Editorial: How many vaccines does a child need?

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As is increasingly evident from the growing literature, the central tragedy of immunization in India is that there is no straight answer to this innocent and innocuous question of parents facing the ever increasing number of vaccines, their irrational combinations and their skyrocketing prices. What is worse, the answer changes depending on who is asked: The govt paediatricians would go by whatever is recommended by the government,¹ and the private paediatricians would go by whatever is recommended by their academies/associations.² Both the government and the academies have largely relied on whatever is produced and promoted by the industry, or provided by industry-funded non-governmental organizations, whether national or global, or the World Health Organization.³⁴ Therefore, the most straight-forward answer to the parent's questions should be that every vaccine made by any industry should be given to every child, regardless of whether they are needed or not. But that doesn't sound credible and no parent would easily accept that for an answer, which is why the question is never answered straight. Unfortunately, this proliferation of new vaccines coexists with the perpetual shortage of essential vaccines under the Universal Immunization Programme (UIP) and the poor coverage (~60%) under the government's routine immunization.⁵ Thus, pushing every new vaccine to the population within reach has somehow become more important than achieving 'universal' immunization with essential vaccines. Public health experts have criticized this supply-push approach and argued for a demand-pull approach to establish the need for new vaccines based on disease burden, cost-benefit, risk-benefit and overall effectiveness in disease prevention. But who is listening?

Thanks to International Monetary Fund - World Bank promoted austerity measures on government expenditure,⁶⁷ financial burden is the only reason why many new vaccines have not yet been included in the government's UIP, despite being recommended by the National Technical Group on Immunization (NTAGI)⁸. But because WHO promotes all vaccines,⁹ and the government does not explicitly categorize any vaccine as "not required for mass immunization", private doctors are having a field day giving every new vaccine to anyone who can afford it, enjoying hefty margins from industry as well as from parents.¹⁰

An informed scientific community committed to evidence-based medicine and science-led policy can easily intervene to change this scenario. It has been attempted in the past¹¹,¹² and a lot of scientific literature has already accumulated prior to this special issue of the MFC Bulletin. However, there are many in the medical community who are trapped willy-nilly by manufactured consent.¹³,¹⁴ New terms like vaccine-preventable diseases, under-utilized vaccines, barriers to vaccination, innovative financing, advance-market commitments, public-private partnerships etc., have entered the lexicon of immunization in the past decade to justify the above practice, and terms like selective immunization have disappeared.¹⁵,¹⁶ Sweeping claims or outright misleading terms are now allowed - such as calling a cocktail vaccine as multivalent, anti rotaviral vaccine as anti-diarrheal, anti-pneumococcal as anti-pneumonia, anti-meningococcal as anti-meningitis, anti-HPV as anti-cervical cancer etc. Indeed, recent Indian research showed that 'neglected and emerging' enteroviruses could contribute to diarrhoea as much as Rotavirus, as well as to non-polio acute flaccid paralysis.¹⁷

Things were not always like this. During the British rule, India was among the global pioneers in the development and production of vaccines and antisera.¹⁸ For decades after independence, public sector had near monopoly on vaccine production and their prices were never a financial burden.¹¹,¹⁹ The entire scenario of immunization changed consequent to liberalisation, privatization and globalization. The public sector suffered systematic neglect and closure,¹⁹,²⁰ while the private sector grew at its expense, but the government emphasised new vaccines and their
combinations, rather than filling the shortfall in UIP vaccines. It is no wonder that the lack of regulation on combining UIP and non-UIP vaccines has enabled the entry of new vaccines into UIP through the backdoor as combinations. Then, it is no longer surprising if the government procurement moves away from individual UIP vaccines made by public sector to the combination vaccines made by private sector. It is no wonder that the revived public sector units are reduced to component suppliers for the private sector and cheap vaccines made by public sector are purchased by the people at huge 'value-added' prices from the private sector. The issue is no longer about enhancing our procurement budgets from the hundreds of crores at present to thousands of crores in the future, but about which industry should get the lion's share in it. It is also not just about ideological shift towards free markets, since neither is the vaccine market a free market, nor do consumers have a free choice in it. It is about increasing conflicts of interest.

Being one of the single largest buyers of vaccines in the world, we expect that the Indian government should be free to take its own sovereign decisions and even shape the market in accordance with its buying needs, especially when all the techno-economic capacity for decision-making is available within the country. The government interacts closely with a large number of industry-funded foreign NGOs and international alliances. International NGOs like the Bill and Melinda Gates Foundation, PATH, International AIDS Vaccine Initiative, Child Vaccine Initiative, Malaria Vaccine Initiative, all recommend uncritical adoption of new and combination vaccines not only to many national governments but also to WHO, UNICEF and other multilateral health organizations. Over a hundred individuals on the pay roll of such organisations work closely with the Union health ministry, often under the same roof! BMGF funds fully the Immunization Technical Subunit of National Technical Advisory Group on Immunization (NTAGI-the highest advisory body of the government of India on immunization), though it is officially run by an Indian NGO, the Public Health Foundation of India since 2012. Even in these days of nationalism and intense scrutiny of foreign NGOs, the role of foreign-funded individuals and NGOs entrenched deep in the strategically important health ministry did not invite ANY scrutiny!

Just as the nature of vaccines and the nature of the vaccine industry have changed, the nature of scientific evidence and the way it is used is also undergoing a sea change in the vaccine policy circles. Waiting for hard evidence is now viewed as a 'barrier' in vaccine decision making even in countries like India, which have all the technical capacity, manpower and funds to collect such evidence. The WHO guidelines on the introduction of new vaccines in UIP suggest that the government use estimates from available data, mathematical models, or the proxy data from other countries with similar social, demographic and environmental conditions, and grade the system to assess the quality of evidence if a country does not have evidence on disease burden. For instance, it states "... It is possible for a strong recommendation to be made with low or very low quality evidence because it is the net result of how all the factors come into play that is important."

The above approach of WHO is in total contrast its own previous recommendation of 2% prevalence as the threshold for adopting mass immunization against Hepatitis-B13 which has since been dropped. Now the threshold has shifted from prevalence to safety and efficacy. But WHO's propensity for changing definitions was most noticed when it declared H1N1 as a pandemic in 2010 using diluted criteria, forcing member countries to stock up tons of Tamiflu made by a MNC. It turned out that neither did H1N1 affect so many people not was Tamiflu effective on H1N1. Similarly, the case definitions on adverse events following immunization (AEFI) have also been changed by WHO/CSIMOS's new classifications as 'non-AEFI,' or 'un-related' or 'unlikely', replacing the earlier Brighton classification definitions of 'probably' or 'possibly' or 'likely'. The changed case definitions make it difficult to establish the causality between vaccine and injury and allow companies and government to escape compensation in case of damage or death following vaccination either during clinical trials or after mass immunization. Such actions compromise both biosafety and bioethics.

Unfortunately, rather than addressing all these issues highlighted in the ICMR-NISTADS framework for a national vaccine policy based on broad-based consultation, the then government adopted a vaccine policy to justify its ongoing practice and was held to account for its various omissions and commissions by scientists, parliamentary committee (34th, 38th, 43rd, 52nd Parliamentary standing committee reports on Health and Family welfare), government committee report, media and the courts (High
Court order 2011). It is now up to the government, medical fraternity, scientific community and the larger civil society to prove that we are not a banana republic and can defend our public health on our own terms and answer the queries of hapless parents without fear or favour.

Disclaimer: The views expressed in this article are those of the author rather than her institution.

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Eradication of polio: no end to the game

C. Sathyamala

My interest in immunization was triggered in the mid 1980s when the Expanded Programme of Immunization (EPI) was being upgraded into the Universal Immunization Programme (UIP), and at the request of a bilateral Funding agency, I wrote up a concept paper on the UIP. It was when the funding agency wrote back after my submission asking my explicit advice on whether or not they should fund UNICEF India for their UIP that I came to know that the assignment had a purpose other than what had been stated on paper. The funding agency was in a quandary because my paper raised critical questions about the UIP as a public health strategy without directing them with a clear-cut yes or no recommendation on financial support. Sticking to my mandate of a concept note, I wrote back that it was for them to decide based on the conclusions I had arrived at in my paper. Later, over the grapevine, I heard that UNICEF India had refused to comment on my concept note and that the funding agency did finally decide to fund the UIP.1

This paper examines the context in which the global polio eradication was initiated as a vertical single vaccine strategy and the efforts that were made by a group of us. The issues of contestation are only briefly touched upon.

At first there was the Universal Immunization Programme

UNICEF’s decision to launch the vertical UIP was in contravention to the principles of Primary Health Care (PHC) laid down at the Alma Ata conference jointly called by the WHO and UNICEF in September 1978. The first strike against the Alma Ata declaration came from a meeting of a select group at the Bellagio Study and Conference Center of the Rockefeller Foundation in April 1979, barely six months after the Alma Ata conference. The meeting entitled “Health and Population in Developing Countries” was sponsored by the Rockefeller Foundation, Ford Foundation and the International Development Research Center (Black 1996). A paper entitled “Selective Primary Health Care - An Interim Strategy for Disease Control in Developing Countries” authored by Walsh and Warren (1979), the latter being the Director of Health Sciences at the Rockefeller foundation, had formed the focus of discussion in this meet. The authors, though commending the “goal of Alma Ata [to be] above reproach”, cast it as an unreachable utopian ideal as “...its large and laudable scope [made] it unattainable in terms of its prohibitive cost and the number of trained personnel required” (ibid: 145). The authors recommended that, “in an age of diminishing resources… instituting selective primary health care directed at preventing or treating those few diseases responsible for the greatest mortality in less developed areas and for which interventions of proven high efficacy exist” was the most beneficial strategy for the poor (ibid 145); a policy of vaccination (against measles, and DPT vaccination for children and Tetanus Toxoid for pregnant women) was suggested as one of the most cost-effective interventions.1 Among the attendees were Robert McNamara (former secretary of defense in the Kennedy and Johnson administration and the then President of the World Bank), and the administrator of USAID (Cueto 2004). But, most importantly, it was the presence of a Harvard trained economist cum lawyer, James Grant, “son of a Rockefeller Foundation medical doctor who worked in China” (ibid: 1869)4 that was to play a critical role. Grant took over, a few months later in January 1980, as the executive director of the UNICEF and played a decisive role in converting the document by Walsh and Warren into the blueprint for the UNICEF programme and in internationalizing the strategy of selective primary health care. It was Grant who was said to have single handedly sold the idea of the UNICEF’s child survival programme5 (GOBI - Growth monitoring, oral rehydration, breast feeding and immunization) which later became GOBI-FFF (food supplementation, female literacy and fertility reduction) to the heads of states and governments and Rajiv Gandhi was one of them. As Adamson (2001) put it,

'[James Grant’s] approach was always to look for leverage points... Soon after the assassination of Indira Gandhi, Jim flew to New Delhi. He saw the new Prime Minister Rajiv Gandhi. And he proposed to [Rajiv Gandhi] that the immunization of India’s children should be the living memorial to his mother Indira. Rajiv Gandhi agreed…’ (29).

Thus, the launching of UIP in India on Indira Gandhi’s birthday, the year following her death, had more to do with its emotional appeal to a son at a point of great vulnerability than its necessity for a country on account of its sound epidemiological rationale.

In Feb 1987, the UIP became one of the technology missions of Sam Pitroda. The Technology Mission had as its objective the reduction of morbidity and mortality due to six vaccine-preventable diseases (whooping cough, tetanus, poliomyelitis, tuberculosis and measles among infants and a reduction of mortality...
due to tetanus among pregnant women). In 1989, my paper on Immunization was published in a special issue of Seminar on Technology Missions (Sathyamala 1989). The key phrases in the Walsh and Warren's paper as well as in the rhetoric on UIP were, “greatest mortality”, and “interventions of proven high efficacy”. These contentions were unsubstantiated and debatable. Though there was extreme paucity of data, what was clear was that the “vaccine preventable” diseases accounted for, at best, 10-12% of mortality in the under-five population in India; it was diarrhoea and respiratory infections which accounted for 60-90%. In 1983, Kamala Jaya Rao in her editorial in the MFC Bulletin, had discussed the Chingleput study which had shown BCG to be of little value in preventing disease in older children and adults, although it may protect against miliary and tuberculous meningitis in infants and young children (Jaya Rao 1983). Further, among the ‘vaccine-preventable’ diseases, measles was a negligible disease in well-nourished children but the mortality was 400 times higher in undernourished children. There were other important concerns regarding the impact of immunization at a population level on the natural history of disease. For instance, in Aug 1985, two months before the UIP was launched, there had been a big outbreak of measles in the small village of Singanikuppam, Tamil Nadu, with a population of less than 700, which had left 27 children dead and 72 hospitalized with serious complications and importantly this took place two years after a mass immunization camp had been held by a charitable organization (Sathyamala 1987). However, by the time the district administration came to know about this, the outbreak had run its course. The outbreak with such a high case fatality rate was a consequence of a onetime mass campaign. The affected children were from those born after the immunization programme and those who had not received the vaccine during the camp. In two years time the accumulation of susceptible children was large enough for the outbreak of an epidemic and this time it was more serious than the others the village had witnessed earlier because of the disruption of the natural immunity cycle. This phenomenon had been reported in 1968 in Tampa (USA) as well. I do not think the Singanikuppam tragedy figured in any academic writings or debate; I had come to know of this only because I was doing a study on sub-centres in that Taluk.

A similar possibility existed with polio as well. In the July 1987 issue of the MFC Bulletin, I had published a paper by Gloria Burrett (Burrett 1987) who worked in the Spastics Society of Northern India. In this paper, she wrote about the rising paralytic poliomyelitis cases in a population they served through a rural centre housed in one of the Primary Health Centres in Faridabad district. This was some 10 kms from the District Hospital at Ballabgarh which functions as a rural training centre for students and interns from AIIMS. The paper raised three important questions on a recent outbreak they observed in one of their villages: half of the children who had paralysis had received three doses of OPV; the village was barely half an hour from two government hospitals and no one seemed to be aware of this outbreak; and there was no attempt to educate the local private practitioners about the association between intramuscular injections and paralysis.

Surprisingly there were few dissenting voices from mainstream academia, and mfc, even with diverging viewpoints among its members, seemed to be the only organization that was consistently raising specific questions about the immunization strategy that was being adopted by the government. UIP went on to become the focus of rural health programmes at the cost of other priorities in health as could be seen from allocation of funds. In the 7th Plan, the single vertical programme of the Technology Mission on Immunization was allotted Rs 240 crores which was 55% of the amount allotted for the control of communicable diseases. I concluded my 1989 paper on the Immunization Mission with,

The six vaccine preventable diseases form a small proportion of diseases which cause death and illness in the underfive population. Both diarrhoea and respiratory infections, although the most common causes of death, are multifactorial in etiology and not preventable by vaccines available today, and an attack on these diseases is not possible without an attack on poverty. On the other hand, immunisation is a biotechnology which can be implemented on a wide scale without the need to challenge the social and economic causes of disease. Therein lies its attraction. Immunisation which is necessary and important at the level of an individual child and is an essential component of primary health care cannot be allowed to become the political weapon it has or to supersede the other important components of primary health care. (Sathyamala 1989)

And then there was the Global Polio Eradication Initiative (GPEI)

Although Walsh and Warren (1979) had not included polio in their list of priority diseases, polio came to be included as part of the EPI and then the UIP. From the time of the success of the smallpox eradication, plans had been afoot to identify another disease
suitable for eradication along the same lines, … in 1980 a meeting took place at the National Institutes of Health in Bethesda, Maryland. Drawing its inspiration from the smallpox eradication campaign, the meeting was intended to identify future eradication targets. Two of the principal architects of smallpox eradication, Frank Fenner and DA Henderson, argued that there simply were no feasible eradication targets. The organisers of the meeting were undeterred. It was a matter of ideology, of faith, rooted in opposition to post-Alma-Ata emphasis on strengthening primary health and belief in eradication. It was this small group of influential American public health experts, committed to eradication, who drove things along. It was essential that the smallpox campaign be followed up: it mattered less which disease was targeted. Measles and polio were identified as the most promising candidates, and in 1983 a symposium on polio control took place at Pan American Health Organization (PAHO) Headquarters in Washington DC. Virtually no speakers at the meeting argued in favour of eradication. Polio was not a major public health concern in the developing world, and ‘control’ was a more appropriate goal. Nevertheless, thanks to the efforts of a small group of men, a mere 5 years later the WHA was to endorse polio eradication. (Blume et al. 2013)¹²

'A conference in Bellagio, Italy, in 1983 first put forward the notion of global polio eradication as a goal for the Expanded Program of Immunization. In 1984, Rotary International set up a consultative committee to consider the potential of a global effort against poliomyelitis. Based on the committee's report, Rotary International declared the goal of poliomyelitis eradication by 2005, the Rotary's centenary year, giving itself 20 years for achieving the target. In 1985, the Pan American Health Organization adopted a resolution to eradicate polio from the Western Hemisphere by 1990. In 1988, at the Forty-first World Health Assembly, urged by the World Health Organization (WHO), the 166 member-states committed themselves to eradicate polio worldwide by the year 2000. The achievement was to be an “appropriate gift, together with the eradication of smallpox, from the twentieth to the twenty-first century”' (Sathyamala et al. 2005)

In 1983, Jonas Salk was said to have 'broached' with Robert McNamara an idea of a campaign to eradicate polio worldwide (Black 1996:43) but it was the Sabin's live attenuated vaccine (Oral Polio Vaccine -OPV) that was included in the eradication initiative.¹³

Although, India had committed itself to polio eradication at the World Health Assembly, it was only from 1995 onwards that serious efforts were made for the intensification of the programme. Onkar Mittal who had worked in a bilateral agency for many years as a consultant and had witnessed the action backstage felt compelled to raise technical and political questions regarding the programme that was beginning to be prioritized among the donors and to which the bulk of funding on health was being allocated. For more than a year (in 2002-03) he tried to get many academics and activists interested in these questions by circulating a paper setting out the major concerns. I was one of those sensitized by this paper. The People’s Health Assembly in Mumbai (14-15 January 2004) was the first group we took our concerns to. Although, we were unsuccessful in obtaining a slot to present it to the assembly, we were able to discuss it with several members on the side-lines of the meeting and to get individuals and organizations like DAF-Karnataka interested. We also presented a paper at the World Social Forum that followed the PHA meeting in a panel organized by Ritu Priya. I had just joined as a visiting faculty at the Centre of Social Medicine and Community Health, JNU, and an elaborate memorandum against the polio eradication initiative was drafted and endorsed by several faculty members as well as others who supported it.¹⁴ It was submitted to the World Health Organization, the UNICEF, and the Government of India, on 7 April 2004, the World Health Day. It was also sent by mail to several of the UNICEF functionaries at the regional level and to Jacob John and others from the academia who supported the GPEI. The memorandum raised critical issues against the Global Polio Eradication Initiative, including the rising number of paralysis in children, an elimination programme being passed off as an eradication programme, and the stage being set for an exorbitantly expensive IPV for routine immunisation in the coming years. By then more than Rs 2500 crores had already been spent and more than Rs 400 crores/year was being allocated in the Tenth plan. Thus, a vertical immunization programme had been whittled into a vertical single vaccine programme absorbing massive resources of money and personnel, in contravention to the original rationale for selective PHC which was a lack of resources. We put forward three demands: an independent enquiry, compensation and rehabilitation of paralysed children with both vaccine induced and non-polio Acute Flaccid Paralysis. There was no response from anyone.
The next two years, beginning with a publication (Sathyamala et al. 2005) in the peer-reviewed, International Journal of Health Services, a concerted effort was carried out by individuals and several organizations in the health movement, to raise this issue in the government, academic, and activist circles by engaging them in debates and by publishing in journals. Journalists were also briefed (See Epilogue)

Using the data from UP, we could show that there was high death rates among children classified as AFP (Puliyel et al. 2007; Sathyamala 2007). Though GPEI was allegedly to reduce the mortality and morbidity in children, its consequence was an exponential increase in the incidence of AFP, particularly in UP, and high death rates, only now not seen as important because it was not "polio" paralysis or deaths.

**Concluding remarks**

Though considerable time and effort went into creating a counter discourse to the dominant narrative of the GPEI within the academia and the government, it became clear that in the race to achieve a mythical goal of polio eradication, the odds were so heavily stacked against the interests of the children that no dent could be made in the programme. That even today (two decades after the intensification programme) the incidence of non-polio AFP continues to remain high as can be seen from the latest reports of the NPSP (National Polio Surveillance project). Non-polio AFP is now endemic in several states in India. Our efforts to get health NGOs to take up the issue of the non-polio AFP children for study, compensation and rehabilitation also has not borne fruit. Part of the reason could be a lack of consensus among those who are in the health movement, notwithstanding passing of resolutions in national level organisations. Non-access to funds could be another reason. The current counter discourse is more in terms of engaging with cost-effective debate or the negative impact on the health services. But there are only a few takers to counter it on epidemiological basis. In all this everyone appears to have conveniently forgotten the reason that GPEP was rolled out in the first place: It was so that there would no longer be any need for polio immunization, but now it is obvious that there will be no end to it.

In her book on the history of UNICEF, Black (1996:37) describes the conflict as that between the protagonists of "selective PHC" and those of "comprehensive PHC". Although initially selective PHC was proposed as a short term interim project, the ideology of selective PHC has come to be accepted as the project for PHC, not only among the establishment but among the movement groups as well. Initially, perhaps, the intention of selective PHC was only to jettison the "comprehensive PHC", but later on with the phenomenal success in its implementation, it could now serve as yet another way for capital accumulation as in the formation of new corporate fronts such as the Global Alliance for Vaccines and Immunizations (GAVI).

**Epilogue**

A few important events in this post 2005 campaign to critically sensitize people on the polio eradication programme were:

1. In the National Hearing on Health and Human Rights in Delhi in December 2005, which was a culmination of regional hearings, co-organised by Jan Swasthya Abhiyan (JSA) and National Human Rights Commission (NHRC), JSA demanded compensation for VAPP (Vaccine Associated Paralytic Polio) cases. This point was included in the NHRC recommendations.

2. A National Consultation on the Polio Eradication Initiative (and Hepatitis-B) was held on 14th May 2006 by the Indian Medical Association (IMA) and Plan International.

3. In 2006 JSA published the booklet - "New Technology in Public Health - Who pays and who benefits?” as a preparation for the second National Health Assembly in Bhopal in February 2007, there was a section on polio eradication. It radically critiqued this strategy.

4. A national consultation on 26 October 2006, Delhi, by JSA along with Medico Friend Circle (MFC), Centre of Social Medicine and Community Health (CSMCH), Jawaharlal Nehru University, New Delhi, (both constituents of JSA), Swasthya Neeti Samvad, New Delhi, and the People's Report on Health (PROH) Council for Social Development, New Delhi.

5. Visit to Lucknow to meet with Mr. A.K. Misra the then Principal Secretary, Health, Govt. of UP and Ms. Renuka Kumar, Secretary, (November 2006) to discuss the situation in UP and to carry out a short field level survey on the children with AFP as well as to help with the analysis of data.


8. In February 2007, in the National Health Assembly of JSA, a parallel session was organized on the GPEI.

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Notes:

1Needless to say that was my first and last association with this funding agency!
2 The declining interest in population issues was said to be one of the concerns that prompted the Bellagio conference (Cueto 2004).
3 The basis of cost-effective persuasion relied on previously published calculations in several World Bank reports.
4 Previously, James Grant had also served in the USAID.
5 His salesmanship was described as 'tireless, peripatetic proselytizing' (Eckholm 1985)
6 This was not because a protective effect of BCG in infants and young children was demonstrated but because the study design had not included this age group.
7 Tamil Nadu has also reported deaths due to measles vaccination in the latter years.
8 A friend who knew of my concerns related to UIP had introduced Gloria to me and it was at my request that she wrote up their experiences at the field level.
9 When the article was brought to the attention of the then head of the department of Social and Preventive Medicine, AIIMS, the response was astounding. I got to know that the HOD called up the head of the Spastics Society of Northern India which employed Gloria to reprimand her.
10 I am not sure if the donor funding for UIP was included or in addition to this.
11 MFC Bulletin No. 126 (March 1987) carries the case for and against global measles eradication.
12 MFC Bulletin No. 126 (March 1987) carries the case for and against global measles eradication.
13 The decision to use OPV needs to be investigated. One theory was that live vaccine was chosen in order to use up the old stock. While the high cost of IPV (Inactivated Polio Vaccine given as an injection) has been cited for choosing OPV, it defies epidemiological rationale for eradication.
14 See Strebel et al. 1995 on intramuscular injections as a risk factor for paralysis.
15 AFP Surveillance Bulletin - India, Report for week 42, ending 22 October 2016 shows 37,347 cases of AFP.
16 For a well substantiated book on the politics of GPEI see Muraskin (2012).
17 This is only indicative; the whole campaign needs to be written up properly.
18 However, there was no progress thereafter despite JSA’s raising the issue again in December 2006 in the follow up National Hearing with NHRC.
19 Members of the Sub-Committee: Prof. S.K. Mittal (Chairman); Dr. Jacob Puliyel and Dr. Onkar Mittal (Co-Chairman); Dr. C. Satyamala Dr. Joseph Mathew Dr. Tarun Gera Dr. Ajay Gambhir(Members). Full report http://jacob.puliyel.com/download.php?id=48
19 Anant Phadke was involved in the drafting of this booklet.
20 This consultation was coordinated by Indira Chakravarthy.
21 Visit by C. Sathyamala, Onkar Mittal, and Jacob Puliyel.
22 Presentation by C. Sathyamala, Onkar Mittal, Dr Rita Priya, Indira Chakravarthi and Vandana Prasad, representing, JSA, PRoH, MFC, and Swasthya Neeti Samvad. Representatives of UNICEF and WHO were present at this meeting.
23 The resolution was drafted by C. Sathyamala, and Rita Priya, with inputs from David Saunders and Prem Chandran John.

References
Is the polio virus more important than the child? A reflection

Antony Kollannur

Polio eradication strategies were on a war footing in 2001 towards its end game stage in India. We were only focusing on the polio virus. WHO or UNICEF does not have any data base on how many of those unfortunate children recovered from transient paralysis and how many received ambulatory support like crutches and wheel chairs. I was the Project Officer Health for UNICEF fully responsible for the social mobilization for polio Eradication in Uttar Pradesh and closely associated with the National Polio Surveillance Project. My plea was: look after the immediate treatment and welfare of the child paralyzed in a comprehensive package of polio eradication by State/National government and UNICEF/WHO and other overseas donors.

Bombs are dropped and missiles are fired with only the target in view. Collateral damage is not their concern or is the least of worries in a war.

Polio eradication strategies too were on war footing towards its end game stage in India. We were only focusing on the polio virus, to get that enemy uprooted from its hideouts. The foot soldiers of polio eradication were also strictly instructed and regimented to just get the wild virus out and exposed. Then block all the possible colonizing sites among children in their guts with harmless polio virus contained in the oral polio drops. These steps were called outbreak response, ring immunization, mop-up rounds, pulse-polio campaign etc. Though the National Immunization days were regularly conducted since December 1995, it was with National Polio Surveillance Project coming into force in 1997 that the eradication got its boost and assumed the nature of a war.

There was huge under-reporting of paralytic cases by the health system before this period. It was this author’s field visit to Katra Bazar in Gonda district of UP in July 1996 and subsequent media explosion in Times of India, Lucknow edition that led to the formation of first polio surveillance cell by a State government in the country. On that single day itself I had reported 17 cases in a charitable mission hospital whereas the official total reporting from 85 districts in UP for the previous six months was only 18 cases.

During this campaign mode of oral polio drops administration and simultaneous surveillance activities, the child was given less importance in my view. The virus got all the attention because the villain was the wild virus and the global funds were generated to eradicate that enemy. The number of viruses identified and contained was the priority for health staff of local governments and global agencies. To illustrate: there were a caravan of vehicles and officers rushing to the flaccid paralytic child, interviewing the parents, examining the sick child and even transporting the child to nearest hospital and waiting for the first excretion of precious stool. The moment the stool samples are obtained for transportation to nearest regional lab for identification of wild virus, the child is forgotten. The sudden onset of trauma of the healthy child following the vaccination (OPV) with the pain, fever and the continued paralysis is the least priorities of the polio crusaders. Not to talk about the facilitation of physiotherapy for the paralytic child, arrangements for crutches, and wheel chairs for the mobility of the physically challenged child. The children affected by the paralysis are not being looked after, the moment the stool samples are obtained for virus isolation; that is all the NPSP doctors or polio Surveillance teams were interested in. The child is abandoned just as a voter is ditched by election agents of candidates soon after the polling!

WHO admits that in 2003 there were 8,000 non-polio paralytic children in India which multiplied every year reaching to almost 60,000 in 2011. But WHO or UNICEF did not have any data base for how many of those unfortunate children recovered from transient paralysis and how many received ambulatory support like crutches and wheel chairs. There has been no evidence to show so far, whether the routine healthcare system and District Social Welfare Board come to their rescue adequately. Media reporting on these were also not available.

When I asked these uncomfortable questions during 1998-2002 period in Uttar Pradesh my own supervisors advised me not to divert the attention from the main issue; i.e., eradication of the wild virus and nothing else. According to them philanthropy and social welfare are not the job of professional organizations, but the responsibility of the respective state governments! I strongly disagreed with the view that it’s not the job of the polio vaccine teams to care for the paralyzed child.

My doubts were more on how come the children who received more than ten doses of oral polio drops still develop paralysis in UP and Bihar? Is there any inadequate immune-conversion because of malnutrition or peculiarities of genetic make-up, ethnic diversity or even chronic intestinal illnesses etc? Again, I was conveniently mentored not to confuse the issue and stay focused to whatever being instructed by experts from Geneva and New York as this vaccine has worked in 125 countries outside India. Quick blames were on the poor quality of rounds of immunization with inadequate coverage and poor cold chain efficiency of vaccine, parents giving false claims of polio vaccine dose coverage, wrong elicitation of history etc. I was not convinced. Even now there are
Kerala is considered as the leader among Indian states in various health indices and the functioning of the public health system. The strengths and weakness of the system can be best assessed when faced with a real challenge. The recent epidemic of diphtheria in Kerala, especially Malappuram and Kozhikode districts provided an opportunity for the same.

Was the epidemic anticipated or unexpected?
Kerala was always in the first place in immunization coverage and known for its low infant and under five mortality rates. But the situation remained static for the last several years and immunization coverage started falling in recent years, while many other states were showing considerable progress. The challenges in improving the malnutrition status and the current decline could be mainly attributed the efforts of an anti-vaccine lobby, which emerged almost a decade ago. Initially it was mainly by many individuals working here and there, however, with the advent of electronic social media like Facebook and Whatsapp, it slowly became an organized movement and with increased reach and influence among the general public. Even though this was noticed by the authorities, they were of the impression that taking action against these individuals could provide more publicity to them and a better option would be just to ignore them. Eventually these groups started working at the grass root level, building on some common fears among many people, of the side effects of vaccines and drugs of modern medicine. In specific pockets certain religious arguments were built against vaccination too, which was actually propagated by quacks who misused religion for their benefit. Naturopaths and some homoeopaths had also joined hands in spreading false allegations against vaccines and vaccination.

On the other hand, steps to combat these and to bring back the trust of people towards vaccination were not adequate. Many front line media houses in Malayalam also were bringing out positions that exaggerated the side effects of vaccines repeatedly. The immunization coverage started falling gradually, especially in some pockets of Kerala, which was noticed in various studies.

We were witnessing a few cases of diphtheria every year, especially from Malappuram district of Kerala. In 2015, there were a few cases and 2 deaths. The affected children were studying in orphanages where majority of children were partially immunized or totally unimmunised. All the experts in public health feared that the situation can worsen to epidemic proportions. At that time, a survey was conducted by the health services department and it was noticed that large percentage of school going children are unimmunised or partially immunised. So in Malappuram district, it was decided to replace TT vaccine with Td vaccine to provide immunity against diphtheria. District health authorities were successful in collecting exact data (individual listing) regarding immunization status of under 15 year old children in the district. Print and visual media were supporting the immunization movement fully at that time. Doctors and health workers also became very active. Mission Indradhanush (national immunization mission) was well underway in Malappuram district, but even with maximum effort, the impact was not substantial. The main reason cited was that the program failed to motivate people from all fields including local self-governments, local leaders, teachers, religious groups etc.

Realising this, a new movement entitled “Mission Mukthi” was formed. It incorporated all individuals and organisations interested in the health of children. Debates were conducted at various places in the district and in visual media, and the anti-vaccine lobby started to lose its grip. Yet the anti-vaccine lobby continued their effort, conducting a public meeting at the collectorate, Malappuram and organizing a rally shouting slogans like “we don't need any vaccines” and against health services department. Even though the entire programme was videographed and complaints launched against them, the authorities failed to initiate any legal action. At the same time, the anti-vaccine campaigners tried to convince people that authorities are afraid of taking action against them because the anti-vaccine arguments are genuine. They even argued that unimmunized children are targeted by authorities in health services department and when these children are brought with minor febrile illnesses, they are admitted, given strong and toxic injections. By this way they are made sick, and when they die, it is attributed to diphtheria or tetanus to induce fear in public and motivate them to take vaccines. Ironically, all this happens in Kerala, which has been known for its good health model and high human development indices.

Malappuram is the most populous district of Kerala. The field-staff of the health services department is inadequate when compared to the population's needs. One junior public health nurse (JPHN) needs to cover 10-15 thousand population instead of 5,000. This prevented them from doing even their usual work. The hostile attitude of some people towards health services staff when they do their field visits; too much of clerical work; poor supervision and lack of a supportive attitude from higher officers have all had a role in the critical situation.

In the present diphtheria epidemic, two boys died during the initial days itself. This created a fear among the public. Media were forced to take a supportive attitude favouring vaccination.

The factors which resulted in the present epidemic
- Anti-vaccine propaganda from various corners
- Inability to create adequate evidence based scientific knowledge regarding immunization among public
- Religious, cultural and social barriers
• Lack of coordination among various governmental and nongovernmental organizations

Remedial measures: The Mission Mukti

First effort was to bring all individuals and organizations that supported immunization under one banner, i.e., Mission Mukti. These associations included District Health Administration of Malappuram, UNICEF, Indian Academy of Paediatrics, Indian Medical Association, Government Medical College, Manjeri, MES Medical College, Perinthalmanna, Kerala Shastrha Sahithya Parishad, Juvenile Justice Commission, Childline, Malappuram, Bar association, Malappuram, Department of Social Justice, Department of Education, Kutumbasree (A women's self-help and leadership initiative in Kerala), Amritha Kiranam Initiative of the Kerala Government Medical Officers Association (KGMOA), Yuktivadi Sangham (Atheist Federation) and Vyapari-Vyavasayi (Traders and Merchants Association).

Data collected by district health authorities showed that 2.6 lakh children under 16 years are either unimmunized or partially immunized in the districts. Names and addresses of these children were also collected.

Leaders of various religious groups were contacted. Many of them had apprehensions about the possible risks of vaccination. Many had the belief that it is programmed to reduce the fertility rate of some specific groups. Explanation of the scientific facts and assurance by a team of doctors helped them to clarify the doubts. As a result, they wholeheartedly supported the vaccination drive and announced it before the visual and print media.

Several programs were conducted in various parts of the district. House visits conducted to educate the parents of unimmunized children. Local leaders and other influential individuals were involved in the process.

Debates were conducted publicly with those who were spreading false allegations about vaccination. The media supported a lot in these initiatives as well.

Other recognized systems of medicine like homoeopathy, Ayurveda, Naturopathy, Siddha, Unani and Acupuncture were also contacted and they also publicly assured their support. According to them, quacks who misuse their system were responsible for anti-vaccine propaganda.

Government of Kerala including chief minister, health minister, health secretary and education minister offered full support to the activities.

A number of articles were published in print media and social media. Leaders of Indian Academy of Paediatrics met all the 140 MLAs of Kerala individually and stressed the need of immunization card to be made mandatory at school entry.

Short films, flash mobs, street theatre, public meetings, awareness classes, training programs for health workers etc. were organized at various parts of the district.

Proper case identification, early referral to health facility, proper investigation, protocol based treatment—everything was streamlined. The work done by the DME and DHS and private health facility need to be emphasized as they could limit the mortality to only two among more than 200 cases. Now the epidemic has almost subsided and newer cases are not being reported.

Conclusions and lessons learned:

• Vulnerability to false propaganda against vaccination in the society is high, despite the high educational status of people, or even progressive nature of the society.
• Many believe that vaccines are programmed by America and Israel to reduce fertility.
• Some even believe that god has given us all the protection needed and trying to enhance this capacity is just like belittling god.
• Several parents believe that they are free to take any decision pertaining to their children, irrespective of child rights as well as the potential dangers associated with such decisions.
• Health workers in the field are not confident enough to impart their duties. They need more support and encouragement. Also, proper monitoring of their work is essential. Shortage in the number of health front line and supervision staff can lead to major setbacks in preventive health measures.
• Government machinery is neither committed nor empowered enough to properly implement national programs, or to take action against those who work or spread false allegations against vaccination.
• The health system has a knee jerk response to public health issues. When there is a vaccine preventable death, everyone is alerted and becomes hyperactive. But continued, sustained effort is lacking to prevent those episodes, even in advanced public health enclaves like those in Kerala.
• In case of an infectious disease outbreak, our hospitals do not have facility to properly admit and isolate the cases so that transmission can be minimized. There were isolation wards for individual communicable diseases once. As the incidence of these cases decreased, such wards were used for other purposes. During this outbreak, we experienced a lot of difficulty in isolating cases.
• Probably the mortality levels reported against this major epidemic was the all-time low (only two deaths—that too from the early reported cases, from more than 200 reported Diphtheria cases). Early detection and prompt treatment, as result of a collective initiative of various constituents of the society, could make this happen.
• Prevention of diseases is not the only responsibility of health department. Its main responsibility is to involve individuals and associations and motivate them to work for the goal. During this outbreak, immunization coverage could be improved by mobilizing massive support from various political, religious and cultural organizations.

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Immunization and control of infectious diseases: Some reflections on the science and scientific thinking in Indian context

Indira Chakravarthi

This article tries to say again some things said about immunization, and also some things as yet unsaid, albeit from a different perspective. The objective is to give some thought to science and scientific principles and thinking in not only the immunization practice, but in our public health measures for control of infectious diseases. An important impetus for this piece is the prevalent tendency, by sections of mainstream and establishment scientists and public health practitioners, to largely dismiss colleagues drawing attention to problems and expressing concerns about flaws in this practice, and label them as being anti-vaccination, anti-science.

In fact this is the first ‘scientific’ point that one wishes to make - that of viewing immunization as one among the preventive measures for control of infectious diseases, a point which seems to have been lost sight of to a large extent.

Microbe-host-ecology interaction

Epidemiological understanding indicates that host population density is critical in determining whether a pathogen can get established and remain endemic in a population.

In a fascinating study of infectious diseases and human population history two authors conclude thus:

Understanding pathogens at the population level is as important in disease prevention and control as understanding pathogens at the microscopic or molecular level. Three ecological processes are crucial in determining the impact, persistence, and spread of pathogens and parasites: the size and spatial distribution of the host population, the movement of infected and susceptible hosts and vectors, and the nutritional status of the human host population. Although medical advances continue to reduce the impact of degenerative and self-inflicted diseases on people who can afford to pay for treatment, the control and prevention of infectious diseases is likely to be increasingly dependent on a solid understanding of the ecology of pathogen transmission and persistence (Dobson and Carper 1996).

One of the studies cited by them is that of population densities for small-pox vaccination coverage in African and Asian countries during the late 1960s and early 1970s, which indicated that smallpox disappeared early from countries in which the density of susceptible (unvaccinated) individuals fell below ten persons per square kilometre (Arita et al. 1986). Infections of small-pox persisted in regions with high number of infected persons, in particular Nigeria with 58 persons, Pakistan with 83 persons; India with 175 persons; and Bangladesh, with 502 persons (per square kilometre in each). To eradicate smallpox in these areas would have required coverage of the order of 98% to reduce the number of susceptible individuals to less than ten persons per square kilometre; such coverage was impractical. By 1970 vaccination policy changed to active case detection, contact tracing, and the breaking of individual chains of transmission. It was this policy change that eventually led to the worldwide eradication of smallpox.

The majority of the infectious diseases, including chronic infectious diseases such as tuberculosis, have spread in all countries of the world as a consequence of industrialization. This spread has resulted from the increase in population density with the growth of cities and the development of rapid means of communication, leading to ease in communicability. Long before the institution of BCG inoculation and the discovery of anti-tubercular drugs, tuberculosis started to decrease, and the chief reasons have been considered to be the development of herd immunity and natural selection against highly susceptible people, improvement in standards of living and improved environment. It is no exaggeration to state that theoretically the means for eradication of this disease have been established. (Okada 1973)

In fact, the Papworth Village Settlement experiment of 1918-1943, conducted in England as a socio-medical experiment to provide comprehensive care to working class families with tuberculosis discharged from a sanatorium, showed substantially reduced active disease in the children living with parents with active TB (discussed in Bhargava et al 2012).

The history of modern public health as it originated in the 19th century in Europe indicates that one of the characteristics of urban areas with high population densities then was the extremely hazardous and unsanitary working conditions, and extremely unhygienic and poor living conditions for large sections of the population, - in other words the genesis of the...
urban slum. Epidemics and fevers were a regular occurrence in the 'hovels and cellars of factory towns and cities'. A reasonable understanding of the nature of these communicable diseases and of socio-economic differences in disease emerged from the large number of studies conducted by doctors and new information that became available from scientists. These formed the basis for co-relation of disease with not just working conditions, but also with the 'filthy environmental conditions, polluted water supplies, and the decaying garbage and wastes clogging the streets'. Many of these studies were highly effective in furthering the cause of sanitary reforms. Measures such as improvements in housing, sewage disposal, sanitary engineering, protected water supplies, wide avenues, setting up diagnostic laboratories for proper identification and isolation of patients and carriers, disinfection, immunization, pasteurization of milk, were being instituted in many places. This Sanitarian Movement laid the foundations for modern public health systems, which as we all know has been the responsibility of the government, implemented through government institutions at various levels. By 1900 there was a general reduction in mortality rates, and deaths due to typhoid, cholera and typhus fever. To summarize this important period in the control of infectious diseases, "Infectious diseases have been the greatest killer in human history. Solving the problems of infectious diseases revealed the underlying relationship between the social and biological determinants of disease and showed that broad-based changes in the social environment as well as specific biological interventions bring disease under control" (Brunham 2009).

**Nutrition-immunity link**

While the resurgence of tuberculosis in some large urban centres in developed countries due to multiple drug resistance is partly due to the persistence of infection (lengthened infectious period) in immunocompromised hosts such as AIDS patients, it is also taken as a reminder that even the most effective drugs will not necessarily eliminate infection without the help of a fully functioning immune system (Anderson 1994 p 458).

It is generally accepted that nutrition can play an important role in the development of a number of infectious diseases. For infections such as pneumonia, bacterial and viral diarrhoea, measles, tuberculosis, there is overwhelming evidence that the clinical course and final outcome are affected adversely by nutritional deficiency. Advances in immunology reveal that nutritional deficiency is commonly associated with impaired immune responses. Malnutrition is the commonest cause of immunodeficiency worldwide, affecting innate as well as adaptive immune responses. Undernutrition is a causal risk factor for development of TB. India has the highest prevalence of undernutrition and the highest number of new cases of tuberculosis (TB), multidrug-resistant TB (MDR-TB), and deaths related to TB. A recent study on undernutrition and TB in India reveals that more than half of the incidence of the disease among adolescents and adults is attributable to malnutrition (Bhargava et al 2014). Very aptly the authors end this study with the observation of well-known microbiologist Rene Dubos, made more than fifty years ago, "It is most unlikely that drugs alone, or drugs supplemented by vaccination, can control TB in the underprivileged countries of the world as long as their nutritional status has not been raised to a reasonable level".

**Is this relevant to us?**

What emerges from this excursion is that over the last century many countries have significantly reduced mortality and morbidity due to infectious diseases by actions and measures based on scientific observations and information about pathogens, hosts, environment, which made possible effective systemic interventions. It also sharply reveals that infectious disease control has not relied upon, and does not rely upon, only immunization; rather several measures have been pursued concomitantly to improve the overall health status of the population through improvements in nutrition, and in living and working environment.

Improvements over time in cellular, molecular and immunology research have often affirmed the observations that have been documented for long, of the links between infectious disease-environment/sanitation-nutritional status-immune system of individuals and populations, in transmission and maintenance of diseases. There have also been considerable improvements in the diagnosis, treatment and prevention of many common infections due to the development and use of drugs and vaccines. The overall approach now is that disease-control strategies in the twenty-first century build upon this understanding of diseases at the population and ecological level as well as at the molecular and cellular level. The challenge before epidemiology is to put things back together again; to view the biologic phenomena within their social contexts, to take account of the role of multiple levels - molecular, individual and social - in shaping outcomes, as well as dynamic interactions within and between the levels.

The nutritional and environmental situation in many parts of India is similar to that of Europe in the
seventeenth, eighteenth centuries. It is now well-known that increased urbanization (leading to high density populations) has facilitated the spread and persistence of many directly transmitted respiratory and gastrointestinal infections, and vector-borne diseases, especially in poor communities without adequate resources to maintain good standards of hygiene and sanitation. So there is much that can be learnt from their history of how the suffering due to infectious diseases has been mitigated.

The point to ponder is: to what extent is our current public health practice for infectious diseases- in which only a vertical immunization program is implemented as preventive measure - based upon sound scientific principles?

Why are nutrition, sanitation and clean water not the public health priorities here? Why is it that the issues of overcrowding, urban slums and their insanitary conditions are not part of disease control here? Why slash funds for child nutrition programmes, anganwadis, and disease control programmes, including immunization? Why deny comprehensive primary health care to our citizens? Why do we so aggressively pursue vertical health programs in the first place, when comprehensive health systems have been shown to be effective at tackling most common illness and diseases? Given the association of undernutrition and TB, how have we translated this into an intervention to reduce suffering from this disease? Why continue to blame population growth and continue with population control strategies when government’s own figures show fall in the growth rates and in fertility rates? Why adopt policies that take away livelihoods and decent work, and lead to precarious work and denial of living wages, medical benefits, maternity benefits, crèches at workplaces, that deny job security to adults and parents of undernourished and hungry children? There is a well-established long-list of things (well within the framework of ‘economic growth for development’) that can be done to reduce the burden of infectious diseases, especially among children, even as we wait for our science establishments to come up with more or better vaccines.

A recent overview of emerging and re-emerging infectious diseases in India, from the National Centre for Disease Control and WHO India Office, talks of the trends in incidence of several known and new infections, and goes on to present the response mechanisms in terms of surveillance, epidemic preparedness and rapid response mechanisms in case of outbreaks (Dikid et al 2013). The review does not discuss any strategy whatsoever to prevent outbreaks of these infectious diseases, even though it describes how they are caused and transmitted. While this is appalling and a matter of great concern that scientists from NCDC do not consider prevention as a priority in the strategies to cope with infectious diseases despite voluminous knowledge on its effectiveness, it is colossal evidence of the deficit in scientific thinking and in application of science to public health among our scientific advisors and policy makers.

In our case, the science of infectious disease control has been reduced to - immunize, immunize, and immunize. Many important issues are unanswered or unaddressed, such as: (i) is there adequate information on causation and disease burden (ii) is vaccination the only option, (iii) is it safe and effective and for whom, (iv) under what conditions will it be effective, (v) the imperative to prevent/minimize adverse effects by ensuring timely medical care, (vi) the need for good quality, continuous monitoring and surveillance, (vii) the importance of studying and reflecting upon accumulating data from such surveillance to look at patterns, construct explanations for the adverse events such as deaths to improve information base about immune response. On the contrary, those who raise such issues are branded anti-vaccination, anti-science (even anti-national in some cases) and very nearly denied the right to exist!

**Immunization in India - limited science**

The polio eradication programme is an example of the narrow approach taken to science, and the ‘collateral damage’ that such a choice can lead to. While India has been declared free of polio due to wild polio virus, there has been a steep rise in acute flaccid paralysis

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implemented and defended have narrowly conceived infectious diseases. We find that the policies and scientific thinking to mitigate the problem of the large amount of available scientific information scientific and medical establishment to effectively utilize. One thus sees that there has been a failure by our state. 

Could the intensity of the polio eradication programme, the administration of as much as 10-12 doses of OPV, have given rise to new, or other strains of enterovirus or poliovirus? The surveillance programme has been only looking for wild polio virus, not for any other viruses. What is the scientific explanation for this public health problem of increasing numbers of AFP? Why is it not a problem that requires an answer and needs prevention as much as polio paralysis? In its obsession with the wild polio virus (one of the many viruses that cause childhood disease), the government has turned a blind eye to the increase in paralysis rates across the country.

A study in India shows an alarming neglect, indeed! An Indian research group studying non-polio enteroviruses (NPEVs - 'cousins' of polioviruses), observes "In spite of the alarming incidence of NP-AFP in the country, prior to our studies, there are no detailed studies to understand the causes of NP-AFP in India" (Rao 2015). An alarming neglect, indeed!

The results of this study on NPEVs point to their association with NP-AFP and acute diarrhoea. About 35% of NP-AFP children were positive for NPEV infections. Association of NPEVs with acute diarrhoea is as significant as that of rotavirus. Lastly, it indicates that "Indian NPEVs in NP-AFP patients exhibited extreme antigenic diversity. We have identified 66 serotypes, by far, the largest number of types identified in a single epidemiological study on NPAFP". Such findings have significant implications for the control of childhood diarrhea in the country, especially the decision to introduce a vaccine for only rotavirus infections. The knowledge of evolution of microorganisms on much shorter timescales than that of humans should also caution us to the limitations and futility-of using vaccines against viral pathogens. The study concludes that there is an urgent need to undertake research on enteroviruses and include these neglected ubiquitous viruses in future epidemiological studies on various diseases for which definitive causes have not been established. Will this advice be heeded?

Relevance of all this

One thus sees that there has been a failure by our state scientific and medical establishment to effectively utilize the large amount of available scientific information and scientific thinking to mitigate the problem of infectious diseases. We find that the policies implemented and defended have narrowly conceived of the problems, exacerbating them and in some cases, creating new ones, such as high rates of paralysis, drug-resistant TB, malaria. Can they be relied upon to practice good, sound science, epidemiology, public health? Can we afford to remain quiet, to stop questioning?

In epidemiology and public health, debates about substantive explanations for disease occurrence "are not simply about solving a puzzle correctly": nor are they merely ivory tower "academic" disputes. Ethically and intellectually, the discipline is bound at the very least "to do no harm". Krieger introduces a higher level of accountability because "at issue are the ways epidemiologic theories and the research they animate contribute-potentially helpfully, potentially harmfully - to efforts to understand and address who and what is responsible for observed burdens and distributions of health, disease, and well-being" (Krieger 2011).

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Note:

1 I use this term to refer to those who do science with the government, as in research centres that exist within government departments, where scientists and policy makers jointly identify issues to be addressed, set the research agenda. This is to distinguish these sections from the larger body of scientific and medical researchers and public health practitioners.

References


Today, international cooperation in science and technology is essential not only for their growth but also for their survival. Such cooperation has become as much of an imperative as science itself. What is, however, not often recognized is that countries, scientists and technologies can cooperate with one another in many different ways. The main recognized modes of scientific and technological cooperation are as follows:

(a) Training of the scientists of the recipient country, in the donor country.
(b) Training of scientists of the recipient country, in the country itself by visiting experts from the donor country.
(c) Financial assistance to the recipient country by the donor country.
(d) Assistance to the needy country through provision of material, equipment, etc.
(e) Transfer of technology and expertise free of cost but in a way, that for subsequent updating, there would be continuous dependence on the donor country, for no steps have been taken by the recipient country to assimilate the imported technology or expertise.
(f) Transfer of technology as above but against payment by the receiving country.
(g) One-time transfer of technology when the recipient country has the capability of assimilating it.
(h) A business agreement where a country sells high-technology products to another. In such cases, it is often (if not necessarily always) a battle of wits, as to who is, in the long run, likely to benefit more.
(i) Survey and collection of information requiring a high level of scientific/technological effort and/or expertise.
(j) Research collaboration where the two parties are unevenly matched so that ‘A’ decides and ‘B’ does. Money and expertise go from A to B and, therefore, for all practical purposes, B does essentially what A wishes even though, on paper, the decision might be made to appear to have been taken jointly and on an equal footing.
(k) Truly collaborative research where there is real intellectual compatibility and an independent commitment to the same problem and objective. Here no transfer of funds or resources is obligatory and there is no giver or taker in terms of money or what money can buy.

As it turns out, in all the above cases excepting the last, there is a donor country and a recipient country, and the responsibilities, rights, privileges, objectives and commitment of the two are not necessarily the same. In fact, in practice, they are rarely the same for the two countries in such cases. By contrast, the last-mentioned type of cooperation is truly collaborative research, as there is no donor and no recipient but a true partnership in an effort to advance knowledge and/or to use it for meeting the objective that are approved jointly.

In (a) to (d), at most an obligation of the privileged to the unprivileged country is discharged with very little gain to the donor country.
In (e) to (j), the gain to the two countries is generally different both qualitatively and quantitatively and, therefore, must be assessed carefully and independently by each of the two countries. For example, in (e), there is always the chance of the donor country providing outdated technology to the recipient which is in no position to judge it. in (f) the donor country could have, as its predominant objective, to make money. This could also be the motive in the case of (g) in respect of the donor country, but if the recipient country has chosen well, it can build on what it has imported and, in course of time, equal or excel the country from which it has received the technology – as, indeed, happened in Japan vis–à–vis the rest of the Western world. In the case of (h), the donor country receives the money while a need of the recipient country for a product is satisfied, the need could, of course, be more apparent and real, and generated by the donor country through high-pressure advertising and use of other methods and techniques which may not always be above board.

In the case of (i), the donor country that helps carry out the survey could use the information obtained for its own purposes, specially if it has the capabilities of collating and interpreting the information, which capability may not exist in the recipient country. In such cases the facilities in the recipient country in terms of men and materials could be used as a tool to acquire information that the donor country might require or merely wish to have. In the case of (j), it could very well be the case of the donor country simply getting a job done, often with lesser investment than what it would need to make at home.

I have stated and discussed the various possibilities above because it is extremely important that we...
distinguish between these possibilities when we talk of international cooperation in science and technology, for the implications of each one of the above possibilities would be different, as would be the exact nature, structure, modalities and function of the cooperation.

Now, to the present agreement—the Vaccine Action Programme (VAP) proposed to be undertaken by India and the United States of America. There are three components of the agreement:

(a) There is the aid or the assistance component under USAID project number 386–0503 titled “Vaccine and Immunodiagnostic Development of the INDO–US Vaccine Action Programme”.

(b) There are plans for testing, in India, of vaccines already developed in the United States. (Such activity would require a totally different set-up from that of cooperative research.)

(c) And there is the plan to develop new vaccines for diseases such as Shigella dysentery, rabies and malaria.

Let us now look at these three components one by one.

As regards the aid component, the US will contribute six million dollars to India. This is what makes it a USAID project. Even though up to three million dollars would be contributed by India, the project establishes a relationship of a giver and a taker between the United States and India respectively. There is nothing wrong in this, in principle but, in some cases, this is not the most desirable relationship to have even between the best of friends. This is one such case. The wordings of the USAID project document clearly indicate that the rights of the two parties would be different. The argument given whenever this has been pointed out is that is the way that USAID operates. The question that such a statement begs is why couldn’t India provide the remaining six million dollars? It will in any case provide three million dollars. And, surely, a country such as India, with a tremendous scientific infrastructure, could provide some Rs 70 million over a period of three years for a programme it has placed on its top priority. It would then have become a no–cost agreement between the US and India, with equal rights and privileges for both the countries. At least to me it is not clear why it has not been conceived as a no–cost agreement.

In regard to the second of the three components mentioned above, namely the testing component, it should be obvious to anyone to anyone who knows anything about vaccines that before a large–scale testing on human objects is undertaken, there would be need for an appropriate survey. Such a survey has not yet been done. The survey should, in every case, given the realities of the world, be done entirely within the country and by the country’s own scientists. If specific help or assistance is required, it could always be obtained by making use of channels of international collaboration between scientists that always exist in open societies.

The first and initial survey would allow one to lay down the strategy for testing the vaccine. The second step would be to test the vaccine according to this strategy. However, before the testing, it would be obviously necessary to make sure that the vaccine is suitable for testing on human beings. This would require availability of facilities in the recipient country for appropriate testing of the vaccine according to its own standards of evaluation (this means that these standards would also need to be laid down). This, indeed, is the practice followed in the United States itself. For example, in one current case, a vaccine developed in India is being tested in the US. However, concerned authorities in the US did not permit the use of batches of vaccine made in India. Therefore, a strange situation has come to exist where the formula of our vaccine is not available easily in India but had to be disclosed to those who are testing it in the US so that they could have it made there itself, under their own supervision. Indeed, no one would blame the US for that. What this implies is that India would be perfectly justified in resorting to the same practice, that is, asking for the recipe of the vaccine, then producing it within the country and testing it itself. We could, at least, set up the testing facilities. That is a job we must do ourselves. Then only would we be justified in asking any country to give us vaccines for testing with or without first making it ourselves. Help which is not deserved, more often than not, turns into a liability.

As regards the third component of the agreement—that is, development of a new vaccine that would require further scientific research—I have already indicated the requirements for a research collaboration; that is, there must have been a commonality of interest amongst the scientists of the two sides before the agreement was thought of. The agreement—or talk of it—alone should not be responsible for initiating the collaboration. The agreement, ideally, should help finishing more quickly and effectively a process of collaboration already started between two intellectually and otherwise compatible groups of scientists from the two sides. This criterion is certainly not satisfied in this case. A great deal of work has been done in regard to the vaccine for Shigella dysentery, rabies and malaria in the United States, but very little—if any—here. Indeed if there were any new ideas in this area in the country, organizations such as Science
& Engineering Research Council (SERC) would have had projects submitted to them on the proposed work in these areas. As the Chairman of the SERC’s Programme Advisory Committee on Genetic Engineering and Molecular Biology for several years (in fact, right from the beginning), I do not believe any such proposal ever came before SERC. In fact, the agreement does not even state who the likely parties from the two sides would be. At least on the face of it, it is not a true scientist–to–scientist agreement. In the area of scientific research, only a de facto scientist–to–scientist agreement can lead to a truly collaborative work.

I believe we have much to learn from the rest of the world, the USA included. And I have the highest respect for American science. Therefore, I believe that we could—and still can—do much better in regard to scientific collaboration between the two countries than the agreement would allow.

Perhaps, it may be wise to defer the present agreement and arrive at separate agreements in regard to the different kinds of activities postulated, each argument being drawn up with much greater care than has been done till now so that all the points that I have mentioned here—and those I haven’t—could be taken care of. I am suggesting this positive step as, indeed, I have no reason to doubt the bona fides of either side: I believe that it is only inadvertently that the present difficulty has arisen—perhaps, because not enough thought was given to it from our side. Justice should not only be done but must appear to have been done.

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**The scene around the Indo-US Vaccine Action Programme**

The Indo-US Vaccine Action Programme, was an MOU between India and USA signed on 9th July 1987. The scope of the agreement signed by John Gunther Dean, US Ambassador to India, and S Ramachandran, then Secretary, Department of Biotechnology, encompassed cooperation across the entire spectrum of vaccine-related technologies, including research to develop new and improved vaccines and vaccine-related diagnostic methodology, field trials and quality control of vaccines, and vaccine delivery methodology. The fine print, however, apart from enabling the US to test several of its advanced and genetically engineered vaccines on Indian people, also gave them access to epidemiological data, as well as sera and blood samples of Indian population. It is common knowledge that samples of blood, sera and cells can tell a lot about the genetic makeup of a population, its immune and antibody profile – collectively known as herd-structure. Such epidemiological data is considered sensitive due to its potential in developing population-specific weapons for biological warfare.

The controversial Indo-US Vaccine Action Programme (VAP), fraught with harmful consequences for the country, was signed bypassing the high-power Scientific Advisory Committee for the Department of Biotechnology set up by the Government, of which PM Bhargava (PMB) was a member. It came under severe attack from a handful of scientists and journalists. PMB was quoted extensively in the national press and in *Nature* (10th September 1987), questioning India’s wisdom in signing an agreement that gives away strategically sensitive data. Much pressure resulted, and a meeting between PMB and the US Ambassador in Delhi was set at 10 pm on 27th September 1987. Asked why he was opposing the VAP, PMB summarized his position and, in turn, asked the Deputy Ambassador the question – what would you do if the roles were reversed?

When the Deputy Ambassador learnt that PMB was going to speak his mind the following day at the Indian Science Writer’s Association meeting, all cordiality in his tone vanished. He handed out to PMB a sheet of paper and simply ordered that the US Ambassador would like PMB to read out the statement typed out on that paper, at the ISWA meeting. PMB took the sheet and replied that what he would say at the meeting would be reasonable and he would be able to defend it anytime anywhere. He quickly got up to leave the room; what ensued then was a battle of wits with the Deputy Ambassador doing his best to retrieve that sheet of paper with the eagle water-mark from PMB who had already made up his mind to not return it. The water-mark proved that the statement was prepared by the US government and probably in the US Embassy.

The following day at the ISWA meeting not only did PMB oppose the VAP, he also narrated on what happened at the residence of the US Deputy Ambassador. Soon a strong Indian contingent was named to represent India in the Joint Working Group of VAP. PMB was named part of this group.

The first meeting of the Joint working Group of the Indo-US Vaccine Action Programme was held in New Delhi on 2nd, 3rd and 4th March 1988. On the evening of the 3rd March, the American Ambassador, John Gunther Dean, threw a dinner for the members of the bilateral group. Nobel Laureate, Fred Robbins, who was a member of the group from the US side, was asked by Ambassador Gunther Dean as to how the meeting went. He replied – ask Dr. Bhargava. The Ambassador turned his back and left!

Excerpts from *Breaking Boundaries* a biography of P M Bhargava by Chandana Chakrabarti (to be published). *Edited by R Srivatsan*
The relationship between public consultation and policy in the area of vaccines is such that the real national consultations had limited impact on policy while the announced policy1 was not based on broad based consultation. This may be a familiar theme in many areas of public policy in India, but it is extremely important for a healthy democracy that it’s informed citizenry document and discuss the strenuous relationship between public consultation and policy in each and every area of public interest.

Background

Vaccine development and production in India dates back to over a century, when the British established the Pasteur Institutes in India to deal with tropical infectious diseases, making India one of the world leaders in the field. The lack of a clear vision and policy for vaccines in independent India led to the loss of the country’s early leadership in vaccine development in the initial decades, followed by the neglect of public sector and decline in vaccine production in the later decades.2, 3 The resulting demand-supply gap for universal vaccines in India2 remains unfilled till date. UNICEF acknowledged this as a global trend (www.unicef.org/supply_index_vaccines_security.html). The government rightly adopted self-sufficiency in vaccine production and self-reliance in vaccine technology as its policy objectives in 1986. However, in the absence of a full-fledged vaccine policy, there was no clarity or consistency on domestic manufacture vs. import, role of public and private sectors, choice of new vaccines and combination vaccines, universal vs. selective vaccination, routine immunization vs. special drives, cost-benefit aspects, logistics etc.

The lack of clear policy also led to the unregulated proliferation of private and foreign companies making and selling several new and expensive vaccines (or their combinations). Most of them were not part of the Universal Immunization Programme (UIP), but were often recommended by private medical practitioners under the unethical influence of private vaccine firms. Combining the new vaccines with UIP vaccines made market penetration easier, especially in an unregulated market.4 Gradually this influence spread to professional associations/academies and eventually found its way into government procurement decisions.

None of these trends caused an alarm as long as public sector units continued to meet bulk of the government procurement of vaccines under the UIP at throwaway prices. Even the fact that only 4 vaccine public sector units (PSUs) remained out of 29 at peak strength nearly went unnoticed.5 But in 2008, all 3 centrally owned vaccine PSUs were suddenly suspended in the name of non-compliance with WHO good manufacturing practices (GMP). The resultant price increases and vaccine shortages due to the failure of the private sector to fulfil its promises came as a rude shock and made headlines.6 The lack of a vaccine policy was beginning to hurt not only the public exchequer but also the children. It was this realization that led to the first ever ICMR-NISTADS National Consultation on Vaccine Policy.

ICMR-NISTADS national consultation

The first ever brain-storming workshop on ‘Sustainable National Vaccine Policy’ was co-organised by Indian Council of Medical Research (ICMR) and National Institute of Science, Technology and Development Studies (NISTADS), an autonomous institute under Council of Scientific and Industrial Research (CSIR) between 4-5 June 2009 at the National Institute of Science, Technology and Development Studies (NISTADS), New Delhi. It was inaugurated by the then Director General (DG) of ICMR & Secretary of the Department of Health Research (DHR) Dr. V. M. Katoch. It brought together scientists, public health experts, paediatricians, policy analysts, lawyers, economists, health activists and others from all over India. After extensive deliberations, they unanimously adopted a draft policy document titled “Framework for an evidence-based National Vaccine Policy”. It was agreed that it should be a part of the disease control strategy under the broader National Health Policy, based on the principles of public health and comprehensive primary health care to enable rational and evidence-based decisions. Follow-up discussions on the draft continued for months over email and the final document was eventually submitted to ICMR and published in India’s best known peer-reviewed, open-access medical journal with 32 authors7. It has been widely cited but did not attract any criticism, barring one commentary8. The policy document comprehensively addressed aspects such as:
Vaccine Types & Categories

Universal vs. selective immunization

Criteria to determine the necessity, suitability, safety, efficacy, coverage, accessibility and affordability, logistics & sustainability of a vaccine at the individual/population levels.

Government vaccine budget and the sustainability of expenditure on immunization

Vaccine decision support system

Vaccine pricing and regulation

Vaccine development and production, access to technology

Intellectual property rights, pathogen diversity, access and benefit sharing

Role of public and private sectors in vaccine development, manufacture and delivery

Distribution, logistics and utilization of vaccines

Policy objectives

The important objectives are reproduced from Madhavi et al\textsuperscript{7} as follows:

1. To contribute to the prevention of mortality and morbidity due to communicable diseases that afflict large populations, especially children; through the use of safe, effective and affordable vaccines, chosen rationally based on scientific evidence.

2. To develop and use the interdisciplinary knowledge base needed for science-based policy and evidence-based practice in the field of vaccines.

3. To achieve pre-eminence in the capabilities and national self-reliance in vaccine R&D, through indigenous public sector and foster a leading role for them in all the aspects of vaccine development, production and immunization for national health security and biosecurity.

4. To maximize the national benefits of international sharing of indigenous biological diversity of pathogens, hosts and knowledge, to the Indian end-users of vaccines on terms that are fair and just.

5. To enable India to play a leading role in the supply of affordable vaccines to the emerging world, considering the declining interest of the multinational sector to make cost-effective vaccines for the emerging world.

6. To promote ethical conduct in the development, trials, adoption and administration of vaccines especially aimed at children and pregnant women.

7. To develop a system for monitoring and where required compensating adverse events following immunization by strengthening disease surveillance & monitoring system, and health management information system (HMIS).

8. To synergize all other relevant policies for effective implementation of the national vaccine policy to fulfil the above objectives.

Approach

The recommended approach from the ICMR-NISTADS national workshop\textsuperscript{7} can be summarized as follows:

- Introduction of any vaccine must be backed by scientific evidence (epidemiological, medical, economic), as well as cost-benefit, risk-benefit and effectiveness on local population taking into account local serotypes and variations in indigenous host-pathogen-environment interactions.

- Being prescription drugs, all vaccines should be deemed un-necessary or selective, unless their universal usage is scientifically warranted.

- Combination vaccines must have strong medical rationale; universal and non-universal vaccines should not be combined and their prices should not exceed their sum total.

- Up-gradation of the National Technical Advisory Group on Immunization (NTAGI) into an expanded, multi disciplinary national vaccine regulatory authority (NVRA) to take all major decisions on vaccines such as disease burden, vaccine development, adoption, production, procurement, distribution, immunization and follow-up.

- Prevention of unethical promotion of vaccines and clinical trials and legislative facilitation to enable Adverse Vaccine Reaction Monitoring & compensation during trials and post-immunization.

- Prioritizing affordable access to vaccine technologies through public sector over IPR issues
and technology transfer considerations in all publicly funded vaccine research, development, production and procurement programmes, including compulsory licensing, wherever necessary.

- Pricing of all vaccines to be brought under Drug Price Control Order (DPCO).
- Thorough and transparent review of all public private partnerships (PPP) in vaccine development, production and delivery including the vaccine park at Chengalpattu.

**Developments that led to the government policy**

Severe criticism in the media, parliament and Court litigations (Annexure 1) on the malafide suspension of vaccine PSUs (during the UPA-I regime) and the resulting vaccine shortages and price increases forced UPA-II regime to rethink. Even as the first day of the ICMR-NISTADS national workshop was in progress on 4th June 2009, the news broke that the President of India announced on behalf of the newly elected UPA-II government that the suspended vaccine PSUs will be revived and upgraded as soon as possible. Later, the Javid Choudhury Committee of the government vindicated the previous criticism and recommended PSU revival and other suggestions similar to the ICMR-NISTADS national workshop. In the meantime, the High Court of Delhi asked the Indian government to consider having a national vaccine policy and even cited the policy document brought out by the ICMR-NISTADS national workshop, while hearing a petition against the pentavalent vaccine

"... A vaccine policy has been framed by some experts (it appears on page 211 of the paper book). The Respondents may examine the policy for framing similar or other guidelines, whenever it becomes necessary at some stage."

**National Vaccine Policy of India (2011)**

Seemingly in response to the interim order of the high court, the Union ministry of health and family Welfare (MOHFW) requested the National Technical Advisory Group on Immunization (NTAGI) to formulate a vaccine policy, which was made by April 2011 and announced in July in a five star hotel with few invitees. The government policy had several positive aspects similar to those that emerged from the ICMR-NISTADS national consultation, such as the emphasis on vaccine security, management, regulatory guidelines, vaccine research and development, and product development.

**Critique of the National Vaccine Policy (2011)**

The national policy carefully avoided mentioning selective immunization, irrational combination vaccines or the importance of indigenous production and public sector. It derided its own PSUs for their ‘limited capacity’ and diminished their role to only those ‘vaccines that have very low profit margins’. Instead, it emphasized the role of private sector, universal immunization for all ‘vaccine preventable diseases’, highlighted ‘new’ and ‘under-utilised’ vaccines produced by the private/multinational sector, termed the need for evidence as ‘barriers to introduction’ of new vaccines, advocated ‘public-private partnerships’ (PPP), mandated ‘advance market commitments’ in the name of ‘innovative financing’ and uncritically accepted the aid politics and the role of industry-funded/friendly international organizations such as Bill and Melinda Gates Foundation (BMGF), GAVI, PATH, WHO, UNICEF etc., thus legitimizing the status quo as the official policy.

A detailed critique of the national vaccine policy is available elsewhere, which highlighted how it was not based on a broad based consultation with the public or parliament, but on a draft originally meant to be prepared by two members of NTAGI but eventually prepared only by a single member despite protests from the other member. A few portions of the national vaccine policy are reproduced below to illustrate its regressive approach

- There is limited production capacity of these vaccines in public sector units and the involvement of private sector manufacturers is required to ensure supply of UIP vaccines is not threatened.
- The pricing policy on vaccines should be based on a realistic assessment to retain the interest of the vaccine industry in research on the new vaccines. The public sector industry should be revived to provide vaccines that have very low profit margins and to make these units competitive, they should be able to hire global consultants...
- It should be mandatory for the Government to support such developments with Advance Marketing Commitments (AMC) and honor these commitments.
- **models must be developed at least for some vaccines such as pneumococcal conjugate vaccine, rotavirus vaccine and HPV vaccine.**
Current scenario

The new national vaccine policy has enabled the government to continue with its approach of vaccine-centric approach to disease control, rather than disease burden-based approach to adoption of vaccines in Universal immunization. Even though the suspended PSUs have been revived and two out of three have even become GMP compliant, their production is yet to be restored to the pre-suspension status. This not because of lack of production capacity, but apparently due to the lack of purchase orders from the government for individual vaccines or DTP combination produced by the PSUs. Instead, there seems to be growing preference for new combination vaccines produced by the private sector (such as pentavalent) despite their high prices and adverse effects.12, 13

Conclusions and prospects

Scholarly literature on the history and dynamics of vaccine development and production in India enabled public understanding and civil society reaction against the arbitrary suspension of vaccine PSUs and the increasing role of private sector in national immunization programmes. The ICMR-NISTADS national consultation7 and its policy draft (2009) had only a limited impact on official policy, whereas the National Vaccine Policy1 was framed and announced without broader consultations. The critical engagement of the media, parliament and civil society was crucial for advocacy and litigation, which eventually impacted a shift in policy to revive the suspended PSUs. However, in the absence of purchase orders from the government, the revived PSUs have no future, unless they become component suppliers to the private sector in the emerging PPP scenario. Considering the orders of magnitude of price difference between the sum of individual PSU vaccines and their private combinations, it amounts to spending public money to procure cheap PSU vaccines at huge value-added prices from private companies. How much real value is added in terms of public health by the privately manufactured new vaccines is anybody’s guess and it suits those committed to PPP to keep it that way.

Annexure

Chronology of events since the suspension of 3 vaccine public sector units (PSUs)

<table>
<thead>
<tr>
<th>Date</th>
<th>Events</th>
</tr>
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<tbody>
<tr>
<td>Jan 2008</td>
<td>DCGI ordered suspension of vaccine production in CRI, PII and BCGVL on GMP</td>
</tr>
<tr>
<td>April 2008</td>
<td>Frontline cover story on “vaccine worries” attacked govt. for PSU closure</td>
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<tr>
<td>July 2008</td>
<td>Health Minister Ramadoss appointed expert committee on the future of vaccine PSUs</td>
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<tr>
<td>Aug 2008</td>
<td>CBI seeks ministry nod to grill PII, BCGVL Chennai lab ex-director, Elangeswaran</td>
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<tr>
<td>Feb 2009</td>
<td>Supreme Court admitted a PIL against PSU closure by S P Shukla &amp; others (HRLN)</td>
</tr>
<tr>
<td>18 Feb 2009</td>
<td>34th parliamentary standing committee report on health attacks govt. on PSUs</td>
</tr>
<tr>
<td>20 Feb 2009</td>
<td>Supreme Court issues notice to the Union Govt. in the vaccine PIL</td>
</tr>
<tr>
<td>4-5 June 2009</td>
<td>ICMR-NISTADS workshop produced a draft National Vaccine Policy</td>
</tr>
<tr>
<td>4 June 2009</td>
<td>President of India’s speech in the parliament mentioned revival of vaccine PSUs</td>
</tr>
<tr>
<td>June 2009</td>
<td>Health ministry prepares an action plan to revive PSUs by 30th June 2010</td>
</tr>
<tr>
<td>Jul-Aug 2009</td>
<td>Govt invests additional Rs 14 crore to make CRI GMP-compliant</td>
</tr>
<tr>
<td>25 Sept 2009</td>
<td>Govt constitutes Javid Chowdhury Committee on vaccine PSUs</td>
</tr>
<tr>
<td>18 Dec 2009</td>
<td>38th parliamentary standing committee report on health criticizes slow PSU revival</td>
</tr>
<tr>
<td>3rd Feb 2010</td>
<td>PIL admitted in the Delhi High Court against pentavalent Vaccine</td>
</tr>
<tr>
<td>5th Feb 2010</td>
<td>Javed Committee submits interim report indicting govt for suspending PSUs</td>
</tr>
<tr>
<td>26th Feb 2010</td>
<td>Health ministry sends revival orders to 3 PSUs</td>
</tr>
<tr>
<td>April 2010</td>
<td>High court issues interim order to govt to formulate a national vaccine policy</td>
</tr>
<tr>
<td>Date</td>
<td>Event</td>
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<tr>
<td>Sept 2010</td>
<td>Final Report of Javed Chowdhury committee severely indicts govt on PSUs</td>
</tr>
<tr>
<td>25th Sept 2011</td>
<td>52nd report of the parliamentary standing committee on health still critical</td>
</tr>
<tr>
<td>11th April 2011</td>
<td>Govt.’s National Vaccine Policy, MOHFW released, announced in July</td>
</tr>
<tr>
<td>Nov 2011</td>
<td>High court interim order to relook into Govt’s vaccine policy document</td>
</tr>
<tr>
<td>29 Nov 2011</td>
<td>Mani (ex-director, CRI) suspended while pending an enquiry, a day before retirement</td>
</tr>
<tr>
<td>Dec 2011</td>
<td>A PIL against introduction of Pentavalent vaccine was filed in Kerala High court following deaths after pentavalent vaccination</td>
</tr>
</tbody>
</table>

On 30th Nov 2012, High court issues a notice to the government to relook into government’s vaccine policy [notice on the petitioners application (C.M. 18416/2011) seeking honourable court to direct the government to look into its vaccine policy in its order dated 30.11.2012].

Another PIL was filed by Dr. Yogesh Jain, Jan Swasthya Sahayog in Supreme Court seeking a ban on pentavalent vaccine due to reported deaths since its introduction in few states in Dec 2011. [Dr. Yogesh Jain vs. Union of India & Ors., WP (C) 697/2013]

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References
10. Interim Court Order no: W.P.(C) 13698/2009, dated 7-4-2010 on PIL against pentavalent vaccine by K. B. Saxena and others vs Union Government and others by Chief Justice, Mukta Gupta, High Court, Delhi.
Economic Evaluation of Public Health Interventions: Some reflections in the context of prioritising vaccines in India.

Rakhal Gaitonde
V.R. Muraleedharan

I. Goal

The goal in any public health programme is the maximization of health of the population, equitability, affordability and relevance to the local settings (drawn from the Alma Ata declaration). In this context where the individual and the community have the inherent right to health, this cannot and should not be automatically and uncritically extrapolated into a "Right to All the Latest Vaccines". The commitment to the right to health is to use the best available knowledge to use the best available interventions to maximise health-the most systematic and broad based way. This needs to be done with reference to the context, including the budgetary considerations, within which this is being articulated. To put the argument more explicitly and up FRONT: all that is effective need not be part of public health system. Prioritization is essential (and inevitable) particularly among those interventions considered effective. Therefore we need some principles to guide us through this process of prioritization. In this short paper, we put forward some of these principles/guidelines that may help us move forward in the Indian context.

II. Context

There has been a general uneasiness at various levels of decision making and among those embarking on building the healthcare system in India that a significant part of public resources is being spent inefficiently and on interventions (vaccines) whose benefits are questionable. This impression has grown stronger over the years, due to many reasons, with the closure of public sector units and significant rise of private manufacturers whose primary motive is predominantly profit making. We have the reputation of having ignored systematically over the past 5 decades effective and efficient preventive and promotive measures to reduce and control "vaccine preventable deaths". The system is not only weak but is covertly destabilized (through careful play of power relations) to worsen our precarious dependence on a number of high-cost, least effective medical interventions, leading to huge health loss, besides bankrupting further those already considerably suffering from avoidable diseases.

III. Are we asking the right questions?

If we consider that the over-arching aim of public health systems as maximisation of welfare, we need to ask three related questions. All three questions are empirical in nature. Robust empirical answers to these questions are essential in order to address whether and to what extent we are spending the limited public resources towards maximisation of welfare arising from various health interventions.

This paper sets out this thinking process as a way of starting a discussion on how to institutionalize such processes in India.

Current thinking on cost-effectiveness studies lays out three questions that need to be asked of every intervention before it is introduced into the public health system.

- The first question / level is - can the intervention work? This question refers to the issue of the efficacy of the intervention that is usually established under laboratory, or strictly controlled circumstances, like a randomised controlled trial.
- The second question / level is - does the intervention work? This question refers to the issue of "effectiveness". This refers to the actual benefit to the population by the intervention under program circumstances.
- The third question / level is - is the intervention worth introducing into the public health system? This question refers to comparing the cost-effectiveness of the intervention in question with other interventions aimed at the same disease, or alternatively other health interventions in general looking at the comparative benefit that the population as a whole derives from each of these competing interventions.

In the rest of the article we shall elaborate on these questions, and present a framework for addressing them, particularly with regard to the third question.

III. A. Can the intervention work?

This is the most frequently asked question, in the decision making process in any public health system. All the randomised clinical trials (Phase III) fall into this category. As per the design of such studies, the aim is to study the efficacy of the intervention (may be a drug or a vaccine) and isolate it from all other random effects. To do this not only are there very strict inclusion criteria (with patients with other inter current medical problems, extremes of ages and diverse life styles etc., usually excluded). Moreover, the
intervention is randomised and controlled, and usually
the provision of the intervention is blinded, i.e., neither
the doctor nor the patient knows whether the drug/
vaccine or a placebo is given. Another significant issue
is that both the sample size and the duration of the
study are based on the positive effects of the drug on
the disease, and the side-effects that are known from
animal studies. In such situations the longer term effect
of the drugs, rare side-effects and those effects that
are unknown are not studied. In sum such studies
merely establish that the intervention has a positive
effect when given to an individual under strictly
controlled conditions. In many circumstances this is
the only information usually used for decision making,
while logically this has to be just the first in a series of
necessary steps, as detailed below.

From the perspective of an evaluation of a candidate
vaccine some of the questions that an efficacy study
does not address are the performance of the vaccine
in a heterogenous population (i.e. populations with
varying levels of nutrition, inter-current infections
etc.), the marginal benefit of the vaccine over other
interventions for the same disease (the additional
benefit of the vaccine compared to other effective
interventions for the same condition), the indirect
effects of the vaccine like the herd effect (the protection
given by a vaccine through the vaccinated group to
the unvaccinated group due to the reduction in the
chance for transmission that ensues when a significant
proportion of the population is covered by the
vaccine), and some of the more important outcomes
from the public health point of view (e.g., reduction
in carrier state in the case of Hep B vaccine) (Clemens
1996).

III. B. Does the intervention work?

In the research relevant to public health decision
making this refers to what are known as 'effectiveness'
studies. In this type of study the question asked is not
whether the intervention is efficacious at the individual
level - as this is has already been addressed under
question 1 above --, but rather whether this
intervention is effective under the programme
conditions in a particular population in a given
geographical setting. A range of methods may be used
for these studies including cohorts (usually
retrospective) and case-control studies. The key issues
that may affect the ways an intervention plays out
under actual (programme) circumstances (with
reference to vaccines) could be related to the
characteristics of the (a) specific vaccines, and/or,
(b) community / population exposed to the vaccines
and/or, (c) the prevailing strength of the health
system. The discussion below will show that it is very
artificial to divide the factors in this way, but we do so
for the ease of discussion.

Vaccine related: These include (a) whether the strains
of the infectious agent that the vaccine is effective
against are the same strains in the particular setting
into which the vaccine is being introduced; (b) whether
the vaccine is equally immunogenic in these particular
populations - this includes issues of genetics, nutrition
as well concurrent infestations among the populations
(these will also be discussed in more detail in the
discussion on community level factors); and (c) also
issues like the way a vaccine is to be administered
(and thus the ease with which peripheral health staff
can be trained etc.,) are other related factors.

Community and Population related: Issues related to
the community and population include the level of
malnutrition, the level of gastro-intestinal infections
and infestations (with worms). While concurrent
infections has an important effect on oral vaccines,
the infestations have a tendency to shift the
predominant response of the immune system from a
Th1 to a Th2 type -- Th1 is required for vaccine related
protection. So worm infestation and other such
underlying diseases may confound the effectiveness
of vaccines. Further, while the literature has shown
till now that malnutrition in itself may not limit
(reduce) the ability of the individual to mount an
immunogenic response to the vaccine, there are some
suggestions that the response in malnourished
individuals may not be as long lasting as that in well
nourished counterparts. This apart, there are other more
socially mediated issues like gender, caste and class
that may affect the effectiveness of the vaccines. It is
well established that more girls are not vaccinated than
boys and that more girls discontinue a vaccine
schedule than boys. Moreover, there are also caste and
class related inequities well established in the literature
with regard to vaccine coverage, in particular.

Given that non-vaccination of the marginalized
communities is well established, it needs to be
underlined that the marginalized communities like the
dalits, adivasis especially are not randomly distributed
in a population, in other words they are clustered. In
such a case it is possible that the herd effect of a
vaccine does not work for this marginalized
community (which is likely to have a larger number
of unvaccinated individuals) because of the clustering.
This can lead to disease outbreaks and a higher disease
burden among such systematically neglected
communities. The other impact of such non-random
vaccine coverage is the effect this has on the
epidemiology of the disease (Fine et al 2011). When a
critical number of individuals in the population are
vaccinated this reduces the transmission of disease
within that population. In such cases it takes longer
for a susceptible population for transmission to build
up (as when the effect of vaccine wanes with age).
This leads to the shift in the population at which
disease usually occurs. Thus, in an unvaccinated
population measles usually occurs in under 5 children;
however, in vaccinated communities the average age at which measles could occur increases to the about 10 or even later. Now, this is fine for a disease like measles in which disease at a later date is much less harmful than at an earlier date. But, it is problematic for a disease like Rubella -- an increase in the age at infection means that women who are unvaccinated will acquire the disease closer to when they are married and have children. This is especially problematic when we know that the more well off will have much higher rates of protection because of their ability to corner the benefits of a public vaccination programme than those in the poorer groups. Thus, we see how community characteristics (like caste, class and gender) can affect the effectiveness of a vaccine. These may well be discussed under the health system effects if the health system is unable to or does not overcome such social issues in the delivery of services. Of course these two are related.

Health systems related: As far as the health system effects are concerned, these include lack of staff capacity, weak cold chain capacity, coverage achieved, overall robustness of the health delivery system, the trust the community has in the health system and related issues.

To sum up thus far: Efficacy of a vaccine does not automatically ensure its effectiveness. A lot depends on contexts: apart from hosts and vaccines specific characteristics, population, geographic and system specific characteristics together could significantly determine effectiveness of a vaccine.

III. C. Should the intervention be included in a publicly funded health system?

Assuming a given vaccine has passed successfully the first two questions (with respect to efficacy and effectiveness), we now turn to the third question - the final step - in the decision making process: Is it worth being provided through a publicly financed health care system? At any point of time, as we have said earlier, there is always a limit to how much can we spend over a period of time. How do we prioritise a given intervention along with a set of other interventions, each of which will demand a portion of the limited budget available?

Process of prioritization

In this section we use Culyer's (2015) framework (book-shelf model, as he calls it) for illustrating the problem of prioritising in the context of a limited budget, and suggest that his line of thinking will bear more fruits in spending public money more wisely. Though Culyer's approach is very demanding in terms of empirical evidence, in fact any economic analysis is very data driven and is not an easy mechanical calculation, we find his way of conceptualizing and exposition of the problem of prioritization is very helpful. We first summarize Culyer's framework and then conclude with suggesting a few initial studies that we need to undertake before we have the capacity to adopt such a framework in decision making.

Book shelf model

The broad question in the health sector is this: we have set of interventions whose effectiveness have been established—we are assuming that there are no interventions with dubious claims - how do we decide which of these should be funded and provided publicly. Some interventions are disease specific, like cancer treatment, some are not disease specific like nutritional interventions, some are preventive and yet others are diagnostics related. "Yet we need a common measure of outcome for all of them" (Culyer, 2016). As he warns, "arriving at a common measure of outcome is not a trivial task". The reason why it is so important is that if "decision makers cannot make reasonable comparisons, they can hardly make reasonable choices". Culyer's book-shelf model first assumes that we have somehow come to a consensus on a measure of health gain of every given health intervention. This could be stated as QUALY (quality adjusted life years) or Disability Adjusted Life Years (DALY) saved. He calls it "Health benefit per $1000" (Y axis, Refer Figure 1, adapted from Culyer 2015). This is easier said than done. We need much more reliable database than we have and of course, we also need a consensus on common measure of outcome of various interventions.

Prioritization and importance of a threshold

First we need to understand better the X-axis and Y-axis of Figure 1. Here we see arrangement of all interventions like a book-shelf ranked according to their effectiveness per $1000 (height, Y axis), with the most effective being on the left extreme, the next less effective on the right, successively in decreasing order of effectiveness. The effectiveness is the expected discounted net improvement in health over the period for which an intervention has effects. And "the fatness of the book is the estimated discounted cost of providing it." This is a "combination of costs of a specific technology, costs of associated procedures (other treatments, diagnosis, community services etc) for as long as treatment continues, and the estimated number of people using the intervention in question." Thus, the area of spine of each book (intervention) reflects the total benefit (health gain) of that intervention.

Estimates of cost-effectiveness ratios alone will not help in deciding which of these should be included for public funding. All interventions (on the x-axis of Figure 1) are effective. We need a threshold level $t_0$ (as shown in Figure 2), a minimum threshold level of
Figure 1: Range of Interventions arranged like a book shelf

Figure 2: The budget and the Threshold

Figure 3: Health loss from poor technology selection

Figure 4: Extreme Health loss from the threshold set too low
effectiveness (a benchmark, least cost-effective ratio) that must be satisfied by an intervention in order to be included. Interventions that fail this test are not cost-effective. Relative cost-effectiveness of each intervention should be demonstrated, keeping in mind t0.

Often we end up close to a situation as Figure 3, where a less cost-effective intervention has replaced a more cost effective intervention, resulting in a net health loss (as shown in the shaded area); or even worse we may be close to a situation as in Figure 4, where the net health loss is much greater due to setting of a much lower threshold and letting several less cost effective interventions replace more cost-effective interventions. (Figures adapted from Culyer 2015)

A quick recap:

We need to spend more wisely, whatever (limited) public resources we have for healthcare. We need to reduce wasteful spending and be more efficient. We need to also make a case for enhancing (or reducing) the budget for introduction (or removal) of new (or existing inefficient) interventions. Pushing the budgetary limits require robust economic analysis and framework for prioritization. Mere effectiveness is not adequate to make a persuasive case for inclusion in public insurance plans. Threshold level cannot be set independently of budgetary limits. Threshold level can be approached from supply side or demand side. Setting threshold too high or low costs lives. We have closed our eyes for too long from setting our own "threshold levels". There is a general uneasiness among several well-informed practitioners of public health and those in the policy-making circles that we are closer to the scenario as in Figure 4.

IV. Way forward?

Setting threshold is a not a direct, and simple exercise. First of all we need a robust cost-effectiveness estimates of various interventions. This is easier said than done. But the way forward is fraught with several methodological issues, both in costing and in arriving at common measure of outcomes (such as time frame and discount rate to be considered, measures of effectiveness to be used for comparisons). Besides these challenges, the credibility of the whole exercise depends a great deal on the credibility of the body and institutional mechanisms participating in the decision making processes, which should be transparent and allow democratic deliberations and consultative interactions towards prioritization.

Many countries (particularly many in Africa) have embarked on conducting costing studies (Refer Special Issues from Vaccines 2015) with a view to help programme managers assess the relative amount of resources being spent per vaccine dose, per child and per facility and regional level.

Our initial steps are therefore obvious: Undertake costing studies of various interventions (vaccines to be prioritised); Undertake effectiveness studies of existing vaccines - design robust retrospective and prospective studies. Build our statistical capacity in undertaking cost-effectiveness studies. These are essential in order to raise questions on the rationality and justification for funding various interventions (vaccines) with public resources. Make economic evaluation of existing and new vaccines mandatory as part of our efforts to strengthen public health system in India.

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It was one of those days either in the last week of February or first week of March in the year 2012 when meetings are held in the Nirman Bhawan (headquarters of the Central Ministry of Health and Family Welfare [MOHFW], Government of India) for disbursal of funds by the Centre to the states for the implementation of what was then known as NRHM (National Rural Health Mission), and is now called NHM (National Health Mission). That was the day designated for NPCC (National Program Coordination Committee) meeting for the state of Uttar Pradesh.

Principal Secretary Health for Uttar Pradesh sought a meaty share of Center’s resources for the state. He threw the weight that the state carries in health policies and programs for improvement of overall health standards of the country. It was stated with aplomb – ‘Uttar Pradesh is to India, what India is to the world’, with a reference to the state’s population. Amidst senior bureaucracy and planners of the health establishment, I was a minion, duly present in that meeting as the consultant in charge for the state at NHSRC (National Health Systems Resource Centre – a technical advisory body to MOHFW).

In due course of the meeting, the discussion veered around to allocation of funds for the NVBDCP (National Vector Borne Disease Control Program); and in UP’s context the first priority was accorded to Japanese Encephalitis (JE). Rather than an occasion for matters of fact, scientific review of the public health strategies adopted and their outcomes, such meetings, as it turned out, are a rather staid affair centering around appraising the state’s performance on a given set of health interventions that are prioritized by the Centre irrespective of the specific context of the state, and the give and take of money for their implementation.

Senior managers of NVBDCP from National Institute for Communicable Diseases (NICD) were at hand to guide the strategy for control of JE. However, a summarily discussion over five to seven minutes regarding the progress made in terms of JE vaccine coverage achieved and resource utilization for the same was all that the JE control program amounted to before further funds were allocated for JE vaccination as part of the UIP (Universal Immunization Programme) in the districts of eastern UP. Sitting next to the expert from NICD, I was bemused at this turn of events and couldn’t help asking him – ‘but sir, isn’t water logging in these areas the crux of the problem, providing fertile ground for breeding of the mosquitoes that act as vector for the spread of JE? Why is it that vector control measures are not part of the plan at all? The response came by way of a laugh and the remark – ‘Oh you mean using larvicidal fish in the stagnant water? Arre ham bhi wahan ke gaon dehat ke hain; log sab bhoon-bhaan ke kha jaenge. Is se kuch nahi hoga; vaccine hi ilaj hai’ (Even I am from the same rural background and know what these people are like. They will simply devour the fish. This is of no use; the only solution is vaccination). The conversation was thus effectively killed. Even then it did show that the farthest they would go to think of the relation between water logging and JE was in terms of larvicidal fish rather than improving water drainage in the area.

Later that year, in August, I was to go on a monitoring visit to district Siddharth Nagar, adjacent to Gorakhpur district in eastern UP – the region that has been in the news as a hotbed of seasonal JE/AES (Acute Encephalitis Syndrome) epidemic for last many years. I took a flight till Gorakhpur. While the plane was hovering over the Gorakhpur air force station, the one thing that struck the eye was a vast sheet of water, gleaming under the sharp monsoon sun that covered much of the countryside around Gorakhpur. The proceedings of the UP NPCC meeting instantly played over in my mind once again.

Before we proceed further, mentioning some elementary facts is essential to facilitate the argument sought to be made here. In India the JE virus has been isolated from more than 15 species of mosquitoes; however the culicine mosquitoes Cx tritaeniorhynchus and Cx vishnui are considered as main vectors of the disease. Stagnant water, ditches, pools, puddles and paddy fields are some of the locales conducive to the breeding of vector mosquitoes. Since humans are not the preferred host for blood feed and less than 2 percent of female mosquitoes feed on humans, hence very high vector densities are believed to be essential for human transmission of JE.3 Neither paddy fields nor puddles and pools are typical only to eastern UP. Indeed, along with puddles and pools some of the most extensive paddy cultivation takes place in the states of Punjab and Haryana, which however are not known for prevalence of JE. It then appears that one major factor that actually makes the difference for bringing about a very high density of vector mosquitoes, resulting in high incidence of JE in eastern UP, is the problem of water logging in the latter region.3

But then JE is just the tip (constituting only about 15 %) of the iceberg that goes by the omnibus category of AES. AES could be caused by about hundred different types of causative agents including different types of viruses, bacteria, spirochetes, parasites etc. Almost 90 % (including JE) cases of viral AES do not
backwardness. This exacerbates the adverse cycle of diseases, JE/AES also disproportionately affect the poor living largely in the rural areas. 

The biomedical phenomenon associated with diseases play out in the social, economic and political context in which people live and ought to be understood as such. Like many other communicable diseases, JE/AES also disproportionately affect the poor living largely in the rural areas.

The significance of water logging however extends far beyond AES. In the absence of any industry, agriculture constitutes the single most important source of livelihood for the population of the region, an overwhelming majority of whom are landless, small and marginal farmers. Water logging has had a devastating effect on agricultural productivity in the region and is said to be a major cause of its overall backwardness. This exacerbates the adverse cycle of environment, poverty, and disease.

The stage is now set for us to evaluate the official strategy to combat JE/AES.

JE caught public attention with a major outbreak of the disease with over 6000 cases and 1500 deaths in the districts of eastern Uttar Pradesh and Bihar in the year 2005. In the aftermath of this disease a decision was taken to start JE vaccination in the districts known to be endemic to the disease with the Chinese SA-14-14-2 live attenuated JE vaccine in children below the age of 15 years. In the year 2011 this vaccination was included in the Universal Immunization Program (UIP) to be administered to the children at an age of 16 to 18 months along with the 1st DPT booster dose. In 2013 one more dose of SA-14-14-2 vaccine was incorporated in the UIP to be given along with the measles vaccine at 9 months of age.

Though the reasons for the shift remain unknown, but it was observed that following mass immunization campaigns with live attenuated JE vaccine among children, in some endemic states the adult JE cases outstripped those in pediatric age group, thereby leading to the imperative of JE vaccination among adults. In July 2014, the Government of India included JE vaccine in the National Immunization Programme for adults in 179 districts with high endemicity, spanning across 9 states.

Thus for all practical purposes, vaccination against JE has become the mainstay of the JE/AIDS control programme. We have already stated that both health and health problems are socially produced and it is not as though the government is not aware of this complexity with respect to JE. In fact the JE/AIDS Control Programme document categorically states that – “nature of the problem suggests that AES should be construed as a broader development and rehabilitation challenge rather than merely a medical problem. Therefore, there is a need to put in place a multi-pronged strategy.” The responsibility of implementation, monitoring and coordination of the programme rests with as many as six government ministries/departments which shall be providing interventions ranging from water and sanitation, to IEC (information, education and communication), to improved nutrition and rehabilitation in addition to the preventive and curative medical interventions. But in the same breath the program document also states that – “The new Programme combines the basic elements of on-going schemes of participating Ministries/Departments”; of course with some new elements and strategies incorporated. In effect then except for vaccination and some other medical measures, there is no real new component in the anti-JE/AIDS strategy.

Moreover, other than vaccination, the worth of other ‘elements’ and ‘strategies’ (both old and new) with respect to JE/AIDS, in the eyes of the health planners, can be judged from the already stated fact that - the discussion on this during the UP NPCC meeting began and ended with fund allocation for ‘JE vaccination.’ Nevertheless, rather than being led astray by our biases, prudence demands taking stock of the present strategy based on empirical realities. Figure 1 presents the trends in JE/AIDS cases and deaths in the country since 1996. The figure clearly shows that irrespective of the success of the JE vaccination, both morbidity and mortality due to JE/AIDS has been consistently on the rise.

It is another thing however that despite these results, there is no dearth of studies that attest to the wisdom of JE vaccination campaign. It could well be that defining the problem narrowly within the ambit of the assumptions made in the study, JE vaccination may have been found to be a cost-effective intervention; however, this conclusion does not sit pretty with the findings of Figure 1. Public health imagination cries for the health problems being conceptualized in their social, economic, political and developmental entirety if such conflict between theory and the empirical reality is to be avoided. There have however been well considered suggestions, flowing from the epidemiology of the disease, that call for treading carefully on the question of propagating JE vaccination. While going into the details of these suggestions is not necessary for the argument being forwarded here it may be noted that for each clinical case of JE, there might be between 250 to 1000 subclinical infections by JE virus, and even the non-clinical infections are known to afford natural immunity among the population to further JE infections. One post marketing surveillance study for JE vaccine conducted by ICMR (Indian Council for
Medical Research) found that 45.7% of the children already had virus neutralizing anti-bodies before vaccination.\textsuperscript{17} Vaccinating such children and adults with post-infection natural immunity is scientifically untenable. In the same study it was also found that at one year the vaccine afforded only 43.1% protective efficacy overall and 35% protection among individuals not having immunity prior to infection.\textsuperscript{17}

The NVBDCP consultant present at the UP NPCC meeting presumed the suggested solution to be the ‘larvicidal fish’ when I was referring to water logging in the districts of eastern UP as the crux of the problem of JE/AES. What I actually had in my mind was the need to develop a comprehensive plan to improve the water drainage in the entire region as a solution to not only the problem of AES, but also for the development of agriculture, the biggest source of livelihood for the people of the region, and thereby facilitate massive reduction in the contribution of poverty to the problem of AES. This can hardly be called extraordinary at a time when the government is thinking of going east to usher in the second green revolution in the country. Add to this the assured massive reduction in the morbidity and mortality due to gastrointestinal diseases, which by any account far outstrip the burden of JE/AES, and we have the framework of mother of all cost-effectiveness analysis in place. But let there be no anxieties; there are no signs yet that any of this is about to happen soon.

This however must lead us to wonder – Why then this ‘blind faith’ for vaccines alone to tide over communicable diseases which primarily have their roots in the impoverishment of the people? After all isn’t it true that along with alleviation of socioeconomic conditions of the people many infectious diseases ceased to be a public health problem in the developed nations much before the first of the tools of modern science to combat these diseases were made available.

The jury could still be out on this question and better informed opinions regarding this ‘blind faith’ couldn’t be welcomed more. The author would like to volunteer a humble opinion of his own in this regard. Apart from the larger political economy of technology in health; technological interventions seem to foster a sense of ‘assuredness’ in face of the insurmountable difficulties; they offer to simplify the complexities of real life health challenges; and weave an illusion of the redundancy of having to persevere the hard way, which even otherwise the powers that be are least inclined to do. There of course are other factors which make the system prone to such glitches, going into the details of which is beyond the brief of this paper. It is true that the health department may find addressing the larger structural determinants of diseases and health to be beyond the pale of its power, but the fact also is that the various policy documents brought out by MOHFW, Government of India since the 1983 health policy bear testimony to the fact that structural determinants of health have been edged out of its vision for health.

To avoid being thought of as a perennial skeptic, I would like to leave you with the following statement that comes from the country’s premier medical teaching and research institute. In their paper titled – ‘Development is not essential to reduce infant mortality rate in India: experience from the Ballabgarh project’, the authors conclude in the abstract of the paper:

It is possible to bring down neonatal mortality before postneonatal mortality. The Kerala model, which focuses on social development, may not apply to northern India for sociocultural reasons.\textsuperscript{18}

Further:

Our study has demonstrated that bringing down the IMR need not wait for the overall development of the community. Environmental, social and educational improvement in the developing countries is likely to be a slow process. Bringing down IMR cannot wait for that long. Developmental issues like literacy campaigns, land reforms, etc, are outside the scope of the health sector. Therefore, without in any way reducing the emphasis on these developmental programmes, we feel that IMR could be brought down faster by more specifically aimed health interventions.\textsuperscript{18}

However, if the people themselves had a real choice between ‘development’ and the ‘silver bullets’ called vaccines, let there be no doubt that they would choose the former. Manish Kakkar of PHFI, who carried out a study on the disease in the Kushinagar district of eastern UP\textsuperscript{19} had this to say of what people themselves might privilege:

But for them the bigger problem is water and sanitation. Therefore, if you start interacting with community leaders, their top most concerns would be diarrhea, chicken pox, measles, and hepatitis. Water is clearly a big problem for them.
Everybody talks about it. If you ask them to rank priorities, JE would not be a priority for them. Vaccines are a useful intervention of modern science which ought to be used with utmost responsibility, and the country can ill-afford the waste of precious resources that follows the launching of vaccination campaigns for infectious diseases that are not in conformity with the epidemiological considerations of the disease.

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References


How a private foundation is taking charge of India's vaccine policy

Sandhya Srinivasan

The choice of vaccine and its use are decisions which governments should be making with scientists, public health experts and civil society organisations, based on factors such as their effectiveness, relevance, alternatives, costs, benefits and risks. Until recently, the universal immunisation programme (UIP) in India was run by the government, with vaccines manufactured in the public sector. Now, however, new vaccines are developed by private industry, promoted in the private sector and strong-armed into the government programme. International organisations and private foundations are calling the shots, on behalf of industry.

Industry, private foundations and international organisations are explicitly called on in the National Vaccine Policy. The Policy proposes that “...the involvement of private sector manufacturers is required to ensure that supply of UIP vaccine is not threatened.” It calls for public private partnerships in vaccine development, using “flexible governing and funding mechanisms”, a pricing policy that will “retain the interest of the vaccine industry”, and the need to explore linkages “between academia, industry and international institutions”. One institution it makes specific reference to is the Bill and Melinda Gates Foundation (BMGF).

The Bill and Melinda Gates Foundation

BMGF is the largest private foundation in the world. In 2011 (the last year for which the website provides summaries on its disbursements), it spent $1.977 billion in its global health programme. It is a major funder of the World Health Organisation. Its funding reaches every possible organisation and institution, at both international and national levels, in its field of interest. It is not surprising that the pharmaceutical industry is well represented on its board. In the last few years, BMGF has come to play a dominant role in decisions at various levels in the research and development of new vaccines and their inclusion in the national immunisation programme. To illustrate, in the case of a vaccine, it might fund (with government) the biotech company that does the research and gets the patent, the academic partner in this research, the community organisation that tests it in clinical trials and even the company that finally manufactures it. It may offer the vaccine to governments at a reduced price, or free, for a few years. It may also offer a volume guarantee to industries unwilling to take the “demand-side risk” – the risk that their vaccine will not be bought.

Its scientific advisory board includes the former head of the Indian government’s department of biotechnology – who also happens to have been involved in developing the rotavirus vaccine recently introduced into the immunisation programme. The deputy director of the Global Alliance of Vaccines and Immunisation (GAVI), which is substantially funded by BMGF, was earlier mission director of the National Rural Health Mission, where she had a voice in the choice of vaccines for India’s immunisation programme.

The BMGF model and strategy

BMGF views its funds as investments, and uses its investments as leverage: by offering relatively small amounts of money for its chosen projects, it gets governments to put money into collaborations with industry for these projects. It funds product development partnerships (PDP) – agreements between government, industry and academia to develop a new technology – and as of 2009 had invested more than $1.9 billion in PDPs. By funding alliances such as GAVI, it generates donations from governments – and investment from industry.

In India, BMGF funding knits together a web of multinational and domestic pharma industry, biotech start-ups (for new research), academic institutions, non-governmental organisations, global alliances, and the government. To illustrate, in the case of a vaccine, it might fund (with government) the biotech company that does the research and gets the patent, the academic partner in this research, the community organisation that tests it in clinical trials and even the company that finally manufactures it. It may offer the vaccine to governments at a reduced price, or free, for a few years. It may also offer a volume guarantee to industries unwilling to take the “demand-side risk” – the risk that their vaccine will not be bought.

The logic of the volume guarantee is explained by Impact Alpha, a media organisation “for the growing number of people who believe our most pressing social and environmental challenges represent the biggest business opportunities of the 21st century” – an apt description of the BMGF agenda. An article in a recent issue of Impact Alpha explains how BMGF is able to use volume guarantees to attract investors “seeking to leverage private capital for large-scale change”:

The Gates Foundation is in a strong position to take on that demand-side risk because it often has a broader perspective on the overall market than the companies themselves. Not only is it
working closely with all the donor governments that provide the bulk of funding for global health campaigns, it is often supporting, through grants, the agencies and on-the-ground organizations that procure and distribute some of the very purchases it is guaranteeing. That market knowledge means that the actual risks to the foundation are lower than the perceived risks to the drug companies.  

Creating a market for new vaccines

It is with this background that one views BMGF’s investment of $4.1 billion⁷ (as of 2016) into GAVI, an alliance of vaccine manufacturers, UN organisations such as UNICEF, and governments, whose agenda it is to get new vaccines added to country programmes. According to the argument advanced by GAVI (and of course BMGF), new vaccines are needed, but they won’t come along unless industry is involved, and is assured of making a return. GAVI creates a market for these vaccines, raising funds by various means: pledges from funding organisations, matching ‘donations’ from the corporate sector, advance market commitments from governments and donors to buy certain vaccines at a specified price for a specific period, and vaccine bonds in the capital markets. Once GAVI support ends, the government must take over all costs of the programme. Thus through a combination of inducement and coercion, GAVI shapes the vaccine market, and vaccine policy.

With a permanent seat on GAVI’s board, BMGF, along with vaccine manufacturers, has a major influence in the choice of vaccines to support. GAVI’s current priorities are the pentavalent vaccine, pneumococcal vaccine and the rotavirus vaccine.

In India, up to October 2016, GAVI had disbursed $437 million, much of which was the cost of specific vaccines to be used over specific periods⁶. It started in 2002 with the Hepatitis B vaccine. $265 million – or more than 60% of all GAVI money disbursed in India— has been spent on introducing the pentavalent vaccine (2011-15). In January 2016, GAVI announced that it would extend its financing up to 2021, with $500 million, for vaccines against rotavirus, pneumonia, measles-rubella, and human papillomavirus (HPV). Of this amount, $180 million was committed to the pneumococcal vaccine (2017-19).⁷

The India vaccine story

Even independent of GAVI, BMGF’s presence is felt at every level of vaccine research and development in India. It has played a key role in steering the shift from the public to the private sector in the research and development of new vaccines, and in promoting new vaccines.

Vaccine manufacture and supply came to be largely controlled by the private sector following the 2008 closure of public sector units (PSUs) on the grounds that they did not meet WHO standards. Though the PSUs were eventually reopened, they now make only a small contribution to the UIP’s needs, leaving it at the mercy of private vaccine manufacturers for its vaccines. This is because, though PSUs make the DPT vaccine, the pentavalent vaccine (against DPT, Hepatitis B and Hib) introduced in the UIP is made by the private sector.

But in any case, the vaccine industry both domestic and international is eying India as a huge market for new vaccines. By 2013, five of the top six revenue-producing vaccine manufacturers in India were private, and all five of them have received funding from both BMGF and the Department of Biotechnology (DBT) for the development of new vaccines.

The DBT’s Biotechnology Industry Research Assistance Council (BIRAC) is a private, not-for-profit company which functions as an ‘industry-academia interface’. It nurtures small companies to collaborate with academia for early stage research and product development through to marketing – the principle again being that the public sector’s role in basic research must be complemented by the private sector to make a commercial success of it. The DBT’s Biotechnology Industry Partnership Programme co-finances high risk ventures for product development, giving industry the patent for any product developed through this research. The DBT-BMGF partnership is implemented by BIRAC.

BMGF and the rotavirus vaccine

The rotavirus vaccine is one prominent instance of vaccine research started in a public sector organisation and taken forward by a private company, supported by the governments of India and the US, and BMGF⁸. The “AIIMS newborn strain” of rotavirus, 116E, that seemed to be protective against subsequent rotavirus disease, was identified in the All India Institute of Medical Science. Interestingly, the strain was characterised through research funded by the Indo-US Vaccine Action Program (VAP). In 1998, DBT and the US secretary of health held a VAP meeting with vaccine manufacturers, where a Hyderabad-based company, Bharat Biotech, was given the rotavirus vaccine project to develop. The project was funded mostly by DBT and BMGF.

BMGF’s influence expanded over the course of the project. For example, an epidemiologist from AIIMS moved to the BMGF-funded NGO Society for Applied Studies (SAS) to run one of the clinical trial sites. The scientist first involved in the vaccine’s research came
to head the DBT and chair BIRAC – and later join BMGF’s scientific advisory board.

The results of the phase 3 trial of the rotavirus vaccine were published in June 2014. In the list of organisations represented in the list of authors, at least three – PATH, SAS and Bharat Biotech – were funded by BMGF. In one of the journal articles\(^9\) reporting on the trial (Bhandari N et al. \textit{Lancet} 2014 Jun 21; 383: 2136-43), what should have been a purely scientific statement on the vaccine’s efficacy and safety makes special mention of the unique history of the vaccine’s development as: “an example of how low-income countries and middle-income countries can... address endogenous infectious diseases of high burden without relying exclusively on multinational pharmaceutical companies”. It indirectly advocates including the rotavirus vaccine in the UIP, despite its “modest” efficacy, at the substantial cost of $3 per child.

The rotavirus vaccine is one of GAVI’s priority vaccines, which should explain its fast-tracking into the UIP. Phase 3 trials were completed in May 2013, the vaccine was approved by 2014, and it was incorporated into the national immunization programme by 2015. Concerns about the vaccine’s efficacy, relevance as well as potential risks have been brushed aside.\(^4\)

\section*{Conclusion}

As can be seen above, BMGF’s footprints are visible everywhere in anything to do with vaccines, from university departments to the national vaccine policy itself. With the introduction of new vaccines in the UIP, the vaccine industry has found entry into a huge market with good future prospects. The central question is: should a private foundation be deciding on the choice of vaccines and who manufactures them?

At present, decisions on a public good are being determined not by the people who stand to benefit – or lose – but by the very industry that profits from it.

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\textit{Email: sandhya199@gmail.com}

\section*{Notes}


\(^3\) Impact Alpha http://impactalpha.com/about-impactalpha/


\(^5\) GAVI Alliance http://www.gavi.org/funding/donor-contributions-pledges/

\(^6\) GAVI Alliance http://www.gavi.org/country/india/


\(^8\) Fogarty International Center https://www.fic.nih.gov/News/Publications/Pages/roger-glass-neonatal-rotavirus-vaccine-project-article.aspx

\(^9\) The Lancet http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2813%2962630-6/fulltext

\textbf{Is polio virus more important ...?}

no scientific answers to this question and no research was done by any stake-holders on polio eradication. The subsequent trend of increasing numbers of non-polio paralysis has caused worry to all and ICMR has assumed responsibility to lead research on the causative mechanism of this phenomenon and the possible role of enteroviruses. Again we have a lower priority than viruses. Nothing is done comprehensively for the child afflicted by the virus, polio or enterovirus; nearly 53,000 in 2012 itself. That was unethical. UNICEF which has got a Global mandate for welfare of children by the UN General Assembly cannot be abdicating its role. A paralyzed child due to polio virus or non-polio virus cannot be discriminated and ignored.

Do not ignore the child today. Give them their due along with your academic pursuits and desire for professional excellence. She/he is tomorrow's voter, policy maker and ruler who may not pardon us during our setting sun phase or twilight existence for our today's neglect.

My plea then was - look after the immediate treatment and welfare of the child paralyzed in a comprehensive package of polio eradication by State/National government and UNICEF/WHO and other overseas donors. Find funds and make an Action Plan. That is our collective duty.

The children are the most important and not the viruses!. As a reflection on lessons from polio Eradication, I find this comprehensive approach is relevant for any Immunization strategies.

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Why clinical data needs to be in public domain

(Excerpts from a PIL filed in the Supreme Court of India, Writ Petition (Civil) No.289 of 2016 (Public Interest Litigation), S. Srinivasan vs Union of India & Others.)

…the petitioner herein is filing the instant writ petition in public interest under Article 32 of the Constitution of India for the enforcement of rights under Article 14 and 21 of the citizens seeking a writ directing the respondents to make public the segregated data (center-wise results) of the Rotavac clinical trial (phase III) that was conducted on 6799 infants at three centres namely Delhi, Pune and Vellore between 2011-2013 to gauge the safety and efficacy of the said vaccine. The petitioner at this stage is not casting aspersions on the efficacy of the said vaccine but is only asking for complete segregated data to be provided. The segregated data is crucial to know if the vaccine is safe in all areas or if some groups are more susceptible to adverse events from the vaccine.

The very raison d’être of such multicenter trials is to compare results among centers. This data should have been examined by the National Technical Advisory Group on Immunization (NTAGI) in public interest but such is the secrecy surrounding it, it has not been provided even to this apex body. The instant petition is asking for the data to be provided to the petitioner or made available in the public domain.

Facts of the Case

On 26th March 2016, the Ministry of Health officially launched Rotavirus vaccine to combat deaths in infants caused due to diarrhea. Before the launch of the vaccine, a clinical trial (phase III) was conducted between 2011 and 2013 at three centres namely Delhi, Pune and Vellore to gauge the efficacy and safety of the said vaccine. Under this clinical trial, 6799 infants were administered the said vaccine to ensure its safety in terms of the number of intussusceptions in the 2-year trial period. Intussusceptions are intestinal obstructions that may need an urgent surgery to prevent death among infants, and is diagnosed by ultrasound examination. The trial was done as per protocol to test the risk of this potentially fatal side-effect of the vaccine over an observation period of 2 years. Multiple trial sites were included to ensure different geographic areas to include a wider range of population groups with allows comparison of results among centers and increases the generalizability of the study…

The aggregated results of the study published in UK Journal “Vaccine” issue dated August, 2014 raised certain questions about the efficacy of the vaccine and the risks associated with it. Through these aggregated results, an expert member of the National Technical Advisory Group on Immunization (NTAGI), which is the apex advisory body of the Government of India on immunization, Dr. Jacob Puliyel deduced that the number of cases of intussusceptions in the infants who were administered ‘rotavirus’ vaccine in Vellore centre were the highest and there was a huge difference in the number of cases of intussusceptions between result in Delhi and Vellore. As a member of NTAGI, Dr. Puliyel considered it his duty to study the segregated results of the clinical trial data from all the three centres to ascertain if a certain population was more susceptible to the side effects of the said vaccine. However, the respondents did not publish the centre-wise results of the said trial.

In his capacity as the member of NTAGI, Dr. Puliyel repeatedly made requests for the said results but the results were not provided to him. Dr. Puliyel made several representations to the Director, CMC Vellore requesting for the data for Vellore limb of the study. His request was not acceded to. He also wrote to the NTAGI by writing emails addressed to Dr. Vijaya Raghavan, Chairperson of Standing Technical Sub-Committee (STSC) of NTAGI (and copying to all members of NTAGI) requesting for the disaggregated data from Vellore in the format provided by him as a member of NTAGI. However, the results from Vellore were not provided.

It is submitted that not providing complete results of clinical trials involving human beings is in violation of ethics of medical research and global norms governing clinical trials. Raising this issue, journal Vaccine published a detailed letter dated 06.10.2014 asking for segregated centre-wise results of the clinical trial to be published. As a result of the letter many newspapers through their science correspondents tried to get the information directly from the Principal Investigator but the respondents did not provide the said data from the three centres.

In the mean time, an NGO also filed an RTI application seeking information on a.) the number of cases of intussusceptions diagnosed as ‘Possible intussusception’ (meaning exhibiting clinical evidence of intussusception diagnosed by the trial doctor as described in the study protocol) and numbers with ultrasound evidence of intussusception in the 1000 infants given the rotavirus vaccine in Vellore limb of study over the period of 2 years and, b.) what is the corresponding figure for the 500 who were placebo recipients. But no reply was given to the RTI application by the respondents.

In response to Dr. Puliyel letter to the Prime Minister dated 16.06.2015, the Prime Minister’s Office made a
therein, who was a member of the NTAGI, cannot entertain the said SLP on the ground that the petitioner, keeping all questions open expressed its inability to Delhi. On 05.02.2016 the Hon’ble Court while Order dated 14.10.2015 of the Hon’ble High Court of to filed an SLP (Civil) No.2532 of 2016 against the Aggrieved by the order, Dr. Puliyel was constrained not made available to members of the NTAGI in spite that the segregated results of the clinical trial were The Hon’ble High Court failed to appreciate the fact that the respondents have shown complete secrecy in the matter and have not disclosed segregated (meaning disaggregated) data from all the centres and have only released aggregated data i.e. the results of all three centres clubbed together. Concealing of this vital data does severe injustice to the thousands of infants who participated in this study, the researchers who painstakingly conducted the trials and the medical/scientific community who depend on this data for their work. It is even more crucial to study the segregated data because the respondents have now launched the vaccine in 4 states in the country where lakhs of infants might be administered the vaccine. It is submitted that informed consent requires the disclosure of safety data, and it would be unethical to proceed with immunisation without informing the public of any risks observed with previous use of the vaccine, and not informing them what adverse effects to look out for.

Earlier petition seeking the same relief
Aggrieved by the attitude and callousness on the part of the respondents, Dr. Jacob Puliyel filed Writ Petition No.6913 of 2015 before the Hon’ble High Court of Delhi praying for the ethical disclosure of the disaggregated data of all the centres where the study was conducted. In the said matter, Vide order dated 14.10.2015, the Hon’ble High Court had dismissed the said writ petition on the ground that segregated trial result of all the three centres was available with the National Technical Advisory Group on Immunization (NTAGI) of which the petitioner is a member and that it was on the basis of this data that the NTAGI approved the said vaccine. The Hon’ble High Court failed to appreciate the fact that the segregated results of the clinical trial were not made available to members of the NTAGI in spite of written requests for the same by Dr. Puliyel. Aggrieved by the order, Dr. Puliyel was constrained to file an SLP (Civil) No.2532 of 2016 against the Order dated 14.10.2015 of the Hon’ble High Court of Delhi. On 05.02.2016 the Hon’ble Court while keeping all questions open expressed its inability to entertain the said SLP on the ground that the petitioner therein, who was a member of the NTAGI, cannot maintain a public interest petition. The Hon’ble Court in the said order dated 05.02.2016 in SLP (C) No.2532 of 2016 stated as under:

Learned counsel for the petitioner seeks leave to withdraw this petition. This petitioner cannot maintain a petition in public interest since he was a member of the National Technical Advisory Group on Immunization which recommended the introduction of the vaccine in question. Leave to withdraw is granted. The special leave petition is dismissed as withdrawn. All questions are left open.

Therefore, the petitioner herein has filed the instant writ petition espousing the same cause of ethical and complete disclosure of clinical trial conducted on human beings. Since the High Court has already expressed its views in the matter, the petitioner herein seeks the intervention of this Hon’ble Court to set aside the Order dated 14.10.2015 of the High Court of Delhi and to direct the respondents to disclose and publish the segregated results of the clinical trial of Rotavac vaccine conducted on 6799 infants in the period between 2011-2013 at Delhi, Pune and Vellore. The petitioner also seeks an interim direction that the segregated results from all the three centres be placed before the NTAGI, which is the expert body on immunization policy, for examination and scrutiny. …

Prayer
It is most respectfully prayed that this Hon’ble Court may be pleased to:
a. Set aside final order/judgment dated 14.10.2015 of the Hon’ble High Court of Delhi in WPC 6913 of 2015
b. Issue an appropriate writ directing the respondents to provide the petitioner the complete segregated results (centre-wise data) of the clinical trial of rotavac vaccine conducted in all three centres, including the number of intussusceptions in the 2-year trial period at each centre
c. Issue an appropriate writ directing the respondents to place before the NTAGI the complete segregated results of the said clinical trial of rotavac vaccine for examination and scrutiny
d. Issue an appropriate writ restraining the respondents from including rotavac from Universal Immunization Policy of the government of India till the complete data from the said clinical trial is not disclosed to the key stakeholders, including the petitioner.
e. Issue an appropriate writ directing the respondents to frame guidelines regarding publication of complete and segregated research results in clinical trials on humans, in accordance with the WHO statement of April 2015 on the issue.
f. Issue such other writ, direction or order, which this Hon’ble court may deem fit and proper under the facts and circumstances of the case…

Filed on 23.04.2016
Information and consent are essential for maintaining credibility of vaccination program and achieving public health goals

Veena Johari

Unfortunately, public health decisions to restrict human rights have frequently been made in an uncritical, unsystematic and unscientific manner. Therefore, the prevailing assumption that public health, as articulated through specific policies and programs, is an unalloyed public good that does not require consideration of human rights norms must be challenged. For the present, it may be useful to adopt the maxim that health policies and programs should be considered discriminatory and burdensome on human rights until proven otherwise.


Prevention of disease has primarily been the responsibility of the public health care sector. The State has a duty to assess the health needs and problems of the population, develop policies and programs to address them, and to implement those programs and policies through a non-discriminatory, systematic health care mechanism, respecting rights of people. Vaccination is one such prevention health care measure, not only for the benefit of the individual but also as a public health measure to prevent diseases.

In the year 1880, the (then colonial) government, as a public health measure, passed ‘The Vaccination Act’ that made the small pox vaccination in certain areas, municipalities and cantonments compulsory, and also allowed the State governments to withdraw a certain area from the purview of the Act. It recognized that some children could be unfit for the vaccine, and a certificate stating the same had to be issued. It recognized that on some children the vaccine would be a failure, and directed the child to be vaccinated again in case of failure. In case the vaccine fails three times, then the child would not be required to be vaccinated again. The Act made non-compliance, without a just cause or excuse, an offence, punishable with imprisonment and a fine. Small pox was endemic in certain areas then and stringent measures to vaccinate and control the spread of the disease was pertinent.

Since then, many more vaccines have been introduced as a public health measure under some policy or program of the Central and State governments, but not all the vaccines are for contagious diseases that require compulsory vaccination to halt the spread of the disease. There are alternative cures, methods, treatments and tests that can detect the disease and treat it, alternative preventive strategies that could be far superior and safer than vaccines. Vaccines have a potential of making a long lasting serious impact on a few individuals who are not suited for the vaccine, but have been vaccinated under the universal programme to provide short term safety as a public health goal.

Therefore, the question that arises is that when public health measures are taken to prevent diseases, does that violate the human rights and the principle of autonomy of the people being vaccinated? The government takes a unilateral decision to vaccinate, which often violates the fundamental and ethical principles of informed consent to be taken from the person being vaccinated or her/his guardian prior to the medical intervention. Are such mandatory measures to prevent diseases and to vaccinate constitutional, and does it violate legal ethical principles and rights of the people?

Is it necessary to mandate vaccination?

In order to achieve public health targets and prevent diseases in the population, it may be necessary to provide for vaccinations in the population. However, it may not be necessary to limit individual rights to achieve the public interest objective. It is well documented and demonstrated in the HIV epidemic that respecting and protecting individual rights, especially of those most vulnerable to the disease, leads to empowerment, enhancement and achievement of the public health goal and curtailment of the spread of the disease. The same can be applicable to all other situations and diseases that require to be controlled through public health measures. The only exception that probably could be carved out is in an emergency when there is a real threat of rapid spread of a highly contagious disease or an outbreak of an epidemic disease.

Mandatory testing, treatment, quarantine and isolation have been legitimized only where it is made with the objective of curtailment of contagious diseases. When mandatory testing is not imposed in the least restrictive and least intrusive means, imposed arbitrarily and is not strictly necessary, it would be a breach of rights of the people affected, and considered to be unconstitutional. Limitation of an individual right must be proportional to the public interest and its objective.

During ‘routine’ vaccinations, more often than not, adequate information is not provided to the parents of the child being vaccinated, no information on side-effects, success, failure, contraindications, alternatives, treatment options in case the child gets the disease for which s/he is being vaccinated, methods of prevention
of disease (other than vaccination), adverse and serious adverse events is given to the persons being vaccinated or their parents/guardians. Public health arguments have been that giving all information prior to the vaccination could create a fear in the minds of the people, and they may not get their child vaccinated. Such a justification to violate an important right to autonomy is unacceptable, as it is well known that there are uncertainties surrounding vaccines with regard to their overall safety and efficacy. Non-disclosure of data showing the deficiencies and links to adverse events and safety of the vaccine violates the principles of informed consent and grossly undermines the rights of persons being vaccinated to make intelligent and informed decisions with regard to their own health, health of their child and health of the community at large.

Is informed consent required?

It is known that no vaccine is absolutely safe. It is also known that the vaccine will fail on some individuals, and it may be contraindicated on others. There maybe some tests to determine allergic reactions, some to determine contraindications, but there may not be any routine tests available to determine if a person will react to the vaccine or not. It therefore becomes imperative for doctors and health care providers to give complete information with regard to the vaccines prior to vaccination. It is also important that proper documentation is done, history of the child, adverse events on previous vaccinations of the child or her/his siblings is taken, so that the health care provider and the parents can discuss the pros and cons of vaccination, with regard to the known and unknown side-effects and take an informed decision whether or not to vaccinate the child. It is necessary that the law and policy carves out exceptions and makes provisions to exempt certain individuals, on whom there is a likelihood of contraindications, or who do not consent for the vaccination. Such refusal should be documented, and parents’ or children’s wishes should be respected.

Whose duty is it to warn of the risks?

In mass vaccinations, where programs are run by the government under the universal immunization program, the question arises about whose duty it is to warn people being vaccinated about the probable side-effects of the vaccine? Is it the manufacturer’s duty, the government’s duty or the health care provider’s duty?

True, the manufacturer may have provided the package insert document that would have the contraindications, and risks involved. However, it cannot be expected that the people who are being vaccinated (or their parents) read the package inserts prior to vaccination. In a case in the U.S.A., Reyes v. Wyeth Laboratories, 498 F.2d 1264 (5th Cir. 1974) an amount of USD 200,000 was awarded to an 18 month child who contracted polio after being vaccinated, even though the package insert carried the warning. It was held that the warning was not conveyed to those receiving the vaccine, and the manufacturer had a strict liability for the child’s injuries. A warning that reaches only the physician is insufficient. The court had defined an “unavoidably unsafe product” if it is defective and is unreasonably dangerous. In the case in point, the benefits outweighed the harm, and the polio vaccine was not defined as unreasonably dangerous, but even so the manufacturer was required to provide adequate warning while marketing the product. Thus, just as manufacturers of drugs are supposed to provide complete and accurate information about the product, the same ought to be applicable for vaccines, and such norms ought not to be relaxed for vaccines.

The government that takes the decision to immunize all persons within a locality with a particular vaccine also ought to be held liable for not providing adequate information about the vaccine, alternatives and benefits and risks of the vaccine. Generally, when there is no outbreak of an epidemic, the decision to vaccinate takes place in an ad hoc manner, more often than not on the persuasion of the pharmaceutical companies who have a vested interest in the large-scale sale of their product. The number of countries using the product is listed and hardly any consideration is taken whether there is a local need to vaccinate or not. Statistics on the number of vaccine shots given and the number of adverse events are considered, rather than the number of persons being vaccinated and the number facing vaccine related adverse and serious adverse events. Multiple shots of a vaccine are given are regular intervals and booster shots are also given. But, the number of persons getting vaccinated could be less than the statistical figure of the number of shots given. Further, no scientific inquiry takes place on the impact of the vaccine on persons and there are too many unanswered questions with regard to the approval, the recording of adverse events, the efficacy and the safety of vaccines. The government being a welfare state needs to make a thorough inquiry into these matters before deciding on vaccination and provide complete and honest information to those being vaccinated. When and who to vaccinate also ought to be a reasoned decision, based on not just economics, but also alternatives, seriousness of the disease, prevalence of the disease and the impact it would have if immunization does not take place or does take place.

It is the medical persons or health care providers who are actually administering the vaccine who have the opportunity to provide adequate information to the recipients of the vaccine or their parents, and they have a duty to do so. Under medical ethics, they have a
duty to warn and to take informed consent prior to any medical intervention. This duty cannot and ought not to be abandoned or discarded under any public health programme, whether mandated or not. It is the duty of the physician to look after the health and safety of all on whom s/he has conducted a medical intervention and warn the patients of the risks, benefits, alternatives and take full informed consent prior to administering the vaccine dose.

The manufacturer, State and medical professionals or health care providers are equally liable for breach of rights of persons and injuries due to vaccination.

**Conclusion**

Principle of necessity should take precedence when decisions to vaccinate are taken. Core principles of informed consent should be followed, and participatory decision making would lead to a greater good for all. Considering the disparity in health care provisions in India, with scarce health care resources in rural and tribal areas and a plethora in urban and semi-urban areas, decisions to vaccinate, should be taken in a non-discriminatory manner, and provisions to handle adverse events should be made in all areas prior to the roll out of the vaccination program.

It is imperative that the link between public health and human rights is recognized, and respect and dignity of human rights be made compatible and complementary to public health goals. A case by case approach is required as not all vaccines are necessary, as some diseases have cures and medicines that could be a more economical and better method, rather than vaccinating an entire population. Individual assessment of disease in each State is also important, and a screening mechanism needs to be put in place, so that harms from vaccination can be minimized. Individual rights and autonomy of individuals need to be respected while implementing public health strategies.
In Europe the safety assessment reports on vaccines are filed confidentially with the regulatory authority namely the European Medical Agency (EMA). The Italian court of Justice Nicola Di Leo has recently ordered that the periodic safety update reports (PSUR) 15 and 16 on Infanrix hexa (combined Diptheria Tetanus and Acellular Pertussis, Hepatitis B, inactivated Poliomyelitis and Haemophilus influenza type B vaccine) – the GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance’s report to the regulatory authority – be made public and this is now available on the internet, hereafter the Report.

It affords a rare opportunity for the public to see first-hand what these reports contain and why there is need for secrecy. It also bears testimony to the lack of due diligence on the part of the EMA, charged with the responsibility for public safety – for accepting these reports filed by the manufacturers at face value without seeking answers to pertinent questions.

In this paper I will concentrate only on the reports of deaths as adverse events after immunization (AEFI) in the PSUR as an illustration of the breakdown of regulation and why everyone needs a healthy dose of skepticism.

**SIDS as AEFI**

Most deaths occurring early in life are attributable to mainly to such causes as infections, congenital defects, malignancies and accidents. Very seldom do apparently healthy children die without any evident cause and these are classified as SIDS (Sudden Infant Death Syndrome) and SUD (Sudden Unexpected Deaths) if the death occurs after infancy.

During infancy, a number of vaccines are administered and some events of unexplained deaths (SIDS-SUD) can occur in temporal association but not causatively related with vaccination (purely by chance). It is acknowledged widely that it is difficult to say whether a death soon after immunization is caused by the vaccine or is a coincidental event. Many analyses are carried out to investigate whether the associations of frequent unexplained deaths following a particular vaccine are causatively related. The PSUR does an Observed/Expected analysis of sudden deaths to evaluate whether the number of sudden deaths reported exceeds what can be expected as coincidence.

**PSUR 15 and observed/expected analysis of sudden deaths (SD)**

The PSUR Report documents the deaths that have happened within 20 days of vaccination. They then look at it against the expected deaths during this period. GSK estimated that of the 60,626,633 doses distributed, 90.6% of all recipients were under 1 year of age. About 54 million doses were administered to infants below 1 year and about 5 million doses were administered to children older than 1 year. They calculate that the incidence of sudden death was 0.454/1,000 live births under 1 year and 0.062/1,000 live births in the second year. They also apply a healthy vaccinee correction factor of 0.8.

**Table 1: PSUR 15 Cumulative number of Observed/ Expected cases of Sudden Death following Infanrix hexa in the first and second year of life**

<table>
<thead>
<tr>
<th>Time since Vaccination (days)</th>
<th>Observed</th>
<th>Expected (1st year)</th>
<th>Observed</th>
<th>Expected (2nd year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 day</td>
<td>10</td>
<td>54.7</td>
<td>1</td>
<td>1.98</td>
</tr>
<tr>
<td>1 day</td>
<td>20</td>
<td>109.3</td>
<td>2</td>
<td>3.96</td>
</tr>
<tr>
<td>2 days</td>
<td>33</td>
<td>164</td>
<td>3</td>
<td>5.94</td>
</tr>
<tr>
<td>3 days</td>
<td>42</td>
<td>218.6</td>
<td>3</td>
<td>7.92</td>
</tr>
<tr>
<td>4 days</td>
<td>49</td>
<td>273.3</td>
<td>3</td>
<td>9.9</td>
</tr>
<tr>
<td>5 days</td>
<td>50</td>
<td>327.9</td>
<td>3</td>
<td>11.88</td>
</tr>
<tr>
<td>6 days</td>
<td>50</td>
<td>382.6</td>
<td>3</td>
<td>13.86</td>
</tr>
<tr>
<td>7 days</td>
<td>51</td>
<td>437.3</td>
<td>4</td>
<td>15.84</td>
</tr>
<tr>
<td>8 days</td>
<td>52</td>
<td>491.9</td>
<td>5</td>
<td>17.82</td>
</tr>
<tr>
<td>9 days</td>
<td>54</td>
<td>546.6</td>
<td>5</td>
<td>19.8</td>
</tr>
<tr>
<td>13 days</td>
<td>54</td>
<td>765.2</td>
<td>6</td>
<td>27.72</td>
</tr>
<tr>
<td>15 days</td>
<td>55</td>
<td>874.5</td>
<td>6</td>
<td>31.68</td>
</tr>
<tr>
<td>16 days</td>
<td>56</td>
<td>929.2</td>
<td>6</td>
<td>33.66</td>
</tr>
<tr>
<td>18 days</td>
<td>57</td>
<td>1038.5</td>
<td>6</td>
<td>37.62</td>
</tr>
<tr>
<td>19 days</td>
<td>58</td>
<td>1093.1</td>
<td>6</td>
<td>39.6</td>
</tr>
</tbody>
</table>

(Source: Table 24 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance Report to Regulatory Authority PSUR 15, page 783 of 1271)

**The ‘cluster of deaths’ paradox**

The fact that rate of deaths is highest immediately after vaccination, and decreases rapidly after that, makes it very likely that the deaths are related to the vaccination episode. There were 42 [42 – 0] deaths in infants in
the first 3 days and only 8 [50-42] in the next 3 days. It is difficult to imagine that reporting bias of a catastrophic event like SIDS is responsible for such a big change in such a short time. These are otherwise unexplained deaths in healthy children. Unexplained deaths will have been investigated by a competent forensic team and the immunization records will have been examined to check if the infant was up to date with its vaccinations or whether there was an element of neglect. Reporting bias has little role under these circumstances.

Exaggerating expected deaths

1. There are other serious problems with how the ‘expected deaths’ are calculated. The safety assessment document has used the number of doses of vaccine distributed as the denominator. This makes no allowance for wastages assuming all the doses of the vaccine distributed, have indeed been utilized.

2. There can be another argument against using this denominator: The Report (page 702) mentions that vaccination could vary between 1 and 4 doses per subject in accordance with local recommendations. It is estimated to be between 15,156,658 and 60,626,633 subjects were exposed to the vaccine. Most babies died with the first dose of vaccination. As each child is given up to 4 doses and they could die after any one of the doses (and you can die only once), perhaps it would be more appropriate to look at the number of deaths against the number of babies vaccinated. Three doses are given in the first year. The number of children vaccinated is one third of number of doses calculated under year 1, and the expected deaths should perhaps be one third of what was sent to the EMA.

The PSUR 16 expected/observed analysis: enlarging expectation to cover the observation

In the PSUR 16 report, Section 9.3.1.1 on pages 246-249 of the document deals with the Observed to Expected analysis. The explanation on the calculation is identical to that in the 15th PSUR cited except for this passage:

“...It can thus be estimated that 75% of all recipients of Infanrix hexa were in their first year of life, and 20% were in their second year of life (5% were not attributable because the age at vaccination was unknown). Therefore the number of doses (since launch) was estimated to be 54.7 million in infants under 1 year and 14.6 millions over the age of 1 year. The estimate of the number of doses in the second year was suddenly pushed up from 9.4% in the 15th PSUR to 20% in the 16th report.”

Table 2: PSUR 16 Cumulative number of observed and expected cases of Sudden Death following Infanrix hexa in children in their first or second year of life

<table>
<thead>
<tr>
<th>Time since Vaccination (1st year)</th>
<th>Observed</th>
<th>Expected</th>
<th>Observed (2nd year)</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16</td>
<td>54.4</td>
<td>2</td>
<td>1.98</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>108.8</td>
<td>5</td>
<td>3.96</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>163.2</td>
<td>6</td>
<td>5.94</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>217.6</td>
<td>6</td>
<td>7.92</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>272</td>
<td>6</td>
<td>9.9</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>326.4</td>
<td>7</td>
<td>11.88</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>380.8</td>
<td>7</td>
<td>13.86</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>435.2</td>
<td>7</td>
<td>15.84</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>489.6</td>
<td>7</td>
<td>17.82</td>
</tr>
<tr>
<td>9</td>
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<td>10</td>
<td>65</td>
<td>598.4</td>
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<td>21.78</td>
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<td>27.72</td>
</tr>
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<td>816</td>
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<tr>
<td>15</td>
<td>66</td>
<td>870.4</td>
<td>8</td>
<td>31.68</td>
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<td>67</td>
<td>924.8</td>
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</tr>
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</tr>
<tr>
<td>19</td>
<td>67</td>
<td>1088</td>
<td>8</td>
<td>39.6</td>
</tr>
</tbody>
</table>

(Source: Table 36 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance 16th PSUR report to Regulatory Authority, Page 249 of 1271)

The expected deaths are in fact much higher than that which is observed - except in children under 2 years where 5 die in the first 48 hours where only 3.96 were expected to die according to their calculations.

The 16th PSUR report had doubled the estimate of those getting the vaccine after 1 year from 9.4% to 20% doubling the figures for estimated deaths. Had the PSUR 15 distribution of doses under 1 year and over 1 year been used for the 16th report, the observed deaths would have been double what was expected for the first 4 days and actual death would exceed expectation in the first 7 days.
Table 3: Expected Death in 2nd Year of Life Using PSUR 15 and PSUR 16 Criteria

<table>
<thead>
<tr>
<th>Time since vaccination (days)</th>
<th>Observed if in the distribution of doses 9.4% were in their second year of life as in the 15th PSUR (%)</th>
<th>Expected deaths assuming 20% used in the second year of life</th>
<th>Expected according to 16th PSUR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1.98</td>
<td>3.96</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>2.79</td>
<td>5.94</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>3.72</td>
<td>7.92</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>4.65</td>
<td>9.9</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>5.58</td>
<td>11.88</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>6.51</td>
<td>13.86</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>7.44</td>
<td>15.84</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>8.37</td>
<td>17.82</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>9.30</td>
<td>19.8</td>
</tr>
</tbody>
</table>

The PSUR merely doubled the ‘expected deaths’ to better match observed deaths and the EMA did not seem to notice.

Evaluation of possible justifications

In the PSUR 15 it is reported 60 million doses of Infanrix had been distributed worldwide since its launch and 5 million doses were administered to children in over 1 year.

72 million doses of Infanrix hexa were distributed during the period covered by the 16th PSUR report and 24 million over 1 year. This will suggest that 9 million children over 1 year (the increase from 5 million of the 15th report to 14 million in the 16th report) were vaccinated with Infanrix Hexa during the year of the 16th PSUR. This is more than a third of the total doses distributed in the year (36.5% of all doses distributed in the period of reporting of the 16th PSUR). Even if every child given Infanrix hexa went on to have all 4 doses and 1 of the 4 doses was given to children over 1 year of age, this figure cannot reach 36.5% of all doses.

If one considers the change to 20% from 9.4% is a correction made for what was historically wrongly calculated at 9.4%, the figure of 20% is still not tenable. Countries like Italy advise only 3 doses and all the doses are given under 1 year.

No matter how one looks at it, the increase to 20% cannot be justified and it seems evident that the motivation for increasing the calculated numbers of those receiving vaccination after 1 year, was a desire to try and cover up the high deaths in children over 1 year of age in the week after receiving Infanrix hexa.

It is clear that Infanrix Hexa caused more deaths than is expected by chance.

Conclusions

1. The reason for keeping safety data on vaccines confidential is prima facie, suspect. If indeed the vaccine were safe, the manufacturer has more to gain by making it public rather than cloaking it in secrecy.

2. As opposed to faith that demands unquestioning acceptance of what cannot be verified, science is fundamentally defined as findings open to scrutiny by anyone. If scientific data is the basis for regulatory clearance, any data that is not open to independent scrutiny (other than by the regulators, who may be lazy or biased) is not science and no different from faith.

3. The EMA did not show due diligence when it accepted in the PSUR 15 and 16 and ‘expected death rate’ in the first year which was three times the likely correct figure – wrongly using a denominator of exposures to vaccine instead of number of children receiving their first dose of the vaccine.

4. The cluster of deaths immediately after immunization did not raise alarm bells and it suggests the EMA merely accepted the interpretations of the vaccine manufacturer without applying its mind.

5. In the 16th PSUR the manufacturer GlaxoSmithKline Biological seems to have deliberately increased (doubled) the projections for expected deaths in the 2nd year to cover-up the excessive deaths observed in the first 7 days after vaccination. The vaccine manufacturer should have been held to account for this possible sleight of hand.

The EMA has arguably been negligent of its duty as a regulator for allowing this to pass (in the 16th PSUR) and has thereby exposed numerous other babies unnecessarily to the risk of death. Opening such data to the public (as the courts eventually did) serves to overcome the limitations of the EMA, as it can benefit from independent external critiques.

6. We as doctors have been naïve to accept such reports on the safety of vaccines. Justifiably doctors are losing the trust of the public and in the process we are endangering public health.

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Email: puliyel@gmail.com

Notes:

1. http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf
Revisiting the Debate on Selective Versus Universal Hepatitis-B Vaccination in India

Anant Phadke

Hepatitis B vaccine is the first in the series of the new generation of vaccines introduced in the Indian market during last 20 years. This introduction is problematic from the perspective of public health because these new vaccines protect from pathogens which have either low prevalence (for example Hep B, Hib, rotavirus), or which mostly cause mild illness, (chicken pox, hepatitis-A), or the vaccines have unresolved safety issues (rota virus vaccine). Most of them are comparatively very costly and yet have been pushed into the Indian market. They are also sought to be introduced into the UIP. We need critical, evidence based discussion about this new trend. It is in this context that this article examines the universal Hep B vaccination in India from a critical perspective.

In India, inclusion of any vaccine in the Universal Immunization Programme (UIP) is now a days seen only in the context of Universal Immunization Strategy, i.e. vaccinating all infants with the vaccine. The option of selective vaccination is not discussed at all. But it may be recalled that in case of Hepatitis B vaccine, selective vaccination (vaccinating a certain section of the infants) was considered when the issue of inclusion of this vaccine in the UIP was being recommended. However, in this debate about selective versus universal hepatitis-B vaccination in India, among the influential experts in India, there was a clear bias in favour of Universal strategy. By way of example, in the latter part of this current article, I have shared our critique of one influential paper in 1996 by Aggarwal R., Naik S.R. – “Cost Efficacy Evaluation of Inclusion of Hepatitis-B Vaccine in Expanded Programme of Immunization” and have shown concretely the bias of this paper in favour of Universal Strategy. Leaving behind this debate which took place at the beginning of the new millennium, this current article argues that this option of selective Hep B vaccination needs to be reconsidered in view of the research findings in recent years on the prevalence of Hep B infection in India and on the outcome of the Hep B universal vaccination in Indian UIP.

Countries with Hep. B-carrier rates of up to 2%, from 2 % to 7% and above 7% have been grouped into low, intermediate and high prevalence zones respectively. It is widely accepted that for low prevalence zone, a selective immunization strategy should be adopted. It was contended by leading experts in India that India belongs to the intermediate zone and hence the option of selective vaccination is not appropriate for India. However, this strategy of Universal Hepatitis B vaccination, which was included in the UIP in 2007, needs to be reviewed because of two reasons -

1. One key assumption behind this inclusion of hepatitis B vaccine in the UIP has been that in India, 4.7% of the population is hepatitis-B carrier and hence that India belongs to the intermediate zone. Now it is quite clear that carrier rate of 4.7% is very much an overestimation. It has also been pointed out that the number of deaths due to hepato-cellular carcinoma in India due to Hep B infection was also grossly over-estimated.

2. A study conducted in 5-11 year-old rural children in five districts in [erstwhile] Andhra Pradesh, showed that in the UIP though the Hep B immunization has increased the antibody titre in significantly high proportion of the vaccinated children, it has not reduced the Hep B chronic carrier rate.

Let us see this new evidence and also explore the option of selective immunization.

Gross overestimation

It was argued that in India 4.7% of the population is hepatitis-B chronic carrier. This estimate was widely accepted and was the basis of the consensus statement in 2000, of Indian Association for Study of the Liver (INSAL) regarding the risk of hepatitis B to Public Health. This claim is based on the paper- ‘Prevalence of HBV in the General Population of India’, in which, Thyagarajan et al summarized the data from studies published between 1983 to1992 (32402 subjects in total) on the prevalence of sero-positivity of Hep-B infection in India. Ashok Kale and myself had pointed out in 2002 itself that this estimate suffers from important errors -

1. Thyagarajan et al calculated the simple average of average Hep-B positivity rates as reported in various studies. Since the number of subjects in each of these studies varied tremendously, it was quite essential to take weighted average of the positivity rates rather than simple average.
2. They included studies on professional donors and one on dental personnel. These studies should have been excluded.

3. Thyagarajan et al mistakenly equated sero-positivity rate with Chronic Carrier rate. It is well known that any survey based on screening test for detection of Hep B infection in the blood gives only the sero-positivity rate and not Chronic Carrier rate. Based on this sero-positivity rate, one has to first estimate the point prevalence by using the Positive Predictive Value (PPV) of the screening test. The Chronic Carrier rate has to be then calculated from this point prevalence.

These mistakes about basic issues related to any survey based on screening test for detection of Hep B infection were surprising. More surprisingly nobody from the galaxy of experts in this field pointed out this mistake. This study was presented in a national seminar funded by an interested pharma company and the book containing various papers presented in this seminar was also funded by this company. Everybody seemed to be keen to believe that India does not belong to the low endemic zone (Chronic Carrier rate of less than 2%). Countries in low endemic zone like U.K, Japan, Netherlands have adopted a strategy of Selective Immunization i.e. vaccination of only those who have high risk of acquiring Hep B infection, whereas others have been advised universal immunization.

Using the same data in the table by Thyagarajan et al, and excluding the four studies of the high risk groups, we arrived at a weighted average of sero-positivity rate of 2.64%, instead of the simple average of 4.7% estimated by Thyagarajan et al. We showed that that the point prevalence was 1.77% and the chronic carrier rate worked out to be 1.42%.

Lodha Rakesh, Jain Yogesh et al also seriously questioned the claim that in India the Hep B chronic carrier rate in India is 4.7%. Based on a systemic review of literature of prevalence of hepatitis B in India, they found that prevalence of hepatitis B in India was 1–2%. However, a limitation of this exercise by Lodha-Jain et al was that no statistical tool was used in this systemic review to synthesize the results of the different studies. This limitation was overcome by a study involving meta-analysis of the available appropriate data. This meta-analysis by Batham A., Narula D et al found that the point-prevalence of HBV in India is 2.4% in non-tribal population and 15.9% among tribal population. (For the purpose of this paper we have limited ourselves to only the non-tribal population.)

This meta-analysis included studies of all the four types of people whose blood is routinely tested for HbsAg (hepatitis B surface antigen) - Voluntary blood donors (VBD), replacement donors (RBD), as well as studies involving antenatal women and community studies. This helped to partly overcome the limitations of each of these types of studies. This meta-analysis excluded studies from high risk groups for hepatitis B infection (professional blood donors, sex workers, drug abusers, dialysis patients, etc). In this study, blood donors formed 85% of the total sample, majority of who were males. Internationally males have a higher prevalence of hepatitis B and hence this analysis may have overestimated the true prevalence of Hep B. Yet, this meta-analysis reported that the prevalence of Hep B infection in India in non-tribal population is only 2.4%, far less than the one assumed by the consensus statement mentioned above.

This meta-analysis was the most comprehensive exercise so far about prevalence of Hep B infection in India. However, disproportionately high amounts of data included in this study are from a few geographical areas. Hence a repeat calculation was done by the same researchers of the prevalence of HBV in India by using population-weights and reported that this exercise revealed that the point-prevalence of hepatitis B among non-tribal was 3.07%. This last meta-analysis includes data from 884,052 hepatitis B antigen (HbsAg) tests done all over the country and is the most comprehensive and largest study so far. However, in this study, surprisingly, the authors have not taken into account the difference between sero-positivity rate reported by various studies using screening test for hepatitis B antigen (HbsAg) and the point prevalence which is to be estimated, as mentioned above, by using the factor of Positive Predictive Value for this screening test. (They had applied this corrective factor in their earlier paper.)

The point prevalence depends upon the Positive Predictive Value (PPV) of the screening test, which in turn depends not only on the sensitivity and specificity of the screening test, but also upon the prevalence of the health-problem in the study population. Different studies use different techniques for detecting HBsAg which have different values of sensitivity and specificity. Assuming that on an average sensitivity of 100% & specificity of 99% for detecting HBsAg, it can be seen from table no.1 that for an estimated point prevalence of 3%, the PPV of HBsAg test would be 75% of the sero-positivity rate. Therefore the average sero-positivity of 3.07% as reported in this exercise by Batham A., Narula D et al by using population-weights would mean a point prevalence of 2.30%. (3.07 x 0.75)
Table – 1: Positive predictive values of a screening test with a sensitivity of 100% & specificity of 99% with varying degree of prevalence in subsets of populations of 10,000 each

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Infected Persons</th>
<th>Sensitivity 100% True Positives</th>
<th>False negatives</th>
<th>Specificity 99% True negatives</th>
<th>False positives</th>
<th>PPV (c/c+g) x100</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>(b)</td>
<td>(c)</td>
<td>(d)</td>
<td>(e)</td>
<td>(f)</td>
<td>(g)</td>
</tr>
<tr>
<td>1%</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>9900</td>
<td>9801</td>
<td>99</td>
</tr>
<tr>
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<td>200</td>
<td>0</td>
<td>9800</td>
<td>9702</td>
<td>98</td>
</tr>
<tr>
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<td>300</td>
<td>300</td>
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<td>9603</td>
<td>97</td>
</tr>
</tbody>
</table>

A carrier of HBV infection is defined as one who has persistence of hep B infection for six months or more. This is indicated by two HBsAg positive tests, six or more months apart. Hence Hep-B point prevalence rate cannot be equated with Hep-B carrier rate. The proper method to estimate the carrier rate is to use data in studies, which have tested blood for HBsAg six months after initial testing. Since such sequential data from large-scale studies from different centres in India are not available, we have to use available single test data by applying the necessary corrective factor to the estimated point prevalence. Studies, which have followed up initial HBsAg positives for six months, have found that about 80% of these positives continue to be positives and hence are carriers. If we extrapolate these findings to the above estimated point-prevalence of HBsAg infection in India of 2.3%, the HBsAg-carrier rate works out to be 1.84% (2.3 x 0.8). Thus India belongs to low endemicity zone and not intermediate zone as regards Hep B chronic carrier rate.

It may also be pointed out that the estimation of number of deaths due to hepatocellular carcinoma due to hepatitis B in India was also highly exaggerated. It was claimed that a Taiwanese study showed that “20% to 27% of carriers will die of cirrhosis or liver cancer.” Extrapolating this to prevalence of Hep B chronic carriers in India (assuming that the chronic carrier rate is 4%), it was claimed by Miller MA, Kane M that in India annually 193,000–261,000 people die of hepatocellular carcinoma due to hepatitis B. It was however pointed out by Jacob Puliyel that the data in the original paper has been misquoted; that in this Taiwanese study it was also found that the rate of HCC in women is one third to one fourth that of males although the carrier rate is the same. Yet Miller MA, Kane M had neglected this fact. Secondly the assumption in this estimation that chronic carrier rate in India is 4% is also highly exaggerated as we have seen that this rate is only 1.84%. Thirdly as has been pointed out by Dr. Jacob Puliyel, data from well maintained, population-based cancer registries in India, project a figure of just 5000 deaths annually in India due to hepatocellular carcinoma.

In 2002, Dr. Ashok Kale and myself had done a detailed exercise in which we used available data on prevalence of HBsAg positivity rates among Indian children, and used data from international literature about long term sequelae of Hep B infection as no such data are available for India. For this purpose we relied on the thorough literature review by Lodha Rakesh, Jain Yogesh, et al. Quality Adjusted Life Year (QALYs) and lives lost due to the five morbid sequelae of Hep B infection (acute hepatitis, chronic persistent hepatitis, chronic active hepatitis, cirrhosis, hepatocellular carcinoma) were estimated in a hypothetical lifetime cohort of 1 million Indian infants. Based on this we estimated life time risk for infants, of dying due to Hep. B infection. We found that average lifetime risk of dying due to the sequelae of Hep. B-infection among the normal population was very low, (0.13%) and among Hep-B-carriers it was 5.6%. This is in contrast to the oft quoted figure of 25% risk of dying for Hep B carriers. It may be noted that our exercise had included deaths due to all the five deleterious sequelae of Hep B infection and not only cirrhosis and carcinoma. This exercise was shared in the Medico Friend Circle but was not published in any journal.

Given the above, it is clear that both the chronic carrier rate of hep B infection in India and it’s deleterious consequences have been highly exaggerated.

Added to this is the problem of failure of the Hep B vaccination in India in the UIP to reduce chronic carrier rate. This is revealed by a study designed to assess the impact of Hep B vaccination in UIP on the Hep B chronic carrier rate. It was conducted in 5-11 year-old rural children in five districts in [erstwhile] Andhra Pradesh. HBV-vaccinated and un-vaccinated children were compared for HBV serology parameters. It was found that prevalence of protective levels of antibody titres was much higher among the vaccinated group - anti-HBs was found in 53% of vaccinated and 18% of un-vaccinated children and the authors concluded that “These data provide evidence supporting efficacy of hepatitis B immunization program in an Indian field setting, justifying the decision to include it in the
universal immunization program.” However, this conclusion is unwarranted as pointed out in the editorial comments in the same issue of Indian Pediatrics – as per the data obtained in this study, immunity to Hep B developed due to vaccination in only 35% of children since 18% of the unvaccinated children also developed protective antibody titres. Secondly at 6 years and 11 years of age, protective levels of anti-HBs antibody (10 mIU/mL) were present only in 59% and 13% respectively of the immunized children! In other countries 95% of those vaccinated have protective antibody levels and this prevalence drops to only 92% at 40 years. Most remarkably this study found that prevalence of Hep B chronic carrier state was almost equal in both the groups - 0.17% in unvaccinated and 0.15% in vaccinated. Whatever may be the cause of this failure, if Universal Immunization in India is unable to reduce the Hep B chronicity rate, then an alternative strategy needs to be thought of. In any case since India belongs to low endemic zone selective immunization strategynedd to be explored.

Rationale and cost-efficacy of selective strategy

Perinatal transmission from mother to infants is a very important route of transmission of Hep B especially in Asian countries including India. It has been estimated that “One-third of the adult asymptomatic HBV carriers in India evolve directly from perinatal infection, whereas the majority becomes infected during childhood or early adulthood.” Chronic infection with hepatitis B is more likely when the infection is acquired in infancy. The newborn can be protected from this perinatal infection by giving Hep B vaccine within 12 hours of birth. Selective immunization of these high-risk newborns is being practiced in low endemic countries like U.K. Japan, Netherlands who have not adopted universal immunization of Hep B vaccine though they can very well afford it. India should also adopt this selective Hep-B vaccination strategy.

The selective Hep B vaccination strategy involves screening of all pregnant women for Hep-B infection and vaccinating all the newborns of Hep-B positive mothers within first 12 hours of birth. We would get many months to screen the pregnant women for presence of HBsAg during one of the ante-natal visits. The card-ELISA test is very easy to perform and can be done by any nurse. The cost of the kit is only Rs. 30 per test. In India only about 3% of pregnant women are HBsAg positive. Hence only 3% of the newborn babies will have to be given Hep B vaccine within 12 hours of birth. In the Universal strategy, a ‘birth-dose’ is supposed to be given to all newborns. However, now it’s almost 10 years that the Hep B vaccine has been included in the UIP and yet most newborns today do not receive Hep B vaccine within 12 hours of birth. Hence the most vulnerable population, the infants and moreover the ones who also contribute substantially to the pool of Hep B chronic carriers in India, are not protected in the Hep B universal vaccination programme in India. Even if the health department has been aiming at increasingly higher proportion of women in India to get delivered in health care institutions, it is difficult to imagine that all of them would do so in the coming years. It is far more practical to find out in the antenatal checkup visits, who among the pregnant women are HBsAg positive and to ensure that these 3% women certainly deliver in a health centre and their newborns receive Hep B vaccine within 12 hours of birth.

The limitation of the ‘selective strategy’ is that since it involves vaccination of only around 3% of the newborns, it would not protect the rest of the 97% children from the risk of Hep B infection. However, it is to be noted that unlike in the developed countries, in India, the most concentrated mechanism of Hep B infection is vertical, perinatal mother to child transmission. What is more important, as mentioned above, the contribution of this perinatal infection to the pool of chronic Hep B infection is very high. In case of mothers who are HBeAg positive (those who have the more pathogenic Hep B envelop antigen) 90% of their newborns who get infection at birth would become chronic carriers. Moreover, some of these newborns would themselves be HBeAg positive and hence are far more likely to infect other children through horizontal transmission. Protecting these vulnerable as well as more infectious newborns of Hep B positive mothers is of paramount importance.

Would the Selective strategy be less cost-effective than the Universal strategy? This issue has been examined in detail below.

Aggarwal –Naik have compared the cost-efficacy of Universal Versus Selective Hep-B vaccination and have concluded that cost per Hep B carrier prevented would be five times in the Selective Vaccination strategy compared to the Universal Vaccination strategy. We found that in this paper, Aggarwal –Naik have not examined the impact of Hep B vaccination on the prevalence of HBeAg positivity rate, have considered only the impact on Hep B chronicity rate; they have therefore not estimated cost per highly infectious carrier (HBeAg positive) prevented. Secondly as pointed out below, some of the empirical assumptions made by Aggarwal-Naik...
in carrying out the cost-efficacy exercise are unjustified.14

1. Inappropriate parameters

Aggarwal-Naik have used data from a study of 8575 infants born in two large hospitals in Delhi and extrapolated these data to a hypothetical cohort of 10,000 newborns to compare the cost-efficacy of Universal and Selective Hep B vaccination in terms of cost per HBsAg carrier prevented.15 In the ‘Delhi study’ used by Aggarwal-Naik, the data for HBeAg positivity were also available. But they chose not to use these data for their cost-efficacy estimation though infants born to HBsAg positive mothers are far more likely to be positive for HBeAg. In this ‘Delhi-study’ it was found that out of the 31 HBsAg positive infants born to the carrier mothers, 13 (42%) were HBeAg positive. In the ‘Delhi-study’ any prevention of HBeAg positivity by Immunizing all HBsAg positive mothers would be double in case of Selective Vaccination compared to Universal Vaccination, “since the newborns of HBsAg positive mothers will have to be specifically located and immunized”. This assumption is again arbitrary and biased. In the Selective Vaccination programme, the HBsAg positive mother would be identified during routine antenatal check-ups. There will be at least 4-5 months available to do this, and no extra human power will have to be employed to locate these mothers as a pregnant woman’s blood is anyway examined in routine ANC checkup. In the Selective Strategy, only the newborns of the HBsAg positive mothers (3%) will have to be reached for giving the first dose within 12-24 hours of birth and it would be known well in advance which women’s newborns will have to be given the vaccine within 12-24 hours of birth. Hence there will be enough time to reach and counsel such a woman so that her delivery takes place in a health care centre and her baby gets the Hep B vaccine in time. The cost of counseling 3% of the pregnant women will be very small.

Thirdly, the unit cost of the material for HBsAg screening in Selective Vaccination programme has been taken as 2 US dollars. No consideration has been given to the fact that annually about 25 million women would undergo HBsAg screening and hence the cost of this screening per test would go down considerably. The cost of the Elisa kit for HBsAg screening was around Rs. 20/- (about 0.5 dollar) per test in September 2001. It was reasonable to assume that with a purchase order running into tens of millions of kits annually, this cost would come down substantially. But Aggarwal-Naik decided to gloss over this.

Aggarwal-Naik’s cost efficacy comparison was thus seriously flawed and hence invalid. There is a need to do this comparison by using reduction in the highly infectious and damaging HBeAg positive pool as the parameter to measure cost-efficacy and by avoiding biased assumptions. We have done this exercise below

3) The cost-efficacy of selective and universal vaccination strategy

We have estimated comparative cost-efficacy of Selective and Universal strategies. The cost-efficacy details of this strategy are given in table II, and the results are seen in rows 5 to 10 in this table.

It is seen from row 10 of table II that the cost of preventing one HBsAg carrier would be Rs. 2211 and 2551 respectively for selective and universal strategy. Row 9 shows that the cost Rs. 9260 per infant protected from HBeAg positivity by Universal Vaccination
Strategy is much more than the cost in case of Selective Vaccination (Rs.5227). Secondly, to cover all the pregnant women and their newborns in a year, the total annual cost of the programme for Universal and Selective vaccination for a cohort of 10,000 would be Rs.500,000 and Rs.1,15,000 respectively.

In the above estimation, we have not accounted for cost of human power, as these factors apply equally to Selective and Universal vaccination. We have also not discussed the cost-effectiveness of these vaccines within the context of social conditions in India and the capacity of the Public Health System in India. There is also the need to discuss the overall strategy of infectious disease prevention in India, of which vaccine strategy is only a part. In this sense this discussion is only the first step in the discussion of the complex issue of overall strategy of infectious disease control in India. The purpose of this article is just to draw attention of the bias that operates among the leading experts in this field which helps the pharma companies to push more vaccines into the UIP, regardless of the scientific rationale for such a decision.

Table II
Comparative Cost Efficacy of Universal and Selective Hep-B Vaccination in a Cohort of 10,000 Pregnant Women and Their Newborns

Notes:

a. The kit cost per test in October 2016 around Rs.30 per test, (with some price variation with different manufacturers). We assume that in the mass screening, this cost would come down to Rs.10/- per test as the gov't would buy millions of these kits in bulk.

b. Kant Lalit, Arora Narendra; Transmission of Hepatitis B Virus in Children: Indian Scenario; in Hepatitis-B in India. Sarin S.K., Singal A.K., (editors) CBS Publishers and Distributors, 1996, Table-2. (We have rounded off this figure)

c. The purchase price for doctors of the vaccine in October 2016 of a multi-dose vial was Rs.20/- per Paediatric dose, i.e. Rs 60 per child for 3 doses. We have assumed that this would come down to Rs.50/- per child in a mass-vaccination programme

<table>
<thead>
<tr>
<th></th>
<th>Selective Strategy</th>
<th>Universal strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cost of ( HBSAg ) screening for 10,000 antenatal cases (@ Rs 10) (^{(A)})</td>
<td>Rs. 1,00,000</td>
<td></td>
</tr>
<tr>
<td>2. ( HBSAg ) Positivity Rate among pregnant women</td>
<td>3% (^{(B)})</td>
<td></td>
</tr>
<tr>
<td>3. Number of ( HBSAg ) Positive mothers</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>4. Number of infants to be vaccinated</td>
<td>300</td>
<td>10,000</td>
</tr>
<tr>
<td>5. Vaccine cost of the vaccination of the newborns @ Rs. 50 per child for 3 doses (^{(C)})</td>
<td>Rs. 15,000</td>
<td>Rs. 5,00,000</td>
</tr>
<tr>
<td>6. Cost of screening and/or vaccination (row 1 + row 5)</td>
<td>Rs. 115,000</td>
<td>Rs. 5,00,000</td>
</tr>
<tr>
<td>7. Number of ( HBeAg ) newborn infections prevented</td>
<td>22 (40%)</td>
<td>54</td>
</tr>
<tr>
<td>8. Number of ( HBSAg ) carriers prevented</td>
<td>52 (26.5%)</td>
<td>196</td>
</tr>
<tr>
<td>9. Cost of preventing one ( HBeAg ) infection (row 6 /row 7)</td>
<td>Rs. 5227</td>
<td>Rs. 9260</td>
</tr>
<tr>
<td>10. Cost of preventing one ( HBSAg ) carrier (row 6 /row 8)</td>
<td>Rs. 2211</td>
<td>Rs. 2551</td>
</tr>
<tr>
<td>11. Total annual cost of the programme</td>
<td>Rs.287.5 million (115,000 x 25 million /10,000)</td>
<td>Rs. 1250 million (25 million x Rs 50)</td>
</tr>
</tbody>
</table>
As seen from row 7 and 8 in table II, Selective Vaccination would directly prevent 40% and 26.5% of the HBeAg newborn infections and HBsAg positive newborn carriers respectively by vaccinating only 3.7% of the newborns. Since we would reduce 40% of vertical transmission of the highly infectious and pathogenic HBeAg positivity, at less than one fourth the annual cost of Universal Vaccination by vaccinating only 3.7% of the newborn babies, this is an excellent bargain.

It may be pointed out that in India, HBV infection is not a priority issue. We therefore need not aim at eradicating HBV-infection but should aim at drastically reducing the HBeAg pool. Secondly, even the Universal HB Vaccination programme will not eradicate HBV in foreseeable future. After 40 years of Universal Vaccination of infants, all the ‘below 40 population’ (i.e. childbearing population) would have been protected, free of hepatitis-B infection and hence vertical transmission would stop completely. Horizontal transmission among ‘below 40 year’ age group would also stop after 40 years of this programme. To stop horizontal transmission from ‘above 40 population’ also, it will take further 25 years of Universal Vaccination because average life expectancy at birth in India is 65 years. During these coming 65 years, the life-expectancy would further increase, with the resultant consequences for this programme.

Conclusion

We conclude that epidemiologically, financially, logistically, the Selective strategy is far more cost-effective compared to the UV strategy, in reducing the Hep B chronic carrier rate in India and the highly infectious, more pathogenic HBeAg infection. But unfortunately the leading experts in the field have not looked at the evidence in a dispassionate, objective manner.

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Rabies - lessons from the Himachal Pradesh experience

Omesh Kumar Bharti,

Each year on September 28 we celebrate the World Rabies Day. The theme for 2016 is ‘Educate. Vaccinate. Eliminate’. Rabies, the disease of the poor, remains a neglected area since centuries as there are no pressure groups in the field which can vie for attention to control rabies or to control the burgeoning population of stray dogs in the country. There have been incidents of foreign tourists bitten by stray dogs in different parts of the country, with few deaths also reported, which may affect tourism and brings a bad name to the country. Sanitation programmes (including appropriate management of food wastes), which are in vogue now, are also important for controlling rabies.

Rabies is a dreaded disease and an estimated 60,000 people die of rabies every year and out of that 31,000 deaths are reported from the Asian continent. About 20,000 deaths are reported from India, i.e. one death every half an hour. The main reason for high death rate in India is high cost of treatment (vaccines and rabies immunoglobulins (RIG) in case of animal bites) and lack of awareness regarding first aid. While Himachal Government has taken a lead in lowering the cost of vaccination through introduction of only intra-dermal technique, the cost of RIG is still beyond the reach of common man.

Our state of Himachal Pradesh is in the North bordering China and is predominantly rural and hilly and villages are near forests where wild reservoirs of rabies exist. Since health facilities are not accessible easily, we were forced to innovate on existing schedules of rabies vaccination keeping in view the compliance of the patients and affordability to give them the best possible option of treatment. Nineteen rabies deaths had been registered from 2009-2015 in IG Medical College, Shimla.

In the years 2006 and 2007, we at Deen Dyal Upadhyaye Hospital, Shimla experienced a severe shortage of rabies vaccine and patients were running from pillar to post. During continued shortage of rabies vaccine in 2008, we contemplated to start an intra-dermal clinic to make vaccine affordable but there were four main hurdles: 1) Non-availability of the appropriate rabies vaccine vials ("For IM/ID use" or Intra-muscular/intra-dermal); 2) Low number of patients visiting the DDU Hospital (sometimes only two a day), which was insufficient to open a vaccine vial; 3) None of the vaccine producing companies were ready to supply cell culture “For IM/ID use” rabies vaccine vials for fear of losses due to more efficient usage; and 4) the reluctance of the hospital doctors to prescribe ID vaccine as this was not the practice at higher teaching institutions including medical colleges.

We contacted a vaccine company in Mumbai (1200 km away from here), which agreed to supply us the appropriate vials. We requested the Chief Medical Officer, Shimla District to write a letter to all health facilities around DDU Hospital to give first aid to patients with animal bites and then refer them to DDU Hospital for vaccination. Now we were able to divide a single 1ml vaccine vial among four patients through pooling strategy. We also consistently advocated that the ID use of rabies vaccine was approved by World Health Organization (WHO) with subsequent approval by the Government of India, which proved to be successful. We innovated a technique of extraction of last drop of vaccine from the vial to reduce wastage.

The first low cost anti-rabies clinic was started on August 2, 2008 after long advocacy with the authorities and doctors. This centre was formally launched as State Intra-dermal Anti-rabies Clinic and Research Centre (ARC&RC) by Mission Director National Rural Health Mission on September 28, 2012. Since then we have continued to innovate based on local requirements and patients’ feedback and have given pre and post exposure prophylaxis to more than 15,000 animal bite victims over more than an eight-year period, saving lives as well as money of the poor patients and the government.

The shift from IM to ID made rabies vaccine accessible to all and since it was affordable to government, the vaccine was made free all over the state to every dog bite patient. However, some doctors continued practicing the costlier IM vaccine and the issue was taken to the high court by an NGO where government gave a commitment to use only ID vaccine in the state. After court orders, new clinics are being established upto PHC level for vaccine and anti-snake venom and upto CHC level for additional RIG application into the bite wounds.

In 2014 there was acute shortage of rabies immunoglobulins (RIG) in Himachal Pradesh and was not available in North India in general (due to limited production and also demand due to high cost). The reports of death due to rabies started pouring in from different states. In 2014, the death of a 32 year old man in Shimla District who was bitten on the lower lip by a stray dog and could not be treated with RIG became widely publicized in local media. Stocks were getting outdated and affordability was another issue. Demand for RIG started coming in from the public, and policy makers were getting worried. There were
patients who said they cannot afford to purchase RIG at all even if costs were lowered. Non-availability of RIGs in the market led us to innovate again for an affordable solution to save lives of the patients.

For post exposure prophylaxis, apart from thorough wound wash with soap and antiseptic and administration of intra-dermal vaccination we decided that the immunoglobulins would be injected into the depth and around margins of the wound/s to neutralize virus locally without giving the remaining RIG into muscles IM as prescribed by WHO. We decided to do a long term follow up of the patients bitten by lab confirmed rabid dogs to assess the clinical efficacy of this method of only local wound infiltration of RIG, based on the existing literature review.

The recent WHO recommendation of giving as much of the RIG as possible around the wound site contradicts earlier recommendation of WHO to inject the rabies immunoglobulins into the muscle as per body weight. Cabasso et al had earlier concluded that 10 IU/kg RIG systemically is insufficient for early protection, that HRIGs at these doses interfered with active immunization, and that 20 IU/kg resulted in minimal interference. This dose was therefore selected for intramuscular inoculation at a site away from the site of vaccination. But if some serum has been injected locally, how logical would it be to give the remaining RIG into a muscle that is already infiltrated with RIG? This dose would be less than that calculated for IM injection and may even interfere with active immunization as detailed above. The WHO recommendations are trapped in their own irrational history.

Over the course of the meeting in WHO/Bill & Melinda Gates Foundation Consultation in 2009, Dr. David C. Anderson, proposed various amendments to the current WHO recommendations on the use of RIG (WHO, 2005) sections A2 and A 3.2). His proposal can be summarized as follows: For passive immunization, the whole dose of RIG is given into the wound(s). The maximum total amount of RIG administered for all individuals, regardless of body weight, should be 1000 IU (normally a 5-ml vial). RIGs may be diluted up to a volume sufficient for the effective and safe infiltration of all wounds. It is not necessary or useful to inject any residual RIG into a distal site (i.e. IM); residual RIG may be used on another patient within 6 hours or otherwise discarded. In case, if it is difficult to administer RIG or the wound has completely healed, then this RIGs can be given as full calculated dose by intramuscular injection in the anterolateral thigh or at a site away from the site of vaccine administration. Other studies have supported infiltration of RIG around injured site.

Dr. Anderson also advocates that rabies endemic countries must take a much more active role in helping with production, standardization and distribution of RIGs. Recognizing that dog bites vary in number, size and location, these recommendations allow RIG to be diluted in saline to ensure there is sufficient volume to inject into all wounds. One 11-year-old boy died of rabies in 1987 when a single puncture wound of the finger was not infiltrated with RIGs, all of the 40-IU/kg dose had been given intramuscularly in the gluteal region.

Therefore it is evident from the above literature review that there is no substitute to local infiltration of RIGs to neutralize virus at the wound site itself and maximize the chances of survival of the patient when RIGs are not affordable or are in scarcity.

Recent pilot study done at DDU Shimla has shown that the local infiltration of wound is effective in saving rabid dog bite patients and this method of only local infiltration continues in DDU Hospital as RIG is still not available in the market and several patients are fine after a year of bite by rabid dogs. The model is also spreading to other district of the state including Indira Gandhi Medical College and appears to be successful as there are no reports of death. We have trained more than 15 batches of doctors and paramedics in the state on intradermal vaccination and local RIG infiltration since 2014.

Sometimes less can be more and we have proved it with intra-dermal rabies vaccination and only local wound infiltration of RIG. This has brought down the treatment cost from about Rs. 50,000 per case to about Rs. 400/- per case. Since this cost is easily affordable by the hospital administration, the Himachal Government has decided to give entire post exposure prophylaxis free to all animal bite victims in the state. This model appears to be successful as patient having even a minor scratch now come to the hospital for post exposure prophylaxis this is free and we have not experienced any death due to rabies this year in 2016. We have replicated the model in Himachal, Let’s replicate the model in other states and rein in this monster of rabies in India for ever.

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Vaccines are given to healthy children as a public health measure to prevent diseases. It is essential that before introducing a vaccine, there should be evidence that it is safe, effective, and has minimal side effects. Moreover, it should also be cost-effective, affordable and feasible in the country as compared to other interventions, that may be equally effective in controlling or curbing the concerned disease.

Early this year, the Delhi government announced the introduction of the Human-Papilloma –Virus (HPV) vaccine in government schools. The intention is to vaccinate girls in the age group of 9 to 13 years. The Delhi government also intends to introduce the vaccine in private schools through a public-private partnership along with Delhi State Cancer Institute and Global Alliance for Vaccines and Immunization (GAVI). Punjab government is also considering introduction of HPV vaccine in the State. However, we see the absence of a caution that needs to be taken before introducing new vaccines in a health care system that is crippled in some areas and in many instances incapable of handling the adverse events that may occur in girls who are administered the HPV vaccine.

The question is whether it is necessary to vaccinate girls mandatorily for HPV or are there alternatives that could be as effective? Also, the question is that once the HPV vaccine is introduced in the Universal Immunization Programme (UIP), or under any State vaccination programme, who will be responsible for the ill-effects or adverse events that the girls may face, and what compensation will be paid to them, and by whom?

Necessity

HPV vaccine is used as a public health measure due to its relation with cervical cancer and related diseases. Exposure to HPV can also be reduced by behavioural change, and therefore mandatory HPV vaccination is not justified in a similar vein as some other vaccines in the UIP.

Mandatory HPV vaccination is also not justified by necessity in the given context. The current HPV vaccine prevents infections from just two of the HPV types (16 and 18) that may cause cervical cancer and also HPV types 6 and 11 which can lead to genital warts. However, there are over 100 HPV types and a critical concern is that if the vaccine was to work and indeed ‘block’ types 16 and 18, other types might become more virulent, and contribute to the carcinogenicity in the absence of these more carcinogenic subtypes.

There is a lack of reliable information regarding the period of immunological protection the vaccine confers against HPV types 16 and 18. Since the highest incidence of cervical cancer in India is in women above 35 years of age, it is not clear whether a 3-dose schedule will successfully provide lasting immunity or boosters will be required when they reach 50 years of age. If boosters are required say once every 3-5 years, the cost of vaccination per woman rises phenomenally.

HPV is a sexually transmitted infection (STI) with varied incidence and mortality rates in different communities of the world. For example, in Australia, a country with low incidence and mortality due to HPV, it is found 4 times higher in its indigenous Aboriginal communities. Around 80% of the women globally are infected with HPV in their life time without any symptoms, without cancer or genital warts as the virus is expelled from the body on its own within 1 to 2 years. The lifetime risk of cervical cancer is 0.8% before the age of 64 in a developed country and 1.5% in a developing country. Time series data indicates that cervical cancer rates are declining and it is low in developed countries compared to developing countries [during 60’s and 70’s, the rates were similar]. Declining cervical cancer rates in the developed world is attributed to the improved living standards, greater access to screening programs and use of condoms since the 1960’s.

In countries that conduct regular testing or screening for HPV, the incidence of HPV has reduced substantially, even without the introduction of the HPV vaccine under any mandatory program of the government.

Universal Immunization Program (UIP)

It is important to carefully consider which vaccines should be added to the national immunization schedule, so that they are offered to all children in the country. Decision to introduce new vaccines should be based on evidence that a particular vaccine is not only effective but is also safe, is also cost effective and feasible to administer when compared to other interventions, and is affordable for the country. Further, the system that delivers this new vaccine should have the organizational capacity to deliver this additional vaccine without a negative impact on the coverage of the previously used vaccines, and it should
be able to monitor its effectiveness and safety. Accordingly, the National Vaccine Policy in India recommends such a detailed evaluation of these factors before a decision to include a new vaccine is taken.

It is important to note that HPV vaccine is not a substitute for cervical cancer screening. All women, including those who are vaccinated, should continue to have regular screening as the prevention capability of the vaccine on cervical cancer has not yet been fully established.

Even for conducting regular screenings, the health system at all levels has to be equipped both in terms of human resources and infrastructure in addition to ensuring the sustainability of the programme. The decision to launch the HPV vaccines under the public health programme in schools in Delhi, without ensuring a robust and functional health care system, preparedness to provide immediate treatment for any of the adverse effects or serious adverse effects of the vaccines, undermines the health of young girls and contravenes their right to healthcare. It is important that the government makes public the arrangement that it has with the companies producing the vaccine. The companies should also be asked to produce reports of the impact, the adverse events and serious adverse events faced by girls who have been vaccinated world over.

Controversies with rDNA vaccines

The HPV vaccines – Gardasil and Cervarix, ever since their introduction, have been surrounded with several controversies. It is recognized by the Drugs and Cosmetics Act & Rules in India, that drugs/vaccines made with rDNA need to be followed up closely, as their side-effects remain unknown, and must be tested in a large population for proper safety and efficacy data.

The approval of the HPV vaccine was fast tracked globally, including in India. It did not undergo the detailed Phase III trials, but only bridge trials on a small population were conducted prior to approval of the HPV vaccine. Significant deficiencies exist in safety data, which have not been investigated nor are the persons being vaccinated informed about them.

Some girls vaccinated in Japan, France, UK, Denmark, India and USA experienced adverse events, that have changed their lives, or that led to death in a few girls. But, due to the lack of an independent scientific inquiry on the real cause of death after vaccination, most inquiry reports summarily dismissed the adverse events as “not related” to the vaccine. The European Medicines Agency (EMA) has confirmed the vaccine’s safety, after it inquired with the manufacturers into only two areas - complex regional pain syndrome and postural orthostatic tachycardia syndrome. Consequently, questions have been raised on the type of inquiry conducted by EMA.

There are a number of countries that have put a moratorium on HPV vaccines, due to the side-effects experienced by some girls, and its unknown safety and efficacy data. Recently the Japanese government has taken such a decision and the Austrian government has rejected the inclusion of HPV in its vaccination schedule. The Green Party MPs at the European Parliament are preparing to call for a moratorium in France. Even in the USA, there are only 3 States that have mandated the vaccine while other States have not included it in their vaccination programme. Canadian academics have called for a moratorium on HPV vaccination. There was a controversy in Australia too and some investigations have taken place in China, UK and Poland. In Australia, the rate of anaphylaxis shock after Gardasil injection has been reported as 2.6 per 100,000 doses.

The Judicial Watch in USA received documents from the Department of Health and Human Services revealing that its National Vaccine Injury Compensation Program awarded about 6 million USD to about 49 victims in claims made against the HPV vaccine. There are about 200 claims filed in which less than half have been decided upon by the authorities. The Judicial Watch also mentioned that “….However, in VAERS reports obtained by Judicial Watch there are 78 separate cases where, after receiving the vaccine, patients experienced outbreaks of warts.” The Judicial Watch in USA states that the facts of so many adverse events contradict the FDAs safety statements on the vaccine. The adverse reaction reports detail 26 new deaths reported between September 1, 2010 and September 15, 2011 of young, previously healthy, girls after Gardasil vaccination in just one year. Moreover, incidents of seizures, paralysis, blindness, pancreatitis, speech problems, short term memory loss and Guillain-Barré Syndrome have also been reported. These documents come from the FDA’s Vaccine Adverse Event Reporting System (VAERS) which is used to monitor the safety of vaccines.

In India, many concerns arise from the HPV vaccine demonstration project done in Andhra Pradesh and Gujarat. These demonstration projects carried out by PATH—an international NGO, had resulted in reporting of deaths of 4 girls from Andhra Pradesh and 2 girls from Gujarat following the administration of the
vaccine. The enquiry committee report appointed by the Ministry of Health and Family Welfare itself had observed that “......Monitoring and management of Adverse Events/ Serious Adverse Events should have been more vigorously pursued”. Informed consent was another essential aspect that came up wherein there was flouting of an ethical informed consent process during these demonstration projects. The enquiry committee too observed it as “the most significant deficiency in the implementation of the project was the obtaining of consent.” However, despite finding serious lacunae in the manner the trial was done, the enquiry committee in its report failed to make any recommendations on actions, neither against those involved in the designing and implementation of these projects nor against the ethics committees which approved of such a design.

The vaccine continues to be marketed in the private sector, and is included under the government program in some countries. It is important to note that these vaccines have not been in use long enough to know the level of protection they will offer to young girls when they are actually exposed to the risk of HPV infection. The manufacturers also recommend regular screening even after vaccination because each vaccinated woman may still not be adequately protected.

**Ethical issues**

The debate on HPV vaccination is located within the complex conundrum of different aspects within public health in the Indian context – introduction of new vaccines in UIP, weakening public health system, lack of policy on compensation mechanisms regarding adverse events following immunization (AEFI), and informed consent process.

HPV vaccine trials and administration from across the world, including India, have provided compelling evidence on reporting of side effects or adverse events. It is only ethical then that compensation policies for HPV vaccines are framed and the informed consent process be seriously implemented. It is unscientific to turn a blind eye on these concerns and rush into the launch of vaccine in the UIP. Further, the Indian public health system being one of the least funded at a global level, faces challenges with regard to establishing a monitoring system to check effectiveness and safety of the vaccines.

Informed consent process is linked to the rights of the individuals who are being administered with vaccines. Children who are the primary recipients of most of the vaccinations, form a vulnerable group, fulfilment of whose rights depend on other persons be it their parents, guardians, or other caregivers. Adolescents too in the case HPV vaccine form a vulnerable group and their rights ought to be protected, the ways of doing which can be challenging and would require the public health system to creatively look into formulating the informed consent process and its implementation.

India currently does not have any official vaccine compensation program, and complainants’ only route to justice is through approaching the legal system which tends to become a lengthy process bearing a lot of expense. On the other hand, India has a compensation policy for clinical trials but ironically in the PATH demonstration project of HPV vaccine in Andhra Pradesh and Gujarat, the health system did not provide any compensation to the families of girls who died after taking the vaccine.

The travesty of informed consent process seen during the HPV vaccine demonstration project presents a volatile nature of procedures that could take place in the absence of a robust monitoring and surveillance system. The preparedness of the health system to implement the IC process needs to be looked into and understood for planning a system of IC for trials as well as for post trial administration of vaccines.

Compensation in the context of clinical trials is a widely debated issue globally. A clear obligation to respect the trial participants needs to be spelt out and that should be based on implementation of fundamental rights and from human rights framework. Clinical trial participants should be provided with all the information on compensation, adverse events reports, and the free medical care ought to be given to them. The issue of compensation for clinical trials related injury or death cannot be viewed in isolation, but as situated in a more complex realm where different legal, ethical, medical advancement, common good, industrial interests and above all the rights of participants intersect. In India though there is a compensation policy in place, yet the ambiguities with regard to who should be given compensation and the quantum of compensation continue unabated. In the PATH demonstration project of HPV vaccine in Andhra Pradesh and Gujarat, the health system did not provide any compensation in cases of reported deaths of girls following the vaccination. Similarly, there is a need to discuss about the compensation with regard to adverse events following immunisation (AEFI). India currently does not have any official vaccine compensation program, and complainants only route to justice is through approaching the legal system which tends to become a lengthy process bearing a lot of expense.
What needs to be done?

It is also important that the government before launching the vaccine ask the Drug Controller General of India (DCGI) and other stakeholders to produce the anonymised raw data of the clinical trials of the vaccine conducted on girls in India for assessment by independent experts on the safety and efficacy issues. This is critical as the approval for the vaccines was given by the DCGI based on bridge trials - Phase IIIB trials - and not Phase III trials.

Comprehensive access to reproductive and sexual health programs and services for adolescents, women and men must be ensured. The focus should be on increasing access to preventive health care services such as pap screenings, visual screening of the cervix with acetic acid (VIA) and Visual Inspection of cervix with Lugol’s Iodine (VILI), pap smear, etc.

It is absolutely essential that sexuality education, and awareness programmes be initiated about HPV, cancer, cervical cancer, risks involved and ways of prevention of sexually transmitted diseases.

In any event, before the vaccine is introduced in any program, it is essential that health systems are equipped enough to handle any adverse events relating to the vaccine, and that full informed consent is taken of the parents of the girls, assent of the girls is taken, and alternatives of preventing the disease, importance of regular screening, etc. be informed to the people, prior to vaccination. It must be informed that the vaccine may not work on some, and that in some it may be contraindicated, and immediate measures need to be taken to help the girls facing adverse events, and where they can find such help must also be given in writing.

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Sunil Kaul and R Srivatsan

Editors

November 11, 2016

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Sunil Kaul and R Srivatsan

Editors

November 11, 2016

Appeal for donations

Dear Readers,

As discussed over the MFC egroup over several weeks a few months ago, the bulletin will be provided online to most subscribers. While those who want a hard copy will get it at a slightly subsidized rate (except institutional subscribers who will pay at cost), it still costs money to compose, upload and maintain the bulletin online. We require about Rs 12000 to 15000 as donations to keep running the bulletin.

We request you to donate money to keep the bulletin running. Kindly address all your donations with a covering letter to:

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15 Archana Apartments
163 Solapur Road, Hadapsar
Pune 411028

We would like to express our gratitude to Madhavi Yenappu who readily agreed to be the guest editor of this issue on immunization. The experience, resources and authors she has brought together have made the issue rich and informative.

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Editors

November 11, 2016
As medical graduates from the ‘progressive’ state of Kerala, adults dying of dehydration, severe malnutrition, an infant mortality near 150/1000 and mothers dying in childbirth so often, were all strange and shocking to us. This was 1993 and the tribals of Sittilingi valley had just finished building a small mud and thatch hut to serve as a “hospital” we would run.

We had dreamt of serving a needy population during our undergraduate days in Alleppey Medical College in Kerala, but “post graduate” pressures forced us to finish our Diplomas in Anaesthesia and Gynecology, after which we decided enough was enough and searched for a meaningful place to work. We found Gandhigram near Dindigul in Tamil Nadu. We worked there as ‘proper’ doctors – but during the five years of work there was always a nagging doubt – is this the way forward, just treating illness without rooting out their causes? Too inexperienced to find an answer, we started a year of exploration.

With a small fellowship amount for “confused people trying to find an answer”, Regi backpacked for a year all through India, visiting organisations and activists; searching, probing, imbibing their wisdom...and learning from their mistakes. Somewhere along the way, the fact that tribals got the worst deal, simply because of their inaccessibility hit us and from then on we started to look only at them. Another year of ‘research’, in an age which didn’t have the internet or Google, looking at places farthest from health care helped us to zero in on Sittilingi, in Dharmapuri Dist of TN.

For 3 years the thatched hut was our hospital – string cots moved to the shade of the nearby tamarind tree while we saw patients in the day, a wooden bench with a solar light and some rudimentary instruments for surgery, deliveries on the floor. From there, with some funds we moved to a 10 bedded facility – but here too, things were pretty rudimentary. Our princely OT was just a small steel table with a 100W bulb – focused light came from a dome which is used for store front display. No oxygen, no suction, no cautery, an anaesthesia machine used in WW2 in the field; but we managed acute abdomens, ruptured ectopics and even ruptured uterus. All with abundant help from Above. Autoclaving was done in a large pressure cooker [the ones they use in small hotels] – and if you don’t mind a slightly wet gown, this works wonderfully. Fumigation of the OT was done with a small bowl of formaldehyde placed next to a table fan and the OT sealed with gummed newspaper. The lab was on a window sill with just a microscope and some test tubes and the neonatal care unit was a cement bed with a 100W bulb.

One of the exciting cases we remember is that of a lady bought in a bullock cart with obstructed labour. Lalitha diagnosed it as impending rupture – we quickly shifted her to the OT, by which time she almost

Kasthuri and her husband were tense. She had just delivered preterm baby girl at 29 weeks weighing just 850gms. Hailing from a remote village, she refused to take the baby elsewhere for treatment. Good nursing care helped save her baby. She is ecstatic holding her small bundle of joy, still underweight, but breast feeding and thriving. We do not use fancy equipment or higher antibiotics – just one to one care, IV fluids, warmth and oxygen if needed.
collapsed. Crash intubation and maintenance with ether on an EMO\textsuperscript{1} anaesthesia machine – we opened her up to find that she had already ruptured; quickly caught the bleeders, took the baby out [dead] and then as fast as possible sutured her up. BP was maintained with fluids and dopamine drip. Lucky for her she ruptured just outside the OT, or she would have lost too much blood to save her.

Our surgical odyssey too is out of the ordinary. We thrive on local anaesthesia and nerve blocks – with a little sedation, all easily learnable and safe. Supplement this “vocal” anaesthesia and some easy banter to ease anxiety, and most rural patients are comfortable during procedures. General anaesthesia is rarely used – but needed for thyroid and breast surgery – and though we now use halothane, ether is still in our repertoire. Investigations are kept at a minimum – haemoglobin, HIV, HbsAg, and simple urine examination are the only ones done for almost all surgeries – blood grouping also for those with major interventions. A good clinical history and examination obviates the need for costly tests, thus bringing down the cost of surgery. No antibiotics except for major surgeries (taking more than 2 hours in operating time), even then only a loading dose, quick discharges and an eagle’s eye for cleanliness and sterility help us to keep surgery costs low. For the rural patient cost is of great consideration and so we use fishing line nylon for sutures instead of prolene and mosquito net mesh instead of prolene mesh for hernias – approved by the International Hernia Society, but mainstream doctors contemptuously shrug at.

Working in a rural hospital means that you are consistently thinking laterally, which keeps life so much more interesting and challenging.

Training of tribals girls as health workers went hand in hand and the tribal women as health auxiliaries. In 10 years, with concentrated training, field work and support of the hospital, we managed to bring down infant mortality to decent levels and achieved a nil maternal mortality. From there we progressed to organic farming, craft revival, women entrepreneurship and peripheral clinics in far off places. More about what we do now on www.tribalhealth.org.

Our suggestions to young doctors with surging adrenaline and in search of challenges –

1. Community medicine is best learnt from the community–most medical college specialists have no clue what is happening in the field; instead specialise in clinical medicine. Be a doctor working with the community rather than a community health professional.

2. Have faith in the wisdom of the people and there is much to learn from them. Live with them – laugh and cry with them, and they will accept you as one amongst them.

3. Never think that health work is limited to hospitals or even community health outreaches – unless you are going to look at the other determinants of health like food, employment, environment, etc., changes you make will never be sustainable.

4. Never hesitate because of lack of funds; there are many donors looking to support good and sincere work.

5. Be brave, close your eyes and jump, that leap of faith is cardinal. Your family and friends will recognise your dreams and worth in time.

6. Find a likeminded partner or group of friends when you start out – remember in this type of work 1 + 1 is not just equal to 2 but 3!

Let me end with a cliché quote, “Traveller, there is no path; paths are made by walking”. Walk the wild road.

Email: regilalitha@gmail.com

Note

\textsuperscript{1} Epstein Mackintosh Oxford – this is an anaesthetic delivery machine used in WW2 for field anaesthesia – uses only air and ether. No need of even oxygen.
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