PERSPECTIVE

India's Research Contributions Towards Polio Eradication (1965-2015)

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Pioneering research has been conducted in India during the past five decades, comprehensively covering epidemiology of poliovirus infection and of polio, efficacy and effectiveness of oral and inactivated polio vaccines (OPV, IPV) as well as pathogenesis of wild and vaccine polioviruses. It was estimated, based on epidemiology data, that India had a very heavy burden of polio, with average 500-1000 cases per day. Prevention was an urgent need, but OPV showed unacceptably low vaccine efficacy (VE) for poliovirus types 1 and 3. Having learned that response to sequential doses followed arithmetic pattern and not prime-boost principle, multiple doses were tested and found to be a simple intervention to increase VE. Eventually this knowledge became critical for polio eradication. Indian research demonstrated that monovalent OPV (mOPV) had nearly three timed higher VE than trivalent OPV (tOPV). Eventually, mOPV type 1 became essential to interrupt wild type 1 infection in many locations where the VE of tOPV was very low. Indian research pointed to the epidemiologic importance of direct person-to-person spread of wild polio viruses and the need and potential of IPV to prevent and control polio. Research on vaccine responses led to the understanding that OPV would become wild-like through back mutations and to the definition of eradication as interrupting transmission of both wild and vaccine-derived polioviruses. By asking and answering the right questions insequence, Indian polio research presaged and guided polio eradication.

Keywords: *Eradication, IPV, OPV, Vaccination.*

Pioneering research conducted in India during the past five decades comprehensively covered epidemiology of poliovirus infection and of polio, efficacy and effectiveness of oral polio vaccine (OPV) and inactivated polio vaccine IPV), as well as pathogenesis of wild and vaccine polioviruses [1-5]. The research findings were essential to explain biomedical barriers against polio eradication and to overcome them by designing suitable tactics [1, 2].

When launched in 1988, polio eradication intended global interruption of only wild poliovirus [WPV] transmission, for which exclusive use of OPV was prescribed for low and middle income (LMI) countries [6]. In 2000, the eradication target year, five countries including India remained polio endemic; initially India's failure was attributed to sub-optimal vaccination coverage – 'failure to vaccinate'. However, WPV type 2 was interrupted in 1999 proving that coverage was adequate to eliminate the type against which vaccine efficacy (VE) of trivalent OPV (tOPV) was satisfactory [1,2,7, 8].

To overcome the barrier of low VE against WPV 1 and 3 — 'failure of vaccine' — findings from old research were applied, reinforced with new studies. Uttar Pradesh (UP) and Bihar had the world's lowest VE; success, finally achieved in 2011, proved that biological barrier to WPV eradication could be overcome everywhere. Research thus proved key to success.

The scientific definition of eradication as interruption of poliovirus transmission, wild and vaccine, and the ideation of using IPV to eradicate vaccine viruses, originated from Indian research [1,9-11]. They form the basis of 'Global Polio Eradication and End Game Strategic Plan 2013-18' of the World Health Organization (WHO), attesting to the pioneering nature of our research [1,9,10,12]. This paper is a look-back on Indian research relevant to polio elimination nationally and eradication globally.

MEASURING THE MAGNITUDE OF POLIO

The model of polio surveillance created in Vellore in 1980 was not nationally up-scaled until 1997 when eradication efforts were failing [13-15]. The lack of nation-wide surveillance had resulted in gaps of information on four fronts: the magnitude of polio burden [13,16-18]; iatrogenic polio [19,20]; barriers to polio prevention/control [1,2,7]; and vaccine-associated paralytic polio (VAPP) [21-23].

The annual incidence of WPV infection prior to vaccine introduction was 48 per 100 pre-school children (range: 63/100 in infancy and 23/100 in 4-year-olds) [24]. Infection occurred in successive waves of the three WPV types — on average 4% of all stool samples were positive in urban and 1.52% in rural children, showing faster spread in towns [2,24,25]. High infection incidence, predictable age distribution and urban-rural

variation of speed of spread, all suggested child-to-child transmission determined by frequency of contacts – houses are more crowded in urban and dispersed in rural communities [24-26].

Different methods measured the prevalence of polio [13,27]. Using denominator-based annual incidence in Vellore and UP, the national disease burden was calculated as 200,000-400,000 per year or 500-1000 per day [13,18,23,28]. The age distribution was: median age at 12-15 months and saturation by age 5-7 years; the steepest part of the curve was during 6 to 12 months when fecal contamination of feeds is least likely [29, 30]. This pattern is consistent only with direct, person-to-person instead of chance fecal-oral transmission, and no known fecally-orally transmitted agent has similar epidemiologic pattern [24-30]. No water-borne or food-borne common source polio outbreak, which should have been inevitable if transmission was mainly fecal-oral, has occurred in India [26].

Iatrogenic polio had received little attention [19,20]. Intramuscular injections, particularly diphtheria-pertussis-tetanus vaccine (DPT), increase the risk of polio paralysis (called provocation polio) several-fold [19,20]. Under Expanded Program on Immunization (EPI), launched in 1978, 27 million DPT injections were given in 1978-79, while no child had been given 3 doses of OPV [31]. In the next 3 years, the numbers of DPT injections were 24, 24 and 29 millions, respectively, while 3 doses of OPV were given only to 0.5, 1.3 and 2.3 millions respectively [31]. After initiating massive scale DPT injections polio cases (reported through sentinel centers) increased; this paradoxical rise of polio after launching EPI was presumably on account of provocation polio [1,2,19, 20].

Extrapolating from European data on frequency of VAPP, at least 2 cases per million birth cohort was predicted in India [32]. Using data from polio surveillance in India, international assessment was very low risk [21]. Re-analysing data using scientific methodology, 6 cases per million birth cohort — five times higher risk than in the USA – were found, demanding upward revision the estimated burden of VAPP in developing countries [22,23]. During 4 decades of exclusive use of OPV, over 3000 children would have developed VAPP in India; ethics demanded shifting the policy to IPV [32, 33].

STUDIES ON VACCINE EFFICACY OF OPV

Until vaccine failure polio was detected in India in 1960s, VE of 3 doses of trivalent OPV (tOPV) was assumed to be 100 per cent universally [29,34]. In India, antibody induction (seroconversion) rates were low for types 1 and 3 (~65%), but satisfactory for type 2 (~96%) [7,35]. Closely similar seroconversion rates were confirmed in a study in Maharashtra; so the problem was widespread [36]. The low VE led to increasing numbers of vaccine-failure polio as tOPV coverage increased, posing one more ethical problem [1,2].

Seroconversion after each additional dose was at the same frequency as after the first dose – a basic phenomenon determining response to OPV, described first in India [1,2,7,37,38]. The responses to sequential doses follow arithmetic proportionality and not prime-boost principle [1,2,7,37,38]. Cumulative VE of multiple doses is obtained by repetition of per-dose efficacy. Thus, VE of two doses, E2 = E1 + [E1[100 – E1]], where E1 is per-dose efficacy; VE of three doses, E3, is E2 + [E1[100 – E2]] [1, 2,37,38]. In this way we calculated the cumulative VE of 5 doses, which closely matched measured antibody responses [1,2,37,38]. To match three-dose VE elsewhere, we needed 9-10 doses [2,7]. The fact that WPV transmission was interrupted in most of India when an average of 8-9 doses per child was reached fits with this observation [39].

The reason for low antibody response was failure to establish infection by vaccine viruses in a substantial proportion, rather than inability to mount immune response after infection [1,2,7,40]. This was contrary to international opinion that our children have suboptimal immune responses to oral live vaccines. Did antibodies in breast milk inhibit intestinal infection with vaccine viruses? [41]. A definitive study showed that such antibodies, although present, did not interfere with vaccine virus take and immune responses [42].

The contrast of easy natural infection with WPV and failure to get infected even with a million vaccine virus inoculum, is probably due to heightened innate immunity consequent to repeated intestinal infections with various microbes. Innate immunity does distinguish between wild and vaccine polioviruses [43].

Several solutions to overcome low VE were successfully tested in Vellore. One was to simply increase the number of doses per child to five [1,2,37]. The immunogenicity of OPV given to neonates was tested and found to be non-inferior to immunogenicity at older ages [44,45]. Thus, five doses could be given under EPI with 5 contacts in infancy starting from the first week of life. Another solution was to give monovalent OPV; against types 1 and 3, VE of monovalent vaccine was 2.5 to 3 times higher [46]. A third solution was pulse immunization, a highly effective method that kept Vellore polio-free from 1982 [47]. Finally the VE and

effectiveness of 2 doses of IPV were shown to be superior to even 10 doses of OPV [48].

In UP, the per-dose efficacy of tOPV against WPV-1 was only 13%, the lowest recorded anywhere [39]. Indeed, very low VE had been described in 1970 in New Delhi [49]. Per-dose VE calculated using the formula described above was 15% against type 1 and 20% against type 3 [31, 49]. In UP, seroconversion after 8 doses of tOPV was only 54% and 65% against types 1 and 3, respectively [50]. Extrapolated, the per-dose efficacy was 10% and 12% against types 1 and 3, respectively [51]. In UP and Bihar, WPV transmission could not have been interrupted using tOPV with such low VE. Comparison of VE of tOPV and monovalent OPV (mOPVs) in Vellore had shown mOPV with two-and-half times higher VE for types 1 and 3 [46]. Based on that observation, the National Regulatory Authority licensed mOPV types 1 and 3 [mOPV-1 and mOPV-3] in 2005. The high VE of mOPV-1 was then confirmed in a fresh study in India [52]. In UP and Bihar, WPV 1 was eliminated using mOPV-1.

Could mOPV types 1 and 3 be combined as bivalent OPV (bOPV) without loss of VE of the components? This question was investigated in India and the result showed non-inferior VE to that of mOPV given separately [53]. Polio elimination in UP and Bihar was sustained using bOPV for sub-national pulses, mOPV for mop up, and tOPV for routine immunization and for national pulse immunization given twice each year.

ISSUE OF SAFETY OF OPV

The textbook definition of attenuation of vaccine polioviruses is loss of neurovirulence while retaining efficiency of infection of the parent WPVs [54,55]. However, there was no evidence for perceptible local transmission of vaccine viruses in India. We had shown that attenuation had resulted in considerable loss of infection efficiency, which would translate to low transmission efficiency between humans [56]. A novel animal model of poliovirus infection and disease had been created in India, in bonnet monkey (*Macaca radiata*) [1,3-5,56-58]. The median monkey oral infectious dose of attenuated poliovirus type 1 was 10,000 times higher than that of wild type 1 Mahoney strain [56,57]. Thus, attenuation had indeed reduced infectivity and transmissibility. This was critical information.

Neurovirulence could be regained by genetic reversion during virus replication in cell culture or human intestine, explaining why OPV causes VAPP. Our finding of low infection efficiency begged the question: would it not also be regained through genetic reversion? It was reasonable to assume it would. If a strain of vaccine virus regained both properties, it would be wild-like in neurovirulence and transmissibility [59,60]. This prediction proved correct in Hispaniola, where a circulating vaccine-derived poliovirus (cVDPV) type 1 caused a polio outbreak in 2000 [61]. Since then cVDPV type 2 outbreaks have occurred in many countries and cVDPV type 1 and 3 infrequently in a few countries [12]. The continued use of OPV is incompatible with true polio eradication, as per our definition of zero incidence of wild and vaccine poliovirus infection [1,9-11].

VACCINE EFFICACY AND EFFECTIVENESS OF IPV

Research on IPV continued during 1970s and 1980s only in Bilthoven (Netherlands) and Vellore (India). Very high VE of IPV (3 doses) in infants was documented in India in early 1980s [62,63]. The Bilthoven group created an improved version of IPV with higher antigenic content in early 1980s [64]. We measured its VE – in Vellore it was named 'enhanced potency IPV (E-IPV); the VE of two doses was higher than that of 5 doses of tOPV [48,65]. Seroconversion rates were better in infants 8 weeks or older at first dose, than in infants 6 weeks old, and, near 100% when interval between doses was 8 weeks or more, instead of the conventional 4 weeks [48,65]. Intradermal inoculation was highly immunogenic [66-68].

In a field study, in nearly 7000 child-years of observation after IPV, none had polio while in equal number of control children without IPV, there were 17 cases; vaccine effectiveness was 100 per cent [1,2,25]. In another study, weekly stool samples were collected from all children in a village, from birth to 3 years. At one point, IPV was introduced in new birth cohorts and fecal shedding of WPVs were compared; there was statistically highly significant reduction (1.52% to 0.52%, $P<0.001$). Retardation of circulation intensity of WPV is the basis of herd effect; IPV exhibits herd effect, the epidemiological marker of mucosa immunity [1,2,25,69].

Mucosal immunity of IPV was explored in the animal model. After immunizing bonnet monkeys with IPV, they were non-susceptible to oral infection with WPV, for one year [56,57]. In 1986, the Indian Council of Medical Research and the Directorate of Health Services commissioned a study to measure the degree of control that could be achieved with IPV in a large population (not published by sponsoring agencies). The schedule of IPV was a dose at 2, 4 and 9 months. In 2.5 million population under IPV, the incidence of polio fell from 14 to 0.3 per 100,000 population (97% decline) when the 3-dose coverage had reached 84 per cent [14,70]. The greater decline relative to the coverage confirmed herd effect [14,69].

The conclusion from these studies was that IPV is highly suited for prevention and control of polio in India. In the face of such important research findings, the exclusive use of OPV during 1980s through 2014 was inconsistent with science and ethics [71-73]. Indian research had predicted the inevitability of introduction of IPV in India and globally [9-11,71-73]. This principle became reality in 2015 as all LMI countries have started introducing IPV in EPI as a prelude to withdrawing type 2 vaccine virus, achieved in April 2016 in globally synchronous manner, according to the current WHO strategic plan [12].

RESEARCH FOR SOLVING PROBLEMS TOWARDS ELIMINATION OF WPV

As WPV elimination was not achieved in 2000, intensive immunization drive with tOPV was applied to improve coverage with multiple doses, assuming that failure to vaccinate was the root cause. By 2005 it became obvious that in UP and Bihar WPVs could not be eliminated using tOPV, whose VE was too low against types 1 and 3 [39]. The per-dose efficacy was only 13% against type 1 [39]. Early research had showed high VE of mOPV-1 and 3 [46]. The National Regulatory Authority granted registration of mOPV-1 and 3 in 2005. A multicentric vaccine trial with mOPVs confirmed the earlier finding of high VE [52]. With intensive application of mOPV-1, circulation of WPV-1 was interrupted in January 2011.

While WPV-1 was targeted for elimination, outbreaks of WPV-3 occurred in Bihar and UP, during 2007-2010. A new bivalent combination of OPV types 1 and 3 (bOPV) was prepared and its VE was found to be non-inferior to VE of mOPV-1 and mOPV-3 [53]. In 2010 bOPV was introduced and UP and Bihar were maintained free of WPV-3 from last quarter of 2010.

RESEARCH IN SUPPORT OF THE END GAME

In 2013, the target of eradication was expanded to include vaccine viruses, for which IPV is essential [10,74]. The WHO Polio Eradication and End Game Strategic Plan 2013-2018 retained the term Eradication to interrupt WPV and the term End Game to eradicate vaccine viruses using IPV, the process that had been named Phase 2 Eradication in Indian literature [9,12,73]. The design of End Game is to introduce at least one dose of IPV in the routine immunization schedule, at the time of the third dose of diphtheria-pertussis-tetanus vaccine and tOPV, followed by the global synchronous withdrawal of type 2 strain from tOPV. This process, called tOPV to bOPV switch would result in two contributions to End Game: there will be no more VAPP due to type 2 and the source of cVDPV-2 will be shut-off.

The immunization schedule in the early End Game period will be bOPV at birth and at 6, 10 and 14 weeks plus one dose of IPV at 14 weeks. This schedule is new and its immunogenicity has been tested in India in a multicentre vaccine trial and confirmed to be highly satisfactory [75]. The seroconversion rates were 99% to types 1 and 3, and 69-78% to type 2. A second dose of IPV closed completely the immunity gap [75]. Earlier research had shown that one dose of IPV given to children who had received several doses of OPV was sufficient to cover any immunity-gap and to boost both humoral and mucosal immunity [76].

EPILOGUE

Research in India on polio was far-sighted, comprehensive and pioneering, presaging polio eradication. However, the application of research findings in policy and programme for control and final eradication of polio in India itself was unduly delayed. An important observation from this saga is a serious fault line in India between science and health-related policy. It is hoped that Government will take note and avoid such disconnect between evidence and policy in all other disease control programmes.

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