"All Sorts of People": The Beginning of Vaccination in America

by

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Part I – A Terrible Choice

One May morning in 1721, a sharp-sighted hawk hovered over colonial Boston, searching for something tasty for breakfast. Looking down, he saw a cloud of dust along the highway, and stooped lower. Within the dust he spied a lone horseman traveling south from Cambridge toward the Boston commons in the center of the town. The man was young and well-dressed, although he wore no finery, no ruffle at his neck or wrist, no special patterns or silver working on his stout riding boots. All that he had was quality, meant to last, but not necessarily to impress. His horse was handsome, but there was no braid on his bridle or ornamentation to the tack. The young man's saddlebags were strained to their limits, stuffed not with extra clothing, but with books! Nothing looked promising to the hawk, so he whirled and turned, backtracking toward Boston. Circling above the harbor, he saw a ship tied up off Bird Island; not among the bustle of loading and unloading and the general traffic of the port, but set aside from the other ships, as if in quarantine. The hawk spotted a small rowboat a hundred yards from the ship, with two gentlemen standing in the prow and a figure wrapped in white lying in the bottom of the boat. Disappointed, the hawk turned away to search for better hunting grounds.

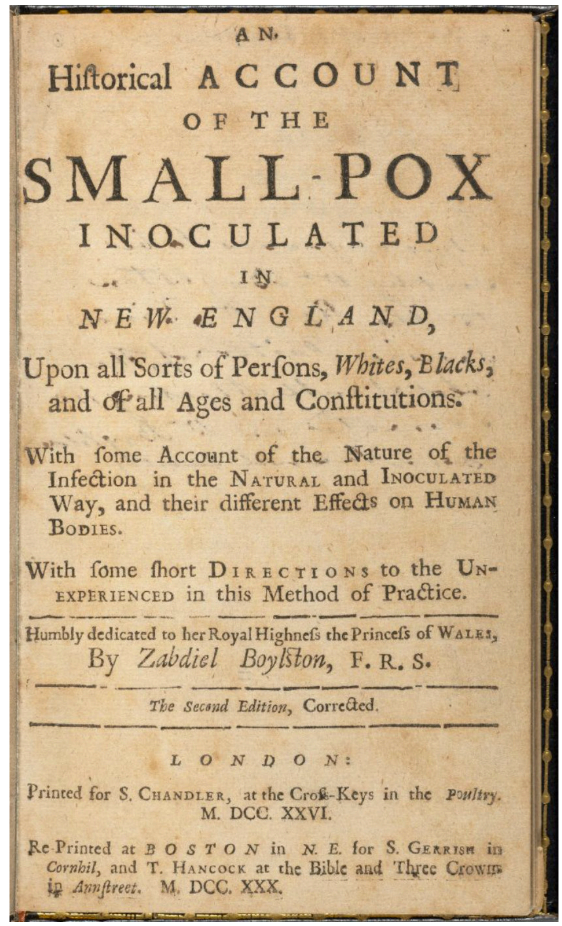

Figure 1. Title page of Zabdiel Boylston's paper.

The rider was Samuel Mather ("Sammy" to his family and friends), returning home for summer holidays from his second year at Harvard University. The distance from his room in Cambridge to his room on the second floor of his family home was between five and ten miles, only a few hours' ride for a kindly person in no special hurry and inclined to spare his horse. And Sammy was gentle with horses, kind with people, but looking forward to seeing his sisters and regaling them with tales of his adventures at college. He was just fifteen years old; young, but not the youngest man at Cambridge. He missed his family, and his dog and his room. He spurred his horse forward for a bit, then relented and rested him. After a few minutes, he patted the horse's neck and clucked to him, encouraging the animal to pick up his pace.

One of the figures in the rowboat was Sammy's father, Cotton Mather. He had a prayerbook in his hand, and was dressed as a minister. He was a brave man, because there was illness aboard the HMS Seahorse, which was indeed in quarantine, and not many people would have gone onboard to comfort the sick seamen. But he did what he considered his duty praying over the poor man. The little boat reached shore, and the shrouded figure was carried off. Cotton Mather's "man" led his horse forward. He mounted hurriedly, especially eager to return home on the day his son would arrive.

In good time, Sammy arrived home, and his mother, sisters, and dog rushed out to greet him. He had barely enough time to wash up and change his clothes before his father arrived, and the family gathered for supper. This was a well-to-do family, and there was plenty of food, cooked all sorts of delicious ways. Mather presided at the table, and began by saying grace, thanking God for the spread. Then the family ate, with Mather and his wife seated, and for the first time, Sammy too was given a chair, while the children, in puritan fashion, stood at the table so that they would not enjoy fleshly pleasures too much and be tempted to linger. As he ate, Mather delightedly watched Sammy, noting the come and go of light in his eyes, and his happy laughter as he enjoyed the company of his family, yet struggled to maintain the even and sober bearing of a plain, godly man. Mather loved his son, and was glad to see him, but the image of that shrouded young sailor was fresh in his mind, and troubling. He almost wished he had made different arrangements for Sammy's summer. Perhaps the young man should have stayed up at Cambridge, relatively safe from the smallpox outbreak that originated with the Seahorse and spread through the port town so quickly. So vicious was this particular outbreak, carrying off so many townspeople so quickly, that the town elders had limited the tolling of church bells upon a death, as the constant peel of bells was both a cacophonous annoyance and a frightening reminder all day, every day, of the smallpox. Cotton Mather had lost a wife and three children in an outbreak of disease in years past. He did not intend to lose Sammy.

That night, Mather's sleep was filled with dreams. Five years earlier, he had learned from Onesimus, a slave in his household, of a strange African practice he called "ye operation." The practice was dangerous, but it seemed to protect people against death from smallpox. Onesimus had shown him a scar on his arm, and described how a village elder had rubbed material from a smallpox sore into a scratch. Curious, Mather had questioned other African-born slaves in the town and heard the same tale. Should he have his son inoculated? Was he brave enough to purposely expose his son to smallpox in the operation?

Question

1. So ingrained is the practice of vaccination in our culture, it is difficult to imagine the terrible risk a colonial person took when undergoing inoculation. It isn't known whether Cotton Mather ordered his son to undergo "ye operation," or simply encouraged him to do so, leaving Sammy to make his own decision. It is known that Dr. Boylston, the local doctor who actually administered the inoculations, included his own slave and the slave's toddler son. The name of the slave has not come down through history, but we do know his child was called Jackie. What dangers did these three people face from the inoculating material itself, or from the procedure and its possible side effects? What may have been their thoughts as they took part?

All Sorts of People

Mather was a man who read widely, and he was not unfamiliar with the idea of "ye operation." The practice was known in ancient Greece, with Thucydides reporting on widespread inoculation against smallpox as early as 525 BCE, and in China by 1000 CE. Variolation (inoculation with smallpox virus) involved making a small incision in the arm of the healthy individual, and introducing matter from pustules of individuals undergoing acute infection. By the 17th century, variolation against smallpox was accepted by some groups in isolated pockets in Europe, and was quite common in many parts of Africa, especially West Africa. But in the Americas, variolation began in Boston, thanks in large part to a black man who was probably born in West Africa and brought to America as a slave.

That slave had been "gifted" to Cotton Mather by the puritan congregation at North Church. He renamed the man "Onesimus." Mather, an influentical Puritan leader, was the son of the founding President of Harvard University, Increase Mather. He was a minister, thinker and writer on theological matters. He rose to prominence amidst the turmoil of the Salem witch trials. Now, another sort of terror was visited on Boston: the smallpox epidemic. Deploring the suffering around him, Onesimus told Mather of his own inoculation with smallpox in his childhood home in Africa. He said it was common practice to transfer pus from the wound of a smallpox patient into a prepared incision. After a brief illness, which most everyone survived, a person was protected against subsequent contacts with the disease. Mather was concerned. He had a large household consisting of a wife, four children, and slaves. If one of them were to become sick with smallpox, and then one-by-one the others were infected, he might lose three, four, five of his household. The 1721 outbreak was a bad one. With a death rate of 10 to 20 percent of people who fell ill, almost everyone knew a family with a brother, mother, father, sister or cousin in quarantine and who had died. It seemed everyone was in mourning. Those who survived a serious fight with the disease were likely to be disfigured by pockmarks, or blind.

Inspired by his remembered conversation with Onesimus, Mather decided to undertake an experiment, enlisting the help of a Boston doctor, Zabdiel Boylston. Mather made a plan. He had his son undergo variolation by Dr. Boylston, and used his influence to convince other men to do the same. Most did not. In fact, most Bostonians had both spiritual and practical concerns, fearing to interfere with the will of God, and fearing they or their families would die as a result of the willful infection with smallpox virus. There were furious arguments in the town among the leaders and everyday people. Hot words were written and spoken, and a rock was hurled through the window of the Mather house where Sammy lay, convalescing after the inoculation.

In the end, Dr. Boylston introduced small amounts of pus from smallpox pustules into scratches on the arms of 282 adults, slaves, and children, and sent them home. Most suffered no ill effect, or only a brief illness from which they recovered. A few did become very sick, and six died. Dr. Boylston, like any scientist, knew he had to make some numerical calculations and comparisons, and publish the results of his thoughtful analysis of the data. A publication allows perusal of the new knowledge by learned societies and influential physicians and scientists and political leaders of the day. Only if Boylston could persuasively communicate with his peers would variolation become widespread and smallpox become a manageable threat that the medical community could successfully combat.

In effect Zabdiel Boylston had conducted the first American clinical trial, and that first American clinical trial was inspired by the knowledge one black slave carried in his head from his African childhood. Now all that was needed was for Boylston to tell people about his study. In his 1726 paper, "An Historical Account of the Small-pox Inoculated in New England, Upon All Sorts of Persons, Whites, Blacks, and of All Ages and Constitutions: With Some Account of the Nature of the Infection in the Natural and Inoculated Way, and Their Different Effects on Human Bodies: with Some Short Directions to the Unexperienced in this Method of Practice / Humbly Dedicated to Her Royal Highness the Princess of Wales," he reported that of about 12,000 to 14,000 inhabitants of Boston, 5,759 people became ill with smallpox in the 1721 to 1722 season. Some 4,915 of these people survived, and 844 became ill and died. But of about 282 people who were introduced to smallpox not naturally but via Boylston's inoculation, only 6 died. Due to this publication and others, word spread, and more and more people asked their doctors for variolation for themselves and their families. As time went by, Bostonians more routinely received vaccinations, and the terrible death toll dropped. In 1777, George Washington ordered mandatory variolation for soldiers in the First Continental army.

Questions

2. Briefly describe Boylston's experimental design by doing the following:
    a. State the hypothesis of the experiment in a single sentence. It may be useful to use an "if : then" type sentence formulation, e.g., *If I work and save my money, then I can buy a car.*
    b. Describe what was done to the experimental group.
    c. Describe the control group.

    Scientists call the variable that is controlled, manipulated or specifically chosen for an experiment, the independent variable. So for Boylston's experiment, the independent variable would be whether or not the person was inoculated. The dependent variable is an outcome that's measured and depends upon the group into which the subject falls, i.e., inoculated or naturally-infected. The dependent variable reported by Boylston was survival or death.

    d. Using the numbers given in the text, make a table of the results of Boylston's experiment.

3. Using the table you made in the previous question, graph the results of Boylston's experiment. (*Hint:* It is probably easiest to work with percent deaths. *Another hint:* Most frequently, the independent variable is arrayed on the X axis, and the dependent variable belongs on the Y axis.)

4. The graphs in Figure 2 (right) tell the story of naturally-acquired and inoculated smallpox deaths in Boston in the 1700s. Consider the findings in the upper part of the graph in light of the findings shown in the lower part. State the overall conclusion to be drawn from the whole graph.

Nowadays, when a new medicine or treatment or practice becomes available, government authorities ask three important questions: a) is the new treatment safe, b) does the new treatment really work, and c) is the treatment practical and is it feasible to make and deliver the vaccine at a realistic cost? Data and graphs from all sorts of experiments on tissue samples and animals in the research lab, and from clinical trials on human volunteers is reported to panels of expert reviewers, who make recommendations to the arms of government that oversee research funding and medical oversight, like the Food and Drug Administration.

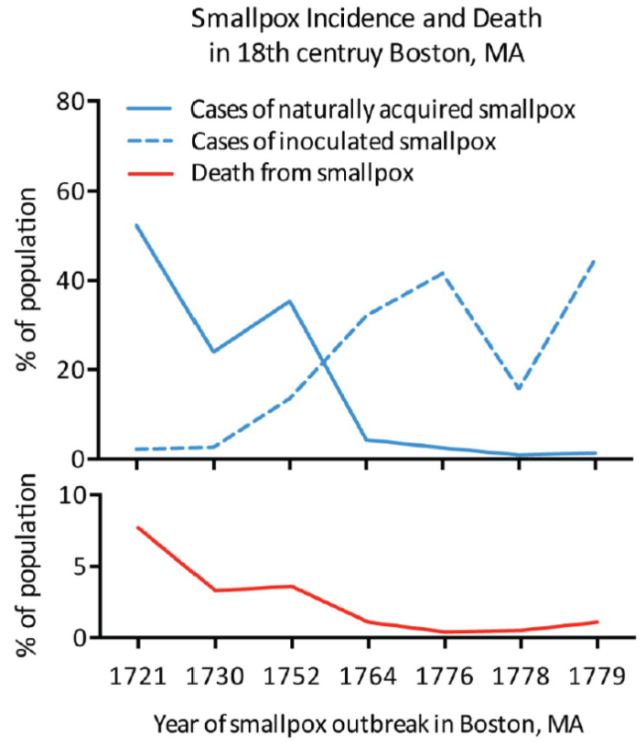

Figure 2. Smallpox incidence and death in 18th century Boston, MA. *Credit:* Niederhuber, M. 2014. The fight over inoculation during the 1721 Boston smallpox epidemic. *SITNBoston*, Harvard University, CC BY-NC-SA 4.0. <http://sitn.hms.harvard.edu/flash/special-edition-on-infectious-disease/2014/the-fight-over-inoculation-during-the-1721-boston-smallpox-epidemic/>.

Question

5. Would Boylston's results in his 1721 clinical trial meet the three basic demands we make in modern clinical trials?

Further Reading on Colonial Boston, Cotton Mather, Onesimus, Zabdiel Boylston, and the 1721 Boston Epidemic

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Part II – Viruses and Vaccines

Viruses, Viruses, Viruses

Smallpox, like many other diseases, is caused by a virus. A virus is not an evil thing. It has no intent to harm anyone or anything at all. Any individual virus particle (called a virion) is just that; a particle, an inert object. On its own, it can't consume plants or other animals and break them down to use the energy stored in their bonds. On its own, the virus can't crawl or fly. It can't reproduce and make more viruses. It seems as though it should be the most harmless of all the microbes, since bacteria, fungi and parasites are all free-living organisms. Unlike the other microbes, a virus must have a host, even if it is an unwilling one. Each virion travels light, and like a bad guest it has to borrow things from the host; tap into its power source, cadge ingredients for meals, appropriate some cellular utensils and hardware. Some viruses are benign; they hurt no one and nothing. Some are harmless to us, but deadly for other species of plant or animal. Some viruses even make their living by invading other microbes. But some do harm people, e.g., measles, mumps, rubella, rhinovirus, rotavirus, influenza virus, human immunodeficency virus, and smallpox. Without an iota of malice, a virus can destroy a life, and a viral outbreak can cripple a community or civilization. If we feel like we're getting a cold or the flu, we lie down, cross our fingers, and wait for it to pass, which is usually a sensible policy. In September of 1918, people all over the world did just that. But about two-thirds of those who did so died during the next ten weeks. That's about 40 million people. In some unlucky communities, like Teller, Alaska, 72 of 80 residents died in a five day period. In the United States, the type A H1N1 flu of 1918 killed about 675,000 people in one year. It took HIV, the AIDS virus, nearly 40 years to kill about the same number of Americans. This is the story of the smallpox virus, once a terrible scourge for humanity, and now extinct.

Do the Math!

Viruses are everywhere. Outdoors and inside, they're part of the invisible world. Feeling a little sick, you skip school or work, and stay home. You sit in a pleasant, clean, book-filled room, in a beanbag chair, and play a video game. Your dog sleeps beside you on the carpet. A quiet day, just you and the pooch. You may think nothing else is stirring. But nothing could be farther from the truth. In fact the virions are everywhere, a veritable crowd of them: $\sim 2.5–5 \times 10^5$ virus-like particles (VLPs) per liter of indoor air. In an easy, unforced inhalation, you breath in about ½ a liter of air, so you're getting about 125,000 to 250,000 virions per breath. How many breaths per minute? How many minutes to the day? If you are indeed sick, the virus will multiply inside your cells, stealing your energy, snacking on amino acids and nibbling nucleic acids from your own cellular pantry, using all your stuff! Eventually new virions will emerge from those airway cells, and eventually you'll exhale them, or spew them out while talking or in an explosive sneeze. From the time an inhaled virion enters an airway cell until hundreds of offspring are released into the space between the cells may be as little as six hours. It takes about three to six hours for a replication round, so after about a day and several rounds of replication, the airway is chock-full of particles. Should you sneeze, cough, or even speak, you add virions to the room's bounty. Those smaller than about five microns in diameter will remain airborne until they encounter someone else's nasal mucosa. Larger particles may settle onto objects (some transmissible by touch) or to the floor, where they can be carried about on shoes and paws from room to room and may be disturbed, and once again, become airborne. It depends on the traffic. It depends on the air in the room. Some viruses persist and are infectious for several days, others are more fragile and only last for minutes or hours outside the body. If others in the home become infected, one after another, withn a few days they will each begin shedding virus at a staggered (and staggering) rate.

On any given day, what sort of viruses are hanging around your house? Adenovirus, enterovirus, IAV, RSV, rhinovirus, rotavirus, just to name some pathogens found in one sampled indoor environment. One virus you won't find in your home is the variola virus, which causes smallpox. The last naturally-occurring case of smallpox, once a greater scourge than influenza or even plague, occurred in 1977 in Somalia. In 1980, the World Health Organization, after a massive concerted global vaccination campaign, declared the virus extinct in the wild, but a few stocks are kept in laboratories in the United States at the Centers for Disease Control (CDC) in Atlanta, Ga., and at the State Research Center of Virology and Biotechnology (VECTOR institute) in Koltsova, Russia. But if you lived in Boston in 1721, you might have millions of virions present in the common area of your home. To a resident of Massachusetts colony, the world must have seemed a perilous place, with spirit and body threatened. Most people believed that witches were out and abroad, and inside there were devilish demons as well.

Questions

1. Assume you have an 8m × 8m × 3m lecture classroom with 25 students. At the start of the experiment, the air is fresh and clean, but you have one student who is actively shedding a rhinovirus that causes the common cold. Assume that once the student enters the room, s/he inhales and exhales normally, taking in about ½ liter of air on inhalation, and releasing about ½ liter of air on exhalation. Assume the person sheds about 2×10^5 virus particles per exhalation, at a rate of about 30 breaths per minute. After one hour, what is the density of virus particles in the room? Express your answer as VLP/room. Show your work.
2. Assuming each of the other 24 students also inhales and exhales at a normal volume and rate, on average how many virus particles would each student inhale/breath by the end of the lecture period? Show your work.
3. *Challenge Question:* Would each student in the room inhale about the same number of virus particles or would it vary from student to student? Do you think every student who inhaled virus particles would become ill? What sort of variables do you need to consider to answer these questions?

A Tale of Two Viruses

There are two distinct viruses involved in the story of vaccination against smallpox. Variola virus causes smallpox, and vaccinia virus causes cowpox. Once inoculated with variola, most people were protected against future outbreaks of smallpox. In England in 1788, some sixty years after the work of Boylston in America, Dr. Edward Jenner, observing that milkmaids who had been sick with cowpox were protected against outbreaks of smallpox, reasoned that he might be able to inoculate people with cowpox preparations, in hopes of protecting them against smallpox. Now cowpox was a much less dangerous disease than smallpox. It's mortality rate was so low it was not feared, while a smallpox outbreak might result in a 30% loss of life. Therefore Dr. Jenner's vaccinia inoculations, just as effective but not as dangerous, quickly became the treatment of choice, and in time the practice of eliciting immunity by inoculation with virus became generally known by the catchall term, "vaccination."

Variola and vaccinia are both "poxviruses." Poxviruses have a rectangular, brick-like shape, rather than the spherical or linear shapes of other families of virus. They carry their genes on a single piece of double-stranded DNA curled at the center of the virion. Poxviruses have humans and other animals as hosts, and usually cause external pustules all over the body. As viruses go, they have relatively large genomes of hundreds of genes. (Smaller viruses may carry as few as five to ten genes; humans carry 30 to 50 thousand genes.) In variola and vaccinia, many of these genes are just alike, and so are the proteins the genes encode. The two viruses differ in a small subset of genes and proteins. Inoculation with vaccinia trains the host to more or less instantly recognize some of the proteins or pieces of proteins that vaccinia shares with variola. When the host encounters the smallpox or cowpox virus a second time, it "remembers" the bad guest, and is more efficient and quicker to show it the door. What accounts for the physical basis of the phenomenon of immune memory? Memory cells.

How to Make a Memory

Virus particles can enter the body through skin, eyes, gastrointestinal tract, or other routes, but the natural route of infection for smallpox virus is by inhalation. The smallpox virus will attach to cells of the upper respiratory tract. After attaching, the viruses can invade the actual interior of the cell. Once the virus is inside the cell, it can borrow host cell resources and use them to replicate and release the new viruses into tissue, where they can go on to infect the next cell, and then the next. This initial breach of the physical barriers provided by skin and mucosal areas becomes the primary site of infection. Immediately, cells of the immune system, like neutrophils, macrophages, and natural killer (NK) cells, home to the site of infection and a race begins. Can the replication rate of the invaders outstrip the "kill" rate of the innate cells? Every infection is like a race between the invading microbes and our immune system. The immune system is the group of cells that deploy an array of different antimicrobial chemicals, working together to protect against invasion.

The bone marrow is the source of all the different cells of the blood. These cells all work together to fight infection, but of all these cells, only two types of cells "remember" the identity of the microbes that cause infectious disease. These are the B and T cells.

B cells are white blood cells that can produce antibodies. Antibodies are proteins that bind tightly, in a lock-and-key fashion, to pieces of foreign proteins that belong to the various bacteria, parasites, and viruses that cause disease. B cells and the antibodies they produce make up the part of our immune system called humoral immunity. When a foreign protein or other molecule of the virus gets "tagged" by an antibody binding tightly to it, then it is easier to remove the virus from the body by a variety of different methods. But humoral defenses are not enough, especially for fighting viruses, since the virus can hide inside our cells where they are safe and protected from antibody attack. B cells partner with T cells, which are also white blood cells, to fight disease. Cell-mediated immunity (CMI) involves the activity of T cells. Humoral and cell-mediated immunity protect us against an impressive array of microbes, each with its own infection strategy.

T cells produce cytokines, which are chemicals that allow the T cells to help B cells to develop into activated B cells. Some T cells can directly attack and kill cells that have been invaded by viruses. T cells work by recognizing and binding to certain foreign peptides (short linear stretches of proteins). Each B cell or T cell is specific to a single little piece of a single protein that's present on a single kind of virus. A particular B cell may only make antibodies that fit with a tiny bit of the hemagglutinin protein, for example, on the surface of a single strain of flu virus. This particular B cell cannot produce an antibody to another piece of the hemagglutinin protein, or to a different protein, or to a different virus. It has one customer only. T cells are similar, except that each T cell is specifically able to recognize a processed peptide that it must first encounter not on the virus itself, but only when the snippet of viral peptide is presented to it on the surface of another cell. But just like the B cell, the T cell can only recognize, and is only effective against, a virus carrying one particular protein.

B cells and T cells make up the portion of bone marrow-derived white blood cells called the lymphocytes. Lymphocytes are highly specific tools, and they're very effective. Unfortunately, it takes a little while for our bodies to generate an army of B and T cells for each specific viral invader, or in other words, to mount an effective immune response. Until a B or T cell encounters its matching viral protein or peptide, we say it is "naïve," and it continually circulates in the blood, stopping from time to time in lymph nodes all around the body. If a lymphocyte discovers evidence that a microbial attack is under way, it must be activated to fight back. It must develop into an "effector" lymphocyte, secreting antibodies or cytokines, and rapidly dividing to produce platoons of B and T cell offspring of identical specificity to the parent cell. The initial stages of effector development occur in a "lymph node," which is a structure that is organized for presentation of foreign matter to T cells in one area and development of effector B cells in another area. Effector B cells can secrete antibodies, and these move out of the lymph node into the lymphatic fluid, as do some effector T cells. The lymphatic fluid empties into the normal blood serum at a structure called the thoracic duct. T cells are able to move from the blood into tissue around infection sites. In humans this process takes about ten days from the beginning of the infection. This phase of immunity is called the adaptive response, or sometimes the acquired response, since it is only activated upon invasion. In fact, if a person is never infected with a particular virus, then effector lymphocytes specific to that virus never even develop.

If pustular matter is taken from an individual whose body is struggling to survive an acute infection, it will likely contain killed and live virus and pieces of virus, as well as dead and active cells of the adaptive system, and elements of humoral and cell-mediated immunity, all in a pus-like mixture.

The effector B and T cells of an ongoing immune response are deadly accurate and can clear the infection with maximal speed and efficiency. The earlier, first ten days of immunity constitute the innate (inborn) response, carried out by a group of white blood cells that are non-specific. These cells, such as macrophages, neutrophils, and dendritic cells, will ingest all sorts of debris including viruses and pieces of viruses. Together they work hard to limit the number of live virus present in the body until the B and T cell response is sufficiently developed. Once that B and T cell response has cleared the virus from the system, the vast majority of the effector B and T cells will die off. But a small group of them will not die at all. Instead, they become memory B cells or memory T cells. Memory cells can live for many years, in some cases for the entire lifetime of the host organism. They are always on patrol, always on surveillance duty, forever looking for any new appearances of their specific virus.

The aim of vaccination is to trick the immune system into developing these memory cells, armed and ready to respond ferociously in an instant. This is done by introducing the virus or pieces of the virus or of viral proteins to the body in a controlled and safe form in an inoculation. A smallpox inoculation leaves smallpox memory T and B cells that will circulate in the blood for many years, always on the lookout for that virus, or pieces of that virus. If ten or twenty years went by and suddenly there was another outbreak of the virus, inoculated people would be re-infected, but the rapid, ruthless memory cell response would likely kill all virus while their numbers were low and before symptoms ever appeared.

Questions

4. Please arrange the terms in the word bank in the order in which they become important in the stepwise story of the development of immunologic memory to an inhaled virus. Briefly list the steps (see sample steps below):

   Word Bank (random order)

   - effector T cell
   - effector B cell
   - antibody
   - lymph node
   - virus
   - naïve T cell
   - naïve B cell
   - bone marrow
   - thymus
   - memory cells
   - lymphatic vessel
   - antigen-presenting cell
   - thoracic duct (in torso, beneath heart)

   Step 1 - Smallpox virus enters by inhalation.

   Step 2 – All of the cells of the immune system are born in the Bone Marrow and Thymus … etc.

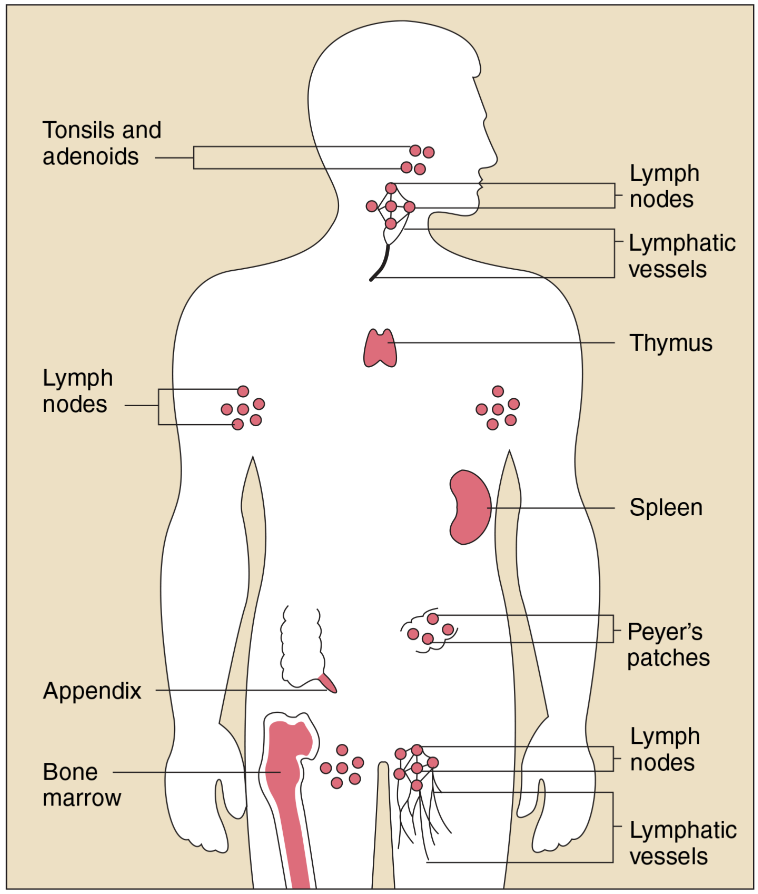

Figure 3. Immune system. *Source: Understanding the Immune System: How It Works*, NIH–NIAID, 2007. <http://static.nsta.org/extras/debatable/theimmunesystem.pdf>.

   Now, label a diagram like Figure 3 with the numbers associated with your steps. For example, you would put a number "1" near the mouth and/or throat for Step 1.

5. *Challenge Question:* Why is the inoculating dose of smallpox less likely to create severe illness than natural infection?

Further Reading on Viruses and Viral Transmission

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Part III – Putting Science in Social Context

Onesimus and Mather

Onesimus was the slave of influential Boston minister, Cotton Mather. The biography we have of Onesimus suggests he was an enterprising and resourceful man. Onesimus saved up the small sums of money he was able to make working extra jobs around Boston and eventually purchased another slave, whom he offered to Cotton Mather in place of himself. Whatever Mather may have thought of this arrangement, by 1711 he had despaired of taming the spirit of Onesimus and decided to free him. He saw that, despite his efforts to persuade his slave otherwise, he remained obstinately determined to live his own life, deploy his talents and labor for his own family's benefit, and enjoy the liberty and opportunities the new land offered. He was enterprising and hard-working enough to eventually purchase his wife's freedom as well. Once established, he ran his own household and raised his own family. But then he disappears from history. Without social standing, without the advantages the Mathers were able to give Sammy, for example, he probably did not build a very big and imposing house. He probably did not become a well-heeled doctor, a respected scientist, or an influential theologian. That's a shame. Paramount in the success of America is a widespread faith in people that is ebullient and above all, optimistic. Optimism looks at the barefoot, poor young man or woman, and at the hungry babe in arms, and sees what each may become and what each may contribute to the American story.

Despite unfortunate beginnings, with two person's interests so much at cross-purposes, not all that came of this clash of two intellects was negative. In 1721, perhaps 10 years after the event, Cotton Mather remembered the conversation he had with Onesimus about inoculation with smallpox, and that memory was useful to him. Onesimus and other slaves Mather went on to question about "ye operation" informed and inspired him to formulate his plans when he tried to construct a defense against the scourge of disease. How unlikely! The experiences of Onesimus and a small group of African men, all unwilling immigrants to America, illuminated the thinking of these early puritan men of medicine.

All Sorts of People Have Something to Contribute

American science has benefited from contributions from continuous influxes of people from all sorts of places. They fled from religious persecution at home, they were brought here in chains against their will, they sought educational opportunities, they fled from violence and persecution at home and were just looking for a safe place to lay their heads. All sorts of people and their children, and their children's children, contributed stories and experiences and ideas from their own cultures to the American conversation, and sometimes they even became the actual scientists and physicians and researchers who moved American science forward.

Essay Prompt

Investigate an immigrant or child of immigrants from the list of not-so-familiar scientists below, or suggest another candidate for your instructor's approval. Tell that person's story in a short essay. Bring a good draft of your essay to class next time to share with a peer editor.

Baruch Benacerraf	Venezuelan American who won the Nobel prize for his work studying surface receptors of immune system cells.
Elizabeth Blackburn	Australian American who won the Nobel prize for her work investigating telomeres, with implications for aging and cancer.
Mamie Clark	African American psychologist who was the first black woman to earn a PhD from Columbia University. Her work on racial identity, racial discrimination, and how children learn played an important role in arguments surrounding Brown vs. Kansas Board of Education of Topeka, Kansas (1954), the landmark Supreme Court case that outlawed school secgregation.
Gerty Cori	Czechoslovakian American biochemist who won the Nobel prize for her work on hormonal biosynthetic pathways. That work touches and informs all fields of biomedicine.

George F. Grant — African American dentist who was the first black man to earn a PhD from Harvard University. He tended the teeth of Bostonians for many years, and invented the first golf tee!

Mario Molino — Mexican American physical chemist whose research informed regulations congress wrote for environmental protection against household chemicals that interfere with the ozone layer and so affect planetary climate change.

Murphy Mnezi — Influential African American educator, physician and biostatician who combined applied mathematics to biomedical subjects, producing impactful contributions to the fields of agriculture, fisheries, and medicine.

Severo Ochoa — Spanish American molecular biologist and physician who won the Nobel prize for discovery of an enzyme important in RNA synthesis, especially of viruses and bacteria.

Helen Rodriguez-Trias — Puerto Rican (American) physician and educator whose lectures on AIDS and maternal health have informed millions of people world-wide on safe sexual practices in HIV/AIDS-infected parents and helped produce thousands of healthy babies.

Aziz Sancur — Turkish American biomedical researcher who won the Nobel prize for his work on the mechanics of the *r* of UV-damaged DNA, which has implications for cancer and aging.

Charles Henry Turner — African American research biologist, zoologist and physiologist who was the first black man to receive a PhD from the University of Chicago, and who discovered that insects can hear, cockroaches can learn, and honeybees can see color.

Jane Wright — African American Professor of Surgery at New York Medical Center. She was a tireless researcher of cancer, and pioneered the use of methotrexate, a highly-effective anti-tumor drug.

Ahmed Zewail — Egyptian American physical femto-chemist whose work on high resolution imaging of transient intermediates in chemical reactions earned him the Nobel prize.