Yersinia pestis, Biological Warfare, and Bioterrorism

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Summary

Yersinia pestis can cause any of three diseases – bubonic plague, pneumonic plague, and Septicemic plague. Bubonic and pneumonic plagues have in the past been weaponized by Japan and USSR. This article analyses whether terrorist groups will emulate these national biological warfare programs and thus will seek to develop weapons armed with Y. pestis.

Preface

I teach a graduate seminar course at the Middlebury Institute of International Studies at Monterey titled "Chemical and Biological Weapons and Arms Control." Last semester a student asked me, "Since the Japanese and Soviet biological warfare programs weaponized *Yersinia pestis*, is it possible that a terrorist group would follow their example and attempt to develop a biological weapon whose payload was *Y. pestis* bacteria"? I did not have an answer to the question, so I decided to conduct research whose objective was to prove or disprove the hypothesis: "It is likely that in the not too distant future, a terrorist group will utilize *Y. pestis* in an attack against a human population."

Introduction

In the historic literature there are many accounts of armies and armed bands having utilized *Y. pestis* for biological warfare (BW) purposes. The methods for waging BW were primitive, such as catapulting plague victims who were sick or had recently died and thus were infested by human fleas (*Pulex irritans*) that, in turn, carried *Yersinia pestis* (*Y. pestis*)[1] into the encampments of enemies.[2] After the plague victim's body landed within the targeted area, the fleas would escape its lifeless host and seek living animals for their meals of blood. When successful, the flea's bite would convey *Y. pestis* cells into the new host. However, no modern military has used such methods for disseminating *Y. pestis* among its enemies, nor are they likely to be so used in the future. For this reason, I chose not to delve into ancient military history but limit my consideration to two BW methods that have been used in the 20th century and, possibly, might again be used in the future.

The first method is to disperse *Y. pestis* via a vector, for example human fleas such as *P. irritans*, amidst a targeted population. The second method involves dispersing *Y. pestis* cells as an aerosol onto the enemy's troop formations or civilian populations.

It must be made clear that when considering BW programs, their main objectives are to conduct research and development (R&D) for offensive purposes; i.e., to develop and produce biological weapons such as spray systems, bombs, rockets, or missiles whose payloads consist of bacterial or viral pathogens. Offensive BW programs are forbidden by international law, mainly the 1972 Biological and Toxin Weapons Convention (BWC).[3]

Conversely, biodefense R&D is permitted under international law, including the BWC. The products of biodefense programs are vaccines, therapeutics, diagnostics, and detectors that are used by nations to defend their populations against attacks utilizing biological weapons and should prevention fail, to treat its victims quickly and correctly. Countries that in the past have acquired offensive BW programs also conducted defensive programs to defend their populations from the BW agents their military scientists produce and from agents possibly possessed by adversaries. Of course, today when emerging infectious diseases and biological terrorism are world-wide existential threats, there are numerous countries that support biosecurity programs whose main objectives are to protect their populations from endemic, introduced, and emerging diseases and by doing so, they also are better prepared to meet the lesser threats of both bioterrorism and BW.

Before describing and discussing national BW programs, I believe it is useful to provide some background. Accordingly, this article has seven sections. First, I describe the pathogen *Y. pestis* and the three forms of the disease it causes. The second section contains a short history of plague vaccines, while the third section contains an even shorter history of therapeutics. The fourth, fifth, and sixth sections address the historical BW programs of, respectively, Japan, the United States (U.S.), and the Union of Soviet Socialist Republics (USSR). Of these countries, Japan and the USSR chose to weaponize *Y. pestis* and use it to arm biological weapons,[4] while the U.S. decided not to weaponize *Y. pestis* but did investigate methods to defend against plague. In the seventh and last section I discuss reasons why *Y. pestis* currently is considered a dangerous threat agent by both military and civilian entities that are responsible for protecting their populations from infectious diseases and consider future developments that may result in weapons based on *Y. pestis* becoming elements of national or terrorist arsenals. By doing the last, the stated hypothesis is supported or refuted.

Yersinia pestis and Plague

In nature, the pathogen named *Y. pestis* can cause any of three forms of plague depending on the route of infection – bubonic, pneumonic, or septicemic. The most common form of plague is bubonic plague, which humans most often contract after having been bitten by a flea infected with *Y. pestis*. After the pathogen enters the host's tissues, it is conveyed through the lymphatic system to lymph nodes where it replicates. The lymph nodes then become inflamed, rigid, and painful. When this occurs, the affected lymph notes are visible as swellings that are called "bubos." In humans, bubos typically are most pronounced in armpits and groin. At advanced stages of the infection the bubos may burst, turning into suppurating open sores. Untreated victims of bubonic plague have a mortality rate between 60 and 80%.

Pneumonic plague is much rarer than bubonic plague and more deadly. Unlike bubonic plague that is spread most often by infected fleas, pneumonic plague is spread by *Y. pestis* cells that are carried in aerosols emitted by coughing and sneezing persons who already are sick with plague. Untreated pneumonic plague has a mortality rate close to 100%. For the purpose of this article, readers should know that the largest known outbreak of pneumonic plague occurred during 1910-1911 in Manchuria, with the first cases being detected in Harbin.[5] The number of persons who died during this outbreak is estimated to have been between 40,000 and 60,000.[6]

Septicemic plague is when *Y. pestis* cells circulate systemically in a victim's blood. Both the bubonic and pneumonic plague can convert to the septicemic form and when this occurs, untreated victims have a mortality rate is close to 100%. Even if treated with antibiotics, patients afflicted with septicemic plague are most likely to die.

History of Plague Vaccines[7]

In the late 1890s, Pasteur Institute scientist Waldemar Haffkine worked for some time to develop a useful plague vaccine. In 1897, he released for general usage a so-called killed whole cell (KWC) vaccine.[8] The KWC vaccine was the main plague vaccine for most of the world for about 40 years and proved to be highly effective against bubonic plague but not against pneumonic plague. It is noteworthy that in 1947, the Department of Bacteriology at the Haffkine Institute, located in Mumbai, India, supplied 23.5 million ml of KWC plague vaccine, the highest production in the history of the Institute.[9] However, since a fairly high proportion of vaccine recipients suffered unpleasant side effects, in the 1940s an increasing number of health agencies prevailed on their governments to forbid the marketing of the KWC vaccine, especially so when more effective and safer live whole cell (LWC) vaccines became available. One exception was that the U.S. developed a KWC vaccine, which is discussed below.

A LWC vaccine was first developed in 1906 by P. Strong who tested it the Philippines. It did not prove effective, but a successful LWC vaccine was developed by L. Otten in 1934 using the *Y. pestis* Tjiwedej strain that had been recovered from a dead rat. It proved highly efficient in South Africa, protecting about 80% of those persons who received it.[10] However, although effective against bubonic plague, it did not protect against pneumonic plague. A more effective LWC vaccine consisting of the *Y. pestis* EV strain was developed by Pasteur Institute scientist G. Girard and colleagues in the mid 1930s.[11] In effect, various variants of the EV strain vaccine continue to be used in many countries of the world to this day, especially by countries that previously were part of the USSR (see below).

The U.S. began a large effort to develop a plague vaccine after it entered World War II and thus sent hundreds of thousands of soldiers into regions of the world where plague was common. The Cutter Laboratories in Berkeley, California, was able to improve on Haffkine's KWC vaccine derived from a virulent strain of *Y. pestis* and produced an effective vaccine named USP. Over the years, Cutter scientists continued to improve on the USP vaccine, with vaccine A being in use during 1942-1951, vaccine B during 1950-1968, and vaccine C during 1968-1998. There were no plague cases during World War II among American soldiers who had been vaccinated. This fine record continued during the Viet Nam conflict. In the 1960s, Viet Nam was the world's leading country in plague incidents, so the exposure of Americans to plague was much greater than in World

War II. All American soldiers received the UPS vaccine C before entering the country and by the time that the conflict ended, just eight soldiers contracted plague, which was a rate hundreds of times less than among the Vietnamese.[12] Production of the UPS vaccine ceased in 1998 and since then, no plague vaccine for human use exists in the U.S.

R&D that aimed to create a LWC vaccine began in April 1943 when the U.S. Navy Medical Research Unit No. 1 located in Berkeley, California, led by Albert P. Krueger, was given the task to "study the offensive possibilities and defenses against the organism of Asiatic plague."[13] By November 1944, the unit had made sufficient progress so that it was ready to attempt small scale pilot plant production of an avirulent strain of *Y. pestis* named A-1122. The largest reactor used for this purpose was 50 gallons (189 liters). The unit continued its work with *Y. pestis* into the 1970s, although in 1946 spun off some of it to the Department of Bacteriology, University of California at Berkeley (UCB).

In parallel with the investigations carried out by Krueger's team, another team led by K.F. Meyer at the George Williams Hooper Foundation, University of California San Francisco, sought to improve both the Haffkine KWC vaccine and the EV LWC vaccine. This work, which continued into the 1970s, was supported by the Commission on Immunization of the Armed Forces Epidemiological Board.[14]

USSR scientists began work to develop a plague vaccine in 1936, when the Scientific Research Institute of Epidemiology and Hygiene at Kirov procured the avirulent *Y. pestis* EV strain from the Pasteur Institute in Antananarivo, Madagascar. By 1941, a team led by M.M. Faybich had developed methodology for keeping high immunogenicity of their line of the EV strain at the initial level. The team developed a dry, live plague vaccine by using this line and methods for its large-scale production. This vaccine was called *Vaccinum pestosum vivum siccum*.[15] The Soviets claim to have produced and distributed 47 million doses of plague vaccine to Soviet armed forces during World War II. They also asserted that when the Red Army was preparing to invade Manchuria in August 1945, 8.5 million doses were manufactured for the specific purpose to vaccine all soldiers in the Far East. Even though plague was endemic to this region, reportedly no Red Army soldier contracted plague on the Eastern front.[16] The researchers M.M. Faybich, I.A. Chalisov, and R.V. Karneev were awarded the State Prize of the USSR in 1945 for having developed the dry plague vaccine.[17] A LWC EV vaccine continues to be used to this day in Russia and most of the USSR's former republics. *The* Stavropol Anti-plague Scientific Research Institute is the only producer in Russia of a LWC vaccine, which now is named EV NIIEG.[18] Western countries have tended not to allow this vaccine to be used by their health providers because other vaccine strains derived from the EV76 line are known to cause a number of negative side effects.[19]

Treating Plague

The German scientist C. Domagk discovered the first sulfa drug, Prontosil, in 1935, which proved to be somewhat effective in treating plague. However, effective treatment of plague only became possible in 1946, when streptomycin, the first antibiotic that proved to be highly efficient against plague became generally available. Although streptomycin remain the drug of choice to treat plague, it can be replaced by the modern antibiotics gentamicin and doxycycline. Whichever antibiotic is used, it must be administered very soon after a person has been infected in order for the antibiotic to be effective.[20]

Japanese Weaponization of *Yersinia pestis*

In the mid-1930s, the Japanese military secretly established the Kwantung Army Epidemic Prevention and Water Supply Department, whose code name was Unit 731, which was staffed with BW specialists drawn from the imperial Japanese army. This unit was commanded by a military physician, major Shiro Ishii, who was particularly interested in plague.[21,22] In 1936, Unit 731 moved from Japan and established its headquarters in the Pingfan district, which was located approximately 24 kilometers south-east of Manchuria's largest city, Harbin. When in 1940 the unit reached its full strength, it comprised of eight divisions that employed an estimated 3,000 persons. In addition to Unit 731, several other Japanese units deployed throughout occupied China were involved in developing biological weapons.[23] For example, Unit 100, headquartered near Hsinking, was established in 1936 and was led by veterinarian Yujiro Wakamatsu. Its responsibility was to develop weapons against animals. Yet another unit, Ei 1644, was established in 1939 under the cover name "Anti-epidemic Water Supply Unit" and headed by medical doctor Masuda Tomosada, was located in Nanking. Like Unit 731, it developed weapons against humans.

After the USSR entered the war against Japan in August 1945, the Red Army quickly overran Manchuria and in the process captured ten of Unit 731's servicemen and two from Unit 100. The 12 were charged with developing, manufacturing and using "bacteriological weapons" and were tried for these war crimes in Khabarovsk city during December 25-30, 1949. The extensive trial record was published in English in 1950.[24] The servicemen confessed that Units 731's and 100's specific functions were to investigate the weapons utility of the pathogens that cause "plague, cholera, gas gangrene, anthrax, typhoid, and paratyphoid."[25] However, it is clear from their testimony that of the pathogens investigated by Unit 731, the highest priority was to weaponize *Bacillus anthracis* and *Y. pestis*. Accordingly, in this article I focus on *Y. pestis*.

The Japanese decided to concentrate on two methods for dispersing BW agents, one that used explosive force to disperse a formulation containing *Y. pestis* as an aerosol over targeted populations and a second type that depended on dispersing fleas infected with *Y. pestis* to cause bubonic plague in population centers. Of the two, more effort was spent on the second.

Unit 731's fermentation facility could produce 300 kg of *Y. pestis* cells in one production cycle. In parallel, the unit's entomologists developed methods for raising large numbers of fleas; they claimed to have been able to produce 40 million infected fleas per month, the weight of which was approximately 10 kg.

In 1947, a team of American investigators led by Herbert H. Fell, Chief of the Planning Pilot-Engineering Division at Fort Detrick, interviewed 24 former Unit 731 scientists and technicians. Team members learned that Unit 731 used captured prisoners of war and kidnapped Chinese citizens as subjects for laboratory and field experiments to determine infectious and lethal doses of *Y. pestis*. In the laboratory, pathogens were introduced into human subjects by direct injection, oral preparations, inhalation of aerosols, or bites by fleas carrying *Y. pestis*. The findings were as follows:

> ID_{50} was 10^{-6} milligrams (mg) subcutaneously and 0.1 mg orally.[26] Respiration for 10 seconds of air containing 5 mg/meter^3 was infectious to

> 80% of exposed persons. The incubation period was normally 3-5 days and death occurred 3-7 days after onset of fever. In most cases of artificially induced plague that terminated fatally, the usual bubonic form became pneumonic three days before death and then was highly contagious.[27]

The Japanese military progressed from conducting such fatal human experimentations against prisoners in a laboratory setting to doing so as part of open air field trials. Human subjects were tied to stakes in open fields and exposed to pathogens in one of three ways. First, they were forced to inhale pathogens that were dispersed as aerosols by sprayers mounted on aircraft or land vehicles. Second, Type 50 Uji bombs whose payloads consisted of pathogens would be placed in the middle of a circle consisting of stakes onto which subjects were tied and an explosive force would disseminated the payloads as explained below. Third, specially adapted Uji bombs would have payloads constituted by fleas infected with *Y. pestis* that would be dispersed by a carefully measured explosive force created by a primacord over a group of tied-up subjects. Briefly, the findings from open field trials were as follows: "The spraying trials proved ...that this method was highly effective, both with subjects held within a room and also exposed to bacilli spread from aircraft at low altitudes. Of the subjects used in these trials, 50-100% became infected and the mortality was at least 60%."[28] However, the two types of bomb experiments gave different results: "The conclusion from all the [explosive] bomb trials was that plague bacilli were not a satisfactory B.W. weapon due to their instability but that it was much more practical to spread plague by means of fleas."[29]

The Type 50 Uji bomb weighed 25 kg and held 10 liters of payload. The nose cone contained an impact delay fuze and a bursting tube loaded with 500 grams of TNT (see Figure 1). In cases when the tail fuze and the primacord failed to function, the explosive train in the nose would detonate when the bomb impacted on the ground and thus would disperse its payload.[30]

Approximately 500 bombs of this model were manufactured in 1940 and 1941, and extensive field trials were conducted during the period 1940 to 1942 at Unit 731's proving ground near Anta, Manchuria. Bombs were tested by static explosion and drop tests from aircraft. For the initial tests, bombs were filled with a dye solution and suspensions of nonpathogenic organisms. Later bomb trials were conducted using a suspension of *B. anthracis* spores as the payload. In drop tests with a wind velocity of 5 meters per second and bombs being detonated at an altitude of 200 to 300 meters, the payload would be dispersed over an area of 40-60 meters by 600-800 meters.

Some of the Type 50 Uji bombs were adapted to carry up to 30,000 fleas infected with *Y. pestis* as payload. The dispersal method for the explosive opening of the bomb had to be reworked so that it did not kill the fleas. The adapted bomb was wrapped with a 4-meter long primacord; a fuze would explode the primacord at an altitude of 200 to 300 meters, thus liberating the bomb's payload.[31] After many trials field trials at Anta, the dispersal method was perfected to the point that 80% of the fleas survived this dispersal method. The adapted Uji bombs probably were the most effective biological weapons developed and used by the Japanese in terms of being able to sicken and kill the largest number of targeted Chinese.

There were two groups of victims of Japanese BW. The first group was constituted by persons that Unit 731 used as subjects in their inhumane laboratory experiments that involved infecting subjects with different pathogens and recording the results. Human subjects were also used in open field tests of candidate biological weapons in order to learn which of them were most effective. According to historical records, more than 3,000 Chinese anti-Japanese patriots, civilians, Soviet citizens, Mongolians and Koreans were used as human subjects and were inoculated with various pathogens by different methods, including passive oral infection, injection, bites by infected vectors, and exposure to aerosols created by exploding bombs.[32] Most of them died almost immediately, but some survivors were vivisected after they contracted various diseases.

The second group was Chinese civilians and soldiers. As noted above, Unit 731 manufactured large quantities of *Y. pestis* cells that were used to contaminate blood fed to many thousands of fleas. The fleas were emplaced in Uji bombs that were carried by aircraft and released on Chinese population centers. As a result, plague among humans and rats became epidemic in Chinese provinces. For example, in the Zhejiang, Jiangxi, Hunan, and Heilongjiang Provinces 1,814 people were infected, and 1,666 of them died.[33] As for the total number of Chinese deaths due to Japanese BW, one estimate by a Chinese scholar is that "...during Japan's invasion of China Biological Warfare activities were carried out in more than twenty provinces and cities, causing more than 200,000 casualties among the Chinese people."[34] As the Chinese public and delivery health systems largely disintegrated during World War II, it is probable that little or no plague vaccine or sulfa drugs were available to the Chinese population, so the casualty rate might even have been higher than estimated by Liu Huaqui. While a large proportion of the Chinese population suffered greatly under Japan's barbarous occupation, it is clear, however, that Japan's usage of its biological weapons brought no advantageous military effects on the outcome of its aggressions in China and elsewhere.

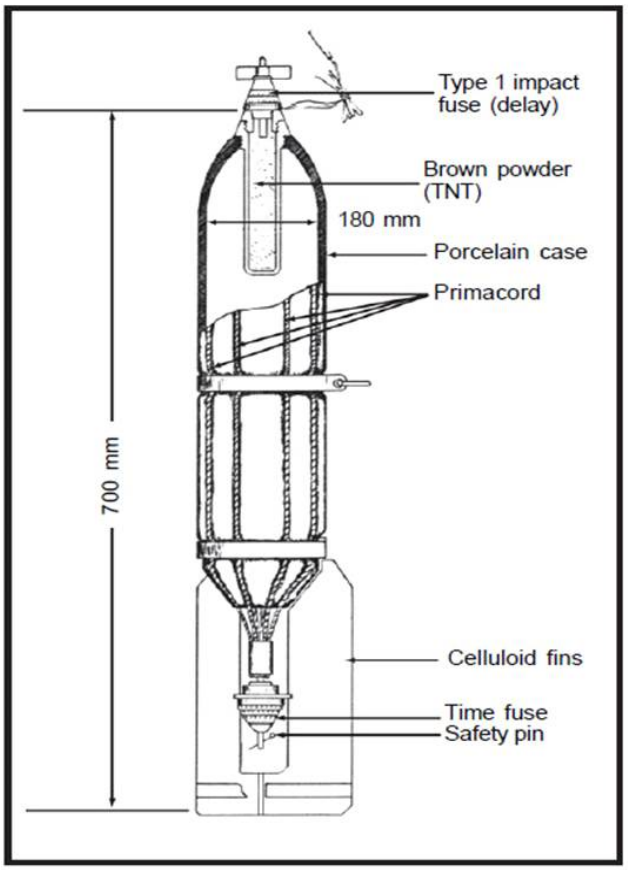

Figure 1: Type 50 Uji Bomb[35]

The United States' Biological Warfare Program

The U.S. started its BW program in 1942, following the precedent set by the United Kingdom (U.K.) and Canada. The reason why these countries did so was that their intelligence agencies had incorrectly concluded that Germany had an operational BW program,[36] so they had to defend against its weapons and develop their own biological weapons so they would be ready to retaliate

in kind. It is ironic that the intelligence agency at the time perceived what did not exist, but they failed to uncover what did exist, namely the Japanese BW program. There certainly were intimations that Japan possessed biological weapons. For example, U.K. intelligence received information from John B. Grant, who at that time was working at the All-India Institute of Hygiene and Public Health, Calcutta, that in December 1941 Japan had used bacteria "...during the Changteh incident in December 1941," the U.K. War Cabinet concluded "...that the allegations were propaganda and were not supported by the technical evidence supplied."[37] A different source appears to have supported Grant's observation. A dispatch issued by U.S. military intelligence reported that "...the Chinese military spokesman, Chungking, was accusing the Japanese of starting germ warfare. He said that on November 4th Japanese planes dropped food and clothing at Changteh, Hunan Province, and that persons who made use of these were taken ill and died with symptoms similar to those of bubonic plague."[38] In the event, the U.S. government decided that information provided by the Chinese was propaganda and therefore should not be taken seriously. So it was that the U.S. and U.K. only learned about the Japanese BW program after its defeat in August 1945.

According to Rosebury and Kabat, after World War II ended, the U.S. BW program conducted a study as to which pathogens should be considered as possible BW agents.[39] Eventually 39 agents were chosen for screening and out of these, *B. anthracis* and *Y. pestis* were given highest priority for weaponization as lethal agents. This is probably the reason why *Y. pestis* was studied intensively within the U.S. BW program and by scientists in other government laboratories as well as academic laboratories. One such project had already started in July 1946 at the UCB, which was funded by the Office of Naval Research. The principal investigator was Albert P. Krueger. Krueger's team studied not only *Y. pestis*, but other pathogens that caused respiratory diseases such as *Mycobacterium tuberculosis*, *Diplococcus pneumoniae*, and *Corynebacterium diphtheria*.[40] Example of studies conducted by the Krueger team were behavior of *Y. pestis* in an airborne cloud, nutritional studies of *Y. pestis*, virulence and viability of *Y. pestis* during prolonged incubation in liquid culture, and the mutation of *Y. pestis* induced by camphor. After Krueger retired in 1957, the project was moved to the UCB School of Public Health where it remained until it was terminated in 1975. All the R&D conducted at the UCB was for defensive purposes.

Sometime during the 1950s, the decision was made by the U.S. BW program to give highest priority to weaponizing *B. anthracis* while *Y. pestis* was given a much lower priority. There seemed to have been four reasons for this decision, and these are spelled out in two reports published in 1952 and 1953 that once were classified but were declassified many years ago:

1. The first testing of *Y. pestis* strains using monkeys had indicated that the LD_{50} was approximately 3,000. However, subsequent testing indicated that the LD_{50} was actually 20,000 – 50,000, or even higher. This meant that *Y. pestis* was much less virulent than other bacterial pathogens such as *B. anthracis*.[41]

2. Substantial laboratory data evidenced that *Y. pestis* stored in wet solution had poor storage characteristics in this form.[42]

3. Laboratory data indicated that *Y. pestis* had been lyophilized and stored successfully, however data was conflicting

as to virulence yields. In some cases, a marked drop in virulence was observed after lyophilization and storage. Data from other tests indicated that *Y. pestis* strains could be lyophilized and stored with little loss in viability and virulence. Due to this conflicting data, more investigations were required to solve this issue.[43]

4. Open air testing done at the Dugway Proving Ground during March 1952 had as its objective to determine the characteristics of the *Y. pestis* A-1122 strain under field conditions. The result was that "low viable counts obtained under the conditions of these tests seem to indicate that this organism loses viability rapidly."[44]

There might have been other reasons than the foregoing four reasons why *Y. pestis* was never weaponized by the U.S. BW program, but the facts speak for themselves; i.e., by the time that President Richard Nixon closed down the BW program, it had weaponized seven agents for use against humans (see Table 2), but *Y. pestis* was not one of them. (The U.S. also weaponized three agents for use against crops – rice blast, rye stem rust, and wheat stem rust).[45]

In view of the U.S. not having weaponized *Y. pestis*, it is worthwhile to review the allegation that has been made by the Chinese and North Korean governments of the U.S. forces having used biological weapons during the Korean War.[46] The report of the so-called International Scientific Commission is filled with allegations of the American having waged BW during the Korean War, of which one example is presented here:

> Since the beginning of 1952, numerous isolated foci of plague have appeared in North Korea, always associated with the sudden appearance of fleas and with the previous passage of American planes. Seven of these incidents, the earliest dating from 11th Feb., were reported in SIA/1, and in six of them the presence of the plague bacteria in the fleas was demonstrated. Document SIA/4 added the statement that after a delivery of fleas to the neighborhood of Au Ju on the 18th Feb., fleas which were shown bacteriologically to contain Pasteurella pestis, a plague epidemic broke out at Bal-Nam-Ri in that district on the 25th. Out of a population of 600 in the village, 50 went down with plague and 36 died.[47]

Although little-remembered now, these charges produced enormous political repercussions at the time, with extensive debate in the United Nations in New York and international protests against the alleged U.S. use. A typical comment by *Pravda* in 1952 was that, "These bandits in generals' uniforms, the butchers in white gloves, the bloody bigots and traders in death who have unleashed the most inhuman carnage in history, warfare with the assistance of microbes, fleas, lice and spiders."[48]

In January 1998, a historian researching the archives of the Central Committee of the Communist Party of the Soviet Union (CPSU) discovered 12 documents containing detailed and authoritative evidence that the Korean War BW allegation was contrived and fraudulent.[49] One document dates from February 21, 1952, and the others from the period of April 13 to June 2, 1953. They describe the way in which the allegations were contrived by North Korean and Chinese officials and Soviet advisers, and include direct communications between the Central Committee of the CPSU to the Chinese and North Korean leaders, Mao Tse-tung and Kim Il-sung, and replies by the latter. For example, one document, from May 1953, opens with the following lines: "For Mao Zedong: The USSR Government and the Central Committee of the CPSU were misled.

The spread in the press of information about the use by the Americans of bacteriological weapons in Korea was based on false information. The accusations against the Americans were fictitious."[50]

More recently, a former Director of the Chinese People's Volunteers' Army Health Division, Wu Zhili, who was directly involved in public health issues during the Korean War had his account of the allegation published. Wu wrote his article in 1997, but it was not discovered until 2005. Furthermore, it was not published until November 2013, when the Chinese journal ***Yan-Huang Chun Qiu/Yan-Huang Historical Review*** did so. It is not possible to here reprint Wu's rather lengthy article, suffice it to state his conclusion:

> This has been my silent regret for decades. There has been no other. I only feel sorry for the international scientists who signed their names. Perhaps I am too naïve, because it is possible they knew the truth but obeyed the requirements of the political struggle. If it was like this then fine, but if not then they were deceived by me. I had unceasingly expressed my apology for them to Huang Kecheng [Chief of Staff in 1952]. Huang said, "You don't need to feel this way, this was political struggle! Furthermore, you have expressed your views on bacteriological warfare from the beginning. It was not an easy situation, and you were given responsibility too late."
>
> I think there will be a day in history to speak clearly about this incidence. Now that I am an 83-years old man who knows the facts and is no longer on duty, it is fitting to speak out: the bacteriological war of 1952 was a false alarm.[51]

In view of the evidence provided here that the U.S. never weaponized *Y. pestis*, the information from the USSR archives that indicates that the USSR ambassador to Peking in 1952 knew that the allegation of the U.S. having waged BW in Korea was false and, most important, by Wu Zhili's thorough account of what really occurred in Korea, which was not BW, but to restate Wu's conclusion, "the bacteriological war of 1952 was a false alarm."

To finish this section, the U.K. and Canada closed down their offensive BW program during the 1950s, but retain substantial defensive capabilities to this day. The U.S. continued its offensive BW program until November 25, 1969 when President Richard Nixon terminated it by executive order.[52] Like the British and Canadians, the U.S. maintains a strong, encompassing defensive BW program to this day.

Weaponization of *Yersinia pestis* by the USSR

The most complete history of the USSR's huge BW program and its implications for today's Russia has been told by Milton Leitenberg and Raymond A. Zilinskas.[53] They explained how this program had two generations with the first spanning 1928-1971 and the second 1972-1992. This article contains an abridged history of this program, with an emphasis on the weaponization of *Y. pestis*.

USSR's First Generation BW Program

In 1925, the director of the USSR Military Chemical Agency, Dr. Yakov Fishman, set up a small BW laboratory in Moscow, eventually to be called the Scientific Research Institute of Health, and appointed Nikolay N. Ginsburg to be its head. In 1928 Fishman submitted a laboratory progress report to Commissar for Defense Kliment Y. Voroshilov that had four parts:[54] (1) a

description of Ginsburg's investigations that demonstrated the feasibility of BW; (2) an assessment of the potential uses of bacteria for purposes of warfare and sabotage; (3) a plan for the organization of military biology and (4) a second plan for organizing defenses against biological attacks. The second part included a description of how a team led by Ginsburg was attempting to increase the virulence and stability of *B. anthracis*, a pathogen they found well suited for purposes of BW since it is both virulent and hardy. The Ginsburg team also investigated the BW potential of *Vibrio cholerae* and *Y. pestis*. Unlike the Japanese BW program which utilized two forms for dispersing *Y. pestis*, by vectors and by aerosols, Soviet military scientists weaponized *Y. pestis* for aerosol dispersal only.

Fishman's report appears to have motivated the Revolutionary Military Council to issue a secret decree in 1928 that ordered the establishment of an offensive BW program.[55] Thus, the USSR's first generation BW program commenced. As a result of the decree's implementation, the USSR came to possess a large BW program before World War II. German intelligence learned from Soviet prisoners of war that this program was conducted in three institutes in the Moscow-region, including Ginsburg's Institute (renamed the Worker's and Peasant's Red Army [RKKA] Biotechnology Institute), four institutes in the Leningrad region, and an open air test site on Vozrozhdeniye Island in the Aral Sea.[56]

As noted above, in 1945 the Red Army captured 12 Unit 731 servicemen and learned a great deal from them about Japanese program. A Soviet BW scientist interviewed by one of the authors recalled some of what was learned:

> Information from the Japanese was used for both BW purposes and for defense. The Japanese reports were meticulously written and had complete information on their experiments involving many pathogens. We particularly found information on plague [bacteria] of interest because they had tested many strains for virulence not only on animals, but also humans. They also conducted experiments using different doses of agents. We [the Soviet Army] never tested on humans. So the Japanese data gave us information on strains that were virulent not only in animal models, but also in humans. So we could compare our strains with theirs and use those that were most virulent in humans for BW. At that time the level of microbiology was not so high, and scientists could not secure highly virulent genetically modified strains. So we worked with what we had from nature. For defense, we used their information on the immunological responses by humans to pathogens in developing vaccines and therapeutics. Moreover, the Japanese had good data on how organisms responded to formulations existing at that time.[57]

The USSR's first generation BW program can be characterized as having assessed known pathogens for the weapons potential and employed the three classical applied microbiology techniques – mutation, selection, and propagation – to weaponize the most promising candidates. By the time the first generation program merged into the second generation program, its scientists had weaponized five bacterial pathogens; *B. anthracis, Burkholderia mallei*, *Coxiella burnetii*, *Francisella tularensis*, and *Y. pestis,* as well as the Venezuelan Equine Encephalitis virus (VEEV), variola virus, and botulinum neurotoxin.

A team at the USSR Ministry of Defense (MOD) Scientific Research Institute of

Epidemiology and Hygiene at Kirov led by V. A. Lebedinsky and Yu.V. Chicherin focused on weaponizing *Y. pestis* in the 1960s. The main objective of this work was to develop an especially virulent *Y. pestis* strain that was resistant to the existing EV vaccine. The USSR BW program did have a *Y. pestis* strain validated for BW, and it is probable that the Lebedinsky-Chicherin team was its developer.[58]

In a related project, the same team in Kirov reportedly developed *Y. pestis* simulants based on strains of *Yersinia pseudotuberculosis* and *Yersinia enterocolitica*. Although strains of these zoonotic pathogens can cause low-order gastrointestinal disease in humans, other strains are non-pathogenic and thus could safely be used as simulants in open-air field tests.

USSR's Second Generation BW Program

In 1971, the Central Committee of the Communist Party (CCCP) and the USSR Council of Ministers issued a decree, stamped "of special importance," that laid the foundation for the organization of a new system to acquire modern biological weapons.[59] The decree formally marked the beginning of USSR's "modern," second generation BW program. Soon thereafter, the MOD's Decree No. 99 established the 15th Directorate to direct the USSR's BW program and appointed Colonel General Yefim I. Smirnov as its head.[60] Further, the Politburo ordered the establishment of an entirely new organization named Biopreparat dedicated to BW that was comprised of five major institutes, as well as an unknown number of production plants and storage facilities. Although an ostensibly civilian organization, it received its orders from the 15th Directorate. Biopreparat's main responsibility was to manage a large program codenamed "*Ferment*" (which translates to "Enzyme") whose objective was "…to develop a second generation of biological weapons using genetically modified strains, which would be of greater military value than existing natural strains. It planned to introduce new properties into diseases organisms, such as antibiotic resistance, altered antigen structure, and enhanced stability in the aerosol form, making delivery of the agent easier and more effective."[61] Further, a new and highly secret Interdepartmental Scientific-Technical Council on Molecular Biology and Genetics,[62] whose cover designation was P.O. Box A-3092,[63] was established to provide scientific direction to *Ferment*, and the highly regarded virologist and academician Victor M. Zhdanov was appointed its chairman.[64] In addition to *Ferment*, the USSR Ministry of Agriculture was ordered to operate a program codenamed *Ekology*, whose objective was to weaponize bacteria, fungi, and viruses for use against agriculturally important animals and crops.

Ferment initially focused on traditional agents, such as *B. anthracis*, *B. mallei*, *F. tularensis*, *Y. pestis*, variola virus, and VEEV, but within a few years its scientists also investigated filoviruses (especially Ebola and Marburg viruses), Junin virus, and Machupo virus.[65] Alongside its offensively directed R&D, Biopreparat Institutes performed defensively directed R&D under a program codenamed Problem 5 whose lead agency was the N.F. Gamaleya Institute of Epidemiology and Microbiology, but Problem 5's R&D was mostly performed by six institutes that comprised USSR's anti-plague system. Its major objective was to develop vaccines and treatments for the pathogens that *Ferment* weaponized and foreign threat agents discovered by Soviet intelligence. Two reports written by

researchers at the James Martin Center for Nonproliferation Studies contain the history and organization of the anti-plague system, including Problem 5.[66]

The USSR's BW program reached its apex in the late 1980s when it had four components. The first component was constituted by three military R&D institutes and an open air test site. The second was Biopreparat, which had five major research institutes and about 35 supporting facilities. The third was the Ministry of Agriculture with six research institutes and an unknown number of supporting facilities. And the fourth was Problem 5 as describe above. The BW program's civilian institutions are listed in Table 1. At that time, an estimated 60,000 persons operated USSR's BW program.

The R&D involving *Y. pestis* was mainly conducted at the MOD's Scientific Research Institute of Epidemiology and Hygiene at Kirov and Biopreparat's State Research Center for Applied Microbiology (SRCAM) located at a secret city called Obolensk. Since there have been no defectors from any of the three MOD's biological institutes, little is known about the BW-related R&D that was conducted within their walls. Conversely, many scientists who once worked for Biopreparat have either defected or, after the USSR dissolved in December 1991, succeeded in relocating to countries such as Israel, United Kingdom, United States, and elsewhere. Accordingly, there is a considerable amount of information about the R&D conducted by Biopreparat institutes.

The first two R&D objectives for SRCAM was for its scientists to (1) eliminate epitopes on the surface of classic BW agents so as to make them unrecognizable to the diagnostic techniques and vaccines possessed by Western countries,[67] and (2) to develop strains of *B. anthracis*, *B. mallei*, *B. pseudomallei*, and *Y. pestis* that were resistant to ten antibiotics.[68]

In 1982, SRCAM scientists V.M. Krasilnikova, A.V. Karlyshev, and P.A. Cherepanov started to investigate the *Y. pestis* F1 antigen and, eventually, they were able to express F1 in *E. coli*.[69] One of outcomes of molecular cloning of *caf1* operon was a development of original method for generation of a so-called "F1 minus" strain of *Y. pestis*.[70,71] The reason for doing so was that in Western countries, standard serological tests have been used for many years to detect antibodies to the F1 protein and these tests are the basis for the surveillance and diagnosis of plague in infected humans and animals. By using a F1 minus strain of *Y. pestis* in their biological weapons, the Soviets would have made it more difficult for the attacked population to identify the causative pathogen of the resulting disease outbreak and begin timely treatment. A F1 minus strain of *Y. pestis* was indeed created, but it was taken over by MOD so its fate as a BW pathogen is unknown.

The first multiple antibiotic resistant strain of *B. anthracis* was successfully created in 1986. During 1987-1988, multiresistant antibiotic strains of *F. tularensis*, *B. mallei*, and *B. pseudomallei* were also created. The research that aimed to develop a multiresistant antibiotic strains of *Y. pestis* initially produced some promising results, but by the time the USSR's BW program was terminated in 1992, this line of research proved to be unsuccessful. It bears stressing that although multiresistant antibiotic bacterial strains were created, they were not tested in the open air at Aralsk 7, so their degree of efficiency as BW agents is not known.

A third approach involving *Y. pestis* was taken by I.V. Domaradsky. He had the idea

of transferring the gene that codes for diphtheria toxin into a militarily useful bacterium. This toxin, which is produced by the bacterial pathogen *Corynebacterium diphtheriae*, had the dual benefit of having a relatively simple chemical structure and being exceedingly toxic.[72] Within a fairly short time, he was able to clone the diphtheria toxin gene and transfer it into *Y. pseudotuberculosis*.[73] This was a substantial accomplishment since at that time *Y. pseudotuberculosis* was more difficult to engineer than *E. coli*. Domaradsky then wanted to undertake the same manipulation using *Y. pestis* as the recipient host for the cloned gene. He was not able to finish this work for unknown reasons, but according to another SRCAM scientist, in 1990 the diphtheria toxin gene was transferred into *Y. pestis.*[74] SRCAM scientists K.I. Volkovoy and P.A. Cherepanov reported that this construct proved to be highly virulent and immunosuppressive in monkeys.

The USSR relied on two mainstay biological weapons: a cluster submunition called the Gshch-304 (*ÃÙ*-304), and a spray system.[75] Both were open air tested at Aralsk-7 with payloads that included *Y. pestis*. [76]

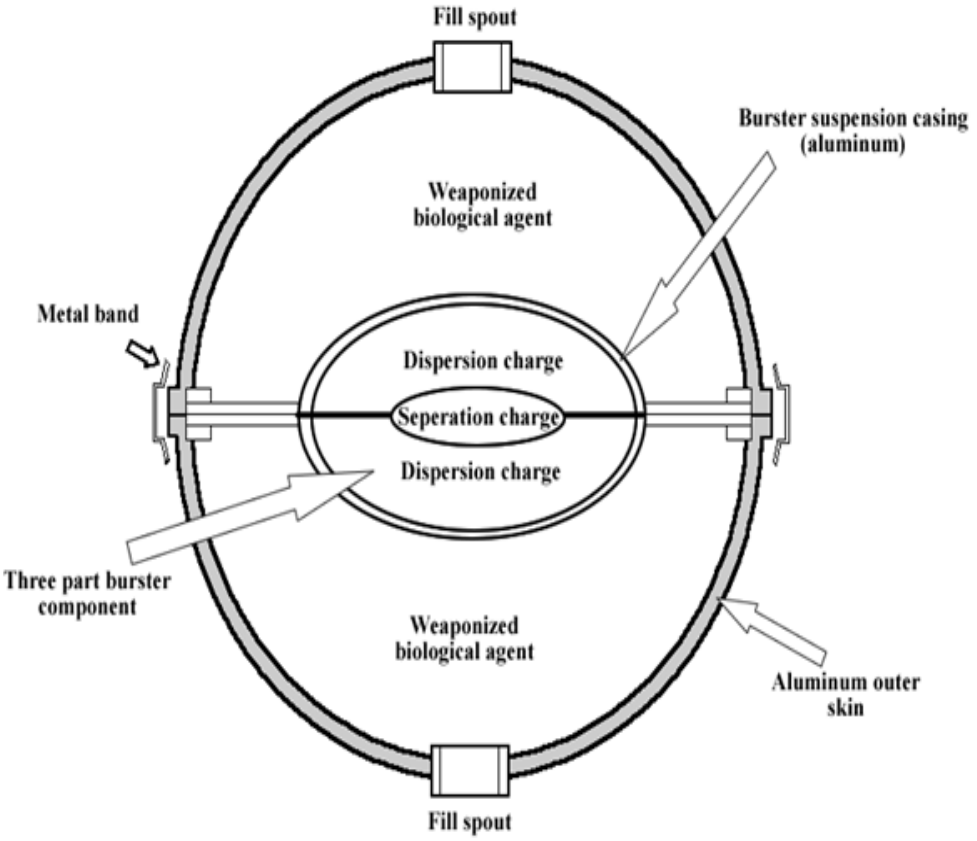

Figure 2. Gshch-304 (*ÃÙ*-304) Bomblet

(6-8 vanes are not pictured)[77]

After the USSR dissolved in December 1991, the new Russian President Boris Yeltsin eventually came to terms with the knowledge that the USSR had operated an offensive BW program in violation of the BWC.[78] In response, on April 11, 1992, he issued Edict No. 390, "On Ensuring the Implementation of International Obligations Regarding Biological Weapons," which ordered that the USSR's BW programs be shut down.[79] At approximately the same time, Yeltsin promulgated a decree that led to a 50% reduction in the staffing levels at the MOD and Biopreparat Institutes and a 30% cut in their funding. In actual practice an even more severe downsizing occurred, with individual institutes undergoing personnel decreases ranging from 50% to over 90%.

On the international level, in accordance with the confidence building measures agreed on by BWC state parties in 1986,[80] the Yeltsin government submitted Russia's confidence building Form F, which is a declaration on past activities in offensive and defensive biological research and development programs. The Form F submitted by Russia briefly described USSR's and Russia's offensive and defensive BW-related efforts from 1946 to March 1992 and identified some of the research institutions that been part of those efforts. It asserted that the USSR began dismantling its offensive facilities in 1986, which was also when Biopreparat was transferred from the MOD to the Ministry of Medical and Microbiological Industries. By April 1992, Aralsk 7 on Vozrozhdeniye Island had been dismantled and its infrastructure had been largely demolished. However, while the second was true, it was not so the first; i.e., the Soviet BW program continued as before until 1992, at which time it shrunk because of the lack of funding noted above.

Finally, it bears noting that despite all evidence to the contrary, the Putin administration has asserted several times that the USSR never had an offensive BW program, claiming that it only operated a defensive program to protect against possible BW attacks. Even more disturbing was that shortly after having taken the oath of president for the second time, Putin forecasted: "What is the future preparing for us? ... In the more distant future, weapon systems based on new principles (beam, geophysical, wave, genetic, psychophysical and other technology) will be developed. All this will, in addition to nuclear weapons, provide entirely new instruments for achieving political and strategic goals. Such high-tech weapon systems will be comparable in effect to nuclear weapons but will be more "acceptable" in terms of political and military ideology."[81]

Table 1: Known Components of USSR's Civilian BW System Circa 1986

R&D Institutes
All-Union Research Institute for Applied Microbiology (SRCAM) in Obolensk
All-Union Research Institute of Molecular Biology (Vector) in Koltsovo
All-Union Scientific Research Foot and Mouth Disease Institute, Vladimir
All-Union Scientific Research Institute of Veterinary Virology and Microbiology, Pokrov
Institute of Engineering Immunology (IEI), Lyubuchany
Research and development facility of unknown name, Vladimir
Research Institute of Highly Pure Biopreparations (IHPB) in Leningrad
Scientific Institute of Phytopathology, Golitsyno
Scientific Institute of Phytopathology, Tashkent, Uzbekistan SSR
Scientific Research Agricultural Institute, Otar, Kazakhstan

Production and Mobilization Plants

Berdsk Chemical Factory, Berdsk

Biokombinat, Georgia (anti-animal agents?)

Biosintez Combine, Penza

JSC "*Sakagrobiomretsvi*" (*Biokombinat*), Tabakhmela, Georgian SSR

Omutninsk Chemical Factory, Omutninsk

Production Facility "Biokombinat," Alma Ata, Kazakhstan SSR

Production plant of unknown name, Pokrov

"Progress" Plant, Stepnogorsk

Scientific and Production Base, Omutninsk

Scientific and Production Base of the Siberian Branch of the Institute of Applied Biochemistry, Berdsk

Scientific Experimental and Production Base (SNOPB), Stepnogorsk

Scientific-Research Technological Institute of Biologically Active Substances (IBAS), Berdsk

Sintez Combine, Kurgan

Special Weapons and Facility Design Units

All-Union Institute for Biological Instrument Development (*Biopribor*), Moscow

Institute of Applied Biochemistry, Moscow

Institute for Biochemical Technological Development (*Biokhimmash*), Moscow

Scientific-Research Technological Design Institute of Biologically Active Substances (IBAS), Berdsk

Special Design Bureau of Controlling Instruments and Automation, Yoshkar-Ola

Special Design Bureau for Precision Machinery Building, Kirishi

State Institute for the Design of Enterprises of the Biological Industry (*Giprobioprom*), Moscow

Unknown name, Posyolok Volginsky (or Poselok Volginsky)

Antiplague Institutes[82]

Central Asian Scientific Research Anti-Plague Institute, Alma Ata

Stavropol Research Anti-Plague Institute, Stavropol

Anti-Plague Research Institute for Siberia and the Far East, Irkutsk

Rostov Research Anti-Plague Institute, Rostov-on-Don

Volgograd Research Anti-Plague Institute, Volgograd

Russian Research Anti-Plague Institute "Microbe", Saratov

Table 2: Lists of Anti-personnel Agents Validated for Biological Weapons by U.S. and USSR

U.S.	USSR
Bacteria	
Bacillus anthracis	*Bacillus anthracis*
Brucella suis	*Brucella* species
Coxiella burnetii	Coxiella burnetii
Francisella (Pasteurella) tularensis	*Francisella tularensis*
	Pseudomonas mallei
	Pseudomonas pseudomallei (?)
	Yersinia pestis
Viruses	
	Marburg virus
Venezuelan Equine Encephalomyelitis virus	Venezuelan Equine
	Encephalomyelitis virus
	Variola virus
Toxins	
Botulinum neurotoxin	Botulinum neurotoxin
Staphylococcal enterotoxin B	Staphylococcal enterotoxin B

Yersinia pestis as a Current Threat Agent

In 2014, the World Health Organization (WHO) reported that in 2013 there were 783 plague cases worldwide, including 126 deaths.[83] Most plague cases occurred in three countries – the Democratic Republic of Congo, Madagascar, and Peru. The low number of plague cases, and their far-off sites, clearly demonstrate that in our time plague has largely disappeared as a major public health threat. Yet, the U.S. Centers for Disease Control and Prevention (CDC) has designated *Y. pestis*, along with four other pathogens and one toxin,[84] as a highly dangerous Category A threat agent. Why is this so?

According to the CDC, all Category A agents possess certain characteristics that add up to them being perceived as posing significant risks to national security. These characteristics are:

- They can be easily disseminated or transmitted from person to person;
- The diseases they cause result in high mortality rates and have the potential for major public health impact;
- Their appearance in a community might cause public panic and social disruption; and
- Their prevention requires special action for public health preparedness.[85]

I maintain that beside the four common characteristics, there is another compelling reason why *Y. pestis* in particular is a dangerous threat agent and that is because two nations have weaponized it in the not too distant past. In other words, Japan and the USSR spent much effort and money to develop *Y. pestis* for the purpose of using it as payload in its biological weapons. They would not have done so unless their military scientists were convinced that biological weapons armed with *Y. pestis* would have been useful to their militaries.

The Potential of *Y. pestis* for Bioterrorism

Y. pestis is a zoonotic pathogen that is widely distributed in natural plague foci in Asia, Africa, western North America, and Eurasia. In the natural plague foci, there are more than 80 reservoirs with different kind of fleas as potential vectors and *Y. pestis* has at time been transmitted between reservoirs by infected fleas biting mammals. In many plague foci, it is not difficult for trained field workers to capture rodents that carry fleas infected with *Y. pestis*. Using standardized techniques still practiced today, a trained microbiologist can subsequently culture and isolate *Y. pestis*. In view of the many natural plague foci spread throughout the world, it is theoretically possible for terrorists to acquire *Y. pestis* from natural sources.

Nature is not the only source for *Y. pestis*; ill willed persons could steal cultures from laboratories and culture collections. In this regard, possibly the most substantial threat is posed by yet another component of the former USSR's BW program; namely, the anti-plague system. Its work, which was mostly defensive in nature, was cloaked in secrecy because the USSR considered information about endemic infectious disease to be state secrets. Actually, the anti-plague system had responsibilities that ranged beyond BW defense, including protecting the country from endemic and imported dread diseases such as plague, anthrax, tularemia, and Crimean-Congo hemorrhagic fever. As such, its researchers were among the few in the USSR that were permitted to work directly with the most dangerous bacterial and viral pathogens, strains which were stored in in-house culture collection.

After the USSR dissolved in December 1991, this system fragmented, with one anti-plague institute and many stations located outside Russia becoming part of the health systems of the newly independent nations. The main problem that attended this development was that Russia stopped funding most of these now foreign anti-plague facilities and their new home governments have not taken up the financial slack. One of the results of lack of funding is that the physical security that once protected facilities and culture collections deteriorated to near uselessness. For the newly independent nations (except Russia), a program initiated by the U.S. called the Cooperative Threat Reduction program has provided sufficient assistance required to safeguard the premises of anti-plague institutes and stations, including their culture collections.[86] Nevertheless, the possibilities exists that outsiders could break into anti-plague facilities and steal cultures of pathogens and use them as a basis for BW programs by terrorist groups. Alternatively, corrupt insiders could be paid by criminals to steal cultures from laboratories or cell culture collections. The proliferation issues posed by the anti-plague system as it now exists in many countries has been reported by CNS researchers.[87]

However, even if pathogens are acquired by terrorists or proliferant nations, it does not mean that the new owners possess a biological weapon. The information about weaponization of *Y. pestis* that emanated from Japan, USSR, and the U.S. indicates that this process is a difficult one, mainly because this pathogen is fragile and therefore has to be formulated; i.e., certain chemicals are added to the bacterial cells that serve to protect them from desiccation and other stresses in order to be effectively disseminated onto targeted populations. The Japanese found that formulations used for a *Y. pestis* aerosol did not work well. As a result, their preferred biological weapon was the Uji bomb carrying fleas infected with *Y. pestis*. I suspect that no terrorist group would have neither the expertise nor the will to deal with the problem of breeding and packaging the thousands of fleas required to disseminate *Y. pestis*.

As for the U.S., its BW program gave up on weaponizing *Y. pestis* and instead chose to weaponize bacterial pathogens that are easier to handle, are more lethal, and survive better as components of aerosols.

Soviet military scientists spent years to develop a formulation that protected the *Y. pestis* cells so instead of the half-life of unprotected cells being a few minutes in the open air, the formulated cells would have a half-life of 10-20 minutes depending on temperature and humidity.[88] No terrorist group would possess the expertise in aerobiology that the USSR had, and so even if they tried to produce a *Y. pestis* aerosol, they undoubtedly would fail. In addition, they probably would face substantial problems with biosafety; i.e., protecting their own operators from exposure to this deadly pathogen.

Based on lessons from the Japanese, U.S., and USSR BW programs, I conclude that it is not likely that *Y. pestis* will be used by a terrorist group in the near future to attack a human population. The more likely scenarios are that terrorists will use food-borne or beverage-borne pathogens or toxins to contaminate food items or beverages that are utilized by their targeted populations. Since botulinum neurotoxin can be purchased from Internet sources and because it is comparatively easy to manufacture, it might be the agent of choice for terrorists.[89] Another possibility is that a terrorist group will have learned from Aum Shinrikyo's failed approach to disperse aerosolized quantities of the avirulent Sterne strain of *B. anthracis* over Japanese urban

areas and instead conduct similar attacks but with a virulent *B. anthracis* strain.[90]

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Endnotes:

1 For a long time, the pathogen that causes plague was called *Pasteurella pestis*. In 1944, it was proposed to change this name to *Yersinia pestis*, after its discoverer Alexandre Emile Jean Yersin. The name change became official in 1970. For convenience, in this article only the new name is used. Further, following common scientific convention, I spell out the genera and species of microorganisms the first time they are named, but shorten them thereafter; for example, *Yersinia pestis* is shortened to *Y. pestis*.

2 B.L. Ligon, "Plague: A Review of Its History and Potential as a Biological Weapon," *Seminars in Pediatric Infectious Diseases* 17(3):161-170 (2006).

3 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction, 1972: <http://www.unog.ch/80256EDD006B8954/(httpAssets)/C4048678A93B6934C1257188004848D0/$file/BWC-text-English.pdf>.

4 eaponizing is the process of researching and developing a pathogen or toxin to the point where it becomes suitable for use in a weapons system.

5 Richard P. Strong, ed., *Report of the International Plague Conference Held at Mukden, April, 1911* (Manila, Philippines, 1912).

6 Mark Gamsa, "The Epidemic of Pneumonic Plague in Manchuria 1910-1911," *Past & Present* No. 190:147-183 (February 2006).

7 For a rather complete history of plague vaccine, see: Valentina A. Feodorova and Vladimir L. Motin, "Plague vaccines," in Valentina A. Feodorova and Vladimir L. Motin (eds.), *Vaccines Against Bacterial Biothreat Pathogens*, (Kerala, India: Research Signpost, 2011), pp. 175-233.

8 V.A. Feodorova and M.J. Corbel, "Prospects for New Plague Vaccines," *Expert Reviews of Vaccines* 8:1721–1738 (2009).

9 Haffkine Institute, "Bacteriology," no date: <http://www.haffkineinstitute.org/bacteriology.htm>.

10 Feodorova and Motin, p. 185.

11 B.N. Mishankin and N.V. Lopatina, "Problems and Prospects: Plague Vaccine, Past, Present, and Future" (in Russian), *Biotekhnologiya* No. 4:3-9 (April 1996).

12 George W. Christopher, et al., History of U.S. Military Contributions to the Study of Bacterial Zoonoses," *Military Medicine* 170:April Supplement 2005, p. 40.

13 Rexmond C. Cochrane, *History of the Chemical Warfare Service in World War II (1 July 1940 – 15 August 1945. Biological Warfare Research in the United States, Volume II*, Office of Chief of Chemical Corps, Camp Detrick, November 1947, p. 359. Secret. (Declassified September 18, 1975.)

14 K.F. Meyer, et al., "Plague Immunization. I. Past and Present Trends," *Journal of Infectious Diseases* 129 (Supplement 1):S13-S18 (1974).

15 Epidemiolog.ru, "Plague Vaccine Live Dry (Vaccine Plague), *Catalogue of Vaccines Registered in Russia* (in Russian); http://www.epidemiolog.ru/catalog_vac/?SECTION_ID=&ELEMENT_ID=476.

16 V.A. Lebedinsky, T.G. Abdullin, V.I. Yevstigneev, N.S. Garin, and Ye.P. Lukin, "Contribution Made by the Scientific Research Institute of Microbiology of the USSR Ministry of Defence to Research Into the Problems of Infective Immunology" (in Russian), *Voenno-Meditsinskiy Zhurnal* 8:67-71 (1989).

17 Work to improve the plague vaccine continued after the war. A team led by two military scientists, V.A. Lebedinsky and V.I. Ogarkov, are said to have developed a small-particle aerosol form of the dry EV vaccine that was administered by inhalation and showed marked

advantage over all other vaccines in preventing pulmonary plague (see N. I. Nikolayev, "History of Development of Plague prevention in the USSR" (in Russian), *Zhurnal Mikrobiologii, Epidemiologii i Immunobiologii*, no. 4:110-115 (1979).

[18] NIIEG is the acronym for Scientific Research Institute for Microbiology of the Russian Federation Ministry of Defense in Kirov city, which was the first in the USSR to develop a LWC plague vaccine.

[19] Feodorova and Motin, pp. 187-193.

[20] Jack D. Poland and D.T. Dennis, "Treatment of Plague," in the World Health Organization's *Plague Manual Epidemiology, Distribution, Surveillance and Control*, WHO/CDS/CSR/EDC/99.2, 1999, pp. 55-61; http://www.who.int/csr/resources/publications/plague/whocdscsredc992b.pdf.

[21] Sheldon Harris, *Factories of Death: Japanese Biological Warfare 1932-1945 and the American Cover-up*, (New York: Routledge, 1994).

[22] Peter Williams and David Wallace, *The Japanese Army's Secrets of Secrets*, (London: Hodder & Stoughton, 1989).

[23] A Japanese researcher has made a thorough study of Japanese BW activities in China and thus has identified the major facilities; See Takashi Tsuchiya, "The Imperial Japanese Experiments in China," in Ezekiel J. Emanuel, Christine Grady, et al. (editors), *The Oxford Textbook of Clinical Research Ethics*, Oxford, Oxford University Press, 2008, pp. 31-45.

[24] Union of Soviet Socialist Republics, *Materials on the Trial of Former Servicemen of the Japanese Army Charged With Manufacturing and Employing Bacteriological Weapons*, (Moscow: Foreign Languages Publishing House, 1950).

[25] Ibid, p. 12.

[26] ID_{50} is the number of microorganisms required to infect 50% of exposed individuals.

[27] Herbert H. Fell, *Brief Summary of New Information About Japanese B.W. Activities*, report submitted to Chief of Chemical Corps, HHF/ars/3, June 20, 1947, p. 6. Dugway Proving Ground Technical Library, File No. 005.

[28] Ibid, p. 7.

[29] Ibid.

[30] Arvo T. Thompson, *Report on Japanese Biological Warfare (BW) Activities*, Army Service Forces, Camp Detrick, May 31, 1946, p. 15. Secret. (Declassified September 10, 1970.)

[31] A primacord is a brand of detonating cord that could be used to affect a near instantaneous linear charge.

[32] According to Tsuchiya, the estimate of 3,000 is a gross underestimate since it did not include victims before 1940, nor of victims of experiments conducted by units other than 741 (Tsuchiya, 2008, p. 33).

[33] Anonymous, *History of Plague Epidemics in China,* Institute of Epidemiology and Microbiology, (Peking: Chinese Academy of Preventive Medicine, 1964).

[34] Liu Huaqui (ed.), *Arms Control and Disarmament Book*, (Beijing: National Defense Industry Press, 2000), p. 368.

[35] Thompson, 1946, Supplement 4G.

[36] Biological Section, Experimental Station, Porton, "Bacteriological Warfare: Evidence of the Interest of Other Countries in Bacteriological Warfare," Porton Down, April 14, 1943, Most Secret, (Document Unclassified JCP-1,DPG, no date), pp. 5-7.

[37] Ibid, p. 7.

[38] Sherman Miles, Acting Assistant Chief of Staff, G-2, "Memorandum for the Chief of Staff: Subject: Recent Developments in the Far East," November 27, 1941, Page 1368, section 13; <http://www.ibiblio.org/pha/pha/pt_14/x14-033.html>.

[39] Theodor Rosebury and Elvin A. Kabat, "Bacterial Warfare," *Journal of Immunology* 56:7-96 (1947).

[40] Albert P. Krueger, "Investigations of Factors Involved in the Epidemic Spread Of Respiratory Diseases," University of California, Naval Medical Research Unit No. 1, March 31, 1949. Confidential (Declassified in 1961.)

[41] Arthur L. Olender and Ira Abelow, *Compilation and Evaluation of Pasteurella pestis*, Chemical

Corps Engineering Agency, February 1, 1953, p. 17. Secret (Declassified on June 22, 1961.)

[42] Ibid.

[43] Ibid.

[44] BW Division, *Limited Evaluation of Pasteurella pestis Strain A-1122, DPG 54-51*, Dugway Proving Ground Report 105, October 20, 1952. Secret. (Declassified September 3, 1957.)

[45] Melvin R. Laird, *Memorandum for the President. National Security Decision Memoranda 35 and 44. Tab A: Material to be Destroyed (Biological and Toxin)*, Washington, D.C.: Office of the Secretary of Defense, July 6, 1970. Secret. (Declassified on May 1, 2001.)

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[47] Ibid, p. 26.

[48] "Fury of the People (in Russian), *Pravda*, May 30, 1952, p. 4. *Pravda* was an organ of the Central Committee of the Communist Party of the USSR until 1991.

[49] This record was published in the following sources: Milton Leitenberg, New Russian Evidence on Korean War Biological Warfare Allegations: Background and Analysis," *Cold War International History Project Bulletin*, Issue 11, Winter 1998, pp. 180-200; Milton Leitenberg, "The Korean War Biological Allegations: Additional Information and Disclosures," *Asian Perspectives* 23(3):159-172, (2000).

[50] Milton Leitenberg and Raymond A. Zilinskas, *The Soviet Biological Weapons Program: A History*, (Cambridge: Harvard University Press, 2012), pp. 298-410.

[51] Zhili Wu, "The Bacteriological War of 1952 is a False Alarm" (in Chinese), *Yan Huang Historical Review* (ŽpÄž%fËy) 2013; http://news.ifeng.com/history/zhongguoxiandaishi/detail_2014_01/01/32643206_0.shtml. The translation used here was done by Drew Casey at the Center for the Study of Chinese Military Affairs, Institute for National Strategic Studies, National Defense University; http://www.ndu.edu/inss.

[52] Richard M. Nixon, "Statement by the President," Office of the White House Press Secretary, November 25, 1969.

[53] Leitenberg and Zilinskas, 2012.

[54] Valentin Bojtzov and Erhard Geissler, "Military Biology in the USSR, 1920-45," in *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945*, ed. Erhard Geissler and John E. van Courtland Moon, (New York: Oxford University Press, 1999), pp. 156-157.

[55] Ken Alibek with Stephen Handelman, *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World – Told From Inside by the Man Who Ran It*, (New York: Random House, 1999), p. 33.

[56] Walter Hirsch, *Soviet BW and CW Preparations and Capabilities ("The Hirsch Report")*, (Edgewood, Maryland: United States Army Chemical Warfare Service, 1951).

[57] An anonymous Soviet scientist quoted in Leitenberg and Zilinskas, p. 36.

[58] "Validating" refers to establishing documented evidence that an agent, used within established parameters, will perform effectively, reliably, and reproducibly to meet its pre-determined specifications and attributes.

[59] Leitenberg and Zilinskas, p. 64.

[60] Some scholars refer to it as the 15th Directorate for Biological Protection of the General Staff. It also was known as P.O. Box A-1968. See Gulbarshyn Bozheyeva, Yerlan Kunakbayev, & Dastan Yeleukenov, *Former Soviet Biological Weapons Facilities in Kazakhstan: Past, Present and Future*, CNS Occasional Paper No. 1 (Monterey, California: Center for Nonproliferation Studies, 1999).

[61] Igor V. Domaradskij and Wendy Orent, *Biowarrior: Inside the Soviet/Russian Biological War Machine*, (Amherst, NY: Prometheus Books, 2003), p. 178.

[62] Also translated as the Inter-Agency Scientific and Technical Council (Alibek with Handelman, p. 43).

[63] Domaradskij and Orent, p. 301.

[64] Like other civilian scientists who were to work for Biopreparat, Zhdanov concealed his

important role in the USSR's illegal BW program from foreign colleagues. A WHO executive who worked with him for a long time wrote: "[Zhdanov was] a member of the WHO Executive Board and various WHO panels on infectious diseases. He was a dedicated supporter of efforts to establish a BWC which were often at variance with USSR's official policies. At WHO he strongly encouraged the development of a network of collaborating laboratories for communicable diseases, and the smallpox eradication program." Source: Martin M. Kaplan, "The efforts of WHO and Pugwash to eliminate chemical and biological weapons – a memoir," *Bulletin of the World Health Organization*: 77(2):153 (1999).

[65] Alibek with Handelman, pp. 41-42.

[66] Sonia Ben Ouagrham-Gormley, Alexander Melikishvili, and Raymond A. Zilinskas, "The Soviet Anti-plague System: An Introduction," *Critical Reviews in Microbiology* 32(1):15-14 (2006). Also accessible on the CNS website: http://cns.miis.edu/antiplague/index.htm; Raymond A. Zilinskas, "The Anti-Plague System and the Soviet Biological Warfare Program," *Critical Reviews in Microbiology* 32(1):47-64 (2006); Mahoney, Casey W., James W. Toppin, and Raymond A. Zilinskas, *Stories of the Soviet Anti-Plague System*, Occasional Paper No. 18 (Monterey Institute of International Studies, August 2013); http://cns.miis.edu/opapers/pdfs/130904_soviet_antiplague.pdf.

[67] An epitope is a region on the surface of a bacterium or virus that elicits a protective antibody reaction by the invaded host.

[68] Sergei Popov, personal communication, 2007.

[69] Andrey P. Anisimov, "Molecular-genetic mechanisms of the formation and functional significance of the capsule of *Yersinia pestis*" (in Russian), *Research Gate*, November 1999; https://www.researchgate.net/publication/256288214_Molecular-genetic_mechanisms_of_the_formation_and_functional_significance_of_the_capsule_of_Yersinia_pestis_Molekularno-geneticeskie_mehanizmy_obrazovania_i_funkcionalnaa_znacimost_kapsuly_Yersinia_pe.

[70] I.G. Drozdov, A.P. Anisimov, et al., "Virulent non-capsulate *Yersinia pestis* variants constructed by insertion mutagenesis," *Journal of Medical Microbiology* 42(4): 264-268 (1995).

[71] Each *Y. pestis* cell is surrounded by a capsule that is comprised of the Fraction 1 (F1) protein. F1 is only fully expressed at 37° C, which is the normal human body temperature. Thus, when *Y. pestis* invades the human host and is exposed to its 37° C environment, it mobilizes F1 whose major effect is to protect the pathogen from phagocytosis (ingestion by white blood cells).

[72] D. Michael Gill, "Bacterial Toxins: A Table of Lethal Amounts," *Microbiological Reviews* 46(1):86 (March 1982).

[73] Domaradskij and Orent, 231.

[74] Popov, 2007.

[75] For more complete descriptions of USSR's biological weapons, see Leitenberg and Zilinskas, pp. 298-303.

[76] Venturi effect – as the aircraft moves through air, wind blows over the top of the container thus reducing the air pressure at its top which results in the dry or wet formulations it contains being drawn out. The formulation is then dispersed by the aircraft's slipstream.

[77] Leitenberg and Zilinskas, p. 299.

[78] *Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction*, April 10, 1972; http://www.unog.ch/80256EE600585943/(httpPages)/04FBBDD6315AC720C1257180004B1B2F?OpenDocument.

[79] Viktor Litovkin, "Yeltsin Bans Work on Bacteriological Weapons. This Means: Work was Under Way, and We Were Deceived" (in Russian), *Izvestiya*, April 27, 1992, p. 1.

[80] United Nations Office at Geneva, "The Confidence-building Measures (CBMs)"; http://www.unog.ch/bwc/cbms (accessed April 29, 2015).

[81] Original article in Russian was reprinted by the following source: Vladimir Putin, "Being strong: National security guarantees for Russia," *Rt.com*, February 20, 2012; http://rt.com/politics/official-word/strong-putin-military-russia-711/.

[82] Yu.A. Knirel, V.A. Fedorova, and A.P. Anisimov, "Struggling for Control over the Plague: The Past and Present of the Black Death," *Herald of the Russian Academy of Sciences* 81(1):35-43 (2011).

[83] World Health Organization, “Plague,” Fact sheet No. 267, November 2014; http://www.who.int/mediacentre/factsheets/fs267/en/.

[84] The four pathogens and one toxin are *Bacillus anthracis*, *Francisella tularensis, variola major virus, viral hemorrhagic fever viruses, and botulinum neurotoxin.*

[85] Centers for Disease Control and Prevention, “Bioterrorism Agents/Diseases,” 2000; http://emergency.cdc.gov/agent/agentlist-category.asp.

[86] Joseph P. Harahan, *With Courage and Persistence: Eliminating and Securing Weapons of Mass Destruction with the Nun-Lugar Cooperative Threat Reduction Program*, DTRA History Series, (Washington, D.C., U.S.: Department of Defense, 2014).

[87] Ben Ouagrham-Gormley, Sonia, Alexander Melikishvili, & Raymond A. Zilinskas, “What Non-proliferation Policy for the Soviet Anti-plague System?” *Critical Reviews in Microbiology* 32(1):65-67 (2006).

[88] To learn about the USSR’s weaponization process of *Y. pestis*, see Leitenberg and Zilinskas, pp. 295-298.

[89] Ken Coleman and Raymond A. Zilinskas, “Fake Botox, Real Threat,” *Scientific American* 302(6):84-89 (June 2010); <http://www.scientificamerican.com/article.cfm?id=fake-botox-real-threat>.

[90] Philipp C. Bleek, “Revisiting Aum Shinrikyo: New Insights into the Most Extensive Non-State Biological Weapons Program to Date,” Nuclear Threat Initiative, December 11, 2011; < http://nti.org/3974A >.