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Polio vaccine development in Canada: Contributions to global polio eradication

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Abstract

The paper briefly describes Canada's distinctive experience in the control of polio and offers some lessons for governments and health policy leaders in other jurisdictions, particularly as they consider immunization policies for the post-polio-eradication era.
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1. Introduction

Beginning in 1910, and especially between 1927 and 1953, Canada was among those nations hardest hit by major epidemics of paralytic polio. Canada was also one of the first countries to successfully eliminate polio after the introduction of the Salk inactivated polio vaccine (IPV) in 1955 and the Sabin oral polio vaccine (OPV) in 1962.

The Canadian success story can be attributed to three major factors:

1. the active involvement of both provincial and federal governments in disease management and in the provision of social supports for polio victims and their families (who were predominantly middle class) during the pre-vaccine era;
2. the development, production and global distribution of both IPV and OPV, with an essential role played by the Toronto-based Connaught Medical Research Laboratories (a self-supporting part of the University of Toronto from 1914 to 1972, and now, the Connaught Campus of Sanofi Pasteur Limited); and
3. the implementation of universal immunization strategies by Canada's provinces, using either IPV or OPV or both in mixed schedules [1].

An historical understanding of Canada's encounter with polio and its control—representing the independent experience of 10 provinces and 3 territories and employing at least three different immunization strategies (IPV or OPV alone, or IPV followed by OPV)—can help in the formulation of immunization policy and program development for the final push towards global polio eradication and for the post-polio-eradication era.

2. Canada's response to the "middle class plague"

During the first half of the 20th century, in a context of marked progress in infectious disease control generally, the North American understanding of paralytic polio was shaped by several factors:

- a frustrating lack of knowledge about polio's cause and spread;
- the unpredictability of ever-worsening epidemics;

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- a fearful popular imagery of polio's physical effects; and
- the potentially catastrophic financial risk for its primary victims—middle class children and their families.

Despite the ''modern'' medical science of the period, epidemics of paralytic polio continued to escalate throughout the industrialized world. Ironically, we now know that the great strides made in improving public health and personal hygiene standards at the time in fact abetted the spread of polio. Rising health status among segments of the population inevitably increased the pool of non-polio-exposed, *and therefore non-polio-immune*, individuals, especially children. This, coupled with a number of geographic, demographic and epidemiological factors, made Canada's middle class particularly vulnerable to paralytic polio.

In the wake of Canada's first significant ''infantile paralysis'' outbreaks in 1910, as the disease was popularly known, Canadian child health authority Dr. Helen MacMurchy wrote about the particular vulnerability of the middle class to this new disease in a popular magazine article, ''Paralysis: The New Epidemic'' [2]. Ten years later, the threat to the ''better off'' and increasingly adult populations became even more apparent after Franklin D. Roosevelt was stricken with ''infantile paralysis'' while vacationing off the coast of New Brunswick [3]. Over the next decade, despite his polio disability, Roosevelt became governor of New York and then President of the United States, holding the latter position from 1932 to 1945.

As President, Roosevelt championed early polio control and social support efforts, although not through the government. An oil tycoon and friend of FDR, along with the President's public relations man, helped catalyze interest in a series of fund-raising dances to celebrate the President's birthday and raise money for a polio rehabilitation facility in Warm Springs, Georgia. Building on this successful effort, in 1938 Roosevelt established the National Foundation for Infantile Paralysis (NFIP) as a private voluntary organization. The NFIP was created not only to raise money ''a dime at a time'' through its annual ''March of Dimes'' fundraising campaigns for a polio vaccine, but also to provide protection against polio's increasing financial threat to American middle-class families. It directly paid the medical, hospitalization and rehabilitation costs on behalf of all polio victims who asked for it [4].

Several public health and political factors guided the Canadian response to the rapidly growing polio problem of the 20th century. The close personal and institutional links between political and public health leaders in health departments across all levels of government were of greatest significance. Supporting those personal links, the Connaught Medical Research Laboratories and the School of Hygiene [5] were two intimately linked institutions within the University of Toronto, under the leadership of Dr. Robert D. Defries (1889–1975) [6]. Connaught stood at the center of Canada's public health network and the evolution of the nation's response to polio. Of particular note, most local health officers and provincial and federal deputy ministers of health were trained at the School and/or spent time at Connaught, and thus shared a common professional education and proactive public health vision driven by Defries and Connaught's founder, Dr. John G. FitzGerald (1882–1940) [7].

The early years of the polio response further strengthened a steadily increasing public-sector investment in public health in Canada, first at the provincial level and then increasingly at the federal level. Beginning in the late 1920s, several provincial governments assumed considerable responsibility for protecting families from the physical and financial effects of polio through specific and non-discriminatory polio hospitalization and after-care policies.

Based on the success of the NFIP in the US, the Canadian Foundation for Poliomyelitis (CFP) was established in 1948–1949. However, by this time, the remarkable success of the NFIP and the breadth of its support of research and patient care for American polio victims had reinforced and helped shape Canadian provincial and federal government interest in undertaking similar work in Canada. By the early 1950s, the CFP played a considerably smaller role than its American counterpart. Its focus was limited to providing support for orthopedic appliances and rehabilitation of individual polio victims, particularly adults not covered by provincial polio policies. Moreover, the CFP had to carefully manage its ''turf relations'' with other voluntary organizations and some provincial governments already helping the disabled in Canada. By 1951, these political tensions resulted in the restructuring of the CFP into independent provincial organizations, such as the Ontario March of Dimes [8].

In contrast, investments in the polio problem in the U.S. were almost exclusively private, focused primarily through the NFIP with minimal involvement of state and federal resources. However, the successful development of the Salk vaccine would require support from both private and public funds, as neither type of investment alone would have sufficed. The involvement of both sectors remains critical to the completion of today's global polio eradication work.

3. Polio and Canadian public health policy, 1927–1953

In 1927, after a decade of relatively low incidence, British Columbia and Alberta were hit by significant polio epidemics. The disease then seemed to march eastward each summer, striking Manitoba in 1928, Ontario in 1929 and 1930, and Quebec in 1931 and 1932. As these epidemics took on increasingly provincial proportions and seemed to move relentlessly eastward, the reality of this disease grew more frightening to the public and public health authorities. Yet the practical effectiveness of medical research and clinical science to combat the disease was increasingly undermined. Beginning in 1927, a human convalescent serum—a passive immune serum collected from the blood of recovered polio patients for use as a prophylactic agent in subsequent cases—was touted as the answer to polio. It was prepared by most provincial governments and stockpiled at public health depots across the Dominion for use during polio outbreaks and in anticipation of the next one [9]. Nevertheless, by 1934 almost half of Canada's disabled population could be traced to polio, a poor testament to the efficacy of this so-called answer to polio.

Canada's second worst polio year was 1937, with a reported case rate of 35.4 per 100,000, or almost 4000 cases across the country, hitting Alberta, Manitoba, New Brunswick, Saskatchewan and, most severely, Ontario. A total of 2546 cases were officially reported in the province, with 119 deaths [10]. The province's newspapers, especially in Toronto, detailed school closings and other desperate public health measures imposed by local and provincial health departments [11].

The 1937 epidemic, unlike previous Canadian epidemics, was characterized by an alarming number of bulbar polio cases. This form of the disease is the most severe. The poliovirus attacks the brain stem's motor neurons, impairs breathing and without the use of an ''iron lung'' respirator results in death. At the start of the epidemic, only one iron lung was available in Canada. It was an original ''Drinker'' iron lung (invented in 1928 by Harvard medical researcher, Philip Drinker) brought to the Hospital for Sick Children in Toronto in 1930. Faced with mounting respiratory paralysis cases across the province, technicians hurriedly assembled a total of 27 iron lungs in the basement of the hospital over a period of six weeks. Each iron lung was paid for by the provincial government and rushed to where it was most needed in Ontario, and also to several other parts of Canada where polio was raging that summer [12].

Faced with an unprecedented number of disabled children after the epidemic, the Ontario government established a program of free standardized treatment and specialized hospitalization for three weeks for all paralytic cases. Parents were instructed on how to care for their polio-stricken children at home following their hospitalization. Doctors and the provincial government worked closely with the Ontario Society for Crippled Children and several visiting nurse organizations to provide follow-up care across the province [13]. A similar pattern of special polio hospitalization policies emerged after polio epidemics elsewhere in Canada during the late 1930s and early 1940s, including a special ''Poliomyelitis Sufferer's Act'' brought in by the Alberta government in 1938 [14].

By the close of 1937, still very little was known about polio. Researchers were entirely reliant on studying the experimental disease in laboratory monkeys, which correlated poorly with the natural human disease. A clear indicator of the dearth of hard science on the subject was the premature use of two polio vaccines in the U.S. in 1935: a ''killed'' vaccine developed by Canadian Maurice Brodie while at the New York Department of Public Health, and an ''attenuated'' type developed by John Kolmer of Philadelphia. Both of these vaccines were quite primitive and based on an inaccurate understanding of the poliovirus. As a result, the Brodie and Kolmer vaccines were ineffective in preventing polio and bore only tragic results [15]. Meanwhile, doctors giving treatment were limited to recommending rest and strict immobilization, and could offer only the convalescent serum, the real value of which was increasingly doubted and debated.

During Ontario's 1937 epidemic, the newest hope of polio prevention was a prophylactic nasal spray that had been first tried in Alabama, and later in Manitoba with unclear results [16]. Public pressure to act was great. The Ontario Department of Health, along with the School of Hygiene and the Hospital for Sick Children, quickly approved a plan to test the spray on 5000 Toronto children in a scientifically controlled clinical trial under Dr. R.D. Defries, Director of the School of Hygiene and Director of Connaught Laboratories. After two rounds of spray treatments, the results proved not only disappointing, but alarming. The spray did not appear to prevent the disease, and many of the children involved in the study lost their sense of smell temporarily, and in some cases, permanently. These results also contradicted the prevailing scientific model of polio's transmission to the nervous system in humans via the nasal portal, based on laboratory research with monkeys [17].

In 1940, Sister Elizabeth Kenny, an Australian nurse, came to North America, bringing a 'radical approach' for the treatment of acute-stage polio [18]. Based in Minneapolis, she made several trips to Canada to instruct local nurses in her methods. She emphasized an early start for the treatment of paralytic polio, the use of ''hot packs'' to relieve pain, and passive movement of the affected limbs to 're-educate' the muscles. These methods were quickly adopted by most Canadian governments and integrated into their polio hospitalization and treatment policies [19].

However, a wave of even larger polio epidemics occurred during the late 1940s and early 1950s in Canada, putting great strain on hospital infrastructure and staff to manage the cases, as well as government financial support to cover the growing costs of care. In 1948, Minister of National Health and Welfare, Paul Martin Sr., introduced an annual $30-million Federal Health Grants Program to assist public health work in Canada. During this pre-Medicare era, the Health Grants Program doubled the federal government's health budget and provided a variety of matching provincial grants to support, among other programs, public health research and development, hospital construction and services for crippled children. Martin's personal experience with polio in 1907 and that of his son, Paul Jr., in 1946 had already raised the Minister's awareness of the great need for boosting polio services through the new grants program in the face of the growing polio threat [20].

Canada's polio epidemic era came to a climax in 1953. During that summer and fall, epidemic polio was felt in Canada from coast to coast, causing nearly 9000 cases and claiming some 500 lives. Ontario experienced its worst epidemic since 1937, while every province from Manitoba west felt the full effects of epidemic polio. In some communities, like Winnipeg, the incidence climbed beyond that seen anywhere in the world up to that time [21]. Most disturbing were the high numbers of bulbar cases among young adults, with many hospitals having to provide rooms filled with iron lungs. The Royal Canadian Air Force was enlisted to make emergency deliveries of iron lungs across the country as the need grew. At the peak of the polio crisis in Winnipeg, 92 cases were dependent on respirators at the same time. This dramatic and desperate situation was repeated, though on a somewhat lesser scale, in many parts of Canada in 1953 and into 1954 [22].

4. Canadian science and the Salk vaccine story, 1947–1955

The University of Toronto's Connaught Medical Research Laboratories had considerable research and production experience with biologicals, such as antitoxins, immune serums and vaccines, as well as insulin. Connaught had produced convalescent serum during the 1920s and 1930s and received its first funding from the NFIP for poliovirus studies in the early 1940s [23]. Connaught's growing involvement in Canada's polio problem was facilitated by its unique, self-supporting, non-profit, university-based organizational structure, and by the close links it had built with and between scientific and public health staff and local, provincial and federal health authorities across Canada. Professional collaboration and collegiality between the public sector and Connaught had clearly evolved since the laboratory's 1913 founding in a humble backyard stable [24].

In 1947, Dr. Andrew J. Rhodes (1911–1995), a leading virologist from England with a special interest in polio, arrived at Connaught Laboratories at a time when a substantial postwar renewal of scientific energies and funding for polio was underway. Increased support came from the NFIP, the Canadian government and the private sector, particularly the Canadian Life Insurance Officers Association. Outside grants for Connaught's polio research work grew sharply from 16% to 48% of all outside grants between 1947–48 and 1953–54 [25]. Rhodes' polio studies were initially focused on developing laboratory methods for polio diagnosis and epidemiological studies of the poliovirus in river waters and sewage [26]. Of special interest were immunological investigations of a dramatic and highly unusual polio epidemic that struck adult Canadian Inuit in Chesterfield Inlet, NWT, near James Bay, during the winter of 1948–49 [27].

Despite the encouraging results of Rhodes and others working on the polio problem, significant progress towards a safe and effective polio vaccine remained stymied until 1949 when a method was developed to grow poliovirus in test tubes using non-nervous tissue cultures. This discovery finally freed researchers from their dependence on laboratory monkeys to cultivate the poliovirus. The Nobel Prize-winning advance—made by a research group in Boston led by Dr. John F. Enders—greatly motivated polio researchers in their work, including Rhodes' group at Connaught [28].

By 1951, Rhodes' research team was able to grow all three types of the poliovirus in a variety of human and monkey tissues [29]. However, this tissue and virus cultivation work depended upon the use of traditional animal-based sera, which could not be used as a human vaccine base, particularly because of potential allergenic reactions to proteins in the sera. None the less in the fall of 1951, a key advance was made at Connaught to overcome this problem when a member of Rhodes' research team, Dr. Arthur E. Franklin, tried a new synthetic nutrient base known as "Medium 199." A complex and chemically pure mixture of over 60 substances, this medium was the first of its kind and originally developed at Connaught in 1949 by Dr. Joseph F. Morgan, assisted by Helen J. Morton, as part of a cancer cell nutrition project under the direction of Dr. Raymond C. Parker [30]. As fellow biochemists, Franklin and Morgan had become friends by 1951 and after hearing about Franklin's poliovirus cultivation research, Morgan suggested he try Medium 199. It worked beautifully [31].

It was not long before Dr. Jonas Salk of the University of Pittsburgh heard about "199" and its ability to provide a non-allergenic base for a human vaccine, a major development that made him confident that he could demonstrate that an inactivated polio vaccine (IPV) could stimulate the immune system enough to prevent polio in humans, just as it seemed to do in laboratory monkeys [32]. Events moved very quickly from that point. In late 1952, the residents of a disabled children's institution near Pittsburgh were the first to receive Salk's vaccine, which was produced with Medium 199 supplied by Connaught. The encouraging results of the trial were presented to the NFIP's Immunization Committee in January 1953 and published in March of that year [33].

In the meantime, Rhodes' research team at Connaught shifted its focus towards the problem of cultivating the poliovirus on an ever-larger scale. The breakthrough came in 1952–53, when Connaught senior researcher, Dr. Leone Farrell, developed the 'Toronto technique' to cultivate bulk quantities of poliovirus fluids. Monkey kidney cells were first grown in Medium 199 using large 'Povitsky' bottles that were gently rocked in specially designed rocking machines. Technicians then carefully infected each bottle of cells with live poliovirus by means of thin glass tubes controlled by mouth. The bottles were further incubated on the rocking machines until the virus infected and destroyed all the cells, leaving a solution of poliovirus in Medium 199, which was then filtered, pooled and precisely tested for potency [34].

With the confirmation of the safety of Salk's experimental IPV vaccine, and reeling from the largest polio epidemic in the U.S. to date in 1952, the NFIP quietly commissioned Connaught to expand its new poliovirus production methods. In July 1953, the NFIP then asked the laboratories to provide all the poliovirus fluids required for an unprecedented, double-blind polio vaccine field trial that was to begin in the U.S. in the spring of 1954 [35]. There was no American counterpart with the facilities or experience to take on such a project.

Through the fall and winter of 1953–54, under the personal supervision of Connaught's Director, Dr. R.D. Defries, large bottles of poliovirus fluids produced by the lab were regularly shipped across the border to be inactivated and processed into a finished vaccine at the pharmaceutical firms Parke, Davis in Detroit and Eli Lilly in Indianapolis. Salk described Connaught's efforts of preparing the fluids in time for the field trial as "Herculean" in magnitude [36]. For Connaught, while a major challenge, the project was similar to its large-scale development of insulin and diphtheria toxoid in the 1920s; heparin and pertussis vaccine in the 1930s; and typhus vaccine, dried blood serum and penicillin in the 1940s [37].

In Canada, the first news of a possible polio vaccine in the U.S. emerged during the summer of 1953, in the middle of the country's worst polio season. The prospect of a vaccine generated intense publicity and raised challenging political issues

for the Canadian federal and provincial governments given the substantial Canadian involvement in the vaccine's development at Connaught.

While a few in his Department were aware of it, Paul Martin, the Minister of National Health and Welfare, first found out about the NFIP's polio vaccine trial and Connaught's major role in it by reading about it in the newspapers [38]. It is possible that a federal election, which occurred on August 10, 1953, in the midst of the 1953 epidemic, played a role in keeping Martin in the dark [39]. Martin's early awareness might have created a difficult election issue and further inflamed public demands for the vaccine that were even more impossible to meet than was the case with gamma-globulin—a concentrated immune serum that, like convalescent serum earlier, was touted as the great polio hope during 1952–53, but was only available from Connaught in limited quantities.

As Dr. G.D.W. Cameron, Deputy Minister of National Health, explained to Martin, Connaught's involvement with the NFIP's trial plans had been kept secret. This substantial involvement was a concern for Cameron, but he did not feel that a separate Canadian trial should be attempted until after the American experiment. A concurrent Canadian trial ''might have some political appeal,'' but he felt it could not be justified on any other grounds. Moreover, as Cameron stressed to the Minister, Canada was ''in an advantageous position since the most difficult part of vaccine production is actually going on in Canada and we can secure supplies for local use as soon as a sound production is established'' [40].

Martin, however, argued that because Connaught's activities with polio had also been financed by the federal government, ''it seems to me we ought to make some arrangement at once to have some of it made available to us'' [41]. Cameron disagreed. Since the vaccine was untested and its safety not yet adequately established, he advised his Minister to watch the American scheme with interest as ''[t]hey will provide the answers and we can benefit from them as quickly, if not more quickly, than any place else in the world'' [42].

The NFIP polio vaccine trial began in the southern U.S. on April 26, 1954 with an elaborate tracking system of some 1,800,000 children who were given: (a) the vaccine, (b) the harmless ''Medium 199'' as a placebo, or (c) nothing and were simply observed to see if they contracted polio. In May, the Canadian government was invited to take part in the trial. However, given the late offer, Canadian involvement was limited to two provinces and one city. The seriousness of the 1953 epidemic catalyzed interest in the field trial on the part of Manitoba, Alberta, and the City of Halifax [43]. At the same time, Connaught focused on preparing and testing its own finished vaccine. In concert with federal and provincial health authorities, Connaught set its sights on planning for a national, all-Canadian, observed/controlled trial of its vaccine to begin in early April 1955, regardless of the results of the 1954 trial in the U.S. [44].

On April 12, 1955, the announcement of the highly anticipated IPV field trial results in the U.S. turned into a major media event. Depending upon the type of poliovirus (I, II, or III), the new vaccine was 60–90% effective in protecting children against the paralytic disease. After licensure by regulators in Washington, six U.S. vaccine producers rush-released their vaccines to meet the demand. Unlike in the field trial experience, the U.S. government did not test each batch of new vaccine produced [45]. Meanwhile, the Canadian trial of the Connaught vaccine had begun on April 1, with the federal and provincial governments sharing the full cost of the vaccine and distributing it free to children in grades 1 to 3 (6- to 9-year-olds), who were considered most susceptible to polio [46].

But at the end of April, public euphoria over the Salk vaccine was shattered when 79 American children, given the polio vaccine produced by Cutter Laboratories in California, contracted paralytic polio. This development forced Cutter's vaccine off the market, and on May 8, the U.S. Surgeon General suspended the entire American vaccination program. The problem was limited to Cutter Laboratories, and later found to be caused by incomplete inactivation of the poliovirus in selected lots.

In Canada, Paul Martin faced one of his most difficult political decisions. Should he follow the example set by the U.S. Surgeon General and call off the Canadian polio vaccine clinical trials? Prime Minister Saint-Laurent wanted to follow the American lead and cease the immunization program. Based on Connaught's long experience with the development of the vaccine, coupled with his personal experience of the disease, Martin maintained his confidence in the Canadian-produced vaccine. Moreover, he was hesitant to bring the issue to Cabinet, where other Ministers may well have forced a cancellation of the program based on unsubstantiated fears and minimal knowledge of the facts. Thus, after consulting with Defries (who was sent to the U.S. to investigate the situation), senior officials in his Department, as well as provincial health authorities, and with no reports of polio cases associated with the vaccine in Canada, Martin, under his own authority, insisted the Canadian immunization program continue. On May 7, he publicly announced his decision, saying ''I am satisfied that the Connaught Laboratories, at present the sole source in Canada of the vaccine, is engaged in doing everything it can to provide the maximum amount for the use of our children'' [47].

The Canadian success in manufacturing and freely distributing a safe polio vaccine contrasted sharply with the tragic events south of the border. It generated considerable media attention and political debate in the U.S., in particular highlighting the differing levels of government funding for public health between the two countries and the contrasts in planning, testing, distributing and paying for the vaccine [48]. The Canadian decision to continue also meant a great deal to Jonas Salk personally and played a major role in ensuring the future international use of the IPV vaccine in the control of polio.

5. From Salk to Sabin, 1955–1962

Immunization with the Salk vaccine clearly struck a crippling blow to paralytic polio, but did not definitively end all

outbreaks of the disease. By June 1956, Connaught had delivered 2.3 million doses of Salk vaccine in Canada, enough to bring the total population of vaccinated children less than 10 years of age to 1,800,000. Of this group, 90% had received at least two doses [49]. By this time, Connaught's vaccine was clearly demonstrating its effectiveness in preventing paralytic polio among those who received it, reinforcing the results of the original American field trial. Based on evidence collected in several provinces during and after the 1955 Canadian polio immunization program began, it was clear that those children receiving two or three doses of the vaccine in 1955 experienced significantly less paralysis in 1956 than those who did not.

Nevertheless, assessing the impact of the Salk vaccine on wild poliovirus infection rates in Canada and the timing and geographic scope of polio outbreaks was difficult. During the 1950–55 period there were wide natural variations in incidence of paralytic polio in Canada that peaked in 1953 and then sharply declined in 1954 and 1955. National incidence remained low during 1956 and 1957, when it dropped to an attack rate level not seen since 1926. In 1957, of more significance was the substantially higher paralytic attack rate among children under 5 than any other age group, the highest being among 2-year-old children. At the same time, the paralytic attack rate for adults from 20 to 39 was as high or higher than reported among school-age groups. This situation fueled an unexpected wave of polio outbreaks and epidemics in several provinces in 1958, 1959 and 1960, these events prompting more aggressive polio immunization campaigns across the country, especially among adults [50].

As part of a broader strategy to boost polio, as well as general pediatric immunization levels in Canada, in 1956 Connaught researchers began working on adding the Salk polio vaccine to its standard diphtheria/pertussis/tetanus (DPT) product. In 1958–59, the federal and provincial governments extended their shared-cost payment arrangement for the Salk polio vaccine to the newly licensed DPT–Polio vaccine combinations (including DT–Polio and T–Polio) to reinforce free and universal polio immunization among older age groups [51]. Meanwhile, beginning in 1957, and once a stable and sufficient Canadian supply was available, Connaught's Salk vaccine was exported to Czechoslovakia and Great Britain, and soon to some 44 other countries that had limited or no local vaccine supply and would otherwise be without protection against the growing global threat of polio [52].

While expanding the production and use of the Salk polio vaccine nationally and internationally, Connaught also intensified its research focus in 1958 on the development of a trivalent oral polio vaccine (OPV), using attenuated poliovirus strains developed by Dr. Albert Sabin of Cincinnati [53]. While developing OPV production methods, Connaught played an important role in facilitating the evaluation and international supply of the Sabin vaccine by conducting a well-coordinated series of field ''demonstrations'' of the vaccine in Quebec, Saskatchewan, Nova Scotia and Manitoba in 1960–61 [54]. In particular, a series of pioneering genetic stability studies of attenuated polioviruses were conducted in Quebec City and Montreal [55]. Based primarily on these Canadian demonstrations—held under the supervision of a special technical advisory committee of the Dominion Council of Health headed by Dr. A.J. Rhodes—a trivalent Sabin vaccine was licensed in Canada in March 1962 [56].

During this period, the international politics surrounding the live polio vaccine (OPV) became more challenging. Several countries hosted large scale oral vaccine field trials based on rival vaccine strains, although Sabin's seemed the safest. Deep in the Cold War period, Sabin's vaccine attracted the most attention when the Soviet Union boldly vaccinated its entire population with the vaccine in 1959, and then offered to give it away to any country willing to accept it. This situation was further politicized since no American vaccine could be exported without a federal license: it had to first meet domestic standards. In Canada, an export license for the vaccine was not required at the time, and Connaught had only to satisfy the requirements of the importing country. This provided Connaught with an advantage over American OPV producers. Connaught was thus freer to export its still unlicensed vaccine to countries desperate for any kind of protection from epidemic polio. For example, in 1961 a 3-million-dose supply of OPV was rushed to Japan to bring a major polio epidemic under control [57].

6. From Sabin to Salk, 1962–1995

By 1962, to have not one, but two, highly effective vaccines available against a dreaded disease was unique in medical history. The Salk inactivated injected (IPV) and the Sabin attenuated live oral (OPV) vaccines were quite different in approach, production and administration. In some jurisdictions, it was clear to public health authorities that both vaccines could work well together, utilizing their relative strengths to prevent polio and limit the risks of inadvertently causing the paralytic disease. Such a view was common in Canada by the time OPV was licensed. In other countries, such as the U.S., choosing and maintaining the use of one type of polio vaccine over the other seemed preferable for various practical, epidemiological, political and legal reasons.

After the Canadian licensing of OPV, research and development efforts at Connaught did not stop with OPV and IPV. Both vaccines could be further perfected. Rapidly changing national and international regulatory standards, new technologies, and growing international demand for polio protection drove scientists at Connaught towards developing better polio vaccines of both types. For example, Connaught licensed a concentrated and purified IPV in 1965. By 1976, a new large-scale poliovirus cultivation technology called the Multi-Surface-Cell-Propagator (MSCP) was developed at Connaught. One MSCP unit had a cell growth surface area equal to between 31 and 55 of the ''Povitsky bottles'' used in the original Toronto method of ''rocking bottle'' cultures [58]. In 1989, Connaught introduced an enhanced potency inactivated poliomyelitis vaccine (eIPV), produced on a cell substrate of MRC-5 human diploid cells using microcarrier

cultures in large 1000-litre fermentors. After a complex and precise production process lasting 18 months, one small vial of MRC-5 cells produced some 700,000 doses of eIPV.

Beginning in 1955, all provinces and territories in Canada used polio vaccines produced by Connaught. After January 1959, they all adopted the combined DPT–Polio (diphtheria, pertussis, tetanus, polio vaccine) product, and its variations, DT–Polio (diphtheria, tetanus and polio vaccine) and T–Polio (tetanus and polio vaccine) for adults. In 1962, with the licensing of Connaught's trivalent OPV, some provinces switched exclusively to this product, while others switched to a mixed Salk/Sabin schedule. Nova Scotia and Ontario have used IPV exclusively since 1955 (except during Ontario's IPV shortage in the early 1990s). Newfoundland, Saskatchewan, Manitoba, Alberta and Prince Edward Island adopted a mixed schedule of IPV and OPV as of 1962. Newfoundland, Saskatchewan and Manitoba then switched to an exclusive OPV schedule during the 1970s, as did Alberta in the 1980s. Newfoundland switched back to an exclusive IPV schedule in 1979. British Columbia, New Brunswick, Quebec and the northern territories adopted an exclusive OPV schedule in 1962 [59]. In 1985, Connaught introduced a new line of ''adsorbed'' polio combination vaccines, which contained an aluminum phosphate adjuvant. This improvement increased the potency of the tetanus and diphtheria components and permitted a reduction in the dose volume from 1 ml to 0.5 ml.

Between 1994 and 1997, all Canadian provinces and territories transitioned to the exclusive use of the new enhanced potency eIPV in a new pentavalent pediatric vaccine combination product known as Penta™, which also included DPT and Hib (*Haemophilus influenza* type b vaccine). By 1998, all provinces had shifted to using eIPV in an improved pentavalent combination product, Pentacel™, which included the less reactogenic and more efficacious 5-component acellular pertussis vaccine.

All of these immunization strategies have proved to be highly effective in eliminating polio. At the peak of Canada's polio epidemics in 1953, almost 9000 cases were reported. By 1965, a decade following the introduction of polio immunization in 1955, only three cases were reported nation-wide, and no cases of wild poliovirus were reported in Canada in 1968. Indeed, by the time that OPV was introduced in 1962, Canada was well on its way to eliminating polio. A total of 89 cases were reported in 1962, 123 in 1963, and only 19 in 1964. Annual cases of wild poliovirus since 1968 have ranged from 0 to 9. An additional 12 cases of paralytic polio have occurred in contacts of OPV recipients, and four OPV recipients have experienced vaccine-associated polio paralysis.

Thus, the Canadian experience with polio vaccines can be divided into two periods: the initial elimination of endemic polio and the maintenance of polio immunization. The greatest reduction in the incidence of polio was achieved between 1955 and 1964 when total annual cases were reduced from a high of 1886 in 1959 to 19 cases in 1964. This was achieved primarily with IPV, which was used by all provinces between 1955 and 1962 in the form of the combination DPT–Polio vaccine product. Ontario and Nova Scotia, maintaining an exclusive IPV schedule beyond 1962, achieved an equally effective control of polio as the other eight provinces that introduced OPV alone or with IPV.

The last outbreak of wild polio in Canada was caused by an imported, unimmunized case from the Netherlands in 1978 and then spread among local groups in Ontario, Alberta and British Columbia that, like the original Dutch case, had refused the vaccine on religious grounds. A total of nine polio cases were the result. In 1992–93, a similar episode involved a polio outbreak in the Netherlands among the same unvaccinated religious group as in 1978, resulting in 68 cases of polio caused by the wild virus. While there was an isolation of wild-type 3 poliovirus in southern Alberta linked to the Netherlands outbreak, unlike in 1978, there were no cases of polio reported in Canada [60]. Since 1993, no cases of wild polio have occurred in Canada. Based on extensive experience using both IPV and OPV, polio immunization in Canada has been an unqualified public health success, completely eliminating the disease.

Canada has been fortunate to have utilized multiple immunization approaches in various provinces over the last 50 years: OPV alone, IPV alone or in combinations, mixed schedules, IPV followed by OPV, and IPV combinations with DPT or DTacP and Hib combinations. This experience provides much food for thought with respect to post-eradication plans for the use of polio vaccines under consideration by different countries.

Like many other industrialized countries, Canada is now in the unprecedented situation of having a large cohort of children and adolescents that are fully immunized against polio, but have grown up un-challenged from natural exposure to polio. Most Canadian adults received a full series of immunization in childhood, but have not been boosted since. Waning polio immunity today is due to the lack of adult boosting, growing anti-immunization tendencies among some parents, and general complacency about the now nearly invisible polio. Ontario is the only province where Td-Polio boosters were offered to high school children routinely until 2003. Thus, at a time of complete polio elimination in Canada, the number of susceptible individuals could actually be increasing, placing those individuals at risk for imported cases of polio. Public health officials must remain vigilant to ensure that post-polio-elimination immunization strategies, including boosting strategies, are in place in Canada for any future polio outbreaks.

7. Canada and global polio eradication

Building on the success of the global smallpox eradication effort during the late 1960s and 1970s, the World Health Assembly in 1988 resolved to eradicate polio globally. At the forefront of the eradication effort is the Global Polio Eradication Initiative (GPEI). The GPEI is spearheaded by the World Health Organization (WHO), UNICEF, Rotary International, and the U.S. Centers for Disease Control and Prevention (CDC) and is the world's largest-ever public health endeavor.

In addition to the key organizations noted above, the initiative includes national governments; private foundations (e.g., United Nations Foundation, Bill and Melinda Gates Foundation); development banks (e.g., World Bank); donor governments (e.g., Australia, Belgium, Canada, Denmark, Finland, Germany, Italy, Japan, UK, USA) and corporate partners (e.g., sanofi pasteur, De Beers). Volunteers in developing countries also play a key role, with thousands participating in mass immunization campaigns every year.

Through the work of the GPEI, health authorities and their partners have pledged to make polio the first disease of the 21st century to be fully eradicated. When the GPEI began in 1988, wild poliovirus was endemic in more than 125 countries on five continents, paralyzing more than 1000 children every day. Since then, GPEI has slashed polio cases by more than 99%, and indigenous polio has been eliminated from all but six countries of the world. Roughly two billion of the world's children have been immunized against polio with the cooperation of more than 200 countries and 20 million volunteers, and funded by an international investment of US$3 billion. The expected gains from global polio eradication, apart from alleviating an estimated 350,000 annual cases of polio, have been evaluated at a savings of US$1.5 billion annually.

From its Connaught Campus, sanofi pasteur has supplied a large percentage of the OPV used in global eradication efforts. Much of the vaccine has been purchased through UNICEF, including 7.2 million doses in 1998 and another 20.8 million in 1999–2000. In March 2000 after 40 years of provision, OPV production ended at the Connaught Campus as even larger OPV production capacity became possible within Aventis Pasteur (now sanofi pasteur) facilities in France. The Connaught Campus, however, has since boosted its IPV production to meet growing global demand.

The global eradication of polio requires a broad program of initiatives, ranging from massive immunization activities to aggressive laboratory containment of poliovirus stocks. The GPEI has relied on four strategies to achieve its goals: routine immunization, mass campaigns (National Immunization Days or NIDs), surveillance and house-to-house ''mop-up'' campaigns. Using these strategies, GPEI seeks to eradicate polio by 2008.

In 1994, the WHO Region of the Americas was certified polio-free. In 2000, the WHO Western Pacific Region (including China) was certified polio-free, and the WHO European Region has been free of polio since 2002. However, the GPEI suffered setbacks in Africa in 2004 when Nigeria suspended vaccination in some states, and a multi-country epidemic broke out. By end of December 2004, a total of 1113 polio cases had been reported in the six endemic countries and in 10 African countries in which the disease was imported. Fortunately, immunization efforts had resumed in Nigeria in July 2004, and mass campaigns in 22 African countries are now targeting 74 million children.

In a unique situation, Egypt, a polio-endemic country, has succeeded in eliminating two of the three types of poliovirus. However, despite repeated vaccination campaigns with trivalent OPV, type 1 poliovirus continues to circulate in two densely populated regions of Egypt (Menia/Assiut and Cairo/Giza). In response, GPEI and Egypt's Ministry of Health have decided to go beyond the traditional eradication approach of vaccinating against all three types of polio at one time. Egyptian health authorities and WHO, in collaboration with sanofi pasteur, have developed a monovalent oral poliovirus type 1 vaccine (mOPV1) for use in addition to trivalent OPV. Experts believe that administering the monovalent vaccine will mean that more children in Egypt will develop immunity to type 1 poliovirus, thus reducing the opportunities for further transmission. The monovalent OPV will be used in specific targeted campaigns in the two regions mentioned above, along with trivalent OPV that will be used for routine immunization activities in these two regions and in the rest of Egypt.

In part because of its own history with polio, Canada has been particularly sensitive to the world's needs for combating the disease. Canada has an international reputation as a world leader in global smallpox and polio eradication efforts, and vaccine development. Since 1988, Canada has been one of the top five donors to the GPEI, contributing a total $110 million to polio immunization efforts.

The Canadian International Development Agency (CIDA) committed $10 million annually for 5 years (1998–2002) to support the Canadian International Immunization Initiative (CIII) and renewed that commitment in 2003, with an additional $80 million for the period 2003–2008. CIII is Canada's contribution to the Expanded Programme of Immunization (EPI). EPI is a WHO program, in partnership with governments, UNICEF, other United Nations agencies, bilateral development agencies and non-governmental organizations (NGOs), to immunize the world's children against six vaccine-preventable diseases: measles, diphtheria, pertussis, tetanus, tuberculosis and polio.

In another example highlighting the deep personal links in Canada to polio elimination, polio survivor and then federal Minister of Finance, Paul Martin Jr., invited Canadian big business CEOs attending a Rotary International reception in May 2002 to donate a further $5 million for polio eradication. Any funds raised at this event were matched dollar-for-dollar by the Bill and Melinda Gates Foundation, and by 150% by the WHO. Highlighting his personal polio story and the work of his father in introducing the Salk vaccine, Martin was joined in his advocacy presentation by GPEI's director, Dr. Bruce Aylward, a Canadian epidemiologist from Newfoundland [61].

As indicated above, the world witnessed a resurgence of polio outbreaks in central and western African countries in 2004 caused by low immunization coverage and the importation of wild poliovirus. In response, the GPEI— together with the WHO, affected countries and the international community—is dramatically expanding polio immunization activities in 2005 and 2006 to meet its eradication targets and halt the spread of the disease. At the same time, GPEI launched an appeal for funding to support these efforts, indicating that an additional US$200 million would be required through the end of 2005,

with an initial US$35 million urgently needed by mid-January 2005. On January 17, 2005, the government of Canada announced $42 million in funding to support the GPEI and meet the immediate shortfall.

Canada's humble beginnings in the fight against polio have brought the world forward to what all had hoped for—a world without polio. The fight had begun in earnest with the development of the first inactivated polio vaccine at Connaught Laboratories in the early 1950s. Now, the world prepares for the last stages of polio eradication and must address the complex questions surrounding global post-eradication vaccination policy. It must also struggle with managing the long-term after-effects of the disease, including post-polio syndrome.

Sustained collaborative support is critical to achieve the ultimate goal of certification of a polio-free world. As long as a single child has polio, children in all countries remain at risk of contracting the disease, given that the virus can be imported easily and spread rapidly. Therefore, in preparation for the vaccine needs of the post-polio eradication era, sanofi pasteur, at their Connaught Campus, has already increased production of acellular pertussis vaccine combinations containing IPV. Moreover, sanofi pasteur is actively working with WHO and various other partners to assist in the development of policies and strategic plans for the use of inactivated polio and combination vaccines, and stockpiling of oral polio vaccines—including monovalent OPV—to ensure that the risk of polio is minimized for children and adults in the future.

A polio-free world will be, in part, a testament to the great Canadian scientists who helped to develop the world's first polio vaccine. It will also speak to the courage of Canada's Minister of National Health and Welfare, the Honorable Paul Martin Sr. And finally, it will be an acknowledgment of all Canadians—through the contributions of their governments and the many individual public health and health care professionals, vaccine industry experts and academics who worked hard to bring Canada's freedom from polio to the rest of the world.

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