

## **The Genetic Engineering of Smallpox**

### **WHO's Retreat from the Eradication of Smallpox Virus and Why it Should be Stopped**

**A BRIEFING PAPER BY THE SUNSHINE PROJECT  
FOR WWW.SMALLPOXBIOSAFETY.ORG**

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*“Some things need be done only once in the entire history of the world. The development of smallpox vaccine and the eradication of smallpox disease are on the list...”*

- William Foege and Walter Dowdle, emeritus directors of the US Centers for Disease Control in an editorial celebrating two decades since the last endemic case of smallpox, Oct. 1997<sup>1</sup>

*“We urge you to consider the threshold at which we all stand and to remember our common humanity.”<sup>2</sup>*

- Appeal of the International Committee of the Red Cross on Biotechnology, Weapons, and Humanity, Sep. 2002.

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The World Health Organization (WHO) is justly proud of the global effort that brought about the eradication of smallpox in 1977; but the truth of the matter is that the job was never finished. The United States and Russia still retain smallpox virus (*Variola major*), an easily transmitted disease and ancient scourge of humanity that is a potent biological warfare agent. Smallpox kills one quarter or more of the people it infects and leaves many who do not die disfigured and blind.

In 1999, the remaining stocks of smallpox virus were slated for imminent destruction. But Russia and the US balked at the World Health Assembly (WHA) resolution calling upon them to destroy the virus. Instead, the US has accelerated smallpox research. Now, it wants to open the Pandora's Box of genetically-engineered smallpox. A US plan to genetically-engineer the virus could be approved by the WHA in May 2005. The plan also includes the expression of smallpox genes in related poxviruses, and unlimited distribution of segments of smallpox DNA up to a certain size. If implemented, this plan would pose serious biosafety risks and open the road to an artificial reconstruction of the virus for biowarfare purposes.

Fewer and fewer people, and their leaders, have personal memories of the horror of smallpox, or even the scars left by vaccination, which had ended in most countries by the late 1970s. As if the world is condemned to repeat history through forgetfulness, WHO has now lost the political will that it once had to finish the job of smallpox eradication. Much of the blame can be laid at the feet of WHO's decision to leave oversight of smallpox research in the hands of an unbalanced and highly politicized “technical” advisory committee that is dominated by a small number of countries and scientists with a personal interest in pursuing smallpox

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<sup>1</sup> Editorial Note by William F Foege, Director Emeritus, CDC and Walter R Dowdle, Deputy Director Emeritus, CDC in MMWR October 24, 1997 / 46(42):990-994

<sup>2</sup> Appeal of the International Committee of the Red Cross on Biotechnology, Weapons and Humanity. September 2002 (online at [www.icrc.org](http://www.icrc.org)).

research. It was US pressure that rammed the proposal for GM smallpox through that committee, and now the World Health Assembly is in the inglorious position of being on the verge of endorsing what may prove to be the undoing of one of WHO's greatest achievements

Civil society and like-minded governments must urgently come together to turn the tide. The creation of genetically engineered smallpox and hybrids of smallpox and other viruses (called chimera) pose serious public health, biosafety, and biological weapons dangers to the entire world. With increased smallpox experimentation, the world stands closer to an accident or deliberate act that would cause a release of the virus.

Because many poxviruses are closely-related and, in their natural state not entirely species-specific, the insertion of smallpox genes into related poxviruses has the potential to create dangerous new human (and animal) pathogens. Through genetic engineering or targeted mutations, labs that receive pieces of the smallpox genome may develop the ability to create smallpox or a novel virus with its characteristics without ever receiving an actual sample of *Variola major*. Moreover, laboratory safety practices and technology cannot erase human error and equipment failures that lead to accidents, as evidenced by a recent string of lab-acquired infections and environmental releases of SARS, Ebola, tularemia, and other dangerous diseases. In fact, the last reported human cases of smallpox were laboratory-acquired (see page 3).

Contained to only two labs in Russia and the US, smallpox has a multilateral research oversight structure that has no parallel with any other disease. Because of the unique situation of smallpox research, if WHO approves these experiments it will not only increase the threat posed by smallpox itself. WHO will also broadcast the signal that genetic engineering of other pathogens, including experiments in which new and more dangerous forms may result – or even be intended are internationally-acceptable.

If endorsed by the WHA, the intergovernmental encouragement of the creation of designer disease will come at a particularly dangerous time. Globally, the number of high containment facilities handling dangerous disease agents is expanding and the hazardous applications of biotechnology are increasing. These trends are reflected in a growing number of lab accidents in a variety of countries in recent years involving highly pathogenic agents in high containment facilities.

Individuals and civil society organizations should take action and voice their opposition to WHO and their national public health authorities, urging them to reject the recommendations of the technical advisory committee and to instead ensure prompt destruction of all remaining virus stocks. This briefing provides a political overview of smallpox eradication, the WHO processes that led to the present state of affairs, and related issues of biosafety and prohibitions on biological weapons.

### The Almost Eradication of Smallpox<sup>3</sup>

*Last Cases:* The last reported human smallpox cases<sup>4</sup> occurred in 1978 at the University of Birmingham in the United Kingdom. A medical photographer who worked above a laboratory where smallpox virus was being studied contracted the disease from a laboratory leak. Before dying, the photographer infected her mother. Although the mother survived, the photographer's father died of a heart attack after visiting his daughter in the hospital. The head of the leaky laboratory came under intense criticism and committed suicide.<sup>5</sup> It was a tragic episode that should humble researchers to this day; but it has been frequently downplayed, even by well-known virologists specializing in the most dangerous diseases.<sup>6</sup>

Smallpox is thought to have killed around 300 million people in the 20<sup>th</sup> Century alone. Into the 1960s, it still killed more than 2 million people every year. Smallpox was defeated by a WHO-led public health surveillance and targeted vaccination program that began in 1967. The final natural outbreak came a year before the tragedy in the UK. It occurred in Somalia's Kurtunwaarey District in October, 1977. Two years earlier, in October 1975, smallpox was eliminated from its last Asian refuge in Bangladesh. The last endemic case in the Americas occurred in Brazil in 1971.

Eliminating natural transmission of smallpox had taken more than 180 years since Edward Jenner scientifically confirmed, in 1796, the traditional knowledge that inoculating humans with the relatively benign cowpox virus conferred immunity to smallpox infection. Later vaccinations relied upon *Vaccinia* virus, another close relative of smallpox virus.

*Smallpox in the Lab:* While smallpox has not occurred in nature for more than 25 years, it hasn't really been eradicated. The causative virus has been contained in laboratories.

At the end of the eradication drive, WHO convened a global commission to certify that the disease was no longer transmitted in nature. In December 1979, WHA adopted the commission's conclusions in Resolution 33.4, which states: "*No more than four WHO collaborating centres should be approved as suitable to hold, and handle, stocks of variola virus*" and that "*other laboratories should be asked to destroy any stocks... or transfer them to an approved WHO collaborating centre.*" In accordance with WHA 33.4, in the late 1970s and early 1980s smallpox samples were eventually transferred to only two labs, one at the US government's Centers for Disease Control (CDC) in Atlanta and the other at the Institute for Viral Preparations in Moscow.

In 1996, Russia alarmed WHO by admitting that - in 1994 - it had unilaterally transferred its collection of smallpox virus from the WHO collaborating centre in Moscow to Vector, a lab near Novosibirsk, Siberia. WHO had no direct control over the move and was forced to accept it as a *fait accompli* with WHA Resolution 49.10. A disturbing fact was that Vector had been a center of the offensive biological weapons program of the Soviet Union. Despite US suspicions that Russia had hidden smallpox virus samples at another facility, the US

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<sup>3</sup> For much of the detail in this section about post-eradication WHO oversight of smallpox, particularly the Technical Advisory Committee on Variola Virus Research, the authors are indebted to Jonathan B. Tucker for providing his unpublished paper "Managing the Dual-Use Dilemma: Lessons from the International Oversight of Smallpox Virus Research" (January 2005).

<sup>4</sup> "Human" because US military researchers have recently developed a technique to infect monkeys by injecting them with large quantities of Variola virus.

<sup>5</sup> A article with detail on the last reported human cases of smallpox can be found here: Pennington, H. "Smallpox Scares" in the *London Review of Books*, 5 September 2002, URL: [http://www.lrb.co.uk/v24/n17/penn01\\_.html](http://www.lrb.co.uk/v24/n17/penn01_.html)

<sup>6</sup> PROMEDMAIL, 29 May 2004 and 6 June 2004, *RFI: Laboratory safety & disease dissemination*, archived online at <http://www.promedmail.org>

government funded live smallpox virus research at Vector from 2000 through 2002; but has since withheld funding, citing proliferation concerns.

Most of the smallpox virus research at CDC is conducted by in-house researchers as well as visiting scientists from the US Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland.

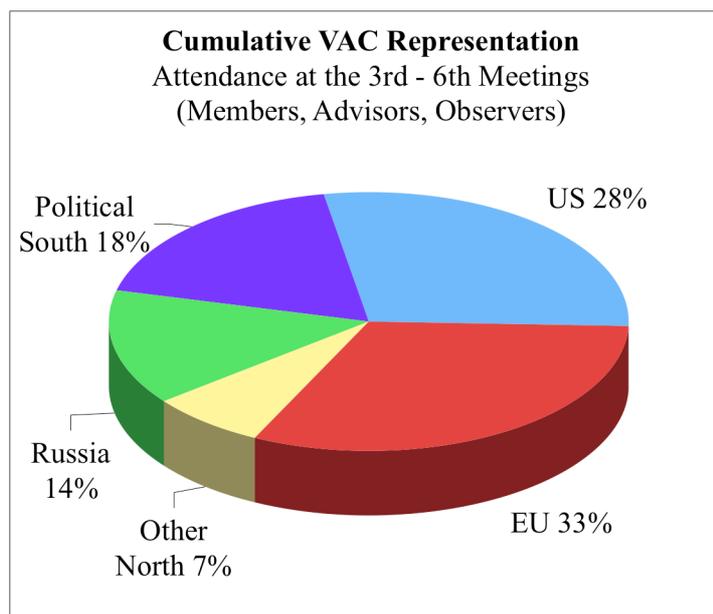
Like Russia's transfer of its smallpox virus collection to Vector, the US has produced its own smallpox surprises. In 2002, it admitted that it holds viruses that are combinations of smallpox virus with animal poxviruses such as rabbitpox and cowpox. The US says that these hybrids were created in the late 1970s in the United Kingdom (and then deposited at CDC). Underscoring the risks of horizontal gene transfer, the hybrids were produced by co-infecting cells with different kinds of poxviruses – prompting the different species to exchange genes and create new types of viruses known as “chimeras”.

Both the Russian Vector and the US CDC submit lists of their smallpox stocks to WHO; but the US did not list the hybrids until 2002, when it started working with them in the CDC lab. WHO quickly called for their immediate destruction; but the US has refused and now says that it wishes to increase experimentation with the hybrid viruses.

*Aborted Destruction and the Variola Advisory Committee:* After declaring smallpox eradicated, WHO established the Committee on Orthopoxvirus Infections to oversee smallpox issues post-eradication. This Committee established guidelines for research with smallpox virus (precluding genetic engineering of the virus) and, in 1994, recommended that all remaining smallpox virus be scheduled for destruction. In 1996 WHA adopted this recommendation and set June 30 1999 as the destruction date. Before June 1999 arrived, the US signaled that it was not prepared to follow through on the decision because its national security demanded more research on defenses against smallpox used as a biological weapon.

Pressured by the US and Russia, in May 1999 the WHA retreated. It agreed to a time-limited “temporary retention” of live smallpox in Resolution 52.10, rescheduling destruction for the end of 2002. Because the Committee on Orthopoxviruses Infections no longer had funding and had been reduced to “Ad Hoc” status, Resolution 52.10 also established a technical advisory committee to oversee smallpox studies in the interim period before the new destruction date. Called the WHO Advisory Committee on Variola Virus Research, or Variola Advisory Committee (VAC), this committee has had a part-time staff and meetings funded by the US since its establishment in 1999.

The VAC has 18 members plus “Advisors to the Committee” and observers. The political North dominates the committee (see chart) and attendance has not even remotely reflected a regional balance. For example, the US and



EU each typically send ten to twelve representatives to a meeting, several times more than the entire representation of major regions such as Asia and Africa. The advisors, in particular, have been overwhelmingly from the North. This imbalance is said to be because WHO cannot find experts in poxviruses in the political South. Since at least the third meeting of the VAC, no advisor has come from anywhere but the US, Russia, or Western Europe.

Some regions have been entirely unrepresented. Since the VAC's third meeting (attendance lists are not available for the first two), no member, advisor, or observer from Southeast Asia, Central America and the Caribbean, the Middle East, or the Pacific has attended a meeting. The entirety of the Americas, excepting Canada and the US, has been represented by a single person.

In addition to its regional bias, the committee – particularly its advisors – is weighted towards scientists with a personal interest in conducting smallpox research. These include a number of US Army, US CDC, and Vector staff who are actively involved in research with the virus and who wish to see restrictions relaxed. This conflict of interest problem has increased over time as fewer of the scientists who participated in the WHO eradication programme and who personally witnessed the devastating effect of smallpox epidemics remain professionally active and able to travel to Geneva for meetings.

The result is a slow substitution of those with real-world experience with smallpox outbreaks (who frequently favor destruction of the virus) with a new generation of researchers whose personal ambitions include smallpox research. Consequently, these researchers frequently have a personal bias towards retaining smallpox stocks and relaxing research restrictions. Over time, the ratio of smallpox “destructionists” to “retentionists” has changed, becoming lopsided in favor of those that, for personal or institutional reasons, would prefer to keep smallpox virus stocks and expand research with the live virus.

The VAC has met six times, beginning in December 1999. By the third VAC meeting (December 2001) the roster of advisors had begun expanding from its initial ten, and a Scientific Subcommittee, which “meets” by electronic mail, had been established to review proposed research projects.

The December 2001 meeting, held in the wake of the US anthrax letter incidents, took critical decisions leading to the situation today. First, the VAC determined that the (mainly) US smallpox research agenda could not be completed by the end of 2002, suggesting that ongoing experiments and planned research would have to be terminated in order to comply with WHA Resolution 52.10. Second, the meeting's report records the first discussion of the US proposal to genetically engineer smallpox. The meeting concluded that a detailed risk analysis was necessary in order for the Scientific Subcommittee of the VAC to consider the proposal.

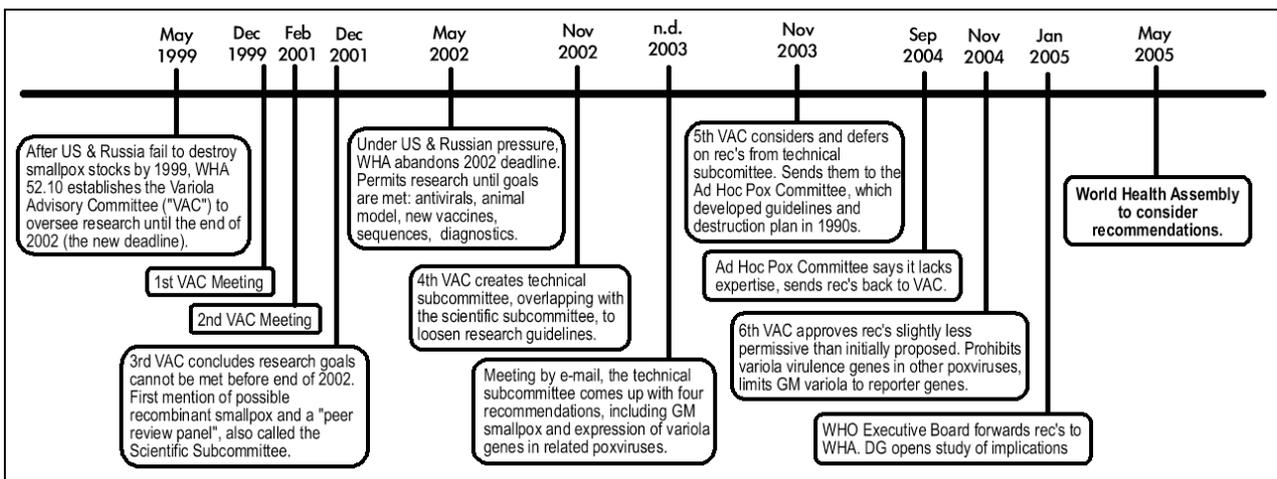
In May 2002, the WHA considered the VAC's report and again yielded on the smallpox destruction deadline. Rather than again postponing the date, this time the WHA took an even larger step backwards and agreed to an indefinite extension of the destruction order, until the US and Russia completed an ambitious research agenda including the development of new antiviral drugs, a new smallpox vaccine, sequencing more strains of smallpox virus, and developing a monkey model of human smallpox infection.

At the fourth VAC meeting in November 2002, the US returned with proposals to genetically engineer smallpox and to insert smallpox genes in other poxviruses. The VAC responded by establishing a new subsidiary body, called the Technical Panel. This panel overlapped by at

least 50% with the Scientific Subcommittee, and its purpose was to modify smallpox research guidelines set up in 1994 that forbade the activities proposed by the US.

Like the Scientific Subcommittee, the Technical Panel (also called the technical subcommittee in some WHO documents) “meets” by e-mail. During 2003, the Technical Panel developed recommendations conducive to the US research proposals, and which allowed inserting smallpox genes into related poxviruses and genetic engineering of smallpox itself. The exact membership of the 2003 Technical Panel is not public. As of late 2004, however, it was comprised of two Americans, two Europeans, one Canadian, and one Russian.

The VAC fleetingly showed an ability to resist US pressure at its fifth meeting in November 2003. Faced with the Technical Panel’s recommendations to substantially relax restrictions on smallpox research, the committee stalled. It deferred on a decision and instead sent them to the Ad Hoc Committee on Orthopoxvirus Infections (called the “Ad Hoc Pox Committee” in the graphic below), the same committee that had developed destruction plans and research guidelines in the early 1990s. But the Orthopoxvirus Committee, meeting in September 2004 for the first time in five years, declined the challenge. Instead, it kicked the ball back to the VAC, saying that it was unable to review the proposed changes to its guidelines because it lacked the appropriate expertise.



Thus, in November 2004, the proposals to allow genetic engineering of smallpox went back to the VAC. The proposals were no longer stalled. The VAC approved the Technical Panel’s recommendations, qualifying them by recommending that the genetic engineering of smallpox be restricted to the insertion of reporter genes and prohibiting the expression of smallpox “virulence” genes in other poxviruses. This meeting set the stage for final approval of the genetic engineering of smallpox virus.

In January 2005, the WHO Executive Board agreed to forward the VAC recommendations to the World Health Assembly; but, because of controversy when the recommendations were made public,<sup>7</sup> the WHO Director General announced that he would also conduct a study of the issue. Little is known about this study, however, it will presumably be tabled prior to the World Health Assembly in May 2005, when a decision will be taken.

<sup>7</sup> US National Public Radio broke the story of the VAC’s recommendations from November 2004 before WHO finalized and released minutes of the meeting. NPR’s story (on 11 November 2004) prompted additional coverage in other media. See: “WHO Allows Smallpox Research”, <http://www.npr.org/templates/story/story.php?storyId=4164567>.

### **Fear Peddlers: Vaccine Salesmen and Maverick Bioterror Researchers**

Every person has reason to be concerned about smallpox and ending the threat that it poses. Some, however, see the threat as an opportunity for gain and fan fears in search of money or attention.

Acambis, a vaccine maker based in Cambridge, UK and Cambridge, Massachusetts, US, quickly implemented a sophisticated marketing campaign after September 11, 2001. Co-opting academic researchers, the company's marketing subsidiary has sponsored international conferences and "preparedness workshops" in Geneva, Athens, Kuala Lumpur, and Mexico City. The conferences play up fears about bioterrorism. The take-home message is that stockpiling large quantities of vaccines is the answer. The company's sponsorship of the conferences is kept very low-key. Acambis secretly sponsored a website, called [smallpoxbiosecurity.org](http://smallpoxbiosecurity.org), that was aimed at convincing government officials to buy batches of smallpox vaccine. It was not until an investigation by non-profit organizations that Acambis acknowledged that it was behind the website.

Meanwhile in Missouri (US), Mark Buller, a St. Louis University researcher previously supported by Acambis grants, assigned himself the task of performing an experiment (with mousepox) that was deliberately designed to demonstrate how smallpox virus might be genetically engineered to make it an even more deadly pathogen. Buller chose to unveil his findings at an Acambis-sponsored conference in Geneva. He explained his actions by saying that they were a contribution to the US biodefense program.

The University of Texas in Galveston, a medical school, promoted its ambition to construct a giant new maximum containment laboratory to study biological warfare agents in a television news segment with the disturbing title "Warriors in Lab Coats". Although the smallpox virus is restricted to CDC (and Vector) by WHA resolution, a University scientist terrorized viewers with dire predictions of the effects of a terrorist attack with smallpox virus. The suggestion was that residents should support the proposed facility in order to protect themselves against smallpox, a dubious assertion indeed.

### **Security Issues: On the Road to Weaponized Smallpox**

The primary US argument for expanding work with live smallpox virus is the fear that it might be used as a weapon. But at the same time, the proposed research projects themselves will add significantly to the risk of smallpox virus being released.

Currently, tightly limited access to smallpox virus reduces the chances of its use as a weapon. There is no evidence that any country other than Russia and the US have maintained stocks of the virus. All claims to the contrary have so far turned out to be untrue. For example, the fear that Iraq may have retained stocks of smallpox virus was raised in early 2003 by the US government. Two years later the CIA reported that it had "*found no evidence that [Iraq] retained any stocks of smallpox or actively conducted research into this agent for BW intentions*".<sup>8</sup> The smallpox fear was misused to support the case for war, but it was not based on fact.

Independent bioweapons experts generally agree that the current risk of a deliberate release of smallpox virus is low because the states or non-state actors with a putative interest in smallpox weapons have most likely have no access to the virus. Any steps that would ease the access to smallpox virus, including expanding the number of individual persons with access and performing research on it, will consequently increase the chances of abuse. Unfortunately, the recommendations of the VAC head in this dangerous direction as they would, if adopted,

<sup>8</sup> Report of the CIA's Iraq Survey Group, September 30, 2004. Online at [http://www.cia.gov/cia/reports/iraq\\_wmd\\_2004/](http://www.cia.gov/cia/reports/iraq_wmd_2004/).

facilitate the creation of the virus in a laboratory, either through synthesis or through the more immediately technically feasible route of targeted mutagenesis of a related virus. Under the VAC's recommended research regime, the number of countries and organizations that would be able to practice all steps necessary for a genetic resuscitation of the virus will greatly increase.

### **A Nuclear Analogy**

If compared to the nuclear field, the current smallpox proposal would amount to allowing unlimited and uncontrolled research and development of nuclear weapons, including uranium enrichment, bomb design and all other steps... short of actually putting the bomb together.

In the same way as Parties to the Nuclear Nonproliferation Treaty are currently discussing restrictions on R&D, e.g. in the field of uranium enrichment, the WHO should prohibit smallpox R&D that may significantly ease the access to this virus. In addition, until the last stocks of smallpox virus are destroyed, all labs working with the virus or parts thereof should be subject to regular WHO inspections to ensure that the safeguards and limits are complied with.

The VAC recommendations would allow any lab in the world to possess up to 20% of the total genome of smallpox, in sequences of up to 500 contiguous base pairs each. The recommendations prohibit only the final step of synthesizing the entire smallpox virus. Synthesizing smaller fragments, splicing them together, and introducing them into related viruses will be permitted.<sup>9</sup>

Under the regime recommended by the VAC, techniques of engineering and mutating related poxviruses could be refined by a potential perpetrator of biological warfare. These methods will enable countries with an interest in smallpox weapons to practice the necessary steps that would enable them to weaponize smallpox virus within a short

time frame. The VAC's recommendations will also make it extremely difficult to detect such programs, as the presence of smallpox DNA, the splicing of smallpox DNA fragments, and the expression of smallpox viral genes or their fragments in other poxviruses in themselves will be permitted.

If the WHA is concerned about the possible hostile use of smallpox virus, it should decide to destroy all remaining smallpox virus stocks and to prohibit any work with smallpox DNA fragments, rather than giving potential proliferators a green light to practice the genetic resuscitation of the virus.

### **Biosafety issues**

The VAC recommendations raise two serious biosafety issues: the accidental escape of smallpox virus during experimental lab work, and the construction of dangerous new viruses through genetic engineering. These are not theoretical or remote scenarios but have been shown in recent years to be much more real than previously imagined.

#### Accidental release

As outlined above, the last reported human smallpox cases in 1978 resulted from an accidental release of the virus during laboratory experiments in the UK. While biosafety practices have been much strengthened since, human error and equipment failure are factors that cannot be eliminated, even if the highest containment practices and barriers are applied. This danger has been highlighted by various lab accidents and accidental escapes of pathogens from high

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<sup>9</sup> While the VAC recommendations place limits on full gene transfers of smallpox genes, they do not limit transfer of smaller smallpox DNA fragments that are not genes.

containment labs in the recent past, including accidents at BSL-4 (P-4) facilities in the US, Russia, Taiwan, and South Africa.

### Some Recent Publicly-Disclosed Laboratory Accidents (excluding nosocomial infections)

Organism (year)	Type	Country	Lab
SARS (2004)	Lab-acquired infection	China	Centers for Disease Control
Ebola (2004)	Lab-acquired infection	Russia	Vector
SARS (2003)	Lab-acquired infection	Singapore	Environmental Health Institute
Marburg (unknown)	Aerosolization incident	South Africa	National Inst. for Communicable Diseases
SARS (2003)	Lab-acquired infection	Taiwan	Institute of Preventative Medicine
Tularemia (2004)	Lab-acquired infection	USA	Boston University
Anthrax (2004)	Accidental release	USA	Southern Research Institute
Tuberculosis (2004)	Lab-acquired infection	USA	Infectious Disease Research Institute
Ebola (2004)	Human exposure	USA	USAMRIID Fort Detrick
Q Fever (2005)	Human exposure	USA	Rocky Mountain Labs
Glanders (2000)	Lab-acquired infection	USA	USAMRIID Fort Detrick
Anthrax (2002)	Lab-acquired infection	USA	Undisclosed (Texas)
West Nile Virus (2002)	Lab-acquired infection	USA	Undisclosed
<i>E. coli</i> O157:H7 (2004)	Lab-acquired infection	USA	Beltsville Agricultural Research Center

Reported accidents – and it should be noted that few countries require mandatory public disclosure of lab accidents – include institutions whose researchers handle live smallpox virus. Last year at Vector, where Russia holds smallpox virus stocks, a researcher stabbed herself with an Ebola virus-infected needle and later died. The CDC lab that holds smallpox virus has not reported any recent accidents; but public disclosure is not required by US law. US Army researchers studying smallpox are from the US Army Medical Research Institute of Infectious Disease (USAMRIID, at Fort Detrick, Maryland). At USAMRIID, lab-acquired infections of glanders and Q fever bacteria as well as vaccinia, chikungunya, and Venezuelan equine encephalitis viruses have occurred in recent years.<sup>10</sup> In addition, the USAMRIID facility, which performed analysis of the anthrax letters, did not safely manage the weaponized germs. An internal investigation revealed widespread contamination of the facility, including areas outside of the high-containment laboratories, by anthrax spores.

Considering these events it is obvious that every additional experiment involving live smallpox virus increases the risk of an accidental release. While the 1978 accident in the UK was contained (after secondary transmission), this was attributable to a large extent to the high degree of smallpox vaccination/immunity in the British population at that time. A similar accident today could well wreak havoc in a large population because fewer and fewer persons have strong immunity to smallpox. Even if all experiments with live smallpox virus are conducted under maximum containment conditions, there is always the risk of an accidental release.

#### Unexpected outcomes of genetic engineering experiments

Every researcher working in a genetic engineering lab is well aware of the fact that more often than not the results of a specific genetic intervention are not entirely predictable. This fact also holds true for the genetic engineering of pathogenic microorganisms. In an official document submitted to a UN body, the UK government stressed in 2001 that “*the risk of unexpected outcomes with genetically modified micro-organisms must increase with the increase in the*

<sup>10</sup> Rusnak JM et al. *Experience in the medical management of potential laboratory exposures to agents of bioterrorism on the basis of risk assessment at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID)*. J Occup Environ Med. 2004 Aug;46(8):801-11.

*number of laboratories both in developed and developing countries that routinely apply recombinant technologies to micro-organisms. (...) unforeseen consequences (...) could be disastrous for example if such organisms escaped from the laboratory.”<sup>11</sup>*

The danger of inadvertently constructing highly lethal pathogens was recently demonstrated by an Australian research team experimenting with a virus that is closely related to the smallpox virus. The team genetically engineered the mousepox virus in an attempt to create a fertility control vaccine to control mouse populations. Unintended and unforeseen, all of the mice infected with the new virus strain died, even those that had been vaccinated against mousepox. It turned out that the additional gene had the unanticipated effect of turning off the immune system of the mice, making them vulnerable to lethal infection by the otherwise harmless virus<sup>12</sup>. The prospect of a genetically engineered smallpox virus overcoming vaccinations and the immune system is disturbing.

Similarly, the introduction of single genes from smallpox virus into related poxviruses may well lead to new highly pathogenic strains. This danger is exemplified by an experiment with the influenza virus that was published in 2002. US researchers introduced two genes from a particularly virulent and pathogenic strain – the so called “Spanish” flu strain of 1918-19 – into another, less dangerous flu strain. In animal experiments, the artificial strain proved to be much more deadly to mice than other viruses containing genes from contemporary influenza virus.<sup>13</sup>

### **The WHO Biosafety Advisory Group**

VAC documents refer to the submission of smallpox recommendations to the WHO Biosafety Advisory Group (BAG), but do not explain what this group is and the extremely limited role and activities of the WHO laboratory biosafety program.

WHO has one staff member working on laboratory biosafety with the daunting task of managing WHO activity on all labs, from Australia to Zambia, ranging from hospital diagnostic benches to maximum containment research facilities, and from issues of physical infrastructure to personnel training and operating procedures.

There are no WHO advisory committees dedicated to lab biosafety. The BAG is an informal group that provides e-mail suggestions to WHO staff members. It is not constituted by WHA resolution, nor does it report to WHA or any its subsidiaries, nor is it empowered to advise WHO. As of early 2005, the BAG consisted of five persons, two from the US, one from Canada, one from Australia, and one from the UK.

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<sup>11</sup> United Kingdom. Background paper on new scientific and technological developments relevant to the convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction. BWC/CONF.V/4/Add.1, 26 October 2001.

<sup>12</sup> Jackson RJ, Ramsay AJ, Christensen CD, Beaton S, Hall DF, Ramshaw IA (2001) Expression of mouse interleukin-4 by a recombinant ectromelia virus suppresses cytolytic lymphocyte responses and overcomes genetic resistance to mousepox. *J Virol* 75:1205-1210.

<sup>13</sup> Tumpey TM, Garcia-Sastre A, Mikulasova A, Taubenberger JK, Swayne DE, Palese P, Basler CF (2002) Existing antivirals are effective against influenza viruses with genes from the 1918 pandemic virus. *PNAS* 99:13849-13854.

### Inadequate safeguards

The Variola Advisory Committee has made a number of recommendations intended to limit the risks posed by the introduction of smallpox genes into other viruses.<sup>14</sup> These safeguards, however, are inadequate, ambiguous, and at times scientifically flawed:

- The Advisory Committee recommends that “*experiments are performed at BSL-3 or higher containment*”. Experiments involving live smallpox virus are currently restricted to BSL-4 (or P-4, maximum containment) facilities. There is no scientific reason to lower the containment requirements for poxviruses that contain genes inserted from the smallpox virus. The Advisory Committee is well aware that the introduction of smallpox viral genes poses a high biosafety risk (otherwise they would not recommend containment measures in the first place). It cannot be excluded that a resulting chimeric virus would be as dangerous as smallpox virus, requiring the same level of containment. At the BSL-3 (P-3) level, researchers in the laboratory are not fully protected from exposure to the virus and hence are a possible avenue of escape for any new virus. The only rationale for lowering the biocontainment level is the fact that more research laboratories would then be able to perform such experiments. The expansion of smallpox research has been explicitly stated by VAC members as a reason for lowering the biosafety level. Indeed, the expansion of smallpox virus research was explicitly stated by VAC members as a reason for lowering the biosafety level. This recommendation highlights the fact that the Advisory Committee is more concerned with expanding smallpox virus research than with safeguarding such work.
- In another recommendation, the Advisory Committee suggests that all researchers handling recombinant virus “*should have their smallpox vaccination status approved*”. Smallpox vaccination provides protection against some other orthopoxviruses; but it is not known to provide protection against all of them. Transfer of smallpox genes to other orthopoxviruses may alter the virus’ host range. There is abundant scientific evidence, as indicated by the example of mousepox, that the immunological properties of a chimeric virus cannot be predicted. It is thus not certain that smallpox vaccination will provide protection against chimeric viruses created in the proposed experiments..
- The Advisory Committee recommends that research smallpox protocols should be reviewed by “*appropriate institutional authorities*” to address “*biosafety and recombinant DNA concerns*”. A recent survey of institutional biosafety committees in the US, however, revealed that a system based on voluntary self-control by scientists is ill-equipped to conduct proper biosafety assessments and to ensure confidence in biosafety reviews.<sup>15</sup> With no mandatory requirements and no mandatory standards for biosafety reviews in many WHO member states, it would be inappropriate for the WHA to rely on institutional biosafety committees or their equivalent when it comes to experiments of high international public health and biosafety concern such as the deliberate introduction of smallpox viral genes into other orthopoxviruses.
- In the same paragraph, the Advisory Committee also recommends approval by “*WHO in accordance with national regulations and WHO resolutions and recommendations*”. It is unclear which WHO body and which WHO resolution is addressed in this paragraph, opening a dangerous ambiguity in view of the Advisory Committee’s politicization and

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<sup>14</sup> WHO/CDS/CSR/ARO/2005.4. Report of the Sixth Meeting of the WHO Advisory Committee on Variola Virus Research, 4-5 November 2004, page 11, para 8.5.

<sup>15</sup> The Sunshine Project. *Mandate for Failure: The State of Institutional Biosafety Committees in a Age of Biological Weapons Research*. October 2004. URL: <http://www.sunshine-project.org/biodefense/ibcreport.html>

unbalanced nature. In another paragraph, the Advisory Committee recommends WHO approval only for experiments involving two or more smallpox genes.<sup>16</sup>

In addition, these safeguards are only applicable to the expression of entire smallpox viral genes in other viruses. Work with large smallpox DNA fragments that do not comprise a full gene – but major, active parts thereof – would not be subject to any safeguards. The recommendations put forward by the Advisory Committee would thereby open the door to a multitude of experiments in which orthopoxviruses are equipped with significant parts of the smallpox virus that may be related to pathogenicity and may pose a serious risk to human health.

It is obvious that the Advisory Committee recommended a broad range of experiments with smallpox viral genes without giving appropriate attention to the risk of the creation of dangerous new pathogens and their escape from the laboratory. The Advisory Committee exhibited a strong bias towards so-called “freedom of research”, reflecting the fact that a majority of the members and advisers of the Committee are themselves involved in smallpox related research and may have confused self-interest with the public interest.

The devastating effects of the smallpox virus and the hundreds of millions of victims of this highly contagious and deadly pathogen, are increasingly forgotten. One step at a time, WHA has moved from destruction of smallpox virus to retention to limited research and finally to genetic engineering.

The world’s governments and peoples have a profound interest in the final eradication of smallpox. For centuries, the scourge of smallpox has affected nearly all countries and its specter will continue to haunt them so long as the smallpox virus stocks remain undestroyed. Unfortunately, the public and most governments were kept out of the closed-circuit of conversations within the Variola Advisory Committee that led to the recommendations for genetically engineered smallpox and smallpox chimera. The May 2005 World Health Assembly is a time when most governments and people can come forward to claim their rightful seats at the table. A decision by the WHA to reject the Advisory Committee’s recommendations would prevent a dangerous policy change and strengthen the integrity of WHO’s processes and its international credibility, whereas approval could signal the undoing of one of its greatest achievements.

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<sup>16</sup> *ibid*, bullet point 3.