

T. Jacob John

T. Jacob John is a noted virologist and emeritus Professor of Virology at the Christian Medical College (CMC), Vellore. He was the Chief of the Virology Service of CMC from 1967 till 1995. He was also Chief of the National HIV/AIDS Reference Centre, CMC Hospital, Vellore for 10 years and chief of the Centre for Advanced Research in Virology, CMC Hospital, Vellore for 15 years. He discovered the problem of oral polio vaccine (OPV) failure in India leading to the 'Pulse Polio' immunization campaign and elimination of the wild polio virus (WPV) in the country. He is also chairman/member/advisor of several national committees and international organizations like WHO.

Please provide a brief history on the elimination of polio in India and your involvement in this initiative

In 1967, I found children developing polio (virologically confirmed) despite taking the recommended three doses of trivalent oral polio vaccine (tOPV, Sabin). Such 'vaccine-failure polio' had never been documented in countries using tOPV, mostly in North America and Europe. Polio was a serious problem in India. We did epidemiological studies and showed a heavy burden, amounting to an average of 500 cases per day in India. Many children were getting polio in spite of three doses of tOPV.

I attempted to improve protection by vaccination. Increased number of doses improved vaccine efficacy; for example, five doses in infancy as there are five infant-contacts in EPI (expanded programme on immunization) for other vaccines. However, the rule of three doses was not modified by the Ministry of Health (MoH), Government of India (GoI). Three doses of inactivated polio vaccine (IPV, Salk) were predictably and completely protective, but MoH did not license it for use in the country. Another trick was to pulse vaccinate in annual campaigns, three rounds, for all children below five years of age. This technique was successful, keeping Vellore free of polio for nearly 2 years. Pulse polio vaccination disturbs the balance of vaccinated and susceptible children at one point in time, thereby blocking the ease of transmission of WPV. However, MoH

did not approve vaccination by campaigns. As pulse vaccination was conducted by Rotary Club of Vellore in collaboration with Municipal Health Officer and CMC, it became well known in the Rotary world and a former President of Rotary International, Clem Renouf of Australia, came to Vellore to watch Rotary volunteers giving tOPV to children in camp clinics. He was impressed and requested Rotary International to consider targeting polio control as a Rotary project for its centenary year in 2005. When a global committee to design the project was made at Rotary HQ in Evanston, Illinois, USA, I was invited to be a member. As Rotary International launched its 'PolioPlus' project to raise funds to give OPV to all children of the (developing) world, the Pan American Health Organisation resolved to eliminate polio in all of Americas using in part, Rotary funding, given to all developing countries proportional to the birth cohort numbers. The World Health Organization was caught by surprise and in 1988, it moved a resolution in the World Health Assembly to 'eradicate polio globally by the year 2000'.

IPV was developed and licensed in USA in 1955 and soon thereafter in many European countries. OPV was licensed in the US in 1962. Both vaccines were found to be effective in preventing polio and further research declined in US and Europe, as polio experts believed that the problem had been solved. In 1987–88, India still was endemic for polio, and about 50% cases were in children 'fully vaccinated' (with three doses of tOPV). Due to such problems persisting in the country, we continued intensive research on polio – epidemiology, animal model, vaccine efficacy of IPV and OPV, pulse polio immunization, splitting OPV as mono component (monovalent type-1, type-2 and type-3 vaccines) and measuring vaccine efficacy, and so on. Globally, Vellore was the only centre conducting such basic and problem-solving research on polio from mid-1960s.

India found it tough to eliminate polio despite intensive efforts, including pulse polio immunization during the 1990s and into the 2000s. Using many research findings of Vellore studies and with me being appointed as Chairman of the India

Expert Advisory Group on polio eradication, particularly using monovalent OPVs, India was able to document the disappearance of WPV type-2 in 1999, type-3 in 2010 and type-1 in 2011.

This is a thumbnail sketch. Full credit for success goes to all field workers who traced and vaccinated children repeatedly, supervisors who maintained high-quality pulse and routine vaccinations, GoI for showing determination and political will and providing all the funding support, Rotary movement for advocacy, social mobilization, volunteering in pulse polio campaigns, WHO for full technical backing and UNICEF for fully supporting with communications and pre-empting negative propaganda by miscreants. The guidance of Vellore research findings was a crucial element not only in India, but in other countries as well.

What were the reasons for the introduction of IPV into routine immunization in India? When did this happen?

During in-depth research and literature searches, I found two major flaws of OPV. In India and many developing countries, especially in the tropical belt, there was unacceptably low vaccine efficacy. Children could get polio (by remaining non-immune) even after 5, 7, 10, 15 and 20 doses of tOPV. That problem could be surmounted by pulse and monovalent vaccines.

However, the second flaw was more serious. OPV contains attenuated live polioviruses. Attenuation is incomplete and some children get polio caused by these vaccine viruses. It is called vaccine-associated paralytic polio (VAPP). In Norway, VAPP occurred in one child per 100,000 children. In India VAPP frequency was one per 150,000 children; in USA one per 750,000 children. VAPP is indistinguishable from WPV. While wild polio was occurring at the rate of 500/day, the risk–benefit ratio of OPV was good. As the numbers dwindle, the risk–benefit ratio becomes unacceptable. While a safe and effective alternative vaccine is available, it becomes unethical not to use it in preference to the unsafe vaccine.

From the characteristics of vaccine viruses, we could predict that among children, some are exposed to secondary

and tertiary transmission of vaccine viruses – and in rare instances continue circulation. With every transmission the vaccine virus loses attenuation and becomes more neuro-virulent. While global experts defined polio eradication as zero transmission of WPV, and accepted the risks of OPV as a price in public health, I insisted that polio eradication must be defined as zero transmission of wild and vaccine viruses (1993). Further understanding of the ethical and epidemiological problems led me to declare that not only should vaccine viruses be stopped and be replaced by IPV, but also that vaccine viruses in transmission must be eradicated using IPV (1996). I advocated introduction of IPV universally and discontinuation of OPV in phases, throughout the late 1990s and all through 2000s. In 2012, global experts accepted my definition of polio eradication and the need for introduction of IPV. The 2013–18 strategy of global polio eradication is called the eradication of vaccine viruses or the ‘endgame’ of polio eradication. This gives me immense personal satisfaction.

The first step was to introduce IPV in all countries using OPV during 2015–16. Then, during the second half of April 2016, a globally synchronous withdrawal of type-2 vaccine virus was accomplished – tOPV to bOPV switch. Wild type-2 had been eradicated in 1999 and since then all type-2 polio was due to vaccine virus type-2. Bivalent OPV contains types 1 and 3, and not type-2. So India introducing IPV into routine schedule was part of a global shift in policy. It happened in a staggered manner from 2015 through 2016. Currently, due to shortage (more demand than supply), only one dose is offered – at or after 14 weeks of age. This age as the best was an old Vellore research finding, recently confirmed elsewhere such as Cuba. Currently, type-2 immunity is due exclusively to IPV.

As shortage of IPV has been a problem, India began giving fractional dose intradermally (ID). Two fractional doses at 6 and 14 weeks are equal or superior to one full IM dose at 14 weeks. So one IM dose can be used for two children ID. One dose of IPV (or 2 ID at 6–14 weeks) is not enough for full protection against type-2. As supply improves (hopefully in 2018), the IPV schedule may be at least two doses at 14 weeks and 9 months, using 9 month contact for measles vaccine.

A polio-eradicated world will use only IPV and not OPV. India contributed to meeting the IPV shortage. Under the Rajiv Gandhi Technology Mission, an IPV manufacturing unit was established in Manesar, Gurgaon, Haryana in 1987–88. After, the assassination of Rajiv Gandhi, the unit was closed by MoH believing that IPV will never be needed again. However, we knew that IPV would become necessary.

When and why did the switch from tOPV to bOPV occur? What challenges did India face during the switch?

The switch was globally synchronized to the two weeks from 17 April to 1 May 2016, with freedom for each country to fix one day for the switch within the time slot. India chose 24 April.

Why? This is a crucial question. As you know Sabin viruses are not fully attenuated, and can cause paralytic polio, indistinguishable from WPV. That is VAPP. A multi-country study by WHO, published in 1982, warned all countries using OPV to monitor VAPP. India simply ignored the alert. Sabin type-3 caused maximum VAPP in directly vaccinated children followed by type-1 and type-2. However, VAPP also occurred in unvaccinated contacts of vaccinated children – so called ‘contact VAPP’ which was most frequent for type-2, followed by type-1 and type-3. So we knew that Sabin 2 had a tendency to spread more than other types and also cause VAPP in secondarily infected children. During my research I also found an important phenomenon, hitherto unrecognized. In our monkey model, the infectivity of Sabin type-1 was far lower than that of its wild counterpart. It took 4 log 10 more Sabin virus to match wild virus. I interpreted this to suggest that infectivity may increase due to genetic reversion during transmission and prolonged residence in the intestines of children. So, if one Sabin strain reverted to neurovirulence and infection efficiency, you have wild-like virus – a real danger ahead. That worry became true in 2000 in Hispaniola with a Sabin-derived type-1 outbreak of polio. This was named circulating vaccine-derived poliovirus (cVDPV); I called them vaccine-derived wild-like virus.

October 1999 was the last wild type-2 isolation globally – in Aligarh, Uttar Pradesh (UP). Five years passed without

any natural wild type anywhere (except a man-made spread in UP), and I proposed to WHO that we must withdraw Sabin 2. My letter was published in *Lancet*: two good reasons to drop type-2 from OPV. That was the best time since several adults and older children were immune due to wild type-2 infection just a few years earlier. No other expert agreed with me. From 2006, cVDPV type-2 outbreaks began in Nigeria – many times, for many years. We had really missed the boat.

In 1993, I defined polio eradication as zero incidence of poliovirus infection, wild and vaccine. The WHO definition was zero incidence of WPV. According to my definition unlike that of WHO, IPV and not OPV was the answer. We maintained our independent views, till 2012, when WHO experts agreed that OPV must be phased out and IPV brought in. So, a 2013–18 strategic plan was prepared. IPV introduction in 2015 began as a prelude to the switch. The switch went on smoothly, but companies could not keep up with the surge in demand.

So the switch was the first step towards the withdrawing of OPV. In future, when WPV 1 is gone, Sabin 1 and 3 will also be withdrawn. By then, IPV supply will improve. It is a pity, that in 1992, GoI closed a state-of-the-art IPV unit. cVDPV polio had been occurring here and there – the largest of 48 confirmed cases in Syria during March to August 2017. This occurred because we continued to distribute Sabin 2, when there was no justification whatsoever.

November 2012 was the last date of wild type-3 detection (Nigeria). I had proposed bOPV to mOPV1 switch after 5 years – in 2018, but other experts expect wild type-1 to disappear in 2017 – so that eventually the switch can be bOPV to no OPV in 2022. I have not given up hope of removing Sabin 3 first and later Sabin 1. As I mentioned, most VAPP is due to Sabin 3.

Switch implementation itself went on like clockwork. There was good preparation with wide publicity and good arrangements to destroy withdrawn tOPV. Supplies of bOPV were in good shape. Monitoring was done and everything was almost fine. Certain private clinics did not stop tOPV as they did not want to waste vaccine. But all that is in the past. However, the real challenge was shortage of IPV. Only two major

manufacturers – Sanofi Pasteur (France) and Bilthoven Biologicals (Holland) stuck it out during the period when IPV was considered as poison for developing countries; but honey for rich countries. Both companies protected their traditional market and tried to upscale production by building new blocks for the emerging 120 countries market. Both failed quality and hence the global shortage.

India Universal Immunization Programme (UIP) resorted to dose sparing by intradermal fractional dose – two ID fractional doses instead of one full IM dose. That is what UIP is doing, but there is no IPV in the private market. So, we have been creating large immunity gaps for type-2 – no OPV-2 and no IPV for privately seen children. IPV coverage in UIP is probably no more than 75%. We hope no cVDPV-2 will be imported. And none will appear *de novo* in India. This is a big risk, but there is no way out.

What were the steps taken in India to ensure that cVDPV outbreaks did not occur post-switch?

As mentioned above, we are fortunate that no cVDPV outbreak has occurred in India, post tOPV–bOPV switch. My guess is that risk is low, but not zero and risk period is up to 3 years from April 2016, i.e. up to April 2019. If a strain emerges, we will be in some trouble, since type-2 immunity is not adequate in the community – having created wide gaps in cohorts born since April 2016. Ideally we should be monitoring type-2 immunity prevalences in different parts of India, but as you know the country is not scientifically strong to think autonomously and with foresight.

There is also some risk of importation of cVDPV from Pakistan or Syria – again low, but not zero. The Syrian cVDPV outbreak is not over yet; so we have to be vigilant. Surveillance of AFP (acute flaccid paralysis) must continue and sewage screening in different parts of India must also continue. So far, only one sewage sample in Delhi was positive for VDPV type-2 in March 2017.

What steps have been taken in India toward strengthening immunization services?

Not much. Mission Indradhanush is only an effort to improve coverage in

poorly performing districts, but not for ‘strengthening immunization services’. UIP as a system is incomplete and not managerially designed. The system has inputs or infrastructure, but does not monitor output. No business will succeed if output is not monitored and inputs not targeted where output is less than optimal. Output is reduction of target diseases. Take diphtheria, for example. Diphtheria toxoid vaccine is highly effective – but diphtheria occurs in many places. Unless UIP is transformed from being a vaccine delivery platform to a disease control platform, UIP will not be justified financially or socially, nor can it succeed in disease control. Disease control is not the mandate of UIP and it has no skill or infrastructure to become a disease control platform. Disease control is a public health agenda in all countries where disease control is the government’s programme. Unless India creates a public health infrastructure and manages control of all vaccine target diseases, plus many like typhoid and cholera, and integrates TB and malaria control, none of our vertical one-disease control programmes and UIP (another vertical programme) will become functionally effective.

Essential functions of the polio programme will need to continue to maintain immunity after polio eradication has been certified. What is being done in India with respect to this?

Indeed. Polio eradication is not yet complete in the world and in India. We have a few threats/risks.

- VAPP paralysing children. This has been totally neglected. Since April 2016, we probably have no VAPP type-2. However, VAPP types 1 and 3 continue. Once IPV is universal, the problem will be mitigated; after switching off bOPV, there will no longer be any VAPP.

- VDPV polio continues as a risk; small, but not zero. Some B-cell immuno-deficient children are probably chronically infected with vaccine viruses (iVDPV), posing future risks of transmission.

- Importation of WPV 1 or cVDPV 2 is unpredictable; vigilance is being sustained.

- Containment failure: Wild and vaccine viruses may be in stored faecal specimens in some institutions, in spite

of containment activities conducted by ICMR/Department of Health Research in the country

- Finally, deliberate introduction by miscreants. India had faced a small outbreak of type-2 polio in UP a few years after the last case was detected in 1999 October. How do we know it was introduced? The virus strain was one that India has not had in nature. Called MEF-1 Old Middle East Forces virus of 1950s – now confined to labs alone. No Indian lab was found to have that strain. And where did we find it in addition to children? In OPV. Obviously added between company despatch and end-use.

So we will have to continue with IPV for a fairly long time, post-eradication

How are the polio resources, capacities and experiences that support overall ongoing immunization being transitioned towards other public health priorities in India?

In the parlance of polio eradicators, this is called ‘legacy’. Since India chose to entrust polio eradication to a newly established agency called NPSP (National Polio Surveillance Project), polio eradication has not impacted UIP very much. Since India chose exclusive use of OPV, we had to go by repeated pulse immunization, instead of routine immunization. Therefore, a simple transition is not possible. Measles elimination and rubella control activities have started, but the responsibility rests on UIP, but not NPSP. Since GoI took polio eradication as a one-time, one-disease job, transitioning for other public health priorities is not in the design. What India needs is a public health infrastructure that can take on such priorities – if we had one, NPSP would have been redundant. Since we do not have one, NPSP cannot be expanded to all diseases. Thus the main lesson we have learned is India will get what she wants. If India wants typhoid, cholera, leptospirosis, dysenteries, TB (yes, TB for the control of which there is not even a national policy), malaria, etc. controlled, GoI should listen to experts demanding the creation of a public health infrastructure.

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