

## Review

# A Personal Recollection of Smallpox Eradication with the Benefit of Hindsight: in Commemoration of 30th Anniversary

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**SUMMARY:** This year 2010 marks the 30th anniversary of smallpox eradication, as declared by the WHO Assembly in 1980. As someone who worked for this program for many years, I would like to present my recollection of how it succeeded and what lessons can be learnt, with the added benefit of hindsight. The program achieved the global unification of mankind despite differences in race, nationality, religion, and politics, and research contributed significantly to building the effective strategy that ultimately led to success. These lessons should be useful in a designing a planning solution for many of the problems we face in today's changing world, including problems regarding health security and even those in current and future socioeconomic regions.

## 1. Introduction

In its discussion of global public health security in the 21st century, the World Health Report 2007 notes that the "greatest fear is that in the absence of global capacity to contain an outbreak rapidly, smallpox might reestablish endemicity, undoing one of the public health greatest achievement" (1). This fear is heightened by concerns that the current HIV epidemics in sub-Saharan Africa may reduce the effectiveness of smallpox vaccination, should immunization be necessary to control imported epidemics, and the limited health resources available in that region.

I worked for the World Health Organization (WHO) global smallpox eradication program from 1962 to 1966 (the preparatory period), 1967 to 1980 (the intensified program), and 1981 to 1984 (post-eradication preparation and documentation). Eradication was declared successful by the World Health Assembly (WHA) on May 7, 1980.

Today, on the 30th anniversary of smallpox eradication, I would like to share my recollections of how eradication of this disease was achieved and suggest some lessons that this unprecedented event in the history of human biological evolution might have for the future of global health security and even, perhaps, the future of humanity itself.

## 2. Smallpox eradication from 1958 to 1966

In 1958, in response to a proposal by the Russian delegate, the WHA resolved that WHO member states should launch a global smallpox eradication initiative. This initiative was considered technically feasible as man is the only reservoir of smallpox virus and an effective vaccine was available. Although reporting completeness was very low, 61 countries reported a total of 276,000 cases in 1958. Of these, more than 95% were from South Asia and sub-Saharan Africa; India, with 85,000 cases, reported the highest number, followed by Bangladesh, Pakistan, and Nigeria.

Over the following 10 years, many countries attempted eradication programs, and almost every year the WHA encouraged member states with endemic smallpox to reach 80% vaccination coverage of the total population (WHA 17.43, 1964). After this period, however, there were still 47 countries reporting smallpox, with a global reported total of 132,000 cases.

Many smallpox endemic countries were not able to support the vaccination program due to shortage of vehicles, personnel, vaccine, and local funds to support operating costs such as petrol, per diem, etc. Indeed, the WHO itself was short of full-time officers, with only one at Headquarters (HQ), no officers in the regional offices, and only a few at county level. Furthermore, there was no regular WHO budget to support countries' programs, and only donated vaccine was available.

**With hindsight:** During this period, the eradication initiative was characterized by several features, including

1. The eradication strategy was based on the assump-

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tion that 80–100% coverage in the general population would be sufficient to interrupt transmission in 3–5 years.

2. Resources for expanded activities, such as vaccination of newborn infants, were limited.
3. Countries with low levels of routine coverage faced severe resource shortages, thus limiting their ability to reach such high levels of population coverage.
4. There was no research strategy, plans, capacity, or activity.
5. There was no effective surveillance in developing countries, thus resulting in an inability to evaluate the progress of eradication correctly.

The strategy and resources available during this period were able to reduce smallpox incidence to some extent, although the goal of complete eradication remained remote. However, the willingness to improve the situation still remained in both smallpox endemic as well as non-endemic nations, therefore the program was intensified over the period 1967 to 1980. To my mind, the factor that most encouraged countries to persevere with this project was that smallpox was clinically very well understood, therefore any small or seemingly insufficient preventive measures, such as occasional vaccination campaigns, always provided promising results. Furthermore, the disease was so disastrous that its eradication would be worthwhile, which encouraged both rich and poor nations to work together, as we will see below.

### 3. WHO Executive Board (EB) debate in 1966

In 1966, I was a member of a WHO assessment team which visited Mali, Nigeria, Afghanistan, and Burma to study how to strengthen the program; only Burma was implementing the eradication work as planned. Our team confirmed the difficulties mentioned above and, in 1966, the WHO proposed to the EB that a 10-year regular budget, with 5% annual increases, be established to strengthen the WHO Secretariat and national eradication programs. Of the total WHO annual budget of US\$50 million, the estimated budget for the intensified smallpox eradication program was US\$2.5 million. Many EB members were critical of such a significant budget increase targeted at the eradication just one disease, namely smallpox. Indeed, a compromise budget increase of US\$1 million was proposed by one member. Fortunately, the original proposals were finally approved by a margin of just two votes. This vote provided the resources for the intensified smallpox eradication initiative to begin in 1967.

**With hindsight:** Despite strong objections by many EB members, Marcolino G. Candau, the WHO's Director-General, remained a firm supporter of the proposal and stressed that unless the total proposed budget was made available, he would not be able to implement the existing WHA resolution. A delegate from Eastern Europe reminded the EB members that the size of the budget proposed was much less than what was being spent by many industrialized countries in continuing smallpox vaccination, dealing with vaccination complications, and containing importations.

Looking back, I continue to be amazed at the Director-General's firm support of the smallpox eradication

initiative. The WHO malaria eradication program, the harbinger of global priority programs, was behind schedule, and I was personally aware that he was not totally confident of the technical feasibility of eradication. He was from Brazil and knew how poor health services were in regions such as the Amazon basin. At the same time, Candau was fully aware that if the WHO eradication initiative were to succeed, funds from industrialized nations would be necessary to assist developing nations—the phrase “international cooperation” was still new to the world community in 1966. As I look back I realize that Candau was an excellent leader and played a definitive role in smallpox eradication.

### 4. Smallpox eradication from 1967 to 1980

The intensified smallpox eradication began in 1967. The earlier strategy 80% vaccination of the entire population remained unchanged initially, but then vaccine supply as well as logistic support, such as vehicles, field equipment, etc., were considerably intensified by the WHO and other international agencies under a newly established Smallpox Eradication Unit at WHO HQ. Special teams were set up in four WHO regional offices, namely the Americas, Africa, the Eastern Mediterranean, and South East Asia, and, more importantly, in nations where smallpox remained endemic.

Field research led to the development and implementation of new strategies, which, in turn, led to the last naturally occurring smallpox infection in Somalia, in October 1977, and the subsequent global certification of zero cases at the end of 1979.

#### 4-1. Ensuring vaccine quality

In 1967 the WHO requested all manufacturers of smallpox vaccine used by the program to submit samples for testing by the WHO reference centers in Bilthoven, the Netherlands and Connaught Laboratory in Toronto, Canada. The results were astonishing; only 30% of samples met WHO standards. The major problems were unsatisfactory potency and heat stability. A special committee was immediately formed by the WHO with experts on vaccine production and assay from laboratories all over the world, including the two WHO smallpox reference centers mentioned above, the Wyeth Laboratory, USA, The Lister Institute, UK, the Research Institute of Virus Preparations (RIVP), then USSR, and others. The committee made a travelling seminar, which visited several vaccine manufacturers and produced the relevant production manuals, including practical production technology. Distribution of this manual, along with the provision of reference preparations for vaccine quality assays, improved this situation notably. Furthermore, a global vaccine assay system was organized with help from the above-mentioned WHO reference centers.

It took 3 years to raise the acceptable rate from 30 to 80% using the WHO assay system. Only freeze-dried vaccine was acceptable. Thus, only vaccine lots of satisfactory quality were used for the program from that point up until the end of the eradication program. A total of 26 manufacturers donated quality vaccine to the program. Among them, the substantial vaccine donation by the then USSR to the WHO helped greatly to stabilize vaccine procurement for this global emergency

operation. The assistance by WHO reference centers is also worthy of note.

During the period mentioned above, a new vaccination method, namely bifurcated needles, which reduced the vaccine dose down to 20% and, although it required 15 skin punctures, could be learned by normal health staff in 20 min, was introduced. The advantages of this new method were confirmed by WHO smallpox staff in field studies. D. A. Henderson subsequently noted this advantage and strongly recommended the introduction of such needles into the program. The needles were manufactured by Wyeth Laboratory, which provided them free of patent charges when used for the WHO smallpox eradication program.

**With hindsight:** As I had once worked in the vaccine control section at the Ministry of Health, Japan, I was delighted to be personally involved in this activity. It was an exciting and enjoyable period at the onset of the intensified smallpox eradication program. Those manufacturers who failed the WHO test were shocked, especially when they came from some of the more developed countries. Incidentally, Japan's donated vaccine never met WHO standards, as far as I remember, due to its minimum requirements. The WHO reference centers tested the large number of vaccine samples submitted free of charge, and other laboratories, such as the Lister Institute, provided their know-how regarding production techniques to facilitate these improvements. I will comment on how we all came to work hard in close harmony below.

#### 4-2. Development of the surveillance and containment strategy

In 1966, the USA initiated a bilateral program for smallpox eradication and measles control in 19 countries in West and Central Africa. During this period, Rafe Henderson (USA) and M. Yekpe (Benin) studied the epidemiology of smallpox in a small village that situated in Benin (then Dahomey), West Africa and found that smallpox spreads slowly, needs close contact between infected and susceptible individuals, and that the transmission tends to be circumscribed in densely populated communities (2). Likewise, A. R. Rao (India) reported that only 35% of non-vaccinated family contacts with smallpox patients developed the disease (3).

These findings roused keen interest among US and WHO staff working on the eradication program. During my visit to Bangladesh, one of the heavily endemic countries, we discovered that cases were only being reported in the northern districts, with no cases in the rest of the country. Based on these findings, in 1970 we finally decided to stop the 80% nationwide vaccination strategy to conduct special vaccination campaigns in affected areas of the northern region only. The results of this strategy change were that no cases were reported between mid-1970 and the end of 1971. Regrettably, the Indo-Pakistan war broke out at this time and there was no way to verify the nil reports, but the government and I believed that transmission had indeed been interrupted. In early 1972, following the ceasefire, a massive importation from India took place in all the Bangladeshi territories and smallpox again became endemic in Bangladesh until the last case was found in 1975. Indeed, this was subsequently found to be the last case in all Southern Asia.

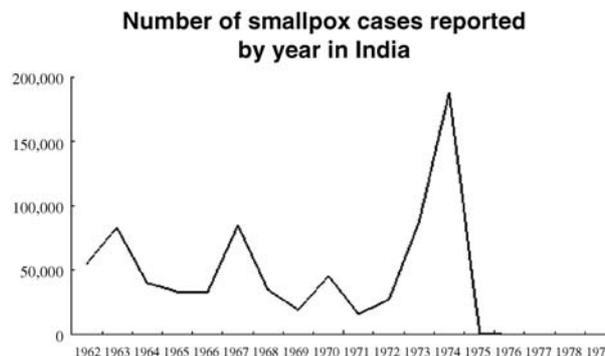


Fig. 1. Smallpox cases reported in India by year. India reported 188,003 cases in 1974 as the intensified surveillance discovered the hidden focus and only 1,436 cases in 1975 as the containment measures intensified. And zero report in 1976 thus having interrupted the smallpox transmission. Source: WHO photographic slide series, History of Smallpox and Its Eradication 1980.

Additional evidence regarding the effectiveness of our surveillance and control strategy came from India. In 1973, the Indian Government abandoned its strategy of targeting the entire population—a strategy that had been failing since the 1960s—and adopted the surveillance and containment method to speed up their smallpox eradication efforts. Practical methods, whereby each health center would stop its routine work for 1 week per month to conduct an active search of smallpox cases and vaccinate 50 households surrounding each case discovered, were put into practice. By chance I was visiting Muzafangar District, Uttar Pradesh, at that time and verified that their relatively developed basic health services were capable of doing this. Another WHO epidemiologist, V. Zigmund, from Czechoslovakia, who was working in Southern India, had made similar observations. The new strategy was subsequently introduced in autumn 1973 throughout India, which had a population of 600 million at that time. Smallpox incidence declined rapidly, with the last case occurring in May 1975 despite the large number of cases due to the detection of a hidden focus, which peaked in May 1974 (Fig. 1), just 1 year prior to the last case.

#### 4-3. Surveillance: how to make it effective?

A significant advantage for surveillance was that, for smallpox, there is no sub-clinical infection of epidemiological significance: the clinical presentation is distinctive and clearly indicates the need for emergency vaccination action. We decided that no laboratory testing was needed to confirm cases and that cases could be reported based simply on the distinctive rash, as shown by smallpox recognition cards, which were widely distributed in smallpox reporting countries. Lay reporting was also facilitated by the smallpox recognition cards invented by the Indonesian smallpox program staff (Fig. 2).

The exception to this was that once the number of smallpox cases had declined to such an extent that there was a real chance that the surveillance containment action was leading to discovery of the probable last case, laboratory verification of smallpox was recommended either by national diagnostic laboratories or one of two WHO designated laboratories, namely the CDC in

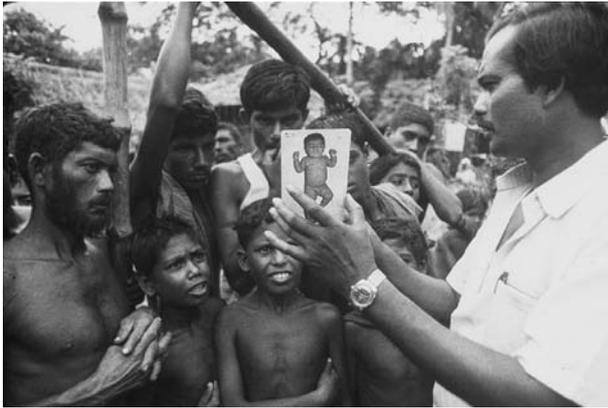


Fig. 2. A surveillance team member holding a recognition card questions villagers in Bangladesh. Source: WHO photographic slide series, History of Smallpox and Its Eradication 1980.

Atlanta, USA and the RIVP in Moscow. In addition, as discussed below, special studies on smallpox virus had been in progress in various laboratories. However, by around 1974–75, when the number of smallpox reporting countries had decreased from 37 in 1967 to 9 in 1974 and then 5 in 1975, diagnostic accuracy became of primary importance as smallpox eradication appeared to be approaching the endpoint of global eradication.

Several new measures were taken, including the requirement that all specimens taken from clinical smallpox or suspected smallpox cases had to be sent to WHO HQ, Geneva, which would then pass them by the fastest possible airline to one of two WHO designated laboratories, namely the CDC and RIVP. Special specimen collection kits were produced and distributed to the countries so that specimens could be transported as safely as possible. This intensified laboratory verification system continued right up until the end of the program, namely declaration of smallpox eradication in 1980. It is interesting to note that the WHO and national programs offered rewards for those people reporting new smallpox cases (Fig. 3).

#### 4-4. Last battle: the Horn of Africa

As smallpox was slowly eradicated from the major endemic regions in South Asia, sub-Saharan Africa became the last battlefield. Luckily, joint national and US bilateral assistance (1966 to 1971) had cleared endemic smallpox from the 19 nations in Western and Central Africa much earlier. Following the surveillance and containment strategy, the WHO program was supposed to succeed in clearing the remainder of sub-Saharan Africa. However, in 1976, when Ethiopia appeared to be the last endemic nation, unexpected smallpox foci were discovered in the Ogaden desert, which borders three countries, namely Ethiopia, Kenya, and Somalia. The last major battle in the fight against smallpox therefore took place in these three countries, which cover the semi-desert area known as the Horn of Africa.

The most frequent strategy used by the WHO was to mobilize global resources in this area. The WHO was able to obtain, through the arrangement by the United Nations Disaster Relief Operation (UNDRO), the fund totaling \$470,000 from member states, including the airlift of 16 vehicles to Somalia. In addition, within 1 month, the WHO transferred smallpox eradication



Fig. 3. Poster announcing US\$ 1,000 global reward for reporting smallpox cases in 1978–79. Source: WHO photographic slide series, History of Smallpox and Its Eradication 1980.

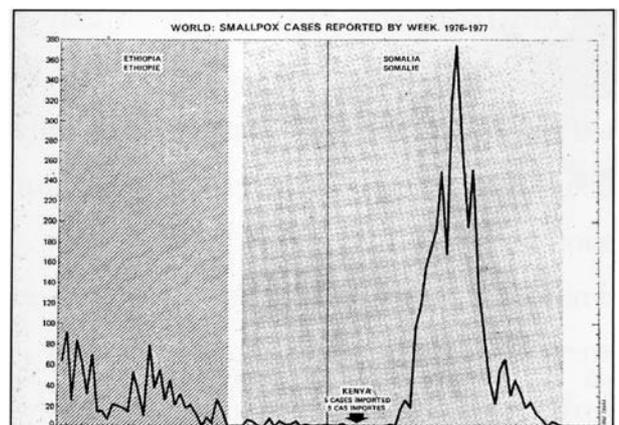


Fig. 4. Graph: Horn of Africa, smallpox cases reported by week, 1976–1977. Source: WHO photographic slide series, History of Smallpox and Its Eradication 1980.

officers from India to Somalia to complement the staff already working there. The fact that many volunteers also joined the operation meant that both the Ogaden and Somalia were saturated with WHO and national program staff. The epidemic was controlled rapidly and the last case occurred in October 1977 (Fig. 4).

#### 4-5. Virological research

Several reports shed doubt on the assumption that smallpox virus has no natural reservoir and is genetically stable. The first, as early as 1971, was the discovery of

human monkeypox patients by S. Marrenikova (Russia). Monkeypox viruses, which belongs to the orthopox group of viruses, causes an exanthema in man and monkeys similar to that of smallpox. Thus, while the known natural reservoir was rodents in the tropical rainforest of sub-Saharan Africa, there was concern that it might behave like smallpox in the human population in Africa. Fortunately, careful laboratory as well as epidemiological studies revealed that human monkeypox is rare in nature and that person-to-person transmission is difficult (4,5).

The second concern was that smallpox virus had been discovered during the passage of monkeypox virus or in the passage of kidney tissue cultures from healthy monkeys. Sixteen viruses, known as white poxviruses, have been isolated. These isolates were reported by several laboratories, including the WHO smallpox reference laboratories. The question therefore remained as to whether monkeypox virus mutated to smallpox virus or whether the isolation of smallpox virus from healthy monkey kidneys meant that the natural infection of monkeys by smallpox virus was circulating in the African forest. Studies in this field were continued even after the declaration of smallpox eradication in 1980, and all results to date indicate that the mutation of monkeypox virus into smallpox virus is genetically impossible (6). The white poxvirus was therefore judged to be most likely a laboratory contaminant.

**With hindsight:** As the snapshots have shown, the newly intensified program (from 1967 to 1977) benefited significantly from dedicated research or special action cum research. This is an important lesson, which may be obvious but is often overlooked in many large programs. The importance placed on research could perhaps be explained by the research backgrounds of the WHO Smallpox Eradication Unit staff. Thus, D. A. Henderson, from the CDC where he worked closely with Alexander Langmuir, the top expert who developed the concept of epidemiological surveillance. Ehsan Shafa, from the East Mediterranean Regional Office, was interested in field practice and studied the effectiveness of the bifurcated needle. Frank Fenner, who led the eradication and certification commission was the author of the book “Medical Virology” and a top virologist in the West. I myself was trained in vaccine standardization at the National Institute of Health, Ministry of Health, Japan, and at the Paul Ehrlich Institute, Germany. Unfortunately, I am only able to mention a few of the many hundreds of national and international staff members who contributed to the studies mentioned above.

The Smallpox Eradication Unit was small, with only a few medical officers at HQ and in regional offices. This could have led to a difficult working environment, but as far as I recall its management was effective due to a lack of bureaucracy. Decisions were swift and, once taken, were enacted rapidly. Sometimes we broke WHO rules; for instance, when over an outbreak was reported, we boarded the next available flight to that country without official approval. During the final phase, many consultants joined operations voluntarily, as needs arose, and left as these needs disappeared.

The Horn of Africa operations were undertaken amidst the Ethiopian-Somali war in 1976 and 1977.

However, rapid mobilization was needed—as we knew that smallpox eradication in Bangladesh had been delayed for 4 years due to the Indo-Pakistan war. Luckily, operations in the Horn of Africa were completed in just 1 year. Furthermore, excellent community cooperation prevented the spread of infection due to population movement by pilgrims and others at that time. Notably, in 1997, during the Dahlem workshop in Berlin, William Foege made the unique point that eradication does not need a grandiose organization—it is enough to have a small yet effective team which is not restrained by bureaucracy (7), as was the case with the WHO Smallpox Eradication Unit.

All in all, however, the program was fortunate in that political unrest, civil conflicts, and inaccessible areas were infrequent. Indeed, there were only three major wars—the Biafra war in Nigeria in 1966–1967, the Indo-Pakistan war in 1971, and the Ethiopian-Somali war in 1976–1977—during 13 years of this program. Perhaps the cold war contributed to the swift implementation of actions needed for the program.

## 5. Global certification of smallpox eradication

The WHO established a certification strategy to verify the last case of smallpox in a region. This involved the absence, for at least 2 years, of a reported case while maintaining continual surveillance. Confirmation had to be made using several methods, including house-to-house searches for cases, laboratory confirmation of suspect cases, the announcement of smallpox report rewards, pockmark surveys, and the evaluation of program records by an independent assessment team. These methods evaluated surveillance sensitivity to ensure that if smallpox virus was circulating it would be discovered. All these were undertaken by WHO certification commissions, who visited those countries with no recorded smallpox cases in more than 2 years.

Additionally, all laboratories which might have stores of smallpox virus (based on reviews of the publication of smallpox research since 1960) were either visited or referred to by independent teams so that unnecessary virus stocks could be destroyed or transferred to the WHO smallpox reference centers in the USA and Russia. Variolation specimens had once been kept in cold climates by local variolators in Afghanistan and China. However, studies of some of these samples showed that they were no longer viable; the remainder were destroyed.

The global certification committee verified that smallpox had been eradicated by the end of 1979, and the WHA declared the success of its eradication program on 8 May 1980. This report was signed by delegates from all nations attesting that there was no smallpox in their individual nations. Virus stocks are only kept in two laboratories under strict controls as of September 2010.

**With hindsight and foresight:** Certification work was aimed at documenting the absence of smallpox throughout the world. Despite the fact that the eradication program appeared ambitious to say the least, it went well surprisingly and encountered few major obstacles. Full international corporation was undoubtedly a key factor behind this. Furthermore, a clear manifestation of a

clinical picture with no sub-clinical infections made the surveillance effective. The quality of this work is further highlighted by the fact that no smallpox has been discovered over the last 30 years despite more than half of the global population being susceptible to smallpox due to the suspension of smallpox vaccination since 1980 or before. This figure will reach 100% by the end of this century.

The cost benefit in relation to the intensified program was estimated by the report of the global commission (1980) as follows: total program expenditure (1967–1980): \$313 million, including \$81 million from the WHO budget, \$32 million bilateral agreements, and an estimated national expenditure of \$200 million. This total estimate can be compared with estimated annual savings (1981 onward) of around \$1,000 million as a result of suspension of smallpox vaccination, no treatment of complications caused by vaccination, no quarantine service, no control of international travelers, and so forth.

Some uncertainty still remains regarding the fate of the smallpox virus stocks kept by the two WHO certified laboratories: they may be destroyed in the near future, but we cannot be completely sure that these two laboratories are only ones keeping stocks of virus. Also, it is likely that smallpox virus could be synthesized using ordinary laboratory techniques in the near future (8), if someone wishes to do so. In the current changing world, it is hard to predict what may happen.

An alternative strategy would be to keep the virus strains in a symbolic place, such as a UN office, with special safety arrangements and accompanied by a statement such as—“the symbol of collaboration of human efforts having won the battle with the worst enemy” with a sub-statement “if any virus is newly discovered, it must be placed here”. Meanwhile, prospective preventive measures, such as the establishment of an international vaccine stock and preparation for emergency response should be instituted, although, as mentioned at the beginning of this article, it would difficult to expect such a large degree of global effectiveness in the current changing world.

I have focused on my memories of these events in this paper, although the future of the smallpox virus itself, as well as legacy programs, such as the eradication of other diseases, for example polio, may be discussed elsewhere in the near future.

## 6. Conclusions and lessons learnt

The global eradication of smallpox can be considered to be a significant event in the history of public health

and, in a broader context, an epoch-making incident in the history of biological evolution, namely the fact that the human species has won the fight against one of the most vicious enemy species, namely variola virus, which has resulted in it becoming extinct on this planet.

Of all the lessons that can be learnt from this achievement, I believe the most important is that the success of this eradication program required both global collaboration irrespective of race, nationality, religion, and technical development, and a focused and coordinated research strategy, in which WHO leadership was indispensable.

The lessons mentioned above could prove useful to those who want to improve the quality of life in their, and other, countries in today’s changing and confusing world.

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**Conflict of interest** None to declare.

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