

ADULT IMMUNIZATION – A NEGLECTED ISSUE IN SOUTHEAST ASIA

Ilina Isahak

Department of Medical Microbiology and Immunology, Faculty of Medicine, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia

On behalf of the Steering Committee for Prevention and Control of Infectious Diseases in Asia: Graham Cooksley (Chairman), Clinical Research Center, Royal Brisbane Hospital, Queensland, Australia; Veronica Chan, College of Public Health, Manila, Philippines; Ilina Isahak, Department of Medical Microbiology and Immunology, Faculty of Medicine, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia; Jacob John, Department of Clinical Virology and Immunology, Christian Medical College Hospital, Tamil Nadu, India; Prayura Kunasol, Department of Communicable Disease Control, Ministry of Public Health, Nonthaburi, Thailand; Lee Bee Wah, Pediatric Department, National University Hospital, Lower Kent Ridge Road, Singapore; Somsak Lolekha, Pediatric Department, Ramanthibodi Hospital, Bangkok, Thailand; Ng Han Seong, Department of Gastroenterology, Singapore General Hospital, Singapore; Estrella Paje-Villar, Faculty of Medicine and Surgery, University of Santo Tomas, Manila, Philippines; H Ali Sulaiman, Department of Internal Medicine, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia; Yong Poovorawan, Pediatric Department, Chulalongkorn University, Bangkok, Thailand; Sofyan Ismael, Department of Child Health, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia; Ha Ba Khiem, Pasteur Institute, Ho Chi Minh City, Vietnam.

Abstract. Adult immunization is a neglected and underpublicised issue in Southeast Asia. Vaccine-preventable diseases cause unnecessary morbidity and mortality among adults in the region, while inadequate immunization results in unnecessary costs, including those associated with hospitalization, treatment, and loss of income. Childhood vaccination coverage is high for the EPI diseases of diphtheria, tetanus and pertussis; however, unvaccinated, undervaccinated, and aging adults with waning immunity remain at risk from infection and may benefit from vaccination. Catch-up immunization is advisable for adults seronegative for hepatitis B virus, while immunization against the hepatitis A and varicella viruses may benefit those who remain susceptible. Among older adults, immunization against influenza and pneumococcal infections is likely to be beneficial in reducing morbidity and mortality. Certain vaccinations are also recommended for specific groups, such as rubella for women of child-bearing age, typhoid for those travelling to high-endemicity areas, and several vaccines for high-risk occupational groups such as health care workers. This paper presents an overview of a number of vaccine-preventable diseases which occur in adults, and highlights the importance of immunization to protect those at risk of infection.

INTRODUCTION

Immunization policies in Southeast Asia have been primarily directed towards vaccinating infants and children. With the focus on childhood immunization, the importance of adult immunization has been overlooked, making it a neglected and under-publicised issue in this region. A substantial proportion of vaccine-preventable morbidity and mortality occurs among adults worldwide (Fedson, 1994; Marth, 1997; Bouvet and Micoud, 1997).

While many infections predominantly affect younger adults, others occur more commonly among middle-aged and older adults. Inadequate immunization against these infections results in substantial and unnecessary costs, both in terms of hospitalization and treatment, and in lost income (Fedson, 1994).

A range of factors contribute to low immunization levels among adults. (Fedson, 1994; Marth, 1997; Zimmerman and Clover, 1995; Gardner *et al*, 1996). Many adults are not aware of the need for immunization, others are concerned about potential side-effects, while the cost of vaccination and access to vaccines and vaccine delivery services may be a barrier for some. Health care providers may miss opportunities to offer vaccination, and overlook indications based on lifestyle

Correspondence: Ilina Isahak, Department of Medical Microbiology and Immunology, Faculty of Medicine, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

Tel: 60-39702203; Fax: 60-39737336

or occupational exposures. While pediatricians routinely consider the vaccination status of their patients, many physicians treating adult patients do not. However, specialist physicians may have heightened opportunities to identify indications for immunization; for instance, practitioners specializing in the treatment of geriatric patients are more likely to consider the need for vaccination against influenza and pneumococcal infections than physicians treating younger patients.

Adult immunization could do much to reduce morbidity and mortality associated with vaccine-preventable infections. Catch-up immunization against the Expanded Program on Immunization (EPI) diseases is important to protect adults who were not vaccinated as children, while others may require boosters to provide ongoing immunity as they age (Zimmerman and Clover, 1995; Hewlett, 1992; Keitel and Edwards, 1993; Laforce, 1993). Those at increased risk of infection, such as individuals prone to occupational or travel-related exposure, may be additional candidates for immunization, while older adults may benefit from immunization against infections primarily affecting the elderly (Zimmerman and Clover, 1995).

This paper presents an overview of several vaccine-preventable infections which occur in adults, and highlights the importance of immunization to provide protection against unnecessary illness and death. Additional vaccine-preventable infections that relate specifically to travellers and not to the general adult population, such as Japanese encephalitis and yellow fever, have not been included.

Diphtheria

In the late 1970s, the introduction of diphtheria into the EPI in Southeast Asian countries brought about a marked decrease in the incidence of this disease. However, high childhood vaccination has led to a decrease in circulation of the causative organism, *Corynebacterium diphtheriae*. As a consequence, adults who were not vaccinated against diphtheria as children have limited opportunities to acquire natural immunity and therefore remain susceptible to infection. Those who were vaccinated as children experience waning immunity, becoming susceptible to infection over time. This phenomenon has led to a major shift in the age-distribution of the disease in all countries where a high vaccine coverage has been attained. In the USA, for example, the proportion of cases among adults rose from 18% in 1958 to more than 80% in 1977 (Galazka and Robertson, 1995). Serologic

studies suggest that 20-60% of American adults older than 20 years are susceptible to infection (Pinner, 1996), while in France, an antibody survey of over 1,000 adults found just under half to be protected against diphtheria, with a lower level of protection among women and people over 65 years of age (Bouvet and Micoud, 1997).

Recent outbreaks in Europe and Asia have indicated the potential for the re-emergence of diphtheria if appropriate protective measures are not taken. In the former Soviet Union, reported cases increased from 839 in 1989 to approximately 48,000 in 1994 (Pinner, 1996). In Jordan, Sudan, Algeria and China, outbreaks have occurred despite the fact that vaccination coverage has been high for a number of years (Galazka and Robertson, 1995). The impact of immunization is evident in the age distribution of cases in these outbreaks, with many more adolescents and adults affected than in pre-vaccine years.

In the Southeast Asian region, vaccine coverage is generally high and the incidence of diphtheria is low. However, outbreaks in the region have occurred. In Thailand, despite a DTP-3 coverage rate of 90%, small outbreaks of diphtheria have been reported in several provinces in recent years. In 1994, a cluster of 18 cases were reported in the Saraburi Province, where no cases had been reported in the previous year (Centers for Disease Control, 1996). In 1996, diphtheria was reported in 7 provinces, the total number of cases reaching 53, up from only 19 cases in the previous year (Department of Communicable Disease Control, 1996). Such outbreaks indicate that, despite infant vaccination, a proportion of the population remain susceptible to infection. Further evidence of adults' susceptibility to diphtheria has arisen from seroprevalence studies in the region. A survey in the Phrae Province of Thailand found an overall seroprevalence of 80% among people 0-59 years of age, with the lowest levels among those aged 50-59 years (Udom, 1996). Serological studies in India have also demonstrated declining seroprotection; in one such study, 53% of adults 21-30 years of age and 83% of those over 30 years of age were found to have antibodies below the protective level (Nivsarkar *et al*, 1994).

Declining seroprevalence among adults, evidence for a recent shift in the age-distribution of cases, and the potential for outbreaks among susceptible populations provide support for the immunization of adults against diphtheria. Only a fraction of the childhood dose of diphtheria

vaccine is required for adults, and it is preferable that the diphtheria-tetanus booster (Td) be used rather than the monovalent diphtheria vaccine, so that immunity against both infections is boosted at the same time.

Tetanus

In Southeast Asia, the success of childhood immunization programs has led to a marked decline in the incidence of tetanus. However, this infection continues to occur in adults who are under-immunized or unimmunized, and in neonates born to unimmunized mothers.

Neonatal tetanus

Despite a dramatic decline in the incidence of neonatal tetanus (NT) since the early 1980s, a considerable number of cases continue to occur in some Southeast Asian countries, largely as a result of incomplete vaccination coverage (Gasse, 1995). In the Philippines, a recent case-control study revealed inadequate tetanus toxoid (TT) vaccination coverage among mothers, with lack of information about the vaccine and low availability given as the primary reasons for non-immunization (Baltazar and Sarol, 1994). Results of the study indicated that infants born to mothers who have received less than two doses of TT are 15 times more likely to develop neonatal tetanus than those born to fully vaccinated mothers. In Indonesia, interviews with health workers and birth attendants revealed a low awareness of the importance of TT immunization of pregnant women (de Haas *et al*, 1994). Similarly, a Thai survey found evidence of incomplete vaccination coverage in those provinces with the highest incidence of NT (Chongsuvivatwong *et al*, 1993). In India, a recent evaluation in Rajasthan revealed only 46-57% of mothers to be fully immunized with TT (Singh *et al*, 1996) while a study in a rural area identified maternal immunization as the single most effective intervention for the prevention of NT, finding two doses of TT to be associated with an 88% reduction in risk (Gupta and Keyl, 1998).

Adult tetanus

Aside from NT, the incidence of tetanus among adults is far higher than among children. While high DTP coverage ensures that most children are protected, immunity against tetanus wanes over time, leaving older adults susceptible to infection. Particularly vulnerable are elderly persons, who not only lack immunity but are liable to ac-

cidents and injuries (Dey and Chaudhury, 1997). In the USA and Europe, tetanus has become a geriatric disease, with the majority of cases occurring in persons aged 60 years or older, particularly women (Laforce, 1993; Bouvet and Micoud, 1997).

Several surveys in a number of countries, including the USA (Laforce, 1993) and Germany (Doller, 1993) have indicated that at least half of adults aged 65 years and over have tetanus antibody levels below that considered to be protective. Susceptibility among adults has also been demonstrated in Southeast Asia. A 1993 serological study in Singapore found that antibody prevalence declined with age, falling from 99% among children aged 5-9 years, to 79% in those aged 30-39 years, and only 50% in those aged 40 and above (The Committee on Epidemic Diseases, 1995a). In a serological study among young adults in Delhi, India, only 76% of those surveyed had protective antibodies to tetanus (Ichhpujani *et al*, 1993).

To address the problem of waning immunity in adults, booster vaccinations (preferably with the Td vaccine) are advisable for all adults on a ten-yearly basis, as recommended in the USA, Europe and other industrialized countries. In addition, tetanus toxoid vaccination is clearly indicated for all seronegative pregnant women, to protect both mother and infant from tetanus infection.

Pertussis

Despite a substantial decline in incidence since the inclusion of pertussis in the EPI, the World Health Organization (WHO) estimates that more than half a million deaths continue to result from pertussis each year. Recently, attention has been drawn to the increasing incidence of pertussis among adolescents and adults (Keitel and Edwards, 1995). In the USA, for example, the proportion of cases of pertussis in people over 10 years of age rose from 15% in 1977-1979 to 27% in 1992-1993 (Centers for Disease Control, 1995).

The increased recognition of post-childhood pertussis is attributable in part to the more widespread availability of appropriate microbiological testing. However, the true incidence of pertussis among adults is likely to be greatly underestimated, as cough in adults is under-reported, and the non-specific nature of pertussis symptoms in adults leads to difficulty in diagnosis (Hewlett, 1992; Keitel and Edwards, 1995; Cherry, 1998; Edwards, 1993). Several studies investigating the incidence

of pertussis in adults have found that between 12-32% of those presenting with prolonged cough have clinical pertussis, independent of childhood vaccination status (Cherry, 1998). Moreover, adults and adolescents are thought to be an important reservoir of infection for infants and children, including newborn babies unable to benefit from either passively acquired antibodies or scheduled immunization (Rothstein *et al*, 1993).

There is a lack of epidemiological data on pertussis in Southeast Asian countries. Although the current incidence of pertussis in the region is low relative to pre-vaccine years, it is likely that – as elsewhere – the true incidence among adolescents and adults is much higher than reported, and that individuals in these age groups are an important source of infection for infants and children. A 1993 serological survey of 0-40 year old people in Singapore found an overall pertussis antibody prevalence of 70%, with the lowest prevalence (50%) among adolescents in the 15-19 year age group (Ministry of the Environment, 1995).

It is well known that immunity against pertussis wanes over time, and that neither natural infection nor immunization can provide life-long immunity. Available evidence suggests that individuals fully immunized as children become susceptible to infection within 10 to 12 years (Keitel and Edwards, 1995). Numerous documented outbreaks have confirmed that outbreaks can occur within highly immunized populations, and that the likelihood of developing clinical pertussis increases with the number of years since immunization (Keitel and Edwards, 1995). Boosters may therefore be necessary to counter waning immunity in adulthood, providing the additional benefit of protecting unimmunized infants who might otherwise be infected by carrier adults. The availability of immunogenic acellular pertussis vaccines – developed in response to concerns about the reactogenicity of whole-cell pertussis vaccines – is likely to play an important role in future adult immunization against this infection.

Hepatitis B

Hepatitis B virus (HBV) is widespread throughout the developing world, where it is a serious public health concern due to both acute and chronic disease. It is estimated that approximately 2 billion people have been infected with the virus worldwide, of which approximately 350 million are chronic carriers, at risk of long-term sequelae and premature death (Kane *et al*, 1993). In countries with a

low rate of infection, HBV is transmitted primarily through sexual contact, injecting-drug use, occupational exposure, or regular household contact with a chronically infected person (American Academy of Pediatrics, 1997). By contrast, HBV infection in highly endemic countries is regarded as primarily resulting from vertical or perinatal transmission.

In Southeast Asia, carrier rates as high as 15-20% in the 1980s prompted the introduction of mass immunization programs in many countries, including Taiwan (Hou *et al*, 1993), Thailand (Chunsuttiwat, 1996), Malaysia (Department of Health, 1995), and Singapore (Goh, 1996), resulting in a marked reduction in HBV incidence and carriage rates. In addition, studies in Taiwan have demonstrated a reduction in both the incidence and number of deaths from primary hepatocellular carcinoma in children (Chan *et al*, 1997).

Despite the success of mass immunization programs, a substantial proportion of the adult population remains susceptible to HBV infection. For example, although universal immunization of infants was introduced in Taiwan in 1986, it is estimated that approximately 20% of adults remain susceptible to infection (Hou *et al*, 1993). Recent epidemiological data from Taiwan indicate that heterosexual contact has become the predominant mode of HBV transmission among adults living in endemic regions (Hou *et al*, 1993). These findings provide strong support for extending the mass HBV vaccination program to susceptible adults, not only to reduce the risk of perinatal transmission to their children, but to reduce the risk of transmission between adults. Further incentive for vaccination of non-immune adults arises from evidence that overt clinical disease and mortality from acute fulminant hepatitis is far more likely to occur in adults than in children (Hollinger, 1996).

Hepatitis B vaccine has been shown to be highly immunogenic in young adults when administered in various three-dose schedules, although antibody responses are diminished among older adults (Gardner and Schaffer, 1993). While use of the vaccine in all seronegative adults is desirable due to the prevalence of sexually transmitted infections, it is particularly important that adults at particularly high-risk of exposure, such as health care workers and people travelling to regions of higher endemicity, receive HBV immunization. Members of these groups are likely to also be at risk of hepatitis A infection, and may therefore be candidates for the combined hepatitis A and B

vaccine which offers a convenient alternative to the monovalent vaccines (Bak and Ruff, 1998).

Varicella

While varicella zoster virus (VZV) is generally regarded as little more than a nuisance infection in children, the clinical presentation is entirely different in adults who are at increased risk of pulmonary and central nervous system complications (Gardner *et al*, 1996; Pugh *et al*, 1998). Advancing age is a particularly important risk factor for severe infection, pneumonia and death (Preblud, 1981). In the US, it has been estimated that the risk of death associated with VZV infection increases from 2.7 per 100,000 among persons 15 to 19 years of age, to 25.2 per 100,000 among persons 30 to 49 years of age (Ventura, 1997). Pregnancy and immunocompromized states are associated with increased severity of illness (Gardner *et al*, 1996), while intrauterine infection may result in stillbirth or congenital varicella syndrome, characterized by eye defects, limb hypoplasia, skin lesions, and neurological abnormalities (Katz *et al*, 1995).

Although VZV is an extremely common infection worldwide, its epidemiology is markedly different in tropical and temperate climates. While in temperate countries, the vast majority of the population have seroconverted by adolescence (Wharton, 1996; Fairley and Miller, 1996) in tropical countries, seroconversion generally occurs in late adolescence and adulthood (Garnett *et al*, 1993). Several seroprevalence studies in Southeast Asia have indicated that a significant proportion of the population remain susceptible to VZV infection well into adulthood. In Singapore, serological surveys have revealed that only 41% of those aged 15-24 years have protective antibodies to VZV, while >90% seroprevalence is not reached until the age of 35 years and over (Ooi *et al*, 1992). Similar results have been obtained in Malaysia (Malik and Baharin, 1995), the Philippines (Barzaga *et al*, 1994) and Thailand (Migasena *et al*, 1997). Incidence data reflect low seroprevalence among adolescents and adults in the region (Ooi *et al*, 1992; Balraj and John, 1994).

In the US and the UK, concern has been expressed that the incidence of varicella among adults is increasing, and that hospitalization rates for adult varicella are substantially higher than a decade ago (Streuwing *et al*, 1993; Choo *et al*, 1995; Miller *et al*, 1993). It has been suggested that this may be a result of increasing numbers of immigrants from

tropical countries (especially Southeast Asia) where fewer adults have immunity to VZV (Ross and Lantos, 1995). Adults of Southeast Asian origin comprise most of the adult varicella cases in the United Arab Emirates, where an increase in the incidence of varicella and frequency of hospitalized cases has led to a call for all new immigrants who are seronegative to be offered the varicella vaccine (Pugh *et al*, 1998).

The Oka strain varicella vaccine, developed over 20 years ago, has proven to be well tolerated and effective in preventing VZV infection in adolescents and adults, with a seroconversion rate of 99% after two doses (Gardner *et al*, 1996). As an additional benefit, preliminary evidence suggests that the vaccine may reduce the likelihood of the development of herpes zoster in later life (Hardy *et al*, 1991).

The susceptibility to VZV of many adults in Southeast Asia due to late seroconversion, together with the heightened risk of complications, hospitalization and death, provide strong support for the vaccination of seronegative adults. Ideally, all adults and adolescents who did not have chickenpox as children should receive the vaccine, as should all health care workers, who are at increased risk of VZV infection through occupational exposure.

Hepatitis A

In many Asian countries, the incidence of hepatitis A among adults is increasing in parallel with socioeconomic development (Shapiro and Margolis, 1993), as occurred earlier in European and other industrialized nations (Bouvet and Micoud, 1997). As the sanitation of countries improves, a shift tends to occur from high to low endemicity and this is reflected in changing age-related seroprevalence patterns. For example, in Singapore, age-related seroprevalence has changed significantly since the mid 1970s. While in 1975, a hepatitis A virus (HAV) seroprevalence of 80% first occurred in the 20-29 year age group, this shifted to the 45-54 year age group in 1985 (Goh *et al*, 1987), then to the 51-60 year age group in 1991 (Yap and Guan, 1993). These changes correlate with age-related incidence; In 1994, 65% of all acute hepatitis A cases occurred among adolescents and adults 15-34 years of age, while only 10% occurred in children under 15 years of age (Ministry of the Environment, 1994). Malaysia (Malik and Baharin, 1993) and Thailand (Poovorawan *et al*, 1993) have also shown declining endemicity in recent years.

In contrast to HAV infection in children, acute infection in adults is often clinical, tending to become progressively more severe with age (Shapiro and Margolis, 1993). As a result, the incidence of clinical disease is often seen to increase in countries undergoing socioeconomic development. The shift in age-related seroprevalence of HAV, together with the susceptibility of many non-immune adults to clinical disease, provide support for adult immunization against this infection.

Hepatitis A vaccine has been shown to be highly immunogenic in adults, with an exceptional safety profile (Gardner *et al*, 1996). While the vaccine should ideally be available for all seronegative adults, health care workers and people travelling to regions of higher endemicity – particularly where hygiene and sanitation are poor – are high-risk groups who should be specifically targeted for HAV immunization.

Typhoid

Typhoid fever is endemic to Southeast Asia, where it has been and remains an important public health problem. In contrast to more developed countries, such as the USA and the UK, where the incidence of typhoid is well below one per 100,000, incidence rates in less developed countries range from 10 to 1,000 per 100,000 population (Yew *et al*, 1993; Thong *et al*, 1995). Recently emerged features adding to the magnitude of the problem include an aggravated clinical picture during concomitant HIV infection, and an increased risk for cancer among chronic carriers (Arya, 1996).

Where typhoid is highly endemic, early contact with the infection often results in seroconversion in childhood (Prokopec *et al*, 1991); however, a substantial number of cases are seen among adolescents and young adults. A study of hospitalized typhoid cases in Ujung Pandang, Indonesia revealed a peak in incidence among young adults 20 to 24 years of age, with a steady decline after 30 years of age (Velema *et al*, 1997). The study highlighted the importance of hygiene in the spread of infection, finding that consumption of food from stalls in the street was strongly associated with risk of infection. While the majority of cases in high-endemicity countries are locally acquired, cases in low-endemicity countries may be predominantly imported. Recent evidence from Singapore – where incidence has been declining in parallel with improved hygiene – indicates an increasing proportion of cases imported by local residents returning from travel to high endemicity countries, particu-

larly Indonesia and India (Yew *et al*, 1993).

Attention has recently been drawn to the movement of isolates of *Salmonella typhi* within Southeast Asia, attributed to extensive reciprocal movements of migrant workers as a consequence of economic growth (Thong *et al*, 1995). Of particular concern is the exchange of antibiotic resistant strains between Malaysia, Thailand and Indonesia, and the observation of severe clinical disease – which may be associated with more virulent strains – among typhoid fever cases in Indonesia.

Antibiotic resistance by the typhoid organism is becoming an increasing problem. Since 1989, several outbreaks caused by multi-drug resistant (MDR) strains of *S. typhi* have been reported in India (Jesudason *et al*, 1996) and other countries in the Southeast Asian region (Rowe *et al*, 1997). The widespread dissemination of MDR strains has severely restricted options for the effective treatment of typhoid fever, and vaccination is becoming increasingly important as a means of controlling this infection.

Several typhoid vaccines that are better tolerated than the old whole-cell typhoid vaccine have become available in recent years, including the single-dose Vi polysaccharide vaccine (Vi CPS) and the Ty21a (liquid formulation) vaccine (Ivanoff *et al*, 1994; Conrad and Jenson, 1996; Levine and Noriega, 1995). A 1998 meta-analysis of studies on typhoid vaccines revealed that efficacy ranged from 51-73%, was unaffected by the age of the recipient, and remained significant for two to five years (Engels *et al*, 1998). Today, typhoid vaccines are primarily used in travellers from industrialized nations to endemic countries. Although typhoid fever is endemic to the Southeast Asian region, vaccination should be considered in adults who did not seroconvert in childhood and who are likely to be exposed to typhoid during travel to higher endemicity areas, especially remote areas with poor sanitation.

Rubella

Rubella is usually a mild and self-limiting infection in children and adults. However, exposure to the virus during the first trimester of pregnancy can increase the risk of spontaneous abortion, and may cause congenital rubella syndrome (CRS), characterized by severe malformations in the developing fetus. The overall risk of fetal damage associated with rubella is estimated to be as high

as 85% (Miller *et al*, 1982), making vaccination against this infection most important for women of child-bearing age.

In industrialized nations, the introduction of rubella vaccination in the late 1960s and early 1970s resulted in dramatic reductions in the incidence of rubella and CRS. However, the success of childhood immunization programs has resulted in a shift in the disease burden, with a greater involvement of adults and adolescents (Galazka, 1991; Stevenson *et al*, 1996). In the USA, 75% of reported cases of rubella from 1994-1997 occurred among persons 15-44 years of age, in contrast to 23% from 1966-1968 (Anon, 1997). Although on the verge of elimination in the late 1980s, a number of clusters of CRS occurred during the 1990s, and it is estimated that in the USA approximately 11 million women of child-bearing age remain susceptible to rubella (National Coalition for Adult Immunization, 1993).

In the Southeast Asian region, the precise burden of CRS is not known. Available evidence suggests that CRS often goes unreported, and outbreaks can occur with no clinical recognition (Miller, 1991). A review of published studies by the World Health Organization identified high rates of susceptibility to rubella (30-47%) among women of child-bearing age in Malaysia, Thailand, India and Sri Lanka (Cutts *et al*, 1997) comparable to those in industrialized countries in the prevaccination era. In Singapore, a seroepidemiological survey found that although the overall prevalence of antibodies to rubella had increased from 48% in 1990 (prior to the introduction of MMR vaccination) to 72% in 1993, one fifth of females in the reproductive age group remained susceptible to infection (The Committee on Epidemic Diseases, 1995b). In Taiwan, an even higher level of susceptibility (37%) was found among females aged 20-29 years, leading to a call for mass vaccination to prevent possible future outbreaks of CRS (Lin and Chen, 1993).

A highly immunogenic and relatively cheap vaccine against rubella has been in use for over 30 years. Over this time, a number of vaccination strategies have been employed by various countries with the aim of reducing the incidence of CRS (The Children's Vaccine Initiative, 1998). These include selective vaccination of schoolgirls and women, universal childhood vaccination, or a combination of the two. A recent review of strategies by the WHO concluded that it is essential to include vaccination of women of child-bearing age

– achieved by either routine vaccination or a one-time mass immunization campaign – in any rubella control strategy, as childhood immunization alone may not control the incidence of CRS (Robertson *et al*, 1997). Experience from the USA (Kaplan *et al*, 1990; Lee *et al*, 1992) and the UK (Lawman *et al*, 1994) indicates that CRS will continue to occur while ever opportunities to identify and immunize susceptible women are missed. Furthermore, males may serve as an important source of infection for non-immune pregnant women (Stevenson *et al*, 1996) and susceptible males should be offered immunization.

Rubella vaccination – either alone or preferably as a combined vaccine containing measles and mumps vaccine – is recommended at 12-15 months and 4-6 years of age. Those who did not receive the second dose at school entry should be administered it at 11-12 years of age or earlier. Vaccination is also recommended for susceptible post-pubertal females and males. Women should be informed of the theoretical risk to the fetus if they are pregnant or become pregnant within three months of vaccination. As an additional preventative strategy, immunization of health care workers (Rose, 1998), particularly those providing obstetric services (Schoenhoff *et al*, 1997) is advisable.

Influenza

Influenza is recognized as a significant cause of adult morbidity and mortality, particularly among middle aged and older adults. In temperate countries, influenza has been extensively studied and the burden of the disease well-established (McBean *et al*, 1993). In the USA, 19 of the annual influenza epidemics to have occurred since 1957 have been associated with over 10,000 excess deaths each; two of these epidemics were associated with over 40,000 excess deaths each (Gardner *et al*, 1996). Approximately 80-90% of deaths during these epidemics occurred in adults 65 years of age or over, especially those with underlying cardiac or pulmonary disease.

In contrast to the USA and other temperate countries, the impact of influenza on public health in non-temperate countries is unknown. However, all Asian countries with established WHO surveillance programs have demonstrated the presence of the virus, and influenza is known to be a substantial cause of morbidity and mortality in some Southeast Asian countries. In the Philippines, influenza is consistently rated as one of the top three

leading causes of morbidity (Robles, 1995); in Vietnam, over 140,000 cases were reported in 1996 (Government statistics) and over 55,000 cases were reported in Thailand in 1995, with the highest rate among adults 35 years of age and over (Ministry of Public Health, 1995).

Although data relating to the impact of influenza on adults in Southeast Asia is sparse, the importance of the disease where it has been evaluated, the known presence of the virus throughout Asia, the emergence of pandemic strains over the last few decades in the region and the opportunity for new strains to emerge make it likely that there is an unrecognized disease burden in Southeast Asia. Annual vaccinations for adults at high risk of infection – including those in high-risk occupational settings such as health care workers and those in close contact in industrial environments, people with cardiopulmonary disease, and all persons 65 years of age and over – would be likely to significantly reduce this burden.

Where evaluated, influenza vaccines have consistently been shown to be effective in reducing health and economic burdens, provided that there is suitable matching between circulating strains and those contained in the virus. Although the vaccine is less efficacious in preventing clinical illness in older adults than in young adults, it lessens the severity of the infection, and is 80% effective in preventing death in this population (McClennan Reece, 1995).

Pneumococcal infection

Streptococcus pneumoniae is a major cause of pneumonia, meningitis and bacteremia worldwide (Jamal *et al*, 1987). It is well recognized that pneumococcal infection and its complications are a special problem among the elderly, as well as those with chronic debilitating and immunosuppressive disease. In the USA, mortality rates for pneumonia have increased substantially over the past decade, particularly among older adults (Pinner, 1996). Moreover, the increasing number of ageing citizens and the emergence of antibiotic resistant strains of *S. pneumoniae* indicate that deaths due to invasive pneumococcal infection will continue to rise (Anon, 1990; Gardner *et al*, 1996).

Currently available pneumococcal vaccine contains 23 serotypes accounting for nearly 90% of the isolates causing serious infection. The vaccine is recommended in the USA for persons 65 years of age or older as well as those who are at increased risk of complications due to chronic

cardiac, renal or respiratory disease (Zimmerman and Clover, 1995). Protection offered by the vaccine has been shown to vary considerably with the age and immune status of the recipient; overall efficacy has been estimated at 56-57% (Gardner *et al*, 1996; Zimmerman and Clover, 1995). Although limited in efficacy, the vaccine offers considerable benefit and it is estimated that if vaccination guidelines were fully implemented, the number of cases of pneumococcal invasive disease in the USA could be halved (Gardner *et al*, 1996). As with the influenza vaccine, the pneumococcal vaccine is greatly under-utilized, with an estimated 14% of persons 65 years of age or older, and 5-7% of those predisposed to pneumococcal infection receiving the vaccine (Gardner *et al*, 1996). Pneumococcal vaccine has recently been evaluated for use in pregnant women to prevent invasive pneumococcal infections in newborn infants (O'Dempsey *et al*, 1996).

In a four-year study of pneumococcal infection in hospitalized patients in Malaysia, type surveillance of *S. pneumoniae* was carried out (Jamal *et al*, 1987). Although typing was carried out on only a small proportion of strains, the authors concluded that the 23-valent pneumococcal vaccine would be likely to offer a reasonable degree of protection against infection.

There is a need for further studies to be conducted in the Southeast Asian region, both to establish the true burden of pneumococcal disease and to assess the potential impact of vaccination on morbidity and mortality among adults. Despite the current lack of data, the use of pneumococcal vaccine among those at most risk of invasive disease is likely to be beneficial based on the results of studies performed in other countries. Such high risk groups include health care workers, people with a history of chronic obstructive pulmonary disease or congestive heart failure, those who have undergone splenectomy, and all persons 65 years of age and over.

Challenge for the future

The data presented in this review indicate that many adults in Southeast Asia are susceptible to a range of vaccine-preventable infections, and that adult immunization could reduce the burden of disease in this population. The following vaccination guidelines (Table 1) are proposed on the basis of currently available data for the region. It is recognized that appropriate vaccination advice will vary from country to country.

Table 1
Vaccination guidelines.

Disease	Vaccination guidelines
Diphtheria	In countries where diphtheria continues to occur, immunization with the Td vaccine is advisable for seronegative adults.
Tetanus	Vaccination is advisable for all non-immune pregnant women. Booster vaccinations with the Td vaccine are recommended for all adults on a ten-yearly basis. (The WHO, however, recommends that it is unnecessary to give more than five boosters.)
Pertussis	Vaccination is advisable for health care workers. Booster vaccination may be required in other adults; however, more epidemiological data is required before specific recommendations can be made.
Hepatitis B	Vaccination is advisable for health care workers, travellers to high-endemicity areas, and all seronegative adults (as HBV can be sexually transmitted).
Varicella	Vaccination is advisable for health care workers and all susceptible adolescents and adults who do not have a history of chickenpox.
Hepatitis A	Vaccination is advisable for people with chronic liver disease, health care workers, travellers to high-endemicity areas, and susceptible adults and adolescents in higher socioeconomic groups living in areas of mixed endemicity.
Typhoid	Vaccination is advisable for seronegative travellers to higher-endemicity areas.
Rubella	Vaccination (either alone or preferably as a combined MMR vaccine) is recommended for all susceptible post-pubertal females and males, including health care workers. (Women should be informed of the theoretical risk to the fetus if they are pregnant or become pregnant within three months of vaccination.)
Influenza	Annual vaccination is advisable for all persons 65 years of age and over, people with cardiopulmonary disease, and those in high-risk occupational settings <i>eg</i> health care workers and those in close contact in industrial environments.
Pneumococcal infection	Five-yearly vaccination is advisable for all persons 65 years of age and over, people with a history of chronic obstructive pulmonary disease or congestive heart failure, those who have undergone splenectomy, and health care workers.

ACKNOWLEDGEMENTS

The authors acknowledge financial assistance from SmithKline Beecham Biologicals for expenses associated with meetings of the Steering Committee.

REFERENCES

- American Academy of Pediatrics. Immunisation of Adolescents: Recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the American Academy of Family Physicians, and the American Medical Association. *Pediatrics* 1997; 99: 479-88.
- Anonymous. Public health burden of vaccine preventable diseases among adults: standards for adult immunization practice. *MMWR* 1990; 39: 725-9.
- Anonymous. Rubella and congenital rubella syndrome: United States, 1994-1997. *MMWR* 1997; 46: 351-4.
- Arya SC. Cholera and typhoid vaccines: a review of current status. *Clin Immunother* 1996; 6: 28-38.

- Bak N, Ruff T. The combined hepatitis A and B vaccine: who should receive it? *Modern Med Aust* 1998.
- Balraj V, John TJ. An epidemic of varicella in rural southern India. *J Trop Med Hyg* 1994; 97: 113-6.
- Baltazar JC, Sarol JN Jr. Prenatal tetanus immunization and other practices associated with neonatal tetanus. *Southeast Asian J Trop Med Public Health* 1994; 25: 132-8.
- Barzaga NG, Roxas JR, Florese RH. Varicella zoster virus prevalence in metro Manila, Philippines. *JAMA (SE Asia)* 1994; (suppl): 633-5.
- Bouvet E, Micoud M. Policy making for vaccinations of adolescents/adults. *Biologicals* 1997; 25: 143-5.
- Centers for Disease Control. Diphtheria outbreak - Saraburi Province, Thailand, 1994. *MMWR* 1996; 45: 271-3.
- Centers for Disease Control. Resurgence of pertussis - United States. *MMWR* 1995; 42: 952-60.
- Chan MH, Chen CJ, Lai MS, *et al.* Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997; 336: 1855-9.
- Cherry JD. Pertussis in adults. *Ann Intern Med* 1998; 128: 64-6.
- Chongsuvivatwong V, Bujakorn L, Kanpoy V, Treetrong R. Control of neonatal tetanus in southern Thailand. *Int J Epidemiol* 1993; 22: 931-935.
- Choo PW, Donahue JG, Manson JE, *et al.* The epidemiology of varicella and its complications. *J Infect Dis* 1995; 172: 706-12.
- Chunsuttiwat S. Progress of hepatitis B control in Thailand. *Commun Dis J* 1996; 22: 177-86.
- Conrad DA, Jenson HB. New and improved vaccines: promising weapons against varicella, hepatitis A and typhoid fever. *Postgrad Med* 1996; 100: 113-25.
- Cutts FT, Robertson SE, Diaz-Ortega JL, *et al.* Control of rubella and congenital rubella syndrome (CRS) in developing countries, part 1: burden of disease from CRS. *Bull WHO* 1997; 75: 55-68.
- De Haas I, Moes N, Wolffers I. Prevention of neonatal tetanus in developing countries hampered by local organisation and limited knowledge of health personnel and traditional midwives; North Sulawesi. *Ned Tijdschr Geneesk* (Netherlands) 1994; 138: 1032-5.
- Department of Communicable Disease Control, Thailand, Government statistics, 1996.
- Department of Health, Ministry of Health Malaysia, Annual Report, 1995.
- Dey AB, Chaudhury D. Infections in the elderly. *Indian J Med Res* 1997; 106: 273-85.
- Doller PC. Vaccination of adults against travel-related infectious diseases, and new developments in vaccines. *Infection* 1993; 21: 1-17.
- Edwards KM. Acellular pertussis vaccines - a solution to the pertussis problem? *J Infect Dis* 1993; 168: 15-20.
- Engels EA, Falaagas ME, Lau J, *et al.* Typhoid fever vaccines: a meta-analysis of studies on efficacy and toxicity. *Br Med J* 1998; 316: 110-16.
- Fairley CK, Miller E. Varicella-zoster virus epidemiology - a changing scene? *J Infect Dis* 1996; 174 (suppl 3): S314-9.
- Fedson DS. Adult immunization: summary of the National Advisory Committee Report. *JAMA* 1994; 272: 1133-7.
- Galazka A, Robertson SE. Diphtheria: changing patterns in the developing world and the industrialised world. *Eur J Epidemiol* 1995; 11: 107-17.
- Galazka A. Rubella in Europe. *Epidemiol Infect* 1991; 107: 43-54.
- Gardner P, Eickhoff T, Poland G, *et al.* Adult Immunizations. *Ann Intern Med* 1996; 12: 35-40.
- Gardner P, Schaffer W. Immunisation of adults. *N Engl J Med* 1993; 328: 1252-8.
- Garnett GP, Cox MJ, Bundy DAP, *et al.* The age in infection with varicella-zoster virus in St Lucia, West Indies. *Epidemiol Infect* 1993; 110: 361-72.
- Gasse F. Neonatal tetanus: review of progress. *Int J Gynecol Obstets* 1995; 50 (suppl 2): S67-72.
- Goh KT, Wong LYM, Oon CJ, *et al.* The seroprevalence of antibody to hepatitis A virus in Singapore. *Asia Pac J Public Health* 1987; 1: 9-11.
- Goh KT. Hepatitis B immunisation in Singapore. *Lancet* 1996; 16: 1385-6.
- Gupta SD, Keyl PM. Effectiveness of prenatal tetanus toxoid immunisation against neonatal tetanus in a rural area of India. *Pediatr Infect Dis J* 1998; 17: 316-21.
- Hardy I, Gershon A, Steinberg S, *et al.* The incidence of zoster after immunization with live attenuated varicella vaccine: a study in children with leukemia. *N Engl J Med* 1991; 325: 1545-50.
- Hewlett EL. Pertussis in adults: significance for disease transmission and immunisation policy (Editorial). *J Med Microbiol* 1992; 36: 141-2.
- Hollinger FB. Comprehensive control (or elimination) of hepatitis B transmission in the United States. *Gut* 1996; 38 (suppl 2): S24-30.
- Hou MC, Wu JC, Kuo B, *et al.* Heterosexual transmission as the most common route of acute hepatitis

- B virus infection among adults in Taiwan – the importance of extending vaccination to susceptible adults. *J Infect Dis* 1993; 167: 938-41.
- Ichhpujani RL, Grover SS, Joshi PR, *et al.* Prevalence of diphtheria and tetanus antibodies in young adults in Delhi. *J Commun Dis* (India) 1993; 25: 27-9.
- Ivanoff B, Levine MM, Lambert PH. Vaccination against typhoid fever: present status. *Bull WHO* 1994; 73: 957-71.
- Jamal F, Pit S, Isahak I, *et al.* Pneumococcal infection in hospitalised patients: a four year study in Malaysia. *Southeast Asian J Trop Med Public Health* 1987; 18: 79-84.
- Jesudason MV, John R, John TJ. The concurrent prevalence of chloramphenicol-sensitive and multidrug-resistant *Salmonella typhi* in Vellore, S India. *Epidemiol Infect* 1996; 116: 225-7.
- Kane MA, Clements J, Hu D. Hepatitis B. In: Jamison DT, Mosely WH, Measham AR, *et al.*, eds. Disease control priorities in developing countries. New York: Oxford University Press, 1993: 321-30.
- Kaplan KM, Cochi SL, Edmonds, LD, *et al.* A profile of mothers giving birth to infants with congenital rubella syndrome: an assessment of risk factors. *Am J Dis Child* 1990; 144: 118-23.
- Katz VL, Kuller JA, McMahon MJ, *et al.* Varicella during pregnancy: maternal and fetal effects. *West J Med* 1995; 163: 446-50.
- Keitel WA, Edwards KM. Pertussis in adults: time to reimmunize? *Semin Resp Infect* 1995; 10: 51-7.
- Laforce FM. Routine tetanus immunisations for adults: once is enough [Editorial]. *J Gen Intern Med* 1993; 8: 458-60.
- Lawman S, Morton K, Best JM. Reasons for rubella susceptibility among pregnant women in West Lambeth. *JR Soc Med* 1994; 87: 263-4.
- Lee SH, Ewert DP, Frederick PD, *et al.* Resurgence of congenital rubella syndrome in the 1990s: report on missed opportunities and failed prevention policies among women of childbearing age. *JAMA* 1992; 267: 2616-20.
- Levine MM, Noriega F. A review of the current status of enteric vaccines. *PNG Med J* 1995; 38: 325-31.
- Lin D-B, Chen C-J. Current seroepidemiology of rubella virus infection among female residents in Taiwan. *J Med Virol* 1993; 41: 174-8.
- Malik YA, Baharin R. Prevalence of varicella zoster virus infection in Malaysia. Johannesburg. Fifth International Congress on the Impact of Viral Diseases in the Developing World, 1995.
- Malik YA, Baharin R. Changing seroprevalence of hepatitis A in Malaysia. Manila: 4th Western Pacific Congress of Chemotherapy and Infectious Diseases, 4-7 September, 1994.
- Marth E. Booster policy for adults. *Biologicals* 1997; 25: 199-203.
- McBean AM, Babish JD, Warren JL. The impact and cost of influenza in the elderly. *Arch Intern Med* 1993; 153: 2105-11.
- McClennan Reece S. Preventing influenza and its complications: a public health initiative for the year 2000. *Nurse Pract* 1995; 20: 33-44.
- Migasena S, Simasathien S, Desakorn V, *et al.* Seroprevalence of varicella zoster virus antibody in Thailand. *Int J Infect Dis* 1997; 2: 26-30.
- Miller CL. Rubella in the developing world. *Epidemiol Infect* 1991; 107: 63-8.
- Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982; 2: 781-4.
- Miller E, Vurdien J, Farrington P. Shift in age in chickenpox. *Lancet* 1993; 341: 308-9.
- Ministry of Public Health, Thailand. Annual epidemiological surveillance report, 1995.
- Ministry of the Environment, Singapore. Communicable Disease Surveillance in Singapore, 1994.
- Ministry of the Environment, Singapore. Communicable Disease Surveillance in Singapore, 1995.
- National Coalition for Adult Immunization. Standards for adults immunization practice. *Am J Infect Control* 1993; 21: 331-2.
- Nivsarkar N, Pathak AA, Thakar YS, Saoji AM. Study of diphtheria antibody levels in healthy populations. *Indian J Pathol Microbiol* 1994; 37: 421-4.
- O'Dempsey TJ, McArdle T, Ceesay SJ, *et al.* Immunisation with a pneumococcal capsular polysaccharide vaccine during pregnancy. *Vaccine* 1996; 14: 963-70.
- Ooi PL, Goh KT, Doraisingham S, Ling AE. Prevalence of varicella zoster virus infection in Singapore. *Southeast Asian J Trop Med Public Health* 1992; 23: 22-5.
- Pinner RW. Addressing the challenges of emerging infectious diseases. *Am J Med Sci* 1996; 311: 3-8.
- Poovorawan Y, Theamboonlers A, Chumdermpadetsuk S. Changing seroepidemiology to hepatitis A virus infection in Thailand. *Southeast Asian J Trop Med Public Health* 1993; 24: 250-4.
- Preblud SR. Age-specific risks of varicella complications. *Paediatrics* 1981; 68: 14-17.
- Prokopec J, Müllerová H, Šerý V, *et al.* Typhoid fever survey in two localities in Vietnam. *J Hyg Epidemiol Microbiol Immunol* 1991; 1: 9-16.

- Pugh RNH, Omar RI, Hossain M. Varicella infection and pneumonia among adults. *Int J Infect Dis* 1998; 2: 205-10.
- Robertson SE, Cutts FT, Samuel R, *et al.* Control of rubella and congenital rubella syndrome (CRS) in developing countries. Part 2. Vaccination against rubella. *Bull WHO* 1997; 75: 69-80.
- Robles CG. Influenza as zoonosis – an overview. *Philippine J Sci* 1995; 124: 233-43.
- Rose VL. ACIP releases recommendations for the immunization of health care workers. *Am Fam Physician* 1998; 57: 1426-9.
- Ross LF, Lantos JD. Immunisation against chickenpox. *Br Med J* 1995; 310: 873.
- Rothstein EP, Bernstein HH, Long SS. Immunisation of adults [letter] *N Engl J Med* 1993; 329: 1046-7.
- Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant *Salmonella typhi*: a worldwide epidemic. *Clin Infect Dis* 1997; 24 (suppl 1): S106-9.
- Schoenhoff DD, Lane TW, Hansen CJ. Primary prevention and rubella immunity: overlooked issues in the outpatient obstetric setting. *Infect Control Hosp Epidemiol* 1997; 18: 633-6.
- Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. *J Hepatology* 1993; 18 (suppl 2): S11-4.
- Singh J, Jain CD, Sharma RS, Verghese T. Evaluation of immunisation coverage by lot quality assurance sampling compared with 30-cluster sampling in a primary health centre in India. *Bull WHO* 1996; 74: 269-74.
- Stevenson J, O'Brien S, Christie P, *et al.* Resurgence of rubella. *Lancet* 1996: 980-1.
- Streuwing JP, Hyams KC, Tueller JE, *et al.* The risk of measles, mumps and varicella among young adults: a serosurvey of US Navy and Marine Corps recruits. *Am J Public Health* 1993; 83: 1717-20.
- The Children's Vaccine Initiative. Action needed now to stop the rubella tragedy. *CVI Forum* 1998; 15: 2-8.
- The Committee on Epidemic Diseases. Immunity of the Singapore population to tetanus. *Epidemiol News Bull* 1995a; 21: 11-4.
- The Committee on Epidemic Diseases. Prevalence of antibodies to measles, mumps and rubella in Singapore. *Epidemiol News Bull* 1995b; 21: 25-9.
- Thong KL, Puthuchery S, Yassin RM, *et al.* Analysis of *Salmonella typhi* isolates from Southeast Asia by pulsed-field gel electrophoresis. *J Clin Microbiol* 1995; 33: 1938-41.
- Udom M. Diphtheria immunity prevalence in population of Phrae province. 1996. Msc Thesis (Public Health).
- Velema JP, van Wijnen G, Bult P, *et al.* Typhoid fever in Ujung Pandang, Indonesia – high-risk groups and high-risk behaviours. *Trop Med Int Health* 1997; 2: 1089-94.
- Ventura A. Varicella vaccination guidelines for adolescents and adults. *Am Fam Physician* 1997; 55: 1220-24.
- Wharton M. The epidemiology of varicella-zoster virus infections. *Infect Dis Clin North Am* 1996; 10: 571-81.
- Yap I, Guan R. Hepatitis A seroepidemiology in Singapore: a changing pattern. *Trans R Soc Trop Med Hyg* 1993; 87: 22-3.
- Yew FS, Goh KT, Lim YS. Epidemiology of typhoid fever in Singapore. *Epidemiol Infect* 1993; 110: 63-70.
- Zimmerman RK, Clover RD. Adult immunisations – a practical approach for clinicians: Part I. *Am Fam Physician* 1995; 51: 859-67.