Article ID: WMC004111 ISSN 2046-1690

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Article ID: WMC004111

Article Type: Review articles

Submitted on:06-Mar-2013, 09:30:06 AM GMT **Published on:** 06-Mar-2013, 11:40:41 AM GMT

Article URL: http://www.webmedcentral.com/article_view/4111

Subject Categories:PUBLIC HEALTH

Keywords: Immunisation, Infant Feeding, Infectious Diseases

How to cite the article: Gupta A, Dadhich JP. Should Developing Countries Incorporate Pneumococcal and Rotavirus vaccines in their National Immunisation Programmes . WebmedCentral PUBLIC HEALTH 2013;4(3):WMC004111

Source(s) of Funding:

No external funding

Competing Interests:

All authors declare that they have no relationships with any company that might have an interest in the submitted work in the previous 3 years; nor do their spouses, partners, or children have any financial relationships that may be relevant to the submitted work; and they have no nonfinancial interests that may be relevant to the submitted work.

Should Developing Countries Incorporate Pneumococcal and Rotavirus vaccines in their National Immunisation Programmes

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Abstract

In recent times there has been an unprecedented global focus on addition of newer vaccines like Rotavirus and Pneumococcal vaccines(PCV) to reduce diarrhoea and pneumonia mortality and enhance child survival. Many issues need to be resolved before introducing these vaccines in resource poor developing countries. There is a need to know how effective these vaccines are for decreasing mortality due to childhood pneumonia and diarrhea in developing countries. The concern is that introduction of these vaccines is likely to divert the meagre resources available away from more beneficial, evidence based cost-effective interventions such as supplying safe water and sanitation, promotion of early and exclusive breastfeeding, and improving health systems which are crucial to control morbidity and mortality due to childhood diarrhoea and pneumonia more sustainably.

Introduction

In the global quest to achieve the Millennium Development Goal (MDG) 4 to reduce child mortality by two thirds by 2015, the World Health Organisation (WHO) has proposed introduction of vaccines for pneumococcal and rotavirus infections in all national immunization programmes (1). The proposal requires more scrutiny of its relevance, effectiveness, cost, and possible contribution to reducing deaths in resource poor countries. The benefits of these vaccines are blunted by low absolute risk reduction in developing countries and the phenomenon of strain shifts, which we discuss in this paper. We discuss the comparative cost effectiveness of providing safe water & sanitation and promoting breastfeeding to reduce early childhood mortality. We argue that developmental assistance currently used to assist introduction of these vaccines in developing countries could be put to better use elsewhere.

Review

The case of pneumococcal vaccine and pneumonia

Pneumonia is the leading cause of mortality in children under five. Studies from developing countries have identified many organisms like Streptococcus pneumoniae, Hemophilus influenzae b, and Respiratory Syncytial Virus as causative agents (2,3). Pneumonia mortality in children is strongly linked to poverty, malnutrition, inadequate health care, low birth-weight, non-exclusive breastfeeding during the first 4 months of life, lack of measles immunization, indoor air pollution and over-crowding. (4,5).

Preventing childhood pneumonia with pneumococcal vaccine

Streptococcus pneumonia may cause invasive pneumococcal disease (IPD), which includes pneumonia, meningitis and febrile bacteraemia. (6) There are 93 known serotypes of this bacterium. A variety of vaccines including a 23-valent polysaccharide vaccine and three conjugate vaccines namely heptavalent conjugate pneumococcal vaccine (PCV 7), ten valent conjugated pneumococcal vaccine (PCV10) and a thirteen valent conjugated pneumococcal vaccine (PCV13) are available to prevent pneumococcal disease. The Cochrane review for PCV showed pooled vaccine efficacy 80% (95% confidence interval (CI) 58% to 90%, $P < 0.0001$); all serotypes-IPD, 58% (95% CI 29% to 75%, $P = 0.001$); World Health Organization X-ray defined pneumonia was 27% (95% CI 15% to 36%, $P < 0.0001$); clinical pneumonia, 6% (95% CI 2% to 9%, $P = 0.0006$); and all-cause mortality, 11% (95% CI -1% to 21%, $P = 0.08$). There was no statistically significant reduction in all cause mortality (7). This data suggests that the PCV is unlikely to reduce childhood mortality to the extent to enable achievement of the MDG-4. The impressive sounding reductions in relative risk quoted in the Cochrane review as vaccine efficacy against vaccine serotype IPD masks a much smaller reduction in absolute risk. According to a trial using 9 valent pneumococcal vaccine, vaccinating 1000 children will prevent 3.6 cases of radiologically confirmed pneumonia (8).

Phenomenon of serotype replacement

There has been a significant increase in pneumococcal disease due to non-vaccine serotypes particularly 19A disease after introduction of PCV7 and the Table 1 shows how the incidence of IPD due to non-PCV strains increased in the UK from 150 to 375 during a four year period when the incidence of IPD due PCV7 strains came down from 400 to 25 (9). A retrospective review from Singapore reveled that IPD incidence remained uncahnged even with increased coverage of PCV7. (10). More alarmingly, there is now an increase in the incidence of Penicillin resistance.(11) The benefits from the vaccine are at risk of being wiped out with the emergence of these new strains which need treatment with more expensive antibiotics. Temporarily this is being countered by the new PCV 13 vaccine, which covers the newly emergent strains but it has been suggested that the strain shifts would continue to evolve with even newer strains likely to emerge in the future (12) .

Cost and cost- effectiveness of PCV

Some economic evaluations of the PCV from developed countries have suggested that it is cost-effective (13,14,15). However, an evaluation in Korea found it was not cost effective (16). The phenomenon of strain shifting makes the cost utility ratio even worse as the costs of treating more virulent replacement-strains must be factored into the costing. An evaluation from Netherlands, which factored-in added costs due to an increase in non-vaccine serotype IPD found PCV 7, was not cost-effective. (17)

In real terms the cost per life saved with PCV has been calculated to be US$ $47,220. (18). On the other hand, saving neonatal deaths utilizing a bundle of 16 interventions in sub-Saharan Africa and South Asia costs only US$1100-3900 per death averted (19). Low-income countries will find the cost of pneumonia control using vaccines unaffordable. In addition, low-income countries lack the strong and fully functioning health system needed to universalize the coverage of pneumococcal vaccine (20). All these factors suggest that pneumococcal vaccine is unlikely to make an impact in terms of reducing childhood mortality in developing countries.

The case of rotavirus vaccine and diarhhoea

Diarrhoea remains the second leading cause of morbidity and mortality among children under five. Diarrhoea is caused by a variety of pathogens including viruses, bacteria, and protozoa. About 88% of deaths due to diarrhoea have been attributed to unsafe water, inadequate sanitation and poor hygiene (21). Rotavirus is responsible for about 40% of all childhood diarrhoea hospitalisations(22). The WHO and UNICEF recommend a 7-point action plan to reduce diarrhoea-related-disease and mortality that includes both a prevention and a treatment package, and vaccines are only one of these measures. The preventive measures include early and exclusive breastfeeding for the first six months, Vitamin A supplements, hand washing, safe and adequate water supply, and sanitation (23). In developed countries and in Latin America, use of rotavirus vaccines has resulted in decline in hospitalization due to diarrhoea and diarrhoea-related-mortality (24,25). However, a Cochrane review on rotavirus vaccine suggests that efficacy of rotavirus vaccines is lower in countries in Africa and Asia compared to high-income countries. The review also reveals that with the 5 valent rotavirus vaccine, at two years follow-up, there was no statistically significant difference in severe rotavirus diarrhoea between vaccine and placebo groups. (26)

Rotavirus strain differences/ Phenomenon of serotype replacement

Rotavirus strains in developing and developed countries are different. This is also responsible for the differences in vaccine efficacy seen in these contrasting environments. A multi-centre study in India, looking at the local rotavirus strains found that only 22.1% of strains identified were covered in Rotarix (GSK), while 47.9% were covered by RotaTeq(Merck) (27). Studies from India have also shown that there has been continuous re-assortment between the human and bovine viruses and the strains causing human infections are evolving continuously(28). This makes the task of developing appropriate vaccines for India a challenge. It is also known that passively transferred maternal antibodies against rotavirus through the placenta and breastmilk may inactivate the vaccine; malnutrition and other enteric co-infections may also be contributing to the lower efficacy(29).

Role of other preventive and therapeutic interventions, coverage and cost-effectiveness

An analysis of the available evidence suggests that provision of safe water is likely to reduce diarrhoeal disease prevalence by up to a third.(30) Still greater reductions (up to 63%) are associated with supply of piped water to homes (31). In developing countries 'not breastfeeding' resulted in an excess risk of diarrhoea mortality in infants 0-5 months of age (RR: 10.52) (32). Oral rehydration therapy (ORT) has proved to be an effective intervention to decrease mortality in childhood diarrhoea. Prior to availability of rotavirus vaccines, annual diarrhoeal deaths consistently deceased in children below 5 years of age, from the estimated 4.6 million in 1980 to about 1.5

million in 2000. Case studies from Brazil, Egypt, Mexico, and Philippines have confirmed that an increase in the use of ORT (15% in 1984 to 40% in 1993) was concomitant with marked falls in mortality due to diarrhoea (33). The WHO briefing suggests that exposure to indoor air pollution more than doubles the risk of disease and is responsible for 900,000 of 2 million annual deaths from pneumonia and other ALRI.(34)

Coverage of essential interventions like supply of safe water and sanitation was 100% in developed countries since 1990s. In contrast in Africa and the South East Asia region, status of preventive and therapeutic intervention like safe drinking water supply, sanitation, are far from satisfactory and remain slow in progress(35) (See Table -2). Exclusive breastfeeding rate for first six months is 37% in developing and 39% in least developed countries. Oral rehydration therapy with continued feeding is available only to 39% of children with diarrhoea in developing countries and 43% children in least developed countries (23). Similarly, Table 3 shows coverage of interventions in India, cleraly showing how much needs to be done to put in place basic health care in the hands of all people.(35,36,37). A recent study from Niger on the impact of introduction of either rotavirus vaccine or PCV7 on health systems storage, transport, and refrigerator space revelas that it will reduce the vaccine reach to the clinics. The study predicted that WHO EPI rates might decrease from an average of 69% to 28.2% (range = 10%–51%). These issues need to be addressed before introducing rotavirus vaccine in Africa and Asia. (38)

In a cost effectiveness study among the interventions against diarrhoeal disease, breastfeeding promotion programs cost US$ 527 to US$ 2,001 per disability adjusted life years (DALY) averted, oral rehydration therapy costs US$132 to US$ 2,570 per DALY averted, improved access in areas with little access to water cost US$ 94 per DALY averted and sanitation US$ 270 per DALY averted. These interventions are more cost effective compared with rotavirus immunizations costing US$ 1,402 to US$ 8,357 per DALY averted during first year of life. (39). For these reasons it will be prudent not to extrapolate efficacy data from developed countries on to other countries.

Conclusions

Any public health strategy must have a place for vaccines but only if the vaccine is proven to be very effective in terms of absolute risk reduction, and is affordable. We believe that interventions like pneumococcal and rotavirus vaccine are likely to compete with the efforts to provide other interventions which could save more lives and be sustainable. In the above analysis and discussion it is clear that both pneumococcal vaccine and rotavirus vaccines have low utility but high costs. For the same expenditure more lives could have been saved by alternate use of the money and this is the opportunity forgone. While GAVI alliance provides co-funding for vaccines there is no such coordinated source of funding for the other interventions in the resource poor countries (20). Considering the critical and sustainable role breastfeeding, water-supply and sanitation can play, and their ability to reduce overall disease-burden, it seems more logical to invest in these interventions. Similar is the case for treatment with ORT.

It is also clear that presence of strong and well functioning health system is required without which it would not be possible to achieve meaningful coverage of any vaccine. Considering strain problems, lack of country specific data on effectiveness and absolute risk reduction of these two vaccines in developing countries, such an initiative can be put on hold. The advice of the Cochrane review on effect of pneumococcal conjugate vaccines for preventing vaccine type IPD and X-ray defined pneumonia is worth taking note of "….policy makers should look into existing data on burden of pneumonia disease or risk of disease in children under two years of age, serotype-specific disease, drug resistance in the local setting, and the cost of the vaccine to make informed decisions on the inclusion of the vaccine into national immunisation programmes.."(7). To make the task easy for programme planners and decision makers, calculations on absolute risk reduction and cost-effectiveness should be generated. Universalising access to these effective interventions other than vaccines could be the game changer for the developing countries to rapidly achieve Millennium Development Goal 4.

References

1. WHO recommendations for routine immunization - summary tables Available at: http://www.who.int/immunization/policy/Immunization_routine_table2.pdf Accessed on May 28, 2012.
2. Mathew JL, Patwari AK, Gupta P, Shah D, Gera T, Gogia S, Mohan P, Panda R,Menon S. Acute respiratory infection and pneumonia in India: a systematic review of literature for advocacy and action: UNICEF-PHFI series on newborn and child health,

India. Indian Pediatr. 2011 Mar;48(3):191-218.
3. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ et al.. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet. 2010 May 1;375(9725):1545-55
4. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. Bull World Health Organ. 2008 May;86(5):408-16.
5. World Health Organization/UNICEF. Global action plan for prevention and control of pneumonia (GAPP). Geneva, Switzerland: World Health Organization; 2009. A vailable at http://whqlibdoc.who.int/hq/2009/who_fch_cah_nch_09.04_eng.pdf. Accessed April 15, 2012
6. WHO. Pneumococcal V accines. A vailable at: http://www.who.int/vaccines/en/pneumococcus.shtml Accessed on May 5, 2012.
7. Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreño RA, Nohynek H, Riley ID, Makela H. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004977
8. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003; 349:1341-8.)
9. Gladstone RA, Jefferies JM, Faust SN, Clarke SC. Continued control of pneumococcal disease in the UK - the impact of vaccination. J Med Microbiol 2011 Jan; 60(Pt 1):1-8.
10. Thoon KC, Chong CY, Tee NW. Early impact of pneumococcal conjugate vaccine on invasive pneumococcal disease in Singapore children, 2005 through 2010. Int J Infect Dis. 2012 Mar;16(3):e209-15
11. Hicks LA, Harrison LH, Flannery B, Hadler JL, Schaffner W, Craig AS, Jackson D, Thomas A, Beall B, Lynfield R, Reingold A, Farley MM, Whitney CG. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998-2004 J Infect Dis. 2007 Nov 1;196(9):1346-54. Epub 2007 Oct 4.).
12. Principi N, Esposito S. Use of the 13-valent pneumococcal conjugate vaccine in infants and young children. Expert Opin Biol Ther. 2012 May;12(5):641-8.
13. Hoshi SL, Kondo M, Okubo I. Economic evaluation of vaccination programme of 7-valent pneumococcal conjugate vaccine to the birth cohort in Japan. Vaccine. 2012 May 9;30(22):3320-8.
14. Blank PR, Szucs TD. Cost-effectiveness of 13-valent pneumococcal conjugatevaccine in Switzerland. Vaccine. 2012 Apr 19. [Epub ahead of print]
15. Wu DB, Chang CJ, Huang YC, Wen YW, Wu CL, Fann CS. Cost-effectiveness analysis of pneumococcal conjugate vaccine in Taiwan: a transmission dynamic modelling approach. Value Health. 2012 Jan-Feb;15(1 Suppl):S15-9.
16. Sohn HS, Suh DC, Jang E, Kwon JW. Economic evaluation of childhood 7-valent pneumococcal conjugate vaccination in Korea. J Manag Care Pharm. 2010 Jan-Feb; 16(1):32-45.
17. Rozenbaum MH, Sanders EA, van Hoek AJ, Jansen AG, van der Ende A, van den Dobbelsteen G, Rodenburg GD, Hak E, Postma MJ. Cost effectiveness of pneumococcal vaccination among Dutch infants: economic analysis of the seven valent pneumococcal conjugated vaccine and forecast for the 10 valent and 13 valent vaccines. BMJ. 2010 Jun 2; 340: c2509.
18. Puliyel J. Cost of pneumococcal vaccine underestimated ten-fold. Hum Vaccine. 2011 May 1;7(5).
19. Darmstadt GL, Neff Walker N, Lawn JE, Bhutta ZA, Haws RA and Cousens S. Saving newborn lives in Asia and Africa: cost and impact of phased scale-up of interventions within the continuum of care. Health Policy Plan. 2008 23:101-117)
20. Cohen AL, Hyde TB, Verani J and Watkins M. Integrating pneumonia prevention and treatment interventions with immunization in resource-poor countries. Bull World Health Organ 2012, 90: 289-294.
21. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? Lancet 2003 Jun 28;361(9376):2226-34.
22. WHO. Global networks for surveillance of rotavirus gastroenteritis, 2001-2008. Weekly Epidemiological Record. 2008;83(47):421–5.
23. The United Nations Children's Fund, World Health Organization, 2009. Diarrhoea: Why children are still dying and what can be done. Available at: http://www.who.int/maternal_child_adolescent/documents/9789241598415/en/index.html Accessed on May 8, 2012.
24. Cortes JE, Curns AT, Tate JE, Cortese MM, Patel MM, Zhou F,Parashar UD. Rotavirus vaccine and health care utilization for diarrhea in U.S. children. N Engl J Med. 2011 Sep 22;365(12):1108-17.
25. Centers for Disease Control and Prevention (CDC). Progress in the introduction of rotavirus vaccine--Latin America and the Caribbean, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011 Dec 2;60(47):1611-4.

26. Soares-Weiser K, Maclehose H, Bergman H, Ben-Aharon I, Nagpal S, Goldberg E et al. Vaccines for preventing rotavirus diarrhoea: vaccines in use. Cochrane Database Syst Rev. 2012 Feb 15;2:CD008521
27. Kang G, Arora R, Chitambar SD, Deshpande J, Gupte MD, Kulkarni M, et al. Multicenter, hospital-based surveillance of rotavirus disease and strains among Indian children aged <5 years. J Infect Dis. 2009; 200 Suppl 1:S147-53.
28. Ramani S, Kang G. Burden of disease & molecular epidemiology of group A rotavirus infections in India. Indian J Med Res. 2007 May; 125(5): 619-32)
29. Patel M, Shane AL, Parashar UD, Jiang B, Gentsch JR, Glass RI. Oral rotavirus vaccines: how well will they work where they are needed most? J Infect Dis 2009;200 Suppl 1:39-48.
30. Bartram J, Cairncross S (2010) Hygiene, Sanitation, and Water: Forgotten Foundations of Health. PLoS Med 7(11): e1000367. doi:10.1371/journal.pmed.1000367
31. Esrey SA, Potash JB, Roberts L, Schiff C (1991) Effects of Improved Water Supply and Sanitation on Ascariasis, Diarrhoea, Dracunculiasis, Hook- worm Infection, Schistosomiasis and Trachoma. Bull World Health Organ 69: 609–621.
32. Lamberti LM, Fischer Walker CL, Noiman A et al. Breastfeeding and the risk for diarrhea morbidity and mortality. BMC Public Health 2011;11 Suppl 3:S15-27.
33. Victora CG, Bryce J, Fontaine O, Monasch R. Reducing deaths from diarrhoea through oral rehydration therapy. Bull World Health Organ. 2000; 78(10):1246-55.).
34. WHO .Indoor air pollution, health and the burden of diseases: Indoor air thematic briefing 2 www.who.int/entity/indoorair/info/briefing2.pdf Accessed September 7,2012)
35. WHO. World health statistics 2012. Available at: http://www.who.int/gho/publications/world_health_statistics/EN_WHS2012_Full.pdf Accessed on May 29, 2012.
36. UNICEF Coverage Evaluation survey, 2009 National Fact Sheet. Available from: http://www.unicef.org/india/National_Fact_Sheet_CES_2009.pdf. Accessed on May 4, 2012.
37. UNICEF – India. Statistics – Basic Indicators. Available at: http://www.unicef.org/infobycountry/india_statistics.html Accessed on May 22, 2012
38. Lee BY, Assi T, Rajgopal J, Norman BA, Chen S I, Brown ST, Slayton RB, Kone S, Kenea H, Welling JS, Connor DL, Wateska AR, Jana A, Wiringa AE, Van Panhuis WG, and Burke DS: Impact of Introducing the Pneumococcal and Rotavirus Vaccines Into the Routine Immunization Program in Niger American Journal of Public Health February 2012, Vol. 102, No. 2 : pp. 269-276 doi: 10.2105/AJPH.2011.300218
39. Jamison DT, Breman JG, Measham AR, et al., editors.In Disease Control Priorities in Developing Countries. 2nd edition. Washington (DC): World Bank; 2006. Chapter 2, p 41.)

Illustrations

Illustration 1

Table 1

Illustration 1: Trends in approximate number of IPD reports in children under five in UK

(Adapted from reference 9)

Week 20 of the Year	Number of IPD cases due to Pneumococcal strain in PCV7	Number of IPD cases due Pneumococcal strain not in PCV7	Total cases
2006	400	150	550
2007	275	175	450
2010	25	375	400
Increase ↑/decrease ↓	↓	↑	↓

Illustration 2

Table 2

Illustration 2: Progress on key preventive interventions for diarrhoea and pneumonia (adapted from reference 35)

WHO region/ Income group	Population using improved Drinking-water sources (%)		Population using improved sanitation (%)		Population Using solid fuels (%)
	1990	2010	1990	2010	2010
Developed countries	100	100	100	100	
African Region	50	63	29	34	77
South-East Asia Region	71	90	25	43	61
Low income	54	65	21	37	91
Lower middle income	70	87	29	47	54
Global	76	89	49	63	41
Ranges of country values	14-100	29-100	3-100	9-100	<5 - >95

Illustration 3

Table 3

Illustration 3: Status of Child health indicators / Child survival interventions in India (Adapted from Ref. 35,36,37)

Child health indicators / Child survival interventions		Status/Coverage (%)
Infant and Young Child Feeding practices (36)	Initiation of Breastfeeding within one hour of birth	40.5
	Children age 0-5 exclusively breastfed	46.8
	Children age 6-9 months receiving solid/semi-solid food and breast milk	57.1
Child health care services (37)	Under-fives with diarrhoea receiving oral rehydration and continued feeding	33
	Under-fives with suspected pneumonia taken to an appropriate health-care provider, 2006-2010	69
	Under-fives with suspected pneumonia receiving antibiotics	13
Routine immunization coverage (36)	Bacille Calmette Guerin (BCG) Oral Polio Vaccine Diphtheria-Tetanus-Pertussis (DTP) 3 doses Measles	86.9 70.4 71.5 74.1
Population using improved sanitation facilities (35)		34
Population using improved drinking water sources (35)		92

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