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Study on the effectiveness and impact of pentavalent vaccination program in India and other south Asian countries

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Penta-valent-vaccine is a combination vaccine administered in a 3-dose schedule, offers protection against diphtheria, tetanus, pertussis (DPT), hepatitis B, and *Haemophilus influenza* type B (Hib). The vaccine is widely recommended by WHO and GAVI as a substitute for prevailing vaccination practices against the above mentioned diseases and viruses. The vaccine has met with both positive and negative responses, which leads to uncertainties about the vaccine's safety. The pros and cons of the vaccine are to be evaluated carefully before the same is added to routine immunization schedule.

Dear Sir,

Vaccination has played a pivotal role in the war against diseases since the time they became first available. History shows medical science as the clear victor of this war thus far, having reduced the incidence of many diseases, and controlled and contained the outbreak of many more. Still, increasing population and the wide variety of causative organisms are putting up an ever-rising challenge, pushing for further improvisations and innovations to be made. Out of this need arose the concept of combination vaccines.

The concept of combination vaccines cannot be labeled as recent. The technology has been in use for over 50 y and has proven quite effective. So vast is its potential that it cannot be written off as obsolete. Eliminating the pain and problems involved in the need for multiple injections, considerably reducing the cost involved (**Table 1**) cumulative exposure to preservatives and stabilizers like gelatin,[1] and maximizing the compliance with immunization schedules, combination vaccines are recommended by the American Academy of Pediatrics, American Academy of Family Physicians, and the Advisory Committee on Immunization practices.[2]

But combination vaccines have one major drawback. While they do combine the positives of the individual vaccines, these combinations at times result in unexpected side effects. These side effects may be of major proportions, thereby making the vaccine unfit for administration. Incidents of this nature, which happened in the past, raise questions about the safety of combination vaccines. The need thus is to reach an optimal conclusion. The vaccines have to be analyzed individually, with the only rationale involved in the analysis being experimental evidence and experience.

In this article, we are proposing a review into the pros and cons of one of the most talked-about vaccines, the pentavalent vaccine (PVV). Although this cannot be taken as a typical example on the topic of combination vaccines, this particular combination calls for special attention due to its potential, both positive and negative.

Details and Applications

Launched in 2001 at Guyana by the Global Alliance for Vaccines and Immunization (GAVI), it took WHO another 10 y to introduce the vaccine in India.[3] As the name suggests, the pentavalent vaccine, administered in a 3-dose schedule, offers protection against 5 diseases, viz., diphtheria, tetanus, pertussis (DPT), hepatitis B, and Hemophilus influenza type b (Hib).

Scope and Need

The CDC traveler's health yellow book groups India under "intermediate zone" in the hepatitis B prevalence chart. The hepatitis B virus (HBV) carrier rate in India is estimated at 4.7%, and HBV carrier load between 37.5 and 42.5 million.[4] In a study conducted by WHO, it was found that in the year 2006 alone, there was 2472 cases of Diphtheria, 2587cases of tetanus, and 22 616 cases of Pertussis.[5]

The estimated annual incidence of Hib infection in Indian children (age <5 y) is 50–60 per 100 000 of which 7.6% infected are infants (<1 y of age).[6,7]

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Table 1.

Sl.no.	Vaccine	Cost
1	Pentavalent vaccine	Rs. 500 = $8.10
2	BCG vaccine	Rs. 150 = $2.50
3	DPT	Rs. 250 = $4.15
4	Hib	Rs. 350 = $5.75
5	Hepatitis B	Rs. 200 = $3.25

In a country of 1.20 billion people, more than 15% of whom are children, these statistics are absolutely unacceptable. Along with the ever-present threat raised by HBV, these data clearly indicate that the vaccination practices in use sorely lack efficiency and competence.

India was not alone in this matter. The scenario was similar to this in most developing countries. WHO and GAVI responded by recommending the administration of Pentavalent Vaccine. The vaccine was introduced in India through the National Immunization Program.[3,8] The financial projections cleared the program as economically feasible. It was started as a pilot study in Kerala and Tamil Nadu and so far has been subjected to many studies and clinical trials on safety and efficacy.[9]

Administration

DTP and HBV vaccines comes in liquid form and Hib in lyophilized form. Hib and HBV vaccines are mixed to DTP just before administration together.[10]

Trials and Tests

Although the safety profile of each component is well known and documented, there was virtually no proof on the safety of the combined PVV. Therefore, some trials and subsequent studies were performed in order for the vaccine to be added to routine immunization programs. The first (of many) study was conducted in Ghana, following the introduction of the vaccine in 2002. The study showed that the vaccine was safe and tolerable.[11] Encouraged by the success of the first study, an open, randomized, controlled trial was conducted in Myanmar, and it was reported that PVV has high immunogenicity for all component antigens and some reactogenicity.[12] Similar results were obtained from many studies, which indicated that the safety profile of the combination vaccine is (at least) comparable to that of the component antigens.[13-15] In India, the study conducted by the Serum Institute of India Ltd (SIIL) noted that the common local reactions reported after the administration of the PVV were pain, swelling, and redness (>2.5cm) at the injection, which subsides in 2 d. The common systemic reactions were fever, irritability, and unusual crying. Also, no cases of neurological hypersensitivity or Serious Adverse Effects (SAE) were reported in any infant.[16] These and similar positive results from many countries prompted WHO to release a statement commenting that the combined application of the vaccines does not, affect the efficacy of each of the components in any way.[17]

Rising Shadows

From being celebrated as a potential life saver, PVV suddenly fell out of favor with general public following a series of adverse results. PVV vaccination was even accused of being fatal in some instances. Even though the majority of the claims lacked strong clinically evidence, it caused a general panic among the public.

Negative Reviews

During the 10 y from 2002 (when the PVV was tested in Ghana) to 2012 (when it reached India), the vaccine was tested in some of the other Asian countries.[18] These tests, their results and subsequent analysis had a curious pattern of repetition.

Stage 1: Sri Lanka

PVV marketed by the Dutch company Crucell was implemented in the immunization programs in Sri Lanka from Jan 2008 onwards. Expectations were high after the successful trails, but the results were far from satisfactory. The outcome of the program was dominated by four cases of fatality reported during a period of only 2 mo. Even though the media celebrated it as the fall of PVV, the government stayed strong and continued with the program until 2009.[19] However, the results went from bad to worse, with 5 cases of serious AEFIs (adverse events following immunization) and 20 cases of HHE (hypotonic and hypo-responsive episodes following immunization) forcing the government to suspend the program and cal for an investigation by WHO. However, the break was only brief. The investigative committee report failed to establish any direct link between AEFI and vaccines. The suspension was removed, and the immunization schedule resumed in 2010. But along with it resumed the fatalities, with a total of 14 deaths being reported afterwards.[20]

Stage 2: Pakistan

The involved was Crucell. The program started 7 mo after its launch in Sri Lanka in Sept 2008. Results were not much different, with 3 deaths in Muzaffarabad alone. The vaccine was suspended from use in December 2012. Again, the ban was temporary, with the committee appointed to investigate the deaths reporting that in no case was the vaccine was responsible.[21]

Stage 3: Bhutan

A change in the manufacturers was tried, to the Delhi-based company Penacea. The result was catastrophic. The campaign was suspended in Oct 2009 shortly after its introduction (in September 2009) following 5 cases of serious AEFIs (reported from 10 to 23 Oct 2009). This also included 4 deaths, all within 1–4 d of administration of vaccine.[22]

The authorities reverted to Crucell, and in June 2010 vaccination with PVV of Crucell was started in Bhutan. The pattern was similar to those in Sri Lanka and Pakistan. During its 3 y in use, the vaccine was implicated in 43 cases of serious AEFIs including

27 deaths. Bhutan finally stopped the controversial program following a series of 9 deaths reported within a period of only 4 mo (Dec 2012 to March 2013).[18]

Next stage: Vietnam

With slight changes in numbers and dates, the same pattern was repeated. On May 4, 2013, the Ministry of Health of Vietnam suspended Quinvaxem, the PVV used in that country, after it had caused 12 deaths and 9 non-fatal serious AEs.[23] Skipping the details, let's go straight to India.

Main stage: our backyard

Eager to avoid an episode as in Bhutan, NTAGI in India suggested that the PVV be introduced only in 2 states, and the harms and benefits would be evaluated for one year before it would be rolled out to other states.21 This was the pilot study (in Kerala and Tamil Nadu) mentioned earlier. Encouraging result that the study yielded led the Serum Institute of India Limited (manufacturer and distributer of Pentavac) to extend the program to other states. Goa, Pondicherry, Haryana, Jammu and Kashmir, Karnataka, Gujarat, and Delhi were included in the program.[18]

Within 20 h of the launch of the PVV program on Dec 14, 2011, (by the Central Ministry of Health and Family Affairs), the first death was reported. This was followed by a series of reports on several cases of serious AEFIs including infant deaths. A total of 34 deaths (at least) were reported.[24]

From good to bad

Safety of the vaccine was no longer assured and the program, backed by WHO and the Bill and Melinda Gates Foundation, started to attract criticism from notable sources. Prof. B.M. Hegday (Retired Vice Chancellor, Manipal Academy of Higher Education [Deemed University] Manipal) was the first person who requested (to the secretary of Central Ministry of Health) a detailed study on the reported AEFIs.[25] Doubts on the safety of the vaccine increased further with even the strongest believers, like Dr Jacob Puliel (Head of Pediatrics, St. Stephan's Hospital, Delhi), who was a member of NTAGI that supported the inclusion of PVV in the routine immunization program at the beginning, voicing their concern. In an editorial to IJME, he depicted the current status of the issue and warned not to extend the vaccine to other states without proper studies.[26]

Dark shadow

In truth many academicians and health specialists protested against introduction of PVV in Kerala. As a result, before starting of PVV program, the Kerala government had set up a commission under Dr Noel Narayanan for a detailed study on children immunized with PVV. But a government affidavit to the Delhi High Court suggested that the study was not done in a systematic way.[27] This incident, along with the fact that this combination vaccine is not licensed for use in USA or any developed countries, led to further speculations on the intentions and ethics behind the administration of the vaccine.[26]

Hib vaccine was the only new inclusion to universal immunization program in which DTP and HBV were already a part. The interesting fact is that even after immunization with Hib vaccine, a child may still get pneumonia, meningitis, or flu caused by other bacteria and viruses,[28] given that the vaccine provides protection only against diseases caused by Hib bacteria. In India there is no clear epidemiological evidence for the burden of Hib infection in children, and so there is no real evidence to prove that this combination is unavoidable in routine immunization program.[26,29]

Conclusion

In all cases, the vaccine itself has never been proven to be bad. But the facts such as proven low incidence of invasive disease, absence of benefit from Hib vaccination, and reported deaths cannot be disregarded so easily. While these cases may be due to some reason totally unrelated to the PVV, we cannot totally rule out the possibility of some (so far unidentified) secondary effect of the vaccine having a role in these unfortunate incidents. Much is unknown and unclear on this issue. What is clear is that the vaccine, originally intended to be a lifeline against disease, resulted in the death of almost 100 healthy infants (in an attempt to cure a disease that the child did not even have in the first place). On the other hand, these deaths may also be the evidence of some potential adverse effects of the vaccine which are dormant. If so, to go forward any further would be to throw the future into uncertainty.

In this scenario wherein the safety and tolerance of the vaccine is in serious debate, the uncertainties have to be cleared before any more attempts are made for its administration. To overcome errors and ambiguities in vaccine combinations, improved systems are needed which can enhance the convenience and accuracy of vaccine-identifying information. Further scientific and programmatic research is needed to answer specific questions related to the use of combination vaccines.[30] These and other necessary steps should be undertaken rapidly, clearing the problems circling the vaccine.

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