Smallpox Vaccination: STS Model for Global Immunization Campaigns

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Abstract

More than 400,000 people in 18th century Europe died of smallpox each year. Today, smallpox has become a distant memory due to successful global vaccination campaigns. The smallpox vaccine led to the eradication of an entire virus from humanity, a feat thought to be impossible. Although the vaccine itself was efficacious, it alone would not have been able to combat the disease. Global vaccination campaigns incorporated a multi-dimensional strategy to ensure that this successful vaccine was administered to individuals all across the globe, including areas with limited access to resources. This paper highlights the microbiological, material, textual, legal, and bioethical dimensions of the immunization campaigns. By describing each dimension in isolation as well as in conjunction with one another, this paper describes how future eradication efforts can utilize interdisciplinary, STS (science, technology, society) approaches to combatting vaccine-preventable infectious diseases.

Introduction

The smallpox vaccine revolutionized healthcare and preventative medicine by eradicating an entire virus. The last naturally occurring case of smallpox was discovered in Somalia on October 26th, 1977 ("WHO | Statue Commemorates Smallpox Eradication," n.d.). On May 8th 1980, the World Health Organization (WHO) declared the eradication of smallpox, and since then, there have been no reported cases. Smallpox, a fatal disease with a 30% mortality rate, often leaves survivors with permanent scars across their faces and bodies ("WHO | Smallpox," n.d.). Before the creation of the vaccine, more than 400,000 people died from smallpox each year in 18th century Europe (Riedel, 2005). Today, smallpox is merely a distant memory.

The successful smallpox vaccination efforts serve as the prime example for current campaigns to eradicate polio, measles, and other vaccine-preventable diseases (Aylward & Tangermann, 2011; Hopkins et al., 1982). The global health community utilized a multidimensional science, technology, and society (STS) approach to develop an efficacious vaccine and achieve widescale immunization. This paper will analyze the following dimensions in the context of the smallpox eradication campaign: microbiological, material, textual, legal, and ethical dimensions. These dimensions ought not to be analyzed in isolation; therefore, this paper will synthesize multidimensional intersections as footnotes and images. Through an interdisciplinary analysis, this paper highlights why smallpox immunization campaigns were successful and how future eradication efforts can utilize multidimensional approaches to combat vaccine-preventable diseases.

Microbiological Dimension

Developing a vaccine requires an understanding of the human immune system, which is one of the most resilient living systems that withstands millions of pathogens' attacks every day (Alberts et al., 2002). While most microbes are immediately recognized by the immune system and destroyed by white blood cells, some pathogens successfully replicate and cause disease. One of those pathogens is smallpox, a DNA virus that is highly adaptable to the human immune system (Institute of Medicine (US) Committee on the Assessment of Future Scientific Needs for Live Variola Virus, 1999). Two viral gene products, CKBP-II and SPICE, inhibit chemokines and complement enzymes respectively, and allow the virus to evade the host immune system (Dunlop et al., 2003). Inhibiting chemokines prevents white blood cells from going to infected areas (Groves & Jiang, 1995). Inhibiting complement enzymes prevents pathogens from being targeted for destruction by immune cells. By doing so, the virus successfully infects squamous epithelial cells and uses the host cellular machinery (e.g. enzymes, nutrients) to produce two types of virions – complete viruses created from the original virus. The first type of virion is shed by infected necrotic cells in skin debris and saliva droplets,

which promotes transmission to other individuals. The second type of virion acquires an additional membrane and is released at the cell surface, causing cell-to-cell infection and systemic dissemination (Bray & Buller, 2004). Because the smallpox virus is adept at intra- and inter-organismic transmission as well as immune evasion, vaccination was key to tackling this disease.

As demonstrated by the first type of virion, smallpox viruses are transmitted via respiratory droplets, skin-to-skin contact, saliva, and fomites ("Transmission | Smallpox | CDC," n.d.). Global smallpox epidemics demonstrated the indiscriminate nature of these viruses. Smallpox infected people from all over the globe regardless of race, ethnicity, socioeconomic status, or gender (Riedel, 2005). Pandemics and epidemics reminded the world that humanity is tied through an underlying biology. This universality was also the reason why the smallpox vaccine could be used to vaccinate people around the world.

The vaccine prepares the body for future exposures to smallpox by inducing humoral immunity against a related but non-pathogenic poxvirus: the cowpox (vaccinia)[1] virus. The cowpox virus activates the production of antibodies[2] and cytokines[3] that "elicit long-lived memory responses capable of recognizing and clearing subsequent variola [pathogenic smallpox] infections." (Kennedy et al., 2009) Humoral immunity consists of B cells and T cells[4] crucial for developing memory against the vaccinia virus; therefore, immunocompromised individuals[5] could not receive the vaccine because they have fewer B and T cells compared to healthy individuals. Other contraindicated populations – those who cannot use vaccinations because of the harm they could cause the patient – included pregnant women, patients with a history of atopic dermatitis, people with "cardiac risk factors" or "serious allergies" against the vaccine, and children under the age of one ("Contraindications to Vaccination | Smallpox | CDC," n.d.). Therefore, unvaccinated people were most at-risk

[1] **Intersection with the Textual Dimension:** The words "vaccine" and "vaccination" were created by Edward Jenner to describe the process of using the non-pathogenic "vaccinia" (cowpox) virus to immunize healthy individuals against variola (smallpox) virus. This link between smallpox and the term "vaccine" may have increased familiarity with global eradication efforts (Riedel, 2005).

[2] Antibodies are proteins that are produced by the human immune system to identify and label foreign pathogens for degradation by white blood cells ("Antibody | Biochemistry | Britannica.Com," n.d.).

[3] Cytokines are proteins that are released by cells (including white blood cells) that influence cell-to-cell communication. (Zhang & Jianxiong, 2007).

[4] B and T cells are two types of immune cells. Examples of T cells include CD4+ and CD88+ T cells.

[5] Examples of immunocompromised patients include HIV patients, cancer patients, and transplant patients.

of contracting smallpox and are currently protected due to herd immunity.[6,7]

The smallpox vaccine represents how science equips people with tools to fight pathogens that would otherwise win microbiological battles against the human immune system. Hundreds of thousands of people died each year due to the frequently evolving smallpox virus. By understanding how vaccines influence our immune systems, researchers combined their microbiological and immunological knowledge with technological innovations to conquer the virus.

Material Dimension

Different types of vaccines include live-attenuated, inactivated, and recombinant vaccines ("Vaccine Types | Vaccines.gov," n.d.). Live-attenuated vaccines use a weakened version of the pathogen to induce an immune response. Examples of live-attenuated vaccines include the smallpox vaccine, MMR (measles, mumps, rubella) vaccine, and the Yellow Fever vaccine. Inactivated vaccines used a killed version of the pathogen to induce an immune response. Examples of inactivated vaccines include the influenza vaccine, polio vaccine, and the Hepatitis A vaccine. Recombinant vaccines use the outermost proteins of a virus (e.g. capsid proteins) to induce an immune response. Examples of recombinant vaccines include Hepatitis B vaccine, Human Papilloma Virus vaccine, and Whooping Cough vaccine. The smallpox vaccine is a live-attenuated vaccine that uses live vaccinia[8] virus to elicit an immune response against variola[9] virus. For smallpox vaccines used during the eradication efforts, vaccinia virus was mass-produced using infected cow lymph (Fulginiti, 2003).

Before mass vaccination efforts, a scalpel or knife was used to administer the smallpox vaccine; however, due to this invasive method of scarification, vaccinated individuals were more prone to infection, especially in areas without proper sanitation (Weniger & Papania, 2013). In 1966, the WHO initiated the Smallpox Eradication Programme, and the use of scalpels for mass vaccination was no longer sustainable. Therefore, from 1967-1969, jet-injectors administered the smallpox vaccine intradermally using a less invasive route (Millar et al., 1969). Jet injectors were "cumbersome, expensive to maintain, and not well adapted for use in sparsely populated areas," so the bifurcated needle quickly replaced them

[6] Herd immunity describes the phenomenon when enough people are vaccinated against the disease that the pathogen is not able to be easily transmitted; therefore, un-vaccinated individuals are protected against the disease due to the vaccination of others (Kim, Johnstone, & Loeb, 2011).

[7] **Intersection with the Legal/Bioethical Dimension:** The ethics of global vaccination involves an analysis of deontological versus utilitarian ethics. Should healthy individuals who are able to be vaccinated against smallpox be legally mandated to do so in order to protect contraindicated patients who are not able to receive the vaccine?

[8] Vaccinia is the scientific name for the cowpox virus that infected milkmaids.

[9] Variola is the scientific name for the smallpox virus.

(Figure 1) (Kennedy et al., 2013). In the early 1960s, Benjamin Rubin invented the bifurcated needle, which delivered the smallpox vaccine subcutaneously. Starting in 1969, all countries began using the bifurcated needle because it "required only one fourth as much vaccine" as the jet injector, was extremely easy to use and sanitize, and could successfully vaccinate 500 people a day.

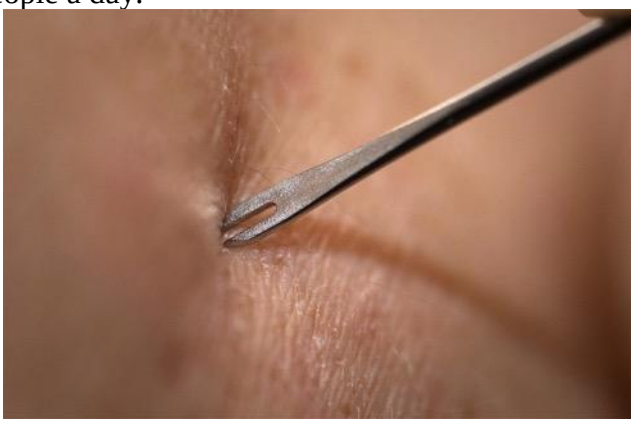

FIGURE 1. Intersection with the Microbiological Dimension: To effectively vaccinate a healthy individual against smallpox, the cowpox virus only had to be administered subcutaneously to induce an immune response. As long as an infected pustule developed on the skin, the person would be considered successfully vaccinated. The pustule would heal, leaving a small scar on the area of vaccination.

Because smallpox vaccines used live-attenuated virus, transport and storage of the vaccines were critical in global eradication efforts, especially in developing countries lacking proper infrastructure and resources. To decrease the amount of refrigeration, researchers created heat-stable, freeze-dried smallpox vaccines by collecting centrifuged suspensions of the virus to be freeze-dried in ampules (Belongia & Naleway, 2003). The Iced-Line Refrigerator (ILR), which is still in use today, stored vaccines in rural areas that had electricity for less than eight hours a day. The ILR contained an internal lining of water containers that could be frozen to maintain cold temperatures when electricity was not available (Lloyd & Cheyne, 2017). For transport, the National Bacteriological Laboratory in Sweden developed a wooden transportable cold box that could refrigerate vaccines for more than five days even when outside temperatures were greater than 43^{o}C.

New methods of smallpox vaccine administration, storage, and transport were crucial to global eradication efforts. These techniques, such as the freeze-dry method, are still used today to vaccinate against other pathogens including polio and measles (Kraan et al., 2014; Peetermans et al., 1978). As shown by the success of the smallpox vaccine, this drive for innovation ought to be emulated in future global eradication efforts.

Textual Dimension

FIGURE 2. Intersection with the Legal and Bioethical Dimensions: This drawing reflects the skepticism by the general public who feared that cows would begin growing from areas of vaccination, since Jenner's smallpox vaccine uses cowpox virus. Because of this drawing and related drawings, people were reluctant to receive the vaccine. Due to this skepticism many unvaccinated individuals died of smallpox. Should legislation be implemented to regulate "Fake News" if people's lives are at risk?

When Edward Jenner first developed the vaccinia smallpox vaccine in May 1796, the public was extremely skeptical, and his publications were not taken seriously by academics who believed that only inoculation using live smallpox (variola) virus would confer protection (Smith, 2011). Similar to the concept of Fake News described by Jacob Soll in *Politico*, this skepticism led to works of satirical art discounting the effectiveness of the vaccine (Figure 2) (Soll, 2018; Fenner et al., 1988). An article titled "Smallpox vaccine triggered AIDS virus," written by Pearce Wright and published in *The Times* on May 11th, 1987, falsely claimed that the smallpox eradication efforts "awakened unsuspected, dormant human immune defense virus infections (HIV)." (Wright, 1987) Wright continued to assert false claims that "some experts" (these "experts" were never confirmed nor identified) feared that obliterating smallpox transformed a minor HIV epidemic into a global pandemic. No scientific publications supported Wright's claims. In 2010, Weinstein et al. published their research in *BMC Immunology* suggesting that "prior immunization with vaccinia virus may provide an individual with some degree of protection to subsequent HIV infection." (Weinstein et al., 2010) Rather than leading to the spread of HIV, smallpox vaccines may have prevented an even larger AIDS epidemic.

Just as tattoos are a form of text technology that allow individuals to express their identity (Kang & Jones, 2007), scars can serve as texts that communicate information about an individual (Jennings, 2009). People who received the smallpox vaccine were marked with a small scar on their arm, where the vaccine was administered; therefore, the absence of a scar

indicated that a person cannot receive the vaccine for medical reasons. The scar played a crucial role in identifying unvaccinated individuals during the eradication efforts (Kennedy et al., 2016). Before the development of the vaccine, survivors of smallpox were left with pockmark scars all over their face and bodies, but today, the only smallpox-associated scars are the small "takes"[10] on people's arms (Figure 3).

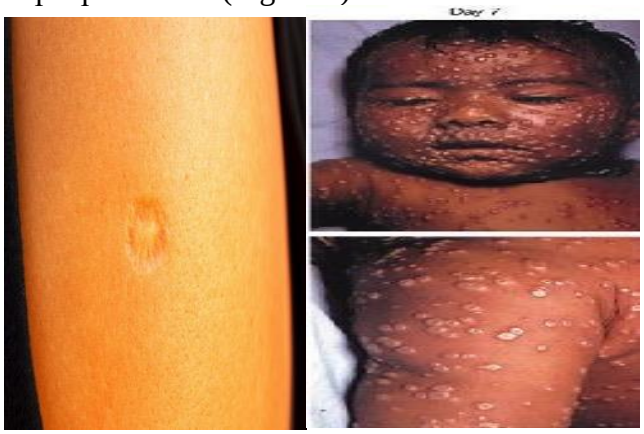

FIGURE 3. The image on the left demonstrates the permanent pockmarks that result from a smallpox infection. The image on the right is a picture of a "take" after administration of the smallpox vaccine.

The smallpox eradication efforts would not have been possible without effective propaganda. Photographs of pockmarked patients were the medium of choice to instill fear within the public ("WHO | The Smallpox Eradication Programme - SEP (1966-1980)," n.d.). Each nation crafted unique posters incorporating national colors, messages, and cultural items. As the WHO Eradication Programme approached the last remaining cases of smallpox, posters publicized a $1000 reward for people who found confirmed cases. In 1979, the WHO released a "Smallpox Zero" poster to celebrate the eradication of smallpox.

The textual dimension of the smallpox eradication efforts allowed people to achieve the seemingly insurmountable goal of eradicating an entire disease. Posters inspired people to receive the vaccine and directly participate in the global smallpox eradication efforts. However, one must remember that the textual dimension can be a dangerous double-edged sword, as shown by the spread of fake news regarding the vaccine. As future eradication efforts are implemented, healthcare leaders must ensure that the textual element of a vaccine is used with great caution and scrutiny.

Legal and Bioethical Dimensions

Smallpox is considered a "dual-use research of concern" (DURC), since DURC is life-sciences research that can become weaponized (Imperiale & Arturo, 2015; Barras & Greub, 2014). After the WHO's official

[10] "Take" is another word for the characteristic scar left by the smallpox vaccine.

declaration of a "smallpox-free world" in 1980, routine vaccination efforts ceased ("Smallpox Questions and Answers: The Disease and the Vaccine," 2003); therefore, populations today are no longer protected against smallpox used as a weapon of bioterrorism. After the 9/11 anthrax attacks, there has been increasing concern about smallpox as a DURC (Cohen, Gould, & Sidel, 2004). There is currently no international legislation overseeing smallpox research; therefore, anyone who has access to a laboratory space and knowledge of the viral sequence is able to reconstruct a highly pathogenic smallpox virus via de novo synthesis – creating the virus from less complex proteins (Trounce, 2018). This gap in legislation ought to be addressed immediately before a potential biosecurity threat arises.

As a medical countermeasure for smallpox bioterrorism attacks, the U.S. maintains a vaccine stockpile to treat 2 million people; however, 2 million people is an infinitesimal fraction of the U.S. population. Therefore, specific legislation should be crafted to determine who would receive the vaccine during biosecurity threats. During the global eradication efforts, Dr. Donald Henderson, Commanding General of the WHO Intensified Smallpox Eradication Programme ("Donald Ainslie (D. A.) Henderson, MD, MPH (1928–2016) Smallpox Eradication: Leadership and Legacy," 2017), used the ring vaccination method to immunize the most susceptible individuals first. In ring vaccination, contacts of confirmed patients are vaccinated first followed by those in close contact with the infected patient. Other individuals who receive priority include pregnant mothers, children, elderly patients, immunocompromised individuals, and healthcare providers. Ring vaccination requires rapid and meticulous surveillance as well as epidemiologic case investigations ("Smallpox-Ring Vaccination," 2017). During a biosecurity threat, ring vaccination could be one protocol for addressing who receives the vaccine.

As demonstrated by the Supreme Court ruling on *Association for Molecular Pathology vs. Myriad Genetics Inc.* ("The Genes You Can't Patent | by Daniel J. Kevles | The New York Review of Books," 2013), the vaccinia (cowpox) virus itself cannot be patented because it is a product of nature; however, isolated cDNA from the virus can. Because the smallpox vaccine used natural vaccinia virus, the vaccine itself was not patented; however, the technologies used to administer the vaccine were eligible for patents. The patents on the bifurcated needle and jet injector reflect John Locke's philosophy in *The Two Treatise of Civil Government* that "the labour of his body, and the work of his hands, we may say, are properly his." (Rubin, 1962; Lockhart, 1945; Locke, 1689) The patent process encouraged engineers to develop improved methods of safe vaccine delivery to aid the eradication efforts.

Since the WHO declaration of the global eradication of smallpox, all countries were mandated to destroy any remaining stocks of live smallpox virus; however, two locations were granted exceptions: Center

for Disease Control and Prevention (CDC) in Atlanta, Georgia, U.S.A. and Vector Laboratories in Russia (Reardon, 2014). The CDC and Vector Laboratories were granted exceptions on the grounds that the viruses be used only for biomedical research and vaccine development. The WHO Committee on Orthopoxvirus Infections (COI) has repeatedly pushed for the complete destruction of the stocks, yet U.S. and Russia continue to possess live smallpox virus. The COI believes that "the risk of keeping the virus outweighs the potential benefits" gained from research (Institute of Medicine (US) Committee on the Assessment of Future Scientific Needs for Live Variola Virus, 1999). These exceptions demonstrate the biased and political nature of legislative decisions; therefore, current systems of legislation regarding DURC should be questioned, evaluated, and changed to ensure parity and justice.

The Legal Dimension of the smallpox vaccine highlights weaknesses of the current legislative system to protect people against DURC. To address these gaps, the U.S. must act now to draft protocols for potential biosecurity threats. As microbes such as polio and measles are eradicated through global immunization campaigns, DURC will be scrutinized as populations are no longer vaccinated against these diseases. Future legislative decisions surrounding DURC should be carefully crafted to eliminate bias and objectively implement policies that place the safety of the public first. By establishing a legal precedent regarding DURC pathogens, future eradication efforts can ensure that the public is protected against a pathogen even after routine vaccinations are no longer necessary.

Conclusion

The smallpox vaccine transformed the world we live in today by extinguishing an entire disease from the globe. The WHO Smallpox Eradication Programme should serve as a model for on-going and future eradication efforts; however, in order to successfully emulate the Programme, one must analyze the smallpox vaccine from a multidimensional STS lens. Today, polio has been eradicated in all countries except for Afghanistan, Nigeria, and Pakistan. A multidimensional comparison of the Polio Global Eradication Initiative and the WHO Smallpox Eradication Programme can provide insights about the strengths and weaknesses of the current polio eradication initiative that were previously overlooked. An interdisciplinary understanding will not only be key to organizing future vaccination efforts but also for devising preventative measures against potential biosecurity threats. By discussing five dimensions of smallpox vaccination, this paper aims to open a multi-disciplinary forum on how the smallpox vaccine has impacted our lives and how we can conquer other vaccine-preventable diseases.

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