Research Article

Lessons from vaccine-related poliovirus in Israel, UK and USA

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Detecting genetic variants of Sabin vaccine virus type 2 in sewage in Israel, London and New York in 2022, is disturbing information. Wild poliovirus type 2 was eradicated in 1999. Sabin virus type 2 was discontinued globally in 2016. Yet, type 2 vaccine virus variants are still circulating in many low income countries from where they were imported into these new locations, showing that the immunisation tactics of polio eradication programme was flawed. Outbreaks of polio caused by type 2 vaccine virus variants occurred in 35 countries during 2018 to 2021, paralysing 2296 children. Immunisation tactics must be corrected urgently.

The tactics was designed assuming that the route of wild virus transmission was faecal-oral, for which the orally fed Sabin vaccine was promoted in low income countries, despite its low efficacy and safety. Vaccine variant viruses mimic wild-virus behaviour of contagiousness and neurovirulence. The sustained circulation of imported viruses in London and New York cannot be via faecal-oral route, but via respiratory route. There is no evidence supporting faecal-oral transmission in low income countries; all evidences support respiratory route.

Exclusive use of Sabin vaccine has resulted in the conundrum of persistence of type 2 vaccine-derived virus, delayed eradication of wild virus type 3 (13 years after type 2) and failure to eradicate type 1 even now. Salk inactivated poliovirus vaccine (IPV) is completely safe and exquisitely efficacious to prevent polio. Both UK and USA give only IPV during the last two decades. There is no polio case in London and only one in New York in an individual who had refused vaccination. The world should be weaned off the live vaccine under cover of immunity induced by IPV.

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Introduction

The Global Polio Eradication Initiative (GPEI) announced on 29 July 2022, the recent detection of type 2 poliovirus genetically related to Sabin type 2, in sewage in Jerusalem, London and New York.[1] One unimmunised person in New York developed polio paralysis in July. In New York State, at first Rockland County and New York city were affected, later Orange County and in August Sullivan County also.[2]

Wild poliovirus (WPV) type 2 was eradicated in 1999.[3] Sabin virus 2 is no longer in use anywhere, since April 2016, after the global switch from trivalent oral poliovaccine (tOPV) to bivalent OPV (bOPV) containing only types 1 and 3.[4] Against this background, importations of variants of Sabin-2 virus in 2022, attest to flawed immunisation tactics of GPEI.

The silver lining is that 'circulating vaccine-derived poliovirus' (cVDPV) type 2 in low income countries, from where it was imported, has received global attention. We hope that course-correction will be demanded of GPEI by global opinion leaders and funders of the eradication efforts, without delay.

Genetic variants of Sabin 2 virus

Poliovirus genome is single-stranded positive sense RNA, highly prone to mutations. After many centuries of human adaptation, wild poliovirus (WPV) types 1, 2 and 3 have relatively stable genes for structural proteins. WPVs are highly contagious and neurovirulent, the two properties Albert Sabin managed to attenuate through repeatedly selecting and propagating variants with reduced virulence in monkeys.[5]

Thus OPV contains 'wild-virus-derived polioviruses'. Sabin's original attenuated strains (Sabin original, SO) and WPVs are at polar ends of genetic variation within the same species and antigenic type. During every cycle of multiplication, either in cell culture or human intestines, SO virus mutates in the direction of the parental WPV genotype. Neurovirulence is regained after very few mutations. OPV is manufactured using SO passaged twice (SO+2) or thrice (SO+3) as seed virus, and next harvest as final product. As a result, the presence of mutated neurovirulent virus particles in very small amounts in every dose of OPV, is inevitable.[6][7]

Currently the entire VP-1 region of poliovirus genome of all field isolates is amplified and compared with that of the virus in OPV, designated 'Sabin virus', to distinguish variants drifted further from it. Genetic drift up to 0.5% for type 2 and up to 0.9% for types 1 and 3 are the criteria to classify as 'Sabin-like' (SL).[8] The virus in Israel was SL.[1] Genetic drift of 0.6% and more for type 2 and 1% or more for types 1 or 3 denotes that they are 'vaccine-derived polioviruses' (VDPVs) that have regained neurovirulence and contagiousness. When epidemiological evidence shows community circulation of a VDPV, it is designated cVDPV, which is nearly fully de-attenuated, and wild-like. About 1% drift denotes approximately one year of community circulation – as if a 'molecular clock' exists. In Egypt, Sabin-2 virus with genetic drift circulated from 1983 till 1993, causing polio, until stopped with tOPV campaigns – the drift from Sabin-2 was about 10% in ten years, validating the molecular clock concept.[9] The genetic distance from SO to WPV is >15%.[10]

The shorter drift distance of type 2 indicates it to be less attenuated than Sabin 1 and 3 viruses as far as transmission efficiency is concerned. Sabin-2 regains transmission efficiency fast if let loose among susceptible children. For Sabin-1 and 3, it takes longer; they regain neurovirulence early, but often without transmission efficiency. Globally cVDPV1 and cVDPV-3 emergence has been few and far between.

Every dose of tOPV contains very small amounts of neurovirulent mutants. They cause 'vaccine-associated paralytic polio' (VAPP), apparently proportional to their numbers, hence very infrequently. Among the three antigenic types, 3 is the commonest cause of VAPP -- it is the least attenuated for neurovirulence. Thus, the two 'attenuation genetics'—transmission efficiency and neurovirulence -- are dichotomous and regained independently at different frequencies. If one neurovirulent mutant gains first entry into the body, VAPP may follow, its probability determined by the 'case-to-infection' ratio of the virus. As the reverted variants are only about 0.0001% in the vaccine, the risk of VAPP is lower than WPV's by a factor of 1000 to 10,000.

Eradication tactics vis-a-vis genetic variants of Sabin 2 virus

These data had warned polio experts that Sabin-2 had to be very carefully managed as it could emerge as VDPV and cVDPV, if allowed to spread where and when population immunity is not high. High population immunity is the safety wall to block their emergence and spread. Original time frame for eradication was 1988 to 1999 when population immunity against type 2 was induced by both WPV-2

and tOPV.[11] Coverage level of tOPV peaked in 1999, resulting in eradication of WPV-2 in October 1999.[3]

From vaccinology viewpoint, that was the best time, indeed the only safe time, to withdraw Sabin-2, because of the wall of highest achievable population immunity ever. Such a moment was once in history, never to happen again. Sadly, knowledge, courage or wisdom did not prevail; tOPV was continued, as business as usual, with the consequences we are concerned with today.

There was another simpler reason why Sabin-2 had to be withdrawn. When a vaccine (like tOPV), with rare serious adverse reaction (namely VAPP) is used, benefit-risk balance had to be assessed. When WPV-2 was widely prevalent, benefit of Sabin-2 was greater than its risk of VAPP. As WPV-2 was eradicated, the balance reversed: risk remained while benefit disappeared. Continuing Sabin-2 beyond its need, ignoring the negative benefit-risk balance, was against common sense. That knowledge and common sense were absent is incredible.

Iatrogenic polio vis-a-vis polio eradication

Polio caused by Sabin virus (VAPP) or its variants, is iatrogenic. WHO had issued clear warning and guidance regarding VAPP in 1980s.[12][13] Countries were asked to monitor VAPP and modify vaccination policy (such as choice between tOPV and IPV), according to what frequency of VAPP was acceptable.[12][13] GPEI did not follow WHO guideline: VAPP was not monitored, creating the impression of its absence.

Eradication is precision public health -- zero polio and zero poliovirus transmission. The end point was now obfuscated by sweeping VAPP under the carpet. Had it been monitored, Sabin-2 VAPP would have alerted countries of its risk without benefit. Not monitoring VAPP was another flaw in eradication intervention tactics.

Should GPEI have used OPV in the twenty-first century at all, as eradication target was 2000? Continued occurrence of WPV polio was failure-- passive error. Causing iatrogenic polio was due to error of commission. When a country (eg India) or a WHO Region (eg. South East Asia) or a continent (eg Africa) is declared as polio-free, most people accept it to be true.

Rationale and consequences of withdrawal of Sabin-2 in 2016

To withdraw type 2 vaccine virus from tOPV was necessary. GPEI waited 16 years to collect 'evidence' of polio due to Sabin-2 variants to get convinced of the need. Was evidence necessary?

The probability of emergence of cVDPV lineages was high due to gaps in type 2 immunity in children born since 1999. It was imperative that a wall of high population immunity be created before Sabin- 2 withdrawal. Already many lineages of cVDPV were in circulation and all of them had to be interrupted. The 'Mogilev experiment' (described below) had given us sufficient warning about the silent persistence of Sabin-2 unless precaution was robust.

Those who do not learn from history tend to repeat the mistakes of history. In 2016 polio was under eradication mode in a globalised world. There was only one sure way to build a wall of population immunity robust enough to interrupt all existing lineages and to pre-empt the emergence of any new lineages. It was to use both IPV and tOPV strategically. IPV had to be in 3 doses through EPI. Since six-antigen (hexavalent) vaccine including whole-cell pertussis and IPV was available, there was no need for additional injections of IPV. It had to be supplemented by multiple campaigns of tOPV. After measuring and ensuring very high population immunity, Sabin-2 could be withdrawn, country by country. These were formidable tasks, but without them Sabin-2 withdrawal in 2016 was too risky.

GPEI was caught in the horns of a dilemma; cVDPV cases were too many but proper preparations were labour-intensive. GPEI took a gamble -- with one dose of IPV plus tOPV campaigns. Population immunity was not monitored. Sabin-2 was withdrawn from all countries irrespective of population immunity levels.

When fresh cVDPV-2 lineages became visible after a lag time of one year, we knew that cutting corners was most unwise. Even when new lineages emerged in multiple locations, 3 doses of IPV were not introduced. No child anywhere has developed polio after taking 3 doses. Preventing polio in individual children and interruption of cVDPV-2 transmission were both important, but GPEI neglected the former and tried its best to achieve the latter, so far in vain.

Was documenting cVDPV as evidence necessary before withdrawing Sabin-2? In public health, foresight to pre-empt problems is standard. For the uninitiated, evidence was needed. Evidence-based approach is fine for healthcare, not public health, as illustrated by the present, globalising, conundrum of cVDPV-2. Wise public health leaders should have protected people from such 'evidence' that are truly tragic events for the paralysed children.

Polio due to type 2 VDPV in low income countries

cVDPV is currently endemically prevalent in many countries. In the last four years (2018-2021) outbreaks of cVDPV-2 polio were recorded in 35 countries -- 25 in Africa and 10 in Eurasia – polio cases totalling 2296.[14]

In Democratic Republic of Congo cases occurred every year; in Niger, Nigeria, Somalia and Pakistan during three years; Afghanistan during 2020 and 2021. There were more cVDPV2 polio cases (513) in Afghanistan and Pakistan than natural polio (354). When polio cases occurred due to importation of cVDPV-2 into Iran, Malaysia, Tajikistan, Ukraine and Yemen, during these four years, there was hardly any discourse about it in International media.

Families of children with cVDPV polio would not have realised that the tragedy was due to human error, not by Nature's vagaries. No compensation was offered in spite of the root cause of human error. During these four years, cVDPV-1 polio cases were 90 in 8 countries and cVDPV-3 polio cases 7 in one country.[14]

History of polio due to Sabin-2 variants goes back five decades

"Those who cannot remember the past are condemned to repeat it", said George Santayana. There was ample information in the twentieth century about the problem of Sabin-2 virus mutating and becoming contagious and neurovirulent, if allowed to circulate. If GPEI leaders knew history, in all probability they would have avoided the risk of cVDPV-2 replacing the eradicated WPV-2. None of the successive GPEI leaders was experienced in polio epidemiology in low income countries, or well versed with vaccinology of IPV and OPV. "Superficial knowledge is potentially more dangerous than ignorance. It gives a false sense of security encouraging an ignorant man to persevere in his efforts that can result in huge damage."[15] What damage, in polio eradication, can be greater than causing life-long paralysis of 2296 children?

OPV was introduced in USA, in 1961-62, without assessing safety by clinical trial. Within one year, polio within one incubation period, was noticed in several vaccine recipients – and confirmed as VAPP.[16] VAPP was re-confirmed by WHO in European countries during 1970s and 1980s;[12] [13] Surprisingly some unvaccinated children also had polio due to Sabin-2 virus following horizontal transmission from vaccinated children. If there was direct contact with recently vaccinated child, it was 'contact VAPP.' If no such contact was present, it was 'community-acquired VAPP.' This sinister

potential of community spread of Sabin-2 variants was known since 1964. The episode of Sabin-2 variants causing polio during ten consecutive years in Egypt was another reminder of the sinister potential.

Mogilev experiment

USSR had been using Sabin tOPV since 1959 in nation-wide campaigns, followed by age-based routine immunisation. With abundant forethought, they planned the experiment in Mogilev District in Byelorussia. After building up high population immunity through two nation-wide OPV campaigns (covering 2 months to 10 years once and 7 years next), tOPV was not given in the entire district from March 1963 till March 1966.[17]

The objective was to monitor the duration of immunity and duration of virus circulation in the absence of continued vaccination. Midway, in March 1965, 40 children in six 'nurseries' were given one dose of tOPV. During May to October 1965, poliovirus type 2 was detected in 9 of 392 randomly selected children below 3 years -- not from the six nursery cohort, but from others. One of them had facial palsy, which is a well-known form of polio.[18]

No type 1 or 2 virus was detected. Antibody studies showed wider prevalence of type 2 and limited prevalence of types 1 and 3 during the lull period. Vaccination with tOPV resumed in April 1966.

This story was reviewed and data and viruses re-analysed in 2003.[19] Having undertaken the world's largest and most expensive public health programme of polio eradication in 1988, no international consultation was conducted to learn from old hands and from those with different viewpoints.

Sabin-1 or Sabin-3 vaccine could be withdrawn without (or with very little) risk of variants surviving in the community – but Sabin-2 could not be withdrawn at will, as it or its variants may already be in transmission silently and may 'blow up on our faces' as emerging VDPV and cVDPV. That is exactly what happened to the under-prepared GPEI. We already said that it should have been withdrawn immediately after WPV-2 eradication. A wiser course was to begin planning for it in 1993 when the Egypt experience was fresh in memory. That was the ideal time to introduce IPV into EPI, with a view to wean the world off OPV by 1999.[20] Since that was not done, the next best time was in 2002, three years after the very last case of WPV-2 polio was documented.[11] The next signal was in 2006 when cVDPV-2 polio caused an outbreak in Nigeria.[21]

Route of infection VDPV-2 in London and New York

One important lesson from the importations of VDPV-2 into London and New York, and its sustained spread locally over several weeks, is about the route of transmission. London and New York have high standards of sanitation and hygiene and contagious transmission is most unlikely to be faecal-oral but most likely to be via the respiratory route. The GPEI tactics was built on the assumption of faecal-oral transmission, against which intestinal immunity was considered essential, for which OPV was the vaccine of choice.

OPV is given by mouth, but the resultant intestinal infection is not contagious despite viral shedding in stools for several weeks. Only rarely do vaccinated children infect their contacts. Had secondary infection been more frequent, partial coverage of children with OPV should have sufficed for achieving high population immunity. On the contrary children had to be reached again and again and given OPV repeatedly, many times, for building up population immunity. On the other hand, WPV and cVDPV are contagious. Polio is a disease of infants and pre-school children with median age below 15 months, typical of respiratory transmitted infectious diseases like measles.

This stark contrast is explained as: OPV is adapted to intestinal infection, while WPV is adapted to nasopharyngeal infection as well as intestinal infection. It is during the period of nasopharyngeal virus shedding that WPV is transmitted to others. We are not aware of any research by GPEI to explore if cVDPV-2 is pharyngeal adapted. There is no evidence for faecal-oral transmission of WPVs.[22][23]

The difference between the transmission efficiencies of OPV and cVDPV can be explained by the acquisition of transmissibility by respiratory route, by de-attenuation. Before Sabin promoted OPV, the general teaching was respiratory transmission, for which there is much epidemiological evidence. [23][24] Historically OPV and the notion of mouth as the natural portal of entry of poliovirus were promoted as a package by Sabin.[22] Polio was prevalent in all countries irrespective of standards of sanitation and hygiene. Sabin discovered that poliovirus infection occurred in the intestines, resulting in virus shedding in stools. He did not pursue the phenomena of pharyngeal infection, early upper respiratory symptoms of infected children, shedding via droplets/aerosol, and the consequent contagiousness. The main argument Sabin put forth was the absence of WPV in the olfactory bulbs of children dying of severe polio to discredit the respiratory route of transmission.[25]

In communities highly endemic for WPVs, Sabin OPV is not highly infectious – had it been otherwise, population immunity would have been near-100 per cent by the time tOPV coverage was more than

50%. Infected children shed virus in stools for 4-6 weeks, but despite that vaccine viruses are not contagious. When one million infectious type 1 viruses are fed in tOPV, only 10% of infants in Northern India became infected.[26] In spite of such observations in many low income countries in the tropical belt of Africa and Asia, clearly negating the belief of faecal-oral transmission, GPEI seems to have considered the assumption to be "dogma" that had to be simply believed without argument.

The epidemiology of polio in the pre-vaccine era was typical of respiratory-transmitted diseases. All 'exclusively vaccine-preventable diseases' like polio, measles, rubella, influenza etc are respiratory-transmitted – sanitation and hygiene did not stop or reduce their transmission. WPVs had circulated ubiquitously in all high income and low income countries, prior to the introduction of IPV and OPV. Even countries known for very high standards of sanitation and hygiene had outbreaks of polio, prevented, controlled or eliminated by vaccination. Thus there was ample evidence for respiratory transmission but none for faecal-oral transmission.

The importation of wild virus from Pakistan to Malawi and Mozambique in 2021 and the importation of VDPV-2 into London and New York and its sustained transmission are reminders that the assumption of faecal-oral route is without any evidence. In both cases, it was probably adults who carried the virus to new territories; if so, re-infected adults were the likely transmission vectors. This will explain the paradoxical decline of WPV polio in Afghanistan and Pakistan in 2021 when all immunisations declined. In 2020 there were 149 cases but in 2021 only 6. When adults wore face masks against the coronavirus epidemic, WPV transmission declined drastically – this is only speculation.

The role of IPV in polio eradication

Obviously, Sabin OPV cannot be used in the polio eradicated world, but IPV can be. If IPV is included in EPI, OPV can be withdrawn in any country that achieves high coverage – 90% is reasonable as high coverage. The original World Health Assembly resolution had stated: "...eradication efforts should be pursued in ways which strengthen the Expanded Programme on Immunisation..."[27] IPV as hexavalent vaccine is EPI-friendly, whereas OPV by campaigns is not.[20] Every country that graduates to the withdrawal of OPV will be 'polio eliminated'.

When all countries eliminate polio, eradication is complete. The polio eradicated world will be using IPV exclusively.

The first step in course correction of GPEI immunisation tactics is the introduction of IPV, three doses, in all countries that are using OPV. The second step is withdrawal of OPV as stipulated above. Once OPV is removed, no new lineage of VDPV will emerge. As IPV will protect children against polio disease, we can wait for population immunity to interrupt cVDPV transmission. IPV offers better mucosal protection against respiratory transmission than OPV. .

Once OPV is globally withdrawn, any poliovirus, WPV, VDPV or Sabin-like is signal of sub-optimal population immunity that must be reinforced urgently. There will be no further need to classify each virus isolate by molecular analysis, thereby saving on expenditure.

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