

Appendix E - UNIVERSITY HONORS PROGRAM
SENIOR PROJECT - APPROVAL

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PROJECT TITLE: Risk/Benefit Analysis of
Nationwide Smallpox Vaccinations

I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

Signed: Robert N Moore, Faculty Mentor

Date: 4/25/03

General Assessment - please provide a short paragraph that highlights the most significant features of the project.

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Re: University Honors Program
Senior Project-Approval

Mr. Corey Cudzilo has thoughtfully addressed an issue of exceptional contemporary importance, the smallpox vaccination program. This program was begun in response to the terrorist acts at the World Trade Center as part of the government's actions to protect the nation from terrorism, including bioterrorism. Although a selection of biological agents have been identified as potential terrorism threats, anthrax and smallpox have received the most attention. Anthrax is a proven threat; however, if smallpox poses a threat is an arguable issue.

Mr. Cudzilo has analyzed available information and has concluded that the proposed smallpox vaccination program may pose a greater threat to the citizens of this nation than a potential bioterrorism action using the smallpox virus. His argument is sound, and his recommendations are viable and supportable. There is no available evidence that smallpox is possessed by terrorist groups, but the potential harm of the vaccine is established. The nation can be protected with a dramatically modified version of the vaccination program that does not require mass immunization of the general population.

Robert N Moore

Risk/Benefit Analysis of Nationwide Smallpox Vaccinations

Corey Cudzilo
Senior Honors Project
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4/23/03

Abstract:

In an age of heightened concern over bioterrorism and biowarfare, smallpox stands out as a threat if for nothing else than the severity of the disease it causes. In response to this threat, the Bush Administration has announced a Smallpox Vaccination Program, but questions and concerns abound from health care workers, military personnel, and the general public. The average American has had no reason to know the basics of the disease and the risks and benefits of the vaccine against it until now. However, most Americans *aren't* educated on the crucial information, and thus cannot make an informed decision or form an objective opinion. This paper seeks to educate the reader on smallpox and its vaccination while discussing the Smallpox Vaccination Program—to determine whether it is necessary, efficient, or warranted.

Fifteen, ten, or even five years ago the words “bioterrorism” and “biowarfare” were not part of this country’s everyday vernacular. We, however, live in a new world and a different time. Yes, biological agents have been used in wars and against people for centuries, but the threat of bioterrorism or biological warfare has never been so public, so sensationalized in the media, or such a part of our government’s agenda. As cliché as it is, September 11, 2001 really *did* change our nation and made it almost fearful of *what else* could be done. Immediately after the attacks the Office of Homeland Security was created. Our country experienced terror alerts for the first time, five levels of increasing risk for terrorist attacks, compiled from unknown sources and information. President Bush designated an “Axis of Evil”: Iran, Iraq, and North Korea. These countries are believed or are known to have nuclear, chemical, and biological weapons and the capacity and the will to use them. The FBI went on a nationwide manhunt for members or associates of Al Qaeda, the terrorist group responsible for the attacks on the World Trade Center. Almost weekly the news is dominated by the arrest of an individual involved with terrorism, domestically or abroad. Iraq, a nation designated by the President to possess Weapons of Mass Destruction (WMD) and ruled by a heartless dictator whose regime raped its country and its citizens is no longer a nation as it once

was, due to an invasion of Coalition Forces led by United States and British armed forces.

It appears as if the United States either has terrorists running away with their tails between their legs or irritated like a hive of wasps, depending on one's point of view. The use of biological agents in terrorism or warfare is still a concern for our nation, both in the government and the general public. In December of 2002 the President announced the Smallpox Vaccination Program, a plan to "better protect the American people against the threat of smallpox attack by hostile groups or governments" (1). At first glance this statement seems directly in line with the policy of our government to protect the United States from bioterrorism. Smallpox is a deadly virus that could be used in bioterrorism; however, a second glance and two minutes of research would tell someone that smallpox has been officially eradicated from this planet since 1980 (2). So why vaccinate America? Is there any real threat? What are the risks? What are the benefits? This paper seeks to determine if nationwide smallpox vaccinations are warranted, necessary, and/or efficient, and to conduct a risk/benefit analysis of the proposed Smallpox Vaccination Program. If nothing else, the average American probably does not know enough information about smallpox and its vaccination to make an informed decision on whether or not to be vaccinated. This paper also seeks to inform the average American on the basics of the smallpox virus and the vaccine against the disease.

History

Smallpox is without question the most devastating disease known to humans. The smallpox virus has killed, crippled, or disfigured nearly one-tenth of all humankind. In the 20th century alone, more than 300 million people died due to smallpox. It dwarfs

other illnesses such as the plague (Black death), cholera, and yellow fever in terms of its universal impact and destructive results.

The emergence of smallpox can be traced back to early settlements in Africa around 10,000 BC (6). From there it was spread outward to India and Egypt. Evidence of facial lesions are present in mummies dating 1570-1085 BC. The first epidemic occurred in 1350 BC during the Egyptian-Hittite war. Egyptian prisoners spread the disease to the Hittite population, eventually causing the decline of the Hittite civilization. There were epidemics in ancient Greece (430 BC) and in the Roman Empire. The early stages of Rome's decline were partially due to a large epidemic that killed between 3.5 and 7 million people. The disease spread west as a result of the Arab expansion, the Crusades, and the discovery of land across the Atlantic Ocean. Smallpox was instrumental in the fall of the Incan and Aztec empires, brought to the New World by Spanish explorers. It decimated the Native American population, brought here by English colonialists and even used against resisting tribes of Indians (6).

Royalty or wealth was not a barrier to infection. Smallpox killed the Roman emperor Marcus Aurelius in AD 180; Aztec emperor Ciutlahuac in 1520; Emperor Ferdinand IV of Austria in 1654; Emperor Gokomyo of Japan in 1654; Queen Mary II of England in 1694; Tsar Peter II of Russia in 1730; and King Louis XV of France in 1774. In some ancient cultures, infants were not named until they caught the disease and survived. Smallpox was the cause of one-third of all blindness in 18th century Europe, when 400,000 people died from smallpox every year. During the 18th century, one-seventh of all Russian newborns died from smallpox, and one-tenth of children born in Sweden (2)(6)

It was known that if an individual survived a smallpox infection they were immune to any further infection. With that knowledge, it was the common practice of the day to infect healthy individuals by intentionally exposing them to persons with mild cases of the disease, in hopes that the resulting infections would be less severe yet still provide immunity. Also, various parts of infected persons, from pus to pustules to scabs, were routinely used to “immunize” healthy individuals. This method was named “variola” and comes from the designation of smallpox as *variola* in 570 AD. That word comes from the Latin *varus*, meaning “mark on the skin”. Variolation was practiced in the East for over a hundred years before it was introduced and became an accepted method in Europe. Lady Montague was an English aristocrat and was responsible for the acceptance of variolation in England. Variolation soon traveled across the ocean to America and was used extensively by the mid-18th century. Fatality rates of variolated persons were ten times lower than those of naturally occurring smallpox. However, two to three percent of variolated people died; many more developed other illness like tuberculosis from infected donors (6). Nonetheless, in 1722 the fatality rate from smallpox was 1:14 in naturally occurring cases and 1:91 in variolated children (7).

It was also known during the 18th century that persons previously infected with cowpox experienced no reaction to variolation, and seemed to be immune to smallpox. Cowpox infected few humans, usually milkmaids or farmers who were in close contact with cows. A few citizens toyed with experiments involving cowpox and variolation, but gave up before any conclusive evidence was found. By 1788 an English scientist named Edward Jenner had begun to compile information, study cases, and design experiments to

test if prior infection of cowpox provided immunity from smallpox. In 1796 he began his experiments by using fluid drained from a cowpox pustule on an infected milkmaid to inoculate an eight-year-old boy. Subsequent attempts at variolation produced no visible results, suggesting immunity. At the end of 1796, Jenner brought his findings, now totaling 13 cases, to the Royal Society. His theory was rejected and Jenner was sent away. Jenner decided to personally finance the publication of his findings and soon appeared with this as the title of his paper: “An inquiry into the causes and effects of the *variole vaccinae*, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of cow pox”. Jenner had used the word *vaccinae*, from the Latin *vaca*, meaning “cow” to describe the phenomenon that conferred immunity to 13 persons previously infected with cowpox. After initial skepticism, the practice of vaccination became extremely popular. By 1800, an estimated 100,000 people had been vaccinated against smallpox. Vaccination spread from England to the rest of Europe and to the United States (6).

Jenner went on to receive numerous accolades, preside over an institute named after him, and gain worldwide popularity over his discovery. He technically did not discover the practice of vaccination, but brought a scientific approach to the procedure and determination to spread knowledge of its success.

Smallpox

The smallpox virus (*Poxvirus variolae*) is one of the largest and most complex viruses known. It is a DNA virus, Baltimore classification class I, and a member of the Poxviridae family, Chordopoxvirinae subfamily, and Orthopoxvirus genus. It is

characteristically a brick-shaped structure with a diameter of about 200-400 nanometers. The Poxviruses were the first viruses to be “seen”—the aggregation of viral particles (elementary bodies) in an infected host are large enough to be seen by a powerful light microscope when stained. Poxviruses are extremely complex antigens and they induce both specific and cross-reactive antibodies. This antigenic property is what allows for a relatively harmless vaccination for smallpox using another Orthopoxvirus, *Vaccinia* virus, which will be discussed in more detail later (3).

The smallpox genome consists of about 250 genes and replicates in the cytoplasm of the host cell upon entry. After entry, smallpox follows the lytic cycle of viruses, meaning it 1) uncoats from its envelope 2) replicates its genome into concatemers 3) transcribes its genome 4) expresses its genome using viral enzymes 5) assembles the viral particles in the cell’s cytoskeleton 6) matures in the golgi complex of the cell and 7) is released from the cell along with other mature virions, causing cell lysis and death (3).

There are two clinical forms of smallpox. *Variola major* is the strain most associated with the smallpox disease. The minor strain causes similar symptomology but has a mortality rate of less than 1%. There are four types of *variola major* smallpox: ordinary (~90% of cases); modified (occurs in individuals vaccinated previously); flat; and hemorrhagic. Both the flat and hemorrhagic types are rare and severe, usually resulting in death (4)(www.cdc.gov/smallpox).

There are many identified clinical features of a smallpox infection. Initially there is a 12-14 day incubation period when the individual looks and feels healthy and is unable to transmit the virus to others. The incubation period is followed by the sudden onset of flu-like symptoms (called the prodrome) characterized by fever, a temperature

usually exceeding 101 degrees, headache, malaise, back pain, and occasionally vomiting and general abdominal pain. After two to three days the individual's temperature drops and symptoms are relieved. The characteristic rash begins to appear, initially on the face and extremities and later progressing to the trunk. Lesions develop in the mucous membranes of the nose and mouth that soon ulcerate and release large amounts of virus into the mouth and throat. At this time the individual is the most contagious. The rash on the body develops into raised bumps by the third day, and soon the bumps fill with a thick opaque fluid. The bumps often have a depression in the center, which is a distinguishing characteristic of smallpox. The bumps become pustules and are firm to the touch and sharply raised from the skin. Most of the pustules will scab over after about five days of their appearance. The scabs will fall off, leaving pitted scars in their place. Death occurs in 30% of individuals infected with variola major, usually resulting from immune complex mediated shock. Between 65-80% of survivors are marked with the deep-pitted scars caused when the scabs fall off, usually most notable on the face. Scabbing and the eventual scarring of the eyes can cause blindness and historically has been a major cause of blindness (2) (5).

The history of the disease suggests that the human population is universally susceptible to infection of the smallpox virus. Transmission of the virus is possible through direct contact with a symptomatic person. Individuals with the characteristic cough can spread aerosols and air droplets containing the virus. The virus can also be transmitted through contaminated bedding and clothing, although not as prevalently as face-to-face contact. It is important to note that infected persons in the incubation period cannot transmit the virus. Infectivity is the highest during the prodrome stage of the

disease and the first week of the rash. The infected individual remains contagious until the last scab falls off. Typically the disease spreads rather slowly, infecting only close contacts in small vicinity, unless a ventilation system exists in a building such as an apartment complex. Today it is estimated that an initially infected person, called an index case, could infect as many as ten other individuals (2)(4).

Modern Vaccination

The modern version of Jenner's cowpox vaccination contains live vaccinia virus, another member of the orthopoxvirus family. Vaccinia is closely related to variola virus but confers immunity to smallpox while not causing smallpox. Most vaccine consists of pulp scraped from vaccinia-infected animal skins of sheep or cattle (4). The Vaccinia virus vaccine proved to be more effective and obtainable than Jenner's cowpox-based vaccine. But despite 20th century advances in medicine and vaccination specifically, in the 1950's an average of 50 million people were still infected with smallpox per year. Gradual increase of emphasis for vaccination reduced the number of infections to 10-15 million per year (2).

The smallpox vaccine is unique because it is not administered by a hypodermic needle. Instead, the vaccine is given using a bifurcated needle that is dipped into the vaccine solution. The skin (usually the arm) is then pricked several times with the two-pronged needle. Successful vaccination results in a red, itchy bump that develops at the penetration site within three to four days. The bump progressively swells, becomes a large blister filled with pus, and then begins to drain. In the second week the blister dries and a scab forms. The scab falls off a week later, leaving a scar. Special care is taken to

prevent the spread of the vaccinia virus from the site of vaccination, since the virus can cause rash, fever, and body aches. Serious side effects are possible in certain groups of people, which will be discussed later (4).

In 1967 the World Health Organization began an intensified plan to eradicate smallpox through vaccination. In ten years the WHO's campaign reduced smallpox from a worldwide threat to human livelihood to the African country of Somalia. There, in the village of Merka, a cook by the name of Ali Maow Maalin developed the characteristic rash associated with smallpox. He survived and recovered and became the last naturally occurring documented case of smallpox in the world; global eradication of smallpox was confirmed by the World Health Assembly on May 8th, 1980.

Unfortunately, the book on smallpox has never been altogether closed. The Center for Disease Control in Atlanta and the Institute for Viral Preparations in Moscow are the only known locations where smallpox exists. The remaining stocks have been slated for destruction on several occasions, but a lack of consensus by board members of the WHO has delayed destruction. Those in opposition to the destruction of the remaining virus contend that future study of the virus would be impossible and that destroying the stocks does not guarantee the absolute eradication of the virus. Those in favor of destruction argue that any escape of the virus from its two known homes raises a risk of use in bioterrorism and/or biowarfare, which is something that some feel may have already happened (6).

New Concerns

This country is currently in an unfamiliar position regarding terrorism on U.S. soil. The September 11th attack on the World Trade Center were the apparent culmination of years of pent-up hatred for Americans and their way of life. Soon after 9-11, the country was again terrorized by anthrax sent through the postal system. The U.S. government has taken new steps to protect its citizens and resources. The Center for Disease Control has listed smallpox as a Class A Bioterrorism Agent, the highest concern and most dangerous classification. Reasoning for this classification and concern stem from the discontinuation of smallpox vaccinations over 20 years ago and resulting susceptibility to the virus (8). It is estimated that 80% of the population has no prior immunity to infection. There is also concern that despite the documentation that only two facilities possess the smallpox virus, it is possible that a terrorist group or rogue nation could have smallpox samples (5). This concern from the scientific community appeared several years before September 11, 2001. The variola virus meets several criteria of any potential bioterror weapon:

1. It is highly transmissible by the aerosol route from infected to susceptible persons.
2. The civilian populations of most countries contain a high proportion of susceptible persons
3. Smallpox is associated with high morbidity and about 30% fatality
4. Initially, diagnosis of a disease that has not been seen for 25 years would be difficult
5. A person may transmit the disease before exhibiting characteristic features of the disease such as the rash and pustules
6. Other than the vaccine, which can still be effective in the first few days of infection, there is no known and proven treatment for smallpox (5).

In response to these concerns, which emerged in the late 1990's but were amplified after the September 11th terrorist attacks, President Bush announced a plan for

a Smallpox Vaccination Program in December of 2002. The plan called for the formation of Smallpox Response Teams, voluntary health care workers vaccinated against smallpox that would “provide critical services to their fellow Americans in the event of a smallpox attack” (1). Also included in the plan are certain military and civilian personnel working or deployed to “high risk” areas. The Bush Administration acknowledges in the plan that smallpox is not an imminent threat, but believes it is wise to “strengthen the preparedness for bioterror attacks by expanding the national stockpile of smallpox vaccine” (1). The Program does not recommend that members of the general public be vaccinated at this point, but is steadily working to procure sufficient doses of the vaccine for every citizen of this country.

The Controversy Begins

Immediately following Bush’s announcement, vocal sides formed on the issue. Some welcomed the program as a necessary protective measure against one of the most serious potential bioterror weapons. The chief of the CDC, Dr. Julie Gerberding, favors the program--“The President’s decision to recommend this vaccine...was really based on the fact that we need urgent and efficient action because we live in a dangerous world these days, where a terrorist attack with smallpox is possible” (9). Asked about the threat of a smallpox attack, virologist Dr. Don Francis said “It scares me. It’s a dangerous disease, and we have little immunity” (10). Others, however, vehemently opposed the program as dangerous in itself and not worth the risks. “We’re not sure anybody has smallpox virus,” contends Dr. Daniel Blumenthal, a specialist once involved in the WHO’s smallpox eradication program, “and yet now we are reinstituting vaccination”

(9). Several union groups, including the American Federation of State, County and Municipal Employees (AFSCME) and healthworkers.org, oppose the plan because of the risks involved in vaccination (11) (12).

There are health risks involved in receiving the vaccination. It is estimated that for every one million people vaccinated, up to fifty would experience life-threatening complications and one or two would die(13)(9). Also, 1,000 people for every 1 million people vaccinated would experience serious but not life-threatening reactions (4).

The program got off to a slow start on January 24, 2003 when only four doctors out of a twenty member “Genesis Team” from Connecticut turned out to be vaccinated (14)(story.news.yahoo.com/news/2003122). Connecticut was the first state to take part in the program, which began with Smallpox Response Teams from each state and eventually 500,000 more health care workers. Similar turnouts have been seen in most other states. As of April 4 2003, only about 31,000 health care workers and about 350,000 military personnel had received vaccinations (15) (16). The plan contained three phases: the first phase was to vaccinate the emergency teams, numbering some 400,000 health care workers, and approximately half a million military personnel. The second phase seeks to inoculate 10 million “first responders”. The third phase, with an unknown timetable, is to vaccinate the general public.

The program has experienced several setbacks in the last few months. Most visible is the lack of participation by the majority of the country’s health care workers. Also, as of 4/04/03, about seventy people vaccinated experienced moderate to severe reactions to the vaccine, while three people have died from heart complications believed to have been aggravated by the vaccine (15). More recently, the United States led a

coalition invasion of Iraq, which has taken precedence over the program and a shift in the Bush administration's focus. These factors have led to an increased vocalization from those opposed to the program, or at least the program as it now exists. Opponents note the increased risk of complications from persons with heart disease, immune disorders, or a history of eczema. There have also been calls for the development of an improved vaccine, one that does not have the potential for serious or life-threatening reactions. "We would like to see a less-toxic vaccine," says Dr. Roger Pomerantz, director of the Center for Human Virology at Thomas Jefferson University (17). The Noravax Company claims that its version of the vaccine, a killed instead of live virus, is safer, although its effectiveness is unproven. Recently the Department of Health and Human Services signed a second contract with the British firm Acambis to produce 209 million doses by the end of 2004. The Acambis contract totals more than \$850 million (17).

The Bush Administration has reacted to some of the concerns. It recently implemented a compensation plan for individuals injured from a vaccination. The CDC has also issued a ten page *Smallpox Response Plan and Guidelines*, updated to deal with a possible attack and smallpox emergency. Still, some states have suspended their vaccination programs until health risks and potential reactions can be further investigated.

My Two Cents Worth

Much of the opposition appears to stem from a lack of education on smallpox, the vaccine, or the threat of attack. The general public has been informed repeatedly on the possibility of a rogue nation or terrorist group possessing smallpox, but no specifics are ever given. "My concern is we had a politicization of the scientific process," says Dr.

Linda Rosenstock, dean of the UCLA School of Public Health, "...one might defend making national security actions and war plans on information that can't be shared with the public. I just can't see any justification making public health policy in that same mindset of secrecy" (9). It appears that policy is being made without sufficient education of health care workers, much less the general public. There is a fear, which is somewhat justified, of the unknown concerning this virus and this vaccine. Americans should no sooner blindly believe their government about a given issue than should the media. Both are capable of spinning the facts and emphasizing what they choose. Public opinion, which so far has been less than receptive to the program, is almost certain to shift if the Bush Administration would provide some specific details on the possible possession of smallpox by a terrorist group or rogue nation. Combine a mysterious virus that has not appeared in 25 years with a vaccine that could seriously harm and probably cause some pain, and you get 30,000 out of 400,000 people following a plan. If Bush and his Administration want this program to succeed, America needs first to be educated and provided with real information. A terror alert of orange is not sufficient.

None of this is to say that Bush's plan is a bad plan. Smallpox is certainly a serious disease and the questions surrounding its availability to terrorist groups are real enough to warrant some measure of national protection against a smallpox attack. However, it does not appear that mass, nationwide vaccinations are a necessary or cost-efficient measure. A more efficient plan would certainly axe phase three of the program, and very possibly phase two as well.

A simulation of a deliberate smallpox attack created by biostatistics professors at Emory University's Health Science Center concluded that targeted vaccination of close

contacts of smallpox-infected individuals would rival that of mass vaccinations. The scientists based their conclusions on their knowledge of community interactions and immunity existing from new vaccinations of Smallpox Response Teams, residual immunity from prior vaccination, and voluntary vaccinations in the general public. In this model, additional vaccinations would only be administered to those in close contact with an infected individual, such as household members, school or daycare centers, neighborhoods, and communities. The simulation also factored in varying levels of residual immunity, where transmission was likely to highest (households), and the likelihood of interaction and transmission within a community each day after infection occurred. They also assumed that smallpox is most likely to be transmitted in close contact rather than casual or indirect contact on the street or in a subway (18). If such a simulation is accurate, hundreds or thousands of people could avoid serious side effects from the vaccine, and hundreds of millions of dollars saved from not vaccinating the entire nation.

The Program also seems to be getting ahead of itself, launching huge initiatives to vaccinate before even enough vaccine is produced to vaccinate the entire country. Information about the disease and vaccine is changing as well. The CDC rewrote part of its website that stated that the vaccine only protects for three to five years. Studies show that people vaccinated even fifty years ago still have some protection and a much lower risk of dying from a smallpox infection than someone that has never been vaccinated (17). With that information known, does that exclude someone born before 1972, the year the U.S. ended its smallpox vaccination program, from needing to receive a vaccination if Phase three is carried out? What about the thousands of Americans that do

not even know they have a heart condition? What are the chances that terrorists would attack America with smallpox after everyone has been vaccinated?

With so many variables, questions, and unknowns, the Bush Administration needs to be first concerned with educating health care workers, military personnel, and the general public alike about the disease and vaccine. Smallpox Response Teams are a good idea, and have been shown through simulation to be effective against a smallpox attack. Hundreds of millions of dollars could be diverted towards research for a safer vaccine, apprehension of terrorists, or back to the general budget. Yes, smallpox is quite possibly the worst disease humans have ever seen, but an entire generation has never even seen the disease or the effects it leaves. Smallpox has been absent for a quarter of a century, and most Americans educated on the topic do not believe we should all be protected from it.