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TOPIC OF INTEREST - "UPDATE ON VACCINES"

GENERAL ARTICLE

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UPDATE ON VACCINES

CURRENT SCENARIO OF VACCINE PREVENTABLE DISEASES IN INDIA

***Raju C Shah**
****Pratima Shah**
*****Khanjan Shah**

Abstract: *India being the second most populous country in the world, has a significant population of under 5 children and significant birth cohort each year. Vaccination is the most cost effective health intervention available, but still the coverage is not complete. It is difficult to get exact incidence of all vaccine preventable diseases in India because of suboptimal health access, diagnostic services and information systems available across the country. In this article we would like to share available literature and present statistics of vaccine preventable diseases in India.*

Keywords: *Vaccines, Vaccine preventable diseases, Incidence, Immunization*

India is the second most populous country in the world with over 1.271 billion people (2015), more than a sixth of the world's population[1] with 26 million birth cohort. Ten percent of India's population is below 5 years.[2]

Vaccination is one of the most cost effective preventive measures which is offered to children.[3] Introduction of vaccines has changed epidemiology of various vaccine preventable diseases; best example is world declared free of small pox.[4]

Children are said to be fully immunized if they have received one dose of BCG,3 doses of DPT and polio vaccine each and one dose of measles vaccine. In India, only 44% of children aged 12–23 months are fully vaccinated and about 5% have not received any vaccination at all.[5] In spite of 20 years of efforts and millions of dollars poured into Universal Immunisation programme (UIP), our coverage rate has still not crossed the 50% mark. Immunization coverage showed improvement since National Family Health Survey-1 (NFHS-1), when only 36% of children were fully vaccinated and 30% had not been vaccinated at all. But, there was very little change in immunization coverage between NFHS-2 (42%) and NFHS-3 (44%).[5] Coverage for BCG, DPT and polio (except "at birth" polio dose) is much higher than all other vaccines. BCG, DPT-1, and polio-1, -2, -3 doses have been received by at least 76% of children, while only 55% of children have received all three doses of DPT. Although DPT and polio vaccinations are given at the same time as part of routine immunization programme, the coverage rates are higher for polio than for DPT (all three doses), undoubtedly because of the pulse polio campaigns. Not all children who begin the DPT and polio vaccination series go on to complete them. The difference between the percentage of children receiving the first and third doses is 21% for DPT and 15% for polio. Around 59% of children aged 12-23 months have been vaccinated against measles. The relatively low percentage of children vaccinated with the third dose of DPT and measles is mainly responsible for the low percentage of fully vaccinated children.[5] In this article we would like to share trend and current status of vaccine preventable diseases in India.

Polio (Fig.1)

In the last century, polio was one of the most feared diseases across the globe and responsible for significant morbidity and mortality amongst children every year. In 1970s routine immunization was introduced world wide as part of national immunization program. In 1988, when the Global Polio Eradication Initiative (GPE1) began, polio paralyzed more than 1000 children worldwide every day. Since then, more than 2.5 billion children have been immunized against polio thanks to the cooperation of more than 200 countries and 20 million volunteers, backed by an international investment of more than US$ 9 billion.

There are now only 3 countries (Pakistan, Afganistan and Nigeria) that have never stopped polio transmission. Global incidence of polio cases has decreased by 99%. In 2015, 24 cases have been reported, 23 from Pakistan and 1 from Afghanistan, as opposed to over 350,000 in 1988.

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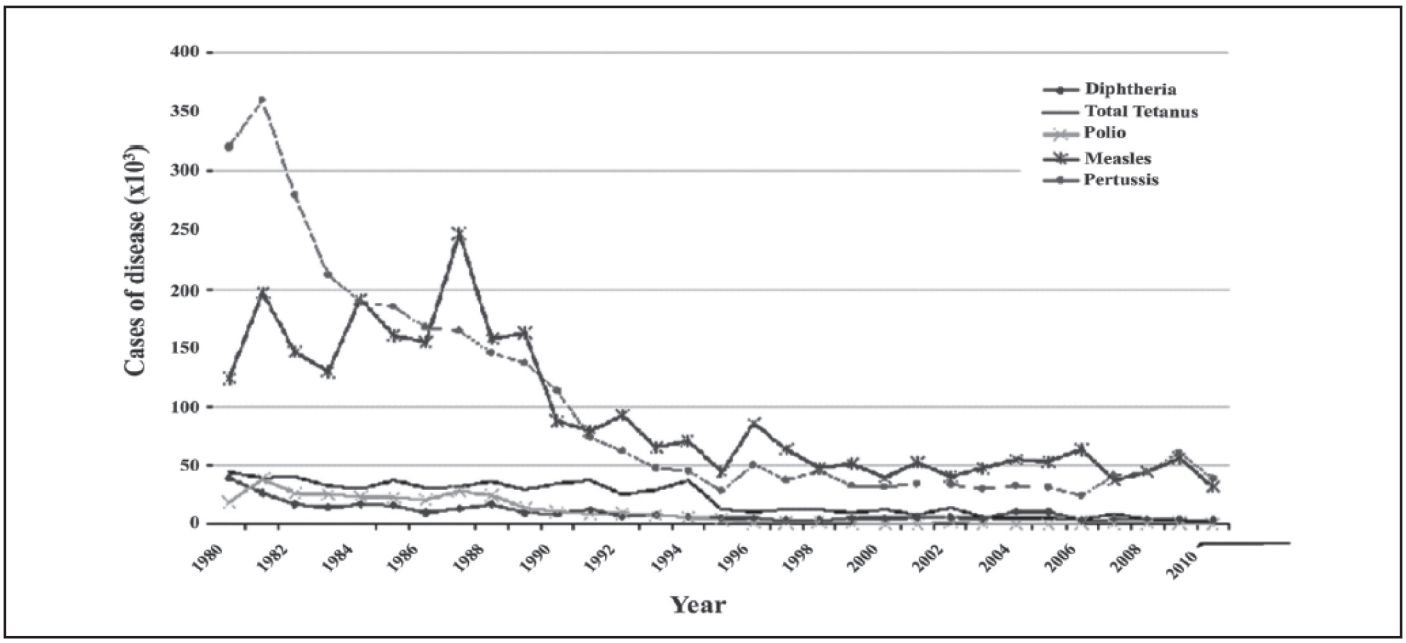

Fig.1. Reported cases of major vaccine preventable diseases in India (1980-2010)[32]

In February 2012, India, long-regarded as the nation facing the greatest challenges to eradication, was removed from the list of polio-endemic countries, convincing doubters that global polio eradication is feasible. The last case of wild polio from India was reported on 13 January 2011 and from being hyper endemic for polio, India was certified as polio free on 27th March 2014.

Tuberculosis

India is the country with the highest TB burden accounting for one fifth of global incidence. The actual magnitude of childhood TB disease is not known in India. Regional data from the WHO in 2007 showed that smear positive TB in children aged< 14 years accounted for 0.6 to 3.6% of reported cases. However, because more than 95% of cases in children <12 years of age are smear negative, these data underestimate the true burden of TB though it is estimated that childhood TB has incidence of 10% of adult TB disease.[6] BCG has an efficacy of 75-86 % for prevention of miliary and meningeal form of the disease. Protective efficacy for pulmonary tuberculosis is 50%.[7] Widespread coverage with BCG vaccine (Fig.2) has led to modification in the pattern of clinical manifestations. Indian experience suggests an increase in the proportion of cases of extra pulmonary TB over the last 3 decades, predominantly due to increase in lymph node TB. The severe form of tubercular meningitis decreased over the last three decades.[8]

Diphtheria (Fig.1)

Diphtheria is an acute bacterial infection caused by Corynebacterium diphtheriae (C. diphtheriae) primarily involving tonsils, pharynx, nose, occasionally other mucous membranes or skin and rarely vagina and conjunctiva. Vaccine has a great impact in prevention of diphtheria. As compared to 39321 cases in 1980, India reported 6094 cases of diphtheria in 2014.[9] The data on vaccine-preventable diseases provided by the Government of India to the World Health Organization (WHO)[10] during 1980-2008 indicate persistence of diphtheria without much decline over the last 25 years. India accounted for 19-84% of the global burden from 1998 to 2008. These reports bring out certain important features about the epidemiology of diphtheria in India. First, the disease, which was common among under-five children in the past[11] is now affecting older children (5-19 years) and adults. Second, in certain states, the disease is common among females and Muslims.[12,13] Third, the majority of the cases are reported from children who were un-immunized/partially immunized against diphtheria. Persistence or resurgence of diphtheria in the country was mainly due to low coverage of primary immunization as well as boosters. According to the WHO-UNICEF estimates, the DPT3 coverage was 66% in 2008, whereas as per the three National Family Health surveys, DPT3 coverage during 1992–2006 was only 52-55%. Because the immunity acquired through

primary immunization wanes in early childhood, adequate coverage of booster doses is equally important. Unfortunately in India, data about coverage of first and second boosters is not routinely collected under the Universal Immunization Programme (UIP) as well as the National Health Surveys.

Measles (Fig.1)

SEAR countries resolved to eliminate measles and control rubella/congenital rubella syndrome (CRS) by 2020. With the help of vaccination reduction in death by measles is 71%.[14]

In 2014 India reported 24977 cases of measles compared to 89612 in 1990.[9] Measles elimination contributes significantly in achieving Millennium Development Goal 4 (MDG-4). "One of the three indicators for monitoring progress towards achieving MDG 4 is the "proportion of 1-year-old children immunized against measles".[15]

Tetanus (Fig.1)

In 1983 the Indian government introduced two doses of tetanus toxoid vaccine to all pregnant women during each pregnancy as nationwide expanded programme on immunisation. In 1990 neonatal tetanus still accounted for almost 80,000 deaths. But in 2013 and 2014 fewer than 500 cases were reported.[9] The elimination of neonatal tetanus is defined as less than one case in 1000 live births in every district across the country(World Health Organization). India was finally declared free of maternal and neonatal tetanus on May 15, 2015.

Pertussis (Fig.1)

Pertussis continues to remain a significant health problem across the globe. Evidence about accurate incidence and burden of pertussis is sparse in most countries including India.. However, the disease is widespread, even if not adequately measurable. Pertussis incidence has been increasing steadily in the last decade especially in industrialized countries. Outbreaks are reported from many developed countries in recent years despite widespread use of acellular pertussis vaccines with high coverage. In India, the incidence of pertussis decreased sharply after launch of Universal of Immunization Program (UIP). Prior to UIP, India reported 200,932 cases and 106 deaths in the year 1970 with a mortality rate of <0.001%. During the year 1987, the reported incidence was about 163,000 cases which came down to 40, 508 in 2010 and 39, 091 in 2011 reflecting a decline of about 75%.[16]

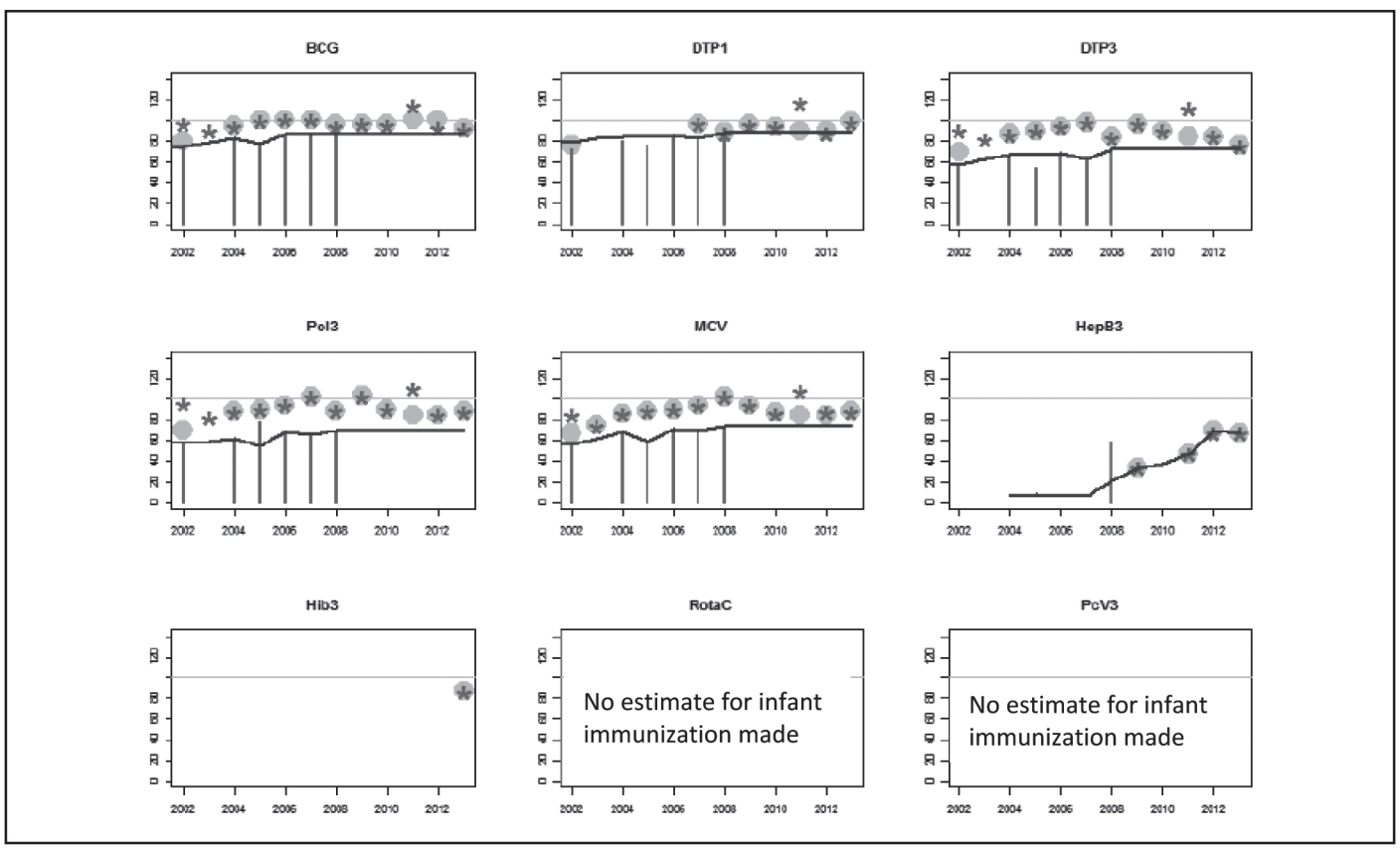

Fig.2. India: WHO and UNICEF estimates of immunization coverage in India: 2013 revision[33]

Hepatitis B infection

Vaccination for Hepatitis B in infants has been started nationwide in 183 countries. The coverage till 2013, with 3 doses of hepatitis B is estimated to be 81% globally.[17] Presently in India, 2-4 % of the population has chronic HBV infection. Under the National Universal Immunization program the Hepatitis B vaccination was started in 2002 for 10 states and scaled up for entire India by 2011-2012.[18] Hepatitis B vaccine is also part of the government's ambitious child immunization programme - Mission Indradhanush against seven vaccine preventable diseases. Besides hepatitis B, Mission Indradhanush will include diphtheria, whooping cough, tetanus, polio, tuberculosis and measles. Immunization coverage has increased by merely 1% since 2009, when it was estimated at around 61%, as per government data. The latest data for 2013 shows vaccine coverage at 65% (Fig.2), whereas there are over 26 million infants across the country. The government has adopted the mission mode to achieve a target of full coverage by 2020.[19]

Streptococcus pneumoniae infection

Streptococcus pneumoniae is a Gram-positive, encapsulated diplococcus. The polysaccharide capsule is an essential virulence factor and the >90 distinct pneumococcal serotypes are defined on the basis of differences in the composition of this capsule. Every year approximately 875,000 Strept pneumonia associated mortality occur world wide.[20-21] In India there is scarcity of evidence reporting accurate incidence and diseases burden of invasive pneumococcal disease. The large population and geographic area, lack of system to report cases, limited medical centers with appropriate diagnostic facilities and rampant use of antibiotics prior to hospitalization. In one study conducted in Bangalore it has been shown that disease burden due to invasive pneumococcal disease in children is high and local institutes have capacity for population based surveillance.[22]

Chicken pox

Varicella-zoster virus, is a member of the herpesvirus family. Humans are the only reservoir of the virus, and disease occurs only in humans. After primary infection as varicella (chickenpox), the virus remains dormant in the sensory-nerve ganglia and can get reactivated at a later time, causing herpes zoster (shingles). Eaxct incidence of chicken pox is not known because of under reporting of cases but few extrapolated data suggest 472327 cases out of 1065070607 population.[23]

Rota virus diarrhea

Diarrhoeal illnesses are a major cause of hospitalizations in children globally. Of India's more than 2.3 million annual deaths among children, about 334 000 are attributable to diarrhoeal diseases.[24-25] Rotavirus is the leading cause of severe diarrhoea in children in developed and developing countries.[26,27] Two rotavirus vaccines have been shown to be effective against rotavirus and have been licensed in more than 100 countries, including India.[28-30] Introduction of these vaccines is expected to reduce child mortality by decreasing the incidence of severe diarrhoea and the frequency of death from diarrhoeal disease. Exact incidence of rota virus diarrhoea is difficult to obtain in developing country like India because of suboptimal diagnostic facility available and under reporting. According to one study conducted by Indian Rotavirus Surveillance Network estimate that 11.37 million episodes of rotavirus gastroenteritis occur each year in India, requiring 3.27 million outpatient visits and 872,000 inpatient admissions when health access is unconstrained, resulting in a need for Rs. 10.37 billion each year in direct costs. An estimated 78,000 rotavirus-associated deaths occur annually of which 59,000 occur in the first 2 years of life.[31]

Points to Remember

- ***With effective immunization strategies, India was certified polio free on 27th March 2014 and maternal and neonatal tetanus free on 15th May 2015.***
- ***With reference to TB, while there is a reduction in the severe forms of tuberculosis like tuberculous meningitis, there is an increase in the incidence of extra pulmonary TB and India continues to contribute one fifth of global burden.***
- ***Persistence or resurgence of diphtheria is mainly attributed to low coverage of primary and booster immunization and there is an increase in cases in the age group of 5 to 19 yrs.***
- ***There is a decline of about 75% cases of pertussis.***
- ***While there are measles cases reported still, there is a substantial reduction in measles related deaths.***

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BOOK REVIEW

FAQS IN PEDIATRIC AND ADOLESCENT PRACTICE

Authors: Parthasarathy A, Anupama S Borker, Alok Gupta, Dhanya Dharmapalan.

Publishers: Jaypee Brothers Medical Publishers (P) Ltd, New Delhi.

Pages: 927

Price: 1295/-

I was amazed to see a book which could answer all the queries that would arise in the minds of postgraduates and practicing pediatricians.A glance at the book reveals that the recent updates of all aspects are covered adequately. A lot of hard work by the authors has gone into the compiling of the book which is worth its weight in gold.

Dr. Janani Sankar, DNB, (Ped), Ph.D,
Senior Pediatric Consultant,
Kanchi Kamakoti CHILDS Trust Hospital, Chennai.
Email: janani.sankar@yahoo.com

ERRATUM

Article titled "Adolescent sexuality" Indian J Pract Pediatr 2015; 17(2): Page 109 - 115

It is regretted that the name of co-author 'Dr.Tuteja JS' was missed in the above article. The authorship of the article should read as 'Chandrika Rao, Tuteja JS'. The error is deeply regretted.

Editorial Board
Indian Journal of Practical Pediatrics

UPDATE ON VACCINES

POLIO VACCINATION - END GAME

*Naveen Thacker
**Ashish Pathak
***Deep Thacker

Abstract: *The World Health Assembly (WHA) in 1988 launched the 'Global Polio Eradication Initiative (GPEI)', a partnership between World Health Organization, UNICEF, Center for Disease Control and Prevention (USA) and Rotary International. Later, the Bill and Melinda Gates Foundation joined this partnership. Since 1988 the number of polio-endemic countries has decreased from 125 to 3 (Nigeria, Afghanistan and Pakistan). Under the guidance of 'Strategic Advisory Group of Experts' (SAGE), the GPEI has developed a comprehensive and long-term plan entitled the 'Polio eradication and endgame strategic plan 2013-2018'. Its goal is the complete eradication and containment of all wild, vaccine-related Sabin polioviruses, so that no child ever again suffers paralytic poliomyelitis. The four main objectives of the plan are 1) poliovirus detection and interruption of transmission 2) strengthening of immunization systems and withdrawal of OPV 3) containment and certification and 4) legacy planning.The plan lays out a road map to interrupt the transmission of wild polio virus (WPV) and achieve the long-term goals of the post-eradication era, including the eradication of vaccine derived polio viruses (VDPVs).*

In accordance with the above strategy in India, a single, full dose of IPV at DPT3/OPV3 contact will be introduced by end of 2015 in routine immunization throughout the country. The evidence base for the above strategy and challenges that India might face in implementing the 'End game poliomyelitis' strategy are discussed in the article.

Keywords: *Poliomyelitis, Injectable polio vaccine, Eradication, Endgame, Policy, India.*

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Abbreviations

WHA	World health assembly
GPEI	Global polio eradication initiative
WPV	Wild polio virus
VDPV	Vaccine derived polio virus type1
VDPV2	Vaccine derived polio virus type2
cVDPV	Circulating vaccine derived polio virus
SAGE	Strategic advisory group of experts
VAPP	Vaccine associated paralytic polio
tOPV	Trivalent oral polio vaccine
bOPV	Bivalent oral polio vaccine
NTAGI	National technical advisory group on immunisation
GOI	Government of India
WMF	Wastage multiplier factors

Since its launch at the World Health Assembly (WHA) in 1988, the GPEI has reduced the global incidence of polio by more than 99% and the number of countries with endemic polio from125 to 3. More than 10 million people are walking today who otherwise would have been paralyzed.[1]

On 26 May 2012, the WHA declared ending polio a 'programmatic emergency for global public health'. The WHA noted India's success in the eradication of wild polio virus (WPV) by using appropriate tools and technology. However, the threat to the global community of ongoing WPV transmission in the last three endemic countries-Afghanistan, Nigeria and Pakistan remains. Apart from the threat of importing WPA from the above three countries, the risk of circulating vaccine-derived polioviruses (cVDPVs), which can cause outbreaks of

paralytic disease, prompted the WHA to call on the World Health Organization (WHO) Director-General to develop and finalize a comprehensive polio endgame strategy.[1]

Advances against polio in 2014

The year 2014 saw tremendous advances for the programme, setting up the possibility to end polio for good. The significant advance is that India has been declared a polio free country by WHO and the country remains polio free today. In 2014, the total numbers of wild poliovirus Type 1 cases worldwide were 356 (Fig.1). A large number of cases have been reported from Pakistan in the year 2013.[2]

Further, to tackle circulating vaccine derived polio viruses (cVDPVs), initiation of inactivated polio vaccine (IPV) vaccination options have been suggested. VDPV2 causes more than 90% of the cVDPV outbreaks in the world including India and more than 40% of vaccine associated paralytic poliomyolitis (VAPPs).Hence the strategic advisory group of experts (SAGE), the world's chief immunization guidance body has recommended the withdrawal of type 2 component of OPV vaccine and facilitated the introduction of at least one dose of IPV.

Polio eradication and end game strategic plan 2013-2018

The plan was created by the GPEI in extensive consultation with national health authorities, global health initiatives, scientific experts, donors and other stakeholders. Its goal is the complete eradication and containment of all wild, vaccine-related or Sabin polioviruses, so that no child ever again suffers from paralytic poliomyelitis. Discussions to create the plan started with a frank assessment and acknowledgement of the reasons for missed deadlines, past failures and lessons learnt from previous eradication plans. The important lessons learnt are that one strategy may not help all regions and technological innovation alone cannot help to overcome gaps in community programmes. Also, a combination of innovations when tailored to a country's context can deliver success even in the most challenging conditions.[1]

Major elements that distinguish this plan from previous GPEI strategic plans include: 1) strategic approaches to end all polio disease (wild and vaccine related), 2) an urgent emphasis on improving immunization systems in key geographic areas, 3) the introduction of new affordable IPV options for managing long term poliovirus risks and potentially accelerating wild poliovirus eradication, 4) risk mitigation strategies to address new threats, particularly insecurity in some endemic areas and contingency plans should there be a delay in interrupting transmission in such reservoirs and 5) a concrete timeline to complete the programme.[1]

Main objectives of plan

The four main objectives of the plan are: 1) poliovirus detection and interruption: Stop all WPV transmission by

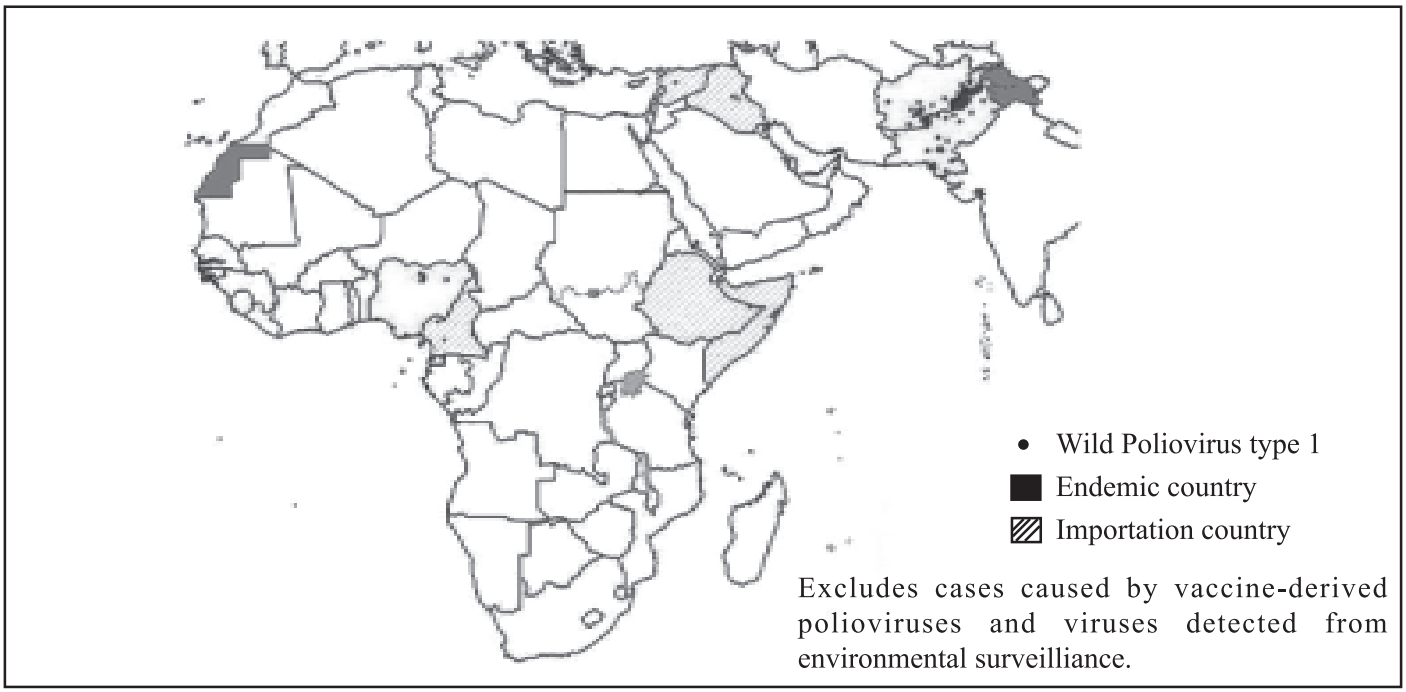
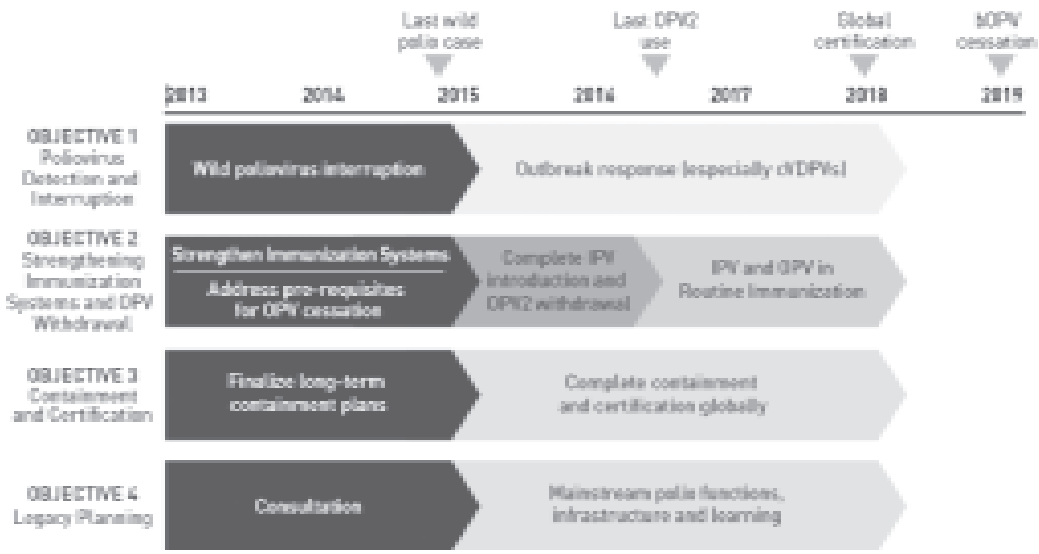


Fig.1 World Map of wild poliovirus circulation in the year 2014



Essential activities (e.g.surveillance, laboratory network and IPV in routine immunization) will be mainstreamed beyond 2019

Fig.2 Main objectives and time line of global end game strategic plan 2013-2018

the end of 2014 and new cVDPV outbreaks within 120 days of confirmation of the first case, 2) immunization systems strengthening and OPV withdrawal: hasten the interruption of all poliovirus transmission and help strengthen immunization systems 3) containment and certification: certify all regions of the world polio free and ensure that all poliovirus stocks are safely contained 4) legacy planning: ensure that a polio free world is permanent and that the investment in polio eradication provides public health dividends for years to come (Fig.2).[1]

Challenges in Global Polio Eradication Initiative: Why OPV use needs to stop?

Since the eradication of WPV2 in 1999, cVDPVs caused by type 2 Sabin strains (VDPV2) have been reported from 14 countries, causing 404 reported paralytic cases. Since the year 2012 there have been more cases of paralytic poliomyelitis caused by Sabin vaccine polio viruses than caused by WPVs.[3,4] VDPV2 causes more than 90% of the cVDPV outbreaks in the world including India and more than 40% of VAPPs. This burden of disease related to vaccination has become increasingly unacceptable to immunization policy makers and to parents. Risk of imported WPV is significant for India as its neighboring countries Pakistan accounted for 176/224 global cases of WPV reported in 2014 and Afghanistan account of 24/224 cases. Thus, we continue to need very high levels of "population immunity to prevent circulation of imported WPV in India".[3]

Stopping OPV without boosting immunity - unsafe

The world needs to ultimately stop using trivalent oral polio vaccine (tOPV) containing type 2 Sabin virus because of risk of VDPV2. Currently, widespread use of OPV is killing off any chains of VDPV before they cause outbreaks (ie. cVDPV) and we also know that the main risk factor for cVDPV is low tOPV coverage. Thus, stopping tOPV will increase the risk for cVDPV, unless the high population immunity is sustained. There can be multiple options for sustaining this high immunity in the population. In the global polio eradication end-game plan there will be planned cessation of the type 2 component of OPV (ie, the switch from trivalent OPV [tOPV] to bivalent OPV [bOPV]) and after the global introduction of at least one dose of IPV into every country's routine immunization schedule.[4,5]An advantage of bOPV is that sero-conversion after 1 dose of bOPV was found to be significantly superior when compared with tOPV for types 1 and 3[6]and bOPV is also attributed to India's successful eradication of polio.[1]

Can a single dose of IPV boost population wide immunity and reduce the risk for cVDPVs?

There are multiple studies to support this: 1) A study in Cuba demonstrate that vaccinating infants with a single dose of IPV can induce sero-conversion and priming in 63% of infants without even being OPV primed.In OPV primed infants the priming response was 98% and first dose sero-converion and priming was seen in 99%.[7]

2) An Indian study from CMC Vellore gave a single supplemental dose of IPV to children last vaccinated with OPV at least 6 months previously. Single dose IPV resulted in boost of mucosal immunity, resulting in a 40% reduction in the prevalence of poliovirus shedding 7 days after bOPV challenge compared with children who did not receive a supplemental dose of IPV.[8] 3) Another Indian study from Muradabad showed that one dose of IPV triaged almost all remaining immunity gap against all serotypes among children immunized with multiple tOPV doses and decreased viral shedding by as much as 75%.[9] The above evidence shows that single dose of IPV can be effective as a risk mitigation factor in controlling cVDPVs. Thus, the use of IPV for controlling cVDPVs is unprecedented, but an essential risk mitigation strategy.[6]

India's current end game strategy

The three main components of the policy are:1) Plan for introduction of IPV in November 2015 in all states and Union Territories in India 2) Potential switch from trivalent OPV to bivalent OPV in 1st year 3) Eventual cessation of oral polio vaccine from EPI.

The National Technical Advisory Group on Immunization (NTAGI), the highest decision making body of GOI for immunization related issue in its meeting in June 2014 recommended that IPV be introduced in routine immunization as single dose at DPT3/OPV3 contact by mid-2015. This single IPV dose is in addition to OPV. NTAGI also recommended strengthening the routine immunization to ensure high coverage with all vaccines. Thus, it should be understood that the decision to introduce at least one dose of IPV is interim from one NTAGI recommendation to next. With the current strategy a birth cohort of 27 million will be benefited with vaccine requirement of about 40 million doses for first year (2015-16) if 5 dose presentation is followed. This includes 35% wastage (WMF 1.53) and additional 25% buffer stocks.The current routine vaccination coverage is above 70% as an average for India, but inequity exists in rural and urban areas, between states and within states. The GOI recognizes these inequities and will address them by strengthening the routine immunization, multiple advocacy efforts for the process to begin and capacity building activities like national orientation for state officials, state and district orientation for medical officers and operational and communication training of health workers.

What communication challenges India faces in its polio end game strategy?

India will face tremendous communication challenges after successful implementation of previous very popular campaign line 'Do buund zindigi ke' (Two drops for life). In some group discussions with the grass root health care workers (HCW) it was found that HCWs were hesitant to believe that the end game strategy needed an injectable vaccine in the form of IPV, when previously they were advocating 'Do buund zindigi ke'.

What are the challenges in India's end game strategy?

We know we can eliminate wild polio viruses, but we have no experience in eliminating vaccine polio viruses. We hope it can be done by using IPV, but we face a challenge of achieving high immunization coverage.

In summary, the destination of polio eradication has changed from exclusively WPVs to vaccine viruses also. The tools of intervention are also changing - instead of exclusive tOPV, we use monovalent OPVs and bOPV; in the near future we will add IPV also.

Points to Remember

- ***Global polio eradication initiative has reduced the burden of polio by more than 99%with only three countries in the world having circulating wild polio virus.***
- ***Since 2012 there have been more circulating vaccine-derived polioviruses (cVDPVs) cases than wild polio cases in the world.***
- ***Polio Eradication and End Game Strategic Plan 2013-2018 is a strategy that lays the roadmap for eradication of wild and cVDPVs by stepwise but simultaneously implemented global policies. The aim is to stop the use of OPV, introduce IPV and strengthen the routine immunization.***
- ***Government of India will introduce single dose IPV along with third dose of DPT for every child from November 2015 as a risk mitigation strategy to boost immunity against any imported cases of wild polio or cVDPVs.***

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CLIPPINGS

Nader Shaikh, Jessica L Borrell, Josh Evron, MG Leeflang .Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children . Cochrane Renal Group. DOI: 10.1002/ 14651858.CD009185.pub2.

In children with urinary tract infection (UTI), only those with pyelonephritis (and not cystitis) are at risk for developing long-term renal sequelae. If non-invasive biomarkers could accurately differentiate children with cystitis from children with pyelonephritis, treatment and follow-up could potentially be individualized.

Published studies that evaluated the results of an index test (procalcitonin, CRP, ESR) against the results of an acute-phase DMSA scan (conducted within 30 days of the UTI) in children aged 0 to 18 years with a culture-confirmed episode of UTI were included . The following cutoff values were used for the primary analysis: 0.5 ng/mL for procalcitonin, 20 mg/L for CRP and 30 mm/h for ESR. Two authors independently applied the selection criteria to all citations and independently abstracted data. We used the bivariate model to calculate pooled random-effects pooled sensitivity and specificity values.

A total of 24 studies met inclusion criteria. Seventeen studies provided data for the primary analysis: six studies (434 children) included data on procalcitonin, 13 studies (1638 children) included data on CRP, and six studies (1737 children) included data on ESR (some studies had data on more than one test). The summary sensitivity estimates (95% CI) for the procalcitonin, CRP, ESR tests at the aforementioned cutoffs were 0.86 (0.72 to 0.93), 0.94 (0.85 to 0.97), and 0.87 (0.77 to 0.93), respectively. The summary specificity values for procalcitonin, CRP, and ESR tests at these cutoffs were 0.74 (0.55 to 0.87), 0.39 (0.23 to 0.58), and 0.48 (0.33 to 0.64), respectively.

Authors' conclusions: The ESR test does not appear to be sufficiently accurate to be helpful in differentiating children with cystitis from children with pyelonephritis. A low CRP value (< 20 mg/L) appears to be somewhat useful in ruling out pyelonephritis (decreasing the probability of pyelonephritis to < 20%), but unexplained heterogeneity in the data prevents us from making recommendations at this time. The procalcitonin test seems better suited for ruling in pyelonephritis, but the limited number of studies and the marked heterogeneity between studies prevents us from reaching definitive conclusions. Thus, at present, do not find any compelling evidence to recommend the routine use of any of these tests in clinical practice.

UPDATE ON VACCINES

ALL ABOUT PERTUSSIS VACCINES

***Vipin M Vashishtha**
****Puneet Kumar**

Abstract: *Pertussis continues to be a significant cause of morbidity and mortality in pediatric age-group globally, despite having a vaccine in our armamentarium for nearly a century. This is in sharp contrast with diphtheria and tetanus that have virtually vanished in well-immunized populations with the use of the vaccine. The persistence of pertussis is not only due to the issues of quality and efficacy of the available vaccines, but also to their adverse-effect profile, peculiar characteristics of the pathogen, complex and incompletely understood pathogenesis and difficulties in diagnosis and research. Availability of various types (1, 3 and 5 component) of acellular vaccines in last 2 decades and recent outbreaks of pertussis in well-immunized populations in the West have made the scenario much more complex. This article summarizes the current knowledge on these vaccines.*

Keywords: *Pertussis, Vaccines, Acellular.*

Epidemiology : Disease Burden

Global

Though pertussis continues to be a significant public health problem globally, there is a large discrepancy between the official reported figures and actual incidence. As per WHO, the official number of reported cases globally in the last 5 years ranges from 0.14 to 0.25 million / year, it is estimated that the actual figure is about 100 times: in the range of 16 million / year, with 95% cases occurring in developing countries.[1] The average case-fatality rate for pertussis is estimated at nearly 4% in infants aged <1 year and at 1% in children aged 1-4 years whereas in industrialized countries it is around 0.2%.

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Classically pertussis has been a childhood infection affecting mainly children aged under 5 years. However, it is increasingly being recognized in older children, adolescents and adults. According to a serological study from US, 21% of adults with prolonged cough had pertussis. The annual incidence of pertussis in adults globally is believed to be in the range of 0.6 million.[2]

Outbreaks of pertussis: Pertussis is a worldwide endemic-epidemic infectious disease, with outbreaks occurring every 3-5 years, as the number of susceptible persons in the population crosses a threshhold level. A summer-autumn seasonality is also notable. However, large outbreaks in highly immunized countries like USA, UK, Australia and New Zealand in the last 5-6 years have been of great concern. The number of cases reported in all these outbreaks have been typically 4-5 times the baseline levels and have surpassed the incidence rate of previous outbreaks. For example, the California epidemic in 2010 experienced the highest number of pertussis cases in over 60 years and the currently ongoing outbreak in California has broken the 2010 records.[3,4] Similarly, an outbreak in Western Australia in 2011 recorded almost double the number of cases in the previous large outbreak 2004.[5] In fact, pertussis has become the most common vaccine-preventable infection in many of these countries. Age-wise distribution of cases in all these outbreaks has shown two peaks: one in young infants (<6 months) before the completion of primary immunization and the second in adolescence: a few years after the last pertussis vaccine booster. Maximum rate of hospitalization and mortality has been recorded in infants.

Elucidation of reasons of such unprecedented outbreaks in highly immunized populations is currently under intense research and debate. It has been found that pertussis resurgence is not a universal phenomenon. The incidence trends, even in countries with superficially similar demography, socioeconomic conditions and vaccination programmes, are very heterogenous. It has been suggested that improved diagnostic aids like ELISA and PCR and increased awareness might have contributed to the surge, rather than real increase in incidence. However, epidemiological patterns of the surge, such as limited age groups affected, documented increased rate of bacteriologic

confirmation, unchanged severity of illness and different timings of the surge in different areas of the same country (e.g., different states in USA) that does not correlate with the introduction of the newer diagnostic tools refute this theory.[6,7]

Another factor that might have contributed to these outbreaks is introduction of acellular pertussis vaccines since most of these outbreaks have followed replacement of whole cell vaccines with acellular vaccines in the national immunization programs. All the three components of immune response: the strength, type and duration of immune response to acellular vaccines vis-a-vis whole-cell vaccines have been implicated. Recent studies and re-analysis of older studies on acellular pertussis vaccines have shown that these vaccines may not be as efficacious as whole cell vaccines, as was originally thought. Epidemiological data from 54 countries has demonstrated that there is a statistically significant correlation between use of DTaP vaccine used as the first (priming) dose and resurgence of pertussis in the respective countries in last 2 decades.[6] The duration of immunity conferred by acellular vaccines is also lesser than that by whole-cell vaccines. It is believed that immunity after acellular vaccines wanes within 4-12 years of primary immunization,[8] leading to pooling of susceptibles. Meta-analysis published recently has suggested that duration of immunity after acellular vaccines might be even lesser than this.[9] To make the matters worse, recent animal studies have also shown that the immune response to currently available DTaP vaccines is much less effective in preventing infection/ colonization with B. pertussis than current DTwP vaccines. They are also less effective in mucosal clearance of pertussis infection. Thus, current DTaP vaccines might be less effective in reducing transmission of infection as compared to currently available DTwP vaccines, even though the difference might be less in preventing pertussis disease.[10] Nevertheless, long-term epidemiological trends in USA and the Netherlands show that some surge in pertussis cases has been noted at least a decade before the introduction of acellular pertussis vaccines, although large outbreaks have occurred only recently.[11,12] Hence, introduction of acellular vaccines is possibly not the only factor responsible for these outbreaks, but just might have acclerated the surge.

Another factor that is being considered is antigenic shifts in circulating Bordetella pertussis strains due to vaccine selection pressure and other factors.[13,14] This has led to the appearance of strains with novel or previously rare alleles in a number of countries[6] and explains some of the outbreaks in Finland, Sweden, the Netherlands and Australia where the outbreaks have coincided with appearance of certain strains. However, it does not explain other larger outbreaks. Moreover, if genetic changes had increased the rates of vaccine failure, one would expect to see those effects first in Denmark, which has for the past 15 years used a 'narrow spectrum' monocomponent acellular pertussis vaccine rather than other countries using 5-component acellular vaccine like USA or countries using whole cell pertussis vaccines. To date, however, there is no evidence of increased vaccine failure in Denmark.[15,16] Thus, whether the observed antigenic shifts have played a significant role in increasing incidence rates and large outbreaks is still an open question.

It is also to be noted that most of the cases of pertussis reported globally have been 'diagnosed' on clinical grounds alone. Confirmatory tests are not available widely. Thus, there is an additional risk of over-reporting. For example, using culture and PCR in a study on children with pertussis-like symptoms in Pakistan revealed that a vast majority of cases were positve for Bordetella parapertussis rather than Bordetella pertussis, against which none of the vaccines might be effective.[17] Pakistan, incidentally, is using whole-cell vaccine in its National Immunization Program (NIP) since 1980s.

Thus, it is plausible that emergence of new strains in combination with low-efficacy acellular vaccines, faster waning of immunity with these acellular vaccines, reduced efficacy of acellular vaccines in preventing transmission ('leaky' vaccine protection-when the vaccine is able to prevent disease in the subjects, but is less efficacious or ineffective in preventing transmission of infection from the subject to other susceptible contacts), relatively low penetration of adolescent booster (TdaP), improved diagnosis and increased awareness has led to the current situation. Additional, yet unknown factors might also be contributory.

Indian scenario

In India, the incidence of pertussis declined sharply after the launch of Universal Programme of Immunization (UIP). Prior to UIP, India reported 2,00,932 cases and 106 deaths in the year 1970 with a mortality rate of <0.001%. During the year 1987, the reported incidence was about 1,63,000 cases which came down to 40,508 in 2010 and 39,091 in 2011 reflecting a decline of about 75%.[15] Amongst different states, AP, MP, Jharkhand, WB and Bihar reported the maximum cases in 2010. In 2010 only 6 and in 2011 a total of 11 deaths were reported.[15] However, there is gross under reporting of cases and actual number may be too high since the DTP3 coverage of three doses of DTP vaccine in 12-23 months old infant was found

to be 71.5% and only 41.4% children in the age group of 18-23 months had received DTP first booster.

Almost all of the cases reported from India have been diagnosed on clinical grounds alone. In the last 30 years, there has been no report of laboratory-confirmed B. pertussis from India! Few studies were published before the implementation of the UIP by the WHO in India in 1978. According to one small study conducted in 2007 at AIIMS, New Delhi, 2 out of total 21 children had positive isolates of Bordetella pertussis in their respiratory secretions.[18] The culture-positive rate of about 8%-10% was same as in older pre-UIP studies. In all these studies it was observed that the frequency of pertussis cases in India was higher during the months of November to June.

Pathogen and pathogenesis

Pertussis is caused by a Gram-negative coccobacillus, Bordetella pertussis. It is transmitted from infected persons to susceptible individuals through droplets. In its early catarrhal stage, pertussis is highly communicable, with a secondary attack rate of up to 90% among non-immune household contacts. The disease is highly infective and its basic reproduction number (Ro) (number of secondary cases resulting from one case introduced into a fully susceptible population) is estimated to be particularly high -about 12 to 17. Untreated patients may be contagious for 3 weeks or more following the onset of typical coughing attacks. Thus, vaccine coverage needs to be particularly high to prevent outbreaks.

Bordetella species have a unique property of the ability to alter their phenotypic state depending upon environmental conditions and may show different expression of virulence factors. These factors include pertussis toxin (PT), filamentous haemagglutinin (FHA), pertactin (PRN), fimbriae (FIM) type 2 and type 3, adenylate cyclase toxin (ACT), tracheal cytotoxin (TCT), BrkA (Bordetella resistance to killing genetic locus, frame A), lipooligosaccharide and B. pertussis endotoxin.[1] PT is the only B. pertussis-specific antigen. Multiplicity of virulence factors and alteration of phenotypic state confers the bacterium a high degree of immune escape.

Pertussis has an incubation period of 9-10 days, but detailed pathogenesis is still incompletely understood. The organisms attach strongly to the ciliated cells through several adhesins. Although PT and FHA are important attachment proteins, FIM, PRN and BrkA participate in this process as well. The bacteria normally do not invade beyond the epithelial layers of the respiratory tract, but PT enters the bloodstream and exerts its biologic effects on systemic sites. Although this sequence may explain the respiratory manifestations of pertussis, the pathogenesis of the encephalopathy that can complicate clinical disease remains unclear. Severe disease and death have been reported mainly during neonatal period and early infancy, while older children, adolescents and adults often have subclinical disease with atypical presentation. Thus, epidemiological shift of cases to higher age-group with good vaccine coverage would contribute to continued circulation of the pathogen in the community that might be less well detected. Whether this also is a factor in current surge also needs to be investigated.

Following natural infection, antibodies to PT are found in only 80%-85% of patients. Neither the type nor the concentration of antibodies is well correlated to immunity. So far, no protective role has been observed for cell-mediated immunity. Natural infection does not confer long-lasting protection against pertussis.[1] Thus, it is no suprise that immunity accorded by the vaccine is not long-lasting.

Pertussis vaccines

There is no stand-alone pertussis vaccine that is licensed anywhere in the world. It comes as a combination vaccine along with diphtheria and tetanus toxoids, thus called DTP or DPT vaccine. Some brands have, in addition, one or more of following components: Hib, Hepatitis B and IPV. Broadly, DTP vaccines are of two types: whole-cell (wP) vaccines based on killed B. pertussis organisms and acellular (aP) vaccines based on highly purified, selected components of this agent: labelled as DTwP and DTaP vaccines respectively. For immunization of adolescents and adults, there is another type of pertussis vaccine that has standard quantity tetanus toxoid and reduced quantity diphtheria and acellular pertussis component called as TdaP vaccine.

DTwP vaccine

It is one of the old combination vaccines developed as early as 1920s during World War II and introduced for mass vaccinations in 1940s. It is composed of 20-30 lf of diphtheria toxoid, 5-25 lf of tetanus toxoid and inactivated whole cell pertussis bacilli adsorbed on insoluble aluminum salts as adjuvant.

Immunogenicity and efficacy: For diphtheria and tetanus, the protective levels of their respective antitoxins has been well defined. In contrast, the scenario of pertussis is complex. Unlike C.diphtheriae and C.tetani, B.pertussis has multiple virulence factors, it shows different expression of virulence factors under different environmental

conditions and its pathogenesis is still incompletely understood. Thus, the relative role of various virulence factors is still unclear. There is no single absolute or surrogate correlate of protection known for pertussis disease and vaccines till date. Antibody levels against PT, PRN and FIM can be used as markers of protection, but no established protective antibody levels are known. Hence, it is difficult to define 'immunogenicity' of pertussis vaccines accurately.[8]

Assessment of clinical efficacy of pertussis vaccine is equally complex, since laboratory diagnosis of pertussis is difficult and the facilities are virtually absent in the developing world. The diagnosis invariably remains clinical and the sensitivity and specificity vary with the case definition used. Accordingly, the efficacy estimates also vary considerably with different case definitions used in different studies. This also makes the comparison between different studies difficult. The efficacy estimates have varied from 83%-98% in higher efficacy trials to as low as 36%-48% in lower efficacy trials. According to a 2003 systematic review, the pooled efficacy of wP vaccine against pertussis in children was 78%, but efficacy varied significantly among vaccines. The efficacy of wP alone ranged from 61% to 89%.[19]

The effectiveness data of wP vaccine also comes from the developed countries which used the vaccine with good coverage in the past. The widespread use of wP vaccine in these countries has been associated with a remarkable decline in reported pertussis. Another evidence of the benefits of wP vaccine was provided by unintended experiments that occurred in three developed countries when vaccine use was curtailed or abandoned. Japan, England and Wales and Sweden utilized wP vaccines in their NIPs which led to remarkable decline in the morbidity and mortality of pertussis in all these countries. However, when the vaccination was suspended owing to high incidence of side effects and perceived poor efficacy of wP vaccines, the epidemics of pertussis recurred with resultant high mortality. A review of the French experience with wP vaccine over a period of 30 years showed persistent high efficacy of the product. Further evidence of the efficacy of wP vaccine is provided by the observation that the reported incidence of pertussis disease varies inversely with vaccine acceptance rates.[15]

There is no data on the effectiveness of wP vaccines among older age groups since pertussis was previously perceived as a problem only of young children, and the reactogenicity of wP vaccine was thought to be too high to permit routine use in older children, adolescents and adults.

Duration of protection: Immunity has been documented to wane over 6-12 years, thus requiring multiple boosters.[20]

Adverse effects: Minor adverse effects like pain, swelling and redness at the local site, fever, fussiness, anorexia and vomiting are reported in almost half the vaccinees after any of the 3 primary doses. Serious adverse effects have been reported with DTwP vaccines but are rare. The frequency of these side effects/1000 doses is 0.2-4.4 for fever more than 40.5°C, 4-8.8 for persistent crying, 0.06-0.8 for hypotonic hyporesponsive episodes (HHE), 0.16-0.39 for seizures and 0.007 for encephalopathy. The frequency of systemic reactions reduces and that of local reactions increases with increasing number of doses. Children with history of a reaction following vaccination are more likely to experience a reaction following future doses. Catastrophic side effects such as sudden infant death syndrome (SIDS), autism, chronic neurologic damage, infantile spasms, learning disorders and Reye's syndrome were attributed to use of the wP vaccines in the past. It has now been proved beyond doubt that the wP vaccine is not causally associated with any of these adverse events.[21]

Contraindications and precautions: Absolute contraindications to any pertussis vaccination (including DTwP vaccine) are history of anaphylaxis or development of encephalopathy within 7 days following previous DTwP vaccination. In case of anaphylaxis, further immunization with any diphtheria/tetanus/pertussis vaccine is contraindicated as it is uncertain which component caused the event. For patients with history of encephalopathy following vaccination, any pertussis vaccine is contraindicated and only diphtheria and tetanus vaccines may be used. Events such as persistent inconsolable crying of more than 3 hours duration/hyperpyrexia (fever >40.5°C)/ HHE within 48 hours of DTwP administration and seizures with or without fever within 72 hours of administration of DTwP are considered as precautions but not contraindications to future doses of DTwP because these events generally do not recur with the next dose and they have not been proven to cause permanent sequelae. Progressive/evolving neurological illnesses, is a relative contraindication to first dose of DTwP immunization. However, DTwP can be safely given to children with stable neurologic disorders.[21]

DTaP vaccines

Good coverage of DTwP vaccines in developed countries led to remarkable decline in incidence of all the three infections in second half of the last century. With only few cases being reported, the frequent local side effects of the vaccine became increasingly unacceptable

to the society leading to decline in coverage of the vaccine in some of the developed countries and resurgence of these infections, especially pertussis. This led to the development of less reactogenic acellular pertussis containing DTaP vaccines starting with Japan in 1981 and then by 1996 in USA with many western countries following suit.

DTaP vaccines contain at least one of the separately purified antigens pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN) and fimbrial hemagglutinins 1, 2 and 3 (FIM type 2 and type 3), in addition to diphtheria and tetanus toxoids as in DTwP vaccines. Although DTaP vaccines contain only a subset of 1-5 antigens, in contrast to DTwP vaccines that contain entire complement of about 3000 antigens, the concentration of the antigens in DTaP vaccines is much higher. Hence, while DTwP vaccines can be considered as vaccines with 'broad coverage' but low titres, DTaP vaccines have 'narrow coverage' but high titres.[8] Among different DTaP vaccines also there are a number of variations. The varied antigenic formulation of aP vaccines approved for human use is a distinctive and unusual feature with respect to all other bacterial vaccines for human use. They differ from one another not only in the number and quantity of antigen components, but also with regard to the bacterial clone used for primary antigen production, methods of purification and detoxification, incorporated adjuvants, and the use of preservatives, such as thiomersal. Nearly two dozen DTaP vaccines have been designed and tested, but direct comparison between these products is almost impossible due to several variables listed above. Further, the exact contribution of the different aP antigens to protection is not clear and thus there is no consensus as yet on the antigenic composition of an ideal aP vaccine, although it is clear that PT is the most important antigen.[8] Among the DTaP vaccines that are licensed in India, Pentaxim® is 2-component DTaP (in combination with IPV and reconstituted with Hib conjugate vaccine), Infanrix® is 3-component, while Tripacel® is 5-component DTaP vaccine.

Efficacy: This is the topic of heated debate globally in view of outbreaks of pertussis in highly vaccinated countries. The efficacy trials conducted in Europe and Africa have brought out variable results and are not strictly comparable due to lot of variation between different DTaP vaccines tested, variation in the DTwP products with which former have been compared and variations in case definition used. Moreover, no study has evaluated a multi-component vaccine directly against versions of itself that contain alternate components or different quantities of each component. Although these limitations have precluded a formal meta-analysis of the efficacy data, a recent Cochrane review[22] has suggested that the efficacy of multi-component (≥three) vaccines varied from 84% to 85% in preventing typical whooping cough(characterized by 21 or more consecutive days of paroxysmal cough with confirmation of B. pertussis infection by culture, appropriate serology or contact with a household member who has culture-confirmed pertussis), and from 71% to 78% in preventing mild pertussis disease (characterized by seven or more consecutive days of cough with confirmation of B. pertussis infection by culture or appropriate serology). In contrast, the efficacy of one- and two-component vaccines varied from 59% to 75% against typical whooping cough and from 13% to 54% against mild pertussis disease. Multi-component acellular vaccines are more effective than low-efficacy whole-cell vaccines, but may be less effective than the highest-efficacy whole-cell vaccines.

Recent studies have also suggested that the efficacy of DTaP vaccines is especially low when they are used in primary series of the vaccination. Kids who had been 'primed' with whole cell pertussis vaccine were better protected from pertussis during the recent outbreaks in comparison to those who received acellular pertussis vaccines throughout. Those who received even one (first dose) of whole cell pertussis vaccine, followed by acellular vaccine in subsequent doses were found to be better protected, and this difference was statistically significant in many studies conducted as a part of retrospective analyses in USA and Australia after the recent outbreaks.[23-25] Recent analysis of epidemiological data of 54 countries has also clearly demonstrated that there is a statistically significant correlation between use of DTaP vaccine used as the first (priming) dose and resurgence of pertussis in the respective countries in last 2 decades.[6] Thus, it is being suggested that the immune response to acellular and whole-cell priming might be different. The lesser protection provided by acellular pertussis vaccines, both as the initial vaccine or full primary course, may be due to 'linked epitope suppression', when the initial exposure locks in the immune response to certain epitopes and inhibits response to other linked epitopes on subsequent exposures.[15] It has also been shown that in contrast to DTwP vaccines that induce immune response with Th1 and Th2 bias, DTaP vaccines induce predominantly Th2 (antibody producing) immune response.[26] This might also in some way be involved in different 'priming' when DTaP vaccine is used as the 1st dose. Immune responses in aP vaccine recipients could change from a mixed Th2/Th1 profile to a robust Th1 profile following a natural booster. Thus, if long-term protection by aP vaccines depends on natural boosters, those aP vaccines which are more effective in

retarding the circulation of B. pertussis could be less efficacious in the long run![27]

Recent animal studies have also shown that the immune response to currently available DTaP vaccines is much less effective in preventing infection /colonization with B. pertussis than current DTwP vaccines.[28] It is also less effective in mucosal clearance of pertussis infection. These two factors make current DTaP vaccines less effective in reducing transmission of infection as compared to currently available DTwP vaccines, even though the difference might be less in preventing pertussis disease. This is of great concern, since such 'leaky protection' cannot be compensated even by giving more boosters.[29]

Duration of protection: Data from developed countries suggests that protection after DTaP vaccination wanes after 4-12 years. Recent meta-analysis suggests that the waning might even be faster than this.[8] Similar data from developing countries is lacking as on date.

Adverse effects: The incidence of minor adverse effects (pain, swelling and redness at the local site, fever, fussiness, anorexia and vomiting) is about 66% less than with DTwP vaccine, but incidence and severity of local adverse effects increases with each successive dose of DTaP vaccine, as with DTwP vaccines. The incidence of severe adverse effects (persistent crying, hypotonic hyporesponsive episodes, seizures and encephalopathy) is same as with DTwP vaccines.[21]

Contraindications and precautions: They are same as with DTwP vaccines.

Tdap vaccines

Good coverage with DTP vaccines in a population breaks the transmission cycle and reduces natural circulation of these infections in young children. Moreover, the immunity to all the three infections is known to wane 6-12 years after the last booster (more rapidly with DTaP vaccines). This results in pooling of susceptible adolescents and adults in these populations. Thus, infrequent 'natural boosting' and rapid waning of immunity acquired from childhood vaccination increases the incidence in adolescents and adults. Secondly, the partly protected adolescents and adults also act as 'reservoirs' of disease transmission to unvaccinated / partially vaccinated young infants. Thirdly, when childhood vaccination programs break down as it happened in the former Soviet Union in the early 1990s, massive outbreaks involving primarily adults can occur. Recent outbreaks of pertussis in several countries have affected mostly adolescents. Thus, it is desirable to regularly boost adult immunity. In addition, vaccination is also needed for catch up vaccination in unimmunized / partially immunized children. Moreover, vaccinating pregnant women with diphtheria and pertussis vaccine (in addition to tetanus) can also protect their newborn babies against these infections before the age of 6-8 weeks when routine immunization begins. However, DTP vaccines (both DTwP and DTaP) have increased reactogenicity in older children and are thus not recommended in children above 7 years of age. Thus, Tdap vaccines were developed. Tdap vaccines contain standard quantity tetanus toxoid and reduced quantity diphtheria and acellular pertussis vaccine. The two brands available in India are Boostrix® and Adacel®.

Efficacy and effectiveness: Tdap vaccine was licensed first time in USA in May 2005 and the coverage of this vaccine even in the developed world was low until recently. The US National Surveys (NIS) have revealed that coverage of Tdap vaccine in year 2008 was just 40.8% which has increased to 86% in 2013. Hence, the efficacy and effectiveness data is also limited. This limited data suggests only modest efficacy (in the range of 65%-75%) of the pertussis component of Tdap. The preliminary data suggests effectiveness wanes very rapidly (within 3-4 years) among aP vaccine recipients and there was no evidence of herd immunity.

Adverse effects: Commonest side effect with Tdap is pain at the local injection site in about 70% of vaccinees, followed by other local adverse effects such asredness and swelling. Systemic side effects like fever, headache and fatigue are rarely seen. Serious adverse events have not been reported. The data on safety of Tdap vaccine in pregnant women is limited; however, existing data from the CDC, US FDA and the pharmaceutical pregnancy registries do not indicate any adverse effect.

Precautions and contraindications: The Tdap vaccine needs to be used with caution in following conditions: (a) Moderate or severe acute illness (b) History of an Arthus reaction following a previous dose of tetanus toxoid and /or diphtheria toxoid containing vaccine, including meningococcal conjugate vaccine (c) Gullain Barre Syndrome (GBS) within 6 weeks of previous dose of tetanus-toxoid containing vaccine and (d) Progressive or unstable neurological disorder or uncontrolled seizures, until these are stabilized with medical therapy. The contraindications are serious allergic reaction to any component of the vaccine or history of encephalopathy not attributable to an underlying cause within 7 days of administration of a vaccine with pertussis component.[8]

IAP Recommendations for use of DTP/ Tdap vaccines[21,30]

Routine vaccination

Three primary doses of DTP vaccines are recommended at 6, 10 and 14 weeks and two boosters at 15-18 months and 4-6 years of age. Only DTwP should be used in primary series. DTaP vaccines may be preferred to wP vaccines only in those children with history of severe adverse effects after previous dose(s) of wP vaccines or children with neurologic disorders, if resources permit. The parents should be counselled about the probable efficacy related disadvantages of using aP vaccines for the primary series. In booster doses, DTaP can be considered, considering reactogenicity of DTwP vaccines. However, DTwP is preferable even in booster doses. Whenever DTaP is chosen, the vaccine with at least 3 aP components should be chosen, the more the better. DT vaccine is recommended only in cases where pertussis vaccine is contraindicated.

Children who have received DTaP as primary doses should be offered DTwP for all subsequent doses. They may be associated with a risk of adverse reactions. Single dose of Tdap vaccine is recommended at 10 years of age.

Vaccination in specific circumstances

Catch up vaccination

For unimmunized children below 7 years of age, three doses of DTwP/ DTaP should be used (preferably DTwP) at 0, 1 and 6 months interval. The 2nd childhood booster is not required if the last dose has been given beyond the age of 4 years. It is essential to immunize even those recovering from pertussis as natural disease does not offer complete protection.

For children above 7 years of age, the first dose should be of Tdap and subsequent doses of Td vaccine. This is followed by Td vaccine every 10 years. If Td is not available, then TT can be used. These children do not require Tdap vaccine dose at 10 years of age.

Adolescents / adults who have never received Tdap vaccine in the past must be given a single dose of the vaccine. Tdap can be given regardless of time elapsed since the last vaccine containing tetanus toxoid or diphtheria toxoid.

Pregnancy

Maternal immunization, particularly of pregnant women, may be an effective approach to protect very young infants and neonates from pertussis. IAP now recommends immunization of pregnant women with a single dose of Tdap during the third trimester (preferred during 27 through 36 weeks gestation) regardless of the number of years since prior Td or Tdap vaccination. Tdap has to be repeated in every pregnancy irrespective of the status of previous immunization (with Tdap). Even an adolescent girl who had received Tdap one year prior to becoming pregnant will have to take it since there is rapid waning of immunity following pertussis immunization.

The way forward...

Since the 'pertussis riddle' is not yet fully solved, the way forward is not straight-forward. Many novel alternative strategies are being researched to outsmart this difficult bacterium. Vaccination of newborns, additional booster doses given to older adolescents and adults, maternal immunization, post-partum immunization and 'cocooning' (vaccinating household members and close contacts to protect the unimmunized young infant from pertussis) are being actively researched. However, as of now, none of them seems to be entirely successful in reducing the disease burden in children either owing to lower vaccine efficacy than desired, less than optimal vaccine coverage or rapidly waning immunity.[15] Cost-effectiveness is also a concern. Out of these strategies, maternal immunization has found most favour among experts[31] and thus is now a standard recommendation of AAP and IAP. However, with maternal immunzation, there is some concern regarding potential interference of maternal pertussis antibodies with infant immune response to primary DTP vaccination. Results of a recently published trial[32] does not support this theory. Another trial is currently underway in Canada.[33] Yet another line of research is the development of better vaccines to overcome the shortcomings of currently available acellular and whole cell vaccines. Inclusion of new antigens (like adenylate cyclase toxin, the autotransport BrkA or IRP1-3) to the current acellular vaccines, replacing alum with other adjuvants (like Toll-like receptor agonists) that induce more potent Th1 and Th2 responses and development of live-attenuated vaccines are under way. Stand-alone acellular pertussis vaccines are also being attempted, that could be more frequently administered as boosters at shorter intervals, without the local adverse events seen with more frequent administration of currently available combination vaccines.[15,27,34]

Points to Remember

- ***Pertussis continues to be a significant public health problem with endemic-epidemic pattern globally, despite having a vaccine in our armamentarium for nearly a century.***

- ***Large outbreaks in highly immunized countries last decade have greatly surpassed the incidence rate of previous ones and thus have forced the scientific community to revisit pertussis epidemiology and vaccines.***
- ***A combination of various factors such as emergence of new strains, lower efficacy and faster waning of immunity of acellular vaccines, reduced efficacy of these vaccines in preventing transmission ("leaky" vaccine protection), relatively low penetration of adolescent booster (TdaP), improved diagnosis and increased awareness of pertussis have led to re-emergence of pertussis.***
- ***Currently IAP recommends use of DTwP vaccines, especially for primary series. In booster doses, DTaP can be considered, considering reactogenicity of DTwP vaccines. However, DTwP is preferable even in booster doses.***
- ***Single dose of Tdap vaccine is recommended at 10 years of age and in third trimester of every pregnant woman.***

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CLIPPINGS

Preterm Surgeries May Impair Later Cognition.

A significant reduction in composite IQ scores was found at age 3 to 6 years when preterm infants had two or more surgeries before term-equivalentage.There has been growing concern about potential adverse effects of general anesthesia on the developing brain. In a prospective cohort study of infants born before 33 weeks gestational age, researchers evaluated the effect of preterm anesthesia exposure on neurodevelopment at ages 3 to 6 years.

Two or more general anesthesia exposures before TEA in small premature infants are associated with reductions in IQ scores during early development. A growing body of evidence supports careful scrutiny of when and whether to consider early neonatal surgical procedures and discussingthe potential risks with parents.

F. Bruder Stapleton. Preterm Surgeries May Impair Later Cognition. Pediatrics and Adolescent Medicine 2015 Sep.

NEWS AND NOTES

15th Chhattisgarh PEDICON

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UPDATE ON VACCINES

CONJUGATE TYPHOID VACCINE

Monjori Mitra

Abstract: *Typhoid fever is a global concern and the increase in prevalence over the years has established that the prevention through vaccination should be a priority. Because of the limitation of the polysaccharide vaccine the innovation of conjugating the polysaccharide with carrier protein has been developed and clinical studies in different parts of the world has shown higher efficacy along with long term persistence of immunogenicity. The first conjugate vaccine developed used recombinant Pseudomonas aeruginosa exotoxin A with the Vi polysaccharide which in the various dose ranging studies done over the years has shown good efficacy in 2 to 5 years old children. The other carrier proteins used in the different vaccines were CRM197, DT, TT etc.*

The two vaccines, which have got license in India have used TT as the carrier protein and have shown good immunogenicity. The clinical study of persistence of immunogenicity is being continued over the years with one of the vaccines. Based on this outcome, the IAP immunization committee has recommended the use of the vaccine .

Keywords: *Conjugate typhoid vaccine, Immunogenicity,*

The disease burden of typhoid fever worldwide is high even to the present day inspite of addressing various hygienic and sanitary issues. A systematic review of studies estimated the incidence of typhoid fever as 21,650,974 illnesses and 216,510 deaths during 2000.[1] A study of all endemic areas showed that the disease was highest among children in the age group of 5-19 years.[2]

A surveillance study in India, at Kolkata, recorded an annual incidence of 340.1 and 493.5 per 100,000 person per year among 2-4 year and 5-15 year age groups respectively. An outbreak of typhoid was reported in the Thar Desert, Rajasthan, with an attack rate of 104 cases per 1000 population. Besides the disease burden, the existence of multidrug-resistant bacteria is a serious growing problem in the developing world and this leads to more complicated typhoid fever.[3]

The wide spread disease burden has become a real public health problem and has globally become an area of concern. WHO and various other organizations' coalition against typhoid foundation and the Bill and Melinda Gates Foundation have been focusing on the disease burden and looking for preventive solution through vaccination. Vaccination has proven to be an effective way of controlling typhoid in resource-poor countries, especially in vulnerable age groups, mainly in children under 15 years of age.[4] As the age group at highest risk of infection by typhoid fever has been established to be between 2-3 years of age, it is suggested that the immunization program against typhoid fever should be thoughtfully reassessed in its attempt to immunize children below 2 years of age.

Over the years various typhoid vaccines have been developed to enhance prevention of the disease. The initial parenteral whole cell inactivated vaccine was included in the EPI schedule of India but was withdrawn due to increased reactogenicity. Since then multiple vaccines were developed. Both inactivated polysaccharide and live oral vaccines are being used globally above 2 years of age. Since the polysaccharide vaccine was T cell independent it needed repeat dosing every three years, as there was no boosting effect and had moderate immunogenicity around 70%, particularly in children less than 5 years of age.

It was seen that the limitations of polysaccharide vaccines could be overcome by conjugation of the polysaccharide vaccines with carrier protein as was done in H influenzae type b, pneumococcal and meningococcal vaccines thereby increasing their immunogenicity in young children and infants. Various conjugation techniques have been experimented with different carrier proteins such as tetanus or diphtheria toxoids, cholera toxin, cholera toxin B subunit or recombinant exotoxin A of Pseudomonas aeruginosa to Vi. It was observed that the immunogenicity of Vi conjugate depends more on the technique and less on the type of carrier protein.[5]

The main advantage of vaccines with polysaccharide antigens conjugated to proteins is the stimulation of T-cell dependent immune responses. The implication of this is

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that infants with relatively less mature immune systems would respond, which does not happen with polysaccharide alone. Most of the efficacy studies have shown that the typhoid conjugate vaccine confers superior protection as compared to the currently available polysaccharide vaccines.[6] According to the World Health Organization (WHO),conjugate vaccines demonstrate greater efficacy and effectiveness, longer persistence of immunity, immunogenicity across all age groups, including infants and toddlers aged younger than 2 years, perhaps some degree of herd immunity and induction of immune memory with initial dosing, leading to anamnestic responses to a subsequent dose or doses.[5]

The first conjugate vaccine study was done in Vietnam to elicit the efficacy of the Vi vaccine bound to non-toxic recombinant Pseudomonas aeruginosa exotoxin A (rEPA) among children 2 to 5 years of age. The study revealed that the vaccine was safe and immunogenic and has more than 90% efficacy in this age group. In the study both school and preschool children from the highly endemic areas received both Vi conjugate vaccine and Vi polysaccharide vaccine in different groups and it was seen that the conjugate group achieved and maintained higher levels of anti-Vi IgG serum antibodies compared to the polysaccharide group.[6,7] The immunogenicity of this Vi conjugate vaccine was observed to be dose-dependent. In the Phase II study, 2- to 4-year-olds were randomly divided into two groups receiving either one or two doses of Vi-rEPA. At 26 weeks post-injection, the antibody levels of 2 to 4 year-old children receiving either one or two doses of Vi-rEPA were higher than those of the school-age children who received one injection of Vi. There was a gradual decline in the antibody gap between one and two injections, at 26 weeks, the titers were 37.9 versus 25.3 mg/mL ($p = 0.2$) and there was no difference at the 3 years interval (5.65 vs 5.84).[8]

In another study the efficacy trial of Vi-rEPA was conducted as a double blind randomized controlled study amongst 11,091 children of 2- to 5 years age group in the high endemic region in Vietnam. Two injections of either Vi-rEPA or saline at 6 weeks apart were given to each child. Less than 2% of children had adverse reactions and none of the reactions was considered serious. Typhoid cases, diagnosed by the isolation of S. typhi from blood cultures after 3 or more days of fever, were identified by active surveillance over a period of 27 months, and by passive surveillance for an additional 19 months after the vaccine code was opened.[6] At the end of active surveillance, Vi-rEPA demonstrated 91.5% protection and 82.4% during the passive surveillance. Over the entire 46-month period, the vaccine efficacy was 89.0%. The typhoid cases in the Vi-rEPA group appeared to be milder since none of the sick children in the vaccine group were hospitalized compared with 34% in the placebo group. The serologic response from this study helped to estimate the antibody protective level as benchmark for future reference.[6,7]

Following the administration of a single dose, detectable antibody levels were maintained for as long as 10 years in adults and 8 years in children. At crossover vaccination of the efficacy trial, children were between 5 and 8 years old and received only one injection of Vi-rEPA. The persistence of the antibody levels of this cohort was re-examined 8 years after the vaccination in 75 randomly selected children. The geometric mean (GM) anti-Vi IgG level remained high at 17.7 mg/mL and a majority of the children (84%) had greater than the estimated protective level. These data demonstrated that, similar to that observed in adults, Vi-rEPA elicited long-lasting protection in school-age children.

Though the conjugate typhoid vaccine with the carrier protein rEPA has been most studied over the last 25 years it has not been licensed till now. However, based on the understanding of immunogenicity and safety, several conjugate typhoid vaccines are being developed and manufactured.[7,8]

Lanzhou Institute of Biologics, China, synthesized Vi-rEPA and conducted a double-blind, placebo-controlled (Vi polysaccharide), randomized Phase I and II studies in a high typhoid endemic region. The results showed that their conjugate was safe and immunogenic, and the levels of anti-Vi IgG in 2- to 5-year-old children (25 mcg/mL, 2 doses at 8 weeks apart) are similar to those observed in Vietnamese children.[9]

A typhoid conjugate vaccine developed by Novartis Vaccines Institute for Global Health used Vi prepared from Citrobacter freundii and CRM_{197} as the carrier protein has been demonstrated to elicit a significantly higher level of anti-Vi IgG in European adults who had never been exposed to typhoid fever. Subsequently, phase 2 trials was conducted at Pakistan, India and Philippines amongst adults, children, older infants, and infants aged 6–8 weeks who had received either 5mcg Vi-CRM_{197} or 25 mcg Vi-polysaccharide vaccine (or 13-valent pneumococcal conjugate vaccine in children younger than 2 years).[10] From an immunogenicity perspective, the data showed that one dose of Vi-CRM_{197} induces a strong anti-Vi immune response than the Vi polysaccharide, in adults, children, and infants aged 9-12 months, both in terms of geometric mean

concentrations and of seroconversion rate, which was100% after vaccination in all three age groups despite the difference in the dose of the two vaccines 5mcg and 25mcg. However, in both children and older infants, a second Vi-CRM_{197} dose, given 2 months after the first one, did not induce a booster response. Additionally, Vi antibody titres fell significantly 6 months after the last dose and in adults and children, they were no longer higher than in recipients of the Vi-PS vaccine. Immunogenicity in infants aged 6-8 weeks was less than in older age groups, particularly in Pakistani infants whose titres 6 months after the third dose decreased to pre-vaccination concentrations, whereas antibodies remained significantly higher than baseline in Filipino infants. Likewise, 6 months after last vaccination, rate of seroconversion fell to 25% in Pakistani infants, whereas it remained at 70% in Filipino infants. It was seen from various evidences that there has been an overall reduced immunogenicity in Pakistani infants compared with Filipino infants for some routine EPI vaccines, including H influenza type b, hepatitis B and measles, suggesting that genetic, nutritional, or other environmental factors might also have a role. Further studies are being conducted with the vaccine to address all these issues.[10]

There are other several Vi conjugates prepared with licensed toxoids such as tetanus (TT) or diphtheria toxoids (DT) or recombinant DT CRM_{197}. One Vi-TT conjugate was licensed for local distribution in India in 2008. The immunogenicity results of the vaccine based on its package insert, showed that the conjugate Vi-TT elicited similar level of anti-Vi IgG in infants and in older children (2- to 5-year-old), the Vi dose of the vaccine was 5 mcg/ 0.5 mL. Currently this Vi -TT vaccine is also undergoing a randomized controlled school-based efficacy trial amongst approximately 2000 children in an urban slum in Kolkata, India, (CTRI/2012/06/002719).Culture positive typhoid fever 1.27% (11 subjects) was seen in the control group and none in the vaccine group in the active surveillance period of 12 months there by demonstrating a 100% efficacy in the study population. Immunogenicity of a subset of the population was assessed from the vaccine arm. There was a 100% seroconversion of fourfold rise and a GMT rise from baseline 1.8EU/mL to 32 EU/mL at 6 weeks post first dose. After 12 months following two doses 6-8 weeks apart the seroconversion considering four fold rise from baseline was 83%and GMT was14EU/mL, which was significantly above the cut off [7.4 EU/mL seroprotected level (unpublished data)].[9]

The second conjugate typhoid vaccine Typbar-TCV was officially launched in 2013 in India. The Vi conjugate prepared using ADH as a linker has efficient immunogenicity with administration of a single dose containing 25 mcg per dose.[11]

The results of Phase I and II clinical trials of Vi-TT were presented at the 8th International Conference on typhoid fever and other invasive salmonellosis (2013).It was shown to be safe in 6-month to 2-year-old children (n = 307) with 98% having had seroconversion 6 weeks after one injection, the GMT of anti-Vi IgG level were significantly higher than those in the Vi group.[10] The phase III study showed a significant rise in GMT amongst both the cohort 6 months to 2 years and 2 to 45 years age group, from 9.44 and 10.41 EU/mL to 1952.03 EU/mL and 1301.44 EU/mL respectively. The antibody titre was 50.49 and 78.80 EU/mL after 18 months and persisted till 24 months. A booster dose was given to a subset after 2 years and there was a significant boosting with high avidity antibodies generated with TCV (unpublished data).[11]

Recently, a Vi conjugate using the Vi purified from Citrobacter freundii sensulato and linked through ADH to CRM_{197}, a mutant non-toxic diphtheria toxin, was studied.[12,13]Vi-CRM_{197} was compared with Vi vaccine in Phase I and dosage studies in European adults. Four weeks after the immunization, the group injected with Vi-CRM_{197} elicited approximately six-times higher anti-Vi IgG levels than those injected with Vi alone (304 vs 52 EU). At 6 months, the difference in the antibody levels was reduced (69 vs 51 EU). The reason for this fast decline of antibody elicited by Vi-CRM_{197} as opposed to the long persistence of Vi-rEPA is yet to be investigated. Similar to those observed in the Vi-rEPA dosage study in young children, the immune response induced by Vi-CRM_{197} was also dosage dependent: within the range tested between 1.25 and 25 mcg, there was a direct correlation between the dosage and anti-Vi IgG response.[14] As reported at the typhoid conference in 2013, the Vi-CRM_{197} conjugate when injected to 9-month-old infants (5 mcg/0.5 mL, 2 injections 8 weeks apart) the level of anti-Vi IgG elicited significantly higher than those in adults immunized with Vi (25 mcg/mL injection) (preliminary results presented). Laboratory investigation of Vi conjugated to DT was attempted by International Vaccine Institute (IVI) and showed to be successful in mouse immunization study. The Vi polysaccharide purified by IVI had a lower molecular weight and in turn the final conjugate Vi-DT could be successfully sterile filtered without blockage or loss. Vi-DT technology was transferred to several pharmaceutical companies in Asia, including India, Indonesia and Korea. Clinical trials of the Vi-DT are underway and their clinical outcome is much anticipated.

If successful, the vaccine will be part of the affordable vaccine program sponsored by Bill Melinda Gat9es Foundation aimed for the most impoverished populations in the typhoid endemic regions.[9]

It is worthwhile to make a note on the wide range of Vi conjugate dosages, from 5 to 25 mcg per dose, used in the clinical studies by the four manufactures mentioned above. In addition, the age and number of injections also vary. A systematic comparison of the short- and long-term immune responses will be helpful for better assessment on these important issues.[14]

Dosage: According to the vaccine schedule of the Indian Academy of Paediatrics, 2014, currently available conjugate typhoid vaccine should be given at 9-12 months of age followed by a booster at 2 years.[15]

Post-exposure prophylaxis and therapeutic vaccination

Post-exposure prophylaxis is not practised with typhoid vaccines because the incubation following ingestion of a large inoculum may be a week or less and the organisms rapidly gain their intracellular niche (within 24 hours). Thus, following exposure there would be insufficient time to mount an effective immune response after administration of the currently licensed vaccines. There have been anecdotal reports of unsuccessful attempts to immunize chronic gall bladder carriers with the intent to interrupt chronic carriage.[16]

Adverse Events: The vaccines were well tolerated in all the forms and various doses and except local reactions including mild pain, tenderness and swelling there were no serious events.

Vaccination in special situation

If immune compromised individuals, including persons with human immunodeficiency virus (HIV) infection, must travel to endemic areas, Vi vaccine should be administered. It is important to immunize such travelers because studies of HIV-infected individuals in typhoid-endemic areas have revealed that they are at greatly increased risk of developing typhoid fever.[16]

Conclusion

The result of the various conjugate typhoid vaccines studied so far shows good immunogenicity and safety outcome. The study results are not uniformly equal. The outcome was seen to be dependent on the dose, number of administrations, genetic background of individuals as seen in the Pakistan study where ethnicity mattered compared to the Filipino group, where background of endemicity mattered which may give rise to boostering effect thereby less number of doses being required. Hence, it may be difficult to come to a uniform consensus for all the vaccines, rather the dosage schedule may vary with the outcome and immunogenicity based on the strength of the vaccine. All the studies are being continued to evaluate the follow-up effect in long term immunogenicity. It has been seen that all the conjugate vaccines have shown better immunogenicity than their polysaccharide counterpart. Globally the vaccines are being evaluated and newer vaccines are being developed to consider in the immunization schedule particularly in developing countries. The only two vaccines globally available and licensed by the regulatory body are in India and being marketed in India only. Ongoing studies for evaluation of long-term immunogenicity for both the vaccines are being conducted across India.

Points to Remember

- ***Prevalence of disease burden in younger age group warrants effective immunization in this age. To control overall disease burden in all age groups an efficacious typhoid vaccine is required.***
- ***Conjugate typhoid vaccine with high immunogenicity and good efficacy should be the choice of vaccine over polysaccharide vaccine.***

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NEWS AND NOTES

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UPDATE ON VACCINES

HEPATITIS A VACCINES

*Ashish Bavdekar
**Amita Sapru

Abstract: *Hepatitis A disease is increasingly being seen in older age groups in India, as the country becomes a region with intermediate endemicity for Hepatitis A infection. Prevention of Hepatitis A through immunization of children is the most effective strategy for control and prevention of the disease. Inactivated and live attenuated hepatitis A vaccines with excellent immunogenicity are available. Inactivated hepatitis A vaccines are recommended to be given intramuscularly at 12-23 months age in a two-dose schedule, 6-18 months apart. Live attenuated hepatitis A vaccine is recommended subcutaneously in a single dose schedule between 12-23 months of age.*

Keywords: *Hepatitis A, Immunization, Prevention, Vaccine*

Hepatitis A virus infects more than 80% of the population in developing countries by late adolescence and is also common in developed countries. It is caused by hepatitis A virus (HAV), which is a non-enveloped RNA virus that spreads predominantly by feco-oral transmission, either through ingestion of contaminated food and water or through direct contact with an infectious person. Despite the multiple genotypes of HAV, there is only one recognized serotype.[1] The incidence of hepatitis A is strongly correlated with socioeconomic indicators; decreasing with increasing incomes and access to clean water and adequate sanitation.[2] Where high standards of hygiene and sanitation apply, most children reach adult life without encountering the virus. The clinical outcome is strongly correlated with age, with young children usually having asymptomatic infection while older children and adults commonly experiencing symptomatic disease. Young children with unrecognized asymptomatic infection constitute a major reservoir for HAV transmission.

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In children less than 5 years age, 50-90% of infections will be asymptomatic, while in adults only 5-30% would be asymptomatic.[1] Nevertheless, hepatitis A infection is still the commonest cause of acute sporadic viral hepatitis and fulminant hepatic failure in Indian children. Reports from South America and the Republic of Korea also signify that HAV infection has become the leading cause of fulminant hepatic failure.[2] Recently, atypical manifestations like moderate or significant ascites, edema, pleural effusions, skin rashes, firm to hard hepato-splenomegaly, slow recovery, severe anemia and coagulopathy are commonly being seen in younger children. Co-infections of HAV with hepatitis E virus (HEV) or hepatitis B virus (HBV) or with other infections viz. typhoid fever, dengue fever, malaria, etc. are also increasingly being encountered.[3]

Hepatitis A in India

Most regions of India are endemic for hepatitis A infections. Recent studies in India have indicated evidence of epidemiological shift of HAV infection from children to older age groups, especially in the higher socioeconomic groups.[4] With continuing economic development and improvement in sanitation and hygiene, such populations are at risk for epidemic outbreaks, due to exposure to endemic areas or persons from these areas or improper water sanitation as was reported in Kerala.[5] Under the Integrated Disease Surveillance Program, 315 outbreaks of viral hepatitis (HAV and HEV) have been reported from 2010 to 2013 and the number of cases reported yearly is increasing. In vulnerable populations, HAV vaccination has a definite role to prevent and protect against HAV infections.

Hepatitis A vaccines

Development of a vaccine against HAV disease started after successful cultivation of HAV in cell lines in 1979. Two types of hepatitis A vaccines are currently used worldwide: i) Formalin inactivated, cell culture produced whole virus vaccines (produced in several countries and used globally) and ii) Live attenuated HAV vaccines (produced in China and used in several countries).Several inactivated HAV vaccines are marketed worldwide (Table I). The different strains of HAV used by different vaccine manufacturers are HM175, CR326FN, GBM and

RG-SB. For vaccine production, the virus is cultured on the cell lines, going through numerous passages for attenuation and then concentrated and purified by sterile filtration, ultrafiltration, chromatography, diafiltration and/or ultracentrifugation. The HAV is then inactivated by formalin and then conjugated to adjuvants (aluminum salts or influenza virosomes). All the inactivated HAV vaccines contain a specified quantity of HAV antigen, but the antigen content in different vaccines is expressed in different units and measured by different assays, and so the antigen content cannot be compared between vaccines.[1]

Live attenuated HAV vaccines are manufactured in China and available in several other countries. They are derived from either the H2 strain or the LA-1 strain of the virus. The attenuated H2 strain HAV vaccine was developed from HAV grown from the feces of a 12 year old child with hepatitis A and which was propagated in human diploid cells through a series of technological processes including culture, harvesting, purification and freeze drying.

Preparations, formulations and storage

The inactivated vaccines are usually available in both pediatric (half of adult dose) and adult formulations (except one, which has the same formulation for all persons above 1 year age). The vaccine is also available in formulations where it is combined with hepatitis B vaccine or typhoid vaccine. The live attenuated vaccine is a freeze-dried vaccine (with diluent), which is available in one formulation for all age groups. HAV vaccines require to be stored at 2-8° C. Freezing destroys the inactivated vaccine and causes aggregation of the adjuvant particles.

Route and schedule of vaccination

The inactivated vaccines are recommended for children from 1 year age, though in certain countries they are licensed for use above 2 years age. They are recommended to be given intramuscularly in a two-dose schedule at 6-12 months or 6-18 months interval depending on manufacturer. The second dose of the vaccine schedule can be given up to 5-10 years after the first dose, as per different manufacturers.Combination formulation of hepatitis A and B vaccine can be used for catch–up vaccination in a three-dose schedule (0, 1 month and 6 month) or in an accelerated four dose schedule (Day 0, Day 7, Day 21/30 and month 12)when vaccination against both diseases is lacking. Another Hepatitis A and B combination vaccine, with a 2-dose schedule (0, 6-12 months, intramuscular) is licensed for use in children 2-15 years age in Europe. Hepatitis A and typhoid combination vaccines are also recommended in a 2-dose schedule.[1] All inactivated hepatitis A vaccines are interchangeable, including the combination hepatitis A vaccines.[2]

Table I. Common Hepatitis A vaccines

Vaccine	Age	Strength	Dose and Route	Recommended Doses, Interval	Strain	Available in India
Inactivated HAV vaccine	1-15 yrs.	80 units	0.5mL, IM	2 doses, 6-18 months apart	GBM	Yes
	≥16yrs	160 units	0.5mL, IM	2 doses, 6-18 months apart	GBM	Yes
Live attenuated HAV vaccine	> 1yr	> 6.5 Lg $CCID_{50}$	0.5 mL, S/C	Single dose	H2	Yes
Inactivated HAV vaccine·	1-18 yrs.	720 ELISA units	0.5 mL, IM	2 doses, 6-12 months apart	HM175	Yes
	≥ 19 yrs.	1440 ELISA units	1 mL, IM	2 doses, 6-12 months apart	HM175	Yes
Inactivated HAV vaccine	≥ 1yr	24IU	0.5mL, IM	2 doses, 6-12 months apart	RG-SB	No
Inactivated HAV vaccine	1-18 yrs.	25 U	0.5 mL, IM	2 doses,6-18 months apart	CR326FN	No
	≥19yrs	50 U	1 mL, IM	2 doses,6-18 months apart	CR326FN	No

The inactivated vaccines can be given concurrently with vaccines for diphtheria, polio, tetanus, hepatitis B, typhoid, cholera, Japanese encephalitis, rabies or yellow fever, without adversely affecting immunogenicity or safety. It is recommended that the injections be given at different sites. The vaccine can be given with immune globulin, if given at different sites. Live attenuated HAV vaccine is recommended to be administered by subcutaneous route in children >1 year of age in a single dose.

Correlates of protection

For assessing the immune response to HAV vaccine, the anti-HAV antibodies are generally measured using enzyme immunoassay or radioimmunoassay and the concentrations are expressed in milli-International units per milliliter (mIU/mL). The absolute lower level of antibody needed to prevent HAV infection has not been determined, but as anti-HAV antibody concentrations of 10-20mIU/mL, achieved 1-2 months after administration of immune globulin are known to protect against hepatitis A, this level is considered as protective. Because no absolute protective level has been defined, generally the lower limit of detection of the assay being used is considered as the protective level.[1] It is suggested that vaccinees who have once seroconverted will be protected even if their antibody levels have fallen below protective levels, as an anamnestic response to second dose of vaccine is quick and robust, while incubation period of disease is longer.[1]

Immunogenicity, duration of immunity and efficacy of vaccine

Most studies of inactivated HAV vaccines demonstrate a seroconversion rate of 95-100% after vaccination in both adults and children. A study in Korean adults using two licensed vaccines has shown an immunogenicity of 70-82% in men and 90-93% in women, eleven months after a single dose. Seroconversion rate is less in chronic liver disease (93%), immune-compromised persons (88%), HIV infection (77%), transplant recipients (26%) and elderly (65%).[2] Infants with maternally transferred antibodies also demonstrate reduced immunogenicity of vaccine.[1, 2] Anti-HAV antibodies have been shown to persist after vaccination, for 10-12 years in adults and for 5-6 years in children. Mathematical models predict that protective antibody levels could persist for 25 years or longer in adults and 14-20 years in children.[1] The inactivated vaccines have an observed efficacy of 94-95%. Large-scale immunization programs in several countries have demonstrated 90-97% reduction in disease incidence.[2]

In Israel, universal HAV immunization program using inactivated hepatitis A vaccine was introduced in 1999 in all 18-month-old children, without catch-up immunizations. The program had a first-dose immunization rate of approximately 90%, and a 2-dose immunization rate of approximately 85%. Dramatic decline in the reported incidence of hepatitis A was seen. There was a more than a 98% reduction in disease in children 1–4 years of age, compared with the pre-vaccination period, a more than a 95% reduction in hepatitis A disease in all age groups including infants and adults, and elimination of outbreaks of hepatitis A associated with daycare and school settings This vaccination program demonstrated that exclusive vaccination of toddlers creates herd immunity and decline in infections and disease in the whole community.[6]

In USA, routine HAV immunization was introduced in 1999, in children 2 years age or older in states, which had a higher incidence of HAV infection. In 2005, the incidence of HAV infection in USA was reduced by 6-7 times. The states with traditionally high incidence rates showed dramatic decline in incidence of hepatitis A, despite vaccine coverage below 50%, though the states with lower incidence of hepatitis A cases showed an increase in proportion of cases. Routine immunization of children was seen to be a highly effective immunization strategy that not only protected children, but also reduced spread of the virus in community. Subsequently, the Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP) and the American Academy of Family Physicians recommended routine hepatitis A immunization of all children in 2006. The first dose was recommended at age 1 year (12–23 months), followed by a second dose at least 6 months later.[7]

Live attenuated HAV vaccine has undergone extensive field trials in China. It induces not only neutralizing antibody but also cell-mediated immune responses. The vaccine is highly immunogenic. The primary study for the H2 strain vaccine shows sero-conversion of 98.6% and 81.3%, 2 months and 15 years after vaccination respectively.[8] In regions in China where mass vaccination programs have been introduced, there has been over 95% reduction in hepatitis A related morbidity and no cases of HAV infection have been reported since 1999. Another study in children aged 1-12 years in China showed persistence of immune response in 72% and 98% children, eight years after single and two dose schedules, respectively.[9] A single center, long term follow-up study in India, has documented a seroprotection rate of 95.8%, 92.3% and 87.6% at 2 months, 30 months and 10 years after a single dose of live H2 strain HAV vaccine.[10]

A multi-centric study of the same vaccine in India has also demonstrated similar excellent immunogenicity.[11] The vaccine was licensed in India in 2005, on the basis of an excellent immunogenicity and safety profile.

Adverse events

In case of inactivated hepatitis A vaccines, the local injection site reactions are pain, tenderness and redness, but they are mild, transient, seen more in adults (56%) but less in children (21%). Systemic reactions are headache, seen in 5-15% of vaccinees and fatigue, fever, diarrhea and vomiting seen in <5% of vaccinees.[1] These vaccines are well tolerated in patients with mild to moderate chronic liver disease, in liver and renal transplantation recipients and in dialysis patients. Apart from severe allergic reaction to the previous dose, there is no contraindication to the use of inactivated hepatitis A vaccines.

Live attenuated HAV vaccines are also well tolerated causing mild local symptoms (pain, redness, pruritus and swelling) and systemic symptoms (mild fever, headache and gastrointestinal disorders). No major side effects or elevation in serum transaminases are seen in studies on this vaccine. Severe allergy to components, included in the live attenuated hepatitis A vaccine is a contraindication to their use. As a rule, live vaccines should not be used in pregnancy or in severely immune compromised patients.

Single dose vaccination schedule with inactivated HAV vaccine

In Argentina, after a nationwide hepatitis A outbreak in 2003-2004, a single dose universal hepatitis A immunization program was started in June 2005 in children aged 12 months. The overall vaccine coverage in 2006 for the single dose was 95%. The annual incidence rate of reported hepatitis A disease declined from 70.5-173.8/100 000 in 1995–2004 to 10.2/100 000 in 2007. An 80-87% decline in hepatitis A disease was seen in all age groups below 50 years.[12] The success of the program in reducing hepatitis A infections with a single dose is encouraging evidence for advocating single dose schedule for national public health programs. As per WHO, countries may consider inclusion of single-dose inactivated hepatitis A vaccine schedule in National immunization programs. This option seems to be comparable in terms of effectiveness, and is less expensive and easier to implement than the classical 2-dose schedule. However, until further experience has been obtained with this schedule, in individuals at substantial risk of hepatitis A, and in immune-compromised individuals, a 2-dose schedule is preferred.[2]

Post exposure prophylaxis/ Outbreak control

Immunoglobulin in dose of 0.02 mL/kg and 0.06 mL/kg is recommended for short term (1-2 months) and long term (3-5 months) protection against HAV infection respectively.The use of a single dose regimen of inactivated hepatitis A vaccine to control community-wide outbreaks has been very successful in small closed communities, when vaccination was started early in the course of the outbreak, and when good coverage of multiple age-cohorts was achieved. Vaccination efforts should also be supplemented with health education and improved sanitation. In USA, the Advisory committee on Immunization practices (ACIP) recommends use of vaccine in preference to immune globulins for post exposure prophylaxis of healthy persons aged ≥12 months to 40 years age. The efficacy of hepatitis A vaccine as post exposure prophylaxis in outbreak settings without accompanying immunoglobulin is still unclear. One small study has shown a protective efficacy of 79% when given within 8 days of symptom onset of the index case while other studies have shown that vaccine alone may be insufficient.[1]

WHO recommendations on use of HAV vaccine

WHO recommends that vaccination against HAV be integrated into the national immunization schedule for children aged ≥1 year on the basis of incidence of acute hepatitis A, change in the endemicity from high to intermediate and consideration of cost effectiveness. In highly endemic countries large-scale vaccination programs are not recommended as almost all persons are asymptomatically infected with HAV in childhood, which effectively prevents clinical hepatitis A in adolescents and adults. In countries with improving socioeconomic status, hepatitis A endemicity may rapidly move from high endemicity (≥90% seroprevalence by age 10 years) to intermediate endemicity (>50% seroprevalence by age 15 years, but <90% by age 10 years). In these countries, a relatively large proportion of the adult population is susceptible to HAV and large-scale hepatitis A vaccination is likely to be cost effective and is therefore encouraged. Targeted vaccination of high-risk groups should be considered in low endemicity (≥50% by age 30 years, with <50% by age 15) and very low endemicity(<50% by age 30 years) settings to provide individual health benefits. Groups at increased risk of hepatitis A include travelers to areas of intermediate or high endemicity, those requiring life-long treatment with blood products, men who have sex with men, workers in contact with non-human primates and injection drug users. In addition, patients with chronic

liver disease are at increased risk for fulminant hepatitis A infection and should be vaccinated. Inactivated hepatitis A vaccines should also be considered for use in pregnant women at definite risk of HAV infection.[2]

IAP recommendations on use of HAV vaccine

Immunization against HAV should be given at 12-23 months age. Single dose is recommended for live attenuated H2-strain Hepatitis A vaccine and two doses 6-18 months apart for all inactivated Hepatitis A vaccines.[13]

Points to Remember

- ***Hepatitis A vaccine is recommended in countries transitioning from high to intermediate endemicity.***
- ***Universal immunization with hepatitis A vaccine is the best strategy in control of hepatitis A in the community.***
- ***Both inactivated and live attenuated vaccines have good immunogenicity and safety.***

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NEWS AND NOTES

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UPDATE ON VACCINES

HPV VACCINES: AN UPDATE

Srinivas G Kasi

Abstract: *Worldwide, 3 Human papilloma virus (HPV) vaccines are available of which 2 are marketed in India. Both, bivalent HPV (B-HPV) and quadrivalent (Q-HPV) have demonstrated excellent immunogenicity, safety and efficacy against all the clinical endpoints studied. While B-HPV has demonstrated superior immunogenicity and cross protection, both vaccines have demonstrated undiminished efficacy in the long term follow up studies. In 2014, the Strategic Advisory Group of Experts (SAGE) of the WHO recommended a 2-dose schedule for girls 9 to 14 years of age. Population impact studies have shown a significant reduction in genital warts and high-grade cervical abnormalities. New HPV vaccines are under development, which aim to broaden protection and reduce the cost of vaccines.*

Keywords: *Human Papilloma Virus Vaccine, Safety, Bivalent, Quadrivalent, Efficacy Immunogenecity, Schedule.*

Genital infection with human papillomavirus (HPV) is associated with almost all cases of cervical cancer and a significant proportion of other anogenital cancers (anus, vulva, vagina and penis) and head and neck cancers. HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide. It is estimated that cervical cancer affects approximately 5,27,624 women each year and 80% of them live in developing countries.[1]

Cervical cancer in India ranks as the second most frequent cancer among women. Current estimates indicate that every year 1,22,844 women are diagnosed with cervical cancer and 67,477 die from the disease. Based on Indian studies performing HPV detection tests in cervical samples, about 5% of women in the general population are estimated to harbor cervical HPV-16/18 infection at a given time and 82.7% of invasive cervical cancers are attributed to HPV 16 or 18. The crude incidence rate is 20.2 and more than half of them die from the disease, with a crude mortality rate of 11.1 which is one of the highest in the world.[2]

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Human papilloma virus vaccines

The presently available HPV vaccines Cervarix and Gardasil (Table I) are produced by recombinant technology in which the L1 gene of the HPV is inserted into a host (baculovirus or Saccharomyces cerevisiae). This results in the production of large quantities of L1 proteins which undergo self-assembly into "virus-like particles (VLPs)" that resemble the outer capsid of the whole virus. These VLPs are noninfectious and nononcogenic as they do not contain viral DNA, but are highly immunogenic.

Cervarix is indicated for the prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) grade 2 or worse and adenocarcinoma in situ, and cervical intraepithelial neoplasia (CIN) grade 1, caused by HPV types 16 and 18.[3]

Gardasil is indicated for the prevention of cervical, vulvar, vaginal, and anal cancer caused by HPV types 16 and 18, genital warts caused by HPV types 6 and 11 and the following precancerous lesions caused by HPV types 6, 11, 16, and 18 which includes (a) cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS), (b) cervical intraepithelial neoplasia (CIN) grade 1, (c) vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3, (d) vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3 and (e) anal intraepithelial neoplasia (AIN) grades 1, 2, and 3[4]. Gardasil 9 is approved for the same indications as Gardasil for types 6,11,16,18,31,33, 45,52 and 58.[5] This vaccine is presently not available in India.

Since cervical cancer has a long incubation period and CIN2/3 or adenocarcinoma in situ (AIS) are necessary precursors of cervical cancer, for vaccine licensure, the World Health Organization (WHO) has recommended these endpoints as a proxy for cervical cancer. Moreover, these endpoints can be studied feasibly and ethically among women. In children or young adolescents, bridging studies are conducted by comparing antibody responses in this population with those in the young women for whom data on the clinical endpoint of CIN2/3 or AIS are available.[6]

The efficacy trials have not established any immune correlates of protection. Neutralizing antibodies are

Table I. HPV vaccines - Main characteristics

	2vHPV	4v HPV	9vHPV
Brand name	Cervarix	Gardasil	Gardasil 9
VLPs	16,18	6,11,16,18	6,11,16,18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck & Co	Merck & Co
Production system	Baculovirus	Saccharomyces cerevisiae	Saccharomyces cerevisiae
Adjuvant	50 mcg of monophosphoryl lipid A, and 0.5 mg of aluminum hydroxide.(ASO4)	Proprietary aluminium hydroxyphosphate sulfate (225 µg)	Proprietary aluminium hydroxyphosphate sulfate (500µg)
Route	IM	IM	IM
Volume	0.5mL	0.5mL	0.5mL

considered to be the primary effectors of vaccine-induced protection. Direct exudation of serum antibodies at sites of trauma is considered as the primary mechanism of protection. High levels of anti-VLP antibodies prevent binding of the virion to the basement membrane, while lower levels prevent transfer of the virion to the keratinocytes.[6]

Vaccine schedules

Both vaccines were initially recommended in a 3-dose schedule.[3,4] which is B-HPV: 0-1-6 months; Q-HPV: 0-2-6 months. The minimum recommended intervals between dose 1 and 2 is 4 weeks and between dose 2 and 3 is 3 months. Both vaccines are recommended from the age of 9 years, while the upper age limit of administration, in some countries is 26 years and 45 years in others. While the B-HPV has a female only recommendation, the Q-HPV is also recommended, in some countries, in males 9-26 years. In India, the upper age limit is 45 years and is presently not approved for administration in males.

Two dose schedule

In April 2014, the HPV working group of the SAGE[7,8] recommended a 2-dose schedule for girls 9-14 years of age. This recommendation was based on studies which demonstrated the non-inferiority of 2 doses of HPV vaccine in girls aged 9-14 years compared to 3 doses in girls aged 9-14 years or 3 doses in women aged 15-24 years in terms of immunogenicity. When two 2-dose schedules with different intervals (0, 2 vs 0, 6 months; 0, 6 vs 0, 12 months) were compared, a 6-month interval resulted in superior geometric mean antibody concentrations (GMC) compared with the 2-month interval a month after the last vaccine dose in all the study age groups. HPV vaccine schedule is as follows

- For adolescent / pre-adolescent girls aged 9-14 years: 2 doses at an interval of 6 months
- For girls 15 years and older, current 3-dose schedule will continue.
- For two-dose schedule, the minimum interval between doses should be 6 months. If the interval is less than 6 months, a 3rd dose should be administered. For programmatic reasons, the interval between the first and second dose may be extended upto 12 months.
- When the first dose is administered before the age of 15 years, even if older at the time of second dose, a two-dose schedule will be applicable.
- For immunocompromised individuals, including HIV-infected, the three-dose schedule is recommended, irrespective of age.

Immunogenicity and duration of immune response[6]

The highest immune responses are observed in young girls aged 9–15 years, with both vaccines being highly immunogenic. Vaccine induced antibody titres against HPV16 and 18 were several fold higher than after natural infection. With the bivalent vaccine, both anti HPV 16 titres and anti HPV 18 titers remain at high levels for at least 8.4 years with maintainence of 100% seropositivity. With the quadrivalent vaccine, anti-HPV 16 titers are maintained at high levels for at least 8 years with 98.8% seropositivity

maintained. For Q-HPV 18 months after first vaccination, anti HPV18 antibody titers return to the level of natural infection, with a further reduction in seropositivity over time. However, the efficacy has remained undiminished for the Q-HPV vaccine.

The immunogenicity of the bivalent and quadrivalent vaccine was compared in a head-to-head trial. Neutralising antibodies against HPV16 and HPV18 were significantly higher for the bivalent vaccine compared to the quadrivalent vaccine in women of age 18-26 years and in older age groups at month 7, 24 and 48 after receiving the first dose.[9]

Immunobridging studies done in young adolescents 9-15 years of age have shown that the neutralizing antibody responses in boys and girls were statistically noninferior and observationally higher (1.7-2.7-fold) than those observed in 16-23 year-old females. The neutralizing antibody responses and seroconversion rates in boys were noninferior to those in girls.[6]

Prophylactic efficacy

The prophylactic efficacy of both vaccines have been studied in large phase II and III studies and followed up for 3-5 years. However, the clinical endpoints assessed and the study population characteristics were different. Hence direct comparison of efficacies would be inappropriate (Table II).[10-13] The B-HPV has demonstrated superior efficacy against infections irrespective of HPV type. This may be related to the unique adjuvant and superior cross protection.[10]

Cross protection[6]

Although, immunity to HPV is type-specific, HPV16 is phylogenetically related to HPV types 31, 33, 52 and 58 (A9 species); and HPV18 is related to HPV45 (A7species).

Table II.: Prophylactic efficacy of B-HPV and Q-HPV

Abbreviations: ATP- According to protocol, TVC- total vaccinated cohort, PP- per protocol, ITT- intention to treat, CIN- cervical intraepithelial neoplasia, GW- genital warts, VIN- vulvar intraepithelial neoplasia, VaIN- vaginal intraepithelial neoplasia, AIN-anal intraepithelial neoplasia, PIN- penile intraepithelial neoplasia. NR- Not Reported

Some cross protection has been demonstrated with both vaccines. For B-HPV, statistically significant cross-protection against 6-month persistent infection and CIN 2 endpoints was demonstrated against HPV-31, HPV- 33 and HPV-45, while for Q-HPV statistically significant efficacy against disease was demonstrated against HPV-31 only. The clinical significance and longevity of this cross-protection is unclear.

Duration of protection

Both vaccines have demonstrated long-term protection against clinical end points. While B-HPV has demonstrated undiminished protection till 9.4 years[14], the Q-HPV has demonstrated protection till 10 years in the Nordic registry follow up.[15]

Vaccine safety[16]

Apart from local reactions, which is more common with the B-HPV vaccine, both vaccines have demonstrated excellent safety profiles in various phase II and III trials both in females and males. With > 175 million doses distributed worldwide, the World Health Organization - Global Advisory Committee on Vaccine Safety (WHO-GAVACS) in 2014, extensively reviewed all the potential signals associated with these vaccines and found no causative link with any of them including, Guillain Barre syndrome, venous thrombo embolism, seizures, stroke and other severe allergic reactions. No adverse outcomes reported when vaccines were inadvertently administered during pregnancy and lactation.

The 9vHPV Vaccine[17]

The 9vHPV contains the VLPs of HPV 6, 11, 16, 18 and 31, 33, 45, 52, 58. This new vaccine received the US Food and Drug Administration (FDA) approval on December 10, 2014, for use in females aged 9 through 26 years and males aged 9 through 15 years. In USA, 10% of the HPV burden is attributable to the five additional types in 9vHPV. This vaccine was licensed on the basis of studies of the vaccine efficacy against clinical endpoints and comparison of immunogenicity with the 4vHPV vaccine (Table III). The noninferiority criterion for GMTs was met for all four HPV types ($p<0.001$). (The dosing schedule is the same as the 3-dose schedule of the 4vHPV vaccine. Alternate dosing schedules are under investigation.

Population impact of HPV vaccination programs[18]

HPV vaccines were licensed in 2006 and are approved in 132 countries. 62 countries, including some low and middle income countries have introduced HPV vaccines into NIPs. In 2011, the GAVI Alliance decided to support HPV vaccination and 10 low-income countries propose to introduce these vaccines by 2017. Six countries, such as the USA and Australia, vaccinate boys as well.

Analysis of data from nine high-income countries is now available. In countries with female vaccination coverage of at least 50%, a significant reduction of HPV type 16 and 18 infections of 68% (RR 0.32, 95% CI 0.19-0.52) and anogenital warts of 61% (0.39, 0.22-0.71) in girls 13-19 years of age was reported. Infections due to HPV types 31, 33, and 45 in this age group of girls also showed significant reductions (RR 0.72, 95% CI 0.54-0.96), suggesting cross-protection. Herd effect was demonstrated by significant reductions in anogenital warts in boys younger than 20 years of age (0.66 [95% CI 0.47–0.91]) and in women 20-39 years of age (0.68 [95% CI 0.51-0.89]). In countries with female vaccination coverage lower than 50%, significant reductions in HPV types 16 and 18 infection (RR 0.50, 95% CI 0.34-0.74]) and in anogenital warts (0.86 [95% CI 0.79-0.94]) was reported in girls younger than 20 years of age, with no indication of cross-protection or herd effects.

HPV Vaccines in development[19]

Newer HPV vaccines in development have attempted

Table III.: Comparison of 9vHPV and 4vHPV immunogenicity for 4 common types:

	9v HPV		4v HPV	
	Seropositivity %	GMTs(mMU/mL)	Seropositivity %	GMTs(mMU/mL)
Anti HPV 6	99.8	893	99.8	875
Anti HPV 11	100	666	99.9	830
Anti HPV 16	100	4062	100	3157
Anti HPV 18	99.8	4541	99.7	679

to reduce the cost and induce broader protection. The newer vaccines under study include: a) L2 Vaccines: L2 protein elicits antibodies which can neutralize a wide variety of HPV types. Being weakly immunogenic, various strategies are being assessed to improve the immunogenicity. These include combination with novel adjuvants e.g. alum+ MPL, the generation of polymeric L2 antigen, generation of a synthetic consensus region of high-risk HPV L2 sequences, utilizing L1 capsomers as a platform for cross-presentation of L2 epitopes and chimeric VLP vaccines, b) L1 capsomer vaccines: L1 capsomers can be produced in bacteria, which is cheaper than using the conventional virus and yeast based systems.

Therapeutic vaccines[19]

The HPV early proteins, E6 and E7 are expressed in all HPV infected cells, and are up-regulated in cancer cells. Thus E6 and E7 have been the choice for therapeutic vaccines. Different strategies are being investigated including the use of live viral or bacterial vectors, peptides, proteins, DNA and dendritic cells. Recently a phase I trial using recombinant HPV16E7 and HPV18E7 established the safety of the product and has progressed to a phase 2 trial.

The Indian scenario[20]

About 25% of all new cervical cancer cases and cervical cancer deaths occurring in the world is accounted by India. While the cost per dose in developed countries is 100 USD, with GAVI support, the cost is as low as 4.5 USD per dose. However numerous barriers exist towards its acceptance in the NIPs. Most available data on incidence is generated from regional cancer registries, while population based data is scanty. The high cost of HPV vaccines render it far beyond the reach of most Indians and precludes its consideration for inclusion in the NIP. Sociocultural issues associated with the HPV vaccine, because it targets a sexually transmitted infection and primarily targets female adolescents and young adults, are a great barrier to wider acceptance. In the developed countries, routine screening with pap smear at regular intervals and early treatment of precancerous conditions have been very effective in preventing squamous cervical cancer. These measures are difficult to implement in low-resource settings. Thus, prevention of HPV infections by vaccination has assumed great public health importance.

It is heartening to note that IAP[21] and FOGSI[22] have unequivocally recommended these vaccines.

Points to Remember

- ***Genital infection with human papillomavirus (HPV) is associated with almost all cases of cervical cancer and a significant proportion of other anogenital cancers and head and neck cancers.***
- ***Worldwide, cervical cancer imposes a tremendous burden while in India it ranks as the second most frequent cancer among women.***
- ***HPV types 16 and 18 are responsible for about 70% of all cervical cancer cases worldwide.***
- ***In India two highly effective vaccines bivalent vaccine containing the VLPs of types 16 and 18 and a quadrivalent vaccine containing the VLPs of types 6, 11, 16 and 18 are available***
- ***Both vaccines elicit robust immune responses and have excellent efficacy and safety.***
- ***Newer HPV vaccines are under development which are expected to provide broader protection and be more economical.***

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UPDATE ON VACCINES

JAPANESE ENCEPHALITIS VACCINES

Digant D Shastri

Abstract: *Japanese encephalitis (JE) is a mosquito-borne viral infection and is the leading cause of viral encephalitis in Asia. Vaccination of humans is one of the most effective preventive strategies in endemic areas. Available JE vaccines belong to four different classes and all of them have been demonstrated to elicit adequate protective levels of neutralizing antibody. Live attenuated vaccine, based on the SA14-14-2 strain confers a high degree of protection after a single dose and is more cost effective and convenient for use. A live attenuated, recombinant (chimeric) JE vaccine is licensed for use in many Asian countries. WHO recommends integration of JE vaccine into national immunization schedules in areas where JE is recognized as a public health priority. Travellers from non-endemic countries having extensive outdoor exposure during the high transmission season or having extended stay should be offered pre-travel vaccination.*

Keywords: *Japanese encephalitis, JE vaccine*

Japanese encephalitis (JE) is a mosquito-borne viral infection and is the leading cause of viral encephalitis in Asia. Infection leads to overt encephalitis in 1 of 250 cases. As per the WHO estimation, currently three billion people living in 24 countries, mainly in south east Asia and western pacific regions are at risk of JE. In these 24 countries with JE risk, overall incidence rate is 1.8/ 100000 with around 67,900 severe clinical cases and 13,600 to 20,400 annual deaths due to JE.[1]

Japanese encephalitis virus (JEV) is transmitted primarily by Culex mosquitoes and has enzootic cycle chiefly among domestic pigs and in some areas, wild Ardeid (wading) birds. Principally the disease transmission occurs in rural agricultural areas, most often associated with rice cultivation and flood irrigation. Recently the disease is also seen in some urban areas because of similar ecologic conditions.[2] In temperate areas of Asia, transmission is seasonal and human disease usually peaks in summer and fall. In the subtropics and tropics, seasonal transmission varies with monsoon rains and irrigation practices and may be prolonged or even occur year round. In endemic countries, because of natural infection adults usually are immune and hence disease is primarily a disease of children in the age group of 1-15 years.

In India, JE is reported from all states and union territories except Arunachal Pradesh, Dadra Nagar Haveli, Daman, Diu, Gujarat, Himachal, Jammu & Kashmir, Lakshadweep, Meghalaya, Orissa, Punjab, Rajasthan, and Sikkim. Highly endemic states include West Bengal, Bihar, Andhra Pradesh, Karnataka, Tamil Nadu, Assam, Uttar Pradesh, Manipur and Goa. Annual incidence is between 2000 to 3000 cases with around 500-600 deaths.[3]

Prevention

A. Mosquito control: Difficult to achieve in rural agricultural setting.

B. Personal protection measures: Like other mosquito borne diseases avoidance of mosquito bites by wearing clothes that covers most of the body, using an effective insect repellent and use of mosquito net are low cost prevention strategies.

C. Vaccine: Vaccination of humans accounts for one of the most effective measures for prevention of Japanese encephalitis in endemic areas. In China, Korea, Japan, Taiwan and Thailand routine immunization of school children is currently practiced. Currently approximately 15 JE vaccines are in use and they fall into 4 classes.[4,5]

I. Inactivated Vaccines

a. Mouse brain-derived, purified vaccine

b. Primary hamster kidney (PHK) cell derived vaccine

c. Vero-cell derived vaccine based on the P-1, P-3, SA14-14-2 or any other strains as virus seeds

d. Vero cell derived Kolar vaccine

II. Live attenuated cell culture derived SA 14-14-2 vaccine

III. Live recombinant (chimeric) vaccines

IV. Other upcoming vaccines

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Serum neutralizing antibody titre of at least 1:10 as determined in a 50% plaque reduction neutralization assay (PRNT50) is accepted as immunological surrogate of protection. The available evidence demonstrates that all four classes of vaccines elicit protective levels of neutralizing antibody. Vaccine effectiveness data for live attenuated vaccine suggest over 95% effectiveness five years post vaccination.[5]

I. Inactivated vaccines

1. Mouse brain-derived inactivated JE vaccine

In 1930s the first mouse brain-derived inactivated JE vaccine was produced in Russia and Japan. During World War II, a simple uncentrifuged 10% suspension of infected mouse brain, inactivated with formalin, was produced for military use in the United States. The modern vaccine is prepared from either of the Nakayama/ Beijing strains of JE virus grown in mice brain, purified, inactivated by formalin, stabilized with gelatin and sodium glutamate and preserved with thiomersal. No myelin basic protein is detectable in the final product. A study conducted in Taiwan about evaluation of efficacy of this vaccine used in last 30 years empirically concluded that even immunization with one dose of mouse brain derived Nakayama strain JE vaccine provided sufficient protection to the population.[6] With availability of better and safer vaccines, production of this vaccine and availability has markedly declined.[4, 7]

2. Inactivated primary hamster kidney cell-derived JE vaccine

Inactivated JE vaccine prepared in primary hamster kidney (PHK) cells is produced exclusively in China with an annual use of more than 75 million doses. The P-3 strain of JE virus, recovered from brain of a human case, is the base for vaccine. Vaccine is prepared in primary cell cultures derived from kidneys of golden Syrian hamsters which is inactivated with 0.5% formalin, stabilized with 0.1% human albumin. The vaccine is more immunogenic than mouse brain-derived inactivated JE vaccine, but was not available outside China. The vaccine is no longer manufactured.

3. Inactivated vero cell derived SA 14-14-2 strain vaccine

This inactivated JE vaccine is based on SA14-14-2 strain of JEV. The formalin-inactivated, whole virus is cultivated in vero cells. The vaccine was licensed for use in the United States, Australia and Europe during the spring of 2009 for use in children more than 2 months of age. The vaccine has been evaluated extensively through clinical trials in India and abroad in children as well as in adults. The vaccine is marketed in Australia and New Zealand as JESPECT and elsewhere as IXIARO. By transfer of technology agreement to another manufacturer, the vaccine is produced in India by Biological Evans Ltd (JEEV) and is licensed in 2012 in India and subsequently in other countries in Asia. The vaccine is WHO pre-qualified.

Immunogenicity and effectiveness: In phase II study conducted among healthy Indian children aged 1-2 years living in an endemic setting, 95.7% seroprotection was found one month following second dose of vaccine. In multiple studies in adults and children in non-endemic settings seroprotection rates have been found ranging from 93% to 99% one month following completion of the 2-dose primary series.

Doses and route: The primary immunization schedule is 2 doses administered intramuscularly on days 0 and 28. The age to commence the vaccination varies. For children less than 3 years the dose is 0.25 mL, and for children aged ≥3 years the dose is 0.5 mL.

In the case of pre-travel prophylaxis the 2 dose series should be completed at least 1 week before travel. Those travellers who are ≥17 years old and have received primary immunization >1 year ago may be given a booster dose if there is ongoing exposure to JE or re-exposure to JE is expected.

Advisory Committee on Immunization Practices of IAP (ACVIP) recommends two dose schedule in the dose of 0.25 mL for children ≥ 1 to ≤ 3 years and in the doses of 0.5 mL for children more than 3 years, adolescents and adults.[8]

Adverse reactions: Post-marketing data for the first 12 months following introduction of the vaccine in Europe, USA and Australia reported AEFI rate as 10.1/100 000 with rash, fever and headache being the most frequently reported AEFIs. Hypersensitivity reactions were observed at a rate of 3.6 per 100 000 doses compared to 8.4 per 100000 doses reported for the mouse brain-derived vaccine.[9]

4. Inactivated vero cell derived Kolar strain vaccine

National Institute of Virology, Pune isolated the JE virus from a patient in Kolar, Karnataka, India. This virus seed has been used by the Bharat Biotech International Ltd. to prepare inactivated vero cell derived JE vaccine. Phase II/III study of the vaccine conducted in 644 healthy individuals showed 93.14% seroconversion and 98.67% seroprotection at 28th day from the first dose; 96.90%

seroconversion and 99.78% seroprotection at 56th day. No serious adverse events were observed.

ACVIP recommends two dose schedule in the dose of 0.5 mL for children more than 1 year with 1st dose at 1 year of age and 2nd dose at 28 days from the 1st dose.[8] In view of waning seroconversion and seroprotection following two primary doses the ACVIP feels the need for a booster dose at a later age.

II. Live attenuated cell culture derived SA-14-14-2 vaccine

The only currently available live attenuated vaccine, the SA 14-14-2 vaccine is based on a stable neuro-attenuated SA 14-14-2 strain of the JE virus. The SA 14-14-2 vaccine strain was obtained from its wild-type SA 14 parent by serial passages in cell cultures (primary hamster kidney cells) and in animals (mice, hamsters) with successive plaque purifications in primary chick embryo cells. The vaccine was licensed in China in 1988 and so far more than 200 million children have been vaccinated. Chengdu Institute of Biological Products is the only authorized manufacturing company to export the vaccine from China. The countries primarily using this vaccine include China (since 1988); Nepal (since 1999); South Korea (since 2001); India (since 2006) and Thailand (since 2007). The vaccine should not be used as 'outbreak response vaccine'. The vaccine is to be stored between 2-8°C. The vaccine is stable for 7-10 days at 37°C and for 4 months at room temperature.

Immunogenicity: In infants, seroprotection rates at 28 days post-vaccination ranged from 90.6% (95% CI: 85.3-94.4) to 92.1% (95% CI: 84.3-96.7) following a single dose of vaccine at 8-12 months.[8] Studies have shown 85-100% antibody response in non-immune children of 1-12 years age group. Minimal standard for vaccine infectivity is $10^{6,8}$ PFU/mL and low seroconversion has been observed with vaccine with low infectious titer than this. Vaccine has demonstrated good effectiveness in children vaccinated at 1-15 years of age in endemic settings, with 99.3% (95% CI: 94.9–100) at 1 week-1 month and 98.5% (95% CI: 90.1–99.2) at 1 year post-immunization.[10]

Dose and schedule: The vaccine is to be administered subcutaneously in the dose of 0.5 mL starting from 8 months age. The dose remains same for all the age groups. In China the 1st dose of vaccine is administered at 8 months and 2nd dose at 2 years. In some areas, a booster is given at 7 years. Catch up vaccination can be offered to all children who are susceptible, up to 15 years age. ACVIP recommends two doses- first dose at 9 months and second dose at 16-18 months along with first booster of DPT vaccine.[8]

Adverse reactions: Studies in children in Thailand and the Republic of Korea assessed the safety of the vaccine in children and found only mild local and systemic reactions-fever (7%), vomiting (1%), skin rash (1%), loss of appetite (1%) and irritability (1%) during the first month after immunization.[5]

Post-marketing surveillance carried out by the Chinese Centre for Drug Evaluation during 2009-2012 reported 6024 AEFIs of which 70 were considered severe. The severe events included febrile convulsions, thrombocytopenic purpura and encephalitic / meningitic illness. Of the nine encephalitis cases, one was considered vaccine-related while the others were classified as coincidental illnesses.

III. Live recombinant (chimeric) Japanese encephalitis (JE) vaccine[5, 11]

A live attenuated, recombinant (chimeric) JE vaccine was first licensed in Australia in 2010 and since then licensed and used in many Asian countries-Malaysia, Philippines and Thailand. This vaccine is a live vaccine using the yellow fever (YF) 17D and JE SA-14-14-2 strains. Construction of the vaccine involves insertion of the nucleic acid sequences encoding the envelope proteins (prM and E) of the JE SA 14-14--2 strain into the YF17D backbone, resulting in a chimeric vaccine virus which is attenuated and lacks neurotropic properties. The vaccine is marketed by different manufacturers as IMOJEV®, JE-CV®, ChimeriVax-JE®.

Immunogenicity: High seroprotection rates have been reported one month after administration of a single dose of live recombinant vaccine in children from endemic countries and from adults from non-endemic countries. The seroprotection rate has been found to be 99.3%, 100%, 95.0% and 89.7% in 9-18 months, 12-24 months, 12-18 months and 36-42 months respectively. The vaccine immunogenicity does not appear to be affected by concomitant administration of the measles/mumps/rubella (MMR) vaccine.[11]

Dose and schedule: Primary immunization is with 1 dose given subcutaneously at 9 months of age or older. A booster dose is recommended by the manufacturer 12-24 months later for those less than 18 years of age (currently, there are no booster recommendation for adults).[5, 11]

Adverse reactions: Short-term safety data for injection site and systemic reactions showed that in the adult

Table I. Japanese encephalitis vaccines

Strain	Dose	Comments
Live attenuated 14-14-2	First: At 9 months 0.5 ml SC Second: 15-18 months 0.5 ml SC	Used in Government programmes in selected districts
Inactvated Vero cell culture derived Kolar strain	Two doses at one month interval Dose: 0.5 ml	Used in private sector marketed as JENEVAC@ in India.
Inactivated Vero cell culture derived attenuated JE virus strain 14-14-2	• 1-3 yrs 0.25 ml per dose; given 2 doses at 28 day interval • 3 yrs 0.5 ml per dose at 28 days interval.	Used in private sector. Marketed as JEEV® in India
Live vaccine using the yellow fever (YF) 17D and JE SA 14142 strains recombinant chimeric vaccine	First dose given SC at 9 months of age or older. A booster dose 12-24 months later for those <18 years of age	Marketed as IMOJEV®, JE-CV®, ChimeriVax-JE (Not available in India)

population, adverse reaction rates were significantly lower with the chimeric vaccine than with a mouse brain-derived vaccine. There is limited post--licensure safety experience with the chimeric vaccine, with approximately 49,000 doses administered to date, and a larger safety database will be necessary to evaluate the risk of rare adverse events.

IV. Other upcoming vaccines

1. Second generation recombinant vaccine
2. Chimeric vaccine using swine flu and West Nile virus
3. Formaldehyde inactivated vaccine manufactured from P20778 Indian strain

The JE vaccines currently in use in India and outside are summarized in Table I.

WHO Position[5]

In areas where JE is recognized as a public health priority, vaccination should be integrated into national immunization schedules and even if the number of JE confirmed cases is low, vaccination should be considered where there are chances of transmission of JE because of suitable environmental conditions. In endemic settings immunization of children less than 15 years of age through incorporation of JE vaccine in the routine immunization program is the most effective preventive strategy. Need for booster dose in endemic settings has not been clearly established. Vaccinating older age group is to be considered only if the disease burden in such groups is sufficiently high.

Recommendations for special risk groups[5]

1. Immunocompromised persons: In immuno compromised persons inactivated JE vaccine can be used, but the immune response may be lower.
2. Pregnant and lactating women: In situation where there is high risk of JE, pregnant woman may be offered inactivated Vero cell-derived vaccines. Inadvertent administration of live attenuated or live recombinant JE vaccine to a pregnant woman is not an indication for termination of pregnancy.
3. Health-care workers: Healthcare workers involved in vector control activities and working in laboratories should be vaccinated with JEV.
4. Travellers: Travellers from non endemic countries having extensive outdoor exposure during the high transmission season or is migrating to JE endemic areas are candidates for JEV. Inactivated Vero cell-derived vaccines and live recombinant vaccines are generally used for prevention. Travellers, at high risk of further exposure to JEV are immunized with a booster dose of inactivated Vero cell derived vaccine if vaccinated more than 1 year ago.

Points to Remember

- ***Advisory committee on vaccines and immunization practices (ACVIP) recommends two dose schedule for both inactivated vero cell derived vaccines and live attenuated cell culture derived SA-14-14-2 vaccine.***
- ***JE vaccine should not be used as 'outbreak response vaccine'.***
- ***For pre-travel prophylaxis, 2 dose series of inactivated vero cell derived SA 14-14-2 strain***

vaccine should be completed at least 1 week before travel.

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BOOK REVIEW

MANUAL OF NEWBORN NURSING

Authors: Ranjan Kumar Pejaver, Rhishikesh Thakre.

Publishers: The Neonatology Chapter of Indian Academy of Pediatrics.

Pages: 490

Price: 480/-

A wonderful initiative indeed from Dr.Pejavar and Dr.Thakre and their team consisting of Dr.Naveen Bajaj, Dr.Ashish Jain, Dr.Nandkishor Kabra and many neonatologists from across the country. No amount of expensive equipment in neonatal intensive care can replace the painstaking bedside work by the neonatal nurse and without question, effort should be put into training this very vital segment. Though tomes on neonatal nursing are available abroad, this very delightful little book catering to the angels of neonatal intensive care in our country fills the void in the Indian context. A very good primer for the neonatal nurse, the book is thoughtfully sectioned into 7 very easily readable parts. The chapters on essential nursing skills, nursing care of newborn and nursing checklist / protocols and appendices are very well set out. The chapter on 'Coping with death' is very thoughtful. It is an everyday manual not just for the nurses but also a good overview of neonatology for interns and pediatric residents working in NICUs. A few spelling errors can be remedied, a section on "Communication" and an index may be thought of in the next much awaited edition!

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UPDATE ON VACCINES

VACCINATION IN SPECIAL SITUATIONS

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Abstract: *Vaccination is vital and life saving. However, in select special situations the schedule has to be altered with preferential use of some and avoidance of a few others. The present article aims at describing the vaccination schedule in special situations in children.*

Keywords: *Vaccination, Special Situations, Vaccines*

Children in special situations include preterm babies, immunosuppressed children (Immune deficiency, children on steroids and chemotherapeutic drugs) and transplant recipients. These children need vaccines more than immunocompetent children for protection from infections. At the same time as their immune system is either deficient or suppressed vaccines may not produce the expected response. Besides some live vaccines may cause severe infections in them. Hence, the schedule needs to be modified accordingly. Healthcare providers who care for immunocompromised children should be knowledgeable about the indications, contraindications, and precautions for vaccine administration in patients with altered immunocompetence.

Immunization in preterm/low birth weight infants

All vaccines should be administered as per schedule irrespective of birth weight or gestational age except hepatitis B which can be given after a delay of 1 month in babies weighing less than 2 kg.[1]

Hepatitis B positive mother

Hepatitis B immunoglobulin (HBIG) is given preferably within 12 hours of birth with the maximum of 72 hours. In neonates ≥ 2kg, hepatitis B vaccine is given at birth followed by 2 doses at 1 and 6 months. In neonates < 2kg hepatitis B vaccine is given at birth followed by 3 more doses at 1, 2 and 6 months. If HBIG is not available / affordable then Hep B vaccine is given at 0, 1, and 2 months and additional dose is given between 9-12 months.

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Immunization in immunocompromised

In children with severe immunodeficiency all live vaccines are contraindicated. Inactivated vaccines are given at a higher doses and more number of doses and antibody titers are checked and regular boosters are given if needed.

B cell immunodeficiency

In severe B cell deficiency live vaccines except measles and varicella are contraindicated while inactivated vaccines can be administered safely but are ineffective.[1] In less severe B cell deficiency (IgG & IgA subclass deficiency) only OPV is contraindicated.

T cell deficiency

In severe T cell deficiency live vaccines are contraindicated and all vaccines are ineffective.

Combined immunodeficiency

Inactivated vaccines may be given while all live vaccines are contraindicated.[1]

Household contacts of immunocompromised

Transmissible vaccines like OPV are contraindicated in household contacts of immunocompromised children while non transmissible vaccines like varicella and MMR are safe. They should be immunized against varicella and influenza (Table.I).

HIV Infection

In asymptomatic HIV positive children all vaccines can be given including BCG and OPV. In symptomatic HIV positive children, BCG and OPV are contraindicated while IPV can be given instead of OPV. Measles, MMR and varicella can be given if CD4 count is more than 15%. All other vaccines can be administered safely.

Children receiving corticosteroids

Live vaccines are contraindicated in children taking "high dose" oral/iv corticosteroids (>20mg/day in children weighing >10kg or >2mg/kg/day) for a duration of more than 2 weeks. However they can be safely administered the vaccines if they are on low dose steroids, alternate

Table I. Immunisation of caregivers and household contacts of immunocompromised children [3]

Vaccine type	Specific vaccine	Comments
Live bacteria	BCG Ty21a Salmonella typhi	Contraindicated Contraindicated
Live virus	OPV MMR	Contraindicated Indicated
	Varicella	Indicated. If a vesicular rash develops after vaccination, avoid contact with immunosuppressed individual until rash resolves.
	Rotavirus	Indicated. All family members should practice good hand hygiene for atleast 1 week after vaccination
Inactivated	IPV, influenza	Immunise all household contacts

Table II. Vaccine schedule : Infants and children fully vaccinated at cancer diagnosis[3]

Vaccine	Timing of immunisation
Live attenuated	
MMR Varicella	Give an additional booster dose to patients off chemotherapy for 6 months Give booster dose to patients incontinuous remission for at least 1 year with lymphocyte count >700/cumm and platelet count >1 lakh/cumm
Inactivated/Recombinant	
Influenza	Give a booster dose to all patients irrespective of chemotherapy status
DTaP	Give a booster dose to all patients who are 3 months post chemotherapy
IPV	Give a booster dose to all patients who are 3 months post chemotherapy
HBV	Give 2 booster doses at 3 months interval regardless of chemotherapy in all patients who have epidemiological risk factors
Hib	Give a booster dose to all patients who are 3 months post chemotherapy
PCV	Give a booster dose to all patients who are 3 months post chemotherapy
MCV4	Give a booster dose to all patients who are 3 months post chemotherapy
HAV	Give a booster dose regardless of chemotherapy in the presence of epidemiological risk factors

Table III. Vaccine schedule : Infants and children not vaccinated or only partially vaccinated at the time of cancer diagnosis

Live attenuated	
MMR	Give 2 doses, at 3 months interval, atleast 6 months off chemotherapy
Varicella	Give 2 doses, at 3months interval, in patients in continuous remission for at least 1 year with lymphocytecount >700/cumm and platelet count>1 lakh/cumm
Inactivated/Recombinant	
Influenza	Recommended for all patients including those receiving chemotherapy
DtaP	Start primary vaccine series in patients who are 3months off therapy
IPV	Start primary vaccine series in patients who are 3months off therapy
HBV	Start primary vaccine series in patients who are 3months off therapy
Hib	Start primary vaccine series in patients who are 3months off therapy
PCV	Start primary vaccine series in patients who are 3months off therapy
MCV4	Start primary vaccine series in patients who are 3months off therapy
HAV	Give 2 doses at 6months interval regardless of chemotherapy in the presence of epidemiological risk factors

day steroids, inhaled or topical steroids and 4weeks after stopping "high dose"steroids.

Cancer Chemotherapy

Vaccine schedules in children on cancer chemotherapy are shown in Table II and III.

IVIG recipients

Live vaccines are contraindicated up to 6 to 11 months after receiving IVIG based on the dosage and indications while there is no contraindication for inactivated vaccines.

Transplant recipients

Hematopoietic stem cell transplant recipients are like unimmunized as they lose all memory cells and hence vaccination should be restarted with killed vaccines after 6 -12 months .

Asplenia /Hyposplenia

As these children are more prone for infections with capsulated organisms they should receive pneumococcal, Hib and meningococal vaccines along with all routine live and inactivated vaccines. In cases where elective splenectomy is planned vaccination is initiated 2 weeks prior to splenectomy.

Vaccines for travelers

Those visiting endemic areas for meningococcal infections like USA/UK/ Saudi Arabia and Africa, 2 doses of meningococcal vaccine - should be given 4-8 weeks apart. Yellow fever vaccine should be given for those travelling to yellow fever endemic zones 10 days before travel.[2]

Oral cholera vaccine should be given to those travelling to endemic area or when there is an outbreak; 2 doses 1 week apart.

Japanese B encephalitis is administered for those travelling to endemic areas and planning to stay for more than 1 month; Single dose (upto 15 years).

Rabies vaccine (pre exposure prophylaxis): For adolescents going on trekking where there is a risk of exposure to wild mammals; 3 doses at 0,7 and 28.

Points to Remember

- ***Vaccination schedule is different in children in special situations***
- ***Live vaccines are usually contraindicated in immunocompromised children***

- ***Optional vaccines are recommended in children undergoing splenectomy and in travelers to endemic areas.***

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CLIPPINGS

Rebecca Normansell,Kayleigh M Kew,Amy-Louise Bridgman.Sublingual immunotherapy for asthma. Cochrane Airways Group DOI: 10.1002/14651858.CD011293.pub2 Assessed as up-to-date: 25 March 2015.

Approximately half of people with asthma have an important allergic component to their disease, which may provide an opportunity for targeted treatment. Sublingual immunotherapy (SLIT) aims to reduce asthma symptoms by delivering increasing doses of an allergen (e.g. house dust mite, pollen extract) under the tongue to induce immune tolerance. However, it is not clear whether the sublingual delivery route is safe and effective in asthma.

Fifty-two studies met our inclusion criteria, randomly assigning 5077 participants to comparisons of interest. Most studies were double-blind and placebo-controlled, but studies varied in duration from one day to three years. Most participants had mild or intermittent asthma, often with co-morbid allergic rhinitis. Eighteen studies recruited only adults, 25 recruited only children and several recruited both or did not specify (n = 9).

With the exception of adverse events, reporting of outcomes of interest to this review was infrequent, and selective reporting may have had a serious effect on the completeness of the evidence. Allocation procedures generally were not well described, about a quarter of the studies were at high risk of bias for performance or detection bias or both and participant attrition was high or unknown in around half of the studies. One short study reported exacerbations requiring a hospital visit and observed no adverse events. Five studies reported quality of life, but the data were not suitable for meta-analysis. Serious adverse events were infrequent, and analysis using risk differences suggests that no more than 1 in 100 are likely to suffer a serious adverse event as a result of treatment with SLIT (RD 0.0012, 95% confidence interval (CI) - 0.0077 to 0.0102; participants = 2560; studies = 22; moderate-quality evidence).

Within secondary outcomes, wide but varied reporting of largely unvalidated asthma symptom and medication scores precluded meaningful meta-analysis; a general trend suggested SLIT benefit over placebo, but variation in scales meant that results were difficult to interpret.

Changes in inhaled corticosteroid use in micrograms per day (MD 35.10 mcg/d, 95% CI -50.21 to 120.42; low-quality evidence), exacerbations requiring oral steroids (studies = 2; no events) and bronchial provocation (SMD 0.69, 95% CI -0.04 to 1.43; very low-quality evidence) were not often reported. This led to many imprecise estimates with wide confidence intervals that included the possibility of both benefit and harm from SLIT.

More people taking SLIT had adverse events of any kind compared with control (OR 1.70, 95% CI 1.21 to 2.38; low-quality evidence; participants = 1755; studies = 19), but events were usually reported to be transient and mild. Lack of data prevented most of the planned subgroup and sensitivity analyses.

Authors' conclusions: Lack of data for important outcomes such as exacerbations and quality of life and use of different unvalidated symptom and medication scores have limited ability to draw a clinically useful conclusion. Further research using validated scales and important outcomes for patients and decision makers is needed so that SLIT can be properly assessed as clinical treatment for asthma. Very few serious adverse events have been reported, but most studies have included patients with intermittent or mild asthma, so cannot comment on the safety of SLIT for those with moderate or severe asthma. SLIT is associated with increased risk of all adverse events.

UPDATE ON VACCINES

VACCINES IN PIPELINE - MALARIA, DENGUE AND EBOLA

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Abstract: *Among infectious diseases, malaria is arguably the most important one due to the huge disease burden, rising incidence of resistance to first line therapy and high mortality in the absence of appropriate therapy. Dengue is another mosquito borne disease on the rise. Though the fatality in dengue is not as high as untreated malaria, a substantial proportion (50% of world population according to WHO) is at risk for dengue. Ebola was recently in the news because of the epidemic proportions it reached in West Africa. It has an extremely high case fatality rate and can spread across international borders without appropriate measures to control it. An appropriate vaccine against all these diseases would be of great help to curb the disease burden and protect vulnerable population.*

Keywords: *Malaria vaccine, Ebola vaccine, Dengue vaccine*

Malaria vaccines

Malaria is caused by Plasmodium species; an intracellular protozoan parasite and is transmitted by female anopheles mosquito. Despite decades of research an effective malaria vaccine still eludes mankind. The malaria vaccine technology roadmap process is a WHO initiative which has laid down 2 main goals: (a) To develop a vaccine with minimum 50% efficacy against severe malaria; lasting for more than a year - target 2015 and (b) To develop a vaccine with 80% efficacy lasting for more than 4 years - target 2025.[1] Most of the malaria vaccines are only in early trials and yet to reach even phase III trials, let alone human use. It is only recently that the most advanced malaria vaccine, the RTS, S/AS01 has completed phase III trials and offers modest protection. So hopefully the WHO initiative as of now appears to be on track to provide a successful malaria vaccine. Malaria vaccine is practically feasible but difficult. Practical feasibility is possible because of the fact that natural immunity occurs in people living in endemic areas. It is difficult because of multiple reasons relating to the host and the parasite. First, the parasite has a life cycle that transcends 2 hosts and secondly, inside human host the parasite has a lifecycle that spans across liver and blood. To complicate matters further there are 5 different species that cause clinical disease out of which vivax and falciparum are more common. Thus to develop an effective antigen and to identify a clinical correlate of immunity are both difficult. The vaccines are categorised according to the stage at which they target the malarial parasite. This section will cover important clinical stage vaccines for P falciparum. There are several more pre-clinical and inactive vaccines; details of which will be found in the "WHO Malaria Vaccines Rainbow Tables".[2]

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Pre-erythrocytic vaccines

These vaccines target the hepatic stage of the parasite, thus in theory leading to disease prevention and possible abolition of clinical manifestations. Immune mechanism of protection is due to both humoral immunity and cell mediated immunity (CMI). Humoral immunity targets parasites before they enter hepatocytes and CMI targets intracellular pathogens. Ruth Nussenzweig had developed the idea of this kind of vaccine and in his trials he had experimented with the circumsporozoite protein (CSP). The CSP antigen is the most advanced antigen and hence the RTS,S/AS01 vaccine based on CSP is the only vaccine to complete phase 3 trials. The RTS,S antigen is based on P. falciparum CSP (Amino Acids 207 to 395 of the CSP from the NF54 strain of P. falciparum) and is developed by GSK (First developed in the year 1987). RTS,S antigen consists of 2 proteins RTS and S; both derived from CSP of P. falciparum. RTS further is a chimeric protein derived from genetic fusion of carboxy terminal of CSP (RT) and hepatitis B virus surface protein (S). Saccharomyces cerevisiae yeast cells are then used to express RTS and S proteins; resulting in virus-like particles (VLPs) which express these proteins on their surface. To enhance the immune response, the vaccine is administered in combination with a novel adjuvant system; AS01 (liposomal based adjuvant) or AS02 (oil in water based

adjuvant). Immunological studies during phase II trials have shown that anti - CSP IgG provides a good correlate of protection and efficacy. A major phase III trial of this vaccine has been completed. The results were published in 3 sets in 2011, 2012 and 2014.[3,4,5] This study was done on 15,460 children across 7 African countries. The study population included young infants aged 6 - 12 weeks and children aged 5 - 17 months. The key results of this study are summarized in Table I. The vaccine does provide modest protection against malaria. Another fact evident especially after the 2014 data is that, the efficacy of RTS, S/AS01 is greater in children as compared to infants. Even the mean geometric titers of anti - CSP antibodies were higher in children as compared to infants (348 to 787 EU/mL in children vs 117 to 335 EU/mL in infants). The immunity waned over time in both the groups of children. Immune interference from other EPI vaccines, maternal antibodies and immature immune system of infants are responsible for poor efficacy in infants. About half of these infants have been enrolled further by giving a booster after 18 months. These results will be available over time.

Meningitis was one serious adverse event (SAE) reported more often in vaccinated group as compared to the control group (25 - 0.24% in treatment group vs 4 - 0.078% in control group). The exact reason for this is not clear and the authors have not been able to establish or refute a causal relationship between the vaccine and meningitis. During the study period no other significant SAEs were reported. There are several other pre-erythrocytic stage vaccines as summarized below:

1. Adenovirus (Ad35) vectored CSP and RTS,S/AS01 in heterologous prime-boost regimen – Phase IIa trials. The rationale here is to combine 2 different antigens in a sequential schedule with an aim to enhance immunity.
2. ChAd63/MVA ME-TRAP Vaccine – 12 different trials in phase I and II. Multiple Epitopes (ME) of falciparum derived from B and T cells are fused to TRAP (Thrombospodin Related Adhesion Protein). TRAP is another malarial antigen expressed on the surface of sporozoites and infected hepatocytes. This particular fusion protein is expressed in simian adenovirus (ChAd63) boosted with modified vaccinia virus Ankara (MVA).
3. ChAd63/MVA ME-TRAP with Matrix adjuvant system – Phase I trial.
4. PfSPZ (Plasmodium falciparum sporozoite) based vaccines – 3 trials in phase I/II.
5. CSP based DNA vaccines – Polyepitope DNA EP3100 (phase I trials).
6. Recombinant vaccines - PfCelTOS FMP012 (phase I trial).
7. ChAd63/MVA ME-TRAP in combination with RTS,S/AS01B (phase I/II trials).
8. ChAd63/MVA ME-TRAP in combination with AMA1 (Apical membrane antigen of falciparum) – Phase I/II trials.

Table I. Efficacy of RTS, S/AS01 candidate malaria vaccine - A phase III RCT across 11 African Sites

Age	Age	Number	Vaccine efficacy against clinical malaria	Vaccine efficacy against severe malaria
2011 Results[3]	5 – 17 months	6000	1. 50.4% in intention to treat population 2. 55.8% in per protocol population	1. 45.1% in intention to treat population 2. 47.3% in per protocol population
2012 Results[4]	6 – 12 weeks	6537	1. 30.1% in intention to treat population 2. 31.3% in per protocol population	1. 26% in intention to treat population 2. 36.6% in per protocol population
2014 Results[5]	Both age groups	15460	1. 45% in intention to treat – Children 2. 27% in intention to treat – Infants	1. 34% among intention to treat - Children 2. There was no significant benefit in infants

Blood stage vaccines

The vaccines targeting this stage would be based on antigens expressed on merozoites. Since RBCs do not express major histocompatibility (MHC) molecules on their surface; immunity to these vaccines is antibody mediated. The most commonly researched molecules for this stage are the merozoite surface protein (MSP) and AMA. All these vaccines are in early phase I/II trial stage.

1. FMP2.1/AS01B (AMA-1 3D7 E. coli expressed in ASO1B adjuvant).
2. ChAd63 MSP1/MVA MSP1 vaccine.
3. pfAMA1-DiCo vaccine.
4. MSP3 [181-276] field.
5. ChAd63 AMA1/MVA AMA1.
6. NMRC-M3V-D/Ad- PfCA Prime/Boost – Falciparum CSP in combination with AMA based vaccine.
7. ChAd63/AMA MVA/AMA1 + alhydrogel/CPG7909.
8. EBA175 RII vaccine.
9. GMZ2 – A MSP3 based vaccine.

Sexual stage vaccines / Transmission blocking vaccine

Elimination of malaria burden globally involves control of mosquitoes and also interruption of disease transmission between the 2 hosts. These vaccines aim to disrupt the malaria life cycle in the mosquito by targeting the gametocyte. An ookinete specific surface protein Pfs25 has been used as antigen to develop these vaccines. After human inoculation anti Pfs25 antibodies block the infectivity of the parasite to the mosquito. Pfs25-EPA (Recombinant vaccine with detoxified Pseudomonas aeruginosa exoprotein A [EPA]) and Pfs25 VLP are two such candidate vaccines in phase I/II trials.

P vivax vaccines

Vivax species is known to produce hypnozoites which re-infect the liver and lead to disease relapses. This makes it technically more difficult to formulate a vivax vaccine in comparison to falciparum vaccine. ChAd63/MVA PvDBP is the only vivax vaccine in phase I clinical trials currently.

Dengue vaccines

Dengue is an arboviral disease (Genus - Flavivirus, Family – Flavivirdae) caused by any of the 4 prevalent serotypes (DENV 1, 2, 3 and 4). The vector is female Aedes mosquito. The clinical spectrum of the disease can range from simple undifferentiated viral fever to severe dengue hemorrhagic fever with shock. The latter can result in significant morbidity, prolonged hospital stay and even death. Similar to malaria, vector control strategies form the cornerstone of prevention; but so far have been unsuccessful. Modernization, international travels, climatic changes, poor hygiene, drinking water supply and lack of social motivation have all contributed to the explosion of the vector, Aedes. A safe, efficacious and cost effective dengue vaccine will go a long way in curbing the disease burden. However, the disease pathogenesis and immunological mechanics of dengue are complex. Homologous serotype specific neutralizing antibodies provide long lasting immunity. However, the severe manifestations of dengue are due to heterologous non neutralizing antibodies which are responsible for antibody dependent disease enhancement. Thus a vaccine for dengue should be able to produce balanced immunity; effectively for all the 4 serotypes, failing which the vaccine itself may trigger a severe dengue infection. This makes the development of an effective vaccine a challenge. A live vaccine also raises safety concerns. If any one serotype of the 4 in a live vaccine replicates unequally, it can lead to unequal titres of neutralizing antibodies. Waning immunity over time, can also in theory lead to severe dengue infection after a subsequent natural infection. The lack of suitable animal models and a lack of a definite / clinical / immune correlate of efficacy are further hurdles towards successful vaccine development. At present several dengue vaccines are in development as follows:

1. Live attenuated vaccines (includes live chimeric vaccines).
2. Purified inactivated vaccines.
3. Subunit vaccines.
4. DNA based vaccines.
5. Viral vectored vaccines.

The development of dengue vaccines dates back to as early as 1929. The virus was attenuated by serial passages through animal cells or suckling mouse. Current techniques of attenuation involve serial passage in animal cell lines, reverse genetic technology to introduce targeted mutations (targeted mutagenesis) and developing chimeric vaccines.

Live attenuated vaccines

The cell culture based dengue vaccines were first developed at Mahidol University, Bangkok. DENV1, 2 and 4 were serially passaged in dog kidney cells and DENV3 was passaged in African green monkey kidney cells / fetal

rhesus monkey lung cells. The resultant tetravalent vaccine however failed to show adequate immunogenicity and there were serious safety concerns.[6] The development of this vaccine was stalled, but it provided researchers a path for future vaccine research. Another cell culture based tetravalent vaccine developed at Walter Reed Army Institute of Research (WRAIR) also failed due to poor efficacy and had serious adverse events. The failures of cell culture vaccines lead to development of novel techniques to produce more stable live attenuated dengue vaccines. The WRAIR strain was further developed by GSK vaccines (Now called TDEN vaccine) and recently phase II trials of 2 vaccine formulations (designated F17 and F19) were published. The TDEN vaccine was immunogenic and had an acceptable safety profile.[7] The US National Institute of Health (NIH) developed the concept of targeted mutagenesis by genetically altering the DNA of DENV. The resultant strains were more stable, more immunogenic and had fewer adverse events.

Live attenuated chimeric vaccines

The DENV2 and DENV3 strains could not be attenuated by the targeted mutagenesis techniques described above and hence chimeric vaccines were introduced. The first type of chimeric vaccine was developed by US Center for Disease Control (CDC). The DENV2 PKD53 strain developed by Mahidol University, Bangkok was used to develop this chimera. The prM and E genes of DENV2 strain were replaced with genes from DENV1, 3 and 4 viruses; resulting in a tetravalent vaccine (DENVax 2). In a phase I trial by Takeda vaccines DENVax was found to be immunogenic and well tolerated.[8] Phase 2 trials are underway.

The second type of chimeric vaccine involves replacement of prM and E genes of another flavivirus (live attenuated 17D strain of yellow fever) with wild type DENV. This was conceptualized by NIH and further developed by Acambis Inc., Paris. Sanofi Pasteur combined all the 4 serotype chimeras into a single tetravalent vaccine now known as CYD-TDV. Similar to malaria vaccines this is the only advanced dengue vaccine to have entered phase III trials.[9] 10,275 healthy 2 - 14 year chidren in Asia Pacific region were included in the study. 6,851 children received the CYD-TDV vaccine and 3,424 children received placebo; in 0, 6 and 12 month schedule. The vaccine showed an efficacy of 56.5% with the primary end point being virologically confirmed dengue occurring after 28 days of last dose. Vaccine efficacy against DENV1 was 50%, against DENV2 was 35%, against DENV3 was 78%, and against DENV4 was 75%. 402 serious adverse events (not related to vaccination directly) - mostly injuries and infections were reported in the treatment group thus making the vaccine safe for use. The Latin American results made available in later half of 2014 enrolled 20,869 children aged 9 to 16 years.[10] Vaccine efficacy against all serotypes in per protocol (PP) analysis was 60.8%. Efficacy against DENV1 was 50.3%, against DENV2 was 42.3%, against DENV3 was 74.0%, and against DENV4 was 77.7%. In an intention to treat analysis (ITT) the vaccine efficacy was 83.7% in seropositive subjects and 43.2% in seronegative patients. Further research and trials are underway and in coming years will provide a hope for a clinically useful dengue vaccine.

Inactivated dengue vaccine

Inactivated vaccines have the advantage that they cannot revert to virulent form and they are free from viral interference seen with live vaccines. Initially monovalent vaccines were developed by WRAIR and are now being researched by WRAIR/GSK/Oswald Cruz foundation.

Subunit dengue vaccine

Structural envelop proteins of dengue virus elicit immune response and one such protein being developed is envelope glycoprotein (E). Recombinant E protein antigen is being produced in various expression systems like E. coli and vaccinia virus. Merck & Co. and Hawaii Biotech in US are in the process of conducting trials.

DNA based dengue vaccines

Genes encoding for NS1 antigen, E antigen and prM antigen are incorporated onto a vector. These vaccines are engulfed by antigen presenting cells and lead to intracellular generation of dengue antigens. WRAIR has developed a candidate vaccine and phase I trials are underway.

Vector based dengue vaccines

DENV genes are inserted and expressed using viral vectors. The candidate viral vectors are adenovirus vectors, Venezuelan equine encephalitis (VEE) virus vector and attenuated measles virus. These vaccines are still in pre-clinical stages.

Ebola vaccines

The new found interest in Ebola vaccines is due to the outbreak in Africa and the nature of disease to spread across international borders. The disease spreads easily by contact with body fluids and fomites. Adding to further woes is the extremely high case fatality rate of the disease.

According to WHO, as on January 21st 2015, there have been 21,689 confirmed cases with 8626 deaths at a case fatality rate of 40%. In 1967, the first outbreak of Marburg hemorrhagic fever occurred and since then there have been about 18 outbreaks of Marburg / Ebola virus outbreaks. The present outbreak has been the largest one so far. Ebola virus along with Marburg virus belongs to the group of hemorrhagic RNA viruses of the family Filoviridae. Early on, live attenuated vaccines were tried without any success. Recently genetic vaccines are being researched by NIH and other institutes in the US and UK. It usually takes years, perhaps decades to develop a vaccine, but the recent epidemic has led to unprecedented developments. At least 3 vaccine candidates have reached phase I trials within a span of 18 months.

The first vaccine is a recombinant vaccine developed from chimpanzee adenovirus expressing Ebola virus proteins (cAd3-EBO) from Zaire and Sudan species of Ebola. This vaccine is being developed by GSK in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID). A single dose of this vaccine was found to be efficacious for up to 5 weeks in a trial in non-human primates. The immunity could be boosted by using modified vaccinia virus Ankara (MVA) based vaccine; which provided immunity lasting for greater than 10 months. Immunity is provided by Ebola glycoprotein specific antibodies and T cell responses. In a phase I trial 20 healthy adults were administered the bivalent cAd3-EBO.[11] 10 participants received $2x10^{10}$ particle units and remaining 10 received $2x10^{11}$ particle units. Vaccine safety and immunogenicity were monitored for a 4 week period. The vaccine was immunogenic at higher dose and no safety concerns were identified. A monovalent variant of the vaccine developed from the Zaire strain (ChAd3) was studied separately at the centre for Clinical Vaccinology and Tropical Medicine at the University of Oxford.[12] Similar to the above trial this one was also an open labelled, dose escalation study to assess the safety and immunogenicity. Sixty healthy adults in 3 groups of 20 each received the monovalent ChAd3 vaccine at doses of: 1×10^{10} viral particles, 2.5×10^{10} viral particles, and 5×10^{10} viral particles. Fever, prolonged PTT and transient hyperbilirubinemia were the only reported adverse events. The highest dose group had the best GMTs of antibody levels and a 100% T cell response. Another trial of the monovalent vaccine is going on at Switzerland.

The second vaccine running head to head in clinical trials with the adenovirus based vaccines is a recombinant vesicular stomatitis virus vaccine (rVSV). The rVSV vaccine has been developed by the Public Health Agency of Canada and US-based New Link Pharmaceuticals and licensed to Merck for further trials. The vaccine now called rVSV-ZEBOV (Zaire EBOV)is undergoing three phase I clinical trials, one at WRAIR; second one at NIAID and third one at University Hospitals of Geneva, Switzerland.[13] The NIAID is testing the vaccine in a prime boost strategy and WRAIR is evaluating it in a single dose injection. A press release dated January 6th 2015 indicated that trials of this vaccine have been halted at both the places due to some unexpected adverse events. It will be resuming shortly with a lesser particle titre dose.

The third vaccine to enter phase I trial is being developed by Bavarian Nordic and Janssen (a subsidiary of Johnson and Johnson). The vaccine is called as HuAd26 / MVA-BN-filo is an adenovirus based vaccine along with modified vaccinia Ankara to boost immunity and provide long lasting protection. Two trials are underway, one in US and another in UK. Another trial in UK is evaluating combination of this vaccine with the GSK cAd3-EBO in a prime-boost technique.[14,15,16]

Conclusion

One malaria vaccine and one dengue vaccine have completed phase III trials. Both the vaccines have shown modest efficacy without any major safety concerns. There are few other vaccines related to these diseases which are already in phase II trials. Soon we may see malaria and dengue vaccines reach clinical use. It is Ebola vaccine which is of concern. WHO had convened an emergency meeting in January 2015 to speed up the development of Ebola vaccines. Phase I results are out and already the strategy for phase II and phase III trials are laid out. The phase III trial proposal has the study design with 3 prongs; cAd3 based vaccine, rVSV-EBOV and placebo. Global alliance for vaccine initiative (GAVI) has already funded US$ 300 million which can support 12 million doses for these further trials. A step forward has been taken and alongside malaria and dengue, Ebola vaccine might soon see the light of the day.

Points to Remember

- ***The RTS,S/AS01 malaria vaccine is the most advanced malaria vaccine in trials as of today; with a modest efficacy.***
- ***RTS,S/AS01 will soon be available for clinical use, starting first with the African sub-continent.***
- ***Live attenuated chimeric dengue vaccine CYD-TDV is the only dengue vaccine to reach phase 3 clinical trials.***

- ***Ebola vaccines are still in early trials. WHO is speeding up the process of these vaccines in the light of the global threat from Ebola disease.***

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NEWS AND NOTES

27th RESPICON 2015

Date: 12th & 13th December, 2015

Venue: Hotel Grand Hyatt, Santacruz (East), Mumbai

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GENERAL ARTICLE

PRIMARY CILIARY DYSKINESIA: DIAGNOSIS AND MANAGEMENT

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Abstract: *"Primary ciliary dyskinesia (PCD)", is a rare, ciliopathic, autosomal recessive genetic disorder that causes a defect in the action of the cilia lining the respiratory tract, fallopian tube and the flagella of sperm cells. It should be suspected when chronic lung disease presents with pancreatic insufficiency, heat intolerance, male infertility, situs inversus and emphysema at young age. Referral to tertiary care center with facilities for genetic evaluation can help in early diagnosis and offer therapies which can delay progression and even decrease severity of disease.*

Keywords: *Primary cilary dyskinesia, Situs inversus, Chronic lung disease.*

"Primary ciliary dyskinesia (PCD)", previously known as immotile ciliary syndrome, is a rare, ciliopathic, autosomal recessive genetic disorder that causes a defect in the action of the cilia lining the respiratory tract (lower and upper, sinuses, eustachian tube, middle ear) and fallopian tube, as well as the flagella of sperm cells. This condition is inherited as an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The symptoms and severity of PCD vary from person to person and over time.

Respiratory epithelial motile cilia, which resemble microscopic "hairs" (although structurally and biologically unrelated to hair), are complex organelles that beat synchronously in the respiratory tract, moving mucus toward the throat. Normally, cilia beat 7 to 22 times per second and any impairment can result in poor mucociliary clearance, with subsequent upper and lower respiratory infection. When accompanied by the combination of situs inversus (reversal of the internal organs), chronic sinusitis and bronchiectasis, it is known as Kartagener syndrome which is seen in 50% of PCD cases. The phrase "immotile ciliary syndrome" is no longer favoured as the cilia do have movement, but may be inefficient or unsychronized.[1] Splenic abnormalities such as polysplenia, asplenia and complex congenital heart defects are more common in individuals with situs ambiguus and PCD, as they are in all individuals with situs ambiguus.[2] The true incidence of the disease is unknown.It is estimated to be 1 in 32,000,[3] although the actual incidence may be as high as 1 in 15,000. The recurrence risk is approximately 25%.

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Genetics

PCD is a genetically heterogeneous disorder affecting motile cilia[4] which are made up of approximately 250 proteins. Around 90% of individuals with PCD have ultrastructural defects affecting protein(s) in the outer and / or inner dynein arms which give cilia their motility, with roughly 38% of these defects caused by mutations on two genes, DNAI1 and DNAH5, both of which code for proteins found in the ciliary outer dynein arm.[5] The role of DNAH5 in heterotaxy syndromes and left-right asymmetry is also under investigation.

Pathophysiology

Structures that make up the cilia including inner and/ or outer dynein arms, central apparatus, radial spokes, etc. are missing or dysfunctional and thus the axoneme structure lacks the ability to move. Secondary ciliary defects, including ultrastructural defects, may be seen following viral infection or pollution exposure but they are transient and ciliary structures are essentially normal.[6] The main consequence of impaired ciliary function is reduced or absent mucus clearance from the lungs and susceptibility to chronic recurrent respiratory infections, including sinusitis, bronchitis, pneumonia, and otitis media. Progressive damage to the respiratory system is common, including progressive bronchiectasis (beginning in early childhood) and sinus disease (sometimes becoming severe in adults). However, diagnosis is often missed early in life despite the characteristic signs and symptoms.[7] In males, immotility of sperm can lead to infertility, but conception remains possible through the use of in vitro fertilization.[8] Many affected individuals experience hearing loss and show symptoms of glue ear which demonstrate variable responsiveness to the insertion of myringotomy tubes or

grommets. Some patients have a poor sense of smell, which is believed to accompany high mucus production in the sinuses (although others report normal - or even acute - sensitivity to smell and taste). Susceptibility to infections can be drastically reduced by an early diagnosis.[8]

Clinical features

Clinical features of PCD are variable and include chronic otitis media, sinusitis and chronic cough. Neonates with PCD are mostly diagnosed as persistent or aspiration pneumonia unless situs inversus or positive family history is associated. 33% children have nasal polyps. In PCD cough reflex is preserved and typical presentation is non-specific bronchodilator non-responsive cough. The commonest organisms causing infections are H. influenzae, Staph aureus, Strep viridians, P aeruginosa. Though infertility in males are common, fallopian tube movement incordination in females are rare. Situs inversus occurs presumably due to abnormal ciliary function in normal visceral rotation during embryogenesis.[9] There have been a few cases of hydrocephalus due to ciliary defect in ventricular ependymal cells.[10] On clinical examination, nasal congestion and polyps, recurrent otitis media, clubbing, variable crackles in both lungs and situs inversus may be observed.[11] Chest radiology and CT scan may show hyperinflation, bronchial wall thickening, segmental atelectasis, bronchiectasis and situs inversus. Usually middle lobe and lingula are involved in PCD while apices are commonly affected in cystic fibrosis (CF). Box 1 gives details of when to suspect PCD.

Box.1 When to suspect PCD[11]

- Family history of PCD
- Respiratory distress in a newborn
- Sinusitis / nasal polyposis
- Chronic cough and wheeze
- Recurrent pneumonia, bronchitis and bronchiectasis (H. influenzae, Staph aureus, Strep viridians, P aeruginosa)
- Excess mucus / difficulty clearing mucus
- Middle ear infections
- Hearing loss
- Lack of response to common antibiotics
- Male infertility
- Hydrocephalus (occasional).

Investigations

For diagnosis of PCD

1) Nasal mucosal biopsy: Nasal mucosa can be easily and non-invasively obtained in a clinical setting using a proper otoscopic head and a disposable thermoplastic curette. A gentle curettage of the inferior surface of the inferior nasal turbinate under direct vision will retrieve small fragments of ciliated epithelium which are optimal for diagnosis and can be processed for electron microscopic

Table I. Genetic testing in PCD

GENE	Axonemal / cellular structure/ function	Routine TEM	Routine Immuno Fluroscence
RSPH4A, *RSPH9*		Often normal components	Abnormal staining with antibodies against
CCDC39, *CCDC40*	NL/DRC factor	Microtubular disorganisation + IDA-defect	DRC components + IDA components
CCDC164, *CCDC65*	NL subunit	NL defect only rarely discernible	NL components
DNAH11	ODA subunit	Normal	

DRC, dynein regulatory complex; IDA, dynein arm; IF, immunofluorescence microscopy; NL, nexin link; ODA, outer dynein arm; TEM, transmission electron microscopy;

examination. Abnormal ciliary ultrastructure and motility in nasal brush or bronchial biopsy by electron microscope in a child with history and clinical examination consistent with PCD may confirm the diagnosis.

2) Video microscopy of ciliary movement, removal of inhaled radio-labelled particles in bronchus and measuring mucociliary clearance of saccharin applied to anterior nares are some of the research tests not applicable in practice.[12,13]

3) Low nasal nitric oxide: May be used as a screening tool in PCD.

4) Genetic Testing: Some examples are given in Table I.

Follow up of progression of PCD

1) Sputum cultures

PCD is a progressive lung disease. Progressive lung disease potentially means progressively worse bugs and hence routine 'surveillance' cultures are recommended. The recommendation from the European Task Force on PCD is that routine sputum cultures be collected at least every 6-12 months when healthy and every time there is an active lung infection.[14]

2) Pulmonary function tests (PFT)

Their utility in PCD is not as clear at this point, but the European Respiratory Task Force on PCD still recommends that PFTs be done every 3-6 months.[14]

3) Imaging

CT scans are the most reliable way to assess for early changes in the airway that might suggest bronchiectasis. The current recommendation is to consider a baseline CT scan to assess the level of lung involvement when the diagnosis is first made. Regular x-rays pose a much smaller radiation exposure risk, but they are not particularly good at picking up bronchiectasis until it is quite advanced. They are an important tool for monitoring infections like pneumonia.

4) Bronchoscopy

Bronchoscopy can be useful in exploratory, diagnostic or therapeutic aspects in PCD. Bronchoalveolar lavage (BAL) can help in identifying infection in resistant pneumonia or bronchiectasis.

5) Upper airways (Ears and sinuses)

PCD-related conductive hearing loss is very common in young PCD patients and routine hearing tests should be performed to assess level of loss. Cultures of the drainage from ears or sinuses can sometimes be helpful for determining a course of treatment.

Differential diagnosis[11]

It is always a diagnosis of exclusion following early suspicion. Cystic fibrosis (intestinal malabsorption, positive sweat test, positive genetic mutation), lung allergies (positive skin allergen test, seasonal and high IgE) and immunodeficiencies (abnormal immunoglobulin, T cell defect, absent thymus or positive NBT test and complement deficiencies) are the common differential diagnosis.

Treatment

Aim

1) To increase mucocilary clearance by airway clearance techniques (chest percussion, postural drainage, regular breathing exercise.
2) Cough remains effective in PCD; encourage coughing, avoid cough suppressants, bronchodilators, DNAse and other anti-inflammatory agents.[15]
3) Prevent respiratory infections with immunization against pertussis, measles, H influenzea, S.pneumoniae and yearly influenza vaccine.
4) Treat for bacterial infection (with suspicion) with appropriate antibiotics of full course. Sputum, bronchoalveolar lavage (BAL) may add to diagnosis. May need prophylactic antibiotics in selected cases.
5) Surgical tymphanoplasty and grommet for chronic ear infection if needed.
6) Nasal polypectomy, sinus drainage and lung lobe resection in end satge disease.
7) Avoid environmental pollutant exposure (tobacco smoke, fungus etc.)

Prognosis[11]

Prognosis is variable, though most children do slowly develop chronic lung disease with bronchiectasis and some degree of pulmonary disability.

Points to Remember

- ***Primary cilary dyskinesia (PCD) is an autosomal recessive disorder with defect in ciliary motility of respiratory tract, middle ear, fallopian tube and ventricular ependyma in brain.***
- ***Clinical features of PCD are of multisystem involvement and present with sinusitis, otitis media,***

bronchitis and pneumonia and ultimately chronic lung disease.

- ***Treatment is to enhance mucociliary clearance, chest percussion and drainage to prevent cough and resist infections.***
- ***Early referral to a tertiary care center with genetic diagnostic facilities can improve the course of the disease.***

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GENERAL ARTICLE

ASTHMA MEDICATIONS IN CHILDREN AND ADOLESCENTS

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Abstract: *There is no 'cure' for asthma but there are various medications that could help control symptoms and thereby preserve good lung function in children and adolescents with asthma. This article is an overview of the latest GINA guidelines for management of asthma. The need for accurate diagnosis and early introduction of low dose inhaled corticosteroid is emphasized as the best treatment practice.*

Keywords: *Asthma, GINA guidelines, Inhaled corticosteroids, Leucotriene receptor antagonist, Long acting beta agonist, Short acting beta agonist, Anti IGE*

Wheeze is a common health problem in infants and children. It is important to note that the clinical presentation of wheeze has considerable overlap with that of pneumonia. Bacterial pneumonia or a mixed viral-bacterial lower respiratory tract infection could present with wheeze.[1,2] Hence, some children with 'asthma' may be prescribed antibiotics.

Asthma is among the most common chronic diseases of childhood. Prevalence is increasing in many countries, especially in children. Asthma is a major cause of school and work absence. Due to the paucity of accurate data in India, the true prevalence of asthma may be grossly under-estimated. Management of pediatric asthma, including evidence based use of medications for the disease, requires an understanding of the issues that uniquely affect children.

Goals of asthma management

- To achieve good control of symptoms and maintain normal activity levels
- To minimize future risk; to reduce risk of exacerbations, maintain lung function and lung development as close to normal as possible

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Categories of asthma medications

There are 3 categories of medications used for pediatric asthma

a) Controller medications: Drugs that help to treat the underlying inflammation of the airways in a child with asthma. By controlling the inflammation, asthma symptoms will diminish and exacerbations are prevented, thereby reducing the risk of a decline in lung function.

b) Relievers or rescue medications: These are fast acting medications that give quick relief of asthma symptoms. They are also used for the short term prevention of exercise induced asthma. Reduction and ultimate elimination of the need for reliever medication is the goal of asthma management and the measure of the success of asthma control.

c) Add-on therapies: These are prescribed in severe asthma that is not controlled with high dose controller medications and elimination of risk factors.

Controller medications

Best results are achieved if daily regular controller medications are started as soon as a diagnosis of asthma is made. Lung functions are superior in children initiated as early as possible on low dose inhaled corticosteroids (ICS) than in those in whom it was started 2-4 years after onset of symptoms.[3,4] Further, those started late on ICS required high dose ICS to start with.[5] The final lung function was also poorer in this group of children. It is also known that a greater long term decline in lung function is noted after a severe exacerbation in children not on regular ICS than in those who are on regular ICS.[6]

Children less than 5 years - Stepwise approach[7]

Step 1: Infrequent viral wheezing and no or few interval symptoms – Does not require controller medication.

Step 2: Symptom pattern consistent with asthma and asthma symptoms not well-controlled, or ≥3 exacerbations per year. Indications for regular low-dose ICS (or Leukotriene receptor antagonist [LTRA] Intermittent ICS).

Symptom pattern not consistent with asthma but wheezing episodes occur frequently, e.g. every 6–8 weeks. Give diagnostic trial for 3 months

Step 3: Asthma diagnosed, and not well-controlled on low dose ICS: after rechecking diagnosis, inhaler skills, adherence and elimination of exposures - Indications for double 'low dose' ICS (or regular low dose ICS + LTRA).

Step 4: Not well-controlled on double ICS – after rechecking diagnosis, inhaler skills, adherence and elimination of exposures - Indications for continuing controller and considering referral for specialist assessment (or additional LTRA, increasing ICS frequency and/or adding intermittent oral corticosteroid.

Children 6 yrs and above – Stepwise approach

Step 1: No controller medication as in under-fives (or may consider low dose ICS)

Step 2: Asthma symptoms more than twice a month; Waking due to asthma more than once a month; Any asthma symptoms plus any risk factors for exacerbations:

Indications for regular low-dose ICS (or LTRA; low dose theophylline; except in children 6-11 years – theophylline not recommended)

Step 3: Not well-controlled on low dose ICS alone – after rechecking diagnosis, inhaler skills, adherence and elimination of exposures; Troublesome asthma symptoms on most days; Waking from asthma once or more a week, especially if any risk factors for exacerbations: Indications for low dose ICS; 6-11yr medium dose ICS preferred/ LABA (or med/high dose ICS; low dose ICS+LTRA [or+theophylline; except in children 6-11 years – theophylline not recommended])

If initial asthma presentation is with an exacerbation: Give a short course of oral steroids and start regular controller treatment (e.g. high dose ICS or medium dose ICS/LABA, then step down).

Step 4: Not responding to Step 3:

Indications for med/high ICS/LABA (or high dose ICS + LTRA [or+theophylline; except in children 6-11 years – theophylline not recommended])

Step 5[8]: If symptoms uncontrolled or exacerbations persist despite Step 4 treatment, check inhaler technique and adherence before referring: Refer for add-on treatment e.g. anti-IgE (or Add low dose oral corticosteroids [OCS]); Preferred option is referral for specialist investigation and consideration of add-on treatment.

Add-on omalizumab (anti-IgE) is suggested for patients with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment.

Other add-on treatment options at Step 5 include:

Sputum-guided treatment: this is available in specialized centers; reduces exacerbations and/or corticosteroid dose; Add-on low dose oral corticosteroids (<7.5mg/day prednisone equivalent): This may benefit some patients, but has significant systemic side-effects. Assess and monitor for osteoporosis.

Before starting initial controller treatment - Record evidence for diagnosis of asthma, if possible; Record symptom control and risk factors, including lung function; Consider factors affecting choice of treatment for the given child/adolescent; Ensure that the child/adolescent can use the inhaler correctly; Schedule an appointment for a follow-up visit

After starting initial controller treatment - Review response after 2-3 months, or according to clinical urgency; Adjust treatment (including non-pharmacological treatments).

Consider stepping down when asthma has been well-controlled for 3 months of initial controller and the treatment risk for exacerbations is low. Consider stepping up if uncontrolled symptoms, exacerbations or risks, but check diagnosis, inhaler technique and adherence first.

Facts about ICS

What is low dose ICS?

A low daily dose is defined as the dose that has not been associated with clinically adverse effects in trials that included measures of safety. Table 1 provides information on what is accepted as low dose ICS in under-fives. Tables I to III give the low, medium and high dose for ICS in children 6-11 years and >12 years, respectively.

ICS in children less than 5 years

Children on regular ICS have significantly less wheezing, fewer exacerbations, less salbutamol use, more clinical improvement compared to placebo in preschool children. For children whose asthma is not well controlled with low dose ICS in spite of good technique, can be found good response by giving twice the low dose. The clinical response may differ based on specific device used for delivery and the child's ability to use it correctly.

ICS in 6 to 11 years

Very few children require moderate or high dose ICS; most are well controlled with low dose ICS with good technique and delivery system. High doses are arbitrary, but for most ICS are those that, with prolonged use, are associated with increased risk of systemic side-effects.

Symptom control and improvement in lung function is expected in 1-2 weeks. Deterioration of asthma control, if it is to occur, is to be expected within weeks to months of stopping ICS. Daily ICS is superior to intermittent ICS in several indicators of lung function, airway inflammation, asthma control and reliever use.[9] Both treatments appeared safe, but modest growth suppression was associated with daily, compared to intermittent, inhaled budesonide and beclomethasone. Clinicians should carefully weigh the potential benefits and harm of each treatment option.

ICS above 12 years

Regular ICS use leads to significantly less asthma symptoms, fewer exacerbation, less salbutamol use, improves quality of life, lung function, reduces exercise induced broncho-constriction and decreases asthma related mortality. Patients not receiving ICS are at increased risk of asthma exacerbations, airway remodelling, and loss of lung function. To achieve good control adding LABA is preferred over increasing dose of ICS.

Adverse effects of ICS in < 11 years

Daily use of ICS 100-200mcg is found to be safe without any adverse effect on growth. High dose is associated with detectable systemic effect on growth in 1st year of life and on hypothalamic-pituitary axis in < 5years. Uncontrolled or severe asthma adversely affects growth and final adult height. Growth retardation is dose dependent, both moderate and high dose of all ICS may affect the growth. In several studies, children with asthma treated with ICS found to attain the final adult height, except one randomised controlled trial (1 RCT) of 5 years treatment with inhaled budesonide 400mcg per day found that initial 1.2 cm reduction in height persisted to adulthood.

No studies have demonstrated the increased risk of fracture in children taking ICS. Controlled studies for 2- 5 years of ICS have shown no effect on bone mineral density.

Low dose ICS has not shown any change in hypothalamic-pituitary axis (HPA). Moderate dose have shown minimal changes but no clinical significance, while very high dose ICS have shown few adrenal crisis cases. Hoarseness and candidiasis were rare in children < 5 years, very rarely a problem in children. ICS is not associated with bruising, dental side effects or increased incidence of respiratory tract infections including tuberculosis.

Adverse effects of ICS in adolescents

Local side effects like candidiasis, dysphonia, and cough from upper airway involvement have been reported. Mouth rinsing after inhalation, use of prodrugs (ciclesonide, HFA beclomethasone) and proper use of devices may reduce these local complications**.** Systemic side effects are not significant if dose is < 400mcg budesonide. Systemic side effect at high dose include easy bruising, adrenal suppression, decreased bone mineral density, non vertebral fracture, cataracts. High dose ICS increased the risk of tuberculosis and respiratory tract infection, but ICS is not contraindicated in active tuberculosis.

Table I*. 'Low dose' inhaled corticosteroids (mcg/day) for children ≤5 years

Inhaled corticosteroid	Low daily dose (mcg/kg)
Beclometasone dipropionate (HFA)	100
Budesonide (pMDI + spacer)	200
Budesonide (nebulizer)	500
Fluticasone propionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studied below age 4 years
Triamcinolone acetonide	Not studied in this age group

*This is not a table of equivalence of doses of the various ICS molecules

Table II. Low, medium and high dose inhaled corticosteroids in children 6–11 years

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (HFA)	50–100	>100–200	>200
Budesonide (DPI)	100–200	>200–400	>400
Budesonide (nebules)	250–500	>500–1000	>1000
Ciclesonide (HFA)	80	>80-160	>160
Fluticasone propionate (DPI)	100–200	>200-400	>400
Fluticasone propionate (HFA)	100–200	>200–500	>500
Mometasone furoate	110	≥220 - <440	≥440
Triamcinolone acetonide	400–800	>800-1200	>1200

*This is not a table of equivalence of doses of the various ICS molecules

Table III. Low, medium and high dose inhaled corticosteroids in adolescents (≥12 years)

Inhaled corticosteroid	Total daily dose (mcg)		
	Low	Medium	High
Beclomethasone dipropionate (HFA)	100–200	>200–400	>400
Budesonide (DPI)	200–400	>400–800	>800
Ciclesonide (HFA)	80–160	>160–320	>320
Fluticasone propionate (DPI or HFA)	100–250	>250–500	>500
Mometasone furoate	110–220	>220–440	>440
Triamcinolone acetonide	400–1000	>1000–2000	>2000

*This is not a table of equivalence of doses of the various ICS molecules

Leucotriene receptor antagonist (LTRA) in children less than 5 years

Montelukast reduced the number of days with symptoms and need for rescue beta 2 agonist by 6% in comparison to placebo. In a 12 month placebo controlled study of 549 young children with recurrent viral induced wheezing, regular montelukast improved some asthma outcomes compared to placebo, but did not reduce frequency of hospitalization, use of courses of steroids, or symptom free days. Two studies which compared LTRA vs ICS in pre-school children favoured ICS to be superior in several asthma outcomes. There is no evidence to suggest use of LTRA - antihistamine combinations.

Leucotriene receptor antagonist (LTRA) in 6 - 11years

LTRAs provide benefit at all levels of asthma symptoms, but the benefit is less than low dose ICS. LTRAs provide partial protection against exercise induced broncho-constriction with no loss of protective effect over time. Add on montelukast therapy was less effective in children with uncontrolled persistent asthma than increasing ICS to moderate dose. Montelukast has not been demonstrated to be a effective ICS sparing alternative in children with moderate to persistent asthma. There is no evidence to suggest use of LTRA - antihistamine combinations in this age group also.

Adverse effect - no potential side effect; post marketing surveillance showed mild increase in neuro-psychiatric behaviour which later was not confirmed by case-controlled study.

Long acting beta agonist (LABA)

Effect of LABA alone or with ICS has not been adequately studied in children <4 years. LABA is always preferred in combination with ICS. Above 6 years LABA are used as add on therapy for those whose asthma is insufficiently controlled with medium dose ICS. No significant difference in exacerbations requiring systemic steroids when LABA was added to ICS when compared to double dose of ICS in children < 11 years.

When medium dose ICS fails, adding LABA in combination with low dose ICS improves clinical asthma outcomes, and reduces the number of exacerbations in adolescents and adults. Low dose combination of rapid acting formoterol and ICS combination may be used for both maintenance and reliever treatment. Formoterol and ICS when used as reliever had an enhanced protection compared to SABA as reliever. Salmeterol and formoterol are similar in efficacy except formoterol has rapid onset of action which can be used as reliever.

Short acting beta agonist (SABA)

SABA drugs include salbutamol, terbutaline, levosalbutamol, reproterol and pirbuterol. They are available as metered dose inhaler (MDI), nebulized respules, dry powder inhaler (DPI) and oral syrups and tablets. Indications and used during flare-ups, and for preventing exercise induced bronchoconstriction. Dose - Salbutamol 100mcg or levosalbutamol 50 mcg, 4-10 puffs every 20 min for first hour, later 4-10 puff every 1-2 hour to 3-4 hour. Both have similar efficacy.

Delivery of SABA via pressurised MDI with spacer leads to similar improvement as delivery via nebulizer. Dry powder inhalers are as effective as spacer and puff for delivery of SABA in worsening asthma or exacerbations.[10] SABA are recommended only in mild and moderate flare-ups and not in acute severe asthma.

Adverse effect: Tremors, tachycardia, head ache, agitation are common complaints in children and is not recommended for prolonged continous use. It can increase asthma morbidity and mortality. It is very important to teach when and how many doses of SABA to be used in a given situation.

Short acting anti cholinergics

Anti-cholinergic drugs include ipratropium bromide and oxitropium bromide. Available as pMDI, DPI, nebulized respules. Its use during flare-ups along with SABA has shown better improvement in lung function and decreased hospital admission. Dose: Ipratropium bromide 250mcg per mL. Not recommended for routine asthma management in children less than 5 years age. Adverse Effects: Dryness of mouth and bitter taste.

Oral corticosteroids (OCS)

Short term use of OCS is necessary to prevent acute flare-ups, hospitalizations, prevent early relapse after emergency treatment, and reduce morbidity. If OCS are to be used for long term basis then utmost precautions should be taken to prevent adverse effects. Oral therapy is as effective as IV hydrocortisone. Prednisolone may be initiated at 1-2mg/kg/day in acute flare-ups. OCS can be stopped abruptly except if taken for > 2 weeks

OCS can be used for acute exacerbations even if triggered by viral infection. Even short course of OCS if used repeatedly causes side effects. Short courses of oral steroids were associated with reduced bone density and the risk of fracture is increased with ≤ 4 courses of steroids. The systemic side effects of long term OCS are osteoporosis, arterial hypertension, diabetes, HPA suppression, obesity, cataracts, easy bruising etc.

Anti IgE

Recommended as add on treatment for severe persistent allergic asthma above 6 years of age, if asthma symptoms are uncontrolled in spite of optimum pharmacological, non pharmacological treatment and allergen avoidance. Anti IgE treatment was associated with significant lower exacerbation rate and improved quality of life. Therapy is expensive and need to be administered under supervision. Adverse events include injection site pain, urticarial rash, pruritis and anaphylaxis.

Other Medications

Long acting anti-cholinergics: Add-on tiotropium by soft-mist inhaler is a new 'other controller option' for Steps 4 and 5, in patients ≤18 years with history of exacerbations.

Oral Theophyllines - not recommended for use in children unless ICS is not available. Side effects include, anorexia, nausea, vomiting, head ache and more serious side effects include seizures.

Oral beta agonist: Oral bronchodilators are not the preferred mode of reliever therapy for acute symptoms. Adverse effects that include tremors, anxiety and cardio vascular stimulation are significant enough to prevent its long term usage.

Conclusion

It is important to understand the reasoning behind the updated GINA guidelines. Developing economies like ours are likely to face increased demand in health care with regard to asthma due to its increasing prevalence. The economy should not be burdened with poorly controlled asthma as its management is expensive. Investment in preventive medication is likely to yield cost savings in emergency care.

Points to Remember

- ***Best results are achieved if daily regular controller medications (low dose ICS) are started as soon as a diagnosis of asthma is made.***
- ***For children <5yrs whose asthma is not well controlled with low dose ICS in spite of good technique, good response is expected by giving twice the low dose.***
- ***In older children, especially those >12 yrs, whose asthma is not well controlled with low dose ICS in spite of good technique, better response is achieved by adding LABA than by increasing dose of ICS.***
- ***Daily ICS is superior to intermittent ICS.***
- ***Symptom control and improvement in lung function are expected in 1-2 weeks.***
- ***Deterioration of asthma control, if it is to occur, is to be expected within weeks to months of stopping ICS.***

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DERMATOLOGY

MANAGEMENT OF ATOPIC DERMATITIS

*Madhu R

Abstract: *Atopic dermatitis (AD) is a chronic, inherited, inflammatory, itchy skin disorder seen in infants and children characterized by remissions and exacerbations. Increasing prevalence of atopic dermatitis has been reported worldwide including developing countries. Sometimes, children with atopic dermatitis may develop allergic rhinitis and or asthma, this sequence of events being named as "Atopic March." Atopic march is less prevalent in the developing countries. Atopic dermatitis is precipitated by many triggers such as infections, aeroallergens, food allergens, environmental factors and emotional stress. Clinical presentation varies in infants, children and adults. There is no gold standard laboratory diagnosis for atopic dermatitis. The most important step in the management of atopic dermatitis is patient/parent/care giver education and counseling regarding the chronic nature of the disorder and about the precipitating factors. Emollients form the cornerstone of therapy of AD both during the active phase and maintenance phase. Topical corticosteroids continue to remain the mainstay of treatment followed by topical calcineurin inhibitors. Severe and refractory AD warrant the use of short course of systemic corticosteroids / cyclosporin.*

Keywords: *Atopic dermatitis, Emollients, Topical corticosteroids, Topical calcineurin inhibitors, Children*

Introduction

AD has a huge impact on the psychological status, quality of life of the child and the parents and financial position of the family. The term, "atopy" derived from the Greek word, atopia which means "different" or "out of place" was first used by Coca and Cooke in 1923.Wise and Sulzberger coined the term, 'atopic dermatitis' in 1933 to denote the association of cutaneous manifestations along with the other atopic disorders.[1] There is an increase in the prevalence of atopic dermatitis worldwide including India which has been attributed to the small family norms, lack of exposure to infectious organisms and increased urbanization and industrialization resulting in higher exposure to pollutants.[2,3] The incidence and severity of atopic dermatitis is lower in developing countries. International study of asthma and allergies in childhood done in 56 countries has found the prevalence to vary between 3% and 20.5 %. Same study done in 16 centres across India reported a prevalence of 2.4% to 6% except in Kottayam where 9% was observed.[3] Increased incidence of AD has been observed in children born to immigrant parents who have moved to developed countries in comparison to the native population and children in the country from which the parents emigrated.[2,4]

Etiopathogenesis

Atopic dermatitis results due to complex interplay between epidermal barrier dysfunction, immune dysregulation, defective innate immune system and exaggerated immunologic response to allergens and infectious organisms in genetically susceptible individuals with a strong influence of the environment. There is a strong family history in most of the children with atopic dermatitis, with the child being more susceptible, when the mother is atopic. Patients with AD have been found to have mutations in Filaggrin gene which contributes to barrier dysfunction.[5] Barrier dysfunction results in increased transepidermal water loss, enhanced absorption of allergens and increased inflammation. In healthy individuals, there exists a healthy balance between Th1 and Th2 type of T helper cells. Acute AD is associated with increased production of Th2 mediated cytokines namely IL-4,IL-5 and IL-13 which result in increased IgE and lowered interferon gamma levels.[6] Increased levels of IL-4 and IL-13 further reduce the ceramide level which affects the epidermal integrity in patients with AD.[7] Increased levels of IL-31, a novel Th2 cytokine has been found to correlate with the severity of AD. Elevated levels of cAMP phosphodiesterase activity has been observed which leads to increased production of prostaglandin (PGE2) and IL-10. This in turn, results in inhibition of Th1 function and increased IgE production. Chronic AD is characterized by increased production of granulocyte macrophage colony stimulating factor and Th1 cytokines namely IL-12 and IL-18.With regard to the

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climate, there is exacerbation of symptoms during winter.[2,3]At the same time, increased sweating during summer can also worsen the pruritus of AD which is a major symptom in these patients. Pruritus is said to be due to IL-31, stress induced neuropeptides, proteases, eicosanoids and eosinophil derived proteins.[6] There is a strong colonization of Staphylococcus aureus (S. aureus) in more than 90% of patients with AD. Staph aureus derived toxins contribute to the inflammation in AD.[1,4] With regard to the autoallergens, an Indian study by Dhar et al had observed that aeroallergens like house dust mite, pollens, Aspergillus fumigates and insects were common. In the same study, common food allergens found were egg white, fish, milk, brinjal, dhal, groundnut and banana.[2]

Clinical features

Clinical manifestations of atopic dermatitis vary according to the age of the patient. Hill and Sulzberger categorized AD into 3 clinical phases namely the infantile phase, childhood AD and the adult phase. AD is characterized by the presence of pruritus, which is chronic, relapsing in nature, with age - specific morphology and distribution of the lesions. Hanifin's clinical criteria for the atopic dermatitis complex (2001) is given in Box 1.

Infantile phase

In the infantile phase of AD which extends up to 2 years of age, lesions may start in the first few weeks of life. About 50% of patients of AD present with clinical manifestations by the first year of life. In the infants, early lesions begin as erythematous papules on the cheeks and scalp. Forehead, ears and neck may also be involved. Vesicles, oozing and crusting may be present.

Box 1. Hanifin's clinical criteria for the atopic dermatitis complex (2001)[1,4]

Essential features

1. Pruritus
2. Eczematous changes
   i. Typical and age -specific patterns - a) face, neck and extensor involvement in infants and children; b) current or prior flexural lesions, especially in older children and adolescents; c) sparing of groin and axillaeii.
   ii. Chronic or relapsing nature

These features must be present and if complete are sufficient for diagnosis

Important features (seen in most cases)

1. Early age of onset
2. Atopy (IgE reactivity)
3. Xerosis

These features seen in most cases add support to the diagnosis

Associated features (clinical associations) – too non-specific to define atopic dermatitis

1. Keratosis pilaris/ ichthyosis/palmar hyperlinearity
2. Atypical vascular responses
3. Ocular /periorbital changes
4. Perioral/periauricular lesions
5. Perifollicular changes

Exclusions

The diagnosis of atopic dermatitis depends upon the exclusion of conditions such as scabies, allergic contact dermatitis, seborrheic dermatitis, cutaneous lymphoma, ichthyoses, psoriasis and other primary disease entities.

Skin is rough and dry. Generalised xerosis is a halmarkof AD. Face and neck are involved in more than 90% of infants with AD. Generalised xerosis is a hallmark of AD. Infants with AD present with intense itching which is usually worse in the early evening and night. Infants will be irritable, roll over or rub themselves against the bedding and clothing of the parents. Scalp scales will be dry in contrast to the yellow greasy scales seen in seborrhoeic dermatitis which is common during the first 3 months of life. Persistent cradle cap beyond 3 months points towards atopic dermatitis. During infancy, groin and diaper area are typically spared in atopic dermatitis unlike seborrheic dermatitis. As the baby grows, lesions may extend to the trunk and extremities. Symmetric, ill-defined erythematous patches may present on the extensor aspect of the legs and arms and the gluteal regions during the crawling stage. Though involvement of the antecubital and popliteal fossa is commonly seen in older children and adolescents, it may be seen in infants and young children.[1,3,8]

Childhood phase

Childhood phase of AD follows the infantile phase and extends from 2 years of age to puberty. Involvement of the flexures is the characteristic feature of childhood phase of AD. Antecubital fossa, popliteal fossa, flexures of the wrists and ankles, hands, feet, creases of the buttock and thigh are the usual sites affected. Lesions are erythematous, ill-defined or circumscribed scaly patches which when associated with intense itching may become lichenified. Periorbital and perioral involvement is commonly seen in the childhood phase of AD. Lymphadenopathy may be present. Frictional lichenoid eruption characterized by multiple, skin colored, flat topped papules on the elbows and at times knees and the dorsa of hands. An “inverse pattern” of AD has been described in which the extensor aspects of the elbows/knees and dorsa of the hands and feet are affected in contrast to the classical flexural involvement. Shiny nails, nail pitting and dystrophic nails have been observed in these children.[1,4,8]

Associated clinical features

Various clinical features that may be associated are pityriasis alba, ichthyosis, palmar hyperlinearity, keratosis pilaris, chelitis, recurrent conjunctivitis, Dennie-Morgan infraorbital fold, anterior neck folds, facial pallor/erythema, white demographism and cutaneous infections (Staphylococcus aureus and herpes simplex). Eczema herpeticum may occur due to the dissemination of herpes simplex virus infection. There could be itching while sweating, intolerance to wool and lipid solvents and food intolerance. Elevated serum IgE levels is found in more than 80% of patients with atopic dermatitis. Course of AD is influenced by environmental and emotional factors. Growth retardation has been observed in children with severe atopic dermatitis. There is no laboratory gold standard for the diagnosis of atopic dermatitis.[1,2,4,9]

Differential diagnosis

Differential diagnosis of atopic dermatitis includes seborrheic dermatitis, scabies, irritant/allergic contact dermatitis, Langerhans cell histiocytosis and various immunodeficiency syndromes such as Wiskott-Aldrich disease, hyperimmunoglobulinemia E syndrome, agammaglobulinemia, Netherton syndrome and Omenn syndrome. Though it may be difficult to differentiate between seborrheic dermatitis (SD) and AD in infants, presence of greasy scales, predilection for intertriginous areas and rare presence of pruritus may point towards seborrheic dermatitis, while presence of xerosis, irritability and intense itching may suggest atopic dermatitis. Presence of pustules in the palms and soles and history of itching in other family members are characteristic features of scabies.[1,4]

Treatment

Atopic dermatitis being a chronic relapsing disorder with remissions and exacerbations, the first and foremost duty of an attending physician is to educate the parents/ care giver/ child (if old enough to understand) about the nature of atopic dermatitis, triggering factors, course, prognosis and most important of all the basic skin care. The main goals of treatment include the prevention of exacerbating factors, restoration of skin barrier function by constant use of emollients and control of inflammation and infection.

General measures

Atopic skin is highly vulnerable to irritants and infections. Hence, it becomes imperative to prevent all the triggering factors including stress to abate atopic flares. In children with AD, while winter causes worsening of xerosis and pruritus, sweating during summer induces itching. Hence appropriate clothing is very important. Cotton clothing is ideal while woolen clothes are best avoided. As exposure to aeroallergens worsens the dermatitis, measures such as wet mopping of floors, vacuum cleaning and avoidance of aerosols/ cigarettes/pet animals are to be encouraged. In children who are hypersensitive to food, eggs, peanuts, soy, wheat, fish and those with coloring agents and preservatives are to be avoided.[10]

Cleansing in AD

Dry skin associated with intense itching is the most important problem faced by children with AD. Therefore it becomes important to provide proper advice to the parents/children with AD with regard to bathing and use of cleansers in day to day life. Lengthy/ frequent baths result in the removal of cutaneous lipids, worsening the dermatitis. Daily bath of 10 minutes (5-15 minutes) duration in cold water or lukewarm water depending on the season is preferable, as it helps in the rehydration of the stratum corneum. Use of hot water is to be strictly avoided. As soaps with alkaline pH tend to cause loss of lipids from the stratum corneum resulting in dryness of skin, they are best avoided in children with AD who already have a dry, vulnerable skin. Synthetic detergents are ideal for these children as they do not cause dryness of skin. In case of cost constraint, minimal use of mild soaps especially for the flexures and feet may be advocated.[1,10,11]

Emollients

Emollients form the mainstay of treatment of atopic dermatitis. For best results, emollients are to be applied within 3 minutes after a quick bath in lukewarm water and soft pad drying. Frequency of application should be two to three times a day or more depending on the degree of dryness. An emolient is to be applied 15 minutes before the application of a topical corticosteroid or topical immune modulator cream. Various factors such as the extent of dryness, degree of inflammation, climate and the site of involvement have an impact on the use of emollients. While greasy ointments are preferred in dry skin, emollient creams are most suitable for inflamed skin. Preservatives and fragrances used in emollients may cause irritation. Adequate quantity of the emollient has to be applied all over the body. Emollient creams containing urea, lactic acid and salicylic acid are best avoided on inflamed skin. Emollients containing ceramides, lipids and N-palmitoyl ethanolamine have been studied to possess anti-inflammatory action. Studies have shown that topical preparations containing natural colloidal oatmeal help to restore the epidermal barrier and to reduce the use of topical corticosteroids and topical calcineurins.[1,4,12,13,14]

Topical corticosteroids[1,4,10]

Topical corticosteroids (TCS) are a big boon in the treatment of AD. TCS should be chosen based on the age of the child, site and extent of involvement, degree of severity, potency and formulation. Saline compresses/wet wraps with saline are beneficial in crusted lesions with oozing. Steroid phobia is a major concern which an attending physician has to confront with, while prescribing topical or systemic steroids. Hence parents /care givers have to be properly educated about the quantity, frequency and duration of application of topical steroids. Finger tip unit (FTU) measurement is used to calculate the requirement of steroids for the various sites. One finger- tip unit is defined as the amount of cream/ointment expressed from a tube with a nozzle 5 mm in diameter, applied from the distal skin crease to the tip of the index finger. FTU weighs approximately 0.5 gm. The mean number of finger- tip units required to treat various anatomical regions is presented in Table I. Steroid ointments are more potent than creams. Desonide, hydrocortisone and fluticasone preparations have been safely used in infants who are 3 months of age and above. Mid potent steroid, mometasone furaote is to be used in children above 2 years of age, once daily. Mild atopic dermatitis may be treated with low potent steroids and emollients. Children with moderate to severe atopic dermatitis may be treated with emollients, mid potent steroids and topical calcineurin inhibitors. Severe atopic dermatitis, may in addition warrant systemic therapy, which shall be discussed later. Daily regimen of topical steroids may be followed for a period of 2 - 4 weeks until control of acute inflammation and thereafter maintenance regimen of twice weekly application may be practiced. Tapering of steroids should be initiated only after disappearance of itching, because itch is the main symptom to assess the clinical response to treatment.[13] Studies have shown that after control of acute symptoms is achieved, twice weekly application of fluticasone on 2 consecutive days, on healed sites and new lesions helps to sustain the improvement and delays the relapse. Fluticasone application on uninvolved skin twice weekly has helped to prevent further flares.[15] In 2007, National institute for health and care excellence gave guidelines for holistic assessment of children with atopic eczema as in Table II.

Table I. Finger tip units for various anatomical sites (1 FTU= 0.5g)

Anatomic Area	3-6 mths	1-2 yrs	3-5 yrs	6-10 yrs
Face and Neck	1	1.5	1.5	2
Arm and Hand	1	1.5	2	2.5
Leg and Foot	1.5	2	3	4.5
Anterior Trunk	1	2	3	3.5
Posterior Trunk	1.5	3	3.5	5

Table II. Holistic assessment[16]

Skin/physical severity		Impact on quality of life andpsychosocial wellbeing	
Clear	Normal skin, no evidence of active atopic eczema	None	No impact on quality of life
Mild	Areas of dry skin, infrequent itching (with or and without small areas of redness)	Mild	Little impact on everyday activities, sleep psychosocial wellbeing
Moderate	Areas of dry skin, frequent itching, redness (with or without excoriation and localised skin thickening)	Moderate	Moderate impact oneveryday activities and psychosocial wellbeing, frequently disturbed sleep
Severe	Widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking and alteration of pigmentation)	Severe	Severe limitation of everyday activities and psychosocial functioning, loss of night sleep

Do's and dont's - Topical steroids

1. Super potent steroids like clobetasol/ halobetasol propionate should not be used in children below 12 years of age.
2. Only low potent steroids (1-2.5% hydrocortisone acetate, desonide) are to be used on the face and intertriginous areas.
3. Treatment may be started with a mid potent steroid once a day for a period of 2 weeks and then changed to low potent steroids.
4. Mid potent steroid is to be used on a short-term basis, followed by intermittent long-term treatment.
5. Patients who require continuous topical treatment should be instructed to use the least potent agent that allows for disease control.
6. Overzealous application to large body surface area may result in systemic absorption and adverse effects.

Topical Calcineurin inhibitors(TCI)[12]

Tacrolimus and pimecrolimus are topical non - steroidal immunomodulators that are very useful in the long term treatment of children with AD.They have an advantage over TCS in that they can be used over the eye lids, perioral region, genital area and flexures. In addition, TCI are devoid of steroid induced side effects. TCI have been considered as second line therapy for short term and intermittent therapy of AD where steroids are contraindicated. Tacrolimus 0.03% ointment has been approved for the treatment of moderate to severe atopic dermatitis in children aged 2 years and older. Pimecrolimus 1% has been considered effective in the treatment of mild to moderate atopic dermatitis in children above 2 years. Tacrolimus 0.03% has been found to be safe and effective in the treatment of recurrent facial involvement in infants with AD. Tacrolimus ointment may be used as prophylactic treatment for AD. Thomas Lugger et al after extensive evaluation over 8 years period have concluded that pimecrolimus cream and tacrolimus ointment are safe and effective in the treatment of infants at least 3 months of age with AD.[17]

Systemic therapy

Anti microbial therapy

Children with AD are prone to develop secondary infection with various microbial organisms, namely staphylococcus (most common), streptococcus, herpes simplex, molluscum contagiosum, human papilloma virus etc. Parents/care givers should be educated to recognize the symptoms and signs of bacterial/viral infections, as these may impede the clinical response to topical TCS/ TCI. In fact, a secondary bacterial or viral infection should be excluded, if there is no response to mild or moderately potent steroid applied over a period of 7-14 days. Topical steroid-antibiotic combination may be useful in localised infected AD. Flucloxacillin has been considered as the first-line therapy for pediatric AD by the 2007 NICE guidelines. Systemic antibiotics like cephalexin and erythromycin have been found to be effective. However, one should keep in mind the local pattern of clinical resistance.Herpes simplex infections may be treated with acyclovir.[12,16]

Antihistamine therapy

Oral antihistamines should not be used routinely in the management of atopic dermatitis as there is no evidence to support the regular use of both first and second generation anti histamines. In children less than 2 years age with sleep disturbance, sedating anti histamine may be useful. Studies have shown that cetrizine has displayed steroid sparing effect evidenced by a reduction in the duration of treatment with moderate to potent steroids. Antihistamines may be useful in children with AD who also have associated allergic rhinitis and bronchial asthma. Guidelines state that antihistamines may be used in children with sleep disturbance on a short term basis.[12,13,16]

Systemic immunosuppressive therapy

Systemic therapy is the treatment option in children with severe and refractory atopic dermatitis.

Oral glucocorticosteroids may be used on a short term basis for a period of 1 week. Cyclosporin is used as the main crisis buster as it produces a quick clinical response compared to other drugs like methotrexate and azathioprine which take at least 3 weeks to be effective.[18,19]

Course and prognosis

Atopic dermatitis occurs in about of 45% of children during the first 6 months and in 60% during the first year of life. Almost 85% of children have their onset before 5 years of life. Twenty percent of children with onset before 2 years tend to have persistent symptoms.[15] AD tends to resolve in 43% of children before 3 years and 70% by puberty.[1]Indian studies have shown that when the onset is in infancy, there is a gradual reduction in the severity over the next 10–12 years and, by 12-15 years, there is complete resolution. Some of these children may present with hand eczema during adulthood. Early onset, severity and concomitant family history of asthma/hay fever are points for poor prognosis.[20] Evidence based guidelines have recommended the continued use of either topical corticosteroids (1-2 times/week) or topical calcineurin inhibitors (2-3 times/week) after disease stabilization to previously involved skin in order to prevent further flares or relapses.[21] In a randomized controlled trial done in the United States and United Kingdom in 124 neonates at high risk for atopic dermatitis, it was concluded that emollient therapy from birth would be a safe and effective measure towards primary prevention of atopic dermatitis.[22]

Conclusion

Atopic dermatitis is on the rise worldwide, including India. However, it is not so severe in the developing countries compared to the western world. Regular use of emollients plays a very important role during both the active phase and maintenance phase. Topical corticosteroids continue to be the mainstay in the treatment of AD. Topical calcineurin inhibitors are effective in the maintenance phase and in prevention of relapse. Severe and recalcitrant AD may be treated with short course of oral corticosteroids or cyclosporine.Considering the fact that atopic dermatitis is a chronic relapsing, highly morbid disorder that affects the physical, psychological and social wellbeing of not only the child, but also of the parents, it is highly important that the attending physician, be it a pediatrician or dermatologist, offers counseling and treatment with empathy.

Points to Remember

- ***Atopic dermatitis (AD) is a chronic, inherited, relapsing, inflammatory, itchy skin disorder seen in infants and children, often in association with a family or personal history of atopic dermatitis.***
- ***Though there is increased incidence of atopic dermatitis worldwide, the severity is less in the developing countries.***
- ***AD is characterized by age specific clinical morphology in infants, children and adults.***
- ***Epidermal barrier dysfunction, xerosis and persistent pruritus are the major issues in AD.***
- ***There is no gold standard laboratory test for the diagnosis of atopic dermatitis.***
- ***Education/ counseling regarding the basic skin care, triggers and course of AD is the first and foremost step in treatment.***
- ***The main goals of treatment include the prevention of exacerbating factors, restoration of skin barrier function by constant use of emollients and control of inflammation and infection.***
- ***Topical corticosteroids form the cornerstone in the treatment of AD. Topical calcineurin inhibitors do not produce steroid induced side effects and are hence most useful in treatment of lesions over face, genitals and for long term therapy.***
- ***Mild atopic dermatitis may be treated with emollients and low potent steroids.***
- ***Children with moderate to severe atopic dermatitis may be treated with emollients, mid potent steroids and topical calcineurin inhibitors. Severe atopic***

dermatitis, may in addition warrant systemic therapy with oral corticosteroids/cyclosporine.

- ***Secondary bacterial and viral infections have to be treated appropriately.***

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RADIOLOGY

EPIPHYSEAL DYSPLASIAS

** Vijayalakshmi G*
***Natarajan B*
***Jeya Rajiah*
***Ganga Devi R*

The growing long bone of a child, unlike that of the adult, has five parts - epiphysis, metaphysis and diaphysis with the growth plate and provisional zone of calcification. In this and the following issues we will see some dysplasias that involve these specific sites in a prominent way.

The striking feature in epiphyseal dysplasias is poorly formed or dysplastic epiphyses. The epiphyses appear late, are small and irregular. The autosomal recessively inherited condition is the rhizomelic type where there is proximal shortening. Both femurs and humerii show bilateral, symmetric shortening. The epiphyses are spotty giving the name "stippled epiphyses" (Fig.1). The D-L spine shows coronal clefts in the vertebrae (Fig.2). Children with this dysplasia present early with cataracts, skin lesions, joint contractures, delayed development and die in infancy. The Conradi Hunermann type is the x-linked dominant variety and is marked by asymmetric shortening (one side more than the other). Stippling resolves in infancy and the epiphyses may develop normally. This type is associated with a normal life span.

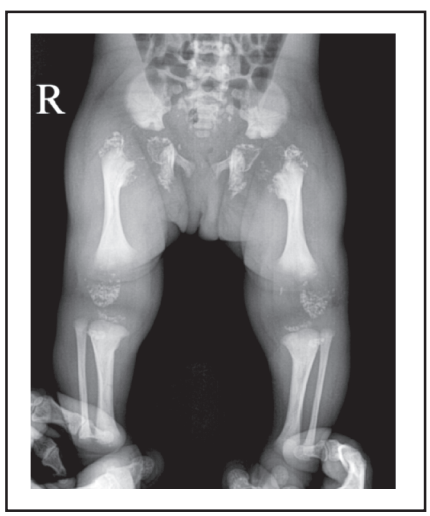

Fig.1. Stippled epiphyses

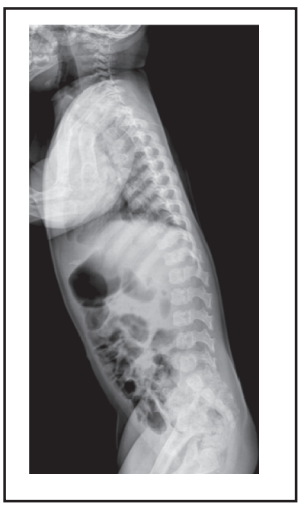

Fig.2.Coronal clefts in body of vertebrae in epiphyseal dysplasia

The spondylo-epiphyseal dysplasias are seen quite commonly and are grouped under Type 2 collagenopathies. Type 2 collagen is not only essential for growth of the epiphyseal plate but also for hyaline cartilage, nucleus pulposus and the vitreous of the eye. In this group of conditions, small and irregular epiphyses are associated with platyspondyly. The inheritance is autosomal dominant. (Fig.3) shows poorly developed upper femoral epiphyses. Long bones are shortened. The spine (Fig.4) shows oval vertebral bodies that will later become flattened. The tarda variety is an X-linked disorder presenting in the

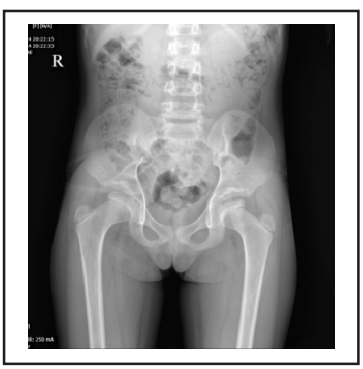

Fig.3. Spondyloepiphyseal dysplasia - Small femoral epiphyses

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Chennai.

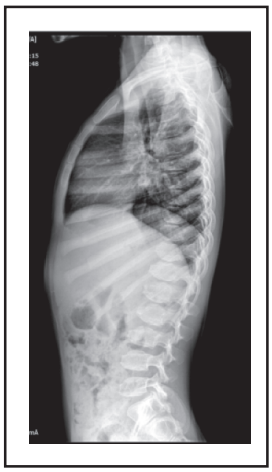


Fig.4. Spondyloepihyseal dysplasia - Oval vertebral bodies

young adult with short stature. The features are the same but of milder severity and the hands and feet are spared.

"Kniest dysplasia" is a rare type of epiphyseal dysplasia. The x-ray of the pelvis (Fig.5) shows dysplastic upper femoral epiphyses just like the spondyloepiphyseal dysplasias but there is marked widening of the metaphyses likened to dumb bells. Coronal clefts are seen in the vertebrae. These children have cleft palate, deafness, myopia and progressive kyphoscoliosis- all part of type 2 collagenopathy.

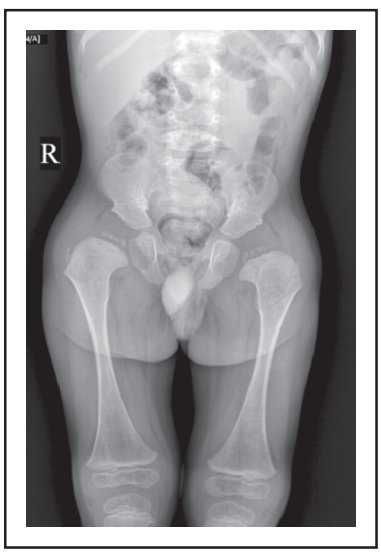


Fig.5. Kniest dysplasia - Dysplastic epiphyses and dumb-bell metaphyses.

Another interesting spondyloepiphyseal dysplasia showing metaphyseal changes in addition to epiphyseal changes is Dyggve-Melchior-Clausen syndrome. The iliac crest in this condition has a peculiar lacy pattern (Fig.6) that is not seen in any other dysplasia. The upper femoral epiphyses as you can see are only a speck. All long bones

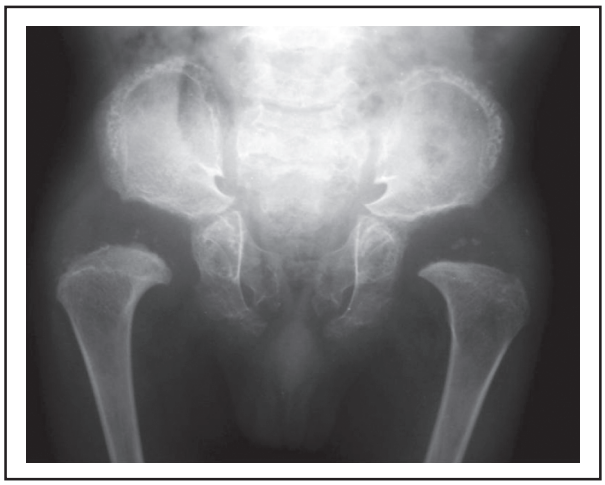


Fig.6. Dyggve Melchior Clausen syndrome-lacy iliac crests

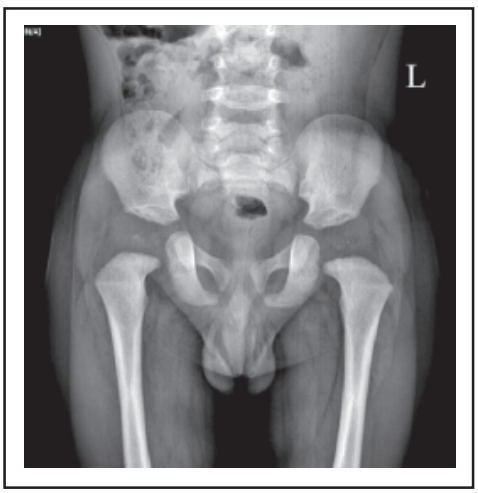
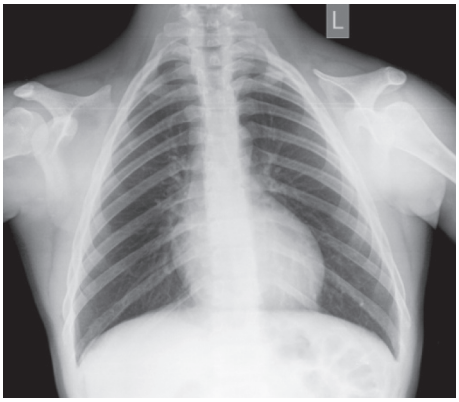


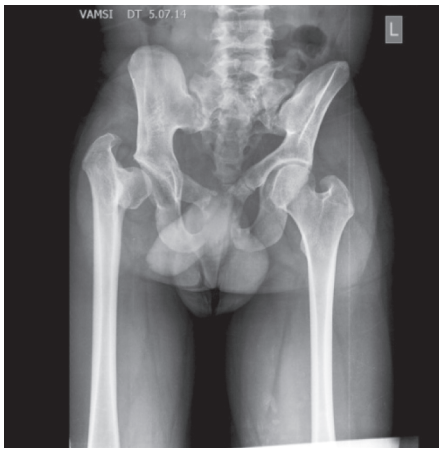
Fig.7. Hypothyroidism

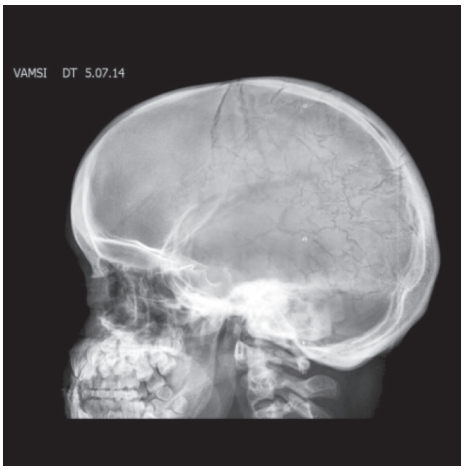
are shortened. There is microcephaly and severe psychomotor retardation. Clinically they can appear like Hurler's syndrome but are radiologically very different. There is no tapering of the lower ilium and no proximally pointed metacarpals that are seen in the mucopoly-saccharidoses.

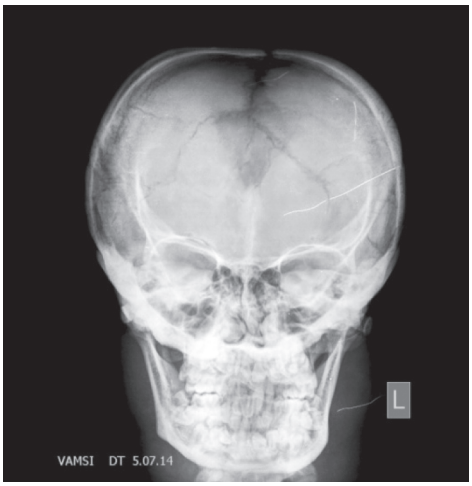
Finally, a word of caution when one encounters the small for age and dysplastic or fragmented epiphyses. Fig.7 is the pelvis xray of a 5 year old child who presented with short stature and mental retardation. The pelvis radiograph shows tiny femoral epiphyses with fragmentation. The pelvic bones are otherwise normal. The metaphyses are normal. This is a case of hypothyroidism - a treatable condition not to be written off as a dysplasia. The vertebrae may be normal or show mild inferior beaking in the dorso-lumbar region due to strain on the spine because of hypotonia, again not to be mistaken for Hurler's syndrome.

PICTURE QUIZ









A 8 year old boy presented with abnormal facies. Radiographs of chest, pelvis and skull are given. Spot the diagnosis.

Compiled by : Dr.P.Venkateswarlu, MD (Pediatrics), Dy. CMO, Golden Jubilee Hospital, Visakhapatnam.

Answer on Page: 256

CASE REPORT

ANTI-N-METHYL D-ASPARTATE RECEPTOR ENCEPHALITIS IN AN ADOLESCENT GIRL WITH OVARIAN TERATOMA

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*Sumant Prabhudesai
*Viswanathan V
**Ramachandran B

Abstract: *Anti N-methyl-D-aspartate (NMDA)-receptor antibody associated encephalitis is a rare form of encephalitis that has a favourable chance of complete recovery. We report the case of an adolescent girl who presented with febrile encephalopathy, orofacial dyskinesia and abnormal behaviour. She was found to have an ovarian teratoma and tested positive for anti-NMDA receptor antibodies in cerebrospinal fluid. She underwent an oophorectomy and received a course of steroids after which she made a complete neurological recovery.*

Keywords: *Autoimmune encephalitis, Orofacial dyskinesia, Anti-N-methyl-D-aspartate, Ovarian teratoma*

Anti-N-methyl-D-aspartate-receptor (anti-NMDAR) encephalitis is a life-threatening form of autoimmune encephalitis (AE) with excellent chances of complete neurological recovery. Though reportedly rare, about 40% patients are below 18 years of age.[1] We report an adolescent girl with an ovarian tumour and anti-NMDAR encephalitis.

Case report

A 17-year-old girl presented with a 10-day history of fever, abnormal behaviour and orofacial dyskinesia. She had aggressive behaviour, irrelevant speech, sialorrhea, chewing movements and tongue-bite and saluted repeatedly. Her blood counts, liver and renal function tests, cerebrospinal fluid (CSF) analysis and MRI brain were normal. She was referred to our hospital as she became drowsy. At admission, she had profound encephalopathy and persistent orofacial dyskinesia. After an emergency intubation, ceftriaxone, acyclovir and azithromycin were started suspecting meningoencephalitis. Electro-encephalography (EEG) showed seizures which were treated with fosphenytoin, levetiracetam and midazolam infusion. Repeat CSF analysis was normal. From this clinical and CSF picture, autoimmune encephalitis (AE) was suspected. CSF was tested for anti-NMDAR antibodies which were positive (titre 1:10); CSF was negative for anti-Voltage Gated Potassium Channel (VGKC) antibodies, herpes simplex virus-PCR and enterovirus-PCR. Abdominal ultrasonography showed a left ovarian cyst. CT abdomen showed a cyst arising from the left ovary with solid components and calcification suggestive of a dermoid cyst. Tests for Wilson disease (serum ceruloplasmin and 24 hour urinary copper excretion) and acute intermittent

Fig.1. Gross specimen of the resected ovarian mass

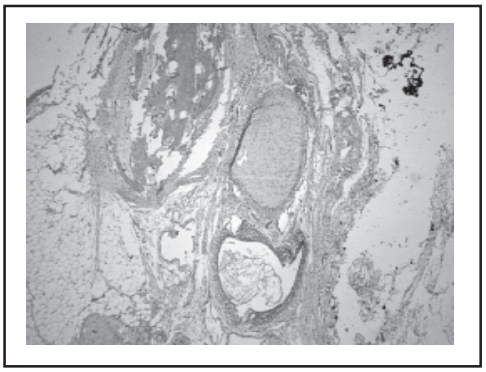

Fig.2. Histopathology of the ovarian mass suggestive of mature teratoma

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porphyria (urinary porphobilinogen) were negative. Laparoscopic left oophorectomy was performed (Fig.1). Intravenous methylprednisolone was given for 5 days. Ten days later, her fever and dyskinesia subsided and sensorium showed improvement. Transient hypertension was noted that responded to nifedipine. After 28 days of ventilation she was extubated. Her sensorium was normal. She was discharged from hospital with no residual neurological deficits. Histopathology of the excised cyst showed a mature teratoma (Fig.2).

Discussion

Paraneoplastic encephalitis associated with ovarian teratomas has been related to the development of antibodies to the NR1/NR2B heteromers of the NMDA receptor.[2] Underlying ovarian teratomas are observed in 56% of females above 18 years but only 9% of girls below 14 years with AE.[3] Clinical manifestations include a nonspecific febrile prodrome; a psychotic phase with emotional and behavioural disturbances, amnesia and cognitive decline; an unresponsive phase with catalepsy-like symptoms and athetoid dystonic posturing; a hyperkinetic phase with orofacial, limb and orolingual dyskinesia; and a recovery phase with slow complete recovery.[4] Autonomic dysfunctions including hypoventilation, urinary incontinence, tachycardia, hypertension and hyperthermia are uncommon in children.[3] The differential diagnoses of anti-NMDAR encephalitis in children are viral encephalitis, new-onset psychosis, limbic encephalitis and reaction to some drugs.[5]

The presence of anti-NMDAR antibodies in CSF or serum confirms the diagnosis. Moderate pleocytosis and mildly increased proteins are common and some patients may have CSF-specific oligoclonal bands. Few have a normal CSF at presentation. EEG usually shows non-specific slow and disorganized activity.[6] This helps to differentiate encephalitis from a psychiatric disorder in children who present primarily with psychiatric manifestations. About 50% patients may have a normal MRI brain while others may have hyperintensities in the hippocampus, cerebellum, cerebral cortex, basal ganglia and brain stem on T2 and FLAIR sequences.[2,5] Brain biopsy findings are often normal or non-specific.[6,7] No standard treatment has been established. Tumour resection and immunotherapy including corticosteroids with intravenous immunoglobulin or plasmapheresis, cyclophosphamide and rituximab have been described. Outcomes are better when a tumour is identified and removed compared to children in whom no tumour is identified[1]. About 80% of patients have substantial or full recovery.[2]

Anti-NMDAR encephalitis, a strong possibility when children present with encephalopathy, behavioural changes and orofacial dyskinesia, has an excellent prognosis. Evaluation including a pelvic ultrasonography should be considered with a high index of suspicion for an ovarian tumour.

Points to Remember

- ***Anti-NMDA receptor encephalitis is rare but life-threatening***
- ***Encephalopathy, orofacial dyskinesia and the presence of a tumour are strong pointers towards this diagnosis***
- ***Diagnosis is confirmed by demonstrating antibodies in CSF***
- ***Immunotherapy and resection of an identified tumour are mainstay of therapy***
- ***Complete neurological recovery is possible with therapy***

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CASE REPORT

NEONATAL ORGANOPHOSPHORUS COMPOUND POISONING - A CASE REPORT

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Abstract: *Organophosphorus compound (OPC) poisoning in neonates with its characteristic presentation of apnea, copious oral secretions, diarrhea, lethargy and seizures often mimic sepsis and requires a high index of suspicion and skillful history taking for diagnosis. This is a report of a neonate with OPC poisoning admitted in the neonatal intensive care unit of our hospital who survived the misfortune.*

Keywords: *Organophosphorus poisoning, Neonate, Cholinergic syndrome.*

A 46 hrs old female neonate of 2.250kg delivered by full-term normal delivery (FTND) in a district headquarters hospital, developed sudden onset of respiratory distress and excessive frothing, following cow's milk feeding. The antenatal and intra partum periods were uneventful and the neonate was apparently well with the mother until the feed.

The neonate was resuscitated with oral suctioning and bag mask ventilation with oxygen.

Systemic examination revealed normal air entry in the lungs with bilateral crackles, pin-point pupils and generalized hypotonia. Baby developed convulsions and respiratory failure; was intubated and ventilated. Baby was given 4.5 mL of 10% dextrose, calcium gluconate and IV phenobarbitone to control seizures. As the pesticide smell was noted from the caregiver, possible OPC poisoning was suspected. Gastric contents were collected by stomach wash. The baby was referred to our hospital after administration of Inj. Atropine (0.03 mg/kg) and empirical antibiotics at the referring hospital.

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On admission at our hospital, the baby was on mechanical ventilation with no spontaneous respiration. Baby was normothermic with features of shock [weak pulses, tachycardia (HR170/min), prolonged capillary refill time] and SpO_2 was 96%. Skin was not sweaty. Systemic examination showed pin-point pupils and generalized hypotonia. Baby was treated with normal saline (NS) bolus and mechanical ventilation was continued. History revealed that the baby was fed with cow's milk using utensils brought from home. The father was an agricultural labourer and there was stock of pesticide at home. Suspecting that the feeding utensils may have been contaminated with pesticides skin and gastrointestinal (GI) decontamination was done. The stomach contents were aspirated and gastric lavage was done with normal saline. Skin was decontaminated with saline soaks in view of the OPC smell. Inj. atropine (0.05mg/kg / IV) Q 30 min initially and later every 2 to 4 hours till atropinisation (given for three days) and pralidoxime 25mg/kg IVstat over 30 min, then Q10 hourly (given for two days) were administered following which the baby's activity improved. The blood sugar and the serum calcium values were within normal limits. During the course of hospitalization, baby had altered gastric aspirate, lethargy and abdominal distension with chest radiograph suggestive of pneumonia, for which antibiotics were stepped up. Fresh frozen plasma was transfused twice. The screening tests for sepsis were normal and blood culture showed no growth. Chemical analysis of stomach contents showed OPC compound - "Quinal phos". Pseudo cholinesterase levels could not be done due to lack of facilities.

The baby was gradually weaned to room air over a period of 7 days. Enteral feeds were started, initially as tube feeds, then as paladai feeds and put on direct breast feeds from 15th day of life. The baby was discharged on 27th day of life and parents were counseled about the risks of OPC poisoning.

Discussion

OPC poisoning is extremely rare in neonates. The common route of poisoning being transplacental, and the others being ingestion (accidental/homicidal), transdermal, inhalational[1,2,3] or contamination of medicines

(herbal/native) with OPC.[4,5] Organophosphate compounds are cholinesterase inhibitors which bind with acetylcholinesterase and pseudocholinesterase enzymes and result in their inactivation. This binding is initially reversible but can become irreversible by the process called ageing, leading to accumulation of the neurotransmitter acetylcholine which results in the classical toxidrome comprising of muscarinic and nicotinic effects.

The onset and severity of symptoms depend on the specific compound, the route of exposure, dose and individual's ability to degrade the compound which in turn depends upon the level of the enzyme paraoxonase (PON1). Neonates have less PON1 activity resulting in severe poisoning.[5] Unlike adults the classical symptoms of organophosphate poisoning does not occur in children. Infants mainly present with acute CNS depression and typical effects such as fasciculation and bradycardia are absent.[6,7]

Diagnosis is based on history of exposure and characteristic features of cholinergic overdose confirmed by a reduction in serum and RBC cholinesterase levels. A 40% decrease in cholinesterase level from baseline produces symptoms and 80% fall results in severe symptoms. Laboratory values of serum cholinesterase levels of 50% or less than normal is consistent with the diagnosis of organophosphate poisoning,[8] though not in correlation to severity of poisoning. However, the trends in enzyme levels indicate the response to treatment.[9] Mother's serum or breast milk cholinesterase levels aid in confirmation of transplacental poisoning.[8] Moderate to severe hyperglycemia has been reported in patients with organophosphate poisoning, which is believed to be due to secondary release of catecholamines from the adrenal medulla and may require insulin. The relative risk of death has been reported to be increased when the blood glucose level is over 150 mg/dL on admission.[10]

Early recognition is paramount in preventing fatality. Decontamination is the essential step in the management. Specific antidote for OPC poisoning consists of intravenous atropine and oximes. Atropine which does not bind to the nicotinic receptors may not be very useful in reversing the neuromuscular toxicity[3]. Presence of tachycardia is not a contraindication to atropine and combination with an oxime may reduce atropine toxicity. Oxime is more useful early in the presentation (36-48 hours) and is recommended when the plasma pseudocholinesterase level is 25% below normal.[10] Certain drugs such as phenothiazines, antihistamines, CNS depressants, barbiturates, xanthenes (theophylline), succinylcholine, aminoglycosides and parasympathomimetic agents are best avoided, as their combination with OPC can increase toxicity. CNS symptoms, hypotension and need for ventilation are poor prognostic indicators in neonates. Death in OPC poisoning often results from respiratory complications[11], with an overall mortality of about 6.4%.[12]

Conclusion

In this neonate OPC poisoning was suspected based on the smell noted from the caregiver. Feeding utensils should be washed thoroughly prior to use. An awareness about hazards of exposure to pesticides must be created among agriculturists with emphasis on prevention of poisoning.

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NEWS AND NOTES

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PICTURE QUIZ ANSWER

Cleidocranial dysostosis (Characterised by drooping shoulders, approximation of shoulder joints over the chest, mild short stature, brachycephaly, delayed closure of anterior fontanelle, dental abnormality, scoliosis and normal IQ. Radiographs reveal delayed closure of sutures with wormian bones, absent clavicle, narrow pelvis and abnormal femoral head with short neck.]