

## Consensus Recommendations on Immunization, 2008

### INDIAN ACADEMY OF PEDIATRICS COMMITTEE ON IMMUNIZATION (IAPCOI)

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#### ABSTRACT

**Justification:** There is a need to formulate recommendations regarding use of new vaccines which have become recently available/ will soon be available and to review/revise recommendations about existing vaccines in light of recent information. **Process:** Following an IAPCOI meeting in March 2008, a draft statement was prepared and circulated among the meeting participants to arrive at a consensus. **Objectives:** To formulate recommendations pertaining to use of Tdap, human papilloma virus (HPV) vaccines and rotavirus vaccines and to revise recommendations pertaining to use of pneumococcal and inactivated poliovirus vaccines (IPV). These recommendations are primarily for pediatricians in office practice. **Recommendations:** IAPCOI recommends (i) offering Tdap vaccine instead of Td/TT vaccine to all children/adolescents who can afford to use the vaccine at the age of 10-12 yrs; (ii) offering HPV vaccine to all females who can afford the vaccine at the age of 10-12 years; (iii) offering both seven valent pneumococcal conjugate vaccine (PCV 7) and 23 valent pneumococcal polysaccharide vaccine (PPV 23) in all high risk children who can afford the vaccine; (iv) offering IPV in addition to oral poliovirus vaccine (OPV) in all children who can afford the vaccine at the age of 6, 10, 14 weeks and a booster at 15-18 months; (v) the use of oral rotavirus vaccines after one-to-one discussion with parents beginning age 6 weeks; and (vi) the use of PCV 7 in healthy children aged below 2 years after one-to-one discussion with parents at the age of 6, 10, 14 weeks and booster at 15-18 months.

**Key words:** India, Indian Academy of Pediatrics, Committee on Immunization, Recommendations.

## I. INTRODUCTION

The IAPCOI met on 22nd and 23rd March 2008 in Mumbai. IAPCOI members and expert invitees who attended the meeting are listed in Annexure 1. The aim of the meeting was to discuss recommendations for vaccines, which have recently become available/ will soon be available and to revise recommendations about existing vaccines in light of recent information. This document presents the consensus recommendations, which arrived out of that meeting.

### *Process for Issuing Recommendations*

This process involves an exhaustive review of published literature including standard text books, vaccine trials, recommendations of various countries, World Health Organization (WHO) position papers, literature from the vaccine industry,

post-marketing surveillance reports, cost-effective analysis, epidemiology of disease in India and if available Indian studies on vaccine efficacy, immunogenicity and safety. If knowledge gaps are present then expert opinion is sought to fill the gaps. The existing national immunization schedule and government policies are also considered. The recommendations of IAPCOI are primarily for pediatricians in office practice. In addition, IAPCOI also submits its position on incorporation of various new vaccines in the national immunization schedule.

### *Categorization of New Vaccines*

The IAPCOI has categorized vaccines into four categories(1).

1. Vaccines covered under Expanded Program on Immunization (EPI).

2. Vaccines not covered under EPI but recommended by IAP.
3. Vaccines which are to be given after one-to-one discussion with the parents.
4. Vaccines to be given in special circumstances.

Category 2 vaccines are those that are unequivocally recommended by the IAP-COI for an individual child if parents can afford the vaccine. Category 3 vaccines are those where the benefits versus cost are not overwhelming as of currently available data and hence are to be administered after one-to-one discussion with parents.

When any new vaccine is introduced in the market (and is not part of EPI), IAPCOI has to take decision about categorization of the vaccine in category 2 or 3. This decision is based on the likely disease burden (morbidity and mortality) in the individual child, vaccine efficacy, and cost-benefit ratio for the individual child; all in the Indian context. Unfortunately, for most new vaccines, reliable data specific to India is not available. Hence, this categorization is largely based on expert opinion (Level III). Also it is dynamic and as new information becomes available, transition between categories may occur.

## II. AIMS AND OBJECTIVES

- To formulate recommendations pertaining to use of Tdap, HPV and rotavirus vaccines.
- To revise recommendations pertaining to use of IPV and pneumococcal vaccines.
- To review and reiterate recommendations pertaining to use of Measles mumps rubella (MMR), typhoid, rabies, chicken pox and hepatitis A vaccines.

## III. SPECIFIC RECOMMENDATIONS

### A. Tdap

#### *Burden of Disease*

Immunity following primary/ booster DTwP/DTaP vaccination wanes over the next 6-12 years(2). Surveillance studies from the developed world, chiefly US have shown a gradual increase in

adolescent and adult pertussis cases over the past decade(3). This has been attributed to more awareness, better diagnosis and a real increase in pertussis cases due to loss of vaccine induced/natural immunity further reduced by lack of natural boosting(3). Adolescent/adult pertussis infections are responsible for considerable morbidity/loss of working days and are a reservoir for disease transmission to unvaccinated/incompletely vaccinated neonates and young infants. Henceforth, several developed countries have instituted routine booster immunization of adolescents and adults with standard quantity tetanus toxoid and reduced quantity diphtheria and acellular pertussis vaccine instead of tetanus and reduced quantity diphtheria (Td) vaccine(3,4). The standard strength DTwP and DTaP vaccines cannot be used for vaccination of children 7 years and above due to increased reactogenicity.

Around 22,616 cases of pertussis were reported in India in 2006(5). This probably reflects a fraction of actual disease incidence as DTP3 coverage in India is only 55% and coverage with the 1st and 2nd booster even lower(6). There is no data on incidence of adolescent and adult pertussis in India.

#### *The Vaccine*

In India the available Tdap vaccine is Boostrix™ (GSK)(7). It contains tetanus toxoid 5 Lf, diphtheria toxoid 2 Lf and the three acellular pertussis components namely, pertussis toxoid 8 µg, filamentous hemagglutinin 8 µg and pertactin 2.5 µg. It contains aluminium hydroxide as adjuvant and no preservative. An efficacy trial done in adults aged 15-65 years using a single dose of acellular pertussis vaccine (same antigens as Boostrix™ without tetanus and diphtheria toxoids) versus single dose of hepatitis A vaccine as placebo, in a randomized double blind trial with 2.5 year of mean follow up showed efficacy of 92% (95% CI 32-99) against the primary definition of pertussis(8). Immunogenicity studies have also shown that antibody response to a single dose of Tdap booster in previously vaccinated children/adolescents is similar to that following 3 doses of full-strength DTwP or DTaP vaccines(7). Commonest side-effect with Tdap is pain at the local injection site in about

70% of vaccinees, followed by redness and swelling. Systemic side-effects like fever, headache and fatigue are rarely seen. Serious adverse events have not been reported. The contraindications are serious allergic reaction to any component of the vaccine or history of encephalopathy not attributable to an underlying cause within 7 days of administration of a vaccine with pertussis component. The dose is 0.5 mL intramuscular in the deltoid muscle.

### ***IAPCOI Recommendations***

There is no reason to believe that the disease burden of pertussis is low in adolescents in India. A safe and efficacious vaccine is available. The IAPCOI therefore recommends offering Tdap vaccine instead of Td/TT vaccine in all children/ adolescents who can afford to use the vaccine (Category 2) in the schedule discussed below. It also recommends that multicentric studies be conducted which aim to determine the prevalence of pertussis in children/ adolescents/ adults presenting with prolonged cough.

### ***Dose and Schedule***

- In those children who have received all three primary and the two booster doses of DTwP/DTaP, Tdap should be administered as a single dose at the age of 10-12 years. Catch-up vaccination is recommended till the age of 18 years; however a single dose of Tdap may also be used as replacement for Td/TT booster in adults of any age if they have not received Tdap in the past(4,7). A gap of 5 years should be maintained between Tdap and previous TT/Td vaccine. A gap of 2 years between Tdap and TT/Td is acceptable in those children/adolescents:
  - who are at high risk for contracting pertussis such as during an outbreak,
  - who are at high risk for pertussis complications such as those with neurological or pulmonary diseases, and
  - who are in contact with infants less than 12 mths of age as infants are at the highest risk for pertussis complications.
- It is also acceptable to use Tdap as a replacement for TT/Td in wound management of children

aged 10 and above if they have not received Tdap in the past and at least 5 years have elapsed since receipt of Td/ TT vaccine.

- In children who have missed the 2nd booster of DTwP/DTaP and who are 7 years of age or more Tdap single dose is recommended at the time of presentation.
- In children who have not completed primary immunization with DTwP/DTaP and are more than 7 years of age, 1 dose of Tdap and 2 doses of Td at 0, 1 and 6 months are recommended.
- The single booster dose of Tdap may be followed by Td boosters every 10 years. There is no data at present to support repeat doses of Tdap (Austria is an exception where Tdap is recommended every 10 years)(4,7). No tetanus prophylaxis is required for minor wounds if less than 10 years have elapsed since receipt of Tdap. No tetanus prophylaxis is required for major wounds if less than 5 years have elapsed since receipt of Tdap; if more than 5 years (but less than 10 years) have elapsed a single dose of TT may be given.
- In the absence of sufficient data on the efficacy, immunogenicity and duration of protection against pertussis with Tdap used as 2nd childhood booster, the IAPCOI does not recommend the use of Tdap vaccine as an alternative to DTaP/DTwP for the 2nd childhood booster in children below the age of 7 years at present.

## **B. HUMAN PAPILLOMA VIRUS (HPV) VACCINE**

### ***Disease Burden***

Globally, cervical cancer is the second most common cancer in women with approximately 5,00,000 cases annually and 350,000 deaths(9). Unlike many other cancers cervical cancer occurs early and strikes at the productive period of a woman's life. It is well recognized that HPV is a necessary cause of cervical cancer. 100 serotypes of HPV have been discovered of which 15-20 are oncogenic. Types 16 and 18 account for 70% of the cases of invasive cervical cancer globally(9). The lag period between infection with oncogenic HPV and invasive cervical cancer is 15-20 years. Oncogenic

HPV serotypes have also been implicated in causation of anal, vulvar, vaginal, penile and oropharyngeal cancers(10). Additionally, non-oncogenic HPV serotypes 6 and 11 are responsible for more than 90% of anogenital warts(10).

Data from national cancer registries in India indicate that cervical cancer is the most common cancer/ cause of cancer related death in Indian women(11). Approximately 1,32,000 cases occur annually with 74,000 deaths. Indian women face a 2.5% cumulative lifetime risk of cervical cancer and 1.4% cumulative risk of death from cervical cancer. HPV types 16 and 18 account for 76.7% of cervical cancer in India. There is no data on burden of anogenital warts in the general community; warts have been reported in 2-25.2% of STI clinic attendees in India(12).

### ***The Vaccines***

Two vaccines have been licensed globally; a quadrivalent vaccine from Merck marketed as Gardasil™ and the other a bivalent vaccine from GSK marketed as Cervarix™. Both are manufactured by recombinant DNA technology that produces non-infectious virus like particles (VLP) comprising of the HPV L1 protein, the major capsid protein of HPV. Clinical trials with both vaccines have used efficacy against cervical intraepithelial neoplasia (CIN) 2/3 and adenocarcinoma in situ (AIS) caused by HPV strains contained in the concerned vaccine as primary end points, and both vaccines have also looked at cross protection against HPV strains not contained in the concerned vaccine. Both vaccines do not protect against the serotype with which infection has already occurred before vaccination. Both vaccines have been licensed in several countries world over.

Gardasil™ is a mixture of L1 proteins of HPV serotypes 16, 18, 6 and 11 with aluminium containing adjuvant. Clinical trials with three doses at 0, 2 and 6 months in more than 16,000 women aged 16-26 years from 5 continents including Asia have shown 100% efficacy at a median follow up of 1.9 years against types 16, 18 related CIN-2/3 and AIS in per protocol analysis (women who received all three doses of the vaccine and who remained uninfected with vaccine HPV type at onset and for 1

month after completion of the vaccine schedule). Additionally 99-100% efficacy was seen against vaccine type related genital warts, vaginal intra-epithelial neoplasia (VaIN) and vulvar intra-epithelial neoplasia (VIN). Follow-up studies in a subset of participants over 5 years show persistent protection, and good response to booster immunization indicative of immune memory(13). Immunogenicity studies in females 9-15 years showed antibody titers non-inferior to those aged 16-26 years(13). Local adverse effects reported were pain at the injection site in 83% of vaccinees (mainly mild-moderate intensity) and, swelling and erythema in 25%. Systemic adverse effects such as fever reported in 4% of vaccines. No serious vaccine related adverse events have been reported.

Cervarix™ is a mixture of L1 proteins of HPV serotypes 16 and 18 with AS04 as an adjuvant. Clinical trials with three doses at 0, 1 and 6 months in more than 18000 women globally has shown 90% efficacy against type 16/18 related CIN2/3 and AIS at 15 month follow up in modified intention to treat analysis (included women who were at baseline negative for HPV DNA of vaccine type virus and who received at least 1 dose of the vaccine)(14). Follow up studies in a subset of participants over 4-5 years show no evidence of waning immunity(15). Local side effects reported were pain (mild and moderate intensity) in 90% and swelling and erythema in 40%. Systemic side effects such as fever were seen in 12%. No serious vaccine related adverse effects were observed.

### ***IAPCOI Recommendations***

Cervical cancer is responsible for significant morbidity/ mortality in Indian women and affects women of all socio economic strata. Compliance with cervical Papanicolou (PAP) smear screening is low in India(11). The currently available vaccines are safe and efficacious. The HPV vaccines are thus of public health importance. The IAPCOI recommends offering HPV vaccine to all females who can afford the vaccine (Category 2) in the schedule discussed below. Since protection is seen only when the vaccine is given before infection with HPV, the vaccine should be given prior to sexual debut. The vaccine should preferably be introduced

to parents as a cervical cancer preventing vaccine and not as a vaccine against a sexually transmitted infection (STI). Vaccines are not 100% protective against cervical cancer and not a replacement for periodic screening(13). Hence, screening programs should continue as per recommendations. Both the available vaccines are equally efficacious and safe for protection against cervical cancer and precancerous lesions as of currently available data. The quadrivalent vaccine has in addition, demonstrable efficacy against vaginal and vulvar cancers, and protects against anogenital warts.

### ***Dose and Schedule***

The dose is 0.5 mL intramuscular in deltoid. Manufacturer's instruction for storage and administration of vaccines should be followed. The recommended age for initiation of vaccination is 10-12 years. Catch up vaccination is permitted up to the age of 26 years. Three doses at 0, 2 and 6 months are recommended with Gardasil™ (minimum interval between 1st and 2nd dose is 4 weeks and second and third dose is 12 weeks) and 0, 1 and 6 months with Cervarix™(13,14). HPV vaccines can be given simultaneously with other vaccines such as hepatitis B and Tdap. As a precaution against syncope following any vaccine in adolescents, the vaccinee should be counseled prior to vaccination, vaccine be administered in a sitting/ lying down position and the patient observed for 15 minutes post vaccination. Both vaccines are contraindicated in those with history of previous hypersensitivity to any vaccine component and should be avoided in pregnancy. The vaccines may be administered in the immunocompromised but immunogenicity and efficacy may be lower(13). At present there is no data to support use of boosters.

## **C. ROTA VIRUS VACCINE**

### ***Disease Burden***

Rotavirus is a major cause of diarrhea related morbidity and mortality in children worldwide. Although rotavirus illness rates are similar in both the developed and developing world and in children of all socioeconomic status, mortality due to rotavirus disease is more in the developing world and in the poor and malnourished(16). It has been

estimated that rotavirus causes 6,10,000 under five deaths globally every year(17). Rotavirus is an icosahedral RNA virus and seven serogroups have been described (A-G); Group A rotaviruses cause most human disease. The viral outer capsid made of VP7 and VP4 proteins. The VP7 protein determines the G serotypes and the VP4 protein the P serotypes. Variability of genes coding for the VP7 and VP4 proteins is the basis for classification into genotypes. All G genotypes correspond with serotypes; there are more P genotypes than serotypes. Each rotavirus strain is designated by its G serotype number followed by P serotype number and then P genotype number in square brackets i.e. G1P1A(8).

Epidemiologic studies from India indicate that 6-45% (median 20%) of all childhood diarrheas that need hospitalization are due to rotavirus(17). It is further estimated that rotavirus causes around 100,000 deaths in children below age 5 years annually in India(18). Seroepidemiologic studies show that G1, G2, G3 and G4 in combination with P8, P6 and P4 account for 65-70% of rotavirus infections in India(17). In addition to the common G and P serotypes, newer serotypes, mixed forms and untypable serotypes are frequently seen(17). Intra country differences exist between North, South, East and West(17).

### ***The Vaccines***

The observation that initial infection with rotavirus prevents from subsequent severe infections has been the rationale for vaccine development. The first clinically licensed rotavirus vaccine (1998) was Rotashield, a live oral tetravalent vaccine comprising of three rhesus human reassortant and one rhesus rotavirus strain. This vaccine was withdrawn soon after licensure due to occurrence of vaccine associated intussusception(19). Currently, two live oral vaccines are licensed and marketed worldwide, Rotarix™ and RotaTeq™. A vaccine based on Indian neonatal strains is undergoing clinical trials(20).

Rotarix™ is a monovalent attenuated human rotavirus vaccine derived from the human Rota virus strain 89-12 and contains the G1P1A(8) strain administered orally in a 2-dose schedule to infants of approximately 2 and 4 months of age. RotaTeq™ is a

Human Bovine reassortant vaccine and consists of five reassortants between the bovine WC23 strain and human G1, G2, G3, G4 and P1A(8) rotavirus strains administered orally in a three dose schedule at 2, 4 and 6 months. Large phase 3 double blind placebo controlled trials with both vaccines in around 70,000 infants each (11 countries mainly US, Finland for Rotateq™ and Latin America and Finland for Rotarix™) have shown 85-98% efficacy against severe rotavirus gastroenteritis and 42-59% efficacy against hospitalization due to diarrhea of any cause(21,22). Both vaccines have been demonstrated to be extremely safe with no increased risk of intussusception as compared to placebo. Shedding of the vaccine virus was observed in 10% of vaccinees with Rotateq and more than 50% of vaccinees with Rotarix. Similar high efficacy extends into the second year of follow up with the vaccines. Results from a recent trial with Rotarix™ in 10,000 infants in Hong Kong, Singapore and Taiwan showed efficacy and safety similar to that seen in earlier trials(23). Both vaccines have been licensed and introduced into the national immunization program of several countries worldwide(16). Efficacy trials in developing countries of Africa and Asia are ongoing and results are awaited.

Studies show no interference between rotavirus vaccines and other childhood vaccines including IPV, pneumococcal, Hib, DTaP and Hep B(21,22). Data is insufficient for pertussis immunity. Immunogenicity studies about simultaneous administration of rotavirus vaccines with OPV are available for Rotarix™ and Rotateq™, which show no reduction in immunogenicity against polio and no significant reduction in immunogenicity against rotavirus(24,25). Additionally an efficacy study shows no reduction in efficacy of Rotarix™ against severe rotavirus gastroenteritis when co administered with OPV(26).

### **IAPCOI Recommendations**

The IAPCOI acknowledges the morbidity and mortality burden of rotavirus and need for a rotavirus vaccine. Such a vaccine would be most needed in the national immunization program as the disease consequences are the most serious in the

underprivileged. However, the IAPCOI is concerned about (a) lack of immunogenicity studies from India where response to other oral vaccines such as OPV has been observed to be suboptimal; (b) lack of efficacy studies from India where there is tremendous diversity in circulating strains and thus results from studies abroad cannot be readily extrapolated.

Till such data is available IAPCOI recommends use of the vaccine after one to one discussion with parents (Category 3). If the decision to administer the vaccine is taken, either vaccine may be chosen as they have similar efficacy and safety profiles as of currently available data.

### ***Dose and Schedule***

Vaccination should be strictly as per schedule discussed below, as there is a potentially higher risk of intussusception if vaccines are given to older infants. Vaccination should be avoided if age of the infant is uncertain. Manufacturer's instruction on storage and administration of vaccines should be followed. There are no restrictions on the infant's consumption of food or liquid, including breast-milk, either before or after vaccination. Vaccines may be administered during minor illnesses. Though there is limited evidence on safety and efficacy of rotavirus vaccines in preterm infants, vaccination should be considered for these infants if they are clinically stable and at least 6 weeks of age as preterms are susceptible to severe rotavirus gastroenteritis. Vaccination should be avoided in those with history of hypersensitivity to any of the vaccine components or previous vaccine dose. Vaccination should be postponed in infants with acute gastroenteritis as it might compromise efficacy of the vaccine. Immunocompromised infants are susceptible to severe and prolonged rotavirus gastroenteritis but safety and efficacy of either of the two vaccines in such patients is unknown. Risks versus benefits of vaccination should be considered while considering vaccination for infants with chronic gastrointestinal disease, gut malformations, previous intussusception and immunocompromised infants.

*Rotarix™*: The first dose can already be administered at the age of 6 weeks and should be given no later than at the age of 12 weeks. The

interval between the 2 doses should be at least 4 weeks. The 2-dose schedule should be completed by age 16 weeks, and no later than by 24 weeks of age. It is available as a lyophilized vaccine to be reconstituted with liquid diluent prior to administration. If the infant spits out or regurgitates the entire vaccine dose then the dose may be repeated at the same visit (as per drug insert of Rotarix™).

*RotaTeq™*: The recommended schedule is 3 oral doses at ages 2, 4 and 6 months. The first dose should be administered between ages 6-12 weeks and subsequent doses at intervals of 4-8 weeks. Vaccination should not be initiated for infants aged >12 weeks. All 3 doses should be administered before the age of 32 weeks. The vaccine is available as a liquid virus mixed with buffer and no reconstitution is needed. The manufacturer does not recommend re administration of vaccine if a dose is spit out or regurgitated.

#### D. PNEUMOCOCCAL VACCINE

##### *Burden of Disease*

*S. pneumoniae* is responsible for 15-50% of all episodes of community acquired pneumonia, 30-50% of all cases of acute otitis media and a significant proportion of bacterial meningitis and bacteremia(27-29). It is estimated that 50% of the 2 million deaths due to pneumonia globally every year are attributable to *S. pneumoniae*(27). Ninety serotypes of *S. pneumoniae* have been described of which a handful are responsible for most cases of invasive pneumococcal disease (IPD). Serotypes 14, 6, 19, 18, 9, 23, 7 are responsible for 85% of invasive pneumococcal disease in the developed world(29). Children under the age of 2 yrs are at greatest risk for invasive pneumococcal disease.

Data on prevalence of pneumococcal disease is scanty in India but it has been estimated that *S. pneumoniae* causes 6.6-22 million episodes of pneumonia and 200,000 deaths yearly from pneumonia in India(27). Results of the IBIS study in patients with invasive pneumococcal disease (IPD) indicate that serotypes 6, 1, 19, 14, 4, 5, 45, 12, 7, 23 are the most prevalent with serotypes 1 and 5 accounting for 30% of invasive pneumococcal disease(30). It is also known that serotypes causing

pneumonia and otitis media differ from that causing invasive pneumococcal disease and usually reflect those serotypes present in the nasopharyngeal carriage.

##### *The Vaccines*

Two vaccines are available; the unconjugated pneumococcal polysaccharide vaccine and the conjugate vaccines.

The unconjugated polysaccharide vaccine is a 23 valent vaccine (PPV 23) containing the following serotypes - 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F(31). It is a T cell independent vaccine that is poorly immunogenic below the age of 2 yrs, has low immune memory, does not reduce nasopharyngeal carriage and does not provide herd immunity. It has at best 70% efficacy against prevention of invasive pneumococcal disease in the high-risk population but offers no protection against non bacteremic pneumonia/ otitis media(31). It is a safe vaccine with occasional local side effects. Not more than two life time doses are recommended.

Conjugate pneumococcal vaccines (PCV) were developed primarily to address the problem of low immunogenicity of the polysaccharide vaccine in children below the age of 2 who are at high risk for pneumococcal disease(29). The 7 valent pneumococcal conjugate vaccine (PCV 7) containing polysaccharide antigen of serotypes 4, 6B, 9V, 14, 18C, 19F and 23 linked to a protein carrier has been licensed for universal immunization in the US since the year 2000 and in 19 more countries in the developed world since then. It covers 85% of the serotypes causing invasive disease in the US. Efficacy trials showed excellent safety, more than 95% reduction in IPD in those vaccinated and 30% reduction in radiologically proven pneumonia(32). The efficacy of PCV7 against acute otitis media was 8%(32). Apart from the direct benefits a significant decline in pneumococcal disease in unvaccinated contacts of the vaccinees was noticed following introduction of the vaccine in the immunization program due to herd effect resulting from reduced nasopharyngeal carriage(33). Though increase in disease due to non vaccine serotypes has been small till date compared to a vast decrease in overall

burden of disease; continued surveillance to monitor serotype replacement is crucial(33,34). Trials with an experimental 9 valent vaccine which incorporates serotypes 1 and 5 in South Africa showed a 20% decline in radiologically positive pneumonia in HIV non infected children and 13% decline in HIV infected(35). A trial in Gambia with 3 primary doses of the 9 valent vaccine showed reduction in the incidence of invasive disease due to all serotypes by 50%, radiologically diagnosed pneumonia by 37% and all cause childhood mortality by 16%(36). 10 valent and 13 valent vaccines are under development(37).

### IAPCOI Recommendations

*For EPI:* The burden of pneumococcal disease is the greatest among the underprivileged children in India. The conjugate pneumococcal vaccines are thus of public health importance and ideally should be available to all children. However the high cost of PCV vaccines is an impediment to this approach. GAVI has offered to supply PCV at a cost of 0.15 - 0.3 USD/ dose to India for inclusion in the national immunization schedule and commits to extending this support till the year 2015(38). Also, broader serotype vaccines will be available in future. IAPCOI feels that Government of India should avail of this opportunity and apply for GAVI support, establish a pneumococcal disease surveillance system and set into motion a process for inclusion of PCV in EPI.

*High-risk children:* Children at high risk of pneumococcal disease are listed in **Table I**(31). The

**TABLE I** CHILDREN AT HIGH RISK FOR PNEUMOCOCCAL DISEASE

- 
- Congenital immunodeficiency, HIV
  - Immunosuppressive therapy, Organ transplant recipients
  - Sickle cell disease, asplenia/ hyposplenia
  - Chronic cardiac disease
  - Chronic pulmonary disease excluding asthma unless on high dose oral steroids
  - Chronic liver disease
  - Chronic renal failure, nephrotic syndrome
  - Diabetes mellitus
  - Cerebrospinal fistula, cochlear implants
- 

IAPCOI recommends administration of both PCV and PPV 23 in all high-risk children who can afford the vaccine in schedules discussed below. The PCV vaccines provide robust immune response and immune memory while PPV 23 provides expanded serotype coverage(28). If PCV is not affordable, at least PPV 23 should be given to high-risk children above 2 years of age.

*Healthy children:* Pneumococcus is a cause of significant morbidity and mortality in children (especially those less than 2 years) and merits prevention. However, as of current data, seven valent PCV covers only 55% of pneumococcal serotypes prevalent in India(38). Therefore, IAPCOI recommends the use of the currently available conjugate pneumococcal vaccine (PCV 7) after one to one discussion with parents in healthy children aged less than 2 years (Category 3) in schedule discussed below. The risk of invasive pneumococcal disease is significantly lower in healthy children above the age of 2 years and thus benefit achieved with vaccination of these children is likely to be low. Vaccination with single dose of PCV vaccine may be considered in children aged 2-5 years if demanded by parents. Since induction of immune system memory, reduction in carriage, efficacy against serotypes causing most invasive disease, and effectiveness against noninvasive syndromes (e.g., non bacteremic pneumonia and AOM) are superior with PCV, PCV is preferred to PPV 23 in this setting(29). There is no data to support pneumococcal vaccination in healthy children aged 5 years and above and is not recommended.

### Dose and Schedule

#### *Healthy children (PCV vaccine)*

- Dose is 0.5 mL IM.
- Routine vaccination: 3 doses at 6,10,14 weeks and 1 booster at 15-18 months.
- Catch up vaccination:
  - 6-12 months: 2 doses 4-8 weeks apart and 1 booster at 15 -18 months.
  - 12-23 months: 2 doses 8 weeks apart.
  - 24-59 months: single dose.



*High risk children (PCV and PPV 23)*

- If affordable, PCV should be given first. For children aged less than 5 years follow the schedule mentioned above. For children older than 5 years a single dose of PCV is recommended (Currently available PCV 7 though licensed upto age 9 years, has been shown to be safe and immunogenic in children older than 9 years as well)(29).
- In children aged 2 years or more, PPV 23 should also be given as a single dose of 0.5 mL IM. If PCV has been given earlier, a gap of 2 months must be maintained between PCV and subsequent PPV 23.
- A high-risk child who has received PPV 23 in the past but not PCV vaccine may be offered a single dose of PCV vaccine at the time of presentation if 2 months have elapsed since receipt of PPV 23.
- Only one repeat dose of PPV 23 is recommended only for children who have sickle cell disease, hyposplenia, asplenia, congenital/acquired immunodeficiency, those on immunosuppressive therapy, renal failure and nephrotic syndrome. The repeat dose of PPV 23 may be given after 3-5 years if the child is less than 10 years of age and after 5 years if child is aged more than 10 years.

**E. INACTIVATED POLIOVIRUS VACCINE (IPV)***The Vaccine*

All currently used IPV vaccines are enhanced potency IPV (eIPV) that contains 40, 8 and 32 D antigen units of type 1, 2 and 3 respectively. It is highly immunogenic. Seroconversion rates are 90-95% after two doses given after the age of 2 months at 2 months interval and 99% after three doses when it is started at 6 weeks of age and given at 4 weeks interval(39). IPV can be used in combination with DTwP and Hib vaccines without compromising seroconversion or increasing side effects. IPV produces excellent systemic/ local pharyngeal immunity and some intestinal immunity(39). Observations from use of the vaccine in the USA and other developed countries indicate that IPV has excellent herd effect(40). The vaccine is very safe.

***IAPCOI Recommendations***

The latest recommendations of the polio eradication committee of the IAP have been published (41). This document highlighted the potential utility of IPV in two key areas (a) to curb wild virus transmission in UP and Bihar (b) switch to IPV DPT combination in polio free states in preparation for the post polio eradication era (in this era OPV use will have to stop but vaccination against polio cannot stop i.e switch to IPV is inevitable). Here we discuss the latest recommendations of IAPCOI regarding use of IPV by IAP members in office practice.

In its earlier update (May 2007) IAPCOI had recommended use of IPV in conjunction with OPV in children after one to one discussion with parents(42). The IAPCOI now recommends offering additional use of IPV with OPV in all children who can afford the vaccine (Category 2) in the schedule discussed below. This change in categorization of IPV and recommending wider use of IPV is for the following reasons:

- Excellent immunogenicity, efficacy and safety of IPV.
- Switch to IPV is inevitable in post polio eradication era. This switch cannot happen overnight due to large number of doses that will be required and has to be in a phased manner. IAP-PEC has already recommended that the government gradually introduce IPV in polio free states to facilitate this switch. By promoting use of IPV in the private sector, the committee hopes to create a demand base for the vaccine, increased supply and lower cost of the vaccine.

The committee recommends continuing OPV use for the following reasons:

- In concordance with the government policy of using OPV for polio eradication.
- Mucosal immunity as measured by stool excretion of virus after mOPV1 challenge is superior with combination of OPV and IPV as compared to IPV alone(43).
- By not giving OPV we might create confusion in the minds of the parents whose children receive

only IPV about the efficacy and safety of OPV and interfere with OPV uptake on the national Immunization Days (NID's) and Sub National Immunization Days (SNID's). Also as a cascade effect there might be some individuals who might not give immunization with OPV due to fear of side effects and neither give IPV due to non-affordability.

- The risk of VAPP with this combined OPV and IPV schedule is extremely low as the child receives OPV at the time when he/she is protected against VAPP by maternal antibodies(44). Subsequently, he/she is protected from VAPP by IPV. Even if we adopt an all IPV schedule the child may still be at a small risk for VAPP through exposure to the oral polio vaccine virus through contacts/ environment before he/she receives his/her first dose of IPV.

The IAPCOI feels that in the current scenario where polio eradication in India is at the cross roads and a highly sensitive issue, the combined OPV and IPV schedule strives to provide the best of protection to an individual child while not deviating from the national immunization policies.

#### ***Dose and Schedule***

It may be administered singly (0.5 mL IM) or as a combination (currently marketed in India with DTaP/ Hib). Schedules are as discussed below:

*Child who has not received any polio vaccination so far:* OPV at birth, OPV and IPV at 6, 10 and 14 weeks. OPV and IPV at 15-18 mths and OPV at 5 years. OPV on all NID's and SNID's. An alternative to this schedule is birth dose of OPV, OPV at 6 weeks, OPV and IPV at 10 weeks, OPV at 14 weeks and IPV at 18 weeks. OPV and IPV at 15- 18 mths and OPV at 5 years. OPV on all NID's and SNID's. In this schedule though the number of IPV doses have reduced from 4 to 3 but it (a) is logistically more demanding as number of visits increase (b) not feasible if combination vaccines are chosen (c) delays the introduction of IPV and thus lowers protection against VAPP.

*Child who has completed primary series of OPV:* IPV may be offered as catch up vaccination for

children less than 5 years of age who have completed primary immunization with OPV. IPV can be given as three doses; 2 doses at 2 month interval followed by a third dose 6 months after the first dose. OPV need not be given with these IPV doses. OPV should be given with the first and 2nd boosters of DTP and on all NID's and SNID's.

*Immunodeficient children and their close contacts:* IPV should be the preferred vaccine if resources permit. OPV should be avoided especially in patients with B cell immunodeficiency. The schedules are as discussed earlier with the exception that a second booster dose of IPV at 5 years is also recommended.

#### **F. OTHER VACCINES**

##### ***MMR***

IAPCOI recommends two doses of MMR vaccine, the first dose at 15 months and the second MMR dose given from 8 weeks onwards after the 1st dose of MMR. This recommendation for two doses is mainly to take care of primary vaccine failure (failure to seroconvert) to the mumps and rubella component of the vaccine.

##### ***Typhoid***

The IAPCOI recommends the administration of the currently available Vi polysaccharide vaccine 0.5 mL IM every three years beginning the age of 2 years till age of 18 years.

##### ***Rabies***

Effective post exposure prophylaxis is available for rabies. Human rabies immunoglobulin (HRIG) is required in addition to the vaccine for most animal bites. However, availability, cost and knowledge regarding use of HRIG is a problem. Henceforth IAPCOI recommends offering pre exposure prophylaxis against rabies (0,7,21 or 0,7,28 schedule) to all children at high risk for rabies. Pre exposure prophylaxis will obviate the need for use of HRIG and will restrict the number of post exposure doses to 2 on day 0 and day 3.

##### ***Chickenpox***

IAPCOI is aware of the increasing number of reports of breakthrough varicella following

varicella vaccination in India. However in the absence of sufficient data on changing epidemiology of chicken pox, it continues to recommend single dose of varicella vaccine in children aged below 13 years.

### Hepatitis A

The IAPCOI concludes that 2 doses 6 months apart of all available brands of hepatitis A vaccines are of similar efficacy and safety.

## IV. CONCLUSIONS

IAPCOI has attempted to modify/evolve recommendations for vaccines which have recently been available/ those which will be available shortly based on currently available data. The revised categorization of vaccines and the new immunization schedule is mentioned in **Tables II** and **III**. Modifications of these recommendations is possible in future based on new data as it becomes available.

*Conflict of interest:* This IAP COI meeting was funded by a scientific grant from GSK. The brands are listed in this policy document only for clarity and does not imply endorsement from the IAP.

## Annexure

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**TABLE II** IAP CATEGORIZATION OF VACCINES

Category 1 Vaccines in EPI		Category 2 IAP recommended vaccines (in addition to EPI vaccines)		Category 3 Vaccines to be given after one to one discussion with parents		Category 4† Vaccines under special circumstances
Dec 2006	New additions*	Dec 2006	New additions*	Dec 2006	New additions*	
BCG	Hepatitis B	MMR	Tdap (instead of Td)	Hepatitis A	Rotavirus	Influenza
DTwP	Hib	Typhoid	HPV	Varicella		PPV 23
OPV	MMR in certain districts	Hib	IPV	PCV 7		Meningococcal
Measles		Hepatitis B		DTaP		Japanese encephalitis
TT		Td				

\* As of July 2008; † No new additions; BCG: *Bacillus Calmette Guerin*; DTwP: *Diphtheria, tetanus, whole cell pertussis vaccine*; OPV: *Oral poliovirus vaccine*; TT: *Tetanus toxoid*; MMR: *Measles, mumps, rubella*; Hib: *Hemophilus influenzae type 'b' vaccine*; Td: *Tetanus, reduced dose diphtheria*; PCV 7: *7 valent pneumococcal conjugate vaccine*; PPV 23: *23 valent pneumococcal polysaccharide vaccine*; DTaP: *Diphtheria, Tetanus, acellular pertussis vaccine*; Tdap: *Tetanus, reduced dose diphtheria & acellular pertussis vaccine*; HPV: *Human papilloma virus*; IPV: *Inactivated poliovirus vaccine*.

**TABLE III** REVISED IAP IMMUNIZATION TIMETABLE

Age	Vaccines
Birth	BCG OPV0 HepB 1
6 weeks	DTWP1/DTaP1 OPV1*/OPV1 + IPV1 Hib1 HepB2
10 weeks	DTWP2/DTaP2 OPV2/OPV2 + IPV2 Hib 2
14 weeks	DTWP3/DTaP3 OPV3/OPV3 + IPV3 Hib3 HepB3**
9 months	Measles
15-18 months	DTWPB1/DTaPB1 OPV4/OPV4 + IPV4 Hib B1 MMR1
2 years	Typhoid#
5 years	DTWPB2/DTaPB2 OPV5 MMR2\$
10 years	TdapHPV^

\* OPV alone if IPV cannot be given

\*\* The third dose of Hepatitis B can be given at 6 months

# Revaccination every 3 years

\$ The second dose of MMR vaccine can be given at any time 8 weeks after the first dose

^ Only females, three doses at 0, 1-2 and 6 months

Vaccines to be given after one-to-one discussion with parents

Age	Vaccine
> 6 weeks	Rotavirus vaccine*PCV 7#
> 15 months	Varicella \$
> 18 months	Hepatitis A^

\* Rotavirus vaccine (2/3 doses (depending on brand) at 4-8 weeks interval)

# PCV 7 (three doses at 6, 10 and 14 weeks and 1 booster at 15-18 months)

\$ Varicella (< 13 yrs single dose, > 13 yrs two doses at 4-8 weeks interval)

^ Hepatitis A (2 doses at 6 months interval)

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