BACK TO THE FUTURE. PUBLIC HEALTH POLICY AND IMMUNOLOGY TECHNOLOGY IN THE FIGHT AGAINST INFECTIOUS DISEASES

Introduction

During the past 16 months, a pandemic caused by a newly emergent virus has spread throughout the world causing death and disrupting the economies of most nations. However, at the turn of the 20th century, epidemics of infectious diseases were part of everyday life. That time also marked a time when the understanding of infections and the development of treatments for them was rapidly advancing. Using the history of Columbia, Lancaster County, let's examine how that knowledge led to the treatments and vaccines that are helping to control the current pandemic of COVID-19.

On October 9, 1893, Lena Agle, age 2 1/2, died of diphtheria. One week earlier, Dr. William Taylor had reported her illness to the newly formed Columbia Board of Health. Lena was just one of 153 cases of diphtheria recorded by the board in the 16-month period between September 1893 and December 1894. The outbreak peaked in November 1893 when the secretary of the board of health reported 47 new cases and 14 deaths, a mortality rate of 30%. The good news was that within a year, scientists in Europe would prove that a new treatment with diphtheria antitoxin would reduce the mortality drastically. The ideas that led to the antitoxin eventually produced a vaccine that prevented diphtheria.

On March 10, 1902, smallpox arrived in Columbia, carried by a transient named George Anderson, whose address was recorded as "earth." Despite rapidly recognizing the illness and transferring Mr. Anderson to the infectious disease hospital in Lancaster, an epidemic developed during which 161 people contracted the disease over a 6-month period. Luckily, this was a mild form of smallpox and only 2 people died. However, it did cost the borough over $7,000 to fight epidemic including immunizing over 10,000 citizens of Columbia with vaccine from the Marietta Vaccine Farm. Almost 100% of the population received the smallpox vaccine in a very short period of time. Smallpox was the only infectious disease that could be effectively prevented at the time of this outbreak. This prevention was so effective, that in less than 100 years, smallpox would be completely eradicated.

In December 2019 the CDC reported a cluster of unusual cases of pneumonia in the Chinese city of Wuhan. In less than two months, the virus responsible was identified and the disease caused by it was given the name, COVID-19. Fourteen cases of COVID-19 were identified in the US from January 21 – February 23, 2020, all related directly to China. In retrospect, a coroner in Santa Clara County, California showed that a death on February 6, 2020 was caused by the novel coronavirus and was not linked to China. This newly identified disease has spread worldwide causing millions of illnesses, over 2 million deaths, and disrupting the economy on a wide scale. The good news is that modern science has been able to elucidate the structure of the virus, decode its genome, and rapidly develop effective vaccines, and to a lesser extent, therapies for the disease.

Treatments and vaccines that are available now to affect the course of Covid-19 infection are based in the same science that produced therapies to treat and prevent diphtheria and to prevent smallpox over 100 years ago. Despite not knowing the exact nature of the diphtheria toxin, an effective treatment was developed and quickly became available. Similarly, without any knowledge of the causative agent, a century earlier Edward Jenner had proved the usefulness of cowpox vaccination to prevent smallpox.

The results of progress made in the last 30 years of the 19th and early 20th centuries eventually resulted in vaccines against many of the most common, and sometimes deadly, infectious diseases known. A child born today can be protected from diphtheria, tetanus, pertussis (whooping cough), measles, mumps, rubella (German measles), rotavirus (the most common source of serious viral gastroenteritis), hepatitis A (infectious hepatitis), hepatitis B (serum hepatitis), polio, chicken pox, Haemophilus influenzae type b (formerly the most common cause of meningitis in young infants), pneumococcus (a common cause of ear infections, pneumonia, and meningitis in children), and influenza. HPV (human papilloma virus) vaccine has the potential to markedly reduce cervical cancer. Ironically, smallpox vaccine has not been part of the routine vaccination schedule since the 1970s.

Using science similar to that developed to treat diphtheria, antibodies can be used treat anthrax, botulism, rabies, and tetanus, as well as Covid-19. Fortunately, one does not need to collect serum from horses to treat Covid. We can now use monoclonal antibodies produced in a lab, or convalescent serum from people who have recovered from an infection

I am not going to discuss current vaccines or vaccine controversies in detail. I think we are all aware of the issues. Rather, we will examine the science and public health policies that heralded the advances of bacteriology and immunology at the end of the 19th century by looking back at Columbia from 1893 to 1903. These early discoveries laid the foundation for our current fight against the novel coronavirus causing COVID-19.

How and why do we have so much information about infectious diseases in this small town from over 100 years ago?

More than 14 years ago, while browsing through the shelves of the Lancaster County Archives, I found an old book entitled Infectious and Contagious Diseases. I was looking for information about ancestors who lived in Columbia. As part of that research, I had discovered a smallpox epidemic that occurred in Lancaster in 1883. The book I found had evidence of another smallpox epidemic almost 20 years later. After ten years of research and investigation, I published a book about infectious diseases and public health based on the experiences of Columbia at the end of the 19th and beginning of the 20th centuries.

This was a period of explosive growth in bacteriology and immunology resulting in new ways of viewing human diseases and opening the door to an important effort to control infectious disease. The role of public health and government grew out of this new knowledge. Today, I will review some of the important discoveries of the latter 19th century, show how the new science

of immunology allowed some of these illnesses to come under control, and explore the role of public health in all of this. Finally, I will explore what happens when confidence in public health and immunization breaks down. To do this, I will focus on two of the diseases reported in the book – smallpox and diphtheria – one, a disease that most of us have never seen, and the other a triumph of public health that has been eliminated.

How did the Record Come to Exist

Columbia borough formed its first Board of Health as a direct result of Pennsylvania Act No. 42 - "To Enable Borough Councils to Establish Boards of Health - that passed the General Assembly on May 8, 1893. Each borough was to be divided into 5 districts with a board member representing each one. Act 42 also required physicians to report infectious diseases to the board and mandated the board maintain a record of infections, births, deaths, and marriages. This was a first attempt to keep a statewide record of vital statistics. Although the board members served without compensation, the board did hire a secretary and a Health Officer. The first board, appointed July 6, 1893, was made up of two physicians, Drs. John Lineaweaver and William Brenholtz, and three businessmen, Frederick Bucher, Abraham Guiles and Daniel Calnan. On August 1, the rules governing the board passed borough council and were published. The following diseases required notification of the board: smallpox, cholera, scarlet fever, diphtheria, typhus, yellow fever, meningitis, rabies, glanders, and leprosy. The Columbia record initially only recorded 3 of these illnesses – diphtheria, scarlet fever and smallpox – along with 2 others noted later – typhoid fever, and tuberculosis. The rules also mandated smallpox vaccination for every citizen of the borough and required proof of vaccination within the seven years prior to school enrollment.

The Columbia Board of Health, in turn, reported to the state Board of Health. The state board was established in 1885 after over 30 years of trying to form a state agency to safeguard the health of the commonwealth. It took a severe epidemic of typhoid fever in Plymouth, Luzerne County to force the General Assembly to act. In a population of about 8,000 over 1,000 residents were sickened and 114 died. This epidemic was traced to one of the two water sources for the town, and specifically to runoff of waste from a single resident living along a stream supplying the town. In 1905, the state board was replaced by the Pennsylvania Department of Health.

Smallpox - History

Now let's turn our attention to smallpox, the first of two diseases that we'll look at in some detail. Smallpox can be dated to at least 1000 BCE. Three Egyptian mummies have evidence of a rash and pathological changes consistent with the disease. It likely spread by trade, migration and war from Egypt to the Middle East, South Asia and China by 250 BCE. Hindu medical texts from 400 CE clearly describe smallpox: " Fever occurs, with pain over the body, but particularly in the back ... pain is felt in the large and small joints, with coughing, shaking, listlessness and languor ... the pustules red, yellow, and white and they are accompanied by burning pain."

Further spread by trade, Islamic conquest, and the crusades brought smallpox to Europe by end of the 6th century.

Smallpox came to the Americas with European exploration and conquest. It had been endemic in Europe for centuries, and many Europeans coming to the New World had been previously infected. Here we have the first record of what happens when an infectious disease encounters a population with no prior exposure. It was devastating. The first two outbreaks occurred on Hispaniola in 1507 and 1518 where it killed up to a third of the native population. The second outbreak spread to Cuba and Puerto Rico in 1519 where about half of the native residents died.

Perhaps as a small measure of cosmic revenge, Columbus' crew is thought to have introduced syphilis to Europe upon their return. The army of French King Charles VIII carried syphilis into the heart of Europe after the siege of Naples in 1494. Eventually, syphilis became known as the great pox, in distinction from smallpox.

Smallpox arrived in the North American colonies in the early 17th century. A major epidemic on the New England coast in 1617-19 reportedly killed over 90% of the indigenous population. There is debate over the exact nature of the illness with some favoring bubonic plague and others favoring smallpox. Regardless, the coast of Massachusetts was largely depopulated when the Mayflower landed in 1620. Another epidemic, this time definitely smallpox, started in Plymouth in 1633 and spread inland through the Great Lakes and St. Lawrence over the next 7 years. Once again, the indigenous population was decimated. Increase Mather, one of Boston's leading Puritan clergymen, saw the hand of God in the destruction of the indigenous population: "About the same time the Indians began to be quarrelsome ... but God ended the controversy by sending the small-pox amongst the Indians at Saugust, who were before that time exceedingly numerous. Whole towns of them were swept away ..."

Later, smallpox largely affected the large coastal population centers of Boston, New York and Philadelphia. Most often it was imported by a sick passenger or crew member who brought the illness from Europe. Epidemics occurred every 5 to 7 years when the population of non-immune people grew large enough to sustain an outbreak.

Smallpox Control – Inoculation

1721 marked the beginning of attempts to prevent smallpox in Europe and North America with a practice known as inoculation or variolation. There is historical evidence that this practice was known and used in China and India centuries earlier. Inoculation involved purposely infecting patients with material taken from victims of smallpox by either scratching it into the skin or blowing it into the nose. Dr. Emanuel Timonius wrote a letter to the Royal Society about the practice in Constantinople in 1713, and Dr. Jacobium Pylarium reported a similar practice in Venice in 1716. Both extolled the safety and effectiveness of the procedure.

Lady Mary Wortley Montague introduced inoculation to Europe. She had a personal interest in smallpox as her brother had died from the disease and she had been scarred by it. At about the

same time, inoculation was brought to the American colonies by a collaboration between Rev. Cotton Mather and Dr. Zabdiel Boylston in Boston in 1721. Rev. Mather, a Fellow of the Royal Society, had read the letters published by Drs. Timonious and Pylarium with great interest. He also had heard of the practice from his servant, Onesimus as he explained in a letter to the Royal Society in 1716: "Inquiring of my Negro-man, Onesimus, who is a pretty Intelligent Fellow, whether he ever had the Small-Pox, he answered, both, Yes, and No; and then he told me, that he had undergone an Operation, which had given him something of the Small-Pox, and would forever preserve him from it ..." Mather stated his desire to use the operation when smallpox came again to Boston.

He got his chance in 1721. Sailors brought the illness from Europe, and despite efforts to contain it by quarantine, it soon spread throughout the city. (As an aside, the word quarantine originates from the Italian *quaranta giorni,* meaning forth days. It came into use during the black death when Venice imposed a 40-day isolation on passengers and crews of ships entering the harbor) Mather wrote to the medical establishment of Boston, urging them to try the new practice. The best educated physician in Boston, Dr. William Douglass, angrily rebuffed Mather, basically telling him to “stay in his lane.”

One little known country doctor, Zabdiel Boylston, agreed to proceed and inoculated his own son and two slaves. All did well. Rev. Mather also had his son, Sammy, inoculated. Despite a severe reaction, Sammy survived and was the only one of Mather's 16 children to outlive him. Nevertheless, a great controversy erupted with angry arguments on both sides. The Boston selectmen reprimanded Boylston and forbade further inoculation. By the end of this outbreak, almost 6,000 of the 12,000 residents of Boston had been infected with 844 deaths. Boylston inoculated 242 people of whom 6 died. Five years later he published his account of the experience while living in England. For his efforts to halt the spread of smallpox, a major street in Boston is named for Boylston, while Dr. Douglass has been forgotten.

Smallpox not only caused epidemics in cities, it also threatened the success of the American revolution. It directly caused the failure of the American attempt to capture Eastern Canada and Quebec in 1775 when smallpox sickened almost half of the colonial armies. Fear of smallpox also slowed recruitment and increased desertion from the Colonial Army. In February 1777 a committee of the Continental Congress authorized mass inoculation of the army. One inoculation center was in Morristown, New Jersey. Despite attempts to isolate the soldiers, smallpox did spread to the surrounding population resulting in 68 deaths.

Smallpox Control – Vaccination

Fortunately, the use of inoculation came to an end in 1798 when Dr. Edward Jenner self-published his manuscript describing the use of cowpox to prevent smallpox: *An Inquiry in the Causes and Effects of Variolae Vaccinae.* The name, vaccination, is derived from the Latin for cow, *Vaca*. Jenner had been told by a patient that she considered herself safe from smallpox because of an earlier infection with cowpox. He began collecting a series of cases from others who had had cowpox and who seemed impervious to either natural or inoculated smallpox.

Finally, he took "matter from a sore on the hand of a dairymaid who was infected by her master's cows and it was inserted, on the 14th of May 1796, into the arm of the boy by means of two superficial incisions." After the sore healed, Jenner inoculated the boy with smallpox. There was no reaction.

Dr. Benjamin Waterhouse introduced cowpox vaccination to the United States when he vaccinated his son with material sent from England. He also provided material to Dr. John Redman Coxe who brought the practice to Philadelphia, and convinced Thomas Jefferson of the importance of the practice.

This is not to say that there were not problems. Initially, there were no commercial producers of vaccine. Because cowpox was not common, the practice of vaccination most often occurred by passing the infection from one person to another. This was known as using "humanized lymph" or arm-to-arm transmission. Systemic infections, like syphilis, could be transmitted along with the vaccine. Sometimes, naturally occurring smallpox was mistaken for cowpox resulting in a smallpox outbreak.

Eventually, arm-to-arm transmission was replaced by vaccine propagated in calves in large vaccine farms. Despite this progress, problems remained. There was no oversight of these producers. Some produced a vaccine that was totally inactive while others produced vaccines that were contaminated. In several instances, fatal outbreaks of tetanus were linked to infected vaccine. All this led to resistance, particularly to mandatory vaccination.

One of the most prominent vaccine producers in the United States was the Marietta Vaccine Farm founded by Hamil Marr Alexander. He founded his enterprise in East Donegal township in 1883. By 1889, he gave up his medical practice to devote himself to the vaccine farm. Later, he expanded with vaccine farms in Omaha, Nebraska, and McEwensville, Northumberland County. Eventually, he also added production of diphtheria antitoxin to the business. His company supplied the vaccine used to stem to 1902 epidemic in Columbia. Parts of the original building are still standing on the property of GlaxoSmithKline along River Road in Marietta.

Despite the use of vaccination, smallpox continued to affect millions of people every year until it was finally eradicated. Lancaster suffered through two outbreaks in the early 1800s; in 1819, at least 70 were infected with 20 deaths. As late as 1883, an epidemic that began in the county jail sickened over 80 with 16 deaths. Major seaports, like Philadelphia, continued to be hard hit. In 1871, there were over 1,200 admissions to the Municipal Hospital and 361 deaths.

The outbreak in Columbia in 1902 was the result of the slow march of smallpox from South America slowly northward through the South into the mid-Atlantic states. You can almost imagine watching the progress much like we watch hurricane prediction maps now. The board of health knew that it was approaching. In February 1902, the health officer noted: 'We have escaped thus far from the pestilence of smallpox, for this boon we are all very thankful ..." The main fear was that a transient would bring the infection to Columbia. Borough council passed a resolution on February 4, 1902. "Resolved: That the Secretary be directed to call attention of

Borough Council to the danger of Small-Pox contagion from tramps who daily visit Columbia, and we recommend that some stringent measures be taken to prevent tramps from occupying the Borough Lockup at night and if possible from entering the town and as a precautionary measure the Board of Health further advises and urges that these people be apprehended and vaccinated." The prominence of the railroad made Columbia particularly vulnerable. Smallpox arrived on March 10, 1902 carried by just such a transient.

Let's look at the response of local authorities in Columbia. Despite efforts to locate and vaccinate contacts, Harry Shackenbach, a local resident developed smallpox on March 28. By the time of a special meeting of borough council on April 16, at a time when only 8 cases had been reported, a program of mass vaccination was authorized, and planning for a municipal hospital for isolation was begun. Two weeks later the hospital opened. Further efforts by borough council reached a climax on May 28, 1902, with adoption of the following resolution:
First–That Council hereby prohibits all public gatherings in the Opera House, Halls, Parks, Streets and other public gatherings.
Second–That it fully approves the action of the Board of Health in ordering Compulsory Vaccination, and the action of the Sanitary Committee in employing Patrolmen for the infected districts, and in adopting the stringent measures for the enforcement of quarantine laws, and regulations, and for the punishment of their violation.
Third–That the Sanitary Committee instruct patrolmen to disperse all gatherings in the Highways.
Fourth–That Council urges all the people of Columbia to co-operate effectively with the Sanitary Committee and with the Board of Health and its officers, in the observance and enforcement of the Sanitary and Health regulations, and to render cheerful and complete obedience thereto.
Fifth–That Council invoke the aid of all local physicians in this work, and urges them to impress upon their patrons and patients the gravity of the present conditions, and the necessity for strict observance of health regulations.
Sixth–That the Sanitary Committee be instructed to prosecute all persons guilty of violating the quarantine laws.
Seventh–That all persons declared infected with Smallpox be required to go to the Municipal Hospital for treatment, and upon their refusal, the Borough to withdraw all assistance, medicinal and provisional.

Six physicians were employed to administer a mandatory vaccination, each paid 25 cents for every dose. Looking back, it is obvious that Columbia had the good sense to follow the advice of Dr. Wertenbacher in Public Health Reports, a forerunner of the CDC's Morbidity and Mortality weekly Report:
It is advised that whatever measures are adopted they should be made thorough.
Measures, good or bad, half done are worse than useless as they give a fancied security.
Smallpox cannot be suppressed without the expenditure of money.
The more promptly you act the less it will cost.
When in doubt act on the safe side.
Finally, the following is offered for your banner in smallpox work: ISOLATE, VACCINATE, DISINFECT."

We can compare the actions taken in Columbia in 1902 with those taken in Lancaster in the 1883 outbreak using Dr. Wertenbacher's directions as a basis. The epidemic in Lancaster started on May 15, 1883, in the jail, a place ideally suited for isolation. However, it quickly escaped the confines of the prison without plans for an alternative site for isolation. Quarantine in houses failed. The infectious disease hospital proposed in June 1883 was not completed until November when the outbreak was over. It also seems that Lancaster was not willing to invest a lot of money in the fight. It was not until July, that free vaccination was offered to those unable to afford it, and that vaccine physicians were appointed for each of the city's nine wards. Columbia managed to do this within a couple weeks of the outbreak.

One of the first major public health campaigns was approved and funded by King Carlos IV of Spain between 1803 and 1813. Spain's American colonies were severely affected by smallpox among the indigenous population. Dr. Jose Flores proposed expeditions to the Caribbean, Central America, and South America and co-led the expeditions along with Francisco Xavier de Balmis. Jenner's cowpox vaccine was carried across the Atlantic by serially vaccinating 22 orphan boys under the care of a nurse. An extension of the plan allowed a group to travel from Central America to the Spanish colonies in the Philippines.

Often greeted with celebrations, and sometimes with resistance, the leaders of this endeavor instructed local physicians in the proper technique of vaccination, propagation of the vaccine, and established local vaccine boards to manage the procedure. Eventually, they managed to directly vaccinate over 500,000 people throughout the Americas and in the Pacific.

In an article published in 1800, Dr. Waterhouse added a super-title: "A prospect of Exterminating the Smallpox," and in 1801, Jenner wrote "that the annihilation of the Small-Pox, the most dreadful scourge of the human species, must be the final result of this practice." However, as late as 1950, there were 50 million cases of smallpox worldwide, and about 300 million people died of smallpox throughout the 20th century. It would take until 1977 for the prediction to come true when the last case of naturally occurring smallpox was found in Somalia in a man named Ali Maow Maalin. After he recovered, he spent his life campaigning for polio vaccination in an attempt to eliminate it. In a cruel twist of fate, Mr. Maalin died of severe malaria, another disease for which there is an active ongoing search for an effective vaccine.

The smallpox virus exists today only in two laboratories, the CDC in Atlanta, and a lab in Moscow. Routine vaccination was suspended in 1971 and for health workers in 1978. However, concern about use of smallpox as a bioweapon has led to continued research into improved vaccine. A very recent report describes the development of a new vaccinia variant vaccine.

Now let's see how the coronavirus vaccine compares with smallpox. Historically, viral vaccines have been of two types: killed, or inactivated viruses – like the Salk polio vaccine; or live attenuated viruses – like the Sabin oral polio vaccine. Smallpox vaccine essentially uses an attenuated virus similar to smallpox to induce immunity. The vaccines to prevent COVID-19 are different. The first two vaccines approved for emergency use in the US use messenger RNA to

trick the body into producing a viral protein – the spike protein – allowing the body to recognize it as foreign and produce antibodies against it. A third approved vaccine, Johnson&Johnson's, uses a different virus engineered to carry genetic material for the spike protein, as does the AstraZeneca/Oxford vaccine.

Reports of a rare coagulopathy involving the J&J vaccine caused a temporary pause in its use. Similar reports led the EU to reassess the use of the AstraZeneca vaccine. In the US, J&J's vaccine may have caused 15 reported cases of unusual clotting in over 7 million recipients. For comparison, smallpox vaccine has about 1 serious reaction per thousand doses, and 14-52 life threatening reactions per million. So far, all approved coronavirus vaccines appear to be safe in pregnancy. Smallpox vaccine is absolutely contraindicated in pregnancy due to fetal vaccinia, a fatal infection. The vaccines in distribution now are very effective but must be given to large numbers of people to stop the pandemic.

The borough of Columbia, led by its Board of Health, was able to dispense vaccine to almost its entire population within weeks of the outbreak. They organized quickly, designated physicians to give the vaccine and provided it free to any who could not pay. The citizens of Columbia cooperated with the effort thus ensuring its success.

Diphtheria – History

Now let's turn our attention to diphtheria. While smallpox often affected the course of wars and fates of monarchies, diphtheria killed children and caused personal tragedy for many families. The history of prevention and treatment of this illness is much less complicated than that of smallpox. However, it was a much more prevalent threat at the time that the record in Columbia was kept. As late as 1900, diphtheria was the tenth leading cause of death in the United States. If one uses the Columbia death record to construct a table showing the causes of death over the seven years of its data, one finds a similar but not identical list. Diphtheria was a constant threat to the health of children throughout this time. The average age of all cases in the 1893-94 epidemic was 8.5 years. Only five adults contracted diphtheria and none died. All were mothers of young children with diphtheria.

Diphtheria was recognized since the time of Hippocrates. He described an illness with fever, a sore throat, a peculiar nasal voice, regurgitation of liquids through the nose, and death on the fifth day. Spanish physicians named the illness, "*garrotillo*." A terrible epidemic of "throat distemper" spread through the New England colonies in 1735. Hampton Falls, New Hampshire was particularly hard hit suffering the deaths of 160 of the 404 children under the age of ten. Preachers throughout the region spoke of the illness in their sermons, blaming the outbreak on a loss of Puritan faith.

Diphtheria – Early Treatment

Since death from diphtheria was caused by airway obstruction, most early treatments focused on trying to remove the obstruction. These included hydrochloric acid, papaine, Monsel's (ferric

subsulfate) solution, cocaine; steam inhalation with eucalyptus, turpentine, or carbolic acid; alcohol as a stimulant; or even tracheostomy. Monsel's solution, a cauterizing agent; papaine, which is an enzyme found in meat tenderizer; and hydrochloric acid were applied topically to try to limit the growth of the membrane. Cocaine was used as a topical anesthetic and vasoconstrictor that could have reduced swelling. Steam with various additives was used to soothe the airways. Vicks Vaporub is still a popular remedy for congestion.

A physician at New York Foundling Hospital, Joseph O'Dwyer, pioneered the use of endotracheal intubation as an alternative to tracheostomy. He described the situation he encountered as follows: "Dante's inscription over the portals of the infernal regions – Hope abandon all who enter here – might well have been placed over the door of the croup room in the Foundling Hospital. All we could say in favor of the operation is that it allowed the little sufferers to die easier." His technique improved survival without surgery to thirty percent. When used with antitoxin in 1897, survival improved to 75%.

Diphtheria – Anti-toxin

The real breakthrough in treatment for diphtheria depended on basic microbiologic research carried on in the 1880s. Edwin Klebs and Freiderich Löffler, working separately, identified the causative organism of diphtheria – initially named the Klebs-Löffler bacillus. Four years later, two researchers in the Pasteur Institute Alexandre Yersin and Pierre Paul Emil Roux, were able to prove that clinical diphtheria was caused by a toxin produced by the bacteria and not as a direct result of the infection itself. Nearly a century later, the structure and action of diphtheria toxin has been elucidated. It is a protein that blocks protein synthesis and is lethal in a dose of 0.1 microgram per kilogram.

Together, Yersin and Roux guided the way forward by suggesting, "Is it possible to acclimate the animal to diphtheritic toxin and to produce immunity against diphtheria by this method?" Progress came rapidly. In 1892 Emil von Behring published a paper proving the ability to produce serum that protected experimental animals. Soon thereafter, trials in humans confirmed its utility. In August 1894, serum from horses became commercially available from a German manufacturer. Soon, large American cities with Boards of Health established their own antitoxin production facilities. After reviewing over 7,000 reported cases treated with anti-toxin published by 1895, Dr. William Welsh of Johns Hopkins concluded: "Anti-diphtheritic serum is a specific curative agent for diphtheria, surpassing in its efficacy all other know methods of treatment for this disease. It is the duty of the physician to use it. By Dr. Alexander's death is 1904, the Marietta vaccine farm was producing anti-toxin.

This treatment was not entirely safe, however. It needed to be used early in the disease, often within the first 24 hours to be most effective. At that point it could be very difficult to accurately diagnose diphtheria. Because the serum was most often produced in horses, exposure to non-human proteins could result in severe reactions including rashes, fever, joint pains, and kidney disease. Injection site abscesses also occurred. These were large volume

injections given intra-muscularly. Diphtheria anti-toxin was the first specific treatment for an infectious disease.

The importance of diphtheria antitoxin is demonstrated by the history of the Idiatrod trail dog sled race held in Alaska annually since 1966. It is held in commemoration the 1925 delivery of antitoxin serum to Nome that prevented an outbreak of diphtheria. In January 1925, Dr. Curtis Walsh of the US Public Health Service recognized an outbreak in Nome. He only had enough antiserum to treat 5 patients. After locating an adequate supply in Anchorage, he had it sent by train to Nenana, 674 miles Nome. From there, 20 teams of dogs and drivers worked in a relay to bring the serum to Nome in only 5 days. The final leg was run by Gunnar Kaasen and his lead dog, Balto. Both became heroes, and Balto was honored with a statue in Central Park in New York City.

Emil von Behring won the first Nobel Prize in Physiology or Medicine in 1901 for his work on diphtheria antitoxin, as did Paul Ehrlich in 1908. Of note is that a non-European coworker of Dr. von Behring, Shibasaburo Kitasato, was instrumental in the development of diphtheria antitoxin as well as a serum therapy for tetanus. Although he was nominated for the 1901 Nobel Prize along with Behring, he was not awarded the honor.

Diphtheria – Prevention

If animals could be immunized against diphtheria toxin, why not children? Initially, anti-toxin was used to provide passive immunity to household contacts of sick children. Smaller doses of anti-toxin were effective in providing a month of protection from the illness. However, exposure to the serum increased the likelihood of severe reactions if anti-toxin had to be used for treatment later.

The use of antitoxin – an antibody against the toxin – was a way to passively immunize against diphtheria toxin. Two similar approaches are used to fight COVID-19. The first is using convalescent serum to treat the infection. This uses naturally occurring antibodies from patients who had been infected and recovered from COVID-19. A second, more modern approach uses antibodies produced using recombinant DNA technology to fight the virus. Even though these are technologically much more sophisticated than horse serum, it is really the same principle.

The search turned to efforts to provide active immunity. The problem was the extreme toxicity of even minute amounts of the toxin. In 1907, Dr. Theobold Smith was able to show that a mixture of antitoxin with the toxin resulted in active immunization. Experimental animals remained immune for up to 2 years. In 1913, Behring did the same thing with humans. Dr. William Park in New York conducted a trial in children giving three injections of the mixture at weekly intervals. Over the next 15 years New York City Department of Health immunized over 500,000 school age children and 250,000 preschoolers and infants. As a result, deaths from diphtheria declined from 800 in 1920 to 198 in 1930.

The search went on for an even safer and more effective alternative. In 1923, Gaston Ramon demonstrated that diphtheria toxin could be made harmless by treating it with formalin and heat, and that the product produced immunity. This became known as diphtheria toxoid. It was more effective, had a long shelf life, and produced long lasting immunity. Its use continues to this day. In the United States, diphtheria was no longer in the top ten causes of death by 1901. Today, diphtheria toxoid is always used in a combination vaccine, usually with tetanus toxoid, and a pertussis (whooping cough) vaccine – DTaP.

The importance of immunization is emphasized by what began in the former Soviet Union in 1991. Prior to universal vaccination in 1958, the USSR reported over 750,000 cases of diphtheria during the early 1950s. By 1978, only 198 cases were reported as a result of mandatory immunization with 5 doses of high potency toxoid prior to school entry. Through the 1980s less potent toxoid was used and the mandatory program was relaxed. When the USSR collapsed, the vaccine supply was disrupted. In 1991, there were over 3,100 cases, and at the peak in 1996, 50,000 cases of diphtheria were reported. Re-institution of a rigorous program of immunization cut the reported cases to 2,875 in 1997. Prevention really worked. I would guess that almost all physicians listening today have never treated a case of diphtheria.

I hope that this brief review of medical history illuminates the path of medical progress from Jenner, Klebs, Loffler, Yersin, Roux, Behring, Kitasato, and Ehrlich to the present development and deployment of Corona virus vaccine and monoclonal antibodies. While I did not spend a lot of time on public health measures like quarantine and isolation, it is clear that the Columbia Board of Health followed the advice of the experts of their day to employ these tactics early and aggressively to help slow the spread of smallpox. The importance of public health infrastructure and its consequences of its absence is clearly illustrated by the diphtheria epidemic that spread through the former Soviet Union after its collapse. This has also been shown by the slow and uneven response to the COVID-19 pandemic caused by years of underfunding and neglect of public health.