Influenza Vaccination in India: Position Paper of Indian Academy of Pediatrics, 2013

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Burden of Influenza is significantly higher in developing countries as compared to developed countries, but the data on the disease burden is less well defined in most of the developing countries including India, and consequently, constraints evolving strategies for prioritization of measures to prevent and control it. The 'swine flu' or 'A(H1N1)' pandemic is on the wane but the virus continues to circulate causing sporadic outbreaks even in 2013. The A(H1N1)pdm09 has replaced the previous circulating seasonal A (H1N1) virus and acquired the status of a seasonal virus. Limited influenza activity is usually seen throughout the year in India with a clear peaking during the rainy season. The rainy season in the country lasts from June to August in all the regions except Tamil Nadu where it occurs from October to December. IAP recommends the ideal time for offering influenza vaccines is just before the onset of rainy season. The efficacy/ effectiveness data of trivalent inactivated influenza vaccines are also presented in different age groups and different categories of individuals. The IAP maintains its earlier recommendations of using the current trivalent inactivated influenza vaccine in all children with risk factors but not as a universal measure. IAP has now prioritized different target groups for influenza vaccination based on contribution of the group to the overall influenza burden, disease severity, and vaccine effectiveness in different age groups and categories. The current trivalent inactivated influenza vaccines incorporate the 2009 pandemic strain also, hence avert the need of a separate 'A (H1N1)' vaccine. IAP stresses the need of more refined surveillance; large scale studies on effectiveness of seasonal influenza vaccines in Indian children, and more effective, properly matched, higher-valent influenza vaccines.

Keywords: *Influenza vaccines, Swine flu, Indian Academy of Pediatrics, Recommendations.*

There are three types of Influenza viruses A, B and C. The subtypes of type A Influenza virus is determined by haemagglutinin and neuraminidase. Both A and B viruses are responsible for seasonal influenza epidemics, and out-of season sporadic cases and outbreaks [1]. The Influenza type A causes moderate to severe illness in all age groups in humans and other animals whereas type B primarily affects children and causes usually a milder illness. The illness by type C Influenza virus is rarely reported in humans [2].

BURDEN OF DISEASE

Seasonal influenza

Global: Influenza occurs globally with an annual attack rate estimated at 5%–10% in adults and 20%–30% in children [1]. Children aged <5 years, and particularly those <2 years of age, have a high burden of influenza. According to a recent estimate, in 2008 there were 90 million (95%, CI 49-162 million) new cases of seasonal influenza, 20 million (95%, CI 13-32 million) cases of influenza-associated acute lower respiratory infections (ALRI), and 1-2 million cases of influenza associated severe ALRI, including 28 000-111 500 deaths [3].

Developing countries: The incidence of influenza episodes and associated ALRI is significantly higher in developing countries as compared to developed countries [3]. A systematic review of seasonal influenza epidemiology in sub-Saharan Africa showed that on average, influenza accounted for about 10% (range 1%-25%) of all outpatient visits and for about 6.5% (range 0.6%-15.6%) of hospital admissions for acute respiratory infections in children [4]. Recent studies from many developing countries of Asia have shown the importance of burden of influenza-related illness in the region [5-13].

India: Adequate data on the prevalence and burden of influenza in India is lacking. According to published data in India, it contributes to around 5-10% of all acute respiratory infections (ARI). The reported incidence of influenza URI was found to be 10/ 100 child years and that of ALRI to be only 0.4/100 child years [2]. According to an Indian review, influenza virus was responsible for about 1.5% to 14.5% of all ARIs

episodes [14]. A community-based study from north India estimated incidence of influenza episodes among children with ARI around 180 and 178 per 1000 children per year, amongst children below 1 and 2 years, respectively. Similarly, the incidence of influenza-associated ALRI was calculated as 33 and 44 per 1000 children per year [3,15].

Swine flu or A (H1N1)

H1N1 pandemic in 2009-10: The pandemic of H1N1 in 2009 had several characteristics that differentiated it from seasonal flu. Globally, the illness rates were highest in children and young adults (20-40% of the population), the hospitalization rates were highest in children below one year of age, and the 'case fatality rates' (CFR) varied tremendously and were estimated to be between 0.0004-1.5%. The risk factors for severe disease and death were pregnancy, morbid obesity, asthma, children below 2; however, 25%-30% of those who died had no underlying risk factor [2, 16, 17]. During the 2009 pandemic, pregnant women were documented as an important risk group for severe disease across the globe [16,17].

According to the data from Government of India, 22.8% of the samples out of the total samples from 202,790 persons who had been tested have been found positive for A (H1N1) [18]. In the majority, the illness was self-limited with recovery within a week. Among those tested, 94% cases recovered and 2,728 deaths were reported till December 2010 [18]. Maximum cases were reported during the months of August and September. Though the attack rate was highest in the age groups of 20-39 years and 10-19 years, the highest case-fatality was seen in the age group 20-39 years, followed by young children less than 5 years old [18]. According to a recent study (2007-2010) conducted in and around Delhi, the percent positivity of Influenza A(H1N1)pdm09 influenza virus was highest in >5–18 years age groups [19].

'Seasonal' versus 'pandemic flu': 'Seasonal flu' usually has severe disease in children below 2 years, individuals above 65 years, and in persons with chronic medical conditions whereas 'pandemic flu' more severely affected children and caused deaths in young adults having no risk factors [16, 17]. Sparing of elderly and very rapid transmissibility and high attack rates were other differentiating features. Overall, the severity and mortality of 'pandemic flu' was higher than seasonal flu (CFR of 0.89% *vs* 0.13%) [2, 16].

A (H1N1) influenza outbreaks during 2013 in India: The pandemic virus continues to circulate and cause waves of infections leading to hospitalization and complications in different parts of India despite the fact that the pandemic stage of the H1N1 virus had ended in August 2010. Once a pandemic has occurred, it is expected to have sporadic outbreaks of smaller magnitude in subsequent few years. Northern India had an unusual heightened activity of A (H1N1) influenza in first quarter of 2013 that led to 261 deaths till February 28, 2013 [20].

DYNAMICS OF SEASONAL INFLUENZA VIRUS CIRCULATION IN INDIA

Seasonality: In temperate regions, outbreaks consistently occur during the late autumn and winter months; in November–March in the Northern Hemisphere; and in May–September in the Southern Hemisphere [21]. In India, limited influenza activity is usually seen throughout the year with a clear peaking during the rainy season all over the country. However, northern India has a secondary albeit a smaller peak in cooler winter months with pattern similar to temperate regions [13,19]. The rainy season in the country lasts from June to August in all the regions except Tamil Nadu where it occurs from October to December.

Genetic surveillance of Influenza virus circulation, 2009-13: In India, there is change in the genetic makeup of circulating influenza viruses since 2009. According to Global Influenza Surveillance and Response System (GISRS) 2009-13 [22], from second half of 2009, A(H1N1)pdm09 was the most predominant influenza virus till first quarter of 2011. Second half of 2011 showed lower activity of this strain while A (H3N2) and B group viruses predominated in this half. However, from the beginning of 2012, the pandemic strain, A(H1N1)pdm09 reappeared and co-circulated with group B and A(H3N2) viruses. A recent study clearly revealed that clade VII has been identified as recent circulating clade in India as well as globally [23].

Group B influenza virus, mainly the undetermined lineage along with both Victoria and Yamagata lineages (to some extent) had circulated almost in equal quantity. There were two clear-cut peaks available, one during rainy season (June to September) and another during winter months. The national laboratories from Kasauli, Mumbai, and Pune regularly collaborate with GISRS. So, in 2012 and in first few months of 2013, A (H1N1) pdm09 and type B (mainly undetermined) were the main flu virus strains responsible for influenza outbreaks. However, it is difficult to predict the future circulation of different types/subtypes of influenza viruses in the country. Furthermore, the yearly type/subtype distribution varied significantly from region to region, and from site to site.

VACCINATION AGAINST INFLUENZA

Influenza Vaccines

Most of the current seasonal influenza vaccines include 2 influenza A strains and 1 influenza B strain. Globally, trivalent inactivated vaccines (TIV) and live attenuated influenza vaccines (LAIV) are available [1]. However, in India, LAIV is not available and a monovalent vaccine containing single pandemic strain, A(H1N1)pdm09 is also available. All currently available trivalent vaccines now have the influenza strain that is antigenically similar to 2009 pandemic swine flu strain i.e. A(H1N1)pdm09. Hence, there is no need to go for separate 'swine flu' vaccine.

The antigenic composition of the influenza vaccines is revised twice annually and adjusted to the antigenic characteristics of circulating influenza viruses obtained within the WHO's GISRS to ensure optimal vaccine efficacy against prevailing strains in both the northern and southern hemispheres [1]. The most recent WHO recommendations are available at *http://www.who.int/influenza/vaccines/virus/recommendations/en/index.html*.

I. Trivalent inactivated influenza vaccines (TIVs): The trivalent influenza vaccines are produced from virus growth in embryonated hen's eggs and are of three types: whole virus, split product, subunit surface – antigen formulations [1]. In most countries, whole virus vaccines have been replaced by less reactogenic split virus vaccines and subunit vaccines. Trivalent influenza vaccines are the only influenza vaccines licensed for vaccination of children <2 years of age, persons aged ≥50 years, and for pregnant women. Current trivalent influenza vaccines are not licensed for children <6 months of age [1].

II. Live attenuated influenza vaccine (LAIV): Live attenuated influenza vaccine provides broader and higher levels of protection than trivalent inactivated vaccines in healthy children aged 2-5 years of age. A Cochrane review of RCTs evaluating live vaccines in healthy children aged >2 years found an overall efficacy against laboratory confirmed influenza of 82% (95%, CI 71% -89%) and an effectiveness against influenza-like illness (ILI) of 33% (95%, CI 28%-38%). Inactivated vaccines had a lower efficacy of 59% (95%, CI 41%-71%) but similar effectiveness at 36% (95%, CI 24%-46%) [24]. A quadrivalent live attenuated vaccine for intranasal application containing 2 influenza A strains and 2 influenza B strains was licensed in the USA in 2012 [1]. Live attenuated vaccine is not recommended below 2 years of age, in high risk individuals and in pregnant women. Non-pregnant individuals aged 2–49 years may receive either TIV or LAIV in accordance with national policy.

III. Adjuvanted trivalent influenza vaccines (aTIVs): In order to enhance immunogenicity, some current formulations of trivalent vaccines include adjuvants such as oil-in-water adjuvants or virosomes [25]. Adjuvanted vaccine shows enhanced priming and boosting, as well as efficacy in infants, although need for two doses remains [25]. It also demonstrates an increased 'breadth' of response. Currently data on adjuvanted vaccines are limited.

IV. Quadrivalent influenza vaccines: The development of quadrivalent influenza vaccine formulation for seasonal influenza vaccine is of interest in providing comprehensive protection against influenza B viruses. Global influenza surveillance system has also recommended that there should be further research on the fourth strain (another influenza B virus of different linage). It was noted that for 4 of the previous 8 seasons, use of quadrivalent influenza vaccine instead of trivalent would have had substantially improved match of global circulating strains and there is definite potential public health benefit for quadrivalent vaccine [26].

Dosage Schedule

Trivalent influenza vaccine is administered intramuscularly, injected into the deltoid muscle (for vaccinees aged >1 year) or the antero-lateral aspect of the thigh (for vaccinees aged 6–12 months). Children aged 6-35 months should receive a pediatric dose, and previously unvaccinated children aged <9 years should receive 2 injections administered at least 4 weeks apart. A single dose of the vaccine is appropriate for school children aged >9 years and healthy adults [1,2].

Live attenuated vaccine is given as nasal spray, 1 dose only, but children aged 2-8 years who have not received seasonal influenza vaccine during the previous influenza season should receive 2 doses, at least 4 weeks apart. Annual vaccination (or re-vaccination, if the vaccine strains are identical) is recommended, particularly for high-risk groups [1].

Efficacy

Efficacy and effectiveness of Trivalent Influenza vaccines: In general, HI antibody titers of 1:40 or greater have been shown to provide 50% efficacy of protection in healthy adults [1]. However, a cutoff of 1:110 for antibody titers may be preferable to predict the conventional 50% clinical protection rate in children, and a titer of 1:330 would predict an 80% protective

level, which would seem to be more desirable from a public health perspective [27].

The reported efficacy/effectiveness of influenza vaccines varies substantially with factors such as the case definition (*e.g.* laboratory-confirmed influenza disease or the less specific influenza-like illness), the 'match' between the vaccine strains and prevailing influenza strains, vaccine preparation, dose, prior antigenic experience, and age or underlying disease conditions of an individual [1]. ***WebTable* I** summarizes the efficacy/effectiveness of trivalent influenza vaccines in different age groups and categories along with grading of evidence. However, most of these conclusions and summaries are based on studies done in temperate climate countries. There is no data on efficacy/ effectiveness of influenza vaccines from India.

Duration of serum antibody response to seasonal influenza vaccines: Following vaccination, anti-HA antibody titers peak 2-4 weeks post-vaccination in primed individuals but may peak 4 weeks or later in unprimed individuals or older adults. Serum antibody titers may fall by 50% or more by 6 months after vaccination, with the degree of reduction being proportional to the peak titers achieved. Vaccine-induced serum antibody titers then remain stable for two to three years. Evidence from clinical trials suggests that protection against viruses that are similar antigenically to those contained in the vaccine extends for at least 6–8 months [28].

Efficacy and effectiveness of monovalent A (H1N1) pdm vaccines: There is no study on performance of A (H1N1)pdm i.e. pandemic 2009 vaccines from India. A case-control study of Arepanrix (AS03) in Canada showed very high effectiveness [29]. In Germany, a study of single-dose Pandemrix in individuals 14 and above was limited due to vaccines becoming available very late, coinciding with peak activity [30]. Another study in seven European countries of multiple vaccines also had a narrow window between circulation of cases and availability of vaccine. Analysis did not distinguish between the different vaccine-types used. The vaccine efficacy increased as delay between vaccination and symptom onset increased [31]. In US, a study of inactivated and live vaccines in 4 communities found that the number of cases dropped coincidentally with the availability of vaccines [32]. The inactivated vaccine effectiveness point estimate was 88.6% among individuals 10-49 years, lower in those 6 months-9 years and over 50 years. Live vaccine had an increased effectiveness in children 6 months-9 years [32].

Safety of Trivalent Influenza and Monovalent A (H1N1) vaccines: Transient local reactions at the injection site occur frequently (>1/100), and fever, malaise, myalgia, and other systemic adverse events may affect persons without previous exposure to the influenza vaccine antigens, trivalent influenza vaccines are generally considered safe [1]. No vaccines against seasonal influenza contain the AS03-adjuvant which has been associated with rare cases of narcolepsy/cataplexy following large-scale use of an AS03-adjuvanted pandemic H1N1 vaccine, primarily in the Nordic countries [33] and in England [34].

During some influenza seasons, seasonal trivalent as well as monovalent Influenza A (H1N1) pdm 2009 vaccines have been associated with a slight increase in the risk of Guillain-Barré syndrome [35, 36]. A brand of seasonal trivalent vaccine from M/s CSL 2010 batch was associated with febrile seizures in children <5 years of age in Australia [26]. In US also, a higher risk for febrile seizures was found from Fluzone, another brand of M/s CSL during December 2010-January 2011. Analysis of these observations concluded that risk was only present among 6-23 month olds when trivalent vaccine was given along with PCV13 [26]. Apart from these few product-specific issues, there are no generic safety issues for influenza vaccines in young children.

IAP RECOMMENDATIONS ON INFLUENZA VACCINATION

IAP has recommended seasonal influenza vaccine (including the earlier monovalent A (H1N1) vaccine) only for the category of 'high-risk children'. This category contains the following:

- Chronic cardiac, pulmonary (excluding asthma), hematologic and renal (including nephrotic syndrome) condition, chronic liver diseases, and diabetes mellitus
- Congenital or acquired immunodeficiency (including HIV infection)
- Children on long term salicylates therapy
- Laboratory personnel and healthcare workers

Vaccination against 'swine flu' (A (H1N1)pdm) during ongoing outbreaks (2013): There is no need to get unduly worried about the recent spurts in the activity of influenza A (H1N1) virus in few northern states. Though it is expected to have A (H1N1) infections slightly more severe with higher mortality than seasonal influenza caused by other co-circulating strains; still the situation is not as alarming as it was in previous few years when the country was in the grip of the ongoing pandemic. Considering the fact that the available influenza vaccines are going to have much better effectiveness against the circulating

A(H1N1)pdm09 strain than other influenza viruses owing to more 'complete match' between the strain circulating in the community and the strain contained in the vaccines, IAP justifies its earlier recommendation of using the influenza vaccine in all children with risk factors as mentioned above and also wherein the vaccine is desired/ requested by parents [2].

IAP recommendations on 'target group prioritization' for seasonal influenza vaccination:

Though the risk groups for influenza in low- and middle-income countries including India are less well defined, still, based on global estimates for developing and low-middle income group countries, IAP believes that influenza vaccination should aim primarily at protecting vulnerable high-risk groups against severe influenza-associated disease and death. However, there is lack of effectiveness data in few categories of individuals and in different age groups. The suggested prioritization (***Table* I**) is based on following attributes: contribution of risk group to the overall influenza disease burden in population, disease severity within individual risk group, and vaccine effectiveness in different age groups and categories. Accordingly, following groups of individuals should be targeted for seasonal annual vaccination (in order of priority).

Prioritization of target groups: (1-Highest priority, 4-Lowest priority)

1. Elderly individuals (>65 years) and nursing-home residents (the elderly or disabled)
2. Individuals with chronic medical conditions including individuals with HIV/AIDS, and pregnant women (especially to protect infants 0-6 months)
3. Other groups: health care workers including professionals, individuals with asthma, and children from ages 6 months to 2 years.
4. Children aged 2-5 years and 6-18 years, and healthy young adults.

Amongst pediatric population, apart from the children with chronic medical conditions (see above), the children below 2 years of age should be considered a target group for influenza immunization because of a high burden of severe disease in this group.

Ideal time for influenza vaccination: The data on seasonality of influenza in India, illustrate the difficulty in having uniform vaccination timing for a vast country like us and have implications when formulating vaccination policies. The evidence of antigenic drifts of circulating influenza viruses in India; together with the temporal peaks in seasonality of influenza in different parts of the country illustrate the need for a staggered approach in vaccination timing. Hence, the best time for offering vaccine for individuals residing in southern states would be just before the onset of rainy season, i.e. before October while for rest of the country, it should be before June [37].

'Northern' versus 'Southern' Hemisphere recommendations: Vaccines elicit a relatively strain specific humoral response, have reduced efficacy against antigenically drifted viruses and are ineffective against unrelated strains. It is of utmost importance, therefore, that vaccine should incorporate the current strain prevalent during that time. Influenza vaccination is recommended annually to ensure optimal match between the vaccine and prevailing influenza strains, and because, unlike the long-lasting, strain-specific immunity following natural infection, influenza vaccines induce protection of relatively short duration, particularly in the elderly [38]. To ensure optimal vaccine efficacy against prevailing strains in both the northern and southern hemispheres, the antigenic composition of the vaccines is revised twice annually and adjusted to the antigenic characteristics of circulating influenza viruses obtained within the global influenza surveillance network.

WHO classifies India under the 'South Asia' transmission zone of Influenza circulation and reviews strain circulation in the country during both the meetings, i.e. February (for northern hemisphere) and September (southern hemisphere). Though India lies within the northern hemisphere, parts of the country have a distinct tropical environment being located close to the equator and behaves much like southern hemisphere seasonality with almost year round circulation and monsoon months peak, still northern India experiences another peak during winter just like northern hemisphere pattern [13, 19]. But these patterns and strain circulation dynamics are not fixed and exclusive to one particular hemisphere and strains usually 'spill' from one to another. Hence, IAP believes it will not be prudent to stick to strain formulations recommended for one hemisphere, but one should use the vaccine that has the 'most recent strains' irrespective of the hemisphere-specific formulations.

WHY HAS IAP NOT RECOMMENDED 'UNIVERSAL INFLUENZA VACCINATION?

There are several reasons why IAP has not offered universal recommendations, i.e. routine use of available Influenza vaccines:

The burden is less defined: Sufficient data to estimate precisely the contribution of influenza to childhood mortality in India is not available. Data on morbidity and mortality of influenza in India is very limited and current

TABLE I SUMMARY OF DISEASE BURDEN, EFFICACY/EFFECTIVENESS OF TIVS, AND PRIORITIZATION OF INFLUENZA VACCINATION IN DIFFERENT AGE GROUPS AND CATEGORIES OF TARGET POPULATION

Age group/ Category	*Burden of disease*	*Fatalities/Severe disease*	*Effectiveness/efficacy of vaccine*	*Level of evidence*	*Prioritization*
0-6 months	High (+++)	Very high (++++)	Not eligible	NA	2*
6-23 months	High (+++)	High (+++)	Not effective/Very low	Moderate	3
2-5 years	Substantial (++)	Moderate (++)	Moderate	Limited	4
6-64 years	Low (+)	Low (+)	Moderate to High	Moderate	4
>65 years	High (+++)	Very high (++++)	Low	Low	1
Pregnant women	Substantial (++)	High (+++)	Moderate**	Limited to high**	2
Individuals with asthma	Not known	Moderate (++)	Not effective	Limited	3
Individuals with HIV/AIDS	Not known	High (+++)	Moderate	Low	2
Individuals with other underlying medical conditions	Not known	High (+++)	Low	Limited	2
Health-care workers	Substantial (++)	Moderate (++)	High	High	3

**Not eligible to receive currently licensed influenza vaccines and should be protected through vaccination of their mothers during pregnancy; **Effectiveness varies for maternal and neonatal protection; Prioritization: 1-Highest; 2-High; 3-Moderate; 4-Low.*

status does not justify the prioritization of strategies for influenza prevention and control.

Target groups less well defined: The attack rates of seasonal influenza is although greatest in young children, the highest mortality and morbidity are observed in the elderly, individuals with certain underlying chronic health conditions, pregnant women, and health care workers. In recent pandemic H1N1 outbreaks, healthy young adult population was more severely affected. The risk groups for influenza in India are less well defined and we do not have data on burden of influenza in different age groups.

Issues related to vaccine availability, timing, suitability and effectiveness: Data are limited on the effectiveness of trivalent influenza vaccines in tropical regions including India. There is no large scale study on effectiveness of influenza vaccines in Indian children. In tropical regions, it is not always clear which formulation is best, and what time of year is optimal. Would vaccine be available round the year? Would trivalent vaccines' effectiveness be different in tropical countries like India with year-round circulation, or could existing effectiveness data be generalized to apply to tropical settings? Further, there is little evidence regarding effectiveness of influenza vaccines in children below 2 years of age even from industrialized countries [39]. In conclusion, the reliable evidence on influenza vaccines is thin. Furthermore, the available influenza vaccines leave a considerable amount of circulating influenza virus strains uncovered, hence IAP believes there is not only need of large scale studies on effectiveness of seasonal influenza vaccines in Indian children, but more effective (adjuvanted), properly matched (region specific) with broader coverage (higher valent) influenza vaccines are also needed before a more liberal recommendation is contemplated.

Need for a more extensive, region-specific surveillance: Though India is regularly participating in global influenza surveillance through a network of national laboratories, still there is diversity in prevailing virus types/sub-types at sub-regional levels. A significant section of circulating viruses belongs to undetermined lineages, hence not represented in available vaccines.

ANNEXURE

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