Smallpox revisited

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Smallpox has been a major epidemic disease since the dawn of history. Caused by the variola virus – a large DNA virus, which is a strict human pathogen with no carrier state. The virus belongs to a related group of viruses causing pox-like infections in other mammals. The milder infections caused by these animal viruses in humans generate excellent immunity against smallpox, as does natural or artificial-induced smallpox infection. These properties enabled a worldwide eradication programme and smallpox became the first human epidemic disease to be eradicated. However, the high infectivity of the virus, its transmissibility, high mortality of the major variety and lack of specific chemotherapeutic agents makes the virus an important biological weapon. The apprehension that some unauthorized stocks are extant and available to terrorist groups has generated some anxiety. This review attempts to revive the knowledge about an important (albeit non-existent) infection and trace the international effort that achieved a public health landmark. The weapon potential of the variola virus has been discussed and possible remedies outlined.

HISTORY is replete with accounts of massive epidemics that have decimated populations. Smallpox has been a leading epidemic disease in the old world since the dawn of history. Both India and Egypt had the disease as early as the 14th and 12th century BC. In India the disease was accepted as a fact of life and periodic epidemics swept across the country. Folklore created a Goddess of smallpox who was propitiated to protect the population from the scourge (see Box 1).

The virus causing smallpox has a brick-shaped virion and belongs to the large family of Poxviridae. These viruses are the largest animal viruses and the only ones within the range of the light microscope. The family Poxviridae is classified into two subfamilies, Chordopoxvirinae and Entomopoxvirinae, subdivided into eight and three genera respectively. They possess a complex virion containing mRNA-synthesizing enzymes, a double-stranded linear DNA molecule of about 200 kbp with terminal hairpin loops. The poxviruses replicate in the cytoplasm of the host cell and are released as enveloped particles. They exist in two forms – the intracellular mature virions (IMV) and extracellular enveloped virions (EEV). Both these forms are infectious. The entry of the virus is by attachment to the plasma membrane and subsequent endocytosis. Studies with the vaccinia virus have incriminated a virus-encoded protein, the vaccinia growth factor binding to the cellular EGF receptor. The cellular receptor for the variola virus, which has a more restricted host range, has not been defined (Figure 1).

For centuries, Shitala Mata has been propitiated in India as the Goddess of smallpox. Temples dedicated to her are scattered all over the countryside and, where there are no such temples, it used to be the custom to display iconographs of the dreaded goddess whenever an epidemic broke out. Traditionally, Shitala Mata is represented as a woman of commanding presence with large penetrating eyes riding a donkey. With one hand she holds up a pitcher full of water and with the other, a broom. On her head she balances a basket full of grain. It has been the general belief that whenever Shitala Mata shakes her head, she spills grain all around and each grain turns into a smallpox pustule, leading to an outbreak of the awful disease. The victims survived if she used the water from her pitcher to clean the spilt grain; they did not, if she used only the dry broom.

Box 1.
Pathogenesis and pathology

Viruses are disseminated by the aerial route from the oropharynx of infected subjects. The virus then spreads to the regional lymphnodes. After a couple of days, there is a blood-borne spread to the lymphoid tissue elsewhere in the body. The virus multiplies in the reticuloendothelial system during the incubation period. The second phase of viraemia is associated with the prodromal symptoms and involvement of the mucous membranes of the mouth and pharynx, followed by the characteristic lesions in the skin. In the skin, the capillaries of the papillary layers of the dermis are infected first. Signs of inflammation and endothelial swelling follow this. The middle layers of the overlying epidermis then show a 'reticulating degeneration', originally described by Unna. The well-demarcated degenerated area shows epithelial cells with basophilic inclusions – the Guarneri bodies. The lysis of the infected cells leads to the accumulation of fluid, which becomes evident as the characteristic vesicle. The vesicle increases in size to 2–5 mm in diameter. After four to seven days, the clear vesicles become filled with purulent material due to neutrophile infiltration. The pustular fluid is usually bacteriologically sterile at this stage. The umbilication characteristic of the mature smallpox vesicle is due to persistent septa and fixed dermal adnexa, like hair follicles. Once the host immune responses control the infection, the vesicular fluid is resorbed and a scab is formed 10–15 days after the appearance of the rash. The scabs fall off after the basal epithelium is replaced. By three weeks the last scabs have usually fallen, leaving scars proportional to the depth of dermal involvement. Mucosal lesions are similar, except that they are covered by slough.

Clinical features

A typical case of smallpox shows clinical manifestations after an incubation period of seven to 17 days (mean 12 days). A prodromal phase with abrupt onset of fever, severe headache and backache heralds the disease. The fever remains high for a day or two, dropping to moderate levels when the mucous membrane and skin lesions appear. The tongue, mucosa of the oropharynx and mouth show ulcers before the rash appears. The rash first appears as macules or a maculopapular eruption of 2–3 mm diameter, evolving to vesicles of 2–5 mm over the next two days. The subsequent evolution has already been described. The distribution of smallpox lesions is classically described as 'centrifugal'. They start first on the face and extremities, though, in severe cases may cover the entire body. The palms and soles are usually involved and these lesions heal the slowest. In nearly three-quarters of the cases of variola major scars were left when the scabs fell off. Panophthalmitis (following perforation of corneal ulcers), arthritis and encephalitis were occasionally seen. The viral infection per se precipitated toxic shock in the majority of fatal cases. Deaths due to secondary bacterial infection of the skin lesions or bacterial pneumonia occurred later in the disease.

While the well-recognized ordinary variola vera accounted for nearly 90% of the cases, atypical manifestations could be misleading, specially if they occurred as sporadic cases. On the basis of a study of 3544 patients in India, five types of smallpox have been described (see Box 2).

The course of variola minor was milder and of a shorter duration than that of variola major, with a mortality of < 1% as against up to 30% in the major form. Marsden’s analysis of 13,686 cases seen by him in London between 1928 and 1934 describes the clinical features. The overwhelming majority (86.85%) had fewer than 100 discrete vesicles on the face, confluent lesions were seen in only 0.13%. Haemorrhagic disease did occur rarely (three cases, 0.02%), but did not end fatally in all cases (one out of three recovered). Residual scarring was much less in the milder infection.

The low (1%) mortality in smallpox outbreaks justified the label variola minor in most cases. When, however, both the varieties coexisted, the distinction was not always clear. It was shown by Chapin and Smith that even in such situations, the two varieties bred true to type.

The haemorrhagic type has often been misdiagnosed even in the context of an outbreak. I had a similar experience, in 1967, in the case of a medical student who fell ill after attending the Infectious Diseases Hospital (IDH) in the course of his training. The 20-year-old male came down with high fever, suffused conjunctivae and petechial rash. Smallpox was not thought of, till a careful examination revealed a single vesicle in the lumbar region. The vesicular fluid showed the typical brick-shaped viruses under electron microscopy. This case, like the majority of early haemorrhagic smallpox cases, died within 72 h of diagnosis. The student had been successfully vaccinated recently (as a pre-requisite for his IDH
posting). Rao (quoted in ref. 5) had noted a few such cases in his large Madras series. Their prognosis was not modified by their vaccination status.

The differential diagnosis of smallpox, particularly in the present post-eradication situation, would cover the large number of causes of papular, vesicular and maculopapular eruptions. Drug eruption and chickenpox would, however, be the most important conditions to exclude. A good history would usually clear the picture. Chickenpox, particularly in the adult, could be quite confusing. The distribution of the rash, morphology of the vesicles, occurrence of skin lesions of the same maturity in a region (in smallpox), helps. Nevertheless, in our experience in the late 1960s and early 1970s, a quick electron microscopic examination of the vesicular fluid or even light microscopy after staining for elementary particles was needed in difficult cases. These methods cannot be employed easily nowadays due to the low herd immunity and also the lack of experience. Interestingly, majority of the confusing cases were adults hailing from Kerala or contiguous parts of Tamil Nadu—an observation supported by the observations of White.

At the start of the 20th century, smallpox was present in all the countries of the world. It was regarded as a severe disease with a high case-fatality rate. The infection maintained itself by spreading from one outbreak, (a few being mild and involving small numbers) to another. Variola minor was described first in 1904 in South Africa. It was realized that a similar mild form of smallpox (called alastrim) was prevalent in the Americas, having spread from the North to the South, and also to Australia and Europe. In Africa, both the forms coexisted in the mid-20th century. The smallpox virus has no host other than human beings, and does not produce sub-clinical infections. Variola sine eruptione, seen in vaccinated individuals in endemic areas, is the nearest. A natural or artificial infection (as in variolation) confers lasting immunity, and there is no carrier state. Jenner’s9 discovery of the efficacy of cowpox in preventing smallpox infection led to the universal adoption of vaccination. The vaccine strain itself underwent a change over the next few decades. The origins of the presently used vaccinia virus strains are unclear. They certainly are not derived from the original cowpox strain used by Jenner. They have probably arisen from the variety of pox virus-infected animals that were used to produce the vaccine ‘lymph’ for immunization against smallpox10,11.

Variola major has been classified into five clinical categories:

1. **Ordinary type**: This comprised >70% of the cases. It was characterized by raised pustular skin lesions which could be divided into three categories;
   
   (a) **Confluent** rash present on face and forearms.
   
   (b) **Semiclouent** rash present on face with discrete rash elsewhere.
   
   (c) **Discrete** rash on all involved areas with normal skin between pustules.

   In unvaccinated patients, mortality was 62% for confluent infection, 37% for semiclouent and 9% for discrete infection.

2. **Modified type**: This form of smallpox was similar to the ordinary disease, except that the course was accelerated and pustular lesions were smaller. Modified smallpox was common in vaccinated patients who developed lesions, in health-care workers exposed by accidental inoculation and in those intentionally infected by variolation, a procedure once widely used as a method of vaccination.

3. **Variola sine eruptione**: Patients had fever but no rash. This was seen in vaccinated patients or those previously infected. Laboratory confirmation of the diagnosis was required.

4. **Flat type**: Pustules remained flat and were usually confluent or semiclouent in distribution. This form of infection occurred mainly in children and was often fatal.

5. **Haemorrhagic type**: Skin lesions and mucous membranes became haemorrhagic. Pregnant women were predisposed to this form of smallpox, which was rare but severe. Profound prostration, heart failure, diffuse bleeding and bone-marrow suppression resulted, and most infections were fatal within three to four days, earning the name ‘sledgehammer smallpox’.

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**Box 2.**
Europe

Universal vaccination eliminated smallpox from Europe by 1953. The countries which were well vaccinated, such as Austria, Germany and the Scandinavian countries achieved near-zero rate in the 1920s. In fact, Norway and Sweden were free from endemic smallpox before the dawn of the 20th century. The social disruption of the First World War did exacerbate the situation, with epidermics in Italy, Portugal, Germany and Russia between 1918 and 1920. While variola major remained under control, the 1920s saw the incursion of alastrim from North America. This smallpox variant was brought under control by the mid-1930s in the United Kingdom and elsewhere in Europe. The Iberian Peninsula, particularly Portugal, remained infected till 1953, after which smallpox (major and minor) ceased in Europe.

Though in the pre-Second World War period imported cases did occur in Europe (largely from Russia and Iberian Peninsula), the highly infected colonies of European states in the tropics had no role in spreading smallpox to Europe, due to the long travel time from the mainland. An exception was the alastrim spread from North America (the trans-Atlantic passage time from North America to Europe was around seven days).

The Americas

In the case of North America, extensive vaccination had decreased the incidence to about 100 cases (with 30 deaths) in 16 states by 1897. These small outbreaks were easily contained. In 1897, variola minor re-entered USA through Pensacola, Florida. It spread all over USA in four years (with spreads to Eastern Canada). At the same time, variola major re-entered from Mexico and to a smaller extent from Canada. Thus, in the first three decades of the 20th century, both forms of smallpox coexisted. The numerous epidemics were analysed by Chapin and Smith and the different forms of smallpox were defined. Alastrim became the dominant form of smallpox in USA in the 20th century and the sole form after 1926 till 1949, when it was eliminated by extensive vaccination, despite strong opposition to the procedure in the 1930s.

Mexico had a continuous epidemic situation in the first three decades of the 20th century. Even the appearance of variola minor in 1932 (from USA) did not displace variola major. The 1942–43 epidemic (with 8000 deaths) stimulated an extensive vaccination effort that resulted in the elimination of smallpox in 1951.

The Central American states eliminated smallpox between 1924 and 1951 (variola major was prevalent all over the continent at the beginning of the 20th century). A concerted action by the countries of the continent, following the decision of the Pan American Sanitary Organization (in 1950), resulted in the elimination of the infection in most countries by the early 1960s. Brazil, the largest and most populous country of the continent, continued to harbour smallpox till 1971. However, fatalities had come down earlier since variola minor, introduced into Brazil in 1910, gradually displaced variola major all over South America.

Australia and Oceania

Australia and Oceania remained somewhat insulated from the ravages of smallpox, but for initial outbreaks amongst aborigines and a couple of entries of alastrim to Australia and New Zealand. Likewise, the Pacific Ocean islands including Hawaii had the occasional rapidly controlled outbreak.

Africa

The eradication process in most of Africa moved more rapidly than in Asia, despite the poorer developmental infrastructure. The programme in Western and Central Africa was handled by the United States Agency for International Development in collaboration with the Centers for Disease Control. The national programmes started in 1967, and by September 1969 all the countries of the region except Nigeria, were free from smallpox. Nigeria had its last case in May 1970 – five years before the disease was controlled in Asia. This programme was coupled with measles vaccination and jet injectors were used widely. It was also the first programme in which active case finding and containment were used, even at the cost of achieving less than targeted levels of mass vaccination. Experience in Zaire and countries of East Africa was similar. Sudan had the paradoxical predicament of being one of the earliest countries to attain zero incidence, but becoming re-infected due to population movement.

The states of southern Africa posed a different type of problem. The world community ostracized the main state of the region, Republic of South Africa due to its apartheid policy. This dragged the adjacent countries into obscurity. The popular feeling that the variola minor prevalent in the region did not warrant the intensive action that variola major required, compounded this lack of approachability. Nevertheless, smallpox was eliminated in southern Africa when the last case occurred on 13 April 1973, in an obscure Christian Sect (Maze zuru) who concealed their smallpox cases and objected to vaccination.

The Horn of Africa provided a major challenge to smallpox eradication. The Ethiopian highlands and the Ogaden desert were geographically tough terrains coping with natural catastrophes like the famine and man-made disasters like the Ethiopian–Somali war. The situation engendered the comment, ‘Global smallpox eradication
was in jeopardy on numerous occasions and in many countries, but nowhere was the outcome so greatly in doubt, and for so long, as in Ethiopia. Additionally, the endemic variola minor was regarded as a fact of life. Public and governmental support was meagre. The ultimate success of the effort was a tribute to the ‘dedicated WHO staff and small band of extraordinarily capable Ethiopian health officers and sanitarians’.

The Ogaden desert was the last bastion of smallpox. The Somali nomads of the desert managed to keep the infection alive till October 1977. Two infected persons travelled through Merca, a post town of 30,000 inhabitants. They infected a 23-year-old cook, Ali Maow Maahin, who had a few minutes contact with the two patients. He remained out of contact with the surveillance teams for eight days, but in contact with a large number of local people. An intensive search campaign was launched covering 50 houses, and all persons residing in, leaving or entering Merca were vaccinated—a total of 54,777 persons. No other natural case of smallpox occurred in the world after this. In the final analysis, elimination of variola minor from this region represents as great an achievement as the apparently larger effort in South Asia. Ingenious devices were resorted to in the programme. A novel method is described in Box 3.

Asia

Only five Asian countries harboured smallpox in 1967. Four (after 1971, five) of these were the countries of South Asia: Afghanistan, Pakistan, India, Nepal (and Bangladesh). These contiguous countries were separated from the other country that continued to be endemic—Indonesia. With little communication between these two blocks, it was logical to tackle Indonesia first and then go on to the mainland states. That is how the Asian strategy was planned and executed.

Indonesia: The programme was started in July 1968 and achieved its objective in January 1972. It was an achievement by any standards, considering the complex logistics in a nation of 13,000 islands strung across a length of 4800 km and 5° latitude on both sides of the equator. The endemicity at that time was the result of reimportation of smallpox into the country in May 1947 (Indonesia had achieved zero transmission status in 1936). The need for a critical population density for continued endemicity ensured that the infection remained confined to the western part of the country, with no spread occurring beyond Sulawesi. The programme was largely indigenous with limited international resources.

The Indonesian programme used the search and containment strategy so extensively that the programme director questioned the value of routine vaccination (Kowara in WHO/SE/72.30 quoted by Henderson). The use of the WHO smallpox recognition card and offering a reward for reporting cases was used successfully in this programme. The extensive interaction between this programme and the South Asian programmes (particularly India, Nepal, Bangladesh and Bhutan) resulted in a paradigm shift in the latter, leading to successful eradication. The last cases in Indonesia got infected in January 1972 when smallpox was still raging in South Asia.

Smallpox eradication in South Asia: The region is a contiguous land mass across which the smallpox virus moved with impunity. The partition of British India and the subsequent animosity between Pakistan and India created a barrier that split the region into two zones, Afghanistan and Pakistan to the west and the rest of the countries of the region to the east. East Pakistan (later Bangladesh) had a porous border with eastern India, which offered no barrier to the spread of smallpox. The story of the last natural case of variola major amply illustrates this (see Box 4).

Afghanistan and Pakistan: Afghanistan and Pakistan freely exchanged smallpox. However, the level of organization and health facilities differed considerably. Nevertheless, the Afghan programme moved forward rapidly once a national commitment arose. Extensive use of variolation was an impediment that was converted to an advantage once the variolators were absorbed into the vaccination drive. The high illiteracy, religious orthodoxy and the lower status of women in the society were overcome, and Afghanistan saw its last indigenous cases in September 1972. Three outbreaks (due to imported cases from Pakistan which was still endemic for smallpox) occurred in 1973. One of these was imported from as far away as Sukkur in Sind, a distance of 600 km.
Pakistan, on the other hand, was a more developed country that had good communication, a more sophisticated health service and administrative infrastructure. Since inception, the two wings of Pakistan had parallel administration. After 1971, East Pakistan as Bangladesh interacted intimately (in smallpox terms) with the eastern part of India. Smallpox vaccination had been in operation in the region of present Pakistan for nearly 100 years before the 1970s. The programme of vaccination resulted in annual vaccination of from 14 to 38% of the population, and more than the number of newborn infants. However, smallpox was still endemic with a four-yearly epidemic cycle. Like in India, even a sustained general vaccination programme since the late 19th century did not control the infection. There were cases reported regularly and epidemics occurred every 4–6 years. This paradox was analysed in a one-year study covering a 1–2 million rural population (around Lahore) and, additionally, urban areas of Lahore. The study conducted by Pakistan Medical Research Centre, Lahore in association with the US National Institutes of Health commenced in May 1966 (refs 14 and 15). The findings challenged the belief that mass vaccination with coverage of close to 100% of the population was the key to smallpox eradication. The study brought out that reporting and surveillance followed by containment were as important for success.

While the study argued strongly for priority application of the strategy to West Pakistan, in reality, other countries benefited before the region. Pakistan did accept its own findings ultimately. It took on the surveillance/containment strategy in 1971 and achieved complete success in 1974. On 16 October 1974, the last case of smallpox was recorded in Pakistan from Multan City. Interestingly, the urban centres of Punjab (Pakistan) harboured the last few cases.

**India**: The Indian subcontinent has been regarded as the home of smallpox based on the writings in ancient literature and its deep imprint in folklore. The disease was regarded practically all over the country as a divine dispensation by a Goddess (with slight local modification). The view prevalent in knowledgeable circles was, ‘...because of population density, or for other ill-defined socio-cultural or epidemiological reasons, the eradication of smallpox would ultimately prove impossible’\(^{16}\). A parallel was drawn with the other pandemic infection exported from India – cholera. (The seven global pandemics of cholera have all originated from the Gangetic plains to die out elsewhere each time, but, remaining endemic in the Gangetic delta.) Interestingly, I held the same pessimistic view till mid-1975 and even questioned the veracity of the elimination reports that emanated later in the same year.

Historically, vaccination became established in British India by 1868, after starting as far back as 1802 (just a few years after Jenner introduced it in England!). The vaccination programme resulted in a gradual decline in the numbers of smallpox deaths well into the 20th century. The larger princely states had some similar programmes, but probably not always as good as the main one. Following the decision of the 12th World Health Assembly to undertake global smallpox eradication, the Government of India resolved to fall in line by extending the vaccination coverage. This resulted in an extensive programme that covered all but the most isolated villages. The possibility of the programme achieving its goal of interrupting smallpox transmission was put in doubt, when it was noticed that Delhi, an area that had documented > 80% (vaccination) coverage, had 346 cases of smallpox between December 1962 and May 1963. Sample reappraisal surveys were, consequently, conducted in 18 ‘representative areas’. They showed actual vaccination of 63% of the population with 86% success, i.e. effectively 54% coverage\(^{16}\). This finding at a time when the programme was progressing from the ‘attack phase’ to the ‘maintenance phase’ resulted in the initiation of other studies by the National Institute of Communicable Diseases (NICD) in five districts reporting 80% coverage. The NICD study showed gross deficiencies. Nevertheless, against professional advice the Government of India terminated the attack phase. At this stage India contributed a third of all the smallpox cases worldwide. An
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intensified smallpox eradication programme was taken up in 1967. A joint WHO–India assessment done at that time generated the comment ‘(smallpox programme) is still far from achieving its objective of smallpox eradication in most areas and in fact, a very considerable epidemic potential exists in India at the present time’.17

The conclusions of the report brought out the deficiencies in the programme and recommended to the Central Government the need for ‘a new and long-term strategy to meet (the) problem’. The policy of case detection and containment was recommended along with other administrative measures. The Government did take cognizance of the report and undertook some measures, though the fervour in evidence later had not yet developed. The two major advances that occurred during this time were the setting up of four units for the manufacture of freeze-dried smallpox vaccine under a Central Director. By 1974 the country became self-sufficient, producing more than 9.4 million doses18,19. The thermolability and consequent unreliability of the liquid vaccine was overcome. The USSR donated 5 to 6 million ampoules of vaccine annually beginning from 1962 up to 1974. This was a major input. Gradual adoption of a neonatal vaccine policy decreased the number of susceptible infants. Earlier, A. R. Rao in Madras had shown that vaccination of neonates was effective and safe20.

The second major input was the introduction of the bifurcated needle into India. Its superiority over the traditional rotary lancet was convincingly shown by Pattanayak et al.21. Nevertheless, the bifurcated needle was not fully adopted till 1973. The switch, however, raised a curious issue. The economy of the bifurcated needle (100 vaccinations v/s 15 by rotary lancet/0.2 ml vaccine) attracted the audit objection of vaccine wastage, when the balance left after 40–50 vaccinations/day had to be discarded!

The next phase of the Indian programme was the Intensified National Campaign 1971–1973. This phase managed to substantially decrease the number of cases in the southern and parts of the western region. The epidermics were moving on to the central region. As the programme went on to zero smallpox, the number of reported cases rose sharply. It appeared that the campaign would go the way sceptics had envisaged. Funds were also a major problem. The determination of the government, WHO and Corporate Sector (largely Tatas) paid-off. The most important contribution was the dedication of the smallpox eradication staff at all levels. The diverse contributions are indicated in Table 1. It was a unique cooperative effort of public, private, governmental, NGO and international organizations. The Tata District of Bihar (now Jharkhand) contributed handsomely.

The intense detection and containment programme yielded results and by December 1974, the number of pending outbreaks decreased to less than 500, and only 285 out of the 575,000 villages of India had the infection (Figure 2a and b). From January 1975, Operation Smallpox Zero was taken up. After 1 March 1975, 70 outbreaks occurred in India. Seven states were affected, including only one state outside the central and eastern regions. They were all dealt with by the detection and containment process. Most of the cases were detected promptly. The last indigenous outbreak occurred in Katihar District of Bihar. The first case of this outbreak was detected on 8 May 1975 and after the detection of 16 cases, with one death, containment procedures abated the outbreak.

The last case of natural variola major was detected in the Government Hospital at Karinganj. Saiban Bibi, a 39-year-old migrant beggar woman was infected in Itauri village of Sylhet District, Bangladesh on 13 May, and showed signs of the disease on 24 May 1975. Detection and containment turned up cases of chickenpox and no smallpox.

East Pakistan: East Pakistan had succeeded in interrupting transmission of smallpox in August 1970 after an 8-month programme of surveillance and containment. The next peak season too did not throw up any fresh cases. The civil war of 1971 resulted in a movement of 10 million people out of East Pakistan. These migrants were housed in camps along the border with India on the Indian side, and only a few were vaccinated. When East Pakistan became Bangladesh (on 16 December 1971), the refugees started returning carrying the infection to all

Table 1. Estimated expenditure for smallpox eradication 1965–1977, by source (thousands of US$) in India (after ref. 16)

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†Excludes the estimated value of vaccine provided between 1965 and 1974, which amounted to 701 million doses from the USSR and 5 million doses from WHO.

§Value of contributions in cash and in kind from Tata Industries (US$ 600,000), USA (US$ 402,000), UNICEF (US$ 380,000), and OXFAM (US$ 100,000).
parts of the new country. Transmission persisted year after year, till a concerted effort in 1975 eliminated the infection in October 1975. The last case of variola major in Asia was that of a 3-year-old girl, Rahima Banu, who became ill on 16 October 1975.

Nepal: Nepal started its control activity on a national scale in 1968, and in 1971 monthly winter vaccination was started. The strategy bore fruit and after November 1973, the cases detected were imports from India. These were contained and the last cases occurred in April 1975.

Sikkim and Bhutan were isolated areas which did have outbreaks, but these usually died out, especially in Bhutan. Sikkim had a good vaccination programme. Both the areas probably did not have any case after 1970.

The last case of human variola major in the world was the result of a laboratory outbreak in Birmingham, England. Janet Parker, a medical photographer in the Anatomy Department of the Medical School of University of Birmingham became ill with smallpox on 11 August 1978 and died a month later on 11 September. Her father died of heart attack after developing fever, and her mother had a mild secondary infection. Tragically, Bedson from University Department of Microbiology, who held strains of the variola virus, died after attempted suicide.

After the definition of the last cases in each country, an intense surveillance system was put in place. These included periodic searches in the market place, active searches in high-risk areas and surveys in remote localities of difficult areas, continuous routine surveillance by public health staff, solicitation of reports from non-medical governmental staff and the public by offering an inducement in the form of rewards. An International Commission, set-up for the purpose, finally declared India free from smallpox on 23 April 1977. The WHO-appointed International Commission certified global eradication of smallpox on 9 December 1979. A parchment has been issued.

The Global Commission for the certification of smallpox eradication made 19 recommendations that prescribed various actions to ensure that the confidence the health professionals had of having eradicated smallpox percolated down to the public domain. This was necessary, as the very idea of eradicating a traditional killer disease was novel. These recommendations resulted in the gradual discontinuation of routine national vaccination programmes. By 1982, all the countries of the world, except Albania and France (permitted revaccination only) had stopped vaccinating routinely. In 1984, even these two countries gave up vaccinating routinely.

Discontinuation of routine vaccination of military personnel did not necessarily follow suit. Political considerations dictated the decisions. The reports of the spread of vaccinia from new military recruits to close contact (as in the case of National Guards vaccinees in Wisconsin, USA) prompted the WHO committee on orthopoxvirus infections to issue a specific recommendation of segregation of military vaccinees in their bases for two weeks.

Thus, at the present time vaccination is required only in the case of investigators at ‘special risk’. Other recommendations covered maintenance of a WHO reserve stock of vaccine, investigation of suspected smallpox cases and the holding of laboratory stocks of variola virus.

The potential hazard of holding laboratory stocks of the variola virus was brought out clearly by the 1978 Birmingham outbreak (loc.cit.). Starting from 75 collections all over the world, only two repositories were left in 1983. These two laboratories, constructed according to WHO-authorized plan, were in USA (Centers for Disease Control, Atlanta, GA) and the former USSR (Moscow Research Institute for Viral Preparations, Moscow). They are periodically inspected. It was originally envisaged

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Figure 2. Distribution of outbreaks in 1974 (ref. 1).
that variola DNA would be cloned into a suitable bacterium (e.g. *Escherichia coli*) and the residual infective stocks would also be destroyed. However, this has not happened and the two authorized stocks are still held. The Moscow stocks were transferred to the Russian State Center of Virology and Biotechnology (Vektor Institute) in Novosibirsk. The ‘Biopreparat’ programme of the Soviet Union involved massive cultivation of the variola virus as a biological weapon. There is considerable apprehension that unauthorized stocks of variola exist in other repositories. The post-USSR scenario has been reviewed by Henderson\(^{(22)}\), and by Preston in his sensational novel *The Cobra Event*\(^{(25)}\).

As the years passed and investigations of suspicious outbreaks and follow-up of rumours all over the world did not yield a single confirmed case of smallpox, the elimination of the disease has come to be accepted. It was felt at this juncture that the following three questions needed to be answered, if humanity is to be assured that the variola virus has vanished in nature outside the known legitimate (and covert) laboratory confines:

(a) Is there any natural source of the smallpox virus left?
(b) Can a new strain of variola evolve from the different orthopoxviruses infecting other mammals?
(c) Is there an animal reservoir of the variola virus?

Fortunately, it now appears that the answers to all the three questions are negative and smallpox eradication is permanent. Some of the evidence is discussed further.

The passage of time and the infectivity decay pattern of the variola virus left two possible sources of the natural virus worth considering. One of these was the stock held by variolators, particularly in cold countries like Afghanistan. An examination of the practice in Afghanistan revealed that, even in suitable conditions in the country, infected scales or pustular fluids used by variolators did not retain their infectivity beyond a year. The absence of any fresh variolation – triggered outbreaks in all these years rules out the source. Ewart (quoted by Fenner and Arita\(^{(26)}\)) pointed out the possibility of smallpox remaining preserved under permafrost on the shores of Hudson Bay in Northern Canada, in the bodies of six Indian victims of a 1782 outbreak, buried in wooden coffins. It was postulated that the viable virus could contaminate the natural waters when the graves eroded. The speculation has had no scientific support.

The animal poxviruses have all been examined in depth for their capability to revert or mutate to variola. While most of them like cowpox, camelpox or buffalopox do produce single or multiple lesions in humans who are exposed to them, they do not cause generalized disease or have a sustained human infection chain. The one infection that has been under great scrutiny is the causative agent of monkeypox (see Box 5). The demonstration of ‘whitepox’ mutants (referring to the colour of the pocks produced on the chorioallantoic membrane of the developing chick embryo) of the monkeypox virus by Marennikova and Shelukhina\(^{(27)}\) raised serious apprehensions. However, a detailed study into the laboratory practices and DNA maps has convinced that the dangers of variola arising as a white virus mutant do not exist.

The third question has likewise been examined in depth. Variola is infective to the apes, and occasional infections of rhesus monkeys in close contact with humans have been recorded. Experimental infection and monkey-to-monkey transmission have been described by Noble...

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**Human monkeypox**

The first case was seen in the Equateur Province of Zaire amongst primitive farmers and hunter-gatherers living in small villages in dense tropical rainforest\(^{(28)}\). The area did not have smallpox after 1968. The material from the skin lesions yielded a virus that differed from variola in producing haemorrhagic pocks on the chorioallantoic membrane and in producing large lesions in the rabbit skin. Extensive surveys in the rainforest region of Central and West Africa showed that pockets of infection were present in the entire region.

The infection itself occurred predominantly in children (of both the sexes). The primary infections were common, though person-to-person transmission did occur, particularly in adults. Though four transmission cycles have been reported, usually a single secondary spread is the rule.

Clinically, the distribution of skin lesions is similar to that of discrete smallpox. There is concomitant swelling of the lymph nodes in the axillary, inguinal or submandibular regions. The case-fatality rates could be as high as 10%, with largest number of deaths in the under 4-year age group. A large outbreak of 92 cases in the Kasai Oriental province of Zaire\(^{(29)}\) demonstrated some changes in the post-vaccination era. A large number of older patients were seen and longer person-to-person chains were demonstrated. A lower fatality rate of 3%, all in children under 3 years of age was seen. It also demonstrated the value of vaccination in protecting against the infection.

Monkeypox has been identified as a zoonosis, with arboreal squirrels of the genus *Funisciurus* being the major reservoirs. Fears of the virus mutating to variola have been unfounded (so far!)

**Box 5.**
and Rich\textsuperscript{28}. They managed to serially passage, but ultimately the virus died out. Whitepox isolates from animal tissues have also been recorded in a number of laboratories, but like the whitepox mutants of monkeypox described above, they have been tracked to laboratory contaminations. The strongest argument against an animal reservoir of smallpox has been the absence of outbreaks in Africa, where the infection remains endemic and the degree of contact of human beings with domestic and wild animals continues. Likewise, in parts of Asia, communities living in close association with animals as before, have not experienced smallpox infections after the disease was eliminated.

Thus, the chances of smallpox re-emerging from natural foci appear extremely remote (since impossible can never be used in biology\textsuperscript{1}). The only way in which smallpox can return is by a deliberate introduction from known or unknown repositories under human control. In the present smallpox zero state, that could happen when biological warfare or bioterrorism is resorted to.

The relative stability of the virus, its ability to infect by the aerial route, its capacity to produce a severe disease with significant (up to 30\%) mortality and establish an outbreak in susceptible populations makes smallpox a favoured biological warfare/terrorism weapon. It poses at least as great a threat as anthrax. In fact, in view of its transmissibility and there being no antibiotic against it and with nearly 80\% of the population of all countries susceptible, smallpox is the greatest bioterror threat. The \textit{modus operandi} developed by Preston\textsuperscript{27} makes frightful reading. It is in this context that one needs to revisit this extinct disease.

While the dangers of biological attacks were already realized, the ruthlessness and audacity of the 11 September 2001 attacks on the Twin Towers in New York have brought the issue into sharp focus. The article by Breman and Henderson\textsuperscript{2} in a widely read medical journal, underscores the anxiety.

It is envisaged that whenever a biological attack would be launched, the ability of variola to cause a visible infection, create panic and severely strain the medical and public health systems would have a major social impact. The current US National Interim Smallpox Response Plan and Guidelines envisages the use of the ring vaccination strategy, that was used successfully during smallpox eradication\textsuperscript{29}. The vaccination strategy would be coupled with case-detection, segregation and epidemiological studies. The premises on which the policy is developed have, however, been questioned on the basis of the Yugoslav and German outbreaks in the 1970s where each infected case had 11 to 38 contacts against the CDC assumption of two contacts per case\textsuperscript{30,31}. A case for voluntary vaccination of the general population is put forward. The restriction on the mobility imposed by the disease on infected subjects (as a factor limiting its spread) during the early infective stage has also been questioned.

Apart from the cost and logistics, particularly in the developing countries, the well-recognized hazards of vaccination have to be taken into account in the background of the absence of the natural disease and an ‘imaginary’ risk (see Box 6). At the present juncture, global stocks of smallpox vaccine are limited. Some countries like USA hold national stocks, but the vast majority would rely on the WHO stocks maintained in Geneva. USA has started action to become self-sufficient for the entire population by the end of 2002, by acquiring privately held stocks (in pharmaceutical stores) and by ordering fresh production\textsuperscript{32,33}.

A silver lining in the cloud is the demonstration that the freeze-dried vaccines prepared according to the standards laid down during the eradication days, can be diluted five-fold without affecting their efficacy. This would enhance the amount of vaccine available to face emergencies\textsuperscript{34}.

The question that would arise is the following: is India in any danger from smallpox?

Natural smallpox has been eradicated from the entire subcontinent, convincingly. Any smallpox that may arise would be the result of deliberate introduction to disrupt the society. In the present political milieu, such an attack is not impossible. If so, are we prepared?

In the final years of the smallpox eradication programme, India was self-sufficient in freeze-dried vaccine. The production facilities have closed down for over 25 years. There is no mention in governmental communications about a stock. If that is true, we are open to attack and will face a major catastrophe, if it materializes. It is sobering to realize that nearly 64\% of our population of 1027 millions\textsuperscript{35} has never been vaccinated, and the remainder has not been revaccinated for the past 26 years. If we assume that 50\% of the once vaccinated individuals have lost their immunity, the total susceptible pool in India is over 800 million! It is, therefore, necessary for the nation to debate this issue and arm itself with an appropriate action plan.

Finally, if at all smallpox reappears amidst human populations, it would need to be countered vigorously. Biotechnology has progressed considerably since the late 1970s and the re-eradication process can be approached

### Box 6.

<table>
<thead>
<tr>
<th>Hazards of smallpox vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US national data for 1968</strong></td>
</tr>
<tr>
<td>Total number vaccinated</td>
</tr>
<tr>
<td>Deaths attributed to vaccination</td>
</tr>
<tr>
<td>Post-vaccinal encephalitis</td>
</tr>
<tr>
<td>Progressive vaccinia</td>
</tr>
<tr>
<td>Eczema vaccinatum</td>
</tr>
<tr>
<td>Complications rate</td>
</tr>
</tbody>
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\textsuperscript{29-35}
different. The legitimately held stocks of the virus can be of some use in this context. Le Duc et al. have reviewed the present position regarding the matter. The major aspects to be researched are: (a) obtaining sequence data, (b) developing a variola-specific detection test, (c) developing new drugs to prevent or treat smallpox infections, (d) developing effective and safer vaccines and (e) validating an animal model of human smallpox. With these objectives in sight, it would be sometime before the last vestiges of smallpox (in legitimate repositories) will be destroyed.

This article has tried to project the fascinating story of smallpox with a view to educate. I sincerely hope that it does not portend the return of the disease.

22. See ref. 5, pp. 1097–1098.

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