4-5-2018

Vaccines: History and Science

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HNR 499

April 5, 2018

Introduction

Vaccines have changed how most of the world encounters and thinks about deadly diseases. Two groundbreaking vaccines that have made an impact world-wide are the polio and pertussis vaccines. These vaccines not only protected against contracting disease, but they also provided groundbreaking research for understanding how to develop effective vaccines in general. The science behind vaccines is both complicated and simple. It is easy to observe that once a disease has been contracted, you cannot contract it again. However, it is challenging to make a vaccine that will protect an individual from disease without causing harm. Understanding the process of how to confer protection without being infected takes some knowledge of the immune system.

Vaccines are a balancing of risks and benefits, and public perception of the need for a vaccine can change over time. When all of the information is understood, the best decisions can be made. Today, there are many questions raised about the efficacy of vaccines and how they work. This document is designed to serve as a reference to answer some of the questions about vaccines and their historical context.

How were vaccines developed?

In order to develop vaccines, it was critical for germ theory to be understood and accepted, which was not until the late 1800s. Louis Pasteur and Robert Koch were able to isolate pathogens and show that infection was the result of exposure to specific germs. Prior to germ theory, most people thought that bad air and unbalanced internal humors were the cause of illness (Smith, 2011). Even before germ theory was completely understood, however,

individuals empirically discovered a way to protect others and themselves from smallpox in some areas of the world.

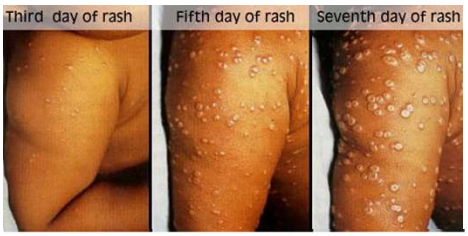


Figure 1. Smallpox rash on a child's arm.

Smallpox is a deadly disease that is highly contagious and, for those who survive it, it is also highly disfiguring due to scarring. A smallpox infection starts as many infections do with a fever and some achy muscles. Then a rash appears and the individual becomes very contagious. Red bumps (pox) begin to appear on the infected individual's tongue and mouth, and spread to the face and limbs. The bumps are filled with fluid and the fluid carries the smallpox virus. The bumps that are in the mouth often burst and breathing or speaking spreads the virus like a viral mist machine (at the time of the first vaccine, people were unsure what exactly caused the illness and just knew that it was contagious). The infected individual might start to feel better once the rash begins to appear, furthering the problem of spreading the virus to others. Approximately four days after the rash appears, a high fever begins again and the bumps from the rash develop into hard pustules. After another week the pustules scab over and then begin to fall off. Typically, four weeks after the rash first appears, all the scabs are gone and the individual is no longer contagious (CDC, 2016). Before the development of vaccines, the fatality rate was 90% for smallpox victims under the age of five, and was even higher for infants under one year (Rusnock, 2009).

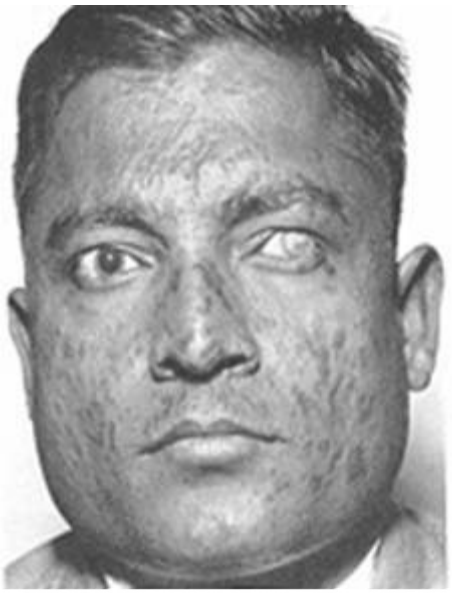


Figure 2. Smallpox scarring can cause blindness.

The first form of protection against smallpox was gained through purposeful inoculation. It was observed that once someone had smallpox and survived, they could not be re-infected. There were also varying degrees of severity in smallpox cases, yet even the mildest cases were protected from reinfection. Inoculation was performed first and most frequently in China and Turkey. To inoculate an individual, pox scabs were ground into a powder and inserted into the nose of a healthy individual. Others inoculated by inserting pus from the pox into a deep scratch. Both the scabs and the pus were collected from mild smallpox cases, and usually from younger children. China and Turkey were the most regular users of inoculation, necessitated by the epidemic nature of smallpox in those regions of the world (Rusnock, 2009).

Much of Europe was impacted by smallpox as well and, due in large part to Lady Montagu, they eventually adopted the practice of inoculation also. Lady Montagu was married to the British ambassador to Turkey and learned of inoculation through her correspondence with prominent Turkish physicians. Lady Montagu herself survived smallpox in 1715 and had the scars to show it (note the heavy make-up in the picture, a popular practice among aristocrats of the eighteenth century for covering up smallpox scars). She became an advocate for inoculation and her children were the first people of Britain to be inoculated. Britain was resistant to accepting the practice of inoculation for several reasons. The smallpox outbreaks were sporadic and infrequent due to their distance from the trade routes; there were also objections from the church. However, the rise in colonization began to cause more frequent outbreaks and soon inoculation became standard practice (Rusnock, 2009).

Figure 3. Lady Montagu

Edward Jenner of England is credited with creating the first vaccine in 1798. The vaccine was for smallpox and worked differently from inoculation. Inoculation, as described above, consisted of infecting an individual with a mild case of the actual disease, in this case smallpox. In contrast, the vaccinations performed by Jenner used a similar disease that was able to provide protection against smallpox. Jenner observed that individuals who contracted cowpox (usually dairy maids, as the udders were where cowpox pustules appeared) were unable to be infected with smallpox. Conversely, those who had had smallpox were not able to contract cowpox. Since cowpox was fairly mild and hardly ever resulted in death, Jenner's idea was to infect individuals with a 'safer' disease, in this case cowpox, in order to prevent the deadlier disease of smallpox (Jenner, 1798).

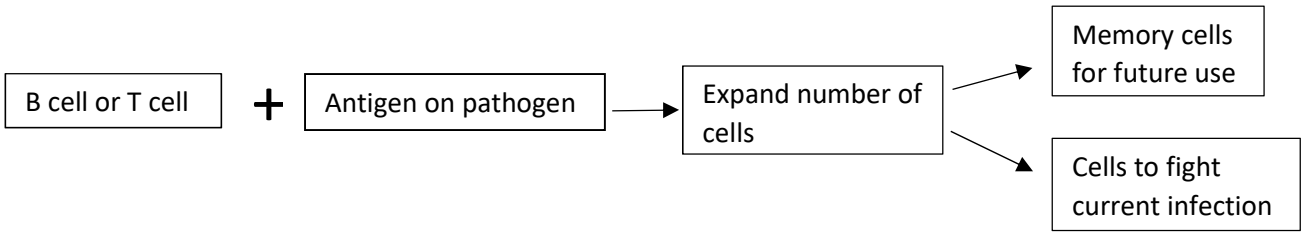
There was resistance to Jenner's smallpox vaccine, just as there had been resistance to inoculation. Worries about cross-contamination from other diseases, religious fears about somehow combining cows and humans, and difficulty understanding how the vaccine worked were common. However, because the deadly smallpox was becoming so commonplace and was killing so many children, many individuals were willing to receive the cowpox vaccine. The cowpox vaccine was so well received that after only three years, 100,000 people in England were vaccinated. By 1802 the Royal Jennerian Society was established through funding from the English government in order to disseminate the vaccine around the world. England had a particular interest in encouraging the use of the vaccine because it had colonies all over the world. Reducing smallpox in the colonies served to protect the English who ruled over them. (Rusnock, 2009).

Vaccination was mostly safe, but there was a still a chance that individuals could die from the cowpox contained in the vaccine. With the first successful vaccine came many

questions, some of which are still relevant today. Can the government mandate vaccination? How much can be asked of an individual for the benefit of the 'greater good'? Why would a doctor want to purposely give a disease to a healthy person? How does the vaccine work? What are the specific risks and benefits of vaccination compared to the risks of the disease?

Why does getting the disease protect me from getting it again?

The immune system recognizes the structural patterns (antigens) of pathogens (germs) and creates a response to them. B cells and T cells of the immune system have receptors and when those receptors bind to the structural patterns on the pathogen, the cells are triggered to divide. Some of the new cells then produce and release antibodies and other cell products that help fight the infection while others cells are produced and held in reserve for fighting future infections.



During infection after the first exposure to a disease, there are very few immune cells that can detect the pathogens, but when the cells divide, many of the them will be saved as "memory cells" to protect from future exposures to the same disease. For example, in the first infection there may be ten cells that recognize the pathogen. These ten cells divide to produce 100 cells; 50 will be kept for memory use while the other 50 will fight the current infection. (These numbers are for illustration purposes only.) Therefore at the time of a second infection there will be five times the original number of cells (50) and this can subsequently expand to even greater

numbers (500). These cells quickly stop the infection from taking hold, and the person is unlikely know they have even been exposed.

How does a vaccine protect from ever getting the disease?

With the first successful vaccine came the acceptance of germ theory. Germ theory was proposed in the mid-sixteenth century, but was difficult for people to accept because the germs could not be seen. When Louis Pasteur and Robert Koch in the mid-nineteenth century began to actually identify germs using a microscope and demonstrated that a healthy animal could be infected with a specific type of germ to cause a specific illness, the germ theory was finally able to gain acceptance. Expanding upon the work of Pasteur and Koch, others identified the routes of infection that pathogens took to cause common diseases. As pathogens were identified, vaccines could start to be developed. The major challenge of this work was to confer protection from the disease without causing harm, but as more research was done in bacteriology and immunology, vaccines continued to improve (Plotkin, 2014).

The immune system is complex, with many different molecules and cells all meant to do specific jobs. B cells and T cells are the ones being used in vaccinology (Dellabona, et al. 2014). B cells and T cells are the memory cells that provide long term protection against pathogens (Parham, 2015). Vaccines work by causing the B cells and T cells to respond to pathogens that have been made safe and harmless by killing them, inactivating them, or dismantling the germ into its component parts.

The antigens do not give cause the disease because they are not the intact pathogen. Since the immune system is able to respond to the antigens given in the vaccine, the B cells and T cells will divide and create more cells as they would with a true infection. When the real pathogen is subsequently encountered, the immune cells will already be more numerous and able to respond quicker and better than if no vaccine had been given (Parham, 2015).

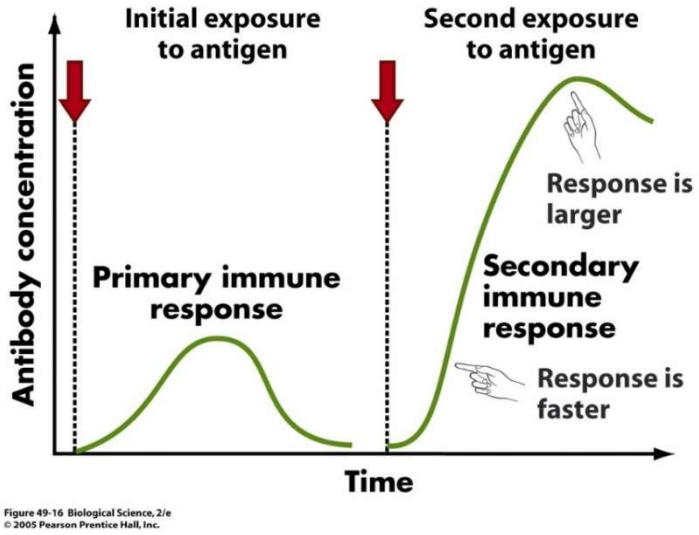


Figure 4. Antibody concentrations after exposure to antigen

What is herd immunity?

There are some individuals who have immune systems that do not respond normally and these individuals will not be able to generate a strong immune response to a vaccine. Encounters with a pathogen, or even a vaccine, would be unwise for these individuals. However, they can still achieve some protection from the disease through the practice of herd immunity (Rashid et al. 2012).

Herd immunity is the idea that when the majority of people are vaccinated and protected from disease, the one unvaccinated person who gets the disease is unlikely to pass it to the next unprotected person because the chance of those two unvaccinated people coming into contact with each other is slim. Each of the unvaccinated individuals is surrounded by protected individuals who cannot pass along the disease onto others (Rashid et al. 2012).

However, when large numbers of individuals begin refusing vaccination, the protection of herd immunity begins to weaken or disappear. This leaves many individuals vulnerable to potentially deadly diseases, beyond those who chose not to get vaccinated (Rashid et al. 2012). Notice in Figure 5 that vaccine coverage (red line) never reaches 100% yet the rate of infection (blue line) remains pretty close to zero. This illustrates herd immunity providing protection for the few unvaccinated individuals.

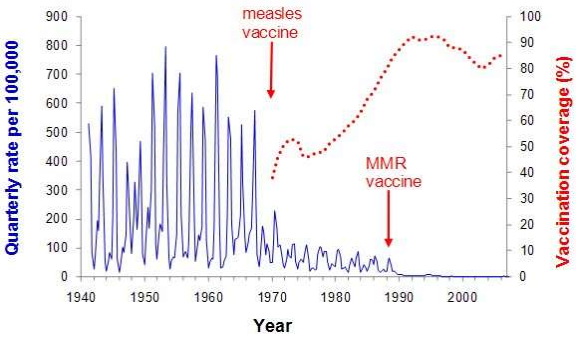


Figure 5. Vaccination vs. infection

How do mutations affect vaccine efficacy?

Herd immunity prevents a disease from getting a 'foothold' in the population. However, every time a bacteria or virus reproduces, there is the potential for mutations to occur. Mutations that are advantageous to the organism are generally retained and persist, just as natural selection explains. Because bacteria and viruses replicate very quickly, they can also accumulate mutations quickly. Because viruses are always mutating, it is possible to catch a cold many times a year. Even though it is the same general cold virus, it may now have enough mutations that the immune system cannot recognize it and provide protection, so the person gets sick and the body has to start all over in generating an immune response and storing up memory cells (Parham, 2015).

Vaccines are often manufactured with a combination of virus strains exhibiting a variety of mutations. For example, the rotavirus vaccine has elements from the five most common variations of the virus and the flu vaccine has three or four variations within it. If the virus

cannot infect individuals, it cannot replicate and mutate. This means that the vaccine not only protects the current population, but will also be effective for the new generation being born (Parham, 2015).

When there is no herd immunity or even personal immunity, the chance increases that the pathogen will mutate out from the protection the vaccine gives. This could mean that even formerly vaccinated individuals will now be susceptible to the pathogen, as their immune systems can no longer recognize the new forms of the virus. From history, we have seen that when a new disease arises, the mortality rate increases. For example, the Native American population in the sixteenth century was devastated when Europeans and their diseases arrived because all the diseases were new to the Native Americans and their immune systems (Crosby, 1976).

What are attenuated and killed vaccines?

Vaccines fall into one of two categories, live-attenuated vaccines and killed vaccines. The goal of the vaccine is to expose patients to a "safe" version of the pathogen in order to generate an immune response. When the vaccine contains killed organisms, there is no danger of the patient getting the actual disease because something that is not alive cannot grow and produce an illness (Parham, 2015).

On the other hand in a live-attenuated vaccine, the infecting organism is still alive, but with some of its disease-causing properties removed. Because the infectious agent is still alive and able to reproduce, it can mimic a true disease more effectively and create a more robust immune response, thus providing better protection against any future infections (Parham, 2015).

The polio vaccine is an example where both a killed virus and a live-attenuated virus vaccine are available. In the United States, children receive three doses of the vaccine. The first dose of the vaccine is the killed virus, producing a beginning level of protection against the real disease by activating B cells to produce memory cells. The second and third doses of the vaccine are the attenuated version. With the attenuated vaccine, a person becomes infected with the weakened virus, which activates additional components of the immune system, while increasing the memory B cells made from the first dose. With this method of vaccination, the chance that the attenuated vaccine will cause the real disease is low because the person is already protected from the first dose of the vaccine (Parham, 2015).

Case studies: polio and pertussis vaccines

The polio and pertussis vaccines have interesting creation stories and taught the medical community and the public a great deal about vaccines. The polio virus vaccine was researched and developed in the 1950's and had a lot of public support. The pertussis vaccine was developed in 1926 when researchers saw a need for it in their communities (Plotkin, 2014).

Polio Vaccine and the Cutter Incident

Polio was a terrifying disease to the American public. Every summer for almost twenty years, polio swept through the United States and affected thousands of children. Parents were afraid to allow their children to go to public pools or to have birthday parties for fear of contracting the disease. There was no cure for polio. Doctors and researchers only knew that polo was caused by a virus and that it affected the motor nerves of the body, often causing paralysis. If the paralysis was in the limbs, patients underwent extensive physical therapy and surgery and many were crippled for life. However, if the diaphragm was affected, the patients could no longer breathe on their own and had to be placed in an "iron lung" (Figure 6) that would breath for them (Kurlander, 2015).

Figure 6. Picture of a toddler in an iron lung due to the paralytic effects of polio.

In the 1930's a polio vaccine was developed but was unsuccessful. In fact this vaccine actually spread polio and killed many children because the thought at the time was that to generate an effective immune response, the vaccine had to hold a live virus. Salk, on the other hand, believed it would be possible to create an effective vaccine using a killed virus (Kurlander, 2015) and his strategy ultimately proved to be successful. Due to the widespread fear and knowledge that any child could get polio, parents were more than willing to help with the development of the vaccine, and thus The March of Dimes organization was started to create funding for research to develop polio vaccines. In its first year, the March of Dimes collected over a million dollars. These dimes came from everyone, not just from the upper class. When the Salk vaccine was ready to be tested, parents were scared they could be harming their children, especially with the memory of the failed vaccine from the 1930's (Kurlander, 2015). Yet even

though parents were scared, the promise of living without the fear of contracting polio was a draw and the Salk trials enlisted almost two million volunteers to test the vaccine and record the data. In 1955, the Salk vaccine containing killed polio virus was deemed both safe and effective (Brandt, 1978).

Six companies were given licenses to produce and distribute the vaccine around the United States but unfortunately there were insufficient regulations and safety measures in place and a big mishap occurred (Brandt, 1978). Two weeks after the vaccine was deemed safe and effective, five children who had recently received the vaccine developed paralytic polio. Batches of the licensed vaccine were not subject to the strict safety measures that were used during the original field trials and the Cutter Laboratory accidentally distributed vaccines contaminated with the live polio virus. In the end, thousands of cases of polio, with more than 200 cases of paralysis and 11 deaths, occurred due to the Cutter incident (Offit, 2005).

Regulations and safety measures for vaccine production have since been established and between 1955 and 1962, 400 million doses of inactivated polio were distributed in the United States. During that time, cases of polio decreased drastically and now it is on the verge of being eradicated worldwide (Offit, 2005). In 2017 there were only twenty-two known cases of wild-type polio (GPEI, 2018).

Pertussis vaccines: Cellular to acellular

The first pertussis vaccines were developed in the early twentieth century and contained killed whole *Bordetella pertussis* bacteria. The vaccine for pertussis was later combined into a DTP shot that contained diphtheria and tetanus toxoid as well. Problems with the DTP vaccine arose in the 1950's due to the pertussis component. The vaccine was highly reactogenic, leading

to injection site pain and redness, and sometimes causing high fevers and systemic reaction. Licensed vaccines also had varying efficacy rates which led to decreases in vaccine compliance. In Japan, after several children died, the vaccination rates plummeted (Figure 7) and the pertussis vaccines were temporarily suspended (Klein, 2014).

A new whole cell pertussis vaccine was developed in Japan, along with an acellular pertussis vaccine in Japan and other countries. The acellular vaccine includes one to five individual pertussis antigens instead of the whole bacteria. This generates an immune response to the actual bacteria without having to include the whole organism, providing a much higher degree of safety for those immunized. When the acellular vaccine was released, vaccine compliance increased once again and cases of the disease declined (Klein, 2014).

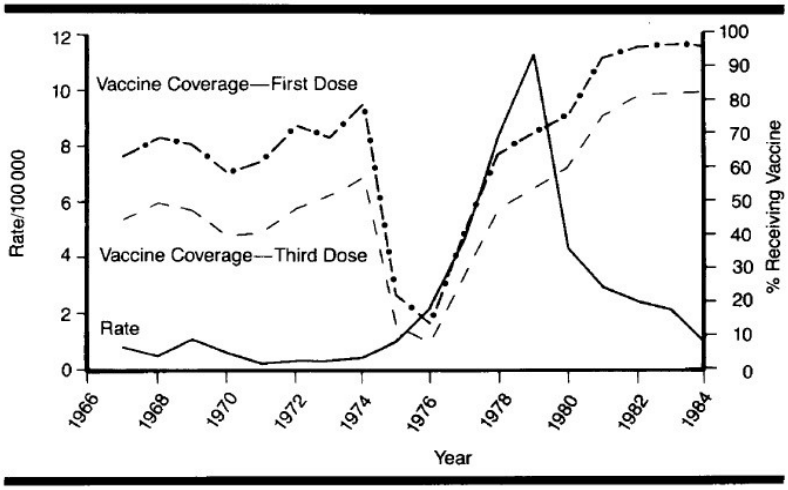


Figure 7. The solid line indicates the rate of pertussis infection per 100,000 individuals. The broken lines indicate the percentage of eligible children that were vaccinated. Notice when vaccine coverage drops, it is followed by an immediate rise in rates of infection.

The one concern about using the acellular vaccine instead of whole cell pertussis is the length of protection provided by the vaccine. There have been numerous studies done that indicate acellular pertussis provide protection against *Bordetella pertussis* for a shorter span of time than the whole cell vaccine did. Shortened protection times could lead to recommendations to increase the number of booster shots required to achieve full protection (Kimura and Hikino, 1985).

Vaccine schedule

The CDC creates a schedule for physicians and a schedule for parents, but it looks daunting. Both schedules have all the information needed about vaccines, but they are not the easiest documents to read and comprehend. Doctors and other medical professionals encourage questions and listen to parents' concerns when viewing the vaccine schedule (CDC, 2017).

The vaccine schedule is made with consideration of many factors, such as how many doses are required for the vaccine to generate a sufficient number of memory cells to achieve protection. It also considers when the child is most vulnerable to the effects of the disease and when the child is most likely to be exposed. For instance, polio can be contracted at any time during an individual's life, from infancy to adulthood. Therefore the vaccine schedules reflect this possibility of infection by scheduling the vaccine dosages early in life and prior to possible exposure (CDC, 2017).

Conclusion

Vaccines are a medical achievement that protect against deadly diseases. Smallpox and polio are diseases with no known effective treatment, but they are preventable with vaccines. The vaccines prevented these diseases so well that smallpox is eradicated and polio is almost eradicated with only seven cases as of April 2018 and 22 cases during all of 2017 (GPEI, 2018). Vaccines provide protection for both the vaccinated individual and the population in general, but have always required a balancing of risks. When parents were faced with a yearly summer epidemic and lived in fear for their children's wellbeing, it was easy for them to see the need for a polio vaccine. The public contributed their own money freely and signed up to voluntarily

receive the polio shot because they believed the polio vaccine was a worthy cause and held fewer adverse outcomes than the actual disease.

The theory behind vaccines is to be able to give protection against a disease without giving the full illness. This is achieved most often by tricking the immune system into making a response against killed or weakened pathogens. If the diseases that vaccines protect against are more prevalent and immediately dangerous, the public tends to have a higher compliance rate for vaccination. However, vaccine compliance needs to always be high in order to prevent mutations from accumulating in the pathogens, causing epidemics. Without vaccines our modern developed world would look much different. It can be imagined that it would look more like developing nations with high birth rates, low life expectancy (largely due to early childhood death) and epidemic diseases (Figure 8).

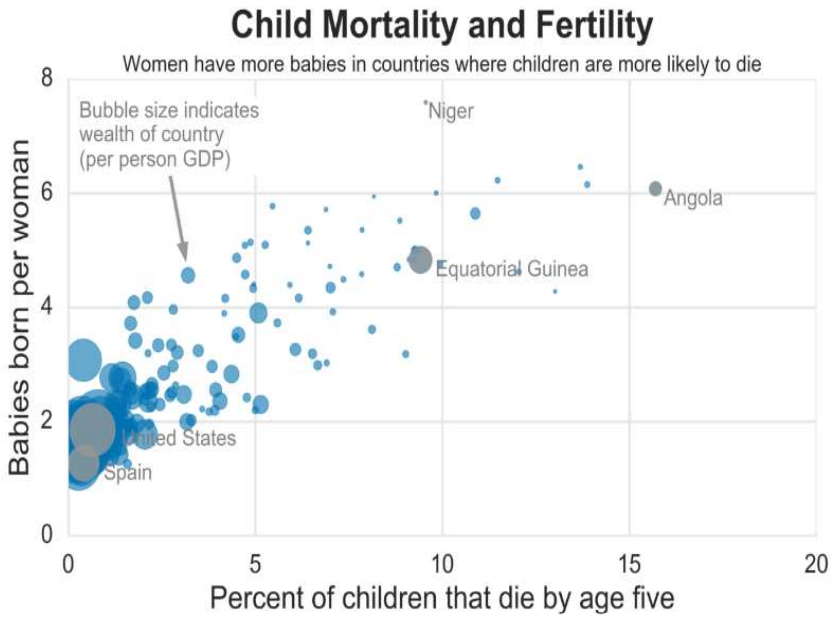


Figure 8. Each dot indicates the percent of children that die by age five for a given country. The size of the dot reflects the wealth of the country.

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