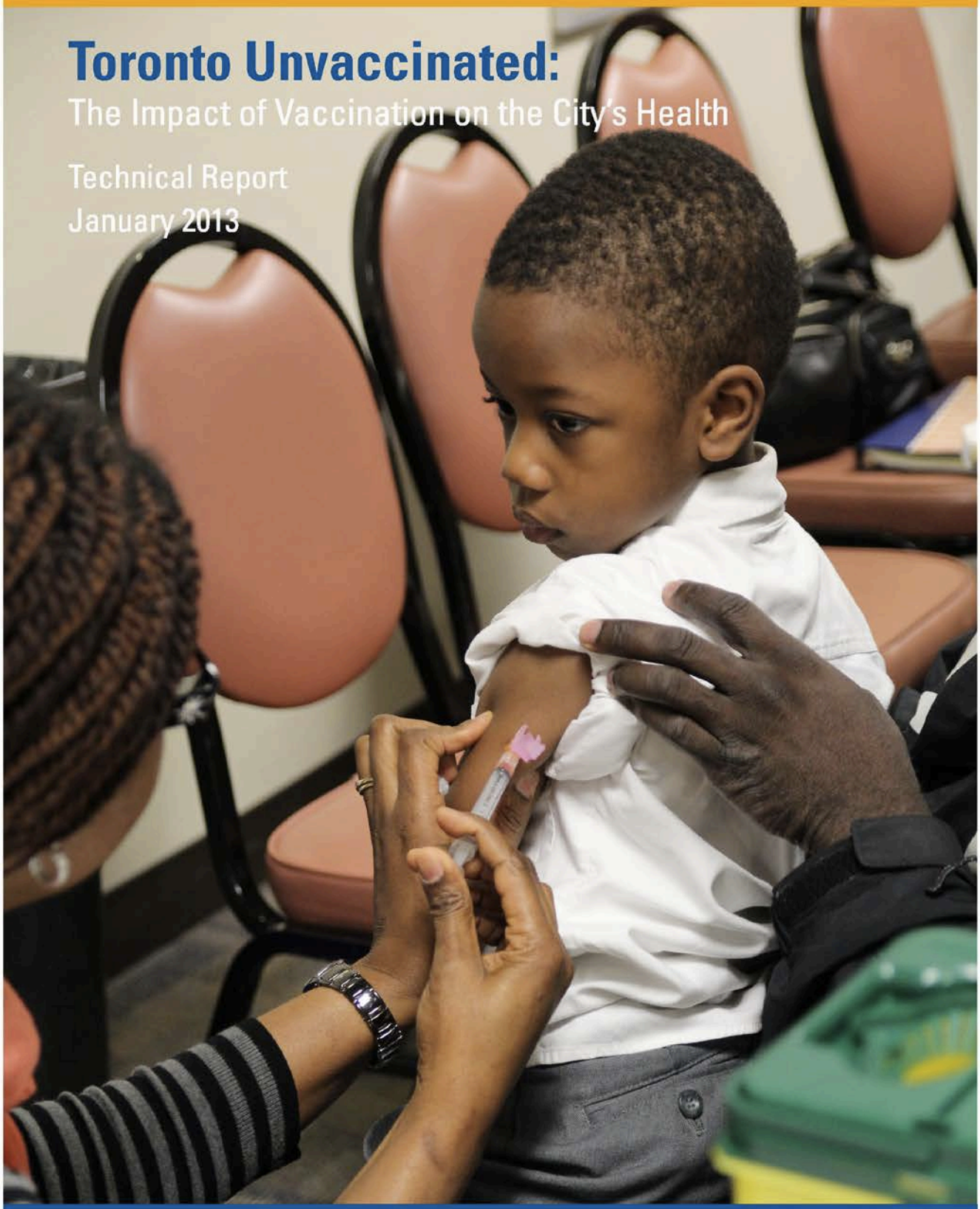
Toronto Unvaccinated:

The Impact of Vaccination on the City's Health

Technical Report

January 2013



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Executive Summary

Vaccines have saved more lives in Canada in the last 50 years than any other health intervention. As the threat of infectious diseases receded with the widespread vaccination, public understanding of the impact and importance of vaccination has also declined. Most families with young children have never seen a child with measles; most have no fear of the paralysis brought on by polio. This is a very different reality from the one that existed when these vaccines were first introduced. Today, many parents are concerned about vaccine safety. Some may decline or refuse one or more vaccines for their children.

This report is in response to a growing trend for vaccine hesitancy among parents, increased rates of vaccine exemptions across the U.S.A. and large outbreaks of diseases prevented by vaccines, such as measles in recent years in Canada, the U.S.A. and Europe. This report also outlines some of the successes and ongoing challenges associated with vaccination.

The goal of the current project was to estimate the benefit created by vaccination in Toronto, by comparing our current disease trends to the expected disease trends in a (simulated) identical city where vaccination is withdrawn. Mathematical modeling has been used to estimate this impact on the health of Torontonians if vaccine coverage were to decline. The three diseases of polio, measles, and pertussis have been chosen to estimate this impact. Even though wild polio has been eradicated in North America, it still circulates in a number of countries. Travel to and from these countries means that unvaccinated individuals are at risk. Measles is highly infectious and requires very high immunization coverage in the population to stop disease from spreading. Outbreaks occurring in Europe, and the U.S.A are also a threat in Toronto, if our immunization coverage drops even by a small amount. Pertussis continues to be found in Toronto. Including this disease in the mathematical model demonstrates the impact of reduced vaccination coverage on the health of infants and young children primarily.

Key Findings

- Our models show that the health gains provided by vaccination in Toronto are large, but would not persist if vaccination coverage were to decline. Large costs in both health and economic terms, would be incurred by the city if levels of vaccination were permitted to decline sufficiently. As such, control of diseases via vaccination (even against diseases that are not currently circulating in the city) should be regarded as an ongoing “work in progress”, rather than a “mission accomplished”. Continued investment and resources are needed to maintain the health gains that vaccination has provided in our city.
- Both for diseases that currently cause minimal morbidity and mortality (measles and polio) and for pertussis, which continues to cause significant disease in Toronto, declines in vaccination are projected to cause increases in illness and disease outbreaks in the near term. Following large declines in vaccine coverage, we would expect to start seeing significant disease outbreaks in as few as 5 years.
- In the long term, even small reductions in vaccination coverage below current levels are sufficient to create significant public health hazards in Toronto.
- Although polio has been eliminated in Canada, the highly connected nature of Toronto, as a result of international commerce, immigration, and tourism, means that asymptomatic polio

cases are likely already arriving in the city on an infrequent but ongoing basis. Current high vaccine coverage in the city is preventing disease spread, but polio could return to Toronto if vaccine coverage were to decline significantly. At extremely low levels of vaccine coverage, Toronto could expect to observe a case of paralytic polio in 5-10 years.

- The highly infectious nature of measles, combined with measles persistence elsewhere in the world, makes local measles outbreaks and hundreds or thousands of illnesses likely following even small declines in vaccine coverage.
- Pertussis remains a common cause of illness in Toronto at the time of writing, and it is possible that both the short duration of protection by new pertussis vaccines and transmission by teens and adults contribute to ongoing risk even with high levels of vaccine coverage. Nonetheless, reduced pertussis vaccine coverage, even under such suboptimal circumstances, would result in as much as a six-fold increase in the risk of severe disease in infants.

Table of Contents

List of Figures and Tables

Section 1: Introduction

Vaccination is one of the major public health success stories of the last century.

In the early 20th century communicable diseases were the leading causes of death in Toronto and other large cities. The enormous decline in infectious disease which occurred over that century began before most vaccines were available, due to improvements in sewage disposal, drinking water safety, nutrition and housing. However, many infectious diseases continued to cause significant morbidity and mortality until they were brought under control by widespread vaccination (**Figure 1.1**).

Unfortunately, since that time vaccination has become a victim of its own success. As the incidence of vaccine-preventable diseases (VPD) declined, the level of public concern about these diseases, and consequently public willingness to accept vaccination (and its small but finite risks) has declined as well.

Figure 1.1. Infectious disease deaths have declined dramatically in Toronto

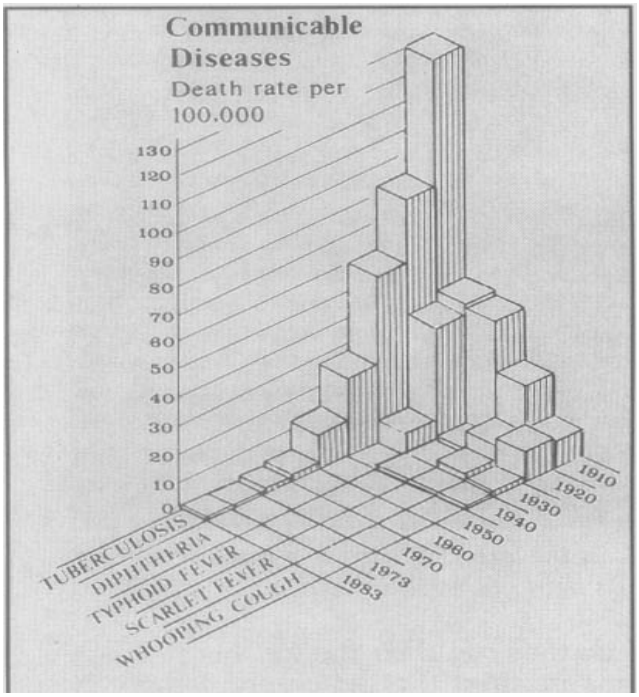


Figure Details: Communicable disease mortality rates in Toronto, 1910-1983. From: Toronto Department of Public Health – Annual statement, as reproduced in (1).

Many cities, including Toronto, have seen cases of diseases, such as measles, which had all but vanished a decade ago. Misperception of actual vaccine risk may have contributed to a decline in vaccine acceptance. Other factors that may contribute to public distrust of vaccination include: challenges in the management and communication of uncertainty about vaccine risks; less risk tolerance for vaccines given to healthy individuals than for drugs used to treat an illness;

difficulty in distinguishing adverse events that are coincidental from true cause-and-effect relationships following vaccination; mistrust of the business and financial motives of the vaccine industry and their perceived pressures on public institutions; misinformation about vaccines and vaccine safety, and outright non-acceptance of scientific evidence (2). We further discuss challenges to vaccination in **Section 3** of this report.

Vaccines work best when they are widely accepted.

A parent who vaccinates their child against an infectious disease not only lowers that child's risk of infection, but also makes it unlikely that this child will serve as a source of infection for others in the community. Once a critical fraction of the population receives the vaccine (achieving so-called 'herd immunity', which depends on how easily a disease is spread to others), the introduction of that infection (for example, via importation from a region where disease transmission is ongoing) into a community no longer results in a self-sustaining chain of disease transmission. The disease is then eliminated from that community. If individuals believe they can gain the benefits of vaccination (as a result of herd immunity), without themselves accepting the small, and often exaggerated, risks associated with vaccination, some will choose not to get vaccinated. But, as vaccine coverage rates decline, pockets of individuals that are not protected against infection are created; if a disease is introduced into a community that has groups of unvaccinated individuals, there is a possibility that the infection will spread and a community will experience a disease outbreak.

A globally connected city such as Toronto needs to be particularly vigilant against novel and established infectious disease threats.

Toronto is home to a diverse population; almost 50% of our residents were born outside Canada (3) and 55% of Ontario's newly arrived permanent residents settled in Toronto in 2010 (4). This diversity presents challenges to infectious disease control for two main reasons: (i) the epidemiology of some diseases varies by country (e.g., individuals from the tropics are less likely to be exposed to chickenpox during childhood; individuals born in some countries are more likely to be carriers of hepatitis B) and (ii) immunization schedules, products, and records in other countries may differ from Canada, making it challenging to determine the immunization status of newly arrived immigrants to Canada (5).

As the 2003 SARS outbreak demonstrated (6), the city's role as a global travel hub makes it vulnerable to emerging infectious disease threats. Toronto is a destination for many international travelers, and in turn, Torontonians travel extensively across the globe. A unique class of traveler is immigrants to Canada who return to their country of origin to visit friends and relatives. Research has shown that these travelers have an increased risk of acquiring infections, compared to other tourists (7). This class of travelers is less likely to seek pre-travel health advice and receive recommended vaccinations, is more likely to stay in remote rural areas, consume high-risk foods, and have longer trip durations (8). All of these factors may contribute to their increased likelihood of acquiring an infectious disease during their travels (8). The rapidity and ease of international travel creates the opportunity for isolated infectious disease outbreaks in far-flung regions of the world to directly impact our own communities, via case importation. Maintaining population protection against infectious diseases through vaccination is the most

effective way of ensuring that vaccine-preventable diseases that have been eliminated in Canada do not become reestablished.

Mathematical models are tools that can help us understand how infectious diseases spread in a population.

A model is a simplified representation of a complex real-world event or structure, whose goal is to explain or predict observed phenomena (9). Mathematical models of infectious diseases are tools that capture the dynamic nature and spread of diseases from infectious to susceptible individuals and are based on a system of equations that describe observed data (9). Epidemic models are often composed of "compartments" that describe the susceptibility (able to be infected with a particular infectious disease), infectiousness (infected with a disease and able to spread it to others), or immunity (protected from being infected) of individuals in a population, and "parameters" (numbers) that describe how individuals move between these different health states (10).

We can use models to build an "alternate future" where vaccination coverage in Toronto declines and look at the impact this would have on the health of Torontonians.

Mathematical modeling provides an important tool for demonstration of the "silent good" (absence of disease occurrence) that has been created by high levels of vaccine coverage. When considering vaccination, models allow us to look at alternate scenarios that would not be possible to replicate in the real world; we can represent, an "alternate future" in which vaccine coverage declines sharply, and project the impact on Torontonians that such a decline would have. Some key concepts that emerge from mathematical models of infectious diseases are described in **Appendix 1**.

To quantify the benefit created by vaccination in Toronto, we focus on polio, measles, and pertussis, three vaccine-preventable diseases that exemplify specific disease control challenges faced by public health and medical professionals.

The goal of the current project is to quantify the benefit created by vaccination in Toronto, by comparing our current disease trends to expected disease trends in a simulated, identical city where vaccination levels are declining. To do this, we have focused on three vaccine-preventable diseases: poliomyelitis, measles, and pertussis (whooping cough). The rationale for focusing on these diseases relates to each highlighting a particular challenge faced by public health and medical professionals at the time of writing.

Poliomyelitis: This much-feared disease has been eliminated in Canada, with the last (asymptomatic) case reported in 1996. However, polio remains endemic in other parts of the world, and nearly half of all paralytic polio cases reported in 2009 to 2011 occurred in people living in polio-free countries who were infected by virus imported from an endemic country (11). Global connectedness makes polio reintroduction into previously polio-free regions an ongoing concern.

Measles: This extremely contagious disease has also been eliminated in Canada, but measles activity elsewhere remains high and there continue to be cases of imported and import-related measles cases in Canada (12). Measles cases in the city are uncommon, and outbreaks have been rare in recent years. Measles' high transmissibility means that even small decreases in vaccination coverage could lead to reestablishment of endemic transmission in Toronto, given the high frequency of travel between Toronto and countries with ongoing measles transmission. Additionally, the false linkages between measles vaccine and autism, which have been amplified via media coverage, have created a real danger of decline in measles vaccine coverage.

Pertussis: Pertussis incidence has decreased dramatically in Canada since the implementation of vaccination programs, but it has not been eliminated and recent outbreaks in many regions have been a source of considerable concern. In pertussis, we find a disease that demonstrates the ongoing disease control challenges that can exist even in the face of high levels of vaccine coverage, and in the context of changing vaccine preparations and vaccine schedules.

In the sections that follow, we first describe some vaccination success stories and vaccination challenges. We then focus on each of the above infectious diseases in turn, describing historical and current disease trends, details about the vaccines used to protect against these diseases, and use mathematical models to demonstrate the impact that changes in vaccine uptake in the Toronto population would be expected to have on future disease occurrence.

Section 2: Vaccination Success Stories

Toronto and the advent of the vaccination era

Before vaccination, infectious diseases were rampant in Toronto.

To understand the dramatic impact of vaccination on the health of Canadians, it is informative to consider what the infectious disease landscape in Canada, and Toronto in particular, looked like in the era before vaccination and how vaccination dramatically altered that landscape. We will focus on smallpox and diphtheria, two formerly common and devastating communicable diseases that have been controlled with the help of vaccination, and illustrate some of the challenges and successes associated with their elimination.

Typhoid, smallpox, lack of basic sanitation facilities: these were just some of challenges facing Toronto's first Medical Officer of Health, Dr. William Canniff, when he was appointed in 1883 (13). Early on, public health practitioners in Toronto recognized the importance of social determinants of health (14) for controlling infectious disease, and conversely, the importance of controlling infectious diseases for social progress (1). Public health in Toronto focused on providing clean water and air, and adequate housing and nutrition, recognizing that these social reforms were critical for maintaining health and preventing disease (1). Prior the advent of vaccines and antibiotics, the major tools available for disease control during outbreaks were isolation of infected individuals and quarantine of individuals exposed to infected cases. Both of these control measures relied on prompt reporting of disease occurrence to public health authorities to effectively limit disease spread. The consequences of these interventions could be both emotionally and financially distressing, frequently requiring the removal of ill individuals to city-sponsored isolation facilities (1).

Smallpox

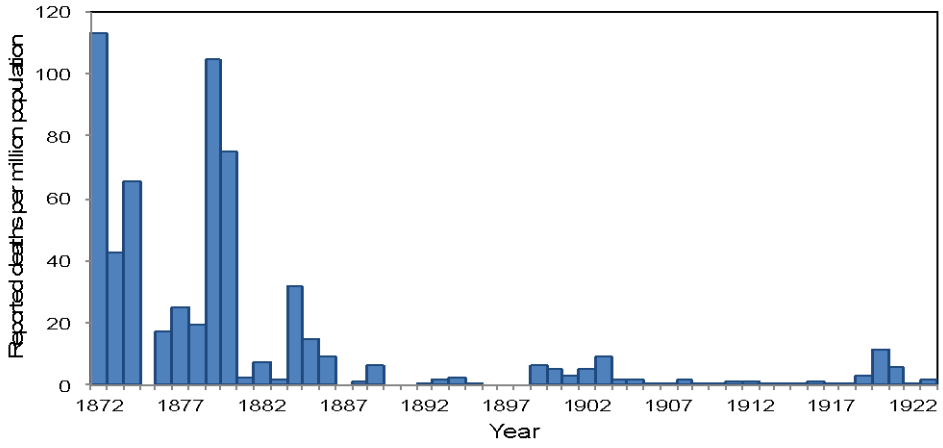
Although smallpox vaccine had been available in North America since the late 18th century, it was the widespread use of smallpox vaccination in the mid-1880s that provided a novel infectious disease control tool for public health practitioners, allowing them to focus on disease prevention rather than outbreak control.

Smallpox epidemics were once common and devastating.

Throughout the 19th century, epidemics of smallpox, a viral infectious disease, were a common and devastating occurrence (**Figure 2.1**). The severe form of smallpox, variola major, had a mortality rate of 20-50% (15). Between 65-80% of survivors were marked with deep, pitted scars, most prominent on the face, and blindness was another serious complication (16).

Figure 2.1. Smallpox epidemics were once common, resulting in deaths in (a) Ontario and (b) Toronto (formerly York County).

(a)



(b)

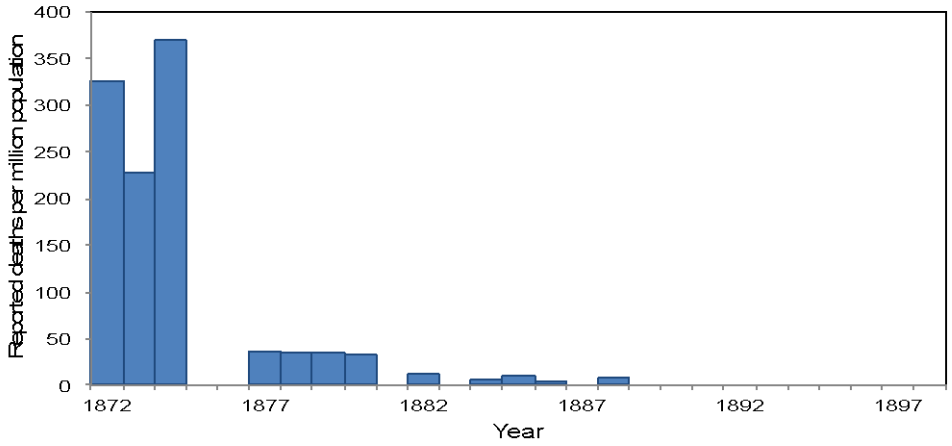


Figure Details. Reported smallpox deaths per million population in (a) Ontario (1872-1923) and (b) York county (1872-1898). Case data were obtained from the Annual Reports of the Department of Heath (17) and population data were obtained from the Canadian census (18). Note that smallpox vaccination became widely available in the 1880s.

Travel contributed to the spread of smallpox.

The role of travel in helping to spread communicable diseases was a recognized concern; an outbreak beginning in Montreal in 1885 led to the development and refinement of many of Toronto's disease control polices, as the city attempted to prevent a widespread outbreak. Edward Jenner had demonstrated that inoculation with cowpox could protect against smallpox, leading to the first use of vaccination as a disease prevention tool; its first documented use in Canada was in 1796 (19). In response to the Montreal epidemic, the first efforts at smallpox vaccine production in Ontario began in 1885, with the establishment of the Ontario Vaccine Farm (20). Ontario passed legislation to make smallpox vaccination compulsory during epidemics, but Toronto's Medical Officer of Health maintained vaccination as a voluntary act, in an effort to establish public support of vaccination (1). Vaccine uptake tended to wax and wane with the threat of smallpox outbreaks. With the introduction of vaccines also came public concerns about vaccine safety and vaccine legislation, leading to the establishment of an anti-vaccination league in Toronto (1).

The availability of a safe and effective vaccine led to a dramatic decline in smallpox, eventually resulting in disease eradication.

Over time, with improvements in vaccine quality and safety, and as the effectiveness of the vaccine became evident, routine smallpox vaccination in children and re-vaccination among older age groups became the norm (20). Smallpox incidence decreased, but unvaccinated individuals remained. The dangers of complacency about vaccination were highlighted by a particularly virulent outbreak that occurred in Windsor, Ontario in 1924. There were 67 smallpox cases and 32 deaths reported; all of the deaths occurred in unvaccinated individuals and no cases were reported in individuals who had been vaccinated in the previous 12 years (20). A rapid vaccination campaign was started, leading to an abrupt end to the outbreak (20).

Endemic smallpox was eliminated in Canada in 1943, but 7 imported cases occurred in 1945 and 1946 (20). Canada's last smallpox case was reported in Toronto in 1962 in a 14-year old male returning from a smallpox-endemic area of Brazil (21). The occurrence of this case prompted a commentary in the Canadian Medical Association Journal on the importance of maintaining adequate vaccination coverage in Canadians as long as smallpox remained prevalent in other parts of the world, given the ease with which disease can spread via transit (22). Through the use of aggressive vaccination campaigns, the World Health Assembly announced the global eradication of smallpox in 1980, with the last naturally-occurring case reported in Somalia in 1977 (16).

Diphtheria

Diphtheria was once a common and much-feared disease in Canada.

Caused by the bacteria *Corynebacterium diphtheria*, it is spread via the respiratory droplets of infected individuals or contaminated objects and foods. It most commonly infects the nose and throat, with throat infection causing a tough fiber-like covering that can block airways. It can also cause skin infections, producing skin ulcers and sores.

Toronto played a critical role in demonstrating that a newly developed diphtheria vaccine prevented illness and death.

As with other communicable diseases, mortality due to diphtheria began to decline prior to the availability of a vaccine, likely representing improvements in living conditions and sanitation, including water treatment and sewage disposal (23, 24). Nonetheless, the burden of disease remained substantial. Early in the 20th century, diphtheria antitoxin was being used to treat disease identified in its early stages and was given to contacts of cases. It was less effective in the later stages of disease, limiting its overall impact on disease control. By the 1920s, a researcher at the Pasteur Institute in France had identified a novel technique to modify the exotoxin of the causative agent of diphtheria, removing its toxicity while still producing an immune response in vaccinated individuals. The Connaught Laboratories were established in Toronto in 1915 to produce diphtheria antitoxin, and they began producing diphtheria toxoid in 1925 (25). In his capacities as Director of both the Toronto Institute of Hygiene and the Connaught Laboratories, John FitzGerald led a program of field trials to evaluate the effectiveness of childhood immunization with toxoid, placing Ontario at the forefront of modern infectious disease control innovations. In 1926, following a severe outbreak of diphtheria in a Toronto school, the Department of Public Health offered immunization with diphtheria toxoid to public school children. Approximately 46,000 children were involved in this study between 1926 and 1932, which showed that immunization dramatically reduced diphtheria incidence and mortality (**Figure 2.2**) (26). These pioneering Canadian field trials were the first scientifically rigorous demonstration of the effectiveness of a non-live vaccine in preventing a specific disease (25)

Figure 2.2. Diphtheria infection and death rates in Toronto declined rapidly following the introduction of the diphtheria vaccine.

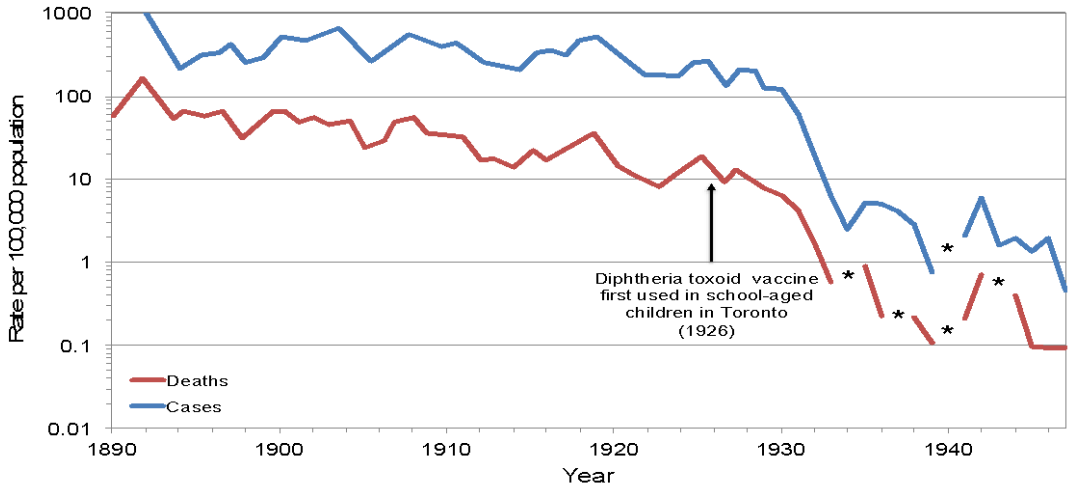


Figure Details. Diphtheria infection and mortality rates per 100,000 population in Toronto, 1890-1947. Years without reported cases (1940) or deaths (1934, 1937, 1940, and 1943) are indicated by asterisks. Data sources: (25) and (27). Note that rates are presented on a log scale.

Section 3: Challenges to Vaccination

Contributors to declining vaccine acceptance and vaccine coverage

Given the remarkable improvements of population health caused by the introduction of vaccines, it may seem surprising that efforts to maintain current levels of vaccine coverage are needed at all. Several factors are now acting to decrease vaccine acceptance, and increase the risk of resurgence of vaccine-preventable disease. Recent data suggest that vaccine coverage is declining. For example, data from the U.S. Centers for Disease Control suggest that declines in vaccine uptake are occurring across the United States, and that the rate of vaccine refusal is increasing (28, 29). Furthermore, the rate of vaccine refusal is 150% greater in jurisdictions that permit vaccine refusal for philosophical (as opposed to religious) reasons (28, 29). Predictably, declining vaccination coverage for highly transmissible, but previously well-controlled, diseases has been associated with the resurgence of these diseases in many jurisdictions (30-35). Factors likely to contribute to falling rates of vaccination are described below.

Success of Vaccination Programs

The degree to which vaccine acceptance has declined partly in response to the success of vaccination programs themselves has been alluded to in Section 1. When sufficient vaccine coverage is achieved, the result is an "immune herd", or a population where a case of disease introduced from outside (e.g., through travel) will not result in an outbreak or epidemic. For many vaccine-preventable diseases this has until recently been the case. It has been pointed out that in a situation where herd immunity is present, and disease risk is negligible, any risk associated with immunization will (over the short term) outweigh risk associated with disease, and some individuals will choose to opt out of vaccination programs. This process is expected to continue until levels of coverage drop low enough that disease re-emerges, resulting in a change in the risk-benefit ratio for vaccination, and resulting in greater vaccine uptake. Vaccine misinformation, as described below, may further enhance the perception that risk of vaccination outweighs risk of disease (36).

Hesitancy to immunize, in this context, does not represent parental disregard for child health, but is more likely to reflect parental concern that vaccines may be harmful. For example, a recent study found that vaccine hesitancy was more common in parents who had a higher degree of interest in their child's nutritional status (37). Indeed, whereas in earlier eras children from disadvantaged social backgrounds may have been less likely to be immunized, the current situation is more complicated, with low-income countries lacking universal access to vaccines due to impoverishment (38), while upper income individuals *within* high-income countries appear more likely to decline publicly-funded immunization by choice (39). As with communicable diseases themselves, concerns about vaccine safety appear themselves to be "contagious", with a high degree of clustering observed in geographical studies of vaccine refusal (40).

Proliferation of Vaccines

The current Canadian immunization schedule as formulated by the Canadian National Advisory Committee on Immunization now recommends immunization against 11 different pathogens, to be conferred through administration of over 25 different injections between birth and 16 years of

age (5). Many parents appear to find this overwhelming. A national telephone survey conducted in the United States in 1999 found that approximately 25% of parents endorsed the statements "children get more immunizations than are good for them" and "I am concerned that my child's immune system could become weakened as a result of too many immunizations" (41). The increased availability of combination vaccines against multiple pathogens results in fewer shots for children than would otherwise be the case. "Vaccine-hesitant parents" refers to parents who accept vaccination but have significant concerns about vaccinating their children; they may delay vaccination or choose only some vaccines (42). Although there are no precise estimates of the number of vaccine-hesitant parents, the use of alternate immunization schedules by some care providers, which eliminate vaccines against diseases regarded as non-serious, appears to be increasingly common (43).

Vaccine Misinformation

Perhaps the greatest consequence of vaccine misinformation in the past half-century occurred as a result of publication in a prestigious medical journal of work purporting to demonstrate a link between receipt of measles-mumps-rubella (MMR) vaccine and autism. This paper has subsequently been retracted by the journal (44, 45). Its lead author has been accused of falsifying data and engaging in scientific misconduct and numerous studies that were subsequently undertaken to investigate this claim have found no link between MMR vaccine and autism (46-48). Nonetheless, this misinformation appears to have had a significant impact on attitudes towards immunization, perhaps in part as a result of amplification by the Internet (49). In a 2010 survey of American parents, 24% of respondents listed the internet as an important source of information about childhood vaccination (50). Approximately 75% of North Americans are Internet users, and 4/5 of these use the Internet to obtain health-related information (49). The Internet provides a means for the amplification of the volume and reach of messages from local groups, and it appears likely that the Internet has contributed substantially to the growth of anti-vaccine sentiment in North America (49). As described by Kata, the fraction of Internet sites that may be classed as "anti-immunization" is substantial; for example, it has been suggested that a U.S. Internet search using the keyword "vaccination" identifies twice as many "anti-immunization" sites as "pro-immunization" sites. Common themes on anti-immunization sites include reports of associations between immunization and health conditions including HIV infection, autism and cancers; text trivializing the burden of vaccine preventable diseases; and text questioning the effectiveness of vaccines (49). Suggestions of conspiracies involving the medical community and pharmaceutical industry are common (49). In countries where access to the Internet is uncommon, rumors or edicts from community leaders may be similarly impactful in causing parents to decline immunization for their children. For example, ill-founded concerns regarding the health effects of vaccines, voiced by religious leaders in northern Nigeria, resulted in large-scale declines in immunization in that area, and may have contributed substantially to the resurgence of paralytic polio in that country (51).

Deterioration of Public Health Infrastructure

Effective vaccination programs depend on a highly skilled workforce, safe and reliable injection supplies, and a cold-chain that maintains live vaccines in an effective state. Economic decline and political instability make such conditions hard to maintain. This was illustrated by the resurgence of diphtheria in Russia in the early 1990s; diphtheria had become a rare disease, but the collapse of the former Soviet Union and associated economic disarray disrupted vaccination efforts, with reappearance of diphtheria at epidemic levels (52, 53). War and related political instability may

be similarly disruptive, as can be seen in recent tragic events in Pakistan, where immunization workers were recently murdered by Taliban gunmen (54). Such a lack of security obviously makes ongoing immunization efforts difficult. Furthermore, while horrifying, such attacks on aid workers and healthcare providers in conflict zones are not uncommon (55). While as Canadians, we are relatively sheltered from the direct effects of such social and economic disruption, the status of Toronto as a major hub for global immigration and travel means that disrupted vaccine delivery systems in other countries may enhance disease risk in our city.

Section 4: Poliomyelitis

Background

Paralytic poliomyelitis was one of the most feared childhood diseases of the 20th century.

Before the introduction of polio vaccines in the late 1950s, paralytic poliomyelitis was one of the most feared childhood diseases of the 20th century in Canada (**Figure 4.1**). Polio first emerged as an epidemic disease in the early 1880s, with Canada experiencing four major epidemics (56). Polio's emergence as an epidemic disease in developed countries is thought to be due to improved hygiene and sanitation standards resulting in children being exposed to infection later in life, when immune protection against infection derived from an infant's mother had waned.

Figure 4.1. In the era before vaccination, poliomyelitis cases and deaths were common in Ontario.

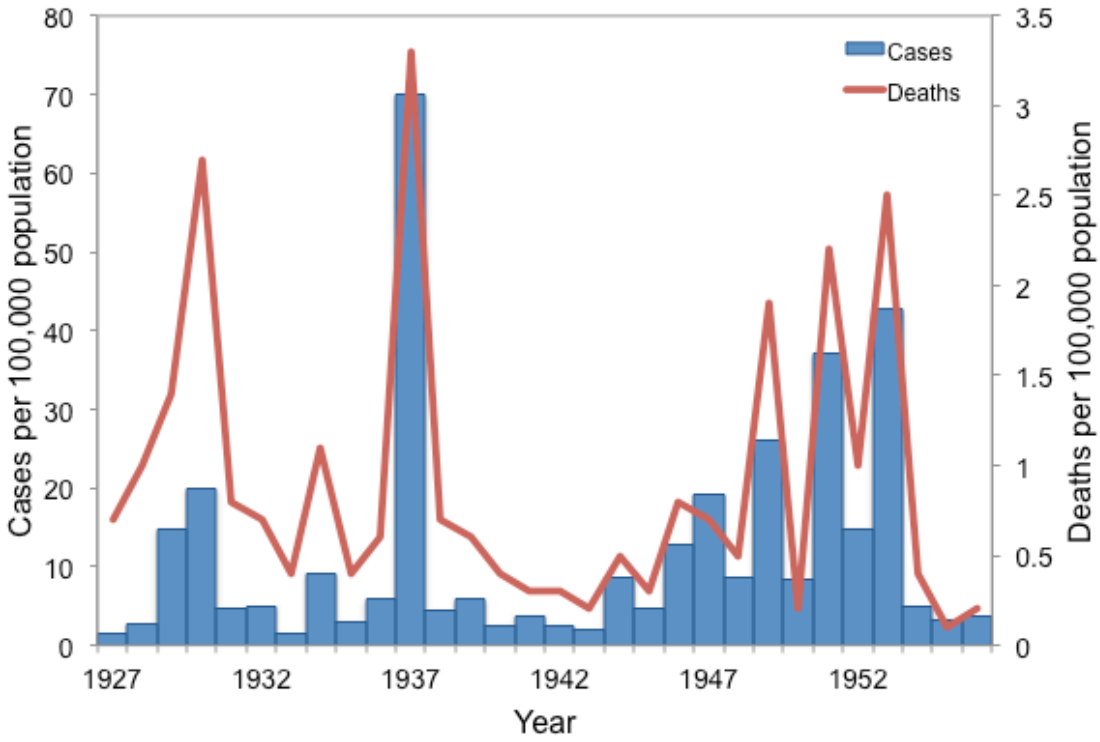


Figure Details: Poliomyelitis infection and mortality rates per 100,000 population in Ontario, 1927-1956. Adapted from (56).

Poliovirus is a member of the picornavirus family, which also includes some common cold viruses and hepatitis A. It only infects humans and a few subhuman primate species (57). Polio displays marked seasonality in temperate climates, with incidence tending to peak in the summer

and autumn. It is most commonly transmitted by ingestion of contaminated food or water, although when hygiene standards are high, it is mainly transmitted by the respiratory route, following infection of the tonsil and pharynx (57). Most people infected with poliovirus display no symptoms; in these individuals, the growth of the virus is restricted to the gut. However, even if infected individuals do not show symptoms, poliovirus is excreted in the feces, allowing for the spread of the virus to others (57). In some cases, the poliovirus can enter the bloodstream (viremia) and cause symptoms such as sore throat and fatigue. In less than 1% of infections, the virus invades the central nervous system, infecting and destroying motor neurons and causing severe disease, including muscle weakness and acute flaccid paralysis (AFP). Paralysis is permanent in approximately 80% of severe cases, with 10% of cases resulting in death, and the remaining 10% recovering (57). The likelihood of developing paralytic polio increases with age.

Vaccines have dramatically reduced the global burden of polio and polio was declared eliminated from the Americas in 1994.

Two types of vaccine are used globally to prevent polio by inducing immunity: inactivated polio vaccine (IPV, also known as the Salk vaccine) and oral polio vaccine (OPV, also known as the Sabin vaccine). First introduced in Canada in 1955, IPV is made by chemically inactivating poliovirus and is administered by subcutaneous or intramuscular injection (**Table 4.1**). After two doses, 95% of individuals develop protective immunity to poliovirus, and after three doses, 99% are immune (58). Serious systemic adverse reactions following immunization are rare (5). Short-lived local reactions at the site of injection (redness, swelling, pain at the injection site) and less frequently, systemic reactions (fever and irritability) are the most common adverse reactions associated with receipt of the inactivated polio vaccine.

Table 4.1. Characteristics of the inactivated polio vaccine.

Characteristic		Details
Number of doses		5
Age at vaccination for each dose:		
	1	2 months
	2	4 months
	3	6 months
	4	18 months
	5	4-6 years
Vaccine efficacy		95-99%
Duration of immunity following primary series		Assumed lifelong, but unknown

OPV is produced by selecting attenuated poliovirus that can grow efficiently in the gut but is unable to grow in the nervous system. In addition to inducing systemic immunity and protecting from paralytic poliomyelitis (as with IPV), OPV induces enteric mucosal immunity. Three doses of OPV provide immunity in greater than 95% of individuals (59). Licensed in 1962, OPV was widely adopted globally. Despite being less expensive and easier to administer than IPV, the attenuated virus in OPV can, in approximately 1 case per 750,000 vaccine recipients, revert to a form of virus that can cause paralysis, which led most high-income countries to switch to using

IPV as the vaccine of choice. Vaccine programs in Canada switched from OPV to IPV in 1995/96, although Ontario used IPV exclusively except for a short period during 1990-1992 (60, 61).

The last major Canadian polio epidemic occurred in 1959, resulting in 1,886 paralytic cases (56). Sporadic outbreaks continued, mainly in clusters of unimmunized individuals. In 1978-79, there were 11 paralytic polio cases among unimmunized individuals who had contact with imported cases in religious groups in Ontario, Alberta and British Columbia and in 1996 an asymptomatic case was reported in Ontario (61). Most recent cases of paralytic polio in Canada have been associated with OPV use; eleven of 12 paralytic cases in Canada reported between 1980 and 1995 were vaccine-associated paralytic polio (61).

Despite great successes, polio continues to circulate in some countries and global connectedness makes the reintroduction of polio into currently polio-free regions an ongoing concern.

In 1994, elimination (reduction to zero of the incidence in a defined geographical region (62)) of indigenous wild poliovirus transmission was certified in Canada and elsewhere in the Americas (61). Although wild poliovirus has been eliminated in Canada, and there have been many recent successes, including interruption of wild poliovirus circulation in India (63), efforts to eradicate (permanent reduction to zero of the worldwide incidence) polio have proven to be challenging, with polio remaining endemic in Afghanistan, Nigeria, and Pakistan (62). Global connectedness makes polio reintroduction into previously polio-free regions an ongoing concern; nearly half of paralytic polio cases occurring between 2009-2011 occurred in people living in polio-free countries who were infected by virus imported from an endemic country (11). Responding to polio outbreaks in polio-free countries cost over $330 million (CDN) in 2011 (11).

The risk of spread of polio following reintroduction is dependent on immunization rates in polio-free regions. When immunization rates are high, risk of ongoing transmission is low. We sought to estimate the risk of a poliovirus-infected individual traveling to Toronto and to quantify the size of a potential outbreak following re-introduction, under varying levels of vaccine coverage in the Toronto population.

Methodology

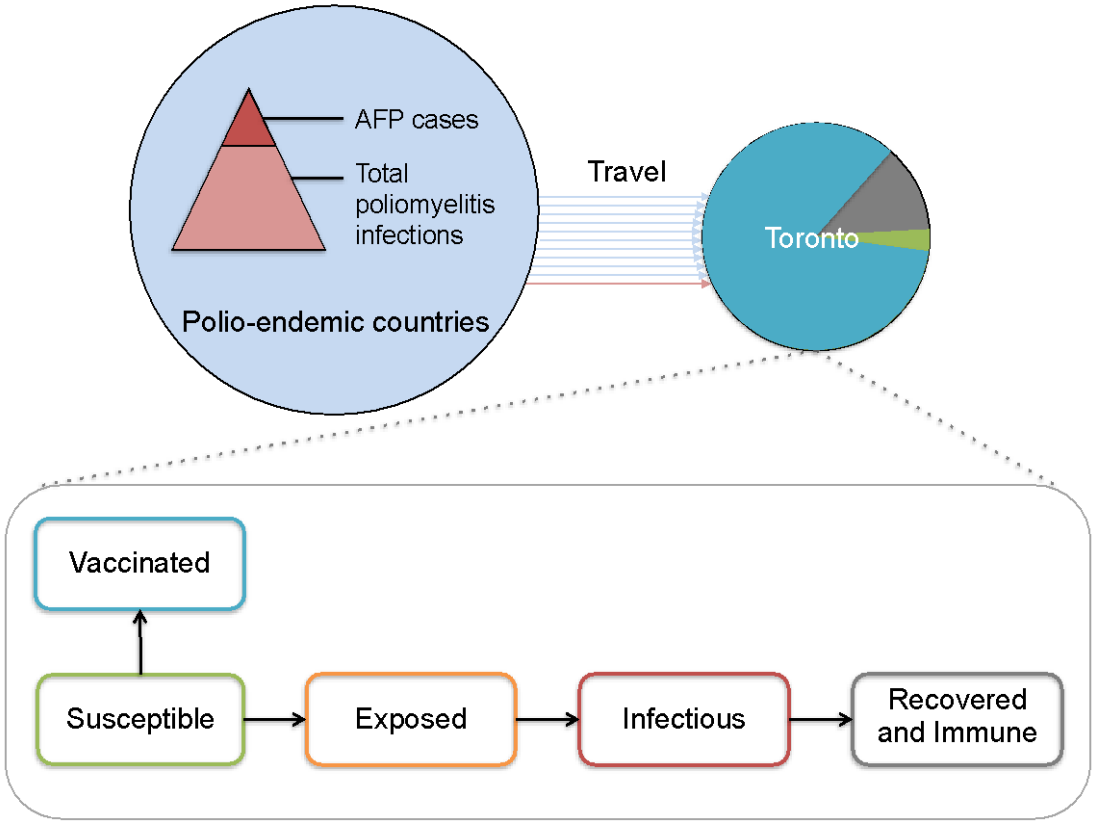
We used a combination of modeling approaches to determine (i) the chance that a polio-infected person will arrive in Toronto and (ii) the chance that polio will spread in Toronto following the introduction of an infected person, assuming varying levels of vaccine coverage (**Figure 3.2**).

Polio Importation Model

We used statistical methods and data on travel patterns to estimate the likelihood that a person infected with polio will arrive in Toronto over the next year.

We used information on the total number acute flaccid paralysis cases reported in 2011 for the three countries (Afghanistan, Nigeria, and Pakistan) where polio remains endemic (that is, circulation of polio has never been interrupted) (64). Since most people with polio will not have symptoms or will have only mild symptoms, we can use acute flaccid paralysis cases as a marker of polio activity in these countries, and use estimates of the total number of polio cases that we would expect to see for every severe case to determine the total burden of polio in these countries. It is estimated that for every case of paralytic polio that is seen, there are approximately 200 additional people who have been infected without displaying symptoms (65). Note that although other countries, such as Chad and the Democratic Republic of Congo have also reported significant polio activity in recent years, the amount of travel between these countries and Toronto is negligible, and so we excluded them from this analysis. The International Travel Survey collects data on the amount of travel between Canada and other countries (66). We use this information to estimate the number of visitors to Toronto from each country of interest and the number of travelers from Toronto returning from these polio-endemic countries in 2011. If Torontonians are not vaccinated against polio, their risk of becoming infected while traveling to countries with polio is much higher, and this also increases the chance that they will return to Toronto with an infection. To understand how reducing vaccine uptake in Torontonians would change the likelihood of a polio case arriving in Toronto, we looked at different vaccination rates and measured how this changed the chance that we would see a polio case in Toronto. Complete details of how we calculated the probability of importation are presented in **Appendix 2.1**.

Figure 4.2. Overview of the models used to measure the chance that a polio-infected individual arrives in Toronto and the expected disease burden following case appearance.



Estimating the Likelihood of Polio Importation for Varying Levels of Travel and Disease Risk

The chance that a person infected with polio will arrive in Toronto will change over time, as polio is eliminated in some countries and is reintroduced in others. We looked at different scenarios to understand how travel patterns and the infection burden in countries with polio will impact the risk that polio will return to Toronto.

The importation analysis described above estimated the current risk of importation of polio case to Toronto, based on current travel patterns and countries with endemic polio cases. Given that this situation is likely to change over time, we also conducted a more theoretical analysis, where we calculated the risk of disease importation in hypothetical countries with low (500 trips per year), medium (5000 trips per year), or high (20,000 trips per year) levels of travel to Toronto and polio incidence of 0.1 (low), 0.5 (medium), or 2 (high) AFP cases per million population. We assumed that the number of people travelling to and from each country was equal. As with the previous analysis, we varied vaccine coverage in Torontonians.

Toronto Poliovirus Transmission Model

We built a model that represents the Toronto population to determine what would happen

Figure Details: Schematic overview of polio model. Reported paralytic polio (acute flaccid paralysis, AFP) cases represent a small but easily detectable subset of the total burden of polio occurring in countries with endemic polio, since most people infected with polio have no or mild symptoms. These infectious cases (both AFP and asymptomatic) are indicated by the triangle, with the rest of population of the country uninfected. When people travel from endemic countries to Toronto (either Torontonians returning from visiting these countries, or individuals from these countries visiting Toronto), we expect that most of them will not be infected with polio (indicated by blue arrows connecting polio-endemic countries to Toronto in the top half of the figure). If a person infected with polio travels to Toronto (indicated by the red arrow), there is a chance that polio may spread within the Toronto population. Whether or not this occurs depends on the health status of the Toronto population (top right, and with health states described in further detail in bottom half of figure). We expect most of the population to be protected against infection because they are vaccinated (blue) or have previously been infected with polio and are now immune (grey). The susceptible population (green) is not protected against polio infection; these individuals can become infected with polio and transmit the infection to others. The fraction of the population that is susceptible will determine whether or not we will see an outbreak of polio if a polio-infected person

if a case of polio were to arrive in the city. This model allows us to look at how changing levels of vaccination in the Toronto population impact the expected outcome of a polio importation event.

The arrival of an individual infected with polio does not mean that Toronto will experience a polio outbreak. An outbreak will only occur if not enough people are protected against infection. People are protected from infection because they have previously been infected with polio or because they have been immunized. We built a model to show how changing levels of vaccination in the Toronto population can change the likelihood and size of an outbreak following the introduction of a polio infected into the city's population.

We modeled the transmission of poliovirus in the Toronto population following infection reintroduction from a polio-endemic country using an age-structured, deterministic compartmental model that included vaccination. A detailed description of the model is provided in **Appendix 2.2**.

Model Scenarios and Outcomes

If polio vaccine uptake declines in infants and children, what would the impact be in the near and distant future? We used our model of the Toronto population to answer this question.

To look at the impact of a decline polio vaccine uptake on outbreak size following the arrival of a person infected with polio in Toronto, we asked the following question: if vaccination coverage were to abruptly and immediately drop to a certain level in all newly vaccinated infants and children, what would be the impact be in 5, 10, 25, etc., years time? **Figure 4.3** shows how the proportion of the Toronto population that is vaccinated would change over time, assuming different levels of vaccine uptake.

We estimated the total number of infections and polio-attributable acute flaccid paralysis cases that we would expect to see over a one-year time period. We restricted the time period to a single year because we assumed that once a polio outbreak was identified in Toronto, there would be a surge in vaccine uptake in the population, so polio circulation would not continue in the population and future polio outbreaks would be prevented. Given that the appearance of a single polio-attributable AFP case would be expected to trigger a public health response, we also evaluated the time at lower vaccination coverage until one or more AFP cases would occur in the Toronto population.

Figure 4.3. The proportion of the Toronto population that has been vaccinated against polio will decrease over time following a decline in vaccine uptake in infants and children.

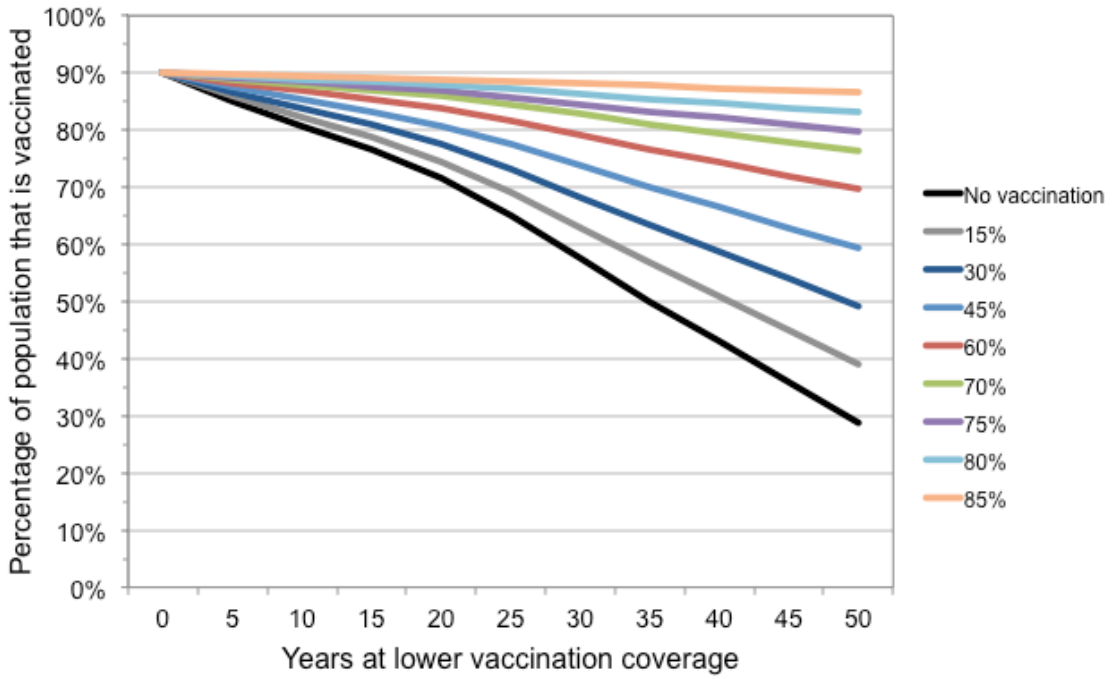


Figure Details: Change in proportion of population vaccinated over time. We modeled reduced vaccine uptake in the population by assuming that infants and children started getting vaccinated at lower levels or not at all (uptake in these younger age groups is indicated in the figure legend). As the amount of time that children are vaccinated at these lower levels increases (shown on the x-axis), the percentage of the total population that has received the polio vaccine decreases (y-axis). For instance, if parents stopped immunizing their children today (no vaccination), in 50 years, less than 30% of the Toronto population will have been vaccinated against polio. Current estimates place population immunity (due to immunization and previous infection) against polio at approximately 90%.

Results

There is a significant risk that a person infected with polio will arrive in Toronto.

Based on current estimates of global burden of polio, we estimate that there is an approximately 15% chance that a person infected with poliovirus will arrive in Toronto in a given year (**Figure 4.4**). Polio may be imported either by the arrival of an infected visitor to Toronto or by the return of a Toronto resident who acquired polio infection while visiting a polio-endemic country. Since most people with polio infections display no symptoms or are only mildly symptomatic, this person will most likely have no symptoms and will not be detected by disease surveillance systems. However, they can still transmit the infection to others. The risk of a polio-infected

person coming to Toronto depends on vaccination coverage in Toronto travelers. With lower vaccination coverage in Torontonians traveling to countries with endemic polio, it becomes more likely that an unvaccinated Torontonian will return to the city with a polio infection.

Figure 4.4. The chance that a person infected with polio will arrive in Toronto increases when fewer Torontonians are vaccinated against polio, as there is an increased likelihood that an unvaccinated Torontonian will become polio infected after travelling to a polio-endemic country.

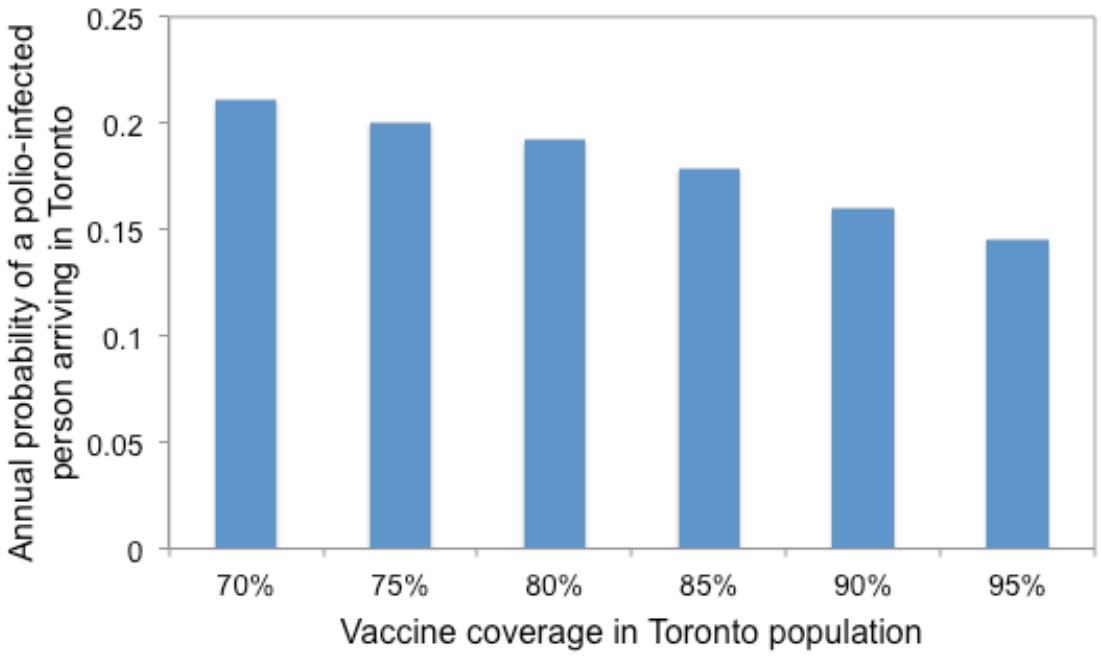


Figure Details: Annual risk (y-axis) that a person infected with poliovirus arrives in Toronto is shown for different levels of immunization in the Toronto population (x-axis). Importation risk was estimated using country-specific data on polio incidence and travel frequency to and from Toronto for Afghanistan, Nigeria, and Pakistan, the three countries with ongoing polio transmission. Current estimates place vaccine coverage in Toronto above 90%. Results are based on 10,000 simulations for each scenario.

Global connectedness is a major driver of polio importation risk.

Unsurprisingly, the biggest driver of importation risk is the degree of connectedness between Toronto and each country. Although Afghanistan has a higher estimated disease burden than Pakistan (2.3 vs. 1.1 reported acute flaccid paralysis cases per million population), the volume of travel between Pakistan and Toronto is much greater. For example, when vaccination coverage is 95% in the Toronto population, there is a less than 1% chance that a person infected with polio in Afghanistan will arrive in Toronto, compared with a 13% chance that a person infected with polio in Pakistan will arrive in Toronto over the course of a year.

The estimates above are based on current trends in polio cases. As people forget about the devastating health impacts of polio, vaccination uptake may decline and we may start seeing

polio in countries that are currently polio-free. We wanted to explore how the volume of travel between Toronto and different countries would influence the likelihood that people infected with polio arrive in Toronto. Since we cannot predict where we may see polio cases in the future, we repeated our analysis for hypothetical countries with different rates of polio and amounts of travel to and from Toronto (**Figure 4.5**). Even with moderate levels of disease activity and travel connectedness, there is a possibility that an individual with poliovirus infection will visit or return home to Toronto.

In the short-term and at current levels of vaccination, there is little risk of a polio outbreak in Toronto. But if there is a sustained decline in vaccination uptake, the introduction of a polio-infected individual into the population could result in a large outbreak.

The arrival of a person with infectious polio in Toronto does not mean that a polio outbreak will occur in the city. If this infectious person only comes into contact with people who cannot be infected with polio, either because they have been vaccinated against polio or have previously been infected and are now immune, there will be no disease spread. Based on our current estimates of the fraction of the Toronto population protected from polio infection and the ease with which polio can be spread in a population, a polio case that arrived in Toronto today would be expected to be a `dead end', causing no or undetectable further spread in the community. However, if vaccine uptake in children declines, there will be more people in the population who are not protected from polio infection. If an infectious polio case were to come into contact with people who are not protected from infection (this is, they are susceptible to polio infection), there is a chance that the infected case will spread the infection, In turn, these newly infected cases can spread the infection to other susceptible people. This can cause in a chain of polio transmission, resulting in an outbreak. Since most people infected with polio will not have symptoms, it may take a while until an outbreak is detected. The occurrence of cases of acute flaccid paralysis would be a signal that polio transmission is occurring in the Toronto population.

Since the Toronto population currently has high polio vaccine coverage, if vaccine uptake in children was to decrease, it would take time until there were enough people susceptible to polio infection in the population to allow for polio to spread in the population and cause an outbreak. **Figure 4.6** shows the number of poliovirus infections (asymptomatic and symptomatic) expected over the course of a year, following a given number of years with children being immunized at rates lower than our current levels.

Figure 4.5. Frequent travel between a country with polio and Toronto results in a large risk of a polio-infected person arriving in Toronto. This risk is significant even when the amount of polio in the source country is small.

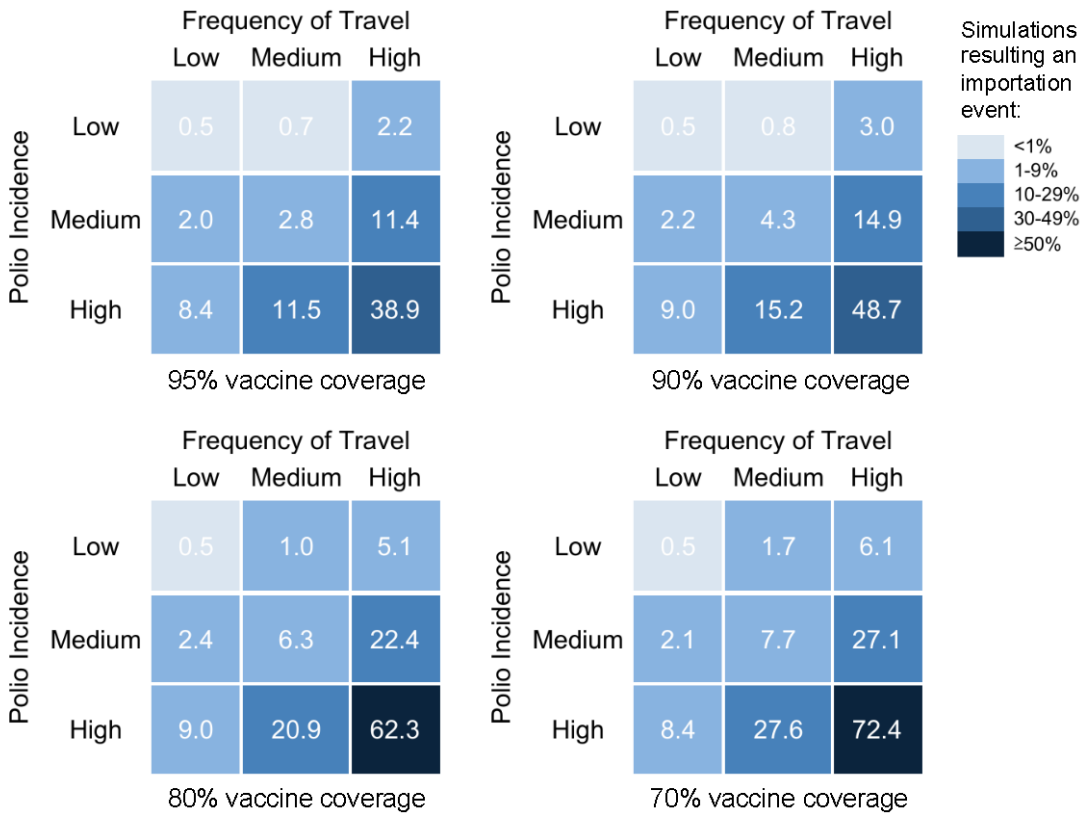


Figure Details: The percentage of simulations that resulted in one or more poliovirus importation events (for 10,000 simulations) in a year is shown for the different vaccination coverage levels (ranging from 70 to 95%) in the Toronto population. Darker shading indicates a greater likelihood that polio will be introduced into Toronto from a country with a given combination of polio burden and amount of travel. Travel frequencies were based on data on travel to and from Toronto, with the number of annual trips classified as low (500 trips), medium (5000 trips), or high (20,000 trips). Polio incidence was classified as low (0.01 paralytic polio cases per million population), medium (0.5 paralytic polio cases per million population), or high (2 paralytic polio cases per million population).

Figure 4.6. When vaccine coverage declines in the Toronto population, large polio outbreaks are expected following the arrival a polio-infected person in Toronto. Outbreak size increases as the amount of time at lower vaccination uptake increases, because the number of people protected against infection is decreasing.

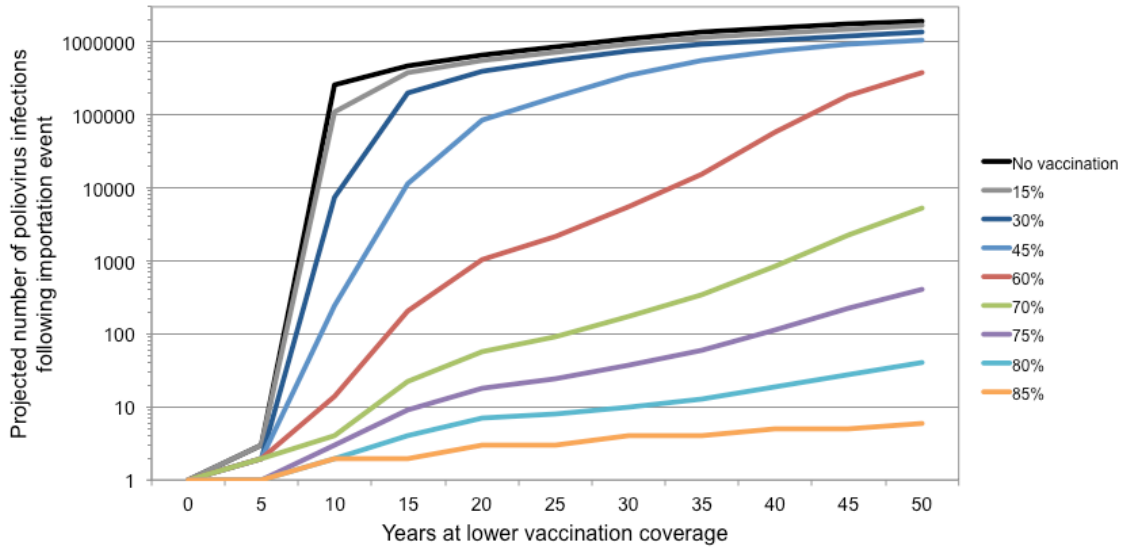


Figure Details: Model-projected total number of infections is shown for different vaccination levels (shown in figure legend) and durations of reduced vaccination coverage (x-axis). It was assumed that 90% of the Toronto population was protected from polio infection before vaccine coverage began to drop. At vaccination levels of 85% and greater, no outbreak is expected to occur during the 50-year time horizon under consideration. Note that total infections are plotted on a logarithmic scale.

Figure 4.7 shows the number of years at lower vaccine coverage that pass until a polio-importation event would result in the occurrence of at least one case of polio-attributable acute flaccid paralysis. At lower coverage, AFP cases would occur as early as 5-10 years following the decline in uptake. When coverage remains above 75%, we would not expect to observe an AFP case, even after 50 years at lower uptake. Our model estimates that we would see very large outbreaks in the Toronto population if vaccination rates were to decline. The sizes of these projected outbreaks are actually much larger than what was typically seen in the era before polio vaccine was available. This relates to the fact that poliovirus is no longer seen in the Canadian population. Reintroducing polio following its elimination and after allowing the number of people who are susceptible to infection to build up has a similar effect to introducing a new pathogen into population.

Figure 4.7. A case of polio-attributable acute flaccid paralysis in Toronto would generate tremendous national and international concern. If an importation event occurred after 5 to 10 years with low vaccination uptake, we would expect to start seeing AFP cases. Time to occurrence of one or more AFP cases increases with increasing vaccine uptake.

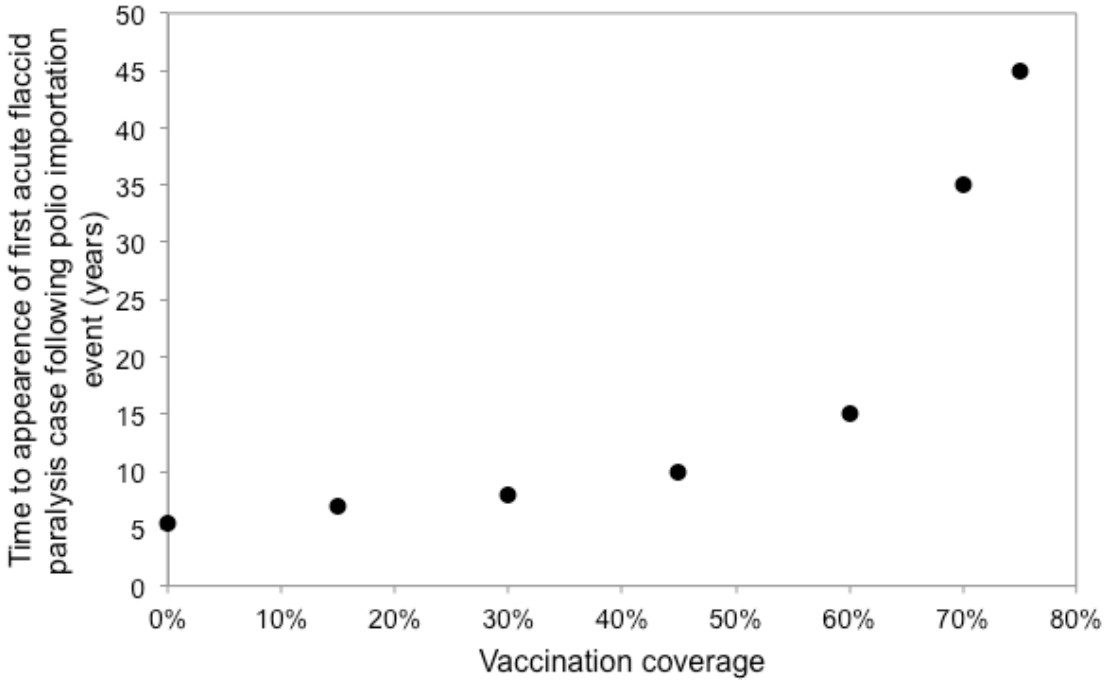


Figure Details: Time until occurrence of the first case of acute flaccid paralysis following a polio importation event is shown for different vaccination levels (x-axis). It was assumed that 90% of the Toronto population was protected from polio infection before vaccine coverage began to decrease. The vaccination threshold for detection of an AFP case was 75%; a case was only detected after 45 years at this level of coverage, with no AFP cases detected over a 50-year time horizon with higher vaccination levels.

Key Findings

- Although polio has been eliminated in Canada, the highly connected nature of Toronto, as a result of international commerce, immigration, and tourism, means that endemic cases of polio, including paralytic polio, are likely to result from declines in vaccine coverage.
- Individuals with asymptomatic polio are likely arriving in Toronto with some regularity.
- High levels of polio vaccine coverage are will ensure that Canada maintains its status as a polio-free country, notwithstanding the occasional arrival of asymptomatically infected individuals. Without polio vaccination, Canada could expect to lose this designation in 5-10 years.

Section 5: Measles

Background

Measles is a highly contagious infectious disease that caused epidemics every two to three years in the pre-vaccine era.

Measles is a highly transmissible viral infection of the respiratory system. It is spread via droplets from the mouth, nose, or throat of an infected person. Symptoms include fever, runny nose, cough, red eyes, and a generalized maculopapular, erythematous rash. In the pre-vaccine era, measles epidemics occurred every two to three years (**Figure 5.1**) and deaths from measles complications were common. Before measles immunization was available, most people acquired infection during childhood. Between 1880 and 1929, an average of 5.5 measles deaths per 100,000 population were reported in Ontario annually (67).

Figure 5.1. Measles epidemics were a regular occurrence in Ontario before vaccination was introduced.

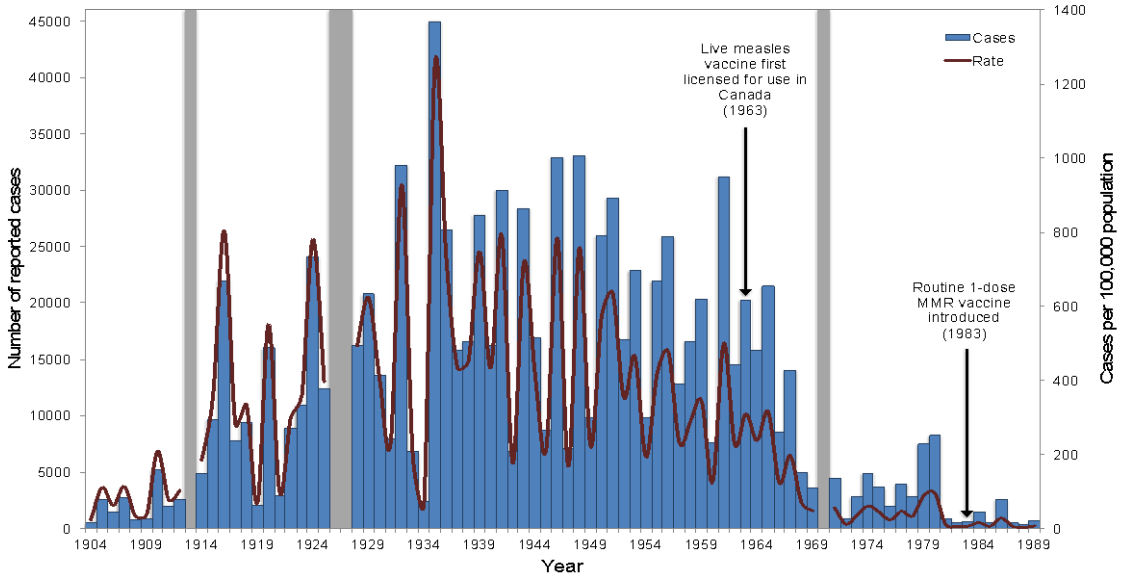


Figure 5.1. Annual reported measles cases and rates in Ontario, 1904 – 1989. Total reported cases (left-hand axis) and cases per 100,000 population (right-hand axis) are shown. No data were available for the years 1913, 1926, 1927, and 1970 (indicated by grey bars). Data were obtained from the International Infectious Disease Data Archive (http://iidda.mcmaster.ca).

Complications including bronchopneumonia and otitis media (middle ear infection) occur in approximately 10% of cases (5). Encephalitis (acute inflammation of the brain) occurs in 1/1,000 cases; 15% of these cases are fatal and 25% result in neurologic complications (5). The case fatality rate is currently less than 0.05%, although in developing countries it has been reported to be as high as 5-15% (68). Malnourished children are at particularly elevated risk of severe complications from measles (69).

Measles vaccine dramatically reduced the burden of measles in Canada.

Live measles vaccine was first licensed in Canada in 1963, with publicly funded immunization programs introduced across Canada by the early 1970s. It was initially administered as a single dose, typically at one year of age. Although measles vaccine is highly effective in preventing infection, cases have been reported in previously vaccinated individuals (70, 71). Large measles outbreaks continued to occur in Canada in the 1980s and 1990s, even though vaccine coverage rates were high; it was estimated that 10 to 15% of children could still become infected with measles, despite being vaccinated (72). As a result, since the mid-1990s, a second dose of measles vaccine is given before a child begins his first year of school. Measles vaccine is given in combination with mumps and rubella (MMR) (**Table 5.1**).

Table 5.1. Characteristics of the measles vaccine.

Characteristic		Details
Number of doses		2
Age at vaccination for each dose:		
	1	1 year
	2	4-6 years
Vaccine efficacy		95% with one dose, 99% with two doses
Duration of immunity following primary series		Lifelong in most; cases of waning immunity after one dose

Side effects associated with MMR vaccine include: malaise and fever, with or without a non-infectious rash, (5%); swollen glands, stiff neck, or joint pains (5%); parotitis (inflammation of salivary glands) (1%); transient thrombocytopenia (decrease of platelets in blood) (1/30,000); and encephalitis (1/1 million) (5). A comparison of the risks the most common complications associated with measles infection and immunization is presented in **Table 5.2**.

Global measles activity remains high, leading to ongoing imported and import-related measles cases in Canada, primarily in unimmunized individuals.

Although measles was eliminated (defined as the interruption of endemic measles transmission and failure to reestablish endemic transmission following measles importation) in the World Health Organization Region of the Americas in 2002, measles activity elsewhere remains high and there continue to be cases of imported and import-related measles cases in Canada (12).

Table 5.2. Risk of complications from measles infection compared to known risks of vaccination in immunocompetent individuals. Table source: (73).

Complication	Risk after infection (per case)	Risk after vaccination (per vaccine dose)
Otitis media	7-9%	0
Pneumonia	1-6%	0
Diarrhea	6%	0
Post-infectious encephalomyelitis	0.5-1 per 1000	1 per 1,000,000
Subacute sclerosing panencephalitis	1 per 100,000	0
Anaphylaxis	0	1 per 100,000-1,000000
Thrombocytopenia	– [a]	1 per 30,000[b]
Death	0.1-1 per 1000	0

[a]Cases reported after measles infection, but risk has not been properly quantified

[b]Risk reported after MMR vaccination and cannot be only attributed to the measles component

Canada's success in interrupting endemic measles transmission is due to high vaccine uptake, as demonstrated by recent isolated outbreaks where the majority of cases occurred in unimmunized individuals. In 2010, a measles outbreak of 82 confirmed and clinical cases occurred in British Columbia, likely following importation of measles cases during the Vancouver Winter Olympics. The three co-primary cases had a common exposure of attending Olympic-related events in downtown Vancouver (74). The mean age of the cases was 23, with 61% born after 1980. 75% of these cases were unimmunized or had no record of immunization (75). 23% of cases required hospitalization and one was admitted to the intensive care unit (74). Quebec has been experiencing a large measles outbreak since the beginning of 2011, believed to have been initiated by an infected visitor from France, where MMR vaccine uptake is much lower than in Canada (60% vs. >90%). The majority of cases were 10 to 19 years of age, 11% required hospitalization, and 8% of cases experienced complications (mainly respiratory) (64). It is estimated that approximately 80% of cases were not vaccinated (either did not receive the vaccine or were under the minimum age to receive the vaccine) (64). Between 2001 and 2011, 53 measles cases were reported in Toronto. Twenty-five of these cases were linked to a province-wide measles outbreak that occurred in 2008 (76).

These recent examples of Canadian measles importations and outbreaks highlight the fact that as long as measles remains endemic in other parts of the world, Canadians are at risk. Importation of measles virus in Canada is expected to be an ongoing concern, with outbreaks occurring in communities with pockets of unvaccinated individuals. Given this likelihood of ongoing measles importation, we sought to quantify the effect that declining vaccination uptake in Toronto would have on future community outbreaks.

Methodology

Measles cases are likely imported into Toronto on a regular basis.

The high transmissibility of measles means that very high population vaccination coverage (~94%) is required to achieve herd immunity (described in **Appendix 1**). Even small decreases in vaccination coverage could allow measles to become re-established in the population. Based on the high frequency of travel between Toronto and countries with ongoing measles transmission, we expect that measles infected cases are arriving in Toronto on a regular basis. The question is: when a measles case arrives in Toronto, will there be an outbreak, and if yes, how large will this outbreak be?

Measles Transmission Model

We developed a model of the Toronto population to help understand how vaccine coverage impacts the risk that an imported case will cause an outbreak.

We built a mathematical model **(Figure 5.2**) to help understand how declining vaccination rates over time in the Toronto population would affect the size of a measles outbreak, following the introduction of an infectious case (refer to **Appendix 2.3** for a description of the model). We also compared the vaccine-associated adverse events averted with reduced vaccine uptake to the number of severe cases expected following an outbreak.

Figure 5.2. The model describes the different health states that an individual can transition between when measles is spreading in the Toronto population.

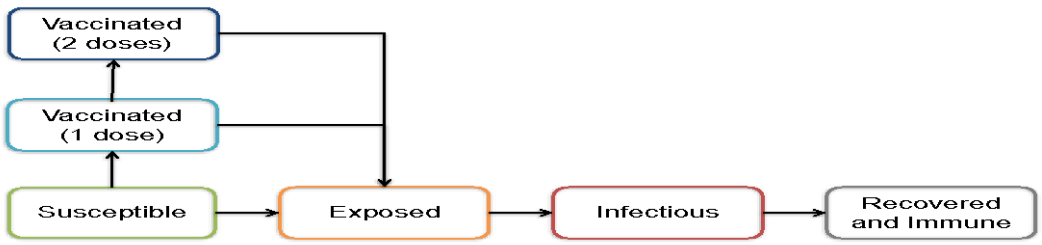


Figure Details: Schematic of the measles transmission model. People can be susceptible (able to be infected with measles), vaccinated (with one or two doses), infectious (infected with measles and able to spread the infection to others in the population), or recovered (previously infected with measles and protected from getting infected again). People who are vaccinated can still become infected with measles, but their chance of being infected is much smaller than it is in individuals who have not been vaccinated. A person who has received two doses of measles vaccine receives more protection against infection than a person with only one dose.

Model Scenarios and Outcomes

How would declining MMR vaccine uptake in infants and children impact the size of future measles outbreaks? We used our model of the Toronto population to answer this question.

To see how a decline in MMR uptake would affect the size of a measles outbreak following the introduction of an infectious measles case in Toronto, we estimated the total number of measles infections and severe cases that would occur following a given number of years of vaccinating children at lower levels than current uptake. We limited our analysis to a one-year time horizon, under the assumption that a surge in measles cases in Toronto would result in an increase in vaccine uptake to baseline levels.

We estimated that the current proportion of the population that is protected from measles infection is 97% in individuals born in or prior to 1970 (due to previous measles infection) (77) and 95% in individuals born after 1970 (due to immunity acquired from immunization). To model the impact of declining MMR uptake over time, vaccine coverage was decreased as described in **Figure 5.3**. This resulted a cohort of individuals with increased susceptibility to measles that increased in size over time.

Results

The arrival of measles infected individuals in Toronto is inevitable, given the high global burden of disease and the high volumes of travel between Toronto and countries with ongoing measles transmission.

Measles incidence has increased in countries frequently visited by Torontonians. For instance, France, Germany, Italy, Spain, and the United Kingdom are among the ten overseas countries mostly frequently visited by Canadians (78); these same countries accounted for more than 57% of the over 10,000 measles cases reported in Europe in 2011 (79), representing a significant potential source of measles exposure in unvaccinated individuals. Given the large global burden of measles and the high degree of global connectivity, we did not formally determine the risk of a measles-infected individual arriving in Toronto. The question of interest is not *if* measles cases will appear, but rather, *when* measles cases appear in Toronto, will there be high enough levels of vaccination in the population to prevent sustained transmission or will there be an outbreak?

Even small declines in vaccine uptake in Toronto may lead to an outbreak in the future, due to the ease with which measles is spread in a population.

The high transmissibility of measles results in dramatic increases in the size of outbreaks as vaccination uptake declines, even after as few as five years at decreased coverage (**Figures 5.3** and **5.4**). When we look over longer time periods (**Figure 5.5**), we see that even with a modest decline in vaccine uptake to 90%, within 20 years, we would expect to see over 10,000 infections following case importation, and this number increases 10-fold after additional 10 years at reduced uptake.

These estimates represent worst-case scenarios, since we have assumed that no individuals infected with measles arrive in Toronto in the interim. This allows the number of people able to be infected with measles to accumulate in the population. Note that even with 95% vaccine coverage, the size of outbreaks is expected to increase over time. This occurs because we assumed that older individuals who were previously infected with measles (before vaccination became widespread) were completely protected from getting re-infected with measles. This contrasts with fully vaccinated individuals, who can still be infected with measles, albeit at $1/100^{th}$ the risk of unvaccinated individuals.

Figure 5.3. We would expect to see measles outbreaks of varying sizes after 5 years at lower vaccine uptake than current levels (assumed to be 95%).

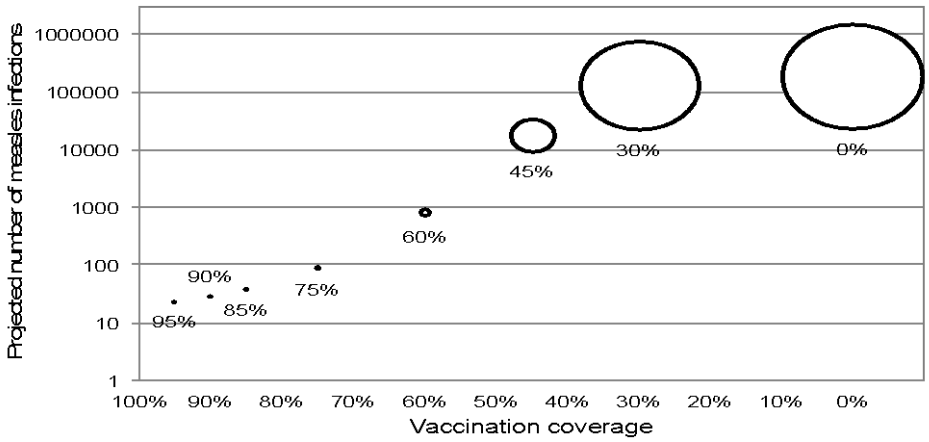


Figure Details: Projected outbreak size is shown following the arrival of a measles-infected person in the Toronto, assuming 5 years of vaccine uptake at the levels indicated by the percentages in the figure. The size of the circle represents the relative size of the projected outbreak. Note that infections are plotted on a logarithmic scale.

Figure 5.4. The size of measles outbreaks depends on the length of time with lower vaccine uptake in the Toronto population. After a few years with low or no vaccine uptake in Toronto, we would expect to see measles outbreaks.

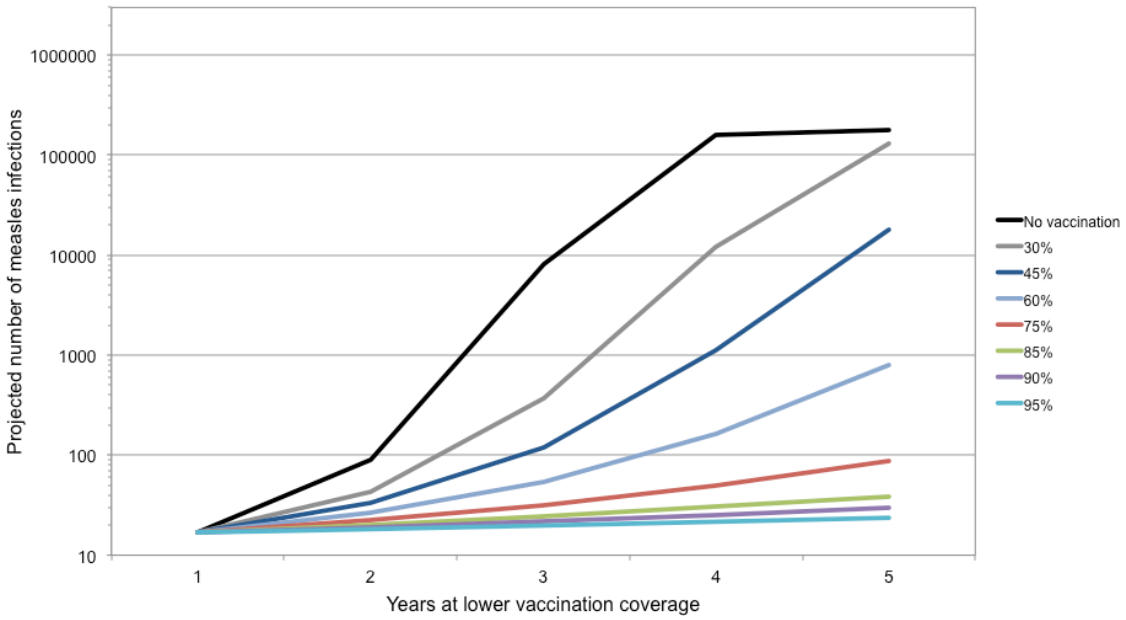


Figure Details: Projected outbreak size is shown following the arrival of a measles-infected person in the Toronto, assuming different levels of vaccine uptake for up to 5 years. Note that infections are plotted on a logarithmic scale.

Figure 5.5. Over longer time periods, even relatively modest declines in vaccine uptake would lead to measles outbreaks if a person infected with measles arrived in Toronto.

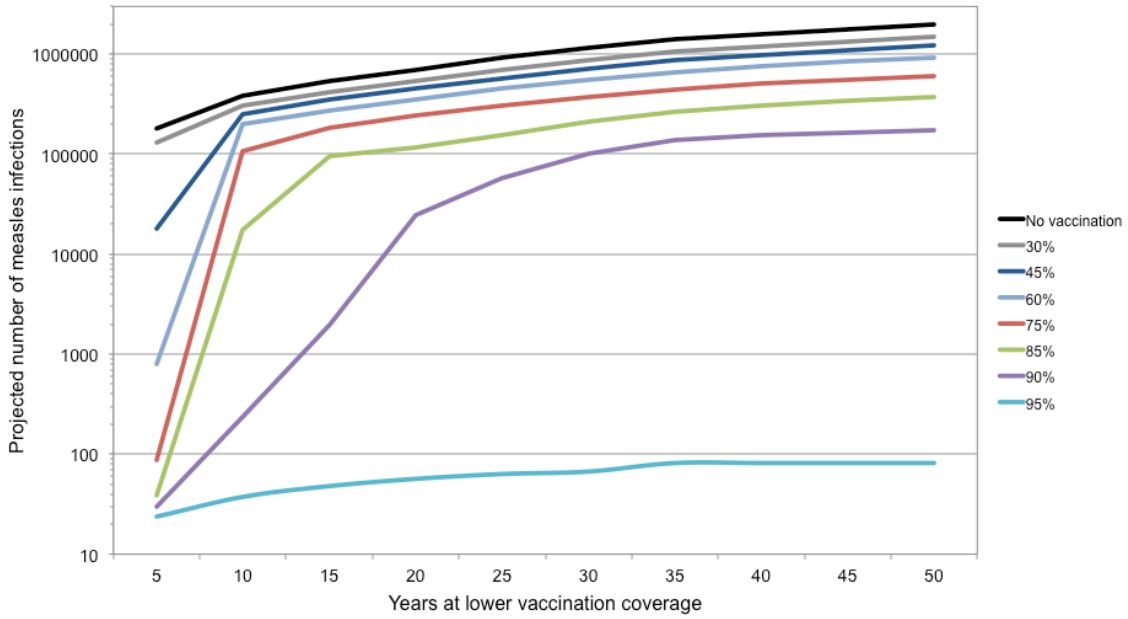


Figure Details: Projected outbreak size following the arrival of a person infected with measles in the city of Toronto, assuming different levels of vaccine uptake for up to 50 years. Note that infections are plotted on a logarithmic scale.

Key Finding

- The highly infectious nature of measles, combined with measles persistence elsewhere in Canada and globally, makes local measles outbreaks and large numbers of illnesses highly likely in the face of small declines in vaccine coverage.

Section 6: Pertussis

Background

Pertussis (whooping cough) is a bacterial respiratory infection caused by the organism *Bordetella pertussis.* It is highly contagious and spread through respiratory secretions from infected individuals.

The typical pertussis infection is multiphasic, with progress from a catarrhal phase with mild cough to a spasmodic cough with an inspiratory whoop and post-tussive vomiting in the paroxysmal phase, followed by a convalescent phase (80). While mortality is greatest in infants, who are at highest risk of pertussis-related encephalopathy and pneumonia (80, 81), many adolescents and adults present with atypical and milder disease symptoms, and are likely to be under-diagnosed.

Among children, symptoms of pertussis include development of a fever, vomiting, and excessive coughing, typically with a 'whooping' noise on inspiration. For adults, a persistent cough is the most common symptom of pertussis infection. In fact, it is estimated that between 12% and 32% of prolonged coughs in adolescents and adults are attributable to pertussis infection (82). The onset of symptoms usually occurs 6 to 20 days after effective contact with an infectious individual. Antibiotics can be given to reduce the severity of disease symptoms and to reduce the duration of infectiousness (83). However, vaccination remains our best defense against the spread of pertussis.

Pertussis is associated with severe outcomes, including death, in children under the age of 2.

Pertussis infection can have severe complications, especially in infants less than 2 years of age. Commonly, these complications include bradycardia, apnea, weight loss, pneumonia, atelectasis, convulsions, encephalopathy, and death (84, 85). In adolescents and adults, reported complications of pertussis include sinusitis, urinary incontinence, rib fracture, and pneumonia with complications occurring more frequently in older adults (86). Among infants less than 6 months of age, the case fatality rate is approximately 1% while in adults, this is estimated to be much lower, approximately 0.2% (87). Risks of pertussis complications among hospitalized children under 2 years of age can be found in **Table 6.1**

Table 6.1. Risk of complications from pertussis infection for children under age 2. Table source: (88).

Complication	Risk after infection (per case)
Pneumonia	9.4%
Atelectasis	3.0%
Pneumothorax	0.1%
Inguinal Hernia	4 per 1000
Umbilical Hernia	4 per 1000
Seizures	2.3%
>5% Weight Loss	1.3%
Death	0.9%

Before the pertussis vaccine was introduced in 1943, Canada had high rates of pertussis.

Prior to the advent of the pertussis vaccine, approximately 160 cases per 100,000 were reported in Canada (5). Widespread Canadian immunization campaigns with whole cell pertussis vaccine began in the 1940s, with subsequent introduction of the adsorbed whole cell vaccine in the 1980s, and acellular preparations in 1997-98 (**Figure 6.1)** (5).

Figure 6.1. Pertussis was a common disease in Ontario before vaccination began in 1943.

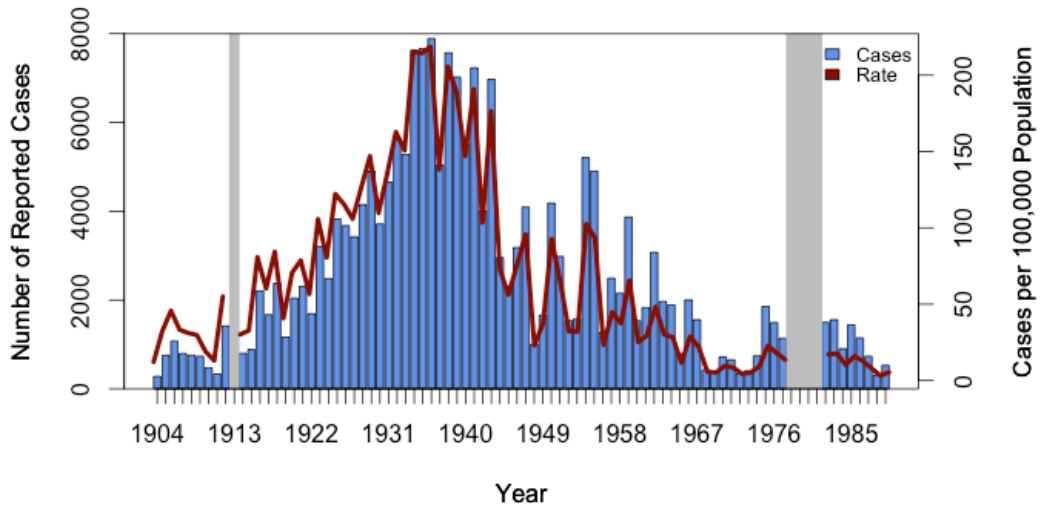


Figure Details: Annual reported pertussis cases and rates in Ontario, 1904 – 1989. Total reported cases (left-hand axis) and cases per 100,000 population (right-hand axis) are shown. No data were available for the years 1913, 1978, 1979, 1980, and 1981 (indicated by grey bars). Data were obtained from the International Infectious Disease Data Archive (http://iidda.mcmaster.ca).

Currently, only acellular pertussis vaccines are approved for use in Canada. There are two formulations: one for infants and children (2 months – 7 years of age) and another with a lower concentration of antigens for adolescents and adults (11-54 years of age). The pertussis vaccine

preparations in Canada are typically given along with diphtheria and tetanus toxoids. Some preparations also contain inactivated polio vaccine and/or Hib conjugate vaccine (5). The recommended vaccination schedule and other vaccine-specific attributes can be found in **Table 6.2.**

Table 6.2. Characteristics of the pertussis vaccine.

Characteristic		Details
Number of doses		7
Age at vaccination for each dose:		
	1	2 months
	2	4 months
	3	6 months
	4	18-24 months
	5	4-6 years
	6	14-16 years
	7	Once as an adult
Vaccine efficacy		~90%
Duration of immunity following primary series		Unclear. Range for whole cell vaccine: 4-12 years. Range for acellular vaccine estimated to be similar (89).

While the pertussis vaccine is considered safe and effective to protect against pertussis infection, the vaccine is associated with minor adverse events. In particular, pain and swelling at the injection site, headache, tiredness, and fever have all been reported as side effects of the vaccine (90). The newer acellular vaccine preparations are considered much safer than the whole cell preparations and have fewer attributed adverse events (91).

While immunization has reduced the burden of pertussis in Ontario, there have been recent surges in the number of reported pertussis cases.

Although the implementation of vaccination programs resulted in a dramatic reduction in the incidence of pertussis in Canada (92), pertussis elimination has not occurred. Pertussis epidemics tend to occur every 2-6 years and this pattern has continued even with the introduction of vaccination (93).There has been a recent surge in the number of reported pertussis cases **(Figure 6.2)** (94-96). This is likely because the pertussis vaccine itself is not 100% effective (97) and has been shown to have waning immunity (89). The United States is currently experiencing a large outbreak of reported pertussis (98). Since November 2011, there have been outbreaks of pertussis throughout southwestern Ontario, although, to date, Toronto has not seen a significant increase in disease activity, with reported rates in 2012 similar to those observed in 2010-11 (99).

Figure 6.2. There has been a recent surge in the number of reported pertussis cases in Toronto.

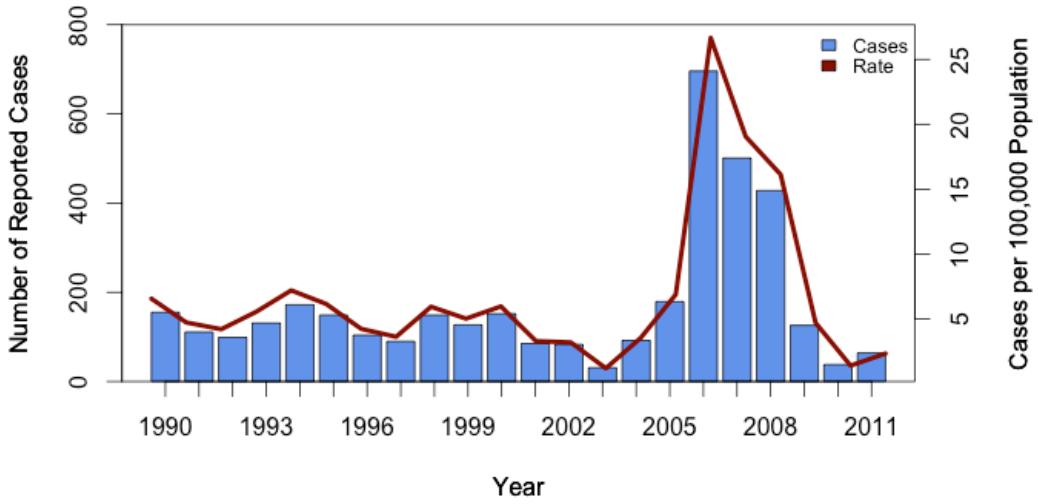


Figure Details: Annual reported pertussis cases and rates in Toronto, 1990 – 2011. Total reported cases (left-hand axis) and cases per 100,000 population (right-hand axis) are shown. Data were obtained from Toronto Public Health.

Immunization against pertussis is not part of the Immunization of School Pupils Act, but coverage rates for pertussis in Toronto remain high among school age children. Recent estimates suggest pertussis coverage among younger children approximates 80%, but coverage is lower for adolescents and adults (100). We sought to estimate the burden of pertussis if vaccination rates for children were to decrease.

Methodology

Pertussis remains endemic in Toronto, despite high vaccination coverage.

Pertussis is an endemic disease with epidemics occurring in the population with regular periodicity. Given that pertussis is continually circulating in the Toronto population despite relatively high vaccination coverage, it might be argued that declining vaccination coverage is immaterial, as the disease has not been eliminated. However, elevated levels of population immunity would still be expected to attenuate the impact of pertussis on vulnerable individuals. We used this model to see how declining vaccine uptake would impact disease trends.

Pertussis Transmission Model

We used a deterministic mathematical model to assess the impact of declining vaccination rates over time on the number of pertussis cases reported in Toronto.

We developed an age-structured compartmental model to simulate the effects of pertussis vaccination in Toronto, Ontario (see **Appendix 2.4** for model details). The model is comprised of susceptible, exposed, infectious, recovered, re-susceptible, re-exposed, re-infectious, and re-recovered compartments as well as 7 vaccination compartments as outlined in **Figure 6.3.** Each vaccination compartment represents a different level of conferred immunity due to vaccination as children, adolescents, and adults progress through the 7 recommended pertussis vaccines (5).[†]

Model Scenarios and Outcomes

We looked at the impact of declining childhood pertussis vaccination on the projected number of infections, neurological complications, and deaths in the Toronto population.

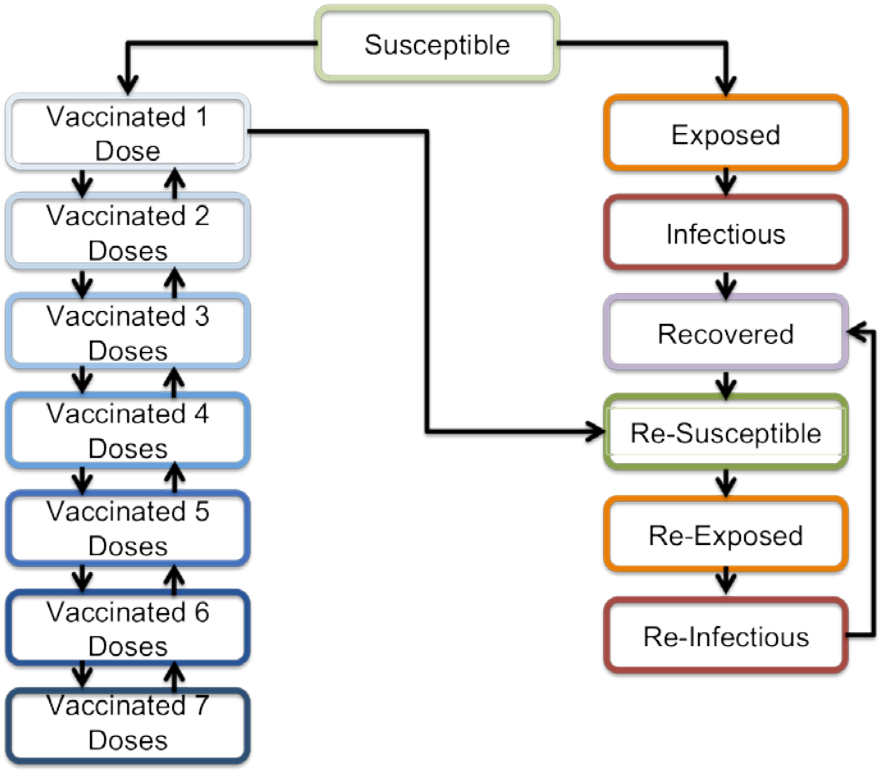
We modeled a series of potential scenarios where immunization coverage for childhood pertussis varied from 20% to 95%. Individuals who were not immunized were considered completely susceptible to pertussis infection. For all scenarios, the adolescent 'booster' vaccine was assumed to be given to 50% of all children who had completed their childhood pertussis vaccination series. Similarly, we assumed that 10% of adults who had completed their childhood and adolescent vaccination series would be given a 'booster' vaccine at least once in their lifetime. To model decreasing vaccination coverage through time, we included a probability of vaccination parameter in the model.

The main outcomes measured were total reported infections, deaths, and pertussis-related neurological complications in children under 2 years of age. The expected number of deaths were calculated based on the estimated 0.9% mortality rate in children under two (88). Neurological complications included development of new seizures, worsening of existing seizures, and

[†] The deterministic nature of this model results in outputs that represent average pertussis incidence over time; clusters and small outbreaks are not explicitly represented.

encephalopathy. The predicted neurological complications assumed a 3.5% neurological complication rate among pertussis patients under the age of 2 (88).

Figure 6.3. The pertussis model schematic. Model is further stratified by age (not shown).



Results

Pertussis is highly communicable and even small decreases in vaccination coverage can have a large impact on outbreak size and associated morbidity and mortality, particularly in children under age 2.

The impact of decreased vaccination coverage can be seen within the first 5 years. After 5 years of vaccination decline, the pertussis-related risk of mortality for children under 2 was found to increase considerably (**Figure 6.4**). At 50% vaccination coverage for 5 years, the pertussis-associated risk of mortality was projected to increase three-fold, relative to that seen with 95% coverage over the same time period. Similarly, pertussis cases in this age group are projected to increase markedly over that time period as vaccine coverage falls. Predicted trends in disease incidence over the next 50 years are shown in **Figure 6.5**. As well, incidence of pertussis-related severe neurological sequelae in children under 2 is expected to dramatically increase as vaccination coverage rates decline (**Figure 6.6**).

Figure 6.4. If decreased vaccination coverage was maintained for 5 years, we would expect higher pertussis-related death rates in children under age 2.

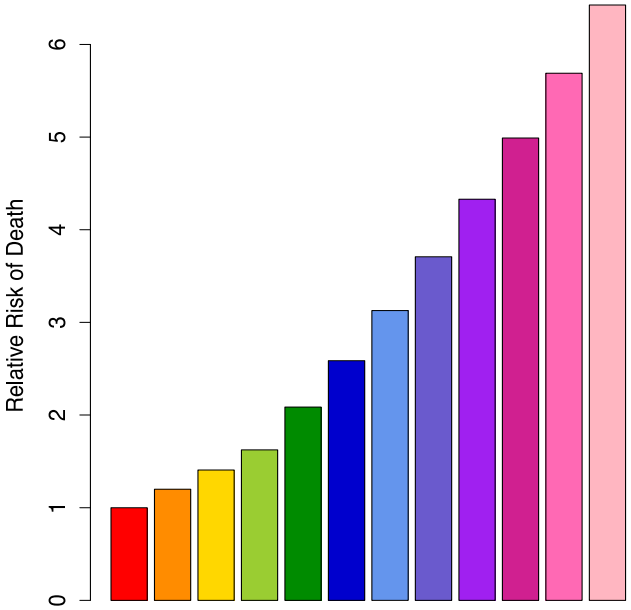


Figure Details: The predicted pertussis-related death rates at 5 years of lower vaccination coverage for children under 2 years of age are shown above. For comparability, the death rates are standardized to the expected death rate if 95% of the population is immunized.

Figure 6.5. Decreasing vaccination coverage rates has a large impact on outbreak size for children under age 2.

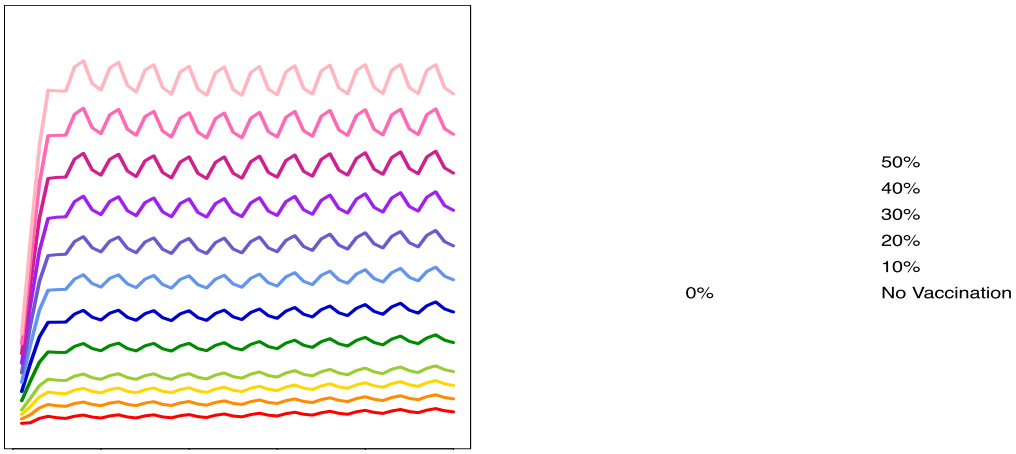


Figure Details: The predicted number of pertussis cases per 100,000 for children under 2 years of age in Toronto is shown for different levels of vaccination coverage

Figure 6.6. Decreasing vaccination coverage rates for pertussis is associated with increased risk of severe pertussis-related complications in children under 2.

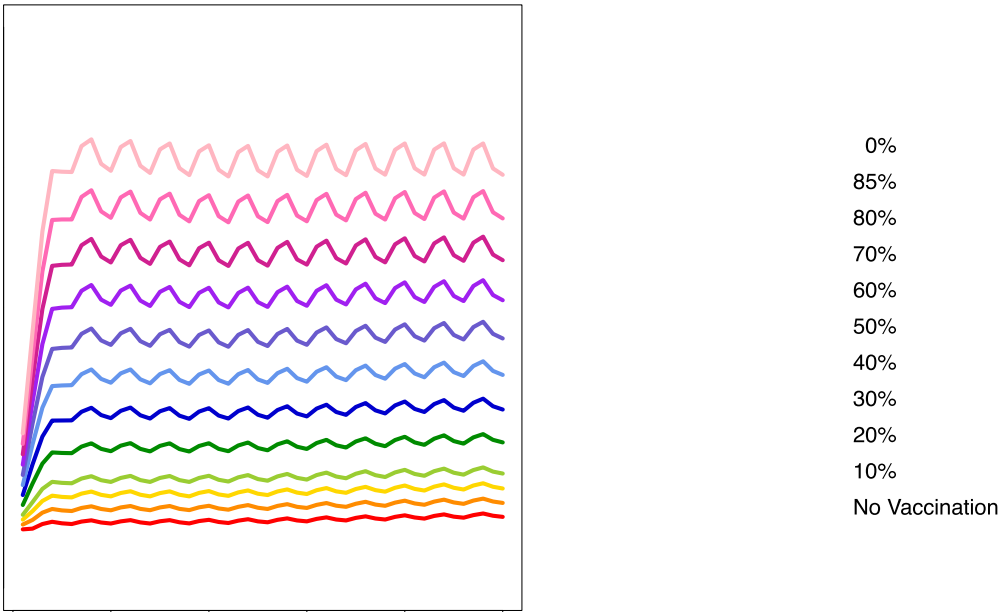


Figure Details: The predicted number of pertussis-related neurological complications per 100,00 in children under 2 in Toronto is shown for different levels of vaccination coverage. Neurological complications include new and worsening seizures and encephalopathy.

Key Finding

- Pertussis remains endemic in Toronto at the time of writing, and it is possible that both short duration of protection by new pertussis vaccine preparations and risk due to transmission by teens and adults results in ongoing risk even with high levels of vaccine coverage. Nonetheless, declines in pertussis vaccine coverage, even under such suboptimal circumstances, could result in as much as a six-fold increase in risk of severe disease in infants.

Section 7: Discussion and Implications

As noted in the introductory section of this document, vaccines have been hailed as one of the most influential public health interventions of the last hundred years. Indeed, vaccination against smallpox stands as a singular instance in which application of a health intervention has actually eradicated a human disease from the planet. Dramatic changes in the health status of children and adults have been achieved in Canada and other countries as a result of immunization programs.

The results of models presented above, which are based on the best available information, show that the City of Toronto would be far less healthy and far more vulnerable to disease outbreaks without ongoing immunization of the population at high levels of coverage.

Maintaining high levels of immunization in Toronto is a priority to prevent morbidity and mortality and associated with infectious diseases. As such, immunization can be thought of as an investment for the City of Toronto: the investment of funds and effort in maintaining high levels of vaccination pays large returns by keeping the population safe and healthy.

However, the fact that we need to use tools like mathematical modeling to demonstrate the value of vaccine programs reflects a factor that threatens the success of these programs: as vaccines decrease the burden of illness in our communities, communities without vaccine-preventable illnesses come to be regarded as "normal", leading some to question the need for ongoing vaccines. In other words, the success of vaccination means that we have been deprived of the epidemics, outbreaks, and tragedies that previously served as constant reminders of their importance (101).

Although *all* vaccines can have side effects, the risks to population health from decreased vaccination far outweigh the potential health gains that would result from fewer vaccine adverse events.

The recent resurgence of measles reported in many parts of the world is due in part to lower rates of vaccination against this disease, which may in turn have been spurred by public concern about suggested links (now discredited) between measles vaccine and autism (102). However, all vaccines have potential side effects, and when diseases are well controlled by vaccination it is not surprising to see that safety concerns focus on potential risks of vaccination rather than risks of disease (36). What is often forgotten is that these individual decisions to decline vaccination add up to a critical mass of unvaccinated individuals sufficient to spark outbreaks or epidemics of diseases that had been eliminated. Importantly, these outbreaks would likely cause far more severe health problems in children than would be seen by maintaining vaccination at current levels.

For many diseases, the importance of high levels of vaccination relates to protection of both vaccinated and unvaccinated people. Although loss of vaccination coverage may be a gradual process, the resurgence of infectious diseases can be dramatic and sudden due to "critical thresholds".

Vaccines protect populations both by preventing vaccinated individuals from becoming sick, and also by decreasing the number of infectious people in a population. This prevents infection in individuals who have not been vaccinated, or in whom vaccination has not provided complete protection. This effect is called "herd immunity", and it is one of the factors that make vaccines one of the most cost-effective health interventions in history (103). These herd effects occur when the number of individuals vaccinated in a population crosses a "critical threshold", such that disease transmission can no longer be supported and the disease is eliminated. The flip-side to this effect, which can be seen in our analyses of polio and measles risk, is that explosive increases in disease risk can occur very suddenly with only small declines in vaccine coverage in the population. Current vaccination coverage levels sit near these thresholds for both of these diseases.

Maintaining vaccine-related gains in health is an active process, requiring ongoing efforts by public health officials, and ongoing engagement by the public.

As demonstrated in this report, the failure to sustain current levels of vaccine coverage would likely cause major health problems in Toronto, including the loss of Ontario's status as a polio-free geographical area, deaths from pertussis in infants (as has recently been observed in California) (104), and a dramatic resurgence of measles (as has recently been observed in Quebec) (105). To sustain current high levels of immunization coverage, public health agencies may need to better communicate such complex concepts as maintenance of herd immunity, the potential for explosive resurgence of communicable diseases, and the vulnerabilities created via lack of immunization in a city like ours, with numerous commercial and cultural links to countries where most vaccine preventable diseases continue to circulate at high levels.

In this exercise, we have modeled the City of Toronto as a single homogeneous entity, though age-structured mixing patterns were incorporated into models. It is possible (indeed likely) that low-level random ("stochastic") events, such as neighborhood clusters of disease cases, could occur, even in the face of overall rates of vaccine coverage that are high. Such sentinel events have occurred in the United Kingdom, France, and the Netherlands (106-110), and have often heralded far more widespread outbreaks of disease (31, 111, 112). Thus both ongoing surveillance efforts, and programmatic efforts to ensure that vaccination rates in Toronto are high in all neighborhoods, are critical.

Key Findings

- The current epidemiology of measles, polio, and pertussis in Toronto was readily simulated using mathematical models constructed using the best available data.
- Both for diseases that currently cause minimal morbidity and mortality (measles and polio) and for pertussis, which continues to circulate as an endemic disease in Toronto, declining vaccine coverage is expected to result in dramatic increases in adverse health events and disease outbreaks in the near term (i.e., in < 5 years after reductions in coverage).
- Given the highly transmissible nature of these diseases, small reductions in vaccination coverage below current levels are sufficient to create significant public health hazards in the City of Toronto.
- Our models indicate that the health gains provided by vaccination in the City of Toronto are large, but will not be robust in the face of declining vaccination coverage. As such, control of diseases via vaccination (even diseases that are not currently circulating in the city) should be regarded as an ongoing "work in progress", rather than a "mission accomplished". Continued investment and resources are needed to maintain the health gains that vaccination has provided in our city.

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Appendix 1: Key Concepts in Mathematical Modeling

Basic reproductive number (R_0): the number of secondary infections created by a single primary infectious case introduced into an entirely susceptible population (**Figure 1**). R_0 determines the epidemic potential of a new pathogen. If R_0 is greater than 1, each old case on average causes more than one new case and exponential growth will be observed in a population. When R_0 is 1, each old case creates one new case on average, and a disease is said to be endemic in a population. When R_0 is less than one, a disease will not be able to cause an epidemic in a population.

Effective reproductive number (R_e): the average number of new infections created by a single infectious case in a population in which not all hosts are susceptible (**Figure A1.1**). When R_e is less than one, a newly introduced pathogen will not cause an outbreak in a population; for a disease that is already established in a population, once R_e falls below 1, the epidemic will stop growing.

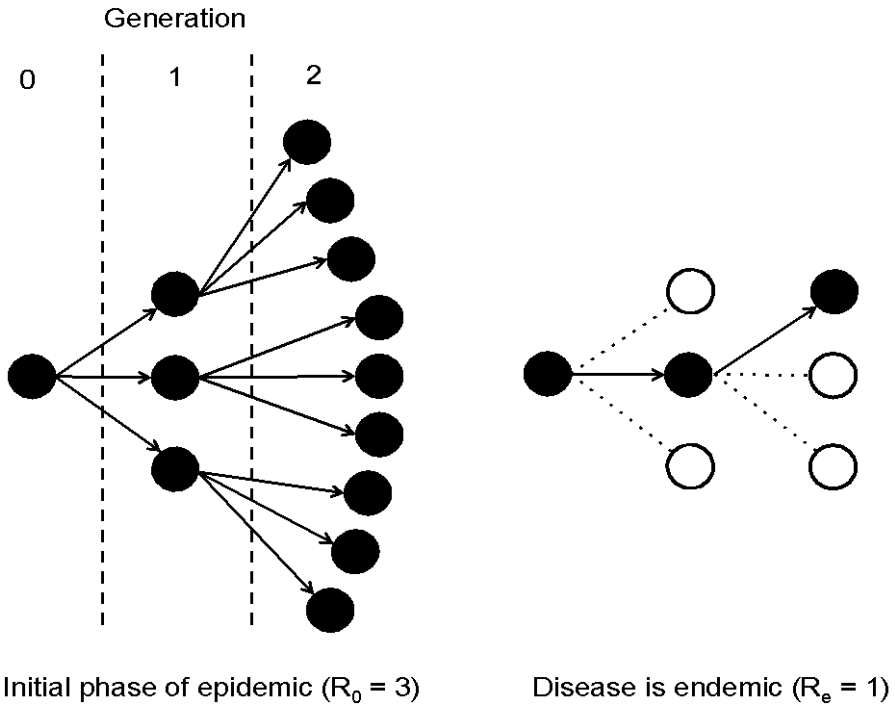

Figure A1.1. The number of new infections generated when the basic reproductive number (R_0) is 3. Infected and immune individuals are represented by dark and open circles, respectively. When there is no population immunity (left), each infectious case generates on average 3 new cases. As individuals acquire immunity, each case generates on average 1 additional case and the disease becomes endemic (effective reproductive number (R_e) = 1). Figure adapted from: (10).

Herd immunity: refers to the indirect population-level effects that vaccinated individuals confer to susceptible hosts, as reduced infection prevalence in vaccinated individuals also reduces the exposure of susceptible individuals to infection (9). The herd immunity threshold (S_h) is the minimum fraction of susceptible individuals that must be immune (typically via vaccination or previous infection) to reduce R_e below 1 and eliminate an infectious disease in a population. It is calculated as $S_h = 1\text{-}1/R_0$. The herd immunity threshold depends on R_0; diseases with higher values of R_0 have a higher threshold. For example, a disease with R_0 of 10 requires 90% immunity, while a disease with R_0 of 2 requires 50% population immunity, for disease elimination or to prevent an outbreak following disease introduction.

Elimination/Eradication: Elimination refers to the reduction to zero of the incidence of disease in a *defined geographical region*, while eradication refers to the permanent reduction to zero of the *worldwide* incidence of disease (62). Although the geographical scales are different, from a modeling perspective, eradication or elimination is achieved by reducing R_0 below 1, maintaining R_e below 1, or keeping the number of susceptible individuals in a population below the herd immunity threshold (9). Note that outbreaks can still occur when R_0 is less than one, due to random fluctuations in the number of new infections generated (9).

Appendix 2: Mathematical Model Details

2.1. Polio Importation Model Calculations

The probability that an individual traveler from a polio-endemic country was infected was modeled as a stochastic process, using a Poisson distribution to account for uncertainty in the AFP reporting data:

$$\_\_\_\_\_$$

where x is the number of infections per paralytic case (assumed to be 200). The risk of a traveler from Toronto acquiring poliovirus infection was calculated by assuming that polio is at endemic equilibrium in the source countries and that the basic reproduction number in low/lower-middle income countries is approximately 10 (113). Under these assumptions, we estimate that approximately 90% ($1 - 1/R_0$) of the population is immune to infection (114), allowing us to calculate the force of infection in the source countries as:

$$\_\_\_\_\_$$

This force of infection acted on unvaccinated travelers from Toronto. Variability was introduced into annual number of travelers arriving from each country by drawing from a Poisson distribution with mean equal to the average number of annual visits. A random number generator was used to determine each traveler's infection status. The expected number of disease importations was determined for a total of 10,000 simulations.

2.2. Polio Transmission Model Description and Equations

Polio transmission in the Toronto population was described using a deterministic, age-structured compartmental model that incorporated demographic processes (births, aging, and deaths) and routine vaccination. The population was divided into five compartments representing different disease states: susceptible (S), vaccinated (V), exposed (E, infected but not infectious), infectious (I), and recovered (R). Transmission of infection occurred through contact between susceptible and infectious individuals. To capture contact patterns within and between age groups and to enable modeling of the recommended polio vaccination schedule, the population of Toronto was divided into age classes with the following cutoffs: <6 months, 6-17 months, 18 months-4 years, 5-9 years, 10-14 years, …, 65-69 years, and ≥70 years. Population size was based on 2011 estimates (115). Mixing within and between age strata was modeled using a population-based prospective study of contact patterns in eight European countries (116). The birth rate was set equal to the death rate to maintain a constant population size and population distribution among age classes. Deaths occurred only in the oldest age group, with continuous aging through the age cohorts. Parameters describing the natural history of polio infection were derived from the literature (**Table A2.1**).

Table A2.1. Poliovirus transmission model parameters.

Parameter	Value	Reference
Latent period (days)	2	(113)
Infectious period (days)	30	(113)
Basic reproductive number (R_0)	6	(114)
Vaccine efficacy (3 or more doses)	99%	(58)
Duration of maternally-derived immunity (months)	6	Assumption
Life expectancy (years)	80	(117)
Number of infections per paralytic case	200	(65)

We assumed that successful vaccination provided complete protection against infection and transmission of poliovirus to susceptible individuals. OPV induces enteric mucosal immunity, such that vaccinated individuals may excrete poliovirus in their feces following exposure to live virus, contributing to ongoing asymptomatic transmission in the population (118). IPV does not induce enteric mucosal immunity, but it does induce systemic immunity (protecting against paralytic poliomyelitis) and reduces oropharyngeal excretion following challenge with live poliovirus. Given that the major mode of poliovirus transmission in Canada is expected to be via the respiratory route (due to high hygiene and sanitation standards), we did not consider the role of individuals successfully vaccinated with IPV in the transmission of poliovirus. We assumed that the level of immunity to poliovirus infection in infants was equal to immunity levels in adults aged 30-34 as a result of transplacental transfer of maternal immunoglobulin, and that maternally-derived antibodies waned by 6 months of age.

We assumed that only a single poliovirus serotype was in circulation. Type 1 poliovirus accounted for greater than 90% of wild poliovirus cases in 2010-2011 (64) and estimates of infections per paralytic case were based on this serotype.

We assumed that population level immunity (due to a combination of vaccination and previous exposure to poliovirus) is currently approximately 90%. To model the impact of declining IPV uptake, vaccine coverage was decreased as a step function, resulting in a cohort of individuals with increased susceptibility to poliovirus infection

We considered a one-year time horizon, under the assumption that following a poliovirus outbreak, there were be a surge in vaccine uptake, such that polio would not re-establish endemicity in the population. Outcomes measured included total infections and AFP cases.

Model equations are presented below, for the jth age group:

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Model parameters

Parameter[a]	Description	Value[b]
$\lambda_{\square}^{*}$	Force of infection	See below
ε	Rate of transition from exposed to infectious	1/latent period
γ	Rate of recovery from infection	1/infectious period
c_j	Vaccine coverage	Estimated from data
VE	Vaccine efficacy	Vaccine efficacy
ρ_j	Aging rate	1/size of age category
μ_j	Mortality rate	1/life expectancy

η_j	Birth rate	1/size of oldest age group

[a]Subscript j indicates age group.
[b]Refer to **Table A2.1** for parameter values.

[*]Force of infection is given by:

where λ_{jm} is the contact rate for infective individuals of age group k (I_k) with susceptible individuals of age group j (based on a population-based prospective study of contact patterns in eight European countries), N is the total population size, and λ_{ks} the probability of transmission given contact (assumed to be independent of age and calculated based on R_0). λ_j is 0 for j>1. For j=1, c_jVE represents maternally-derived immunity and is equal to c_jVE in the 30-34 year old age group (j=9).

2.3. Measles Transmission Model Equations

Measles transmission in the Toronto population was described using a deterministic, age-structured compartmental model that incorporated demographic processes (births, aging, and deaths) and two doses of routine vaccination. The population was divided into six compartments representing different disease states: susceptible, vaccinated (one dose or two doses), exposed, infectious, and recovered.

Transmission of infection occurred through contact between susceptible and infectious individuals. To capture contact patterns within and between age groups and to model the recommended measles vaccination schedule, the Toronto population was divided into age classes with the following cutoffs: <12 months, 1-4 years, 5-9 years, 10-14 years, …, 65-69 years, and ≥70 years. Population size was based on 2011 estimates (115). Mixing within and between age strata was modeled using a population-based prospective study of contact patterns in eight European countries (116). The birth rate was set equal to the death rate to maintain a constant population size and population distribution among age classes. Deaths occurred only in the oldest age group, with continuous aging through the age cohorts. Parameters describing the natural history of measles infection were derived from the literature (**A2.2**).

Table A2.2. Model parameters.

Parameter	Value	Reference
Latent period (days)	8	(15)
Infectious period (days)	5	(15)
Basic reproductive number (R_0)	17	(114)
Vaccine efficacy		(119)
1 dose	0.95	
2 doses	0.99	
Duration of maternally-derived immunity (months)	6	Assumption
Life expectancy (years)	80	(117)

In their first six months of life, infants were assumed to be immune to measles infection due to protection derived from maternal antibodies, with levels of immunity equal to immunity in adults aged 30-34. We assumed that vaccinated individuals had reduced susceptibility to measles infection, with risk relative to unvaccinated individuals equal to (1- vaccine efficacy). Given the uncertainty that exists around waning of vaccine-induced immunity and its impact on susceptibility and disease transmission in vaccinated individuals (120, 121), we did not include this in the model, and considered vaccine-related immunity to be life-long. A 'term time' forced R_0 was used to account for enhanced measles transmission when schools are in session (114).

Based on available data, we estimated that the level of immunity against measles infection was 97% in individuals born in or prior to 1970 (due to naturally-acquired immunity) (77) and 95% in individuals born after 1970 (due to vaccine-acquired immunity). To model the impact of declining MMR uptake over time, vaccine coverage was decreased as a step function, resulting in

a cohort of individuals with increased susceptibility to measles that increased in size over time (see **Figure 4.3** for an example of how declining vaccination rates were implemented in the model).

The main outcomes measured were total infections, severe cases, and adverse vaccine events averted by immunizing at lower levels than the base case. Risks of severe cases and serious vaccine-associated events were based on the data in **Table 5.2**. As a conservative measure, we used lower bound estimates of probability of infection-related complications and upper bound estimates of probability of vaccine-related complications. We limited our analysis to a one-year time horizon, under the assumption that a surge in measles cases in Toronto would result in a return to baseline levels of vaccine uptake.

Model equations are presented below:

For the first age category (j=1, under 12 months):

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For the second age category (j=2, 1-4 years):

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For all remaining age categories (j>2):

Model parameters

Parameter[a]	Description	Value[b]
$\lambda_{\square}^{*}$	Force of infection	See below
ε	Rate of transition from exposed to infectious	1/latent period
γ	Rate of recovery from infection	1/infectious period
$C_{1,j}$	Vaccine coverage, first dose	Estimated from data
$C_{2,j}$	Vaccine coverage, second dose	Estimated from data
VE_1	Vaccine efficacy, one dose	Vaccine efficacy
VE_2	Vaccine efficacy, two doses	Vaccine efficacy

θ	Rate of loss of maternally-derived immunity	1/duration of maternally-derived immunity
ρ_j	Aging rate	1/size of age category
μ_j	Mortality rate	1/life expectancy
η_j	Birth rate	1/size of oldest age group

[a]Subscript j indicates age group.
[b]Refer to **Table A2.2** for parameter values.

[*]Force of infection is given by:

$$\lambda_j = \sum_{k=1}^{16} \beta_{jk} \frac{I_k}{N}$$

where β_{jk} is the contact rate for infective individuals of age group k (I_k) with susceptible individuals of age group j (based on a population-based prospective study of contact patterns in eight European countries), N is the total population size, and β_{jk} is the probability of transmission given contact (assumed to be independent of age and calculated based on R_0). β_j is 0 for j>1. For j=1, c_j represents maternally-derived immunity and is equal to c_j in the 30-34 year old age group (j=8).

2.4. Pertussis Transmission Model Details

In order to realistically model the recommended series of pertussis vaccinations, we stratified the population according to the following cutoffs: <2 months, 2-4 months, 4-6 months, 6 months-2 years, 2-7 years, 7-10 years, 10-15 years, 15-20 years, 20-65 years, and >65 years. In this model, transmission of pertussis occurs when an infectious individual contacts a susceptible or re-susceptible individual according to a mixing matrix based on contact patterns between the age groups, as adapted from the best available data for high-income countries (116).

Pertussis seasonality and multi-year periodicity of epidemics were simulated by incorporating two cosine terms into the model transmission arameter (β_1) to represent annual outbreaks (β_2) and epidemics every 4 years (β_3), such that:

$$\beta(t) = \beta_1 * \left(1 + \beta_2 \cos\left(\frac{2\pi t}{365}\right) + \beta_3 \cos\left(\frac{2\pi t}{4 * 365}\right)\right).$$

To estimate the β seasonality terms in the absence of vaccination, we used data on pertussis mortality in children under 2 years of age in Ontario from 1880-1929 (67) assuming that 16% of cases were reported to the public health authorities. This is consistent with estimates of case-reporting in England and Wales during a similar time period (122). We used data on children less than 2 years old because we thought this age group would have the most complete data, given more typical and severe disease manifestations in young children.

We modeled aging as a continuous process with deaths occurring only in the oldest age category. To maintain a constant population size and proportionate age distribution, we set the birth rate equal to the death rate. We assumed that individuals with repeat infections, or those with pertussis infection following immunization would be 20% as infectious as individuals with primary pertussis infections. This is similar to an assumption made by Van Boven and colleagues (123) and incorporates both the hypothetical vaccine efficacy for infectiousness (124) and the reduced duration of cough in partially immunized individuals (125). Other epidemiological model parameters were taken from the literature, and can be found in **Table A2.3**. The differential equations used in this model can be found in **Figure A2.1**.

Table A2.3. Parameter values used in model.

Parameter	Best-fit value	Range	Reference
Latent period (days)	8		(126)
Infectious period (days)	15		(126)
Duration of immunity following infection (years)	Median= 12.37	10-50	Model calibration; (89), (127)
Duration of immunity following complete immunization (years)	Median= 15.43	2-25	Model calibration; (89)
Relative infectiousness of individuals re-challenged with pertussis (following loss of naturally-acquired or vaccine-induced immunity)	0.2		Assumption, similar to (123)
β_1, base transmission parameter	11.3346	9-12	Model calibration
β_2, relative amplitude of annual forcing	0.05	0.005-0.25	Model calibration
β_3, relative amplitude of seasonal forcing	0.029	0-1	Model calibration
Life expectancy pre-vaccine era (years)	66		Assumption
Life expectancy pre-vaccine era (years)	75		Assumption

Figure A2.1. The differential equations used to model pertussis.

$$\frac{dS_j}{dt} = \eta_j N - \lambda_j S_j + \left(1 - c_{j-1,1}\right)\rho_{j-1} S_{j-1} - \rho_j S_j - \mu_j S_j$$

$$\frac{dV_{2..6,1}}{dt} = c_{j-1,1}\rho_{j-1} S_{j-1} + \left(1 - c_{j-1,k+1}\right)\rho_{j-1} V_{j-1,1} + \omega_v V_{j,2} - \omega_v V_{j,1} - \rho_j V_{j,1} - \mu_j V_{j,1}$$

$$\frac{dV_{2..6,2..7}}{dt} = \left(1 - c_{j-1,k+1}\right)\rho_{j-1} V_{j-1,k} + c_{j-1,k}\rho_{j-1} V_{j-1,k-1} + \omega_v V_{j,k+1} - \omega_v V_{j,k} - \rho_j V_{j,k} - \mu_j V_{j,k}$$

$$\frac{dV_{7..10,1..7}}{dt} = \rho_{j-1} V_{j-1,k} + \omega_v V_{j,k+1} - \omega_v V_{j,k} - \rho_j V_{j,k} - \mu_j V_{j,k}$$

$$\frac{dE_j}{dt} = \lambda_j S_j - \varepsilon E_j - \rho_j E_j + \rho_{j-1} E_{j-1} - \mu_j E_j$$

$$\frac{dI_j}{dt} = \varepsilon E_j - \gamma I_j - \rho_j I_j + \rho_{j-1} I_{j-1} - \mu_j I_j$$

$$\frac{dR_j}{dt} = \gamma\left(I_j + IR_j\right) - \omega R_j - \rho_j R_j + \rho_{j-1} R_{j-1} - \mu_j R_j$$

$$\frac{dSR_j}{dt} = -\lambda_j SR_j + \omega R_j + \omega_v V_{j,1} - \rho_j SR_j - \mu_j SR_j$$

$$\frac{dER_j}{dt} = \lambda_j SR_j - \varepsilon ER_j - \rho_j ER_j + \rho_{j-1} ER_{j-1} - \mu_j ER_j$$

$$\frac{dIR_j}{dt} = \varepsilon ER_j - \gamma IR_j - \rho_j IR_j + \rho_{j-1} IR_{j-1} - \mu_j IR_j$$

Figure Details: These equations represent the susceptible (S), exposed (E), infectious (I), recovered (R), re-susceptible (SR), re-exposed (ER), and re-infectious (IR) compartments as well as 7 vaccination compartments as outlined in **Figure 6.3.** The subscript j indicates age group and k indicates vaccine dose number. The other parameters are detailed in the chart below. Refer to **Table A2.3** for specific parameter values.

Parameter	Description
I_j^*	Force of infection
e	Rate of transition from exposed to infectious
g	Rate of recovery from infection
w	Rate of loss of immunity following infection
w_v	Rate of loss of immunity following vaccination
rr	Relative infectiousness of for individuals with previous exposure to pertussis
$c_{j,k}$	Vaccine coverage
r_j	Aging rate
m_j	Mortality rate
h_j	Birth rate

*Force of infection is given by:

$$\lambda_j = \sum_{m=1}^{10} \frac{\phi_{jm}\beta(t)\left(I_m + rrIR_m\right)}{N}$$

where f_{jm} is the contact rate for infective individuals of age group m (I_m and IR_m) with susceptible individuals of age group j (based on a population-based prospective study of contact patterns in eight European countries), *rr* is the reduction in infectiousness for individuals with previous exposure to pertussis, *N* is the total population size, and *b(t)* is the probability of transmission given contact (assumed to be independent of age):

$$\beta(t) = \beta_1 * \left(1 + \beta_2 \cos\left(\frac{2\pi t}{365}\right) + \beta_3 \cos\left(\frac{2\pi t}{4 * 365}\right)\right)$$

As the duration of vaccine-induced immunity has been debated in recent years (89), we used model calibration techniques to estimate this parameter value. In particular, we fit the model to data on laboratory confirmed pertussis cases found in the Greater Toronto Area during 1993-2003 (32). We used data on children under 2 because we thought this age group would have the most complete data. As underreporting of pertussis cases in Toronto is a critical issue, we used age specific case-reporting probabilities. These probabilities, along with the duration of vaccine-induced immunity, were varied to achieve an optimal fit between the data and the model. The fit between the model and the data can be found in **Figure A2.2.**

After the model was calibrated both in the absence of vaccination and with childhood vaccinations, we introduced adolescent and adult vaccinations to maintain consistency with the guidelines set forth by the Public Health Agency of Canada (5). In particular, we included a booster vaccine for adolescents age 14-16 and a one-time adult booster vaccination.

Figure A2.2. The model was calibrated to cumulative and annual pertussis incidence in the 1993-2003 vaccine era. Cases confirmed by the Public Health Laboratory --Toronto and the Hospital for Sick Children are shown in black and model predicted incidence of detected cases for the four age groups (under 2 months old, 2-4 months old, 4-6 months old, 6-24 months old) is shown in grey.