

NATIONAL SECURITY HEALTH POLICY CENTER

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Study on Smallpox Vaccines and Vaccination

Interim Findings

Basis for study.

- Information described in this report has been derived from the original documents on file at the U.S. Library of Congress and the National Library of Medicine.
- The goals of the study were to:
 - Ascertain the historical basis on which suppliers of smallpox vaccine selected the *Vaccinia* viral strain and the substrate (host cells) for production.
 - Assess the use, and where possible effectiveness, of the various vaccines in country-specific vaccination programs and the World Health Organization (WHO) led worldwide eradication campaign (WEC).
 - Review the historical data relating to smallpox vaccination in humans, with particular regard to assessment of markers for vaccine safety and efficacy.

Major findings.

1. The smallpox vaccines in routine use by countries affected by the disease, and that used during the WEC, can be assigned into subgroups based on the progenitor *Vaccinia* virus strain used to produce the material for human vaccination.
2. The vaccines that were effective against the smallpox disease-state caused by *Variola minor* were not always exposed to the disease state caused by the more virulent *Variola major* virus.
3. Because of the time-dependency and the occurrence of the endemic disease state the widespread use of some vaccines at the time of the WEC meant that they were primarily used in “maintenance programs,” where they provided for herd immunity, and were not exposed to endemic smallpox disease.
4. There was considerable “switching” between vaccines used in many countries that mean that consideration of “time-stamped” data on incidence of disease and the vaccine in use is important in assessing the vaccine performance.
5. The use of vaccines that were derived from the New York City Board of Health (NYCBH) strain in countries where endemic smallpox was significantly more widespread than previously reported. In fact, subject to the conclusion of the National Security Health Policy Center (NSHPC) study, it would appear that the NYCBH vaccine strain was the most widely used progenitor vaccine strain during the vaccination of persons in countries with endemic smallpox.
6. The origin of the vaccine strains, and the performance of smallpox vaccines in India during the eradication campaign, appears relevant to current concerns about the potential for a bioterrorist to obtain and release smallpox virus on an unprotected population.

Progenitor Vaccine Strains and Worldwide Use.

The basis of the smallpox vaccines that were successful in protecting the human population from the disease state was the pioneering work of Edward Jenner and his colleagues in a series of studies that are well documented in the history of annals of infectious disease. The discovery that the *Vaccinia* virus was safe for administration in man and could provide cross-protection against the *Variola* virus, which caused smallpox disease in humans, became the basis on which the disease was at first controlled, and then eradicated, throughout the world. The majority of vaccines that were produced for human use were, in large part, based on two “progenitor” strains of the *Vaccinia* virus. One of the strains was supplied through the auspices of the New York City Board of Health (NYCBH); the other was supplied by the Lister Institute in the United Kingdom. Both *Vaccinia* strains were used in the programs to control and eradicate smallpox; both were used as the starting point for vaccines that have been described as successful in the eradication of the disease. The issue of whether the two strains exhibited any differences in safety and efficacy profiles is an important consideration in the context of the current need to select a strain for reinstating vaccine stockpiles. Of course in any new program it is axiomatic that the select *Vaccinia* strain will produce a vaccine that is effective against the smallpox virus. Given that the disease no longer exists in man and human testing is not possible, the data demonstrating that the selected vaccine strain was used in countries where smallpox was an endemic threat is of vital importance. It is for this reason that NSHPC undertook a program of research into the origin of vaccine strains in the vaccines used to eradicate smallpox.

What is clear from NSHPC research is that the data in the literature that ascribes the major role in controlling endemic smallpox to the Lister strain requires reinterpretation when one considers the history of the many vaccines used around the world. Some of the data reviewed to date in our study is described below.

NYCBH.

The history of the *Vaccinia* virus strain that became the basis for the pioneering work in vaccine production and distribution that the NYCBH undertook in the 19th and 20th centuries has been the topic of significant research for the NSHPC study. The researchers used as source data the contemporaneous scientific publications and original correspondence that are housed in the U.S. Library of Congress and the National Library of Medicine. In the context of the distribution of the NYCBH vaccine strain and its use in controlling endemic smallpox the key findings are as follows:

1. NYCBH, beginning in 1874, acted as a major supplier of authentic strains of *Vaccinia* virus to other organizations thus enabling physicians to administer effective smallpox vaccine.
2. The NYCBH strain was used by Wyeth (a major U.S. pharmaceutical company) and eventually formed the basis for the first freeze-dried product, Wyeth DryVax, a product considered sufficiently stable and efficacious that it is being considered for use as a contingency vaccination nearly 25 years after last manufacture.
3. The NYCBH strain was supplied to Canada (early 1900s) and formed the basis of the extensive Canadian program including in-country eradication of smallpox. This program was important in the WEC as Canada provided significant donations to third-party countries through the WHO (41 million doses between 1964-1984).
4. The use of NYCBH strains in countries with endemic smallpox and the efficacy associated with its use is well established (see data on Africa, India and South America below).
5. Through a circuitous, but documented, route the NYCBH strain can be shown to be the source strain for the EM-63 smallpox vaccine. This is the vaccine that was used widely in the former USSR, replacing the reactogenic strains previously in routine use, and the subject

of the largest donations to the WEC by that country. The donations by the USSR included some through WHO but the vast majority was made through bilateral agreements with individual countries, most notably in the context of eradication of the disease in India, Zaire, Iran and Afghanistan.

6. Prior to the WHO involvement in the WEC, a program initiated by the Pan-American Sanitary Organization (PASO, later PAHO) in the early 1950s in South America, used vaccine based on NYCBH.

Widespread use of the NYCBH strain to develop other smallpox vaccines.

The availability of vaccines that were based on the NYCBH strain as indicated in Figure 1 brought about major reductions in the worldwide incidence of smallpox. Contrary to previous reports that the use of the Lister strain was more widespread than NYCBH the data shows that the latter strain was very widely used in countries where smallpox remained an endemic disease. It is worth noting that the emergence, and apparent preponderance, of the Lister strain at the time of the intensified WEC program (1967) is misleading in the context of efficacy against the endemic disease state. The WHO advocated the Lister strain in the WEC because of its relative ease in manufacture—not because of any perceived performance advantage in the face of the disease. In fact by the time that the Lister strain was being distributed under WHO guidelines, smallpox was only occurring in a few countries around the world. The eradication of smallpox from Europe, the Americas, and the majority of the world (excluding Africa and India) was achieved several decades before the involvement of the WHO, and the intensified WEC program, which targeted the last “pockets” of disease that might act as reservoirs for future outbreaks. In these remaining areas of endemic disease (and notably in Africa and India) the NYCBH strain, together with Lister and other strains eventually succeeded in the desired goal—the defeat of smallpox.

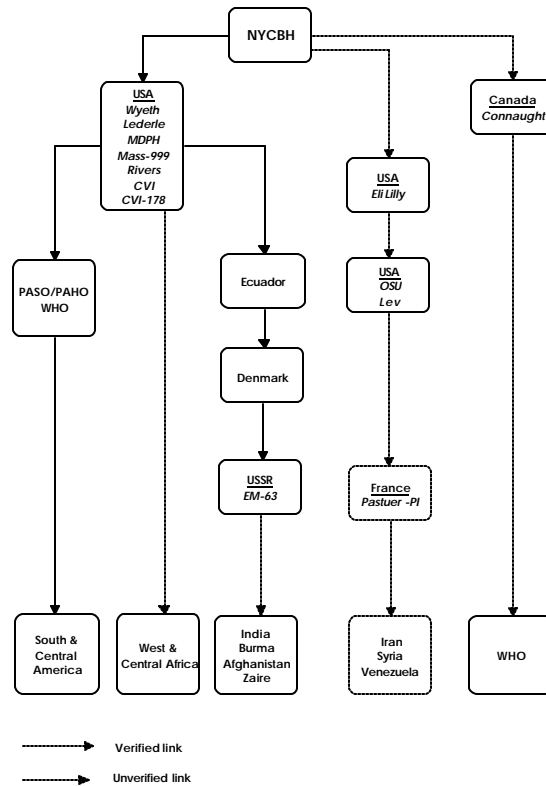


FIGURE 1 – RELATIONSHIP OF NYCBH STRAIN TO MAJOR SMALLPOX VACCINES IN WEC

Selected data, based on the relationships shown in Figure 1, indicate the use and efficacy of vaccines based on NYCBH strains in countries with significant endemic smallpox disease.

West and Central Africa.

In the period of the 1960s the countries comprising the regions of West and Central Africa were suffering major disease problems that included endemic smallpox disease that was caused by both *Variola major* and *Variola minor* viral strains, but principally the *major* variant. In early 1961 the United States had commenced a program that was targeted at eradicating measles, with demonstrable success in this program they initiated an expanded effort to leverage a program to target smallpox. The program sponsored through United States Agency for International Development (USAID) extended through 20 countries comprising 120 million persons and resulted in the use of over 100 million doses of vaccine based on the NYCBH strain. The data on vaccine supplied is summarized in Figure 2.

Table 4. Smallpox vaccinations (in thousands), Smallpox Eradication Programme, West and Central Africa

Country	Year						Cumulative vaccinations Jan. 1967– Dec. 1972
	1967	1968	1969	1970	1971	1972	
Central African Republic	381	405	477	508	558	427	2 756
Chad	1 387	1 345	1 322	1 182	977	666	6 879
Congo	182	581	312	617	288	73	2 033
Dahomey	702	990	934	849	448	184	4 107
Equatorial Guinea	NA ^a	NA	82	238	16	6	341
Gabon	225	146	175	201	105	138	990
Gambia	231	147	40	40	20	3 ^b	481
Ghana	1 342	1 988	2 094	1 909	1 052	481 ^b	8 866
Guinea	1 068	2 063	1 434	1 453	1 200	1 100 ^b	8 318
Ivory Coast	1 580	1 756	1 582	548	619	67	6 152
Liberia	44	231	398	191	120 ^b	268 ^b	1 252
Mali	1 043	1 472	1 193	516	56	111	4 391
Mauritania	NA	NA	430	288	193	297	1 208
Niger	1 610	1 166	936	1 297	850	776	6 635
Nigeria	9 560	23 494	16 155	8 702	5 362	5 454	68 727
Senegal	383	1 468	762	330	507	124	3 574
Sierra Leone	0	965	1 154	258	93 ^b	100 ^b	2 570
Togo	606	608	922	467	507	166	3 275
United Republic of Cameroon	1 611	1 996	1 693	1 443	3 250	2 215	12 208
Upper Volta	2 040	2 208	1 338	1 026	1 568	632	8 812
Total ^c	23 972	43 030	33 431	22 062	17 788	13 288	153 575

^a NA = not available.^b Incomplete and/or provisional.^c Totals do not sum up because figures are rounded off.

FIGURE 2 – SMALLPOX VACCINATIONS 1967-1972, WEST & CENTRAL AFRICA

Source: F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, and I.D. Ladnyi, *Smallpox and Its Eradication*, (Geneva: World Health organization, 1988).

The incidence of smallpox in the region during the major period of vaccination against smallpox is shown in Figure 3. Throughout the region there was an underlying seasonal pattern of smallpox disease (see shaded portion of Figure 3). The incidence began to drop immediately after vaccination commenced and regional control was in place by early 1970.

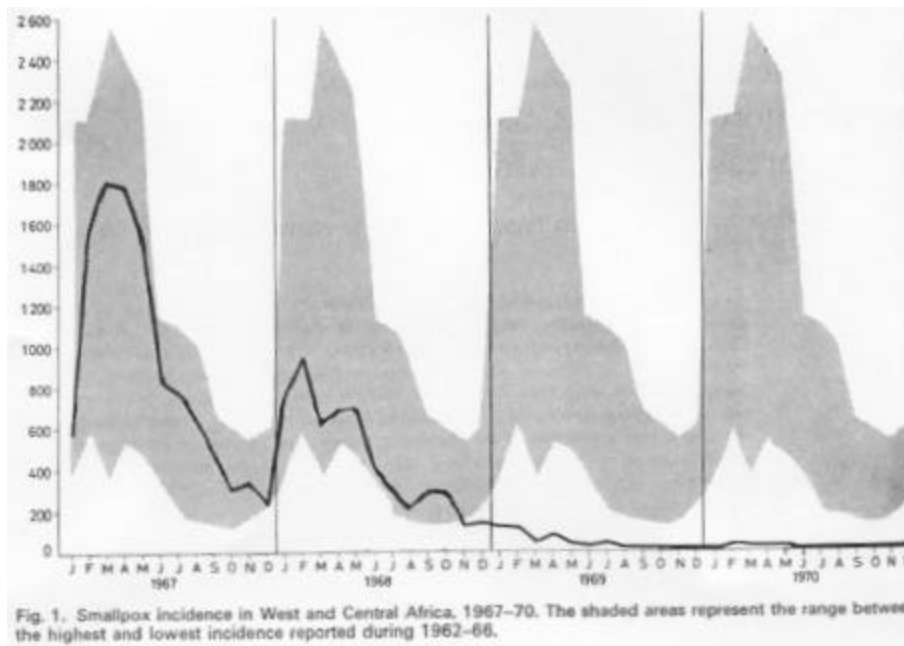


FIGURE 3 – EFFECTIVENESS OF SMALLPOX VACCINE IN WEST AFRICA.

Source: F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, and I.D. Ladnyi, *Smallpox and Its Eradication*, (Geneva: World Health organization, 1988).

The data from individual countries in the region provide even more important information concerning the smallpox vaccines and their time-dependent role in disease management. For example, in Ghana prior to 1964 the country utilized a vaccine based on the Lister-strain but saw only limited success in control of smallpox. From 1965-1967 the Ghanaians switched to a vaccine sourced from Switzerland (Berne strain) with some success but the disease state persisted. In 1967 the country switched again, this time to a vaccine based on a NYCBH strain, and finally achieved control and eradication. This time-dependent pattern of using vaccines from different sources that are derived from different vaccine strains indicates the need for caution in interpreting the data and the claims made in general statements about the WEC and vaccine success.

In Zaire, through 1969, the country had used locally produced vaccine and donations from the WHO in an eradication program that was targeted at smallpox and, through United Nations International Children's Emergency Fund (UNICEF), tuberculosis. From 1969 onwards the country used only smallpox vaccine that met WHO requirements, principally through a U.S. based pilot program involving the use of jet-injectors and combination vaccines and donations under a bilateral agreement with former USSR. The WHO vaccination program utilized some 24 million doses of vaccine throughout the period between 1968 and 1971. The Soviet supplied vaccine, EM-63, was based on the NYCBH strain and continued in use during the dramatic control and eradication that is shown in Figure 4. From 1971 onwards the vaccine supplied by the Soviets was the LIVP strain (based on a Lister strain derivative). But the vaccine was now mainly used for maintenance of the controlled state; the eradication relied on the vaccine that resulted from the use of an NYCBH based strain.

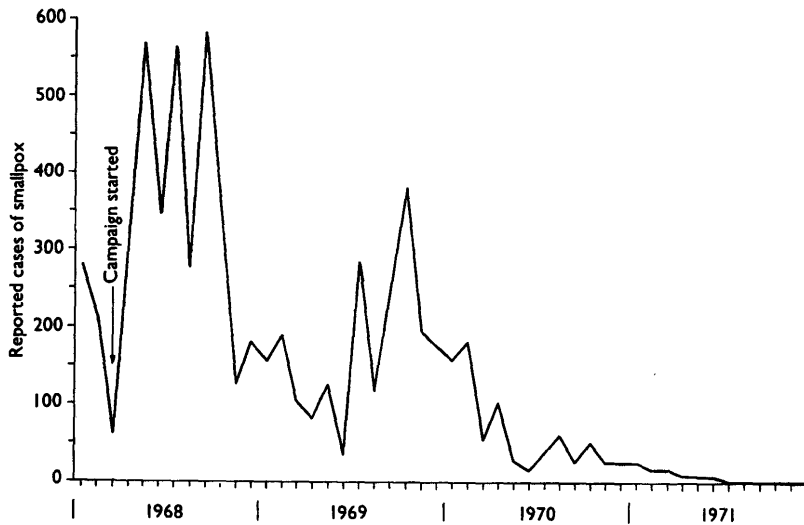


Fig. 18.4. Zaire: number of reported cases of smallpox, by month, 1968–1971.

FIGURE 4 – EFFICACY OF SMALLPOX VACCINE IN ZAIRE

Source: F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, and I.D. Ladnyi, *Smallpox and Its Eradication*, (Geneva: World Health organization, 1988).

Pan American Sanitary Organization (PASO)/Pan American Health Organization (PAHO) Experience.

The Pan-American organizations—PASO and latterly PAHO—under programs of USAID were able to supply vaccines and expertise to develop local production of freeze-dried vaccine for the South American and Central American countries beginning in 1949. These programs led to significant reductions in smallpox disease in many countries and ultimately eradication from the American continent. For example one early success was exhibited by Peru (Table 1) other examples are readily quoted.

Year	1949	1950	1951	1952	1953
Incidence of smallpox	6,305	3,753	1,218	1,370	163

TABLE 1 – SMALLPOX CASES IN PERU

A continual problem in South American countries was the reintroduction of smallpox from Brazil due to that countries inability to implement an effective program of vaccination during the 1950s. Under the auspices of WHO the Brazilian authorities began vaccination using a NYCBH based vaccine that was grown on calves and, unusually, eggs. This program, together with the other vaccines in Brazil, resulted in a successful control and eradication of smallpox in the country.

Lister Institute Vaccines.

The Lister Institute was an early participant in the programs to control and eradicate smallpox but was not a producer of vaccines on a commercial scale for widespread distribution outside of the UK. The role of the Lister Institute in the WEC was based on considerations of vaccine safety long after smallpox had been eradicated from Europe. It resulted from a desire to use smallpox vaccines with less reactogenic properties rather than considerations of a need to increase vaccine efficacy. European countries having achieved eradication of endemic smallpox at the end 19th –early 20th centuries noted that the injuries due to vaccinal complications outweighed the minimal risk of disease and began a review of their collective programs. In reviewing their options, consideration was given to vaccines based on the Lister and the NYCBH strains. Most countries, but with some notable exceptions, decided to utilize a vaccine that used the Lister strain because of the higher potency of the seed stock available and the reactogenicity profile.

The requirement for a recognized seed stock was also recommended by WHO and was implemented by the National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu – RIVM) in the Netherlands based on the availability of the high potency Lister seed stock. RIVM became a major source of seed stock based on production of material from calves. This contrasted with the approach at the Lister Institute where the production of seed stock continued to be based on alternate passage of the seed on rabbits and sheep. Given the viral host adaptation that is exhibited by *Vaccinia* virus the consistency of the vaccines produced by these two different seed stocks is open to some continued debate. The availability of the Lister seed stock from RIVM did not however mean that all smallpox vaccines from this strain were identical. Indeed some programs acknowledged the need to derive their own seed stock from the material supplied by RIVM and further indicating that the production methodology, and in particular the host cell, was a key element in producing an effective vaccine.

In the early 1960s the former USSR was becoming the largest donor of smallpox vaccines based on its contribution to WHO but more importantly on the basis of agreements in place with individual countries still trying to control the disease. The Soviets evaluated a number of vaccine strains including Lister and NYCBH (obtained from Ecuador) in order to develop a new vaccine with reduced complication rates. They selected the NYCBH strain which they renamed “EM-63” – this vaccine strain then became the basis for the large donations made by the USSR to WHO and third-party countries. The vaccine was used in many countries where *Variola major* and *Variola minor* were still prevalent in the endemic disease states. The supplies by the USSR under the bilateral agreements vastly outweighed its role in supplying the WHO. Bilateral donations from the USSR were used to meet the requirements in countries such as India, Burma and Afghanistan.

As stated above the Lister-based vaccines in use from the 1960s onwards in Europe and other countries that also switched due to concerns with reactogenicity, were mainly viewed as “maintenance vaccines” – becoming available long after the endemic disease state had been eradicated. This use provided herd immunity in the general population, not encountering significant challenge from new smallpox cases except where importation of the virus occurred with transit of infected humans.

The Indian Experience.

It is now acknowledged that the story of smallpox eradication in India is one of conquest over some of the most virulent forms of the disease. It is important to consider the India experience given that the virulence of the smallpox outbreaks in the country attracted not only some of the best aspects of

the WEC but also less savory scientific interest. In fact, in commentary by former scientists from the USSR the smallpox viral strain known variously as “India-1967” or “India-1” is described as “excellently suited to weapons production. It was highly virulent and was stable enough to retain its infectious qualities over time. Within a few years... (it) became our principal battle strain of smallpox.”¹ It is now highly-likely that this strain has become the focus of programs aimed at developing BW outside of the former USSR – it is therefore of considerable concern.

In the 1960s the former USSR began a major involvement in the efforts by India to eradicate smallpox through a bilateral agreement with the Indian government. Despite the Indian government having four regional establishments for production of smallpox vaccine the combined output fell woefully short of the needs of the country. In the period 1966-1967 the production facilities in India were able to supply approximately 1.4 million vials, approximating to 20 million doses of vaccine, on an annual basis. The limited supply of vaccine resulted in an annual incidence of smallpox that exceeded 85,000 cases per annum. With the involvement of the USSR in the program from 1967-1970, and their annual donation of over 100 million doses, the rate dropped to 12,700 cases per annum. The vaccine supplied by the Soviets was EM-63 a NYCBH based strain. In the late 1960s with the newly formed recommendations of the WHO concerning the need for higher seed stock potency the Soviet program switched from EM-63 to a derivative of the Lister seed stock. After 1971 the vaccine supplied to India by the USSR was based on this new seed stock and was designated “LIVP”. The introduction of the LIVP vaccine did not however result in an immediate improvement in the reduction of smallpox disease in India. In the northeastern states the disease continued to be a problem, mainly due to failures in compliance with the vaccination programs and difficulties in maintaining effective quarantine and isolation. In fact the number of cases increased, but this may be an artifact and reflect the increased efforts in the region to effect surveillance and disease reporting. In response to this apparent setback the Indian authorities switched again to a local variant of the *Vaccinia* virus – the so-called “Patwadanger” strain. (Note: the origin of this vaccine strain has yet to be verified in our research). The Indian authorities also markedly increased their production capability such that by 1970-1974 the four regional facilities produced in excess of 20.8 million vials versus donations of 6.8 million vials of LIVP. From 1974 onwards the Indian authorities were able to produce sufficient vaccine to meet the needs of the country. The use of the Patwadanger-based vaccine soon surpassed the use of the Lister-based vaccine, and in short order, the entire production in India focused on the locally-produced vaccines, and eventually lead to the eradication of smallpox from the Indian subcontinent.

¹ Ken Alibek and Stephen Handelman. *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World-Told from the Inside by the Man Who Ran It*. Random House, NY, 1999.

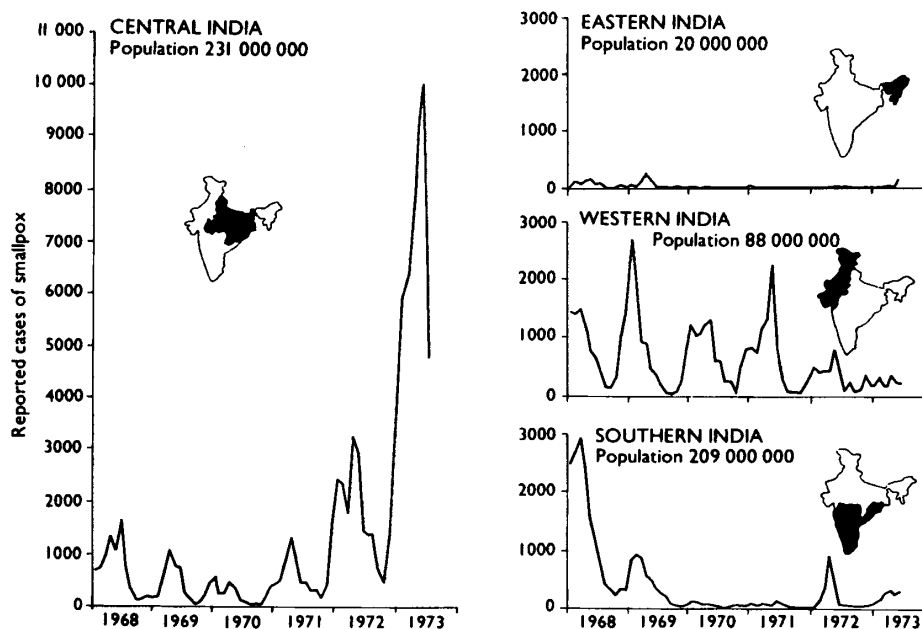


Fig. 15.8. India: number of reported cases of smallpox, by region, by month, 1968–1973. (Population data for 1971 from Basu et al., 1979.)

FIGURE 5 – INDIAN EXPERIENCE WITH SMALLPOX VACCINES

Source: F. Fenner, D.A. Henderson, I. Arita, Z. Jezek, and I.D. Ladnyi, *Smallpox and Its Eradication* (Geneva: World Health Organization, 1988).

In the context of current concerns about the possible use of smallpox as a bioterrorist weapon the data on the Indian experience is particularly striking. Former Soviet Union scientists identified that India was afflicted with some of the most virulent forms of smallpox, so virulent that it is claimed that the Soviets restructured their BW program around “India-1”². It has further been suggested that the large amounts of smallpox material produced by the former Soviet Union is the most likely source of starting material for a bioterrorist group. It would therefore seem logical to have any vaccine-based defense against the threat posed by this material use as its progenitor the vaccine strains that exhibited success during the eradication campaign.

² Biohazard.