Review of: "Polio eradication at the crossroads"

T Jacob John, Dhanya Dharmapalan

Potential competing interests: The author(s) declared that no potential competing interests exist.

Review of "Polio eradication at crossroads"
by Chumakov K, Ehrenfeld E, Agol VI and Wimmer E*

T Jacob John[1], Dhanya Dharmapalan[2]
1. Retired Professor, Clinical Virology
Christian Medical College, Vellore, Tamil Nadu 632004, India.
E mail <tjacobjohn@yahoo.co.in>

2. Consultant in Pediatric Infectious Diseases,
Apollo Hospitals, CBD Belapur, Navi Mumbai- 400614, India.
Email drdhanyaroshan@gmail.com

*Chumakov K, Ehrenfeld E, Agol VI, Wimmer E. Polio eradication at the crossroads. Lancet Global Health. 2021;9(8):e1172-e1175. doi: 10.1016/S2214-109X(21)00205-9. Epub 2021 Jun 9. PMID: 34118192

Review of Polio Eradication at Crossroads

[All direct quotations from the reviewed paper are presented in italics]

The story so far on Polio Eradication

For reasons unknown, the failing global polio eradication initiative (GPEI) has not got the attention it deserves, from global experts of polio epidemiology, vaccinology and public health ethics, the three disciplines involved.

All high-income countries had eliminated polio, decades ago, the disease and poliovirus infection, wild and vaccine, by the tactical use of polio immunisation. Some had started and continued with Salk inactivated poliovirus vaccine (IPV) never allowing the Sabin oral poliovirus vaccine (OPV); some had eliminated wild polioviruses using OPV and then eliminated vaccine viruses with switch to IPV; some started with a mixed

approach and eventually settled with the exclusive use of IPV. These experiences provided proof of principle that polio can be eliminated also in all low-income countries where GPEI was operating. To analyse and extract the common replicable factors of success in high income countries, scientific evidence in other words, in order to apply it in low income countries, expertise in vaccinology and epidemiology was necessary.

Since 2000,the target year for polio eradication, GPEI has been confronting two problems in low income countries– wild virus polio and iatrogenic vaccine-virus-induced polio. Currently wild virus polio is confined to two countries, but iatrogenic polio is rampant in many countries. How high income countries overcame both problems is key to GPEI's eventual success.

By its flawed immunisation tactics, GPEI created an ethical problem. Outbreaks of iatrogenic polio due to circulating vaccine-derived polioviruses (cVDPVs) are confined in low income countries where GPEI is actively involved. No public health agency has any right to cause polio under the flag of its eradication. That goes against medical ethics. The resultant rich-poor divide with more harm and sub-optimal benefit in countries only because they are poor and without voice in GPEI decisions, is unacceptable in a programme run by a United Nations (UN) agency. That contravenes public health ethics. Public health must ensure fair distribution of not only benefits, but risks also.

GPEI's role and responsibility were essentially in the Regions of Africa, Western Pacific and SE Asia. The problems of GPEI are currently confined to the Regions of Africa and Eastern Mediterranean. In Americas, Western Pacific and European Regions, the Regional Offices and member nations had greater autonomy for eradication as they had made, well ahead of 1988, Regional goals for eradication by 2000. GPEI was assigned the role to eradicate in the remaining three Regions by the World Health Assembly (WHA), in 1988, but could not succeed even by 2021.

GPEI's four partner agencies work under its lead agency -- World Health Organisation (WHO). Partner agencies have expertise in science, ethics and programme implementation. When a strategy fails beyond a reasonable grace period after the target year, should not its science basis be reviewed and corrected? When ethics is violated, should not a red flag be raised? Every few years, GPEI comes up with versions of modified 'strategy plan for polio eradication's endgame,' as if eradication was within reach. The first was in 2000, when GPEI had missed eradication goal by a wide margin [1]. The latest of the series was in 2019, operational until 2023[2]. Every endgame document exuded confidence of success, projecting it as within reach, but every time it was only mirage.

A common strain in all endgame documents is blaming the countries with either problem, for faulty implementation of GPEI's strategy. GPEI says the root cause of emergence of cVDPVs is low OPV

coverage[2]. The true root cause is the continued use of OPV – with its three flaws: low immunogenicity where high immunogenicity is essential; genetically unstable vaccine viruses that cause vaccine-related polio – sporadic and outbreaks; and ideological unacceptability to some, who have no objection to IPV used in rich countries[3].

GPEI's plans of immunisation with OPV in unreasonably large numbers of doses are not implementable in many poor countries, as it has learned the hard way. Even where they are implemented well vaccine-induced polio continues sporadically and/or in outbreaks. These lessons stood out in the year 2000 as the time-target was missed, and in every passing year since then, but have not been explored seriously, for which, willingness for *metanoia* was needed –to review concepts and beliefs about the end-point, and means of achieving it, to introspect for lurking biases, to have humility to accept errors, to match science and ethics with interventions, and courage of conviction to re-design tactics to eradicate polio.

This global public health project of gargantuan magnitude, costing about a billion US dollars annually, having missed the time target 21 years ago, and continuing to collect and spend about a billion dollars annually, must be audited for efficiency. Efficiency is the ratio of output to inputs. If internal auditing is not forthcoming, external auditing must be prescribed. Another critical question: does not iatrogenic polio violate human rights? Should not the victims be compensated by the perpetrator? All these deserve urgent appraisal. But who has authority to scrutinise a UN agency's performance?

The paper under review and its importance

The paper under review is 'polio eradication at the crossroads 'by Chumakov K, Ehrenfeld E, Agol VI and Wimmer E, published in Lancet Global Health[4].The journal has high visibility, globally. The authors are renowned molecular virologists, with notable achievements to their credit. Chumakov had shown that every dose of Sabin trivalent oral polio vaccine (tOPV) contains tiny amounts of back-mutated neurovirulent viruses[5]. Wimmer had synthesised replication-competent poliovirus in the laboratory[6]. Ehrenfeld and Agol are renowned for their discoveries in poliovirus-host cell interactions [7][8]. What they write gets global attention. Let us hope that their critique of GPEI's goal, objectives, strategy and tactics will be an eye-opener for many, including GPEI partner agencies themselves.

There is a caveat though, that they are not experts of polio epidemiology, vaccinology or public health ethics. Nonetheless, in a near-vacuum of compassionate, unbiased, third party evaluation of the failing polio eradication saga, this paper is a breeze of fresh air. We as reviewers, and the experts of GPEI, may disagree on specifics, with different reasoning -- but the message that the eradication programme has been stuck at crossroads for 21 years is loud and clear.

The proposals and some of the recommendations for a way forward are in fact a re-hash of the original 1988 WHA resolution for global polio eradication that launched the GPEI. We wish that some high-profile

organisation will be inspired to take the agenda forward and create an occasion for a thorough review and GPEI's course correction. The very definition of eradication, or its end-point, the destination of the pilgrimage, deserves scrutiny for clarity, even for validity[3].

Does not the Lancet Global Health that published the paper in the first place, have a moral obligation to further help resolve this imbroglio? We hope the editors will take note and lead a discussion, if not a debate. An audit by the journal is feasible, as it will be voluntary and disinterested, can be well-meaning and thorough. The need is great and urgent, as cVDPVs are infecting literally millions of children in Africa, thousands of them have been paralysed, but the perpetrators are not paying compensation to their victims [3].

The paper under review deals extensively with the obstacles encountered by the GPEI before spelling out a revised goal and strategy. Only the original WHA resolution of 1988 resolution is binding on all UN member nations. If any recommendation deviates from it, amended resolution has to be presented to the WHA and passed. Ordinarily, WHO drafts and presents resolutions to WHA. The wishes of others, however lofty, are not horses on which to ride on to *Eldorado*.

The gist of the paper reviewed:

The essence of the paper is given in its abstract and we quote: *"We propose that the sustainable protection of the world population against paralytic polio cannot be achieved simply by stopping the circulation of poliovirus but must also include maintaining high rates of population immunity indefinitely, which can be created and maintained by implementing global immunisation programmes with improved poliovirus vaccines that create comprehensive immunity without spawning new virulent viruses. The proposed new strategic goal of eradicating the disease rather than the virus would lead to a sustainable eradication of poliomyelitis, while simultaneously promoting immunisation against other vaccine-preventable diseases "*[4].

The proposal flaunts eradicating the disease polio as a new strategic goal and desires (i) stopping circulation of polioviruses; (ii) high rates of population immunity maintained indefinitely; (iii) using improved poliovirus vaccines without the undesirable properties of Sabin OPV – low immunogenicity and genetic instability; and (iv) synergy with immunisation against other vaccine-preventable diseases.

We present our review as well as critical analysis of each section of the manuscript as presented below.

On the Section: Introduction

The opening statement of the introduction that polio eradication's launch in 1988 was inspired by smallpox eradication [completed in 1977] is not historically accurate. Smallpox eradication's rapid progress was the

inspiration to establish the Expanded Programme on Immunisation (EPI), launched in 1974, as the power of vaccines in public health – not merely for individual protection – was made obvious by smallpox eradication as it was nearing success (reviewed in [3]). With fourteen years of experience with EPI that was adopted by every country that did not have universal healthcare or organised public health, now with access to Sabin trivalent oral polio vaccine (tOPV), polio eradication was in the line of EPI's natural progression.

But what inspired the plunge were two events: the Rotary International's 'PolioPlus' programme launched in 1985 to immunise all the world's children against polio in 20 years, and Pan American Health Organisation's (PAHO) 1986 resolution to eliminate polio from the Americas by 1990, assured of funds from Rotary [3]. PAHO is the Regional Office of the WHO, Geneva. The next year, 1991, WHO Regional Offices of Europe and Western Pacific resolved to eliminate polio in their territories by the year 2000 [3]. With three Regional Offices moving forwards for polio elimination, three others were left behind – South East (SE) Asia, Eastern Mediterranean and Africa. With these events mobilising momentum, the WHO drafted a resolution and got it unanimously passed in the WHA in 1988, for global polio eradication by 2000. These details are relevant to point out some misreading of the eradication goal and its strategy, by the authors of the paper under review.

The GPEI erred in defining polio eradication as the global elimination of only polio due to wild polioviruses (WPV), but tolerating OPV-caused polio as only adverse reaction to vaccine. The same error is apparently repeated by the authors when they propose universal vaccination with Sabin tOPV, stating:*"If and when new vaccines inducing comprehensive immunity without causing VAPP and cVDPVs become available, conventional OPV must be phased out. However, until the new vaccines are available, conventional OPV must continue to be used. The objective of our efforts should be to eliminate the disease, not the virus"*[4]. 'The disease' is polio due to WPVs, and VAPP and cVDPVs are not to be under the eradication radar until the new vaccines become available. We disagree -- VAPP and cVDPV polio are not to be allowed if we take medical ethics seriously, as we will discuss below.

The paper recognises the problem of cVDPVs with *"pathogenicity and transmissibility indistinguishable from those of wild polioviruses"*. To quote: "*The inevitable emergence of cVDPVs means that polio eradication must also include elimination of OPV itself, at least in its present form, which substantially complicates the original task"*. Having recognised the "*global resurgence of cVDPV2 that started in 2016"*, caused by the switch from tOPV to bivalent OPV *sans* type 2, the authors *"attempt to make some recommendations that might help to put the eradication programme back on track for sustainable success* [4]*."* Unfortunately, while cVDPV outbreaks are paralysing hundreds of children in several countries, they have no immediate solution for it, but are very diffident in proposing drastic changes to help the eradication programme back on track.

The authors have identified several obstacles to the present efforts of the GPEI[4]. One is the emergence of cVDPVs that are variants with *"pathogenicity and transmissibility indistinguishable from those of wild polioviruses"*. This is the main obstacle from the year 2005. To single out one badly affected country, namely Nigeria – polio caused by type 2 cVDPV (cVDPV2) was first detected in 2005 (3 cases), and it persisted in subsequent years – 2006 (21cases), 2007 (68), 2008 (63) and 2009 (153 cases)[9] . In 2020 cVDPV2 polio outbreaks were documented in 21 countries in Africa, and four countries in Asia[10]. The same year, polio outbreaks of type 1 cVDPV (cVDPV1) occurred in one Asian and two African countries[10].

The risk of emergence of cVDPV was known to epidemiologists even before 2000, with one decade-long event in Egypt [11]. Then a large outbreak of cVDPV1 in the Hispaniola Island in 2000 [12] really and truly warned GPEI that more will occur unless plans were modified. Timely warnings were not heeded[13][14].There is a time for everything; there was a time for prevention of the emergence of cVDPV2. The seed of cVDPV1 (in Hispaniola) and cVDPV2(Egypt and Nigeria) was in tOPV [5]. There was a time to safely discontinue tOPV. A stitch in time saves nine. Since 2017, cVDPVs have exploded into a major obstacle for GPEI [3][4].

The second obstacle is *"extraordinary persistence of wild poliovirus circulation in some geographic regions"*[4].This is true of only two countries today, and with only type 1 wild virus. Other countries with 'extraordinary persistence' included India and Nigeria; they overcame it with extraordinary numbers of doses of OPV per child and of supplementary immunisation (SI) campaigns. Then why does it persist in Pakistan and Afghanistan? There, a section of the population has real misgivings about the safety of OPV and a group with a particular political ideology rejects OPV altogether[3]. They have killed over a hundred OPV givers and even burned down a hospital for offering OPV[3][15].

The third obstacle is *"that in some regions immunogenicity of trivalent OPV was very low, which was caused by a high prevalence of other enteric infections and interference between serotypes of vaccine virus in trivalent OPV: the OPV type 2 (OPV2) component of trivalent OPV reduced immunogenicity of the other two vaccine strains; therefore, each child had to be vaccinated up to 50 times to reach the population immunity threshold required to stop virus circulation"*[4]. This specific problem was well known to polio epidemiologists and vaccinologists and to WHO, from the time of launching the EPI (reviewed in [3]). The cause is neither other enteric infections nor inter-type interference – but that is the common belief among some scientists [3]. If they were true, children would be less vulnerable to natural polioviruses, particularly types 1 and 3 – facts are the opposite: polio was very common and WPV infections by types 1, 2 and 3 saturated children by age 5[3].

To improve efficacy, a dose of tOPV soon after birth was added to the EPI schedule of 3 doses in infancy, in 1985[16]. One more dose in the second year was routine, adding up to five. Then annual two-dose pulsing

to all children below 5 was introduced for polio eradication, adding up to 15[3]. GPEI very well knew of the problem; it is currently an obstacle only in Pakistan and Afghanistan. India got rid of WPV transmission in 2011 (giving up to 50 doses, as the paper under review states), and Nigeria in 2015[17]**.** There is a reason (explained later) for the obsession and obstinacy, persisting with the most inefficient OPV.

The fourth obstruction is related to the first. *"To increase the immunogenicity of the vaccine, monovalent OPV type 1 (OPV1) and OPV type 3 (OPV3), and a bivalent OPV (bOPV) containing only serotypes 1 and 3 were introduced for supplemental immunisation campaigns. The introduction of these new vaccine formulations finally led to the cessation of transmission of wild type 1 poliovirus in India, but the downside was a reduced immunity against serotype 2, which promoted the emergence of type 2 cVDPV (cVDPV2) ….the number of paralytic cases caused by cVDPV2 has been steadily increasing in many countries in Africa and Asia"*[4].. The causal relationship of rolling out mOPVs and bOPV in India and the emergence of cVDPV2 in Africa is tenuous. In Africa cVDPV2 had emerged in Egypt in the 1980s[11] . In Madagscar it was reported in 2001-02[18] . In Nigeria it emerged in2005 while tOPV was still in wide use[19]. In fact, type 2 was removed from routine immunisation (by tOPV to bOPV switch) only in 2016, but outbreaks of cVDPV2 polio had been occurring even before 2005.

Epidemiologists were aware that until about 2000 WPVs had been circulating in most low income countries resulting in very high level of population immunity in all of them. As time went on, with WPVs drastically reduced, with new additions to the population by birth and growth, population immunity would wane, and had to be kept up exclusively by vaccination. Gaps in population immunity were to be anticipated, making it imperative that wild viruses be eradicated fast, and, most importantly, to withdraw corresponding vaccine viruses before the emergence of cVDPVs[13][14]. Given immunity gaps, and vaccine viruses continued beyond the time of need, cVDPVs emerged, thoroughly confounding the eradication programme. In addition to expertise in vaccinology, epidemiology and ethics, wisdom and forethought were also necessary.

All of the above 'obstacles' can be boiled down to two fundamental undesirable properties of the Sabin OPV. First, low immunogenicity in several low income countries of the tropical zone, and consequent persistence of WPVs in such countries in spite of a reasonable number of doses of OPV. Five doses we count as reasonable. Even 15 doses as we described above borders on the reasonable, but fifty doses, we feel as unreasonable. Even so, fifty does were given to achieve the goal of eliminating the transmission of WPV types 1 and 3. The second undesirable property of OPV that spells danger is genetic instability leading to emergence of variants with regained virulence and transmissibility. We raise a logical question, therefore: is not the exclusive, extensive and extended use of OPV for polio eradication as GPEI policy, then, the root cause of the failure of GPEI to reach the eradication goal?

On the Section : Refocus eradication campaign priorities

The authors have elaborated on their proposals and we quote: *"Since its outset, the GPEI strategy focused primarily on stopping virus transmission to prevent paralytic poliomyelitis; the measure of its success was on the basis of the absence of paralytic disease and asymptomatic circulation of live poliovirus. A crucially important aspect of this approach is the destruction or secure containment of all poliovirus stocks. However, we posit that this strategy is unrealistic and undesirable, and should be replaced with emphasis on protecting the global population by continued immunisation with safe and effective vaccines. The rationale is two-fold. First, proving the absence of poliovirus circulation is a daunting task that cannot be verified reliably because of the limitations of existing surveillance tools, which include acute flaccid paralysis surveillance supplemented by environmental surveillance"*[4].

There is a factual error here: the measure of success of interrupting WPV transmission was quite simple: three consecutive years after the last WPV detection through acute flaccid paralysis (AFP) surveillance supplemented with virological surveillance according to GPEI strategy[20][21][22][23]. The rationale is simple: since one case of WPV polio represented about 160 infections by type 1 or about 1000-2000 by types 1 and 2, the consistent absence of polio for 3 years was accepted by all concerned as surrogate for the interruption of transmission[20][21][22][23]. For this, the quality of AFP and virological surveillance were monitored with precise metrics to ensure adequacy of surveillance to mean interruption of transmission. The destruction of, or secure containment of all poliovirus stocks, is simply because the goal of eradication was achieving zero polio and zero transmission of poliovirus and common sense is to destroy or contain stocks. This is not essential to achieve eradication and conclude 'polio-free' status of countries, but for certification, the empowered certification hierarchy of committees will use it as an additional benchmark. So far five WHO Regions, namely, Americas, Western Pacific, European, SE Asia and African -- have been certified free from WPV transmission (reviewed in 3). Only two countries, Pakistan and Afghanistan in just one Region (Eastern Mediterranean) have yet to reach certification criteria. Under this scenario, the criticism is not valid.

Africa remains with an anomaly: with a multi-country epidemic of cVDPV polio, which did not prevent the Certification committees to refrain from certifying polio eradication status. So, the question remains: is vaccine related polio to be eradicated or not? Both the GPEI and the present paper under review are vague on this matter. We declare unequivocally that polio eradication must be defined as zero polio due to wild and vaccine viruses and zero transmission of wild and vaccine viruses [3][14].

We quote another criticism by authors**:** *"Surveillance of acute flaccid paralysis is based on clinical manifestations of poliovirus infection, which worked well in the initial phases of polio eradication. In a fully susceptible population, acute flaccid paralysis surveillance can detect one in 100 to 1000 infections. However, with increasing population immunity, surveillance for clinical signs of poliovirus infection*

becomes much less sensitive, allowing poliovirus to circulate undetected for many years. Combined with the poor implementation of acute flaccid paralysis surveillance in some regions, this occult circulation was the reason for the emergence of the so-called orphan poliovirus lineages that resurfaced after many years of circulating undetected. Although environmental surveillance is believed to be more sensitive than acute flaccid paralysis surveillance, its global implementation is unrealistic because of the enormous cost and the absence of sewage systems in substantial parts of the world where environmental surveillance is needed most. For the current eradication strategy to work, effective surveillance must be done not only as part of a one-time certification process but must be continued into the future. Therefore, ensuring that there is no silent poliovirus circulation is next to impossible"[4].

There is again a misunderstanding of polio epidemiology and also of the purpose of sewage surveillance. In any community, well vaccinated or not, polio due to wild poliovirus (WPV) can occur only in the non-immune children, and the frequency of one in 100 (wild type 1) to 1000 (WPV types 2 and 3) remains unchanged – that is the basic neurovirulence property of the virus. One case of true polio represents 100 to 1000 non-immune children even if all the rest are immune, even with many break-through infections. The absence of even one polio case in the face of quality clinical and virological surveillance is proof for less than 100 (type 1) and less than 1000 (types 2 and 3) infections among non-immune children. If it is maintained over sufficient time, arbitrarily but liberally fixed as 3 years by GPEI, we can be sure that the circulation of WPVs has been interrupted.

Good quality AFP surveillance with virology had been established in all countries over 20 years ago. The need for sewage surveillance is not to detect 'occult' WPV infection at all. The problem of poor sensitivity of clinical and virological surveillance arose when cVDPVs began to emerge. While one in 100-1000 WPV infections resulted in paralytic polio, cVDPV does not cause polio at the same frequency, as its neurovirulence is much lower. The ratio is unknown, but probably one or two orders of magnitude lower; one polio case per 1000 to 2000 cVDPV1 infections and one case per 10,000 to 20,000 cVDPV2 infections. The clinical AFP surveillance will obviously be far less sensitive to detect cVDPV circulation in the community; therefore the need for sewage surveillance to detect its community circulation [3]. If there were no cVDPV cases, there would have been no need for sewage surveillance at all.

The authors recommend a supposedly clear and specific revised goal or GPEI -- instead of eradication. *"At the core of our recommendation is the replacement of the goal to globally eradicate poliovirus with an emphasis on protecting populations from paralytic disease caused by poliovirus. The only sustainable solution to eliminating paralytic poliomyelitis is to indefinitely maintain the highest possible rates of population immunity through quality immunisation programmes* [4]*."*

GPEI is functioning under the WHA resolution to eradicate polio. GPEI has no freedom to alter the goal of

its establishment, namely polio eradication. By proposing 'a sustainable solution for the failing GPEI, the authors seem to make a U turn by recommending the re-introduction of "*conventional OPV*" which can only mean Sabin tOPV. We concluded earlier that the current major problem GPEI faces is multi-nation cVDPV polio outbreaks. They were seeded by the continued use of tOPV far beyond its legitimate usefulness. The paper's arguments are circular and even contradictory.

Maintaining high levels of population immunity indefinitely is not in the purview of an eradication programme which would logically come to an end with eradication certification. EPI will continue and the call of maintaining immunisation belongs to country EPI policy. It is for WHO to clarify its EPI policy – and it is unlikely that EPI would want population immunity against polio dismantled soon after achieving eradication. In other words this proposal is infructuous as far as GPEI is concerned**.**

The new element in their proposals is to develop improved vaccines with high immunogenicity in low income countries and without reversion to virulence, unlike Sabin OPV. The authors, expert molecular virologists, are confident that today's molecular virology is capable of creating such candidate vaccines, and we agree. One novel OPV 2 -- replication-deficient and safe -- has already received 'emergency use approval' from WHO and is in use in Nigeria[24]. Other similar ones are technically possible. What we cannot know yet, are: how epidemiologically effective they will be against the obstacles described above and how they will be accepted everywhere, including in Pakistan and Afghanistan where there is aggressive antipathy to Sabin OPV. Will they accept another non-Sabin oral poliovirus vaccine?

We caution against counting chicken before eggs hatch and against putting all eggs in one basket. Do we have to wait for improved genetically engineered live oral vaccines, an unproven tool, success not guaranteed, while outbreaks of cVDPV polio are raging since 2017? Protecting children from iatrogenic polio is public health emergency; it cannot wait for future possible solutions. Vaccinologists know polio (wild or vaccine virus) can be predictably prevented in every child, using the exquisitely effective and completely safe IPV, as all high income countries have proven decades ago. Why an illogical tactic of one vaccine for rich countries but another for poor countries, like 'large hole for large cat and small hole for kitten,' attributed to the science genius Isaac Newton? We know IPV will protect children under all socio-economic circumstances. Why perpetuate unethical double standard? Why provide a lame alibi for GPEI for not eradicating polio by 2000? The need to prevent polio in children in children in Africa is now, today, not to be postponed.

The authors continue: *"If and when new vaccines inducing comprehensive immunity without causing VAPP and cVDPVs become available, conventional OPV must be phased out. However, until the new vaccines are available, conventional OPV must continue to be used. The objective of our efforts should be to eliminate the disease, not the virus. A limited transmission of poliovirus might still occur and should not be*

considered a failure of the campaign. Importantly, the proposed strategy does not abandon the goal of eradication because after sustainable vaccination programmes are in place worldwide, strong population immunity will ensure that the virus will no longer be able to transmit and will gradually disappear"[4].

After stating clearly: "*replacement of the goal to globally eradicate poliovirus with an emphasis on protecting populations from paralytic disease caused by poliovirus"* another U turn? Now the end result is accepted as: eradication of polio disease and poliovirus infection.

Suppose it takes five years to come up with new vaccines with the desired properties, then do they argue for GPEI to re-introduce conventional (read Sabin trivalent) OPV now and use it until then? They and we had concluded earlier that the current most important problem GPEI faces is multi-nation cVDPV polio outbreaks[3][4]. They were seeded by the continued use of conventional OPV. If GPEI back-tracks to the status in 2016, pre-tOPV-bOPV switch vaccination tactics, then all the proposals for refining the goal of eradication and wanting to "eradicate polio disease" come to naught.

"A new emphasis on vaccination programmes, as opposed to virus circulation, and the return of trivalent OPV in combination with inactivated poliovirus vaccine (IPV) or a new genetically stable version of the vaccine that is crucial to stopping the current surge of cVDPV2 will make draconian containment measures unnecessary, thus eliminating an undue burden on the pharmaceutical industry and enabling badly needed research and development to expand the availability of critically needed polio vaccines and antivirals."[4].

In their mind-set of wanting to come to an early conclusion of the global polio eradication, confused or confusing recommendations have emerged that will only prolong the agony. Emphasis on vaccination programme, namely EPI was the starting point of the WHA Resolution for polio eradication in 1988 (reviewed in[3]). For several years eradication efforts were nested within EPI and led by senior EPI officers of WHO. When that approach was not getting anywhere near achieving high enough immunisation coverage, did the tactics get changed and the eradication efforts brought under the 'vertical' programme of GPEI working parallel to EPI. EPI target diseases did not come under effective surveillance in most low income countries. If polio eradication efforts are back in the EPI platform, there is no hope of early success.

On the Section : Do not stop immunisation, improve its quality

The authors state:*"Although the original scenario of abandoning all polio immunisations was gradually replaced with a plan to switch from OPV to IPV after detectable circulation of poliovirus is stopped, the 2019 WHO recommendation specifies that this switch is only an interim policy and that, at some point, IPV might become unnecessary"*[4].

According the 2019-2023 endgame strategy, both current lineages of cVDPVs and the risks of further VDPV emergence will persist as long as OPV use continues, and OPV use cannot be stopped globally until after WPV eradication (2). Full OPV withdrawal will take place approximately one year after WPV eradication is certified according to this latest endgame strategy [2]. OPV cessation is critical, according to the endgame strategy, to stop the occurrence of VAPP and to remove the primary risk of emergence of all types of VDPVs. Planning for OPV withdrawal will start two years in advance of expected WPV eradication, 'building on the lessons learned from the switch from tOPV to bOPV'[2]. Pre-cessation SIAs may also be considered for high risk areas in the year prior to withdrawal[2]. Clearly GPEI expresses no hurry to complete and conclude polio eradication[2]. Sadly, the authors of the paper under review also do not propose interventions that were overdue for decades in order to protect children from polio disease as soon as possible[4].

On the Section : Continue poliovirus research and prepare to sustain immunisation

Now the trump is exposed: the authors want research to develop oral vaccine that is highly immunogenic and will not "*spawn virulent variants*". They are not apparently aware of the ethical dilemma of creating polio under the flag of its eradication and the urgency for the need to put a stop to it. Even the enumerated major obstacles are not counted as problems demanding immediate solutions. The first obstacle was: emergence of virus variants called cVDPVs with *"pathogenicity and transmissibility indistinguishable from those of wild polioviruses"*. As we showed earlier, cVDPVs began emerging even before the year 2000, due to the use of tOPV. If very high coverage can be achieved, the emergence of cVDPVs may be infrequent, but not zero as we have seen repeatedly in Nigeria while tOPV was in use until mid-2016. There, tOPV coverage was very high, high enough to stop WPV types 1 and 3[3]. The capacity to achieve such coverage is not in the hands of GPEI but under the purview of EPI, both WHO EPI and country EPI. Any slip up in OPV coverage will lead to emergence of new VDPV lineages. If on the other hand only IPV is in use and no OPV, then vaccinated children will be protected from polio, and they will not contribute to VDPV emergence.

The second obstacle was extraordinary persistence of WPV, currently in Pakistan and Afghanistan. Conventional OPV is not the solution as it is the problem. On the other hand if IPV is given, it is very likely that animosity against it will not develop, especially if IPV is in combination with highly valued EPI vaccines[3]. The reduction of polio incidence will be at a minimum proportional to coverage, and not erratic as under OPV coverage, but more likely far higher[3]. In 2020 there were 84 cases of WPV1 polio and 135 cases of cVDPV2 polio in Pakistan, and 56 cases of WPV1 polio and 308 cases of cVDPV2 polio in Afghanistan[10]. IPV is key to protecting children simultaneously against both WPV1 and cVDPV2 polio in both countries.

Except OPV and Rotavirus vaccine, all other vaccines in EPI are injected. Already many of them are given

as combination products. IPV is used in rich countries as a part of four (quadrivalent), five (pentavalent) or six (hexavalent) vaccines. If IPV is given in EPI schedule, instead of OPV, three problems will immediately be solved: no more polio as a result of low efficacy of vaccine; no more spawning of virulent variants; no more antipathy to OPV. Thus all problems confronting GPEI can be solved in one stroke – a shift in vaccine policy to full schedule IPV in EPI, namely 3 doses. It is the obvious that we tend to miss; it is the simple we tend to undervalue thinking we need complex remedies.

And what stands against IPV? We quote: *"IPV does not induce strong intestinal immunity sufficient to block virus transmission. Despite these shortcomings, if both vaccines were used together, their best properties would be combined to safely create a comprehensive immunity. Immunisation with IPV was shown to prevent VAPP, whereas subsequent doses of OPV boost the formation of mucosal immunity and prevent the emergence and spread of cVDPV"*[4].

If we pinpoint one fundamental reason why the eradication programme has stalled beyond 2000, with WPV1 still persistent in Pakistan and Afghanistan and with uncontrollable polio outbreaks due to cVDPV2, and occasional outbreaks due to cVDPV1, it is the belief that intestinal mucosal immunity is essential to *"block virus transmission."*It is only a belief, without any scientific evidence that it is essential for interrupting poliovirus transmission – and that belief is common both to GPEI and the authors of the paper under review. Lack of scientific evidence in this regard had been extensively reviewed by us earlier[3].

Belief can be a very strong motivating factor, as it often breeds dogma[3]. GPEI, believing that 'strong intestinal immunity' was essential for polio eradication as dogma, shifted the goal, in the mind, ever so subtly, to create 'strong intestinal immunity' as a necessary intermediate goal, and had been chasing it from 1988, rather than eradicating polio paralysis. For that GPEI should have started with protecting every vaccinated child from polio, and by expanding polio protection by increasing 3 dose IPV coverage. Instead, GPEI chose to create strong mucosal immunity with OPV as the goal, and as a result, got stuck at the crossroads ever since 2000.

The two goals are not only technically and scientifically different but also contradictory– polio eradication and creating strong mucosal immunity (albeit in the hope it will one day result in WPV eradication). For creating strong mucosal immunity GPEI had to depend on OPV, thereby seeding VDPVs, which had to be then accepted as inevitable. That was (and is) in fact incompatible with polio eradication. On the other hand, protecting every vaccinated child from polio, caused by WPV or vaccine viruses, using IPV as the primary tool, was the right path towards polio eradication without creating polio. Such was the power of believing in the dogma of mucosal immunity as pre-requisite for WPV eradication. .

Monitoring methods for the two goals are also drastically different. If intestinal immunity is the goal, then

interruption of transmission of viruses becomes the endpoint – but only WPV could be interrupted, not cVDPVs. If eradication is the goal, every case of polio is to be prevented, whether caused by wild or vaccine virus. The choice was GPEI's and the priority was given to the former.

Notice that Africa region is certified 'polio-free' (wild virus in small print) because that was the goal, the contribution of establishing intestinal immunity[25]. Sufficient intestinal immunity to interrupt WPV transmission, types 1, 2 and 3,has been achieved using OPV in all low income countries except Pakistan and Afghanistan. GPEI has achieved success by the 'alternate goal' that was set. The cVDPV outbreaks could not be condoned by GPEI because the vaccination tactics chosen was the only reason for emergence of cVDPVs. The tragic consequences of the belief in intestinal immunity as the necessary route for eradication is suffered by hundreds of paralysed children in 21 countries in Africa and in Afghanistan and Pakistan – not by GPEI.

This belief in intestinal immunity as *sine qua non* for polio eradication, is unfortunately very common even among scientists unconnected with GPEI, including the authors of the paper under review. While chasing this unrealistic and unnecessary goal, even polio paralysis created by interventions to chase that mirage, had to be ignored. Otherwise, to suggest that polio disease must be eradicated reads superfluous since eradication pertains to the disease first and pathogen next. It is true that OPV, when it infects the intestines, induces strong mucosal immunity. If infection happens only on the fiftieth feeding, still, intestinal immunity is induced. To infect most children in low income countries, an unreasonable and impractical number of doses had to be scheduled, and had to accept vaccine-virus polio as inevitable, if polio (read WPV polio) must be eradicated. That is where GPEI has reached, and the authors have not spotted the difference between belief and evidence. So they recommend only OPV, and they desire that OPV ought to be both highly immunogenic and completely safe – hence a new generation OPV emerging from research.

What is the experience of countries outside the sphere of influence of GPEI that includes all countries that use IPV exclusively? Without exception, all of them have achieved zero polio disease and zero poliovirus transmission, not only WPV but vaccine viruses also[3]. Let us be very clear: the problem with GPEI is that it has not defined vaccine-induced polio – that includes VAPP and VDPVs – as polio to be eradicated. Once that objective is subsumed under eradication, it will become obvious that exclusive use of IPV in EPI is the solution to both problems – low immunogenicity and vaccine-induced polio. No child anywhere has been reported to develop polio – be it wild virus polio or vaccine virus polio, after taking 3 doses of IPV. The desire to "*eradicate the disease*", to avoid "*spawning new virulent viruses*", and to create a comprehensive immunisation platform covering all vaccine-preventable diseases can predictably be fulfilled by including IPV-containing vaccines in EPI and achieving high coverage[26].

On the reviewed paper's Conclusion

The authors emphasised in their concluding remarks: *"The modified strategy should be a part of the next phase of the polio eradication campaign that should better synergise and be merged with other global immunisation programmes."* There is something disturbingly disappointing here: they predict there has to be a 'next phase' of eradication campaign. But there is nothing new here, since the 1988 WHA Resolution had stated: "that eradication efforts should be pursued in ways which strengthened the development of the Expanded Programme on Immunisation as a whole, fostering its contribution, in turn, to the development of the health infrastructure and of primary health care". The WHA Resolution had cited the "goal endorsed by the 30th WHA Assembly in 1977—the provision of immunisation for all children of the world by 1990". Universal vaccination was the original strategy (reviewed in[3]). The citation the authors used to describe the original strategy was not authentic, but simply a paper by two USA scientists published in 2002, not reflecting the cited matters accurately.

Universal vaccination is easier said than done in many countries in Africa, Eastern Mediterranean and SE Asia, the three Regions which failed to eliminate wild virus polio by 2000-2001. In 2021, WPV1 is still present in two Eastern Mediterranean Region countries and outbreaks of polio due to cVDPVs occur in many African countries and the same two Asian countries and lately in one European Region country. OPV requires unreasonably large number of doses and near-100% coverage to achieve and sustain mucosal immunity, whereas, IPV through EPI need not have such stringent and virtually impossible conditions to prevent and control polio in the community – even to the point of zero polio (reviewed in 3). Wherever OPV is used on a large scale, VAPP is inevitable because every dose of OPV already contains a tiny amount of mutant viruses capable of causing paralysis[4].

As for the magnitude of annual numbers of VAPP in all countries where GPEI is active, neither GPEI nor its Partner Agencies including WHO puts them in the public domain, for the simple excuse that VAPP is not polio, but merely adverse event following immunisation. Surprisingly many polio scientists and donor agencies do not confront the fact that polio, whether caused by WPV or OPV or cVDPV, is the same to the suffering children.

The authors are committing the same error as that the experts of GPEI made: go by belief instead of evidence. They stated in the last paragraph: *"Although the history of the campaign clearly shows that success cannot be guaranteed regardless of how close it appears to be, we believe that this new strategy will lead to a sustained elimination of paralytic poliomyelitis caused by poliovirus*[4]." GPEI experts believed in their strategy without guarantee of success; the authors believe their proposals may succeed if implemented, but again they are not sure, guarantee is not promised.

When man was sent to moon his return was guaranteed. What the world needs is evidence-based strategy

with guarantee of success, achievable only if the success-factors of countries that have achieved success decades ago are applied everywhere. That is the strategy that worked in Finland, Sweden, Iceland and Francophone provinces of Canada in 1962; in France in 1980; in Germany in 1996 and in USA in 2000, New Zealand in 2002, Australia in 2003, the UK in 2004and in some 50 counties in all continents (reviewed in[3]). In Yogyakarta province in Indonesia IPV replaced OPV in 2007 and it has remained without any polio, WPV or vaccine, since (reviewed in [3]). These provide evidence and guarantee.

The authors conclude in the abstract, *"The proposed new strategic goal of eradicating the disease rather than the virus would lead to a sustainable eradication of poliomyelitis while simultaneously promoting immunisation against other vaccine-preventable diseases"*[4].This is a flawed argument. Polioviruses are highly infectious and in all low and middle income countries all polio (disease) was confined in children below 5 years (until recently), thereby confirming all above 5 were near-100% immune. Yet polioviruses survived. Such infectiousness, with basic reproduction number R_0= 44 [1+ life expectancy 65 years/median age of polio 1.5 years] cannot be allowed to survive in any human community lest it should spread and turn the table against us[27]. Higher the R_0 smaller the required pool of susceptible children for virus survival in transmission.

Just as in 2000, as also today, the polio world map can be marked in two colours – countries using IPV exclusively and have no polio caused by any poliovirus, wild or vaccine-lineage, in one colour and in the other colour all countries using Sabin OPV with or without IPV, always at risk of VAPP. It is unethical to allow VAPP to occur when there is a safe alternative in IPV [28][29]

Now, the efficacy of IPV to prevent polio disease is legendary – no child, to our knowledge had developed polio (wild or vaccine virus) after getting just 3 doses of IPV. *"At the core of our recommendation is the replacement of the goal to globally eradicate poliovirus with an emphasis on protecting populations from paralytic disease caused by poliovirus"*[4], so the authors state. Their goal is the complete elimination of polio disease, irrespective of virus survival in the community – for that IPV is obviously the ideal solution, the only solution, not OPV.

All experts, GPEI and independent, must agree on one crucial point: three doses of IPV can and must be made EPI policy and then no child will develop polio if the schedule is completed. If 3-dose IPV becomes EPI policy, then there will not be any need to give Sabin OPV or any new OPV. As the coverage is increased to a level of 'herd immunity' to provide sufficient 'herd effect', eradication is guaranteed[30]. That coverage level is certainly far below 100% -- hence quite achievable[3].

References

1. ^*Fred Brown. (2001). Progress in Polio Eradication: Vaccine Strategies for the End Game. S Karger Ag*

242 pp. (DEVELOPMENTS IN BIOLOGICALS). ISBN 978-3-8055-7285-9

2. [a, b, c, d, e, f]*World Health Organization, Global Polio Eradication Initiative. (2019). Polio endgame strategy 2019-2023: eradication, integration, certification and containment. Geneva: World Health Organization 2019. Available from: https://apps.who.int/iris/handle/10665/329948*
3. [a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z, ^]*TJ John, Dhanya Dharmapalan. (2021). Polio: the eradication imbroglio; the malady and its remedy. 1st ed. Amazon. (Kindle e-book). Available from: https://www.amazon.in/POLIO-ERADICATION-IMBROGLIO-Malady-Remedy-ebook/dp/B08RC59C9X*
4. [a, b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v]*Konstantin Chumakov, Ellie Ehrenfeld, Vadim Agol, Wimmer Eckard. (2021). Polio eradication at the crossroads. The Lancet Global Health. 9(8):E1172–E1175. doi:https://doi.org/10.1016/S2214-109X(21)00205-9*
5. [a, b]*K. M. Chumakov, L. B. Powers, K. E. Noonan, I. B. Roninson, I. S. Levenbook. (1991). Correlation between amount of virus with altered nucleotide sequence and the monkey test for acceptability of oral poliovirus vaccine. Proc Natl Acad Sci U S A. 88(1):199–203. doi:10.1073/pnas.88.1.199PubMed PMID: 1846038; PubMed Central PMCID: PMC50777*
6. [^]*E. Wimmer, A. Nomoto. (1993). Molecular biology and cell-free synthesis of poliovirus. Biologicals. 21(4):349–356. doi:10.1006/biol.1993.1095PubMed PMID: 8024750*
7. [^]*E. Ehrenfeld, B. L. Semler. (1995). Anatomy of the poliovirus internal ribosome entry site. Curr Top Microbiol Immunol. 203:65–83. doi:10.1007/978-3-642-79663-0_3PubMed PMID: 7555091*
8. [^]*Vadim I. Agol, George A. Belov, Kurt Bienz, Denise Egger, Marina S. Kolesnikova, et al. (1998). Two Types of Death of Poliovirus-Infected Cells: Caspase Involvement in the Apoptosis but Not Cytopathic Effect. Virology. 252(2):343–353. doi:10.1006/viro.1998.9438*
9. [^]*Steven Wassilak, Muhammad Ali Pate, Kathleen Wannemuehler, Julie Jenks, Cara Burns, et al. (2011). Outbreak of type 2 vaccine-derived poliovirus in Nigeria: emergence and widespread circulation in an underimmunized population. J Infect Dis. 203(7):898–909. doi:10.1093/infdis/jiq140PubMed PMID: 21402542; PubMed Central PMCID: PMC3068031*
10. [a, b, c]*WHO. (2021 Aug). Global Circulating Vaccine-derived Poliovirus (cVDPV). 2021. p. 1. Available from: https://polioeradication.org/wp-content/uploads/2021/08/weekly-polio-analyses-cVDPV-20210824.pdf*
11. [a, b]*Chen-Fu Yang, Tary Naguib, Su-Ju Yang, Eman Nasr, Jaume Jorba, et al. (2003). Circulation of endemic type 2 vaccine-derived poliovirus in Egypt from 1983 to 1993. J Virol. 77(15):8366–8377. doi:10.1128/jvi.77.15.8366-8377.2003PubMed PMID: 12857906; PubMed Central PMCID: PMC165252*
12. [^]*Kew Olen, Morris-Glasgow Victoria, Landaverde Mauricio, Burns Cara, Shaw Jing, et al. (2002). Outbreak of Poliomyelitis in Hispaniola Associated with Circulating Type 1 Vaccine-Derived Poliovirus. Science. 296(5566):356–359. doi:10.1126/science.1068284*
13. [a, b]*T. Jacob John. (2004). Two good reasons to drop type 2 virus from oral polio vaccine. The Lancet. 364(9446):1666. doi:10.1016/S0140-6736(04)17351-0PubMed PMID: 15530625*
14. [a, b, c]*T. John, Vipin Vashishtha. (2009). Eradication of vaccine polioviruses : why, when & how? Indian J Med Res. 130(5):491–494.*

15. ^*T. Jacob John, Dhanya Dharmapalan. (2019). Fighting polio in Pakistan. The Hindu. Available from: https://www.thehindu.com/opinion/op-ed/fighting-polio-in-pakistan/article27004837.ece. Accessed 18 Sep 2021.*
16. ^*Global advisory group. (1985). Expanded programme on immunization. Weekly Epidemiological Record. (60):13–20.*
17. ^*GPEI. Nigeria three years free from wild poliovirus. [cited 18 Sep 2021]. Available from: https://polioeradication.org/news-post/nigeria-three-years-free-from-wild-poliovirus/*
18. ^*Dominique Rousset, Mala Rakoto-Andrianarivelo, Richter Razafindratsimandresy, Bakolalao Randriamanalina, Sophie Guillot, et al. (2003). Recombinant vaccine-derived poliovirus in Madagascar. Emerg Infect Dis. 9(7):885–887. doi:10.3201/eid0907.020692*
19. ^*Helen E. Jenkins, R. Bruce Aylward, Alex Gasasira, Christl A. Donnelly, Michael Mwanza, et al. (2010). Implications of a Circulating Vaccine-Derived Poliovirus in Nigeria. N Engl J Med. 362(25):2360–2369. doi:10.1056/NEJMoa0910074*
20. a, b*T. Jacob John. (1985). POLIOMYELITIS IN TAIWAN: LESSONS FOR DEVELOPING COUNTRIES. The Lancet. 325(8433):872–873. doi:10.1016/S0140-6736(85)92231-7*
21. a, b*Centers for Disease Control and Prevention. (1994). International Notes Certification of Poliomyelitis Eradication -- the Americas, 1994. MMWR. 43(39):720–722.*
22. a, b*Centers for Disease Control and Prevention. (2001). Certification of poliomyelitis eradication--Western Pacific Region, October 2000. MMWR Morb Mortal Wkly Rep. 50(1):1–3. PubMed PMID: 11215787*
23. a, b*Centers for Disease Control and Prevention. (2002). Certification of poliomyelitis eradication--European Region, June 2002. MMWR Morb Mortal Wkly Rep. 51(26):572–574. PubMed PMID: 12139184*
24. ^*WHO. First ever vaccine listed under WHO emergency use. [cited 19 Sep 2021]. Available from: https://www.who.int/news/item/13-11-2020-first-ever-vaccine-listed-under-who-emergency-use*
25. ^*WHO. Global polio eradication initiative applauds WHO African region for wild polio-free certification. [cited 19 Sep 2021]. Available from: https://www.who.int/news/item/25-08-2020-global-polio-eradication-initiative-applauds-who-african-region-for-wild-polio-free-certification*
26. ^*T. Jacob John. (2000). The Final Stages of the Global Eradication of Polio. N Engl J Med. 343(11):806–807. doi:10.1056/NEJM200009143431111*
27. ^*Roy M. Anderson. (1982). The Population Dynamics of Infectious Diseases: Theory and Applications. Springer US. (Population and Community Biology Series). doi:10.1007/978-1-4899-2901-3. ISBN 978-0-412-21610-7*
28. ^*T. Jacob John, Dhanya Dharmapalan. (2018). An ethical appraisal of the choice of vaccines against Poliomyelitis. Indian Journal of Medical Ethics; Vol 4, No 1 (NS) (2019): Learning not to repeat the past. Available from: https://ijme.in/articles/an-ethical-appraisal-of-the-choice-of-vaccines-against-poliomyelitis/*
29. ^*T. Jacob John, Dhanya Dharmapalan. (2019). The moral dilemma of the polio eradication programme.*

Indian J Med Ethics. 4 (NS)(4):294–297. doi:10.20529/IJME.2019.060PubMed PMID: 31791935

30. ^*T. Jacob John, R. Samuel. (2000). Herd immunity and herd effect: new insights and definitions. Eur J Epidemiol. 16(7):601–606. doi:10.1023/a:1007626510002PubMed PMID: 11078115*