of laboratory-based incidence assays, such as one based on avidity of antibodies,[5] that alone or in combination may improve estimates.

Hallett and Garnett suggest that we compare risk factors for recent infection (BED OD <0.8) with longer-term infection (OD ≥ 0.8). In this comparison, only geographical region was significantly associated with recent infection (north central compared with central/Kampala, adjusted odds ratio, 2.4; 95% confidence interval, 1.5-3.9; $P < .001$). The limited number of associations may be a result of restricted sample size, little change in risk factors over the past few years, or misclassification. It would be useful to include this type of analysis in national surveys when CD4 cell count and duration of known HIV infection could be used to more precisely define longer-term infections.

Westerhaus noted the importance of civil conflict in HIV transmission. Given the high incidence in the north central region but similar prevalence to other regions, it may be that the BED assay identified an area with increasing HIV incidence, possibly due to ongoing conflict in an area with an existing generalized epidemic. The finding that having recent vs longer-term infection was associated with being from the north central region supports this suggestion.

Ongoing conflict did not restrict access to any of the enumeration areas, although at times our teams traveled with military escort. We did not sample directly from internally displaced camps but included populations from districts in the north central region (Apac, Gulu, Kitgum, Lira, and Pader) and traced potential respondents to camps if they had moved since the 2002 census. Of 2347 potential respondents, 2123 (90%) were included from 46 enumeration areas in the north central region: 275 respondents from Pader, 479 from Gulu, 606 from Apac, 581 from Lira, and 182 from Kitgum. There were no differences in demographic factors between respondents in the north central region and other areas of the country.

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Global Eradication of Polio

To the Editor: In their *JAMA* Classics commentary, Drs Cochi and Kew[1] stated that poliovirus type 2 was eradicated in 1999. However, vaccine-derived type 2 poliovirus has been circulating in Nigeria from 2006 to the present, resulting in 103 cases during the period January 1, 2007, to August 12, 2008.[2] The re-emergence and continued circulation of this type of poliovirus is not consistent with eradication.

Those who worked on smallpox eradication, myself included, labored under the assumption that eradication is forever, not a one-time achievement necessitating an open-ended, long-term strategy for its maintenance. The formidable and resource-intensive challenges facing polio eradication have recently been discussed at a symposium at the US National Institutes of Health in September 2007.[3] These epidemiological, immunological, and virological barriers were not addressed by Cochi and Kew. The global community needs clear communication about the remaining challenges and sizable investments for field operations and research, not only to achieve one-time interruption of circulation and prevention of polio disease but to sustain that achievement.

Although their intent was to "assess the prospects for reaching the goal of a polio-free world," Cochi and Kew have not mentioned one of the biggest challenges. Poliovirus circulation in Nigeria has never been interrupted, despite 2 mass oral poliovirus vaccine (OPV) vaccination campaigns per year from 1996 to 1998 in northern Nigeria, 4 to 8 such campaigns per year for the past 10 years (albeit with a cessation in some northern areas of about 18 months starting in 2003 due to popular resistance), and 6 to 8 such campaigns each year since 2004.[2,4,5]

Yet in stating that pools of susceptible individuals in general accumulate due to failure to reach children through the routine program, Cochi and Kew do not acknowledge the need to improve the quality of the frequent resource-intensive mass campaigns. Nor do they emphasize the need to invest in the neglected routine immunization programs in the remaining polio-endemic countries (indeed in all countries) to sustain eventual eradication and reduce mortality from all vaccine-preventable diseases.

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In Reply: Mr Steinglass correctly points out that we could not explore the full complexity of global polio eradication in our article. Regular, detailed updates are available on the Internet[1] and from weekly publications.[2,3] The cause of all remaining poliovirus circulation worldwide is insufficient population immunity, usually the consequence of low rates of OPV coverage. In northern Nigeria, failure to vaccinate is the reason for continuing poliovirus circulation. Up to 60% of children in certain high-risk states (eg, Kano) have received 3 or fewer doses of OPV despite numerous opportunities either through routine immunization or the many rounds of supplemental immunization activities (SIAs).[2] This large-scale failure to vaccinate is unique among the remaining endemic areas of the world.

All 3 poliovirus serotypes are co-circulating, a situation that has not existed anywhere else in the world since 1999, when wild poliovirus type 2 was eradicated globally. The capacity for wide international spread has been demonstrated for the Nigerian wild poliovirus type 1[2,4] and on a more limited basis for the wild poliovirus type 3.[3] An outbreak of type 2 circulating vaccine-derived poliovirus (cVDPV) in the northern states of Nigeria has been ongoing since 2005.[2,5] Past experience in other countries with either type 2 wild poliovirus outbreaks or type 2 cVDPV outbreaks demonstrates uniformly that such outbreaks have been quickly controlled by increasing OPV coverage.[5]

Efficacy of the basic eradication strategies has been validated repeatedly by the eradication of the indigenous wild polioviruses in almost all countries, including areas of Pakistan, Afghanistan, and Nigeria where the communities are more accessible and the biological risks are at least as high as in the remaining endemic areas. However, low rates of OPV coverage in insecure areas of Pakistan and Afghanistan have resulted in persistent pockets of endemicity for wild poliovirus types 1 and 3.[3] While most of India has been able to stop transmission of wild poliovirus, the situation in northern parts of the country appears to be different than in the other endemic areas. Poliovirus circulation persists despite frequent high-quality SIAs that have increased OPV coverage rates to greater than 90% in the outbreak states of Uttar Pradesh and Bihar.[3] Improved routine immunization and the addition of inactivated poliovirus vaccine given in mass campaigns may help accelerate polio eradication in these states where the biological risks for poliovirus circulation (500 000 or more births per month, poor sanitation, subtropical climate) are very high.[3]

Steinglass also correctly points out the need to improve the quality of delivery of polio vaccines to all children of the world. Indeed, the success of polio eradication, which means the total cessation of all poliovirus circulation, rests on achieving that goal through a proper balance between routine immunization and supplemental mass immunization campaigns. Successful navigation[6] from the current polio-endemic phase, through the posteradication phase, and to the post-OPV phase requires the continued development of a comprehensive endgame strategy for maintaining high population immunity and sensitive polio surveillance.

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RESEARCH LETTER

Thyroid-Stimulating Hormone–Receptor Antibody and Thyroid Hormone Concentrations in Smokers vs Nonsmokers With Graves Disease Treated With Carbimazole

To the Editor: Cigarette smoking increases the risk of complications of Graves disease, such as ophthalmopathy and relapse after treatment with antithyroid drugs.[1] Anecdotally, patients with Graves disease who smoke appear to respond more slowly to treatment with carbimazole. We therefore retrospectively compared the decline in concentrations of thyroid-stimulating hormone (TSH)–receptor antibody and thyroid hormones in smokers and nonsmokers during carbimazole therapy.

Polio Today
Are We on the Verge of Global Eradication?

SUMMARY OF THE ORIGINAL ARTICLE

Studies in Human Subjects on Active Immunization Against Poliomyelitis

Jonas E. Salk, MD; MAJ Byron L. Bennett, US Army (*ret*); L. James Lewis, PhD; Elsie N. Ward, MA; J.S. Youngner, ScD

JAMA. 1953;151(13):1081-1098

In 1953 at the height of polio epidemics in the United States, Salk and colleagues described preliminary findings that led to an inactivated poliovirus vaccine. After review of the scientific evidence favoring artificial immunization against polio, the systematic experimental approach to vaccine development was outlined in detail including the criteria for selection of the vaccine strains, the choice of monkey kidney cells for vaccine virus production in tissue culture, and the inactivation of infectivity by incubation of clarified virus preparations in a 1:250 formalin at 1°C for 7 to 10 days.

Preliminary results were reported on the levels of neutralizing serum antibodies induced in 161 human participants who had been injected with the experimental vaccine just a few months earlier. Antibody levels, measured in both tissue culture and in mice, were higher when the vaccine was emulsified in a mineral oil adjuvant and delivered intramuscularly than when the vaccine was prepared in an aqueous suspension and delivered intradermally. Antibody levels to each of the 3 poliovirus serotypes induced by the inactivated vaccines compared favorably with levels induced by natural infection. Formalin inactivation of infectivity, measured by intracerebral inoculation of cynomulgus monkeys, appeared to be irreversible and the induction of neutralizing serum antibodies in human participants appeared to be entirely attributable to the noninfectious experimental vaccines.

See www.jama.com for full text of the original *JAMA* article.

Commentary by Stephen L. Cochi, MD, MPH, and Olen Kew, PhD

THE MEDICAL WORLD HAS MADE MUCH PROGRESS since the historic efforts in the 1950s of Dr Jonas Salk to develop inactivated polio vaccine (IPV) and of Dr Albert Sabin to develop oral polio vaccine (OPV). Global incidence of poliovirus cases has declined more than 99% from an estimated 350 000 cases at the beginning of the World Health Organization (WHO) Global Polio Eradication Initiative in 1988 to 1315 cases in 2007 and to 866 cases at the time of this publication. [1] Poliovirus type 2 was eradicated in 1999. The number of countries that have never interrupted wild poliovirus transmission (ie, polio-endemic countries) has been reduced from more than 125 in 1988 to 4: Afghanistan, India, Pakistan, and Nigeria. In this Commentary, we review the historical basis for pursuing polio eradication and assess the prospects for reaching the goal of a polio-free world.

History and Background of Polio Eradication Strategies

Most countries in Europe and North America effectively eliminated endemic transmission of wild poliovirus within a few years after introduction of IPV in 1955. In the United States, polio cases decreased more than 25-fold between 1955 and 1961, and some countries in northern Europe eliminated polio using IPV alone. In the United States, OPV gradually replaced IPV after 1961 and endemic circulation stopped in the late 1960s. The strategy of routine childhood immunization, so successful in the developed world, was less successful in the developing world in reaching elimination, which led Sabin to argue for supplemental mass administration

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tration of OPV to supplement routine immunization.[2] Striking results from well-organized national immunization days in Cuba[3] and later in Brazil,[4] Mexico,[5] and Costa Rica[6] resulted in the 1985 regional polio eradication initiative in the Americas.[7] Early successes in the Americas prompted the 1988 resolution of the World Health Assembly to eradicate polio worldwide by the year 2000 by targeting the disease burden in developing countries through a global partnership spearheaded by the WHO, the United Nations International Children's Emergency Fund, Rotary International, and the Centers for Disease Control and Prevention.[8]

In 1994, the Region of the Americas was certified as polio-free. Cessation of poliovirus transmission was achieved through 4 key strategies: surveillance for acute flaccid paralysis; strengthening of routine immunization systems; provision of supplemental doses of OPV through national immunization days and subnational targeted supplemental immunization activities; and house-to-house "mopping up" immunization rounds to eliminate the last foci of polio transmission in affected countries. Successful application of these basic strategies in the Western Pacific region was pioneered by China, which experienced an epidemic in 1989-1990 that affected 10 000 children despite high routine OPV coverage.[9] By 2000, the 37 Western Pacific region countries were certified polio-free,[10] followed in 2002 by the 51 countries of the European region.[11] The 4 endemic countries have persistently delayed certification of the remaining 3 WHO regions.

Polio Eradication Strategies in the Developing World

Naturally acquired immunity through wild poliovirus circulation exists only in the polio-endemic areas of the world and those few previously polio-free countries experiencing ongoing poliovirus transmission because of importation from endemic areas. The remainder of the world relies solely on immunization, whether OPV, IPV, or a combination of both. Even when achievable, high rates of routine immunization alone (>90%) have proven inadequate over the last 40 years to prevent periodic epidemics in tropical countries with high birth rates and poor sanitation.[2] Thus, a consensus emerged within the polio eradication initiative that any eradication strategy in the developing world should consist of the 4 fundamental components that proved so successful in the Americas: improved routine immunization, supplemental mass immunization, poliovirus surveillance, and outbreak response capacity.

Improved Routine Immunization

For either eradication or control, improving the current level of routine immunization against polio in developing countries is crucial. Unfortunately, current global routine immunization coverage is less than optimal. The WHO and the United Nations International Children's Emergency Fund data for 2006 indicate that more than 26 million children worldwide are not vaccinated with 3 doses of polio vaccine through routine programs, and that average global coverage reached only 80% of children.[12] Forty countries have less than 80% coverage—the minimum level needed to significantly reduce the risk of outbreaks following importations.[13] These countries include 3 of the 10 most populous countries in the world: India (58%), Indonesia (70%), and Nigeria (61%). Seven of the 40 countries have coverage that is lower than 50%. Closing this vaccine coverage gap by improving the level of routine immunization will be a major challenge. It is unlikely that the world will reach the 2010 global goal for all countries having at least 90% national vaccination coverage and 80% vaccination coverage in every district.[14]

Supplemental Mass Immunization

In many tropical developing countries, pools of susceptible individuals accumulate from both failure to reach children through the routine program and failure of OPV to uniformly induce an adequate immune response despite the recommended 3 to 4 routine doses. Even countries with relatively high national immunization coverage are at risk for periodic large polio outbreaks in the absence of supplemental immunization. Therefore, any strategy for developing countries must also include the capacity to organize and deliver multiple supplemental doses of polio vaccine each year to prevent large polio outbreaks.

Effective Poliovirus Surveillance

An integral component of global eradication is continuation of nationwide acute flaccid paralysis surveillance, which includes continued operation of the WHO Global Polio Laboratory Network. The 145 laboratories of the Global Polio Laboratory Network are essential for providing information for programmatic action by identifying outbreaks early, assessing the effectiveness of immunization strategies, and guiding response efforts toward global control.

Adequate Outbreak-Response Capacity

Each country must have access to sufficient public health infrastructure and vaccine supply for possible polio outbreak-response. The vicissitudes of economic and political fortunes of low-income countries dictate that this response capacity must also exist at the WHO headquarters and regional level, and rely on external funding.

Resurgence of Polio During 2003-2006

After reaching a record low of 483 reported polio cases globally in 2001, 2 events fueled debate about the feasibility of polio eradication. The first circumstance was the cessation of polio vaccination in northern Nigeria during 2003-2004, which occurred because of unfounded fears about the safety of OPV; the second was reductions in the number and geographic extent of national immunization days and supplemental immunization days in India during 2001-2002, which

resulted in the spread of polio from Nigeria and India during 2003-2006 with importations into 27 previously polio-free countries.[13] At least 92 separate importations were documented by epidemiologic and genomic sequencing data. Control of the ensuing outbreaks required additional supplemental immunization rounds with direct costs of more than $500 million in external funds alone. Cessation of polio vaccination in northern Nigeria resulted in more than 5000 additional paralyzed children during 2003-2006, both within Nigeria and through the spread of poliovirus to 20 of the 27 polio-free countries from West and Central Africa to Indonesia.

Recent Progress, Innovations, and Challenges

The year 2007 marked a turning point as intensified eradication activities in the remaining polio-endemic countries reduced poliovirus spread. During this time, most of the outbreaks in countries that were previously polio-free were successfully stopped through intensified use of outbreak-response guidelines endorsed by the World Health Assembly in May 2006. As of June 2008, transmission continues in the 4 polio-endemic countries but only 6 countries that were previously polio-free have ongoing transmission (Angola, Chad, the Democratic Republic of the Congo, Ethiopia, Niger, and Sudan).

New tools and tactics, in addition to more aggressive outbreak-response guidelines, have contributed greatly to restoring confidence that polio eradication can be achieved, including large-scale use of monovalent OPV formulations to enhance protective efficacy, particularly in tropical countries, compared with trivalent OPV; implementation in the WHO Global Polio Laboratory Network of rapid virus culture techniques and the polymerase chain reaction to reduce the time for poliovirus identification by half, thereby facilitating rapid response capacity; and intensified engagement of national and local political leaders in polio-affected countries.

In polio-endemic countries, type 1 monovalent OPV has been used on a massive scale (>2.5 billion doses since 2005) to prioritize eradication of type 1 poliovirus, which has a greater capacity than type 3 poliovirus to cause paralytic disease, to cause large outbreaks, and to spread over wide geographic areas. Remarkable progress has occurred in India, which has reported a record low of 8 cases of type 1 poliovirus in 2008 and has interrupted indigenous transmission for the first time ever in Uttar Pradesh—its largest state and last remaining original "polio reservoir." Whether this success will be sustained through the 2008 summer high season for poliovirus transmission remains an open question. Other challenges include a new type 1 poliovirus outbreak in 2008 in northern Nigeria with renewed risk of international spread, which is due to persistent failure to fully vaccinate children, and persistent low-level poliovirus transmission in parts of Afghanistan, Pakistan, and a handful of previously polio-free countries now dealing with ongoing poliovirus transmissions due to importation.

In polio-free countries of North America, Europe, and Australia, there has been a transition back to the use of IPV to eliminate the rare adverse events associated with OPV.

More than 5 million children and young adults are walking today because of the efforts of the polio eradication initiative since 1988. After the many setbacks, will the promise of a polio-free world for future generations[15]—first imagined by the availability of polio vaccine beginning in the 1950s—finally be realized? While optimists would say yes, the answer still is not clearly in sight, although it may be just over the horizon.

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