Smallpox eradication—the final battle¹

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If ever there was an appropriate time to pay homage to the remarkable and renowned Dr Jenner, this is it, for today we believe we could be only months away from that day when we will detect and contain the world's last case of smallpox.

If a day and a place could be identified which might mark the nascent beginning of the global campaign, we might select a day in May 179 years ago—and a place not far from Bristol—when Dr Edward Jenner inoculated the boy James Phipps with matter from a cowpox lesion on the finger of the dairymaid Sarah Nelmes. The inoculation was successful. Forty-eight days later Dr Jenner inoculated the boy with smallpox virus and showed that he was protected. Despite the obvious difficulties of travel and communication at that time, it was only a few years before Jennerian vaccination began to be employed in Europe, the Americas, Asia, and Africa. This fact alone bears witness to the significance of the discovery.

And it was Dr Edward Jenner himself who wrote in 1801, 'it now becomes too manifest to admit of controversy that the annihilation of the Smallpox, the most dreadful scourge of the human species, must be the result of this practice (of vaccine inoculation)'. Today, almost 175 years later, the end at last appears to be in sight. Smallpox persists at present in only three countries—India, Bangladesh, and Ethiopia. But India, a vast country with more than 550 million population, detected only seven cases during the fourth week in April 1974—in fact, the last known indigenous case occurred on 20 April in a 5-year-old girl vaccinated early in the incubation period of the disease. Her illness was so greatly modified that in previous years it might never have been detected. Although this may not be the last case, the end is rapidly approaching. In Bangladesh, only 1200 of its 150 000 villages are now infected, and in Ethiopia, 114 villages. For both countries May is the usual peak of the smallpox season. In the heat of summer and during the monsoon rains, smallpox is transmitted from one person to another with difficulty. If no measures whatsoever were taken,

we would expect between May and October a decrease of 80 % in the infected villages as well as in the number of cases. However, today the most intensive campaign ever mounted to detect smallpox cases and to stop the spread of smallpox is now in progress.

With the end in sight there could be no more appropriate time to pay homage to the man whose work and writings made this possible.

I think that to appreciate the importance of Dr Jenner's vaccine to the world in which he lived and to subsequent generations one must appreciate the problem of smallpox in eighteenth century Europe before any form of protection was available.

Razell, in his treatise *Population Changes in Eighteenth Century England*, documents vividly the impact of smallpox in the early 1700s. From parish registers, bills of mortality, and special smallpox censuses of the time he estimates conservatively that not less than 15 % of all children who were born eventually died of smallpox. The figure is almost certainly conservative, for we know now that in unvaccinated populations essentially all who are born eventually contract the disease, its behaviour being somewhat like that of measles in this regard. Sub-clinical infections among the unvaccinated are unknown and there is no treatment even today. Thus, the percentage who died was probably little different from that observed today in Asia—fully 20 to 25 %. One of many contemporary observers commented: 'When smallpox is epidemic, entire villages are depopulated, markets ruined and the face of distress spread over the whole country.' In areas of central Europe at that time it was said that the newborn child was not given a name until after he had experienced smallpox and survived. Blindness was a significant problem and smallpox was reported then to have been its chief cause in Europe. No other disease, past or present, has come close to wreaking such havoc.

But by Jenner's time, smallpox in England had become less of a problem than 50 years previously. The technique of deliberate inoculation of smallpox virus into the skin was introduced in the early 1700s and, after a prolonged period of controversy regarding its use, began to be widely applied in England in the 1760s. Among those artificially inoculated in this

¹The First Jenner Memorial Lecture delivered at Bristol Royal Infirmary on 1 May 1975

manner the proportion who died was far less than among those who acquired smallpox in the natural manner. The data are not precise, but, in contrast to smallpox which killed one in five, artificial inoculation of the virus caused death in perhaps 1 in 100 or even fewer. By 1776, Daniel Sutton alone claimed to have variolated 300 000 persons or 5% of the estimated population of England and Wales. Among the more prosperous the procedure was relatively commonplace. But it was also practised among the poor. Many parish authorities commented that they found it less expensive to pay for the inoculation of all within their parish than to pay the costs of isolating and nursing the sick and burying the dead among the poor afflicted with smallpox. Edward Jenner himself was inoculated (variolated) as a boy at Wootton-under-Edge in 1756.

But variolation was hazardous—a person so inoculated can transmit the natural disease to others, and many outbreaks developed as a result of variolated persons coming in contact with susceptible persons.

Jenner's cowpox offered extraordinary advantages. Death following administration of cowpox was almost unknown, and the cowpox virus could not be spread naturally from person to person as the smallpox virus could.

The technique of Jennerian vaccination spread world-wide. Initially the cowpox virus was transferred from person to person. Matter was taken from the vesicle or pustule of one inoculated person and transferred to the next, an approach called arm-to-arm vaccination. However, there were problems. If only a few were being regularly vaccinated, failure to obtain a satisfactory take meant that fresh material must be obtained—specifically, another individual in the early stages of development of a vaccination reaction. In isolated areas—and there were many—this was not easy. And sometimes when vaccination was performed, syphilis and hepatitis were simultaneously transferred.

Eventually, the technique of scarifying the entire flank of a cow came into practice, thus making available a large quantity of cowpox virus for inoculation. An Indian colleague of mine, now in his 80s, recalls vividly the practice when he was a boy in India of leading from door to door an inoculated cow and scraping off a bit of matter for inoculation at each house.

As vaccination became increasingly common, smallpox began to recede, especially in temperate climates where preservation of vaccine was less of a problem. And the refrigerator played a role. In fact, Dr James Leake attributes the marked reduction of smallpox in the Americas in the 1930s to the widespread introduction of the refrigerator.

The elimination of smallpox in Europe and North America surprisingly did not occur until the 1940s. Primarily, I believe this resulted from the fortunate or unfortunate replacement of the virulent variola major strain of smallpox by variola minor (1% death rate). This strain appears to have originated in South Africa but spread subsequently to the Americas and to Europe about the turn of the century. In Europe and North America, interest in the control and elimination of smallpox waned. As recently as 1927, the United Kingdom alone recorded some 14 900 cases, but only 47 deaths; the United States reached its peak in incidence in 1930 with some 49 000 cases and 173 deaths. For reasons unknown, however, variola minor never extended much beyond the Americas, Europe, and South Africa. In the rest of the world variola major remained the dominant type.

In the 1940s, North America and Europe finally became free of smallpox as a result of more widespread vaccination and as a result of local efforts of varying intensity to stop outbreaks where they occurred. The tropical areas, although beset with the far more malignant variola major, were at a great disadvantage as vaccines of satisfactory stability were not available, health services were limited and transport was a problem.

Jenner's hope for annihilation of the smallpox remained frustrated until in 1950 the venerable proponent of the concept of disease eradication, Dr Fred Soper, propounded a programme for smallpox eradication in the Americas. Smallpox transmission was interrupted in most countries. But Brazil, the largest of the countries in South America, remained a non-participant. Inertia set in, pious resolutions were passed annually at the Pan America Health Organization's Annual Governing Council Meetings but little further progress was made.

Interest in smallpox eradication spread to the World Health Assembly where interminable discussions about smallpox were conducted annually. But neither funds nor a coherent World Health Organization programme evolved. In 1958, the Soviet Union spearheaded a resolution to have the Assembly accept the principle of eradication as a policy, and this was adopted, but most countries were much too preoccupied with a new scheme to eradicate malaria to do more than give a passing nod to a smallpox eradication programme. Between 1958 and 1966, a number of countries undertook programmes, and some in North Africa, Iran, and a few other countries appeared to be successful—I say 'appeared', because at that time not the slightest effort was made to try to improve the reporting of smallpox cases. As we later discovered, some countries reporting a nil incidence during this period

had in fact simply eliminated smallpox by government decree. But finally, in 1966, delegates of several countries proposed to the Assembly that a special budget for smallpox eradication be approved to intensify activities. Some officials in the World Health Organization were less than enthusiastic, having gradually come to an appreciation of the difficulty, if not impossibility, of malaria eradication and were hardly anxious to take on a second eradication programme; a number of prominent delegates were highly sceptical of the theoretical or practical feasibility of such a project; some had reservations in regard to the Organization's ability to execute such an extensive programme. The resolution passed, however, and under this less than auspicious cloud, the programme was launched in January 1967 with the hope expressed that eradication might be achieved in 10 years. As John Hunter had once advised Jenner, the delegates to the Assembly were saying, 'But why think? Why not try the experiment?'

The intensified global programme of smallpox eradication began in January 1967. At that time 42 countries reported cases of smallpox and in 30 of these the disease was considered to be endemic (fig 1). In that year 131 000 cases were reported. However, subsequent surveys in Africa and Asia showed that much less than 5% of all cases were reported. Thus, in all, there occurred that year at least 2 500 000 cases.

The budget provided to the programme by the Assembly was less than US \$3 000 000, a pathetically small sum considering the task set out, but fully 3% of the Organization's total budget.

The vaccine needs alone were estimated to be between 200 and 250 million doses. If purchased, the cost for the vaccine would have been greater than the entire budget for smallpox which was provided to WHO. A number of laboratories in the endemic areas were producing freeze-dried vaccine but examination of specimens showed that almost none of this vaccine met WHO standards in regard to potency, stability, and purity. Some samples of vaccine, in fact, revealed no detectable virus whatsoever. The quandary as to how to provide vaccine to the programme was approached by soliciting donations of vaccine and by providing assistance in the form of equipment and supplies, consultants, and standard production manuals to laboratories in the developing countries. During the first few years of the programme, the Soviet Union donated approximately 140 million doses annually and the United States of America 40 million doses, but donations were also received from almost 20 additional countries. All vaccine which was donated was tested in one of two international reference centres, in Canada and in the Netherlands, and provision was made for testing samples of vaccine produced in other production laboratories throughout the world. Vaccine production in the endemic areas

Fig. 1 Smallpox cases per 100 000 inhabitants, 1967

gradually increased, and now some 80% of the vaccine used in the programme is produced in laboratories in the developing countries themselves. All of this vaccine is subjected to quality control by the countries, and sample batches are regularly assessed by the international reference centres.

A second problem confronting us when the programme began was in regard to vaccine administration. The scratch technique was widely used throughout much of the world, but this technique produced a lower proportion of satisfactory takes than did the multiple pressure technique. Unhappily, the multiple pressure technique was very difficult to teach to vaccinators. An alternative and new technique, the jet injector, was initially introduced for use in programmes in South America and western and central Africa. This device proved most efficient in administering vaccine to large numbers of people, and take rates were as high as those obtained with the multiple pressure technique. However, the jet injector, like any other mechanical apparatus, required maintenance, repair, and a continuing supply of spare parts. In the developing countries, it was difficult to assure adequate repair and maintenance. In 1968, however, Wyeth Laboratories in the United States developed a forked needle intended for multiple pressure vaccination. This needle offered considerable advantages in that only one-fourth as much vaccine was required for vaccination as with the conventional techniques. Studies were undertaken by WHO to determine if the needle could be used for multiple puncture vaccine, a vaccination technique in which the needle is held at right-angles to the skin surface and a series of punctures are made. Studies showed that this technique of vaccination, even when blood was drawn, produced as high a proportion of takes as the multiple pressure technique. The needles could be re-used many times and thus were a very economical instrument. These were introduced late in 1968 and have been employed subsequently throughout the world.

The problems of vaccine supply and vaccine administration having been solved, attention was directed to the strategy of the programme. For many years, the approach in virtually all countries endeavouring to eliminate smallpox was, simply, mass vaccination. Little attention was paid to reporting, to the detection of cases, or to the containment of outbreaks. A WHO Expert Committee considered the question and had initially recommended that a target be established calling for vaccination of 80% of the population. However, experience showed that even when 80% were vaccinated, smallpox often persisted. The only solution which the Committee offered was to suggest vaccination of 100% of the population, an objective which obviously is im-

possible to achieve. However, early in the course of the global campaign it was found in eastern Nigeria that the detection and containment of smallpox outbreaks alone resulted rapidly in a cessation of smallpox transmission even in a population which was poorly vaccinated overall. Similar observations were soon made in other countries of Western Africa and subsequently in Brazil and Indonesia. Because of this, the strategy of the campaign was shifted to emphasize that detection and containment of outbreaks was not of equal but of greater priority than mass vaccination. Gradually this became a policy which was followed throughout the endemic countries. While mass vaccination was still conducted in most countries, it was definitely relegated to a secondary, supporting role.

Just over eight years have passed since the programme began. As noted, the World Health Assembly, when it decided to embark on the programme, expressed the hope that it might be completed within 10 years. This goal we believe can and will be achieved. When the programme began, four areas were delineated—South America, Africa, mainland Asia, and Indonesia. It was considered that the amount of communication between any two of these areas was sufficiently small that if smallpox were eliminated from one of the areas, it was not likely to be re-introduced. In fact the experience of the past eight years has revealed no importation of smallpox from one of these areas into a second. The first of the areas to become free of smallpox was South America, the last case having been reported from Brazil in April 1971. The second area, Indonesia, detected its last case in January 1972 (fig 2). In each of these areas, just over two years after the last case, international commissions were convened to determine whether or not the commission was satisfied that smallpox had been eliminated from the areas. In both cases, after a full review of the programmes and selected field visits, the commissions agreed that smallpox had been eradicated. In all of Africa only one country (Ethiopia) now remains endemic for smallpox, and on the mainland of Asia only two countries (India and Bangladesh).

The smallpox epidemics in India only nine months ago were the subject of international headlines. As of the end of April 1974 only 29 villages had experienced one or more cases of smallpox within the preceding six weeks and so were considered infected—18 of these were due to importations from Bangladesh. The last known case in India had its onset on 20 April. Undoubtedly others will be found, but they should be few. And now with a 100 Rupee (about £5) reward to anyone reporting a previously unknown outbreak, cases are being found very quickly. In the process, literally thou-

Fig. 2 Smallpox endemic countries, 1967 and 1974

sands of cases of chickenpox, scabies, and other skin rashes are being checked daily. To double-check the situation, an India-wide house by house search was conducted. One hundred thousand workers visited 110 000 000 households—and to make sure that the work was really done, a sample of 5 to 10% of all villages was cross-checked by independent field teams. Only one previously unknown outbreak of two cases was discovered. Although importations from Bangladesh will undoubtedly continue to occur, the last indigenous case in India should occur in a matter of days to, at most, a few weeks.

In Ethiopia, despite civil strife and some of the most difficult geographical problems encountered anywhere, the work goes on. Fortunately, Eritrea, where the fighting has been most intense, has been smallpox-free for almost three years. In the remaining highly circumscribed infected areas, over 200 Ethiopian sanitarians and health worker volunteers from Japan, Austria, and the USA are continuing to work. Government support is in fact better than before, and since November 1973 two helicopters have been working in support of the team. Periodically, the staff must now withdraw from localized areas because of civil disorders but, so far,

they have been able to return to these areas to work. Cases are almost 60 % below the number of a year ago, and now just over 100 villages are infected. But the outbreaks are small, and the villages which are comparatively isolated now have higher levels of immunity. When the summer rains begin in June movement becomes difficult, smallpox spreads more slowly, and experience shows that at low levels of incidence, such as we now have, it frequently dies out spontaneously. Such, we hope, is the script that Ethiopia will follow.

The great tragedy and setback for the programme in 1974 occurred in Bangladesh, which at the end of April harboured more than 90 % of the world's smallpox. As long ago as August 1970, smallpox had been eliminated from Bangladesh—the first of the Asian countries to succeed since the intensified programme began. But 18 months later, in February 1972, massive numbers of importations occurred as thousands of infected persons from a refugee camp near Calcutta returned after liberation, and smallpox spread rapidly through the war-torn country. In the summer of 1974 victory again appeared to be within grasp when, suddenly, the worst floods in more than 20 years inundated the northern districts, the only

areas at that time which were still endemic. Health staff were diverted for flood relief work, food distribution, and cholera control, and hundreds of thousands of refugees began to move in search of food and employment, and smallpox began to spread. In January 1975 came the final blow when almost overnight the slums in Dacca, housing some 400 000 persons, were cleared by bulldozers. Fully half the population left for their home districts and, what were limited outbreaks in Dacca, became dozens of outbreaks scattered across the southern districts. In February 1975, an emergency programme was begun under Presidential directive; more than 60 international staff were brought in but only in mid-April was the previously explosive spread stopped. A tough and difficult battle still lies ahead but with a bit of good luck and a great deal of hard work the last case could be found before the end of August. But, even with less than optimal circumstances, it is difficult to foresee smallpox being present after December 1975.

The essence of what has made the programme what it is is, very simply, an imaginative and dedicated field staff, both national and international, who, given scope and encouragement to work out problems according to local circumstances and support in their efforts to do so, have responded with some remarkable solutions to impossible problems.

The primary strategy of the programme, as I noted, is rapid detection of each outbreak and its containment. Since smallpox must spread from man to man in a continuing chain of infection, the objective is to break each of the chains by isolating the case and vaccinating the contacts. In some areas, this is easier said than done. In more primitive areas, villagers resist vaccination. Bihar, India was a special problem last year. Persuasion and sometimes police helped to overcome resistance. Highly effective, however, proved to be what was called the 'dawn raid'. A large vaccination team was formed and this descended on the sleeping villagers at 4.30 am. Vaccination was quickly completed and surprisingly the team then enjoyed a convivial breakfast with village elders who explained that, by tradition, they were supposed to resist vaccination but, once defeated, their tradition called for hospitality. However, in one case, even this and all other efforts failed as the team was repeatedly driven off by spears and arrows. The epidemiologist decided to make one last effort and approached the village one morning for his fifth attempt in as many days. A long and futile discussion ensued with the well-armed chief and his villagers as to whose powers were greater—the chief's or the epidemiologist's. Finally, keeping his eye on his watch, the epidemiologist raised his hand, a great silver bird miraculously appeared,

dived on the village, and dropped a large number of picture cards about smallpox and vaccination. The chief capitulated, the village was vaccinated, and the local flying club received a letter of thanks.

While such events are dramatic, I think we must describe most of the work of both national and WHO staff as arduous and tedious, involving hours and days of walking, of fording rivers, riding on camels, mules or sometimes elephants, and bouncing over rough roads by bicycle, motorcycle or landrover; of living under the most difficult of field conditions and surviving as best they can on the food which is available. Not surprisingly, consultants serving in India and Bangladesh customarily lose 4-10 kg in weight over a three-month period of service. But morale and enthusiasm are high.

A not atypical example is a young woman physician whom I met on leaving India after three months of service, regretting bitterly that her institute would not permit her to stay a further six weeks. She had been posted in a small district capital where she lived in a village house, subsisting on chapattis, vegetables, eggs, and an occasional chicken, and returning to Lucknow two days each month for a state-level planning and coordination meeting. The work was done by bicycle, bullock cart, on foot, and, on two occasions, by rented elephant. But the classic story of transport problems stems from Ethiopia and the report of two cases of smallpox from an area near the Sudan border thought to be free of smallpox. The message had been carried from a small mission station by a runner who travelled for two days to the nearest police radio. At the time the only airstrip anywhere near the area was under water. The only way to check the report was on foot—315 miles. The surveillance officer took 15 days to reach the area—both cases were chickenpox.

The examples are many: an Afghan surveillance team who travelled for four days on foot and horseback through metre-deep snow to reach an outbreak; an Indian District Health Officer and his team who were captured by tribal villagers and saved at the last minute from execution by burning, but who returned to control the outbreak; a Pakistan surveillance agent captured and held for ransom by insurgents, but who on return refused transfer from his assigned area.

Although one might assume that classroom training of the national staff involved in the programme would assure a satisfactory result with much less strain, it has become abundantly clear to all of us that this is at best only a partial answer. Successful execution of the programme consists of perhaps 10 % technical skill and 90 % organization and leadership. But effective leadership to solve the problems faced by field workers cannot be supplied by an army of

physicians and senior supervisors who never leave their desks. Regrettably, these types are all too plentiful throughout the world. A classic illustration of the armchair disease came to light in India when a distinguished Indian professor of social and preventive medicine, who volunteered for three months' service, admitted that never in his life had he visited an Indian village. And perhaps the disease is not so uncommon in WHO, for in 1967, when we undertook our first full assessment of a programme, I asked our Regional Office if they could provide the requisite sleeping bags and mosquito nets. The request was met with astonishment as I was told that consultants never required such things as they *never* ventured *that* far into the field.

With senior national as well as WHO smallpox staff moving actively in the field, many of their hitherto desk-bound counterparts have frequently responded as well, and the effect has been surprising—lower level staff have worked harder and with greater enthusiasm and, in the process, they have found better and more effective methods for coping with the problems.

It is the field staff who have shaped the strategy and tactics of the eradication programme. New concepts and alternate approaches to problems are constantly being experimented with. I can say without qualification that no two national eradication programmes are identical and, further, that in any one country the programme of today is considerably modified from that of a year ago, or even six months ago. More significant is the fact that almost every new development in the programme has stemmed from field staff.

But at what cost has all this been done? In terms of international resources, if one adds together all that has been provided through WHO's regular budget plus all of the funds provided to WHO's

Special Account for Smallpox Eradication, plus all that has been given through bilateral donations, the total over 8½ years is \$57 million, almost precisely the cost of one large C-5 transport plane. The burden of expenditure has been borne by the endemic countries themselves, a total which is several times this figure. But, with few exceptions, the expenditure by the countries has been little more than what they were already spending to *control* smallpox. In other words, WHO and its member countries, with only a very modest additional input in resources, have transformed a neverending control programme to a successful *eradication* programme.

For all of us it has been a revelation in so many countries to find at the periphery such an array of unproductive health staff and facilities. It has been a revelation to discover how effectively they may be mobilized with a comparatively small input involving leadership in the field and definition of a series of activities with defined objectives and a modest element of management. Other health programmes, especially those involving immunization, but others as well, could, I believe, be similarly transformed.

For all of us in the smallpox eradication programme a tough, difficult final battle remains, but the end is in sight. At the same time, for WHO I believe there are new horizons opening as we study the lessons of this programme and apply these to other areas.

Jennerian vaccination antedated the development of any other vaccine by fully 80 years, but the principle employed was the inspiration for Louis Pasteur in his development of the next vaccines. At this time we do not have the technology to permit the eradication of another disease, but hopefully the programme of smallpox eradication will serve to pioneer more effective programmes in public health and eventually the eradication of other diseases as well.