

- 12 Howe SJ, Mansour MR, Schwarzwaelder K, Bartholomae C, Hubank M, Kempinski H, *et al.* Insertional mutagenesis combined with acquired somatic mutations causes leukemogenesis following gene therapy of SCID-X1 patients. *J Clin Invest* 2008;**118**:3143–9.
- 13 Bushman FD. Retroviral integration and human gene therapy. *J Clin Invest* 2007;**117**:2083–6.
- 14 Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, Cassani B, Callegaro L, *et al.* Gene therapy for immunodeficiency due to adenosine deaminase deficiency. *N Engl J Med* 2009;**360**:447–58.
- 15 Kohn DB, Candotti F. Gene therapy fulfilling its promise. *N Engl J Med* 2009;**360**:518–21.
- 16 Aiuti A, Cassani B, Andolfi G, Mirolo M, Biasco L, Recchia A, *et al.* Multilineage hematopoietic reconstitution without clonal selection in ADA–SCID patients treated with stem cell gene therapy. *J Clin Invest* 2007;**117**:2233–40.
- 17 Felice B, Cattoglio C, Cittaro D, Testa A, Miccio A, Ferrari G, *et al.* Transcription factor binding sites are genetic determinants of retroviral integration in the human genome. *PLoS ONE* 2009;**4**:e4571. doi:10.1371/journal.pone.0004571. Available at [www.plosone.org](http://www.plosone.org)
- 18 Raper SE, Chirmule N, Lee FS, Wivel NA, Bagg A, Gao GP, *et al.* Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. *Mol Genet Metab* 2003;**80**:148–58.
- 19 Evans CH, Ghivizzani AC, Robbins PD. Arthritis gene therapy's first death. *Arthritis Res Ther* 2008;**10**:110 (doi:10.1186/ar2411). Available at <http://arthritis-research.com/content/10/3/110>
- 20 Cavazzana-Calvo M, Fischer A. Gene therapy for severe combined immunodeficiency: Are we there yet? *J Clin Invest* 2007;**117**:1456–65.
- 21 Peng Z. Current status of gene therapy in China: Recombinant human Ad-p53 agent for treatment of cancers. *Hum Gene Ther* 2005;**16**:1016–27.
- 22 Guo G, Xin H. Chinese gene therapy: Splicing out the West? *Science* 2006;**314**:1232–5.
- 23 Guinn BA, Mulherkar R. International progress in cancer gene therapy. *Cancer Gene Ther* 2008;**15**:765–75.
- 24 Chen L, Woo SL. Complete and persistent phenotypic correction of phenylketonuria in mice by site-specific genome integration of murine phenylalanine hydroxylase cDNA. *Proc Natl Acad Sci USA* 2005;**102**:15581–6.

S. S. AGARWAL

Formerly Department of Genetics  
Sanjay Gandhi Post Graduate Institute of Medical Sciences  
Lucknow  
Uttar Pradesh  
[agarwal\\_ss2000@yahoo.com](mailto:agarwal_ss2000@yahoo.com)

## Lessons from the Challenges of Polio Eradication in India

In 1988, India resolved to eliminate the transmission of wild polioviruses (WPVs) by the year 2000, but failed; in 2002, the target was revised to 2005.<sup>1</sup> However, the endemic transmission of WPV types 1 and 3 continues even in 2009.<sup>2</sup> India's problems on the polio eradication front are symptomatic of the defects in her health system.<sup>3</sup> The only other countries with uninterrupted endemic transmission of WPVs are Pakistan, Afghanistan and Nigeria, all with weak health systems.

Readers may recall the debate on the proposed health system reforms between two rival political party candidates in the recent election for President of the USA. In India, the political party that wins a majority forms the government, which implements the party's policy on health system. I am unaware whether any political party addresses issues related to the maladies (and the possible remedies) of our health system. So, there is no reform to implement though, in my opinion, reform is urgently required in the health sector.

The inordinate delay in polio eradication suggests systemic deficiencies in our health infrastructure, especially regarding the organization of the health system and the sharing of responsibilities between the Centre and the states.<sup>3</sup>

### *The health system in the context of polio eradication*

India's health system should consist of two arms: 'medical care'—focusing on individuals, particularly after they fall ill, for restoration to health; and 'public health'—focusing on the community and the environment for breaking the chains of transmission of infections to control endemic diseases and outbreaks. Medical care for rural communities is predominantly in the public sector but remains minimalist in spite

of the National Rural Health Mission. While medical care deficiencies in the public sector in urban communities have to a certain extent been mitigated by the private sector, both sectors are guilty of not ensuring quality and equity.<sup>4</sup>

Polio eradication is a global public health programme; India's responsibility is polio elimination within the country. However, there is no Department of Public Health either at the Centre or in the states (with the exception of Tamil Nadu). Thus, many essential functions of public health in India are unmet. Instead of establishing public health infrastructure with a broad agenda of controlling all infectious diseases, we have special vehicles for targeted 'vertical' control of tuberculosis, malaria, leprosy, AIDS, kala azar and lymphatic filariasis (under the Department of Health Services) and of childhood cluster of 6 diseases (Universal Immunization Programme [UIP] under the Department of Family Welfare).<sup>1</sup>

India's official representative at the 1988 World Health Assembly committed to the elimination of WPVs by 2000 and we expected that UIP would achieve it on time.<sup>5</sup> In 1995, when it became clear that this was unlikely to happen, the WHO stepped in and created a new special vehicle called the National Polio Surveillance Project (NPSP) and polio was placed under epidemiological monitoring through detection and virological investigation of all cases of acute flaccid paralysis.<sup>2</sup> No other childhood disease targeted for control under UIP is being epidemiologically monitored.<sup>6</sup>

In 1978, India set out to reach 85% vaccination coverage of infants, but has reached <50% in 30 years.<sup>7</sup> Inter-state disparities are unacceptably wide—some with >95% but others with <30% coverage with 3 doses of DPT (diphtheria–pertussis–tetanus) vaccine and trivalent OPV (tOPV) during infancy. The vaccination coverage in Uttar Pradesh and Bihar is among the lowest, contributing to barriers in interrupting the transmission of WPVs.<sup>3,7</sup>

During the 1970s and 1980s, studies had shown that tOPV had low vaccine efficacy (VE) in India and incomplete safety globally.<sup>8,9</sup> On the other hand, inactivated poliovirus vaccine (IPV) had a superior VE in India and complete safety globally.<sup>9,10</sup> However, on account of a health system flaw, a restrictive policy of the exclusive use of tOPV was continued and the government declined to license IPV.<sup>3</sup> This official stand was mistaken by some global public health agencies to mean that Indian studies on VE of tOPV were not credible. Thus, a cycle was created in which the WHO and the government reinforced each other's flawed policy of exclusive use of tOPV. Escape from this cycle was not easy then and it is not easy even today. The lesson to be learned here is that health-related policies should be supported by evidence, for which technical leadership should be strengthened at the Central and state levels. When in-country studies showed anomalous results, the government should have verified the results by independent investigation, for which a functional public health department with laboratory support was necessary, but not available. The Indian Council of Medical Research did undertake such an investigation and confirmed the low VE, but that was also ignored.<sup>11</sup>

In the absence of case-based disease surveillance, which is an integral function of a public health department, vaccine-failure polio was missed for decades.<sup>3,8,10,11</sup> This shortcoming was recognized by the NPSP only after attempts at elimination of WPVs failed beyond 2004. In 2005, the NPSP conducted independent verification of VE using field epidemiology, for the first time, and re-discovered that 3 doses of tOPV provided protection to no more than 30% of children against WPV types 1 and 3.<sup>12</sup>

In 1982, WHO had warned all countries using OPV to keep vaccine-associated paralytic polio (VAPP) under surveillance.<sup>9</sup> In the absence of disease surveillance and laboratory support services, this WHO recommendation could not be complied with. In summary, the major factor that led to India's failure with polio elimination is the lack of an overarching Department of Public Health and the lack of technical leadership at the highest levels of policy-making. As in the case of similar departments in other fields, the Department of Public Health must also be headed by a technically qualified professional.

In 1999, India took a leading role in a conference on 'Public health in South East Asia in the Twenty-first century' convened in Calcutta (now Kolkata).<sup>13</sup> The outcome was embodied in the 'Calcutta Declaration' in which the importance of public health as a discipline and as a framework for employing public health-trained personnel with a clear career track (in other words a public health department, as in Tamil Nadu) was highlighted.<sup>13</sup> This recommendation needs to be acted upon.

#### *The current situation of polio*

Though by definition, India is still endemic for WPV, the burden of disease has been drastically curtailed by a long, arduous and expensive intervention meant for total elimination. In the 1980s, the mean daily number of cases of polio was 500–1000.<sup>8</sup> In 2006, 2007 and 2008 the mean number was 1.9, 2.4 and 1.5, respectively.<sup>2</sup> The drastic reduction was both numerical and geographical. During the past 5 years, WPVs have continued to circulate only in Uttar Pradesh and Bihar,<sup>2</sup> but, a chain is as strong only as its weakest link. These 2 states together have a population of about 250 million (2001 Census), i.e. over 20% of the national total. Moreover, in recent years WPV types 1 or 3 from Uttar Pradesh and Bihar have spread to nearby areas (e.g. Delhi and Haryana) and faraway states (e.g. Orissa and Maharashtra) and neighbouring countries (e.g. Nepal and Bangladesh) and faraway countries (e.g. Lebanon and Angola).<sup>14</sup> It is imperative that Uttar Pradesh and Bihar succeed soon so that India achieves success, without which global eradication of polio will remain unrealized.

In 2006, there was an outbreak of WPV type 1, predominantly in Uttar Pradesh.<sup>2</sup> An outbreak of WPV type 3 began in 2007 and continued into 2008, predominantly in Bihar.<sup>2</sup> In response, unprecedented vaccine pressure is being applied. Presently, following the outbreaks when transmission efficiency and burden of WPVs are low, there is an opportunity for interrupting WPV types 1 and 3 in 2009–10, which should not be missed.

Of the three serotypes of WPVs, type 2 was eliminated from India in 1999, providing proof that the type 2 component in tOPV performed more efficiently than the types 1 or 3 components. The wide differential in type-specific VE of tOPV were recognized and confirmed by several studies in India.<sup>8,10,11</sup> VE against type 2 is the highest and against 1 the lowest.<sup>8,10,11</sup> The interruption of type 2 WPV showed that adequate coverage of vaccination had been reached through multiple annual tOPV campaigns, but VE was inadequate against WPV types 1 and 3. It took 6 more years for this interpretation to be accepted, highlighting the gaps in epidemiology; since 2005, monovalent OPV types 1 and 3 (mOPV-1, mOPV-3) are being used since they have significantly higher type-specific efficacy.<sup>12</sup>

Taking a cue from the interruption of type 2, the current tactic is to focus on eliminating type 1 and, after ensuring success, to aim for eliminating type 3.<sup>2</sup> As the issue of incomplete safety of OPV became global news, the government allowed the entry of IPV in India and licensed it in May 2006, but without evolving a policy on its use. The government and NPSP are in the process of developing an evidence-based policy on its use to complete and conclude polio elimination, re-defined as zero incidence of poliovirus infection (i.e. not only wild but also vaccine-derived).<sup>3</sup>

#### *Possible solutions: The way forward*

We can either somehow achieve polio eradication and leave the system as it is; or introduce systemic changes while eradicating polio. The former option may seem expedient, but the latter is in our long term interest.

A third option is to accept the current status of polio as 'control' and to discontinue the intensified efforts to interrupt WPV transmission, as has been proposed in a paper in this issue of the *Journal*.<sup>15</sup> The authors advocate conservation of resources and suggest that those resources should be put to better use—to improve the delivery of healthcare in the public sector.<sup>15</sup> They point out that the polio elimination programme has been exorbitantly expensive.<sup>15</sup> When one wages war (on polio) but disallows the use of the more powerful weapon (i.e. IPV) in favour of the

less efficient (OPV), consequent delays and cost-escalations will invariably follow. For controlling polio at the present level, resources will need to be provided perpetually, i.e. resources will not be conserved. Thus, the better option is to complete the operation, eliminate WPVs and thereafter eliminate vaccine polioviruses. This sequence will necessarily be expensive as the elimination of vaccine viruses will require the inclusion of IPV in the UIP.<sup>3</sup> Had IPV been introduced earlier the comparative merits of both vaccines could have been evaluated. Thus, much time and money would have been saved for the elimination of WPVs. As OPV could have been withdrawn earlier, continued seeding of the community with vaccine viruses could have been stopped in time.<sup>3</sup>

In my opinion, the best way forward for us is to complete the task of polio elimination and also take early steps to reform our health system. India's health system must be redesigned to be comprehensive, professional, efficient, responsive to people's needs and oriented to quality and equity. The first step should be to establish a National Commission on Health Systems to assess the lessons learnt from India's problems with elimination of polio and to apply remedies holistically. Appropriate tools of public health must be applied to control the many neglected infectious diseases including cholera, enteric fevers, shigellosis, leptospirosis, rabies and scrub typhus. India needs to graduate and acquire the skills of modern public health to address the new epidemics of diabetes, hypertension, cardiovascular and neurovascular diseases and obesity. The current spending on health, 0.91% of GDP, is woefully inadequate for a self-declared 'welfare state'. India must drastically increase the budget also for appropriate healthcare with equity and quality. The Central and state governments should establish Departments of Public Health, with avenues for training in epidemiology and public health and career tracks for trained officers. Without Departments of Public Health increased fund allocations are unlikely to be absorbed or utilized or to succeed in disease control and health promotion.

### Conclusion

As the prevalence of WPVs decline vaccine viruses show the tendency to fill the niche by evolving into 'circulating vaccine-derived polioviruses' that are wild-like.<sup>3</sup> Thus, true polio eradication requires the elimination of both WPVs as well as vaccine viruses.<sup>3</sup> Therefore, IPV will have to be introduced for the safe withdrawal of OPV, at the earliest opportunity in the future. The original argument that elimination of WPV using the cheaper vaccine (OPV) would be more economical than by using the more expensive IPV was faulty; but as now as it was then, the question was not primarily one of economics but of science guiding policy. Way back in 1981 it was suggested that IPV would be the vaccine of the future and the use of OPV should be considered only as an interim measure.<sup>16</sup>

### REFERENCES

- 1 Available at <http://www.mohfw.nic.in/> (accessed on 6 April 2009).
- 2 National Polio Surveillance Project. AFP and polio data. Available at <http://www.npsindia.org/bulletin.pdf> (accessed on 6 April 2009).
- 3 Polio Eradication Committee, Indian Academy of Pediatrics. Universal Immunization Programme and polio eradication in India. *Indian Pediatr* 2008;**45**:807-13.
- 4 Voluntary Health Association of India. Health services in rural and urban areas. Chapter 8. In: Mukhopadhyay A (ed). *Report of the Independent Commission on Health in India*. New Delhi: Voluntary Health Association of India; 1997:75-95.
- 5 World Health Assembly. Global eradication of poliomyelitis by the year 2000. (Resolution WHA 41.28). World Health Organization, Geneva. 1988
- 6 John TJ. Resurgence of diphtheria in India in the 21st century. *Indian J Med Res* 2008;**128**:669-70.
- 7 National Family Health Survey, India. NFHS-3 Fact sheets. Available at <http://www.nfhsindia.org> (accessed on 6 April 2009).
- 8 John TJ. Poliomyelitis in India. Prospects and problems of control. *Rev Infect Dis* 1984;**6** (Suppl 2):S438-S441.
- 9 World Health Organization Consultative Group. The relation between acute persisting spinal paralysis and poliomyelitis vaccine. Results of a ten-year enquiry. *Bull World Health Organ* 1982;**60**:231-42.
- 10 John TJ. Immunization against polioviruses in developing countries. *Rev Med Virol* 1993;**3**:149-60.
- 11 Pangi NS, Master JM, Dave KH. Efficacy of oral polio vaccine in infancy. *Indian Pediatr* 1977;**14**:523-8.
- 12 Grassly NC, Fraser C, Wenger J, Deshpande JM, Sutter RW, Heymann DL, et al. New strategies for the elimination of polio from India. *Science* 2006;**314**:1150-3.
- 13 Anonymous. Calcutta declaration on public health. *J Health Popul Dev Countries* 2000;**3**:5.
- 14 Anonymous. Progress towards interrupting wild poliovirus transmission, January 2006-May 2007. *Wkly Epidemiol Rec* 2007;**82**:245-51.

- 15 Yadav K, Rai SK, Vidushi A, Pandav CS. Intensified pulse polio immunization: Time spent and cost incurred at a primary healthcare centre. *Natl Med J India* 2009;**22**:13–17.
- 16 John TJ. Towards a national policy on poliomyelitis. *Indian Pediatr* 1981;**18**:503–6.

T. JACOB JOHN  
439 Civil Supplies Godown Lane  
Kamalakshipuram  
Vellore  
Tamil Nadu  
tjacobjohn@yahoo.co.in

---

*The National Medical Journal of India* is indexed in  
*Current Contents: Clinical Medicine* and *Science  
Citation Index*.

—Editor