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# CANADA'S VACCINE LEGACY: INFLUENZA, POLIO & COVID-19 VACCINE(S)

Christopher J. Ruttly | September 24, 2020

The New York Times' Canada Correspondent, Ian Austen, recently wrote a story that focused on the little known, yet essential role that Canadian biochemist, Dr. Leone N. Farrell, played in making the Salk polio vaccine possible during the early 1950s; see <https://www.nytimes.com/2020/07/31/world/canada/leone-farrell-chemist.html> or <https://outline.com/PqFn4L>. Austen's article struck a chord among Canadians in the midst of the COVID-19 pandemic, particularly in the discussions of many potential COVID-19 vaccines, including several being developed in Canada. They also wondered when or whether any COVID-19 vaccines would be produced in Canada, and if Canadians would have timely access to others developed and manufactured elsewhere.

Farrell's story resonates today for several reasons, especially since her critical work at Connaught Medical Research Laboratories of the University of Toronto was conducted in 1953, during Canada's worst polio epidemic year. Indeed, prior to the COVID-19 pandemic, Canada's experience with polio that year was the nation's last most severe epidemic emergency as it affected most provinces and left some 9,000 reported cases and 500 deaths.

However, this was certainly not Canada's only national public health emergency, or threatened emergency, during which an expedited vaccine development and/or production initiative was launched. The story of vaccines prepared in Canada in response to polio and to active or threatened influenza pandemics in 1918, 1957, 1976 and 2009, highlight a legacy of bold public health commitment to providing vaccines as an emergency response. This history also underscores limits in, and a decline of, domestic vaccine production capacity that undercuts Canada's independent ability to produce any of the COVID-19 vaccine candidates.

## Influenza 1918

During the 1918 "Spanish" influenza pandemic, a sixth of the Canadian population, mostly young adults, was attacked by a flu like no other, leading to some 50,000 deaths. With little understanding of the viral cause of the disease (the influenza virus was not isolated until 1933) there was very little that could be done to prevent, control, or treat it. Nevertheless, in early October 1918, as the devastating 2nd wave of the pandemic was emerging, Connaught Antitoxin Laboratories, a unique self-supporting, public-service-based part of the University of Toronto, established in 1914, launched a heroic effort to prepare a vaccine. A small team at Connaught, working day and night in the Labs' modest Medical Building facility prepared what was considered an experimental influenza vaccine, based on the prevailing view that *Bacillus influenza* caused the disease, using samples collected from "flu" cases in New York City, Boston and Toronto. Connaught distributed the vaccine free of charge to provincial health departments, hospitals, medical and nursing staff, the military and other public health services across Canada. Due to this unprecedented emergency, no claims of effectiveness were made, but the vaccine did no apparent harm and Connaught's efforts were widely appreciated across the country.

Connaught's influenza vaccine was supplemented by a supply prepared by the Ontario Provincial Board of Health Laboratories. There were also vaccine production initiatives elsewhere in Canada, most notably in Winnipeg and Kingston. It is important to note that in 1918, few effective and safe vaccines existed beyond smallpox vaccine. Furthermore, vaccine production efforts were quite localized and unregulated

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by governments. In fact, the federal department of health was only established in 1919, its creation largely spurred by the pandemic. For more on the 1918 influenza vaccine production efforts, see: <https://definingmomentscanada.ca/the-spanish-flu/research/>

## **Polio, Paralysis and Expediting Prevention**

By the late 1920s, in Canada, Connaught's development, testing and production of diphtheria toxoid vaccine made significant progress in preventing diphtheria. However, an opposite trend was being observed with poliomyelitis, a human-only gastro-intestinal virus that can invade the nervous system and damage motor-neurons in the spinal cord. Infection causes varying degrees of muscle weakness or paralysis, including of muscles involved with breathing, requiring "iron lung" support. From the late 1920s through the early 1950s, polio outbreaks and epidemics relentlessly increased in Canada while much remained mysterious and misunderstood about "thecrippler." However, starting in the late 1940s, progress accelerated towards a vaccine.

In July 1947, Dr. Andrew J. Rhodes, a leading virologist specializing in polio, was recruited from the U.K. to lead a comprehensive research program at Connaught to investigate the virology, epidemiology and clinical diagnosis of polio. Rhodes' research was funded by the National Foundation for Infantile Paralysis (aka, the U.S. March of Dimes), Canadian Life Insurance Companies, and newly established Federal Public Health Research Grants. In 1949, a Boston research team, led by Dr. John F. Enders, discovered a method to cultivate poliovirus in tissue cultures. At the same time at Connaught, "Medium 199", the first synthetic tissue culture medium was developed, originally for nutritional studies of cancer cells. In 1951, Rhodes' polio research team discovered that Medium 199 could be used to cultivate poliovirus in monkey kidney cells. Meanwhile, Dr. Jonas Salk, based at the University of Pittsburg, showed a formaldehyde-inactivated poliovirus vaccine could prevent polio in monkeys. However, to cultivate the virus, Salk used an animal serum-based medium unsafe for a human vaccine, but when Connaught provided him with Medium 199, the first small-scale human test of a polio vaccine was possible.

It was at this point, in 1952-53, that Connaught's Dr. Leone Farrell developed the "Toronto Method" for large scale poliovirus cultivation, thus enabling an unprecedented field trial of the vaccine. In July 1953, Farrell led Connaught's "herculean task" (as Salk described it) of producing some 3,000 litres of poliovirus fluids, just as Canada's worst polio epidemic was accelerating.

During 1953, most provinces, particularly from Manitoba west, felt the full effects of epidemic polio at record or near record levels. Indeed, Manitoba faced the worst polio crisis in the country, if not in the history of this disease, recording 2,317 cases and 91 deaths. Winnipeg was ground zero with 763 cases and at the peak of the crisis there were 90 iron lungs operating at once in one hospital. In many ways the challenges associated with securing sufficient supplies of ventilators to manage COVID-19 patients has closely echoed the 1953 polio epidemic crisis and the urgent demand for iron lungs around the country.

The poliovirus fluids were shipped from Connaught to two U.S. pharmaceutical firms for inactivation and processing into the finished vaccine in time for the field trial to launch on April 24, 1954. The triple-blind field trial involved some 1,800,000 "polio pioneer" children enrolled across 44 U.S. states; they received either the vaccine, a placebo of Medium 199, or were observed. In May, Alberta, Manitoba and Halifax joined the trial. Meanwhile, Connaught manufactured the full vaccine while the federal and provincial governments planned an all-Canadian observed-controlled trial to start in April 1955, regardless of the trial results. Connaught's original polio vaccine work took place in the Spadina Building (originally Knox

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College) at U of T, that had been used for several purposes until taken over by Connaught in 1943 to expedite penicillin production in time for D-Day. The Building was recently renovated and today is the Faculty of Architecture's Daniels Building.

On April 12, 1955, unprecedented media attention was given to the announcement of the polio vaccine field trial results; the vaccine proved effective and was immediately licensed in the U.S., where production by several firms had been underway so it would be available right away. During the field trial there was U.S. federal testing of each batch of vaccine, but in the rush to commercial production this responsibility was left to company protocols. Unfortunately, a few batches of vaccine prepared by Cutter Laboratories in California containing live virus were not detected by the firm's testing, leading to the vaccine causing polio cases. The "Cutter Crisis" led to the rapid shut-down of the vaccine's introduction in the U.S, and to a potential crisis in Canada. For Paul Martin, Minister of National Health and Welfare, who had personal experience with polio, as did his son, Paul, Jr., the burning question was "What should Canada do?" Connaught was the sole source of the vaccine in Canada and the federal government had maintained the lot-by-lot testing policy of the vaccine. There were no reports of vaccine associated polio cases, so immunizations continued uninterrupted. The vaccine was distributed through a special federal-provincial free program for children, and also subjected to further study of its effectiveness. For more on the Canadian polio vaccine story, see: <http://connaught.research.utoronto.ca/history/> Articles #7 and #8.

### **Influenza 1957**

In 1956-57, as Connaught was increasing polio vaccine production in a new facility, built with federal and provincial funds, to meet both national and international demands, a new pandemic strain of influenza virus was spreading from Asia. This was the first influenza pandemic since 1918 and prompted high global demand for a vaccine. Influenza vaccines had been developed during World War II and used on a limited basis by the early 1950s. Improved vaccine production methods enabled larger, but still limited, supplies in the face of sudden high global demand. The main limiting factor was sourcing the large numbers of eggs in which to cultivate the virus. Concerned about limited vaccine availability, the Canadian government on behalf of the provinces, called Connaught with an urgent request for 500,000 doses to be used on a priority basis to protect armed forces and health services personnel. The Institut de microbiologie et d'hygiène at the Université de Montréal was also asked to contribute to the urgent request for vaccine. The Institute, which was established in 1938 along similar public service lines as Connaught, had focused largely on BCG tuberculosis vaccine research and producing diphtheria and tetanus vaccines; a new polio vaccine production facility, built with federal and provincial funds, opened in 1956.

While Connaught had developed and produced influenza vaccine during WWII for the military, the Labs did not routinely produce it in the 1950s. However, in June 1957, a team that normally prepared veterinary vaccines began cultivating the A/Asia/57 virus in specially secured fertile hen's eggs sourced from disease-free flocks. A further challenge was choosing between several possible production and processing methods, while also developing testing and quality control standards. By August, large-scale production of the inactivated A/Asia/57 vaccine began and by early October, after production of some 10,000 doses per week, the first vaccine was delivered to the provinces. By the end of November, Connaught had delivered 400,000 doses to all ten provinces, but just as the vaccine became available, demand declined as the pandemic threat subsided. However, fearful of a second pandemic wave the following year, Connaught was asked to prepare a further 1 million doses, which the Labs completed by January. Fortunately, a second wave did not develop and the vaccine was stored as a stockpile.

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## Influenza 1976

In early February 1976, a new strain of Influenza A virus, popularly referred to as “swine flu” (a H1N1 pig-origin strain of influenza A virus), caused an outbreak in new army recruits at Fort Dix, New Jersey, leading to one death. There were fears that the strain isolated from the fatal case was closely related to the strain responsible for the 1918 pandemic, and that the young and middle-aged would have little or no immunity. In March, taking advantage of a rare opportunity to mount a pre-emptive strike, President Gerald Ford committed the U.S. government to an unprecedented plan to immunize every American citizen against “swine flu” before November. In Canada, federal health minister, Marc Lalonde, followed suit and approved an expedited swine flu immunization program, ordering 12 million shots, primarily for the chronically ill and people over 65 years-of-age.

However, with U.S. influenza vaccine producers committed to meeting the unprecedented U.S. government order, it became less available for Canada. Thus, Connaught Labs was asked to provide vaccine, although it had not produced influenza vaccine since 1957-58. With limited time and a lack of specialized production equipment, which the federal government declined to help provide, Connaught imported vaccine in concentrated bulk form from producers in Europe and Australia, and would then process, test and finally fill and package the vaccine.

By this time, Connaught had been sold by the University of Toronto to the Canada Development Corporation, a new federal crown corporation, and since October 1972 was known as “Connaught Laboratories Limited.” Institut Armand Frappier, which had evolved and expanded from the Institut de microbiologie et d'hygiène and had moved its vaccine production to the University of Quebec in Laval in 1975, was also asked to supply vaccine. Influenza vaccine production would be an important focus of IAF, but in 1976, sufficient production capacity was not yet in place. Thus, IAF also imported bulk vaccine, sourced from Institut Mérieux in France. Later, in 1989, Institut Mérieux would acquire Connaught Laboratories, while IAF’s vaccine production facilities would ultimately evolve into BioChem Pharma, and then GSK Canada near Quebec City in 2005.

Fortunately, the 1976 “swine flu” pandemic emergency did not materialize and out of the 10 million doses ultimately available in Canada, only about 800,000 people received the vaccine. However, the ramp-up of this unprecedented mass vaccination initiative encountered numerous obstacles on both sides of the border, i.e.: vaccine production delays; securing liability insurance; growing public resistance; and the emergence of rare adverse reactions allegedly associated with the vaccine, most notably Guillain-Barré Syndrome. For Connaught, an important outcome of the 1976 influenza vaccine story was its acquisition of one of the major U.S. vaccine facilities, the Merrill-National site in Swiftwater, PA, in early 1978. The Swiftwater site specialized in influenza vaccine development and production and would provide Connaught with an important supply for Canada.

## Influenza 2009

While the 1976 pandemic threat of “swine flu” did not materialize, the “H1N1” strain of “swine flu” materialized globally in the spring of 2009, beginning in Mexico. Canada’s first confirmed H1N1 case occurred on April 24th, the first death on May 8th, and on June 10th the World Health Organization declared H1N1 influenza a pandemic. By the time it was over there were at least 10,000 confirmed cases and 428 deaths in Canada. As in previous influenza pandemics, a major focus of public health, political

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and popular attention, particularly in Canada, was on expediting the production and free distribution of a vaccine before the worst effects of the pandemic hit.

During the decade prior to the H1N1 pandemic, it was global fears of another potential influenza pandemic, caused by the H5N1 “bird flu,” coupled with growing fears of vaccine supply nationalism, that drove Canadian pandemic vaccine planning. In 2000-01, the Canadian government focused on negotiating an exclusive 10-year pandemic influenza vaccine contract with Canada’s only domestic influenza vaccine producer, BioChem Pharma, in St. Foy, Quebec, which was acquired by GSK in 2005. By 2009, GSK’s influenza vaccine production facility had been upgraded and on May 27th the H1N1 virus seed strain was received, setting in motion the vaccine production process. GSK was focused on preparing an adjuvanted vaccine, which was designed to prompt a boosted immune response.

By June 12, 2009, there were some 28,774 cases and 144 deaths in 74 countries due to H1N1, with 2,446 cases and 4 deaths in Canada. Three more deaths were confirmed on June 22nd, one of which a 6-year-old girl in Toronto. However, by mid-July, plans for rapid vaccine production and roll-out were slowed due to alarmingly low yields of virus cultivation, pushing GSK’s first vaccine delivery target to September-October and full supplies not likely until December-January. Nevertheless, on August 6th, Health Canada formally placed its order to GSK Canada for 50.4 million doses of H1N1 vaccine at a total cost of \$400 million; 60% was paid by the federal government and 40% by the provinces. The expectation was that about 75% of Canadians might want or need to be vaccinated.

However, the production delays, coupled with continuing spread of the pandemic, raised public concerns. There were many questions about the vaccine’s safety and effectiveness once given, exacerbated by wide media attention and social media discussions, especially if the pandemic had passed by the time it was available. Of particular concern was whether or not GSK’s adjuvanted vaccine was safe for pregnant women and children, both groups appearing unusually vulnerable to severe H1N1 infection. The adjuvant GSK used, known as AS03, was not approved for use in Canada, thus requiring a clinical trial. In response to the concerns, in early September, Health Canada placed an order for 1.2 million doses of non-adjuvanted vaccine for pregnant women. Meanwhile, as the global H1N1 death toll reached 3,200, with 74 deaths in Canada, medical and public health concerns grew that the vaccine would arrive too late, following a pattern seen in the 1957-58 pandemic.

On October 21st, Health Canada finally approved GSK’s H1N1 vaccine, coinciding with the start of a second wave of cases in Canada. The first H1N1 immunization clinics opened on October 26th, marking the start of the largest immunization effort in Canadian history. The vaccine was initially offered to people with chronic medical conditions under the age of 65, pregnant women, children between 6 months and under 5 years of age, people living in remote settings, healthcare workers involved in essential service and pandemic response, and caregivers of people at high risk who could not be immunized. However, after months of the pandemic and months of waiting for the vaccine, the initial turnout at the immunization clinics was underwhelming. But following media and public attention in the wake of the sudden death of an otherwise “healthy as can be” 13-year-old boy due to H1N1 on October 27th, vaccine uptake was sharply boosted. Although only 40% of Canadians chose to take the vaccine, it was one of the highest uptakes in the world.

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## Whither a Canadian COVID-19 Vaccine?

As the COVID-19 pandemic has grown on a global scale not seen since the 1918 influenza pandemic, the challenges of mounting an emergency vaccine response are far more complicated than in previous outbreaks. Indeed, the situation we face in our response to COVID-19 is closer to the vaccine context surrounding the 1918 pandemic, and during the major polio epidemics of the early 1950s; vaccines did not yet exist then and had to be developed, tested and then produced on a large scale. In 1957, 1976 and 2009, influenza vaccines existed and other than modifications in production methods and technologies, the challenges were primarily in boosting the scale and speed of manufacturing.

In the Canadian context, meeting these challenges became increasingly problematic as domestic vaccine manufacturing capacity declined and/or fell out of independent Canadian corporate or public control, especially since the late 1980s. Since the COVID-19 pandemic began, there have certainly been several Canadian COVID-19 vaccine research and development initiatives, yet they are separate from any Canadian vaccine manufacturing capacity. Indeed, today, as recent reports have emphasized (ie. <https://www.cbc.ca/news/canada/saskatoon/vido-intervac-university-of-saskatchewan-manufacturing-delays-canada-vaccine-1.5694008> ), there is no independent Canadian vaccine production capacity, at least none able to manufacture a COVID-19 vaccine at any scale. Sanofi Pasteur Canada's Toronto site certainly has substantial vaccine production capacity, but it is committed to meeting Canadian and global demand for existing vaccines, and moreover, the site is not Canadian owned. The same is true at GSK Canada and its influenza vaccine production facility in Quebec.

While much has irrevocably changed in Canadian vaccine research, development and production since the 1950s, the challenges Dr. Leone Farrell faced when she joined Connaught Laboratories' polio research team in 1952 — with the country in the grips of polio epidemics on an unprecedented scale — closely parallel what Canadian COVID-19 scientists face today. However, Dr. Farrell had a significant advantage in that she worked within a seamless vaccine research, development and production environment at Connaught Laboratories within the University of Toronto, which was also a key part of a broadly collaborative international poliovirus research community. Indeed, Farrell and Connaught's seamless polio vaccine work was a, if not the, vital element in expediting the development, production and testing of the Salk polio vaccine.

Connaught Labs was created in 1914 as a bold response to pressing infectious disease threats and an absence of Canadian antitoxin and vaccine research, development and production capacity. Over a century later, something similarly seamless, collaborative, publicly oriented and boldly Canadian is clearly needed to expedite the development and domestic production of one or more of the COVID-19 vaccine candidates that have been identified. Such a new initiative, built on the original seamless model of Connaught Labs, would also prove of great value in bolstering Canada's preparedness for other new infectious disease threats.

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