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Review

Synthesizing evidences for policy translation: A public health discourse on rotavirus vaccine in India

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ABSTRACT

The debate on the relevance of rotavirus vaccine to immunization program in India, where 27 million children are born every year, rages on. We synthesized the issues raised during these debates and reviewed the current literature to identify themes that could inform public health policy decision. The paradigm we used integrated disease burden data, host and environmental factors, vaccine efficacy, immunization program issues, and economic considerations. Our synthesis reveals that substantive country specific information on disease burden and economic impact of rotavirus illness in India is constrained by lack of public discussion and qualitative studies on mothers' perceptions of the vaccine in concern. The need to improve the performance of current immunization program against six major vaccine preventable diseases (tuberculosis, diphtheria, tetanus, pertussis, polio, and measles) is often cited as a priority over introduction of rotavirus vaccine. Health in India being a state subject, we emphasize that the states which are in a position to reap the benefit of rotavirus vaccine, due to their good immunization program performance, should not be restrained from doing so. Meanwhile, the poorly performing states should step up their vaccination program and increase immunization coverage. Scientific, ethical and societal concerns captured through multiple sources indicate that the introduction of rotavirus vaccine would be a good investment for India.

1. Introduction

Rotavirus infection occurs worldwide in children under five years of age. The infection may remain asymptomatic, cause self-limiting watery diarrhea or may lead to acute gastroenteritis with fever, vomiting and severe dehydration that may at times be fatal. Bouts of vomiting associated with severe rotavirus gastroenteritis (SRVGE) also pose a hurdle to the clinical management of these cases with oral rehydration salt and sugar solution. Furthermore, no antiviral medicine is currently considered as "standard of care" for SRVGE. On the other hand, disease burden and cost implications of rotavirus diarrhea have been estimated to be enormous [1,2]. Due attention has therefore been paid by global health policy makers to tackle this challenging situation. Consequently, many countries have introduced rotavirus vaccines in their routine immunization program [3,4] after much deliberation. Key deciding factors for introducing rotavirus vaccine in low-income countries have been cost of immunization, financial support from global alliance for vaccines and immunization (GAVI) and long-term sustainability of the program following withdrawal of external assistance [5]. In India, the issue continues to be debated. While one group of discussants opines that India should [6] introduce the vaccine in her routine immunization program, others take a contrary stance [7].

India's national immunization program has evolved since the 1970s (Fig. 1) leading to the introduction of some vaccines and dropping of others based on scientific evidence and public health considerations. The rotavirus debate pivots on vaccine efficacy. While the indigenous Rotavac[2] vaccine tested in India is being challenged [8], Rotarix[3] and Rotateq[4] – two vaccines that have undergone clinical trials in many developed and developing countries [9–11] – have not undergone trial in India. However, the latter two are currently available through the private health

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[2] Developed from New Delhi strain (116E) isolated from asymptomatic neonates.
[3] Monovalent vaccine that used a human strain.
[4] WC-3-based multivalent human-bovine reassortant vaccine.

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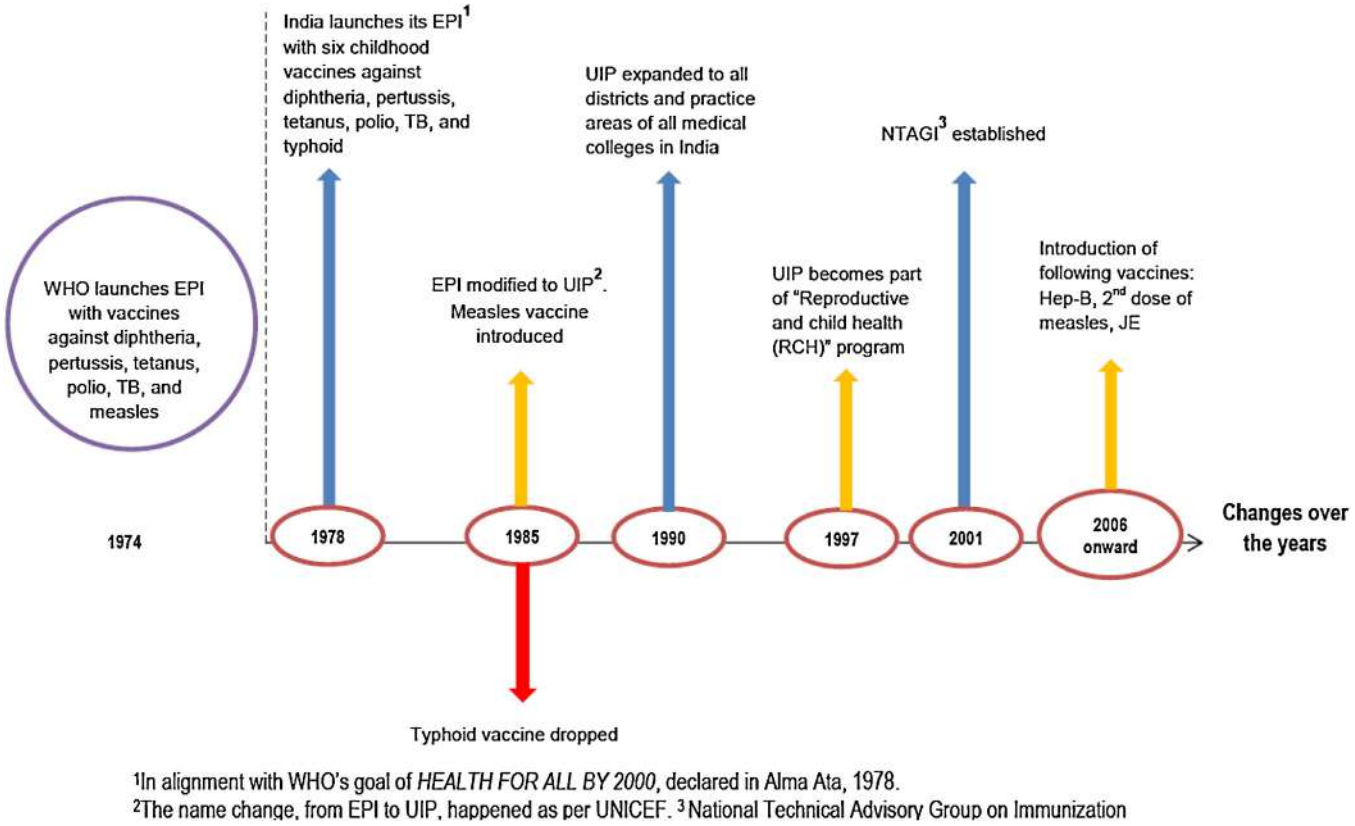

Fig. 1. Evolution of India's national vaccine policy, since introduction of the Expanded Program for Immunization (EPI).

sector. Some health professionals have questioned whether a vaccine should be our only strategy to tackle rotavirus disease burden [12].

Our objective was to understand how evidence was used by different discussants in the aforementioned arguments and to integrate scientific findings with societal and ethical concerns. By categorizing these arguments, we also aimed to inform policy makers in the country for evidence based action.

2. Method

2.1. Literature review

Based on our initial understanding of the debate two key areas were selected for literature review, (a) 'epidemiology' and (b) 'vaccine'; another subsidiary area chosen for review was 'debate'. We adopted a thorough search strategy, followed by data screening.

2.1.1. Search strategy

We searched PubMed and Embase (two bibliographic databases) using identical search terms to retrieve articles on identified areas published in English till September 2013. We did not specify any start-time of publication while conducting this search. Under 'epidemiology' we searched PubMed with 'rotavirus' ('rotavirus' *OR* 'rotavirus infections') as Medical Subject Heading (MeSH) major term, paired with MeSH subheading term 'epidemiology' and text word 'India'. For Embase search, 'rotavirus' and 'epidemiology' as subject heading terms were paired with the text word 'India'.

A similar search strategy as above was followed for 'vaccine' with a single change: the term 'epidemiology' was replaced by MeSH major term 'rotavirus vaccines' *OR* 'vaccines' *OR* 'vaccination' in PubMed. These three subject heading terms were similarly paired for searching in Embase. Articles highlighting 'debate' featured in our rotavirus vaccine search. However, in order to obtain wider perspective of the debate, the terms 'perceptions', 'policy', 'debate', 'importan*', 'necess*' were combined with the terms 'vaccines' *AND* 'India', in both bibliographic databases.

Apart from PubMed and Embase, we searched the Cochrane Library to identify systematic reviews or meta-analyses on rotavirus vaccine. When searched with rotavirus vaccine as a MeSH term, two meta-analyses [13,14] were identified, one published in 2004 and the other in 2012, conducted by the same group of authors. Bibliographies of retrieved articles were reviewed for additional citations and accessed. Experts in the field were also consulted to obtain articles that might have been missed in the above mentioned search.

2.1.2. Data screening

Full texts of the manuscripts were accessed which included articles, letters and short communications. We excluded conference abstracts, studies not focussed on India, rotavirus infection in animals and articles on clinical management. Duplicates in databases were sorted and the numbers of articles finally selected are presented in Fig. 2. Bibliographies were managed by EndNote (version 5.0.1).

2.2. Analysis

The data for our analyses was text obtained through the aforementioned search process. The aim in the first phase of analyses was to familiarize ourselves with the various arguments used to arrive at conclusions. We read the articles line by line to identify threads of arguments which we manually coded without hierarchy and identified cognitive contents (Fig. 3). In the next phase

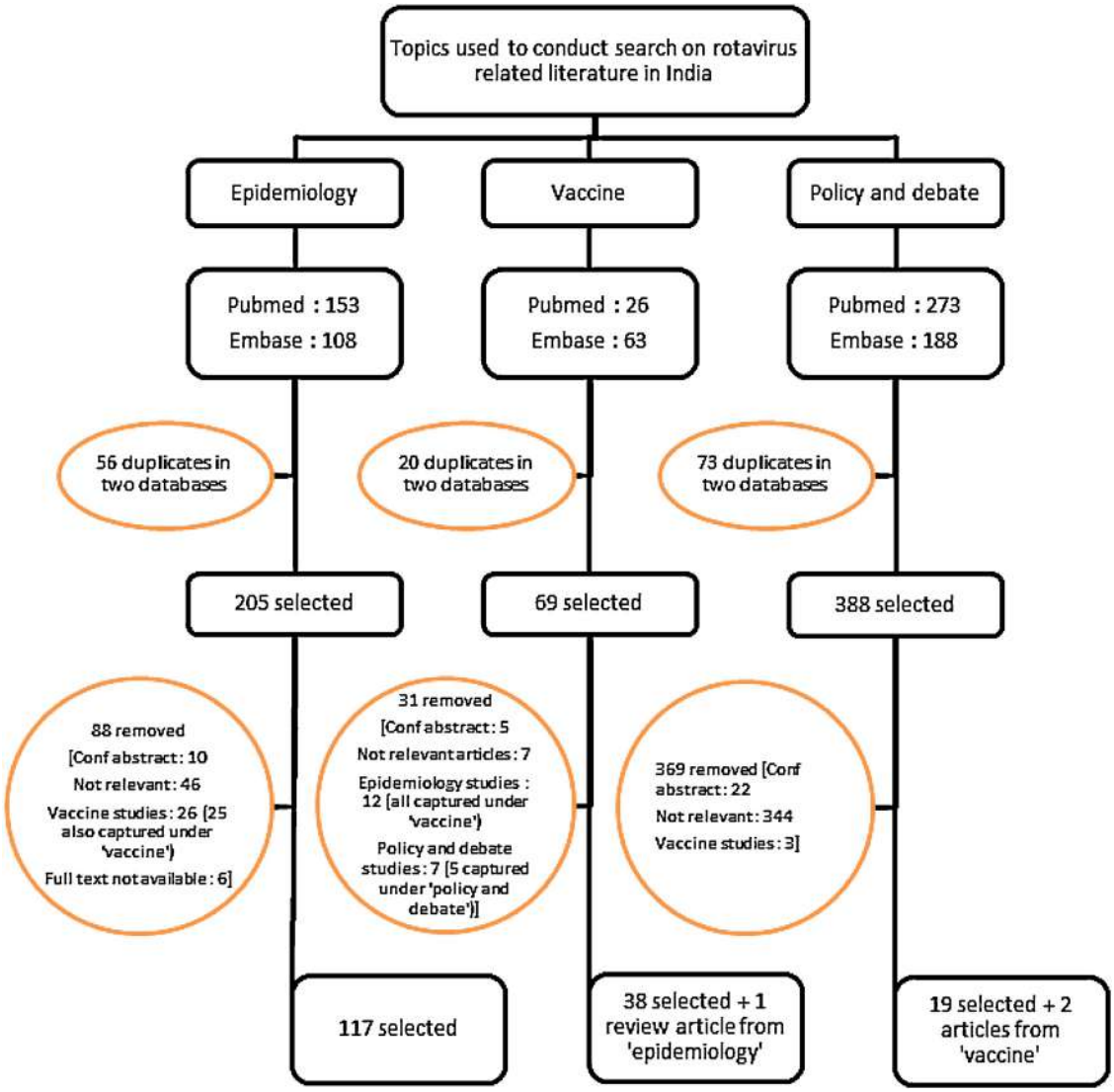

Fig. 2. Results from search algorithm.

of analyses we attempted to identify if different scientific, economic, societal and ethical perspectives led the discussants to arrive at dissimilar conclusions from available evidence base. This required referring to the original articles that the discussants used in building their arguments. Part of this exploration included identifying if same evidence was interpreted differently by different discussants. We also took recent and emerging evidence into account.

3. Results

3.1. Data categorization

Of the 177 articles resulting from the data screening process (Fig. 2), 117 were from the domain of 'epidemiology', 39 from 'vaccine' and 21 from 'debate'. Articles retrieved under 'debate' comprised efficacy, adverse events and immunization performance related discussion, perceptions of pediatricians toward immunization against rotavirus, as well as policy matters. 'Vaccine' articles encompassed clinical trials, mechanisms of action, and inhibitory factors related to oral live vaccines, vaccine uptake by general population in urban and rural settings, as well as economic issues. Most of the articles in 'epidemiology' were on hospital based studies, and only 14 out of 117 articles (12%) described community based investigations. While 10 community based studies were carried out over the last decade, the rest were from an earlier time. Apart from articles referring to rotavirus group A, group B rotavirus studies (occurring rarely and mostly in adults) also featured in our search. Nine articles dealing with infrequent rotavirus genotypes of group A and five about group B were not included during detailed analysis and thus a total of 163 articles (103 from 'epidemiology', 39 from 'vaccine' and 21 from 'debate') were analyzed in-depth. Original research and review articles were used in the citation for the present write-up, as deemed appropriate.

The earliest article documenting rotavirus in children in India appeared from Vellore in Tamilnadu [15] within a year of its first detection in Australia [16]. We noticed that articles on rotavirus diarrhea subsequently started appearing from various parts of the country, including north-eastern states [17–19], all of which appeared under 'epidemiology'.

Cognitive contents in articles used for detailed analyses were arranged into themes as shown in Fig. 3 for synthesizing arguments. The six emerging themes were – (a) disease burden, (b) host factors (mother and child), (c) macro-social environment, (d) the agent (rotavirus) and the vaccine, (e) immunization program issues, and (f) economic issues.

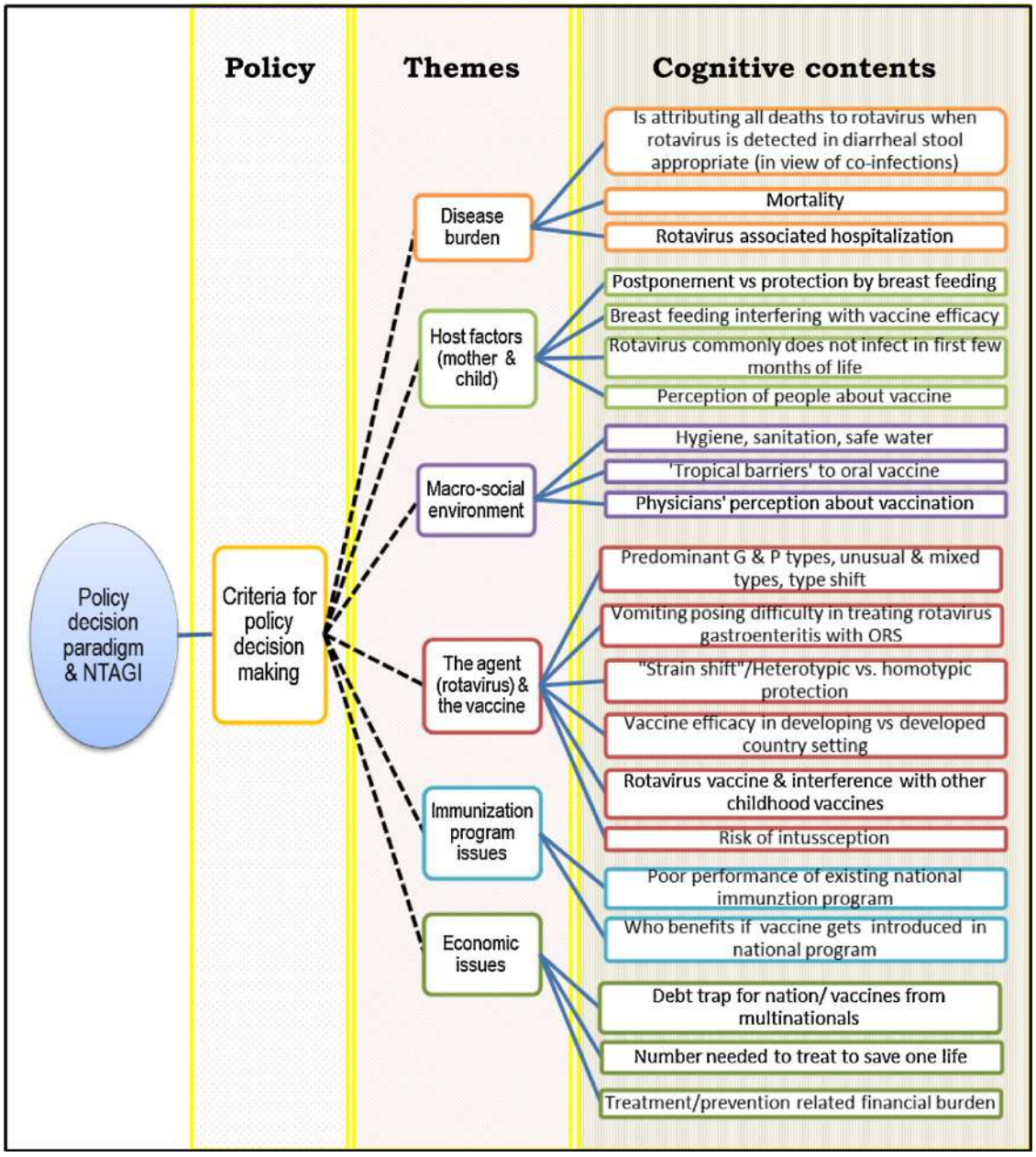

Fig. 3. Issues and themes feeding into policy framework.

3.2. Disease burden

Disease burden is presented here under two major headings, (a) morbidity and (b) mortality due to rotavirus diarrhea in India. Most of the information under this topic came from facility based studies [20], and we identified scarcity of data on morbidity and mortality in communities. As highlighted by some authors [21], community based studies are close to true estimates of rotavirus disease burden and are also representative of circulating strains and serotypes.

3.2.1. Morbidity

A study [22], using data from the Indian Rotavirus Strain Surveillance Network (operating through hospitals) and rate of hospitalizations due to rotavirus diarrhea in a south Indian birth cohort, estimated that 457,000–884,000 hospital admissions occur in India annually due to rotavirus. The same study also estimated that every year rotavirus infection leads to about two million outpatient visits in children under-five years.

We identified four community based prospective cohort studies, conducted in the recent past, to assess rotavirus disease morbidity in the community. One of them, from an urban slum in Vellore, south India [23], investigated the issue of protection conferred by prior rotavirus infection to subsequent infections and rotavirus diarrhea. We examined three other studies [24–26], one each from north (Delhi), east (West Bengal) and south (Tamil Nadu) India, that assessed community based disease burden. In these studies SRVGE constituted 17–33% of all rotavirus diarrheal episodes. Extrapolation of this information to an Indian birth cohort of 27 million reveals rotavirus related diarrhea morbidity in the community to be at least four times higher than what is captured through hospital based surveillance.

In the rotavirus vaccine debate, some discussants have argued that the high morbidity associated with rotavirus diarrhea can

be partially attributed to concomitant enteric infections [12]. A recent multi-country investigation on diarrheal disease in infants and young children informs us on this issue [27]. This matched case–control study estimated burden of disease adjusted for the occurrence of asymptomatic colonization with enteric pathogens often seen in children living in fecally contaminated environments [28]. Despite a wide array of putative pathogens detected, only a few contributed to most attributable moderate-to-severe diarrhea cases and rotavirus was the prime organism detected in multiple age strata in this study [27].

3.2.2. Mortality

Studies offer different estimates (from 81,000 to 113,000) of rotavirus deaths in children under-five years in India. The lower estimate was generated using the World Health Organization's recommended method [29] and the higher figure was obtained on the basis of findings from million death study that used a nationally representative survey conducted in community settings [30]. Worldwide rotavirus associated mortality estimated in 2008, concurred with this range [31]. Using data from a birth cohort of an urban slum in south India, national family health survey (NFHS), national statistics from WHO and UNICEF, and Indian Rotavirus Strain Surveillance Network, Tate et al. generated a higher mortality range (122,000–153,000) [22]. These studies suggest that India contributes the highest number of rotavirus diarrhea deaths in children globally. However, some pediatricians have expressed concern whether all these deaths could be ascertained solely to rotavirus infection, because bacterial co-infections are known to interplay [12] and enhance rotavirus disease severity.

The opponents of rotavirus vaccine in India argued that in efficacy trials of currently available rotavirus vaccines, cumulative mortality was marginally higher among the vaccinated group than the placebo group [7]. They cited Cochrane review [14] in this regard. Upon careful reading, we realized that the review actually reported that protection offered by rotavirus vaccines against mortality could not be established as the studies were mostly conducted in low-mortality countries. Furthermore, the Cochrane review underlined the importance of these vaccines by highlighting three aspects, (a) effectiveness in reducing rotavirus diarrhea (severe cases and cases of any severity), (b) effectiveness in reducing all cause diarrhea, and (c) effectiveness in reducing need for hospitalization due to rotavirus infection.

3.3. Host factors (mother and child)

In the debate on rotavirus vaccines, it has been argued that biological and behavioral host factors have implications for policy on vaccines.

3.3.1. Biological factors

Breastfeeding did not have any protective effect against rotavirus diarrhea in an investigation conducted in rural West Bengal, India [32]. A research from the neighboring Bangladesh has inferred that breastfeeding postpones rather than prevents occurrence of rotavirus diarrhea in children under-two years age [33]. Further, investigations have been carried out to examine inhibitory effect of breast milk on live oral rotavirus vaccine. A study [34] involving breast feeding mothers from India, Vietnam, South Korea and USA, detected the highest IgA and neutralizing titers among Indian mothers against strains present in the vaccines Rotarix, Rotateq and Rotavac. This was a concern because neutralizing antibody in mother's milk might reduce the effectiveness of oral live rotavirus vaccine administered to infants.

The natural history of rotavirus infection in children shows that the virus commonly does not infect neonates and infection rates peak between 3 and 24 months of age [35,36]. The chances of reinfection and severity of diarrhea is thought to decrease following the first infection with rotavirus. However, in a community based study from Vellore [23], levels of reinfection were found to be quite high, with approximately only 30% of all infections identified being primary. Also, protection against moderate or severe diarrhea reportedly increased with the order of infection but was found to be only 79% after three infections. Critics of rotavirus vaccine have cited the above evidence to argue that immunization against rotavirus, similar to primary rotavirus infections, might not prove efficacious in the Indian scenario in preventing repeated rotavirus infections [7].

3.3.2. Behavioral factors

We could not identify any rotavirus specific study addressing host behavioral issues. However, a survey undertaken by UNICEF [37] in India in 2009 is worth noting in terms of perceptions of parents vis-à-vis vaccine uptake. In this study, parents of 12–23 months old children with no or partial immunization were interviewed about the reasons for failing to immunize or partially vaccinating their children. Thirty-six percent of parents living in urban and 26% in rural areas did not feel the need to vaccinate their children while approximately 25% parents did not know their children could be protected with vaccines. About 11% were unaware of where to get children immunized. The pattern of response however differed between urban and rural settings. The reasons cited for partial immunization comprised lack of knowledge about 'what vaccines were needed' and 'when those were to be given'. On the other hand, 'fear of side effects' was one of the major reasons for 'no' immunization.

3.4. Macro-social environment

The macro-social issues raised in the rotavirus vaccine debate in India were (a) sanitary hygiene and access to safe drinking water, (b) 'tropical barriers' to oral vaccines, and (c) physicians' perceptions of vaccination. While physicians' views can influence vaccine dispensation among the public, the other issues (such as microbiota of gastrointestinal tract in tropical countries) influence vaccine uptake at the gut-level.

3.4.1. Infrastructure

Some authors who favored rotavirus vaccine as the principal mode of intervention also recognized sanitation, hygiene, and safe water supply as effective prevention measures against diarrheal diseases caused by bacteria and parasites [38]. They did not assign much weight to the above measures for controlling rotavirus gastroenteritis due to the ubiquitous presence of the virus in the developing *and* developed world. However, others have pointed out that such infrastructural interventions might indeed be useful [12,39] to reduce all causes of diarrheal morbidity and mortality, including that caused by rotavirus. This conviction comes from the fact that the severity of rotavirus gastroenteritis is influenced by the presence of co-infections in the gut, which in turn, is linked with poor civic infrastructure such as water supply and sewerage systems.

3.4.2. Physicians' perceptions

A national survey [40], conducted in 2009–2010 to identify the predictors of administration and attitude about vaccines including rotavirus, revealed that only a tenth of pediatricians had been routinely administering rotavirus vaccines in India. Unfortunately, we could neither locate any Indian study on perception of mothers about rotavirus vaccine nor a public debate.

3.5. The agent (rotavirus) and the vaccines

Diversity of protection (homotypic vs heterotypic) conferred by live oral rotavirus vaccine(s) in Indian setting has been raised as an issue [12]. Since early days of detection, an enormous diversity has been exhibited by rotavirus in India [15,17–19]. A recent review from the subcontinent has revealed that the most common G (G1–G4) and P-types (P [4] and P [8]) globally, accounted for three-fourths of all strains in this region [41]. It is worth noting that the three vaccines that are relevant in the current debate, and vying for inclusion in the national program, have included the following G and P combinations – Rotarix (G1P [8]), Rotateq (G1P1A [8], G2P1B [4], G3P1A [8], G4P1A [8] and G9P1A [8]), and Rotavac (G9P [11]). Rotarix and Rotateq have been found to be safe in multiple prelicensure trials of these two vaccines [10,42,43]. Although, a low risk of intussusception have been documented in post-licensure studies of Rotarix and Rotateq from some countries, such concern is far outweighed by the health benefits of vaccination [44,45].

3.6. Immunization program issues

In 2010 the National Technical Advisory Group on Immunization (NTAGI) played a key role in the development of the draft of the National Vaccine Policy [46]. Established in August 2001 by the Department of Family Welfare, Government of India the NTAGI is the primary advisory committee on all immunization related issues in the country. The policy document observed that since the beginning of the universal immunization program (UIP), India has had six major vaccine preventable diseases (tuberculosis, diphtheria, tetanus, pertussis, polio, and measles) under its ambit for more than two decades (Fig. 1). Importantly, this document identified a major hurdle; the lack of indigenous surveillance data to assess disease burden to make decisions on the introduction of new vaccines. However, as shown earlier, data on morbidity and mortality estimates for rotavirus disease in the country are now available [22,24–26,29–31].

We encountered publications [46–48] relating to criteria for policy decision making in our search. Disease burden, safety and efficacy of the vaccine, affordability and financial sustainability of a proposed vaccination program, program capacity to introduce new vaccines (including cold chain capacity), vaccine production capacity and cost effectiveness were the key issues [46]. In a recommendation paper, the Indian Academy of Pediatrics Committee on Immunization (IAPCOI) [48] mentioned the use of evidence based methodology such as Grades of Recommendation Assessment, Development and Evolution (GRADE). However, we could not identify an evidence based policy framework in any program document that could guide the introduction of rotavirus vaccine in the Indian UIP. Moreover, as highlighted by Nelson and Walker [49], although NTAGI has discussed suitability of rotavirus vaccine in India, no recommendation has yet been made. Meanwhile, critics of the Indian immunization program have highlighted the country's inability to cope with the growing gap between demand and supply of UIP vaccines [50]. It has also been mentioned that vaccine manufacturers have been using trends observed in western countries about introducing new vaccines to influence India's decision [50].

Another major challenge of India's UIP is that fewer than 44% of 27 million newborns in the country receive the full schedule of vaccines [51]. Only 52% receive three doses of diphtheria-tetanus-pertussis (DPT). Further, India spends woefully little on routine immunization [52]. Against this backdrop, critics have argued that India's first priority should be ensuring access to inexpensive UIP vaccines by the poor [7]. On the other hand, public debate on India's poor immunization performance is also lacking. The economists raising this issue have further pointed out the futility of public interventions until children reach school going age, although the first two years of life have a decisive and lasting influence on child's health, well-being, aptitude and opportunities. While explaining such situation, they use the analogy of a gardener allowing anyone to trample on flowers in his garden and later trying to rectify the neglect by giving the plants extra care and heavy doses of water and fertilizer [53].

3.7. Economic issues – interfacing with immunization program performance

In any vaccine policy discussion, economic issues play major role [54]. Those opposing introduction of rotavirus vaccine in India's UIP highlighted that the number needed to be vaccinated for preventing one death and the cost incurred in doing so would considerably exceed per capita income in India, if vaccines produced by multinational companies are used [55]. Furthermore, external financial assistance over a limited period of time extended to the developing countries like India for introducing newer vaccines have been mentioned by this group as a way to lure these countries into a 'debt-trap' [56]. Development of indigenous [57] and low-cost (~INR 180 for 3 doses/child) [8] Rotavac blunts the above arguments.

Regarding economic burden, one study pegged the direct hospitalization related costs to families to be between INR 1530 and 3130 [58]. Another reports that the median direct medical costs due to rotavirus hospitalization in India varies from INR 1800 to 4300 (dependent on the level of care) while the overall economic burden due to rotavirus in India has been calculated in the range of INR 2–3.4 billion [22]. Considering the above figures, it has been projected that a rotavirus vaccination program in India, even at 50% efficacy, would prevent around 44,000 deaths, 293,000 hospitalizations and 328,000 outpatient visits annually, and would save the national exchequer more than US$ 20 million (~INR 860 million) per year (as per 2008 rates) in the cost of medical treatment [59]. In order to predict the economic impact of introducing rotavirus vaccine in the national immunization program in India, researchers considered factors such as disease burden, vaccine efficacy and vaccine cost. Two studies [59,60] reaching similar conclusions envisaged that rotavirus vaccine would likely be a good investment in the country.

Rheingans et al. [61] raised the issues of distributional effects and equity concerns. Their work revealed that the Indian states with the lowest cost effectiveness ratio (CER) – a favorable situation – are those with high pre-vaccination mortality. However, many of these states will also have the lowest proportional reduction in rotavirus mortality due to low vaccination coverage. If national rotavirus vaccination were implemented in India within the existing immunization coverage, then the states with the most favorable CERs and greatest disease burden would benefit the least. Their analysis also suggests that the value for money of rotavirus vaccination could be substantially increased by eliminating differences in coverage between richest and poorest quintiles; the number of deaths averted would increase by 89% among the poorest quintile and could increase the overall number of lives saved by 38%. This is equivalent to increasing vaccine efficacy against severe rotavirus infection from 57% to 79% [61].

4. Discussion

In this discourse, we have critically examined the debate on whether rotavirus vaccine should be introduced in India's immunization program. Our intent was to identify how arguments used by pro- and anti-vaccine lobbies could inform a policy decision process. While both sides have used epidemiological data, economic arguments, and clinical trial results, we could locate very few

references pertaining to challenges in translating these evidences into action. A description of policy making processes for any vaccine currently used in the national immunization program was also scarce.

The first moot point we identified was if the public health problem surrounding rotavirus morbidity was being overestimated. It has been argued that bacterial and parasitic co-infections in the gut are actually responsible for severity of rotavirus diarrhea encountered in our setting [12,62]. In order to obtain clinching biological evidence in this regard, one needs to know which of the gut organisms had harmless presence, which increased the severity of diarrhea and which one was responsible for primary causation. The Global Enteric Multicenter Study (GEMS) focusing on the etiology and population-based burden of pediatric diarrheal diseases in sub-Saharan Africa and south Asia has thrown some light on this issue by identifying that rotavirus was the most common cause of moderate-to-severe diarrhea at every study site during first year of life [27]. It is also important to know that rotavirus vaccines in clinical trials have shown efficacy in reducing 'diarrhea of any severity' and 'SRVGE'. A policy making body may not have answers to all the questions, cited in this paragraph, at a given point in time but they can work under the principle that policy evolves through a process and is not a one-time event [63].

Secondly, the failure of vaccine uptake by the gut mucosa of a child due to anti-rotavirus antibodies in breast milk of mothers and the inability of natural rotavirus infections in preventing subsequent infections (reported from south India) were host related concerns. Preliminary evidence suggests that breastfeeding might not interfere with the immunogenicity of orally administered live attenuated rotavirus vaccines in a clinically significant way [64,65]. Further investigations are ongoing in this area. It is worth mentioning that not only chance of reinfection but also severity of diarrhea has been found to decrease following first infection with rotavirus in north India and abroad [35,36]. The goal that has been pursued to develop live oral rotavirus vaccines [66] is to duplicate the degree of protection against the disease (effect) that follows natural infection [67]. Corroboration regarding reduction in severity of rotavirus gastroenteritis following vaccination has been obtained through clinical trials from Bangladesh and Vietnam [11]. Further supportive evidence come from Mexico and Brazil [68,69], which have witnessed reduction in childhood mortality and hospitalizations due to diarrheal disease – mostly noted among children under two years age – following introduction of rotavirus vaccine. As a proactive policy making process needs to draw evidences from multiple sources, most of the above evidence favors introducing rotavirus vaccine.

Macro-social environmental issues constitute another area of discussion. Infrastructural development is favored over rotavirus vaccine by some as, presumably, such interventions would reduce diarrheal morbidity and mortality, including those caused by rotavirus. We maintain that policy making often takes place in an environment of incomplete empirical evidence. For instance, evidence on effectiveness of improved sanitation, hygiene and provision of safe water in controlling rotavirus diarrhea [12,38] may not be available in the immediate future. We emphasize, 'introduction of rotavirus vaccine in national immunization program in India' and 'infrastructural development ensuring sanitation, hygiene and safe water' should not be pitched against each other as these agenda are not mutually exclusive. While the former is necessary to fulfill the immediate goal of reducing rotavirus induced morbidity and mortality in children under-five, the other will pay dividends in the long-run. As indicated by Anderson et al. [70], it is unrealistic to demand that every decision be based on robust scientific evidence, especially when we know that we are far from having all the information we need.

Many live oral vaccines often elicit reduced immunogenicity when administered in a developing nation, compared to industrialized country settings [71]. This has also been the case with rotavirus vaccines [72,73]. Reasons for this reduced immune response is yet to be clearly understood, although tropical enteropathy, characterized by intestinal inflammation, blunting of small intestinal villi, and mal-absorption, along with poor nutrition have been hypothesized as potential causes [74]. While reduced efficacy due to the above reasons is a reality, work of Rheingans et al. [61] who considered a vaccine efficacy as low as 50%, revealed that a considerable proportion of birth cohort of 27 million children will benefit from introduction of rotavirus vaccine in India. Apart from efficacy and immunogenicity, safety plays a critical role in the considerations of any vaccine. Available evidence does not warrant against introduction of rotavirus vaccine in the national program from this perspective.

Lack of public debate [53] on India's poor immunization performance [75] is an issue under the macro-social environment that has been highlighted. Discussion on utility of rotavirus vaccines in India has remained mostly restricted to public health professionals and clinicians. Although, we could locate studies on pediatricians' perceptions and practices about rotavirus vaccine, qualitative studies on mother's perceptions were lacking. Such investigations should be promoted through committed resources and the findings incorporated in vaccine policy discussion. The current NTAGI of India [76] does not have public representation in it. This gap also needs to be bridged at the earliest.

Whether rotavirus serotype-specific neutralizing antibodies (immunity) play an important role in protection against rotavirus-associated diarrhea is still under discussion. The goal that has been pursued to develop rotavirus vaccines is to duplicate the degree of protection against disease that follows natural infection [67]. Although, some have opined that serotype specific immunity [77] is of central importance, recent evidence from clinical trials and post-licensure studies indicate protection against a wide range of circulating rotavirus strains, even those not included in the vaccine [78–81]. However, monitoring 'strain shift' in the community should be continued in India during post-vaccination period so that the range of protection offered by rotavirus vaccines through the national program can be tracked [20].

Finally, it needs to be appreciated that health in India is a state subject. Heterogeneity exists among Indian states in terms of immunization program performance, and it is estimated that the poorly performing states with low immunization coverage will draw less benefit from introduction of rotavirus vaccines [61]. A pragmatic decision making paradigm is, thus, required in such an environment of heterogeneity. The states which are currently in a position to reap the benefit of rotavirus vaccine should not be restrained from doing so. Meanwhile, poorly performing states should step up their vaccination program. The latter goal should however not be the basis of delaying introduction of rotavirus vaccine in the national immunization program, and may even be considered unethical. Availability of a low-cost indigenous vaccine further strengthens this issue as it would lead to reduced financial burden to the exchequer [82].

Synthesis of evidence within an ethical and rights-based perspective thus led us to conclude that introduction of rotavirus vaccine is justified. Otherwise, the cost of inaction could be overwhelmingly large in the future, compared to the cost of action today. One, of course, needs to evaluate the impact of such a policy decision at regular intervals, and ensure public engagement in the process.

Conflict of interest

The authors declare that they had no competing interests that could have inappropriately influenced this study.

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