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The certification of smallpox eradication and implications for guinea worm, poliomyelitis, and other diseases: Confirming and maintaining a negative

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ABSTRACT

Rigorous, independent, confirmation of disease eradication is necessary to assure credibility of the claimed accomplishment. The criteria and procedures for formal certification of global disease freedom are based on the biological and epidemiological features of the pathogen and its manifestations. Certification activities by previously endemic and at-risk countries include comprehensive documentation focusing on surveillance, reports of national independent review groups, and special field surveys. National and regional results are reviewed by authoritative International Commissions (ICs) which verify the findings by field visits. The ICs present their results to an independent WHO-convened group ("Global Commission" for smallpox), members of which participate in field visits. When fully satisfied, the Global Commission makes conclusions and recommendations to the World Health Assembly (WHA). Smallpox was confirmed eradicated in 1980 by the WHA less than three years after the last naturally occurring case was detected. Dracunculiasis (guinea worm) freedom has been certified in 187 countries. Regional commissions have certified the Americas, Asia, and Europe polio-free; however, re-establishment of endemic foci in countries previously declared disease-free has created special challenges for completing this program. Post-eradication activities require attention to surveillance, maximum security of the microbial agent, and essential research to assure maintenance of disease freedom.

1. Introduction

> "The rule of the final inch consists in this: not to shirk this critical work, not to postpone it . . .One's purpose lies not in completing things faster, but in the attainment of perfection."
>
> Alexander Solzhenitsyn, The First Circle, 1968 [1]

Disease eradication is on an arc running from control to elimination to eradication, with destruction (or extinction) of the causative microbe at the far end of the arc (Table 1). The definitions of elimination (regional) and eradication (global) are reduction of disease transmission, incidence, and prevalence to zero within a surveillance system that could detect cases if they occurred. Well before eradication is in sight, certification activities begin, with a goal to confirm disease absence. These challenging activities comprise the final phase of the program including the "final inch". Rigorous, independent confirmation of disease eradication is necessary to assure credibility for the claimed accomplishment within the lay and scientific communities. While smallpox is the only human disease to have been certified as eradicated [2,3], World Health Organization advisory groups have also established criteria and been developing methods for confirming the eradication of guinea worm (dracunculiasis) and poliomyelitis [4,5].

1.1. Principles and procedures for certifying eradication

The principles of certification derive partly from procedures developed by the malaria eradication program which began in 1955 and include: a time interval after the last recorded case before a country may be certified; collection of national information on the disease history and conduct of the program; surveillance activities, including specimen collection from suspected cases; and, presentation of data to an independent group which assesses and confirms the information [6]. Smallpox had, guinea worm has, and polio continues to develop, highly refined survey and certification procedures and WHO-convened independent committees ("Commissions") to judge whether the evidence fulfills the criteria for certification. The survey procedures are based on the biological properties of the causative microbe, its clinical expression, epidemiological features, national and local surveillance systems, and laboratory diagnosis. The salient clinical and epidemiological features of smallpox, guinea worm and poliomyelitis considered in designing certification approaches are shown in Table 2. The special features of the field surveys used to detect and identify each of these diseases are shown in Table 3. In addition, the

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Table 1
Away all disease: definitions.

Control	Reduction of disease incidence, prevalence, morbidity, mortality, and disability to a locally acceptable level.
Elimination	Reduction of infection and disease to zero in a defined area. Surveillance crucial. Continued efforts required.
Eradication	Permanent reduction of worldwide incidence to zero as a result of deliberate interventions. Surveillance crucial. Continued efforts may not be required.
Destruction	Destruction of all isolates of microbial agent.

Table 2
Clinical and epidemiological considerations for certification: smallpox, guinea worm, and poliomyelitis.

Feature	Smallpox	Guinea worm	Poliomyelitis
Incubation period	14–17 days	9–12 months	7–21 days
Syndrome visible	Yes (eruption)	Yes (worm)	Yes (paralysis)
Recognized by public	Yes (eruption)	Yes (worm)	Yes (paralysis)
Asymptomatic carriers	No	No	Yes
Transmission mode	Respiratory	Water	Fecal–oral
Vector/reservoir	Human	Cyclops/human	Human
Secondary attack rate among susceptibles	High (40–90%)	?Low	High (10–90%)

Table 3
Survey considerations for certification of eradication: smallpox, guinea worm, and poliomyelitis.

Feature	Smallpox	Guinea worm	Poliomyelitis
Surveys	"Fever and rash" Facial pock marks	"Hanging worms" Blisters on legs	"Non-polio" Acute flaccid paralysis (AFP)
Target group	School children	Villages at risk	Children < 15 yrs
Diagnostic dilemma	Chickenpox, monkeypox	Trauma, infection (bacterial)	Vaccine-associated, AFP, Guillian-Barré Syndrome
Environmental surveys for microbe	No	No	Yes
Laboratory confirmation	Yes	No	Yes
Rumor registers	Yes	Yes	Yes
Reward	Yes	Yes	?
Interval before certification	2 years	3 years	3 years
Continuing Research	Yes	Yes	Yes

commissions make recommendations for actions in the post-eradication period, including research, continuing or discontinuing interventions and destroying or keeping the microbe to assure maintaining the achievement.

1.2. Smallpox

For smallpox, a two-year period was designated as the minimum time after alleged interruption of transmission before a country could be certified. Smallpox has a two week incubation period so there would be at least 52 generations of person-to-person transmission during this period. Assuming a secondary attack rate range of 37–88% (mean 65%) in susceptible (unvaccinated) persons (Table 4) [3] and face-to-face contact of each case with possibly five to ten susceptible contacts during the period of contagion, there would be well over two hundred, and possibly several hundred, persons contracting smallpox during the two years; the attack rates would be reduced in vaccinated populations. It is unlikely that these ill patients and community outbreaks would go undetected by local authorities, national, and international health officials, and the press in a country with a functioning eradication program and active surveillance. The smallpox infection to clinical syndrome ratio was consistently one-to-one, unlike polio where the infection to paralysis ratio is 200 or more. Attempts to suppress reporting of cases might delay knowledge of the epidemic, but only for a limited time, assuming there were national incentives to detect cases.

Table 4
First generation secondary attack rates for smallpox in susceptible persons.[a]

Type of smallpox	Location	Number of contacts		
		Contacts	Developed disease	%
Variola minor	Brazil	38	20	53
Variola minor	Brazil	674	466	69
Subtotal *Variola minor*		712	486	68
Variola major	Nigeria	27	12	44
Variola major	Benin	17	8	47
Variola major	Madras, India	103	38	37
Variola major	Pakistan	45	33	73
Variola major	Pakistan	22	10	46
Variola major	Pakistan	43	38	88
Variola major	Calcutta, India	80	61	76
Variola major	Bangladesh	21	9	43
Subtotal *Variola major*		358	209	58
Total		1070	695	65

[a] Modified from Ref. [3]: all persons with vaccination scar absent.

The formal approaches used in the countries and regions for certification of smallpox eradication comprised national and international components. The national responsibilities included petitioning to WHO for certification and documentation of the history of disease and eradication activities. A description of the surveillance systems for routine disease reporting and for detecting smallpox cases was required and was the most scrutinized part of the documentation. Special surveys were performed in areas where, if cases were occurring, they would be found: these were locations where the last cases were recorded, areas of poor surveillance, along borders with countries having had disease outbreaks, and among refugees, nomads, seasonal workers, and other transient populations. Specimens from patients with suspected smallpox ("fever with rash" cases) were collected and sent to a WHO-approved and collaborating laboratory (Centers for Disease Control and Prevention, Atlanta and the Research Institute for Viral Preparations, Moscow) for testing; specimens were collected from each outbreak when transmission was occurring but from each suspect patient during certification. A rumor register was created and available nationally and locally with details of investigations and final disposition. Countries frequently, but not always, formed national evaluation bodies ("national commissions") composed of eminent scientific and public health officials in anticipation of visits by International Commissions designated by

WHO. The national commissions were independent of the eradication program; assessments performed by these groups were quite rigorous, particularly those in India and Bangladesh [7,8]. National commissions supervised special facial pockmark surveys and specimen collections from patients with skin lesions that resembled smallpox.

As national evaluations and certifications occurred many years after the last smallpox cases were detected, local interest had usually waned and few human and material resources were available to complete all of the requirements. WHO regional offices and the Smallpox Eradication Unit at WHO headquarters assisted frequently in the preparation of country documentation and helped with designing the surveys carried out locally. WHO occasionally provided a vehicle and gasoline funds for survey work and consultants who monitored progress and helped with preparations for the visits of the International Commissions. Members of the International Commissions were internationally respected scientists and public health authorities, well-versed in the eradication program and familiar with the health systems, cultures, and languages of the countries to be evaluated. It was common for outstanding directors of smallpox programs in endemic countries to serve on International Commissions and some were members of the Global Commission for the Certification of Smallpox Eradication (The Global Commission), the WHO-designated but independent group that oversaw all certification actions and made recommendations to the World Health Assembly.

Several countries in a geographic area were assessed during the same period, particularly in Africa. The International Commissions would meet first in one country and review all the evidence for the various countries; subgroups would then visit individual countries for anywhere from one to three weeks before reconvening. The subgroup field visits would focus entirely on: (1) seeking answers to questions raised in written and verbal reports presented at the first meeting review, (2) traveling to areas where the risk of continuing smallpox transmission was high, usually including places where the last cases occurred, where questions were raised by the rumor register, and where there was poor surveillance.

1.3. Findings and conclusions from the Smallpox Commissions

Smallpox certifications began in 1973 with the Americas and in Indonesia in 1974. The first certification exercise had flaws. Seven of the 13 countries of the Americas had had smallpox in 1960 or later, yet only Brazil was visited by the International Commission: the assessment was chaired by a Brazilian health official, a mistake not repeated in subsequent evaluations [3,9]. Activities intensified from 1976 to 1979 as the African and then Asian countries completed certification requirements. In Africa, the field surveys concentrated on primary schools to find pockmarked children. The WHO smallpox identification card, which originated in Indonesia, was used to ask persons of all ages (especially children) about suspected smallpox patients in their villages (Fig. 1). Rewards for reporting confirmed smallpox cases were widely publicized (Fig. 2). By the end of 1979, all 200 countries and territories were certified as smallpox-free, of which 35 had been endemic during the intensified program (Table 5) [9]. A total of 79 countries were visited by 21 International Commissions and the Global Commission for the Certification of Smallpox Eradication; the dates showing the last reported case and certification in these countries are shown in Fig. 3. In December 1979 the Global Commission certified the world free from endemic disease and their conclusions and recommendations were accepted by the World Health Assembly on May 8, 1980.

There is no way to prove statistically that an infection does not exist in one person on the globe—it is impossible to prove a negative. Despite theoretical reasoning that at least two years would be adequate before certification, of concern was the question of how long smallpox could persist in a country without being detected. Indeed, evidence of some cases of smallpox occurring up to nine months after elimination was presumed in five countries: Nigeria in 1970, Brazil in 1971, Indonesia in 1971, and Botswana in 1972–1973. The reasons included uneven coverage by the surveillance system, suppression of reports by local staff or communities, and, once, lack of communication between levels of reporting—but all countries detected outbreaks within the two year interval [3].

Fig. 1. Active search for smallpox, Somalia, 1977–1978 by Commissions, 1973–1979.

The most rigorous assessments were performed at the end of the global program building on prior experiences. As an example, facial pockmark surveys performed by the Indian eradication staff

Fig. 2. Reward posters to stimulate reporting a confirmed case of smallpox (WHO).

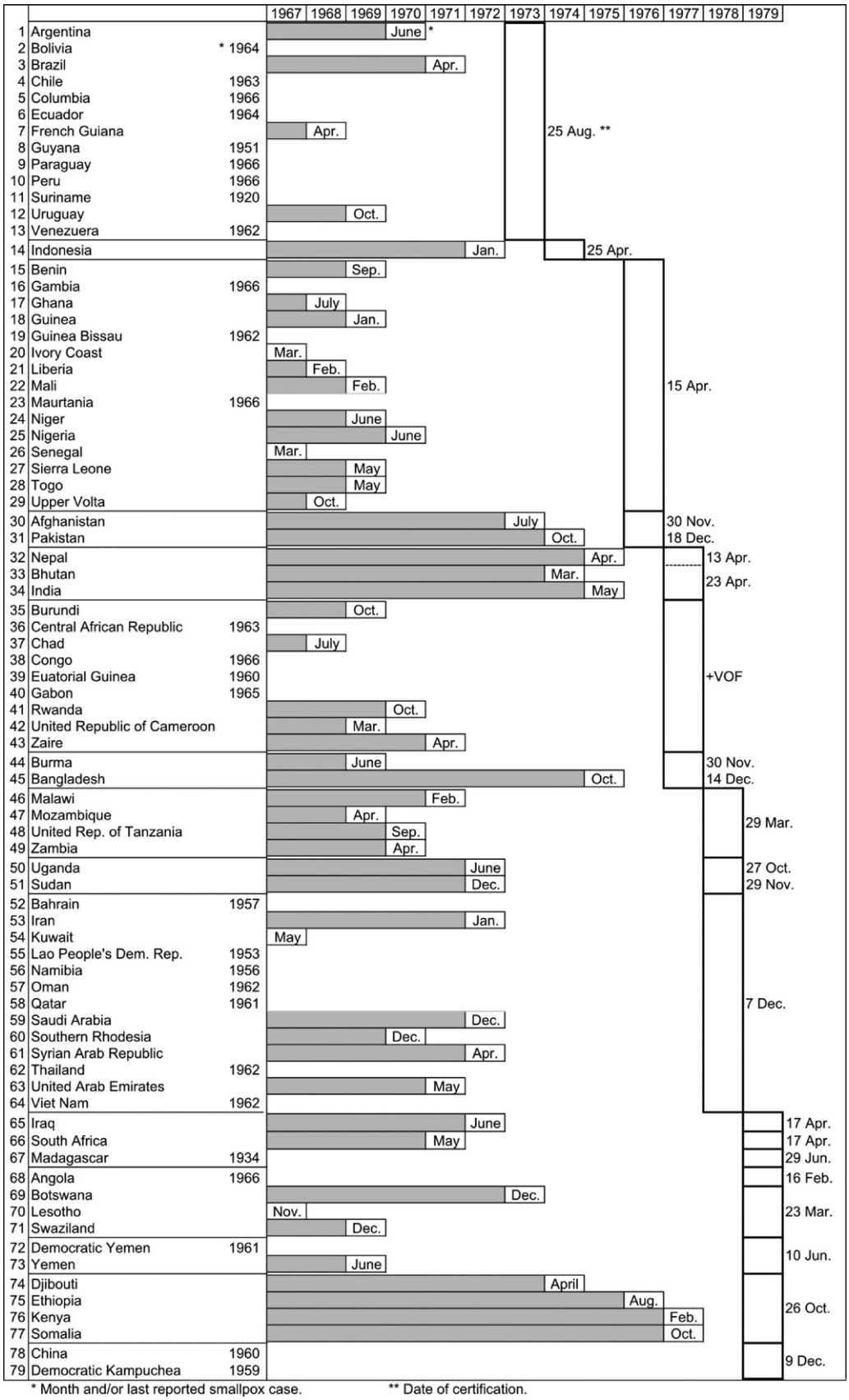

Fig. 3. Seventy-nine countries requiring special procedures for the certification of smallpox eradication: month and year of last case and certification dates are shown. Modified from Ref. [3].

Table 5
Smallpox certification activities in 200 Countries, 1977–1980.

Countries	Number	Population (billions)
Countries	200	4.5
Submitting statements	121	1.5
Visited by commissions	79	3.0
At special risk	44	1.8
Endemic during SEP*	35	1.2
Specimens collected	17,000	

* SEP, Smallpox Eradication Program.

Table 6
Smallpox certification activities in India: facial pockmark surveys, 1977.

Age group	Survey	Number of persons examined	
		Total	With facial pockmarks[a]
Preschool children	National surveys	271,897	0
	International Commission	3139	0
School-age children	National surveys	224,297	38
	International Commission	26,665	18
Adults	National surveys	1,451,125	650
	International Commission	14,307	94

[a] Due to smallpox contracted before 1975.

and national commission are shown in Table 6. By 1977, almost three million persons were assessed for evidence of smallpox having occurred since the last case was recorded in 1975. Of those 688 persons found with residual facial pockmarks, all lesions had occurred before 1975, the year of the last case; no preschool child had facial scarring due to smallpox; the International Commission examined more than 40,000 persons and confirmed these findings [3,7]. A picture of the last case of smallpox caused by *Variola major* is shown in Fig. 4; Rahima Banu, the Bangladeshi child, age three, ill with smallpox in 1975, still had residual facial scarring 27 years later, in 2002. The search for cases using the smallpox identification card is shown being used in Somalia (Fig. 1). Somalia is where the last naturally occurring case of smallpox occurred. Ali Maow Maalin of Somalia, the very last patient with smallpox (October 1977), had *Variola minor* and minimal facial scarring following recovery.

Fig. 4. Rahima Banu from Bhola Island, Bangladesh: the last patient with smallpox caused by *Variola major* in 1975 (WHO) and 2002 (J. Breman).

Two events tied to certification merit special note. During preparations for certification in Malawi in 1978, investigation of a pockmarked person suggested that smallpox may have occurred in 1972, possibly 19 months after the last reported case; however, it was only in 1974 that an active surveillance program was developed there. China, which had claimed eradication in 1961, had had almost no relations with WHO or the United Nations during the eradication decade, until the late 1970s. Due to politics, China did not participate in the eradication program until the intensified certification period began, from 1977 to 1980. Because of the vastness of the country, meager information in an initial report submitted to WHO, and the knowledge that the Chinese retained variola virus, a special report on eradication was requested. After delicate negotiations, a WHO delegation visited China in 1978, comprising Frank Fenner, Chairman of the Global Commission for the Certification of Smallpox Eradication and Joel Breman of the Smallpox Eradication Unit, WHO. All evidence indicated that the disease had been eradicated in the early 1960s. However, in 1985, Chinese colleagues with whom we worked during certification uncovered previously unknown outbreaks occurring during 1962–1965 in northern China that were known locally but not reported to national authorities. These events were associated with the ancient practice of variolation to protect against smallpox; the practice stopped in 1965 [10].

Special findings from the field and laboratory were considered by the Global Commission in making 19 post-eradication recommendations (Table 7); these covered future vaccination policy, maintenance of reserve stocks of vaccine, investigation of suspected cases, laboratories designated to retain variola virus, research on orthopoxviruses, including human monkeypox, and program documentation [2,3,9].

1.4. Status of guinea worm and polio eradication initiatives

Both the guinea worm eradication program and polio eradication initiatives have established independent international commissions convened by WHO to oversee and judge evidence tied to progress toward eradication [4,5]. As for smallpox, the principles of rigorous documentation, scrupulous surveillance, suspect case investigation, rumor registers and, for polio, laboratory confirmation of patients with acute flaccid paralysis, are being used.

Guinea worm. The International Commission for the Certification of Dracunculiasis Eradication (ICCDE) was first convened in 1996 and has since certified 187 countries free of guinea worm (Fig. 5) [11]. Twenty of these countries in southeast Asia and Africa had endemic disease when the program began in 1988 and 3.5 million cases occurred. Residual endemic foci are now in two areas, western Africa (Ghana and Mali) and southern Sudan–western Ethiopia. Recently, an outbreak of 10 cases of guinea worm distributed throughout southwestern Chad has caused alarm because

Table 7
Thematic Recommendations of the Global Commission for the Certification of Smallpox Eradication, 1979.

Vaccination policy
Reserve vaccine stocks
Investigation of suspected cases
Laboratories retaining variola viruses
Human monkeypox
Laboratory investigations
Documentation and dissemination
Committee on orthopoxviruses
Vaccinia virus as a vector for foreign genes

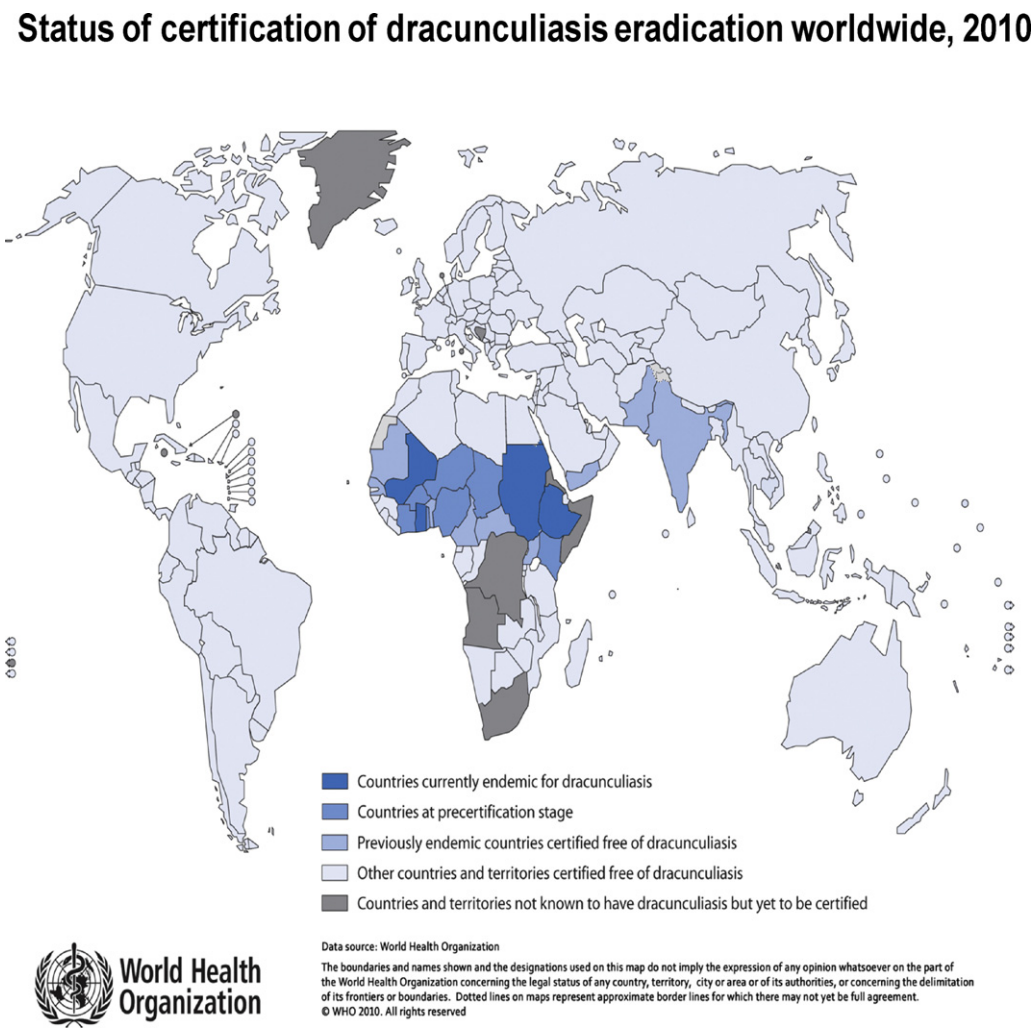

Fig. 5. Status of certification of dracunculiasis eradication worldwide, 2010 (WHO).

Chad had not reported cases since 1998; this outbreak is being investigated carefully as importation is possible [12].

WHO is now reporting the status of guinea worm each month in the Weekly Epidemiological Report (http://www.who.int/wer/2011/WE8613.pdf). Pre-certification activities are occurring in Burkina Faso, Cote d'Ivoire, Kenya, Niger, Nigeria and Togo as well as Chad.

Polio. Polio Regional Commissions certified the American, Western Pacific, and the European WHO Regions as polio-free in 1994, 2000, and 2002, respectively [5]. Type 2 polio has been eradicated since 1999 from all areas of the globe, leaving type 1 and type 3 (Fig. 6). This program faces a special certification conundrum in how to deal with countries that were previously polio-free and became recently re-infected and re-endemic following importations; this has been due to "failure to vaccinate" (low coverage in target groups) or "vaccine failure" resulting, in part, from competing enteric pathogens. Some of the certification ambiguity arises because countries free from polio for two or more years are designated "polio-free" by WHO. Those with re-importations having transmission continuing for more than one year are designated "re-endemic". Hence these latter countries should require three years of polio freedom before certification.

Following stoppage of polio vaccination in endemic northern Nigeria in 2004, 21 previously polio-free countries became re-infected from importations. Recent large outbreaks of polio occurred in Tajikistan, the Democratic Republic of Congo, and Republic of Congo after several years of polio freedom, these events have caused substantial setbacks to the global eradication program. Polio is a special challenge for certification in that there are many asymptomatic but infectious human carriers of wild poliovirus. Early studies showed that for every paralyzed person with polio, there were 100–200 symptom-free persons with wild virus in their gut [13]. It is unknown how many of these asymptomatic persons exist in currently endemic or recently re-infected countries with variable vaccination coverage, competing enteric pathogens, malnutrition, and other mitigating factors.

A number of AFP cases associated with circulating vaccine-derived polioviruses have been reported from previously endemic countries. Attention has recently been given to a number of vaccine-associated polio type 2 cases that have been detected in Nigeria, China, Syria, Somalia, and Afghanistan. Because type 2 polio has been eliminated globally, bivalent (types 1 and 3) vaccines have been produced for dealing with the continuing focus on the Indian subcontinent and Africa.

Both the guinea worm and polio programs are using innovative surveillance approaches, including house, village, community, and health unit searches; special containment procedures and a reward in some countries for guinea worm; and, detection of patients with acute flaccid paralysis (AFP) and collection of stool specimens for viral identification for polio.

Many other disease control programs are moving into elimination and eradication modes, particularly those designated

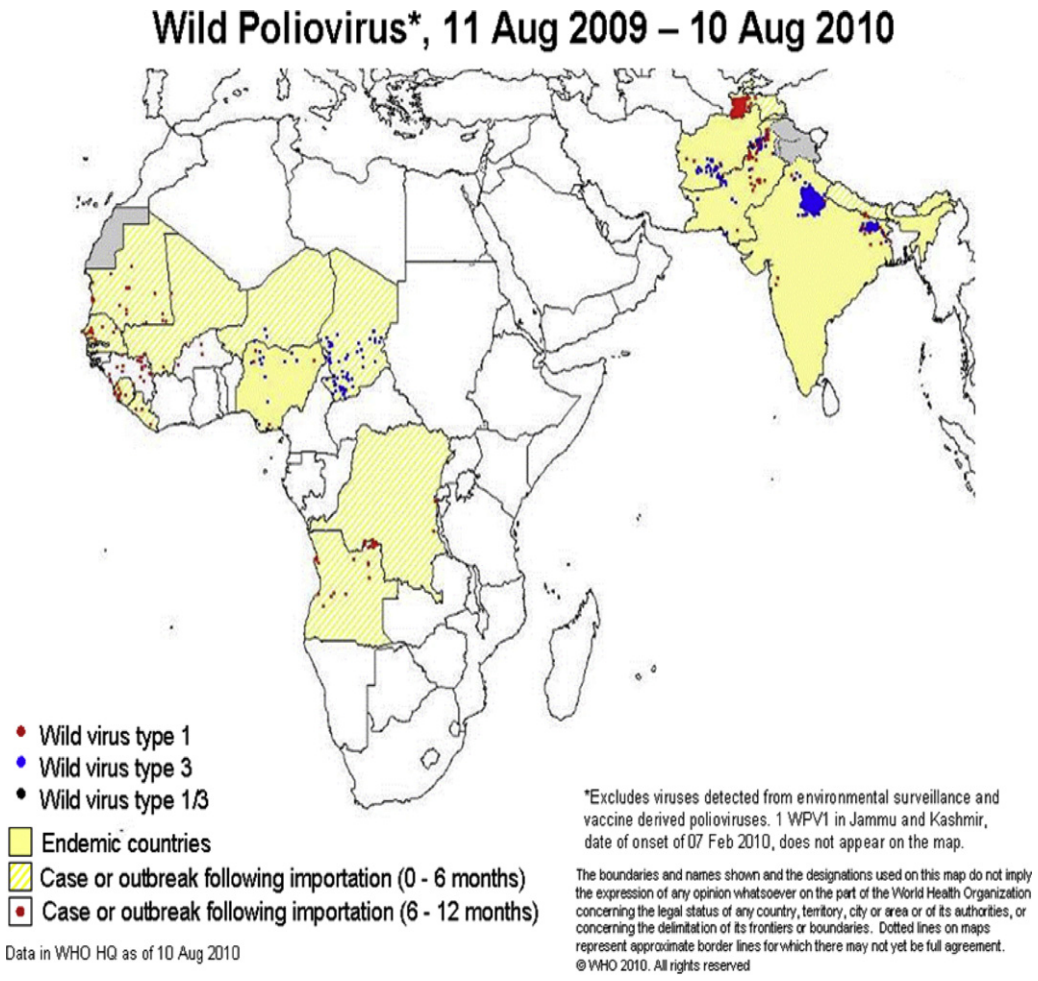

Fig. 6. Wild poliovirus worldwide: 11 August 2009–10 August 2010 (WHO).

neglected tropical diseases (Table 8); we expect they will soon be considering how to confirm officially their claims of elimination and eradication. In 2010, the WHO voted to take on measles elimination as a goal [14]. Rinderpest, the first veterinary disease (of cattle) was reported to have been eradicated officially in 2011 [15]. Details on certification procedures are awaited for this disease.

Table 8
Neglected tropical diseases targeted by the World Health Organization and Pan American Health Organization for elimination or eradication.

Resolution[a]	
Disease	Goal and WHO or PAHO
Dracunculiasis	Global *eradication* (WHA57.9) 2004
Onchocerciasis	Regional *elimination* (interrupting transmission of the parasite) (PAHO CD48.R12) 2008
Lymphatic filariasis	Global *elimination* as a public health problem (WHA50.29) 1997
Trachoma	Global *elimination* of blinding trachoma (WHA51.11) 1998
Leprosy	Global *elimination* (reduction of cases to less than 1 per 10,000 population) (WHA44.9) 1991; elimination as a public health problem (WHA51.15) 1998
Chagas disease	Regional *elimination* of transmission "as technically feasible" (WHA51.14) 1998; "control and elimination" (WHA63.20) 2010
Visceral leishmaniasis	Regional *elimination* (WHA60.13) 2007

[a] Number and year resolution passed: WHA is World Health Assembly resolution and PAHO CD is Pan American Health Organization Communicable Disease resolution.

1.5. Research and microbial destruction

Focused research during the eradication programs, including during the certification and post-certification periods, has been essential for the accomplishment and maintenance of program objectives [16]. The Global Commission for the Certification of Smallpox Eradication advised continued research on human monkeypox and vaccinia (smallpox vaccine) but made no comments in support of research on smallpox [2,3,9]. The recent findings of a large increase in human monkeypox cases in the Democratic Republic of Congo and an outbreak in a non-forested savannah area in central Sudan underscore the importance of continuing post-eradication research, particularly when smallpox vaccination has stopped [17,18].

The most contentious post-eradication issue has been the debate over the destruction of variola virus, a topic not considered by the Global Commission in 1980 [9]. A WHO orthopoxvirus committee beginning in 1986 advised destruction of all virus stocks, thought to exist only at the Centers for Disease Control and Prevention, Atlanta, U.S.A., and the Vektor laboratory, Novosibirsk, in the Russian Federation which received all variola virus isolates from the Research Institute for Viral Preparations, Moscow. This recommendation and others to minimize escape of variola virus was made based on the view that research on the pathogen was unnecessary,

that a large majority of countries supported destruction, especially those endemic nations participating in the eradication program, and retention posed a global public health risk, even if the isolates were kept under maximum security [19,20]. More recently, two arguments have been forwarded for retention of variola virus by scientific bodies in the U.S.A. and the Russian Federation: (1) studies are needed to develop new vaccines and drugs to counter bioterrorists who might use variola virus, (2) and, there are bona fide scientific reasons for doing experiments with variola virus using methods not available a few years ago [20]. Areas of research that have been defined as necessary before destruction are: developing a less reactogenic vaccine; characterizing the genome of variola virus; developing an animal model for smallpox; and, finding an effective anti-viral drug [21,22]. Strong political, economic and public health arguments for destroying the known stocks of variola virus are forwarded in recent papers [23–25]. Because of these questions the World Health Assembly has deferred destruction of variola virus repeatedly, most recently May 2011.

The ICCDE recommended several research themes including genetic characterization of the human guinea worm (*Dracunculus medinensis*) and related animal worms [26]. A detailed research agenda has been defined by the polio research coalition [27]. All eradication programs have established networks of researchers and institutions that establish agendas and priorities in support of the eradication program and these networks should be maintained and their activities assessed periodically. Why? Many arguments for eradication include stopping interventions (vaccination for smallpox and polio, mollusciciding of drinking water sources for guinea worm). Hence, rapid diagnosis and surveillance of pathogens and diseases that resemble those which are being eradicated are essential post-eradication research themes as is maintenance of institutions and trained staff capable of performing these functions.

2. Conclusions

While it is impossible to confirm a negative, there are procedures that have been applied successfully for confirming and maintaining the eradication of smallpox. Certification work is difficult and unheralded as, following assumed interruption of disease transmission, countries have gone on to other public health problems and staff and resources are often meager and borrowed. Only with convincing documentation of eradication will the world's scientific, public health, and lay communities accept a Commission's conclusions and recommendations, particularly when stopping interventions is advised. The entire credibility of the endeavor depends on the rigor of the certification process, the authority and independence of the certifying groups, and the post-eradication steps to assure maintenance of disease freedom. To maintain credibility of the accomplishment, the post-eradication steps must assure continued surveillance for suspected cases which resemble the eradicated diseases, maximum security of etiologic agents that could cause laboratory-associated outbreaks, and essential research.

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