Connecticut: Yale University Press; 1988.
6. Beecher HK. Ethics and clinical research. *N Engl J of Med*. 1966 Jun;274(24):367–72.
7. Petryna A. *When experiments travel: clinical trials and the global search for human subjects*. Princeton: Princeton University Press; 2009.
8. Hoffman S. Beneficial and unusual punishment: an argument in support of prisoner participation in clinical trials. *Indiana Law Review*. 2009 Feb;33(2):475–515.
9. Williams JR. The Declaration of Helsinki and public health. *Bulletin WHO*. 2008 Aug;86(8):650–651.
10. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS; 2002.
11. Indian Council of Medical Research. Ethical guidelines for biomedical research on human participants. New Delhi:ICMR;2006 Oct[cited 2013 Jun 15]. Available from: http://icmr.nic.in/ethical_guidelines.pdf
12. Allen P, Waters WE. Attitudes to research ethical committees. *J Med Ethics*. 1983 Jun;9(2):61–5.
13. De Vries RG, Forsberg CP. What do IRBs look like? What kind of support do they receive? *Account Res*. 2002 Jul-Dec; 9 (3–4):199–216.
14. Department of Health and Human Services, Office of Inspector General. Institutional review boards: their role in reviewing approved research. Boston: The Office of Evaluation and Inspections; 1998 Jun. Report No.: OEI-01-97-00190. Available from: https://oig.hhs.gov/oei/reports/oei-01-97-00190.pdf
15. Indian Council of Medical Research. WHO-ICMR Summary report: status of ethical review of ICMR funded projects in clinical research/clinical trials. New Delhi:ICMR;2007. p14.
16. Kamath G. Making the grade. *Business World* [Internet]. 2007 November 16 [cited 2011 Jan 2]. Available from: http://www.businessworld.in
17. Brahme R, Mehendale S. Profile and role of the members of ethics committees in hospitals and research organizations in Pune, India. *Indian J Med Ethics*. 2009 Apr–Jun; 6(2):78–84.
18. Petryna A. Ethical variability: drug development and globalizing clinical trials. *Amer Ethnologist*. 2005 May; 32(2):183–197.
19. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalisation of clinical trials. *Nat Rev Drug Discov*. 2008 Jan;7(1):13–14.
20. Sunder Rajan K. Experimental values: Indian clinical trials and surplus health. *New Left Review*. 2007 May-Jun;(45):67–88.
21. Nundy S, Gulhati CM. A new colonialism? – Conducting clinical trials in India. *New England J Med*. 2005 Apr;352(16):1633–6.
22. Ravindran D, Nikarge S. Clinical trials watch. *Indian J Med Ethics*. 2010 Oct–Dec;7(4):259–62.
23. Kahn J. A nation of guinea pigs. *Wired* [Internet]. 2006 March 14 [cited 2013 Jun 3]. Available from: http://www.wired.com/wired/archive/14-03/indiadrug.html
24. Rao M, Rao KD, Shiva Kumar AK, Chatterjee M, Sundararaman T. Human resources for health in India. *Lancet*. 2011 Feb;(377):587–98.
25. Nagarajan R. Indore docs flout clinical trial norms, earn lakhs. *Times of India* [Internet]. 2011 Jun 3:17. Available from: http://articles.timesofindia.indiatimes.com/2011-06-03/india/29616513_1_clinical-trials-quintiles-research-doctors
26. Baader G, Lederer SE, Low M, Schmaltz F, Schwerin AV. Pathways to human experimentation, 1933–1945: Germany, Japan, and the United States. *Osiris*. 2005;20(2):205–31.
27. Ravindran D, Ingle G. Clinical trials in India: the needs of the country and the focus of sponsors. Paper presented at: Third National Bioethics Conference; 2010 Nov 17–20; New Delhi.
28. Sengupta S, Lo B. The roles and experiences of nonaffiliated and non-scientist members of Institutional Review Boards. *Acad Med*. 2003 Feb;78(2):212–18.
29. Anderson EE. A qualitative study of non-affiliated, non-scientist institutional review board members. *Account Res*. 2006 Jun;13(2):135–55.

National Vaccine Policy: ethical equity issues

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Abstract

The ministry of health and family welfare published the national vaccination policy in April 2011. The policy document drew severe criticism from several public health experts. A review of the print and web-based literature on the national vaccine policy was done and the issues of ethics and equity involved in introducing new vaccines under the Universal Immunisation Programme (UIP) were studied.

The average coverage of the UIP vaccines at the national level is below 50%. Despite this, the policy document did not state any concrete strategy for increasing the coverage. The main stumbling block for evidence-based vaccine policy in India is the lack of reliable epidemiological data, which makes it difficult for the National Technical Advisory Group on Immunisation to offer sound technical advice to the government. No attempts have been made to prioritise diseases or the selection of vaccines. The policy suggests the introduction of the following vaccines in the UIP: Haemophilus influenzae type b, pneumococcal vaccine, rotavirus vaccines and human papillomavirus (HPV). This selection is on the grounds of the vaccines' availability, not on the basis of epidemiological evidence or proven cost-effectiveness. This is a critical review of the current vaccination policy and the move to include the rotavirus and HPV vaccines in the UIP.

Introduction

Vaccines are important preventive medicines for primary healthcare, are critical for a nation's health security and play a useful role in public health by reducing morbidity and mortality due to communicable diseases (1-3). Every country should have its own immunisation policy that states how the government proposes to universalise the benefits of immunisation to the large sections of the population which do not receive the basic vaccinations, and also describes how new vaccines are to be selected for introduction in the Universal Immunisation Programme (UIP)(3,4).

The ministry of health and family welfare (MOHFW) published the national vaccination policy in April 2011 (5). This policy was drafted by the National Technical Advisory Group on Immunisation (NTAGI), a government - constituted committee of experts. As for the context and framework of the policy, it states, "The document covers all categories of vaccines used in the UIP, vaccines available but not part of the UIP and those vaccines which are likely to become available in future." (5: p 4) The chapter on ethics and equity stresses, "The ethical use and equitable access to prevention and care should be the basic mantra of any programme meant for ameliorating

disease burden in the country."(5: p 28) The document also suggests the introduction of a few new vaccines in the UIP. When the document was published, it evoked severe criticism from several public health experts.

Methods

A review of the literature was made through a search of the published articles, printed and web-based (Pubmed and Google), on the subject from August 1, 2012 to December 30, 2012. The keywords or phrases used for the search were 'vaccine policy', 'cost-effectiveness', 'ethical issues in vaccination', 'rotavirus vaccine', and 'human papillomavirus (HPV) vaccine'. Various appropriate combinations of the keywords or phrases were also used. The references of selected articles were scrutinised further to access more literature. Only articles published in English from January 2000 to December, 2012, were included in the review (Fig 1). These included both original studies and review articles (print 14+web 43).

Review of vaccine policy and current UIP

A vaccine policy would indeed be a welcome development if it succeeded in giving an epidemiologically sound rationale to the vaccination programme in the country (6,7). Unfortunately the policy draft is non-committal in this respect. It was formulated following judicial prompting by the Delhi High Court during the hearing of a public interest petition that alleged that the newly introduced vaccines (pentavalent) in the country lacked sufficient evidence and asked the government to state its policy on vaccines (4).

The UIP in India is one of the largest in the world, targeting 27 million infants and 30 million pregnant women every year. While Indian manufacturers provide 43% of the global vaccine supply, the average coverage of the UIP vaccines at the national level is below 50% (5). Despite this, the policy document does not put forward a concrete strategy to increase coverage and does not propose any mechanism to improve the availability of vaccines for the remaining 50%, except offering incentives for auxiliary nurse midwives. All doses of the currently included diphtheria, tetanus and pertussis vaccine (DPT) cost less than Rs 15, but the production remains erratic and demand–supply gaps continue. The difference between requirement and supply in 2010–11 was 13.7 million doses for the BCG vaccine and 40.9 million doses for the DPT vaccine (50%) (8).The rapid growth (8%–10% per annum) of India's current vaccine market can be attributed mainly to the new, high-priced vaccines, an abundance of which are combination vaccines and are not part of any national programme (2,6,7). As for the vaccine security of the country under the current UIP vaccines, the document states, "Since there is limited production capacity of vaccines in public sector units (PSU), involvement of private sector manufacture is required to ensure supply of UIP vaccines." (5: p 4). There is no word of revamping the PSUs, which have been closed since 2008, or strengthening the public sector (9). There is a mismatch between the stated national health policy of self-reliance and self-sufficiency in vaccine production; supply remains unaddressed.

Newer vaccines and criteria for inclusion

Vaccines cannot prevent all deaths due to communicable diseases, but rationally selected vaccines can cost-effectively reduce the morbidity and mortality associated with some important diseases which are epidemiologically relevant for the country (2). A well thought-out immunisation schedule must be epidemiologically relevant to the country's health status and only target serious diseases or public health problems for which effective vaccines are available, with others being deemed non-universal (10).

The vaccine policy states, "Diseases which are prevalent in developing countries are often different than the ones in developed countries; majority of the vaccine research is being done in developed countries and focus on the diseases prevalent in those countries."(5: p 5) The target diseases for vaccines and research need to be modified according to our situation. The policy should have elaborated on any serious work being undertaken by the NTAGI on this subject and should have prioritised the diseases for vaccine selection in India, instead of merely copying from the developed countries.

The criteria for selection of vaccines for the introduction of new vaccines in the UIP touch upon disease epidemiology only to the extent of mentioning "Disease burden (incidence / prevalence, absolute number of morbidity / mortality, epidemic / pandemic potential)" (5: p17) and "consideration for pathogen, host and environmental interactions and long-term impact of vaccination on disease epidemiology have simply gone missing"(6). Epidemiological discussions on guiding policy should also consider the burden of a particular disease compared to other health problems, as well as the extent to which the disease can be controlled by vaccination and the possibility of the development of more serious infection due to strain replacement, as happened with Haemophilus influenzae type b (HiB) infection in the West, or age-shifting due to sub-immunisation, as in the case of rubella (6, 11).

One of the main stumbling blocks for an evidence-based vaccine policy in India is the lack of reliable epidemiological data. There are insufficient data on the actual prevalence and incidence of disease, pathogen strain/serotype variations, and immunity with and without vaccination among populations of different geographical regions/age groups (2). The policy lays down certain guiding principles for the identification of vaccines/diseases of local relevance as follows: "based on information derived from strong surveillance system within country. Furthermore, the data from the investigator-initiated researches, from modelling studies, and the data from countries with either geographical proximity or similar demography may also be used."(5:p16) The current level of disease surveillance in India is insufficient to support unequivocal scientific decisions based on established principles of public health. These limitations severely affect the task of the NTAGI, on which the Union Government currently relies for all its vaccination

policy decisions (2). The NTAGI depends on extrapolated data from studies with small sample sizes based on a few hospitals, blood banks in India, or studies carried out abroad for decision-making. The latter confounds the problem and benefits interest groups attempting to push all available vaccines into the national programmes, regardless of the necessity, suitability, cost-effectiveness, safety and sustainability of these vaccines and their bearing on our health priorities (2, 4). Beyond the criteria named for the selection of diseases of public health importance, no attempts have been made to prioritise diseases. Our vaccination policy has suffered a great deal on account of these limitations.

As for vaccines to be included in the UIP, the policy declares that the following factors need to be considered: "safety and efficacy of the vaccine; affordability and financial sustainability of the vaccination programme, even if the initial introduction is supported by an external funding agency; programme capacity to introduce a new antigen, including cold chain capacity; availability of a domestic or external vaccine production capacity; the cost-effectiveness of the vaccination programme and also of the alternatives other than vaccination"(5: p17). Vaccine efficacy and cost-benefit/risk-benefit analysis are relevant only when the need for a vaccine is proven. However, there is no evidence that these points were considered while framing the policy.

The policy stresses the introduction of the following vaccines: Hib vaccines, pneumococcal conjugate vaccines, rotavirus vaccines and vaccines for HPV, the burden of which is estimated to be high, with the vaccine having considerable potential to reduce child mortality. No epidemiological evidence favouring the introduction of any of these vaccines is available from India (4,12). An attempt has been made to incorporate the principles of ethics and equity in the inclusion of newer vaccines by saying, "The new vaccines which are relatively more expensive than traditional vaccines are commonly used by the upper and middle class families through personal resources from the private market. Children of poor families who cannot afford these vaccines are at a disadvantage… The introduction of new vaccines in UIP is an approach to make vaccines accessible to the poor and needy."(5: p16) The committee proposes to include these new vaccines on the basis of availability and their use in other countries, but not on the basis of any evidence from India. Once a vaccine is included in the national programme, the manufacturers secure a huge market in a single stroke for years together, unlike in the case of other medicines (1,2). The introduction of more expensive vaccines sold by private manufactures in the public health system requires a transparent evaluation of the need for the vaccine and the health of the children in the country, and should not focus solely on the viability of the vaccine industry (4,6,12).

The methods used by economically well-off nations to gain control over poor countries by accessing their markets and creating a demand for medical technologies, including vaccines, irrespective of local needs, have been documented extensively (1,7,9,12). When a new product is being prepared, research is published to highlight the number of deaths caused in the country concerned due to the absence of that particular vaccine. The estimates are often outright exaggerated or reflect poor research design. The limitations of such models have been pointed out previously (12-14). In the next stage, after a market presence has been established, the equity argument is brought up. Pressure is brought to bear on the government to bring the vaccine under the UIP with the argument that the well-to-do are protected and it is not equitable that the poor should go unprotected (12,15). These methods are used to influence our vaccine policy as well. The following two ethical issues are also to be considered:

1. As vaccines are given to healthy populations, their safety and the need for them should be thoroughly assessed on the basis of various scientific parameters before they are introduced in a national programme (1, 2).
2. The mere availability of a safe and efficacious /affordable vaccine cannot be a good enough justification for its universal use. Vaccines are not consumer goods and should not be advised unless the need for them is proven on the basis of scientific principles of public health (2).

Financial mechanism for newer vaccines

The vaccine policy also contains guidelines for a financial mechanism for the introduction, production and supply of newer vaccines in the UIP programme (5: pp 10, 29). It comes out openly in favour of public–private partnership (PPP) and advance market commitment (AMC). Under AMC, the government promises to buy a certain amount of vaccine at a given price, even if the efficacy of the vaccine is poor or it has a lower market price, thus guaranteeing the market before its production. If we are being asked to make a long-term AMC before evaluating the utility of a vaccine, this policy needs careful scrutiny (2,4).

The policy mentions several models for financing (5). "..in Pakistan, where the rich kids pay a price for the [typhoid] vaccine that allows it to be subsidised to the poor kids. In Bangladesh, the fishery industry finances the cholera vaccine for the poor. Such models need to be studied and similar ones to be developed for India at least for some vaccines such as pneumococcal conjugate vaccine, rotavirus vaccine and HPV vaccine"(5:p 29). Here again, the policy does not discuss the subject of these essential vaccines (6).

The policy suggests flexible governing and funding mechanisms to support vaccine development in the PPP mode because "It unifies the commitment of public sector to develop products to improve health of the population with the private sectors discipline and culture in business development and marketing." (5:p10). According to the policy, "industry must be provided a channel to voice its opinion, to be utilised in framing policy" (5: p11), which might allow the private partners to influence policy for marketing their interests in the future (4,6). It is even suggested that repositories in public sector institutes and platforms in the Indian Institutes of Technology be augmented to support the vaccine industry, to encourage it

to manufacture vaccines whose risks may not justify their use (4,6). An expert committee on vaccination had earlier cautioned that all measures be taken to ensure that PPPs do not lead to public spending and private profit (4). The proposed model for financing and pricing vaccines on the basis of retaining the interests of the private vaccine industry may be ill-advised.

The Global Alliance for Vaccines and Immunization (GAVI), an international coalition of multiple funding agencies with vaccine manufacturers and non-government organisations, was formed in 1999. It decides on the global promotions of vaccination (11). Pharmaceutical companies promote their agendas by funding or otherwise gaining influence over such funding agencies (12,15,16). The dominance of the Bill and Melinda Gates Foundation in GAVI makes it by far the largest contributor to the vaccination programme. It has business interests in at least nine pharmaceutical majors (6). Representatives from private vaccine manufacturers and industry-funded medical associations/academies must be specifically prohibited to prevent conflicts of interest while formulating vaccination policy (2,6).

Together with prioritisation of private sector funding, these policies may undermine the developing countries' self-reliance in vaccine technologies, while jeopardising the sustainability of their vaccination programmes (17). The policy fails to lay any road map for the revival of public sector capacity in vaccines, except for suggesting that the public sector be managed along the lines of the private sector (6). This aim of such a policy seems to be to not have a policy and to utilise vaccines indiscriminately, with epidemiology taking a back seat. The policy is increasingly determined by the supply "push" by the pharmaceutical companies than the "pull" demand of proven public health needs (4,7).

A critical review of the rotavirus and HPV vaccines

The introduction of newer vaccines into the immunisation programmes in India has been the subject of heated debate in recent years (12,15). While a number of concerns have been identified, the one that receives precedence over the others is that the commercial interest of the vaccine manufacturing lobby often overrides public health interest (2, 4, 6,18-20). The author had previously published review articles on the inclusion of the Hib and pneumococcal conjugate vaccines in the UIP (20,21). This article attempts to make a critical review of the inclusion of the rotavirus and HPV vaccines in the UIP.

Rotavirus—disease problem

Rotavirus infection has a wide range of clinical manifestations, ranging from the absence of symptoms to severe diarrhoea (22). Virtually all children, in the developed as well as developing countries, get infected with rotavirus diarrhoea by the age of three (23). The incidence of the first infection, which is most likely to be symptomatic, peaks between the ages of four to 23 months of age and the severity of the infection decreases with subsequent attacks. Milder cases are easily managed with oral rehydration at home and only the severe cases and some moderate ones may require admission (24).

There are limited data regarding the morbidity and mortality of rotavirus infection and no countrywide data are available yet. On the basis of an analysis of 40 studies in India between 1976 and 1997, the median prevalence of rotavirus in hospitalised cases of severe diarrhoea was estimated to be 18% (IQR 15%–23%) (25). According to the Indian Rotavirus Strain Surveillance Network, rotavirus was found in approximately 39% of hospitalised cases, the incidence being the highest among children aged between 6 and 23 months (26).

In a WHO report which is widely quoted by many authors, it was reported that the case fatality rate of rotavirus infection was 1 in 225, with most of the deaths occurring in the Indian subcontinent (27). The report attributes these figures to studies by the epidemiologist Roger Glass but does not specify which studies these are. The studies by Glass (25, 29) do not mention mortality rates due to rotavirus from India. In a study from the West, the case fatality rate of rotavirus infection over a 10-year period was 0.27% (28). Naturally, an early infection imparts acquired immunity to subsequent rotavirus infection (30). A Mexican study reported that two infections in children provided complete protection (31), and an Indian study reported that three infections provided 79% protection (32).

Rotavirus vaccine

WHO has recommended the inclusion of the rotavirus vaccine in the national schedules of countries where the under-5 mortality due to diarrhoeal diseases is ≥10% (33). Currently, two vaccines are available. These are Rotarix (GlaxoSmithKline), a monovalent vaccine administered in two doses, and Rota Teq (Merck), a pentavalent vaccine administered in three doses, starting at 6–12 weeks of age. Both are given orally (33). An indigenous vaccine, 116E (Bharat Biotech), which is based on human rotavirus of serotype G9P (11), is still under phase 2 trials (33). The data from other developing countries show efficacy of Rotarix vaccine ranging from 17.6% in Mali to 61.2% in South Africa (34).There have been no efficacy trials of the licensed rotavirus vaccines available in India (16,34,37). There is a definite gradient in the efficacy of these vaccines when different regions of the world are compared—the highest is in the USA and it is low in Asia (37-40)**.** A recent immunogenicity trial in India for two doses of Rotatrix has shown a low seroconversion rate of 58.3% (39).

The vaccine policy mentions that the 116 E rotavirus vaccine was developed through effective collaboration between Indian and US academia, as well as partnership between the Indian vaccine industry and the Programme for Appropriate Technology on Health (PATH). Safety and immunogenicity studies of two orally administered human rotavirus vaccine candidates, 116E and I321, were done in India (41).

For the evaluation of a vaccine for public health use, what is more important than its efficacy are the absolute risk of infection, absolute risk reduction (difference between the risk of disease in the non-vaccinated and that in the vaccinated), the number needed to treat (NNT), and number needed to harm. These parameters /statistics also give a better idea of the

cost-effectiveness of a vaccine (42). A multicentric randomised controlled trial conducted in different Asian countries to test the safety and efficacy of rotavirus vaccine RIX4414 (Rotarix TM) yielded the following results (34). The experimental group had 5,263 children and the control group, 5,256. Two children (0.04%) among the experimental and 51 (0.97%) among the control group developed severe rotavirus gastroenteritis in the two-year follow-up period, the efficacy of the vaccine being 96.3% (95% CI 86.0– 99.6%). The actual risk difference for rotavirus infection among the control group was only 0.93% (0.97–0.04), which means that the clinical significance was negligible (34). The NNT to get one extra protection was 214 per year. During the two years of follow-up, severe rotavirus infection was not found to recur among infants from either group. This suggests that acquired immunity develops after the first infection and the rotavirus vaccine is not needed for immunity. Eight (14.9/10,000) and four (7.5/10,000) cases of intussusception (an abdominal surgical problem in children) were reported among the vaccinees and control groups, respectively, and the risk was 7.4 /10,000 more among vaccinees (34). The rotavirus vaccine was first withdrawn from the USA due to the risk of intussusception (35). Following the first dose, the risk was reported to be 1–2/100,000) (43). There are no published reports on the incidence or rates of acute intussusception following rotavirus vaccination in India (16). Post-marketing surveillance data revealed that there had been 13 cases of acute intussusceptions till December 2011, and two cases following RV5 during a five-month surveillance period in India (16). A Cochrane database review reported that the rotavirus vaccine failed to achieve mortality reduction among children (36). The diminished immune response and lower efficacy of oral vaccines in developing countries like India are well known, especially among younger age groups, because of the greater interference of maternal antibodies (16,34,44). This has been shown to reduce the immunogenicity of oral poliovirus vaccine earlier (34).

At present, the rotavirus vaccine is not manufactured indigenously, though some Indian companies are trying to manufacture it in collaboration with foreign companies. Compared to the cost of the primary vaccines included in the UIP, the cost of the routine rotavirus vaccine is prohibitive. The cost of one dose is approximately Rs 770 and immunising all children in India with two doses would require Rs 1925 crore. Considering that the total budget for the UIP in India was Rs 1320 crore for the year 2011–12 (36), this option seems impossible. Though a model-based analysis regarding the public health impact of the rotavirus vaccine in India proved it to be cost-effective (22), a re-analysis showed that the absolute risk reduction is only marginal or negligible for the most vital of events, such as severe infections, death, outpatient visits and admission to hospital (29).

In the industrialised countries of the West, general standards of hygiene and improvement in sanitation led to the virtual extinction of diarrhoea due to bacterial and parasitic disease. This led to a proportional increase in the occurrence of diarrhoea due to rotavirus. Hence, the rotavirus vaccine may have been a public health priority for these countries. However, the same conditions do not apply to developing countries like India, where the rotavirus strains are different and 58% of rotavirus infections are associated with other pathogens (29,36). Almost every child gets rotavirus infection by the age of three years and there is little to worry about if dehydration can be managed promptly. Besides, early infection with rotavirus affords good protection against moderate to severe diarrhoea. The following questions are both scientifically and ethically relevant to guide our policy on rotavirus vaccination (29):

- What is the burden of rotavirus morbidity and mortality in the community setting in India?
- Is it more desirable to encourage the acquisition of natural immunity through mild rotavirus infection while focusing on improving the population's nutritional status and the facilities for prompt management of severe dehydration, especially in the case of children between 2 and 24 months of age?

Many experts have opined that the recommendation for the inclusion of the rotavirus vaccine in the UIP in India should wait (16,33). Its inclusion now would be a mistake (36).

HPV vaccine

Persistent HPV infection may lead to the development of precancerous lesions or severe adenocarcinoma *in situ*. These have a high chance of progressing to squamous cell cancer or adenocarcinoma respectively, within an average of about 20 years (45,46). There are more than 100 types of HPV, of which at least 15 are oncogenic, and most of the HPV infections are cleared by the immune system (46). In some women, the infection persists and some may develop precancerous cervical lesions, though the relationship between infection at a young age and the development of cancer 20–40 years later is not clearly known (46).

In a recent study in India, a cohort of 31,488 women (age 30–59 years) were followed up over eight years. The absolute risk of cervical cancer was 2.5/10,000/year and HPV was detected in only 10.3%, with the prevalence being almost similar across different age groups (47). Even among the 'HPV-positive' women, only 36.7% had lesions of cervical intra-epithelial neoplasia (CIN) grade 1 or higher. This raised questions about the magnitude of the risk arising from HPV infection as far as the development of (pre)cancerous lesions is concerned (47). According to the national cancer registry, the number of cases of cancer of the cervix is predicted to reach 113,138 by 2015 and 123,291 in 2020 (48).

The current HPV vaccines target only two oncogenic strains: HPV-16 and HPV-18. These account for the majority of cancers (46). The currently licensed HPV vaccines—quadrivalent HPV 6, 11, 16, 18 (Gardasil(r), Merck & Co., Inc., Whitehouse Station, NJ USA) and bivalent HPV 16, 18 (Cervarix (tm), GlaxoSmithKline Biologicals, Rixensart, Belgium)—are recommended for the age group of 9–26 years. Three doses of these injections are required to be administered in six months. There is a lack

of conclusive data regarding the length of immunological protection afforded by these vaccines (49).

In the case of HPV, no large field trials have been carried out in India and the data submitted before the licensing authorities for marketing approval of Cervarix and Gardasil in the country are not available in the public domain (18,19,49). Approval for the HPV vaccines in India was based on two trials approved by US regulatory agencies. The trials were conducted on small samples, that for Cervarix consisting of 354 "healthy Indian female subjects aged 18–35 years" and that for Gardasil consisting of 110 "healthy females of 9–15 years of age" (18). The MOHFW, Indian Council of Medical Research, PATH and the state governments of Andhra Pradesh and Gujarat conducted a 'demonstration project' to ascertain the feasibility of the introduction of the vaccine among vulnerable girls in India. In these trials, three doses of the HPV vaccine were administered to 16,000 girls of between 10 and 14 years of age in Andhra Pradesh and Gujarat without monitoring adverse reactions This project was widely criticised for its use of unethical practices that violated all scientific norms (18, 19,49).

If we optimistically assume that the vaccine will prevent every case of cervical cancer, the absolute risk reduction is 0.00025. The number needed to be vaccinated to prevent one death is 4,000 and the cost per life saved can be calculated to be Rs 750 lakh (47,50). Currently, there is no evidence on the number of doses of vaccines / frequency of boosters required for lifetime protection and the prevention of cervical cancer (18,19). This can be determined only through clinical trials and long-term follow-up. No studies with relevant results have been published (51).

Currently, one dose of the vaccine costs Rs 3,000 (approximately US$ 60). Thus, if every 10-year-old girl receives three shots initially (Rs 9,000) and needs a booster shot every five years over the next 40 years, amounting to eight shots in all (Rs 24,000), the total cost would come to Rs 33,000 according to the present estimates (49,50).

Besides, information regarding the protection offered by the HPV vaccine 30–40 years after the primary vaccination is not available from anywhere in the world (53). No cost-effectiveness analyses have been carried out to determine whether the proposed vaccination programme will result in fewer deaths from cancer (54, 55). We must also consider that HPV vaccination is not a substitute for screening for cervical cancer. The expenditure required for screening of one woman does not exceed Rs 80–250 and all women, including those who are vaccinated, are advised to continue to get regular Pap test screening and HPV testing done (18).

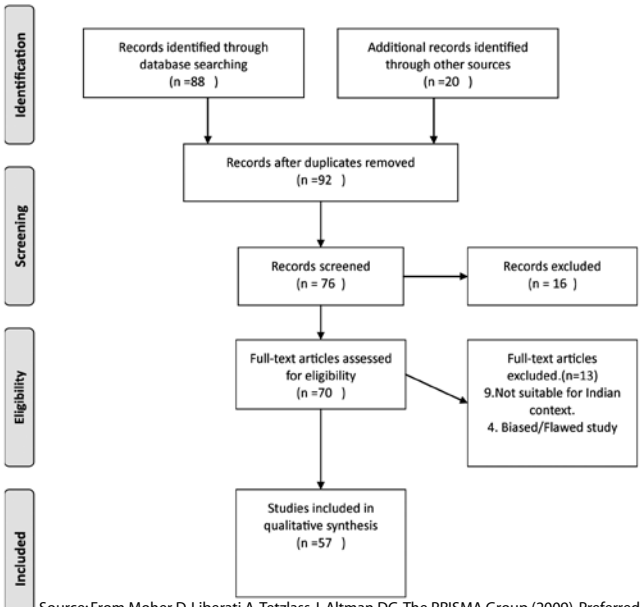
The adoption of more effective measures for the prevention and control of cervical cancer, including better hygiene, early detection through cytology-based screening programmes and the treatment of precancerous lesions, has substantially reduced deaths related to cervical cancer in the developed nations (18, 19,52).

India has several health priorities and the inclusion of the HPV vaccine in the government programme need not qualify among the highest in the list (19,49). Given the unfavourable cost-effectiveness of the vaccine and the present health expenditure of the central and state governments, the cost of introducing the vaccine may not be justified (19,49). In addition, there will be a need to cross hurdles of an ethical, religious, cultural and social nature as well as the vaccine is against a sexually transmitted virus (52). The latest WHO committee on HPV vaccine recommended that further monitoring was needed to learn about the impact of the vaccination on precancerous lesions and cancer of the cervix as the current evidence was insufficient to make decisions related to national-level usages (56).

The additional considerations which must be taken into account are (57): (i) the practical experience from HPV vaccination programmes worldwide has been limited; (ii) there is reluctance to accept a vaccine to prevent a sexually acquired infection that causes cancer only sometimes, and prevents infection only if it is completed before exposure; (iii) vaccination does not confer protection against all causes of cervical cancer; and (iv) an HPV vaccination programme has been rejected by some developed countries for the reasons discussed above (57).

GAVI is the major external funding agency for HPV in India and it has included HPV in its Advanced Market Commitment plan (18). This illustrates how the promotional practices of drug companies, pressure from powerful international organisations, and the co-option of India's medical associations to uncritically endorse a vaccine are influencing public health priorities (18). Therefore, there are several factors that need to be given due consideration before recommending/ prescribing/using HPV vaccines on a large scale in India.

Figure 1: Flow chart



Source: From Moher D, Liberati A, Tetzlass J, Altman DG. The PRISMA Group (2009). Preferred reporting/items for Systematic Reviews and Meta-Analyses. The PRISMA Statement. *PLoS Med.* 6(6): e1000097. doi.10.1371/journal.pmed.1000097

References

1. Madhavi Y. Vaccine policy in India. *PLoS Med*. 2005 May;2(5):e127. Epub 2005 May 31.
2. Puliyel J. Vaccine policy and advance market commitments. *Econ Pol Wkly*. 2011Nov 5;XLVI (44–5):18–19.
3. Bhan A. Ethical considerations in developing a national vaccine policy. *Indian J Med Res.* 2010 Aug;132:226–7.
4. Madhavi Y, Puliyel JM, Mathew JL, Raghuram N, Phadke A, Shiva M, Srinivasan S, Paul Y, Srivastava RN, Parthasarathy A, Gupta S, Ranga U, Lakshmi VV, Joshi N, Nath I, Gulhati CM, Chatterjee P, Jain A, Priya R, Dasgupta R, Sridhar S, Dabade G, Gopakumar KM, Abrol D, Santhosh MR, Srivastava S, Visalakshi S, Bhargava A, Sarojini NB, Sehgal D, Selvaraj S, Banerji D. Evidence-based National Vaccine Policy. *Indian J Med Res.* 2010 May;131:617–28.
5. Ministry of Health and Family Welfare. National Vaccine Policy [Internet]. MoHFW, Government of India. New Delhi: 2001 Apr [cited 2013 May 12]:1–30. Available from: http://mohfw.nic.in/WriteReadData/l892s/1084811197NATIONAL%20VACCINE%20POLICY%20BOOK.pdf
6. Bajpai V, Saraya A. Agenda setting in vaccine policy and social relevance of the emerging vaccine technologies from public health perspective – part 1. *Int J Med Public Health*. 2012;2:7–15.
7. Phadke A, Kale A. Some critical issues in the epidemiology of hepatitis-B in India. *Indian J Gastroenterol.* 2000;19 (Suppl 3):76–7.
8. Dutta AG. What ails Delhi? *Mid-day* [Internet]. 2010 May 31 [cited 2012 Oct 13]. Available from: http://www.mid-day.com/news/2010/may/310510-Delhi-Diphtheria-826-cases-Pertussis-vaccine-scam.htm.
9. Madhavi Y. Vaccine PSUs: chronicle of an attenuation willfully caused. *MFC Bull*. 2008 Jun–Jul;329:1–7.
10. Park K, editor. *Park's textbook of preventive and social medicine*. 19th ed. Jabalpur: Banarsidas Bhanot Publishers; 2007:105–6.
11. Indian Academy of Pediatrics, Committee on Immunization 2005–2006. 4th ed. Mumbai: IAP; 2007 Jan.
12. Lone Z, Puliyel JM. Introducing pentavalent vaccine in the EPI of India: a counsel for caution. *Indian J Med Res*. 2010 Jul;132:1–3.
13. Rao JV, Ganguly NK, Mehendale SM, Bollinger RC. India's response to the HIV epidemic. *Lancet.* 2004;364:1296–7.
14. Hardon A, Blume S. Shifts in global immunization goals (1984–2004): unfinished agendas and mixed results. *Soc Sci Med.* 2005;60:345–56.
15. Puliyel JM, Madhavi Y. Vaccines: policy for public good or private profit? *Indian J Med Res.* 2008 Jan;127:1–3.
16. Indian Academy of Pediatrics committee on immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. *Indian Pediatr*. 2012 Jul:49:549–63.
17. Yamey G. Global Vaccine Initiative creates inequity; analysis concludes. *BMJ*. 2001;322:754.
18. Sarojini NB, Srinivasan S, Madhavi Y, Srinivasan S, Shenoi A. The HPV vaccine: science, ethics and regulation. *Econ Pol Wkly*. 2010 Nov;XLV:27–32.
19. Ramanathan M, Varghese J. The HPV vaccine demonstration projects: we should wait, watch and learn. *Indian J Med Ethics*. 2010 Jan–Mar;7(1):43–5.
20. Jayakrishnan T. Newer vaccines in the Universal Immunisation Programme. *Indian J Med Ethics.* 2011 Apr–Jun;2(2):107–12
21. Jayakrishnan T. Pentavalent vaccine in UIP – a review. *Indian Pub Health Assoc Bull* (Kerala). 2011;2:7–9.
22. Rose J, Hawthorn RL, Watts B, Singer ME. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. *BMJ*. 2009;339:b3653 doi:10.1136/bmj.b3653.
23. Glass RI, Parashar UD, Bresee JS, Turcios R, Fischer TK, Widdowson MA, Jiang B, Gentsch JR. Rotavirus vaccines: current prospects and future challenges. *Lancet.* 2006;368(9532):323–32.
24. Parashar UD, Glass R I. Rotavirus in viral gastroenteritis. In: *Harrison's Principles of Internal Medicine*, 16th edition, Kasper DL, Braun-wald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. New York: McGraw-Hill, Medical Publishing Division; 2005: p 1141–2.
25. Jain V, Parashar UD, Glass RI, Bhan MK. Epidemiology of rotavirus in India. *Indian J Pediatr.* 2001;68:855–62.
26. Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, Naik TN, Mukherji D, Venkatasubramaniam S, Gentsch JR, Glass RI, Parashar UD; Indian Rotavirus Strain Surveillance Network. Multicenter hospital-based surveillance of rotavirus disease and strains among Indian children aged <5 years. *J Infect Dis*. 2009 Nov 1;200 Suppl.1:S147–53.
27. World Health Organization. *Report of the meeting on future directions for Rotavirus Vaccine Research in Developing Countries*[Internet]. *Geneva 9–11 Feb 2000*. Geneva: Department of Vaccines and Biologicals, WHO;2000 [cited 2013 May 12]. Available from: http://whqlibdoc.who.int/hq/2000/WHO_V&B_00.23.pdf.
28. Gil-Prieto R, San Martín M, de Andrés A L, Alvaro-Meca A, González A, de Miguel AG. Hospital acquired rotavirus infections in Spain over a ten-year period (1998–2007). *Hum Vaccin*. 2009 Nov;5(11):748–53.
29. Bajpai V, Saraya A. Agenda setting in vaccine policy and social relevance of the emerging vaccine technologies from public health perspective – Part I1. *Int J Med Public Health*. 2012;2:16–25.
30. Phua KB, Emmanuel SC, Goh P, Quak SH, Lee BW, Han HH, Ward RL, Bernstein DI, De Vos B, Bock HL. A rotavirus vaccine for infants: the Asian experience. *Ann Acad Med Singapore*. 2006 Jan;35(1):38–44.
31. Velazquez FR, Matson DO, Calva JJ, Guerrero L, Morrow AL, Carter-Campbell S, Glass RI, Estes MK, Pickering LK, Ruiz-Palacios GM. Rotavirus infection in infants as protection against subsequent infections. *New Engl J Med*. 1996 Oct 3;335(14):1022– 8.
32. Gladstone BP, Ramani S, Mukhopadhya I, Muliyil J, Sarkar R, Rehman AM, Jaffar S, Gomara MI, Gray JJ, Brown DW, Desselberger U, Crawford SE, John J, Babji S, Estes MK, Kang G. Protective effect of natural rotavirus infection in an Indian birth cohort. *N Engl J Med*. 2011 Jul 28;365(4):337–46.
33. Taneja DK, Malik A. Burden of rotavirus in India--is rotavirus vaccine an answer to it? *Indian J Pub Health Assoc.* 2012 Jan–Mar;56:17–21.
34. Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, Lee BW, Teoh YL, Tang H, Boudville I, Oostvogels LC, Suryakiran PV, Smolenov IV, Han HH, Bock HL. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. *Vaccine*. 2009 Oct 9;27(43): 5936–41.
35. Rose J, Parashar UD. Should India launch a national immunization programme against rotavirus. Yes. Head to head. *BMJ*. 2012 Nov 30:345:e7818.doi:10.1136/Bmj.e7818.
36. Puliyel JM, Mathew J. Should India launch a national immunization programme against rotavirus. No. Head to head. *BMJ*. 2012:345e 7832. doi:10.1136/Bmj.e7832.
37. World Health Organization. Rotavirus vaccines: an update. *Wkly Epidemiol Rec*. 2009;84:533–40.
38. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, Meurice F, Han HH, Damaso S, Bouckenooghe A. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet*. 2007 Nov 24;370(9601):1757–63.
39. Narang A, Bose A, Pandit AN, Dutta P, Kang G, Bhattacharya SK, Datta SK, Suryakiran PV, Delem A, Han HH, Bock HL. Immunogenicity, reactogenicity and safety of human rotavirus vaccine (RIX4414) in Indian infants. *Hum Vaccin.* 2009 Jun;5(6):414–19.
40. PATH, Norwegian Institute of Public Health, CDC and WHO. Proceedings from the 8th International Rotavirus Symposium. Organized by PATH, Norwegian Institute for Public Health, CDC and WHO, Istanbul, Turkey, June 3–4, 2008.
41. Bhandari N, Sharma P, Glass RI, Ray P, Greenberg H, Taneja S, Saksena M, Rao CD, Gentsch JR, Parashar U, Maldonado Y, Ward RL, Bhan MK. Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: results of a randomised controlled trial. *Vaccine*. 2006 Jul 26;24:5817–23. Epub 2006 May 12.
42. Spitalnic S. Risk assessment: relative risk and absolute risk reduction. *Hospital Physician*. 2005 Oct;10:43–6.
43. No authors listed. Rotavirus vaccine and intussusception: report from an expert consultation. *Wkly Epidemiol Rec*. 2011 Jul 22;86(30):317–24.
44. Paul Y. Oral polio vaccines and their role in polio eradication in India. *Expert Rev Vaccines*. 2009;8:35–41.
45. World Health Organization. Human Papillomavirus Vaccines WHO position paper. *Wkly Epidemiol Rec.* [Internet]. 2009 Apr 10[cited 2012 Nov 29];15:118–32. Available from: http://www.who.int/wer/2009/wer8415.pdf 4.
46. Haug C. The risks and benefits of HPV vaccination *JAMA*. 2009;302:795–6.
47. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh

AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA.. HPV screening for cervical cancer in rural India. *N Engl J Med*. 2009;360:1385–94.
48. Time trend of cancer incidence rate 1982–2005.National Cancer registry programme [Internet] ICMR. 2004 Apr[cited 2012 Dec 23]. Available from: http://www.icmr.in/ncrp/cancer_reg.htm.
49. Anjali, Sarojini, Sama, with inputs from various individuals and organisations. Memorandum: Concerns around the human papilloma virus (HPV) vaccine. *Indian J Med Ethics*. 2010 Jan–Mar; 7(1):37–40.
50. Aneja H, Puliyel JM. Selling vaccines: deciding on who can afford HPV. *Indian Pediatr*. 2009;46:647.
51. Sawaya GF, Smith-McCune K. HPV vaccination: more answers, more questions. *N Engl J Med.* 2007;356:1991–3.
52. Somasundaram K. HPV vaccine: end to women's major health problem? *Indian J Med Res.* 2008 Jun;127(6):511–13.
53. Mathew JL. HPV vaccine in the Indian context. *Indian Pediatr*.2009 July;46(7);644–6.
54. Choudhury P. Preventing cervical cancer: pediatrician's role. *Indian Pediatr.* 2009 Mar;46(3):201–3.
55. National Board of Health. Reduction in the risk of cervical cancer by vaccination against human papilloma virus (HPV) – a health technology assessment. Copenhagen: National Board of Health, Danish Centre for Health Technology Assessment, 2007[cited 2013 May 12]; 9:1–14. Available from: www.dacehta.dk
56. World Health Organization. Meeting of WHO human papilloma virus advisory committee – April 2010. *Wkly Epidemiol Rec.* 2011May 27;86(22):221–32.
57. Comeau P. Debate begins over public funding for HPV vaccine. *CMAJ.* 2007;176:913–14.

Innovations in monitoring of adverse drug reactions: the role of a technical advisor

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To undergo treatment you have to be very healthy, because apart from your sickness you have to withstand the medicine. – Molière

Abstract

Adverse drug reactions (ADRs) have ethical implications. These include assessment of the risk–benefit ratio and re-administering informed consent based on the new ADRs identified. The Indian Council of Medical Research ethical guidelines mandate the scrutiny of ADR; and the standard operating procedures of the ethics committee of the authors' medical school endorse this line. However, institutional review board members are often hard-pressed for time and are unable to analyse all the reported ADRs as thoroughly as required. This calls for a dedicated system for the scrutiny of ADRs. This paper seeks to share the experience of development and implementation of a review mechanism for ADR monitoring.

The authors report an innovation in ADR monitoring by appointing a technical advisor on ADR (TA-ADR). During routine assessment, an unusual occurrence of ADRs was noticed from internal and external sites which were related to the study drug, which in turn resulted in the trial being put on hold. This system is being reported here for possible adoption by others.

Introduction

An essential part of the agreed mandate of all human ethics committees is the protection of the human participants. According to the Indian Council of Medical Research (ICMR) guidelines, "an adverse event (AE) or an unexpected adverse drug reaction (ADR) requires expedited review by the ethics committee" (1). ADR monitoring during clinical trials involving investigational new drugs (INDs) plays a critical role in ensuring the safety of participants. In addition, safety monitoring by the ethics committee is important for making an ongoing estimate of risk–benefit, and hence has a bearing on ethical dimensions of the trial as well. If the risk–benefit ratio is found unfavourable, reassessment needs to be done based on the four moral principles of justice, autonomy, beneficence, and non-maleficence and re-administering of informed consent by informing research participants about potential ADRs based on the new problems identified. In spite of this overarching importance of ADRs and safety monitoring, this activity does not receive sufficiently thorough and comprehensive attention and review**.** One of the major reasons for this is the fact that members of the ethics committee have dual affiliations, one with their respective primary departments and the other with the ethics committee. AWHO document titled *Pharmacovigilance in drug regulation* observes that routine review of safety information requires considerable resources, expertise, support and commitment from those involved (2). Too much and uncritical reliance on data safety monitoring boards also dilutes the attention that ADRs deserve.

A systematic evaluation of the ADRs reported by the principal investigators (PIs) as per the norms recommended by the International Conference on Harmonization – Good Clinical Practices (ICH–GCP) (3) and in the format prescribed by the Council for International Organizations of Medical Sciences (CIOMS) (4) and Central Drug Standard Control Organisation (CDSCO), India, (5) is necessary. The ICMR ethical guidelines (1) and the standard operating procedures (SOPs) of the Institutional Human Ethics Committee (IHEC) of the authors' medical school mandate the scrutiny of ADRs.

Against this background, the Institutional Review Board (IRB) conducted a review of the Committee's structure and functions. The report on the review exercise recommended that a technical advisor (TA) on ADR monitoring (TA-ADR)