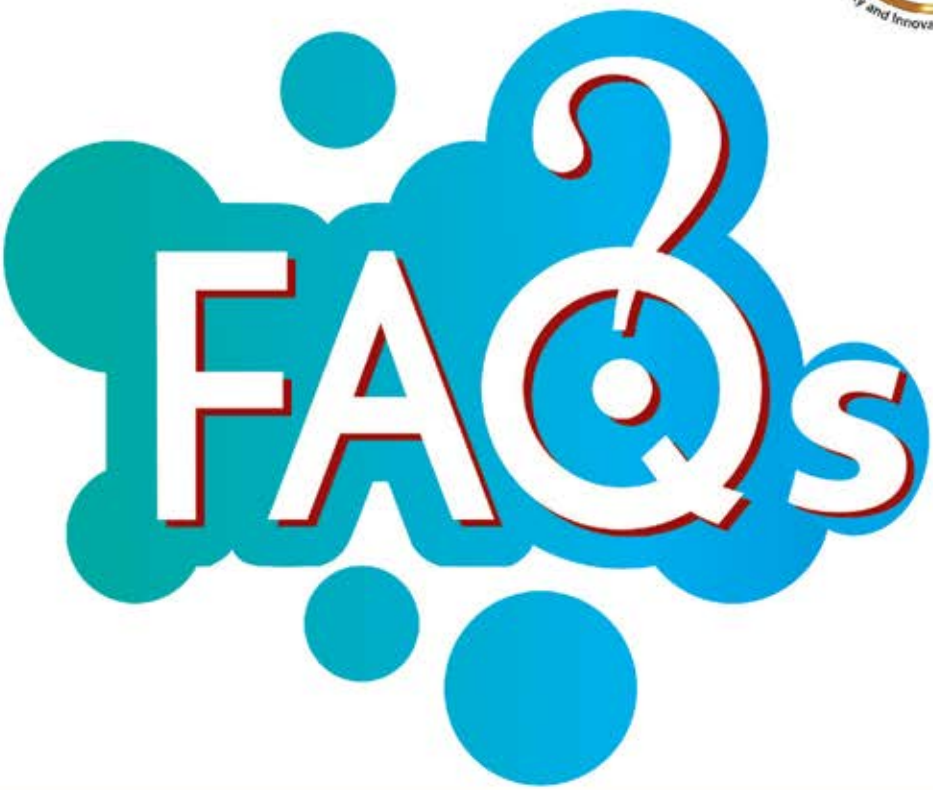
others.com, for detailed information on pediatrics books, visit our website www.jaypeebrothers.com, for detailed information on pediatrics books





on Vaccines and Immunization Practices

Chief Editor
Vipin M Vashishtha

Editor
Ajay Kalra

THIRD EDITION

Foreword
Walter A Orenstein



FAQs
on Vaccines and Immunization Practices

3rd Edition

Chief Editor

Vipin M Vashishtha
MD FIAP
Director and Consultant Pediatrician
Mangla Hospital and Research Center
Bijnor, Uttar Pradesh, India

Editor

Ajay Kalra
MD DCH MNAMS FIAP
Erstwhile Professor
Department of Pediatrics
SN Medical College
Agra, Uttar Pradesh, India

Foreword

Walter A Orenstein

JAYPEE BROTHERS MEDICAL PUBLISHERS
The Health Sciences Publisher
New Delhi | London

JAYPEE BROTHERS

Contents

SECTION 1: GENERAL VACCINATION

1. **Vaccine Immunology: Basics and Beyond** 3
   Yash Paul, Vipin M Vashishtha
2. **Elementary Epidemiology in Vaccination** 28
   Vipin M Vashishtha, Yash Paul
3. **Vaccination Schedules** 39
   Yash Paul, Satish V Pandya
4. **Practice of Vaccination** 48
   Yash Paul, Satish V Pandya, Atul K Agarwal
5. **Vaccine-preventable Diseases Surveillance** 62
   Meeta Dhaval Vashi
6. **Vaccination in Special Situations** 75
   Abhay K Shah
7. **Adverse Events following Immunization, Vaccine Safety, and Misinformation against Vaccination** 93
   Meeta Dhaval Vashi, Vivek R Pardeshi
8. **Cold Chain and Vaccine Storage** 104
   Digant D Shastri
9. **Control and Eradication of Infectious Diseases** 118
   Yash Paul, Priya Marwah
10. **Development and Licensing of Vaccine** 124
    Gautam Rambhad, Canna Jagdish Ghia
11. **National Immunization Technical Advisory Group** 145
    Madhu Gupta, Adarsh Bansal
12. **Medicolegal and Ethical Issues in Immunization** 151
    Satish Kamtaprasad Tiwari, Yash Paul
13. **Vaccine Schedules including National Immunization Program** 158
    Meeta Dhaval Vashi, Vivek R Pardeshi
14. **Vaccine Hesitancy** 167
    Chandrakant Lahariya, Dewesh Kumar

SECTION 2: LICENSED VACCINES

15. **Bacillus Calmette-Guérin Vaccine** 177
    Vipin M Vashishtha, A Parthasarathy, Hitt Sharma

JAYPEE BROTHERS

16. Polio Vaccines **199**
Naveen Thacker, Prem Pal Singh, Vipin M Vashishtha

17. Diphtheria, Tetanus and Pertussis Vaccines **224**
Vipin M Vashishtha, Unmesh A Upadhyay

18. Measles Vaccines **259**
Baldev S Prajapati, Arun Wadhwa

19. Measles, Mumps and Rubella Vaccines **266**
Arun Wadhwa, Baldev S Prajapati, Sudhir Kumar Choudhary

20. Hepatitis B Vaccines **281**
Ajay Kalra, Sanjay Verma

21. Hepatitis A Vaccines **302**
Arun Wadhwa, Nigam P Narain

22. Varicella Vaccines **312**
Vijay N Yewale, Dhanya Dharmapalan

23. Typhoid Vaccines **333**
Chandra Mohan Kumar, Vipin M Vashishtha, Ajay Kalra

24. *Haemophilus influenzae* Type B Vaccines **356**
Jaydeep Choudhury

25. Pneumococcal Diseases Vaccines **363**
Shobha Sharma, Neha Goel

26. Rabies Vaccines **389**
Omesh Kumar Bharti, Jaydeep Choudhury, Vipin M Vashishtha

27. Japanese Encephalitis Vaccines **405**
Vipin M Vashishtha, Chandra Mohan Kumar

28. Rotavirus Vaccines **434**
Rakesh Bhatia

29. Human Papillomavirus Vaccines **446**
Jaydeep Choudhury, Srinivas G Kasi

30. Influenza Vaccines **462**
Sanjay Srirampur, Pritesh Nagar, Vipin M Vashishtha

31. Meningococcal Vaccines **481**
Parang N Mehta

32. Cholera Vaccines **491**
Nupur Ganguly

33. Dengue Vaccines **498**
Dipti Agarwal

34. Malaria Vaccines **509**
Abhay K Shah

JAYPEE BROTHERS

35. Combination Vaccines **519**
Ashok K Dutta

36. Yellow Fever Vaccines **525**
Chandra Mohan Kumar, Obeid Shafi, Shweta Singh

37. Ebola Vaccines **532**
Arun Wadhwa

SECTION 3: VACCINES IN THE PIPELINE

38. Respiratory Syncytial Virus Vaccines **541**
M Surendranath

39. Newer Tuberculosis Vaccines **549**
Sangeeta Sharma

40. Coronavirus Disease 2019 Vaccines **556**
Arun Wadhwa

41. Human Immunodeficiency Virus Vaccines **568**
Dipti Agarwal

42. Cytomegalovirus Vaccines **574**
Unmesh A Upadhyaya

43. Enteroviral Vaccines (EV71) **582**
Piyali Bhattacharya

44. Diarrheal Disease Vaccines other than Rotavirus **588**
Shalabh Agarwal

45. Hepatitis E Vaccines **594**
Dipti Agarwal

46. Hepatitis C Vaccines **599**
Abhay K Shah, Aashay A Shah

47. Zika Virus Vaccines **611**
M Surendranath

48. Chikungunya Vaccines **617**
Sachidanand Kamath, Geeta MG

SECTION 4: NOVEL VACCINE STRATEGIES

49. Deoxyribonucleic Acid Vaccines **629**
Sumit Mehndiratta

50. Chimeric Vaccines **639**
Puneet Kumar

JAYPEE BROTHERS

51. Therapeutic Vaccines **647**
Ajay Kalra, Srinivas G Kasi, Premashish Mazumdar

52. Newer Adjuvants Vaccines **656**
Puneet Kumar, Sanjay Niranjan

SECTION 5: VACCINATION OF SPECIAL GROUPS

53. Adolescent Immunization **677**
CP Bansal, Ashok K Banga

54. Vaccination Strategies for Travelers **691**
Rashna Dass Hazarika

55. Maternal Immunization **700**
Harish K Pemde, Ravitanaya Sodani

56. Vaccines for Healthcare Professionals **711**
Rashna Dass Hazarika

Annexure 1: National Immunization Schedule 2020 *723*

Annexure 2: Indian Academy of Pediatrics— Advisory Committee on Vaccines and Immunization Practices Recommended Immunization Schedule 2019 *727*

Index *735*

JAYPEE BROTHERS

CHAPTER 41

Human Immunodeficiency Virus Vaccines

Dipti Agarwal

JAYPEE BROTHERS

1. What is the biology of HIV virus?

Human immunodeficiency viruses 1 (HIV-1) is an enveloped RNA virus, a lentivirus belonging to the Retroviridae family. The virus was isolated and subsequently identified as the etiologic agent of AIDS in 1983. The viral genome, consisting of two copies of a single-stranded RNA, codes for structural (Gag, Pol, and Env), regulatory (Tat and Rev), and accessory proteins (Vpu, Vpr, Vif, and Nef) **(Fig. 1)**. As in other enveloped viruses, binding of the virus to cell-surface receptors is mediated by the envelope glycoproteins, which play a critical role in initiating the viral infection.

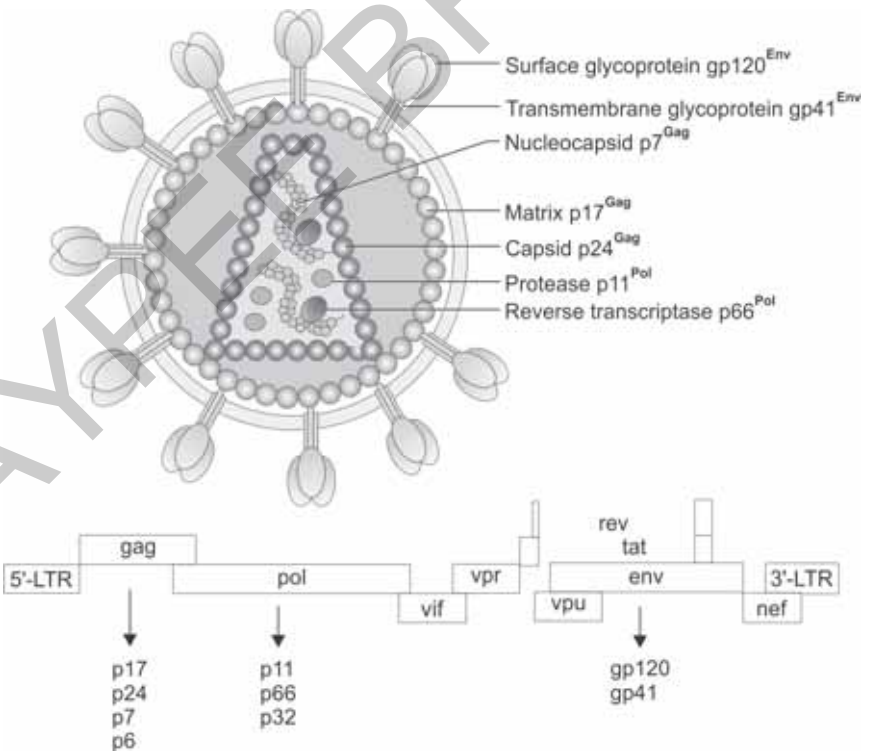


Fig. 1: Human immunodeficiency virus type 1 (HIV-1) genome and virion.

2. What is the need to have an HIV vaccine?

HIV/AIDS is the world's leading infectious disease worldwide. It has been estimated that more than 37.9 million people are living with HIV/AIDS, with about 1.7 million children less than 15 years in 2018. Nearly 32 million people have died from AIDS related illness since the start of the epidemic (end 2018). The extent of prevalence and fatality, therefore, warrants a necessity of the vaccine.

3. Is there any natural protective antibody for the virus?

Broadly neutralizing antibodies or bNAbs have been demonstrated to be naturally produced in some people infected with HIV but have not succeeded in overcoming the virus. Various studies involving neutralizing antibodies in HIV-1 infected individuals can provide information about the response that can help vaccines to be developed to elicit immune responses. Antibodies have been found to bind the CD4-binding region of gp120, gp140 and gp41. It has been shown that these antibodies neutralize the virus by blocking cell receptors. It has been demonstrated that antibodies binding to membrane proximal external region (MPER) of gp41 can prevent virus from fusing with cell and hence can play role in prevention of infection.

4. Is there any passive immunity against HIV?

Passive immunization involves use of intravenous infusions of bNAbs to prevent occurrence of HIV infection. These antibodies have been shown to protect primates. These results suggest that inducing bNAbs by vaccination should provide protection to humans. There are at present no such vaccines which could elicit antibody response. Lack of immunogen is major hindrance in development of such vaccine. Studies are underway to develop antigen-vaccine that can stimulate immune responses and form bNAbs. Studies on immune prophylaxis are also being carried which involves injecting a vector containing bNAbs genes to produce antibodies that may prevent occurrence of HIV infection.

5. Do we already have a vaccine or any possibility to have one in future?

A vaccine should be able to prevent replication of HIV virus and prevent spread of the infection. It should be able to develop both durable cellular and humoral immunity. Currently, none is available but it is possible to have one as the virus is limited to a human host with no known animal reservoir, it is not highly infectious, and natural infection generates both antibody and T-cell responses (body's innate defense mechanisms, which can be instigated/augmented by vaccine).

6. What are the reasons for not having one till now?

Human immunodeficiency virus has many characteristics that make vaccine development difficult: subclinical cases and a carrier state, a long-term

JAYPEE BROTHERS

infection process, a nonspecific acute clinical disease, significant antigenic variation, viral DNA integration into the host genome, transmission through infected cells, and destruction or alteration of immunoregulatory cell function. Some of the reasons are as follows:

- High variability of the virus epitopes, the lack of durable immune correlates of protection.
- Viral antigens induce expansion of CD4 T helper cells, which results in increase in B-cells and plasma cells along with IgG hypersecretion resulting in dysregulated antibody production.
- Classic vaccines mimic natural immunity against reinfection generally seen in individuals recovered from infection; till date, there are no study supporting development of an immune responses in a person infected with HIV infection.
- Most vaccines protect against disease, not against infection; HIV infection may remain latent for a long-period before causing AIDS.
- Most effective vaccines are whole-killed or live-attenuated organisms; killed HIV-1 does not retain antigenicity and the use of a live retrovirus vaccine raises safety issues.
- Most vaccines protect against infections through mucosal surfaces of the respiratory or gastrointestinal tract; the great majority of HIV infection is through the genital tract.
- Limitations with the existing animal models and logistical problems associated with the conduct of multiple clinical trials.

7. What is the progress in the development of HIV vaccine?

Many clinical trials of HIV vaccine have been conducted. The first trial was conducted in 1987 at National Institutes of Health. However, most of the trials have reached Phase I/II and six trials have reached clinical efficacy Phase III/IIb. Multiple vaccine concepts and vaccination strategies have been tested, including DNA vaccines, subunit vaccines, live vectored recombinant vaccines, and various prime-boost vaccine combinations. The six trials are summarized here:

1. VAX004 trial was conducted between 1998 and 2003. Although it reached Phase III but did not demonstrate efficacy.
2. VAX003 trial was conducted during same period and it also aimed at humoral immunity and was not successful.
3. STEP trial reached Phase IIb and was conducted between 2004 and 2007. It was intended to see development of cellular response.
4. Phambili trial was stopped at Phase IIb stage after the results of STEP trial as this trial also aimed at cellular response.
5. RV144 trial was conducted between 2003 and 2009. This trial was aimed at humoral and cellular response. It was conducted using canary Pox vaccine and it demonstrated 31.2% efficacy in preventing infection.
6. HVTN505 trial was conducted between 2009 and 2015. It was prematurely stopped. It used DNA capsid and aimed to develop humoral as well as cellular response.

JAYPEE BROTHERS

The Thai vaccine trial (RV144) was the major breakthrough; for the first time ever, it revealed that vaccine combination demonstrated a modest efficacy in preventing infection in humans.

8. Give more details about Thai HIV vaccine trial.

The HIV vaccine trial, also known as RV144, was the largest HIV vaccine study ever conducted in humans and involved more than 16,000 volunteers in Thailand. RV144 evaluated the safety and efficacy of a prime-boost combination of two vaccine components given in sequence The trial tested a "prime-boost" combination of two vaccines: (1) ALVAC HIV vaccine (the prime), and (2) AIDSVAX B/E vaccine (the boost). Harmless virus was used as a vector to deliver HIV genes and the boost contained a protein found on the HIV surface. The vaccine combination was based on HIV strains that are found commonly in Thailand. Results of the trial show that this (ALVAC-HIV and AIDSVAX B/E) vaccine regimen may reduce the risk of HIV infection in a community-based population. The regimen was found to be safe and demonstrated an efficacy of 31.2% in preventing HIV infection. The trial showed modest success and provided guideline for further clinical research for HIV vaccines. However, the vaccination did not alter the CD4 count or the viral load. The trial guided researchers to identify the factors that protected some of the recipients from HIV infection. Those participants of RV144 trial who produced high levels of immunoglobulin G were found to bind to part of the envelope V1V2 and were protected against virus. Whereas those vaccines with high levels of envelope-binding antibody belonging to the IgA family appeared to have less protection from the virus.

9. How ethical are HIV vaccine trials?

Prevention trials are complex in nature — you are enrolling people at risk of HIV who are HIV-negative. But overall, today's trials are conducted incredibly well. UNAIDS and the World Health Organization have come up with good guidance on conducting clinical trials.

10. What are the innovations in vaccine development?

New strategies examining heterologous vector prime-boost, universal inserts, replicating vectors, and novel protein or adjuvant immunogens are being explored to induce T-cell and antibody responses. HIV vaccine development requires innovative ideas and a sustained long-term commitment of scientists, governments, and the community. Innovations in vaccine development have included the following:

- *Protein subunit:* Vaccine using envelop protein such as gp160, gp120 and gp140 have been developed. They can produce neutralizing antibody and activate CD4 T-cells but do not develop CD8 response.
- *Adjuvants:* AIDSVAX B/B' vaccine (VaxGen), employed recombinant gp120 envelope proteins, and a primary clade B isolate (GNE8), with

JAYPEE BROTHERS

alum salts as adjuvant, showed good safety and immunogenicity in Phase I and II trials.

- *Virus-like particles (VLPs):* They combine a viral vector with the desired antigen. However, recent trials based on VLPs have not been encouraging. AVX101, a VEEV replicon-based vaccine with promising results are in preclinical stage.
- *Live recombinant vaccines:* They involve use of a viral vector with required genes to be introduced into the host cell. The most used viral vectors are poxviruses.
- *DNA vaccines:* They involve use of non-living, non-replicating, non-transmissible plasmids, which are taken up by host cells. They encode proteins expressed by host tissues which can promote antigenic presentation. However, these vaccines have been shown to induce low immunogenicity, due a low DNA uptake.
- *Lipoidal biocarriers:* They improve bioavailability, delay elimination. CAF01, a liposomal system has been shown to build strong humoral and T helper response. Virosomes are reconstituted viral envelop lipid bilayers that function as antigen carriers. Both T helper and CD8 cells are developed in response to it. Antibody production is also stimulated by the virosomes.

11. What is mucosal immunity?

Mucosal immunity will help protecting against entry of virus and hence provide protection against systemic infection also. In rhesus monkeys, administration of oral inactivated vaccine was found to be effective in inducing vaginal and rectal IgA antibody. Studies have also demonstrated mucosal CD8 responses with systemic immunization. Recently virosome in a study was given intramuscularly followed by intranasal route. This effort could be the beginning of a new class of vaccines.

12. What is the way forward for HIV vaccine development?

Since HIV-1 was identified, development of a preventive vaccine has been a major goal. An effective HIV vaccine is a global health priority. Of the various HIV vaccine trials, only Thai trial has showed modest protection in human clinical trial **(Table 1)**.

National Institute of Allergy and Infectious Diseases (NIAID) and its partners have continued to conduct further trials based on modest success of Thai vaccine trial. Numerous investigational vaccines are at different stages of development. Researchers are developing novel prime-boost regimens that elicit strong, long-lasting protective immune responses. The Pox-Protein Public-Private Partnership, or P5, have been working to build on the modest success of RVl44. Results from HVTN 702, a vaccine efficacy trial in South Africa are to come by the end of the year 2020. Two investigational vaccines based on "mosaic" immunogens—vaccine components comprising elements from multiple HIV subtype are also being developed so as to provide immune protection against the wide variety of global HIV strains.

JAYPEE BROTHERS

TABLE 1: HIV clinical trials, rationale design and outcome.

Study	*Regimen*	*Participants*	*Aim*	*Outcome*
VAX004 (United States, Netherlands)	*r*gp120 B/B	MSM, high-risk women	bnAbs	No prevention of HIV infection
VAX003 (Thailand)	*r*gp120 B/E	Drug users	bnAbs	No prevention of HIV infection
Step/JVTN502 (USA)	*r*Ad5 HIV-1 gag/pol/nef B	MSM, high-risk women	CD8 + T-cells	Increased infection risk
Phambili/HVTN503 (South Africa)	*r*Ad5 HIV-1 gag/pol/nef B	Heterosexual men, women	CD8 + T-cells	Increased infection risk
HVTN505	*DNA/rAd5	MSM, trangender women	Ab and T-cells	No infection risk, no efficacy
RV144 (Thailand)	*ALVAC-HIV/AIDSVAX B/F gp 120 in alum	High-risk men and women	Ab and T-cells	31.2% vaccine efficacy

(r: recombinant; MSM: men who have sex with men; bnAbs: broadly neutralizing antibodies; *: prime-boost regimen)

Source: Trovato M, D'Apice L, Prisco A, De Berardinis P. HIV vaccination: a roadmap among advancements and concerns. Int J Mol Sci. 2018;19(4):1241.

In 2017, NIAID started large clinical trial to assess safety and efficacy of vaccine against HIV in women in southern Africa. The trial is called Imbokodo or HVTN 705/HPX2008. In 2019, NIAID and partners have started complementary phase III HIV vaccine trial to assess an investigational vaccine regimen for safety and efficacy among men who have sex with men and transgender people. The trial is called HPX3002/HVTN 706 or Mosaico, is taking place at multiple clinical research sites in North America, South America and Europe.

SUGGESTED READING

1. Fast PE, Kaleebu P. HIV vaccines: current status worldwide and in Africa. AIDS 2010;24(Suppl)4:S50-60.
2. Kim JH, Rerks-Ngarm S, Excler JL, Michael NL. HIV vaccines: lessons learned and the way forward. Curr Opin HIV AIDS. 2010;5(5):428-34.
3. Lema D, Garcia A, De Sanctis JB. HIV Vaccines: a brief overview. Scand J Immunol. 2014;80(1):1-11.
4. National Institute of Health. (2020). An Empirical Approach to HIV Vaccine Development. [online] Available from: http://www.niaid.nih.gov/emperical. [Last Accessed August, 2020].
5. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, Paris R, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209-20.
6. Trovato M, D'Apice L, Prisco A, De Berardinis P. HIV vaccination: a roadmap among advancements and concerns. Int J Mol Sci. 2018;19(4):1241.

JAYPEE BROTHERS

for detailed information on pediatrics books, visit our website www.jaypeebrothers.com, for detailed information on pediatrics books, visit our webs

FAQs on Vaccines and Immunization Practices

A must-have desk-top manual for Pediatricians, General Practitioners, and Medical Students

Key Features

- Comprehensive, latest, and in-depth coverage of all the issues related to vaccinology and vaccines in an easy-flowing question-and-answer format.
- Seventeen new chapters including Coronavirus vaccines, Vaccine hesitancy, Vaccine schedules, Vaccines for doctors and travelers, Maternal immunization, etc.
- Up-to-date content, incorporating the IAP ACVIP Recommended Immunization Schedule 2019 and National Immunization Schedule 2020.
- Answers all the real-life situations faced by a busy practitioner in day-to-day clinical practice.
- Often neglected subjects like basic immunology, elementary epidemiology, etc., are also dealt in a simplified manner.
- Provides an insight to the novel vaccine delivery systems and offers a glimpse into the future of vaccines.
- Contributions from leading experts in the field of vaccinology.

Vipin M Vashishtha MD FIAP
Director and Consultant Pediatrician
Mangla Hospital and Research Center
Bijnor, Uttar Pradesh, India

Ajay Kalra MD DCH MNAMS FIAP
Erstwhile Professor
Department of Pediatrics
SN Medical College
Agra, Uttar Pradesh, India

Available at all medical bookstores or buy online at www.jaypeebrothers.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers

Shelving Recommendation
PEDIATRICS

ISBN 978-93-90020-60-7

9 789390 020607