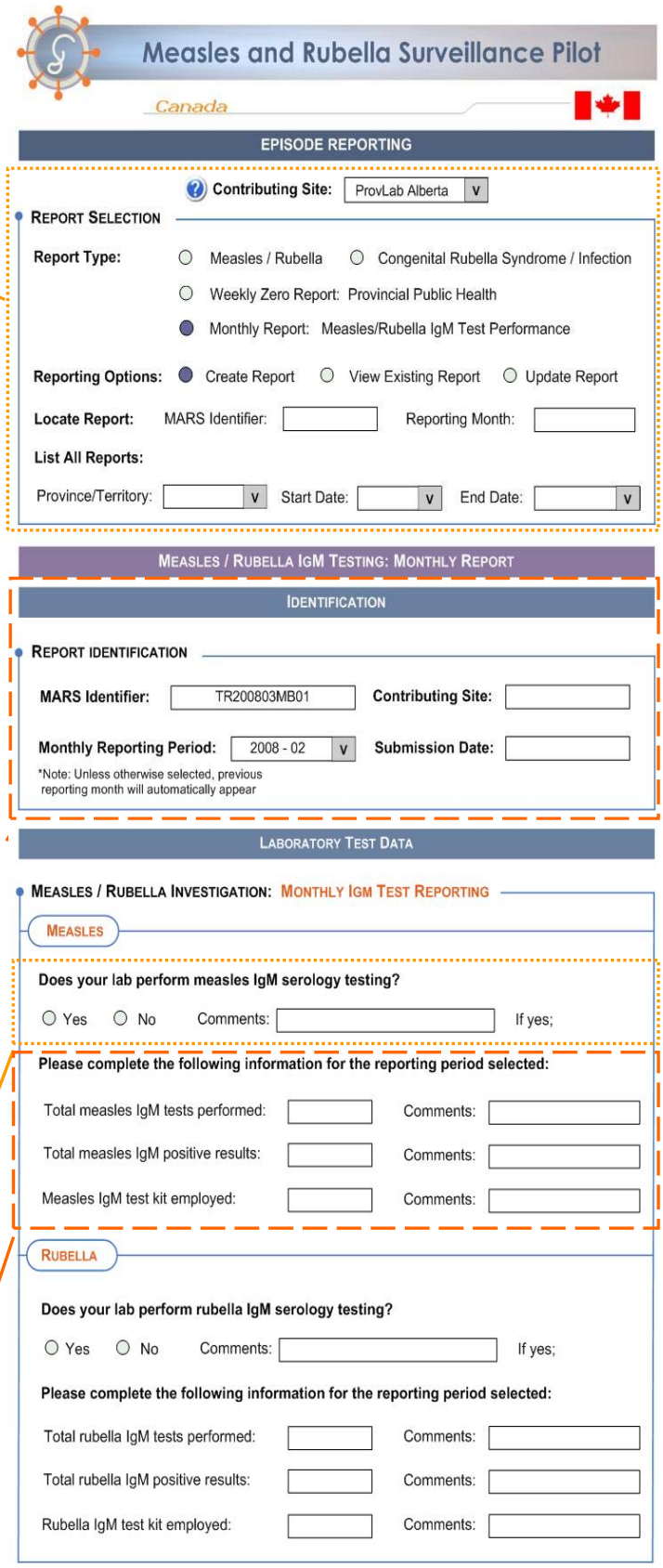
MONTHLY IGM TEST REPORTING

TO CREATE A MEASLES/RUBELLA IGM TEST PERFORMANCE MONTHLY REPORT:

- The provincial laboratory contributing data is specified, and 'Monthly Report: Measles/Rubella IgM Test Performance' is selected as the 'Report Type'
- The user may then create a new report, or view/update an existing report
- Existing reports may be located by their reporting month, unique MARS ID, or a list of existing reports may be generated

MONTHLY REPORT DATA FIELDS:

- 'Report Identification' details captured will include a system-generated unique 'MARS Identifier', the 'Contributing Site' (i.e. provincial lab), 'Monthly Reporting Period', and the report 'Submission Date'
- To report monthly IgM test data, the user selects the 'Monthly Reporting Period' for which data will be entered (note: this field will auto-populate with the previous month unless otherwise selected)
- For both the 'Measles' and 'Rubella' sections of the report, the user specifies whether their lab performs measles/ rubella IgM testing
- If the answer is 'yes' to either, the user then completes the following information for the specified reporting period: 'Total measles/rubella IgM tests performed', 'Total measles/rubella IgM+ results', and the 'Measles/rubella test kit employed'



PERIODIC DATA ENTRY

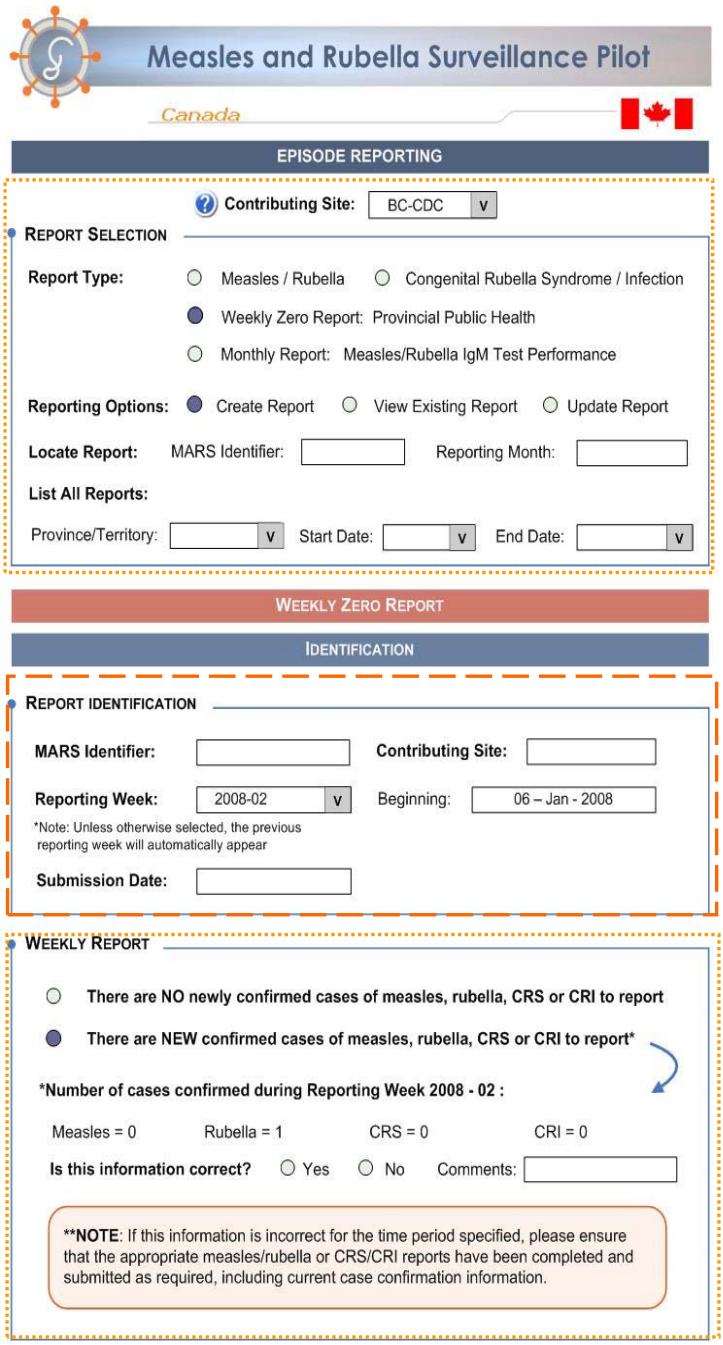
WEEKLY ZERO CASE REPORTING

TO CREATE A 'WEEKLY ZERO REPORT':

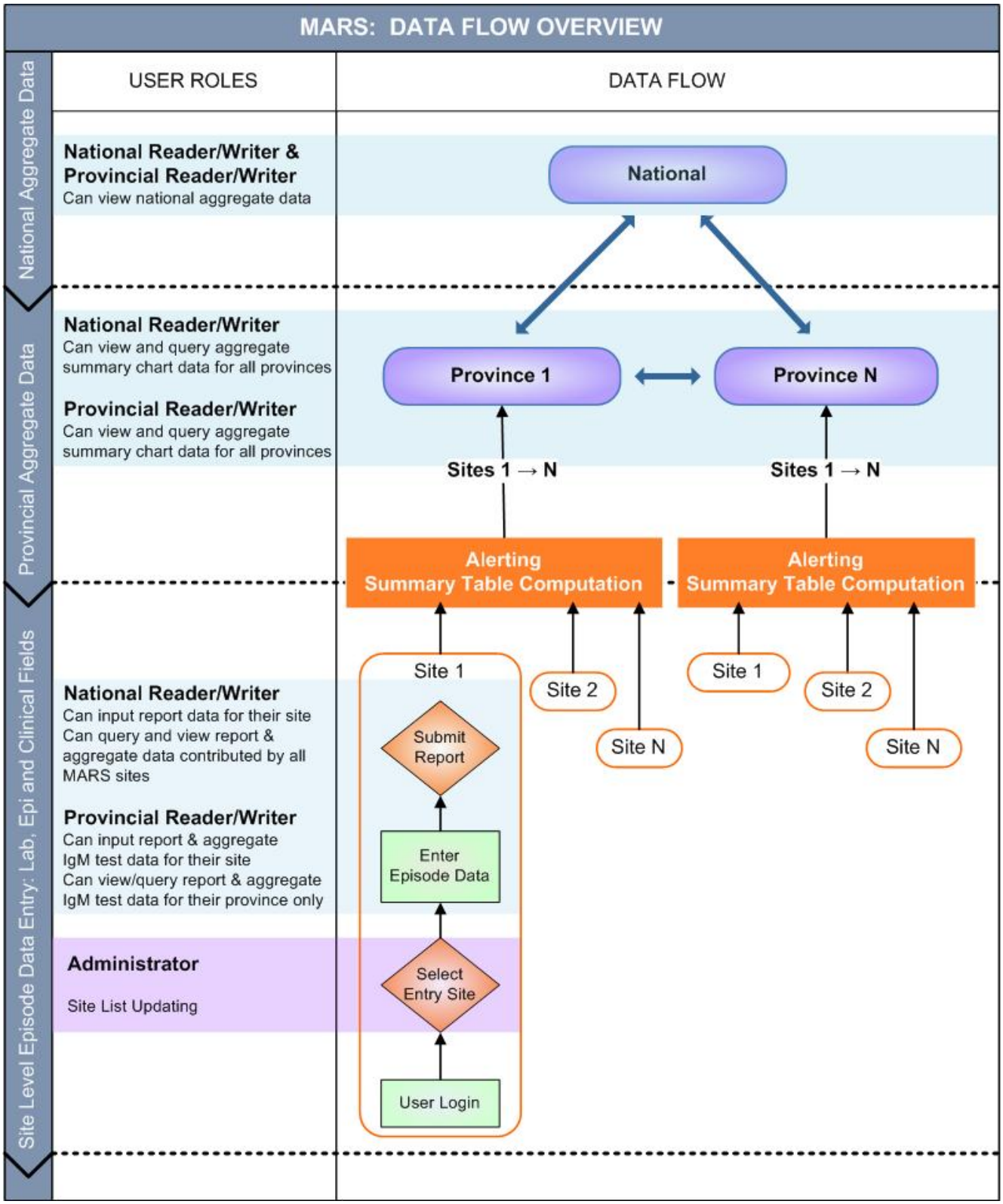
- The provincial public health 'Contributing Site' is captured, and 'Weekly Zero Report' is selected as the 'Report Type'
- The user may then create a new report, or view/update an existing report

'WEEKLY ZERO REPORT' DATA FIELDS:

- **REPORT IDENTIFICATION** details captured will include a system-generated unique 'MARS Identifier', the 'Contributing Site' (i.e. provincial public health), 'Reporting Week(Beginning)', and 'Submission Date'
- In the **WEEKLY REPORT** section, the user selects the 'Reporting Week'; this field will auto-populate with the previous reporting week unless otherwise selected, while the 'Beginning' date will auto-populate based on the 'Reporting Week'
- The user may then either specify that 'There are NO newly confirmed cases of measles, rubella, CRS or CRI to report', or that 'There are NEW confirmed cases of measles, rubella, CRS or CRI to report'
- If there are no new cases, the report is submitted as is
  - If 'no' is selected, but newly confirmed cases or unconfirmed IgM+ investigations are on file for the time period selected, MARS will flag this for review
- If the user indicates that there are new confirmed cases, the application will:
  - Provide a summary of measles, rubella, CRS and CRI cases confirmed during the reporting week specified, and will ask the user to verify this information
  - Generate a prompt, asking the user to 'ensure that the appropriate measles/rubella or CRS/CRI reports have been completed and submitted as required, including case confirmation details'



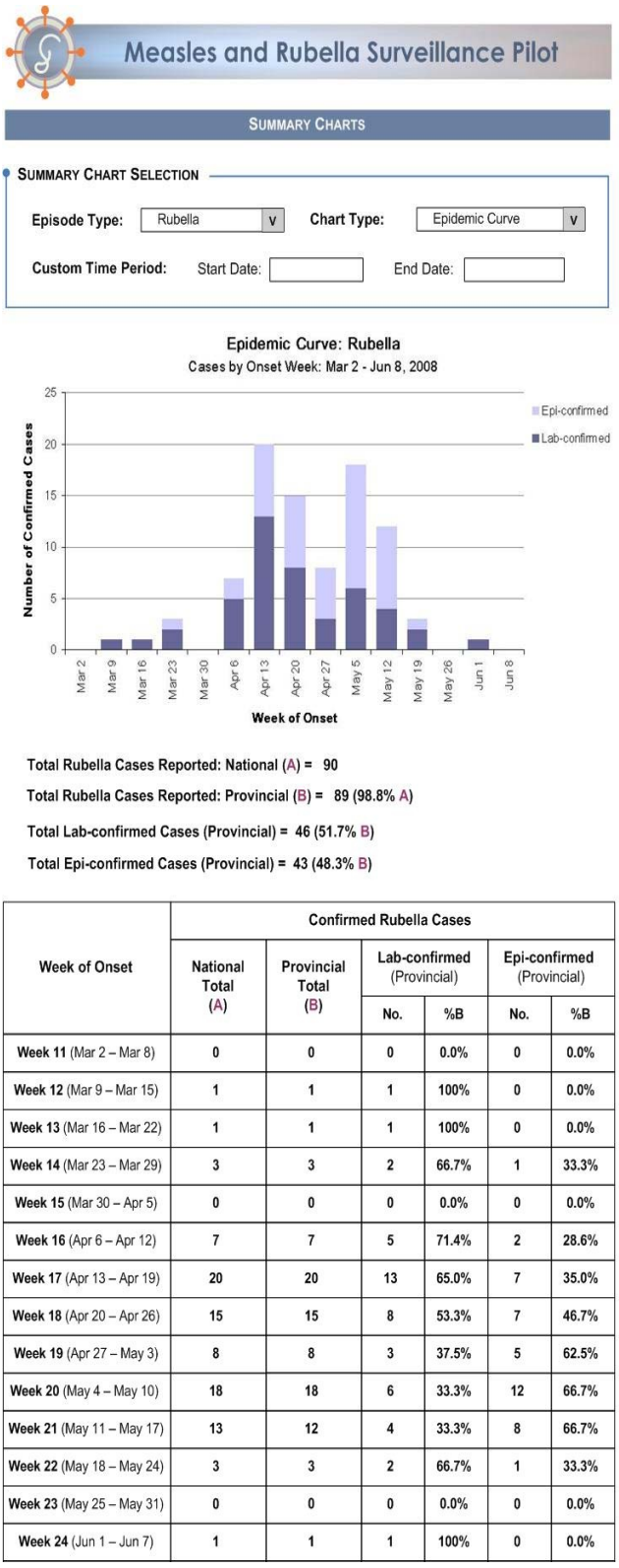
APPENDIX VI: MARS Data Flow Overview



SUMMARY CHARTS

EPIDEMIC CURVE CHART

- The 'Epidemic Curve' chart displays the total number of lab and epi-confirmed cases (e.g. rubella) reported by 'Week of Onset' (i.e. rash onset) over a selected time period; data is displayed at 1-week intervals
- The user selects either measles or rubella as the 'Episode Type' from a drop-down menu, then selects 'Epidemic Curve' as the 'Chart Type'
- The user then selects the 'Start Date' and 'End Date' of the 'Custom Time Period' for which data will be viewed
- The total number of cases (e.g.: rubella) reported over the selected time period is displayed below the 'Epidemic Curve', along with the total numbers of 'Lab and Epi-confirmed' cases; the percent values in brackets show the proportion of all reported cases that are lab/epi-confirmed, respectively
- The table displays the total number of confirmed cases reported according to 'Week of Onset' and by confirmation method (i.e.: Lab/Epi-confirmed) for each week during the specified time period
- Percentage values displayed in brackets for 'Lab and Epi-confirmed' cases indicate the proportion of reported cases confirmed by each method on a weekly basis over the time period specified



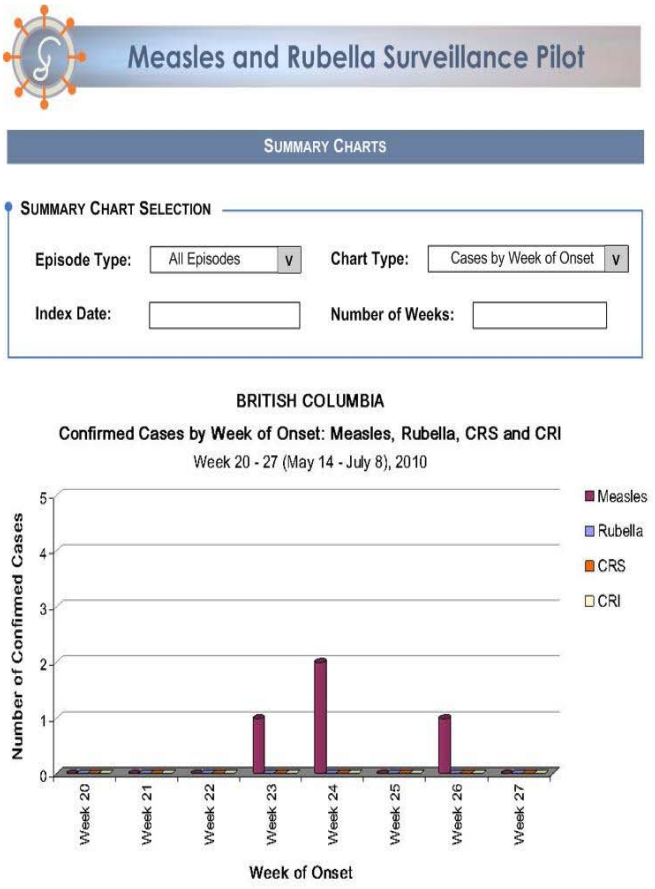
Week of Onset	Confirmed Rubella Cases					
	National Total (A)	Provincial Total (B)	Lab-confirmed (Provincial)		Epi-confirmed (Provincial)	
			No.	%B	No.	%B
Week 11 (Mar 2 – Mar 8)	0	0	0	0.0%	0	0.0%
Week 12 (Mar 9 – Mar 15)	1	1	1	100%	0	0.0%
Week 13 (Mar 16 – Mar 22)	1	1	1	100%	0	0.0%
Week 14 (Mar 23 – Mar 29)	3	3	2	66.7%	1	33.3%
Week 15 (Mar 30 – Apr 5)	0	0	0	0.0%	0	0.0%
Week 16 (Apr 6 – Apr 12)	7	7	5	71.4%	2	28.6%
Week 17 (Apr 13 – Apr 19)	20	20	13	65.0%	7	35.0%
Week 18 (Apr 20 – Apr 26)	15	15	8	53.3%	7	46.7%
Week 19 (Apr 27 – May 3)	8	8	3	37.5%	5	62.5%
Week 20 (May 4 – May 10)	18	18	6	33.3%	12	66.7%
Week 21 (May 11 – May 17)	13	12	4	33.3%	8	66.7%
Week 22 (May 18 – May 24)	3	3	2	66.7%	1	33.3%
Week 23 (May 25 – May 31)	0	0	0	0.0%	0	0.0%
Week 24 (Jun 1 – Jun 7)	1	1	1	100%	0	0.0%

NOTE: For all types of 'Summary Charts' discussed, data may be displayed at either the **provincial** or **national level** provided the user possesses the appropriate 'User Role'

SUMMARY CHARTS

CASES BY WEEK OF ONSET

- The 'Cases by Week of Onset' summary chart displays for a given 'Episode Type' the total number of 'Confirmed Cases' reported during the selected time period; data is displayed at 1-week time intervals
- The 'Episode Type' is selected (i.e. Measles, Rubella, CRS, CRI, or All Episodes), then 'Cases by Week of Onset' is chosen as the 'Chart Type'
- The time period for which data will be displayed is specified by selecting an 'Index Date', followed by the 'Number of Weeks' of data to be viewed (up to 52 weeks maximum)
- The 'Confirmed Cases by Week of Onset' chart will display in bar graph format the number of confirmed cases reported at either the provincial or national level (as selected by the user)
- Totals for the number of 'Confirmed Cases' reported over the selected time period are displayed below the bar graph; if the provincial chart is chosen, both national and provincial totals will be displayed for each case type for comparison purposes
- The table provides the total number of 'Confirmed Cases' by 'Week of Onset' for the time period specified. If provincial data is viewed, the number of 'Confirmed Cases' reported nationally will be displayed along with provincial values, If national data is viewed, only nationally aggregated case data will be displayed.



Total Confirmed Cases:

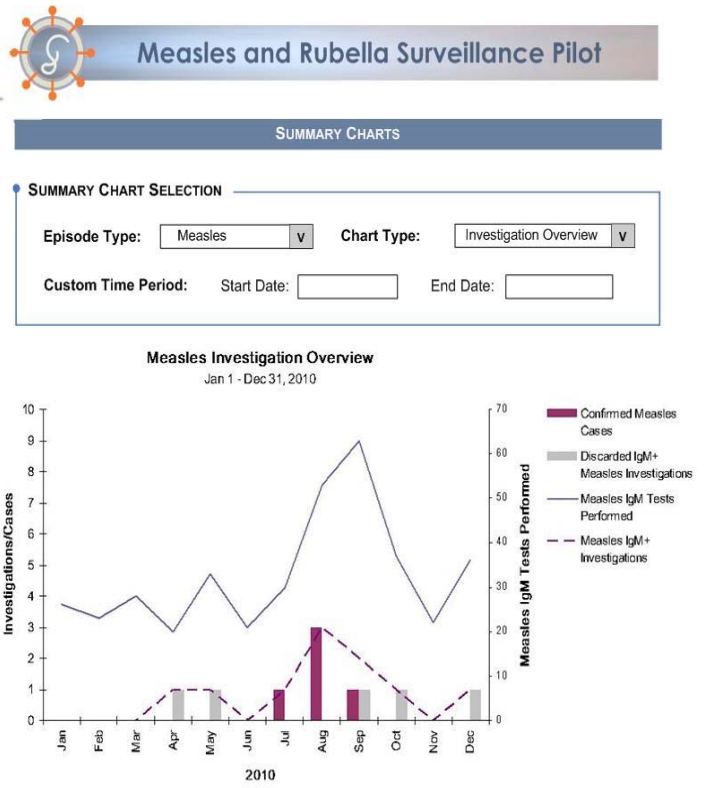
Measles: Provincial = 4, National = 4 **CRS:** Provincial = 0, National = 0

Rubella: Provincial = 0, National = 0 **CRI:** Provincial = 0, National = 0

Week of Onset	Confirmed Cases							
	Measles		Rubella		CRS		CRI	
	Prov.	Nat.	Prov.	Nat.	Prov.	Nat.	Prov.	Nat.
Week 20 (May 14 – May 20)	0	1	0	0	0	0	0	0
Week 21 (May 21 – May 27)	0	0	0	0	0	0	0	0
Week 22 (May 28 – Jun 3)	0	0	0	0	0	0	0	0
Week 23 (Jun 4 – Jun 10)	1	1	0	0	0	0	0	0
Week 24 (Jun 11 – Jun 17)	2	2	0	0	0	0	0	0
Week 25 (Jun 18 – Jun 24)	0	0	0	0	0	0	0	0
Week 26 (Jun 25 – Jul 1)	1	1	0	0	0	0	0	0
Week 27 (Jul 2 – Jul 8)	0	0	0	0	0	0	0	0

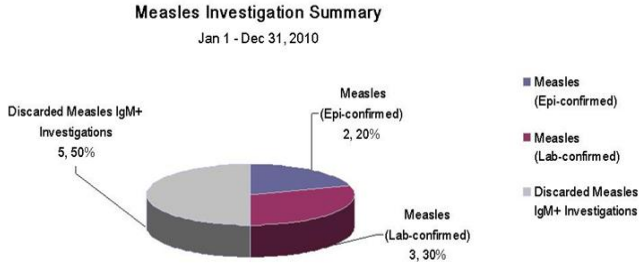
INVESTIGATION OVERVIEW CHART

- The 'Investigation Overview' chart displays for the either measles/rubella the number of 'Confirmed Cases', 'Discarded IgM+ Investigations', 'IgM+ Investigations' and 'IgM Tests Performed' over a selected time period, with data displayed at 1-month intervals
- The 'Episode Type' is selected (i.e. measles or rubella), then 'Investigation Overview' is chosen as the 'Chart Type'
- The 'Custom Time Period' is specified
- Totals for the number of 'IgM Tests Performed', 'IgM+ Investigations', 'Confirmed Cases' and 'Discarded IgM+ Investigations' reported over the specified time period are displayed below the graph
- A 'Case Classification Summary' pie chart is also displayed in this view to summarize the final designation of episodes investigated over the time period selected (i.e. 'Epi-Confirmed', 'Lab-Confirmed', or 'Discarded'); values are expressed as totals, and as a percent of all 'Classified' episodes
- The table summarizes the data displayed in the 'Investigation Overview' and 'Case Classification Summary', including totals for the overall time period and for each 1-month interval
- In the table, letter values (A, B, C) signify data types used as denominator values to calculate proportions (%A, %B, %C) for specific data categories, i.e.:



Total Measles IgM Tests Performed (A): 392 Total Discarded Measles IgM+ Investigations: 5 (50% B)

Total Measles IgM+ Investigations (B): 10 (2.6% A) Total Confirmed Measles Cases (C): 5 (50% B)

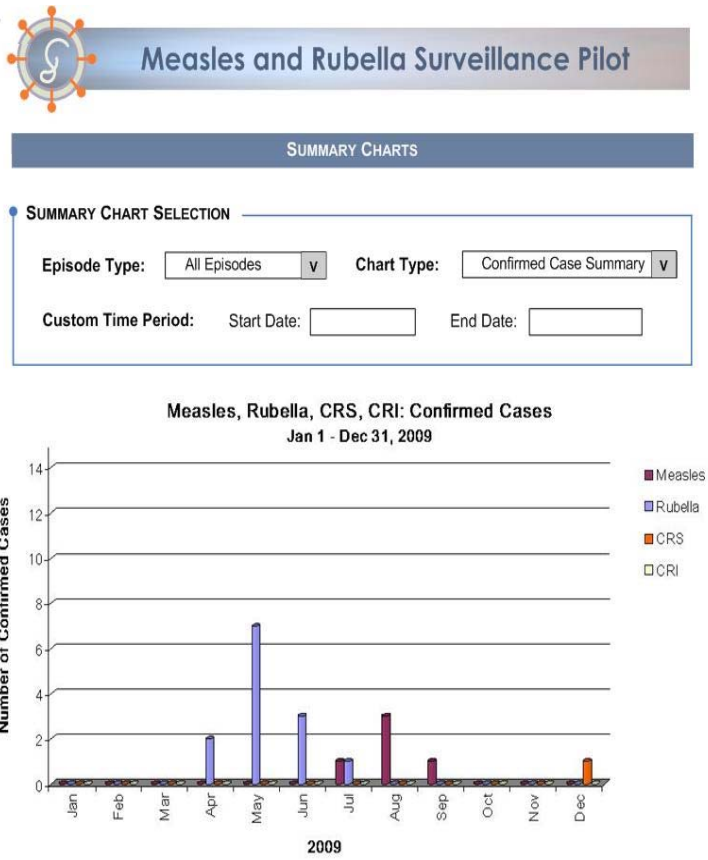


	Measles IgM Tests Performed (A)	Measles IgM+ Investigations		Discarded Measles IgM+ Investigations		Confirmed Measles Cases					
						Total		Lab-confirmed		Epi-confirmed	
		No. (B)	% A	No.	% B	No. (C)	% B	No.	% C	No.	% C
Totals	392	10	2.6%	5	50.0%	5	50.0%	3	60.0%	2	40.0%
Jan	26	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Feb	23	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Mar	28	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Apr	20	1	3.6%	1	100%	0	0.0%	0	0.0%	0	0.0%
May	33	1	3.0%	1	100%	0	0.0%	0	0.0%	0	0.0%
Jun	21	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Jul	30	1	3.3%	0	0.0%	1	100%	1	100%	0	0.0%
Aug	53	3	5.7%	0	0.0%	3	100%	1	33.3%	2	67.7%

- 'IgM+ Investigations' expressed as a proportion of all 'IgM Tests Performed (A)'
- 'Discarded IgM+ Investigations' expressed as a proportion of all 'IgM+ Investigations (B)'
- 'Total Confirmed Cases' expressed as a proportion of all 'IgM+ Investigations (B)'
- 'Epi and Lab-confirmed Cases' expressed as a proportion of all 'Confirmed Cases (C)'

CONFIRMED CASE SUMMARY CHART

- The 'Confirmed Case Summary' chart displays for 'All Episodes' (i.e. measles, rubella, CRS and CRI) the number of of 'Confirmed Cases' reported over a selected time period according to onset; data is displayed at 1-month intervals
- 'All Episodes' is selected as the 'Episode Type', then 'Confirmed Case Summary' is chosen as the 'Chart Type'
- The 'Custom Time Period' is specified
- Totals for the number of 'Confirmed Measles, Rubella, CRS and CRI Cases' reported over the selected time period are displayed below the bar graph
- The table provides the total number of 'Confirmed Cases' reported over the time period selected, and for each 1-month interval during that time period; totals are also provided for the number of 'Lab and Epi-confirmed' measles and rubella cases
- In the table, letter values (M,R) signify the data types used as denominator values to calculate proportions (%M, %R) for specific data categories, i.e.:
  - 'Epi/Lab-confirmed Measles' expressed as a proportion of all 'Confirmed Measles Cases (M)'
  - 'Epi/Lab Confirmed Rubella' expressed as a proportion of all 'Confirmed Rubella Cases (R)'



Total Confirmed Measles: 5

Total Confirmed Rubella: 13

Total Confirmed CRS: 1

Total Confirmed CRI: 0

Episode Type	Confirmed Measles					Confirmed Rubella					CRS	CRI
	Total (M)	Epi-confirmed		Lab-confirmed		Total (R)	Epi-confirmed		Lab-confirmed		Confirmed	Confirmed
		No.	%M	No.	%M		No.	%R	No.	%R	No.	No.
Totals	5	3	60.0%	2	40.0%	13	9	69.2%	4	30.8%	1	0
Jan	0	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0
Feb	0	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0
Mar	0	0	0.0%	0	0.0%	0	0	0.0%	0	0.0%	0	0
Apr	0	0	0.0%	0	0.0%	2	0	0.0%	2	100%	0	0
May	0	0	0.0%	0	0.0%	7	5	71.4%	2	28.6%	0	0
Jun	0	0	0.0%	0	0.0%	3	3	100%	0	0.0%	0	0
Jul	1	0	0.0%	1	20.0%	1	1	100%	0	0.0%	0	0

AGE DISTRIBUTION CHART

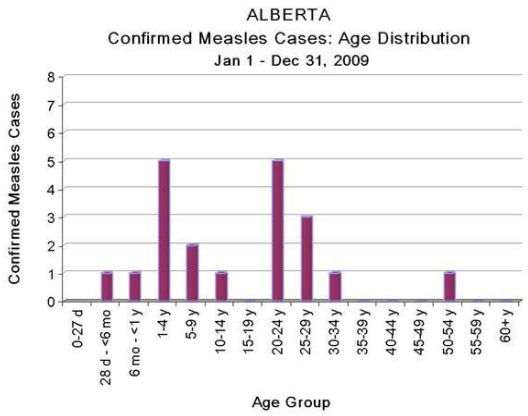
- The ‘Age Distribution’ chart displays the total number of confirmed cases reported for a specified time period by age range
- The ‘Episode Type’ is chosen (i.e. measles, rubella, CRS, or CRI), then ‘Age Distribution’ is selected as the ‘Chart Type’
- The ‘Custom Time Period’ is specified
- The total number of confirmed cases reported over the selected time period is displayed
- The table displays the number of ‘Confirmed Cases’ reported according to ‘Age Range’ for the ‘Custom Time Period’; percentage values indicate the proportion of all cases reported for each age range

SUMMARY CHARTS

SUMMARY CHART SELECTION

Episode Type: Measles | Chart Type: Age Distribution

Custom Time Period: Start Date: | End Date:



Total Confirmed Measles Cases: Provincial = 20, National = 22

Age Range	Confirmed Measles Cases	
	Number	% Total Provincial Cases
0 – 27 d	0	0.0%
28 d - < 6 mo	1	5.0%

IMMUNIZATION STATUS CHART

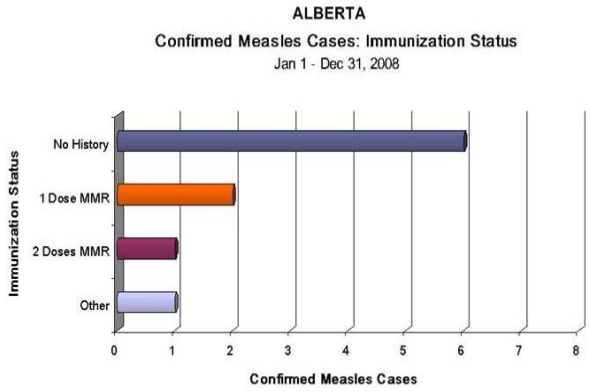
- The ‘Immunization Status’ chart displays the total number of confirmed cases reported for a specific time period according to immunization status
- The ‘Episode Type’ is chosen (i.e. measles, rubella, CRS, or CRI), then ‘Immunization Status’ is selected as the ‘Chart Type’
- The ‘Custom Time Period’ is specified
- Total confirmed cases reported for the selected time period are displayed
- The table displays the number of ‘Confirmed Cases’ reported according to ‘Immunization Status’ for the time period selected; percentages indicate the proportion of all cases with that status (i.e. ‘No History’, ’1 Dose MMR’, etc.)

SUMMARY CHARTS

SUMMARY CHART SELECTION

Episode Type: Measles | Chart Type: Immunization Status

Custom Time Period: Start Date: | End Date:

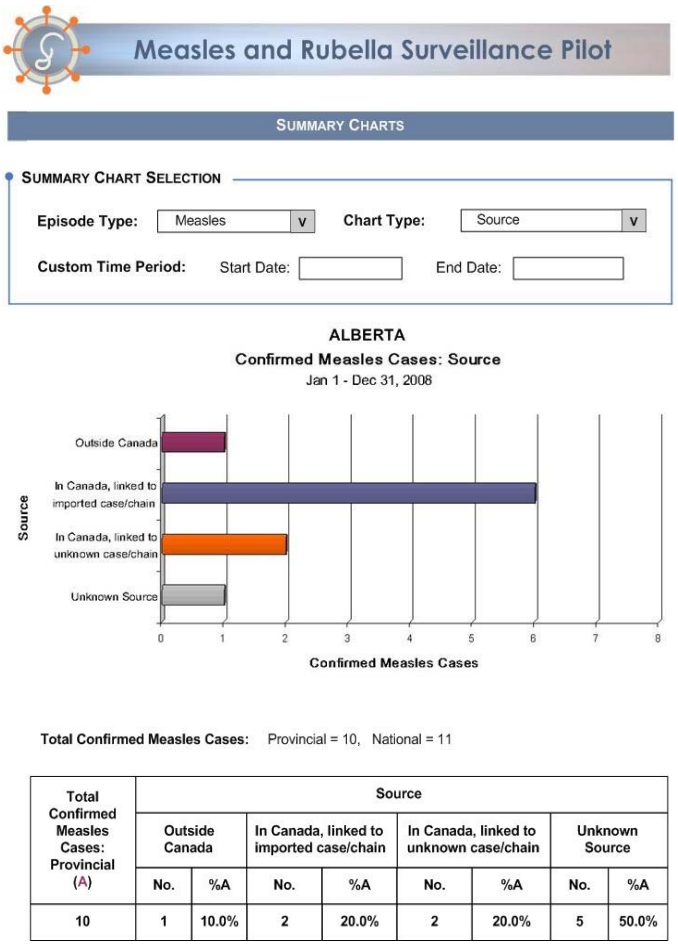


Total Confirmed Measles Cases: Provincial = 10, National = 11

Total Confirmed Measles Cases: Provincial (A)	Immunization Status							
	No History		1 Dose MMR		2 Doses MMR		Other	
	No.	%A	No.	%A	No.	%A	No.	%A
10	6	60.0%	2	20.0%	1	10.0%	1	10.0%

SOURCE CHART

- The 'Source Chart' displays the total number of confirmed cases (e.g. measles) occurring over a specified time period according to the 'Source' of infection, i.e.: 'Outside Canada', 'In Canada, linked to an imported case/chain', 'In Canada, linked to an unknown case/chain', or 'Unknown Source'
- The user selects the 'Episode Type' from a drop-down menu (i.e. measles, rubella), then selects 'Source' as the 'Chart Type'
- The user then selects the 'Start' and 'End' dates of the 'Custom Time Period' for which data will be viewed
- The total number of confirmed cases (e.g. measles) reported over the selected time period is displayed below the graph



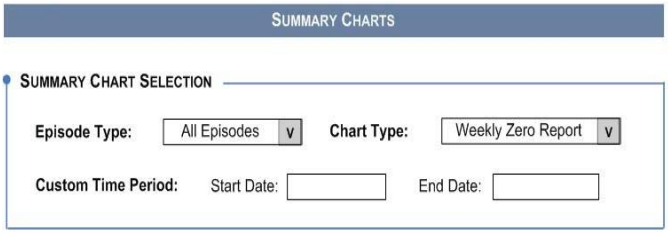
Total Confirmed Measles Cases: Provincial = 10, National = 11

Total Confirmed Measles Cases: Provincial (A)	Source							
	Outside Canada		In Canada, linked to imported case/chain		In Canada, linked to unknown case/chain		Unknown Source	
	No.	%A	No.	%A	No.	%A	No.	%A
10	1	10.0%	2	20.0%	2	20.0%	5	50.0%

- The table below the graph displays the number of 'Confirmed Cases' reported by 'Source' for the 'Custom Time Period' selected; percentage values (in brackets) provide the proportion of confirmed cases attributable to each 'Source' of infection for the time period specified

WEEKLY ZERO REPORT CHART

- The 'Weekly Zero Report' chart displays a summary of weekly national notification activity for all P/Ts, including both zero reports and confirmed cases
- The user selects 'All Episodes' as the 'Episode Type', and 'Weekly Zero Report' as the 'Chart Type', then specifies the 'Custom Time Period' to be viewed
- P/T Reporting results are shown for each jurisdiction by epidemiologic week
- Results are calculated for 'Total Reports', 'Total Missing Reports', 'Average # Weekly Reports', '% P/Ts Reporting Weekly', and 'Minimum / Maximum Weekly Reports'



Epidemiologic Week		Confirmed Cases			P/T Reporting (including zero reporting)												# P/Ts Reporting
Week of Onset	Beginning	Measles	Rubella	CRS/CRI	BC	AB	SK	MB	ON	QC	NS	NB	NL	PE	YT	NT	NU	
2008-01	30-Dec-07				1	0	1	1	0	1	1	1	1	1	0	1	1	10
2008-02	06-Jan-08				1	0	1	1	0	1	1	1	1	1	1	1	0	10
2008-03	13-Jan-08				1	1	1	1	0	1	1	1	1	1	1	1	1	12
2008-04	20-Jan-08				1	1	1	1	0	1	1	1	1	0	1	1	1	11
2008-05	27-Jan-08				1	1	1	0	0	1	1	1	1	1	1	1	0	10
2008-06	03-Feb-08				1	1	1	1	0	1	1	1	1	1	1	1	1	12
2008-07	10-Feb-08				1	1	1	1	0	1	1	1	1	1	0	0	1	10
2008-08	17-Feb-08				1	1	1	0	0	1	1	1	0	0	0	1	1	8
2008-09	24-Feb-08				1	1	1	1	0	1	1	1	1	0	0	1	1	10
2008-10	02-Mar-08				1	0	1	1	0	1	1	1	1	1	0	1	1	10
2008-11	09-Mar-08	1			0	1	1	1	1	1	1	1	1	1	1	1	1	12
2008-12	16-Mar-08				1	1	1	1	1	1	1	1	1	1	1	1	1	13
2008-13	23-Mar-08	3			1	1	1	1	1	1	1	1	1	1	1	0	1	12
2008-14	30-Mar-08	6			1	0	1	1	1	1	1	1	1	0	1	1	1	11
Total Reports		51	0	0	13	10	14	12	4	14	14	14	13	9	9	13	12	
Total Missing Reports					1	4	0	2	10	0	0	0	1	5	5	1	2	

Average # Weekly Reports =	11
% P/Ts Reporting Weekly =	86.50%
Minimum Weekly Reports =	8
Maximum Weekly Reports =	13

APPENDIX VIII: Mars Pilot Application: Monthly Test Report Data Fields v4.4 (DRAFT)

MEASLES / RUBELLA IGM TESTING: MONTHLY REPORT				
REPORT IDENTIFICATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
MARS Identifier	TR/YYYY/MM/PT/##, where: TR = 'test report' YYYY = current year MM = report month PT = 2 letter P/T code (e.g.BC, AB, SK, etc.) ## = report no. 01-99	Periodic, monthly (MARS auto-generates when new record is created)	PHAC/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Contributing Site	Contributing Site (auto-populates based upon user ID)	Periodic, monthly (MARS auto-generates when new record is created)	CIRID, NML, P/T Public Health, P/T Lab /MARS	CIRID, NML, P/T Public Health, P/T Lab
Submission Date	YYYY/MM/DD	Periodic, monthly (MARS auto-generates when new record is created)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab
Monthly Reporting Period	YYYY/MM (auto-populates with previous month unless otherwise selected)	Periodic, monthly (P/T Lab)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab

LABORATORY TEST DATA				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Does your lab perform measles IgM serology testing?	Yes, No	Periodic, monthly (P/T Lab)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab
If yes:				
Total measles IgM tests performed	numeric			
Comments	free text			
Total measles IgM+ results	numeric			
Comments	free text			
Measles IgM test kit employed	drop-down(dd)list, incl. 'Unknown', 'Other'			
Comments	free text			
Does your lab perform rubella IgM serology testing?	Yes, No	Periodic, monthly (P/T Lab)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab
If yes:				
Total rubella IgM tests performed	numeric			
Comments	free text			

Total rubella IgM+ results	numeric
Comments	free text
Rubella IgM test kit employed	drop-down(dd)list, incl. 'Unknown', 'Other'
Comments	free text

APPENDIX IX: MARS Pilot Application: Weekly Zero Report Data Fields (DRAFT)

WEEKLY ZERO REPORT				
REPORT IDENTIFICATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
MARS Identifier	WR/YYYY/MM/PT/##, where: WR = 'Weekly Report' YYYY = current year WW = report week (i.e. :01-52) PT = 2 letter P/T code ## = report no. 01-99	Periodic, weekly (MARS auto-generates when new record is created)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab
Contributing Site	Contributing Laboratory (auto-populates based upon user ID)	Periodic, weekly (MARS auto-generates when new record is created)	CIRID/CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Reporting Week Note: Unless otherwise selected, the previous reporting week will automatically appear Beginning Note: this field will auto-populate based upon the 'Reporting Week'	drop-down list; format YYYY - ##, where week ## = 01-52 Date for the first day of the reporting week, i.e. :DD-Mon-YYYY, where 'Mon' = 3 letter code for month e.g.: 08-Jan-2008	Periodic, weekly (MARS auto-generates when new record is created)	CIRID/CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab

Submission Date	YYYY/MM/DD; auto-populates upon report submission	Periodic, weekly (MARS auto-generates when new record is created)	CIRID/CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab

WEEKLY REPORT				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
1. There are NO newly confirmed cases of measles, rubella, CRS or CRI to report **OR**	If 'NO' is selected, but newly confirmed cases OR unconfirmed IgM+ investigations exist for the time period, MARS will flag this for review	Periodic, weekly (P/T Public Health)	CIRID/ CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
2. There are NEW confirmed cases of measles, rubella, CRS or CRI to report	If 'NEW', MARS will generate a summary of cases confirmed during the reporting week, e.g. Measles = 0, Rubella = 1, CRS = 0, CRI = 0			
Is this information correct?	Yes, No			
Comments	Free text			

APPENDIX X: MARS Pilot Application: Measles/Rubella Investigation Report Data Fields, v4.4 (DRAFT)

MEASLES/RUBELLA REPORT				
EPISODE IDENTIFICATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Case Number Assigned by Province/Territory	Numeric	Real-time, upon IgM+ notification (P/T Public Health, CIRID)	PHAC (CIRID) / CMRSS [1]	CIRID, NML, P/T Public Health*, P/T Lab*
MARS Identifier	MR/YYYY/MM/DD/PT/## where: MR = 'Meas/Rub report' YYYY = current year MM = report month DD = report day PT = 2 letter P/T code ## = report no. (all natural numbers)	Real-time (MARS auto-generates when new record is created)	PHAC / MARS	CIRID, NML, P/T Public Health, P/T Lab
Public Health Identifier	Numeric	Real-time, upon IgM+ notification (P/T Public Health (PH), P/T Lab if on req.)	P/T Public Health/ BC-CDC [9,14]	P/T Public Health, P/T Laboratory
Laboratory Sample Identifier	alpha-numeric, may be >1 per record	Real-time (P/T Lab, NML)	P/T Lab, NML/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Health Unit Reporting/ Geographic Locale	Drop-down / free text	Real-time, upon IgM+ notification (P/T PH)	CIRID, P/T Public Health / CMRSS, BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
City	Drop-down / free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab

Forward Sorting Locator (First 3 Postal Code digits)	alpha-numeric	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Date of Birth	YYYY/MM/DD	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Age	years/months/days	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Sex Comments	Female/Male/Other Free text	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Pregnancy	Yes, No, Unknown drop-down list (0-42 weeks)	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Date Reported to Health Unit	YYYY/MM/DD	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Date Investigation Initiated	YYYY/MM/DD	Real-time, synonymous with serology sample collection date (P/T PH, or P/T Lab)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
BACKGROUND, EXPOSURE & CLINICAL INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Rash Onset Date Comments	YYYY/MM/DD Free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab

Vaccination History Date: Dose 1 Vaccine Type Comments	Yes, No, Unknown YYYY/MM/DD Measles, Measles/ Rubella, MMR (Note: multiple vaccine events may be captured) Free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Hospitalization Comments	Yes, No, Unknown Free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Is this episode epidemiologically linked to another case? **If yes:** Outbreak Identifier Comments	Yes, No, Unknown Provincial Outbreak ID, Federal Outbreak ID (alpha – numeric, free text) Free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Source	Outside Canada; In Canada linked to an imported case/ chain; In Canada linked to case/ chain of unknown source; Unknown source	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab

Comments	Free text			
Incubation Period Measles: 7-21d prior to rash onset[1] Rubella: 14-21d prior to rash onset[1]	YYYY/MM/DD – YYYY/MM/DD	Real-time: MARS automatically estimates using rash onset date and known latency range of measles / rubella	CIRID / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Communicable Period Measles: communicable 4d prior to 4d after rash onset[1] Rubella: communicable 7d prior to minimum 4d after rash onset[1]	YYYY/MM/DD – YYYY/MM/DD	Real-time: MARS automatically estimates using rash onset date and known communicable period of measles / rubella	CIRID / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Travel History ▫ travel during incubation and communicable periods	**(Note**: MARS will capture multiple travel instances)	Real-time, upon IgM+ notification (P/T PH, CIRID)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Within Canada				
Date Range	Yes, No, Unknown			
Setting (s)	YYYY/MM/DD to YYYY/MM/DD			

Province/Territory	drop-down/free text			
Outside Canada	P/T (drop-down)			
Date Range	Yes, No Unknown			
Setting (s)	YYYY/MM/DD to YYYY/MM/DD			
Country	drop-down/free-text			
Comments	Country (drop-down)			
	Free text			
Immigration History ▫ If foreign-born		Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Country of Birth	Country (drop-down)			
Year of Immigration	YYYY			
Comments	Free text			

CLINICAL INFORMATION - SUPPLEMENTAL				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Date of Prodrome Onset	YYYY/MM/DD	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab

Fever Highest recorded temperature	Yes, No, Unknown ^{0}C	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Cough	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Coryza	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Conjunctivitis	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Koplik Spots	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Rash Nature of rash Duration (days)	Yes, No, Unknown macular only, papular only, maculopapular, sandpaper, pinpoint, blotchy, vesicular, reticular/lacey, crusting, acneform, exfoliating, flushed numerical	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Nodes If yes, location	Yes, No, Unknown postauricular, sub-	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab

	occipital, cervical, inguinal			
Sore throat and /swollen tonsils	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Malaise	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Headache	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Photophobia	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Myalgia	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Encephalitis	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Arthritis	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Arthralgia	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Other (specify)	Free text	Real-time, upon IgM+ notification (P/T PH)	P/T Public Health / BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free Text	Real-time, upon IgM+ notification (P/T PH)	PHAC/MARS	CIRID, NML, P/T Public Health, P/T Lab
LABORATORY INFORMATION				
SAMPLE INFORMATION				

DATA FIELD	VALUE SET	DATA INPUT (STAKEHOLDER)	DATA FIELD SOURCE (STAKEHOLDER / SYSTEM)	ACCESS
Sample Information		Real-time (if IgM+) (P/T Lab)	NML/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Laboratory Sample ID	Alpha-numeric			
Sample Type**	serum, cerebrospinal fluid (CSF), urine, throat/ nasopharyngeal (T/NP), amniotic fluid, chorionic villi, placental tissue, products of conception, other (specify)	**NOTE**: ▫ All sample info will be entered prior to specifying results for tests performed on the sample ▫ All test results will be linked to the sample on which they are performed, and the associated sample information		
Sample Collection Date	YYYY/MM/DD			
Laboratory Receipt Date	YYYY/MM/DD			
Rash Onset Date (may be entered with sample info. if provided with test req.)	YYYY/MM/DD			
Viral Culture/ Identification Sample Provided? (with test request, in addition to initial serology sample)	Yes, No, Unknown	▫ Help text will be provided for each test field, specifying the appropriate sample type, and required sampling time frame		
If yes, Sample Type:	**T/NP**, urine, other (specify)			
Comments:	Free text			

LABORATORY TEST RESULTS – PRIMARY INVESTIGATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Measles IgM Serology	Positive, Negative, Indeterminate, Not done	Real-time (if IgM+) (P/T Lab)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD	**NOTE:** IgM+ test result entry will trigger real-time alerting of all stakeholders (P/T PH, CIRID, NML); the alert will contain the MARS generated 'Unique Case Identifier' to enable access by all to the correct episode/record		
Testing Lab	Lab ddlist, plus 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			
Rubella IgM Serology	Positive, Negative, Indeterminate, Not done	Real-time (if IgM+) (P/T Lab)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD	**NOTE:** IgM+ result entry will trigger real-time alerting of all stakeholders (P/T PH, CIRID, NML); the alert will contain the MARS		
Testing Lab	Lab ddlist			
Test Kit	ddlist, 'Internal', Other'			

Comments	Free text	'Unique Case Identifier'		
Parvovirus B19 IgM Serology	Positive, Negative, Indeterminate, Not done	Real-time, if associated with a measles/rubella IgM+ investigation (P/T Lab)	NML,CIRID / MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist			
Test Kit	ddlist, 'Internal', Other'			
Comments	Free text			

LABORATORY TEST RESULTS – SUPPLEMENTARY/CONFIRMATORY (MEASLES)

DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Measles IgG Serology Result i.e.: significant (4-fold) rise in convalescent measles antibody titre	Positive, Negative, Indeterminate, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Acute:				
Titre Result	Free text (e.g. 1:4, 1:64)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, plus 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			

Convalescent:				
Titre Result	Free text (e.g. 1:4, 1:64)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, plus 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			
Measles RT-PCR Virus Detection	Positive, Not detected , Inconclusive, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, plus 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			
Measles Virus Isolated	Yes, No, Not done	Real-time (NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, plus 'Other'			
Comments	Free text			

Measles Genotype[10]	A, B1, B2, B3, C1, C2, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, E, F, G1, G2, G3, H1, H2, other (free text), Not done	Real-time (NML)	NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, plus 'Other'			
Comments	Free text			

LABORATORY TEST RESULTS – SUPPLEMENTARY/CONFIRMATORY (RUBELLA)

DATA FIELD	VALUE SET	DATA INPUT (STAKEHOLDER)	DATA FIELD SOURCE (STAKEHOLDER / SYSTEM)	ACCESS
Rubella IgM Serology Result	Positive, Negative, Indeterminate, Not done	Real-time (if IgM+) Periodic (if IgM-) (P/T Lab)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD	**NOTE:** IgM+ result entry will trigger real-time alerting of all stakeholders (P/T PH, CIRID, NML); the alert will contain the MARS 'Unique Case Identifier'		
Testing Lab	Lab ddlist			
Test Kit	ddlist, 'Internal', Other'			
Comments	Free text			

Rubella IgG Serology Result i.e.: significant (4-fold) rise in convalescent measles antibody titre	Positive, Negative, Indeterminate, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Acute:				
Titre Result	Free text (e.g. 1:64)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist,'Internal','Other'			
Comments	Free text			
Convalescent:				
Titre Result	Free text (e.g. 1:4)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			
Rubella Avidity Result	High, Intermediate, Low, Not done	Real-time (P/T Lab, NML)	NML/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Pregnancy gestation week *at time of sample collection	drop-down list (0-42 weeks)			

Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist, 'Internal', 'Other'			
Comments	Free text			
Rubella RT-PCR Virus Detection	Positive, Not detected, Inconclusive, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			
Rubella Virus Isolated	Yes, No, Not Done	Real-time (NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			
Rubella Genotype[11]	1a, 1B, 1C, 1D, 1E, 1F, 1G, 1h, 1i, 1j, 2A, 2B, 2C, Other (free text), Not done	Real-time (NML)	NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			

Testing Lab	Lab ddlist, 'Other'
Comments	Free text

CASE CONFIRMATION & CLASSIFICATION INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Case Classification		Real-time (CIRID)	CIRID, NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Epidemiologically Confirmed i.e. clinical illness & epidemiological link to a lab-confirmed case	Yes, No			
	Yes, No			
Laboratory Confirmed	Confirmed Measles, Confirmed Rubella, Discarded			
Final Designation				
Case Reviewed By Provincial Public Health Provincial Laboratory CIRID NML	**Note**: When the user confirms review for their jurisdiction, the user's signature (i.e. name, institution and contact information), will auto-populate in the jurisdiction field	Real-time (CIRID, NML, P/T Public Health, P/T Lab)	CIRID, NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			

Case Classification Date	YYYY/MM/DD	Real-time (auto-populates upon review completion)	CIRID, NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free Text			

* PH Identifier for episode/record level data identification in MARS may be limited to the provincial level if required by P/T Public Health

** The 'Sample Type' value set is intended to include all sample types which may conceivably be tested, however not all sample types will be appropriate for the selected test. Bold font will indicate the preferred sample type for each test, with help text provided to outline ideal sampling periods.

APPENDIX XI: MARS Pilot Application: CRS/I Investigation Report Data Fields, v4.4 (DRAFT)

CONGENITAL RUBELLA SYNDROME / INFECTION REPORT				
EPISODE IDENTIFICATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Case Number Assigned by Province/Territory	Numeric	Real-time, upon IgM+ notification (CIRID)	PHAC (CIRID) / CMRSS [1]	CIRID, NML, P/T Public Health*, P/T Lab*
MARS Identifier	CR/YYYY/MM/DD/PT/##, where: CR = 'Cong.Rub. report' YYYY = current year MM = report month DD = report day PT = 2 letter P/T code ## = report no. (all natural numbers)	Real-time (MARS auto-generates when new record is created)	PHAC / MARS	CIRID, NML, P/T Public Health, P/T Lab
Public Health Identifier	Numeric	Real-time, upon IgM+ notification (P/T Public Health (PH), P/T Lab if on req.)	P/T Public Health/ BC-CDC	P/T Public Health, P/T Laboratory
Laboratory Sample Identifier	alpha-numeric, may be >1 per record	Real-time (P/T Lab, NML)	P/T Lab, NML/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Health Unit Reporting/ Geographic Locale	Drop-down / free text	Real-time, upon IgM+ notification (P/T PH)	CIRID, P/T Public Health / CMRSS, BC-CDC	CIRID, NML, P/T Public Health, P/T Lab
City	Drop-down / free text	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Forward Sorting Locator (First 3 Postal Code digits)	alpha-numeric	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab

Date of Birth	YYYY/MM/DD	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Age	years/months/days	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Sex	Female,Male,Other	Real-time, upon IgM+ notification (P/T PH)	CIRID/CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			
Date Reported to Health Unit	YYYY/MM/DD	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Date Investigation Initiated	YYYY/MM/DD	Real-time, synonymous with serology sample collection date (P/T PH, or P/T Lab)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
CRS/CRI BACKGROUND, EXPOSURE & CLINICAL INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Birth Status**	Live Birth, Still Birth	Real-time (P/T Public Health)	P/T Public Health, P/T Lab / CPSP	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			
Vaccination History	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Date: Dose 1	YYYY/MM/DD			
Vaccine Type	Measles, Measles/ Rubella, MMR (**Note**: Multiple vaccine			

	events may be captured)			
Comments	Free text			
Hospitalization	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			
Travel History ▫ travel during incubation and communicable periods	(**Note**: MARS will capture multiple travel instances)	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Within Canada	Yes, No, Unknown			
Date Range	YYYY/MM/DD to YYYY/MM/DD			
Setting (s)	drop-down/free text			
Province/Territory	P/T (drop-down)			
Outside Canada	Yes, No Unknown			
Date Range	YYYY/MM/DD to YYYY/MM/DD			
Setting (s)	drop-down/free-text			
Country	Country (drop-down)			
Comments	Free text			

Is this episode epidemiologically linked to another case?	Yes, No, Unknown	Real-time, upon IgM+ notification (P/T PH)	CIRID / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
If yes:				
Outbreak Identifier	Provincial Outbreak ID (alpha – numeric, free Federal Outbreak ID (alpha – numeric)			
Comments	Free text			

MATERNAL HISTORY

MATERNAL BACKGROUND, EXPOSURE AND CLINICAL INFORMATION

DATA FIELD	VALUE SET	DATA INPUT (STAKEHOLDER)	DATA FIELD SOURCE (STAKEHOLDER / SYSTEM)	ACCESS
Age (at delivery)	Numerical (years) OR Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			
Ethnicity/Immigration History	Aboriginal Canadian-born, Non-aboriginal Canadian-born, Foreign-born, Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Country of Birth	Country drop-down			
Year of Immigration				

	YYYY			
Comments	Free text			
Number of previous pregnancies		Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Gravida	Numerical, ≥ 0 (2 digits)			
Para	Numerical, ≥ 0 (2 digits) OR 'Unknown'			
Comments	Free text			
Immunization with rubella-containing vaccine	Yes, No, Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
If yes:				
Date: Dose 1	YYYY/MM/DD			
Vaccine Type	Measles/ Rubella, MMR			
*Note: Multiple vaccine events may be captured				
Comments	Free text			
Contact with person with rubella or rash during pregnancy?	Yes, No, Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			

History of rubella-like illness or rash during pregnancy?	Yes, No, Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
If yes, week or month of pregnancy	#weeks, OR #months			
Comments	Free text			
Rubella outbreak in mother's area of residence during pregnancy?	Yes, No, Unknown	Real-time (P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			

MATERNAL LABORATORY INFORMATION

DATA FIELD	VALUE SET	DATA INPUT (STAKEHOLDER)	DATA FIELD SOURCE (STAKEHOLDER / SYSTEM)	ACCESS
Routine rubella IgG prenatal screening before or during current/previous pregnancy?	Yes, No, Unknown	Real-time (P/T Lab, P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
If yes:				
Rubella Prenatal IgG Serology	Positive, Negative, Indeterminate			
Result Date	YYYY/MM/DD			
Comments	Free text			

Laboratory confirmation of rubella infection during pregnancy?	Yes, No, Unknown	Real-time (P/T Lab, P/T PH)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Comments	Free text			
Rubella IgM Serology	Positive, Negative, Indeterminate, Not done	Real-time (P/T Lab, P/T PH)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD	**NOTE:** IgM+ result entry will trigger real-time alerting of all stakeholders (P/T PH, CIRID, NML); the alert will contain the unique 'MARS Identifier'		
Testing Lab	Lab ddlist			
Test Kit	ddlist, 'Internal', Other'			
Comments	Free text			
Rubella IgG Serology Result i.e.: significant (4-fold) rise in convalescent measles antibody titre	Positive, Negative, Indeterminate, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Acute:				
Titre Result	Free text (e.g. 1:64)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist,'Internal','Other'			
Comments	Free text			

Convalescent:				
Titre Result	Free text (e.g. 1:4)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist, 'Internal','Other'			
Comments	Free text			
Rubella Avidity Result	High, Intermediate, Low, Not done	Real-time (P/T Lab, NML, P/T PH)	CIRID, NML/ CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Pregnancy gestation week *at time of sample collection	drop-down list (0-42 weeks)			
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Test Kit	ddlist, 'Internal','Other'			
Comments	Free text			
Rubella RT-PCR Virus Detection	Positive, Not detected, Inconclusive, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			

Rubella Virus Isolated	Yes, No, Not Done	Real-time (NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			
Rubella Genotype[11]	1a, 1B, 1C, 1D, 1E, 1F, 1G, 1h, 1i, 1j, 2A, 2B, 2C, Other (free text), Not done	Real-time (NML)	NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			

CRS CLINICAL INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
CRS: Clinically Compatible Manifestations CRS confirmation requires two clinically compatible manifestations; any combination from columns A		Real-time (P/T Public Health)	P/T Public Health, P/T Lab / CPSP	CIRID, NML, P/T Public Health, P/T Lab

and B, (below) plus laboratory confirmation of infection	
Column A	
Cataracts/congenital glaucoma	Yes, No, Unknown Yes, No, Unknown
Congenital heart defect	Yes, No, Unknown
Sensorineural hearing loss	Yes, No, Unknown
Pigmentary retinopathy	
Column B	
Purpura	Yes, No, Unknown
Hepatosplenomegaly	Yes, No, Unknown
Microcephaly	Yes, No, Unknown
Micropthalmia	Yes, No, Unknown
Mental retardation	Yes, No, Unknown
Meningoencephalitis	Yes, No, Unknown
Radiolucent bone disease	Yes, No, Unknown
Development of late conditions such as diabetes and progressive pan-encephalitis and any other conditions possibly caused by rubella virus	Yes, No, Unknown
	Free text
Comments	

CRS/CRI LABORATORY INFORMATION				
SAMPLE INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Sample Information Laboratory Sample ID Sample Type***	Alpha-numeric serum, cerebrospinal fluid (CSF), urine, throat/ nasopharyngeal (T/NP), amniotic fluid, chorionic villi, placental tissue, products of conception, other (specify)	Real-time (if IgM+) (P/T Lab) **NOTE**: ▫ All sample info will be entered prior to specifying results for tests performed on the sample ▫ All test results will be linked to the sample on which they are performed, and the associated sample information ▫ Help text will be provided for each	NML/ MARS	CIRID, NML, P/T Public Health, P/T Lab
Sample Collection Date	YYYY/MM/DD			
Laboratory Receipt Date	YYYY/MM/DD			
Rash Onset Date *may be entered with sample info if provided with test req.	YYYY/MM/DD			
Viral Culture/ Identification Sample Provided? (with test request, in addition to	Yes, No, Unknown			

initial serology sample)		test field, specifying the appropriate sample type, and required sampling time frame		
If yes, Sample Type:	**T/NP**, urine, other (specify)			
Comments	Free text			
LABORATORY TEST RESULTS – CRS/CRI INVESTIGATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
Rubella IgM Serology	Positive, Negative, Indeterminate, Not done	Real-time (P/T Lab, P/T PH)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD	**NOTE:** IgM+ result entry will trigger real-time alerting of all stakeholders (P/T PH, CIRID, NML); the alert will contain the unique 'MARS Identifier'		
Testing Lab	Lab ddlist			
Test Kit	ddlist, 'Internal', Other'			
Comments	Free text			
Persistent Rubella IgG Elevation (CRS/I) i.e.: persisting for longer than expected from passive transfer of maternal antibody; in the absence of recent rubella immunization	Yes, No, Not Done	Real-time (P/T Lab, NML)	P/T Public Health, P/T Lab / CPSP [12, 13]	CIRID, NML, P/T Public Health, P/T Lab
	Free text			

Titre Result	YYYY/MM/DD			
Lab Result Date	days			
Duration of Elevation (post-natal) i.e. interval b/t DOB and sample collection date (calculated field)				
Comments	Free text			
Rubella RT-PCR Virus Detection	Positive, Not detected, Inconclusive, Not done	Real-time (P/T Lab, NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			
Rubella Virus Isolated	Yes, No, Not Done	Real-time (NML)	CIRID, NML / CMRSS, MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			
Comments	Free text			
Rubella Genotype[11]	1a, 1B, 1C, 1D, 1E, 1F, 1G, 1h, 1i, 1j, 2A, 2B, 2C, Other (free text), Not done	Real-time (NML)	NML / MARS	CIRID, NML, P/T Public Health, P/T Lab
Result Date	YYYY/MM/DD			
Testing Lab	Lab ddlist, 'Other'			

Comments	Free text			

CASE CONFIRMATION & CLASSIFICATION INFORMATION				
DATA FIELD	**VALUE SET**	**DATA INPUT** (STAKEHOLDER)	**DATA FIELD SOURCE** (STAKEHOLDER / SYSTEM)	**ACCESS**
CRS Case Classification**		Real-time (Following case discussion by stakeholders; P/T PH, P/T Lab, CIRID, NML)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Laboratory Confirmed	Yes, No			
Two clinically compatible case manifestations	Yes, No			
Final Designation	Confirmed CRS, Discarded			
Comments	Free text			
CRI Case Classification****		Real-time (Following case discussion by stakeholders; P/T PH, P/T Lab, CIRID, NML)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab
Laboratory Confirmed	Yes, No			
No clinically compatible case manifestations	Yes, No			
Final Designation	Confirmed CRI, Discarded			
Comments	Free text			
Case Reviewed By	**Note**: When the user	Real-time	CIRID / CMRSS	CIRID, NML, P/T Public

Provincial Public Health Provincial Laboratory CIRID NML Comments	confirms review for their jurisdiction, the user's signature (i.e. name, institution and contact information), will auto-populate in the jurisdiction field Free text	(Following case discussion by stakeholders; P/T PH, P/T Lab, CIRID, NML)		Health, P/T Lab
Case Classification Date Comments	YYYY/MM/DD Free Text	Real-time (MARS auto-populates once review is complete)	CIRID / CMRSS	CIRID, NML, P/T Public Health, P/T Lab

* Access to the PH Identifier for episode/record level data identification in MARS may be limited to the provincial level if required by P/T Public Health

** Live Birth CRS Confirmation Criteria: Two clinically compatible manifestations (any combination from columns A and B of the CRS Table plus laboratory confirmation of infection, through 1) isolation of rubella virus from an appropriate clinical specimen, or 2) detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine, or 3) rubella–specific IgG persisting at elevated levels for longer than would be expected from passive transfer of maternal antibody; or in the absence of recent immunization. Still Birth CRS Confirmation Criteria: Two clinically compatible manifestations with isolation of rubella virus from an appropriate clinical specimen. [12, 13]

*** The 'Sample Type' value set is intended to include all sample types which may conceivably be tested, however not all sample types will be appropriate for the selected test. Bold font will indicate the preferred sample type for each test, with help text provided to outline ideal sampling periods.

**** CRI Confirmation Criteria: A case with laboratory confirmation of infection but with no clinically compatible manifestations: (1) isolation of rubella virus from an appropriate clinical specimen, or (2) detection of rubella-specific IgM in the absence of recent immunization with rubella-containing vaccine, or (3) persistence of rubella-specific IgG at elevated levels for longer that would be expected from passive transfer of maternal antibody; or in the absence of recent immunization [12, 13]

Measles & Rubella Laboratory Investigation Survey, 2007

Background

Enhanced measles and rubella surveillance in Canada is conducted through the Canadian Measles and Rubella Surveillance System (CMRSS), and requires laboratory confirmation of all clinically suspect cases of measles/rubella-like (febrile-rash) illness lacking an epidemiologic link to a laboratory confirmed-case. IgM serology is the standard front-line test most universally performed for rapid diagnosis, and may therefore be the best representative indicator for the investigation of measles/rubella-like illness (MRLI) in the Canadian setting.

The purpose of this brief survey is to estimate the current level of investigation into MRLI in Canada by gathering information regarding the testing protocols employed by all Canadian laboratories performing measles and rubella IgM serology testing.

1. Contact Information

1.1 Please provide the following laboratory contact information:

Laboratory:
Address:
City:
Province:
Postal Code:

1.2 Please provide contact information for the provincial/regional laboratory director or designate to whom correspondence should be directed regarding this survey:

Name:
Position:
Telephone:
Fax:
Email:

2. Laboratory Test Information

2.1 Does your laboratory perform measles IgM serology testing?

❑ Yes ❑ No

Comments:

2.2 Does your laboratory perform rubella IgM serology testing?

❑ Yes ❑ No

Comments:

2.3 What IgM testing protocol is used by the laboratory when screening clinically suspect MRLI cases? Please check the selection that applies; if another screening protocol is used, please provide details in the comments section below.

❑ All MRLI cases are screened for measles, rubella and parvovirus B19 IgM

❑ Only MRLI cases negative for measles IgM are screened for rubella and parvovirus B19 IgM

❑ Rubella and parvovirus B19 IgM testing is performed by the lab only when specifically requested

❑ Other screening protocol used (please provide details below)

Comments:

2.4 Please specify (in the table provided below) the number of measles IgM tests performed and the test kit used during the 2005 and 2006 calendar years, and between January 1st and September 30th of 2007.

YEAR	TEST KIT EMPLOYED (e.g. Behring, Bion IFA, etc.)	NUMBER OF MEASLES IGM TESTS PERFORMED	NUMBER OF MEASLES IGM-POSITIVE RESULTS
2007 (Jan.1 – Sept. 30)			
2006			
2005			

Comments:

2.5 Please specify (in the table provided below) the number of rubella IgM tests performed and the test kit used during the 2005 and 2006 calendar years, and between January 1st and September 30th of 2007.

YEAR	TEST KIT EMPLOYED (e.g. Behring, Bion IFA, etc.)	NUMBER OF RUBELLA IGM TESTS PERFORMED	NUMBER OF RUBELLA IGM-POSITIVE RESULTS
2007 (Jan.1 – Sept. 30)			
2006			
2005			

Comments:

Measles & Rubella Laboratory Investigation Survey, 2012

Background

Enhanced measles and rubella surveillance in Canada is conducted through the Canadian Measles and Rubella Surveillance System (CMRSS), and requires laboratory confirmation of all clinically suspected cases of measles and rubella lacking an epidemiologic link to a laboratory-confirmed case. IgM serology is the standard front-line test most universally performed for rapid diagnosis, and may therefore be the best representative indicator for the investigation of measles-like illness (MLI) in the Canadian setting.

The purpose of this brief survey is to estimate the current level of investigation into MLI in Canada by gathering information regarding the testing protocols employed by Canadian laboratories performing measles and rubella IgM serology testing.

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1. Contact Information

1.1 Please provide the following laboratory contact information:

Laboratory:
Address:
City:
Province:
Postal Code:

1.2 Please provide contact information for the provincial/regional laboratory director or designate to whom correspondence should be directed regarding this survey:

Name:
Position:
Telephone:
Fax:
Email:

2. Laboratory Test Information

2.1 Does your laboratory perform measles IgM serology testing?

❑ Yes ❑ No

Comments:

2.2 Does your laboratory perform rubella IgM serology testing?

❑ Yes ❑ No

Comments:

2.3 What IgM testing protocol is used by the laboratory when screening clinically suspect MLI cases? Please check the one selection that best applies*

*Note: If another screening protocol is used, or if the protocol has changed between 2007 and the present, please provide details in the comments section below.

❑ All MLI cases are screened for measles, rubella and parvovirus B19 IgM

❑ All MLI cases are screened for measles and rubella IgM

❑ Only the specific IgM test(s) requested will be performed initially; if negative, additional measles/rubella and parvovirus B19 IgM testing will be performed

❑ The lab will perform only the specific IgM screening test(s) requested

❑ Other screening protocol used (please provide details below)

Comments:

2.4 Please specify the number of measles IgM tests performed, measles IgM-positives and the test kit used during the June 1, 2011 - May 31, 2012 reporting period, and for the 2007 - 2011 calendar years.

YEAR	NUMBER OF MEASLES IgM TESTS PERFORMED	NUMBER OF MEASLES IgM-POSITIVE RESULTS	TEST KIT EMPLOYED (e.g. Behring, Bion IFA, etc.)
Reporting Period 2011/June/01-2012/May/31			
2011			
2010			
2009			
2008			
2007			

Comments:

2.5 Please specify the number of rubella IgM tests performed, rubella IgM-positive results, and the test kit used during the June 1, 2011 - May 31, 2012 reporting period, and for the 2007 - 2011 calendar years.

YEAR	NUMBER OF RUBELLA IgM TESTS PERFORMED	NUMBER OF RUBELLA IgM-POSITIVE RESULTS	TEST KIT EMPLOYED (e.g. Behring, Bion IFA, etc.)
Reporting Period 2011/June/01-2012/May/31			
2011			
2010			
2009			
2008			
2007			

Comments:

2.6 Does your laboratory perform any of the following confirmatory tests to further investigate measles or rubella IgM-positives? Please check all that apply.

- ❑ Measles RT-PCR detection
- ❑ Measles paired acute/convalescent IgG serology
- ❑ Measles virus isolation
- ❑ Rubella RT-PCR detection
- ❑ Rubella paired acute/convalescent IgG serology
- ❑ Rubella virus isolation
- ❑ Other confirmatory testing is performed (please provide details below)
- ❑ Some or all confirmatory testing is referred (please specify)

Comments:

Your participation is greatly appreciated. Please submit the completed survey to the attention of Tracie EisBrenner at the following email address: tracie.eisbrenner@phac-aspc.gc.ca by **Tuesday August 13th 2012**. Kindly enter all responses directly on the form provided.

APPENDIX XIV: MARS PILOT USER SURVEY, 2013

Measles and Rubella Surveillance (MARS) Pilot User Survey: March 2013

The purpose of this survey is to gather input from MARS pilot participants regarding their experience in using the measles and rubella surveillance (MARS) application for national reporting purposes during the June 2011 - May 2012 MARS pilot period. This information will be used to inform next steps with respect to the broader implementation of real-time, integrated measles/rubella surveillance at the national level.

Please note that individual MARS user responses will remain strictly confidential, and all survey data will be assessed at the aggregate level.

The MARS application is hosted by the Canadian Network for Public Health Intelligence (CNPHI) on their website at https://www.cnphi-rcrsp.ca. Please note that it may be helpful to access the MARS application for reference purposes when completing the survey.

Estimated Completion Time: 20-30 minutes

*Required

1. Contact Information

Please provide your name and current contact information.

First Name: *

Last Name: *

Email: *

Telephone: *

i.e. (Area Code) 7-digit phone number

2. Pilot Site Information

Please confirm your position and organizational affiliation at the time of your participation in the MARS pilot project (June 2011 - May 2012).

Position Title: *

Organization: *

Address:

City: *
Vancouver

Province: *
BC

Postal Code:

3. MARS User Role

3.1. Please specify the public health organization(s) for which you contributed data during the MARS pilot period (June 1, 2011 – May 31, 2012). *
Check all that apply

- ○ Provincial Public Health Laboratory (PHL)
- ○ Provincial Public Health (PH)
- ○ Both Provincial PHL and PH organizations
- ○ National Microbiology Laboratory (NML)
- ○ Centre for Immunization and Respiratory Infectious Diseases (CIRID)
- ○ Other:

3.2. In which of the following general activities did you participate during the MARS pilot period? *

Check all that apply

- [ ] Laboratory data entry
- [ ] Epidemiological and clinical data entry
- [ ] Review of MARS report data
- [ ] Classification of measles/rubella investigation reports (i.e. to confirm or discard)
- [ ] Data query, export and analysis
- [ ] Other:

Measles/Rubella Investigation Reports

Please indicate your level of agreement with the following statements pertaining to use of the 'Measles/Rubella Investigation Report' form, which was designed to support real-time, integrated reporting of measles/rubella investigations. Check the selection that best applies.

4.2. The 'Measles/Rubella Investigation Report' form is well structured and easy to follow.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.3. The 'Measles/Rubella Investigation Report' form is intuitive, requiring minimal training to use.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.4. 'Measles/Rubella Investigation Report' data field names are clearly described and easy to understand.

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable

4.5. The report form includes all laboratory data fields required to investigate and confirm measles and rubella.

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable

4.6. The report form includes all epidemiological and clinical data fields required to investigate and confirm measles and rubella.

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable

4.7. The report form effectively integrates laboratory, epidemiological and clinical measles/rubella data contributed by national and provincial public health and laboratory users.

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable

4.8. The 'Review' page, which summarizes the report data entered, includes all measles/rubella data fields needed for review and classification purposes.
Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.9. The time required to create and submit a new 'Measles/Rubella Investigation Report' is approximately:
Please estimate based on a single, uninterrupted data entry session from the time of MARS access to report submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.10. The time required to complete a single update to an existing 'Measles/Rubella Investigation Report' is approximately:
Please estimate based on a single, uninterrupted data entry session from the time of MARS report access to 'update' submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.11. The time required (by provincial public health) to complete and submit a measles/rubella 'National Case Report' form via the established Canadian Measles and Rubella Surveillance System (CMRSS) is approximately:
Please estimate based on a single, uninterrupted data entry session.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.12. To support national measles/rubella case reporting during an outbreak, the addition of a MARS 'bulk upload' function to enable line listed data entry is:
Check the selection that best applies.

- ○ Very Important
- ○ Important
- ○ Moderately Important
- ○ Of Limited Importance
- ○ Not Important
- ○ Not Applicable

4.13. Are there any changes to the 'Measles/Rubella Investigation Report' form that you would recommend to support broader national adoption of the MARS application?
If 'Yes', please provide details in the 'Comments' section below.

- ○ Yes
- ○ No

Comments:

***Survey Completion Status = 38%**

*Based on longest possible 'survey path'

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Congenital Rubella Syndrome/Infection (CRS/I) Investigation Reports

The 'CRS/I Investigation Report' form was designed to support real-time, integrated reporting of CRS/I investigations by provincial and national laboratory and public health stakeholders.

4.14. Did you use the 'Congenital Rubella Syndrome/Infection (CRS/I) Investigation Report' form during the pilot period? *

Note: 'Use' is defined as accessing a report for either data entry or review purposes.

- (•) Yes
- ( ) No

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Congenital Rubella Syndrome/Infection (CRS/I) Investigation Reports

Please indicate your level of agreement with the following statements pertaining to use of the 'CRS/I Investigation Report' form, which was designed to support real-time, integrated reporting of CRS/I investigations. Check the selection that best applies.

4.15. The 'CRS/I Investigation Report' form is well structured and easy to follow.

Check the selection that best applies.

- ( ) Strongly Agree
- ( ) Agree
- ( ) Undecided
- ( ) Disagree
- ( ) Strongly Disagree
- ( ) Not Applicable

4.16. The 'CRS/I Investigation Report' form is intuitive, requiring minimal training to use.

Check the selection that best applies.

- ( ) Strongly Agree
- ( ) Agree
- ( ) Undecided
- ( ) Disagree
- ( ) Strongly Disagree
- ( ) Not Applicable

4.17. 'CRS/I Investigation Report' data field names are clearly described and easy to understand.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.18. The report form includes all laboratory data fields required to investigate and confirm CRS/I.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.19. The report form includes all epidemiological and clinical data fields required to investigate and confirm CRS/I.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.20. The report form effectively integrates laboratory, epidemiological and clinical CRS/I data contributed by national and provincial public health and laboratory users.
Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.21. The time required to create and submit a new 'CRS/I Investigation Report' is approximately:
Please estimate based on a single, uninterrupted data entry session from the time of MARS access to report submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.22. The time required to complete a single update to an existing 'CRS/I Investigation Report' form is approximately:
Please estimate based on a single, uninterrupted data entry session from the time of MARS access to report submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.23. Are there any changes to the 'CRS/I Investigation Report' form that you would recommend to support broader national adoption of the MARS application?
If 'Yes', please provide details in the 'Comments' section below.

- ○ Yes
- ○ No

Comments:

***Survey Completion Status = 54%**

*Based on longest possible 'survey path'

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Monthly Test Reports

The 'Monthly Test Report' form was designed to capture aggregate measles and rubella IgM serology test data contributed by provincial laboratories to support national surveillance indicator estimation.

4.24. Did you access or use the 'Monthly Test Report' form during the pilot period? *
Note: 'Use' is defined as accessing a report for either data entry or review purposes.

- ○ Yes
- ○ No

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Monthly Test Reports

Please indicate your level of agreement with the following statements pertaining to use of the 'Monthly Test Report' form, which captures aggregate measles and rubella IgM serology test data contributed by provincial laboratories to support surveillance indicator estimation. Check the selection that best applies.

4.25. The 'Monthly Test Report' form is well structured and easy to follow.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.26. The 'Monthly Test Report' form is intuitive, requiring minimal training to use.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.27. 'Monthly Test Report' data fields are clearly described and easy to understand.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.28. In addition to capturing 'Positive' and 'Negative' measles/rubella IgM serology results, it would be helpful to capture 'Indeterminate' results as a defined field. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.29. The time required to complete and submit a new 'Monthly Test Report' is approximately:

Please estimate based on an uninterrupted data entry session from the time of MARS access to report submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.30. The time required by the provincial public health laboratory to contribute aggregate measles and rubella IgM serology test data on a monthly basis is approximately:

Please estimate based on the person time required by the site to obtain the requested test data.

- ○ <30 minutes/month
- ○ 30 - < 60 minutes/month
- ○ 1 - < 2 hours/month
- ○ 2 - < 3 hours/month
- ○ >3 hours/month
- ○ Not Applicable

4.31. Are there any changes to the 'Monthly Test Report' form that you would recommend to support broader national adoption of the MARS application?
If 'Yes', please provide details in the 'Comments' section below.

- ○ Yes
- ○ No

Comments:

***Survey Completion Status = 66%**

*Based on longest possible 'survey path'

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Weekly Zero Reports

The 'Weekly Zero Report' form was designed to support routine weekly 'zero' and aggregate 'confirmed case' measles/rubella reporting by provincial public health via the MARS application.

4.32 Did you access or use the 'Weekly Zero Report' form during the pilot period? *
This includes accessing a report for either data entry or review purposes.

- ○ Yes
- ○ No

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Weekly Zero Reports

Please indicate your level of agreement with the following statements pertaining to use of the 'Weekly Zero Report' form, which was designed to support routine weekly 'zero' and aggregate 'confirmed case' reporting by provincial public health via the MARS application. Check the selection that best applies.

4.33. The 'Weekly Zero Report' form is well structured and easy to follow.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.34. The 'Weekly Zero Report' form is intuitive, requiring minimal training to use.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.35. 'Weekly Zero Report' data fields are clearly described and easy to understand.

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable

4.36. The time required to complete and submit a 'Weekly Zero Report' via MARS is approximately:
Please estimate based on an uninterrupted data entry session from the time of MARS access to report submission.

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.37. The time required to complete and submit a 'Weekly Zero Report' via the established Canadian Measles and Rubella Surveillance System (CMRSS) is approximately:
Please estimate based on a single uninterrupted data entry session..

- ○ < 30 minutes
- ○ 30 - < 60 minutes
- ○ 1 - < 1.5 hours
- ○ 1.5 - < 2 hours
- ○ ≥ 2 hours
- ○ Not Applicable

4.38. Are there any changes to the 'Weekly Zero Report' form that you would recommend to support broader national adoption of the MARS application?
If 'Yes', please describe in the 'Comments' section below.

- ○ Yes
- ○ No

Comments:

***Survey Completion Status = 77%**

*Based on longest possible 'survey path'

5. MARS Application

Please indicate your level of agreement with the following statements pertaining to MARS application features and functionality. Check the selection that best applies.

MARS Electronic Notification System

The MARS application includes an electronic notification system which automatically generates an email notification when a report is created or updated. The email notification includes a link to the relevant MARS report form, and is received by all MARS users within the submitting province and at the national level in keeping with jurisdictionally specified business rules.

5.1. It was easy to access newly submitted and updated reports through automated MARS email notifications. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree

5.2. MARS automated email notifications effectively support interjurisdictional communication regarding measles/rubella reports. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree

5.3. Are there any changes to the MARS email notification/alerting system that you would recommend ? *

If 'Yes', please describe in the 'Comments' section below.

- ○ Yes
- ○ No

Comments:

MARS Integrated Reporting

The MARS application was designed to allow national and provincial laboratory and public health users to centrally access and contribute site-specific data to common measles/rubella investigation reports in keeping with established surveillance roles, thereby providing investigators with role-based access to the same investigation data at the same time.

5.4. Centralized reporting of measles/rubella investigation data via MARS supports improved linkage of laboratory and epidemiological data. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable/ Did Not Use

5.5. The ability to report measles/rubella investigation data in real-time via MARS enables more timely national surveillance. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable/ Did Not Use

5.6. Using the MARS 'Summary Reports' function, it is easy to view aggregate measles/rubella report data of interest for a specified time period. *

Check the selection that best applies.

- ○ Strongly Agree
- ○ Agree
- ○ Undecided
- ○ Disagree
- ○ Strongly Disagree
- ○ Not Applicable / Did Not Use

5.7. Using the MARS 'Query Builder', it is easy to perform custom data queries for export into Excel. *

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable / Did Not Use

5.8. Overall, the MARS application is easy to use. *

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree

5.9. Overall, the MARS application successfully supports integrated national measles and rubella surveillance and reporting. *

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree

5.10. The web-based MARS application on CNPHI was consistently available for use as needed for reporting purposes. *

Check the selection that best applies.

- Strongly Agree
- Agree
- Undecided
- Disagree
- Strongly Disagree
- Not Applicable

5.11. During the pilot period, approximately how often did you access the MARS application to create, update or review MARS reports for your site? *

Check the selection that best applies.

- ○ Very Frequently, ≥ 2 times/week
- ○ Frequently, ~1 time/week
- ○ Occasionally, ~1 time/ 2 week period
- ○ Infrequently, ~ 1 time/month
- ○ Rarely, < 1 time/month

5.12. At my site, the number of users concurrently responsible for MARS data entry was: *

Check the selection that best applies.

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ ≥ 5

5.13. At my site, the number of users involved in the routine review of MARS report data was approximately: *

Check the selection that best applies.

- ○ 1
- ○ 2
- ○ 3
- ○ 4
- ○ ≥ 5

5.14. In your experience, what site-based factors were most important in facilitating the implementation of real-time surveillance using the MARS application?

e.g. site-based personnel support for enhanced laboratory data entry, compatibility of existing IT infrastructure with CNPHI platform

5.15. In your experience, what were the most significant challenges in implementing real-time surveillance using the MARS application?

e.g. site-based personnel support for enhanced laboratory data entry, compatibility of existing IT infrastructure with CNPHI platform

***Survey Completion Status = 100%**

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Thank you for your participation in the MARS User Survey.

All individual survey responses will remain confidential. Should you have any questions regarding the survey, please contact Tracie EisBrenner at tracie.eisbrenner@phac-aspc.gc.ca

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