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* NOTE: Many trade names of the vaccines are included in the text for the sake of clarity.

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VACCINOLOGY II

COVID VACCINES - AN UPDATE

***Vidya Krishna**

Abstract: *From the time COVID-19 infection was first reported from Wuhan, China by the end of December 2019, vaccine production and trials geared up globally and have been successful in bringing out vaccines for use in the community in a year's time. This was made possible as the genome of the SARS-CoV-2 was released by Chinese researchers on 11th January 2020. The scientific advancements and lessons learnt from the previous pandemics due to H1N1(Spanish flu), H2N2(Asian flu), H3N3 (Hong Kong Flu) and SARS outbreak also helped in this regard. This article highlights conventional and newer technologies used in the development of vaccines and the types of vaccines available.*

Keywords: *SARS-CoV-2, Vaccines, Technologies.*

The COVID-19 pandemic started with the report of a cluster of pneumonia cases that first emerged in relation to a seafood market in Wuhan, China towards the end of December 2019.[1] The virus, initially called 2019-nCoV, belonging to the family of coronaviruses like the SARS and MERS CoV viruses, was later named SARS-CoV-2. On 11th January, 2020, the genome sequence of the pandemic virus was released on the public domain by Chinese researchers. The WHO declared a pandemic situation on 11th March, 2020 and the ensuing year has seen an unprecedented health and economic crisis. Till date, about 115 million cases have been reported globally with nearly 2.5 million deaths.[2]

Virology

SARS-CoV-2 belongs to the betacoronaviridae genus of the orthocoronaviridae subfamily. It is a large, enveloped, positive sense, single stranded RNA virus. The viral genome has 11 open reading frames (ORFs) of which ORF2 encodes the spike (S) surface glycoprotein while the ORF4, ORF5 and ORF9 encode the envelope (E) protein, the membrane(M) protein and nucleocapsid (N) protein respectively.[3] The S protein facilitates the viral binding to angiotensin converting enzyme 2 (ACE2) receptor on host cells and entry into them. The E and M proteins help in viral assembly and release.

Pathogenesis

Following binding of S protein to ACE 2 receptor found on type II pneumocytes in the lungs and various extra-pulmonary tissues including gastrointestinal tract, liver, kidney and brain, the S protein is cleaved by host cell serine protease called Transmembrane protease, serine (TMPRSS2). The virus then enters the cell and undergoes replication. Activation of renin-angiotensin aldosterone system (RAAS), thrombo-inflammation and dysregulated immune response leading to cytokine storm contribute to the disease pathogenesis.[4]

Immunology

Both cellular and humoral immunity have a role in the protection against the disease. While T helper type 1 (Th1) response is associated with a protective effect, Th17 and Th2 response is responsible for the cytokine storm and adverse outcomes. T cell responses can be longer lasting and against a broad range of antigens like S, M, N and ORFs.[3] Humoral immunity is probably important in protection against re-infection. Neutralizing antibodies against the receptor binding domain (RBD) of SARS-CoV-2 have protective effect.

In natural infection, antibody response is profound in severe cases while it can be mild / absent in asymptomatic cases. Re-infection risk after natural infection is low (<1%). A large prospective cohort study among healthcare workers in the UK reported 83% protection after natural infection up to a period of 5 months.[5]

While re-infection is generally milder than first infection, antibody mediated disease enhancement can be a serious concern leading to concerns in vaccine mediated immunity as well.[3]

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Vaccine development

The genome of the SARS-CoV-2 was officially released by Chinese researchers on 11th January 2020 and by end of March 2020, human trials for the first vaccine had already begun. Armored with the scientific advancements and lessons learnt from the previous epidemics like H1N1, SARS, Zika, Ebola, the race for developing a SARS- CoV-2 vaccine began quite early in the current pandemic. There has been ongoing research on creating vaccine platforms that could support development and manufacturing of the vaccine to handle a new pandemic caused by "Disease X". An ideal platform would not only enable rapid development of the vaccine but also elicit good immunogenic response and facilitate large scale manufacturing. While conventional technologies producing inactivated, live attenuated and protein subunit vaccine with their relative merits and demerits abound, this pandemic ensured that newer technologies like nucleic acid (DNA/RNA) based and viral vector based vaccines made a major breakthrough.

Vaccine development generally takes years, while in COVID vaccines it could be successfully and speedily carried out due to the readymade platforms for the different stages (Table I).

Vaccine types

1. RNA vaccines: The first research on RNA vaccines took place in France in 1990s when influenza antigen was delivered to mice in liposomes.[6] Though it produced an immune response, the toxicity of the lipid delivery system had been a major challenge till lipid nanoparticles (LNPs) were discovered.[7] While a killed virus or protein subunit is introduced into the body to elicit an immune response in conventional technologies, in the newer technology the mRNA sequence coding for the antigen production is delivered into the body. The body produces the antigen which is then presented on the cell surface leading to activation of the immune response. In the case of RNA vaccines, they carry the advantage of eliciting a potent combined T and B cell response like live vaccines versus only a humoral response in killed or subunit vaccines.[8]

RNA vaccine technology is particularly well suited in pandemic situations with new pathogens as the RNA vaccine candidates can be developed rapidly, within days, once the genome sequence of the pathogen is known.[9] The potential antigen-producing sequence is first identified, for example the S protein sequence in SARS-CoV-2 and this sequence is introduced into a DNA template. The corresponding mRNA which is produced is packaged into an appropriate delivery system. RNA vaccines are considered safe as they do not integrate with the host genome.[8] However, they can elicit significant reactogenicity due to contamination during vaccine synthesis or in the Lipid nano particles (LNP) delivery system. Also, as they are unstable, they need strict cold storage precautions to avoid disintegration. However, it seems likely that RNA vaccines can be engineered to be thermostable.[10]

Conventional mRNA vaccines also need multiple doses to elicit good immune response.[9]

Self- replicating RNA vaccines have the advantage of using lower doses as in addition to the genome sequence for the target protein, these vaccines contain replicons which direct self-replication through production of RNA dependent RNA polymerase. As multiple RNA copies are produced, it elicits higher antigen load, albeit with a lag phase and hence, they elicit equivalent protection at lower

Table I. Phases of vaccine development

Phases of vaccine development	Purpose
Pre-clinical	Vaccine testing in laboratory
Phase 1 Clinical trial (small group of healthy volunteers)	Assessing vaccine safety, assessing major adverse events
Phase 2 Clinical trial (larger group of targeted population usually in 100s)	Assessing vaccine immunogenicity and dosing
Phase 3 Clinical trial (larger group of 1000+ volunteers, vaccine group randomized against a placebo controlled group usually).	Assessing vaccine efficacy – how well it protects against the disease when compared to a placebo.
Phase 4 Post marketing surveillance	Monitoring long term adverse events, vaccine effectiveness (ability to prevent disease or transmission in real world).

doses. The self -replicating RNA vaccines can use viral vectors or synthetic RNA platforms and typically do not produce viral infectious particles as they do not include viral structural proteins.[10]

The two mRNA vaccines developed against SARS-CoV-2 are BNT162b2 mRNA vaccine (Pfizer Bio-NTech) and mRNA-1273 vaccine (Moderna). Both vaccines are nanoparticle-formulated, nucleoside-modified RNA (modRNA) encoding the SARS-CoV-2 full-length spike protein.

i) BNT162b2 mRNA COVID-19 vaccine (Pfizer Bio-NTech)

Interim analysis from the global phase2/3 trial evaluating the safety, immunogenicity and efficacy of 30 μg of BNT162b2 in preventing COVID-19 in persons 16 years of age or older showed that a two dose regime, 21 days apart, showed 95% protection (95% confidence interval [CI], 90.3 to 97.6) after seven days of the second dose. Efficacy after first dose was 52% (95% CI, 29.5 to 68.4) with early protection starting as soon as 12 days after the first dose. Incidence of severe COVID was very low even with one dose indicating that the vaccine protects against severe disease and alleviating to some extent the concerns regarding vaccine mediated disease enhancement. Safety profile data with follow-up up to two months after the second dose showed mild-moderate local reactogenicity, especially in those aged under 55 years, with pain being the most common reported symptom and in most cases, it resolved within two days. Systemic reactogenicity was commoner after second dose in the 16-55 years age group. Fatigue and headache occurred in about 2% after the second dose. No vaccine or COVID-19 associated deaths were reported.[11]

ii) mRNA-1273 SARS-CoV-2 vaccine (Moderna).

Preliminary analysis of phase 3 COVE (COVID Vaccine Efficacy) trial with a two dose regimen 28 days apart in the age group 18 years and above has shown that the vaccine has 94.1% efficacy (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. This trial done in the USA between July to October 2020, recruited 30,420 participants with 15,210 in each group- placebo and mRNA vaccine. More than 96% received the second dose and follow-up data for up to two months has been published.[12] The vaccine efficacy to prevent COVID-19 was consistent across subgroups such as age (18 to <65 years of age and ≥65 years), presence of risk for severe COVID-19, sex, race and ethnicity. There were no severe COVID-19 cases among the vaccinated group. Safety data showed mild local reactogenicity with predominant reaction being pain lasting for 2-3 days and systemic symptoms including headache, fatigue, myalgia and chills were common, especially in the 18-65 years age group. There was one COVID-19 related death in the placebo group and none in the vaccine group.[12]

2. Viral vector Vaccines: Viral vector vaccines typically use a virus like adenovirus, to carry the genome sequence of the target antigen into the host cell. The host cell machinery produces the target antigen which then elicits a strong immune response just like in a natural infection. Viral vectors can be replicative or non-replicative. Non-replicative vectors pass on the genome sequence to the host cells , cannot replicate or cause infection per se as the replication genes have been removed from their genome sequence. Replicating viral vectors can undergo replication in the host but at a slower rate than normal. This allows the host to elicit a stronger immune response to the target antigen while also containing the infection by the viral vector. Adenoviruses are preferred viral vectors as they have a wide range of tissue tropism, are stable, do not integrate into the host genome, can accept large DNA insertions and elicit mucosal and systemic immunity.[13] However, pre-existing host immunity to adenoviruses might reduce the immunogenicity.

i) ChAdOx1 nCoV-19 (AZD1222) [Oxford-Astra Zeneca vaccine, Covishield (Serum Institute of India)]

This is a non-replicating chimpanzee adenovirus vectored vaccine expressing the full length SARS-CoV-2 glycoprotein gene. Preliminary data has been published from phase 2/3 trial comparing standard ($3.5\text{-}6.5 \times 10^{10}$ virus particles) vs low dose (2.2×10^{10} virus particles) and single vs double-dose 28 days apart across various age groups (18-55 yrs, 56-69yrs and ≥70 years). Immunogenicity, measured by assessing both humoral and cellular immune responses, was found to be similar across age groups after the boost vaccination.

Local adverse events included pain and tenderness at injection site and systemic effects included fatigue, headache, feverishness and myalgia. As with the mRNA vaccines, reactogenicity was of grade mild-moderate, higher in the 18-55 years age group than the older age group and greater after first dose compared to second dose. No serious adverse events or deaths were attributed to the vaccine.[14]

Interim analysis from phase 3 trial data has shown efficacy of 79% in preventing symptomatic disease,

100% against severe disease and hospitalisation and 80% efficacy in age group above 65 years. The vaccine has favourable reactogenicity and safety profile. Review by Data Safety and Monitoring Board (DSMB) has found no increased risk of thrombosis or events characterised by thrombosis including cerebral venous sins thrombosis among the 21,583 participants receiving at least one dose of the vaccine.[15]

ii) Ad26.COV2.S COVID-19 Vaccine (Janssen Pharmaceuticals Companies of Johnson & Johnson)

Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector vaccine encoding a full-length and stabilized SARS-CoV-2 spike protein. Phase 1/2 trials have been done in healthy adults above 18 years and have shown good safety and immunogenicity against the wild-type virus. Both humoral and cellular responses were documented with predominantly Th1 response. Fever, headache, myalgia and injection-site pain were the common adverse effects and were less common above 65 years.[16]

It has obtained emergency use authorisation in the US as a single dose vaccine for age group above 18 years having shown 66.3% efficacy in preventing laboratory confirmed COVID-19 infection. It had high efficacy in preventing severe disease, hospitalisation and deaths.[17]

iii) Gam-COVID-Vac (Sputnik V)

It is a heterologous recombinant adenovirus based vaccine, based on rAd type 26 (rAd26) and rAd type 5 (rAd5), carrying the full length SARS-CoV-2 glycoprotein S. It is administered as a two dose regime 21 days apart. The vaccine has been developed in two forms: liquid (to be stored at -18°C) and freeze dried (to be stored at 2-8°C). Storage at 2-8°C has been approved by the Ministry of Health of the Russian Federation.

Interim analysis from phase 3 trial has shown that the vaccine has 91.6% efficacy (95% CI 85.6 - 95.2) and none-mild reactogenicity. No vaccine related serious adverse events or deaths were reported.[18]

3. Protein subunit vaccine

NVX-CoV2373 (Novavax) vaccine: NVX-CoV2373 is a recombinant SARS-CoV-2 nanoparticle vaccine containing trimeric full-length SARS-CoV-2 spike glycoproteins optimized in the established baculovirus Spodopterafrugiperda (Sf9) insect cell-expression system. It also has Matrix-M1, a saponin based adjuvant. Both vaccine and adjuvant are stored at 2-8°C and packaged as ready-to -use liquid formulations in 10-dose vials. It is given as two doses, 21 days apart. Phase 1 trial data has shown none to low local and systemic reactogenicity. No serious adverse events were reported. Immunogenicity as measured by neutralising antibody titres was similar to convalescent plasma. T-cell response showed a predominant Th1 phenotype.[19]

Phase 3 trial data from UK have shown 96.4% (95% CI: 73.8, 99.5) efficacy against mild, moderate and severe disease caused by the original COVID-19 strain and 86.3% (95% CI: 71.3, 93.5) efficacy against the B.1.1.7/ 501Y.V1 variant circulating in the U.K.[20]

Phase 2b trial taking place in South Africa has demonstrated efficacy of 55.4% among the HIV- negative trial participants in a region with predominantly B1.351 escape variants. In both trials, NVX-CoV2373 has demonstrated 100% protection against severe disease, including all hospitalization and death.[20]

Phase 3 trial (PREVENT-19) is also ongoing in US and Mexico and Phase1/2 trial is being continued in US and Australia.

4. Inactivated vaccines

BBV152 Vaccine (Covaxin, Bharat Biotech): BBV152 is a whole-virion, β- propiolactone inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule (TLR), a imidazoquinoline molecule (IMDG), adsorbed to alum (Algel). The NIV-2020-770 strain, isolated from a patient with COVID-19, was sequenced at the Indian Council of Medical Research-National Institute of Virology, and provided to Bharat Biotech.

In a double-blind, randomised, phase 1 trial, the safety and immunogenicity of three different formulations of BBV152 (3 μg with Algel-IMDG, 6 μg with Algel-IMDG, and 6 μg with Algel) were studied against placebo, as two doses 14 days apart. The two formulations,3 μg with Algel-IMDG and 6μg with Algel-IMDG, were chosen for phase 2 trial. Neutralising antibodies and T cell responses were found to persist at 3 months follow up. Based on interim analysis from phase 2 trial, the 6μg with Algel-IMDG has been chosen for phase 3 trial. The dosing interval has been modified to 28 days in phase 2 trial. The vaccine appears to be safe and immunogenic though large scale data are yet to be published.[21]

Type, required doses and interval between the doses of available vaccines are given in Table II.

Table II. Different types of COVID vaccines

	Type	Doses	Interval between doses
a) BNT162b2 mRNA COVID-19 vaccine (Pfizer BioNTech)	RNA vaccines	Two doses	21 days
b) mRNA-1273 SARS-CoV-2 vaccine (Moderna)	RNA vaccines	Two doses	28 days
c) ChAdOx1 nCoV-19 (AZD1222) (Oxford- Astra Zeneca vaccine) (Covishield, Serum Institute of India)	Viral vector vaccine	Two doses	Minimum 28 days apart, ideally 6-8 weeks
d) Ad26.COV2.S COVID-19 Vaccine (Janssen Pharmaceuticals	Viral vector vaccine	Single	
e) Gam-COVID-Vac (Sputnik V)	Viral vector vaccine	Two doses	21 days
f) NVX-CoV2373 (Novavax) vaccine	Protein subunit vaccine	Two doses	21 days
g) BBV152 Vaccine (Covaxin) Bharat Biotech	Inactivated vaccine	Two doses	28 days

Indications

Ministry of Health and Family Welfare (MOHFW) has prioritised vaccines for the following groups: [22]

1. Health care workers (public and private), including ICDS workers
2. Frontline workers: Personnel from state and central police department, armed forces, home guard, prison staff, disaster management volunteers and civil defense organization, municipal workers and revenue officials engaged in COVID-19 containment, surveillance and associated activities.
3. Population ≥60 years of age and people aged 45-60 years with co-morbidities like diabetes, hypertension, cancer, lung diseases etc.

Precautions and Contra-indications

Allergy: The vaccine should not be given to those who have had a previous systemic allergic reaction (including immediate-onset anaphylaxis) to a previous dose of the same COVID-19 vaccine or any component of the COVID-19 vaccine e.g. polyethylene glycol / polysorbate-80.[23] All recipients of vaccines should be placed under observation and monitored for at least 15 minutes post vaccine.

Immunocompromised hosts: As they are at increased risk for severe COVID-19, the Advisory Committee on Immunization Practices (ACIP) from USA and Joint Committee on Vaccination and Immunization (JCVI) from UK have recommended the non-live viral vaccines (mRNA and viral vector vaccines) in this group. The complete immunization course should be preferably completed two weeks before starting immunosuppression.[23,24]

Pregnancy: Safety data is not available for COVID vaccines in pregnancy. However, ACIP and JCVI have recommended that non- live virus vaccines may be offered in pregnancy if the pregnant woman is considered to be at risk of contracting the infection or at risk for severe disease. The risk-benefits of immunization and absence of safety data in humans should be explained.

Breastfeeding: There is no known risk with administering non-live viral vaccines and hence, vaccine may be offered after informing that there is no safety data in humans.

Previous COVID-19 infection: Vaccine can be taken anytime once acute infection is resolved and period of isolation is completed. In periods of vaccine shortage, vaccination may be delayed for them as risk of re-infection is low in the initial few months after infection.

Patients with bleeding disorders, anti-coagulants and anti-platelet drugs: COVID vaccines may be given intramuscularly to patients with bleeding disorders. If patient is on replacement therapy to reduce bleeding (e.g Hemophilia), vaccine administration can be planned shortly after this therapy. The vaccine can also be safely administered intramuscularly in patients on warfarin with INR below upper level of therapeutic range and patients who are stable on directly acting oral anti-coagulant (DOAC) like apixaban, dabigatran etc. It is advisable to

use a fine needle (23G/25G) and apply firm pressure to the injection site without rubbing for at least a couple of minutes. The patient should be explained about the risk of hematoma formation at injection site.[23]

Children: Currently approved vaccines have not been recommended in children as they are at lower risk of disease and no clinical trial data are available on safety and efficacy in this group.

Points to remember

- ***SARS-CoV-2 is an enveloped, positive sense, single strand RNA virus , that is responsible for the current COVID-19 pandemic.***
- ***Humoral and cellular immune responses in the form of neutralizing antibodies to the receptor binding domain of ACE 2 receptor and Th1 response respectively, have protective effect against the disease and re-infection.***
- ***Several mRNA, viral vector, protein subunit and inactivated vaccines have entered phase 2/3 trials and based on interim safety and efficacy data, obtained emergency use authorization.***
- ***While these vaccines do not have a live virus component and should be safe in the immunocompromised, pregnant and lactating women, we still await safety and efficacy data from trials enrolling these sub-groups.***
- ***COVID-19 causes mild / asymptomatic infections in majority of the children. Currently, no COVID vaccine is approved in children below 16 years of age.***

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CLIPPINGS

Integration of artificial intelligence for retionpathy of prematurity screening programme

Childhood blindness from retinopathy of prematurity (ROP) is increasing as a result of improvements in neonatal care worldwide. The effectiveness of artificial intelligence (AI)-based screening in an Indian ROP telemedicine program evaluated and differences in ROP severity between neonatal care units (NCUs) identified,related to differences in oxygen-titrating capability. External validation study of an existing AI-based quantitative severity scale for ROP on a data set of images from the Retinopathy of Prematurity Eradication Save Our Sight ROP telemedicine program in India. Images were assigned an ROP severity score (1-9) using the Imaging and Informatics in Retinopathy of Prematurity Deep Learning system. The area under the receiver operating characteristic curve, sensitivity and specificity for treatment-requiring retinopathy of prematurity was calculated. Using multivariable linear regression, the mean and median ROP severity in each NCU as a function of mean birth weight, gestational age, and the presence of oxygen blenders and pulse oxygenation monitors was estimated. The area under the receiver operating characteristic curve for detection of treatment-requiring retinopathy of prematurity was 0.98, with 100% sensitivity and 78% specificity. The authors concluded that Integration of AI into ROP screening programs may lead to improved access to care for secondary prevention of ROP and may facilitate assessment of disease epidemiology and NCU resources.

Campbell JP, Singh P, Redd TK, Brown JM, Shah PK, Subramanian P, et al. Applications of Artificial Intelligence for Retinopathy of Prematurity Screening. Pediatrics 2021; 147 (3): e2020016618; DOI: https://doi.org/10.1542/peds.2020-016618.

VACCINOLOGY II

INFLUENZA VACCINES – INDIAN CONTEXT

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Abstract: *Influenza is a single stranded RNA virus belonging to orthomyxovirus family. Influenza virus is classified into subgroups A,B,C and D. Influenza A and influenza B viruses cause respiratory illness leading to significant mortality and morbidity in children and adults. Influenza can cause epidemics and pandemics due to antigenic shift in the genetic structure of viruses. Influenza B is also capable of causing serious disease in children. Influenza illness can be prevented by hand hygiene, cough etiquette, safe social distancing and yearly vaccination with influenza vaccine. Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices has recommended yearly quadrivalent inactivated influenza vaccination for routine immunization for children above 6 months of age through 5 years to prevent influenza in children. Live attenuated vaccine can be given intranasally for the age group above 2 years through 49 years. In the year 2020 Indian Academy of Pediatrics Advisory Committee on Vaccines and Immunization Practices has recommended a uniform dose of 0.5ml of inactivated influenza vaccine for all age groups above 6 months.*

Keywords: *Influenza virus, Inactivated vaccine, Live attenuated vaccine, Quadrivalent, Trivalent, Children.*

Influenza viruses are RNA viruses of Orthomyxoviridae family causing a broad array of respiratory illnesses which account for significant morbidity and mortality in infants and children. There are four types of influenza viruses A, B, C and D. The subtypes of type A influenza virus are determined by haemagglutinin and neuraminidase. Both A and B viruses are responsible for seasonal influenza epidemics, non- seasonal sporadic cases and outbreaks.[1] The influenza type A causes moderate to severe illness in all age groups in humans and other animals. Influenza A viruses are known to cause pandemics due to antigenic shift. A pandemic can occur when a new and different influenza A virus with a different antigenic structure emerges due to antigenic shift that can infect many people as they do not have immunity against the new virus and the new virus (for pandemics the term used is new virus) which has the ability to spread efficiently across the population. Influenza B can cause similar illness like influenza A and sometimes causes severe infection and death. Antigenic shift is not seen in influenza B viruses and hence they do not cause pandemics.[2] Influenza B is also not classified into subtypes.

Type C virus causing mild illness is rarely reported in humans. Influenza D viruses primarily affect cattle and are not known to infect or cause illness in human beings.[3]

Influenza A viruses are classified into sub groups based on two surface envelope glycoproteins on the virus, hemagglutinin (H) and neuraminidase (N). There are 18 hemagglutinin sub types (H1 to H18) and 11 neuraminidase subtypes (N1 to N11). There are 198 different influenza A subtype combinations but only 131 subtypes have been detected in nature. Currently circulating subtypes of influenza A viruses are (H1N1) and (H3N2). Influenza A subtypes are further divided into clades and subclades (can be alternatively called "groups" and "sub-groups," respectively) depending on genetics. Influenza B is classified into two lineages as B/Yamagata and B/Victoria and these lineages are further classified into clades and subclades.[3]

Influenza A viruses are found in animals, ducks, chicken, pigs, whales, horses and seals. Wild birds are the primary natural reservoirs of influenza A and are considered as the source of influenza A viruses for all other animals.[4,5]

Major changes in antigenic structure of influenza A virus can lead to antigenic shift and a new virus formed will lead to pandemic as the new virus has the ability to spread from person to person rapidly as the people would not have immunity against the new virus. The reassortment of genetic material occurs in animals such as pigs which

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Table I. Subtypes of influenza A viruses associated with pandemics and epidemics

Year	Common name	Subtype	Severity	Mortality
1918-19	Spanish flu	H1N1	Severe pandemic	50 million affected and 14 million died in India
1957	Asian flu	H2N2	Severe pandemic	>1 million affected
1968-69	Hong Kong flu	H3N2	Moderate pandemic	1-3million affected
2009-10	2009 H1N1	H1N1	Mild to moderate	Approx. 285000 affected

Source: Seasonal and Pandemic influenza vaccines. In: IAP Textbook of vaccines. Vashishtha VM, Kalra Ajay, eds, 2nd edn, Jaypee Brothers Medical Publishers, New Delhi 2020; pp448-466.

are the common host for avian influenza viruses and human influenza viruses, when these animals are coinfected with both viruses.[6] Minor changes in hemagglutinins (HA) and neuraminidase (NA) can cause antigenic drift which may cause limited outbreaks of influenza A.[7]

The nomenclature of influenza virus is in order of virus type, geographic origin, strain number, year of isolation, and virus subtype. e.g. nomenclature of the A H1N1 pandemic influenza virus 2009 is A/California/7/2009/H1N1. (Table I).

Incidence

Influenza occurs globally with an annual attack rate estimated as 5%-10% in adults and 20%-30% in children. In India, it contributes to around 5%-10% of all acute respiratory infections. Reported incidence of influenza upper respiratory infection (URI) was found to be 10 per 100 child years and that of acute lower respiratory infection (ALRI) to be only 0.4 per 100 child years.[8]

Seasonal flu usually causes severe disease in children below 2 years, individuals above 65 years and in persons having chronic medical illness whereas pandemic flu affects children more severely and causes deaths in young adults without any risk factor, sparing adults and rapidly transmit the disease with high attack rate.[8,9]

During the post pandemic period, last major outbreak in India occurred in 2015 with 42,592 cases reported with 2990 deaths. This was followed by low transmission period in 2016 with 1786 cases reported and only 265 deaths recorded. In 2017, a total of 38811 laboratory confirmed cases and 2266 deaths are reported by Integrated Disease Surveillance Programme (IDSP) under National Centre for Disease Control (NCDC).

Maximum number of cases were from Gujarat (7709 cases and 431deaths) followed by Maharashtra (6144 case and 778 deaths), Rajasthan (3619 and 279) and Madhya Pradesh (802 and 146). Together, 4 states contributed to 47% of cases and 69% of total deaths in India. During 2017, some cases were reported from north-eastern states for the first time. Based on molecular analysis of isolates from Chennai and Pune, the dominant flu strain in India during 2017 was A/Michigan/7/2009(H1N1) pdm09 virus, replacing A/California/7/2009(H1N1)pdm09 seen during 2016 and was isolated for the first time in India. In 2018, 15266 cases and 1128 deaths were reported. About 28798 cases of seasonal influenza A H1N1 and 1218 deaths were reported during the year 2019 in India and the maximum number of cases (approximately 5000) was reported from Rajasthan by Central Surveillance Unit, IDSP NCDC. In the year 2020, the reported number of cases decreased to 2752 and deaths to 44. The reduction in number of cases may be due to COVID -19 pandemic which made people to follow safe distancing, wearing masks and hand hygiene.

Globally, in spite of continued testing or increased testing for influenza in some countries, influenza activity remained at lower levels than expected for this time of the year. Between February 2020 and March 2020, influenza activity increased in most of the countries of northern hemisphere consistent with typical influenza season. Starting from middle of March, influenza activity decreased sharply, with spread of SARS-CoV-2 infection. Worldwide, influenza B accounted for majority of influenza reports. Between September 2020 and January 2021, influenza A (H1N1)pdmo09, A(H1N2) and influenza B viruses circulated in very low numbers, influenza activity was mostly reported from countries in the tropics and sub tropics and some countries in temperate zone of northern hemisphere. Percentage of positivity was less than 0.2% in contrast to three previous seasons (2017-2020) percentage, which was 17%.[10]

Surveilance data of circulating influenza virus subtypes both globally and in India is shown in Fig.1 and 2.

Seasonality of influenza in temperate regions occur as outbreaks during late autumn and winter months;

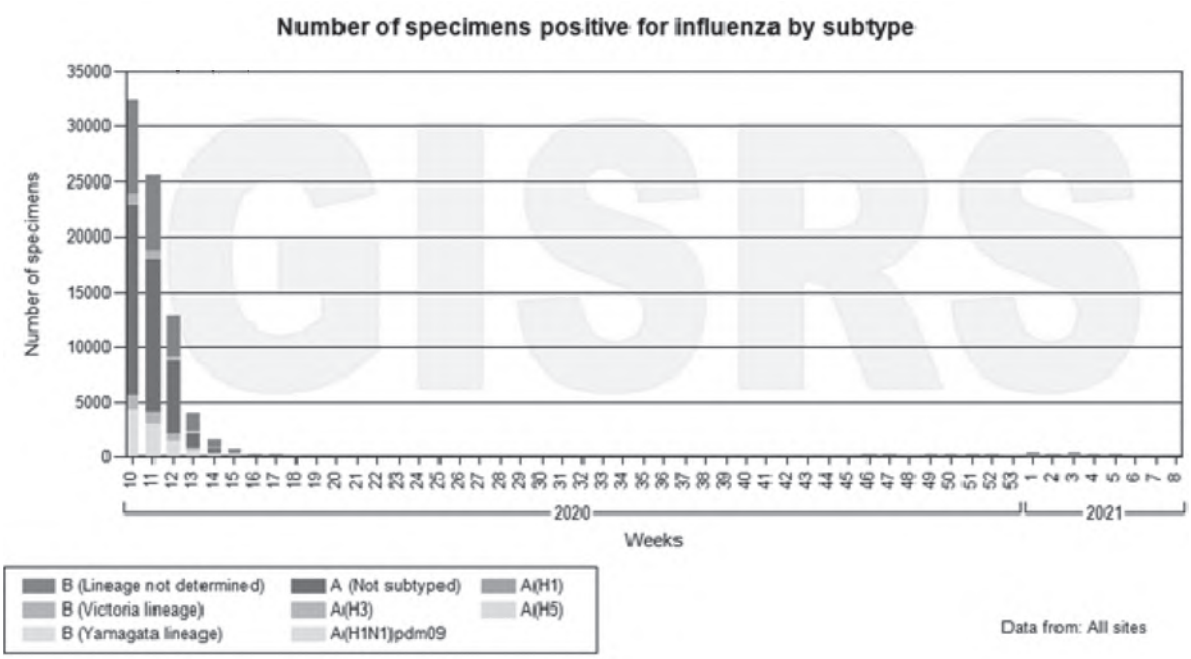

Fig.1. Global flu data 2020. Number of specimens positive for influenza by subtype

Source: World Health Organization. Flunet Summary. 29th March, 2021. Available from https://www.who.int/influenza/gisrs_laboratory/updates/summaryreport/en/

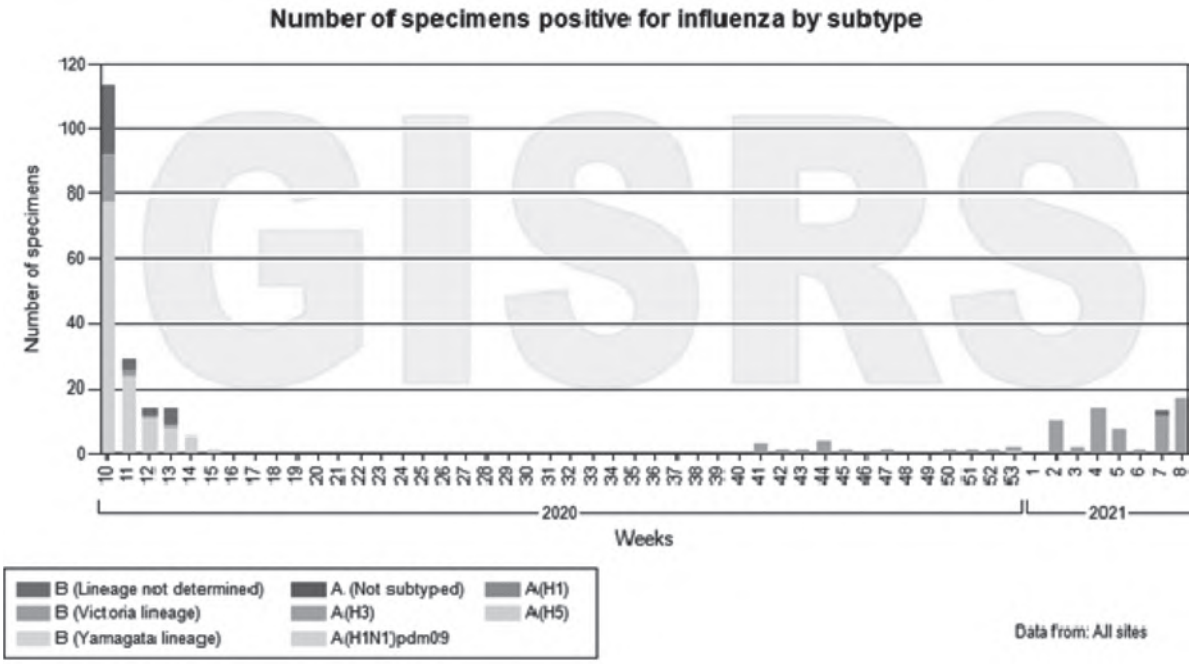

Fig.2. Indian data 2020. Number of specimens positive for influenza by subtype

Source: World Health Organization. Flunet Summary. 29th March, 2021. Available from https://www.who.int/influenza/gisrs_laboratory/updates/summaryreport/en/

November to March in Northern Hemisphere and May to September in Southern Hemisphere. In India, limited influenza activity occurs throughout the year with peaking during rainy season all over the country with a small peak in winter months in North India. In northern parts of India, influenza infection peaks between January and March which is similar to Northern hemisphere. In central India, (Delhi, Lucknow, Nagpur and Pune), influenza peaks between July and September and in southern part of India (Chennai, Vellore), influenza peak is in September to November.[11] Multisite virological influenza surveillance in India 2004-2008 has shown seasonal influenza A(H1N1),

(H3N2) and influenza B co-circulated in all regions without any particular pattern of movement of any subtype. Year- round limited influenza activity occurs with peaks during rainy season. Peak influenza activity is seen from July to August in Delhi, Pune and Kolkata and October to December in Chennai.[12]

Study of epidemiology of influenza B in a temperate region of northern India from 2010-2016 has shown co-circulation of B/Victoria (35.4%) and B/Yamagata (53.8%) and peak activity seen in winter months. The circulation in each season is dominated by one lineage which correlated with the vaccine strain, but up to 37% consisted of a different lineage. The study concludes that the preferred vaccine should be a quadrivalent vaccine with two B lineages.[13]

Box 1. Recommended composition of Influenza virus vaccines for use in 2021 Southern Hemisphere Influenza season

Composition of Southern Hemisphere 2021 quadrivalent vaccine

Egg based vaccines

- A/Victoria/2570/2019(H1N1) pdm09-like virus
- A/Hongkong/2671/2019 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage) -like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Cell or recombinant based vaccines:

- A/Wisconsin/588/2019 (H1N1) pdm09- like virus
- A/Hongkong/2671/2019 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage) -like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

Recommendation for trivalent vaccine:

Egg based vaccines:

- A/Victoria/2570/2019(H1N1) pdm09-like virus
- A/Hongkong/2671/2019(H3N2)-like virus
- B/Washington/02/2019(B/Victoria lineage)-like virus

Cell or recombinant based vaccines:

- A/Wisconsin/588/2019(H1N1) pdm09- like virus
- A/Hongkong/2671/2019(H3N2)-like virus
- B/Washington/02/2019(B/Victoria lineage)-like virus

Influenza vaccines

WHO recommendations provide a guide to national public health and regulatory authorities and vaccine manufacturers for the development and production of influenza vaccine for the next season. Unlike other vaccines, the content of influenza vaccine needs to be updated regularly because the circulating viruses evolve continuously every season. Recommendations are usually made in February for the following influenza season for northern hemisphere and in September for the following season for the southern hemisphere (Box 1 and Box 2). It takes 6-8 months for the manufacturer to produce, approve and distribute the vaccine before the influenza season. These recommendations are made based on the data of WHO Global Influenza Surveillance and Response System (GISRS).[14]

Box 2. Recommended composition of 2021-2022 Northern Hemisphere Influenza season[15]

Egg based vaccines

- A/Victoria/2570/2019 (H1N1)pdm09-like virus
- A/Cambodia/e0826360/2020 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage) - like virus

Cell or recombinant - based vaccines

- A/Wisconsin/588/2019 (H1N1) pdm09- like virus
- A/Cambodia/e0826360/2020 (H3N2)- like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus
- B/Phuket/3073/2013 (B/Yamagata lineage)- like virus

Recommendations for trivalent influenza vaccine

Egg based vaccines

- A/Victoria/2570/2019 (H1N1)pdm09-like virus
- A/Cambodia/e0826360/2020 (H3N2)-like virus
- B/Washington/02/2019 (B/Victoria lineage)-like virus

Cell or recombinant based vaccines

- A/Wisconsin/588/2019 (H1N1)pdm09- like virus
- A/Cambodia/e0826360/2020 (H3N2)- like virus
- B/Washington/02/2019 (B/Victoria lineage) -like virus

Flu Vaccine

First inactivated egg-based flu vaccine was developed by Thomas Francis, Jr. and Jonas Salk in 1940 with the support of US army. After the discovery of influenza B virus in 1942, a bivalent flu vaccine containing influenza A and influenza B viruses was developed. In 1978, first trivalent flu vaccine was introduced and in 2012, first quadrivalent flu vaccine was introduced in US. In June 2003 first nasal spray vaccine was licenced in US. In 2012 cell culture vaccines emerged as alternative method of producing flu vaccine.[16]

Vaccine can be an inactivated vaccine, live attenuated vaccine, adjuvanted vaccine or recombinant vaccine. Vaccines elicit a relatively strain specific humoral immune response, and effectiveness is reduced against antigenically drifted viruses and also ineffective against unrelated viruses due to antigenic shift.

A trivalent vaccine contains two strains of Influenza A (H1N1 and H3N2) viruses and one strain of Influenza B viruses - either Victoria or Yamagata virus.

Quadrivalent vaccine contains two influenza A inactivated viruses (H1N1 and H3N2), two influenza B inactivated viruses (Victoria and Yamagata). Reason for inclusion of both the influenza B strains is because of the cocirculation of both influenza B strains during the flu season in the recent years. Other important aspect is that, there is hardly any cross protection between the two strains of influenza B viruses. Presence of only one strain of influenza B in a trivalent vaccine may lead to a mismatch in some seasons with the circulating strain of influenza B virus for that season and this might lead to decreased effectiveness of the vaccine. In a Finland study, it was found that in 4 out of 12 seasons, the vaccine strain of influenza B did not match with the circulating strain of influenza B. These findings support the inclusion of both lineages of influenza B in the flu vaccine for better effectiveness of vaccine and the preference of tetravalent vaccine .[17]

Antigenic composition of the influenza vaccines is revised twice annually and adjusted to the antigenic characteristics of circulating influenza viruses obtained with the help of WHO Global Influenza Surveillance and Response System (GISRS) to ensure optimal vaccine efficacy against prevailing strains in both the northern and southern hemisphere.

Inactivated influenza vaccines (IIVs)

Trivalent inactivated vaccine (TIV) or quadrivalent inactivated vaccine are of three types: a) whole virus vaccine b) spilt vaccine and c) subunit surface antigen. All the standard inactivated vaccines contain 15μg of HA of each vaccine virus. High dose inactivated influenza vaccine (HD-IIV3) contains 60μg of HA of each vaccine viruses. HD-IIV3 is recommended for the age group of > 65 years because of better immunogenicity. HD-IIV3 is not available in India.

Presently, spilt virus vaccine or subunit surface antigen vaccines are available in India. In split virus vaccines, the virus has been disrupted by a detergent. In subunit vaccines, HA and NA have been further purified by removal of other viral components. The immunogenicity of spilt virus vaccine appears to be better than that of sub unit vaccine in children aged 6-35 months[18] and also in adults above 50 years.[19] Trivalent inactivated flu vaccine and quadrivalent inactivated influenza vaccines are the only flu vaccines recommended for children < 2 years of age, persons aged more than 50 years, for pregnant women and people with chronic illness.

Live attenuated influenza vaccine

Live attenuated flu vaccine (LAIV) is made using 2 different technologies - Ann Arbor backbone by Astra Zeneca and Leningrad (Russian) backbone which is produced by Russia and India. An indigenous monovalent pandemic H1N1 vaccine produced by Serum Institute of India was available during 2009 pandemic. A trivalent LAIV was also produced in India. Presently both are not available in India.

Currently, licenced LAIV are based on temperature sensitive(*ts*) cold adaptive (*ca*) which will replicate in at lower temperature of nasopharynx 25°C without replicating in at higher temperature 39°C of lower respiratory tract compared with wild-type viruses (*wt*). Such viruses are derived in a classical method by serial passage of a wild - type virus in eggs at gradually decreasing temperatures. Several live attenuated influenza A and influenza B generated by this method are used for licenced LAIV. In US, these live viruses based on the *ca* A/Ann Arbor/6/60 and B/Ann Arbor/1/66 viruses are developed which are used for re assortment with HA and NA genes from a variety of candidate with viruses of interest to prepare a LAIV.[20]

The USA has a long-standing paediatric influenza vaccination programme, including use of live attenuated influenza vaccine (LAIV). Following evidence of apparent lack of vaccine effectiveness (VE) of LAIV in 2015/2016, particularly against A (H1N1) pdm09,[21] USA suspended the use of LAIV in the 2016/2017 season.

Advisory Committee on Immunization Practices (ACIP) of USA has not recommended LAIV for the flu season of 2016-2017 and 2017-2018 because of decreased efficacy compared to inactivated vaccine. ACIP has reintroduced the recommendation of LAIV4 as an option for vaccine provider from 2018-2019 season.[22] UK introduced LAIV for children in 2013/2014 and Finland in 2015/2016. Both countries have since been closely monitoring the programme performance. In 2015/2016, UK and Finland, unlike the USA, found evidence of significant VE of LAIV against laboratory-confirmed influenza.[23] Several studies, however, reported relatively lower VE of LAIV against influenza A(H1N1)pdm09 infection compared with inactivated influenza vaccine, although not for influenza A(H3N2) or influenza B.[24] The reasons for these apparent differences remain under investigation. Both UK and Finland continue to recommend the use of LAIV in children for the 2017/2018 season and are intensifying further monitoring of their childhood programs against a range of end-points.[25] Canada and Europe did not report any decreased efficacy of LAIV and they continue to use LAIV.[25]

LAIV is recommended for healthy children above 2 years of age and adults up to the age of 49 years. It is not recommended for pregnant women, children below 2 years and in high-risk individuals. LAIV is administered intra nasal as 0.2 ml as a total dose, and administered as 0.1 ml in each nostril.

Adjuvanted TIV (aIIV3): It was introduced in USA in 2015. It was developed to improve immunogenicity. Adjuvanted inactivated vaccine contains oil in water adjuvant, MF59. It is mainly recommended for elderly age group people aged above 65 years. FDA has licenced adjuvanted quadrivalent influenza vaccine since February 2020 for persons above 65 years of age.[26,27,28]

Recombinant influenza vaccine (RIV): Initially licenced as trivalent vaccine (Flublok), now the quadrivalent vaccine is licenced in USA from 2016. RIV4 contains 45µg of HA protein per vaccine virus component (total 180µg); the HA proteins are produced via the introduction of the genetic sequence for the HA into an insect cell line (spodoptera fugiperda) via a baculova virus vector. This process does not use live influenza viruses and eggs.[29] It is recommended for individuals who have severe egg allergy and also for pregnant women and for the age group above 18 years. RIV was found to be safe but less immunogenic in children aged below 36 months compared to IIV. Effectiveness of RIV is 44.6%.[30]

Cell based influenza vaccines: Flu viruses used in the cell based inactivated flu vaccines grown in cultured cells of mammalian origin instead of hens' eggs. The cell based vaccine manufacturing process uses animal cell (Madin-Darby Canine Kidney, or MDCK cells) as a host for growing flu viruses instead of fertilized eggs. The potential advantage of this technology is that it might permit faster start-up of vaccine manufacturing process in the situation of pandemic. It is recommended from 4 years of age onwards.[2]

Differences between inactivated and live Influenza vaccine are given in the Table II.

Dosage schedule

In 2020, IAP ACVIP has recommended the use of uniform dose of 0.5ml dose for all the children above six months of age as studies have shown comparable reactogenicity and superior immunogenicity in comparison to 0.25ml dose.[31] For the brands (Sanofi) which have not yet got approval for 0.5ml dose for less than 3 years by Drugs Controller General of India (DGCI), it is prudent to follow the product insert information.

Children above 6 months through 8 years, who have not received any dose of influenza vaccine should receive 2 doses with 4 weeks interval between the 1st and 2nd doses. If the child has previously received 2 or more total doses of any influenza vaccine, need only one dose. The two previous doses need not be given during the same season or consecutive seasons.

Children 6 months through 8 years who have previously received only one dose of influenza vaccine, need two doses of vaccine 4 weeks apart for protection

Intradermal flu vaccine is recommended for adults 18-64 years of age, the immune response is similar to intramuscular flu vaccine.[32] A high dose trivalent inactivated flu vaccine containing 60 micrograms of hemagglutinin per strain has shown significantly higher antibody response and provided better response against laboratory confirmed influenza illness than the regular flu vaccine in persons above 65 years.[33] Intradermal and high dose flu vaccines are presently not available in India.

Timing of flu vaccine

With available data on seasonality in India, it is difficult to have uniform timing for flu vaccination.

The best time for people living in the southern states of India would be just before the onset of the rainy season

Table II. Comparison between LAIV and IIV

Factor	LAIV	IIV
Age	Above 2 years to 49 years	Above 6 months to above 65 years
Route of administration	Intranasal spray	Intramuscular injection
Number of viruses in vaccine	Four (2 influenza A and 2 influenza B)	Three (2 influenza A and 1 influenza B) TIV, or four (2 influenza A and 2 influenza B) QIV.
Vaccine strain updated	Yearly	Yearly
Frequency of administration	Yearly	Yearly
Interval between the dose if 2 doses are given in a year	4 weeks	4 weeks
For persons with medical risk factors related to influenza	Cannot be given	Can be given
Children with asthma	Cannot be given	Can be given
Family members and close contacts of immunocompromised	Can be given	Can be given
Contacts of immunocompromised in protective environment	Cannot be given	Can be given
Simultaneous administration with other vaccines	Can be given	Can be given
Interval between the administration with other live vaccines	4 weeks if not administered on same day	Can be given any time
Persons on influenza antiviral medication Oseltamivir, Zanamvir Peramavir, Baloxavir	Cannot be given if taken within 48 hours for Oseltamivir and Zanamivir, for 5 days for Peramivir, 17 days for Balaxovir	No specific recommendation
Interval between the other inactivated vaccines if not administered on the same day	Can be given any time	Can be given any time
Children less than 2 years	Cannot be given	Can be given
Pregnancy	Cannot be given	Can be given
Child on salicylate therapy	Cannot be given	Can be given

i.e., October and rest of country, it should be in June. Southern hemisphere vaccine which will be released in March is suitable for most of states in India to get protection against the influenza peak which occurs in monsoon. WHO classifies India under South Asia transmission zone of influenza circulation; circulating strains are reviewed in both meetings of northern and southern hemispheres. Though India lies in northern hemisphere, parts of the country have tropical environment and has southern hemisphere like influenza seasonality with round the year circulation and peaks of monsoon and India also experiences winter peaks of influenza in North India like Northern hemisphere. With these patterns of strain circulation not being fixed there may be spill over from one to another circulating strain.[34]

It is not prudent to stick to vaccines recommended for one hemisphere, one should use the vaccine which contains most recent strains preferably 2 weeks prior to the onset of flu season.

ACVIP recommendations for flu vaccine

Influenza vaccine (IIV) is routinely recommended for the children in the age group above 6 months to 5 years. Latest available vaccine can be administered after 6 months of age as two doses in the first year followed by once in a year from 2nd year onwards. Vaccine should be administered 2-4 weeks prior to the influenza season. Routine influenza vaccine is introduced in India by IAP ACVIP because of the influenza activity round the year with seasonal peaks, high morbidity and mortality in young children and high-risk groups, paucity of facilities for laboratory diagnosis, high transmission rate, substantial economic burden, limitation of antiviral drug oseltamivir and availability of moderately efficacious vaccine. IAP ACVIP recommended the vaccine in immunisation schedule (2018-19) and update on immunisation for children aged 0 through 18 years.[35]

Influenza vaccine is also recommended for children above 5 years of age with following high risk conditions:

1. Chronic cardiac, pulmonary, hematological, renal conditions (including nephrotic syndrome), chronic liver diseases and diabetes mellitus.
2. Congenital or acquired immunodeficiency (including HIV infection).
3. Children on long term salicylate therapy.
4. Laboratory personnel and healthcare workers.
5. Also, wherein the vaccine is desired or requested by parents.

IAP believes that influenza vaccination should aim primarily at protecting vulnerable high-risk groups against severe influenza associated disease and death. However, effectiveness of vaccine is different in various age groups and different categories of individuals. Prioritisation is done on basis of influenza disease burden and severity in a particular group of individuals, effectiveness of vaccine in various group of individuals. These group of individuals at high risk should be targeted for flu vaccination.

Prioritisation of target groups: Group 1 highest priority and Group 4 lowest priority

1. Elderly individuals of age more than 65 years and nursing home residents (elderly and disabled).
2. Individuals with chronic medical conditions including individuals with HIV/AIDS and pregnant women specially to protect infants below six months of age.
3. Other groups: health care workers, individuals with asthma, and children of 6 months to 2 years age.
4. Children from 2 years to 18 years and healthy young adults.

Children less than 5 years, and particularly less than 2 years of age should be considered for target group for vaccination because of severe disease burden of influenza in that age group.[36]

For countries considering the initiation or expanding immunisation programme for seasonal influenza vaccination,WHO recommends that pregnant women should have highest priority. Year-round maternal immunisation significantly reduced maternal influenza-like illness, influenza in infants, and low birthweight in a RCT trial in Nepal.[37]

Maternal vaccination was associated with statistically significant reduction in febrile respiratory tract infections (RTI) and higher mean birth weight of babies, 63% reduction in lab confirmed influenza and 29% reduction in febrile RTI in infants. Passive transfer of anti-influenza antibodies from vaccinated women to neonates has been documented. Protection of infants though maternal vaccination has been observed in several studies. In a randomized controlled trial conducted in Bangladesh, vaccination of pregnant women during the third trimester resulted in a 36% reduction in respiratory illness with fever among these women, as compared with women who received pneumococcal polysaccharide vaccine. In addition, influenza vaccination of mothers was 63% effective (95% CI 5 to 85) in preventing LCI(Laboratory confirmed influenza) in their breastfed infants during the first 6 months of life.[38]

In India, vaccine uptake among pregnant women is extremely poor;12.8% in pandemic influenza vaccine and none for seasonal vaccine.[39]

Efficacy

Hemagglutination Inhibition (HI) antibody titres of 1:40 or greater have been shown to provide 50% protection in healthy adults.[36] However, a cut off of 1:110 for antibodies is preferable to conventional 50% clinical protection rate in children, a titre of 1:330 would predict an 80% protective level, which is more desirable from public health perspective.[40]

Following vaccination, anti-hemagglutinin (anti-HA) antibody titre peaks in 2-4 weeks in primed individuals. Antibody titre peak takes 4 weeks or more in individuals and older adults who are not primed. Serum antibody titre falls by 50% or more by 6 months after vaccination, with a degree of reduction proportional to the peak titres achieved

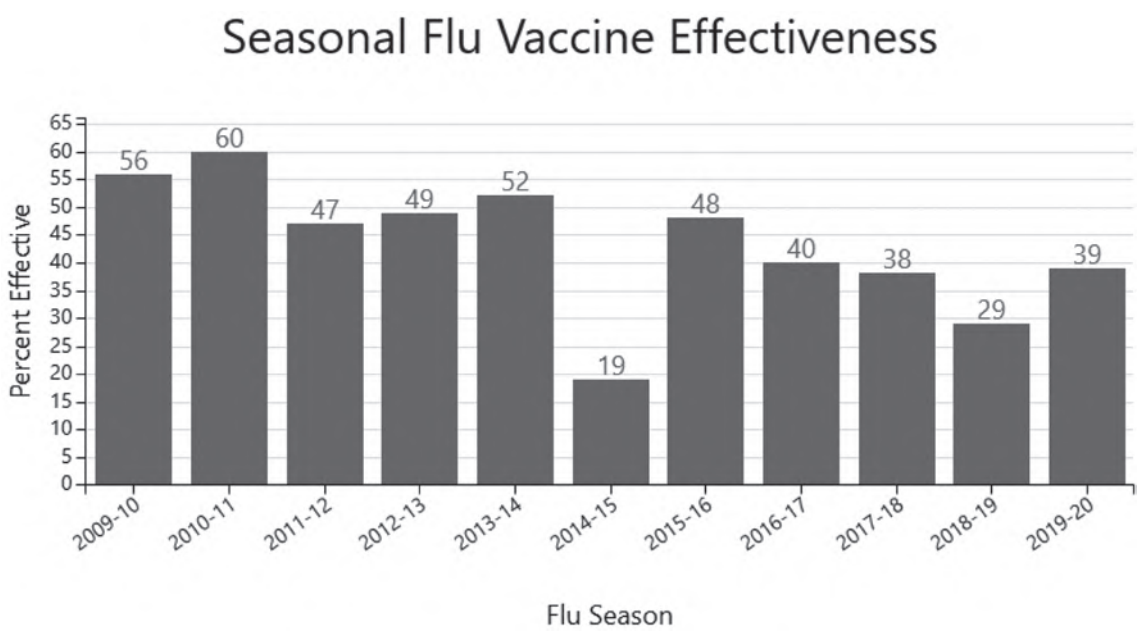

Fig.3. Effectiveness of seasonal Flu vaccine during various seasons.

Table III. Various brands of Influenza Vaccines available in India

Brand name	Manufacturer	Type of vaccine	Valency	Composition
Flu quadri	Sanofi Pastuer India Ltd	Inactivated Spilt virion	Quadrivalent	H1N,H3N2, B/Victoria, B/Yamagata
Influvac tetra	Abbot India Ltd	Inactivated Sub unit	Quadrivalent	H1N1,H3N2,B/Victoria, B/Yamagata
Fluarix tetra	GlaxoSmithkline Pharmaceuticals Ltd	Inactivated Spilt virion	Quadrivalent	H1N,H3N2, B/Victoria, B/Yamagata
Vaxiflu	Zydus Cadilla	Inactivated Split virion	Quadrivalent	H1N1, H3N2,B/Victoria, B/Yamagata
Zuviflu Not available	Zuventus	Inactivated	Trivalent	H1N1, H3N2,B/Victoria or B/Yamagata
Nasovac Not available	Serum Institute of India	Live attenuated	Monovalent / Trivalent	H1N1 (monovalent)
Vaxigrip Not available	Sanofi Pastuer India Ltd	Inactivated Spilt virion	Trivalent	H1N1.H3N2, One of Influenza B virus

and may remain stable for 2-3 years. Protection against viruses that are antigenically similar to those contained in the vaccine, extend for a minimum 6-8 months.[36]

The reported efficacy and effectiveness of influenza vaccine varies substantially with factors such as case definition e.g., lab confirmed or less specific “influenza like illness”, the match between the vaccine strains and circulating strains of viruses, vaccine preparation, dose, prior antigenic exposure, age and underlying medical condition.[36] A meta-analysis has shown efficacy of Live influenza vaccine (LIV) for similar antigen as 83.4% using per protocol analysis and 82.5% using intention to treat analysis; for any antigen 76.4% for per protocol and 76.6% for intention to treat. Vaccine efficacy for inactivated vaccine, for similar antigen was 67.3%.[36] Efficacy of flu vaccine for each year is shown in the graph of CDC (Fig.3). The vaccine effectiveness estimated included in the chart and below are vaccine effectiveness estimates from the U.S. VE Network (Fig.3).

Various brands of Influenza vaccines available in India are given in Table III.

Safety of influenza vaccine

Influenza vaccines are safe with only minimal mild side effects. Transient local reactions at the injection site occur often and fever malaise, myalgia and other systemic adverse events may occur in persons who are not exposed to influenza antigens.

Flu vaccine and egg allergy[41]

a) A person with a history of egg allergy, who has experienced only urticaria after exposure to egg should receive influenza vaccine.

b) Persons who report having had reactions to egg involving symptoms other than urticaria, such as angioedema, respiratory distress, light headedness, or recurrent emesis, or who required epinephrine or another emergency medical intervention, may receive flu vaccine. The vaccine should be administered in an inpatient or an outpatient medical setting. Vaccine administration should be supervised by a healthcare provider, who is able to recognise and manage severe allergic reactions.

c) A previous severe allergic reaction to influenza vaccine, regardless of the component suspected being responsible for the reaction, is a contraindication to future receipt of vaccine. Post vaccination observation of patient is not required; however, observation for 15 minutes may be considered as required for other vaccines.

Persons who had Guillain-Barre Sydrome:[41]

A history of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous dose of any type of influenza vaccine is considered a precaution to vaccination. Persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks of a previous influenza vaccination generally should not be vaccinated. As an alternative to vaccination, physicians might consider using influenza antiviral chemoprophylaxis for these persons. However, the benefits of influenza vaccination might outweigh the risks for certain persons who have a history of GBS and who also are at high risk for severe complications from influenza (populations at higher risk for medical complications attributable to severe influenza such as chronic pulmonary, cardiovascular, renal, hepatic, neurologic, hematologic, or metabolic disorders and diabetes mellitus).

Concurrent administration of influenza vaccine with other vaccines:[36,41]

Data regarding potential interference following simultaneous or sequential administration for the many potential combinations of vaccines are limited. Therefore, following the general guidelines for immunization is prudent. IIVs and RIV may be administered concurrently or sequentially with other inactivated vaccines or with live vaccines. LAIV can be administered simultaneously with other live vaccines. If LAIV in not administered simultaneously with other live vaccines, they should be administered with an interval of 4 weeks between the two live vaccines. Concomitant administration of non aluminium adjuvanted vaccines may be avoided if other option of non adjuvanted vaccine is available, as there is no data for concomitant administration non aluminium adjuvanted vaccines. If two non aluminium adjuvanted vaccines are given concomitantly they should be administered at separate anatomic sites.

Recommendations for seasonal flu vaccine for healthy children

Number of studies suggested that in healthy children, particularly those below two years of age, influenza may have a serious and complicated course and frequently lead to hospitalisation and sometimes death. Moreover, preschool and school aged children were found to be important cause of transmission to the community, as they shed the virus for longer time and they have frequent contact with greater number of children and individuals. These findings led a number of health authorities to modify the seasonal flu vaccine recommendations for healthy children. Several factors seem to indicate that vaccination against influenza in healthy children of any age and pregnant women could be effective in preventing the disease in entire pediatric population and in providing herd immunity in adults and old people as well. The direct advantage of vaccine seems to be greater in younger children, particularly of less than 2 years of age.[42]

It was observed that that immunising healthy siblings and household hold contacts with seasonal flu vaccine can prevent influenza hospitalisation in infants below 6 months of age.[43]

SARS-CoV-2 (COVID-19) and Flu vaccine

SARS-CoV-2 is a novel virus. Clinical experience with influenza vaccination of persons with COVID-19 is limited. For persons with acute illness or suspected or laboratory confirmed COVID-19, the influenza vaccination should be delayed until the person is no longer acutely ill.[41,44]

In the present ongoing pandemic of Covid-19, it is important to get influenza vaccine as it reduces the risk of flu illness, hospitalisation and death due to flu and can reduce the burden of healthcare, which can be utilised for care of Covid-19 patients. During the Covid-19 pandemic, WHO has recommended seasonal flu vaccine for health workers and older adults as highest priority. Covid-19 patients with recent influenza vaccination had better outcome than those who were not vaccinated in Brazil. Data analysis from 92,664 clinically and molecularly confirmed COVID-19 patients who have been vaccinated with influenza vaccine recently experienced 8% lower odds for intensive care treatment (95% CI 0.86, 0.99), and 18% lower odds of requiring invasive respiratory support (95% CI 0.74, 0.88) and 17% lower odds of death (95% CI 0.78, 0.90).[45]

Points to Remember

- ***Immunisation against influenza may play an important role in reducing the morbidity and mortality in children and adults. ACVIP IAP recommended influenza vaccine for all children from 6 months of age to 5 years as a routine vaccine yearly***
- ***Influenza A and Influenza B cause mild to severe respiratory illness in children and adults leading to significant morbidity and mortality.***
- ***Quadrivalent flu vaccine is recommended routinely for children from the age of 6 months through 5 years of age.***
- ***Uniform dose of 0.5 ml intramuscular quadrivalent influenza vaccine is recommended for all age groups.***
- ***Influenza vaccine is a priority vaccine during COVID-19 pandemic.***

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VACCINOLOGY II

PNEUMOCOCCAL VACCINES - PAST, PRESENT AND FUTURE

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Abstract: *Streptococcus pneumoniae is a major cause of mortality and morbidity among children under five years of age. India is one among the countries with high mortality due to invasive pneumococcal disease. With the emerging resistance of pneumococcus to penicillin, especially in meningeal isolates, the focus is on prevention, which is mainly by pneumococcal vaccines. Since the current vaccines are serotype specific, it protects against invasive pneumococcal disease and is affected by geographic diversity of the serotypes, use of other targets such as pneumococcal surface protein A is explored. This commentary gives an overview of the pneumococcal vaccines that are in use and that are under development.*

Keywords: *Streptococcus pneumoniae, PCV, PPV, India.*

Streptococcus pneumoniae is a major cause of mortality and morbidity among children under five years of age. It is estimated that nearly 2-3 million childhood deaths occurred in India in 2005, mainly due to pneumonia. Childhood pneumonia deaths were also higher in central, east and west India.[1] Even with the several evidences on high mortality in India, the pneumococcal conjugate vaccine (PCV) was not implemented until late 2017, when PCV 13 was first rolled out in two states of North India where mortality was high.

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This is because, Indian data on prevalent streptococcus pneumoniae serotypes are relatively less when compared to other countries.[2] This is mainly due to the high-quality techniques required for the bacterial isolation of this organism, which is further hindered by empirical use of antibiotics.

Burden of pneumococcal disease in children

During the first few years of life, nasopharyngeal (NP) colonization is a necessary precursor for pneumococcal disease.[3] Pneumococcus can spread from the nasopharynx by contiguous extension to cause infection in the middle ear (otitis media), or invade the bloodstream and spread to other sites causing infection such as meningitis, bacteremic pneumonia or sepsis.

The highest burden of serious pneumococcal disease occurs in young infants and the elderly. The childhood peak of invasive pneumococcal disease incidence occurs earlier in developing countries compared to developed countries. Among the pneumococcal diseases, mortality is high in invasive pneumococcal disease (IPD) (meningitis, sepsis, and bacteremic pneumonia) whereas the number of cases are more with non-invasive pneumococcal diseases (non-bacteremic pneumonia, acute otitis media). India is one among the top 4 countries with the greatest number of pneumococcal deaths in children under 5 years.[4]

Pneumonia is the most common non-invasive pneumococcal disease next to acute otitis media. Globally, pneumonia is one of the two diseases that is responsible for 25% of deaths in children under 5 years.[5] Among these, 70% of deaths are reported in fifteen countries, among which India is at the top. The meta-analysis of burden of IPD in South East Asia by Jaiswal, et al in 2014, showed that in children <5 years, 2.98% of suspected invasive bacterial disease (IBD) and 24% of all confirmed IBD had S. pneumoniae infections[6]. It was also observed that 14.87% of all cases of bacterial pneumonia and 36.81% of all cases of meningitis were due to pneumococci. This study also includes meta-analysis of 10 hospital-based surveillance studies in India that showed 10.58% of the invasive diseases, 7.62 % of the severe pneumonia cases and 11.21% of the meningitis cases were caused by S. pneumoniae in children with suspected

bacterial infections aged 1 month to 12 years. S. pneumoniae caused 24.3 % and 32.78% of confirmed pneumonia and meningitis cases respectively.

Prevention and control of pneumococcal disease

Prevention of nasopharyngeal (NP) colonization plays the major role in pneumococcal disease because NP colonization precedes the disease.[7] NP colonization occurs in most children as early as 6 months of age.[8,9] Since pneumonia is the most common infection which can turn serious, empirical use of antibiotics is common. This can accelerate the development of resistance, because of the natural recombination between resistant pneumococci or other commensal streptococci that are present as the normal flora of the nasopharynx, thus diminishing the effectiveness of antibiotics and can lead to the spread of antimicrobial resistance. This will necessitate the use of second and third-line antibiotics that are more expensive and less effective, making it a major economic burden in India. Hence, the best way to prevent pneumococcal disease is by preventing NP colonization. However, the currently available vaccines are based on the polysaccharide capsule that helps protect it from host defences and aids in the development of capsule - type-specific immunity. At present, there are over 100 different serotypes of S. pneumoniae, and hence pose a challenge in formulating vaccines containing the varied serotypes. There has been wide geographical diversity observed in the serotype distribution.[10] Moreover, only conjugate vaccines provide serotype specific protection against IPD and carriage. Thus, country specific sustained and continuous surveillance of carrier and disease-causing serotypes is necessary to identify the prevalent serotypes that can guide in choosing appropriate regional vaccines.

Pneumococcal vaccines: Types and schedule

Two types of vaccines are currently recommended by WHO for routine immunization; pneumococcal conjugate vaccines: PCV10 or PCV13, either a 3 primary doses without a booster (3 + 0 schedule) or 2 primary doses with a booster dose (2+1 schedule).[11] Pneumococcal conjugate vaccines (PCV) contain the capsular polysaccharide which is conjugated to a protein whereas polysaccharide vaccines (PPSV) contain purified capsular polysaccharides. PPSV vaccines generate antibodies against pneumococcal capsular antigen via a T- cell independent mechanism and without memory B- cells, whereas conjugated vaccines can induce a T-cell- dependent and B cell memory response.[12] PPSV is recommended only for children more than 2 years because it is less immunogenic in children less than 2 years of age. PCV, unlike PPSV, allows a more robust immunogenicity with enhanced avidity and memory for the capsular polysaccharides. Thus, immunologic priming with PCV allows for a more enhanced immune response to PPSV when administered as the initial vaccine in adults.[13] In addition, PCV reduces or suppresses nasopharyngeal colonization of vaccine serotypes not only among the vaccinated but also the unvaccinated, suggesting indirect protection through mechanisms of herd immunity.

PCV10 or PCV13 (protects against 10 or 13 serotypes respectively) and PPSV23 (protects against 23 serotypes). The timing of the dosage depends on the disease burden in different age groups. The schedule should be combined with the routine vaccination schedule in each country so as to achieve maximum coverage. In addition, the interval of two months between the primary 2 dose series maximizes the immune response. 3+1 schedule has been primarily used during the introduction of PCV7 as well in PCV 13. Based on the current evidence and WHO recommendations, most of the countries are using either 2+1 or 3+0 schedules.[14] If regional pattern shows disease peaks in less than 8 months of age a 2+1 schedule might not offer optimum individual protection for certain serotypes because higher antibody levels are induced by the 3rd dose. For 2+1 schedule the optimum dosing interval between two primary doses should be a) 8 weeks or more for infants ≤ 6 months b) 4- 8 weeks or more for infants ≥ 7 months and one booster dose between 9- 15 months. In high income countries, either the 2+1 schedule (primary doses at 2 and 4 months followed by booster at 12 months) or 3+1 schedule (primary doses at 2,4,6 months followed by booster at 12-18 months) is followed (In US 3+1 schedule and in Canada, either one of these schedules are used due to provincial differences). Variant of 2+1 schedule is in line with WHO EPI schedule which is 6 weeks, 14 weeks and booster at 9th month because there is no further visit around 12 months. This is followed in the five states (Himachal Pradesh, Madhya Pradesh, Bihar, Uttar Pradesh and Rajasthan) in India under routine immunization from 2016-2017. It is planned to be scaled up all over the country as per 2021 budget by GOI.

The three primary doses schedule early in life (e.g. a 6-, 10- and 14-weeks) is considered the best option in low-income countries, where invasive pneumococcal disease is highest before the end of the first year of life. In other settings, a schedule including a booster dose may address the disease peaks in the second year of life. The additional advantage of the booster doses is the reduction in the NP carriage which is important to reduce transmission. Currently, the emphasis is on herd immunity.

PPSV 23 is not good for herd immunity because of the following reasons: (1) less immunogenic, (2) does not produce mucosal immunity, (3) induces hypo responsiveness with repeat booster doses (4) no effect on colonization or carrier state and does not prevent community acquired or non bacteremic pneumonia. All these disadvantages are not associated with PCV.

Indications for PPSV in high risk populations

A dose of PPSV is recommended in addition to PCV in children more than 2 years with the following high risk conditions.

1. Functional or anatomic asplenia
2. Immunocompetent children with chronic heart or lung disease, diabetes mellitus, cochlear implant, cerebrospinal fluid leak.
3. Immunocompromised children - Those with HIV infection, chronic renal failure, nephrotic syndrome, on treatment with immunosuppressive drugs and congenital immunodeficiency.

PPSV should be administered atleast 8 weeks after the last dose of PCV. A second dose PPSV is recommended after 5 years to children with anatomic/functional asplenia or an immunocompromising condition.

Pneumococcal vaccination in adults

1. All adults 65 years or older should receive one dose of pneumococcal polysaccharide vaccine (PPSV23) regardless of previous history of vaccination with pneumococcal vaccine. Doses of PPSV23 should be spaced 5 years apart from each other in case they have received a PPSV earlier.
2. PCV13 for all adults 19 years of age or older with immunocompromising conditions, cerebrospinal fluid leaks, cochlear implant followed by a dose of PPSV 23 at least 8 weeks later. A second PPSV 23 dose 5 years after the first PPSV 23 dose is indicated for persons aged 19 through 64 years with immunocompromising conditions.

Vaccine impact

The impact of pneumococcal vaccine is measured by a reduction in mortality, invasive pneumococcal disease, pneumonia, AOM and the nasopharyngeal carriage.[15] Among the PCV evaluation end points, IPD is the gold standard since it involves assessment of serotype specific effectiveness, serotype replacement and herd immunity (reduction in unvaccinated groups). The direct effect of PCV is seen as reduction of carriage as well as disease caused by the vaccine serotypes of S. pneumoniae in the vaccinated. Since colonization precedes disease, PCV effect on carriage has a large impact on reducing pneumococcal disease at the population level. Moreover, it also reduces the chance of transmission, number of carriers and progression to disease in the unvaccinated or adults which is the indirect effect or herd effect.[16]

Surveillance of PCV impact in developing countries is challenged by outcome ascertainment, pre-existing rapid decline in mortality and pneumococcal disease in the context of non-vaccine interventions and the maintenance of completeness and quality of reporting over time. Thus, the vaccine effectiveness may not be same when compared between high income (developed) and developing countries.[17] Developing countries differ in distribution of prevalent pneumococcal serotypes and pneumococcal disease surveillance systems.

Table I. Different valent vaccines and serotypes

Name of the vaccine	Serotypes	Added /removed serotypes from existing ones
10 valent GSK	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F	Added 1,5 and 7F to PCV7
10 valent M/s Serum Institute of India Ltd., Pune	6A, 6B, 9V, 14, 19A, 19F, 23F, 1, 5, 7F	removed 4 & 18C from PCV 10; 6A and 19 A added
13 valent Pfizer, US	3, 4, 6A, 6B, 9V, 14, 18C, 19A, 19F, 23F, 1, 5, 7F	3, 6A and 19A are in addition compared to PCV10 GSK
15 valent Merck, US	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A, 19A,22F,33F	Added 22F and 33F to PCV13
20 valent Pfizer, US	4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 3, 6A,19A,22F,33F, 8,10A,11A,12F, 15B/C	Added 8, 10A, 11A, 12F, 15 B and 15 C, 22F and 33F to PCV 13

IPD surveillance is challenging due to requirement of sterile site specimens, lack of proper diagnostic methods in developing countries and culture negativity due to pre-administration of antibiotics. Moreover, IPD is only a small fraction of the pneumococcal disease. Also developing countries have high disease burden and mortality and the patients with underlying predisposing conditions may vary. This will influence the serotypes covered by the vaccine, serotypes replaced and the data available on the incidence of IPD or pneumonia. To identify pneumococcal pneumonia among all cause pneumonia is challenging. In this scenario, the best possible approach in assessment is nasopharyngeal surveillance.[18] Absence of vaccine serotypes in the nasopharynx of pneumonia cases reflects vaccine effectiveness.

Serotype replacement, where vaccine serotypes have been replaced by non-vaccine serotypes has been witnessed in vaccine implemented countries. This has led to the development of newer valent vaccines including the emerging new serotypes. The newer vaccines which are under phase 2 and phase 3 trials are PCV15 (Merck) and PCV20 (Pfizer). Recently, a newer PCV10 (Pneumosil) by Serum Institute of India, Pune was approved by WHO. The different valent vaccines and the respective serotypes are given in Table I.

Future perspectives

The protection provided by the polysaccharide vaccines (conjugate or purified polysaccharide vaccines) are serotype specific. However, currently there are nearly 100 serotypes and the idea of including all the serotypes is not feasible. Another disadvantage is the serotype replacement, which demands developing higher valent vaccines. Currently, the focus is on pneumococcal whole cell and protein-based vaccines which are in the different stages of development. These proteins are tried in various strategies such as stand-alone vaccine, as carrier in conjugate vaccines or in combination with PCV.[19] The various antigens that has been in trials are pneumococcal surface protein A (PspA), pneumolysins, neuraminidases and pneumococcal histidine triad protein D.[20] if successful these can be an economic alternative for countries with high pneumococcal disease burden for the effective control of pneumococcal disease.

Points to Remember

- ***WHO recommends conjugate (PCV10 or PCV13) for routine immunization as three doses (2p+1 or 3p+0) and polysaccharide (PPSV) vaccines for adult immunization.***
- ***PPSV vaccines generate a T- cell independent immune response without memory B- cells, whereas conjugated vaccines can induce a T-cell- dependent and B cell mediated response.***
- ***The pneumococcal vaccine impact is measured by decrease in endpoints such as mortality, invasive pneumococcal disease, pneumonia, AOM and the nasopharyngeal carriage.***
- ***Surveillance of PCV impact in developing countries using endpoints other than nasopharyngeal carriage is challenging, and the best possible approach in such case would be the nasopharyngeal surveillance.***
- ***Continuous pneumococcal surveillance is important in India, so as to monitor the serotype replacement.***

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CLIPPINGS

Role of artificial intelligence (AI) in predicting clinical outcomes in COVID-19 patients, from initial chest radiographs

This retrospective single-center study of adult patients presenting to the emergency department during Feb, Apr 2020, with SARS-CoV-2 infection confirmed on real-time (RT-PCR). Initial CXRs obtained on ED presentation were evaluated by a deep learning artificial intelligence (AI) system and compared with the Radiographic Assessment of Lung Edema (RALE) score, calculated by two experienced radiologists. Death and critical COVID-19 (admission to intensive care unit (ICU) or deaths occurring before ICU admission) were identified as clinical outcomes. Results Six hundred ninety-seven 697 patients were included.: mean age n age 62 years (IQR 52– 75). Multivariate analyses adjusting for demographics and comorbidities showed that an AI system-based score $\geq$ 30 on the initial CXR was an independent predictor both for mortality and critical COVID-19 (HR 3.40 (95% CI 2.35–4.94; $p < 0.001$)). Other independent predictors were RALE score, older age, male sex, coronary artery disease, COPD, and neurodegenerative disease.

Conclusion Our study has shown that initial CXR's severity assessed by a deep learning AI system may have prognostic value in COVID-19 patients, with a performance comparable to a radiologist-assessed score.

Mushtaq J, Pennella R, Lavalle S, Colarieti A, Steidler S, Martinenghi CMA et al Initial chest radiographs and artificial intelligence (AI) predict clinical outcomes in COVID-19 patients: analysis of 697 Italian patients. European Radiology (2021) 31:1770–1779 .

VACCINOLOGY II

VACCINATION IN SPECIAL SITUATIONS

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Abstract: *The concept of immunization is to enable development of immunity in healthy non-immune individuals. However, certain special situations such as immunosuppression, prematurity and exposure to infectious diseases, pose a greater risk to a child who may become unwell or present with serious post-vaccine events and require selective use of vaccines, adopting a different schedule or even vaccine deferral. Specific knowledge of these unique clinical scenarios improves the chances of better immune protection and decreases the incidence of vaccine related adverse events.*

Keywords: *Special situations, Immune-compromised, Transplant, Febrile seizures, Bleeding diathesis.*

A special situation with reference to immunization is a clinical scenario in which administration of a vaccine may either elicit a suboptimal / no immune response or lead to an increased risk of an adverse event following vaccination (AEFI) or both. Clinical conditions like congenital immune deficiencies or acquired immunosuppressive conditions, bleeding diathesis and systemic diseases requiring long-term immune modifying drugs like steroids and cancer chemotherapy necessitate judicious use of selected vaccines and/or vaccine deferral. Similarly, a moderate or severe illness, a previous anaphylactic reaction to a particular vaccine and/or a severe hypersensitivity reaction (e.g. anaphylaxis) to a vaccine constituent are established contraindications to vaccines.[1] Clinical conditions that are not contraindications to administer vaccine are listed in Box 1.

This article discusses vaccinations in special situations in pediatric population.

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Box 1. Clinical scenarios which are not considered special situations

- Convalescent phase of illness
- Current antimicrobial therapy
- Mild illnesses, febrile or afebrile
- Allergy to products not present in vaccine
- Family history of adverse effects to vaccines
- Malnutrition

Vaccination during an acute illness

Mild illness : Children with a mild acute illness, such as a low-grade fever, an upper respiratory infection (URI), otitis media or mild diarrhea, should be vaccinated as per routine. Published data has shown that young children with these illnesses respond to measles vaccine as well as those without these conditions.[2]

Low-grade fever is not a contraindication to vaccination. A temperature check is not necessary before vaccination if the child is well. The Advisory Committee on Immunization Practices (ACIP) has not defined a body temperature above which vaccines should not be administered. The decision to vaccinate should be based on the overall clinical scenario rather than a defined body temperature.

Moderate or severe acute illness : If a person has a moderate or severe acute illness, vaccination with both live and inactivated vaccines should be delayed until the patient has recovered. There is no evidence that a concurrent acute illness reduces vaccine efficacy or increases vaccine adverse events. However, the concern is that an adverse event (particularly fever) following vaccination could complicate the diagnosis and management of a moderate or severe illness.[3]

Vaccination and febrile seizures

According to published data by the Vaccine Safety Datalink (VSD)[4] and Duffy, et al[5] (American Academy of Pediatrics), the incidence of febrile convulsions was high when pneumococcal vaccine is given as a standalone

vaccine as compared to influenza or DTaP vaccines and when these vaccines are given together the incidence of febrile seizures is up to 30 per 100 000 children immunized. However, the authors concluded that the risk of infection from these vaccine preventable diseases is more than receiving the vaccine for the same.

Guillain-Barre syndrome and vaccination

Guillain-Barre syndrome (GBS) has followed vaccinations, especially influenza and meningococcal vaccines. Published data over 12 years showed that there was no increased risk of incidents of GBS following any vaccination and all vaccinations combined, whether using a 6 week or 10 week risk interval prior to GBS.[6]

The small risk of GBS associated with influenza vaccination, to the order of one to two excess cases of GBS per million people vaccinated, is substantially less than the overall health risk posed by naturally occurring influenza. In fact, one of the complications of natural influenza infection is an increased risk of GBS that is several times greater than the risk following influenza vaccination.[7]

Aspirin and influenza vaccine

- Published data recommends that all children and adolescents (aged 6 months through 18 years) who are on long term aspirin or salicylate containing medications (e.g. Kawasaki disease, anticoagulation prophylaxis) and who have an increased risk for Reye syndrome associated with influenza infection, should receive the Influenza vaccine.[8]

Rotavirus vaccine in children with intussusception

Intussusception is a rare potential adverse effect of oral rotavirus vaccination in some settings; however, the risk of intussusception after rotavirus vaccination is much lower than the risk of severe rotavirus gastroenteritis in children who do not receive rotavirus vaccine. Published data of phase IV marketing surveillance of a new rotavirus vaccine introduced in India (ROTAVAC™) indicated that it was not associated with intussusception in the study population.[9]

Established contraindications for rotavirus vaccines are allergy to any of the vaccine ingredients, severe allergic reaction (anaphylaxis) to a previous dose, severe combined immunodeficiency (SCID), certain other primary and secondary immune deficiencies, acute moderate or severe illness, certain pre-existing or acquired gastrointestinal conditions (e.g. congenital malabsorption syndromes, Hirschsprung disease, short-bowel syndrome, previous bowel surgery) and spina- bifida or bladder exstrophy.[10] **(**Latex rubber is contained in the RV1 oral applicator whereas the RV5 is latex-free. Therefore, some experts prefer that infants with spina bifida or bladder exstrophy, who are at high risk for acquiring latex allergy, receive RV5 instead of RV1. However, if RV1 is the only rotavirus vaccine available, it should be administered, because the benefit of vaccination is considered to be greater than the risk for sensitization.[11]

Vaccination in children with bleeding disorders

Children with bleeding disorders and those receiving anticoagulant therapy are at increased risk for bleeding following vaccines given via the intramuscular (IM) route. Published guidelines from the MASAC (Medical and Scientific Advisory Council) recommend the following procedures to be followed while immunizing children with bleeding disorders.[12]

- A 23-gauge or smaller needle should be used for the vaccination and firm pressure without rubbing should be applied at the site for at least 5-10 minutes.
- Vaccines that are recommended for IM injection could be administered subcutaneously - Pneumococcal, injectable polio vaccine, hepatitis-A and B.
- For pharmacological management of pain, paracetamol is a safe alternative, however it should be judiciously used in individuals at risk for liver disease and NSAIDS should be avoided because of the potential risk of bleeding.
- Children receiving recombinant factor (VIII or IX) for prophylaxis and treatment for hemophilia, vaccination could be given within one day afterwards to decrease the risk of developing a hematoma.
- The patient and/or caregiver should be counseled about the potential risk of hematoma development at the site of vaccination. Anticipatory guidance should be given regarding when to report to a hospital if any adverse reactions such as hematoma, fever, warmth and redness develop.

Vaccination in children with history of allergy

a) Children with history of serious hypersensitivity or anaphylaxis to any of vaccine components should not receive the initial vaccine that is contraindicated. The vaccine insert label should always be evaluated for vaccine constituents for antigen, stabilizers or buffers, preservatives, antibiotics and residue present in the final products.

b) Children with history of serious egg allergy like anaphylaxis should not receive influenza and yellow fever vaccines but can safely receive other vaccines including measles and MMR vaccines (Live measles and mumps virus are cultivated in chick embryo fibroblast cell culture).

c) Persons who have had reactions to egg other than urticaria (e.g., angioedema or swelling, respiratory distress, lightheadedness, or recurrent vomiting) or who required epinephrine or another emergency medical intervention may receive any licensed influenza vaccine in a medical setting where the vaccine administration is supervised by a health care provider who is able to recognize and manage severe allergic reactions. Ideally, all children should be monitored for at least 15 minutes after any vaccination for allergy and resuscitation equipment should be available.[13]

d) Majority of anaphylactic reactions to measles, mumps, and rubella (MMR) are due to the gelatin component. There is no relation to egg allergy since the vaccine contains a minuscule to almost negligible amount of, egg protein.[14] Table I depicts relationship between the egg-content of common vaccines and recommendations for children with history of egg allergy.[15]

e) Children with history of any hypersensitivity are at increased risk for allergic reactions with inactivated mouse brain Japanese encephalitis vaccines and hence, should be monitored carefully. A mild reaction is not a contraindication to vaccination.

Vaccination in children on steroid therapy

Children receiving oral corticosteroids in high doses (prednisolone 2 mg/kg/day or for those weighing more than 10 kg, 20 mg/day or its equivalent) for >2 weeks (nephrotic syndrome, connective tissue disorders, auto-immune conditions) should not receive live virus vaccines until the steroids have been discontinued for at least 30 days.

Inactivated vaccines are safe but may be suboptimal in their efficacy. Children on lesser dose of steroids or those on inhaled or topical therapy may be immunized as per schedule. A detailed guide to use of live vaccines with steroid therapy can be found in Table II.[16]

Similar guidelines are to be followed in children who are receiving immunosuppressive agents other than corticosteroids. These children should not receive live virus vaccines during therapy except in special circumstances. Table II highlights the salient features on the relationship between dose and duration of corticosteroids and administration of live vaccines.[16]

Vaccination in children who are receiving chemotherapy

Chemotherapy has a significant effect on the cell-mediated and humoral immunological systems, causing a secondary/acquired immunodeficiency state.

Table I. Guidance for individual vaccine use in children with a history of egg allergy

Vaccine	Grown in	Egg-protein content	Approach to egg-allergic patient
Measles and Mumps	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Purified chick embryo rabies	Chick embryo fibroblast cell cultures	Picograms to nanograms	Administer in usual manner
Influenza (killed and live attenuated nasal vaccine)	Chick extra-embryonic allantoic fluid	Less than 1 microgram	Administer in usual manner, as the ovalbumin content is very low. Children who have had more severe reaction than urticaria, but not anaphylaxis, may receive vaccine in a medical setting supervised by a health care provider who can recognize and manage severe allergic reactions.
Yellow fever	Chick embryos	Micrograms	Skin test with vaccine prior to vaccination

Table II. Steroid therapy and administration of live vaccines

Dose, route and duration of steroid	Guidance for live vaccine
Topical therapy, local injections, or aerosol use of corticosteroids.	No contraindication
Physiologic maintenance doses of corticosteroids.	No contraindication
Low or moderate doses of systemic corticosteroids given daily or on alternate days. Children receiving <2 mg/kg per day of prednisone or its equivalent, or <20 mg/day if they weigh more than 10 kg for <2 weeks	Can receive live-virus vaccines during corticosteroid treatment.
High doses of systemic corticosteroids given daily or on alternate days for fewer than 14 days. Children receiving ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh more than 10 kg	Can receive live-virus vaccines immediately after discontinuation of treatment. Some experts however would delay immunization with live-virus vaccines until 2 weeks after discontinuation.
High doses of systemic corticosteroids given daily for 14 days or more. Children receiving ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh more than 10 kg, for 14 days or more	Should not receive live-virus vaccines until 4 weeks after discontinuation.
Low or moderate doses of systemic corticosteroids or locally administered corticosteroids in children who have a disease (e.g., systemic lupus erythematosus) that, in itself, is considered to suppress the immune response or who are receiving immunosuppressant medication other than corticosteroids	Should not receive live- virus vaccines during therapy, except in special circumstances.

Vaccination in children with cancer needs special consideration as described below:[17]

- Overall, live-vaccines are contraindicated during chemotherapy and for 6 months after completion. Killed/subunit/recombinant vaccines are also best given after 6 months from end of treatment to achieve an optimal immune response.[18]
- Annual inactivated influenza vaccine is the only vaccine recommended for all children during chemotherapy[17,19] whereas hepatitis B vaccine is recommended only for previously unimmunized children with risk of transfusion associated transmission.[20,21]
- Post-treatment re-immunization or catch-up schedule largely depends on the pre-chemotherapy vaccination status.

Vaccination of siblings should continue as per schedule except for oral polio vaccine (OPV), which needs to be substituted by the injectable vaccine. OPV is contraindicated including pulse polio doses. If sibling receives OPV by mistake or because there is no other option, then he/she should stay away from index child for at least 2 weeks.[22,23] Varicella and inactivated influenza vaccines are recommended for all contacts including siblings and parents.

Vaccination of children with human immune deficiency virus (HIV) infection

Children with human immunodeficiency virus (HIV) infection are susceptible to a range of infections including a heightened severity by vaccine preventable pathogens. Overall, the efficacy and safety of vaccines depend on the degree of suppression of the cellular immunity.

Table III. IAP-ACVIP schedule for immunization of children with HIV infection

Vaccine	Asymptomatic	Symptomatic
BCG	Yes (at birth)	No
DTwP/DTaP/Td/ Tdap	Yes, as per routine schedule at 6, 10, 14 weeks, 18 months, and 5 years	Yes, as per routine schedule at 6, 10, 14 weeks, 18 months, and 5 years
Polio vaccines	IPV at 6, 10, 14 weeks, 12-18 months and 5 years If indicated IPV to household contacts If IPV is not affordable, OPV should be given	IPV at 6, 10, 14 weeks, 12-18 months and 5 years If indicated IPV to household contacts If IPV is not affordable, OPV should be given
MMR	Yes, at 9 months, 15 months and 5 years	Yes, if CD4+ count >15%
Hepatitis B	Yes, at 0, 1 and 6 months*	Yes, four doses (0,1,2 & 6months), double dose, check for seroconversion and give regular boosters
Hib	Yes, as per routine schedule at 6, 10, 14 weeks and 12-18 months	Yes, as per routine schedule at 6, 10, 14 weeks, and 12-18 months
Pneumococcal vaccines (PCV and PPSV23)	PCV: Yes, as per routine schedule at 6, 10, 14 weeks and 12-15 months (PPSV23: One dose 2 months after PCV, 2nd dose 5 years after first dose (not more than two doses)	PCV: Yes, as per routine schedule at 6, 10, 14 weeks and 12-15 months (PPSV23: One dose 2 months after PCV, 2nd dose 5 years after first dose (not more than two doses)
Inactivated Influenza vaccine	Yes, as per routine schedule beginning at 6 months, revaccination every year	Yes, as per routine schedule beginning at 6 months, revaccination every year
Rotavirus vaccines	Insufficient data to recommend, to be given as per ACIP/WHO recommendations in asymptomatic	Insufficient data to recommend, to be given as per ACIP/WHO recommendations. Unlikely to be symptomatic in the age group for RV vaccination. Consultation with an immunologist or infectious disease specialist is advised.
Hepatitis A	Yes	Yes, check for sero-conversion, boosters if needed
Varicella	Yes, two doses at 4-12 weeks interval. Use single antigen vaccine** (MMRV in HIV infected children have not been studied)	Yes, if CD4 count ≥15% in children <8 years of age and CD4 count >200/mm3 for > 8 years Two doses at 4-12 weeks apart
Vi-typhoid / Vi- conjugate vaccine	Yes, as per routine schedule	Yes, as per routine schedule
HPV vaccine	Yes (females only), as per routine schedule of 3 doses at 0, 1-2 and 6 months starting at 10 years of age	Yes (females only), as per routine schedule of 3 doses at 0, 1-2 and 6 months starting at 10 years of age

* Hepatitis B virus surface antigen (HBsAg) positive mothers, infants to be given hepatitis B immunoglobulin (HBIG) within 12 hours of birth as per birth weight if status unknown <2,000 g infant to be given both HBV vaccine and HBIG. If >2,000 g to check the status and give HBIG accordingly (not later than 1 week)

** As per ACIP/Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). If varicella vaccine was given before initiation of combination antiretroviral therapy (c-ART), repeat the doses of varicella vaccine after start of c-ART.

(ACIP: Advisory Committee on Immunization Practices; BCG: Bacille Calmette-Guérin; CD: cluster of differentiation; DTP: diphtheria, tetanus, and pertussis; Hib: Haemophilus influenzae type b; HIV: human immunodeficiency virus; HPV: human papillomavirus; IAP: Indian Academy of Pediatrics; IPV: inactivated poliovirus vaccine; MMR: measles, mumps, and rubella; OPV: oral polio vaccine; PCV: pneumococcal conjugate vaccine; PPSV: pneumococcal polysaccharide vaccine; TT: tetanus toxoid; RV- rota virus)

CD4 (cluster of differentiation 4) counts less than 200 cells/ mm^3 is known to elicit minimal or no host response.

Vaccination is usually safe and effective early in infancy before HIV infection causes severe immune suppression. The duration of protection may be suboptimal, as there is impairment of memory response with immune attrition. In older HIV-1 infected children and adults, the immune response to primary immunization may be less but protective immunity to vaccines received prior to the infection is usually maintained. However, immunity to measles, tetanus, and hepatitis B wanes faster than other antigens.[24] Current recommendations from World Health Organization (WHO), American Academy of Pediatrics (AAP), Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control and Prevention (CDC) are that all live vaccines are to be given in asymptomatic HIV-1 infected children except OPV.

In a symptomatic child, all the live vaccines are contraindicated; however some vaccines like measles/ MMR/Varicella may be considered on a case-to-case basis. Monitoring of seroconversion after administration of a killed vaccine is recommended. In a HIV infected child, there is a multifold enhanced risk of diseases like tuberculosis, hepatitis A and B, measles, influenza, varicella and pneumococcal, and meningococcal disease. Hence in such situations a judicious and intelligent decision by the physician is warranted.[25]

The immunization schedule for children with HIV is outlined in Table III.

Vaccination of children with hematopoietic stem-cell transplant (HCT)

Hematopoietic stem cell transplant (HCT) recipients should receive certain routinely recommended vaccines because of loss of memory cells due to marrow ablation and waning of antibody titers over a period of 1 to 4 years after HCT. (For details kindly refer IAP Guidelines page 415) after HCT against tetanus, poliovirus, measles, mumps, rubella, pneumococcus and haemophilus, irrespective of the source of the transplanted cells.[3]

- MMR and varicella-containing vaccines should be administered 24 months after transplantation if the HCT recipient is presumed to be immune-competent.
- 3 doses of tetanus, diphtheria and pertussis vaccines 6months after HCT; for> 7 years, Tdap followed by 2 doses of Td.
- 3 doses of IPV, Hib and Hep B 6-12 months after HCT.
- Revaccination with inactivated vaccines, including influenza vaccine, should start 6 months after HCT. However, influenza vaccine may be administered as early as 4 months after HCT, if needed.
- Three doses of PCV 13 should be administered 6 months after HCT, followed by a dose of PPSV 23.
- A dose of Meningococcal ACWY vaccine should also be administered 6 months after HCT.

Vaccination in children with apslenia/splenectomy

Children with asplenia or hyposplenia (either functional or anatomical) are at high risk of serious infections with encapsulated organisms. Vaccination with pneumococcal (both conjugate and polysaccharide), hib, meningococcal and typhoid vaccines are indicated in addition to all routine vaccines. In children who are scheduled for an elective splenectomy, immunization should be planned at least 2 weeks prior to splenectomy for achieving optimal protective titers. In those who have undergone emergency splenectomy, published data suggests that immunization 2 weeks after splenectomy is associated with a adequate antibody response to vaccines as opposed to vaccination immediately following surgery. All live vaccines may be safely given when indicated.[26, 27]

Vaccination in children with congenital immunodeficiencies

Live vaccines can cause severe or fatal reactions in immunosuppressed persons due to uncontrolled replication of the vaccine virus. Live vaccines should usually not be administered to children with congenital immunodeficiency. Generally, vaccination in an immunosuppressed child should be determined by the severity of that patient's immune suppression.

Inactivated viral or bacterial vaccines cannot replicate, so they are safe for use in immunosuppressed persons. Certain vaccines are recommended as immunosuppression is a risk factor for complications from certain vaccine-preventable diseases (i.e., influenza, invasive pneumococcal and meningococcal disease and invasive Hib disease). However, a functional immune system is required to develop an optimal immune response to a vaccine. Hence the immune response may be poor, depending on the degree of immunosuppression present.[3]

All healthy household contacts of children with underlying congenital immune deficiencies should be offered inactivated vaccines as per the routine schedule.

Published guidelines on live viral vaccines are as follows:

- All healthy contacts should receive varicella, MMR and rotavirus vaccines. MMR and varicella viruses are not significantly shed from the immunized individual after receiving these vaccines. However, after vaccination if the contact develops a rash, the immune-compromised child should be isolated and should be given zoster immune globulin. Strict hand hygiene practices after diaper change of an immunized infant minimizes rotavirus transmission.[28]
- The inactivated influenza vaccine is preferred over the live vaccine.
- Contacts should NOT be given oral polio vaccine, because of the possibility of fecal-oral transmission. Smallpox vaccine is also contraindicated.[29]
- Other live viral and bacterial vaccines, aside from those discussed above (i.e., oral polio, live influenza and smallpox), can be safely given to contacts because there is no evidence of increased risk of transmission of infection to immune-compromised contacts. A summary of acceptable and contraindicated vaccines are highlighted in Table IV.

Vaccination in children with chronic diseases

Children with end-organ damage and long-term neurologic, endocrine (diabetes), liver, renal, hematologic, cardiac, pulmonary and gastrointestinal disease are predisposed to invasive infections by vaccine preventable pathogens. This group of children should be vaccinated with pneumococcal, hepatitis A, varicella, influenza and rotavirus vaccines. The overall protective efficacy of vaccines is suboptimal when compared to healthy children

Table IV. Vaccine recommendation in primary immunodeficiency (PID) states

Category of PID	Example of PID	Not recommended	General recommendation
T cell	SCID WAS Hyper IgM syndrome	All live vaccines, both viral and bacterial Rotavirus in SCID (data available only for SCID among T cell defects)	IPV should be used
B cell	CVID XLA IgG subclass specific	No information on use of VZV vaccine Yellow fever, OPV	All childhood vaccines can be given (DTP, Hib, IPV, meningococcal, MMR) as per routine schedule. IVIG may interfere with immune response to measles vaccine and possibly VZV vaccine. IPV not OPV should be used Conjugated pneumococcal vaccine initially, followed by polysaccharide vaccine aged >2 years Administer inactivated influenza vaccine annually from 6 months of age. BCG when indicated
Complement	C2, C3,C4, C8, C9 deficiencies Properdin, factor B or factor D deficiencies		Many specialists recommend extra vaccinations against Hib, pneumococcus and meningococcus
Phagocytic function	CGD LAD	BCG Live Salmonella typhi vaccine	All other vaccines, including live vaccines can be given

BCG, bacillus Calmette-Guerin; CGD, X-linked chronic granulomatous disease; DTP, diphtheria, tetanus, pertussis; Hib, Haemophilus influenzae *type B; IgA, immunoglobulin A; IgM, immunoglobulin M; IPV, inactivated polio vaccine; LAD, leukocyte adhesion deficiency; MBL, mannose-binding lectin; MMR, measles, mumps, rubella; OPV, oral polio vaccine; SCID, severe combined immune-deficiency, WAS – Wiskott Aldrich syndrome, XLA - X linked agammaglobulinemia*

and hence booster doses may be needed (hepatitis B). Laboratory evidence of protective titers antibody response should be documented. In addition to hepatitis B, children with chronic liver diseases should be vaccinated with hepatitis A vaccine Booster doses of pertussis vaccine should be administered to children with a static neurological condition. Children with cardiac and pulmonary conditions should receive pneumococcal (PCV and PPSV-23) and annual influenza vaccines.[28]

Vaccination after receiving antibody-containing products

Live vaccines

Blood (e.g. whole blood, packed red blood cells and plasma) and other antibody-containing blood products [e.g. Ig, hyper-immunoglobulin, and intravenous immunoglobulin (IVIG)] interfere with the immune response to live vaccines such as measles and rubella vaccines for 3 months and may cause suboptimal response. Other live vaccines like rotavirus, yellow fever vaccines may be administered at any time before, concurrent with or after administration of any Ig, hyper-immunoglobulin, or IVIG.[28] If a dose of injectable live virus vaccine (other than yellow fever and zoster) is administered after an antibody-containing product but at an interval shorter than recommended, the vaccine dose should be repeated unless serologic testing is feasible and indicates a response to the vaccine.

Inactivated vaccines

Antibody-containing products cause less interference with inactivated vaccines, toxoids, recombinant subunit and polysaccharide vaccines as compared with live vaccines. Inactivated vaccines and toxoids given either simultaneously or at any interval before or after receipt of an antibody-containing product should not significantly impair the development of a protective antibody response. The vaccine or toxoid and antibody preparation should be given at different sites using the standard recommended dose. Increasing the vaccine dose volume or number of vaccinations is not indicated or recommended.[28]

Immunization in preterm/low birth weight infants

The BCG vaccine and Zero (birth) dose of OPV can be safely administered to low birth weight and preterm babies after stabilization and preferably at the time of discharge. All vaccines may be administered as per schedule according to the chronological age irrespective of birth weight or period of gestation.[30,31] The birth dose of hepatitis B vaccine needs a special mention here- published data shows that for neonates above 2000 grams it can be administered at any time after birth. However, in babies less than 2000 grams the protective titers generated by the birth dose of the vaccine is suboptimal.[30] Hence, the birth dose of hepatitis B vaccine in these babies should be delayed till the age of 1 month.

Routine immunization and COVID-19 disease

As of November 25th 2020, there were 59,481,313 confirmed cases and 1,404,542 deaths due to COVID-19 disease worldwide.[31] India ranks 2nd in the number of cases (92,66,705 as on Nov 25th 2020).[33] Vaccination across all age groups have been interrupted with an increased risk of emergence of vaccine preventable diseases (The Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics has addressed these issues. The salient points are outlined below.[34]

- Routine immunization to be continued as scheduled amidst the pandemic as it is an effective measure to prevent the emergence of VPDs.
- The risk of exposure is minimal if appropriate infection control policies are reinforced by the hospital/clinic (mask, hand sanitization and social distancing).
- There is no documented risk of vaccinating a healthy child who should be followed up for any adverse events following immunization (AEFI) as per routine.
- There is currently no need for a change in the immunization schedule and the ACVIP recommends that in private practice settings, the existing ACVIP guidelines are to be followed for routine immunization.
- Multiple vaccines in a single visit using the minimum permitted interval can be given to complete the schedule in the shortest possible time.
- At present, the ACVIP does not recommend use of either Bacillus Calmette Guerin (BCG) or the Measles Mumps Rubella vaccine for protection of individuals against COVID-19 infection.

Points to Remember

- ***Routine vaccination schedule can be followed in mild illnesses, febrile or afebrile.***
- ***Egg allergy is not a contraindication for receiving MMR, Rabies and Influenza Vaccines.***
- ***All live bacterial and viral vaccines are to be deferred in children with congenital immune deficiencies.***
- ***In the COVID-19 pandemic era, pediatricians should counsel parents regarding the importance of adhering to routine immunization schedule in order to prevent emergence of Vaccine preventable diseases.***

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CLIPPINGS

Multisystem inflammatory syndrome (MIS-C) in children: A systematic review.

Twenty-four studies were included, with a total of 270 participants. Fever and gastrointestinal symptoms were prominent. Shock, rash, conjunctivitis, lips or oral cavity changes and lymphadenopathy were observed, while respiratory symptoms relatively infrequent. Seventy-eight percent to 100% of patients had evidence of SARS-CoV-2 infection, and patients positive for SARS-CoV-2 by serology 86% were more than those by RT-PCR 36%. Most patients had increased inflammatory markers including C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), ferritin, interleukin-6 (IL-6), and D-dimer, accompanied by neutrophilia and lymphopenia. Impaired cardiac function was seen from elevated biomarkers and abnormal echocardiography. Intravenous immunoglobulin (IVIG), anticoagulants, inotropic agents and glucocorticoids were the main treatments, along with other intensive supportive care. Overall, the outcomes of MIS-C were favourable, and only one death was recorded.

Tang Y, Li W, Baskota, Zhou Q, Fu Z, Luo, et al. Multisystem inflammatory syndrome in children during the coronavirus disease 2019 (COVID-19) pandemic: a systematic review of published case studies. Transl Pediatr 2021; 10(1):121-135. PMID: 33633944.

Monitoring patients with juvenile idiopathic arthritis using health-related quality of life.

In this retrospective monocentric study, experts aspired to explore whether self-assessment with the EuroQol five-dimensional 'youth' questionnaire with five levels (EQ-5D-Y-5 L) inside a mobile E-health application could identify juvenile idiopathic arthritis (JIA) patients in need of possible treatment adjustments. Between October 2017 and January 2019, the EQ-5D-Y-5 L was completed through a mobile application (Reuma2Go). Sixty-eight JIA patients finished the EQ-5D-Y-5 L questionnaire. The results show that in the studied population, the EQ-5D-Y-5 L was able to identify JIA patients in need of possible treatment adjustments. Remote monitoring of the health-related quality of life and patient-reported outcomes via E-health applications could provide valuable additional information for determining the frequency of clinical visits, assessing therapeutic efficacy and guiding treat-to-target strategies in pediatric JIA patients.

Doeleman MJ, de Roock S, Buijsse N, Klein M, Bonsel GJ, Seyfert-Margolis V, et al. Monitoring patients with juvenile idiopathic arthritis using health-related quality of life. Pediatr Rheumatol 2021 Dec;19(1): 1-7. 19:40. https://doi.org/10.1186/s12969-021-00527-z.

VACCINOLOGY II

ADVERSE EVENTS FOLLOWING IMMUNIZATION - PREVENTION, MONITORING AND REPORTING IN INDIA

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Abstract: *The Adverse Event Following Immunization, although considered rare, is not uncommon. Establishing a system to manage it is an important element to ensure the quality of vaccines, safe immunization practices and retaining vaccine confidence in the public. India has established a robust national Adverse Event Following Immunization surveillance system spanning from the lowest level of immunization delivery to the national level with its guidelines updated most recently in 2015. The systematic Adverse Event Following Immunization reporting, investigation, causality assessment, monitoring and taking corrective actions are a crucial part of the system. The participation of private sector immunizations service providers is a key to its success.*

Keywords: *Adverse Event Following Immunization, Surveillance, Monitoring, Reporting.*

Vaccines are one of the greatest boons to mankind due to its pivotal role in preventing infectious diseases. The vaccines provided under the immunization program aim to protect individuals as well as the public from vaccine-preventable infectious diseases that are known to cause significant morbidity and mortality.[1] Modern vaccines are by and large considered to be safe. Nevertheless, Adverse Event Following Immunization (AEFI) does occur albeit it is infrequent and rare.[2] Even if the AEFI is sporadic, when occurs, it has a great potential to influence the immunization program primarily in an adverse way, making it the biggest apprehension among immunization program managers. It can cause anxiety among vaccine recipients and family and shape their views and attitudes towards vaccines and the immunization. This may foster vaccine hesitancy and vaccine refusals making people susceptible to the very disease the vaccine was supposed to prevent. A systematic review published in 2019 showed that adverse events are the biggest concern of parents for their children's vaccination in the United States.[3] A misrepresentation of autism and the measles, mumps and rubella (MMR) vaccine in 1998 in the United Kingdom[4,5] has contributed to the fall of vaccination coverage from 91% in 1998 to 80% by 2004 resulting in several measles outbreaks.[6] India is not an exception; adverse events have created a scare in parents for many vaccines. The recent successful MR vaccination campaign also witnessed a fear of autism and subacute sclerosing panencephalitis (SSPE) towards the vaccine and created social media sensation.[7] Such issues emphasize the importance of prevention, monitoring and timely reporting of AEFI for its effective tackling.

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What is AEFI?

AEFI is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of vaccines. That may include any unfavorable or unintended sign, symptom, disease or even an abnormal laboratory finding.[2,8] Such adverse events may be related to vaccines or the process of immunization or can be coincidental.

Classification of AEFI

The AEFIs are classified by three methods: i) underlying association, ii) the severity of the events and iii) the frequency of occurrence.

i) Based on the underlying association,the AEFI is categorized into five groups namely; vaccine product-related, vaccine quality defect-related, immunization error-related, immunization anxiety-related and coincidental events[2] (Table I).

Table I. Classification of AEFI based on underlying association

Type of AEFI	Cause	Example
Vaccine product - related	Caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product inspite of correct preparation, handling and administration of vaccine.	Extensive limb swelling following DTP vaccination
Vaccine quality defect - related reaction	Caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer.	Failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leads to cases of paralytic polio
Immunization error - related reaction	Caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.	Transmission of infection by contaminated multidose vial
Immunization anxiety - related reaction	Caused by anxiety about the immunization.	Vasovagal syncope in an adolescent during/ following vaccination
Coincidental	Caused by something other than the vaccine product, immunization error or immunization anxiety.	A fever occurs at the time of the vaccination (temporal association) but is in fact caused by any common infection like malaria.

Source: *World Health Organization-Council for International Organizations of Medical Sciences*[2]

ii) Based on the severity of the events, the AEFI is categorized as serious, severe and minor (Fig.1).[2] It is critical to distinguish the 'serious' and 'severe' as they are used interchangeably in common practice. The serious reaction is a regulatory term that results in hospitalization, long-term disability or deaths. A severe reaction is a non-regulatory term and describes intensity. It includes serious reactions that are not categorized as serious.

iii) Based on the frequency of occurrence, the AEFI is categorized into five groups: Very common, common, uncommon, rare and very rare (Table II).[8] Local reactions like fever, pain and redness in children are documented up to 50% (very common) with diphtheria and tetanus toxoids and whole-cell pertussis (DTwP) vaccine and are documented in only 1-6% (common) with the hepatitis B vaccine.

Reporting of AEFI

The government is the main immunization service provider in India, the AEFI reporting system is primarily geared to follow the immunization system.[8] Starting from the health workers at the lowest level (auxiliary nurse midwives-ANMs), the report flows upwards until the national level (Fig.2).[7] Serious AEFI is expected to be reported immediately within 24 hours as well as through a weekly block register-based reporting system and monthly Health Management Information System (HMIS).[8] Any event which raises parental/community concern, associated with the newly introduced vaccine and immunization error-related reactions also needs to be reported immediately. Severe AEFI is expected to be reported through the weekly reporting system and monthly HMIS. Weekly reporting of serious and severe AEFI even if it is zero is mandatory. The minor AEFI is reported through a monthly HMIS even if it is nil.The AEFI committees are set-up at the district, state and national levels to provide technical support to the respective

Table II. The classification of AEFI based on the frequency of occurrence[8]

Frequency group	Frequency %
Very common	≥10
Common	≥1 and ≤10
Uncommon	≥0.1 and ≤1
Rare	≥0.01 and ≤0.1
Very rare	≤0.01

AEFI= Adverse Events Following Immunization

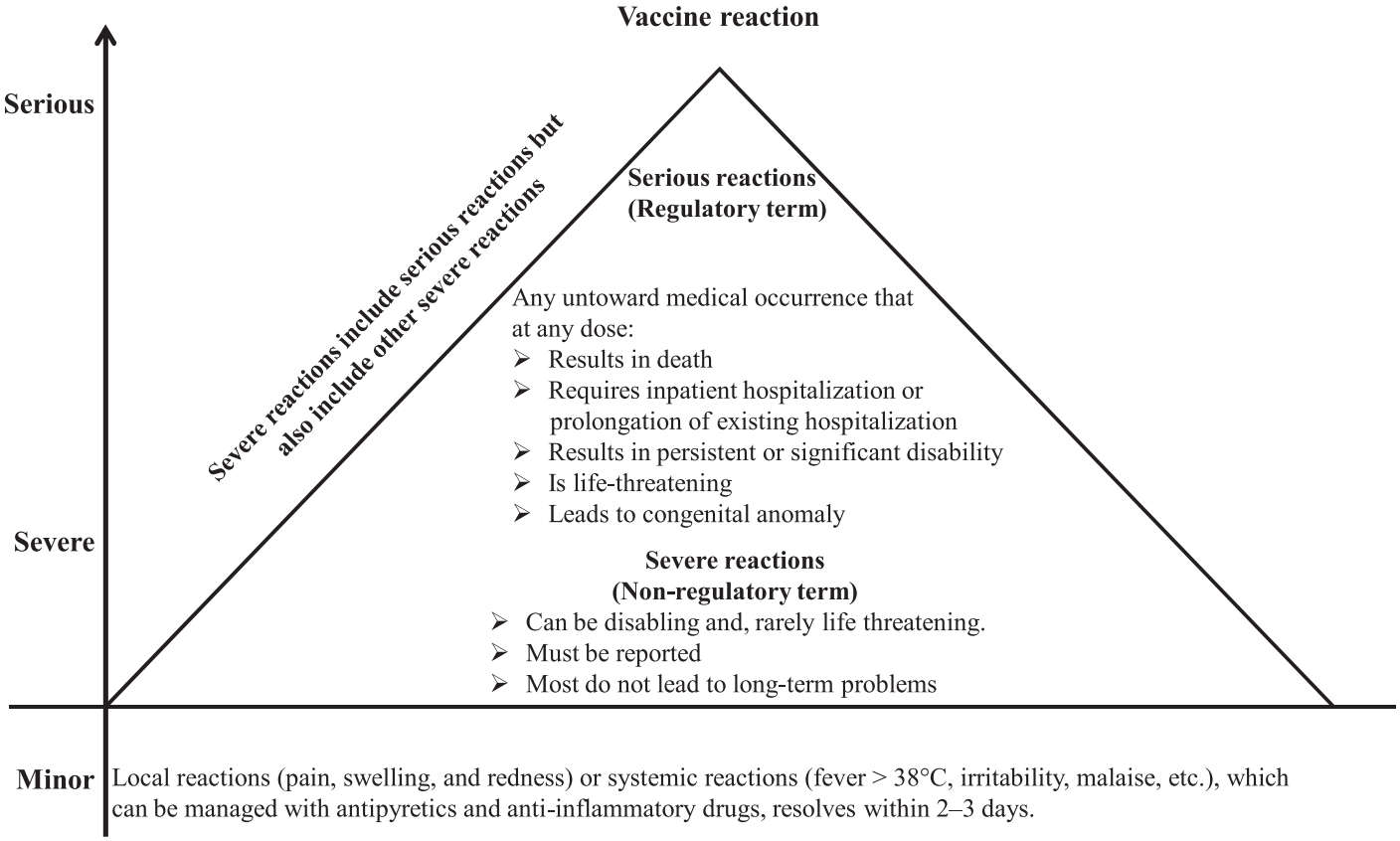

Fig.1.Classification of the AEFI based on its severity

government partners. The committee comprises a multidisciplinary team including pediatricians, epidemiologists, microbiologists, pathologists, pharmacologists, forensic medicine experts , representation from pharmacovigilance program and other immunization partners.[8]

Investigation of AEFI

Investigation of an AEFI to understand the causes and associations is an important step in public trust building and to address preventable causes. The investigation should be able to identify product-related reactions and immunization-related errors so that future AEFI can be prevented. It is critical to identify coincidental events which can be very often a reason for AEFI/ deaths as shown in the case study in Box 1. The case study also demonstrates that understanding background rates of events is important and essential for making informed decisions.

Once a serious AEFI is reported by a health worker, the Medical Officer In-charge confirms and submits the case report form (CRF) to District Immunization Officer (DIO) within 24 hours. The conduct of the investigation is decided by DIO within the next 24 hours and CRF is sent to State Immunization Office with a copy to Immunization Division at the national level (Fig.2). The investigation supported by the district AEFI committee will collect data about the patient, event, suspected vaccine, other persons with similar events if any, assess and observe immunization services and collect specimens from patient and vaccine if necessary. In case of death an autopsy, specimen collection and verbal autopsy to collect information related to death should be completed within 72 hours. It is also important to identify and investigate event clusters when more than two cases of the same adverse events develop in time, place or during the vaccine administration of the same vaccine. A preliminary investigation is to be completed and a preliminary case investigation form (CIF) is to be sent to state and national level simultaneously within 10 days of notification. At the end of the investigation, a conclusion is drawn and a final CIF has to be submitted within 70 days of AEFI notification (Fig.2).

Causality assessment of AEFI

The causality assessment is a systematic approach in collecting and interpreting data around a reported AEFI and drawing a conclusion on the likelihood of causal association between the event and the vaccine received. In defining the AEFI events, a standard case definition should be used such as the one from Brighton

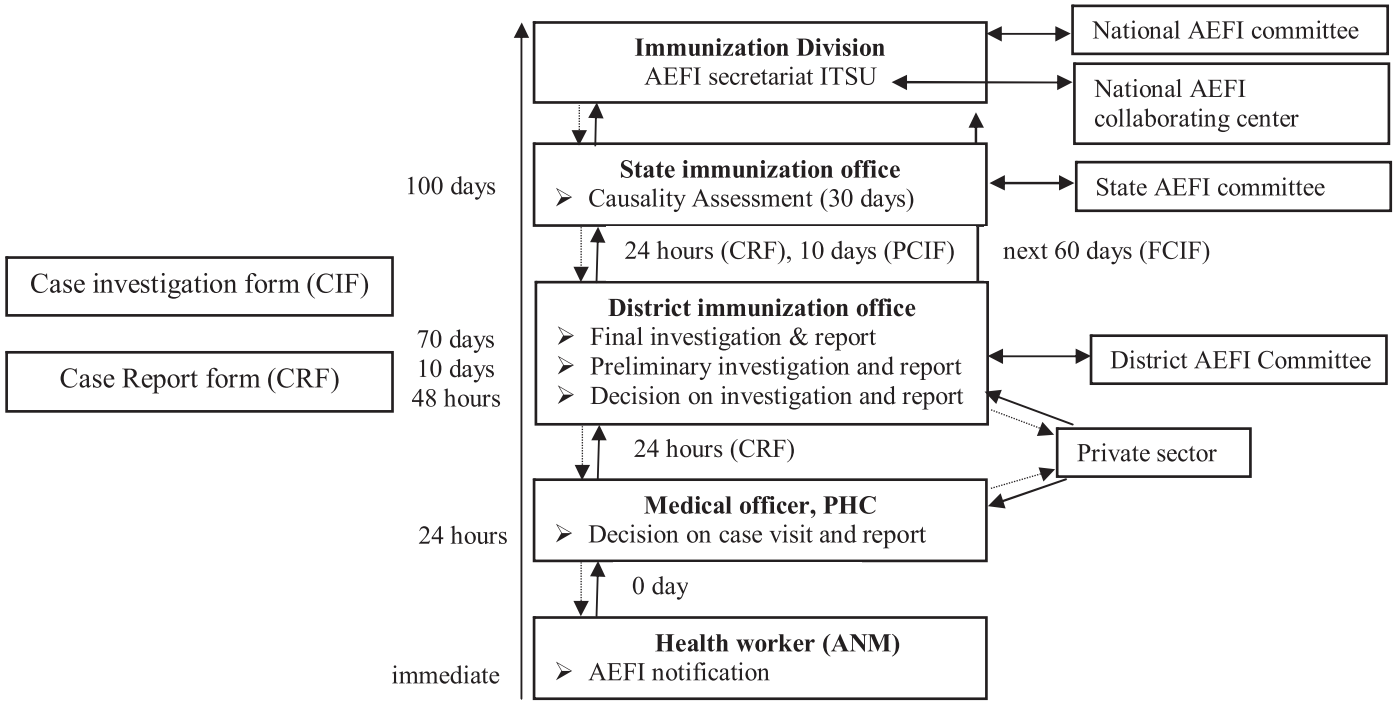

Fig.2. AEFI reporting system in India for serious events

AEFI= Adverse Events Following Immunization; ITSU=Immunization Technical Support Unit, ANM= Auxiliary Nurse Midwife, PHC=Primary Health Centre, CIF= Case Investigation Form, CRF= Case Report Form, PCIF= Preliminary Case Investigation Form, CIF= Final Case Investigation Form

Source: *Adapted from Joshi et al[7] and AEFI operational guidelines 2015[8]*

Box 1. A case study on coincidental AEFI demonstrated by investigation

Case study

Background deaths in the community may be attributed to vaccine AEFI[2]

Issue: In 2006, after the Japanese Encephalitis (JE) vaccination campaign in 4 Indian States, the media reported excessive deaths after JE vaccination which became a sensational issue.

Investigation: The 504 AEFI's following vaccination including 22 deaths were investigated by a special committee set-up that found no link between the vaccine and associated serious illnesses or death.

Fact: About 94 lakh children were vaccinated in a population with background mortality of 8.6 per 100,000. The 22 deaths reported among children constituted only 0.24 deaths per 100,000. The 22 deaths reported, therefore, do not reflect excess mortality caused by the JE vaccine.

Lessons: Know the background rates, conduct proper AEFI investigations, and institute a good AEFI surveillance system to identify and tackle the issues effectively.

Collaboration.[9] At the end of causality assessment, one would be able to say if the event is vaccine-related, immunization error-related, or coincidental and take appropriate corrective steps. However, for many individual events, a definite or absence of causal association may not be established.

The state immunization officer along with the state AEFI committee conducts causality association within one month of receiving the final case investigation form. Generally, the investigation is done on serious events, that are caused by immunization error, significant events of an unexplained cause, events that result in community outrage

and unusual cases. The following criteria are used in causality assessment: Temporal relationships, biological plausibility, strengths of association, consistency of association, specificity, definitive proof that the vaccine has caused the event, alternative explanations and proof of evidence that the vaccine in question could cause similar event.

The causality assessment has 4 steps. i) The first step is to assess if the AEFI case satisfies the minimum criteria based on a predefined checklist and determine its eligibility for causality assessment. ii) Then, all available information will be systematically reviewed for the eligible AEFI case based on a checklist to assess the causal aspects of AEFI. iii) In the third step, an algorithm will be used to get a direction on causality based on information gathered. iv) In the end, the AEFI association is categorized into one of the four groups: (a) consistent causal association with immunization, b) indeterminate, c) inconsistent causal association with immunization (co-incidental) and d) adequate information not available (unclassifiable). Based on the findings appropriate actions need to be taken as described later.

Monitoring of AEFI surveillance

The performance of the AEFI surveillance system needs to be monitored continuously to provide essential inputs to ensure that the system is robust. Monitoring will ensure identifying and preventing immunization error-related adverse reactions and help in extricating coincidental reaction from vaccine-product related one. Moreover, it can act as a guide to formulate an appropriate response during public outrage. The AEFI surveillance system should be sensitive enough to identify, investigate, and respond to AEFI in a timely and effective manner. To ensure these, several indicators are developed (Table III).[8] Continuous tracking of indicators and timely analysis of reports are an essential part of AEFI system monitoring.

Role of private sector in monitoring and reporting AEFI

It is typically believed that about 20%-30% of all immunization in India is delivered through the private sector that includes practicing pediatricians particularly in urban areas.[7] However, recent evidence on vaccines that are available only in the private sector (before they become available in the public sector) shows abysmally low and patchy coverage due to high cost and less affordability. A study conducted in 16 Indian states on Hemophilus influenzae type b (Hib) vaccine that was available only through the private sector showed low coverage in the 2009-2012 birth cohort.[10] Similarly, a model-based estimate of the pneumococcal conjugate vaccine (PCV) in India showed low coverage of 0.33% (statewide range: 0.07% to 2.38%) through the private sector for the year 2012.[11] Considering these points, the proportional coverage through the private sector may be low, correspondingly, the number of AEFI expected from the private sector might be quite low. But from the viewpoint of the absolute number of children vaccinated in the large urban centers with high media penetration and the influence that the private providers carry timely management, responsive crisis communication and counseling of the aggrieved parents by the private providers, even for a single AEFI, would go a long way to allay fears and mitigate vaccine hesitancy in the community.

Table III. AEFI monitoring indicators and target under the surveillance system[8]

Monitoring indicator	Target
1. Percentage of routine reports (zero reports) received on time	≥ 80%
2. Percentage of AEFI cases line-listed	≥ 90%
3. Percentage of serious AEFI cases	No target
4. Percentage of serious AEFI cases reported on time	≥ 80%
5. Percentage of serious AEFI cases with CRF shared with State and Center on time	≥ 80%
6. Percentage of serious AEFI cases investigated on time	≥ 80%
7. Percentage of serious AEFI cases with a completed investigation	≥ 80%
8. Percentage of serious AEFI cases classified for causality by State AEFI committee on time.	≥ 80%

Source: AEFI Surveillance and Response Operational Guidelines by Ministry of Health andFamily Welfare, Government of India 2015.[8]

The private sector immunization partners are encouraged to report AEFI to their respective counterparts in the government immunization system, to the nearest medical officer of the primary health center or directly to the district immunization officer immediately. The occurrence of AEFI is a random event, but their management is driven by easy access to care, which is often the private sector in urban areas. Besides the children vaccinated by the private providers, the suspected AEFI cases from the larger community of children who got the vaccine from the public sector also will seek care for treating AEFI at the private facilities. Therefore, the private sector providers have broader responsibility for reporting such suspected AEFI cases. To enable themselves to do so, the private sector needs to update themselves on the latest national guidelines, build bridges with the relevant government department and include vaccination details as a regular item in taking the history of each patient. From the surveillance perspective, focal persons in private health facilities are oriented by the state and district authorities to participate in the AEFI surveillance. Private immunization partners have only the onus of reporting, but the investigation is done by district health authorities.

There are good examples for the private sector involvement in active AEFI surveillance which should be the way forward. As a part of vaccine safety surveillance after the introduction of the rotavirus vaccine (RVV) in India, a prospective intussusception surveillance study was carried out involving tertiary care hospitals and medical colleges.[12] In this study, seven of 19 facilities (37%) were from the private sector. Similarly, there is a Multi-centre Active AEFI Sentinel Surveillance (MAASS) Network which heavily involves the private sector in monitoring the occurrence of predefined AEFI and evaluating its association with vaccines in hospitalized children under 2 years.[13] The private medical college hospitals with a large immunization footfall can produce useful insights on AEFI through post-vaccination follow-up, monitoring and AEFI causality assessment.[14]

Professional bodies such as the Indian Academy of Pediatrics (IAP), Indian Medical Association (IMA), Indian Public Health Association (IPHA), Medical Colleges and other partner agencies such as the National Polio Surveillance Project (NPSP) are also encouraged to get involved in AEFI surveillance. The IAP has developed a reporting system for Infectious Disease Surveillance and AEFI that aims to generate and act as an early warning system to track infectious disease and AEFI in India. This is an online system accessible through website http://www.idsurv.org/, provided with case definition and other details. The private immunization service providers can report directly on the website.[15] This website was established to produce a combined realtime database to keep its users informed about AEFI/infectious disease status in India.

Prevention of AEFI

The prevention of AEFI and its consequences has several layers starting from pharmacovigilance to risk-communication and media management. The Pharmacovigilance Program of India (PvPI) was set-up in 2015 under the Central Drug Standard Control Organization (CDSCO) to monitor and prevent adverse events related to vaccines and drugs. The CDSCO is responsible for assessing vaccine benefits versus risks and granting permission for vaccine import or licensure to use in the country and closely monitors AEFI causality reports for the needful preventive actions. Good manufacturing practices (GMPs) and systems to ensure adherence help in the prevention of vaccine quality-related reaction. Further, a good AEFI surveillance system that tracks, monitors, investigates and acts on AEFI from the lowest level of the health system to the national level is a key aspect of AEFI prevention. An accurate and timely report from the private sector through this AEFI surveillance system is also important. Furthermore, conducting the causality assessment and taking corrective actions is a key component of the AEFI prevention (Table IV). Moreover, periodic and updated training and continued education of health staff at all levels are crucial. Finally, effective communication around vaccine safety including management of media and public reaction through evidence-based, result-oriented strategic communication is necessary. The immunization system should establish regular and different ways of communication with media, have special media communication for events such as vaccination campaigns and AEFI response protocol for media at each level.

Adverse events of special interest: Covid-19 vaccines

With the prospect of one or multiple COVID-19 vaccines getting introduced, primarily to the adult population that are outside expanded program of immunization (EPI), it becomes imperative to build sensitive AEFI surveillance in the country.[16] In the current emergency, COVID-19 vaccines may need to be deployed after accelerated clinical trials with small sample size. Therefore, identification of events including the rare ones needs follow-up during vaccine development, approval and use. After COVID-19 vaccine deployment, health personnel

Table IV. Corrective actions for the prevention of future AEFI*

Type of AEFI	Corrective actions
Vaccine (product or quality) - related reaction	If a higher reaction rate than expected is observed from a specific vaccine or a lot, inform the immunization division who can update drug regulators to consider : • Withdrawing that lot. • Changing manufacturing specifications or quality control. • Obtaining a vaccine from a different manufacturer. Strengthen the following points at immunization settings • Advising 30 minutes observation is important following any vaccination. • Technical competency in managing anaphylaxis among immunization providers. • Availability of emergency drugs like adrenaline at immunization facility. • Checking contraindications for vaccine product allergy. • Advising on managing common minor reactions like fever and pain,written instructions with a contact number to seek early medical care for any serious symptoms.
Immunization error-related	Correcting the cause of the error; this may mean one or more of the following : • Change in logistics for supplying vaccine. • Change in procedures at the health facility. • Training of health workers. • Intensified supervision. • Confirm correct diluent, expiry date and sterile administrative technique before vaccination. • Ensure that reconstituted vaccine should not be used beyond the recommended time (e.g.BCG & MR/MMR within 4 hrs). • The date and time of opening vaccine vial should be written on the label. • Make certain that no drugs/substances other than vaccines should be stored in the refrigerator at the immunization facility. • Simple measures like checking Vaccine Vial Monitor (VVM), shaking the vial before use and following the recommended route of administration may avert many adverse reactions. Whatever action is taken, it is important to review it at a later date to check that the immunization-related errors have been corrected.
Immunization anxiety-related	Strengthen the following strategies at immunization settings to minimize these reactions : • Ensure comfortable room with adequate privacy, less waiting time, vaccine preparation out of the line of vision of the recipient and effective communication on vaccination procedure.
Coincidental	Main objective is to present evidence to prove that AEFI is not a vaccine-related reaction or an immunization-related error and that the most likely explanation is a coincidental event. This communication can be challenging when there is a widespread belief that the event was caused by immunization. Information on the background rate of reported coincidental events and finding similar events among unvaccinated groups of the comparable population helps in differentiating coincidental from other types of reactions. Sometimes, it may be useful to enlist further expert investigation to convince/ensure that the event truly was coincidental. The potential for coincidental events to harm the immunization program through false attribution is immense.

** Source: Modified from AEFI Surveillance and Response Operational Guidelines by Ministry of Health and Family Welfare, Government of India 2015.[8]*

should be vigilant about such events. Considering this challenge, a standard definition for Adverse Event of Special Interest (AESI) which is specific to the COVID-19 trial vaccines is developed for ongoing monitoring and rapid communication.[17] There needs to be sensitization and involvement of all the health care personnel in this context. The responsibility of detecting, reporting and managing AEFI go beyond the domain of pediatrics and demand the wholehearted active engagement of the entire medical fraternity, in both the public and private sectors and adult physicians and care givers.

Conclusion

"The introduction of new vaccines, organized mass vaccination campaigns and increased routine coverage can lead to an increase in AEFI". Any event of adverse reaction socialized in electronic media has the potential to backfire a long-built immunization program in India. A responsible and reactive AEFI surveillance system should be an integral part of the national immunization program. The systematic AEFI reporting, investigation, causality assessment, monitoring and taking corrective actions play a vital role in ensuring the quality of vaccines, safe immunization practices and retaining vaccine confidence in the public. Sensitization, training and greater participation of private-sector immunization partners in identifying and reporting AEFI is the way forward.

Points to Remember

- ***Understanding the background rates of adverse events in the population is important for informed decisions.***
- ***Management of AEFI is an important activity to retain and gain public trust in vaccines.***
- ***Serious and severe adverse events although used interchangeably, are not the same.***
- ***AEFI surveillance, monitoring and causality assessment are cornerstones for preventive actions.***
- ***Private sector immunization partners have a crucial role in AEFI surveillance and AEFI prevention.***

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CLIPPINGS

SARS-CoV2 Antibodies in Neonatal cord blood after vaccination during pregnancy

Studies evaluating the safety and efficacy of currently available vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) do not include pregnant participants.

A 34-year-old multigravid patient working in health care received the Pfizer-BioNTech (BNT162b2) mRNA vaccine for SARS-CoV-2 in the third trimester of pregnancy. Uncomplicated spontaneous vaginal delivery of a female neonate with Apgar scores of 9 and 9 occurred at term. The patient's blood as well as neonatal cord blood were evaluated for SARS-CoV-2–specific antibodies. Both the patient and the neonate were positive for antibodies at a titer of 1:25,600. In this case, passage of transplacental antibodies for SARS-CoV-2 was shown after vaccination in the third trimester of pregnancy.

RT-PCR for SARS-CoV-2 done pre pregnancy and seven times at various points during pregnancy were negative. A prior antibody test was performed as part of a system-wide effort to determine the incidence of infections among health care professionals were negative. She had no contact with SARS CoV2.

Initial studies of the two currently available mRNA vaccines have shown them to be safe and effective in non pregnant adults.The American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine released a joint statement in January 2021 advocating that pregnant individuals at high risk for contracting the virus should be able to decide whether they will receive the vaccination during pregnancy or while breastfeeding.

Maternal antibodies generated during pregnancy are able to cross the placenta into the fetal circulation, providing immune protection for the neonate. This has been demonstrated previously in pregnant patients receiving several other vaccines in pregnancy. This case report supports the conclusion that this may also be true for the SARS-CoV-2 vaccine. Although it is possible that neonatal antibodies were from undetected maternal infection with SARS-CoV-2, this is unlikely given the frequency and high sensitivity of polymerase chain reaction testing in this case.

This is the first case report that vaccination in pregnancy produced a robust immune response for the patient, documenting transplacental transfer of neutralizing SARS-CoV-2 antibodies in the setting of maternal mRNA vaccine administration. No apparent complications were noted in the patient or the neonate.

Gill L, Jones CW. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Antibodies in Neonatal Cord Blood After Vaccination in Pregnancy. Obstet Gynecol 2021 Mar 8. Issue - 10.1097/AOG.0000000000004367. doi: 10.1097/AOG.0000000000004367.

VACCINOLOGY II

LEGAL AND ETHICAL ISSUES IN IMMUNIZATION

***Satish Tiwari**

Abstract: *Epidemiology, economics and ethics demand that the health professionals and the policy makers should alleviate the misery caused by various infectious diseases and related complications. Adequate immunization is an important and time-tested health intervention in preventing infectious diseases. The need is to prepare a standardized national recommendations or guidelines regarding vaccination. Many pediatricians are facing ethical dilemma regarding the need of costly vaccines for the general population at the cost of basic necessities of life like nutrition, safe drinking water, pollution free environment, etc. Medical graduates should keep themselves updated with the recent advances in the field of immunization. There is a need for strengthening the surveillance of adverse events following immunizations in the country. All the necessary safe guards should be in place and the regulations should be followed in letter and spirit in vaccine trial in vulnerable child population. Right things should be done so that the future generation can live a healthy life.*

Keywords: *Informed Consent, Vicarious liability, Medical Negligence, Child Rights, Conflict of interest, Crosspathy.*

Our universe is full of unique things including living entities ranging from microorganisms to the mammals like human beings. According to theories of evolution the principle of "survival of the fittest" is applicable to most of the living organisms and hence many natural defense mechanisms are available to protect our body. As far as microorganisms are concerned there can be commensals (body friendly microorganisms) or pathogenic (disease causing organisms). The protection of our body depends upon balance between body immune system, dose and virulence of microorganism. The body immunity varies with genetic make-up, immune stimulators and boosters. The vaccines are considered as "Magic bullets" in modern medicine.[1]

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Role of vaccination

Vaccination is one of the ways of boosting the body's immunity. In the present COVID-19 pandemic where we don't have any specific treatment against the virus, the world was eagerly looking for an effective vaccine as an ultimate protective weapon to tackle the menace of this deadly virus. Vaccines are one of the simple, safe, effective and low-cost measures to fight against the various, common infections that are threatening the human life. It helps by improving humoral, cell mediated and other modes of immune mechanism.

Vaccination vs Immunization

These two words are many times used interchangeably. But we know that administering a vaccine is the vaccination and the child can be said to be immunized once the vaccine is taken up and the antibodies are developed. This understanding is very important for legal aspects since failure to take-up the vaccine and development of disease after the recommended doses of vaccines can be a cause of litigation. Hence, chances of failure, possible adverse effects, costs of vaccine, etc should be explained before giving any vaccine and an informed consent shall be obtained (Appendix A). One should remember the axiom "No vaccine is 100% effective and 100% safe." If parents are not willing for some vaccines, a "negative consent" shall be recorded.

The child right issues

Health is one of the basic and fundamental rights as per our constitution. It is also accepted as one of the important child right issues as the children are the future of human race. A healthy child is pre-requisite for a strong and healthy future generation. So, is it child abuse or neglect if a family or parents fail to immunize their children? Should this lead to punishment to the parents or relatives? Will this be violation of human rights under article 21 of the constitution?[2] Considerable inequities have been found in childhood vaccination based on child's gender, birth order, education of parents, religion, caste, area of residence, access to health care, etc.[3]

Vaccination of the children is important as far as the health programs and policies are concerned. In order to prevent serious childhood infections, the government has to decide a policy and schedule of vaccination as per the needs of community and available resources. The need of the vaccines and revision in the schedule is an ever changing concept according to the prevalence of infections.

Ethical Issues in Immunization

The developing countries are reeling under the morbidity and mortality because of various communicable diseases. Vaccination introduced as evidence based program to check the spread of infections. But it may end in commercialization with full of ethical and legal queries. The immunization schedule is full of ethical dilemmas. Do our children need all these vaccines? How many of us can afford the costly vaccines? What is more important nutrition, immunization, education or other basic necessities of life? There is a need for genuine and scientific discussions on this issue.[4]

Various vaccination schedules

The vaccination schedules are decided depending upon the epidemiological factors related to prevalence of disease, available resources, affordability by people and government, evidence based recommendations, chances of adverse reactions, etc. There are different schedules depending upon the priorities by the policy makers and the academicians.

In India, the two distinct schedules are:

i) National Immunization schedule or Universal Immunization Program (UIP) which is followed in Government set-up).

ii) Schedule by Indian Academy of Pediatrics (The Academic organization of Pediatricians)

The various schedules may have their own advantages or disadvantages and we may have to take decisions based on the need, affordability and availability of vaccines in consultation with parents. The controversies and paradoxes should be taken care by considering the standard, acceptable protocols as per the recommendations and evidence based guidelines.

These two schedules (UIP and IAP) are almost accepted by the practicing pediatricians and there are no major controversies including the scheduled primary vaccines at 6, 10 and 14 weeks considering this as the most practical schedule in order to decrease the number of visits and to suit the epidemiology of the diseases in our country. But, the ideal gap between two doses of Penta/ Hexa vaccines is 6-8 weeks for best results or efficacy.[5] But, IAP is recommending the UIP schedule as pragmatic for the above said reasons. A change in disease epidemiology based on continuous surveillance may help the experts to suggest modification of the immunization schedule.

Availability of vaccines

Proper immunization is the birth right of each and every child but, many vaccines may not be available or freely available in our country all the time. Injectable polio and oral typhoid are some of them. The injectable polio is available in combination as hexavalent (costly) combination vaccine but standalone injectable polio has not been available for many years for various reasons. There are also many other low cost vaccines which are in short supply while the costly vaccines are freely available in market. The point of discussion is: Is it possible or advisable to nationalize vaccine manufacture?

The non-inclusion of mumps containing MMR vaccine in government schedule is considered unjustified by pro-vaccine group. Mumps is known to cause fatal or serious illnesses like pancreatitis, orchitis, meningo-encephalitis, etc. Similarly, it is very difficult to understand the non-inclusion of typhoid vaccine in the UIP. Typhoid is associated with prolonged morbidity, mortality and loss of school hours in children or work hours in adults besides increasing drug resistance.

Efficacy and protection

The efficacy and protective effects of many vaccines are doubtful and controversial. The glaring example is of acellular versus whole cell pertussis. The role of vaccine industry and their exaggerated claims are always doubtful. The outbreak of pertussis in some of the western countries resulted in self-introspection, self-discipline and soul searching as far as efficacy of acellular vaccine is concerned.[6] This vaccine was projected as superior, painless remedy for the child.

The practicing pediatrician has to advise the parents on the choice of a particular brand of vaccine when more than one is available in the market. The scientific facts regarding the relative merits of a vaccine are not easily discernible. The role of vaccine industry and their exaggerated claims are also doubtful. Hence, the guidelines advised by experts of professional organizations like Advisory Committee on Vaccines and Immunization Practices (ACVIP) of Indian Academy of Pediatrics (IAP) are relied upon by many practitioners to counsel parents

regarding vaccines. These professional bodies analyze the available relevant literature to base their recommendations for the practicing pediatricians and periodically update these recommendations. Adhering to these recommendations also helps the practitioner from vexatious litigations.

There are discussions about the gestational age (should we give vaccine to a 28-30 weeks gestational age baby) and the minimum weight (can we give vaccine to 1000 gram baby) of the newborn for giving BCG and the hepatitis B before discharge from hospital. Similarly timing of vaccination is debatable in patients who are immune-compromised due to disease/ drugs or during an outbreak of pandemic. During the COVID-19 pandemic in the beginning of 2020, it was decided that the vaccinations should be temporarily stopped as continuation would result in over-crowding of babies and parents. This might result in spread of pandemic as physical distancing cannot be maintained. But, subsequently after about a month WHO, IAP and other organizations came with the guidelines that routine immunizations cannot be stopped as it may result in increased number of cases of vaccine preventable diseases.

Vaccines being biologic products can cause side effects and the vast majorities are minor. Any practitioner administering vaccines should be equipped to institute emergency measures like administration of adrenaline for an extremely rare event of anaphylaxis or bag mask ventilation before shifting to a referral centre. If there are any complications or adverse effects following immunizations (AEFI) the same shall be informed to competent concerned authorities. After instituting the emergency treatment, the child must be referred to a higher center at the earliest. The important issue which needs discussion- How much the practitioner needs to inform the parents regarding the potential side effects-the common minor ones or the extremely rare serious adverse events.

Conflict of interest

This issue has generated lots of discussions amongst academicians, government, non-governmental organizations (NGOs), pro and anti-vaccine groups. Many feel that the various multinational companies are producing the vaccines for the market in developing countries where it is easy to sell any vaccine without significant legal restrictions or problems. Murmurs of dissent are heard whenever a costly vaccine is recommended and creates flutter amongst the hyper-excitable academic experts.[7] Perhaps, all the facts are not presented and controversy, contradiction and confusion prevail resulting in allegations and counter-allegations. The latest COVID vaccines are no exceptions to these issues. Lots of discussions are going on regarding the available brands, their efficacy, availability in open market, interval between two doses and overall duration of protection. Academic organizations should draft an evidence based consensus recommendations and guidelines.[8]

Negligence

Negligence occurs if there is some **d**amage to the patient **d**irectly due to some **d**eficiency in the **d**uty (4 "D") by the treating physician or doctor.[9] The damage can be physical or financial. Hence, we have to be careful and take adequate precautions and follow a standard protocol. Any history of allergies to the components of vaccine should be recorded in writing. In this case, Tapankumar Nayak v. State of Orissa II (1997) CPJ 14 NC, injection of triple vaccine resulted in severe reaction including brain damage. Similar complications were not noted in other children. The National commission confirmed the order by Orissa State Commission and commented that there was no scope for awarding relief under the Consumer Protection Act. It strongly recommended State Government to render all possible assistance and proper rehabilitation of the affected child.

Inadvertent administration of expiry dated vaccine

Administrating expiry dated vaccine may not be negligence unless there is obvious damage. One of the simplest ways to avoid this error is "First in-First out" principle of using any medication or injections. Another simple precaution is checking the date at the time of reconstitution or filling the syringe. In-spite of all these steps if the error occurs inadvertently, accept the error, explain to parents that the chances of any untoward effects are rare and will be taken care if required. The dose can be repeated after recommended interval free of cost.

Research in immunization

Science and research are dynamic processes. Research in vaccination is continuously changing as newer microorganisms are detected. Hence, there is always a need for well-designed, ethical research regarding newer vaccines. An extensive research is required before recommending any vaccines for community. If the vaccine is costly, less effective or has major side effects, the entire planning of the policy makers will get defeated. The recent knowledge that the resurgence in whooping cough in many western countries may be because of acellular vaccine with lesser duration of protection has helped in WHO to advise

countries using whole cell vaccine to continue with the same. The studies showed that protection from disease after a fifth dose of DTaP among children who had received only DTaP vaccines was relatively short-lived and waned substantially each year.[10]

Newer vaccines

Science of immunization is dynamic and ever evolving phenomenon. The newer vaccines are the obvious outcome in the recent scientific developments. Newer vaccines are coming up depending upon epidemiological drift/shift in the disease causing organisms. After knowing the pros and cons of the available vaccines, the concerned person or relatives shall make informed choice.[11] Hence, an informed consent is preferable over implied consent. The newer vaccines or strains must be properly evaluated for their advantages / side effects before using in the community.[12] In the third millennium, though there are many technical advances; still, as far as the availability of many vaccines is concerned it is a tale of "so near and yet so far". Fortunately, in the present COVID-19 pandemic vaccine development was fast tracked and even developing nation like ours has started a massive vaccination exercise, mainly targeting the adults in a sequential manner.

Vaccination certificate

The certificate of vaccination may be required especially at the time of school admission or international travel. This is important to prevent international spread of infectious diseases. Issuing of false certificates may result in legal problems in future. So, the certificates should be issued based on previous records. If the records are not available better option will be to vaccinate the child as per the age and then issue the certificate. The parents should be impressed upfront on the safe-keep of the immunization cards of their children the same way they protect a ration card.

Vaccination camps

The practice of medicine is supposed to be a noble profession. Many people in community consider it as social service and immunization camps as social service activity. Organization of diagnostic camps and distribution of medicines can be done as a routine social service activity. But, vaccinations camps will require extra efforts for transport, cold chain maintenance in order to preserve efficacy of vaccine. Hence, camps should be organized as per the recommendations and guidelines issued by local authorities. If the vaccines are injectable, care should be taken that the same is administered by a person competent, skilled and experienced to give the injections. A qualified medical graduate or post graduate shall supervise the entire camp in order to avoid the allegations of vicarious liability. The doses shall be given at the minimum or subsidized rates and arrangements for subsequent doses shall be made where multiple doses are required. Adequate arrangements should be made to monitor any immediate adverse reaction following immunization and to institute emergency measures.

The issue of crosspathy

Many ayurveda or homoeopathy graduates are practicing vaccination in their set-up. It is often observed that many vaccination camps are held by these graduates. The Honorable Supreme Court has ruled in, Poonam Varma vs Ashwin Patel (AIR 1996 SC 2111) that "The right to practice, medicine, is dependent upon registration permissible only if there is qualification, and that too, a recognized qualification, possessed in that system of medicine. If a physician doesn't have knowledge of a particular system but practices that system is a quack. He is a mere pretender to knowledge or skill, or to put it differently, a charlatan." Hence the vaccines being part of allopathy, its administration in clinics or camps becomes part of crosspathy if done by those not trained in allopathy.

Conclusions

Vaccination is the simplest way to protect vaccine preventable diseases. It helps in decreasing the mortality, morbidity associated with such illness and helps in improving the survival, life expectancy and quality of life. Many parents now question the authenticity and side effects associated with modern drugs and vaccines, such as pain and swelling with DPT and intussusception with rota vaccine. There can be sharp division of opinion amongst the different stake-holders. Hence, standardized guidelines; schedule or recommendations are the need of the hour. Quality control and cold chain maintenance are pre-requisites for effective immunization.

Points to Remember

- ***There is a need to have quality control in the manufacture, transport and storage of vaccines.***
- ***Issue of clear guidelines is an increasing responsibility on the government and the academic organizations in this era of biased and confusing promotions.***
- ***Millions of children suffer from morbidity and mortality for either want of vaccine or optimal, ethical and rational use of vaccines.***
- ***We should understand the various legal issues related to vaccinations, otherwise there may be allegations of negligence in future.***

- ***The profession and commerce need to be separated and conflict of interest of various stake-holders shall be kept in mind.***

Appendix A

Consent for Vaccination

(These forms are to be printed/filled in local/ vernacular language)

I/We have been informed about various vaccines available for my/our child. I / We have also been explained about advantages, side effects or complications of these vaccines. I/ We have been explained that there can be risk to the life of otherwise healthy child during or after vaccination.

Many new vaccines are available recently. It has also been explained that some of the vaccines are costly and optional. We are willing to immunize our child as per our economic condition, affordability, need and our knowledge of various vaccines.

I/We have been informed that most of the vaccines may not give 100% protection and there may be possibility of disease even after vaccination.

I/We have been explained all these in the language known to me/us and I/we are signing this form without any pressure/coercion and after getting satisfied with the clarifications to my queries/doubts.

Name of the patient age/sex

Name of the relatives Witnesses

Relationship

Signature 1)

Date & time 2)

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VACCINOLOGY II

FREQUENTLY ASKED QUESTIONS IN VACCINOLOGY

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**Annamalai Vijayaraghavan
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1. What are 'excipients' in vaccines and what purpose do they serve?

Excipients are ingredients added to vaccines apart from weakened or killed disease antigens (viruses or bacteria), for a specific purpose (Table I)**.** These include preservatives, adjuvants, and stabilizers. Others like residual cell culture materials, inactivating ingredients and antibiotics are used during the manufacturing process and removed but present in trace amounts.

Thimerosal was used only in small amounts and from 2011 has been removed from all childhood vaccines with the exception of inactivated flu vaccine in multi-dose vials.

Adjuvanted vaccines can cause more local reactions (such as redness, swelling, and pain at the injection site) and more systemic reactions (such as fever, chills and body aches) than non-adjuvanted vaccines. Aluminium salts have been used safely in vaccines for more than 70 years.

People with severe egg allergies receiving vaccines containing small amounts of egg protein (Influenza, Yellow fever and Q fever vaccine), should be vaccinated in a medical setting and be supervised by a trained health care professional. Formaldehyde is present in very small amounts in vaccines and does not pose a safety concern.

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2. What is the cause of severe allergy following vaccination? What is a serious adverse event following immunization (AEFI)?

Four types of hypersensitivity reactions may occur related to vaccine constituents: 1) allergy to egg-related antigens 2) mercury or thimerosal sensitivity 3) antimicrobial-induced allergy (eg, streptomycin, neomycin, polymyxin B) and 4) hypersensitivity to other vaccine components, including stabilizers (e.g. gelatin), yeast protein and the infectious agent.

An adverse event following immunization (AEFI) will be considered serious, if it: i) results in death ii) is life-threatening iii) requires in-patient hospitalization or prolongation of existing hospitalization iv) results in persistent or significant disability/incapacity v) requires intervention to prevent permanent impairment or damage. It is important to note that 'serious' and 'severe' are often used as interchangeable terms, but they are not.

Anaphylactic reaction mediated by IgE, occurring within minutes or hours of receiving the vaccine can be a serious AEFI. Anaphylaxis involves two or more organ systems (dermatologic, cardiovascular, respiratory and/or gastrointestinal) simultaneously. Symptoms and signs include generalized urticaria, edema of the mouth and throat, difficulty in breathing, wheezing, hypotension, or shock. Such reactions are rare following vaccination and can often be prevented by appropriate screening questions and mitigated by emergency preparedness.

3. How common is egg allergy in children and what is the relation between egg allergies and vaccination?

Egg allergy affects about 1.3 % of all children. The most common animal protein allergen in vaccines is egg protein. Influenza, Yellow fever and Q fever vaccines have small amounts of egg protein.

Influenza vaccines are prepared using embryonated chicken eggs and contain a small amount of ovalbumin. According to current available evidence, patients with egg allergy (including anaphylaxis) needing influenza vaccine can be vaccinated safely as long as the amount of residual egg ovalbumin is limited to 1ug or less per dose (all vaccines licensed for use in India - Fluquadri, Influvac, Vaxigrip - contain less than 1ug egg ovalbumin).

Table I. Excipients in vaccines

Type of Ingredient	Example	Purpose
Preservative	Thimerosal	To prevent contamination
Adjuvant	Aluminium salts	To help boost body's response to vaccine
Stabilizers	Sugars, gelatin	To keep the vaccine effective after manufacture
Residual cell culture materials	Egg protein	To grow enough of the virus or bacteria to make the vaccine
Residual inactivating ingredients	Formaldehyde	To kill viruses or inactivate toxins during the manufacturing process
Residual antibiotics	Neomycin	To prevent contamination by bacteria during the vaccine manufacturing process

MMR and MMR-V vaccines can be safely given to children with egg allergy since measles and mumps vaccine viruses are both grown in chick embryo fibroblasts-not actually in eggs. It appears that gelatin-not egg-might be the cause of allergic reactions to MMR.

Yellow fever vaccine is grown in chick embryos that are homogenized and has potentially higher amounts of egg protein (about 10-fold that of influenza vaccine) and hence allergy specialist evaluation is recommended before vaccination.

Rabies vaccine presents very little risk to egg-allergic individuals. Of the three available rabies vaccines, only one is grown in chick fibroblasts and contains picogram amounts of egg protein. An alternative would be to use human diploid cell vaccines.

4. If a child is able to consume lightly cooked eggs without reaction, can he take the influenza vaccine? What influenza vaccine should be given if child gets urticaria after eating egg-containing foods?

A reasonable way to screen for egg allergy is by asking persons whether they can eat lightly cooked egg (e.g., scrambled egg) without adverse effects. If so, they are unlikely to have an egg allergy and also if they develop only urticaria after egg exposure, they can receive any licensed influenza vaccine (Inactivated influenza vaccine (IIV), live attenuated (LAIV) or recombinant influenza vaccine (RIV) that is otherwise appropriate for their age and health status. However, if a person has previously experienced a severe allergic reaction to flu vaccine such as anaphylaxis, regardless of the component suspected of being responsible for the reaction, should not get a flu vaccine again.

5. What vaccines are essential before pregnancy and during pregnancy?

Inactivated virus or bacterial vaccines or toxoids can be safely given in pregnancy while live attenuated viral and live bacterial vaccines are generally contraindicated. Benefits of vaccinating pregnant women usually outweigh potential risks when likelihood of disease exposure is high, when infection would pose a risk to the mother or fetus and when the vaccine is unlikely to cause harm. It takes about 2 weeks after getting vaccinated before the body develops antibodies.

Before pregnancy: MMR/Rubella vaccine (avoid pregnancy for at least a month after vaccination)

During pregnancy: Whooping cough: 27^{th} - 36^{th} week of each pregnancy as Tdap (preferably during the early part of this time period).

Influenza: vaccination after 26 weeks. Babies get influenza vaccines at 6 months only and if contracted before this period, can be severe in infants - especially in extreme preterms or babies ventilated for long duration.

Hepatitis A: For pregnant women who have a history of chronic liver disease.

6. What are the permanent contraindications for any vaccine?

There are 4 such situations:

i) Anaphylaxis after any vaccine- is a permanent contraindication to that vaccine. The other three permanent contraindications are vaccine specific.

ii) Encephalopathy not due to another identifiable cause and occurring within 7 days of pertussis vaccination is a contraindication to subsequent doses of pertussis-containing vaccine.

iii) Severe combined immunodeficiency (SCID) is a contraindication to rotavirus vaccine and other live vaccines, bacterial and viral.

iv) A history of intussusception is a contraindication to rotavirus vaccine.

7. When does the process of immunization start?

Immunization process starts when a child is in utero. Immunity develops from tetanus toxoid given to pregnant women, where tetanus antitoxin passes to the unborn child and protects from neonatal tetanus.In the same manner inactivated vaccines like Td, Tdap, inactivated influenza vaccine ,hepatitis vaccine are safe if given during pregnancy and produce immunity. Immunity against measles is transferred as passive immunity (maternal antibodies) and protects from infection for some period after birth.

8. What is the reason that some children suffer from vaccine preventable disease though they have been vaccinated against that disease?

Vaccines have been used for decades and have proven to be effective. Like any other medicine, no vaccine is 100% effective. Immunity varies between children due to malnutrition, repeated episodes of diarrhea leading to diminished immunity, individual specific immune response to vaccine etc. However, in such cases the disease is less severe than in children who have never been vaccinated.

9. If a child is brought late for a subsequent dose of multi dose vaccine should we restart the schedule?

No. If the child is brought late, the next dose of the vaccine is given and parents motivated to bring the child for the remaining doses at the recommended interval as per the immunization schedule.

10. What is "left out"/ "dropout"?

'Left outs' are those children who have never been vaccinated (thus remaining unimmunized). 'Drop outs' are those children who started vaccination but did not complete the schedule (thus remaining partially immunized).

From a behavioral perspective, large percentage of dropouts is a serious problem because it reflects the poor perception of the parents /care givers about the benefits of vaccination or of the immunization service delivery system, or both, combined with other barriers that forces them to give a low priority to immunization.

11. Why are some vaccines not administered after reaching a certain age in the National Immunization Schedule?

Age of administration for different vaccines has been recommended in National Immunization Schedule taking into consideration maximum benefit in terms of immunity generation, reduction in disease incidence, and mortality and morbidity. The schedule has been designed to ensure protection against vaccine preventable diseases to children at ages when they are most vulnerable and when a vaccine preventable disease can be life threatening. With increasing age, most children acquire natural immunity to some infections like poliomyelitis due to repeated subclinical infections.

12. Why are booster doses required after initial doses of some vaccines?

Immunity or protective effect generated by some vaccines gradually diminishes over time and there is increased vulnerability to repeat infections. For such vaccines, booster doses serve to boost immunity and enhance protection level against specific vaccine preventable diseases (VPD). e.g.:- DPT and PCV.

13. If a child has suffered from a VPD in the past, will the child still require vaccination against that disease?

Yes. Most VPDs like diphtheria, tetanus, rotavirus diarrhea, H influenzae *b* pneumonia and Japanese encephalitis, do not confer long term immunity even after an episode of full-blown infection and disease. Therefore, in these cases a child will still require all recommended doses of the vaccine as per the recommended immunization schedule.

Some VPDs are caused by different strains of the same pathogenic organism. In these cases, infection by one strain does not confer immunity against other strains and will require vaccination to ensure full protection. e.g. bivalent OPV as currently given in UIP provides protection against poliovirus types 1 and 3. For a child who got infected with type 1 poliovirus in the past, administration of this vaccine will still be required, as the child is vulnerable to infection by type 3 poliovirus.

14. If fever does not occur after giving an injectable vaccine, does it mean that vaccine has not been effective and needs to be re administered?

No. Though mild fever occurs in majority of children who receive injectable vaccines, there are a few children in whom the immune response elicited by vaccine does not cause rise in body temperature. This is normal and there is no need to re-administer vaccine.

15. Why do pain and swelling occur at the injection site? How to manage?

In case of injectable vaccines like hepatitis B, pentavalent vaccine and IPV, infants may have redness, mild pain, and swelling at the injection site. This is mainly due to rupture of some muscle fibers by the intramuscular (IM) needle. In addition, some of the vaccine components e.g. aluminium adjuvant, stabilizers or preservatives can lead to local inflammatory reactions. These symptoms generally appear on the day after the injection and last up to 3 days.

Cold compresses i.e. a pad of clean cloth dipped in cold water can be used to control swelling and redness. Paracetamol can be used for providing symptomatic relief for severe pain.

16. Can a preterm child receive vaccinations?

All vaccines are administered as per schedule according to the chronological age irrespective of the birth weight or period of gestation. BCG can be given after stabilization in the newborn period and preferably at the time of discharge. The take of BCG vaccine is similar in preterm and low birth weight babies whether given at discharge or later. PCV, rotavirus and influenza are recommended at the appropriate chronologic age. Moreover, preterms are at increased risk of chronic complications from influenza. Hence, health care personnel handling preterm babies and all household contacts of these babies are immunized to protect them till the babies receive influenza vaccine at 6 months.

The birth dose of hepatitis B vaccine can be administered only after the baby reaches a weight of 2 kgs as immunogenicity is suboptimal below this weight. In babies weighing less than 2 kgs born to hepatitis B positive mothers, the vaccine is to be given along with Hepatitis B immunoglobulin within 12 hours and 3 more doses are to be given at 1, 2 and 6 months after birth. Oral polio and rotavirus vaccines are not given to neonates in the nursery to avoid spread of live virus to vulnerable infants and deferred till discharge.

Because of low muscle mass, needle of 5/8 inch or less is preferred for safe deep anterolateral thigh intramuscular injection.

17. What precautions should be taken after vaccination?

One must ensure that the parents /caretakers wait for 30 minutes at the health facility or session site after vaccination. This is required so that immediate care can be sought for side effects or adverse events. Babies may be breast fed after vaccination, even after giving oral vaccines. There is no effect of breast milk on the efficacy of the vaccines. No medicines or herbs must be applied at the injection site.

18. Can Measles /MR vaccine lead to autism in children?

There is strong scientific evidence that measles /MR vaccination is not linked to autism, or any permanent neurological sequelae, which have been wrongly attributed to this vaccine.

19. What specific precautions should be taken during vaccine administration?

The label is checked for expiry date and the vaccine vial monitor (VVM) label of the vaccine vials and expiry date of diluents are checked before use. Auto Disabled (AD) syringes are specialized plastic syringes introduced in Universal Immunization Program (UIP) for administering injectable vaccines. Once used, these syringes get locked, as the plunger cannot be withdrawn to refill the syringe with vaccine again. This avoids reuse or misuse of syringes and prevents transmission of infections from one child or a pregnant woman to another.

Care should be taken that under no condition different vaccines are withdrawn or mixed in the same syringe. A new AD syringe must be used for every vaccine administered. The syringe should be opened from the plunger end and only when vaccine is to be administered.

New syringe is always used for reconstituting BCG, Measles/MR/MMR and Japanese encephalitis (JE) vaccines.

It must be ensured that the vaccine and diluents are of the same temperature and supplied by the same manufacturer before reconstituting.

The expiry date and packaging of AD syringe is checked before opening it.

Two or more injectable vaccines must never be mixed in the same syringe.

Spirit, soap or liquid antibiotic should not be used to clean injection site. Water swab is adequate.

Injection site should not be rubbed after vaccine administration.

The following must be checked:

- Label for type of vaccine, the label must be readable.
- Expiry date.

- Status of VVM
- Cap or bottle is not cracked
- The vaccine is not visibly frozen in case of freeze sensitive vaccine
- Just after opening and reconstituting a multidose vial, vaccinator should mention the date and time of opening on the vial

20. When the expiration date of a vaccine indicates a month and year, does the vaccine expire on the first or last day of the month? What should we do if a dose of expired vaccine is given to a patient?

Vaccine may be used through the last day of the month indicated on the expiration date. After that, it must not be used. Vaccine supply must be monitored carefully so that vaccines do not expire. Expired vaccines and diluents should NEVER be administered, even if it is only 1 day past the expiration date.

If an expired vaccine has been administered, the dose should be repeated. If the error was detected on the same clinic day, the dose may be repeated on the same day. If the error is detected more than one day later and if the expired dose is a live virus vaccine, one must wait at least 28 days after the previous (expired) dose was given before repeating it. If the expired dose is not a live vaccine, the dose should be repeated as soon as possible.

21. What are the key messages that must be given to parents after each vaccination?

Apart from what vaccine was given and what disease it prevents, as per national guidelines, the four key messages that need to be delivered to parents and caregivers are:

- When and where to come for the next visit
- What minor adverse events could occur and how to deal with them
- To keep the immunization card safe and to bring it for the next visit
- To wait for at least 30 minutes after vaccination at the session site. The health care worker at the nearest health facility must be informed in case of any problem faced by the child even after 30 minutes.

22. How to manage biomedical waste?

At the session site, the needle of the AD syringe must be cut immediately after administering the injection, using the hub cutter that cuts the plastic hub of the syringe and not the metal part of the needle. The cut needles that get collected in the puncture proof container of the hub cutter are then autoclaved, boiled or chemically disinfected and should be disposed of in a safety pit/tank and the hub cutter washed properly with sodium hypochlorite.

The plastic part of the syringes after cutting the needle should be discarded into the red bag.

Needle caps /wrappers are collected in the black bag and disposed as municipal waste.

23. What must be done in the following situations - lapsed immunization / unknown immunization / preponed immunization?

For the purpose of calculating intervals between doses, 4 weeks equals 28 days. Intervals of 4 months or greater are determined by calendar months.

There is no need to restart a vaccine series regardless of time elapsed between individual doses due to immune memory. It should be given at the next visit as if the usual interval has elapsed and schedule completed. Vaccines given 4 days or less before the minimum interval are considered valid.

Vaccines administered 5 days earlier or later than the minimal interval or minimum age should not be counted as valid doses and should be repeated as age appropriate. In case of unknown status, to consider as unimmunized and vaccines given accordingly.

24. What measures should be adopted for catch up immunization?

Catch up immunization schedules are individualized. Any number of single or inactivated vaccines may be given on the same day either singly or as a combination vaccines maintaining a gap of at least 2 inches between different vaccines.

Inactivated vaccines can be given at any time in relation to other live or inactivated vaccines. If not given on the same day, a gap of 4 weeks must be maintained between two live injectable vaccines especially MMR and varicella, yellow fever and live attenuated influenza vaccine (LAIV).

OPV and rotavirus may be given at any time in relation to any live or inactivated vaccine. For catch up doses, vaccines are given at the minimum possible interval for early protection.

25. What is the interval to be maintained for vaccines following immunoglobulin administration?

Immunoglobulin does not interfere with immune response to killed vaccines and rotavirus vaccine.

Table II. Immunoglobulins and vaccine interval

Product	Dose	Route	Interval (months) after immunoglobulin
Tetanus Ig	250 units (10mg IgG/kg)	IM	3
Hepatitis A Ig	0.02-0.06ml/kg(3.3-10mg IgG/kg)	IM	3
Hepatitis B Ig	0.06ml/kg(10mg IgG/kg)	IM	3
Rabies Ig	20 IU/kg (22mg IgG/kg)	IM	4
Varicella Ig	125units/10kg(60-200mgIgG/kg) maximum 625 units	IM	5
Measles prophylaxis Ig			
Standard	0.25ml/kg(40mg IgG/kg)	IM	5
Immunocompromised	0.5ml/kg(80mg IgG/kg)	IM	6
IVIG			
Replacement therapy for immune deficiencies	300-400mg/kg	IV	8
Immune Thromocytopenic purpura treatment	400mg/kg	IV	8
Post exposure varicella prophylaxis	400mg/kg	IV	8
Immune thrombocytopenic purpura treatment	1000mg/kg	IV	10
Kawasaki disease	2g/kg	IV	11
Monoclonal antibody to respiratory syncytial virus (palivizumab)	15mg/kg	IM	None
Cytomegalovirus IVIG	150mg/kg maximum	IV	6

It interferes with live vaccines like measles and varicella vaccines. If possible, immunoglobulin when needed, should be given at least 2 weeks after measles vaccine. Depending on the dose of immunoglobulin received, the MMR vaccine should be deferred by as long as 3 to 11 months. Table II.

26. What is the importance of using only diluents provided with the vaccine?

It is important to reconstitute vaccine using only the diluent provided by the manufacturer for each specific vaccine. Using the wrong diluent, substituting even other vials of sterile normal saline or sterile water makes the vaccine ineffective and less effective. Deaths have resulted when vaccines were incorrectly mixed with medications other than diluents specifically approved for use with specific vaccines by the manufacturer.

27. What are some common mistakes that lead health workers to use the wrong diluent to reconstitute vaccines?

i) Saving vials with missing labels, makes correct identification of vial contents impossible.

ii) Storing diluents for different vaccines together in the refrigerator.

iii) Believing that diluents are interchangeable

iv) Storing other medications like insulin or anesthetic agents in the refrigerator where a busy health worker can mistakenly choose them may even result in death.

28.When should reconstituted vaccines be discarded? What may happen if reconstituted vaccines are stored longer than 6 hours after reconstitution?

WHO recommends that reconstituted BCG vaccines, measles-containing vaccines, yellow fever vaccines and

freeze-dried Hib vaccines be discarded within 6 hours of reconstitution. Since freeze-dried vaccines do not have preservatives that limit the growth of microorganisms, vaccines kept longer than 6 hours may have high numbers of bacteria and may lead to deaths from toxic shock syndrome. The vaccine vial monitor (VVM) that is attached to the vaccine vial can serve as a visual trigger to assist a health worker in properly applying the multi-dose vial policy, especially in knowing when the reconstituted product must be discarded.

(**Note: Chickenpox vaccines**- After reconstitution, it is recommended that the vaccine be injected as soon as possible. However, it has been demonstrated that the vaccine may be kept for up to 90 minutes at room temperature (25^0 C) or up to 8 hours in the refrigerator (2^0 C to 8^0 C). If not used within these timeframes, the reconstituted vaccine must be discarded

MMR - To minimize loss of potency, should administer as soon as possible after reconstitution. If not used immediately, the reconstituted vaccine may be stored between 2°C to 8°C, protected from light, for up to 8 hours. Reconstituted vaccine must be discarded if it is not used within 8 hours).

29. How long is a vaccine viable if it is loaded into a syringe and has been stored in the refrigerator?

Most vaccines are available in Single dose vials [SDVs]. SDVs do not contain preservatives to help prevent microorganism growth. Therefore, vaccines packaged as SDVs are intended to be punctured once for use in one patient and for one injection. CDC recommends that vaccines that have been drawn into syringes by the provider be discarded at the end of the clinic day if unused.

Manufacturer-filled syringes that have not been activated (i.e., have not had the needle guard removed or a needle attached) may be kept and used until their expiration date.

30. What is meant by 'Precautions' during vaccine administration?

A precaution is a health condition in the recipient that might increase the chance or severity of a serious adverse reaction, might compromise the ability of the vaccine to produce immunity (such as administering measles vaccine to a person with passive immunity to measles from a blood transfusion) or might cause diagnostic confusion. Injury could result, but the chance of this happening is less than with a contraindication. In general, vaccines should be deferred when a precaution is present.

Permanent precautions include:

- Guillain-Barré syndrome (GBS) occurring 6 weeks or less after a previous dose of a tetanus toxoid vaccine is a precaution for these vaccines.
- GBS occurring 6 weeks or less after a previous dose of influenza vaccine is a precaution for this vaccine.
- History of thrombocytopenia or thrombocytopenic purpura is a precaution for MMR vaccine.
- Chronic gastrointestinal disease, spina bifida, bladder exstrophy, or altered immune competence other than SCID are precautions for rotavirus vaccine.

Temporary precautions include:

- Moderate or severe acute illness (all vaccines); risk-benefit decision exists until the patient is considered recovered.
- Recent receipt of antibody-containing blood products(MMR-II and varicella-containing vaccines, except zoster); risk-benefit decision exists for a predefined interval
- History of Arthus type hypersensitivity reaction after a previous dose of diphtheria toxoid or tetanus toxoid vaccine; risk-benefit decision exists until at least 10 years have elapsed since the last tetanus-toxoid-containing vaccine.
- Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; risk-benefit decision exists until neurologic status has been clarified and stabilized.

31. If the full ampoule of diluted BCG vaccine is injected accidentally, what side effects may occur and how to manage?

The following were reported in different studies: majority developed papule, erythema, axillary lymphadenopathy, large deep ulcers, necrotic lesions, abscesses or regional suppurative lymphadenitis. Some developed fever, headache, malaise, very rarely jaundice or intracranial bleed. There was no report of disseminated tuberculosis.

In one study, the situation was managed by giving Isoniazid 10mg/kg/day and Rifampicin 15mg /kg /day for three months and appropriate drainage of abscess.

32. What are the vaccines recommended for a child with cochlear implant and schedule?

Pneumococcal conjugate vaccine and Pneumococcal polysaccharide vaccine are used in high risk group with

Table III. Recommended vaccinations in children with cochlear implant

Vaccines	Primary	Catch up vaccination (Normal children unvaccinated)		With cochlear implant
Pneumococcal*	Primary series PCV13 /PCV10 6 weeks to 6 month at 6, 10, 14 wks Booster PCV13 / PCV10 12 to 15 months	**PCV 13** **7-11 mths :** 2 doses 4 wks apart and one dose during 2nd year **12 to 23 mths :** Two doses 8 wks apart **> 2 yrs to 5 yrs:** a single dose is recommended	**PCV 10** **7-11 mths :** 2 doses 4 wks apart and one dose during 2nd year **12 to 23 mths :** Two doses 8 wks apart **>2 yrs to 5 yrs :** Two doses 8 wks apart recommended	**24 - 71 mths :** One dose of PCV 13/10 (if 3 doses of PCV13/10 received) Two doses of PCV 13/10, 8 weeks apart (if fewer than 3 doses of PCV 13/10 received) **6-18 yrs unvaccinated** Single dose of PCV13/10 is recommended **PPSV23 :** One dose 8 weeks after the last dose of PCV13/10 must be given to all children above the age of 2 years

* If possible recommended dose of pneumococcal vaccines given at least 2 weeks before the cochlear implant surgery.

PPSV23- Pneumococcal polysaccharide vaccine

cochlear implant. Table III. CDC recommends Hib vaccination for children below 5 years with cochlear implant and meningococcal vaccine for preteens (11 years to 12 years with a booster at 16 years) and teens (16 years to18 years) with cochlear implant.

For normal children the primary schedule for pneumococcal conjugate vaccine for both PCV 13 and PCV 10 is three primary doses at 6 weeks, 10 weeks and 14 weeks with a booster at 12 through 15 months. Catch up vaccination for unvaccinated children aged 7 to 11 months is two doses PCV 13/10 four weeks apart and one dose during the second year. A single dose of PCV 13 is recommended for unvaccinated children 2 years to 5 years. Two doses of PCV10 are recommended for unvaccinated children 12 months to 5 years 8 weeks apart (Table III).

For children aged 24 through 71 months, one dose of PCV13/10 (if 3 doses of PCV received previously). Two doses of PCV13/10 given at least 8 weeks apart (if fewer than 3 doses received). A single dose of PCV 13/10 is given to previously unvaccinated children aged 6 years to 18 years.

Eight weeks after the last dose of PCV 13/10 in children aged 2 years and above, a dose of pneumococcal polysaccharide vaccine (PPSV23) is given. If possible recommended dose of pneumococcal vaccines given at least 2 weeks before the cochlear implant surgery.

33. What is the current recommendation on immunization of health care workers?

COVID-19 - Vaccination against COVID-19 is recommended for all health care workers. It is given intramuscularly 0.5 ml as two doses four weeks apart by the government. It is currently available as viral vector vaccine (genetically modified adenovirus from chimpanzees) and as an inactivated vaccine.

Hep B: If there no serologic evidence of immunity or prior vaccination against hepatitis B one must receive 3-dose series of recombinant hepatitis B vaccine, first dose immediately, second dose after 1 month, third dose 5 months after the second.

Influenza: One must get 1 dose of influenza vaccine annually.

Tdap/Td: A one-time dose of Tdap (tetanus, diphtheria, acellular pertusis as soon as possible if not received Tdap previously (regardless of when previous dose of Td was received). To get either a Td or Tdap booster shot every 10 years thereafter. Pregnant HCWs need to get a dose of Tdap during each pregnancy.

ACIP recommends the following additional vaccines in special circumstances:

MMR (Measles, Mumps, & Rubella): for those born in 1957 or later and have not had the MMR vaccine, or no

Table IV. Recommended vaccinations in splenectomized patient

Vaccines	Primary	Booster	In the unvaccinated or incompletely vaccinated
Pneumococcal	Age appropriate series of PCV 13	PPSV 23 (see next column)	**2-5 yrs** - 2 doses of PCV 13, 8 wks apart; 8 wks after completion of primary series, 2 doses of PPSV23 given, 5 yrs apart **> 6 yrs** - 1 dose of PCV 13 and 8 wks later, 1 dose of PPSV23 given
Meningococcal	2-9 yrs: 2 doses ≥ 8 wks apart and ≥ 4 wks after completion of PCV13 series	Age < 7 yrs: booster given after 3 yr interval and every 5yrs thereafter. Age > 7 yrs : booster given every 5 yrs**	For children > 2 yrs, 2 doses of Menactra should be given 4 wks after PCV 13 series is complete
Hib vaccine	Primary series should be completed		**< 12 mths** : If nil dose or only 1 dose received, 2 doses Hib given If 2 or more doses received, 1 dose Hib given **>15 mths** : 1 dose Hib given

PCV13 - 13 valent pneumococcal conjugate vaccine; PPSV23 - 23 valent pneumococcal polysaccharide vaccine;
**All doses should be completed using same vaccine product

serologic evidence of immunity or prior laboratory confirmed disease Two doses of MMR is recommended (1 dose stat and the 2nd dose 28 days later).

Varicella: If there is no serologic evidence of immunity or prior vaccination or prior laboratory confirmed disease. Two doses of varicella vaccine, are recommended 4 weeks apart.

Other vaccines recommended are hepatitis A vaccine, pneumococcal vaccine PCV13 followed by pneumococcal polysaccharide vaccine one year later for those aged above 65 years (CDC Recommendation) and meningococcal vaccine for microbiologists who are routinely exposed to Neisseria meningitides.

34. What vaccinations are recommended in the splenectomised patient?

Anatomic asplenia (e.g., surgical removal or congenital absence of the spleen) or functional asplenia (as occurs in persons with sickle cell disease) predisposes to increased risk for infection by encapsulated bacteria, especially S. pneumoniae, N. meningitidis (meningococcus) and H influenzae b. Recommended vaccinations are shown in Table IV.

Pneumococcal, meningococcal and Hib vaccinations should be administered at least 14 days before elective splenectomy, if possible. In those who have undergone emergency splenectomy vaccination done 2 weeks after the sugery has good antibody response compared to vaccination immediately following surgery. All live vaccines may be safely given. If the vaccinations are not administered before surgery, they should be administered after the procedure as soon as the patient's condition is stable.

35. Oral rotavirus vaccine has inadvertently been given as intramuscular injection? What adverse effects may be expected?

Nineteen of the 39 reports (49%) documented an adverse event; irritability (seven cases) and injection site redness (five) were the most commonly reported adverse event. An injected dose of RV1 or RV5 is not considered a valid dose, and a properly administered oral replacement dose should be given within the appropriate age and dosing schedule.

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CLIPPINGS

Cardiometabolic risk factors during childhood in relation to lung function and asthma.

In this population based cohort study involving 4,988 children, researchers sought to study the longitudinal correlations of cardiometabolic risk factors with lung function and asthma at school age, as well as to examine whether any association was explained by child's body mass index. At a median age of 6.0 years (95% range 5.6 - 7.6) and 9.8 years 109 (95% range 9.3 - 10.4), cardio-metabolic risk factors including blood pressure, lipids, insulin and 110 Creactive protein (CRP) concentrations have been measured. There were no consistent associations between other cardio-metabolic risk factors and respiratory outcomes. Lung function, but not asthma, was related to blood pressure and CRP, but not lipids or insulin. Further research into the underlying mechanisms and long-term consequences of these associations is required.

Mensink Bout SM, Santos S, de Jongste JC, Jaddoe VWV, Duijts L. Cardiometabolic risk factors during childhood in relation to lung function and asthma. Pediatr Allergy Immunol 2021 24 March 2021 https://doi.org/10.1111/pai.13509.

GENERAL ARTICLE

PRACTICAL TIPS FOR EFFECTIVE PRESENTATION ON THE PHYSICAL AND VIRTUAL STAGE

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Abstract: *Most of us believe that an effective speaker is born that way. But the truth is that public speaking is a skill that ought to be learnt and mastered. As medical teachers and academicians we are routinely required to make presentations both to the medical community and sometimes to the general public. Online presentations have become the rule rather than the exception in these COVID days. The subsequent article aims to elucidate some of the practical tips for an effective presentation both on stage as well as online.*

Keywords: *Public speaking, Presentation, skills.*

Following is the question that haunts every potential speaker, more so a beginner. “Is speaking an art or a science?”. It is an interesting combination of both and every one can improve his oratorial skills. A famous axiom on successful speaking elucidates the sure route to success as “Know what to say, say it and sit down”.

Clarity, depth and brevity are the three corner stones of a good presentation. A good speaker always knows his subject well and will understand the needs of his audience. The needs of a post graduate student are different from those of a consultant. It is ideal to follow a simple, easily understandable approach with as many life examples as possible while addressing lay persons. Talks and deliberations on subjects with personal experience and conviction reach the audience better. However, ifthe talk is based only on knowledge from books, journals or from the internet and if the speaker is unsure and does not practice the principles he advocates, it is unlikely to impress the listeners. It is always prudent, therefore, not to venture on to a subject or a group about which/whom one is neither confident nor comfortable.

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Preparation of The Power Point [PPT] Slides

It is essential to keep the slides to the minimum possible number and time the duration to 1 to 1.5 slides per minute. Accordingly, the number of slides in a thirty-minutes talk be restricted to 30-45. It is suggested to have not have more than 6 lines in each powerpoint slide; should there be more data, it is to be either divided or each line be animated to appear one by one while the previous lines get blurred simultaneously. Using animations is left to the choice and comfort of the speakers. It has the disadvantage of prolonging the time and may complicate the digital presentation. But many young speakers use them effectively. Times new Roman, Calibri, Tahoma and Arial are some of the commonly used fonts and the use of capital letters and abbreviations on the slide is best, if avoided.

The introductory slide containing the Curriculum vitae should be brief and clear indicating the present place of work and important responsibilities held presently.

The speaker’s notes can be utilized to type and store important points relevant to that particular slide. Power point has an option wherein it is visible only to the speaker. Further, another option is the availability of viewing next slide on the computer to guide the thoughts and words. It is ideal to quote references appropriately. References need to be as recent as possible.

Pictures and videos need to be used appropriately. While embedding video, it is better to check if they play on a different computer. It is always necessary to carry a backup in case one needs to use them. It may be prudent to carry own laptop with presentation loaded, if the organizers permit. It is worthwhile to check compatibility of the devices prior to the presentation, for instance, videos require audio synchronization and have to be checked in advance. Adding audience poll survey during presentation involves and interests the delegates. The combination of white background and black letters fits any circumstance. But many speakers use colors to draw the attention as long as they are restricted to two. Pictures and cartoons also can be appropriately used to convey the facts in an

interesting manner. Always the presentation needs to be backed up in additional pen drive or uploaded on Google drive or on cloud storage as additional reserves. Availability of internet connection in the preview room can be utilized whenever necessary. Rarely, the presentation can be disrupted by unexpected technical problems but one should not lose their calm.

Youngsters can experiment with newer formats like Prezi, a virtual presentation software.

Should one rehearse?

It is surprising to know that almost all successful speakers rehearse. Beginners need to rehearse more often to achieve perfection. Further, one can estimate the time duration of their talk to help, complete the talk within the stipulated time. It is better to rehearse in front of well-wishers whenever possible as they may give valuable critical feedback (which one may not always like!); else, rehearsal in front of a mirror could help.

Quality and tone of the voice add strength to the talk

Audience do not relish a speech delivered in a monotonous tone, with the speaker reading from his notes or from the slides. Modulating one's voice according to the occasion, raising it to emphasize, lowering it or pausing at appropriate times adds to the success of the presentation. It is always a good idea to listen to great orators and to learn from them. Many such are easily and freely available on YouTube. However, dramatization during a scientific talk is not accepted by most audience.

On the day of presentation!

It is ideal to dress appropriately, arrive at the venue early, load the presentation and check it along with audio and video. It would be better to introduce oneself to the audience and also try to remember their names. During the presentation, they can be addressed to get useful feedback too. It is better to relax, drink a glass of water, keep mind fresh and finish attending natures'call before the presentation. Collar mike, if available, can be used effectively as one turns to the screen to explain a point. It would be prudent to carry one's own pointer compatible with the regular as well as LED screen. Generally, words are better visualized on the laptop as compared to a large LED screen. A small slip of paper containing major focus points of the talk can be tactfully placed on the podium before one begins.

At the time of delivering the talk!

When the moment arrives and the speaker is asked to take the podium, it would be impressive to stand brisk, walk confidently towards the stage with the visualization that it is a well-prepared talk and will be delivered successfully. On reaching the podium, a smile and greeting the chairperson and the audience will provide a confident start. A stiff posture and hiding behind the podium is best avoided.

Overcoming difficulties on the podium

Some beginners experience thought block as they see the audience; proper practice and rehearsal helps build confidence of the speaker. Taking a deep breath and sipping a cup of water will allay the anxiety.

How one should begin?

The best time to impress the audience is at the beginning of the talk. A good beginning with a quote, a live example, interesting video or a question to the audience are examples of how one can begin successfully. The speaker has to attract the attention of the audience in the very beginning. A mundane beginning like "I don't know why I was invited to give this talk" or "I don't know whether I am eligible to talk to you on this subject" is not an impressive way to begin. A good beginning is a talk, half well done!

Body of the talk

Aristotle's quote on effective communication - "Tell them what you will tell them; Tell them; Tell them what you told them", sums it all. The second important part of any talk is its body. The speaker has to decide on salient points to emphasize in his talk and take the audience on a comfortable and interesting journey thereafter. During preparation of the talk, every speaker should place himself in anticipation of his own response to his talk, if seated among the audience. Most audience would not be interested if the contents are irrelevant to their practice/ life. Involving audience in between to raise their hands for a question or a carefully planned joke relevant to the occasion will help audience sustain their interest.

Conclusion of the talk

The third important part of any talk is it's conclusion. Brief recall of what was discussed and its relevance or ending the talk with relevant questions are some modes of ending a lecture. The ending could also be dramatic like presenting a relevant video, stunning statistics, a rare presentation or an intriguing question like "Can change in practice happen from tomorrow?" etc. It is wise to always end the talk with a concluding summary slide. At conclusion, it is a good gesture to thank the chairpersons, audience and organizers.

How to assess audience response?

The response can be assessed by maintaining the eye contact with section of audience and gradually shifting the point of eye contact to other areas. This is a powerful tool to keep audience interested. It is yet another useful exercise to observe the body language of all sections of the audience while delivering the talk. It is most important to face the audience and not to look at the slides on the screen, as audience generally lose interest if the speaker does not face them.

Answering questions; interacting with audience

The speaker has to stay relaxed and take questions one by one and be specific as far as possible while answering. An open palm gesture is appropriate at this time as it indicates welcome sign for questions. If a question cannot be answered, it is better to accept it and offer to mail the answer to the person who raised the question. It is an appreciative move to acknowledge brilliant questions, to please the audience.

Time Control

Time is precious both during physical and online presentations as it involves many persons. It is very important to be punctual and present in the hall at least 30 minutes earlier and load the presentation.

- The slides visible to the presentor have to be always numbered; adding slide numbers will help the speaker to have control over the time of the lecture.
- Moderators are encouraged to keep a Portable Document Format [PDF] version of the entire PPT open in their mobile device to be shared with all panelists. This easily helps everybody to know contents of the next slide and the timeline of the discussion. [Panel discussions]
- It is advisable to keep all introductions to less than 2-3 minutes and the final 2-5 minutes in the PPT for interaction and completion.
- To convey the key points in few words is an art. The best form is rehearsal. Steve Jobs too, rehearsed 20 times before every presentation to get the perfection. The presentations have to be rehearsed and timed appropriately. This can be done by setting an alarm on the mobile to remind five minutes ahead of completion., to avoid intrusion into the time of the next speaker/event.

Tips for online (Zoom or Google meet) presentations

COVID-19 has given birth to a new level of digital learning, coining an apt terminology 'Glocal' with global speakers coming locally. Unlike in physical presentations, more technical skills are to be learned, to present effectively online (Box 1).

Box 1. Technical challenges and solutions – Musts for an online presention

- High speed uninterrupted internet connectivity-WiFi not local hotspot.
- Backup internet source - A mobile device? Hosting platform to be downloaded beforehand e.g Zoom, Google Meet.
- Laptop for logging in - for best results.
- Presentation open & ready for screen share.
- Ear phones for better audio quality.
- Technical rehearsal beforehand - to share, check videos and audio / video quality.
- Panel discussions - all panelists with moderator who is familiar with the technology to be present and logged in at least 15 minutes prior to the talk; technical glitches including 'not allowed to ente', video audio changing etc. can be corrected.
- Familiarity with the commonly used icons and modes -"mute" "unmute" "camera on" and "camera off", slide sharing, stop slide sharing, chat box, etc.

- It helps if the speaker imagines facing a hall full of interested and positively responding audience.
- It is recommended to sit facing a good light source such as light bulb or tube light and never in front of a bright window and the laptop facing the window as only the silhouette will be visible. The ambience would be better with a plain background, silent area and good seating (Fig.1). Even a fan and AC may produce distracting noise.
- The camera of the laptop should be placed at the same level as the eyes (Fig.2).
- It has to be ensured that other family members including children do not appear in the screen and a place be chosen respecting the privacy of the family members or co-workers, as the case may be.
- An appealing and neat appearance - properly groomed hair, decent attire and a smiling face are rich attributes. It is required to avoid looking sideways and face the camera on the laptop.

Some Do's

- Nodding head in approval in agreement with the other experts.

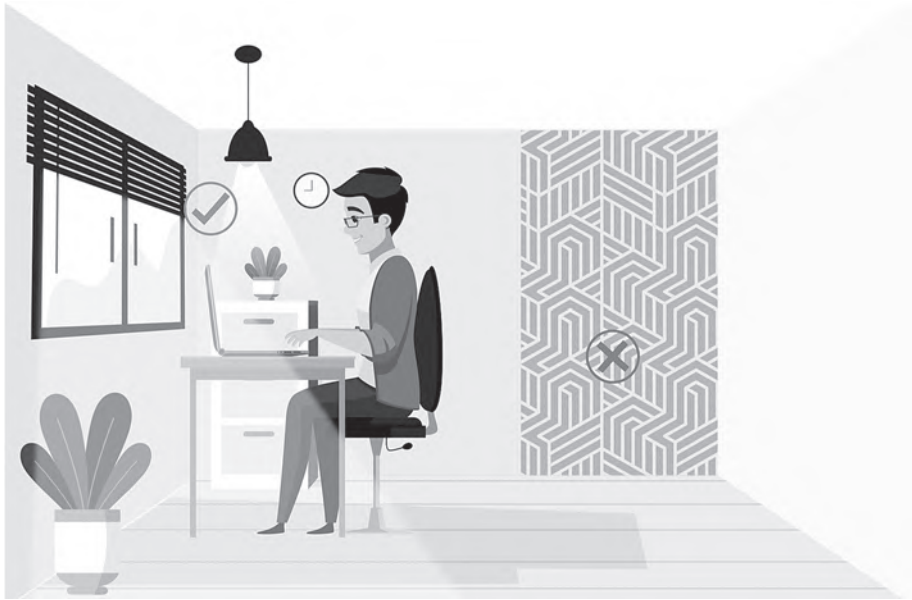

Fig.1. Ideal Environment - Facing the light with a plain background, silent area and good seating.

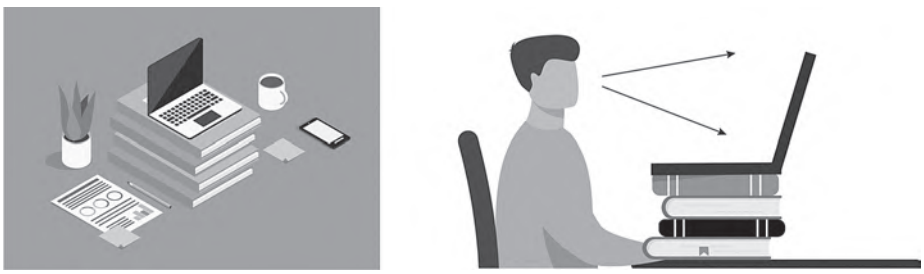

Fig.2. Ensure that Screen is placed at the level of eye

- Raising hand to make a point or wait until the other panelist / speaker completes.
- Writing down salient points to be conveyed is a valuable addition.
- Muting the audio before one needs to unexpectedly talk to someone at office or home.
- Keeping mobile in silent mode to avoid unnecessary disturbances.
- Muting the microphone when not speaking and unmuting it only when speaking.
- Disconnecting the video can help, when internet signals are weak and there are more slides to be added.

Some Don'ts

- Interrupting another panelist.
- Conversing with other panelists or the moderator on the audio phone; messaging services can be opted and this point has to be mutually agreed upon during the rehearsal time.

After the talk

It is a good and rewarding idea to listen to the recorded presentation at leisure. One will indeed be surprised at the omissions which one did not notice while presenting. It is ideal to obtain critical feedback to help plan the next presentation more effectively. Whenever possible, the points learned to improvise the next lecture have to be noted down.

Whenever one delivers a lecture, it has to be considered as an opportunity to improve the speaking skills and over time, it will lead one to be a well sought-after speaker.

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DRUG PROFILE

PARENTERAL IRON PREPARATIONS FOR CHILDREN AND ADOLESCENTS

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Abstract: *Iron deficiency remains the most common nutritional deficiency in Indian children. Oral supplementation of iron is highly effective in prevention and treatment of iron deficiency anemia except in rare conditions where oral supplementation could be rendered ineffective. Parenteral iron therapy is an option in these situations. Serious hypersensitivity reactions are known to occur with parenteral preparations. Judicious use of newer parenteral iron products reduces these events to a great extent.*

Keywords: *Iron deficiency, Children, Parenteral, Iron dextran, Iron sucrose, Ferric gluconate, Ferric carboxymaltose.*

Iron deficiency anemia (IDA) in children is extremely common in Indian scenario and is preventable to a greater extent with iron supplementation. In all age groups, the preferred route for supplementing iron is always the oral route. Parenteral iron is generally reserved for those conditions where oral therapy fails due to inability to tolerate oral iron, poor compliance, ongoing blood loss, chronic kidney disease (CKD) and/or associated malabsorption. It may also be considered if IDA persists despite adequate oral therapy for at least 3 months. Parenteral iron produces a faster haemoglobin response than oral iron only in children on hemodialysis for CKD.[1]

The earlier agents - iron dextran, iron sucrose and ferric gluconate - are associated with significant adverse reactions. The newer third generation formulations like ferumoxytol and ferric carboxymaltose are iron-carbohydrate complexes that slow the release of iron resulting in more favourable safety outcomes.[2]

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Table I. Concentration of elemental iron in various parenteral preparations[5]

Iron preparation	Concentration
Iron dextran	50mg/mL
Iron sucrose	20mg/mL
Ferric gluconate	12.5mg/mL
Ferric carboxymaltose	50mg/mL
Ferumoxytol	30mg/mL

Parenteral iron dose is calculated for the child's body weight with due consideration of the total iron deficit. Depending on the preparation used, parenteral iron can be given either as a single total dose or in divided doses. Further doses are determined after monitoring hemoglobin and serum iron concentrations.[3]

Dosage[4]: The total cumulative dose of parenteral iron required can be calculated by using Ganzoni formula that is, total iron dose = [actual body weight × (15-actual Hb)] × 2.4 + iron stores). Iron stores are calculated as 500 mg for children above 35 kg and 15mg x weight in kg for children < 35 Kg. e.g if the child's weight is 30 kg means 15 x 30 =450 mg. The concentration of elemental iron in various parenteral preparations are given in Table I.[5]

Adverse effects: Serious hypersensitivity reactions, including life threatening and fatal anaphylactic reactions have been reported in patients receiving intravenous iron. These reactions can occur even when a previous administration has been tolerated (including a negative test dose). Test doses are no longer recommended and caution is needed with every dose of intravenous iron. Intravenous iron products should be administered only if appropriately trained staff and resuscitation facilities are available. Patient should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration. In the event of a hypersensitivity reaction, treatment should be stopped immediately and appropriate management initiated. The risk of hypersensitivity is increased in patients with known allergies, immune or inflammatory conditions or those with a history of severe asthma, eczema, or other atopic allergy; in these patients, intravenous iron should only be used if

the benefits outweigh the risks. Intravenous iron should be avoided in the first trimester of pregnancy and used in the second or third trimesters only if the benefit outweighs the potential risks for both mother and fetus.[6]

Iron dextran

Iron dextran was the one of the earliest parenteral iron preparations that was used. Two iron dextran formulations currently available are the high molecular weight (HMW) one and the low molecular weight (LMW) one, both in a 50 mg/mL concentration. However, there is a very high risk of anaphylactic and other adverse reactions to iron dextran especially with the HMW preparation. With the availability of several newer, safer preparations of parenteral iron, the use of iron dextran is much reduced.[7]

Dosing: As a test dose does not rule out the chance of a serious anaphylactic reaction, test dose before administration is no longer recommended. Moreover, majority of the adverse events were noted with HMW dextran and this product is no longer available in the market. Caution is needed with every dose of intravenous iron. Unlike other parenteral iron products, iron dextran is the only preparation approved for intramuscular (IM) and intravenous (IV) administration. When given IV the total dose should be administered as a slow infusion at a rate not exceeding 50 mg/minute and when given IM, should be given via Z-track technique to avoid staining the skin. However, the IM route is not routinely recommended because of injection site pain and local complications.[8]

Iron sucrose

Iron sucrose is a commonly used iron preparation in all age groups. It is available at a concentration of 20 mg/mL (100 mg/ 5 mL or 200 mg/10 mL) of elemental iron in single use vials and contains no preservatives.

Dosing: Divide calculated total cumulative dose and give every 3 to 7 days until total dose is administered. Recommended maximum single dose is 300mg or 7mg iron/kg to prevent adverse effects. Iron sucrose can be given as a slow IV injection over 2 to 5 minutes. The single-use vials can also be diluted and mixed with normal saline to concentrations of 1-2 mg/ml as mentioned.

Administration:[9]

Children (>1 month of age):

Dilute doses ≤100mg 1:1 with normal saline and infuse over 30min.

Dilute 200 mg in 200ml normal saline and infuse over 60 minutes.

Dilute 300mg in 250ml normal saline and infuse over at least 90 minutes

The drug should be neither mixed with other medications nor added to parenteral nutrition. Unlike iron dextran, iron sucrose does not carry a "black box warning" for anaphylactic reactions and test dosing is not required. Anaphylactic reactions, however, are reported. Hypotension has been reported with the administration of iron sucrose and may be linked to rate of infusion or total dose given. Other mild adverse reactions reported with iron sucrose are hypertension, nausea, vomiting, diarrhea, constipation, abdominal pain, edema, fatigue, dizziness, headache, and muscle cramps. It has a terminal half-life of approximately 6 hours, attributed to its rapid distribution out of the serum. Changes in the serum transferrin saturation and ferritin can be accurately measured in a patient receiving IV iron sucrose within 48 hours.[10]

Ferric gluconate

Sodium ferric gluconate was approved by the FDA in 1999 and is currently only indicated for anemia in patients on hemodialysis in conjunction with erythropoietin therapy.[11]

Dosing: The recommended dose in children above 6 years is 8 doses of 1.5 mg/kg (0.12 mL/kg) repeated at sequential dialysis sessions. Adult patients on hemodialysis may receive up to 125 mg (10 mL) per dose to achieve a cumulative dose of 1 gram over 8 sequential sessions. The medicine is administered as a slow IV infusion at a rate not to exceed 12.5 mg/min. No test dose is required prior to initiation of ferric gluconate therapy.

Adverse reactions: Ferric gluconate can be safely given to patients who are iron dextran intolerant, although the rate of ferric gluconate intolerance was noted to be higher in patients who had a prior history of iron dextran intolerance. Patients with multiple drug allergies may similarly be at an increased risk of hypersensitivity reactions.[12]

Ferric carboxymaltose

Ferric carboxymaltose is a relatively new and effective parenteral iron preparation with good safety profile in adults with severe iron deficiency anemia.

Dosing: The recommended dosing is two doses of 15 mg/kg/dose (maximum 750 mg) at least 7 days apart and each individual infusion can be administered over 10 to 15 minutes, without the need for a test dose. Data on its use in children is currently limited.[13] However the available studies in children look very promising.

A recent systematic review and meta-analysis has shown that ferric carboxymaltose was the most effective treatment for iron deficiency anemia in children with inflammatory bowel disease.[14] Given the rapid infusion time and high dosing availability, it is a practical and effective way to reduce the burden of iron deficiency in these patients, and allows for repeated infusions without overt straining on resources.[15]

Ferumoxytol

Ferumoxytol is the latest formulation of parenteral iron, which was approved by the FDA in June 2009 for treatment of iron-deficiency anemia in chronic kidney disease. It is the only isotonic parenteral iron preparation currently available.[16] The major benefit of ferumoxytol over other forms of parenteral iron preparations is the ability to administer as a rapid injection.

Dosing: In adults, 510 mg (17 mL) is given as a single dose, followed by a second dose (510 mg) 3 to 8 days after the initial dose; which is to be administered at a maximum rate of 1 mL/second (30 mg/second).[17]

Another advantage of ferumoxytol is improved bioavailability which helps in correction of iron deficiency within 1 week of administration compared to oral iron and other available IV iron preparations. Dosing recommendations for children are not available for ferumoxytol since studies in this population have not yet been completed.[18]

Conclusion

Oral iron is always the preferred route of supplementation in children with iron deficiency anemia. However, in certain circumstances parenteral iron supplementation may be warranted. Use of parenteral iron has been considered risky in the past when there was only one formulation available and reactions were poorly studied. With the advent of newer preparations, parenteral iron therapy should no longer be considered unsafe and should be prescribed whenever indicated. Administration of the test dose does not eliminate the possibility of a subsequent anaphylactic reaction. Hence all doses should be administered only after ensuring adequate precautions to manage a severe anaphylactic reaction. The newer agents appear reassuring but more studies are underway to establish their efficacy and safety in children.

Points to Remember

- ***Iron deficiency anemia continues to be one of the major public health challenges in Indian children.***
- ***Oral supplementation is the preferred method to treat even severe forms of iron deficiency.***
- ***Parenteral iron supplementation is not superior to oral route but has definite advantages in some clinical settings where efficacy of oral supplementation is compromised***
- ***Intravenous iron preparations carry a risk of allergic reactions or anaphylaxis and careful monitoring of patient is necessary***
- ***Newer iron preparations have better safety profile than older ones like iron dextran or iron sucrose***

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CLIPPINGS

Manifestations and Risk Factors in Children Hospitalized with Respiratory Syncytial Virus Infection

The clinical manifestations of Respiratory syncytial virus (RSV) include both mild upper respiratory infections and severe infections of the lower tract, such as bronchiolitis and pneumonia that can lead to hospitalization and severe complications, including respiratory failure.

The study aimed to evaluate the manifestations of RSV infection in hospitalized children younger than 18 months of age and predictors of disease severity, as well as their comparison with the same age group hospitalized due to ALRI of different etiology.

A retrospective analysis was performed on medical records of 448 children hospitalized due to ALRI. The analysis was performed on the total study group and subgroups of children with positive and negative results of the nasal swab for RSV detection. In each group, clinical data, laboratory test results, and imaging results were analyzed.

The most common manifestation was pneumonia (n = 82; 63.08%). Otitis media was observed mainly in children under six months of age with lowered inflammatory markers ($P < 0.05$), conjunctivitis in those with a positive family history of allergies ($P < 0.05$), and pneumonia in children under six months of age, with lower blood oxygen saturation and inflammatory markers, features of acidosis, and fever-free course ($P < 0.05$). Respiratory failure affected 13 children (10%). However, no predictors of this complication were noted.

It seems advisable to perform the imaging of the lungs on admission and carefully monitor the child's condition during hospitalization. Special attention for the younger children with low inflammatory markers on hospital admission, increased clinical symptoms, and family history of allergies.

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DERMATOLOGY

TOPICAL ANTIFUNGAL DRUGS - AN OVERVIEW

***Madhu R**

Abstract: *In tropical countries like India, there has been an increase in the prevalence of dermatophytosis among adults and children over the last 6-7 years. This has been associated with rampant abuse of irrational topical corticosteroid, antifungal, antibacterial combination creams and change in the etiological agent from Trichophyton rubrum to T.mentagrophytes. Topical azoles, allylamines, benzylamines, hydroxy pyridone, morpholine, tolnaftate, Whitfield's ointment and polyenes are the various antifungals available to treat fungal infections. Topical antifungals are seen as a big advantage in the treatment of superficial mycoses like dermatophytosis, pityriasis versicolor and candidiasis in the pediatric population,especially in neonates and infants. High local concentration, ease of application, negligible systemic absorption and minimal adverse effects are the merits of topical antifungals. Limited infections are treated with only topical antifungals, while extensive lesions, presence of comorbid conditions, immunosuppressive therapy and infection of hair/nail warrant the use of topical antifungal agent along with a systemic antifungal drug. Topical imidazoles, allylamines, ciclopirox olamine and amorolfine are the various options currently in vogue for the treatment of dermatophytosis of skin and pityriasis versicolor. Topical imidazoles and ciclopirox olamine are effective in the treatment of mucocutaneous candidiasis. Various antifungals available for the treatment of onychomycosis are 5% amorolfine and 8% ciclopirox olamine nail lacquers, with the newer options being 10% efinaconazole and 5% tavabarole solutions, which are yet to be available in India. Counselling plays a pivotal role in the management of dermatophytosis of glabrous skin.*

Keywords: *Dermatophytosis, Topical antifungals, Systemic antifungals, Fungistatic, Fungicidal.*

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Fungal infections in children could range from superficial mycoses to subcutaneous and opportunistic invasive mycoses, wherein the treatment may be topical or systemic antifungal drug or a combination of both. There has been a rise in the incidence of invasive fungal infections, in this era of increased immunosuppressive states such as bone marrow/solid organ transplantation, hematological malignancy, prolonged administration of corticosteroids or other immunosuppressive drugs and acquired immunodeficiency syndrome. Medical advances in preterm care have improved the survival of preterm babies, which on the other hand has led to prolonged stay in intensive care units, total parenteral nutrition and use of broad-spectrum antibiotics. All these increase the susceptibility of preterm babies to develop invasive mycoses.[1,2] Systemic antifungal drugs have gained much significance in this context of increasing invasive fungal infections and antifungal resistance. Similarly, the surge in the prevalence of dermatophytosis of the glabrous skin, especially steroid modified tinea as a result of use of irrational topical corticosteroid, antifungal combination creams among children in the recent years in India, has led to increased use of systemic and also topical antifungals in this population.[3,4] This increased prevalence reflects the scenario of dermatophytosis among the adults. There has been a change in the trend of the etiological agent from *T.rubrum to T.mentagrophytes*. Antifungal agents are classified into topical and systemic drugs (Table I). Polyenes, heterocyclic benzofuran, azoles, allylamines and echinocandins are the five major classes of antifungal agents available to combat fungal infections.

Topical antifungal drugs

Topical antifungal agents, by virtue of the ease of application, high local concentration, better bioavailability, minimal side effects, negligible systemic absorption and drug-drug interactions are a much-sought option in the management of superficial fungal infections in children. Moreover, topicals are the only option in children with hepatic failure and concomitant superficial fungal infection and in those in whom systemic antifungals cannot be taken. Therapeutic efficacy will depend on the drug concentration, which is determined by penetration, diffusion and molecular weight.[5] An ideal topical antifungal agent is

Table I. Classification of antifungals

Class	Topical	Systemic
Polyenes	Nystatin	Amphotericin B
Heterocyclic Benzofuran	-	Griseofulvin
Azoles	Imidazoles - Clotrimazole, ketoconazole, miconazole, oxiconazole, bifonazole, fluconazole, luliconazole, sertaconazole, eberconazole, fenticonazole Triazole - Efinaconazole	Imidazole - Ketoconazole Triazoles - Itraconazole, voriconazole, posaconazole, isavuconazole, ravuconazole
Allylamines Benzylamines	Terbinafine Butanefine	Terbinafine
Echinocandins	-	Caspofungin, micafungin, anidulafungin
Antimetabolites	-	Flucytosine
Pyridone	Ciclopirox olamine	-
Morpholine	Amorolfine	-
Oxabarole	Tavabarole	-
Thiocarbamate	Tolnaftate	-
Miscellaneous	Whitfield's ointment, undecylenic acid, selenium sulphide, zinc pyrithione	-

expected to be fungicidal with high mycological and clinical cure rate, possess broad-spectrum activity/ keratinophilic and lipophilic effects/low incidence of side effects/convenient dosing/low relapse rate and in addition should be cost effective. Localised lesions are amenable to treatment with only topicals, while in extensive lesions, topical antifungals compliment the action of systemic antifungal drugs. Topical antifungals are available in various formulations such as cream, lotion, gel, spray, ointment, shampoo, lacquer, soap and powder. Suboptimal concentration of antifungal drugs present in soaps and powders precludes the use of these products, as it may lead to antifungal resistance. Adverse effects associated with topical antifungals are rare and may manifest as erythema, burning or stinging sensation and allergic contact dermatitis. Azoles, allylamines, ciclopirox olamine, amorolfine and Whitfield's ointment are the topical antifungals currently in use. In case of extensive dermatophytosis, while using combination of topical and systemic antifungals, cost factor emerges as the constraint of topical antifungals, wherein the physician can choose the cost-effective options and limit the application to the most pruritic sites and lesions in exposed areas. Duration of treatment varies in the different superficial fungal infections. In case of dermatophytosis of glabrous skin, application of all topical antifungals has to be continued for 2 weeks beyond complete clinical resolution.[6] It would be appropriate to apply the cream from 2 cm beyond the outer margin inwards, as there is radial movement of the dermatophytes.[7] Most of the topical antifungals used in dermatophytosis of skin, except few, require twice daily application."Rule of Two" (The topical antifungals should be applied 2 cm beyond the margin of the lesion twice a day for at least 2 weeks beyond clinical resolution) summarises the technique and frequency of application and duration of treatment of dermatophytic infection of skin.[8]

Azoles

Azoles are heterocyclic aromatic compounds classified as imidazoles and triazoles based on the presence of number of nitrogen atoms. They exert antifungal action by non-competitive inhibition of 14 α lanosterol demethylase resulting in impairment of synthesis of ergosterol and accumulation of 14 α methylated sterols. This leads to disruption and increased permeability of fungal cell membrane, inhibition of cell growth and finally death of fungal cell. Spectrum of activity of azoles include dermatophytes, *Candida* spp., *Malassezia* spp., *Piedraia hortae, Hortaea werneckii, Aspergillus spp., Fusarium, Sporothrix schenckii, Cryptococcus neoformans, Histoplasma* spp., *Blastomyces dermatidis, Coccidioides*

immitis, Paracoccidioides brasiliensis etc.[9] In addition, few azoles possess antibacterial activity, while some have anti-inflammatory action. Most of the azoles have to be applied twice daily, while bifonazole, ketoconazole, oxiconazole and luliconazole are effective with once daily application.

Clotrimazole

Clotrimazole is a broad-spectrum, first generation imidazole with fungistatic action and fungicidal effect at very high concentration.[10] It is also active against few Gram-positive bacteria and Trichomonas species. It was first synthesised by Karl Hienz Buchel (Bayer) in 1969.[11] By virtue of good spectrum of activity against dermatophytes, *Candida* and *Malassezia* species, this topical drug available as 1% cream/ lotion/ gel is effective in children with mucocutaneous candidiasis, pityriasis versicolor, tinea corporis, tinea cruris, tinea pedis and otomycosis.[12] It is not recommended for self-medication by care takers in children less than 2 years of age.

Dosage regimen

Pityriasis versicolor and cutaneous candidiasis - twice daily x 4 weeks

Oral candidiasis - clotrimazole mouth paint 5 times daily for 1 to 2 weeks

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution

Miconazole

Miconazole is a synthetic, benzimidazole derivative with fungistatic and fungicidal effects. Apart from the inhibition of 14 α demethylase, this first-generation imidazole causes oxidative damage and fungal cell death by induction and accumulation of reactive oxygen species (ROS).[13] Miconazole was shown to inhibit thromboxane synthase and aggregation of platelets.[14] It penetrates well into the stratum corneum and is detectable up to 4 days post application. Spectrum of activity and clinical uses are similar to clotrimazole. It is useful in the treatment of erythrasma and is available as 2% cream, gel and powder. Miconazole 2% cream is approved for use in children aged 2 years and above.[15] Miconazole 0.25% cream with zinc oxide and petrolatum was approved for the treatment of diaper dermatitis complicated by candidiasis in immunocompetent infants aged four weeks and above.

Dosage regimen

Pityriasis versicolor - once daily x 4 weeks

Cutaneous candidiasis - twice daily x 4 weeks

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution

Ketoconazole

Ketoconazole (KZ) is a second-generation imidazole drug known for the broad spectrum anti-mycotic coverage, anti-inflammatory potential in par with hydrocortisone acetate and antibacterial activity.[12,16] In addition to the clinical indications similar to that of miconazole, KZ is effective in the management of seborrheic dermatitis, by virtue of good action against *Malessezia* spp and anti-inflammatory effect. KZ lotion, gel, foam and shampoo are approved for use in children aged 12 years and older.[15] As clinical data on the safety and the effectiveness of KZ cream and KZ shampoo in children aged less than 12 years is not available, use is not recommended for self-medication.

Dosage regimen

Pityriasis versicolor and cutaneous candidiasis - once daily x 4 weeks

Extensive pityriasis versicolor - Ketoconazole lotion is to be applied for 10 minutes before bath x 2 weeks

Seborrhoeic dermatitis - short contact lotion or shampoo applied on the scalp for 5 to 10 minutes before hairwash, twice a week for 4-8 weeks

Dermatophytosis of skin - once daily x 2 weeks beyond complete resolution

Bifonazole

Bifonazole (BZ) is a broad-spectrum fungicidal imidazole, with anti-inflammatory property and antibacterial activity against Gram-positive bacteria. Apart from inhibition of 14 α lanosterol demethylase, bifonazole also inhibits HMG-CoA reductase.[17] It penetrates well into the skin, achieves high concentration and is retained for a long duration of about 120 hours. While clinical uses are similar to miconazole, BZ has the advantage of once daily application and shorter treatment duration.

Dosage regimen

Pityriasis versicolor - once daily x 2 weeks

Cutaneous candidiasis - once daily x 2 to 4 weeks

Dermatophytosis of skin - once daily x 2 weeks beyond complete resolution

Oxiconazole

Oxiconazole is a broad-spectrum fungicidal drug with an advantage of reservoir effect. This drug which achieves high concentration in the epidermis and is retained for 7 days, has exhibited good therapeutic efficacy. It also has antibacterial effect against certain Gram-positive bacteria.

Literature states that oxiconazole cream may be used in pediatric population.

Dosage regimen

Pityriasis versicolor and cutaneous candidiasis - Once/twice daily x 2 weeks

Dermatophytosis of skin - once/ twice daily x 2 weeks beyond complete resolution

Sertaconazole

Sertaconazole (SZ), a third- generation imidazole exhibits fungistatic action at low concentration and fungicidal effect at high concentrations. It is active against *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Listeria monocytogenes*, etc. Studies have documented the anti-inflammatory and anti-pruritic potential of SZ.[18,19] Anti-inflammatory action of SZ was found to be the highest when compared with fluconazole, miconazole, ketoconazole, butoconazole, terconazole, tioconazole and ciclopirox olamine.[18] SZ is approved for use in children aged 12 years and above.

Dosage regimen

Pityriasis versicolor and cutaneous candidiasis - twice daily for 4 weeks.

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution.

Luliconazole

Luliconazole (LZ), an analogue of lanaconazole is an imidazole which was first discovered in Japan in 2005. Broad spectrum of activity, unique chemical structure, reservoir effect, once daily application and low minimum inhibitory concentration (MIC) against *T.rubrum* and *T.mentagrophytes* are seen as advantages of luliconazole.[20] This drug has been approved by FDA for use in children aged 12 years and above with tinea pedis and tinea cruris and in those who are 2 years and older with tinea corporis. Therapeutic efficacy of LZ 5% and 10% solutions in the management of onychomycosis have been evaluated in adults. However, published data in children are not available.[21,22]

Dosage regimen

Dermatophytosis of skin - once daily x 2 weeks beyond complete resolution.

Eberconazole

Eberconazole (EBZ) is a broad-spectrum imidazole first approved in Spain in 2015. It exhibits fungicidal action at higher concentrations. EBZ also has anti-inflammatory potential and antibacterial activity like sertaconazole.

Dosage regimen

Pityriasis versicolor /cutaneous candidiasis - once or twice daily x 2 weeks

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution.

Efinaconazole

Efinaconazole (EFZ) is a novel topical triazole, approved by FDA in 2014 for the treatment of toe nail onychomycosis due to *T.rubrum and T.mentagrophytes* in adults. Spectrum of activity includes dermatophytes, *Candida* spp. and non-dermatophytes such as *Aspergillus, Fusarium, Acremonium, Scopuloriopsis* etc. This fungicidal drug permeates through the subungual space and rapidly penetrates into the nail. Low keratin binding of EFZ results in higher levels of the unbound drug and thus contributes to the antimycotic action.[23] EFZ 10% solution was approved for the treatment of onychomycosis of toe nails in children aged 6 years and above, in April 2020.[24]

Dosage regimen

Onychomycosis of toe nails - Once daily application x 48 weeks

Allylamines and Benzylamines

This group of drugs are fungicidal in nature and exert their antifungal action by inhibition of squalene epoxidase in the HMG pathway. This leads to the accumulation of squalene which exerts a direct effect on the fungal cell causing death and depletion of ergosterol, which results in disruption and increased permeability of the fungal cell membrane. Naftifine and terbinafine belong to allylamines, while butenafine is a benzylamine. As the inhibition of fungal squalene epoxidase is selective, propensity for drug - drug interaction is much less compared to azoles.

Terbinafine

Terbinafine (TRB) is a broad-spectrum, fungistatic and fungicidal drug, lipophilic in nature. Terbinafine cream was approved for use in the treatment of tinea pedis due to *T.rubrum or T.mentagrophytes* in 1997. Lipophilicity of the drug leads to high concentration of the drug in stratum corneum, sebum and hair follicles. It is detectable in the stratum corneum, seven days after the last application.[25] Spectrum of activity of TRB includes dermatophytes, *Candida* spp., Gram-positive bacteria (*Staph aureus, Staph.faecalis), Pseudomonas, Trypanosoma cruzi* and

Leishmania mexicana.[12] TRB is approved for sale without prescription for the treatment of tinea corporis, tinea cruris and tinea pedis in patients aged 12 years and above. A study done by Lucio B, et al documented the efficacy of terbinafine in the treatment of tinea corporis and tinea cruris in children aged 2-15 years.[26]

Dosage regimen

Pityriasis versicolor and cutaneous candidiasis - once/twice daily x 2 weeks.

Dermatophytosis of skin - Twice daily x 2 weeks beyond complete resolution.

Butenafine

Butenafine is a broad-spectrum, synthetic benzylamine derivative. It was widely used in Japan as the treatment of choice in patients with tinea corporis, tinea cruris, pityriasis versicolor and cutaneous candidiasis since the introduction in 1992. It achieves high concentration in the stratum corneum and is retained for a long duration. Studies have documented continued improvement after cessation of application of butenafine cream and this residual therapeutic efficacy has been attributed to the strong keratin binding nature of the drug.[12] Butenafine has been approved by FDA for the treatment of interdigital tinea pedis, tinea cruris and tinea corporis in children aged 12 years and above.

Dosage regimen

Pityriasis versicolor/cutaneous canidiasis - once daily x 2 weeks.

Dermatophytosis of skin - once daily x 2 weeks beyond complete resolution.

Ciclopirox olamine

Ciclopirox olamine (CPO), a broad-spectrum antifungal agent with fungistatic and fungicidal effects and anti-inflammatory potential, acts through various mechanisms. CPO chelates with trivalent metal ions such as Fe^{3+} and Al^{3+} and inhibits catalase and peroxidase enzymes. It interferes with the cellular transport of electrons and mitochondrial energy production. Eventually, there is increased permeability of the fungal cell membrane and leakage of cellular contents.[27,28] CPO is active against dermatophytes, *Malassezia* spp., *Candida* spp., *Aspergillus* spp., *Cryptococcus neoformans* spp., *Fusarium solani*, certain Gram-positive and Gram-negative bacteria. Antibacterial action of CPO facilitates the treatment of superficial fungal infections with secondary bacterial infections. It is available as 1% cream, 0.77% gel and 8% nail lacquer.

FDA approval: CPO cream in children aged 10 years and above; CPO nail lacquer in children aged 12 years and above and CPO shampoo in children aged 16 years and above.

Dosage regimen

Cutaneous candidiasis - twice daily x 4 weeks Pityriasis versicolor - twice daily x 2 weeks.

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution.

Seborrhoeic dermatitis - CPO gel and shampoo twice weekly x 4 weeks.

8% CPO nail lacquer - daily application for 48 weeks. It is to be applied over the entire nail bed, under surface of nail plate, hyponychium and 5 mm area of surrounding skin.

Amorolfine

Amorolfine is a broad-spectrum antifungal drug with both fungistatic and fungicidal action. It is a morpholine derivative, which exerts the antifungal effect by inhibition of 2 enzymes namely, delta 14 sterol reductase and cholestenol delta - isomerase, that are a part of ergosterol biosynthesis pathway. Ergosterol depletion occurs resulting in disruption and increased cell membrane permeability, and eventually cell death. Amorolfine and CPO were observed to possess sporicidal activity against microconidia of *T.rubrum* and blastospores of *Candida albicans*.[29] Epidermal retention of the drug for two to three days is seen as an advantage. This drug exhibits good spectrum of activity against dermatophytes and dimorphic fungi and is less active against yeast and moulds. It is available as cream and nail lacquer. Amorolfine nail lacquer is not recommended for use in children aged below 12 years.

Dosage regimen

Dermatophytosis of skin - twice daily application

Onychomycosis - nail lacquer - twice weekly x 6 months for finger nails and 9 to 12 months for toe nails

Tavabarole

Tavaborole, a broad-spectrum antifungal agent, is effective against toe nail onychomycosis due to *T.rubrum* and *T.mentagrophytes* in adults. It inhibits fungal cytoplasmic leucyl-transfer RNA synthetase, for which it has high affinity, compared to the mammalian counterpart. Fungal protein synthesis is thus inhibited and this eventually leads to death of the fungal cell. Unique nature of tavabarole with low molecular weight and hydrophilicity

enables better penetration of the nail, compared to ciclopirox olamine nail lacquer.[30] It has a good spectrum of activity against dermatophytes and non-dermatophyte moulds. Safety and efficacy have not been established in pediatric population.

Dosage regimen

5% Tavabarole nail lacquer - once daily application x 48 weeks. It should be applied over the entire nail surface and beneath the tip of the affected toe nail.

Tolnaftate

Tolnaftate is a thiocarbamate, discovered as early as 1962. The exact mechanism by which this drug exerts its antifungal action is unknown. Though it inhibits the enzyme squalene epoxidase, the mechanism is considered to be different from that of allylamines. It is fungistatic at low concentrations and fungicidal at high concentrations.[7] While it is active against dermatophytes and *Malassezia* species, it does not act against *Candida* and bacteria.

Table II. Topical antifungals - Concentration, formulation, frequency of application and FDA Pregnancy Category

Drug	Drug concentration	Formulation	Frequency of application	FDA pregnancy category
Imidazoles				
Bifonazole	1%	Cream	OD	B
Clotrimazole	1%,2%	Cream, lotion, soap, powder	BD	B
Eberconazole	1-2%	Cream, lotion, gel, powder	BD	C
Ketoconazole	2%	Cream, lotion, soap, powder, shampoo	OD	C
Luliconazole	1%	Cream, lotion, spray	OD	C
Miconazole	2%	Cream, gel, ointment, powder	BD	C
Oxiconazole	1%	Cream, lotion	OD/BD	B
Sertaconazole	2%	Cream, lotion, shampoo, powder	BD	C
Triazole				
Efinaconazole	10%	Solution	Daily	C
Allylamines				
Terbinafine	1%	Cream, gel, lotion, spray, powder	OD/BD	B
Benylamines				
Butanefine	1%	Cream	OD	B
Hydroxy pyridone				
Ciclopirox olamine	1%, 8%	Cream Shampoo Lacquer	BD Weekly twice Daily OD	B
Morpholine				
Amorolfine	0.25%, 5%	Cream Lacquer	BD Weekly twice	Not categorized
Oxabarole				
Tavabarole	5%	Solution	Daily	C

Note: OD - once daily; BD - twice daily

Dosage regimen

Dermatophytosis of skin - twice daily x 2 weeks beyond complete resolution

Pityriasis versicolor - twice daily x 2-4 weeks

Whitfield's ointment

Whitfield's ointment, used for the treatment of dermatophytosis is composed of 6% benzoic acid and 3% salicylic acid in an emulsifying ointment base (half strength). Full strength ointment contains 12% benzoic acid and 6% salicylic acid. Benzoic acid possesses antifungal and antibacterial activity, while salicylic acid is keratolytic and has weak antifungal and antibacterial effects. It should not be applied on inflammatory lesions, flexures and sites with thin skin such as face, as there could be irritation and burning sensation. It is useful in the treatment of dermatophytosis of skin, pityriasis versicolor and tinea nigra.

Dosage regimen

Dermatophytosis of skin - twice daily application x 6 weeks

Pityriasis versicolor - twice daily x 2-4 weeks

Details of drug concentration, formulations, frequency of application and FDA Pregnancy Category are given in Table II.

Synopsis of topical antifungal therapy

Topical antifungals play a pivotal role in the management of the common superficial mycoses namely dermatophytosis, pityriasis versicolor and candidiasis. Decision making with regard to selection of only topical antifungal drug or combination of topical and systemic antifungal drugs depends on the site, extent, involvement of nail/terminal hair, presence of co-morbid conditions, immunosuppressive treatment and failure of treatment with topicals. Topical antifungal therapy is the preferred choice in limited infection, neonates and infants, hepatic failure and multiorgan dysfunction. In children with extensive lesions, hair/ nail infection or steroid modified/chronic/ recurrent dermatophytosis, combination of topical and systemic antifungals is to be prescribed, wherein topical compliments the action of systemic antifungal, by virtue of the high local concentration of the drug. While choosing a topical antifungal drug, cost, compliance, availability and affordability warrant due attention.

Topical imidazoles, allylamines, ciclopirox olamine, amorolfine, butenafine and tolnaftate are effective in the treatment of dermatophytic infection of skin. Cochrane review concluded that all classes of commonly used topical antifungals achieve substantial mycological and clinical cure rates.[31] Head to head comparative clinical trials would be required to determine the real efficacy and superiority of one molecule over the other. However, topical imidazoles with anti-inflammatory potential are preferred in steroid modified and inflammatory lesions of dermatophytosis. In children with steroid modified dermatophytosis, it is of utmost importance to abruptly stop the application of the triple/four/five drug combination of topical corticosteroid, antifungal, antibacterial cream.[6] Emollients play a significant role in the alleviation of itch in patients with

Table III. Topical antifungals and clinical indications

Superficial mycoses	Topical antifungal drug
Dermatophytosis of skin – tinea corporis, tinea cruris, tinea faciei, tinea pedis, tinea manuum	Imidazoles, allylamines, butanefine, ciclopiroxolamine, amorolfine, tolnaftate
Onychomycosis	Amorolfine and ciclopirox olamine nail lacquers Newer drugs - 10% Efinaconazole and 5% Tavabarole
Pityriasis versicolor	Imidazoles, allylamines, butanefine, ciclopirox olamine, amorolfine, tolnaftate
Extensive lesions	Ketoconazole lotion/shampoo - short contact prior to rinsing
Mucocutaneous candidiasis- cutaneous candidiasis, vulvovaginal candidiasis, oral candidiasis	Imidazoles, ciclopirox olamine
Malassezia associated dermatitis - Seborrhoeic dermatitis	Ketoconazole with or without zinc pyrethione/ sertaconazole/ ciclopirox olamine / selenium sulfide shampoo

dermatophytosis, especially steroid modified tinea, as there is epidermal barrier dysfunction (increased transepidermal water loss and decrease in level of ceramides) in steroid modified dermatophytic lesions.[6,32] Emollients could be applied immediately after bath, after patting the skin dry and could be repeated depending on the dryness of skin. Topical antifungal drug could be applied thirty minutes after emollient application. Table III depicts the clinical indications for topical antifungals.

Prescription of a topical antifungal or a combination of topical and systemic antifungals alone would not ensure a successful therapeutic response in patients with dermatophytosis and pityriasis versicolor. Counselling regarding the course of infection, personal hygiene (daily bath, wiping dry), lifestyle modification (avoidance of synthetic tight garments, leggings/jeans, measures to reduce obesity), avoidance of sharing of fomites and washing clothes in hot water at 60^0 C is indeed imperative in patients with dermatophytosis. Persistent hypopigmentation, post-treatment and recurrence are the main issues in patients with extensive pityriasis versicolor. Hence, it becomes important to reassure the children and parents about hypopigmentation of lesions and counsel them about prevention of recurrence.

Points to Remember

- ***Fungal infections in children could include superficial mycoses to subcutaneous and opportunistic invasive mycoses, wherein the treatment may be topical or systemic antifungal drug or a combination of both.***
- ***Topical antifungal agents, are very useful preparations in view of ease of application, high local concentration, better bioavailability, minimal side effects, negligible systemic absorption and drug – drug interactions.***
- ***"Rule of Two" in usage of topical antifungals means it should be applied 2 cm beyond the margin of the lesion twice a day for at least 2 weeks beyond clinical resolution.***
- ***In children with extensive lesions, hair/nail infection or steroid modified / chronic / recurrent dermatophytosis, combination of topical and systemic antifungals are needed.***
- ***Emollients could be applied immediately after bath, after patting the skin dry and could be repeated if there is dryness of skin. Topical antifungal drug could be applied thirty minutes after emollient application.***

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ERRATUM

Article titled “Rotavirus vaccination” Indian J Pract Pediatr 2020; 22(4):37-42.

Page No.40: Box 1. Maximum age for the final dose in the series: 8 months, 6 days. To rewrite as - Maximum age for the final dose in the series: 8 months, 0 days. The typing error is regretted.

Editorial Board
Indian Journal of Practical Pediatrics

ADOLESCENCE

SCHOOL BASED ADOLESCENT HEALTH CARE - CUDDALORE MODEL

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Abstract: *Health care of adolescents is an important aspect of pediatrics and paediatricians play a vital role in supervising their overall well being - physical, psychological, social, reproductive and spiritual. The Cuddalore model of school based adolescent care with emphasis on the ten-point program is a simple, feasible, and acceptable means of achieving this goal. The components include growth monitoring, age appropriate immunization, life skills education, handling peer group pressures and avoiding internet addiction. Our experience in implementing this project is shared in this brief write-up.*

Keywords: *Adolescents, School based care.*

Adolescence is a critical period of life, where the major determinants of mortality and morbidity are largely behavioural. This phase is characterized by immense biologic, psychological and social changes. Adolescents are the pillars of future India and hence Indian Academy of Paediatrics (IAP) in 2004 declared "We promise to look after you till 18 years". The Government of India in the recent national programs has included those up to 18 years as children, to be taken care of by pediatricians. Adolescents are not usually brought to the pediatrician's office and when they do, little time is spent on counselling them on preventive care focusing on physical, reproductive, mental, social, emotional and spiritual wellbeing. It may be more appropriate if pediatricians make school visits and spend time on preventive health care in adolescents thereby laying the foundation for their good all-round health, especially reproductive health of adolescent girls destined to be the future mothers.

We were buoyed by the Thiruvananthapuram experience where a school based study showed that intervention using family life and life skill education package resulted in consistent improvement in knowledge about reproductive health among adolescents of all ages where previously there had existed an overall naivete about such issues.[1]

In a school-based study, menstrual disorders were reported in 21.1% comprising dysmenorrhea (72.4%), oligomenorrhea (11.3%), normal vaginal discharge (81.5%) and abnormal vaginal discharge (5.7%) in spite of adequate menstrual hygiene in the majority of girls.[2] Proper history and simple clinical examination may be sufficient to identify a majority of adolescents with lower reproductive tract infections (RTI). A study of 427 unmarried girls from a community adolescent clinic validating clinical diagnosis of lower RTI against laboratory diagnosis as gold standard showed sensitivity 62.7%, specificity 97.8%, 92.3% overall accuracy and a high 0.96 negative predictive value.[3]

The Cuddalore Model

A project 'Vision-2020 for Adolescents' was prepared, and presented in the National Conference of Indian Academy of Pediatrics (IAP) 2005. It was the work done as a pilot project in Cuddalore District in the year 2005 as District Presidential Action plan which was completed in 2005. With the help of senior pediatricians, adolescent experts and psychiatrists problems of adolescent were identified. All the projects were executed in the year 2005. After completing the pilot project, it was presented in the National conference in 2005. The project has been coordinated with the Government of Tamil Nadu and followed up with Training Program as TOT for Teachers,

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in District level and State level. It is an ongoing project in Cuddalore District in Tamil Nadu state. Salient features of the project were:

(i) Around 10,000 school children enrolled every year and trained in adolescent health care continuously for the last 15 years.

(ii) Five hundred pediatricians trained in adolescent health care as part of central IAP project in 2012.

(iii) Eye screening performed for 12000 school children.

(iv) 'Teens Clubs' started in schools.

(v) Government girls' high schools adopted as part of a district project.

(vi) Training of teachers imparted to give adolescent care at district and state level.

(vii) Model lecture of 60 minutes duration prepared to provide training on the important aspects of adolescent health, family life education and life skills.

The Cuddalore model being presented here includes a ten-point program for maintenance of health, growth monitoring, ability to handle peer pressure, prevention of unhealthy habits like smoking, alcohol and drugs, some aspects of HIV prevention and how to deal with the issue of teenage relationships in an appropriate manner.

Ten-point program - Cuddalore Model

Brief explanation about the following ten common issues was provided to the school children.

1. Personal hygiene: Cleanliness gives protection from infection and promotes self-confidence and a sense of well being. After using the toilet, girls need to wash genitalia from front to back to prevent infection and also practice compulsory hand washing. Community studies in Kerala showed the value of good personal hygiene practices and are worth emulating. A population based survey among adolescent girls and young adults between 10 and 24 years of age from three districts of Kerala showed the following personal hygiene practices - changing sanitary napkins/ cloths more than once a day (94.3%), cleaning genitalia adequately every day (71.7%), washing after using the toilet (69.2%), washing from front to back after defecation (62.2%) and washing hands with soap after defecation (73.2%) with higher percentages in the older groups emphasising the need for adolescent reproductive sexual health (ARSH) and counselling services from early adolescence.[4]

2. Balanced diet: Protein, carbohydrate, fat, vitamins, minerals and water in proper proportions constitute a balanced diet. Proteins are the building blocks of our body and there is an increased need in pre-adolescents on account of the rapid growth spurt. It prevents infection, gives energy and also improves memory. Adolescents need to consume vegetables and fruits. They should not miss breakfast as the morning food is considered the "brain food'. One egg gives 6 grams of first class proteins with high chemical score and the highest protein efficiency ratio of any dietary protein. Carbonated drinks, junk foods and foods with added preservatives should be avoided.

Anemia is quite common in adolescent girls (28.4%) as shown in a study among 14300 adolescents.[5] Poor socio-economic status, fear of gaining weight and irregular eating habits are the main causes of anemia in this population. National programmes tackling anemia in India which will benefit adolescents include : (i) Adolescent girls anemia control programme launched in 2011 in 13 states (ii) National weekly iron (100 mg) and folic acid (500 microgram.) launched in 2012 (iii) Weekly Iron and Folic Acid Supplementation(WIFS) programme and biannual albendazole administration. Anemia prevention efforts should focus on strengthening the existing iron and folate supplementation programmes and prevention of folate and vitamin B12 deficiency anemia.[6]

3. Exercise: At least 30 minutes of exercise per day has innumerable benefits like: (i) prevention of heart attack, (ii) postponement of diabetes mellitus, (iii) increased memory power, (iv) improved blood circulation, (v) increased excretion of waste products through sweat (vi) promotion of physical fitness (vii) reduced abdominal girth.

4. Eye care: During adolescent period there is elongation of the eye ball which can produce refractive error. The pre pubertal growth spurt may involve the optic globe resulting in its elongation and myopia in genetically predisposed individuals. Vision testing should be done before it affects school performance. Four population-based studies and eight school-based studies were included. In a systematic review, including 4 population-based and 8 school based studies from India, overall prevalence of refractive error was 8% per 100 children (CI: 7.4-8.1) and in schools it was 10.8%.[7]

5. Hair and skin care: Adolescents need to apply plenty of oil/moisturizer, particularly to the hands, neck and face. Too much soap can remove naturally occurring sebum allowing moisture to escape while a good moisturizer slows this down by acting as a barrier. Adolescent skin as such is

most attractive and they should not hide it with cosmetics.[8]

6. Dental care: Nearly 10% of the children have dental problems. For healthy teeth, adolescent needs to consult a dentist yearly. We need to promote brushing twice daily and after eating sweets and rinse the mouth with salt water daily. Toothbrush needs to be changed every 3 months. Bad breath is a sign of poor dental hygiene. Food particles get lodged between teeth and gum line, forming plaque and promoting decay. If plaque is not removed, tartar forms, attacking the supporting bone leading to fall of tooth. Good preventive care is better in order to avoid dental implants in later years.

7. Hydration: Adolescent girls need to drink adequate water - at least 8 glasses (approximately equal to 200 mL) per day. Girls often do not drink enough water and for fear of using dirty toilets tend to withhold urine for prolonged periods . This predisposes them to urinary tract infections. Withholding behaviour is to be avoided and adequate local hygiene measures followed after using the toilet. Boys need to wash by retracting the foreskin.

8. Adequate sleep: Sleep for atleast 8 hours a day will re-charge the adolescent brain, improve memory and promote vitality. They need to be counselled on sleep hygiene which includes regular sleep timings and avoidance of TV or electronic gadgets in the bed room.

9. Pleasant communication: Adolescents with a pleasant voice and a sweet smile will have more friends and better self-esteem. A smile costs nothing and improves face value!

10. Menstrual hygiene: Menstruation is the first sign of reproductive maturity. If menarche has not been attained by 14 years, a doctor needs to be consulted. Initial few cycles can be irregular, scanty or profuse. Pre-menstrual symptoms like, irritability, fatigue, breast tenderness, abdominal discomfort, etc. are common. Many girls may curse themselves or feel miserable about the problems that accompany menstrual cycles. They need to be counselled.

Menstrual hygiene needs to be emphasized - regular baths, neat clothes, frequent change of sanitary napkins/ cloth and trimming pubic hair prior to cycles. Good personal hygiene promotes self-confidence. Girls should not use chemical disinfectants over the under garments. Teachers and parents need to adequately educate pre adolescent girls regarding menstrual cycles to prevent anxiety and fear.

After getting trained on these ten points, the students were asked to put up their hands in turn and talk about any one of them - they were rewarded with a small token like a pen, so that they would continue to remember and follow the instructions.

Components of program implementation

1.Growth Monitoring: Weight and height were measured and body mass index (BMI) computed to assess growth and to identify under nutrition and obesity. Growth monitoring was carried out with adolescent health cards and age appropriate immunisation advice was provided. Many adolescents were worried about their appearance, short stature, skin colour, obesity, etc. They need to be told "real beauty is not outside, it is inside". Respectful attitude towards parents and teachers, good conduct in society and positive contributions to the community are what make one 'truly beautiful'. Height and skin colour do not really matter.

2.Anemia prevention: Three questions on adolescent health care were put forth in meetings at girls schools (i) Do you forget everything you read? (ii) Do you feel sleepy in classes? (iii) Does your hair fall during combing? We did hemoglobin (Hb) estimation for 400 girls in the 12^{th} standard and found that majority had Hb less than 10 gm/dL. Deworming was done and biweekly iron tablets was initiated for all girls with the help of the state Government. The National Cadet Corps (NCC) teacher was given the responsibility of administering biweekly iron tablets on Mondays and Thursdays.

3.Vision problems: We screened 12000 school children with the help of Aravind Eye hospital team, who trained one teacher per 300 children from 6 schools to use the Snellen chart. These teachers screened the vision of adolescents and identified nearly 1200 children with refractive errors and later 800 of those children were given spectacles at minimum cost. Adolescents need to read and work in good light and avoid reading in moving vehicles.

4.Family life education: The project was implemented by a trained pediatrician visiting the school and educating the adolescents, in an interactive session for 60-90 minutes. Quoting examples of various unhealthy, risky or exploitative situations and by using role-play, students were asked to enact how to avoid and say NO in a given situation. It was followed by question-and-answer session, where queries are answered in a simple and culturally appropriate manner. On the next day, a one-to-one counselling session for the children in need was organised in the same school.

5.Life skills education: Life skill strategies (WHO) were taught in a culturally appropriate manner for (i) coping with emotions (ii) coping with stress (iii) creative thinking (iv) critical thinking (v) decision making (vi) effective

communication (vii) empathy (viii) interpersonal relations (ix) problem solving and (x) self-awareness.

6.Learning to Say NO: The adolescent is given guidance as to how to refuse a situation while maintaining healthy friendship and relationship. This includes (a) avoiding the situation, (b) giving reasons to the other person, (c) explaining the reason (d) finding others to support oneself (e) politely refusing, (f) repeating the refusal (g) talking about one's own feelings and (h) walking away. Learning to say 'NO' the first time itself will be much easier than doing it later. Remember while saying 'NO', not to hurt the other person, rather make the person feel how much one is hurt to say 'NO'. When an adolescent is trained to say 'No'at home and school, he or she will be able to say no to smoking, alcohol, drugs and premarital sex and unprotected sex which may lead to HIV and other sexually transmitted diseases.[4,8]

7.Psychological problems: All young people today face stress in their lives. Relationship experiences are most important. Nearly one in five adolescents, will have an emotional or behavioural disorder at some point or other. Academic failure and social rejection often have lasting consequences. At least 3% of school aged children suffer from serious mental illness such as depression, obsessive compulsive disorder or psychosis. School is the best opportunity for group counselling and individual counselling for those who need it without being judgemental. Short version of Teen Screen Questionnaire-Mental Health (TSQ-M-Short) was used in schools to identify psychological problems in adolescents.[9]

8.Risk taking behaviour and addictions: Experimenting, experiencing and expanding are the three main characteristics of adolescents. Everyone goes through this stage of risk-taking behaviour and parents have to temper this while maintaining healthy interactions with their teenage children. A case control study among unwedded teenage mothers clearly showed that those with (i) poor parenting, (ii) emotional separation from parents and (iii) lack of age-appropriate sexual reproductive health education had increased risk of teenage pregnancy, highlighting the importance of family on prevention.[10]

The method of protection against HIV infection is to practice healthy sexual and reproductive behaviour such as avoiding sex before marriage.

Adverse adolescent health behaviours are smoking, alcohol use, drug misuse and internet addiction. In India adolescent statistics for alcohol use is reported to be 11% in boys, 1% in girls - and for tobacco use - is 29% in boys and 4% in girls. Average age of initiation for tobacco is 12.3 yrs, 13.6 yrs for alcohol and 11% of cannabis users initiated before 15 yrs. Tobacco use usually starts in adolescence and continues into adult life. A study from Noida, India, in 2011 found some form of tobacco use in 11.2% students.[11]

Internet addiction is a growing epidemic and especially with online instruction being the norm after the covid pandemic, every adolescent has easy access to smart phones and thereby browsing on the internet has increased exponentially. Diagnosis of internet addiction disorder was made by (i) being preoccupied with the internet, (ii) feeling a desire to use the internet for increasing amounts of time in order to achieve satisfaction (iii) having a lack of control in efforts to stop using the internet or to cut back use.[12,13]

Upscaling Cuddalore Model: Role of IAP /Adolescent Health Academy (AHA) District Branches

- Each district branch of IAP or AHA can adopt one or two schools a year to promote adolescent health.
- IAP district branches can coordinate with Governmental efforts to advance the cause of adolescents in the school health program.
- Organize training programs on life skill education and health awareness (like stress management; time management, study skills, anger control) for parents of adolescents.
- Guidance can be provided to form Teens club in each school to showcase their talents, harness their energy and potential in organising camps for immunization, eye donation, blood donation and organ donation campaigns.
- Organization of comprehensive adolescent development in collaboration with Rastriya Kishore Swasthya Karyakram (RKSK) and ICDS network.[12,13]

Points to Remember

- ***Pediatricians need to be trained to educate adolescents in schools on 10 major aspects - cleanliness, balanced diet, exercise, eyecare, hair and skin care, dental care, adequate sleep, hydration, pleasant communication and reproductive health.***
- ***Growth monitoring and regular immunisation to be completed and charted on adolescent health cards.***
- ***Visual problems should be screened as part of school health checks.***

- ***Anemia must be identified early by screening and Iron + folic acid supplementation given especially to adolescent girls.***
- ***Family life education needs to be imparted to adolescents as an insurance against teenage pregnancies, sexually transmitted diseases like HIV and dysfunctional relationships that can ensue from inappropriate interactions.***
- ***Life skill education is an essential aspect of adolescent care which can help protect them from risk taking behaviours like smoking, alcohol and drugs.***
- ***Psychological issues may be prevented by mass counselling in schools and to offer one-to-one counselling to students with specific problems***.

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RADIOLOGY

CYSTIC LESIONS IN NEONATES AND INFANTS ON CRANIAL ULTRASONOGRAM - PART II

Raveendran J

The differential diagnosis of intracranial cystic lesions in cranial ultrasonogram (USG) includes a broad spectrum of conditions:

1. Normal variants.
2. Supratentorial cysts and
3. Infratentorial cysts.

Cranial USG can provide important information about the anatomic location, size and shape of the lesions as well as their mass effect on adjacent structures. Normal variants and supratentorial cysts have been discussed in the last issue. We will discuss in detail about the vein of Galen malformation and infratentorial cysts in this issue.

Infratentorial cysts can be described based on its location as supra, retro or infra cerebellar cysts.

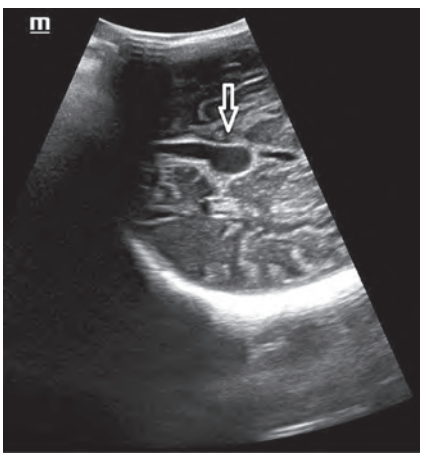

Fig.1a. Sagittal view cranial sonography showing Vein of Galen noted as anechoeic tubular midline structure (white arrow)

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Vein of Galen malformation

This is not a true cyst, but may appear so on ultrasound scan. They are located in supracerebellar region. Dilatation of vein of Galen is caused by a vascular malformation that is fed by large arteries of the anterior or posterior cerebral artery circulation. Hydrocephalus may or may not be present. Calcification occurs especially if there is thrombosis in the malformation.

Vein of Galen malformation appears as anechoic, tubular midline structure located superior to the cerebellum (Fig.1a & b). Colour Doppler (Fig.1c) shows increased flow.

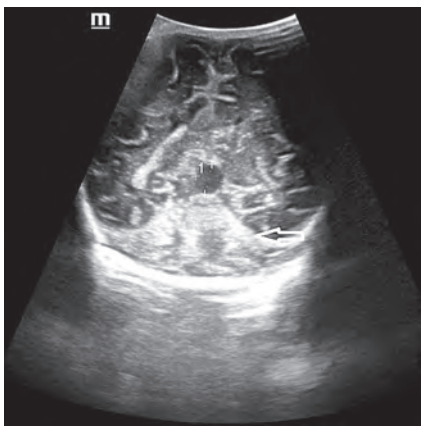

Fig.1b. Coronal view cranial sonography showing Vein of Galen located superior to cerebellum (white arrow)

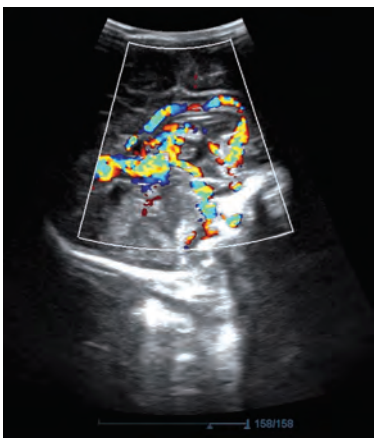

Fig.1c. Colour Doppler shows increased blood flow

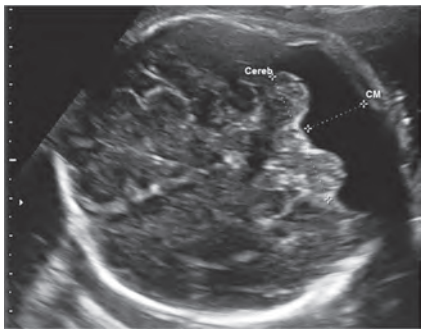

Fig.2. Axial view cranial sonography showing an enlarged retrocerebellar CSF space (mega cisterna magna)

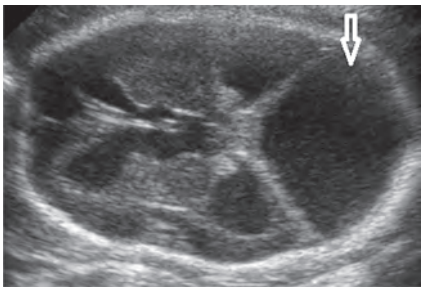

Fig.3a. Cranial sonography shows cystic dilatation of the posterior fossa (white arrow) with enlargement of the posterior fossa.

Infratentorial cysts

Mega cisterna magna

It is a normal variant characterized by a truly focal enlargement of the subarachnoid space in the inferior and posterior portions of the posterior cranial fossa (Retro and infracerebellar). It is CSF filled space with normal vermis and normal cerebellum. It is seen in 1%. On cranial USG, an enlarged retrocerebellar CSF space usually >10 mm is seen (Fig.2). Septae may be seen within it due to Blake's pouch vestigial remnants.

Dandy Walker malformation

Most common posterior cranial fossa malformation and is characterized by the triad of hypoplasia of the vermis, cystic dilatation of the posterior fossa in communication with fourth ventricle. Enlarged posterior fossa with torcular - lambdoid inversion is seen.

On cranial USG (Fig.3a & b), marked enlargement of the cisterna magna (≥10 mm), complete aplasia of the vermis, a trapezoid-shaped gap between the cerebellar hemispheres are the features.

Arachnoid cyst

Arachnoid cyst is seen in posterior fossa most commonly located in retrocerebellar region extra axially. On cranial USG, arachnoid cysts are visible as extremely well circumscribed cysts with an imperceptible wall and displace adjacent structures. No mass effect is observed, as they exert a remodeling effect on adjacent structures and the bone.

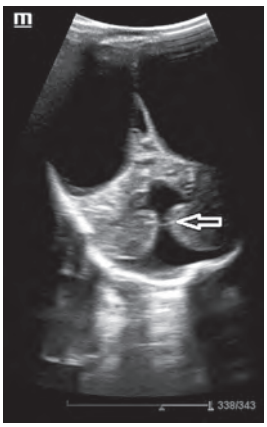

Fig.3b.Cranial sonography-Coronal view shows complete aplasia of the vermis (white arrow and communication with fourth ventricle

The ultrasonogram features of the cystic lesions are correlated with the clinical history. Changes of the appearance of these lesions over time can assist in improving the diagnostic yield. Familiarity with the ultrasonogram features of intracranial cysts is therefore an extremely valuable tool, as it facilitates an accurate diagnosis and treatment when necessary.

CASE REPORT

INSULIN EDEMA AFTER TREATMENT OF DIABETIC KETOACIDOSIS IN A CHILD WITH TYPE I DIABETES

***Deepti Pandit**
****Sujatha Sridharan**
****Antony Jenifer**

Abstract: *One of the lesser known side effects of insulin therapy is the development of generalised edema, especially in underweight patients on intensive insulin regimen. We report the case of a 15 year old type 1 diabetic, who presented with diabetic ketoacidosis, after achieving glycemic control with insulin on day 5, developed generalised edema with weight gain on day 8. As all investigations were within normal limits, a possibility of insulin edema was entertained and child managed conservatively. Edema resolved spontaneously within a week.*

Keywords: *Insulin, Edema, Diabetes mellitus.*

Insulin edema is the development of generalised edema following insulin therapy. It is one of the lesser known side effects of insulin therapy and a diagnosis of exclusion. Generalised edema following insulin administration has been described in the literature as early as 1928 by Leifer.[1] The severity varies widely from minimal pedal edema to generalised edema with pleural and pericardial effusion[2] and most described cases have shown spontaneous resolution without any definitive treatment indicating its transient nature.[3]

A 15 year old girl with type 1 diabetes mellitus, who defaulted on insulin for the past six months, presented to the emergency room history of fever for a week, fast breathing, pain abdomen and altered sensorium for a day. Physical examination at the time of admission showed that she was dehydrated, drowsy and tachypnoeic with acidotic breathing. Her BMI was 14.4 kg/cm^2. Biochemical investigations revealed severe metabolic acidosis, ketonuria and hyperglycemia (blood glucose- 426 mg/dL). Her glycosylated hemoglobin (HbA1c) was 15.7 which reflected the poor glycemic control. The diagnosis of diabetic ketoacidosis as a result of non-compliance of insulin therapy was made and treated with IV fluid (NS in the initial 24 hours and N/2 for the next 48 hours) and insulin infusion as per international protocol was started with short acting insulin which was later changed to basal bolus regimen (NPH + regular insulin). Dehydration correction and electrolyte restoration were achieved by day 4 and IV fluid was stopped. She needed 1.8 U/kg/ day of insulin to achieve glycemic control initially which later came down to 0.7 U/kg/day by day 7, when reasonable glycemic control was achieved with fasting blood sugar levels between 80 to 150 mg/dL and postprandial values 200 to 250 mg/dL.

On day 8 of admission, she had developed facial puffiness and bilateral non tender pitting pedal edema which increased over the next 2 days to generalised edema with ascites. Her weight increased from 37 kg on day 3 of admission to 46 kg on day 10 and urine output was around 1.2 ml/kg/hour and there was no respiratory distress. Total fluid input in first 8 days was 12080 ml and output was 9135 ml. She was extensively worked up for all causes of generalised edema. Cardiac evaluation with chest X-ray, and echocardiogram were normal. Evaluation for renal function with blood urea nitrogen, serum creatinine, serum electrolytes and liver enzymes were within normal limits while ultrasound abdomen revealed moderate ascites. Though there was a mild reduction in serum albumin from 3.7 to 3.1 g/dL, urine examination did not reveal any evidence of proteinuria. She was managed conservatively with salt restricted diet alone as there was no respiratory compromise or significant discomfort. She improved gradually with edema resolving over the next 10 days.

Discussion

After ruling out other causes of generalised edema and possibility of fluid overload, we made the diagnosis of insulin edema since it developed concurrent with the improved glycemic control. While getting into the input output balancing, the positive balance of 2945 mL is for

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dehydration correction and hence it cannot be attributed as fluid overload. Insulin edema is a known but less commonly reported entity observed with adolescent girl who are nutritionally compromised to start with. It has also been previously reported in Type 1 diabetics, with poor glycemic control who are started on intensive insulin therapy and those presenting with DKA which is similar to our child.[4,5]

The pathophysiology of edema still remains elusive though multiple mechanisms have been described. Few of the proposed hypotheses include enhanced renal tubular sodium reabsorption by the action of insulin on Na/K ATPase and Na/ H exchanger 3 in the proximal renal tubule, insulin counteracting the natriuretic effect of glucagon, transient inappropriate hyperaldosteronism, selective increase in vascular permeability in subdermal vessels in response to insulin, intensive fluid resuscitation in an insulin-deficient catabolic state (DKA) and hypoalbuminemia.[6-8]

To conclude, we propose that insulin edema needs to be anticipated and recognised by clinicians treating diabetics, especially in those who are underweight with poor glycemic control and on intensive insulin regimen. Knowledge of this potentially, self-limiting complication will reduce excessive concern and unnecessary interventions.

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CLIPPINGS

Neurologic Involvement in Children and Adolescents Hospitalized in the United States for COVID-19 or Multisystem Inflammatory Syndrome

The spectrum of neurologic involvement in COVID-19 in children and adolescents is unclear.1695 patients (age <21 years) hospitalized over a 9 month period between March and December 15, 2020, with positive severe acute respiratory syndrome coronavirus 2 test result (RT-PCR and/or antibody) at 61 US hospitals were enrolled including 616 patients meeting criteria for multisystem inflammatory syndrome in children.

Documented neurologic involvement was found in 365 (22%) patients. Among those with neurologic involvement, 322 (88%) had transient symptoms and survived, and 43 (12%) developed life-threatening conditions clinically adjudicated to be associated with COVID-19, including severe encephalopathy (n=15), stroke (n=12), central nervous system infection/demyelination (n=8), Guillain-Barré syndrome/variants (n=4), and acute fulminant cerebral edema (n=4). Of 43 patients who developed COVID-19–related life-threatening neurologic involvement, 17 survivors (40%) had new neurologic deficits at hospital discharge, and 11 patients (26%) died.

Many children and adolescents hospitalized for COVID-19 or multisystem inflammatory syndrome in children had neurologic involvement, mostly transient symptoms. A range of life-threatening and fatal neurologic conditions associated with COVID-19 infrequently occurred. Effects on long-term neurodevelopmental outcomes are unknown.

LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams M, Maamari M, Walker TC JAMA Neurol 5th March, 2021. doi:10.1001/jamaneurol.2021.0504.

CASE VIGNETTE - 1

PRIAPISM IN NEWBORN

***Bharani Anand R**
****Binoy Balakrishnan**

A baby boy, born by labour natural with a birth weight of 2950 grams and normal early newborn period, presented on day 26 with multiple crying episodes associated with erection of penis (Fig.1a) lasting for variable durations between 10 mins and 60 mins, followed by flaccidity. These episodes occurred also during night disturbing his sleep. Complete blood count and penile doppler ultrasound were normal (Fig.1b). Progressive detumescence was achieved without any surgical intervention. There were no further episodes on follow up.

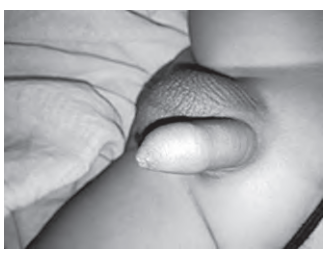

Fig.1a. Priapism

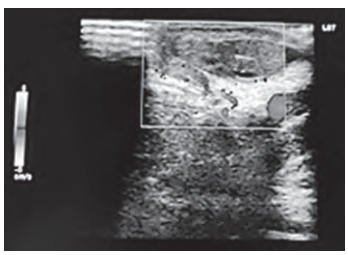

Fig.1b. Penile Doppler USG

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Neonatal priapism is a rare pathology whose actual incidence is unknown and one study describes a rate of 0.15 per 1000 live births between 1974 and 1988. The most common cause for newborn priapism is idiopathic.[1] Other possible causes include blood dyscrasias, malignancy, trauma, neurological pathology and drug-related side effects.[2] Although, sickle cell anemia is common in children, it is negligible in neonates because of the predominance of fetal hemoglobin. Among neonates, polycythemia is the most known detected etiology. In literature, there are reported cases of neonatal priapism attributed to polycythemia and one to blood transfusion, where as all other cases were idiopathic.[3] Suggested management options include observation, intravenous ketamine, phlebotomy and exchange transfusion. Majority of cases improved with observation and spontaneous detumescence was achieved. Hence, it is prudent to do an etiological workup to look for polycythemia, blood disorders in such cases and conservative approach is optimal in majority of cases.

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CLIPPINGS

Overweight is associated with early puberty in boys and girls

It has been clear that overweight and obesity in childhood is associated with onset of puberty at a younger age in girls but for boys, this has been less clear and study results variable. Defining onset of puberty may be more difficult in boys compared with girls. The data from the Boston Birth Cohort Study used to evaluate this question. The objective was to examine the associations between body mass index (BMI) at 2-4 years and 5-7 years and age at peak height velocity (APHV), an objective measure of pubertal timing, among boys and girls from predominantly racial minorities in the US. This prospective birth cohort study found that overweight or obesity during 2-7 years was associated with earlier pubertal onset in both boys and girls. The BMI trajectory analyses further suggest that reversal of overweight or obesity may halt the progression toward early puberty.

Chen L,Wang G, Bennet WL, Ji Y, Pearson C, Radovick C, et al. Trajectory of Body Mass Index from Ages 2 to 7 Years and Age at Peak Height Velocity in Boys and Girls. J Pediatr 2021;230 (E5) :221-229.

CASE VIGNETTE - 2

A CASE OF CHRONIC IMMUNE THROMBOCYTOPENIC PURPURA PRESENTING WITH INTRACRANIAL HEMORRHAGE AND CEREBRAL HERNIATION TREATED WITH DECOMPRESSIVE CRANIECTOMY

***Chaturvedi Vijendra**
****Sharma Ravi**
*****Chaturvedi Anupam**
******Sharma Durga Prasad**

A 12-year-old boy with refractory chronic ITP on treatment presented with acute onset unilateral severe headache, blood-stained vomitus and altered sensorium. He had a GCS of 7/15 (E2V2M3) with bilateral exaggerated deep tendon reflexes and bilateral extensor plantar response, both pupils were equal in size and reactive to light. He had petechiae all over the body. CT of the brain revealed acute parenchymal hematoma in left temporal lobe, with effacement of left lateral ventricle, midline shift of 3mm towards the right side and a mass effect over the midbrain (Fig.1). Platelet count was 10,000/mcL, aPTT and PT/INR were normal. Within hours of admission, there was deterioration of his GCS, development of anisocoria and patient was intubated and put on mechanical ventilation. Emergency decompressive craniectomy with evacuation of bleed was carried out after transfusing multiple units of platelets (single and random donor platelet units).The patient was gradually weaned from ventilator. With the gradual improvement in GCS, right sided hemiplegia and right facial palsy became apparent. By the end of 2 weeks post-surgery patient had made substantial neurological recovery. Since there was no sustained response in platelet levels, he was subsequently started on injection Rituximab and currently on follow up with near normal platelet counts.

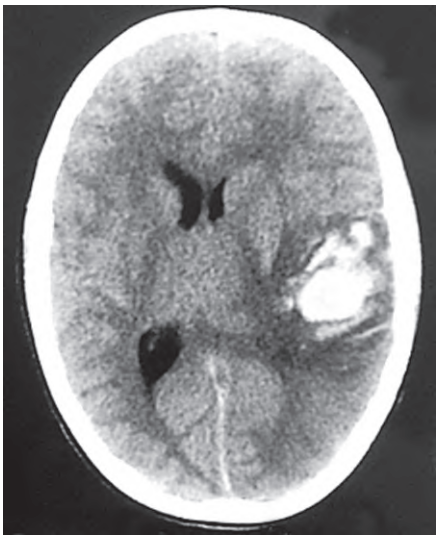

Fig.1. Coronal section CECT head

Majority of patients with ITP have good prognosis, however mortality rate becomes very high in the sub-group who develop intracranial hemorrhage (ICH). Median platelet count at the time of ICH in ITP is 5000/microlitre[1] and 98% of the study subjects have platelet count below 20000/microlitre.[2] This article intends to highlight that early neurosurgical intervention in such cases can be lifesaving and also can help patient to recover with minimal neurological deficits.

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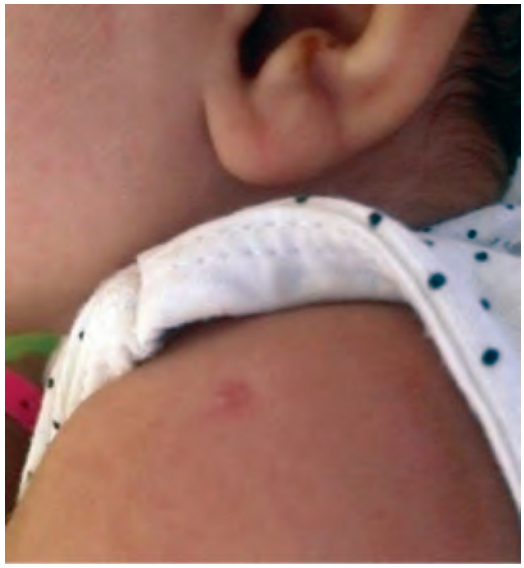
PICTURE QUIZ

***Zahabiya Nalwalla**
****Jayashree Kanthila**
*****Maneesh Rai**
******Nutan Kamath**
*******Suchetha Rao**
*******Sowmini P Kamath**

A 3 months old infant presented with high-grade fever with maculopapular rash, had the feature shown in the figure. Investigations revealed polymorphonuclear leucocytosis, raised ESR and C reactive protein; echocardiogram clinched the diagnosis. Identify the clinical feature shown in the figure and the diagnosis.



Answer : BCG Scar reactivation in Kawasaki Disease

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Department of Cardiology
**** Professor
*****Associate Professor,
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Kasturba Medical College and Hospital, Mangalore,
Manipal Academy of Higher Education, Manipal.

CLIPPINGS

Artificial intelligence-assisted auscultation in detecting congenital heart disease

This study evaluates the accuracy of artificial intelligence-assisted auscultation

In total, 1362 patients with CHD were enrolled in the study (mean age—2.4 ± 3.1 years and 46% female). The samples of their heart sounds were recorded and uploaded to the platform using a digital stethoscope. By the platform, both remote auscultation by a team of experienced cardiologists from Shanghai Children's Medical Center and automatic auscultation of the heart sound samples were conducted and analysed. Compared to face-to-face auscultation, remote auscultation detected abnormal heart sound with 98% sensitivity, 91% specificity, 97% accuracy, and kappa coefficient 0.87. AI-AA demonstrated 97% sensitivity, 89% specificity, 96% accuracy, and kappa coefficient 0.84.

Conclusions The remote auscultations and automatic auscultations, using the AI-AA platform, reported high auscultation accuracy in detecting abnormal heart sound and showed excellent concordance

Lv J, Dong B, Lei H , Wang SG, Zhu et al . Artificial intelligence-assisted auscultation in detecting congenital heart disease. European heart Journal – Digital health. ztaa017. doi:10.1093/ehjdh/ztaa017. Jan 2021.

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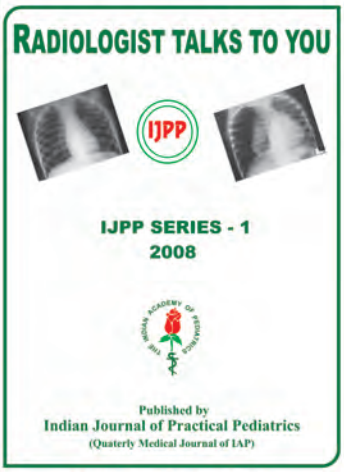

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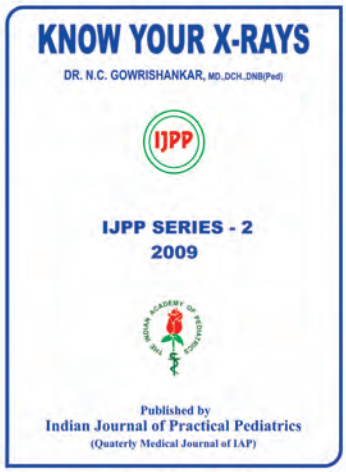

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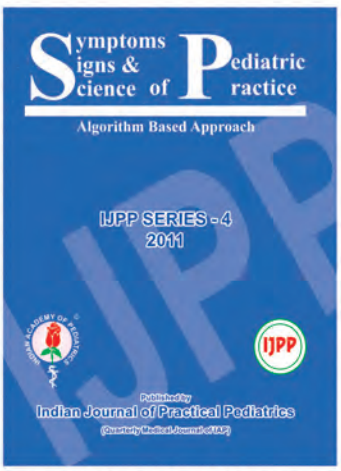

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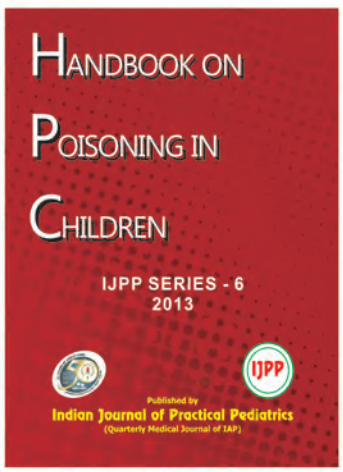

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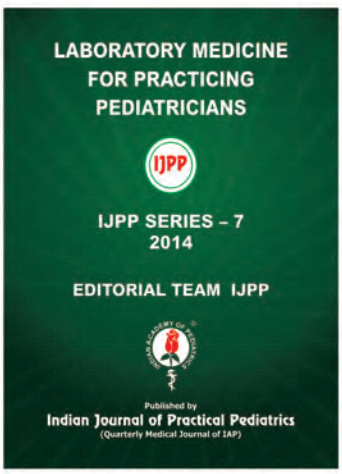

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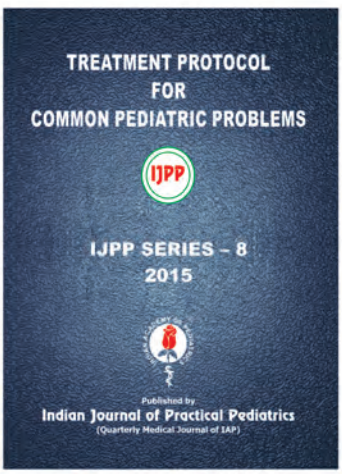

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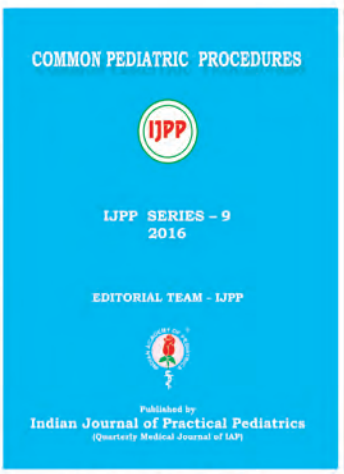

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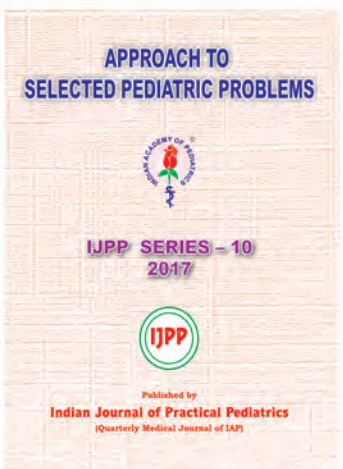

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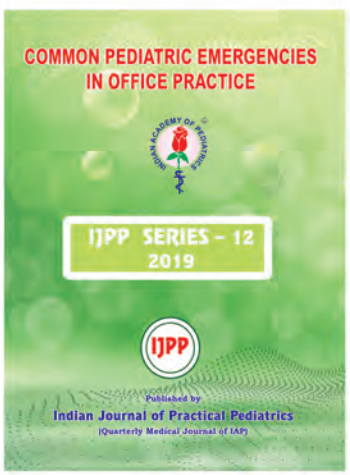

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