Influenza Vaccination for Children in India

JOSEPH L MATHEW

From the Advanced Pediatrics Centre, PGIMER, Chandigarh 160012, India.
Email: jlmathew@rediffmail.com

Recently there has been considerable concern over influenza in our country especially as it has been suggested that in the event of a pandemic, there will be limited management options available(1). Following the availability of influenza vaccine in India some years back, the Indian Academy of Pediatrics Committee on Immunization (2005-06) recommended it for a limited number of high-risk conditions(2). More recently, the Advisory Committee on Immunization Practices (ACIP), USA and the American Academy of Pediatrics expanded the indications for the vaccine to include routine immunization in children between 5-18 years(3), in addition to continuing immunization of all children between 6 months and 4 years. However, not all developed countries have followed suit(4). Current aggressive marketing of the vaccine and consequent inquiries, especially for its role in children with asthma; necessitate scientific evaluation of influenza vaccination in the context of our country. Thus the clinical condition and intervention are both relevant in our setting.

The decision question is whether (or not) to prescribe/recommend influenza vaccination in Indian children, with the goal being to prevent influenza infection and/or its consequences. The clinical question could be framed as, *"In Indian children with or without underlying conditions (population), does influenza vaccination (intervention) as compared to no vaccination (comparator) result in improved clinical outcomes (outcome)?"*

CURRENT BEST EVIDENCE AND CRITICAL APPRAISAL

Vaccination differs from other interventions in three major aspects; first, it is administered to healthy children before the onset of disease, unlike therapeutic and diagnostic interventions; Second, it often involves decisions for a population rather than individual children alone; and third, it usually has an impact wider than those vaccinated owing to population effects, economic issues and political considerations. Therefore, unlike most other interventions, literature search for current best evidence opens up the following lines of inquiry: (*i*) burden and clinical importance of influenza in Indian children, (*ii*) efficacy and effectiveness of influenza vaccination *vis-à-vis* the desired outcome, and (*iii*) appropriateness of vaccine/vaccination in our setting.

A. *Importance of Influenza in India*

A Pubmed search using the terms "*influenza India*" with limits "*humans, All Child (0-18years)*" conducted on 23 February 2009 yielded 48 citations, of which 9 provided relevant data.

Serological evaluation for antibodies against influenza virus strains identified at least one strain in 62% in the age group 5-15 yr, 77% among 16-25 yr, 78% among 26-35 yr, 84% in 36-45 yr and 93% among those older than 45 yr, suggesting progressively increasing infection/exposure with age(5). Although the percentages appear alarming, it is actually heartening because it means that influenza is likely to be a mild infection since commensurate morbidity and mortality have not been reported in our country. This is confirmed by another Indian study of 132 children with clinical and radiological evidence of broncho-pneumonia/pneumonia, using bacterial and viral culture and specific antigen detection tests; the majority (74%) of cases were

attributable to bacteria; of which *H. influenzae* type b(HiB) was predominant(6). A small minority could be attributed to viruses; among these respiratory syncytial virus was the most common(6).

***Table* I** summarizes the isolation rate of influenza viruses using standard methods, from children with acute respiratory infection(7-13). It shows that in India, viruses are responsible for a minority of respiratory tract infection and even among these, influenza forms a small proportion and respiratory syncytial virus appears to be the most frequently identified. This is in stark contrast to data from developed countries where influenza is a major, if not the most important cause of respiratory tract infection in children and adults. It should be noted that only a limited number of these studies simultaneously looked for evidence of bacterial infection; hence the detection of virus/antigen has been assumed, rather than proven to be causal in the remainder.

A recent community-based, longitudinal prospective study followed a cohort of children weekly from birth, looking for respiratory viruses from naso-pharyngeal aspirates among children with acute respiratory infection(14). This study had the advantage of following children over time and reported that over 440 child years of follow-up, viruses could be identified in a significant number of ARI; however only a fraction of these (18%) affected the lower respiratory tract, of which a very small proportion (8%) were severe cases, together accounting for only 1.4% of all ARI. Among those with lower respiratory tract infection (LRTI), influenza was identified in less than one-third and was absent in those with severe LRTI. The data indicates that influenza is responsible for a minority of lower respiratory tract infections in children.

B. *Efficacy and Effectiveness of Vaccination*

A Cochrane Library search on 23 February 2009 with the terms "*influenza vaccine*" revealed 13 systematic reviews and 3 protocols, of which all except three reviews and two protocols were unrelated to children. The review on influenza vaccines in healthy children published in 2008(15) included literature search till September 2007. Additional search beyond September 2007 using the terms *"influenza vaccine"* with limits "*humans, all child*" did not identify any additional randomized trials comparing influenza vaccine with placebo/no vaccination. Thus, the data from RCTs included in

TABLE I BURDEN OF DISEASE DUE TO INFLUENZA IN INDIAN CHILDREN

Site	*n*	Children with	Sample	Virus identification method	% with viruses	% with influenza virus
Pune 2008(7)	385	ARI	NPA	IF for respiratory viruses	37.1%	5.4%
Chennai 2005(8)	240	ARI	TS	Culture, HI, IF	tested only for influenza viruses	10%
Pune 2003(9)	763	ARI	TS, NS,	NPA Culture and HI	tested only for influenza viruses	4.8%
Delhi 2000(10)	200	ARI	NPA	Centrifugation enhanced cell culture	49.5%	14.5%
Lucknow 1991(11)	736	<5yr with ARI	NPA	Culture and IF	22%	6%
Vellore 1991(12)	809	<6yr with ARI	NPA, TS	Culture and IF	49% among LRI; 37% among pneumonia	1.5%
Lucknow 1990(13)	230	Clinical ARI	-	Indirect IF for four viruses	22%	4%

ARI = acute respiratory infection; HI = haemagglutination inhibition; IF = immunofluorescence; NPA = nasopharyngeal aspirate; NS = nasal swab; TS = throat swab.

the Cochrane review is regarded as current best evidence. ***Table* II** summarizes the important findings showing that vaccine effectiveness is considerably lower than vaccine efficacy, which itself does not approach the usual range of 90-95%.

Another Cochrane review examined the effect of influenza vaccines in people with asthma and demonstrated that there was no clinically useful impact on a wide variety of outcome measures(16). It also documented that the vaccine itself was not responsible for asthma exacerbations. No robust evidence was found favouring influenza vaccination in other "high-risk" conditions listed by the IAPCOI(2), suggesting that the recommendations may not be based on robust evidence, but rather an extension of guidelines produced for other clinical settings(17).

C. *Appropriateness of Vaccine*

Continual antigenic drift of the influenza virus necessitates that the vaccine be continually modified/ updated to include the most current strains and administered annually to provide protection. This is done through global virus surveillance at internationally accredited laboratories to identify latest strains and then conveying this information to vaccine manufacturers, in order to get sufficient stocks available by the onset of winter, which corresponds to the peak influenza season in the temperate climate of most developed countries in both hemispheres. In India (as in other non-temperate climate countries), it appears that there is no clearly defined 'influenza season' though winter peaks have been reported. Data on local strains from the reference laboratory in Pune, does not automatically translate into inclusion of these strains in the vaccine; because vaccine is primarily prepared, bearing the needs of developed countries in mind. Further, although India lies within the northern hemisphere, parts of our country have a distinct tropical environment being located close to the equator. The significance of this in terms of a National policy on influenza vaccination has not been considered hitherto. Therefore, for practical purposes, the vaccine currently available here is merely an imported version with a "take it or leave it choice". The significance of this on influenza transmission and prevention is not clear.

EXTENDIBILITY

This is perhaps the first of the EURECA series where the clinical condition as well as the intervention have been examined with an exclusive focus on the local setting. None of the data included in the Cochrane

TABLE II EFFICACY AND EFFECTIVENESS OF INFLUENZA VACCINE COMPARED TO PLACEBO OR NO INTERVENTION

Outcome	Vaccine type	Age group	Trials	Participants	RR (95% CI)
Efficacy	Live vaccine	Overall	5	6001	0.18 (0.11-0.29)
		< 2 years	0	–	–
		< 6 years	5	5941	0.47 (0.23-0.97)
		> 6 years	1	60	0.15 (0.10-0.23)
	Inactivated vaccine	Overall	5	1628	0.41 (0.29-0.59)
		< 2 years	2	786	0.15 (0.18-1.69)
		< 6 years	2	132	0.61 (0.34-1.08)
		> 6 years	3	710	0.31 (0.54-0.76)
Effectiveness	Live vaccine	Overall	8	188418	0.67 (0.62-0.72)
		< 2 years	0	–	–
		< 6 years	5	38646	0.67 (0.57-0.77)
		> 6 years	8	149772	0.67 (0.60-0.74)
	Inactivated vaccine	Overall	5	19388	0.64 (0.54-0.76)
		< 2 years	0	–	–
		< 6 years	3	476	0.39 (0.21-0.69)
		> 6 years	4	18912	0.72 (0.54-0.76)

RR: relative risk; CI: confidence interval

EURECA CONCLUSIONS IN THE INDIAN CONTEXT

- Influenza is not a serious clinical problem among children in India in terms of disease burden and its consequences.
- Influenza vaccination appears to have limited efficacy and effectiveness; hence cannot be recommended for routine use.

review meta-analysis were generated from India; hence, even the limited efficacy and effectiveness demonstrated may not be extendible in our context. This may further lessen the practical utility of influenza vaccination in children in India.

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