Agenda Setting in Vaccine Policy and Social Relevance of the Emerging Vaccine Technologies From Public Health Perspective – PART 2

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ABSTRACT

Part 1 has dealt with agenda setting in vaccine policy, the percepts of a scientific vaccine policy. Part 2 of the paper discusses the case of Rota virus and Hib pentavalent vaccines. The background, methodology and the results / conclusions of Part 2 remain along the line for the first Part. The thrust of the paper is to strengthen the case for an epidemiologically guided decision regarding inclusion of new vaccines.

Key words: Vaccine, Pentavalent, Carcinoma cervix, Hib

ROTA VIRUS VACCINATION

Rota virus vaccine has all the trappings of 'a great philanthropic cause' to become the next happening thing in the world of vaccines. Temptation to recommend its co-option in the national immunization program becomes irresistible when the overwhelming weight of scientific evidence attests to its efficacy.

The Cochrane group published a review of 34 randomized control trials of Rotavirus vaccines that included 175,944 participants to evaluate the most common rotavirus vaccines in use – Rotarix, Rota Teq and Lanzhou Lamb Rotavirus (LLR), for prevention of rotavirus diarrhea.[1] The review included 26 trials (99,841 participants) of Rotarix (the most commonly used vaccine in India) and 8 trials (76,103 participants) of Rota Teq vaccine.

It was found that compared to placebo, both Rotarix and Rota Teq vaccines effectively reduced rotavirus diarrhea while also reducing the frequency of all cause severe diarrhea, hospitalizations and cases requiring medical attention. Effectiveness was continued to be observed even at one and two years follow-up. There was no difference between the vaccines and the placebo in the number of adverse events like deaths and reactions to vaccine.[1]

The authors concluded that – "Rotarix and Rota Teq are effective vaccines, and support the World Health Organization's recommendation to include rotavirus vaccination of infants into national immunization programs, especially in countries with a high burden of diarrheal deaths in children younger than five years."[1]

On face of it, these findings would make an open and shut case for straight away inclusion of Rotavirus vaccination in the National Immunization Program (NIP). However, the scheme of considerations for inclusion of a vaccine in

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NIP drawn out in Part 1 of the paper compels us to have a closer look at the whole picture.

As regards the data analysis, for example the section on efficacy outcomes for Rotarix vaccine mentions – "Rotarix reduced rotavirus diarrhoea by 72% at up to one year (RR 0.28, 95% CI 0.17 to 0.48; 11,121 participants, six trials) and 67% during the second year of follow-up (RR 0.33, 95% CI 0.21 to 0.50; 7293 participants, five trials)."[1]72 % and 67 % in themselves appear as very impressive reduction in risk of rotavirus diarrhea, except that this relative risk reduction rather than (Absolute Risk Reduction) AAR.

Time line of important developments regarding Rotavirus vaccination

The report of the 'Meeting on Future Directions for Rotavirus Vaccine Research in Developing Countries, Geneva 9–11 Feb, 2000', sponsored by Children's Vaccine Program of the Bill and Melinda Gates Foundation informs that prevention of rotavirus disease was listed as one of the goals of the 'Program for Control of Diarrheal Diseases' of WHO in 1979. The Institute of Medicine (IOM) of the CDC in the U.S. declared development of rotavirus vaccine to be a high priority for the developing countries in 1985. Nothing much happened for the next one decade. In 1996, a report prepared under the chairmanship of Dr Tore Godal for the WHO and other agencies, listed rotavirus as a "best buy" for the developing countries.[2]

In 1996, due to dearth of good epidemiological data on rotavirus and the need for disease burden research in the U.S., the IOM issued another report that claimed that rotavirus was not a high priority for prevention in the United States.[2] The fact that epidemiological data on rotavirus was found wanting in 1996 even in U.S where it is a leading cause of diarrheal disease, raises doubts about estimates of rotavirus diarrhea in the developing countries.

WHO recommended in 1997 that further studies be carried out to determine the disease burden of rotavirus and efficacy trials of rotavirus vaccines be conducted in Asia and Africa; as also the need to design surveillance that could be used to evaluate vaccines once introduced.[2] The first rotavirus vaccine 'Rotashield' was recommended by the 'Advisory Committee on Immunization Practices' of the U.S to be administered to all infants in routine immunization and licensed by USFDA in 1998. These developments enthused W.H.O, IOM, GAVI and PATH (Program for Appropriate Technologies in Health), who viewed delays in the introduction of rotavirus vaccines as "morally indefensible, as the majority of disease burden and mortality preventable by these new vaccines are in poor developing countries."[3]

CDC, WHO and their industry partners organized a workshop in Feb 1999 in Bangkok to establish the Asia Rotavirus Surveillance Network. The straight forward message to the participants in the workshop was – "with a newly licensed rotavirus vaccine available, regional decision makers would first and foremost require updated rotavirus disease burden data to evaluate the vaccine's potential use in their locality". By early 2001 nine countries - China, Hong Kong, Indonesia, Malaysia, Myanmar, South Korea, Taiwan, Thailand, and Vietnam, were members of this surveillance network.[3] India was a notable absentee. First results from the network were not available until May 2002. WHO report on 'Future directions for rotavirus vaccine', Feb 2000 presents worrisome data on the burden of rotavirus disease in India.

It was said that "approximately 111–135 million cases of rotavirus infection occur each year, leading to 650 000 deaths (or about 1 in 225 children). Most deaths occur in the Indian subcontinent and sub-Saharan Africa and, to a lesser extent, South America."[2] The report attributes these figures to Dr Roger Glass, but in the absence of any references in the report to the studies by which these estimates have been arrived at, it is not possible to comment on the methodology by which these figures have been possible. Nevertheless, they do present an alarming picture of rotavirus disease burden in India.

Meanwhile, based on the preliminary results of the efficacy trials of the rotavirus vaccine in Africa and Asia, the WHO has recommended the inclusion of rotavirus vaccines in the national immunization programs of these countries in 2009[4] and the rotavirus vaccine was set to be launched in the some of the most vulnerable countries as early as 2010.[5]

The aforementioned sequence of events makes it obvious that rotavirus diarrhea was not a public health problem that was articulated first by the developing countries themselves and almost certainly they were not involved in the rotavirus vaccine initiative. However, in the industrialized West where the general standards of hygiene and sanitation have ensured that other (bacterial and parasitic) causes of diarrheal disease have become virtually extinct, rotavirus diarrhea is the predominant cause of diarrheal disease. Hence, rotavirus vaccine may have been a public health priority for these countries, but

that same is true for developing countries and India needs further examination.

Rotavirus epidemiology

Prominent features of rotavirus epidemiology are:

- Virtually all children in the developed as well as the developing countries will get rotavirus diarrhea by the age of three.[6]
- Though the predominant mode of transmission is through feco-oral route, transmission through respiratory secretions, person to person transmission and through contaminated surfaces of objects is also known; for these reasons it is presumed to be less amenable to improvements in hygiene and sanitation.[7]
- Severe vomiting is a prominent feature of the clinical triad of fever, vomiting and diarrhea, oral rehydration therapy becomes difficult in severe cases, setting dehydration early.[8],[9]
- Not all cases of rotavirus infection get severe diarrhea. Rotavirus infection has a wide range of clinical manifestations – from asymptomatic to severe diarrhea.[10] The first infections are most likely to be symptomatic. Rotavirus diarrhea incidence peaks between the ages of 4 to 23 months of age and the severity of infection is reduced with subsequent infections. Rotavirus infection is relatively rare among older children and adults. Only the severe cases and some moderate ones may require admission. Milder cases can be easily managed with oral rehydration at home.[11]
- In tropical countries rotavirus diarrhea occurs all the year round, while in the temperate countries the incidence is higher in winter.[11]
- Unlike anti-microbial therapies for other diarrheas, there is no specific therapy for rotavirus diarrhea.[7] However, "standard oral rehydration therapy is successful in most children who can take oral fluids…… Intravenous fluid replacement may be required for patients who are severely dehydrated or are unable to tolerate oral therapy because of frequent vomiting."[11]
- Because of these features it is believed that in areas where access to medical facilities is less, mortality due to rotavirus may be high and that "there is wide agreement that effective vaccination represents the most promising prevention strategy against the disease."[12],[13]
- While the prevalence of rotavirus infection may be the same for both the developed and the developing countries, the overwhelming weight of rotavirus mortality lies in the developing countries and principally among the poor in the latter. The relative proportion of rotavirus disease among severe diarrheas has increased due to decline in bacterial and parasitic diarrheas with improvements in sanitation and hygiene.[14]
- An early infection imparts good immunity to subsequent rotavirus infection.[15] A Mexican study demonstrated that a single rotavirus infection could provide protection against the more severe forms of the disease, while two infections provide complete protection against moderate and severe disease.[16] Impact of malnutrition on the outcomes in rotavirus diarrhea is equivocal. Some studies show that malnutrition is more frequently associated with outcomes like severe diarrhea or death,[17],[18] while some other studies show that malnutrition has no particular effect on the outcomes.[19–22]

Rotavirus burden of disease

In 2009 Parashar *et al.* examined the results from seventy six studies from across the world, published between 1986 and 2004. These studies examined the prevalence of rotavirus in severe diarrhea cases among inpatients. The studies were classified into five groups (A to E) on the basis of WHO classification of countries by levels of child mortality and region. The country specific estimates of rotavirus deaths in each country of the group was calculated by multiplying the mean proportion of hospitalizations due to rotavirus diarrhea in each group with the WHO estimates of deaths in less than five years age group due to diarrhea in each country. The study admits that in the absence of reliable data on the etiology of deaths due to diarrhea, the authors have presumed that the etiology of admissions due to severe diarrhea is representative of the etiology of deaths due to diarrhea. For the countries for which reliable data is not available, the country specific estimates have been derived by projecting the data of countries with similar income levels.[23]

In this study the number of rotavirus associated deaths due to severe diarrhea in India stands at a whooping 122, 270 per year. Another interesting observation is that over the years the mortality due to rotavirus diarrhea has been waxing and waning by huge margins even though the overall mortality due to severe diarrhea worldwide has decreased from 3.2 million in 1986 to 1.56 million in 2009.[23] The estimates for rotavirus diarrheal deaths across

the world over the years have varied thus – 873,000 in 1986,[24] 440,000 in 2003,[25] 611,000 in 2006[7] and 527,000 in 2009.[23] Such huge fluctuations in the number of deaths due to rotavirus diarrhea over the years inspite of nearly 50 % decline in the overall mortality due to severe diarrhea between 1986 and 2009 reflects the rather weak quality of data based on which these projections were made. Yet, these figures have so often been quoted by various experts and multilateral agencies to push inclusion of rotavirus vaccines in the immunization schedules around the World. The 2009 study by Parashar *et al.* had only 20 studies from the high or very high mortality countries of Asia and Africa. While the minimum number of children included in each study was 100, the total number of children covered in the studies is not mentioned. This leaves much to be desired as to the comprehensiveness of the estimates made in the study.

Burden in India

In 2001 a paper on "Epidemiology of Rotavirus in India" authored by Vivek Jain, Umesh D. Parashar, Roger I. Glass, and Maharaj K. Bhan was published in Indian Journal of Pediatrics. Of these, two authors Roger I. Glass, and Maharaj K. Bhan had been participants in the 2000 meeting organized by W.H.O on 'Future directions for rotavirus vaccine'. This paper provided the burden of rotavirus disease in India based on the analysis of some 40 studies published between 1976 and 1997. The median prevalence of rotavirus in hospitalized cases of severe diarrhea was found to be 18 % (inter quartile range 15–23 %).[26] Mortality rates among these proven cases of rotavirus diarrhea in different studies have not been mentioned in the paper.

The burden of rotavirus mortality in India has been calculated thus - given a below five years mortality rate of 105 per 1000, a total of 2,590,000 under five deaths occurred in India in 1998. "According to World Health Organization estimation approximately 21% of under-5 deaths in India are attributable to severe diarrhea, leading to an estimate of 544,000 diarrheal deaths in children under five. Based on the finding that rotavirus was detected in a median of 18% of children hospitalized with diarrhea and assuming that this proportion is similar to the percentage of diarrhea associated deaths attributable to rotavirus", the authors estimate that "in 1998, rotavirus caused approximately 98,000 deaths in India."[26] Apparently then between 1998 and 2009 the number of deaths due to rotavirus in India increased by 24,270 (refer to the number of rotavirus deaths in India in Parashar *et. al.* mentioned earlier) inspite of an overall decline in total number of deaths due to severe diarrhea. Case fatality due to rotavirus diarrhea changes over time due to "improvements in health care access, nutrition, poverty alleviation programs, etc."[27] It would be reasonable to presume the same for India as well.

In both studies by Parasher *et al.* and Jain *et al.*, the case fatality of severe rotavirus diarrhea has been supposed to be the same as the prevalence of rotavirus cases among severe diarrhea cases. However, no convincing argument has been given to justify this assumption, except probably the reason that there are no community based studies available that have measured the case fatality rates among severe rotavirus cases. The problem is that once a high burden of disease is so established, it is unquestioningly taken as given by the subsequent studies and the need for empirical evaluation of disease burden through well designed population based studies is lost in the high decibel campaign for the introduction of new vaccines.

The few estimates of rotavirus case fatality from the community based and from the hospital based studies show that case fatality due to rotavirus is highly varied and much less than the incidence rates. A study investigated an epidemic of diarrhea in December 2000-January 2001 in the tribal dominated Jawhar area of Thane district in Maharashtra. Rotavirus was isolated from the stool of 70 % of the hospitalized cases. Case fatality among the 490 cases was only 4%.[28] In a study of hospital acquired rotavirus infection over a ten year period from 1998–2007, the case fatality was 0.27 %.[29] A European study on rotavirus surveillance in some Eastern European countries showed that case fatality due to acute gastroenteritis (all cause) ranged between 0 to .5% in the absence of rotavirus vaccination.[30] On the other hand case fatality in hospital based study of rotavirus gastroenteritis in Guinea-Bissau was as high as 8 %.[31]

These varied outcomes underline the need to have more accurate information on case fatality in India in order to make a informed decision on introducing rotavirus vaccine; especially as case fatality has very direct bearing on the cost-effectiveness of the rotavirus vaccine program – the higher the case fatality, the more the cost-effectiveness.[27]

Implications of these findings for rotavirus vaccination

Both the aforementioned papers by Parasher *et. al.* and Jain *et. al.* argue for the inclusion of rotavirus vaccine in the immunization schedule. Jain *et al.* state - that there is an "urgent need for safe and effective interventions against rotavirus such as vaccines. The significant diversity

of rotavirus strains and young age of hospitalization pose unique challenges to the formulation of a rotavirus immunization program in India, but raise the possibility of utilizing a neonatal vaccine to provide effective coverage."[26] In view of the fact that the last author of this paper Dr M K Bhan later became the Secretary of the Department of Biotechnology, Government of India; the observations made in this paper become very influential for policy. Besides, the IAP (Indian Academy of Pediatirics) Committee on Immunization has reiterated its support for Rotarix vaccine manufactured by Glaxo Smith Kline.[32]

Desirability of rotavirus vaccination

At present the rotavirus vaccine is not manufactured indigenously, though some Indian companies are trying to manufacture it in collaboration with foreign companies. The cost of routine rotavirus detection in children with severe diarrhea as also the vaccine are prohibitive compared to the cost of the primary vaccines included in UIP. Cost ranges from $7.50 per dose to more than $100 per dose;[33] though GAVI's largesse is offered as an assurance, as though aid can stand a guarantee for sustainability of a program. There is considerable variation in the rotavirus strains between those prevalent in the West and in India, as also those prevalent across India. This means that rotavirus vaccine has to be specific to the locally prevalent strains. Besides, vaccine trials in different countries, as also its routine administration in U.S have had to be stopped because of association with intussusceptions. These facts argue for extreme caution and widespread field testing of the vaccine.

The preliminary results of trials of oral rotavirus vaccines from low income countries of Asia and Africa suggest that "they may not work as well."[33] Maternal antibodies present in the breast milk and stomach acid may lower the titer of the vaccine virus in oral live attenuated vaccines by destroying some of it.[33]

The moot point is what is likely to be the specific advantage of the vaccine over what can be achieved through strengthening peripheral health services for administering intravenous fluids to severe diarrhea cases? This can be achieved by training the peripheral health workers and will also lead to strengthening of the health services. The need is for carrying out well planned operations research and cost effectiveness studies for such a strategy.

Cost effectiveness studies

Johnie Rose *et al.* carried out a model based study to "examine the public health impact of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in a birth cohort in India, and to estimate the cost effectiveness and affordability of such a programme." Calculations showed that vaccine would cost Rs 8023 per life year saved and the net cost of rotavirus vaccination program would be 11.6% of the total budget of MOHFW for the year 2006–07.[34] The mathematical model developed by the authors does not include the costs due to numerous factors such as the opportunity costs to the patients, possible increase in public health costs due to strain replacement, costs in terms of possible adverse impact on routine immunization, cost of adverse events following immunization and numerous other factors discussed in Part 1 of the paper that do not lend themselves to straightforward monetary equivalent; still the authors opine that this would be a *cost effective program* (emphasis ours).

Based on the assumptions made, the authors report the expected clinical events and use of health services related to rotavirus infection in a simulated follow up of a birth cohort of 100,000 Indian infants followed for five years under strategies of no vaccination and vaccination with RIX4414, as given in table 1. The figures for ARR have been calculated by us by calculating the difference in risk for different events in the vaccinated and the non-vaccinated infants.

Part 1 of the paper had discussed the significance of expressing the risk benefit outcomes in terms of ARR rather than RRR. We can clearly see from table 1 that even as the relative risk reduction in occurrence of different events is indeed impressive, the ARR is only marginal or negligible for the most vital of the events – severe infections, deaths, outpatient visits and admissions to hospitals. ARR for deaths and admissions to hospitals is a negligible .16 and .8 per cent respectively and is only 7 per cent for both severe infections and outpatient visits; meaning thereby that for the most vital of the outcomes that are often cited as the rationale for introduction of rotavirus vaccine, the real impact of vaccination on disease morbidity and mortality and the treatment costs is least encouraging. Most importantly, a mention of adverse effects has gone missing from the clinical events; as also in the cost-benefit analysis.

Further the authors state that vaccination will cost Rs 8,023 per life year (not per life) saved. One need only reflect on the recent widely publicized Planning Commission affidavit filed in the Supreme Court that stated that Rs 25 constitutes adequate "private expenditure on food, education and health." This means a per capita

Table 1: Benefits in clinical risks and use of health services reported by Johnie Rose *et al* in their model based assessment of the cost effectiveness of RIX4414 rota virus vaccination program for Indian infants.

Clinical events per 100,000 children	No vaccination	Vaccination	Change (%)	ARR (%)
Any infection	278,672	253,657	−25,015 (−9.0)	25
Asymptomatic infection	181,164	185,092	3,928 (2.2)	−4
Symptomatic infection	97,508	68,565	−28,943(−29.7)	29
Severe infection	18,260	11,279	−6,981 (−38.2)	7
Deaths	398	235	−163 (−41.0)	0.16
Use of health services per 100,000 children				
Home treatment with oral rehydration solution	73,221	52,191	−21,030 (−28.7)	21
Outpatient visits	21,582	14,405	−7,177 (−33.3)	7
Admissions to hospitals	2,367	1,555	−812 (−34.3)	0.8

Source: Johnie Rose *et al*[10]

Note: The change in the event of interest has been reported by Johine *et al.* in terms of relative risk reduction. The ARR has been calculated by authors and was not mentioned in the original source. It is calculated as a difference between the probability of an event in the non-vaccinated and the vaccinated.

consumption expenditure of Rs 9,125 in a year. Taking this and the ARR for severe infections, deaths and hospital admissions with rota virus vaccination together, we would rather suggest that the Rs 8,023 that vaccination would cost to save one life year can be better utilized to save many more lives lost due to preventable intestinal infections by providing safe drinking water.

Further, the total outlay for MOHFW for the year 2005–06 was Rs 9332 crores (Approx. 2, 121 million dollars).[35] Of this amount a measly Rs 507 crores (US dollar 115 million), at 5.4% of the total budget, was devoted to routine immunization. Compared to this the outlay for the pulse polio program was Rs 877 crores (dollar 199.3 million approx.), at 9.4% of the total budget. The cost of a rotavirus vaccination program at an allocation of 11.6% of the budget would amount to a punishing sum of Rs 1, 082 crores (dollar 246 million). Actual cost would turn out to be much more because we know by experience that whenever special immunization programs are launched with such enthusiasm, the fate of routine immunization goes for a toss; pulse polio being a case in point.

Guide to further action

In rotavirus infection if dehydration can be managed promptly, there is little to worry. Besides, early infection with rotavirus affords good protection against moderate to severe diarrhea. Almost every child gets rotavirus infection by the age of 3 yrs.[6] Answers to the following questions are required to guide our policy on rotavirus vaccination:

- What is the burden of rotavirus morbidity and mortality in community setting in India?
- What proportion of children less than two years of age are likely to develop severe diarrhea upon first infection of rotavirus, this being the most vulnerable group.
- Can children < 2 yrs with severe diarrhea be managed for dehydration in community setting / at peripheral health centers?
- What is the relationship between underweight babies / malnutrition and rotavirus diarrhea outcomes in India?
- Is it more desirable that a mild rotavirus infection affords a natural immunity to the population while the focus is on improving the nutritional status and facilities for prompt management of severe dehydration, especially in children between 2–24 months of age?
- What will be the impact of rotavirus vaccine on the immunization with the six primary vaccines?

These questions cannot be answered through a set of statistical assumptions. We need to institute sincere studies and operations research to answer them. Time spent and the cost incurred on this will only be a fraction of what it might cost to blindly step into yet another ill-advised vaccine trap. Such costs can hardly be measured sufficiently in purely economic terms.

HAEMOPHILUS INFLUENZAE TYPE B (HIB) VACCINATION

There has been much animated debate for and against the Hib pentvalent vaccine off late that has queered the pitch

for its inclusion in the vaccination schedule. As in the case of Rotavirus vaccines the weight of the scientific evidence generated through the gold standard of Randomized Control Trials of the vaccine suggest that it could possibly be included in the immunization schedule.

The Cochrane group published a review (including 6 RCTs) and a meta-analysis of 4 of these RCTs covering a total of 210,178 participants in 2007.[36] The review included "all randomized controlled trials (RCTs) or quasi-RCTs of conjugate H. influenza type b vaccines compared with placebo or no treatment in children who were followed until at least two years of age"; among the objectives of the study were to determine the efficacy of conjugate Hib vaccines in preventing the Hib infection and death in children less than five years of age.[36]

The review concluded that "Hib vaccine is safe and effective in preventing invasive Hib disease. The findings of RCTs suggest an 80% reduction in Hib invasive disease, although the size of the effect could plausibly be anywhere between a 46% and 93%."[36] These again are relative risk reductions and not the desired ARR, while NNT and NNH that have simply not been accounted for in this Cochrane review. The included studies did not reveal any statistically significant impact on Hib related mortality. Overall, the local burden of disease, cost of vaccine and the cost-effectiveness of vaccine delivery were the factors suggested to guide usage of vaccine in "resource-poor settings".[36]

This review did not include any study from India. Moreover, another important thing to bear in mind about the results of RCTs is that they may just be too good to be true in the real life conditions and may not take into account many clinical and non-clinical factors. In the light of these results we shall proceed towards a more comprehensive discussion on Hib vaccine in light of the scheme laid out in Part 1 of the paper.

The bacterium Haemophilus Influenzae type b (Hib) is an established cause of bacterial meningitis among infants and young children and of pneumonia in children less than five years of age.[37] WHO estimates suggest that between 400,000 to 500,000 deaths in children under five years of age are caused by Hib infections world over annually.[38] There exists a conviction that the morbidity and mortality due to Hib can be drastically cut through universal immunization against the disease.[39–42] The 'Subcommittee on Introduction of Hib Vaccine in Universal Immunization Program' constituted by the 'National Technical Advisory Group on Immunization in India' (NTAGI) "strongly recommended that Hib vaccine should immediately be introduced in India's UIP". Prior to this recommendation recognizing that *"it is the poorest children that are most at risk"* (emphasis ours), the Indian Academy of Pediatrics recommended Hib vaccine for routine use in India. Hib vaccine is to be introduced as an oral pentavalent vaccine in combination with the vaccines for Diphtheria, Pertusis, Tetanus and Hepatitis B.[43]

Rates of pneumonia due to Hib have been estimated to be 2 to 5 times higher than Hib meningitis, though meningitis is the most serious consequence with high case fatality. Claims are that countries using Hib vaccine have virtually eliminated the infection, while it continues in countries not using the vaccine.[43]

The votaries of Hib vaccination in India have cited many hospital based studies from different centers to show that Hib is responsible for significant proportion of cases of bacterial meningitis[44–52] and pneumonia[53–55] in children below 5 yrs of age. Case fatality in Hib meningitis ranges between 20 to 29 %.[46–48],[56] Overall case fatality in invasive infection due to Hib has been reported to be 16 %.[10] Neurological sequelae like seizures, hearing loss, developmental delay or mental retardation have been reported with Hib meningitis.[48],[51],[57] On the basis of systematic analysis NTAGI (National Technical Advisory Group on Immunization in India) estimated the "burden of Hib disease in India in 2000 to be about 2.4 million cases and 72,000 deaths in children <5 years of age, accounting for approximately 4% of all child deaths in India.[43]

However, most of the studies quoted above do not give an idea of the prevalence of Hib infection in the general population, and with the exception of three studies on nasopharyngeal carriage, the rest have very small sample sizes ranging from 51 to 132.[43]

Detractors of the initiative to include Hib pentavalant vaccine in the immunization program have instead pointed out to the studies sponsored by the WHO to show that the incidence of Hib in India is not as much as is projected.[58] As against studies quoted by NTAGI, which with the exception of one study were all done prior to or in 2000; studies sponsored by WHO were done between 2000 and 2010 and were more systematic in their approach to the problem of Hib infection in India.[59] In pre 1998 studies showing pre-vaccination data the Asian studies have been shown to have very low prevalence of invasive disease (3–9/100,000) vis-à-vis an American and a Gambian study which had invasive disease to the extent of 500–1000/100,000.[58]

Particular point of contention was the fact that NTAGI ignored the results of a multi-centric study done by ICMR to establish the prevalence of Hib invasive disease in India, from July 2005 to Dec 2006.[60] Results of this study did not support NTAGI's recommendation of including pentavalent Hib vaccine in EPI. Importantly enough this led to a review of NTAGI's recommendation.

Issues concerning Hib vaccine

Safety and efficacy issues

In recommending the pentavalent Hib vaccine NTAGI has said that the vaccine is safe, efficacious in preventing the infection, induces high immunogenicity and leads to a good herd immunity. Availability of vaccine has also not been viewed as a problem because of its production within the country. Studies from other countries have been quoted to allude cost-effectiveness for Hib vaccine. NTAGI report does not quote any study on cost-effectiveness of the vaccine in India. A personal communication of 2008 from one Ms Ulla Griffiths and price trends of vaccines have been cited to express a hope that the vaccine is likely to be cost-effective in India.[43]

Contrary to NTAGI's position, the detractors of Hib vaccine have pointed out the results from probe studies done in Asia to show that the vaccine does not reduce the burden of disease appreciably compared to placebo.[61] Reference has been made to the role of GAVI, WHO, USAID, John Hopkins and the Hib Initiative in misleading the people about the efficacy of the vaccine.[61],[62] There are no well planned efficacy or cost-effectiveness studies from India yet, to support or refute the efficacy of the vaccine.

What is intriguing is the fact that the expert opinions like – "the lack of local surveillance data should not delay the introduction of the vaccine especially in countries where regional evidence indicates a high burden of disease", that are handed down by WHO have served as a fiat accompli for advisory groups like NTAGI while making their own recommendations regarding Hib vaccine.[43]

Among the more serious aspersions against the vaccine are the reports of deaths subsequent to vaccination in Sri Lanka, Bhutan and Pakistan.[58],[63] WHO expert panel that investigated the vaccine related deaths in Sri Lanka, went to the extent of altering standard WHO classification of adverse effects following immunization (AEFI) to facilitate re-introduction of vaccine after the deaths.[64] W.H.O defended the change in classification on the plea that "the independent experts were free to make up their own classification."[64] The point however is – why is their discretion so sensitive to the interests of the drug companies? Ostensibly, both the NTAGI and the 'Core Committee on Immunization' of the ICMR failed to appraise the government of these important developments.[58]

Strain replacement and the vaccine trap

What a vaccine does to the epidemiology of the other diseases with similar mode of transmission is an important consideration in assessing the suitability of a particular vaccination. Detractors of Hib vaccination have pointed out that in countries like Canada where Hib vaccine has now been given for about two decades Haemophilus Influenzae type b has been replaced with other strains of the bacterium.[58] What this portends in terms of the long term consequences of the vaccine is not known as yet; hence, countries where Haemophilus Influenzae has been nearly eradicated are in a bind over withdrawing the vaccine even though they are free from the bacterium.[58] They are caught in a vaccine trap - if the vaccine is withdrawn then their populations may be liable to more severe attacks of invasive Hib disease in the absence of herd immunity afforded by natural infection. Vaccine detractors opine that the predicament being faced by these countries can serve as a learning opportunity for countries like India.[58]

Backdoor entry into vaccination program

It is already pointed how the new and expensive vaccines are sought to be imposed on people by making them ride piggyback on the primary vaccines in the form of combination vaccines. Pentavalent Hib vaccine is one more such combination which has been described as a "Solution in search of problems."[65] Moreover, meta-analysis has shown that pentavalent vaccine is not as effective immunologically as are the individual vaccines.[64] The expert panel that was asked to review the decision of NTAGI on Hib vaccine has ratified its recommendation and GAVI had been ready with a grant of $ 165 million to unpack the pentavalent vaccine drive to cover around 10 million children in 28 states in 2010,[66] though the same has not started yet. The big question is whose fate hangs by the thread – that of the vaccine or health of the people?

CONCLUSION

The discussion in this paper delineates the forces and the interests we need to watch out for in deciding on the

social relevance of the emerging vaccine technologies. The results of the efficacy trials of the vaccines discussed here leave much to be desired. Instead of unequivocally demonstrating the benefit of the vaccines in terms of absolute risk reduction (ARR), numbers needed to treat (NNT) and numbers needed to harm (NNR, to assess the impact of vaccine adverse events), the actual impact of the vaccines is sought to be enhanced by presenting figures for relative risk reduction as shown above in case of rota virus vaccine. The actual cost-effectiveness analysis has to go even beyond ARR, NNT, NNH and the monetary cost of the vaccine; these parameters have be explored for the alternative intervention strategies as well and the results contextualized in the social, economic, political and environmental milieu of the country or even regions within the country.

In the case of the Hib vaccine this evidence simply does not seem to be present with respect to India and there have been shocking attempts to even suppress the limited evidence that is available. Such lapses are not inadvertent, but are motivated by the numerous commercial interests that are operating in numerous forms to push vaccines.

Even the people in the home countries of the global vaccine manufacturers have not remained immune from their all powerful ability to manipulate public regulators and governments for serving their business interests. In this context, it is really heartwarming that health activists in India have successfully managed to thwart many a push by drug industry and their henchmen in international agencies and government to impose new vaccines on the unsuspecting people. Yet, we know that the threat remains and is very real. The contest here is not between pro vaccine and the anti-vaccine lobbies, but between a rational vaccine science and "corporate greed" that is at large in the name of science. Eternal vigilance and scientific temper towards the desirability of new health technologies, of which vaccines are among the most powerful ones, is the price we must pay to safeguard our health.

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