The Golden Jubilee of vaccination against poliomyelitis
Jonas Salk (1914-1995) in India in 1983 to receive the Jawaharlal Nehru Award.
Inactivated poliovirus vaccine (IPV), developed in the USA by Jonas Salk in the early 1950s, was field tested in 1954, and found to be safe and effective. The year 2004 marks the golden jubilee of this breakthrough. From 1955 IPV was used extensively in the US and polio incidence declined by more than 95 per cent. However, in 1962, when oral poliovirus vaccine (OPV) became available, the national policy was shifted to its exclusive use, for reasons other than science and economics. The World Health Organisation (WHO) also adopted the policy of the exclusive use of OPV in developing countries. Thus IPV fell into disrepute in much of the world, while Northern European countries continued to use it. New research led to improving its potency, reducing its manufacturing costs and combining it with the diphtheria-tetanus-pertussis (DTP) vaccine to simplify its administration and reduce programmatic costs. All countries that chose to persist with IPV eliminated poliovirus circulation without OPV-induced polio or the risk of live vaccine viruses reverting to wild-like nature. IPV is highly immunogenic, confers mucosal immunity and exerts herd protective effect, all qualities of a good vaccine. It can be used in harmony with the expanded programme on immunization (EPI) schedule of infant immunisation with DTP, thus reducing programmatic costs. During the last ten years IPV has once again regained its popularity and some 25 industrialised countries use it exclusively. The demand is increasing from other countries and the supply has not caught up, leaving market forces to dictate the sale price of IPV. Anticipating such a turn of events India had launched its own IPV manufacturing programme in 1987, but the project was closed in 1992. Today it is not clear if we can complete the job of global polio eradication without IPV, on account of the genetic instability of OPV and the consequent tendency of vaccine viruses to revert to wild-like properties. The option to use IPV is complicated since it is not yet licensed in India, we do not manufacture it and imported vaccine would be prohibitively costly. However, in this golden jubilee year we have much to celebrate as the global eradication of wild polioviruses is within sight. Had we strictly followed the principles of science and health economics, perhaps we could have achieved success earlier and cheaper, with the absence of vaccine-induced polio as the bonus.

**Key words** Inactivated poliovirus vaccine - oral polio vaccine - poliomyelitis

The twin purposes of this review are to celebrate the fiftieth year of vaccination against polio and to pay tribute to the scientist who developed the first safe and effective poliovirus vaccine. The innocuity and immunogenicity of the inactivated poliovirus vaccine (IPV) was established in humans (after animal studies) by Jonas Salk in 1952 and 1953. Thereafter a massive field trial for determining its protective efficacy was conducted in 1954, which involved over a million subjects. It confirmed the safety and efficacy of IPV and 2004 is the fiftieth anniversary (golden jubilee) of this breakthrough. IPV was licensed for general use in the USA in 1955. India honoured Salk with the Jawaharlal Nehru Award for International Understanding in the year 1983.
By 1959 Albert Sabin succeeded to attenuate the three serotypes of polioviruses after years of arduous and diligent research, thus developing the live oral poliovirus vaccine (OPV). Within a decade of these developments, several nations used either IPV or OPV or both in combination and successfully controlled or even eliminated polio from their territories. From those beginnings of human mastery over polioviruses and poliomyelitis, the world has progressed much towards eradicating them from humans altogether. This review will focus on the first vaccine namely IPV. A treatise on IPV will be incomplete without noting the contribution of Anton van Wezel, the Dutch scientist who improved and standardised the production and potency of IPV. This review should help dispel some misconceptions that had arisen over the years regarding certain properties of IPV.

Unfortunately, none of the three scientists who developed these vaccines is alive to celebrate with us the impending global victory over polio. As we are nearing the global eradication of wild polioviruses, the need and prospects of IPV to complete it will also be explored. Successful interruption of wild virus transmission and the safe and scientific management of the final phase of eradication to avoid the risk of polio due to vaccine viruses, are the best tributes we can pay to the memory of Salk, Sabin, van Wezel and a number of others who made these achievements possible.

The development of IPV by Salk: The incidence of polio in the USA began increasing perceptibly from about 1916, when the endemic ‘infantile paralysis’ of infants and preschool children transitioned into ‘epidemic polio’ affecting children and adolescents, and occasionally even adults. Franklin D Roosevelt was 39 yr old in 1921 when he developed polio paralysis in both lower limbs. In spite of this physical challenge he was elected President of the USA in 1933. In 1938 Roosevelt’s friend and former partner in a law firm, Basil O’Connor, established the National Foundation for Infantile Paralysis (NFIP), which grew to become one of the most successful voluntary associations ever, dedicated to a health problem. The NFIP raised money from and through a multitude of ordinary people, especially housewives who went house-to-house in annual campaigns of collection that was cleverly called “March of Dimes”. It built up a huge network of volunteers for local activities. The funds were used to pay for the costs of treatment and rehabilitation of polio affected persons, to train nurses and physical therapists to care for them and also to conduct laboratory research to understand more about the virus and eventually to develop vaccines against polio. The funds for research on polio from the NFIP during 1940s and 1950s were an order of magnitude larger than that disbursed by the National Institute (presently Institutes) of Health (NIH), which had access to governmental allocations, but had other priorities.

In 1947 Jonas Salk joined the University of Pittsburgh, in Pennsylvania State, as Associate Professor of Microbiology. He was born in New York in 1914 to parents who had migrated from Russia. After graduating in Medicine in 1939, he worked with Thomas Francis Jr. in Ann Arbor, Michigan, from 1941 to 1947, the main avenue of research being the cultivation (in fertilized hens’ eggs) and inactivation of influenza viruses to make vaccines for use by the defence forces.

By 1948 three serotypes of polioviruses had been identified by cross neutralisation experiments in monkeys. Research to check if there were more than three serotypes was initiated and funded by NFIP. Four laboratories including Salk’s laboratory in Pittsburgh were selected to type a large number of poliovirus isolates to search for unknown type. The plan was to do all the tests in monkeys, since there was no other established method to type the viruses. Infecting monkeys with a known type, waiting for them to recover and to challenge them with untyped strains was slow, laborious and expensive. In 1949 John Enders, Thomas Weller and Frederick Robbins grew polioviruses in human non nervous system cells cultured in laboratory glassware. They shared the 1954 Nobel Prize for this breakthrough work. Salk saw the immense potential of using cell culture system to type strains of polioviruses fast and cheap and also to grow them in large enough quantities to attempt to make a killed vaccine. The then widely held view of experts was that an infectious vaccine would be necessary to protect against polio. Salk knew immunology well enough to predict that actual infection was unnecessary to induce immunity, but injections of killed virus antigen would suffice. He pursued his experiments at relentless pace and proved the principle of immunogenicity and safety of killed virus preparation, first in animals and later in human subjects, in 1952 and 1953.

The vaccine field trial and licensure: The epidemic of polio in the US in 1952 claimed more than 58,000 victims and in 1953 the incidence was 20 per 100,000 population, the highest ever recorded in the US. There was great urgency in the minds of O’Connor and Salk to develop and deploy a safe and effective vaccine to prevent continued devastation by the virus. As stated earlier,
the then prevalent opinion of most poliovirus experts, including Sabin, was that only a live attenuated virus vaccine would be effective against polio, as it is due to an infection that begins on the pharyngeal and intestinal mucosa and later spreads to the spinal cord. Jenner’s smallpox vaccine, Pasteur’s rabies vaccine and Theiler’s yellow fever vaccine – all contained live viruses. Salk was convinced that an inactivated vaccine would work just as well as in the case of influenza. By January 1953 Salk had given one or another version of his killed virus vaccine to 161 persons without incident. He demonstrated not only the development of virus neutralising antibodies but also that the level of induced antibody after three doses of IPV was often higher than what was obtained after natural infection.

The NFIP went ahead and organised what became one of the largest ever vaccine trials, directed by Thomas Francis Jr., a most trusted and respected epidemiologist of his time. The trial participants included 1,829,916 children in different parts of the USA and also in Canada and Finland. The experiment involved both placebo controls and in some areas observed controls. On April 12, 1955 Francis announced the result of the trial in a public function organised jointly by the NFIP and the University of Michigan (where the Vaccine Evaluation Centre functioned under Francis). It also turned out to be a big ‘media event’. The protective efficacy was 80-90 per cent against paralytic polio. The success of the trial confirming the safety and efficacy of the vaccine was publicised widely by the media in the US and Europe. The very same day Ovetta C. Hobby, the US Secretary of Health, signed the papers to license the vaccine for general use. These historical details are essential to highlight some issues that have relevance to the subsequent unfolding of the history of the two vaccines, IPV and OPV.

What is worth noting is that research leading to the development of the vaccine and its field trial were funded entirely by the NFIP, a private voluntary organization. The vaccine trial was also conducted in the private voluntary sector. The Foundation’s volunteers, alumni of NFIP-supported training programmes, members of Parent-Teacher Associations, and State health officers made the field activities of the vaccine trial possible. The Federal government or its agencies such as the NIH or the Communicable Disease Center (CDC, presently the Centers for Disease Control and Prevention) were not involved in either the development or the field trial of the vaccine (except for quality check of the vaccine by the Laboratory of Biologics Control under NIH). During the crucial years of Salk’s intense experiments, he wrote only very few scientific papers for publication. Much of the detailed experiments were not written up for peer reviewed, publications and critique by fellow scientists, as would have been expected of any scientist generating new data and creating new information. On the other hand, the NFIP had regular Round Table review meetings of all research funded by it, thus giving Salk the opportunity to present his many studies in detail to a select group of scientists and managers. Even the vaccine trial results were announced directly to the public and the media, a move that was much misunderstood as sheer publicity seeking. To top it all, Salk became a public hero both in the US and globally. All these seem to have alienated several mainstream polio scientists and officials of the Federal government agencies, many among whom were ardent believers of the popular hypothesis that only a live attenuated vaccine would be effective against polio. Indeed, when Sabin’s live oral vaccine became available, by about 1962, the Public Health leaders promptly adopted it for immunisation, as if they were embarrassed of the killed vaccine.

The negative attitude of the leading scientists was clear from the fact that Salk was never elected to the National Academy of Sciences of the USA. However Salk did get a Congressional medal and a citation from US President Eisenhower as the nation’s appreciation. These were recognitions in the political rather than in the science arena. The only two major awards he was given in the US were the Albert Lasker Award of the American Public Health Association and the Bruce Memorial Award of the American College of Physicians.

The “Cutter incident” and incompletely inactivated vaccine: For preparing the vaccine for trial, polioviruses were grown in cell cultures at the Connaught Laboratories of the University of Toronto, Canada, and shipped to two US manufacturers, the Park Davies and Co. in Detroit, and Eli Lilly and Co. in Indianapolis. They inactivated the viruses, filtered and blended the three types into the vaccine for the trial. Samples from every production batch was tested for absence of residual live virus by the manufacturer, the Laboratory of Biologics Control (LBC) of the NIH in Bethesda and Salk’s own laboratory. The vaccine preparation was exactly as prescribed by Salk. The seed viruses were type 1 Mahoney, type 2 MEF-1 and type 3 Saukett strains. The viruses were inactivated with formaldehyde 1:1000 for 13 days at 37ºC. After the vaccine was licensed, four additional companies also began manufacturing IPV, using supposedly the same protocol as had been approved
by Salk and the NFIP. However, when it was licensed for production there was no government regulation in place for safety testing\(^5\). All manufacturers had sent their vaccines to the LBC for safety tests, but they could sell the vaccine even prior to the completion of safety tests at the LBC. One of the new manufacturers was the Cutter Laboratories in Berkeley, California\(^5\).

The staff of LBC was overworked and could not cope up with the volume of work with the necessary speed to complete safety tests prior to the distribution of vaccines\(^11\). The vaccine samples had to be injected in monkeys to ensure safety; although tests in cell cultures would have been simpler, that method had not yet become routine in the LBC. The vaccine made by Cutter Laboratories was ready for marketing immediately after licensing, indicating that they had worked on vaccine manufacture even while the francis trial was going on. In LBC, the Cutter vaccine caused paralysis in monkeys and the microbiologist Bernice Eddy reported the matter to William Sebrell, the Director of NIH\(^11\). He chose to ignore the information and the Cutter vaccine was not withheld from release as it should have been, based on the safety problem identified in the NIH\(^1\). Two weeks later, reports of children developing polio after taking the Cutter IPV began coming in. Within days, the Surgeon-General instructed the withdrawal of IPV made by Cutter. About two weeks later use of IPV from all other manufacturers was also suspended for completion of safety checks and finding them safe, immunization was resumed\(^6\). Sebrell was held incompetent to handle the situation and had to resign later\(^11\). James Shannon was given charge of managing the Cutter episode and he and O’Conner sharply disagreed on the management, of the problem\(^11\). After Sebrell’s resignation, Shannon was made the Director of NIH. According to the new NIH Director, “it was the forceful personality of O’Connor with the political support he had that was able to override some of the essential details of Federal management of an important biological product”\(^11\). Even the Secretary of Health, Ovetta C. Hobby, had to step down on account of the Cutter incident, the way it was handled, and the embarrassment caused by it\(^5,11\).

The whole Cutter episode lasted for less than two months. Obviously the Cutter Company had made two errors-they had compromised on the manufacturing process and also on safety testing. Based on this experience a Technical Committee developed safety regulations for the production of the vaccine, to be implemented by the companies under the authority of the LBC of NIH\(^5,11\). The new vaccine regulations altered some steps of vaccine production, apparently resulting in some reduction in antigenic potency\(^4\).

The Cutter vaccine indeed had residual live virus, which was the cause of polio in vaccinated monkeys and children and in family contacts and playmates of vaccinated children. A new Poliomyelitis Surveillance Unit was created in the CDC in Atlanta, which investigated the vaccine-related polio cases and concluded that 79 vaccinated children, 105 family members and 20 community contacts had developed polio due to the virus contained in the vaccine\(^5\). Among them, 192 had paralysis\(^6,12\). It was in this unfortunate manner that two of the Federal agencies ultimately got involved with issues related to IPV. The Cutter incident did dent the public’s confidence in IPV for a short while, but with the continued use of quality-assured vaccine, it became popular once again among the public. But the unpleasantness among scientists and Federal agencies seems to have persisted, based on the facts enumerated above. As soon as OPV became available, the American Medical Association recommended it for regular use in the country\(^5\). The Federal government and the American Academy of Paediatrics welcomed this shift. That OPV caused more cases of paralysis globally every year than those caused by the faulty Cutter vaccine, received scant attention from Public Health leaders or was ignored by them, apparently partly on account of their faith in and fascination for the first effective oral live virus vaccine, but also partly due to their displeasure of Salk and his IPV.

There are important lessons India must learn from this episode and how it was handled. First, when a problem arises, its solution must include both short-term and long-term interventions. If one vaccine from a manufacturer failed in quality, other vaccines could also fail. Therefore, a National Regulatory Authority was established to ensure the safety of vaccines and that idea has since been accepted universally. Secondly, since the polio vaccine resulted in the disease it was intended to prevent, surveillance of the disease in order to detect any more such cases was instituted. This was instrumental in detecting the vaccine-associated polio when OPV was introduced\(^13\). Thus every unexpected problem has the seed of the opportunity to make progress beyond the mere solution of the problem. It seems that in our country, punitive rather than corrective interventions are given importance when something goes wrong. For example, in 1974 the Government of India ordered the closure of India’s first and only successful OPV manufacturing unit (at the Pasteur Institute in Coonoor, Tamil Nadu) just because one vaccine candidate batch of type 3 poliovirus did not pass the quality test. Earlier six batches of trivalent OPV had been passed and also released by the Pasteur Institute. Since then India had to import all necessary OPV from other countries.
Soon after OPV was licensed and introduced in the US, stray cases of polio were observed within the incubation period of its administration to children. A Special Advisory Committee was appointed by the Surgeon-General of the USA to investigate if the disease was caused by the vaccine. The Committee reported on the risk of paralytic polio due to Sabin vaccine in comparison with that of disease in the absence of immunization, and concluded that the benefit justified the risk. The Committee did not report on the comparative risk-benefit assessment of the two vaccines, or in other words, it ignored the very existence of IPV. This piece of information seems to confirm the apparent animosity towards IPV, which had unfortunately developed on account of all the reasons stated earlier. These extraneous factors, rather than scientific or economic arguments seem to explain why the Public Health leaders of the US switched to OPV as soon as it became available, and for their unfortunate persistence with it for more than three decades in spite of the fact that it caused polio in 8-10 children every year. Finally in 1996 the US reversed its stand and went back to IPV. By then the US had influenced the rest of the world to believe that there was something wrong with IPV.

The application of biotechnology to improve IPV: Salk did as much as he could do to make a safe and effective vaccine against polio. Once the vaccine was introduced, quite understandably the NFIP was no longer able to raise as much funds as before. As IPV was a product of NFIP, and as OPV became popular, no one in the USA seemed to be scientifically interested in further research to improve on it. However, there were other nations loyal to Salk IPV, such as Finland, Sweden, Norway, Netherlands and Francophone parts of Canada. Finland and Canada had participated in the Francis trial of IPV in 1954 and found it to be completely safe and highly effective. In 1961 Finland gave IPV in a nationwide campaign and eliminated wild virus polio without the risk of vaccine-virus polio of OPV. Norway used IPV from 1961 to 1969 and had eliminated polio. When OPV became available, Norway switched to it, believing it to be superior. During the next ten years OPV-induced polio was recognised at a rate of one case per 400,000 vaccinated subjects and in addition one case among unvaccinated contacts per 100,000 vaccinees. Consequently Norway reverted to the exclusive use of IPV in 1979. Thus, IPV remained or became the vaccine of choice in the Scandinavian and other North European countries. Research to improve IPV was spearheaded by scientists in the Netherlands and France.

Until about the early 1980s IPV continued to be made the way Salk had prescribed. There were two problems to be addressed if it were to be improved. One, the viruses had to be grown on monolayer cell cultures. The method was slow, cumbersome and did not yield large amounts of vaccine per batch. Unlike the live vaccine, which is also made in cell culture, there was much loss of the antigen content with virus inactivation, resulting in the final product remaining relatively more expensive, compared to the live vaccine. Second, the vaccine was not properly standardised for its potency, for which reason there was much variation between products and batches. The IPV used in Finland had low potency of the type 3 component, resulting in immunity gap and an outbreak of polio due to type 3 wild virus affecting vaccinated children, more than a decade after it was eliminated.

In the Netherlands, the Rijks Institute (popularly known as RIVM) in Bilthoven made IPV for the country, but it had no commercial interests. Their biomedical engineer van Wezel realised that cell cultures could be adapted to large-scale production, just like bacteria, in controlled bioreactors, usually called fermenters. Mammalian cells would require a surface on which they had to attach before cell division could take place, unlike bacteria (and some cells) that grow in suspension. The bioreactor was an excellent system to mass-produce cells that grow in suspension. So van Wezel used minute spheres, called microrcarriers, on which the mammalian cells would attach and the rest of the process was like in suspension culture in bioreactors. The cells on microrcarriers could be infected with polioviruses. He grew polioviruses in 1000 litre bioreactors and established sophisticated concentration and purification processes and this new system could produce one to two million doses per production batch. This new IPV had higher potency than the earlier Salk vaccine. The immunogenic potency of IPV is measured as D antigen units. The potency of old IPV varied between manufacturers and batches, and on the average contained 20, 2 and 4 D antigen units of type 1, 2 and 3 polioviruses per dose. The new product of van Wezel was made with 40,8 and 32 D antigen units per dose. The final vaccine contained virtually no extraneous protein and the nucleic acid from the cell substrate was only in picogram quantity. The vaccine safety test in monkeys could be replaced with that in cell cultures. The antigen potency test in monkeys was also replaced with test in rats and cell culture virus neutralisation with enzyme immunoassays. French researchers showed that Vero cells, a continuous cell line of simian origin, was safe for human vaccine production and monkeys could thus be removed from use to produce...
or quality test IPV^{24,25}. On the other hand, most OPV manufacturers use approximately 50-60 monkeys, mostly Indian Rhesus (Macaca mulatta), to manufacture and quality test every batch of OPV that we continue to import and use in our country, even though such use of monkeys is banned within India.

The innovations described above led to markedly reduced cost of production of this highly purified and potent vaccine^{24-26}. The Dutch scientists also showed that IPV could be combined with diphtheria-tetanus-pertussis (DTP) vaccine, making its injections harmonised with that of the usual infant vaccination under the expanded programme on immunization (EPI). By all counts this new formulation IPV was perfectly suited for use in developed as well as developing countries^{25-27}. The advantages were complete safety, excellent immunogenicity after 2 or 3 doses, combinability with DTP and harmony with EPI schedule, markedly lower cost of production than the old IPV and reduced programmatic costs of immunisation. Our studies in Vellore (see below) raised the hope of introducing it in India at least on a limited scale for learning some field experience with it in the country, for which purpose the manufacturer was willing to sell this IPV for about ten rupees a dose. The reason for not using this new IPV in developing countries like India was not based on science or economics, but apparently on personal prejudices of policy makers.

Two manufacturers in France and Canada made (and continue to make) this new IPV for commercial distribution and it has become very popular in industrialised countries^{25,28}. We had the opportunity to investigate its immunogenicity soon after it was made and we named it as ‘IPV of enhanced potency’ (IPVe or E-IPV)^{29,30}. Since only E-IPV is currently available in the market, the term IPV will hereafter mean this new vaccine. The original Salk IPV will be referred to as ‘old IPV’ or ‘Salk vaccine’.

**Immunogenic efficacy of IPV:** The 1954 Salk vaccine trial by Francis had found that the protective efficacy of different batches of IPV correlated with the potency of vaccine, which was measured by antibody response in children, in other words, its immunogenicity^6. On the average, the vaccine efficacy in the trial was 80-90 per cent against paralytic disease and 70 per cent against any disease, non-paralytic and paralytic^6,9. In Texas, the protective vaccine efficacy of Salk vaccine was 96 per cent during two polio seasons^31. The immunogenicity and protective efficacy of Salk vaccine have been of very high order in every industrialised country in which it has been used^{35,37,32}. In their context the anxiety was about the duration of immunity. The then widely held belief was that antibody induced by killed virus antigen would not last long and repeated boosters would be necessary to sustain protection. The need for multiple doses of IPV was counted as a disadvantage, in comparison with OPV, just three doses of which would give life long immunity according to this view. In reality the reverse in true - antibody persistence was prolonged even with the old IPV in the US^{32} and in developing countries the number of doses of OPV needed for ensuring protection was many times more than for IPV^{27,33}.

Swedish children given three primary and one booster doses of the old IPV were all antibody positive when tested 18 yr later^{32}. French children given three plus one doses of E-IPV remained antibody positive even when they were adults^{34}. These studies and the vast experience with IPV in many European countries have shown it to be an excellent immunogen with prolonged (sustained) immunity for decades even in the absence of continued boosters or continued virus circulation to boost antibody level.

On account of the WHO policy of exclusive use of OPV in developing countries, there have been only very few studies conducted on the old or new IPV in such countries, almost all of which showed excellent antibody response, in terms of both the seroconversion rates and antibody titres^{35-39}. We measured the antibody response of infants to three doses of the old IPV during 1979-1980^{16,37}. Since there are three variables (seroconversion rates) for inter-study comparison, we had devised a single variable, namely the seroconversion index (SI), which is the cumulative response of 100 infants to the three polioviruses, or in other words 300 potential seroconversions^{27}. In effect the SI would approximate to the mean of the seroconversion rates to the three types of polioviruses. In the first study in 67 infants given the quadruple vaccine containing DTP and the old formulation IPV, the SI was 94 after three doses given at intervals of 4 wk between doses and 98.5 when the interval was 8 wk between doses^{36}. In comparison the SI after 3 doses of OPV was only 70-78 in several studies in Vellore (Reviewed in Ref. 27). In a larger study of the quadruple vaccine given to 152 infants (6-45 wk old), the SI was 87 when the interval between doses was 4 wk^{37}. The seroconversion rates in the group with 8 wk interval between doses were 100, 98 and 95 per cent to types 1, 2 and 3 polioviruses, respectively and
the SI was 98\textsuperscript{37}. We had found that two factors affected the immune response to IPV. One was the presence of maternal antibody when vaccination commenced and the other was the interval between doses\textsuperscript{29,30,36,37}. The effect of maternal antibody was negligible if the first dose was given at or after 8 wk of age.

We collaborated with the department of paediatrics of the Mysore Medical College (Mysore, Karnataka) in comparing the antibody response of infants given 3 doses of either OPV or IPV, in 1987 (Chetna NC and John TJ, unpublished). The old IPV manufactured by Institute Merieux in France was used in this study. The number of children, seronegative to the three poliovirus types prior to vaccination who completed the study were 49 for OPV and 53 for IPV. Although infants were eligible to commence immunisation at the age of 6 wk, in reality all children were over two months when they received their first dose. The seroconversion rates induced by OPV were 85, 89 and 55 per cent against poliovirus types 1, 2 and 3 respectively, for an SI of 76. The seroconversion rates due to Salk vaccine were 98, 98 and 96 per cent against poliovirus 1, 2 and 3 respectively, with the SI of 97. The Fig. illustrates not only these differences in seroconversion rates but also the contrast between the levels of antibody achieved by the children receiving the two vaccines. The proportions of children with very high antibody titres (512 or more) to poliovirus types 1 and 3 in response to Salk vaccine were indeed higher than the proportions responding to OPV with titres of 8 or even 4 (Fig.). With E-IPV even higher antibody titres would be achieved.

Soon after the RIVM began producing E-IPV, we received the same supplied as quadruple vaccine containing DTP, for field evaluation. Following just two doses of E-IPV in infants 6 to 45 wk of age, the seroconversion rates were 97, 84 and 97 per cent to the three viruses respectively and the SI was 94\textsuperscript{29}. The seroconversion rates were better in infants 8 wk of age and older when the first dose was given than those of 6 or 7 wk of age and also when the interval between doses was 8 wk instead of 4\textsuperscript{29,30}. The SIs achieved by children given the old IPV (3 doses) or E-IPV (2 doses), according to the presence or absence of maternal antibody when the first dose was given, and according to the interval between doses, are summarised in the Table. Although not directly tested by us, data from others show that we could expect near 100 per cent seroconversion to the three types after a third dose, irrespective of the age of the infant or the interval between doses.

In Kenya, the seroconversion rates of infants 2 months or older, given two doses of E-IPV were 94, 88 and 97 per cent to the three types and after three doses 100, 100 and 98 per cent respectively\textsuperscript{38}. The SI was 93 after 2 doses and 99 after 3 doses\textsuperscript{38}. In Cote d’Ivoire, where a proportion of infants had remained seronegative after giving 3 doses of OPV, and in Oman where many infants had remained non-immune even after giving 5 doses of OPV, a single suplemental dose of IPV induced seroconversion in them 2 to 14 times more frequently than what could be achieved by a supplemental dose of OPV\textsuperscript{39,40}. Moreover, the IPV induced superior booster seroresponse in terms of achieved antibody titres, than did OPV\textsuperscript{39,40}.

While most of the studies in developing countries showed excellent immunogenic efficacy of IPV, which was considerably better than that of OPV, there has also been one study in which the results were in the opposite.
been one published large-scale study on the immunogenicity of OPV and IPV in the Gambia, Oman and Thailand. The WHO conducted a study of immunogenic efficacy of OPV and IPV in the Gambia, Oman and Thailand. Seroconversion rates could not be calculated in the Gambia. In Thailand the SI after 3 doses of OPV was 95, but the SI after 3 doses of IPV was only 75. After 2 doses of IPV the SI was only 56. On the other hand, in Oman the same study recorded SI of 84 after 3 doses of OPV and 94 after 3 doses of E-IPV. After 2 doses of E-IPV the SI was 78. The result of the study in Thailand is the one exception to the finding of markedly higher immunogenic efficacy of 3 doses of old IPV or 2 doses of E-IPV than that of 3 doses of OPV documented in every other study. Obviously there was some reason(s) for the very low immune response of children to IPV in the study in Thailand, but there is no scientifically plausible factor to explain it.

For obtaining the best results with 2 doses of IPV it should be given from 8 wk of age or later and the second dose after an interval of 8 wk or more. However, a booster should be given after some interval. Such a sequence does not harmonise with the current infant immunisation schedule of DTP, which is scheduled in 3 doses at 6, 10 and 14 wk of age. Therefore the primary immunisation could be with 3 doses of IPV in the EPI schedule. The WHO study in Oman gave the 3 doses of IPV in the DTP schedule and got excellent seroconversion rates, namely 90, 96 and 95 per cent to types 1, 2 and 3 polioviruses respectively, and SI of 94. Three doses of OPV given in the same schedule resulted in only 81, 97 and 73 per cent seroconversion to the three types and SI of 84.

Being a purified antigen, the E-IPV could be injected intradermally in fractional doses without reducing its immunogenicity, both for primary and for booster vaccination, thus saving on cost. Intradermal immunisation has also been shown to induce rapid and vigorous anamnestic response in case it were to be used for outbreak control in an immunised community. The antibody levels thus achieved were orders of magnitude higher than that are usually achieved with OPV, given either in primary or booster vaccinations. At the present time these observations have only theoretical importance, but in case data were needed in the post-eradication era, they are already available.

**Protective efficacy of IPV in developing countries:** Studies on vaccine efficacy of IPV in developing countries, in terms of protection from polio, have been even fewer than the immunogenicity studies described above. There has only been one published large-scale study on the clinical protective efficacy of E-IPV in a developing country, Senegal. It showed the field level protective vaccine efficacy of two doses of E-IPV to be 89 per cent against paralytic polio. We had conducted a study using E-IPV in one half of the population (5 million) in North Arcot district, Tamil Nadu, India, on behalf of the Indian Council of Medical Research (ICMR), during 1987 to 1992. IPV was given as DTP-IPV combined vaccine replacing DPT, in two doses at 2 and 4 months of age, and the third dose was given at 9 months at the time of measles vaccination. The other half population was given OPV in the regular schedule. The objective of the ICMR was to conduct at demonstration of polio control, including its documentation by disease and virus surveillance. The Government gave permission to conduct the study on condition that the study will not be published; therefore no details will be recorded here. The incidence of polio declined in both populations; the rate of fall was faster and steeper in the IPV area. In the OPV area the incidence declined from 9 to 0.4 per 100,000 population per year in the 5 yr of study, when 95 per cent coverage had been achieved at the required age interval. In the IPV area the annual incidence fell from 14 to 0.3 per 100,000 when 84 per cent coverage had been achieved.

Earlier we had conducted a small study of field level vaccine efficacy of IPV in a rural community of 50,000 population, from April 1980 through March 1983. Quadruple vaccine (DPT-IPV) was given to infants in the routine schedule, at first using the old IPV and later using the E-IPV. Among 3220 vaccinated children observed for 6911 child-years, none developed polio. In the adjacent area, with 50,000 population, 3104 children had received DPT, and were observed for 6612 child-years; 17 cases of polio were recorded among them. The vaccine efficacy was 100 per cent. A much larger study, was conducted by Renu Patel in Mumbai, during 1988 through 1991 (Patel R, personal communication). As Professor of paediatrics in Grant Medical College, she was in charge of the Integrated Child Development Scheme in several slums in Mumbai. Frustrated with the persisting occurrence of polio in spite of achieving over 90 per cent coverage with 3 doses of OPV in infants, she introduced Salk IPV in one population unit of about 100,000 people, in 1988. From 1989 no child developed polio in that population. Earlier, annually about 5 children would get paralysed, and all of them were recipients of at least 3 doses of OPV. In 1989 she expanded the IPV population to another block of about 100,000 and again polio disappeared in that block from 1990. In that year one more block was included under IPV immunisation,
and there also polio incidence fell to zero in 1991. The first block remained polio-free over 3 yr, the second block was polio-free for 2 yr and the third block for one year, while under IPV coverage. At that juncture she was transferred out of Mumbai and the study could not be continued7 (Patel R, personal communication).

In summary, there is sufficient evidence to show not only that IPV is highly immunogenic in developing countries but also to show that its protective efficacy is much superior to that of OPV including in those countries in which OPV provides low immunogenic and protective efficacy.

Does IPV induce mucosal immunity?: It had been widely taught, and stated in many textbooks that IPV induced no mucosal immunity and for that reason it was unsuitable for use in developing countries under the EPI as it would not control its incidence. According to this viewpoint, while humoral immunity induced by IPV is sufficient for personal protection, the lack of mucosal immunity would not protect against infection with wild polioviruses. Unless infection is prevented in the vaccinated, the transmission of the pathogen in the community will not be retarded. Unless transmission is reduced, vaccination programme will not get the benefit of herd effect, necessary to control infection and disease. The conclusion of this argument is that only OPV, which is supposed to induce both humoral and mucosal immunity, is suitable for prevention, control and ultimately elimination of poliovirus infection in developing countries. Facts do not agree with his contention.

There are two aspects to mucosal immunity. One is the presence of mucosal secretory immunoglobulin A (IgA) and the other is the inhibitory effect on mucosal infection upon exposure to infection. A common error has been to equate one with the other. Indeed mucosal infection due to vaccine viruses in OPV would induce mucosal secretory IgA, but the non-infectious vaccine given parenterally would also induce it, albeit not so often or in comparable amounts. Mucosal IgA in response to local infection is neither the only nor the major constituent contributing to inhibition of mucosal infection when exposed. There are other factors in mucosal immunity, particularly if we define it as inhibition of mucosal infection of wild polioviruses when exposed, as a result of any immunisation, rather than the level of IgA. This will be evident in the following paragraphs.

To begin with, it is important to point out that direct mucosal stimulation is not necessary for the presence of secreted antibody on mucosal surfaces. Poliovirus neutralising antibodies are secreted in human breast milk of immune mothers, and continue to be secreted as long as lactation continues48,49. The interesting correlation is that the presence of poliovirus-neutralising antibody in human breast milk is determined by the height of antibody level in the serum48,49. In other words, local/mucosal immunity is a reflection of the height of past immune response, rather than direct mucosal stimulation48,49. It was stated earlier that IPV induces much higher levels of antibodies than OPV. Indeed, secretory IgA response in breast milk has been demonstrated as a response even to the non-replicating antigens in IPV50.

Functional mucosal immunity against wild polioviruses has a spectrum of expression, ranging from a mere reduction in the quantum or duration of virus shedding, to complete resistance to reinfection. It cannot be directly measured since it is unethical to challenge immunised children with wild poliovirus. Therefore mucosal immunity to vaccine viruses has been taken as a surrogate. Passive immunisation due to maternal antibody in infants reduces the frequency of vaccine virus take when the antibody titres are very high, showing again that serum antibody levels determine mucosal protective immunity51.

Mucosal antibody induction by IPV has been investigated by a few researchers52-55. All studies reported the induction of secretory IgA by IPV. After giving two doses of E-IPV to infants, nasopharyngeal virus-specific IgA was detected in 57-65 per cent to type 1 poliovirus, in 62-77 per cent to type 2 and 60-71 per cent to type 34. After three doses, 89 per cent had IgA specific for types 1 and 3 polioviruses and 91 per cent had it for type 24. For comparison, 73-77 per cent of infants had such antibody after taking two doses of OPV and 100 per cent had IgA after three doses54. Moreover, the IgA levels were higher in infants given OPV than IPV54. Nasopharyngeal virus neutralising antibody to poliovirus types 1, 2 and 3 was found in 28, 42 and 49 per cent of infants after two doses of E-IPV and in 43, 60 and 66 per cent after three doses, respectively. On the other hand, 73-77 per cent infants had such activity after two doses of OPV and 100 per cent had it after three doses54.

In one study of children in the USA53, who had earlier received OPV or IPV had equal frequency and levels of secretory IgA antibodies both in the pharynx and in stools, thereby indicating that there is little to show one is superior to the other. In industrialised countries, both OPV and
IPV immunise with the same frequency. In the developing country context 3 doses of OPV immunise only one half to two-thirds of children against poliovirus types 3 and 1; mucosal immunity can only develop in these children. On the other hand, 3 doses of IPV immunise over 95 per cent of children, and even slightly reduced frequency of mucosal immunity will be numerically superior to that of OPV. The usual teaching that IPV does not induce mucosal immunity and that it is not suitable for controlling polio in developing countries is not based on a scrutiny of evidence, but on assumptions believed by many to be true by repeated assertions, quoted in many textbooks and papers.

In the early years several workers had given OPV or the old IPV to children and later challenged them with OPV. In general, children who were naturally immune (due to earlier wild virus infection) had most gut immunity, OPV-immunised had somewhat less, IPV-immunised had still lower and non-immune children had the least degree of gut immunity. In one study, two groups of infants, given two doses of either OPV or IPV, were challenged with a dose of OPV. In the OPV group 13 per cent (3/23) and in the IPV group 20 per cent (4/20) shed vaccine virus(es) in the stools, indicating mucosal immunity of a comparable degree induced by both vaccines. In another study, when the challenge dose of vaccine virus was high, pharyngeal shedding was inhibited more frequently in IPV immunised children, than in OPV-given children. When the challenge dose was low (nearer to natural events), inhibition was complete in both groups of children. Since oral-oral/respiratory route is the more common for transmission of wild polioviruses, the strong pharyngeal mucosal immunity induced by IPV explains the strong ‘herd effect’ in developed as well as developing country settings.

The WHO study in the Gambia, Oman and Thailand had investigated mucosal immunity after immunisation, by challenging with a dose of monovalent OPV type 1 and testing a stool sample for virus shedding after a week. In Oman 13 per cent of children who had earlier received 4 doses of OPV shed virus, but only 10 per cent did so after getting 3 doses of IPV, thereby showing that there was no difference in mucosal immunity between the two vaccines. In contrast, in Thailand 57 per cent of children who had received 3 doses of IPV shed virus, while only 14 per cent of those who had got 4 doses of OPV shed virus after challenge. In the Gambia 4 per cent of children vaccinated with 4 doses of OPV, 9 per cent of children vaccinated with 4 doses of OPV and 3 doses of IPV and 16 per cent of children vaccinated with 3 doses of IPV shed the challenge virus. If the frequency of shedding of challenge virus is taken to reflect mucosal immunity due to IPV it would appear that there was good mucosal immunity in Oman, no mucosal immunity in Thailand and intermediate level in the Gambia. The difficulty of interpreting the results of such experiments in developing countries includes the widely variable frequency of vaccine virus take (and shedding) in different geographic locations. Unless the median infectious dose (MID) is measured and a fixed and predictable infectious dose such as 10 or 100 MIDs is used for challenge, the true differences in virus shedding accounted by mucosal immunity, as against the naturally occurring inhibitory factor(s) influencing the low vaccine virus take after a dose of OPV, cannot be measured with any degree of confidence.

We had conducted just that kind of a study, not in children for obvious reasons, but in Macaca radiata monkeys, which are an excellent experimental animal model for gastrointestinal poliovirus infection. After immunising animals with 3 doses of the old IPV, groups of four animals were challenged with 100 MIDs of wild poliovirus type 1 at various intervals from the time of the third vaccine dose. While every unimmunised control animal got infected and shed virus in the throat and faeces, no vaccinated animal did, when challenged between 4 and 12 months after vaccination, thereby clearly demonstrating the phenomenon of mucosal protective immunity induced by IPV.

Mucosal immunity, either due to secretory antibody or ‘spill over’ of IgG antibody, is a feature in many cases of parenteral vaccination with non-replicating antigen, against diseases caused by mucosal infections. The vaccine we use against diphtheria is a toxoid, and the immunity induced is basically humoral, ‘anti-toxin’ in specificity, not anti-bacterial. Yet, vaccination of children results in decline in the incidence of disease in the community. Humoral immunity somehow contributes to a degree of mucosal immunity, sufficient to reduce infection or at least the quantum and/or duration of bacterial shedding by the vaccinated children. Vaccines against pertussis contain either killed whole bacteria or specific immunogens without bacteria (hence called acellular). The herd effect of the killed vaccine had been well recognised for decades. The acellular pertussis vaccine offers protection against infection among family members of the vaccinated children, thereby indicating mucosal immunity in the vaccinated. Current influenza vaccines are sub-units of inactivated influenza viruses,
and even they cause substantial reduction in virus transmission from the vaccinated, herd effect in other words, thus showing evidence for mucosal immunity resulting in reduced frequency of infection or of virus shedding\textsuperscript{63-65}. Vaccination of staff caring for elderly people has been shown to reduce influenza morbidity and mortality among the elderly\textsuperscript{63,64}. In one study, the reduction of disease was 68-87 per cent among patients exposed to staff with high vaccination coverage\textsuperscript{65}. Even more convincing has been the mucosal immunity induced by vaccines against \textit{Haemophilus influenzae} type b (Hib)\textsuperscript{66}. The immunogen in these vaccines is the capsular polysaccharide, given by injection. Among all vaccines, mucosal and parenteral, against various diseases, Hib vaccine is perhaps the one with best herd effect\textsuperscript{66}.

The general principle can now be enunciated that all parenteral vaccines exhibit herd effect due to mucosal immunity, provided (i) they offer good immunogenicity and individual protection; (ii) the disease in question is due to mucosal infection by human-to-human transmitted pathogen, irrespective of the tissues or organs affected by pathology; and (iii) mucosal immunity is not defined narrowly as secretory IgA. There has been no observation or reason to believe that IPV alone is an exception to this general principle.

\textit{Herd immunity and herd effect induced by IPV:} Herd immunity and herd effect have recently been redefined\textsuperscript{67}. The reduction of incidence of infection or disease as the case may be, in the unvaccinated segment of a population as a result of vaccinating a proportion of that population is herd effect\textsuperscript{67}. Herd immunity on the other hand is the proportion of immune subjects in a defined population\textsuperscript{67}. Herd effect results from the reduction of transmission of the pathogen to the unvaccinated, on account of the retardation of transmission from the vaccinated, due to the induced immunity. Thus herd effect is a reflection of both herd immunity and the inhibitory effect of vaccine-induced immunity on the shedding of the pathogen necessary for new infections to occur. In order to induce immunity to inhibit infection or shedding of the pathogen, the vaccine must have high immunogenicity. Absent or reduced shedding is a reflection of mucosal immunity, which prevents infection or reduces the quantum and/or duration of shedding. Thus, herd effect is manifest due to the development of mucosal immunity\textsuperscript{67}. For obvious reasons herd effect occurs only in infections transmitted human to human, like polioviruses among many others described in the earlier section\textsuperscript{67}.

When vaccination is introduced, the incidence of a disease will decline in parallel with the proportion protected – the proportion being the product of vaccine coverage and vaccine efficacy merely on account of the herd immunity induced by vaccination. This decline is confined to the vaccinated individuals. If the decline of incidence is steeper, which could happen only if the incidence in the unvaccinated segment also declines, then it is a reflection of herd effect of the vaccine\textsuperscript{27}. From 1955, the year the Salk vaccine was introduced in the USA, until 1962 when the national policy shifted to OPV, the incidence of paralytic polio had declined by about 95 per cent, far in excess of the proportion of susceptible persons vaccinated\textsuperscript{6}. The incidence of polio declined in excess of coverage, both at the national level and in particular in specific regions where focussed studies were conducted\textsuperscript{6,68-70}. It is not widely appreciated that the rate of decline in incidence remained about the same even after introducing OPV in 1962, indicating that the herd effect of IPV was not inferior to that of OPV in the USA until 1965, by which time more than 99 per cent reduction in incidence had already occurred\textsuperscript{68-70}. Even less appreciated is the fact that from 1961 till 1965 the coverage of preschool children with 3 doses of IPV had only gradually declined from 74 to 50 per cent while that of OPV increased from 6 per cent in 1962 to 47 per cent in 1964\textsuperscript{68-70}. In other words, more than 99 per cent reduction of incidence of polio had actually occurred in the US mainly under the influence of IPV and its herd effect.

The WHO had investigated the performance, safety and efficacy of OPV and IPV in several European countries and concluded that IPV offered both personal protection and community protection (reflecting herd effect)\textsuperscript{71}. In Finland, the IPV coverage was low at about 18 per cent by 1959\textsuperscript{15,16}. In 1960-61, mass vaccination was given and as the total population coverage with 3 doses reached 51 per cent, polio disappeared in the entire population\textsuperscript{66}. The herd effect of the early and relatively crude (according to modern standards) IPV was quite obvious and remarkable in both USA and Finland. Another demonstration of high herd effect of Salk vaccine was in the Netherlands, in which a particular religious community of 200,000 people, living well dispersed throughout the country, had refused vaccination\textsuperscript{9,72-74}. Two outbreaks of polio had occurred among them, first by type 1 virus (1978, 110 cases) and later by type 3 virus (1992, 71 cases)\textsuperscript{9,72-74}. Even though the viruses had circulated widely in that religious community, only one case of polio had occurred outside their members and there was no laboratory evidence of virus dissemination among the general population\textsuperscript{6,70-73}. Even the estimated 400,000 unvaccinated individuals remained unaffected\textsuperscript{9,72-74}.

We conducted a field study to investigate the herd
effect of IPV\(^2\). The hypothesis was that IPV would not retard the infection rate of polioviruses if it did not induce any mucosal protection of vaccinated children. On the contrary, if the circulation of viruses were to be retarded, it would mean that mucosal immunity was induced. A rural community was chosen and from July 1979, weekly stool samples were collected from all infants. They were continued in the study until they were three years of age. Infants born from January 1980 were also similarly investigated, but were given three doses of Salk vaccine, starting at 3 months of age. The former group of 94 was the control population, from whom 4527 stool samples had been collected. From the vaccinated group, or the study population of 82 children, 8159 stool samples were collected. The reason for lower number of stools in the control group was that their samples were not collected prior to July 1979. The stools were examined for the presence of polioviruses and we found that rate of virus shedding was 1.52 per cent in the control and only 0.52 per cent in the vaccinated group. This difference, attributable to vaccination, was statistically highly significant (\(P<0.001\))\(^2\).

It was stated earlier that herd effect of a parenteral vaccine was dependent upon the degree of immunogenicity. This is illustrated by the experiences in Finland and Belgium\(^5,16,75\). In Finland, where a nationwide three-dose IPV campaign reached 51 per cent coverage, the disease (and infection) disappeared\(^{16}\). In Belgium, on the other hand, where only two doses of IPV were given by campaign, even 75 per cent coverage did not result in interruption of wild virus transmission\(^{75}\). In both countries the same vaccine was used, but the immunogenicity of three doses was superior to that of two doses, as had been shown earlier.

**India’s policy decision to manufacture IPV and its reversal:** India launched the EPI in 1978 and introduced OPV in 1979. During the next 10 yr, the reported annual number of cases of polio did not decline, obviously due to inadequate vaccine efficacy of OPV. The various studies on IPV conducted in India were to stimulate and encourage the Government to make an informed choice on polio control using OPV or IPV or both. Yet, IPV was not licensed in India, except for limited research investigations.

In 1988, after deliberations within the scientific community in India, the Government took a new policy decision to produce E-IPV in India and make it available to the nation by 1991. The intention was to make available sufficient IPV for polio control, and to use it side by side with OPV so that experience with both vaccines could be evaluated and compared subsequently. The IPV manufacturing unit was built in Gurgaon, under the name Indian Vaccine Corporation Limited (IVCOL), funded by the Department of Biotechnology. The training of professional staff and the transfer of technology for vaccine production in large volume bioreactors, using van Wezel’s microcarrier cell culture method, were offered as a gift from the Government of France. The mandate of IVCOL was to use the microcarrier technique to manufacture IPV, inactivated rabies vaccine and live attenuated measles virus vaccine. The intention was to obtain the microcarrier cell culture technology, vaccine quality Vero cells, and to become self-sufficient for various vaccines. It had been deemed unethical to inject sheep brain rabies vaccine in humans and IVCOL would have produced sufficient safe rabies vaccine to replace sheep brain vaccine by 1991. The potential for export of all three vaccines to earn foreign exchange to strengthen our economy was another motivation. Since the Governments of India and France covered the development investment, the vaccines made here would have been extremely competitive in price in the world market and quite cheap within the country, especially for use in national programmes. However, it appears that the Ministry of Health and Family Welfare declined to license IPV in the country and therefore the initiative was effectively blocked. By the end of 1991, the Government rescinded its earlier policy decision to introduce IPV also in India and decided to close down IVCOL.

Earlier attention was drawn to the fact that the Government had closed down the one successful OPV manufacturing unit in India; now history was repeated by closing the IPV manufacturing unit also. The ultimate beneficiaries of these decisions were vaccine manufacturers outside India and vaccine importers within India. But those who suffered the consequences were the hundreds of thousands of children who developed polio paralysis in spite of taking the 3 doses of OPV under the Government programme and also the economically weak members of society who suffered the adverse reaction of encephalomyelitis caused by sheep brain rabies vaccine. Unfortunately, neither group of victims was compensated. Cost was certainly not the constraint since we have closed down the IPV manufacturing unit, incurring huge loss, a national waste. Our polio and rabies vaccine policies were not driven by science.

**The future prospects on IPV in the global setting:** During the last decade several industrialised nations have discontinued the use of OPV in favour of the exclusive
use of IPV. This trend was set by France, which had given the option to medical professionals to use either vaccine. The popularity of IPV increased steadily and eventually France discontinued the use of OPV. Very soon the country eliminated indigenous wild virus polio, transmission of imported wild polioviruses from African countries and also vaccine-induced polio\textsuperscript{76,77}. Germany, USA and Canada also abandoned OPV primarily to avoid vaccine-induced polio\textsuperscript{78,79}. Currently some 25 countries in Europe, North America and the Pacific use only IPV and each year more rich countries are opting for IPV (Wood D, personal communication). Some countries have had to wait two or more years after deciding to switch to IPV in order for the manufacturers to upscale production. European countries prefer combination vaccines containing IPV, such as DTP-IPV or DTP-Hepatitis-B-IPV while the US uses IPV not combined with other vaccines\textsuperscript{78,79}. The major reason for switching to IPV in developed countries is to avoid OPV-associated polio in vaccinated children and also in family and community contacts.

The demand for IPV is increasing steadily among rich countries, but no new manufacturers have begun marketing IPV. Consequently the selling price of IPV is exorbitant and remains unaffordable to low and medium income countries. Thus, the disparity based on the income level of countries, namely rich countries opting for the completely safe IPV while poor countries having to be satisfied with OPV with its attendant risk of vaccine-associated polio is being perpetuated. Neither the World Health Organization nor the Government of India has altered their policy to use OPV exclusively. Without articulating a shift in policy, indicating the expansion of the market for IPV, manufacturers would be reluctant to invest money in new plants to produce it. Fortunately there seems to be new developments in this direction. Some manufacturers have been attempting to prepare IPV using Sabin vaccine viruses as the base, instead of laboratory-maintained fully neurovirulent wild-virus stocks.

The annual numbers of OPV-induced polio in India are in the range of 100-200 cases\textsuperscript{80,81}. This is considered to be unethical by some, especially as a safe and effective alternative vaccine is already available in the world. Others consider this as an acceptable price for preventing a much larger burden of wild virus polio. The future perspective on the need, potential and wider use of IPV is likely to be an evolving scenario as more Public Health and opinion leaders become aware of the issues involved.

In addition to causing OPV-associated polio sporadically, a new risk of the continued use of OPV has come to light recently. Contrary to common belief, the vaccine viruses in OPV are poorly transmitted from the vaccinated to the unvaccinated. However, by genetic mutations and probably genetic recombination with other enteroviruses, vaccine virus may revert to its original parental quality of easy transmissibility, thus giving rise to fully neurovirulent circulating vaccine-derived but wild-like viruses that are virtually no different from wild polioviruses except that they come from the vaccine lineage of ancestry\textsuperscript{82-84}. Such revertant viruses are called ‘circulating vaccine-derived polioviruses’ (cVDPV)\textsuperscript{82-84}. Four such incidents of the emergence of cVDPV have been detected, two with large-scale outbreaks of infection, prolonged circulation over a few to many years causing at least 20 to 30 cases of polio among children\textsuperscript{82-84}.

\textbf{Table.} Seroconversion indices according to the presence or absence of maternal antibody at the commencement of vaccination, and the interval between doses

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Maternal antibody</th>
<th>Interval between doses (wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Old IPV (3 doses)</td>
<td>Present</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>95</td>
</tr>
<tr>
<td>E-IPV (2 doses)</td>
<td>Present</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>96</td>
</tr>
</tbody>
</table>

IPV- inactivated poliovirus vaccine
E-IPV - enhanced potency IPV
The original Salk vaccine was further improved by van Wezel in the Netherlands. This new formulation, then called as E-IPV, is currently the only one in the market. Therefore, today the name IPV denotes this improved version with enhanced and standardised potency. It is a completely safe and highly effective vaccine against poliomyelitis in children. Contrary to common teaching without scrutiny of evidence, it confers excellent mucosal immunity in vaccinated children and provides a high degree of herd protective effect in the community. These properties are expressed both in developed and in developing countries, unlike OPV which has reduced efficacy in polio endemic tropical countries. The reason for developing countries not making use of this excellent choice has more to do with policies recommended by the WHO than on science or economics. The cost of production of IPV is only slightly more than that of OPV, but the selling price is exorbitantly high due to the market forces of high demand from rich countries and inadequate supplies even to meet the current requirements. Having reached the verge of global eradication of wild polioviruses using IPV by some countries and OPV by many, including India, the future course is not clear on account of some potential problems of genetic reversion inherent to the nature of OPV. We have difficult choices ahead of us in terms of the risks, benefits and economics of pursuing the current policy or of altering it. If chosen, IPV will perform well – that is one important message of this review.

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