Executive Summary
The Association of Physicians of India Evidence-Based Clinical Practice Guidelines on Adult Immunization

Expert Group of the Association of Physicians of India on Adult Immunization in India

Introduction

Considerable controversy exists regarding adult immunization especially in developing countries, such as India. Even among the published guidelines from international organizations, like the World Health Organization (WHO) and other professional associations from the developed countries, there is a lack of consensus regarding the optimal strategy for adult immunization. Moreover, these guidelines do not address the issue of adult immunization in developing countries like India.[1-6] On the other hand, pediatric immunization programs have been one of the most successful public health interventions in India also.

Therefore, the Association of Physicians of India (API) decided to fill this void regarding technical guidance for adult immunization strategies in India. To address the issue, an Expert Group Meeting for evolving Consensus Recommendations on Adult Immunization in India was jointly organized by the Association of Physicians of India and the Department of Medicine, All India Institute of Medical Sciences (AIIMS), New Delhi, at the AIIMS on December 6-7, 2008.

Epidemiology, Vaccine Efficacy and Safety

The Expert Group observed that reliable epidemiological data regarding the burden of infectious diseases (also true for non-infectious diseases) from India were lacking. The Expert Group felt that sparse published data are available from India regarding the efficacy and safety of various adult immunization strategies. Furthermore, the issue of paucity of data regarding objective monitoring of the adequacy of immunization (e.g., optimal antibody titre) against various infectious diseases was also discussed.

The Expert Group, therefore, felt that there is an urgent need for collecting and periodically updating reliable epidemiological data; generating efficacy and safety data regarding various adult immunization strategies; and documenting the adequacy of immunization from India. The Expert Group was of the opinion that these recommendations should be periodically reviewed, updated, refined and reissued as and when new data become available.

The Expert Group proposes that the Consensus Guidelines should be reviewed every 3 years to incorporate modifications of any emerging research from our country. It was sincerely hoped by the Expert Group that health care professionals should sensitize themselves regarding operational research as a part of their professional duty so that more indigenous evidence-based interventions can be generated for the benefit of our population. However, the Expert Group fully appreciates the limitations faced by the health care professionals working in resource constrained settings in India.

The current consensus guidelines of the Expert Group are an amalgamation of the available data from our country as well as other countries extrapolated to Indian conditions, keeping in view the cost-effectiveness of immunization in adults in a vast country like India with limited resources.

Depending on the available published data, the different levels of evidence and recommendations cited in these adult immunization guidelines have been given a grading as shown in Table 1. This document can serve as a template to guide national

Table 1 : Different levels of evidence

Grading of evidence	
Ia:	systematic review or meta-analysis of randomized controlled trials
Ib:	at least one randomized controlled trial
IIa:	at least one well-designed controlled study without randomization
IIb:	at least one well-designed quasi-experimental study, such as a cohort study
III:	well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies, and case series
IV:	expert committee reports, opinions, and/or clinical experience of respected authorities
Grading of recommendations	
A:	based on hierarchy I evidence
B:	based on hierarchy II evidence or extrapolated from hierarchy I evidence
C:	based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
D:	directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence

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policy managers regarding adult immunization strategies to be adopted in our country.

The recommendations for adult immunization formed during this meeting are detailed below in alphabetical order. However, it needs to be appreciated that each vaccine has its own specific considerations which may need to be addressed individually by the clinician.

Cholera

Vaccines

Vaccines for cholera are available as [i] injectable killed whole cell vaccine; and [ii] oral cholera vaccine.[7-11] The injectable killed whole cell vaccine has been found to have a poor efficacy (45%) and the protection lasts for a duration of only 3 months (Level Ib). Two doses of the vaccine are administered one week to one month apart. Adverse events include pain, redness and swelling at injection site. The WHO does not recommend the use of the old parenteral vaccine because of its limited protective efficacy and lack of suitability for public health purposes (Level Ib).

Among the oral cholera vaccines, Dukoral (WC/rBS) consists of 1 mg of recombinant cholera toxin B subunit plus 2.5 x 10^{10} of the following V. cholerae O1 organisms: formalin-killed El Tor Inaba (Phil 6973); heat-killed classical Inaba (Cairo 48); heat-killed classical Ogawa (Cairo 50); and formalin-killed classical Ogawa (Cairo 50). It is approved for use in persons aged over two years. Dukoral (WC/rBS) is administered in 3 separate doses, 1 to 6 weeks apart for 2 to 6 year old children and as 2 separate doses, 1 to 6 weeks apart for those aged over 6 years. It confers 85% - 90% protection for 6 months among all age groups (Level II). The protection declines rapidly after 6 months in young children but remains at about 60% after 2 years in older children and adults.

A variant of the WC/rBS oral cholera vaccine that does not contain the cholera toxin recombinant B-subunit is also available as Vabiotech vaccine. It consists of (i) 600 EU LPS formalin-Killed El Tor Inaba (Phil 6973); (ii) 300 EU LPS of the following V. cholerae O1 organisms: heat-killed classical Inaba (Cairo 48), heat-killed classical (Cairo 50), and formalin-killed classical Ogawa (Cairo 50); and (iii) 600 EU LPS of V. cholerae O139 (4260B). It is administered in 2 separate doses given 1 week apart. This vaccine is not approved by the WHO. It is licensed for use only in Vietnam and has been shown to have 66% efficacy at 8 months among all age groups. The only licensed single-dose live attenuated OCV CVD 103-HgR (Orochol) is no longer available in the market.

Recommendations

The two currently available oral cholera vaccines are not recommended for routine adult immunization (Grade C). Dukoral vaccine is associated with the problems of high cost and waning efficacy (Level II); Till date insufficient data are available regarding Vabiotech vaccine. Oral cholera vaccines are not recommended for outbreak control (Grade C) or for prevention of outbreak during emergencies (Grade C).

These recommendations may be modified in the future following the availability of results of an ongoing community-based randomized controlled trial (RCT) of the Vabiotech vaccine involving approximately 70,000 adults and children in Kolkata.[12] Clinicians should remember that basic measures of provision of safe water, sanitation, improved food hygiene and health education are key factors essential for the control of cholera.

Diphtheria, Tetanus, Pertussis

Vaccines

Since 2005, two new tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines (Tdap) are available for use in those who are more than 10 years of age. These include [i] Adacel® that contains tetanus toxoid, diphtheria toxoid, and five pertussis antigens; [ii] Boostrix® that contains tetanus toxoid, diphtheria toxoid, and three pertussis antigens. These vaccines are administered as 0.5 ml intramuscular injection in the deltoid. Efficacy of Tdap vaccine was shown to be 92% in a recent RCT (Grade Ib).[13-17]

Recommendations

The Expert Group recommends routine Tdap vaccination for all adults not immunized earlier. For adults in the age group of 18 to 64 years who have completed their childhood vaccination schedule, a booster dose of Td vaccine is indicated once every 10 years till the age of 65 years; one dose of Tdap vaccine may be administered in place of Td vaccine.

For adults aged over 18 years who have not received prior vaccination against diphtheria, pertussis and tetanus, three doses of Td vaccine are indicated; two doses are administered at least 4 weeks apart and the third dose is given 6 to 12 months after the second dose. The Tdap vaccine can substitute any one of the Td doses.

For adults who have not received Tdap vaccine and are likely to come in contact with infants suffering from diphtheria or pertussis, a single dose of Tdap vaccine (2 weeks before the contact with the infant) is indicated if 2 years or more have elapsed since the last dose of Td vaccination.

Health care personnel, especially those in direct contact with the patients, who have not received Tdap vaccine should receive a single dose of Tdap vaccine if 2 years or more have elapsed since the last dose of Td vaccination.

Women planning pregnancy should receive one dose of Tdap vaccine if they had not received it previously. Pregnant women who have received the Td vaccination more than 10 years ago, should receive one dose of Td vaccine in the second or third trimester of pregnancy. Pregnant women who have received Td vaccination during the preceding 10 years should receive one dose of Tdap in the immediate postpartum period if the last dose of Td was administered more than 2 years ago. For pregnant women who have never received previous vaccination, three doses of Td vaccine are indicated in the second or third trimester of pregnancy; two doses are administered at least 4 weeks apart and the third dose is given 6 to 12 months after the second dose.

During pertussis outbreaks, the subjects who have not received Tdap vaccine earlier should receive a single dose of Tdap vaccine if 2 years or more have elapsed from the last Td vaccination.

The recommended immunization schedule for adults following trauma and injury is shown in Table 2.

Precautions

The Tdap/Td vaccines are contraindicated for persons with a history of anaphylaxis to any component. The Tdap vaccine is contraindicated in adults with a history of encephalopathy not attributable to an identifiable cause within 7 days of administration of a vaccine with pertussis component; these persons should receive Td vaccine.

Table 2 : Tetanus immunization schedule for adults with injury, trauma

History of tetanus toxoid doses	Clean minor wound	All other wounds
Unknown or less than three doses	Tdap/Td	Tdap/Td, TIG
Three or more doses	Tdap/Td if more than 10 years have elapsed since last tetanus toxoid dose	Tdap/Td if more than 5 years have elapsed since the last tetanus toxoid dose

In adults with moderate or severe acute illness, and those with unstable neurologic conditions (e.g., stroke, acute encephalopathies) Tdap vaccination is to be deferred until the acute illness resolves. In adults with a history of Arthus reaction with the previous dose of tetanus/diphtheria containing vaccine, Tdap/Td is administered only after 10 years since the last dose.

Hepatitis A Virus

Vaccines

Vaccines available for immunization against hepatitis A virus (HAV) include [i] inactivated vaccines such as single antigen (HAV antigen) vaccines, e.g., Havrix® (GlaxoSmithKline) and Vaqta® (Merck & Co); and combination vaccine e.g., Twinrix® (containing both HAV and HBV antigens GlaxoSmithKline).[18-20] The vaccination schedule is detailed in Table 3.

Recommendations

The Expert Group felt that universal immunization for hepatitis A is not recommended as yet.[12-14] Not only is the vaccine costly, more epidemiological data are required to ascertain its benefits. The Expert Group was of the opinion that adults at risk for acquiring hepatitis A, and adults who are negative for anti-HAV antibodies are likely to benefit most in view of changing epidemiology. The following adults are considered at high risk for acquiring hepatitis A: persons who use illicit drugs; persons who work with HAV-infected primates or with HAV in a laboratory; people who receive clotting factor concentrates; persons infected with other hepatitis viruses; persons with chronic liver disease who are not already immune to HAV; persons who have received, or are awaiting a liver transplant; food handlers; and men who have sex with men.

Post-exposure prophylaxis

Population requiring protection after exposure to HAV include: close personal contacts; child-care center staff, attendees, and household members of the attendees; persons exposed to a common source, such as infected food handlers. Immune status for hepatitis A should be checked prior to vaccination.

In healthy persons aged between 1 and 40 years, a single-antigen hepatitis A vaccine according to the age-appropriate dose is preferred to anti-HAV immunoglobulin because of the advantages of the vaccine including long-term protection, ease of administration, as well as the equivalent efficacy of vaccine compared to the to anti-HAV immunoglobulin. In persons aged over 40 years, the manifestations of hepatitis A are more severe. Therefore, the magnitude of the risk of HAV transmission from the exposure should be considered in advocating the use of vaccine or anti-HAV immunoglobulin.

Administration of anti-HAV immunoglobulin (0.02 ml/kg, intramuscularly) as soon as possible, within two weeks following exposure is preferred since little information is available regarding the performance of the vaccine in this age group. If the anti-HAV immunoglobulin is not available, the vaccine can be used. In immunocompromised persons, patients with chronic liver disease, and persons who are allergic to the vaccine or its component, anti-HAV immunoglobulin (0.02 ml/kg) should be administered as soon as possible, within two weeks after exposure.

Hepatitis B Virus

Vaccines

The hepatitis B virus (HBV) vaccine is available as a recombinant vaccine. For immunocompetent adults, 20 µg of recombinant vaccine is administered at 0, 1, and 6 months as an intramuscular injection in the deltoid using a 24-38 mm needle (Level A). Protection (defined as anti-HBs antibody titer of 10 mIU/ml or higher) following the first, second and third doses of the recombinant vaccine has been observed to be 20% to 30%; 75% to 80%; and 90% to 95% respectively (Level A).[21-24]

Recommendations

Hepatitis B vaccination is indicated for all unvaccinated adults at risk for HBV infection and all adults seeking protection from HBV infection including post-exposure prophylaxis.

Prevaccination screening

Prevaccination screening in general population has not been found to be cost effective in India (Level B). Prevaccination screening may be cost-effective in adult populations with a prevalence of HBV infection of >20% (Level B) such as household, sexual, and needle-sharing contacts of HBsAg-positive persons; HIV infected persons; injection drug users; men who have sex with men; patients with chronic liver disease (CLD) and end-stage renal disease (ESRD). Where indicated, the Expert Group recommends the prescreening protocol shown in Fig. 1.

Table 3 : Vaccination schedule for hepatitis A virus

Age (years)	Vaccine (Manufacturer)	Dose	Volume per dose (ml)	Route of injection	No. of doses	Schedule (months)
1-18	Vaqta (Merck)	25 U	0.5	IM	2	0, 6-18
	Havrix (GlaxoSmithKline)	720 EL U	0.5	IM	2	0, 6-12
≥ 19	Vaqta (Merck)	50 U	1	IM	2	0, 6-18
	Havrix (GlaxoSmithKline)	1440 EL U	1	IM	2	0, 6-12
	Twinvix (GlaxoSmithKline)	720 EL U (hepatitis A), 20µg (hepatitis B)	1	IM	3	0, 1, 6

EL U = enzyme linked immunosorbent assay units

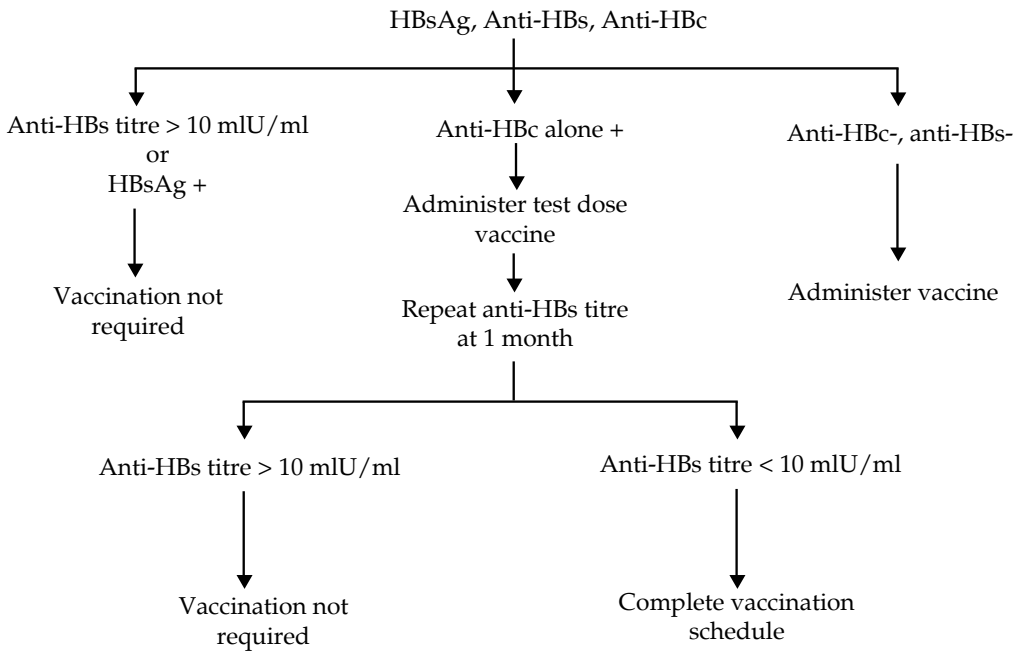

Fig. 1 : Expert Group-recommended prescreening protocol for hepatitis B virus infection. HBsAg = hepatitis B surface antigen; anti-HBs = anti-hepatitis B antibody; anti-HBc = anti-hepatitis B core antibody; + = positive; - = negative

Unvaccinated adults who are at risk for HBV infection include patients with percutaneous or mucosal exposure to blood; patients with sexual exposure. Percutaneous or mucosal exposure can occur in injection-drug users; household contacts of persons with chronic HBV infection; inmates and staff of institutions for developmentally disabled persons in long-term care facilities; persons at risk for occupational exposure to HBV (such as dialysis staff, laboratory staff dealing with blood samples, blood bank staff, nurses working in intensive care units, operation theaters and surgeons and other doctors at high-risk); patients who are HIV-seropositive, patients with CLD, chronic kidney disease (CKD); diseases where blood products or multiple blood transfusions are required such as hemophilia, aplastic anemia, leukemia, hemoglobinopathies, and patients awaiting major surgeries. Sexual exposure is a risk factor for HBV infection in patients presenting to sexually transmitted disease (STD) clinics, homosexuals; promiscuous heterosexuals; commercial sex workers; and sex partners of HBsAg-positive persons.

When the HBV vaccine schedule is interrupted, the vaccine series need not be restarted (Level B). If the vaccination schedule is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 8 weeks (Level B). If only the third dose has been delayed, it should be administered as soon as possible (Level B).

Post-exposure screening

The Expert Group felt that, in India, post-exposure screening was not indicated for most adults (Level A). However, the Expert Group felt that post-exposure screening is required for persons whose subsequent clinical management depends on the knowledge of their immune status, such as patients with ESRD (Level A); CLD (Level B); HIV infection (Level B); other immunocompromised persons (Level B); sex partners of HBsAg-positive persons (Level B); infants born to HBsAg-positive women (Level B); and certain health care workers at high risk for continued percutaneous or mucosal exposure to blood or body fluids (Level B).

When indicated, post-exposure screening should be performed 1 to 2 months after administration of the last dose of the vaccine series. The anti-HBs titre should be maintained above 10 mIU/ml in all groups except in CKD patients on dialysis in whom a titre of over 100 mIU/ml is desired.

Non-responders with normal immunity

Non-responders who are HBsAg and anti-HBc negative should receive a further full course of vaccination as fourth, fifth and sixth doses. Retesting should be done 1 to 2 months after the last dose. If there is no response, 40 µg of recombinant vaccine is administered at 0,1, and 6 months. Retesting should be done 1 to 2 months after the last dose. If the person still remains a non-responder, alternative strategies for protection must be explored.

Special situations

For patients with CKD and other immunosuppressed patients, 40 µg of recombinant vaccine is administered at 0, 1, 2, and 6 months (Level A). Testing for anti-HBs antibody titre must be done at 1 to 3 months following the last dose. If titres are less than 100 mIU/ml [in patients with CKD on dialysis] or 10 mIU/ml [in patients with immunosuppression due to other causes], administer GM-CSF (150-300 µg subcutaneously) followed 24 hours later by an intramuscular booster dose of 40 µg of vaccine while evaluating the patient for factors that have resulted in a poor response (Level A). If retesting at 1 to 2 months reveals that the person is still a non-responder, intradermal injection of the vaccine has been found to be effective in some studies (Level B). The anti-HBs antibody titres should be measured annually in these patients.

Booster doses

Booster doses of HBV vaccine are not indicated in persons with normal immune status (Level A). For CKD patients, the

need for booster doses should be assessed by annual anti-HBs antibody titre testing. A booster dose should be administered when anti-HBs levels decline to less than 10 mIU/ml (Level A) (<100 mIU/ml in patients on dialysis) (Level B). For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. When anti-HBs levels decline to <10 mIU/ ml, annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure.

Herpes Zoster

Vaccines

Herpes zoster vaccine (Zostavax) is a lyophilized preparation of the Oka strain of live, attenuated varicella zoster virus (VZV), the same strain is used in the varicella vaccines. Herpes zoster vaccine is available as a sterile preparation for subcutaneous administration which is reconstituted as directed in the package label using the supplied diluent. Each 0.65 ml dose contains a minimum of 19,400 plaque-forming units [PFU]. Herpes zoster vaccine should be administered as a single 0.65 ml dose subcutaneously in the deltoid region of the upper arm. The vaccine should not be injected intravascularly or intramuscularly and should only be reconstituted and injected using a sterile syringe free of preservatives, antiseptics, and detergents, which can inactivate the vaccine virus. Before reconstitution, zoster vaccine should be protected from light. Once reconstituted, the vaccine should be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes after reconstitution.[25-27]

Recommendations

The Expert Group observes that presently herpes zoster vaccine is not recommended for use in adult population, with or without comorbid conditions as reliable epidemiological data are not available from India regarding the burden of herpes zoster. In developed countries, herpes zoster vaccine is being advocated to adults aged 60 years and above who are at high risk for developing recurrent herpes zoster, such as patients with chronic medical conditions (e.g., CKD, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease); persons who are likely to have severe immunosuppression in near future (Level II; Grade B).

Human Papilloma Virus

Vaccines

Two HPV vaccines are commercially available. These include Gardasil® (Merck, USA), a quadrivalent vaccine containing the HPV virus L1 protein like particles of HPV 6,11,16, and 18; Cervarix® (GlaxoSmithKline, Belgium) is a bivalent vaccine containing L1 VLPs of HPV 16,18. Lack of standardized serologic assays for HPV vaccines does not allow direct comparison of the immune responses with these vaccines. The immunogenicity of the two vaccines is equivalent with respect to HPV 16, but HPV 18 appears to be more immunogenic in the Cervarix® vaccine. The clinical significance of this difference has not yet been determined.

For the Gardasil® vaccine, 3 doses are administered as 0.5 ml intramuscular injection at 0, 2, and 6 months. The minimum interval between the 1st and 2nd doses and the 2nd and 3rd doses should be 4 weeks and 12 weeks respectively. For the Cervarix® vaccine, 3 doses are administered as 0.5 ml intramuscular injection at 0, 1 and 6 months.[28-31]

Recommendations

The vaccine has to be delivered prior to exposure to the HPV virus. Therefore, the immunization must precede the sexual debut. The Expert Group recommends the age for initiation for vaccination to be 10 - 12 years (Level Ib, Grade A). Catch-up vaccination can be advised up to the age of 26 years for Gardasil® vaccine and 45 years for Cervarix® vaccine (Level Ib, Grade A). The HPV vaccines can be given simultaneously with other vaccines e.g., Hepatitis B, Tdap (Level IIa, Grade B).

The HPV vaccine is contraindicated during pregnancy and in patients with hypersensitivity to any of the vaccine components. In case a patient becomes pregnant during the course of vaccination, the subsequent doses should be delayed till delivery, but, should be completed within 1 year.

Currently available data do not support the use of booster doses (Level IIa, Grade B). Screening for cervical cancer should be continued in spite of HPV vaccination.

Special situations

The HPV vaccine is not contraindicated during lactation. The vaccine can be administered to immunosuppressed individuals. However, the immunogenicity and efficacy may be lower (Level IV, Grade C).

Influenza Virus

Vaccines

Trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV) are available for use in adults[32-35]. The TIV (2007-08) contains A/ Solomon Islands/3/2006 (H1N1) like, A/Wisconsin/ 67/2005 (H3N2) like, and B/ Malaysia/2506/2004 like strains. The TIV (2008-09) contains A/ Brisbane/59/ 2007 (H1N1) like, A/Brisbane/10/2007 (H3N2) like, and B/Florida/4/2006 like strains. The TIV is administered by an annual, single intramuscular dose of 0.5 ml. The LAIV is administered by the intranasal use and is approved for use in adults aged up to 50 years.

Recommendations

In the absence of epidemiological surveillance regarding the influenza serotypes in our country, the Expert Group observes that presently the use of influenza vaccine in India is not recommended. However, in the developed countries with robust surveillance protocols, influenza vaccination is being recommended to people at high risk for influenza-related complications, such as the elderly (age > 65 years); and patients with chronic obstructive pulmonary disease (COPD) (Level 1a, Grade A).

The Expert Group also felt that there was no evidence to recommend the use of influenza vaccine in adults (younger than 65 years) with select chronic health conditions, such as cardiac or pulmonary diseases, diabetes mellitus, cancer, immunodeficiency, renal disease, hemoglobinopathies; residents of nursing homes; people aged 50 years or more; pregnant women; health care providers; adult household contacts of people at high risk for influenza complications; people providing care to children under 2 years of age; people who provide essential community services; people who provide services within closed or relatively closed settings (e.g., crew on ships); and people responsible for culling poultry infected with avian influenza (Level IV, Grade C).

Japanese Encephalitis

Vaccines

The vaccines used for immunization against Japanese encephalitis (JE) are (i) mouse brain-derived inactivated vaccine that uses the Nakayama strain (e.g., BIKEN/JE-VAX®) and (ii) PHK cell-cultured, live-attenuated vaccine (e.g., SA 14-14-2 vaccine).[36-40] With effect from 2007, the production of the mouse brain-derived inactivated vaccine has been stopped at the Central Research Institute (CRI), Kasauli and this vaccine is not available for use in India. The SA 14-14-2 live attenuated vaccine is currently in use in China, India, Korea, Sri Lanka and Nepal and is expected to get the WHO prequalification in 2009. It is administered subcutaneously as a single 0.5 ml dose and a booster dose may be given at one year.

Recommendations

The JE vaccine is primarily useful in the pediatric age group as JE is mainly a disease of children. The Expert Group observes that, currently, the JE vaccine is not recommended for routine use in adults. The issue of adult immunization against JE in case of major outbreaks needs to be reviewed in light of the policy that is being followed in the pediatric age group.

Measles, Mumps And Rubella

Vaccines

In India the measles, mumps, rubella (MMR) live attenuated vaccine is manufactured using the following strains: Edmonston Zagreb for measles, L-Zagreb for mumps and the Plotkins RA 27/3 strain for rubella. The measles and the rubella components are produced using human diploid cells while the mumps component is produced from chick embryo. All the forms of MMR vaccine are available as 0.5 ml lyophilized mixed preparations of the various strains. The MMR vaccine should be administered subcutaneously into the upper arm and should never be administered by the intravenous route.[41-44]

Recommendations

The Expert Group recommends that all adults (except those who have medically documented history of having suffered from all the three disease; those who have received two doses of MMR vaccine in the childhood; and those with any contraindications for receiving this vaccine), should receive one dose of the MMR vaccine.

For adult immunization, two doses of the vaccine are recommended for health care workers; in the setting of outbreaks; recent exposure to these infections; women who could become pregnant; and college students. This vaccine is contraindicated in individuals with known hypersensitivity to any component of the vaccine; pregnant women; subjects with previous history of anaphylactic or anaphylactoid reactions to neomycin; patients with febrile respiratory illness or other active febrile infections; and in severely immunocompromised patients such as HIV-seropositive individuals with a CD4+ count of 200/mm^3 or less.

Meningococcal Meningitis

Vaccines

Two types of vaccines are in use for meningococcal meningitis (i) the polysaccharide vaccines and (ii) conjugate vaccines.[45-47] A third type based on outer membrane protein [OMP] has not been found to be very effective and is not widely used. Bivalent (A+C) and quadrivalent (A,C,Y,W135) polysaccharide vaccines are available. There has been no vaccine for serogroup B so far; serogroup C vaccine is considered to be relatively less immunogenic. The vaccine does not induce herd immunity and has no effect on nasopharyngeal carriage.

It is available as a lyophilized vaccine containing 50 µg of polysaccharide per dose. After reconstitution with sterile saline solution, the vaccine has to be used on the same day preferably within 8-12 hours. A single dose of 0.5 ml of the reconstituted vaccine is administered subcutaneously in the deltoid region. In children between 3 months and 2 years of age, two doses at an interval of 3 months are indicated.

Conjugate vaccines have been in use recently in a few developed countries. These vaccines are based on covalent linkage of the polysaccharide to a carrier protein (diphtheria/ tetanus toxoid), which converts the polysaccharide to thymus dependent antigen thus enhancing the capsular antibody formation and memory cells. The conjugate vaccines also provide herd immunity, reduce nasopharyngeal carriage, and provide immunity after 28 days of vaccination which may last longer also. Serum Institute of India Ltd is in the process of developing a conjugate vaccine against Serogroup A. The vaccine is likely to be available in 2009.

Recommendations

The Expert Group felt that routine vaccination of all adults is not recommended in view of low efficacy of meningococcal vaccines in children below 2 years and the short-lived protection provided by the currently available polysaccharide vaccines.

The meningococcal vaccine can be used in selected populations in certain situations, such as (i) during an outbreak; (ii) during inter-epidemic period; and (iii) to travelers, pilgrims, people attending fairs and festivals. During an outbreak, a single dose of vaccine (A+C) may be given to health care workers, laboratory workers and close contacts of cases (family members and immediate neighbors). Mass vaccination may be considered depending on the age-specific attack rate, geographical distribution of cases, and the availability of vaccine.

During the inter-epidemic period, meningococcal vaccination may be given to personnel living in dormitories; military recruits; jail inmates; immunocompromised individuals, such as those suffering from terminal complement component deficiency.

For people attending fairs and festivals, a single dose of bivalent vaccine is recommended 10-14 days before the scheduled visit. For Haj pilgrims, the practice of giving a single dose of quadrivalent vaccine may be continued. For travelers (above the age of 2 years) going to endemic countries, a single dose of vaccine depending on the prevalent serotype in the visiting country is recommended.

As a national policy, the National Institute of Communicable Diseases (NICD), Delhi is administering quadrivalent polysaccharide vaccine to the Haj pilgrims to fulfill the requirements of the Government of Saudi Arabia. On demand, it is also providing the vaccine to Delhi Government/Municipal Corporation of Delhi/ other state health authorities for high risk personnel as and when required. However, the requirement of the vaccine outstrips the demand during outbreaks. Therefore, a formal national policy needs to be developed in this regard.

Pneumococcal Infection

Vaccines

The pneumococcal polysaccharide vaccine (PPV), contains 25 µg each of purified capsular polysaccharide from 23 serotypes

of Streptococcus pneumoniae.[48-51] A single standard dose (0.5 ml) is administered by the intramuscular or subcutaneous route. This vaccine can be co-administered with live vaccine(s) such as the influenza vaccine. Conjugate pneumococcal vaccine (heptavalent) is not recommended for use in adults.

Recommendations

The scientific evidence for the efficacy of PPV has been a very controversial issue. This is attested by the fact that more than 15 meta-analyses with conflicting results have been published so far on the efficacy of PPV in adults.

The Expert Group observed that the available evidence is insufficient to recommend routine use of PPV in adults. Although PPV is efficacious in preventing invasive pneumococcal disease among adults,[48] routine PPV administration to adults is not likely to be cost-effective in India. Moreover, PPV has no proven effect on all-cause mortality.[48] Pneumococcal vaccination is recommended in patients undergoing splenectomy (preferably at least 2 weeks prior to splenectomy) (Level IV, Grade C); and one-time revaccination is indicated after 5 years in these patients. The Expert Group also noted that currently, there is no evidence to support the efficacy of PPV in preventing invasive pneumococcal disease in populations considered at high-risk, such as healthy elderly (aged 65 years and above), particularly those living in institutions; patients suffering from chronic organ fialure; patients with diabetes mellitus, nephrotic syndrome; or immunodeficiency (Level Ia; Grade A).[48]

In fact, the latest published meta-analysis commissioned by the World Health Organization (WHO) concluded that "pneumococcal vaccination does not appear to be effective in preventing pneumonia, even in populations for whom the vaccine is currently recommeded".[52] Given the lack of credible scientific evidence supporting the efficacy of PPV in high-risk populations and a complete lack of published data on the population at risk of invasive pneumococcal disease and community acquired pneumonia among the adults in India, the Expert Group endorses the recent recommendations by the WHO against the use of PPV among adults.[53] The WHO states that "in resource-limited settings where there are many competing health priorities, the evidence does not support routine immunization of the elderly and high-risk populations with PPV".[53] However, these guidelines might change with the availability of better pneumococcal vaccine preparations or more evidence regarding the efficacy/cost-effectiveness of PPV.

Rabies

Vaccines

The rabies vaccines that are available and that have been used in India are shown in Table 4. The equine and human rabies immunoglobulins (RIG's) that are currently available in India are detailed in Tables 5a and 5b respectively.

The tissue culture rabies vaccines are administered in the deltoid muscle or in the anterolateral part of the thigh. They are not to be injected in the gluteal region. Five doses of the vaccine are administered on days 0, 3, 7, 14, and 28. Optionally on day 90 a sixth dose may be given.[52-58] The intradermal regimens are listed in Table 6. Intradermal administration as recommended is however not widely used due to lack of trained personnel for administration.

Table 4 : Rabies vaccines available in India

Brand	Product	Pharmaceutical
Abhayrab	PVRV (0.5ml)	Human Biologicals Institute, Hyderabad
Rabipur	PCECV (1 ml)	Novaritis Vaccines/Sanofi Aventis
Rabivax	HDCV (Liquid) (1ml)	Serum Institute of India, Pune
Vaxirab	PDEV (1 ml)	Zydus Alidac Ahmedabad
Verorab	PVRV (0.5 ml)	Sanofi Pasteur/Ranbaxy Pharma
PVRV*	PVRV (0.5 ml)	Pasteur Institute of India, Coonoor, Tamilnadu
Indirab	Chromatographically purified PVRV (0.5 ml)	Bharat Biotech, Hyderabad

* Limited production, since July 2001

PVRV = Purified Vero cell rabies vaccine; PCECV = Purified chick embryo cell vaccine; HDCV = Human diploid cell culture vaccine; PDEV = Purified duck embryo vaccine

Recommendations

Post-exposure treatment

Definition of categories of exposure and use of rabies biologicals is shown in Table 7. All exposures in wild are considered as category III exposures. Bite by bats or rodents do not ordinarily necessitate rabies vaccination. However, bites by bats or rodents in unusual circumstances may be considered for vaccination in consultation with an expert in the field of rabies

Following exposure, there is no need to wait for laboratory confirmation of diagnosis to start treatment. Immediately after exposure, wound care (Table 4b) is started, and the degree of exposure is classified and the post-exposure treatment is started. The animal is to be observed for 10 days. Post-exposure vaccination can be discontinued if the animal is healthy after 10 days. Persons who present for evaluation and prophylaxis even months after having been bitten should be dealt with in the same manner as if the contact occurred recently.

Passive immunization

Passive immunization is carried out with human rabies immunoglobulin (HRIG) (20 IU/kg body weight; up to a maximum of 1500 IU or equine rabies immunoglobulin (ERIG) (40 IU/kg body weight; maximum of 3000 IU). The ERIG must be given only after administering the test dose as per the

Table 4b : Wound management

Do's		
Physical	Wash with running tap water	Mechanical removal of virus from the wound
Chemical	Washing the wound with soap and water, dry and apply disinfectant	Inactivation of the virus
Biological	Infiltration of immuno-globulins in the depth and around the wound in category III exposures	Neutralization of the virus

Don'ts

- Touch the wound with bare hand
- Apply irritants like soil, chillies, oil, herbs, chalk, betel leaves etc.

Table 5a : Equine rabies immunoglobulins currently available in India

Brand	Product	Pharmaceutical
Anti-Rabies Serum	Purified equine RIG, 5 ml vial (300 IU/ml, 1500 IU potency)	Central Research Institute, Himachal Pradesh
Carig	Purified equine RIG, 5 ml vial (300 IU/ml, 1500 IU potency)	Cadila Pharmaceuticals, Ahmedabad
Equirab	Purified equine RIG, 5ml vial (300 IU/ml, 1500 IU potency)	Bharat Serums and Vaccines Limited, Mumbai
Zyrig	Purified equine RIG 5 ml vial (300 IU/ml, 1500 IU potency)	Zydus Alidac, Ahmedabad
Abhayrig	Purified equine RIG, 5 ml vial (300 IU/ml, 1500 IU potency)	Human Biologicals Institute, Hyderabad

RIG = rabies immunoglobulins

Table 5b : Human rabies immunoglobulins currently available in India

Brand	Product	Pharmaceutical
Berirab-P	Human RIG, 50 IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	Aventis Behring, Cadila Health Care
Imogamrab	Human RIG, 50 IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	Bharat Serums and Vaccines Limited, Mumbai
Rabglob	Human Rabies Immunoglobulins, 50 IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	Bharat Serums and Vaccines Limited, Mumbai
Kamrab	Human Rabies Immunoglobulins, 50 IU/ml; 2 ml (300 IU) ampoule and 5 ml (750 IU) ampoule	Medlife, Thane

RIG = rabies immunoglobulins

Table 6 : Regimens for post-exposure prophylaxis

Route	Regimen	Dose	Schedule (Days)
Intradermal	Two-site*	0.1 ml	Day 0, 3, 7, 28†
Intradermal	Eight-site‡	0.1 ml	Day 0 (8 doses§), 7 (4 doses#), 28¶, 90¶

*Two site regimen signifies right and left upper arm (total 2 sites)

†On each day, one injection is administered in right and left upper arm

‡Eight site regimen signifies both upper arms, both lateral thighs, both suprascapular regions and both sides of the lower quadrant region of the abdomen (total 8 sites)

§One injection each in both upper arm, both lateral thigh, both suprascapular region, and on both sides of the lower quadrant region of the abdomen (total 8 doses)

#One injection each in both upper arm and both lateral thigh (total 4 doses)

¶One dose in one upper arm only

manufacturer's guidelines. The Expert Group observed that the use of immunoglobulins needs to be encouraged after following proper precautions.

The rabies immunoglobulin should be infiltrated as much as possible into and around the wounds; remaining immunoglobulin, if any, should be given intramuscularly at a site away from the site where vaccine has been administered. If the rabies immunoglobulin volume is insufficient, it can be diluted with sterile normal saline (up to equal volume).

Table 7 : Definition of categories of exposure and use of rabies biologicals

Category III
Single or multiple transdermal bites, scratches or contamination of mucous membrane with saliva (i.e., licks), exposure to bats
Wound management plus rabies immunoglobulin plus vaccination is indicated
Category II
Minor scratches or abrasions without bleeding or licks on broken skin and nibbling of uncovered skin
Wound management and use of vaccine alone is indicated
Category I
Touching, feeding of animals or licks on intact skin
No exposure has occurred. Therefore, if history reliable, no prophylaxis is indicated

Management of re-exposure

On re-exposure following a full course of either pre-or post-exposure vaccination, 2 booster doses are to be administered intramuscularly or intradermally on days 0 and 3 irrespective of category of exposure or time that has elapsed since previous vaccination. Rabies immunoglobulin is not indicated in this scenario. All subjects who have received incomplete vaccination should be treated as fresh cases.

If rabies immunoglobulin is not available

If rabies immunoglobulin is not available, double dose of the first dose of vaccination may be administered in the following situations: (i) category III exposure; (ii) patients who are malnourished, patients receiving corticosteroids, anticancer drugs and antimalarials; (iii) patients with HIV/AIDS with severe immunosuppression (CD4+ count < 200/mm^3). If feasible, test for antibody titres and give boosters if titre is less than 0.5 IU/ml. However, doubling the dose of the vaccine should not be considered as a substitute for RIGs.

Pre-exposure prophylaxis

Pre-exposure prophylaxis is recommended for risk groups like veterinarians, laboratory personnel working with rabies virus, medical and paramedical personnel treating rabies patients; others, such as dog catchers, forest staff, zoo keepers; postmen, policemen, courier boys, and school children in endemic countries.

Only modern tissue culture vaccines must be used for pre-exposure prophylaxis. The human diploid cell culture vaccine [HDCV] and purified chick embryo cell culture [PCEC] vaccines (1 ml) or purified Vero cell rabies vaccine [PVRV] (0.5 ml) are administered by intramuscular route in the deltoid region or the anterolateral thigh on days 0, 7, and 28. The reconstituted tissue culture vaccines (0.1 ml, irrespective of the reconstituted volume) can be administered by the intradermal route over the deltoid region on days 0, 7, and 28.

Monitoring

In persons working with live rabies virus in diagnostic, research, and vaccine production laboratories, antibody titres in the serum should be monitored every 6 months and a booster dose of the vaccine should be administered when the titre falls below 0.5 IU/ml. In other professions at permanent risk of exposure to rabies, such as veterinarians, animal handlers, wildlife officers, etc., antibody titres in the serum should be monitored annually and a booster dose of the vaccine should be administered when the titre falls below 0.5 IU/ml.

Special situations

Rabies vaccines and rabies immunoglobulin are safe during pregnancy, lactation and in immuno-compromised states including HIV infection and AIDS.

The post-exposure prophylaxis remains the same on exposure to a vaccinated animal

Other issues

Interchanging modern rabies vaccines is not recommended. When completion of post-exposure treatment with the same modern rabies vaccine is not possible, one of the recommended cell culture vaccines may be used. No study has addressed on vaccine immunogenicity following change of the route of vaccine administration (e.g., from intramuscular to intradermal) during post-exposure prophylaxis.

Typhoid Fever

Vaccines

Vaccines available for typhoid fever include (i) inactivated whole cell vaccine; (ii) live oral Ty21a vaccine; (iii) injectable Vi polysaccharide vaccine; and (iv) Vi-rEPA vaccine.[61-64] The inactivated whole cell vaccine is not recommended for use by the WHO or the CDC. Limited data are available on the Vi-rEPA vaccine.

Live oral Ty21a vaccine is an orally administered, live attenuated Ty2 strain of Salmonella typhi in which multiple genes (including the genes responsible for the production of Vi), have been mutated chemically. The lyophilized vaccine is available in two formulations: a liquid suspension (in sachets) or as enteric coated capsules. The Vi polysaccharide vaccine is a subunit vaccine composed of purified Vi capsular polysaccharide from the Ty2 S. Typhi strain and elicits a T-cell independent IgG response that is not boosted by additional doses. The target value for each single dose is about 25 µg of the antigen.

Recommendations

Typhoid vaccine is recommended as part of routine immunization in adolescents (Grade A). Either Ty21a or Vi vaccine may be used as both have comparable efficacy (51% vs 55% at 3 years) and both are safe (Grade A).

Between the capsule and liquid formulations of Ty21a, the expert group recommends liquid formulation (Grade A). Three doses of Ty21a capsules/sachets (liquid formulation) are administered on alternate days. It is also recommended that this series should be repeated once in every 3 years as a booster dose. The capsule formulation should be taken orally with plain, cold or lukewarm water. The sachet should be given with 100 ml of safe water with buffer to protect the B-subunit against gastric acidity. Following the administration of the vaccine, food should be taken only after one hour. Proguanil and anti-bacterial drugs should not to be given for 3 to 7 days before and after the course of vaccine. The Vi vaccine is given as a single subcutaneous or intramuscular dose of 0.5 ml. A booster is recommended once in every 3 years (Level II). Both these vaccines may be co-administered with other killed/live vaccines.

The expert group also recommends vaccination of the entire community at risk during an outbreak situation (Grade B). If immunization of the entire community is not possible, the group recommends that the individuals aged 2 to 19 years should be specifically targeted.

Due to insufficient data, the Expert Group currently does not recommend routine immunization of adults (Grade C).

Special situations

Pregnancy: The expert group does not recommend the use of Ty21a in pregnancy as data documenting its safety are not available as of now (Grade C).

HIV infection: The expert group recommends that in HIV-seropositive individuals with a CD4+ T-lymphocyte count >200/mm^3, both Ty21a and Vi vaccines can be administered as in the case of immunocompetent individuals. However, in HIV-seropositive individuals with a CD4+ T-lymphocyte count <200/mm^3, Vi vaccine may be used (Grade C).

Varicella Virus

Vaccines

Two vaccines for varicella virus are currently available in India. These are Varilrix (GlaxoSmithKline Biologicals S.A, Belgium) and Okavax (Pasteur Mérieux serums & vaccines, Avenue Le Clerc, Lyon-France). Both contain an attenuated live VZV (Oka strain).[65-70]

Varicella zoster immune globulin (VZIG)

Varicella can be prevented in nonimmune, healthy individuals by the administration of varicella zoster immune globulin (VZIG) (prepared from patients recovering from herpes zoster) within 72 hours of exposure. The VZIG also lowers attack rates among immunocompromised persons if administered no later than 96 hours after an exposure. The recommended dose is 125 units/10

kg of body weight, up to a maximum of 625 units. It is presently not manufactured or distributed in India

Recommendations

Persons aged over 13 years without evidence of varicella immunity should receive 2 doses of the vaccine 4-8 weeks apart. It is recommended to do an antibody titre (if available and affordable, from accredited laboratory) to find out if there is immunity due to subclinical infection before giving two doses (Level IV, Grade D). Dosing schedule consists of administration of two doses (0.5 ml each) of varicella vaccine subcutaneously over the deltoid region. Minimum interval between first and the second doses should be 4 weeks. If more than 8 weeks elapse after the first dose, the second dose may be administered without restarting the schedule. Those who have received one dose of vaccine in childhood are advised to get their second dose (Level Ib, Grade A).

Special situations

Adults at increased risk for exposure

Two doses of varicella vaccine are strongly recommended in adults at increased risk for exposure of varicella such as health care personnel, household contacts of immunocompromised persons, non-pregnant women of childbearing age, persons who live or work in environments in which transmission of VZV is likely (e.g., teachers, day-care employees, residents and staff in institutional settings), persons who live or work in environments in which transmission has been reported (e.g., college students, inmates and staff members of correctional institutions, and military personnel), adolescents and adults living in households with children, and international travellers (Level IV, Grade D).

Postpartum women

Women who do not have evidence of varicella immunity should receive the first dose of vaccine before discharge from the health care facility. The second dose should be administered 4–8 weeks later. Women should be counseled to avoid conception for 1 month after each dose of varicella vaccine (Level IV, Grade D).

HIV-infected individuals

All HIV-infected persons with CD4+ >200 cells/μL should receive two doses of varicella vaccine (Level IV, Grade D).

Individuals receiving corticosteroids

Persons without evidence of immunity against varicella receiving systemic corticosteroids for medical conditions (e.g., asthma) and are not otherwise immunocompromised may be vaccinated if they are receiving less than 2 mg/kg body weight or a total of <20 mg/day of prednisone or its equivalent dose of corticosteroids.

Persons who are receiving higher doses of systemic corticosteroids (i.e., more than 2 mg/kg body weight prednisone or its equivalent) for more than 2 weeks may be vaccinated once steroid therapy has been discontinued for more than 1 month (in accordance with the general recommendations for the use of live-virus vaccines) (Level IV, Grade D).

During outbreaks of varicella infection

Varicella vaccination is recommended for outbreak control. A two-dose vaccination schedule is recommended for optimal protection. Persons who do not have adequate evidence of immunity against varicella should receive their first or second dose as appropriate. Those vaccinated with the first dose as part of outbreak control measures should be scheduled for the second dose after 4 to 8 weeks (Level IV, Grade D).

Post-exposure prophylaxis

Single-antigen varicella vaccine has been shown to be effective in preventing illness or modifying varicella severity if administered to unvaccinated children within 3 days, and possibly up to 5 days, of exposure to rash. Varicella vaccine is recommended for post-exposure administration for unvaccinated persons without other evidence of immunity against varicella. It should preferably be given within 3 days of exposure to varicella rash and can be given up to 5 days of exposure to rash (Level IV, Grade D).

Contraindications for varicella vaccine

Varicella vaccine is contraindicated in individuals with a history of a serious reaction (e.g., anaphylaxis) after a previous dose of varicella vaccine or to a varicella vaccine component; women who are pregnant or may become pregnant within 1 month; patients with malignant conditions, including blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. Varicella vaccines should not be administered to persons receiving high-dose systemic immunosuppressive therapy, including persons receiving on oral corticosteroids >2 mg/kg of body weight or a total of more than 20 mg/day of prednisone or its equivalent for persons who weigh >10 kg, when administered for >2 weeks; HIV-seropositive adult or adolescent with CD4+ T-lymphocytes count <200 cells/μL; persons with a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents, siblings) unless the immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Recommendations for varicella zoster immune globulin

The following patient groups are at risk for severe disease and complications from varicella and can receive VZIG.

Immunocompromised patients

The VZIG can be used primarily for passive immunization of immunocompromised persons without evidence of immunity after direct exposure to varicella or disseminated herpes zoster patients, including persons who (i) have primary and acquired immune-deficiency disorders; (ii) have neoplastic diseases; and (iii) are receiving immunosuppressive treatment.

Pregnant women

Because pregnant women might be at higher risk for severe varicella and its complications, VZIG should be strongly considered for pregnant women without evidence of immunity who have been exposed. Administration of VZIG to these women has not been found to prevent viremia, fetal infection, congenital varicella syndrome, or neonatal varicella. Thus, the primary indication for VZIG in pregnant women is to prevent complications of varicella in the mother rather than to protect the fetus.

Any patient who receives VZIG to prevent varicella should receive varicella vaccine subsequently, provided the vaccine is not contraindicated. Varicella vaccination should be delayed until 5 months after VZIG administration. Varicella vaccine is not needed if the patient has varicella after administration of VZIG (Level III, Grade D)

This statement was prepared by the Expert Group Meeting for forming Consensus Recommendations on Adult Immunization in India jointly organized by the Association of Physicians of India (API) and the Department of Medicine, All India Institute of Medical Sciences, New Delhi, on December 6-7, 2008 at the All India Institute of Medical Sciences, New Delhi, India.

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Conflict of Interest

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