Immunization for persons infected with human immunodeficiency virus

Chitsanu Pancharoen, Jintanat Ananworanich, Usa Thisyakorn

Department of Pediatrics, Faculty of Medicine, Chulalongkorn University

and HIV-NAT, The Thai Red Cross AIDS Research Center

INTRODUCTION

Patients with human immunodeficiency virus (HIV) infection are at risk for several infections that can be prevented by immunizations. The potential benefits of immunization are clear. However, HIV disease may influence the risk for adverse events and the effectiveness of the vaccines.

HIV destroys CD4+ T cells and creates an environment of inappropriate immune activation rendering even the uninfected T cells and B cells dysfunctional. Therefore, both responses to T cell-dependent antigens (e.g. protein-derived vaccines) and T cell-independent antigens (e.g. polysaccharide vaccines) are affected. The immune response decreases as the HIV disease progresses. Fortunately, in this era of highly active antiretroviral therapy (HAART), new evidence suggests that one's ability to mount an immune response to vaccines can be restored to that of HIV-uninfected persons [52,65]

Types of vaccines do influence the nature of immune response. Vaccines using T-dependent antigens stimulate production of long-lasting cell-mediated and humoral immune responses, while T-independent antigenetic vaccines do not induce T-cell memory, and booster doses are not expected to produce substantially increased protection [15]. The response to higher doses of vaccine and the persistence of antibody in HIV-infected persons have not been systematically evaluated. Although higher doses or more frequent boosters may be considered for these patients, firm

recommendation cannot be made [13]. Live viral vaccines evoke a stronger and a more rapid immune response even after a single dose. In contrast, inactivated vaccines usually require more doses and longer time before adequate immunity is produced. However, in immunocompromised hosts, live viral vaccines have to be used with caution. Unlike patients with primary T-cell immunodeficiency such as severe combined immune deficiency in which live viral vaccines are absolutely contraindicated, HIV-infected persons usually have some preserved immunity; therefore, many live viral vaccines can be given to patients with mild HIV disease.

Another important issue is whether vaccines can worsen HIV disease by inducing CD4+ T cell activation, resulting in more production of HIV virions. Several studies have shown transient increase in plasma viremia after immunization [56,63,67,73,78]. However, this phenomenon is not always true according to other studies [25,34] and likely does not bear clinical significance.

The objectives of this article are to summarize principles and suggest recommendations for vaccinating HIV-infected persons.

INACTIVATED VACCINES

In general, there is no harm in vaccinating HIV-infected patients with inactivated vaccines although antibody response may be impaired especially in symptomatic HIV-infected patients. It is universally recommended that HIV-infected patients be immunized as soon as age-appropriate with these inactivated vaccines [3].

Hepatitis B virus (HBV) vaccine

Studies in infants born to HIV-infected mothers showed that children who

became infected with HIV responded poorly to HBV vaccine and the duration of protection was less, as compared to children who were not infected [7,68,76,83,85]. One study showed that the antibody response depended on CD4+ T cell count [68]. After completing vaccination with three conventional doses, the anti-HBs response of such persons should be measured, and those without protected antibody levels should be re-vaccinated with additional doses. Higher vaccine doses or increased number of doses may be required, however, firm recommendations cannot be made.

Watanaveeradej V et al studied antibody response to HBV vaccine in infants of HIV-positive mothers and found that the vaccine was well tolerated. The vaccine response rate of the HIV-infected group was 2/6 (33.3%), which was significantly lower than 20/21 (95.2%) for the HIV-uninfected group. Geometric mean antibody titers (GMTs) were 225.5 and 342.0 IU/L in the HIV-infected and HIV-uninfected groups, respectively [83].

Diphtheria and tetanus toxoids, and pertussis (DTPw/DTPa,DT/dT/dTpa) vaccine.

For HIV-infected children, DTP vaccine is indicated at the same schedule and dosing as for immunocompetent children. Acellular pertussis vaccine in the combined DTPa vaccine is preferred and is commonly used in developed countries because it has fewer side effects whereas whole cell pertussis vaccine in the combined DTPw vaccine is less costly and used more in developing countries. dT or dTpa vaccines can be used as a booster dose in HIV-infected adults.

Immunity against tetanus in HIV-infected patients tended to be similar to that of age-matched normal population, whereas the immunity to diphtheria was usually lower and might require re-vaccination especially in HIV-infected patients living or

traveling to areas where diphtheria exposure is possible [41,42,48,69]. Limited data is known about the antibody response to pertussis vaccine in HIV-infected persons.

Kroon FP et al found that after vaccination with diphtheria and tetanus toxoid, 61-73% and 78-100% of HIV-infected adults developed protective antibody titers of diphtheria and tetanus toxin, respectively. The mean titers of antibodies to diphtheria and tetanus were significantly lower in HIV-infected patients especially in those whose CD4+ T cell count was less than 200 cells/mm^3 [42].

Inactivated poliovirus (IPV) vaccine

IPV vaccine is the preferred poliovirus vaccine for HIV-infected patients. This vaccine eliminates the risk of vaccine-associated polio paralysis (VAPP) seen with oral poliovirus vaccine (OPV). However, the antibody response of IPV vaccine in HIV-infected adults was poor and correlated with CD4+ T cell count [42,79].

Vardinon N et al found that the rise in anti-poliovirus antibody titer after IPV administration was noted in HIV-infected subjects whose CD4+ T cell count was greater than 200 cells/mm^3 whereas the group with low CD4+ T cell count failed to respond [79].

***Haemophilus influenzae* type b (Hib) conjugate vaccine**

HIV-infected children are at risk for invasive Hib infection and should receive Hib conjugate vaccines at the same dosage and schedule as immunocompetent children. Early immunization before the patients develop immunologic suppression may improve the chance for normal antibody responses [84]. Similarly, after immune recovery from HAART, Hib vaccine should be re-administered [48]. Several studies have shown that HIV-infected patients did not respond well after Hib vaccination

especially those with low CD4+ T cell count [10,24,32,43,52,62,84].

Melvin AJ et al found that 14 of 18 (78%) previously immunized children who have HIV infection and were successfully treated with HAART had detectable antibody levels to Hib and 3 of the 4 (75%) without detectable antibodies seroconverted after re-immunization [52].

Pneumococcal vaccine

HIV-infected patients have a high risk of pneumococcal infections [19]. A study from Thailand showed that several children with invasive pneumococcal infection were HIV-infected and a number of cases were caused by drug-resistant pneumococci [58].

There are two types of pneumococcal vaccines, the recently developed protein-derived or pneumococcal conjugate vaccine and the polysaccharide-derived vaccine. In children, the pneumococcal conjugate vaccine is the preferred choice as it can elicit immune responses in children younger than 24 months while the polysaccharide vaccine cannot. Studies in HIV-infected children comparing the two types of vaccines have also demonstrated the conjugate vaccine to be significantly more immunogenic [13]. In HIV-infected Uganda adults, the occurrences of invasive pneumococcal diseases were not different in patients who received polysaccharide pneumococcal vaccine versus those who received placebo. Moreover, the patients who received the vaccine had higher prevalence of pneumonia from all causes [22]. A study comparing antibody responses using pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in HIV-infected adults did not find a significant difference between the two vaccines [20]. Nevertheless, available data suggests superior antibody responses with conjugate vaccine; therefore, it should also be the

preferred choice in HIV-infected adults.

Studies have documented that the antibody production to pneumococci after vaccination with either conjugate or polysaccharide vaccines were lower in HIV-infected patients than in healthy control subjects, and the seroconversion rate was low in patients with low CD4+ T cell count [1,11,35-37,44,64,84]. Slightly better responses were found with the conjugate vaccines [35]. Higher antibody concentrations were achieved after sequential vaccination with conjugate and polysaccharide vaccines [46]. In countries where pneumococcal conjugate vaccine is not available, unconjugate polysaccharide vaccine can be used as an alternative, usually after the age of two. Most evidence supports giving the vaccine as early as possible in the course of HIV infection in order to achieve the optimal antibody response.

Influenza vaccine

Influenza may cause severe complications in HIV-infected patients leading to increases in hospitalization and mortality. Annual influenza vaccine is recommended for HIV-infected children and adults. The antibody response to all types of influenza vaccines may be low in patients with advanced HIV-related illnesses and correlates with the number of CD4+ T cell count [8,16,30,38,39,47].

A review of published studies indicates that vaccination against influenza is well tolerated in both children and adults with HIV, but response to vaccination is lower than that observed in immunocompetent individuals. There have been studies reporting that immunization against influenza may stimulate an increase of HIV viral load and decrease of CD4+ T cell count [56,63,67]. The increased viral replication is usually transient and it is difficult to determine a clear, measurable progression of the

underlying HIV disease [86]. Therefore, vaccination against influenza can be safely administered to HIV-infected patients.

Japanese B encephalitis virus (JEV) vaccine.

JEV vaccine has been part of the Expanded Program for Immunization (EPI) in several countries with high prevalence of JEV including Thailand. There are no evidences supporting an increased risk for JEV infection in HIV-infected patients. The vaccine is theoretically safe and should be recommended in HIV-infected persons who live in or are traveling to areas with high prevalence of JEV. However, the antibody response to the vaccine may be impaired.

The only study on JEV vaccine in HIV-infected persons was done by Rojanasuphot S et al who found that 5 of 14 (36%) HIV-infected children and 18 of 27 (67%) uninfected children had positive JEV antibody titers after 2 doses of immunization [66].

Hepatitis A virus (HAV) vaccine

Generally, HAV vaccine is recommended for children living in areas with increased hepatitis A rates and for people with chronic liver disease. Several developing countries recommend the use of this vaccine in HIV-infected persons.

A study by Santagostino E et al on HIV-infected hemophiliacs who received HAV vaccine showed that seroconversion rates and antibody titers were significantly lower than those of HIV-uninfected patients [70].

LIVE VACCINES

Live attenuated vaccines may cause serious complications in HIV-infected patients with more advanced disease. Additionally, activating the immune system by vaccination potentially increases viral replication and may promote HIV disease progression. However, HIV-infected persons with no or minimal immune suppression can be immunized safely with live vaccines [2].

In some developing countries where routine HIV testing is not performed, the advantages of routine administration of live vaccines i.e. BCG, OPV and measles vaccines far outweigh the theoretical risks of complications from these vaccines. Also, vaccination at birth or early in life often results in an adequate immune response as it precedes HIV-induced immunosuppression. Therefore, the World Health Organization (WHO) and many countries recommend routine universal immunization with these vaccines.

Bacille Calmette-Guérin (BCG) vaccine

BCG vaccine is not routinely recommended for use in the United States for prevention of tuberculosis. However, in developing countries where the prevalence of tuberculosis is high, the WHO recommends that BCG vaccine be given to all neonates born to HIV-infected mothers although complications from BCG vaccine including disseminated BCG infection have been reported [5,9,12,27,29,54,55]. A large study in Zaire showing the low incidence of BCG-associated side effects [69] supports the continuing use of BCG vaccine in EPI of HIV-endemic countries. BCG vaccination should be avoided or administered with caution to symptomatic HIV-infected children and is not recommended for HIV-infected adults. However, it is quite safe in neonates as they usually have relatively

intact immunity immediately after birth. The benefit of the vaccine in protecting HIV-infected persons from tuberculosis are difficult to assess.

Thaithumyanon P et al found that BCG vaccine given to neonates born to HIV-positive mothers was safe. The tuberculin skin responses (BCG scar and tuberculin skin test) of HIV-infected children performed at the age of 9 months were less than those of HIV-uninfected children [74]. A few preliminary studies concerning other mycobacterial vaccines have been done [18,80,81]. These vaccines may have a role for the prevention of HIV-associated tuberculosis in the near future.

Oral poliovirus (OPV) vaccine

The benefits of poliovirus vaccines exceeds the potential risks in HIV-infected children. In most developed countries, OPV vaccine is no longer routinely recommended for use in HIV-infected children and members of their households. However, although a few cases of VAPP have been developed after receiving OPV, many hundreds of thousands of HIV-infected children have been immunized, with no convincing evidence that the risk of developing VAPP is increased in HIV-infected children [17,51,58,69]. Moreover, IPV vaccine is not always available in many developing countries and costs a lot more than OPV vaccine. OPV vaccine also has superior ability to induce intestinal immunity important for protection against wild poliovirus. Thus, many infectious disease experts from limited resource countries accept the use of OPV vaccine in HIV-infected children.

Measles vaccine or Measles-Mumps-Rubella (MMR) vaccine

Measles can be a life-threatening infection in immunocompromised hosts including HIV-infected persons [33]. A frequent complication, pneumonitis, is

associated with high mortality rates especially in the non-immunized.

The benefit of measles vaccine surpasses the potential risk in HIV-infected children. However, there has been a case report of an HIV-infected adult with severe immunologic suppression who developed progressive fatal pneumonitis after receiving measles vaccine [4,14,82].

MMR vaccine should be administered to HIV-infected children at 9 to 12 months of age unless the children are severely immunocompromised (category 3 or CD4+ T cell < 15%). The second dose of MMR vaccine may be administered as soon as 4 weeks after the first dose rather than waiting until school entry. Children receiving routine intravenous immunoglobulin prophylaxis may not respond to MMR vaccine. Children with symptomatic HIV infection, when exposed to measles, should be considered susceptible regardless of their history of immunization and should receive, if indicated, passive immunoprophylaxis.

HIV-infected children frequently respond poorly to measles and MMR vaccination and failure from measles vaccine is common [6,23,40,75]. Thaithumyanon P et al found that 7 of 29 (24.1%) HIV-infected children had detectable measles antibody at 2 weeks post-vaccination. A decrease of antibody was noted in 2 symptomatic HIV-infected children as their disease progressed. Potential predictors of vaccine response including CD4+ T cell count were not statistically different between the responders and the non-responders [75].

Varicella-zoster virus (VZV) vaccine

HIV-infected children may be at an increased morbidity risk from varicella and herpes zoster. Limited data on varicella immunization of HIV-infected in CDC immunologic category 1 indicates that the vaccine is safe, immunogenic, and

effective. Pneumonia caused by varicella vaccine was reported in an HIV-infected patient [72]. Weighing potential and benefit risks, varicella vaccine should be considered for HIV-infected children in CDC categories N1 (no symptoms) and A1 (mild symptoms with CD4+ T cell $\geq$ 24%). Symptomatic HIV-infected persons exposed to varicella should be considered susceptible regardless of their history of immunization and should receive varicella zoster immunoglobulin.

Levin MJ et al studied the safety and immunogenicity of VZV vaccine in children with mildly symptomatic HIV infection (N1 and A1) and found that the vaccine was safe and associated with only mild local and systemic reactions. Vaccination also had no effect on the HIV disease progression or on the HIV viral load. However, the antibody response was impaired, with only 60% of subjects having anti-VZV antibody [49].

OTHERS

Rabies vaccine

Dog bites are a serious public health problem in developing countries. In Thailand, more than a quarter of victims were children [59]. With HAART therapy, HIV-infected children tend to live longer [61], thus they may be at risk for rabies exposure.

The WHO Expert Committee on Rabies recommended using a double dose of rabies vaccine, given at different sites, for subjects who are immunocompromised and have been exposed to rabies. No published study testing this empirical recommendation had been published. Thisyakorn U et al evaluated the safety and immunogenicity of pre-exposure human diploid-cell rabies vaccine (HDCV) in HIV-infected children and found that GMTs of rabies antibody in HIV-infected

children were significantly lower than those in the control healthy group. GMTs in HIV-infected children with CD4+ T cell count less than 15% was significantly lower than those in HIV-infected children with CD4+ T cell count of 15% or more [77]. The vaccines were well tolerated. A transient increase of viral load was found in a few patients [78]. Pancharoen C et al [60] reported a 6-year-old HIV-infected girl with severe immunologic suppression (CD4+ T cell count = 4%) who failed to respond to intramuscular preexposure rabies vaccination on days 0,7,28; and intradermal postexposure rabies vaccination at 4 sites on days 0,3,7 and at 2 sites on days 30,90 (double the usual dose).

If possible, the titers of neutralizing antibodies in all HIV-infected, rabies-exposed patients should be determined on days 14 and 28 after rabies vaccination to ensure adequate response. Use of rabies immunoglobulin may be another solution especially in patients with severe immunologic suppression. Further studies are urgently needed to determine the proper methods of rabies immunization in HIV-infected, rabies-exposed persons.

Typhoid vaccine.

HIV infection is an important risk factor for invasive salmonella infection. A study from Thailand showed that a number of children with nontyphoidal nonparatyphoidal salmonella bacteremia were HIV-infected [57]. However, there is no strong evidence supporting that infection with *Salmonella typhi* is more frequently observed in HIV-infected persons.

Live, attenuated TY21a typhoid vaccine should not be administered to HIV-infected persons. Parenteral inactivated vaccine is a theoretically safer alternative but the immunogenicity of this vaccine may not as good in HIV-infected as that in

immonocompetent persons. The vaccine should be indicated for HIV-infected persons who live in or are traveling to an endemic area for typhoid fever.

Kroon FP et al found that the proportion of the HIV-infected persons vaccinated with typhoid vaccine and had protective antibody against *S. typhi* was lower than that in healthy controls. The antibody response was correlated with CD4+ T cell count [45].

EFFECT OF CO-MORBID CONDITIONS ON IMMUNE RESPONSE

Malnutrition and concurrent infections are common co-morbidities in patients with HIV infection. Both have a deleterious effect on the immune system and can affect how patients respond to vaccines. A vicious cycle frequently develops: cytokine release from infections can increase catabolism and decrease intake leading to wasting while malnutrition-related immune dysfunction can lead to more infections [28,50,71]. In certain infection such as *Mycobacterium avium* complex or tuberculosis, weight loss is almost universally seen.

Malnutrition mainly affects T-cell function; therefore, immune response to T-dependent antigenic vaccines can be diminished [21] while antibody response to polysaccharide vaccines are usually preserved [53].

Opportunistic infections promote the release of inflammatory cytokines, which can increase HIV viral load production and render cells inappropriately activated. Cell-associated organisms such as *Mycobacterium tuberculosis* and cytomegalovirus can reduce mature HLA complexes displayed on cell membrane and interfere with natural killer cell, complement and neutralizing antibody function [26,31]. These can cause an adverse effect on the immune response.

RECOMMENDATIONS

Recommendations for immunization in HIV-infected persons may differ from country to country. Considerations depend on the cost benefit of each vaccine i.e. the availability and affordability of the vaccine and the prevalence and mortality of each vaccine-preventable disease. Recommendations used for developed countries may need to be somewhat different from those recommended for developing countries (see table). A frequently encountered problem in HIV-infected children is incomplete immunization due to frequent illnesses or lack of a committed caregiver. It is very important to provide "Catch Up" immunization to these children as soon as possible. Another common occurrence is the inability to locate immunization records especially in orphans. In such circumstances, one should consider these children un-immunized and provide immunization appropriate for age. Alternatively, antibody levels could be measured to determine protection to different infections. Household contacts of HIV-infected persons should also be immunized against common preventable infections.

Summary of important issues include:

1. BCG vaccine can be used for all infants born to HIV-positive mothers in countries where tuberculosis is prevalent. The vaccine should not be administered in symptomatic HIV-infected children and in all HIV-infected adults.

2. DTP vaccine can be used safely in HIV-infected children. DTPa is preferred in developed countries whereas DTPw is commonly used in developing countries. dT or dTpa may be used as a booster vaccine for HIV-infected adults.

3. IPV vaccine is recommended in HIV-infected children. However, OPV vaccine can be used with caution, especially in HIV-infected children with severe immunologic suppression.

4. Hib, pneumococcal and VZV vaccines are classified as optional vaccines for healthy children from most developing countries including Thailand. These vaccines, if possible, should be used in HIV-infected persons. VZV vaccine is not recommended in HIV-infected children with moderate or severe immunologic suppression.

5. HAV vaccine may be beneficial in HIV-infected persons who live in high prevalence areas.

6. Preexposure rabies vaccination may be offered to HIV-infected persons who live in areas with rabies exposure.

CONCLUSIONS

Immunization is essential for HIV-infected children and adults. Antibody response in these patients is usually not as good as that in immunocompetent persons and correlates mainly with the level of CD4+ T cell count. Certain vaccines activate virus replication, and transiently decrease CD4+ T cell count and increase viral load. Inactivated vaccines are safe whereas certain live vaccines may be harmful when given to severely immunocompromised patients. The use of HAART can restore immune response to vaccines. Each country needs to have its own recommendation for immunizing HIV-infected persons. Vaccine trials are needed to obtain the best immunization strategy.

Table. Recommendations for routine immunization of HIV-infected children in developed and developing countries.

Vaccines	Type of countries		Comments
	Developed	Developing	
BCG	No	Yes	Safe when given at birth. Avoid in symptomatic HIV-infected children and all HIV-infected adults
HBV	Yes	Yes	
DTP	DTPa	DTPw	dT and dTpa may be used in adults.
IPV/OPV	IPV	OPV	OPV may be used with caution.
Hib	Yes	Yes	
MMR	Yes	Yes	Not recommended if severely immunologic suppressed.
JEV	No	Yes	Should be used in endemic area of JEV.
VZV	Yes	Yes	Not recommended if moderately or severely immunologic suppressed.
Pneumococcal	Yes	Yes	
Influenza	Yes	Yes	
HAV	No	Yes	Should be used in area with endemic HAV.
Rabies	No	Yes	Considered if high risk of rabies exposure

Note: HIV=human immunodeficiency virus, BCG= Bacille Calmette-Guérin, HBV=hepatitis B virus, DTPa=diphtheria-tetanus-acellular pertussis, DTPw=diphtheria-tetanus-whole cell pertussis, IPV=inactivated poliovirus, OPV=oral poliovirus, Hib=*Hemophilus influenzae* type b, MMR=measles-mumps-rubella, JEV=Japanese B encephalitis virus, VZV=*Varicella zoster* virus, HAV=hepatitis A virus

References

(1) Ahmed F, Steinhoff M, Rodriguez-Barradas MC, Hamilton RG, Musher DM, Nelson KE. (1996). Journal of Infectious Diseases. 173:83-90.

(2) American Academy of Pediatrics. (2003). Immunization in special circumstances. In: Pickering LK Ed, Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics. pp 66-98.

(3) American Academy of Pediatrics. (2003). Human immunodeficiency virus infection. In: Pickering LK Ed, Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics. pp 360-382.

(4) Angel JB, Walpita P, Lerch RA, Sidhu MS, Masurekar M, DeLellis RA, Noble JT, Snydman DR, Udem SA. (1998). Annals of Internal Medicine. 129:104-106.

(5) Armbruster C, Junker W, Vetter N, Jaksch G. (1990). Journal of Infectious Diseases. 162:1216.

(6) Arpadi S, Markowitz L, Baughman AL, Shah K, Adam H, Wiznia A, Lambert G, Dobroszycki J, Health JL, Bellini WJ. (1996). Pediatrics. 97:653-657.

(7) Arrazola MP, de Juanes JR, Ramos JT, Aragon AJ, Garcia de Codes A. (1995). Journal of Medical Virology. 45:339-341.

(8) Benne CA, Kroon FP, Harmsen M, Tavares L, Kraaijeveld CA, De Jong JC. (1998). Clinical and Diagnostic Laboratory Immunology. 5:114-117.

(9) Besnard M, Sauvion S, Offredo C, Gaudelus J, Gaillard JL, Veber F, Blanche S. (1993). Pediatric Infectious Disease Journal. 12:993-997.

(10) Boudes P, Sobel A, Deforges L, Leblic E. (1989). Journal of American

Medical Association. 262:2386.

(11) Carson PJ, Schut RL, Simpson ML, O'Brien J, Janoff EN. (1995). Journal of Infectious Diseases. 172:340-345.

(12) Centers for Disease Control and Prevention. (1985). Morbidity and Mortality Weekly Report 34:227-228.

(13) Centers for Disease Control and Prevention. (1993). Morbidity and Mortality Weekly Report. 42(No.RR-4):1-18.

(14) Centers for Disease Control and Prevention. (1996). Morbidity and Mortality Weekly Report 45:603-606.

(15) Centers for Disease Control and Prevention. (2002). Morbidity and Mortality Weekly Report 51(No.RR02):1-36.

(16) Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. (1994). Pediatric Infectious Disease Journal. 13:206-211.

(17) Chitsike I, Furth RV. (1999). British Medical Journal 318:841-843.

(18) Collins DM. (2000). Immunology and Cell Biology. 78:342-348.

(19) Dworkin MS, Ward JW, Hanson DL, Jones JL, Kaplan JE. (2001). Clinical Infectious Diseases. 32:794-800.

(20) Feikin DR, Elie CM, Goetz MB, Lennox JL, Carlone GM, Romero-Steiner S, Holder PF, O'Brien WA, Whitney CG, Butler JC, et al. (2001). Vaccine. 20:545-553.

(21) Ferguson AC, Lawlor GJ Jr, Neumann CG, Oh W, Stiehm ER. (1974). Journal of Pediatrics. 85:717-723.

(22) French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K, Moore M, Antvelink D, Mulder D, Janoff EN, et al. (2000). Lancet. 355:2106-2111.

(23) Frenkel LM, Nielsen K, Garakian A, Cherry JD. (1994). Archives of

Pediatrics and Adolescent Medicine. 148:57-60.

(24) Gibb D, Giacomelli A, Masters J, Spoulou V, Ruga E, Griffiths H, Kroll S, Giaquinto C, Goldblatt D. (1996). Pediatric Infectious Disease Journal. 15:1097-1101.

(25) Glesby MJ, Hoover DR, Farzadegan H, Margolick JB, Saah AJ. (1996). Journal of Infectious Diseases. 174:1332-1336.

(26) Griffiths PD. (2001). Encyclopedia of Life Sciences. www.els.net.

(27) Hesseling AC, Schaaf HS, Hanekom WA, Beyers N, Cotton MF, Gie RP, Marais BJ, van Helden P, Warren RM. (2003). Clinical Infectious Diseases. 37:1226-1233.

(28) Hira S, Dupont H, Lanjewar D, Dholakia Y. (1998). National Medical Journal of India. 11:256-258.

(29) Houde C, Dery P.(1988). Pediatric Infectious Disease Journal. 7:810-812.

(30) Jackson CR, Vavro CL, Valentine ME, Pennington KN, Lanier ER, Katz SL, Diliberti JH, McKinney RE, Wilfert CM, St Clair MH. (1997). Pediatric Infectious Disease Journal. 16:200-294.

(31) Janeway CA, Travers P, Walport M, Capra JD. (1999). Immunobiology. The Immune System in Health and Disease. 4th ed. London: Elsevier Science Ltd/Garland Publishing.

(32) Kale KL, King JC Jr, Farley JJ, Vink PE, Cimino CO, Paradiso PR. (1995). Pediatric Infectious Disease Journal. 14:350-354.

(33) Kaplan LJ, Daum RS, Smaron M, McCarthy CA. (1992). Journal of the American Medical Association. 267:1237-1241.

(34) Keller M, Deveikis A, Cutillar-Garcia M, Gagajena A, Elkins K, Plaeger S, Bryson Y, Kaplan A, Zangwill K, Chang SJ. (2000). Pediatric Infectious

Disease Journal. 19:613-616.

(35) King JC Jr, Vink PE, Farley JJ, Parks M, Smilie M, Madore D, Lichenstein R, Malinoski F. (1996). Pediatric Infectious Disease Journal. 15:192-196.

(36) King JC Jr, Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. (1997). Pediatrics. 99:575-80.

(37) King JC Jr, Vink PE, Chang I, Kimura A, Parks M, Smilie M, Lichenstein R, Farley JJ. (1997). Vaccine. 16:361-365.

(38) King JC Jr, Treanor J, Fast PE, Wolff M, Yan L, Iacuzio D, Readmond B, O'Brien D, Mallon K, Highsmoth WE, et al. Journal of Infectious Diseases. 181:725-728.

(39) King JC Jr, Fast PE, Zangwill KM, Weinberg GA, Wolff M, Yan L, Newman F, Belshe RB, Kovacs A, Deville JG, Jelonek M, HIV Influenza Study Group. (2001). Pediatric Infectious Disease Journal. 20:1124-1131.

(40) Krasinski K, Borkowsky W. (1989). Journal of the American Medical Association. 261:2512-2516.

(41) Kroon FP, van Dissel JT, de Jong J, van Furth R. (1994). AIDS. 8:469-476.

(42) Kroon FP, van Dissel JT, Labadie J, van Loon AM, van Furth R. (1995). Clinical Infectious Diseases. 21:1197-1203.

(43) Kroon FP, van Dissel JT, Rijkers GT, Labadie J, van Furth R. (1997). Clinical Infectious Diseases. 25:600-606.

(44) Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. (1999). Vaccine. 18:524-530.

(45) Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. (1999). Vaccine. 17:2941-2945.

(46) Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. (2000). Vaccine. 19:886-894.

(47) Kroon FP, van Dissel JT, de Jong JC, Zwinderman K, van Furth R. (2000). Vaccine. 18:3040-3049.

(48) Kurtzhals JA, Kjeldsen K, Heron I, Skinhoj P. (1992). APMIS. 100:803-808.

(49) Levin MJ, Gershon AA, Weinberg A, Blanchard S, Nowak B, Palumbo P, Chan CY; AIDS Clinical trials Group 265 Team. (2001). Journal of Pediatrics. 139:305-310.

(50) Lin E, Kotani JG, Lowry SF. (1998). Nutrition. 14:545-550.

(51) Moss WJ, Clements CJ, Halsey NA. (2003). Bulletin of World Health Organization. 81;61-70.

(52) Melvin AJ, Mohan KM. (2003). Pediatrics. 111:e641-644.

(53) Neumann CG, Lawlor CJ Jr, Stiehm ER, Swenseld ME, Newton C, Herbert J, Ammann AJ, Jacob M. (1975). American Journal of Clinical Nutrition. 28:89-104.

(54) Ninane J, Grymonprez A, Burtonboy G, Francois A, Cornu G. (1988). Archives of Disease in Childhood. 63:1268-1269.

(55) O'Brien KL, Ruff AJ, Louis MA, Desormeaux J, Joseph DJ, McBrien M, Coberly J, Boulos R, Halsey NA. (1995). Pediatrics 95:414-418.

(56) O'Brien WA, Grovit-Ferbas K, Namazi A, Ovcak-Derzic S, Wang HJ, Park J, Veramian C, Mao SH, Zack JA. (1995). Blood. 86:1082-1089.

(57) Pancharoen C, Thisyakorn U. (1999). Nontyphoidal nonparatyphoidal salmonellosis, an emerging problem in Thailand. In: Proceedings of the Fourth International Symposium on Typhoid Fever and Other Salmonellosis, Taiwan. pp 77-81.

(58) Pancharoen C, Chongthaleong A, Reinprayoon S, Thisyakorn U. (2001). Journal of the Medical Association of Thailand 84:1246-1250.

(59) Pancharoen C, Lawtongkum W, Thisyakorn U, Wilde H. (2001). Wilderness and Environmental Medicine 12:239-243.

(60) Pancharoen C, Thisyakorn U, Tantawichien T, Khawplod P, Wilde H. (2001). Scandinavian Journal of Infectious Diseases 33:390-391.

(61) Pancharoen C, Thisyakorn U. (2003). Expert on Opinion Pharmacotherapy. 4:179-182.

(62) Peters V, Sood S. (1994). Journal of Pediatrics. 125:74-77.

(63) Ramilo O, Hicks PJ, Borvak J, Gross LM, Zhong D, Squires JE, Vitetta ES. (1996). Pediatric Infectious Disease Journal. 15:197-203.

(64) Rodriguez-Barradas MC, Musher DM, Lahart C, Lacke C, Groover J, Watson D, Baughn R, Cate T, Crofoot G. (1992). Journal of Infectious Diseases. 165:553-556.

(65) Rodriguez-Barradas MC, Alexandraki I, Nazir T, Foltzer M, Musher DM, Brown S, Thornby J. (2003). Clinical Infectious Diseases. 37:438-447.

(66) Rojanasuphot S, Shaffer N, Chotpitayasunondh T, Phumiamorn S, Moch P, Chearskul S, Waranawat N, Yuentrakul P, Mastro TD, Tsai TF. (1998). Southeast Asian Journal of Tropical Medicine and Public Health. 29:443-450.

(67) Rosok B, Voltersvik P, Bjerknes R, Axelsson M, Haabeim LR, Asjo B. (1996). Clinical and Experimental Immunology. 104:203-207.

(68) Rutstein RM, Rudy B, Codispoti C, Watson B. (1994). AIDS. 8:1281-1284.

(69) Ryder RW, Oxtoby M, Mvula M, Batter V, Baende E, Nsa W, Davachi F, Hassig S, Onorato I, Deforest A, et al. (1993). Journal of Pediatrics. 122:697-702.

(70) Santagostino E, Gringeri A, Rocino A, Zanetti A, de Biasi R, Mannucci PM. (1994). Thrombosis and Haemostasis. 72:508-510.

(71) Schmidt K. (1997). International Journal of Vitamin and Nutritional Research. 67:307-311.

(72) Sharrar RG, LaRussa P, Galea SA, Steinberg SP, Sweet AR, Keatley RM, Wells ME, Stephenson WP, Gershon AA. (2000). Vaccine. 19:916-923.

(73) Stanley SK, Ostrowski MA, Justement JS, Gannt K, Hedayati S, Mannix M, Roche K, Schwartzentruber DJ, Fox CH, Fauci AS. (1996). New England Journal of Medicine. 334:1222-1230.

(74) Thaithumyanon P, Thisyakorn U, Punnahitananda S, Praisuwanna P, Ruxrungtham K. (2000). Southeast Asian Journal of Tropical Medicine and Public Health. 31:482-486.

(75) Thaithumyanon P, Punnahitananda S, Thisyakorn U, Praisuwanna P, Ruxrungtham K. (2000). Southeast Asian Journal of Tropical Medicine and Public Health. 31:658-662.

(76) Thaithumyanon P, Punnahitananda S, Praisuwanna P, Thisyakorn U, Ruxrungtham K. (2002). Journal of the Medical Association of Thailand. 85:277-282.

(77) Thisyakorn U, Pancharoen C, Ruxrungtham K, Ubolyam S, Khawplod P, Phanuphak P, Wilde H. (2000). Clinical Infectious Diseases 30:218.

(78) Thisyakorn U, Pancharoen C, Wilde H. (2001). Vaccine. 19:1534-1537.

(79) Vardinon N, Handsher R, Burke M, Zacut V, Yust I. (1990). Journal of Infectious Diseases. 162:238-241.

(80) Vuola JM, Ristola MA, Cole B, Jarviluoma A, Tvaroha S, Ronkko T, Rautio O, Arbeit RD, Reyn CF. (2003). AIDS. 17:2351-2355.

(81) Waddell RD, Chintu C, Lein AD, Zumla A, Karagas MR, Baboo KS, Habbema JD, Tosteson AN, Morin P, Tvaroha S, et al. (2000). Clinical Infectious Diseases. 30:S309-315.

(82) Wallace MR, Hooper DG, Graves SJ, Malone JL. (1994). Vaccine 12:1222-1224.

(83) Watanaveeradej V, Samakoses R, Kerdpanich A, Aree C, Nitayabhan S, Viputtikul K, Sukwit S, Simasathien S. (2002). International Journal of Infectious Diseases. 6:240-241

(84) Weiss PJ, Wallace MR, Oldfield EC 3rd, O'Brien J, Janoff EN. (1995). Journal of Infectious Diseases. 171:1217-1222.

(85) Zuccotti GV, Riva E, Flumine P, Locatelli V, Fiocchi A, Tordato G, Giovannini M. (1994). Journal of Pediatrics. 125:70-72.

(86) Zanetti AR, Amendola A, Besana S, Boschini A, Tanzi E. (2002). Vaccine. 20:B29-B32.