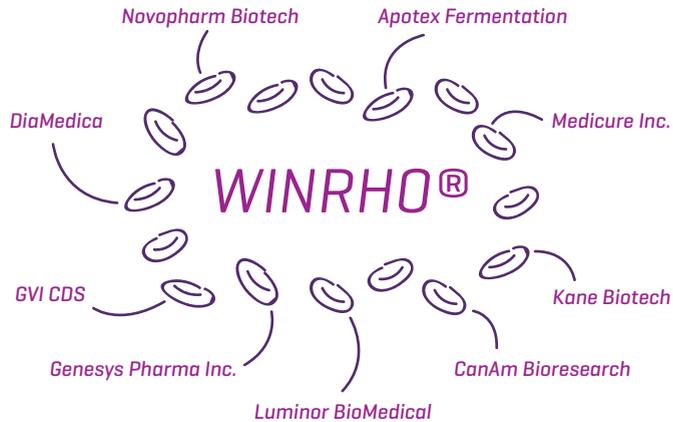

Impact Report // Preventing Rhesus (Rh) Disease in Newborns

Research in Manitoba Saves Infants

Research in Manitoba Creates a Major Industry Sector

WINRHO® SDF Rho[D] Immunoglobulin (Human)'s development laid the foundations for the biomedical sector in Manitoba. The WINRHO® story inspired investment from the Manitoba provincial government into life sciences, which attracted other research and business to Manitoba that are continuing to grow to this day.

Manitoba is now one of the largest biomedical centres in Canada with biopharmaceutical companies like Novopharm Biotech, Apotex Fermentation (formerly ABI Biotechnology), DiaMedica, Medicure Inc., Genesys Pharma Inc., Genesys Venture Inc., Luminor BioMedical (formerly Miraculins), Kane Biotech, CanAm Bioresearch, GVI CDS, and others located here.



Innovation creates High-Value Employment

Employment in Manitoba due to WINRHO® SDF:

In 1975, the Winnipeg Rh Institute employed 20 people. By 1991 it had grown to 125 employees.

From 1989 to 2011, Cangene saw tremendous growth as well.

"Starting off with only 14 people around 1989, Cangene employed more than 900 persons in 2011, and two thirds were in Manitoba," says Dr. John Langstaff, Cangene's former CEO.

ABI Biotech also added 100 jobs to the province when it was operated by Dr. Albert Friesen.

"I am very optimistic about the future life science sector for Manitoba. There are now enough activities that students and young entrepreneurs can see and seize the opportunities, and there are enough employees that staffing the new opportunities is easier."

— Dr. Albert Friesen

Emergent BioSolutions purchased Cangene in 2014. Emergent BioSolutions has remained the Canadian distributor for WINRHO® SDF.

Emergent BioSolutions in Manitoba:

350

people employed.

\$77,000

average annual salary for jobs ranging from research to front-line manufacturing, technical trades and administrative support.

\$100M

approximate annual revenue generated.

90%

of product exported from the Winnipeg site, continually bringing new dollars into the province.

\$15M

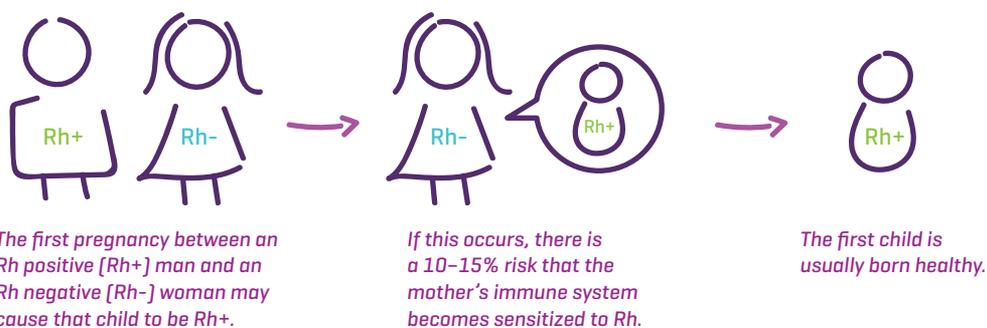
invested in upkeep and replacing equipment over last few years.

2700 hours

approximate annual volunteer time invested in community organizations by Emergent BioSolutions employees.

Rh Disease Devastates Young Families

Before 1940, there were some couples who had a healthy first child followed by multiple lost pregnancies, still births, or babies who died in their first days of life. In 1940, researchers discovered the Rh factor — a type of protein found on the surface of red blood cells, that played a role. Rh disease is an incompatibility of the blood between mother and child. The effects take place in the child as a fetus. Antibodies in the mother's blood destroy fetal red blood cells faster than the body can replace them. Without enough red blood cells, the fetus can't get enough oxygen. This leads to serious problems and may even be fatal to the child.



In a first pregnancy, there's very little danger to an Rh positive baby because the child is usually born before the mother produces substantial Rh antibodies. However, since the woman will continue to produce antibodies throughout her life, during her next pregnancies, maternal Rh antibodies can cross the placenta and reach the fetus.

Before 1940, Rh disease caused 4.2 deaths for every 1,000 live births worldwide and caused permanent brain damage in approximately 20% of surviving children.

The continued loss of pregnancies and babies was devastating for families affected by Rh disease.

These health histories began the focused effort on trying to find a cure.



Manitoba Researchers took up the Challenge

Largely through Manitoba-based research, the incidence of Rh disease has dropped to nearly 0% in Manitoba and the developed world.

To prevent Rh disease, an Rh negative woman receives an injection of WINRHO® SDF Rho(D) Immunoglobulin (Human) around the 28th week of pregnancy, and again within 72 hours of delivering an Rh positive baby. This prevents sensitization in the mother, protecting future babies, for more than 97% of Rh negative women.

The treatment proved so successful that for years, pregnant women travelled to Winnipeg, or New York to access treatment — the only two centres in North America doing this work.

Today, most women in developed countries have a simple blood test done early on, or prior to pregnancy, to determine whether they are Rh negative.



Rh negative woman receives WINRHO® SDF

Children survive birth and lead healthy lives.

Winnipeg's Rh Ladies were Instrumental

In the early 1960s, Dr. Alvin Zipursky recruited four women to donate blood for research on Rh disease. They became the first of the 'Rh Ladies'.

In order to create an injection for pregnant women to protect their babies, researchers needed the blood of women who already had the disease.

The Rh Ladies spent 2-3 hours each week lying down as two pints of blood were drawn.

In 1968, 21 women were doing this — not to help themselves, but to help other families.

Many Rh Ladies donated blood for decades. Their contributions were critical in advancing treatment.

Brave Steps toward Success

OUTSIDE MANITOBA	R&D ACTIVITIES IN MANITOBA	HEALTH OUTCOMES/IMPACTS
1940 Dr. Landsteiner of the Rockefeller Institute for Medical Research, discovered the Rh factor in New York City	1944 Dr. Chown and Professor Marion Lewis began the Winnipeg Rh Laboratory	
1945 Dr. Wallerstein of New York City perfects total blood exchange transfusion for newborns	1945 Dr. Chown of Winnipeg utilizes the exchange transfusion technique to save newborns	
1963 Dr. Liley in New Zealand performs Intrauterine Transfusions	1963 Dr. Rhinehart Friesen of Winnipeg performs the first Intrauterine Transfusions in Canada	Death rate of newborns is halved, bringing it down to 25%
	1963 Dr. Bowman launches the "Rh Ladies" club. It consisted of women with Rh- blood who had had miscarriages and who donated blood weekly for 2-3 hours. Some continued donating for decades	These Rh antibodies provide the basis for Canada's 'first preparation of Rh immune globulin'
	1965 Dr. Zipursky proposes injecting Rh immune globulin before delivery	
	1967 The Winnipeg Rh laboratory begins a clinical trial on the efficacy of Rh immune globulin, which displayed success	The 1,216 women who received the Rh immune globulin did not produce the harmful antibodies at 6 months
	1973 WINRHO® is developed and produced by the Rh Institute WINRHO® is licensed and then distributed throughout Canada by Rh Pharmaceuticals	Deaths due to Rh disease reduced to nearly 0% in Canada

Impacts

Since the advent of Rh immune globulin, Rh disease has been virtually eliminated in high-income countries. From a 50% mortality rate in 1940, deaths from Rh disease reached nearly 0% in Manitoba by the mid-1970s.

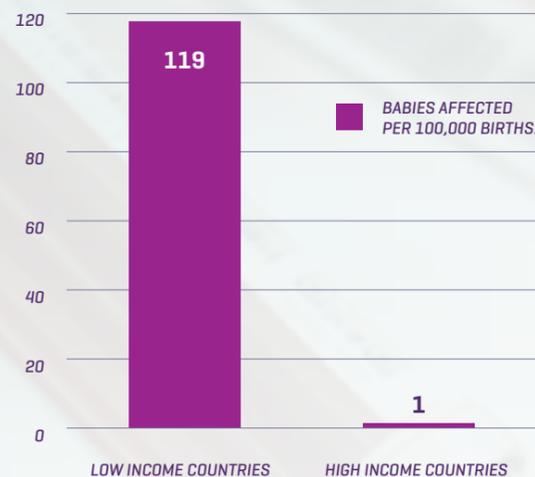


Saving lives across the globe

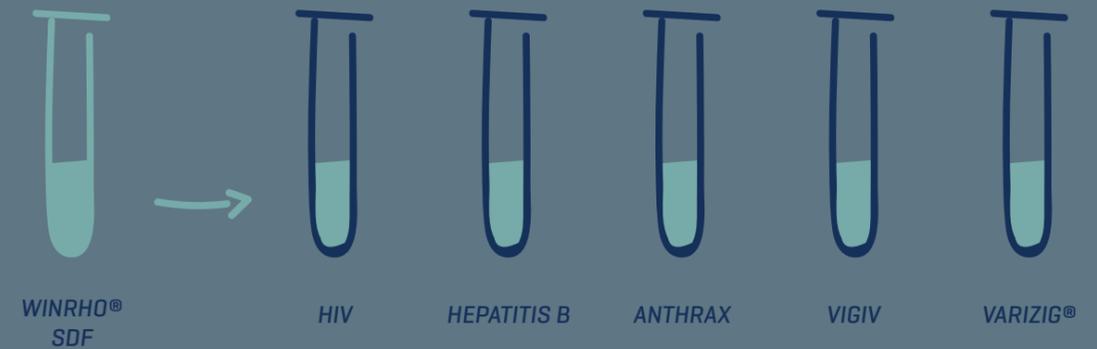
WINRHO® SDF continues to reduce Rh disease across the globe. Due to limited health care access, there is still work to be done for Eastern Europe/Central Asia, Latin America, sub-Saharan Africa, and South Asia, where a combined prevalence of 119 cases per 100,000 live births continues today, compared with 1 case per 100,000 live births in high-income countries.

A recent burden of disease study found that globally, over 100,000 babies die each year from Rh disease, and approximately 20,000 develop permanent brain damage.

The burden of Rh disease continues



Techniques from the development of WINRHO® lead to new treatments and cures:



HIV

In 1995, WINRHO® SDF became a new treatment for HIV related idiopathic thrombocytopenia purpura (ITP). ITP is an immune condition where the antibodies stick to blood platelet antigens, reducing the platelet counts. WINRHO® SDF, as a treatment in ITP, increases and sustains platelet counts to a normal level for up to 125 people per million each year.

Hepatitis B

The techniques developed to create WINRHO® SDF contributed to the development of a specialty hyperimmune product, HepaGam B® (Hepatitis B immunoglobulin). This Hepatitis B immune globulin is the only product of its kind approved in North America for the prevention of Hepatitis B recurrence following Liver Transplantation in Hepatitis (HBsAg)-positive liver transplant patients.

Anthrax

Anthrax is primarily a disease of herbivorous mammals. The disease is regarded as being non-contagious. Humans generally acquire it directly or indirectly from infected animals, or exposure to infected or contaminated animal products. Anthrax causes skin, lung, and bowel disease and can be deadly.

Anthrax Immune Globulin Intravenous is manufactured using a similar technique as WINRHO® SDF and is approved as a treatment for inhalational anthrax in adult and pediatric patients in WINRHO® SDF combination with appropriate antibacterial drugs.

VIGIV

[Vaccinia Immune Globulin, Intravenous]

VIGIV (Vaccinia Immune Globulin, Intravenous) Variola virus, or smallpox, is a highly contagious virus that was eradicated from the world in 1980. Due to fears that it may be used as an effective bioweapon, smallpox vaccines have been stockpiled by many countries and issued to the military. Live virus smallpox vaccines can result in serious adverse reactions including encephalitis, eczema vaccinatum, generalized vaccinia and myopericarditis.

Vaccinia Immune Globulin (Intravenous) (VIGIV) is manufactured on a similar manufacturing platform as WinRho® SDF and is indicated for the treatment of complications due to vaccinia vaccination.

VariZIG®

[Varicella Zoster Immune Globulin (Human)]

Primary varicella zoster virus infection causes varicella (chickenpox) and reactivated infection results in herpes zoster (shingles). Complications are more common in adolescents, adults and immunocompromised individuals. Individuals with impaired immunity are at risk of severe varicella and death.

Based on a similar manufacturing platform as WinRho® SDF, VariZIG® is a varicella zoster (chicken pox) hyperimmune product used when a person is exposed to varicella and has increased risk of getting severe disease.

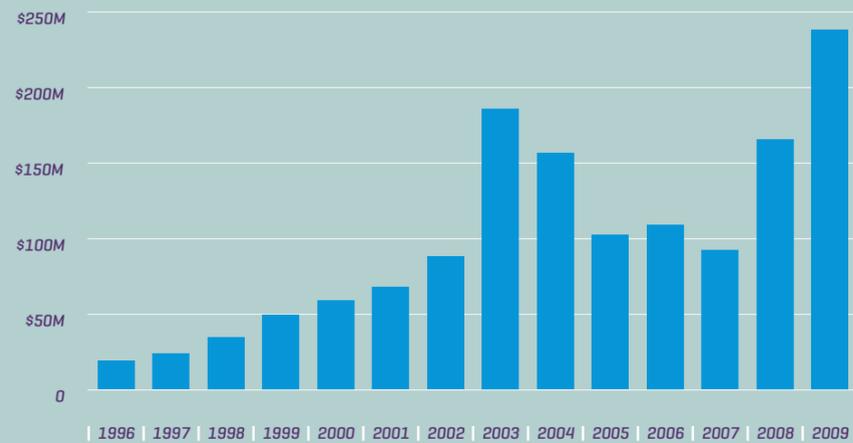
Research in Manitoba is a Good Investment

WINRHO® SDF Rho[D] Immunoglobulin [Human]WINRHO® was first developed in 1974. In 1980 when WINRHO® SDF was commercialized, it immediately dominated the Canadian market as the leading Rh Immunoglobulin, with a 60% share. WINRHO® SDF was the flagship product of Cangene Corporation.

In 1995, Cangene Corporation acquired the Apotex-acquired right to WINRHO® SDF and related technology and continued the production and distribution of WINRHO® SDF.

As a private company, Cangene was one of Canada's largest and earliest biopharmaceutical companies. The company showed continuous growth until it was sold in 2014. The revenues peaked in 2009 at \$239 million.

Cangene total revenues in millions.

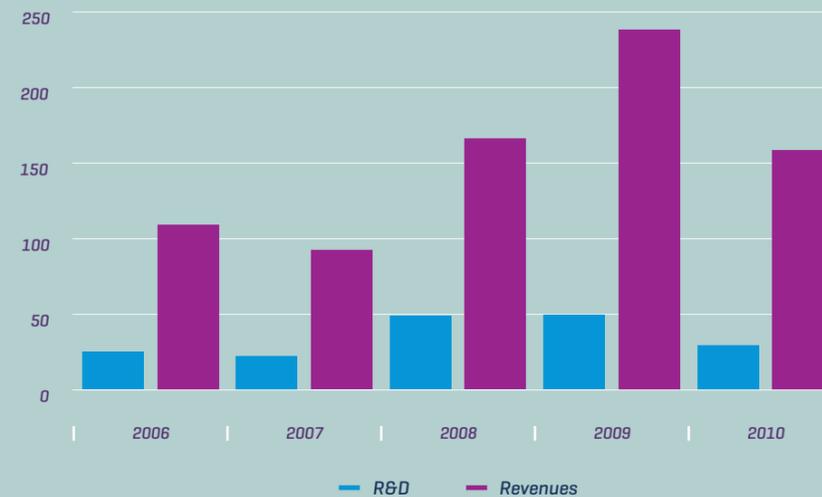


WINRHO® SDF leads Cangene's biopharmaceutical sales.



The Research and Development Payoff

Research and Development (R&D) investments and revenues of Cangene, 2006–2010 (\$ millions).



Over five years:

\$174.7M invested into R&D

\$765.5M Revenues

438% ROI
[Return on Investment]

WINRHO® SDF inspires the growth of Manitoba's bioscience industry.

Cangene's R&D investments peaked at \$49.4 million in 2009 with a corresponding high revenue of \$238.8 million in 2010.

The importance of investment in R&D is recognized by other pharmaceutical companies in Manitoba. Medicare, a specialty pharmaceutical company based in Winnipeg and established in 1997, invested \$140 million in R&D from 1998–2008 [or \$14 million per year.] They expected to earn \$40 million in revenues in 2017.

ABI Biotech and Novapharm invested nearly \$40 million from 1984–1991 in R&D and \$300 million from 1992 to the present, respectively.

Where smart money continues to grow.

In 2018 alone:

\$9 billion total industry revenue. **\$64,548** average salary earned by 13,824 employees.

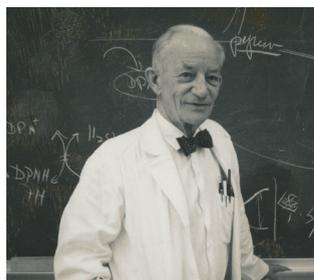
Manitoba bioscience sector

\$73.94 million

Ongoing Research and Development investment.

World Class Research Thrives Here

Our leaders in the elimination of Rh disease include:



Dr. Bruce Chown

One of the most influential and well-known physicians in Manitoba medical research history.

Dr. Chown combined early induction of pregnancy with exchange transfusion in order to prevent Rh disease. This approach was later adopted by other researchers around the world to treat the severely affected babies while in utero.

Professor Marion Lewis

Developed a less invasive, less painful capillary test for mothers and babies that is still used today to detect whether expecting mothers were immunized with various antibodies.

Professor Lewis studied the blood group distribution in the indigenous people of North America and was the first to provide evidence that the ancestors of the indigenous people of North America came across the Bering Strait from Asia.



Dr. Jack Bowman & Dr. Rhinehart Friesen

Through intrauterine transfusion, health care providers in Manitoba brought down the perinatal mortality from Rh disease from 50% to 13% in 1964. Dr. Bowman and Dr. Friesen were instrumental in this — training a team that led to the technique being widely used in Manitoba. This in turn led to women from all over North America coming to Winnipeg to be treated and successfully give birth.

Dr. Alvin Zipursky

Dr. Zipursky's suggestion to inject immune globulin into the mother's body earlier in the pregnancy reduced the chances of the death of a fetus to less than 0.5%. Even after six decades as a physician, Dr. Zipursky is continuing to prevent Rh disease by focusing on accessibility to Rh immunoglobulin in low income countries.

Starting in 1964, and continuing for a few years, women from all over North America came to Winnipeg to be treated for Rh disease and to give birth.

This demonstrated the need, the value and the hope that Manitoba researchers provided at that time.

By adopting, applying, and innovating discoveries made by other researchers, Winnipeg enhanced its capacity to treat sensitized mothers and avert many cases of Rh disease.



Newborn Theresa Ann Seepish, who had her Rh blood replaced via transfusion by Dr. Bruce Chown, surrounded by her siblings (left to right): Kenny, Linda, and Frankie Seepish.

Research to Real Life

Dr. Albert D. Friesen is a Winnipeg bio-entrepreneur who has spearheaded the development of the life-sciences industry in Manitoba. Yet, his career biography does not tell the story of his personal connection in preventing Rh disease.

His biotechnology career began as the first full-time employee at the Winnipeg Rh Institute where he led the development of WINRHO® Rho(D) Immunoglobulin (Human), one of Canada's first successful biotech products.

His leadership in the biotech industry has been instrumental in finding and developing several Canadian health industry companies, including ABI Biotechnology, Novopharm Biotech Inc., Genesys Pharma Inc., Medicure Inc. and KAM Scientific Inc. and was also the driving force behind several others, including DiaMedica, Miraculins and Kane Biotech.

During the development of WINRHO®, Drs. Bowman and Friesen undertook a clinical trial with 1200 expectant mothers, 200 of which were in their second pregnancy. One participant of that trial group was Dr. Friesen's wife, Lee Friesen and her sister Lois Kehler.

The Friesen's now have three healthy daughters who are Rh negative — each of whom had three children, and for each pregnancy received WINRHO®. Today, Dr. Friesen proudly states, "We have nine healthy grandchildren as a result of this work."



Dr. Albert Friesen, his wife Lee, and their family.

RESEARCH MANITOBA

A201 CHOWN BUILDING
753 McDERMOT AVENUE
WINNIPEG, MB R3E 0T6

T: 204-775-1096

F: 204-786-5401

E: INFO@RESEARCHMB.CA

RESEARCHMANITOBA.CA

CREDIT FOR ANY PHOTOS, DATA/CHARTS AND INFORMATION:

GIBLETT, ELOISE R. 1994. "PHILIP LEVINE 1900-1987: A BIOGRAPHICAL MEMOIR". NATIONAL ACADEMY OF SCIENCES, WASHINGTON DC.

LANE, DEBRA. "HISTORY OF THE DEVELOPMENT OF RH IMMUNE GLOBULIN". CANADIAN BLOOD SERVICES, WINNIPEG, OCT 2010 CREDIT THE DISCOVERY OF RH DISEASE TO A FRENCH MIDWIFE IN 1609 AMERICANPREGNANCY.ORG/PREGNANCY-COMPLICATIONS/RH-FACTOR/

THE RH BATTLE — TRAGEDIES AND TRIUMPHS VOICES, UNIVERSITY OF MANITOBA FACULTY OF MEDICINE MAGAZINE (1883-2008).

WARREN, P., JAMIESON, J.C. 2010. JACK BOWMAN: WINNIPEG'S CONTRIBUTIONS TO THE TREATMENT AND PREVENTION OF RHESUS AND HEMOLYTIC DISEASE OF THE NEWBORN. TRANSFUSION MEDICINE REVIEWS, 24 [1] 68-76.

ZIPURSKY, ET AL. 2013. NEONATAL HYPERBILIRUBINEMIA AND RH DISEASE OF THE NEWBORN: INCIDENCE AND IMPAIRMENT ESTIMATES FOR 2010 AT REGIONAL AND GLOBAL LEVELS. PEDIATRIC RESEARCH, 74[51]. P 95 RETRIEVED FROM: CANADA.CA/EN/PUBLIC-HEALTH/SERVICES/PUBLICATIONS/HEALTHY-LIVING/CANADIAN-IMMUNIZATION-GUIDE-PART-1-KEY-IMMUNIZATION-INFORMATION/PAGE-3-BENEFITS-IMMUNIZATION.HTML#P1C272. ACCESSED ON JANUARY 26, 2017

WINNIPEGFREEPRESS.COM/LOCAL/LOCAL-BIO-ENGINEER-TO-BE-HONOURED-204132171.HTML

THESTAR.COM/NEWS/INSIGHT/2016/02/21/MY-GOAL-VERY-MODEST-WIPE-OUT-RH-DISEASE.HTML

CANGENE CORPORATION. 2003 ANNUAL REPORT.

UNIVERSITY OF MANITOBA COLLEGE OF MEDICINE ARCHIVES.

THIS REPORT WAS BASED ON THE FOLLOWING DOCUMENT:
SARKER, SANCHITA AND CATALA JR, AMBROSIO. RESEARCH MANITOBA. PREVENTING RH DISEASE IN NEWBORNS: AN IMPACT NARRATIVE. WINNIPEG, MB.

AMBROSIO CATALA JR. AND RYAN CATTE, CONTRIBUTED TO THE REPORT.

The Research Manitoba Impact Framework guides the development of Impact Reports and Impact Narratives.
For more information visit www.researchmanitoba.ca/impacts/impact-framework/

WINRHO® SDF Rho[D] Immunoglobulin [Human] is a registered trademark of Saal Therapeutics

PREPARED (2019) BY: KATHLEEN ZAWALY, KRISTEN HOOPER, AND NECOLE SOMMERSELL.

