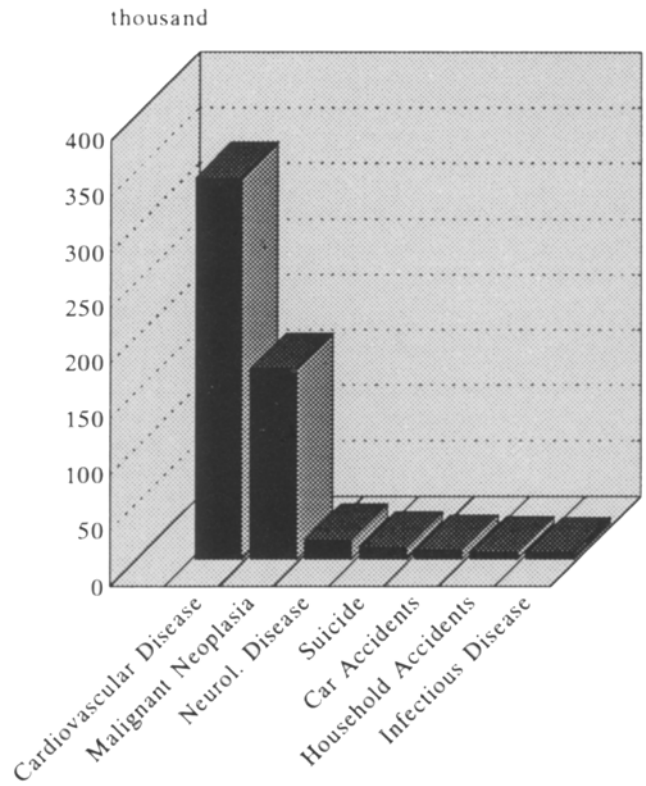
P. C. Döller

Vaccination of Adults against Travel-Related Infectious Diseases, and New Developments in Vaccines*

Summary: The number of people travelling to tropical or subtropical countries, whether for holidays or for business, is steadily increasing. Many of these travellers are at risk of acquiring an infectious disease. Protection against certain infectious diseases is possible by vaccination. Vaccinations required or recommended for adults are reviewed here. Progress in the refinement of available vaccines, as well as the development of new vaccines, is discussed.

Zusammenfassung: *Impfungen gegen Reise-Infektionen bei Erwachsenen und Neuentwicklungen von Impfstoffen.* Immer mehr Menschen reisen zur Erholung oder beruflich in tropische und subtropische Länder. Bei vielen dieser Reisen ist mit einem Infektionsrisiko für bestimmte Krankheiten zu rechnen. Gegen einige Infektionskrankheiten kann man sich durch Impfungen schützen. In der folgenden Übersicht wird auf Impfungen bei Erwachsenen eingegangen, die anläßlich von Reisen in tropische und subtropische Regionen notwendig sind beziehungsweise empfohlen werden. Weiterentwicklungen von bereits vorhandenen sowie Entwicklungen von bislang nicht verfügbaren Impfstoffen werden diskutiert.



according to 1990 World Health Statistics Annual, World Health Organization, Geneva 1991

Figure 1: Death rates in West Germany, 1989.

Introduction

Every year about 4 million Germans travel to tropical and subtropical countries [1]. In order to minimize the risk of acquiring an infectious disease during such journeys, it is important that travellers follow some elementary hygienic guidelines and take appropriate measures of specific prophylaxis. Of the latter, vaccination is one of the most important. The successful eradication of smallpox and the drastic reduction of poliomyelitis are impressive examples of the efficacy of vaccinations.

Most people are not concerned with vaccination against infectious diseases prevalent in foreign countries until they plan a journey outside of Europe. Most travellers consult their physician or a vaccination center for vaccination requirements. Upon consultation, it is frequently discovered that many people received their last vaccination decades previously. Because the risk of certain infectious diseases still exists in industrialized countries, this means that many adults are inadequately vaccinated and may lack protection against these infections.

Vaccination can be classified into three groups: (I) those that are required by law; (II) those that are recommended for all travellers; and (III) those that should be administered only to people at high risk.

All persons should have sufficient protective immunity against tetanus, diphtheria and poliomyelitis (Table 1). Depending on the country of destination, immunization against additional diseases is strongly recommended. Because of the high incidence of hepatitis A in tropical and subtropical countries, persons travelling to endemic areas should have protection against this infection. Yellow fever vaccination is required by law upon entering certain countries.

Vaccinations against typhoid fever, cholera, hepatitis B, rabies, meningococcal meningitis and Japanese encephalitis should only be administered in special circumstances. Vaccination against cholera with the

Received: 18 August 1992/Revision accepted: 29 October 1992

Dr. Dr. *P. C. Döller*, Tropenklinik, Paul-Lechler-Krankenhaus, Paul-Lechler-Str. 24, W–7400 Tübingen, Germany.

* Dedicated to Prof. Dr. *H.-J. Gerth* on the occasion of his 65th birthday.

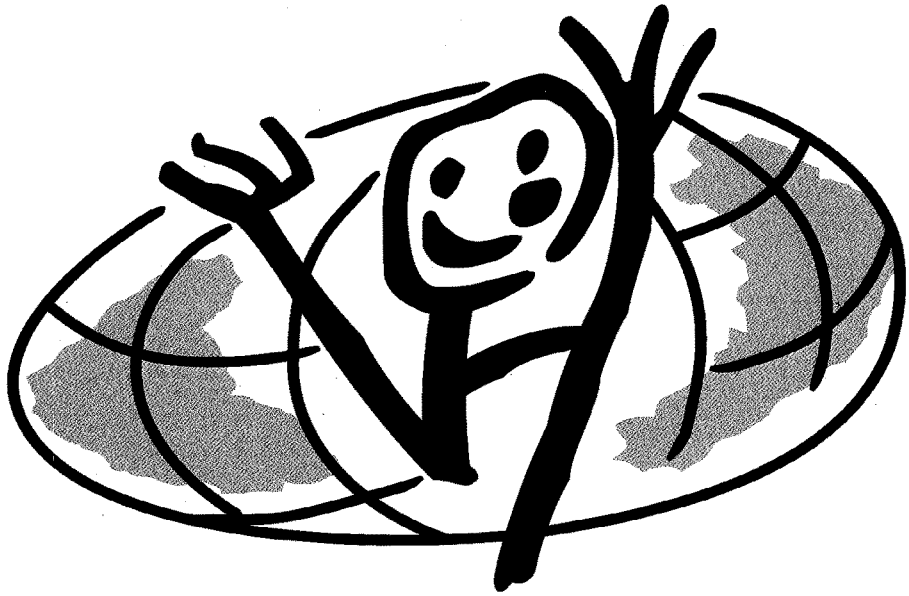
Table 1: Travel-related vaccinations.

Active Immunization								
Disease	Type of vaccine in present use	Mode of Administration	Indication	Traveller class	Pregnant	HIV-infected	Efficacy	Duration of protection
Required by law								
Yellow fever	Live attenuated virus	s. c.	Travel to certain African and South American countries	I, II, III	Only if unavoid.	Depends on current immune status	High	10 years
Recommended								
Tetanus	Toxoid	i. m.	Booster every 10 years	I, II, III	Possible	Possible	High	10 years
Diphtheria	Toxoid	i. m.	Booster every 10 years	I, II, III	Only if unavoid.	Possible	High	10 years
Poliomyelitis	Live attenuated virus	oral	Booster every 10 years	I, II, III	Possible	Contra.	High	> 10 years
	Inactivated virus	s. c.	If oral vaccination is contraindicated. Booster every 5–10 years		Possible	Possible	High	5–10 years
Special indications								
Hepatitis A	Inactivated virus	i. m.	For travel in tropical and subtropical countries; all nonimmune persons should be vaccinated	II, III	Only if unavoid.	Possible	Possibly high[a]	Not known (possibly 5 or more years)[a]
Typhoid fever	Live bacteria	oral	For travel under poor hygienic conditions in tropical and subtropical countries; backpackers	III	Contra.	Contra.	No efficacy against *Salmonella paratyphi* or other salmonellae	1–2 years
Meningococcal meningitis	Polysaccharide	s. c.	For travellers to sub-Saharan Africa, India, Nepal and Saudi Arabia (not necessary for guided tours and travel to urban areas)	III	Only if unavoid.	Possible	High (no efficacy against type b meningococci = prevalent in Europe)	3–5 years
Hepatitis B	Genetically engineered HBsAg	i. m.	High-risk individuals such as medical personnel with high risk of needle and blood exposure and people with sexual exposure in endemic areas	Generally not for tourists	Possible	Possible	High	Dependent on antibody titer
Rabies	Inactivated virus	i. m.	For high-risk individuals such as veterinarians, animal handlers, etc. (pre-exposure and post-exposure vaccination)	III	Only if unavoid.	Possible	High	2–5 years

Infection 21 (1993) No. 1

L&P

Die erste aktive Langzeitimmunisierung gegen Hepatitis A!



Mit ***HAVsorbat SSW*** ist es erstmals gelungen, einen Impfschutz gegen Hepatits A zu entwickeln, der lange anhält und eine Erkrankung zuverlässig und aktiv verhindert.

Durch Grundimmunisierung und Auffrischimpfung kann eine Schutzwirkung von bis zu 10 Jahren erzielt werden – eine Vorsichtsmaßnahme besonders für Reisende in Endemiegebiete.

Damit's gutgeht.

HAVsorbat SSW

Die erste aktive Langzeitimmunisierung
gegen Hepatitis A.

Wirkstoff: Hepatitis A-Impfstoff · **Zusammensetzung:** 1 Impfdosis (1 ml Suspension) enthält: 720 Antigeneinheiten inaktiviertes Hepatitis A-Virus, gezüchtet in Kulturen menschlicher diploider Zellen, 0,95 mg Aluminiumhydroxid-Gel (entspr. 0,5 mg Aluminium), 5,0 mg 2-Phenoxyethanol, max. 0,05 mg Polysorbat 20, max. 0,1 mg Formaldehyd. · **Anwendungsgebiete:** Aktive Immunisierung gegen Hepatitis A; insbesondere für Reisende in Endemiegebiete, beruflich Exponierte wie z. B. Kanal- und Klärwerksarbeiter, Personen, die mit der Herstellung und der Verteilung von Lebensmitteln beschäftigt sind, Mitarbeiter pädiatrischer Einrichtungen und Kliniken, Angehörige von Entwicklungsdiensten, Schutz- und Streitkräften bei Einsätzen in Endemiegebieten sowie andere Risikogruppen. · **Gegenanzeigen:** Bekannte Überempfindlichkeit gegen Bestandteile des Impfstoffes. Akute, insbesondere fieberhafte Infekte. Zur aktiven Immunisierung bei Kindern aufgrund begrenzter Erfahrung nicht empfohlen. · **Hinweis:** HAVsorbat SSW schützt nicht vor durch andere Erreger als HAV hervorgerufene Hepatitiden. Die Impfung verhindert nicht die klinische Manifestation einer bereits bestehenden HAV-Infektion. In der Schwangerschaft und Stillzeit nur nach sorgfältiger Abwägung der Indikation und des Risikos impfen. · **Nebenwirkungen:** Lokale vorübergehende Reaktionen wie Rötung, Schwellung, Induration oder leichte Schmerzen. Gelegentlich Allgemeinreaktionen leichter Art: Kopfschmerzen, Unwohlsein, Mattigkeit, Fieber, Appetitlosigkeit, Übelkeit. Bei unter 1% der Geimpften Schmerzen im Oberarm, Infektion der oberen Luftwege, Erbrechen, Durchfall oder vorübergehend leicht erhöhte Leberenzymwerte. In Einzelfällen allergische Reaktionen möglich. Im Falle des Auftretens eines Schocks übliche Behandlungsmaßnahmen einleiten. · **Wechselwirkungen:** Die gleichzeitige passive Immunisierung mit anti-HAV-haltigem Immunglobulin kann zu niedrigeren Antikörpertitern als nach HAVsorbat SSW allein führen. Bei immungeschwächten Personen kann der Impferfolg eingeschränkt sein. · **Dosierung:** Gebrauchsfertige Impfstoffsuspension zur i. m. Injektion. Empfohlenes Impfschema: 2 Impfungen mit je 1 Dosis (1 ml HAVsorbat SSW) im Abstand von 4 Wochen oder mind. 2 Wochen (für schnelleren Impfschutz) i. m., vorzugsweise intradeltoidal, verabreichen. 3. Impfung nach 6-12 Monaten durchführen. Nicht i. v. injizieren! Nicht mit anderen Impfstoffen oder Arzneimitteln mischen! Bei gleichzeitiger Gabe mit anderen Impfstoffen 2 verschiedene Injektionsorte für die i. m. Gaben wählen! In Ausnahmefällen (z.B. Hämophilie-Patienten) subkutane Injektion mit anschließender Titerkontrolle. Bei immungeschwächten Patienten siehe Gebrauchsinformation. · **Lagerhinweis:** HAVsorbat SSW muß im Kühlschrank bei +2°C bis +8°C gelagert und aufbewahrt werden. Der Impfstoff darf nicht eingefroren werden, da dadurch die Wirksamkeit verloren geht. Gefrorener Impfstoff ist zu verwerfen. · **Handelsformen und Preise:** Originalpackungen als Flasche: 1 Impfdosis HAVsorbat SSW mit 1 ml Suspension: DM 72,55; 2 X 1 Impfdosis HAVsorbat SSW mit je 1 ml Suspension: DM 137,68; 10 X 1 Impfdosis HAVsorbat SSW mit je 1 ml Suspension: DM 670,46 (Apotheken-Verkaufspreise inkl. gesetzl. MwSt. Stand: Januar 1993)

Schutz durch Immunität

Sächsisches Serumwerk GmbH Dresden

Sächsisches Serumwerk GmbH · Zirkusstraße 40 · O-8010 Dresden · Tel.: 03 51/45 61-131 · Fax: 03 51/45 61-166

Table 1 continued

Disease	Type of vaccine in present use	Mode of Administration	Indication	Traveller class	Pregnant	HIV-infected	Efficacy	Duration of protection
Active Immunization								
Japanese encephalitis	Inactivated virus	s. c.	For individuals residing for prolonged periods in endemic areas in China, Korea, Burma, Bangladesh, Nepal, Thailand, Laos, Vietnam	III	Contra.	Possible	Very high	1–4 years
Cholera	Inactivated bacteria	s. c.	No longer recommended by WHO	(III)	Only if unavoid.	Possible	Very low	6 months
Measles	Live attenuated virus	s. c.	Nonimmune individuals	II, III	Contra.	Depends on current immune status	High	Mostly lifelong
Passive Immunization								
Hepatitis A	Human immuno-globulins	i. m.	If active hepatitis A vaccine is not available, for travellers who must depart soon; will be replaced by active immunization; in case of infection immediately after transmission	II, III	Possible	Possible	High	2–4 months
Tetanus	Human tetanus antitoxin	i. m.	In case of injury (simultaneously with tetanus toxoid)	I, II, III	Possible	Possible	High	3–4 weeks
Rabies	Rabies-specific human immuno-globulins	i. m.	In case of bite (simultaneously with active immunization)	I, II, III	Possible	Possible	High when applied immediately after bite	
Hepatitis B	Hepatitis B-specific human immuno-globulins	i. m.	After needle and blood exposure (simultaneously with active immunization)	I, II, III	Possible	Possible	High	2–3 months

[a] Recently licensed in Germany (1992).
s. c. = subcutaneous; i. m. = intramuscular; contra. = contraindicated; unavoid. = unavoidable.

presently available vaccine is no longer recommended by the World Health Organization (WHO), and smallpox vaccine is no longer available after worldwide eradication of the disease.

It is important to recognize that vaccination is only one feature of a comprehensive disease prevention program for travellers. No vaccine is completely safe or effective; therefore, the benefits and risks of all immunizations should be considered. The most common misunderstanding about immunization is the confusion about what is required by law with what is recommended. Currently, only one vaccine, yellow fever, is obligatory for international travel to certain countries. In most such countries, this requirement is enforced mainly to prevent the importation of the disease and not to prevent the incoming traveller from contracting the disease. Other vaccines, such as tetanus, diphtheria, poliomyelitis and hepatitis A, are of greater importance for the health of the individual and should be strongly recommended, even though they are not required by law.

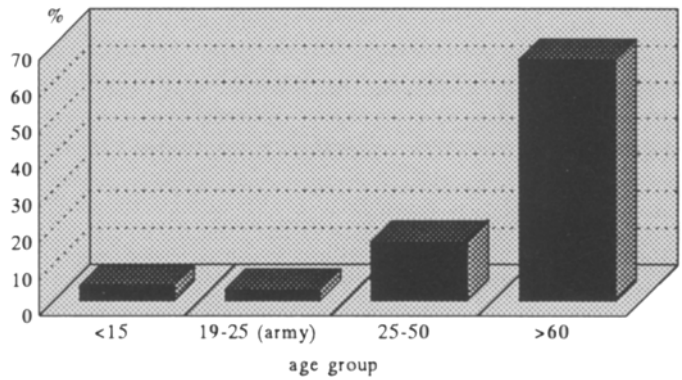
Approximately 5,000 fatal cases of infectious diseases occur in Germany each year (Figure 1), a number equivalent to the number of deaths by household accidents, but fatalities caused by cardiovascular or

Infection 21 (1993) No. 1

Table 2: Cases of infectious diseases preventable by vaccines reported in 1989 in West Germany [2].

Disease	No. of cases	
	Disease	Death
Cholera	1	0
Poliomyelitis	2	0
Typhoid fever	204	2
Diphtheria	4	2
Yellow fever	n. r.	n. r.
Meningococcal meningitis[a]	545	37
Hepatitis A	5007	17
Tetanus	11	6
Japanese encephalitis	n. r.	n. r.

[a] Mainly serotype B (nonpreventable by vaccination).
n. r. = not reported.



according to *Werner* et al. 1987

Figure 2: Individuals without protection against tetanus in various age groups in West Germany.

neoplastic disease exceed these numbers by a factor of 30–60. Only a small number of infections are imported from tropical countries. Infections reported in Germany [2] that are typical for tropical or subtropical countries and preventable by vaccination are listed in Table 2. Hepatitis A causes the highest rate of infection among returning tourists, followed by typhoid fever.

Classification of Travellers

Travellers can be classified into different groups with different risks of acquiring infections. The first group (class I) consists of business people, mainly travelling for only a few days and mostly staying in urban surroundings, and people on a cruise. Both of these types of travellers generally live under very good hygienic conditions. People in the second group (class II) are those attending organized tours in urban and rural areas, where the hygienic conditions vary between quite good and bad. The third group (class III) includes all nonorganized backpackers and adventure tourists, who often travel under the worst hygienic conditions and are thus at high risk of acquiring an infectious disease. Independent of hygienic conditions, vector-borne infections can affect all groups of travellers, but the distribution of risk is generally in accordance with the above classification.

Vaccinations for Travellers

Because not all vaccinations can be given simultaneously and some vaccinations require intervals between injections/doses, a vaccination schedule must be determined early in the planning phase of a journey. Since some vaccines require more than one dose for full protection and some are incompatible with others, the first dose should be administered several months before departure. This is obviously not a problem with vaccines protective for ten years or more. Vaccines that induce only short-lasting protection should be administered shortly before departure.

Currently Available Vaccines

Tetanus

Clostridium tetani is an anaerobic rod-shaped bacterium, ubiquitous in nature and found especially in topsoil. The bacteria invade the human organism through small or extensive skin lesions and grow locally under anaerobic conditions, producing a neurotoxin that causes tetanic spasms. In persons without immunity, the infection results in a high fatality rate. Whereas in industrialized countries tetanus is a rare disease because of protective immunity by vaccination, in developing countries about 1 million cases occur annually, especially among neonates, because of lack of immunity. With vaccination, morbidity could be reduced in Germany to about 11 non-fatal and six fatal cases per year, as reported in 1991 [2]. All fatal cases occurred in patients older than 45 years.

In Germany nearly every child is vaccinated against tetanus, beginning in the third month of life. Many adults (especially older people) have not received a tetanus vaccination in several decades, while many others neither remember their last tetanus vaccination nor have any vaccination documents.

Serological studies have shown that in Germany, immunity to tetanus toxin decreases with increasing age. In the age group 18–65 years, more than 10% were nonimmune [3]. Other studies showed a lack of immunity in 65% of the age group > 60 years [4] (Figure 2). On the other hand, some people have been hypervaccinated after receiving tetanus vaccine too often and are thus at risk of having adverse reactions [5].

After a previous basic immunization with three intramuscular injections of 0.5 ml tetanus-toxoid each, beginning in infancy, a booster dose should be administered every ten years, irrespective of travel. Not only are travellers at risk, but also those persons injured in accidents or involved in gardening. Tetanus-toxoid vaccine can and should be administered simultaneously with diphtheria-toxoid vaccine.

A few years ago, test systems for the determination of the antitoxin level in serum were made commercially available. It is advisable to determine the antibody (antitoxin) level in the serum of persons whose immune status is unknown due to missing vaccination documents.

Diphtheria

Diphtheria is a disease caused by a toxin produced by *Corynebacterium diphtheriae*. Only bacteria bearing certain genetic information are capable of producing this toxin. Infection is acquired by contact with respiratory secretions or by direct contact with infected skin lesions [6].
Diphtheria, previously a major health problem, has been largely eliminated in developed countries by widespread vaccination with diphtheria-toxoid vaccine. Nevertheless, in some countries morbidity and mortality associated with diphtheria have increased during the past decade because of the low vaccination rate among adults. For example, in the former USSR adults account for about 80–90% of diphtheria cases [7,8].
In most tropical and subtropical countries, cutaneous and respiratory forms of diphtheria are still common, however, with cutaneous diphtheria being more common than respiratory diphtheria. Cutaneous diphtheria is also more contagious than respiratory diphtheria, and skin lesions are the most common source of infections in tropical countries. Travellers can be affected, as demonstrated by imported cases in tourists [9]. Appropriate immunization can prevent toxic effects.
Since diphtheria remains a worldwide problem, adults should be immunized, preferably with the combined diphtheria-tetanus-toxoid vaccine for adults. The diphtheria-toxoid vaccine for children up to the age of 5 years should not be administered to older children or to adults, because of adverse reactions. The concentration of diphtheria toxoid in the adult vaccine (d) is only 1/15 of that in the children's vaccine (D). In susceptible individuals, a single dose of diphtheria toxoid does not induce protective levels of antitoxin, but after basic immunization one booster dose given every ten years (preferably simultaneously with tetanus-toxoid) will ensure long-lasting immunity.
Determination of the protective antibody concentration (as with tetanus antitoxin) is possible but is not carried out routinely.

Poliomyelitis

Three types of polioviruses exist. The most common form of infection with poliovirus is a mild asymptomatic episode; severe manifestations are rare. In most cases no clinical manifestations are seen. The ratio of inapparent infection to paralytic cases is 100:1 or less, but paralytic poliomyelitis is a severe disease with serious consequences, which must be prevented [10].
In the early phase of infection with polioviruses, droplets from coughing and sneezing can be a source of infection,

Figure 3: Areas in which poliomyelitis is endemic (incidence > 10/100,000).

but the main route of transmission is fecal-oral. Polioviruses spread where hygiene and sanitation are deficient, as is the case in many areas of tropical countries (Figure 3). Poliovirus infections are more likely to produce serious illness in older individuals, with a rise of the incidence of paralytic poliomyelitis in particular. The case fatality rate of paralytic poliomyelitis is variable, being particularly high in the elderly.
Extensive use of the currently recommended formulation of live attenuated trivalent oral (OPV) and/or injectable (IPV) polio vaccine has resulted in the virtual elimination of paralytic poliomyelitis in industrialized countries and a substantial reduction of cases in many developing countries [11]. Oral vaccination in developing countries is not as effective as in industrialized countries. Even in well-vaccinated countries, however, important gaps in protection may exist. Whereas non-immunized individuals are protected in a well-immunized population, they can be readily infected by imported polioviruses. People refusing vaccination (mostly for religious reasons) are at high risk when wild polioviruses are imported by travellers. Recent outbreaks in Gambia, Brazil, Taiwan and Oman [12] showed that protection against poliomyelitis is important for all people.
The aim of the WHO "Expanded Programme on Immunization (EPI)" is to eradicate poliomyelitis worldwide, as has already been done in the case of smallpox, by the year 2000. In Germany wild polioviruses (autochthonous poliomyelitis) have been completely eradicated, but because of increasing tourism to developing countries and the increasing inflow of people from the Third World requesting asylum, wild polioviruses may be brought to Germany and may infect nonimmune people. The only way to achieve protection of travellers and nontravellers is by periodic booster immunization every ten years, not only for children but also for adults.
In Germany oral vaccination is preferred because of its greater ease of administration, lower costs (IPV is more expensive than OPV), ability to induce not only serum antibodies but also intestinal resistance (secretory IgA antibodies) and the rapidity with which the vaccines develop long-lasting, though not life-long, mucosal immunity [13]. The incidence of side effects and of

Infection 21 (1993) No. 1

Figure 4: Areas in which hepatitis A is endemic.

Figure 5: Areas in which typhoid fever is endemic.

insufficient reaction is low with both types of vaccines [14]. Oral polio vaccine is among the safest and most effective antiviral vaccines in current use [15]. As a live vaccine it is contraindicated in individuals with immunodeficiency diseases and their household associates, as well as in patients undergoing immunosuppressive therapy and their household contacts. These individuals should be vaccinated with injectable polio vaccine.

Hepatitis A

Hepatitis A is a viral infection transmitted by contaminated food and drinking water. In tropical and subtropical countries hepatitis A is endemic, with a very high prevalence (Figure 4). In most countries of the world nearly all people have antibodies against hepatitis A due to an infection in early childhood. Today, prevalence in northwestern Europe and in North America is relatively low due to good hygienic conditions, safe food and safe water supplies. The seroprevalence of anti-hepatitis A virus (HAV) antibodies declined in the years following World War II. Younger people, who mainly constitute the group of adventure and backpacker tourists, often travel with small budgets and under less than optimal hygienic conditions and are thus very susceptible to HAV infection. In Germany about 96% of young adults of the age group 20–27 years are nonimmune to HAV [16]. Other studies have shown that 84% of people between 51 and 65 years of age have antibodies against HAV and are therefore immune [17]. About 5,000 cases of hepatitis A are reported annually in Germany (Table 2), mainly imported cases. The severity of the disease is closely related to age, with increased severity associated with increased age.

Every traveller visiting endemic areas (which encompass nearly the entire world except North America and Northwestern Europe) should be aware of the risk of acquiring hepatitis A. Protection is provided by administering human immunoglobulins to travellers a few days before departure to a tropical or subtropical country, especially to those in groups II and III mentioned above. This protection lasts only for about two to six months; repeated immunoglobulin doses must be administered for prolonged protection.

An inactivated active hepatitis A vaccine was first described in 1989 [16]. In 1992 an inactivated hepatitis A vaccine was licensed in several European countries and has been licensed in Germany since December 1992. It is now recommended for all travellers as an individual protection measure [18]. Different vaccination schedules have been studied and results indicate good immune response. A short-term immunization schedule is most suitable for tourists. However, before immunizing persons over 60 years of age, it may be advisable to determine the antibodies against HAV. Since a previous HAV infection will protect the traveller, vaccination would be unnecessary in some cases.

Typhoid Fever

Typhoid fever [19,20] is a bacterial disease of humans caused by *Salmonella typhi*. Paratyphoid fever is caused by *Salmonella paratyphi* A, B or C. Infection is transmitted by ingestion of bacteria via contaminated water and food. Chronic asymptomatic fecal carriers are an important reservoir of infection. Since gastric acidity is a major barrier to infection, individuals taking H_2-blockers or antacids and those who have had partial gastrectomy are at increased risk.

With antibiotic treatment, typhoid fever has a case fatality rate of less than 1% in developed countries. In developing countries, however, case fatality rates are higher, even when antibiotics are available. Typhoid fever has been almost eliminated in developed countries due to sewage and water treatment facilities, but it remains a common disease in developing countries. In 1980 the yearly number of cases was estimated at about 7 million in Asia, over 4 million in Africa and 0.5 million in Latin America (Figure 5). About 200 cases of typhoid fever are diagnosed each year in Germany, of which most are contracted abroad [2]. Vaccinating travellers against typhoid fever could be an important approach to prevention. In Germany a live oral vaccine (*S. typhi* Ty21a) is available. The vaccine is administered by ingestion of one capsule each on days 0, 2 and 4. The protection is supposed to last for about one to two years, but it is not absolute. The vaccine provides no protection against *S. paratyphi* or enteric salmonellae.

Figure 6: Areas in which yellow fever is endemic.

Because a large inoculum of *S. typhi* can cause typhoid fever, even after prior vaccination, vaccinated persons should also observe dietary constraints and other hygienic measures. Reliance on "immunity" alone is clearly dangerous.

Yellow Fever

Yellow fever is an endemic disease in tropical Africa and tropical South America (Figure 6). Two forms of yellow fever are known. Jungle or sylvatic yellow fever is an infection of monkeys living in the jungle, which can be transmitted by certain mosquitos to humans working or travelling in the jungle. A second form, urban or rural yellow fever, is an infection of humans and may be transmitted from person to person by certain other types of mosquitos. During the last decade, the prevalence of yellow fever has increased in certain countries [21]. Most cases in Africa have been reported from Nigeria, with a high case fatality rate (about 60–80%), and most cases in South America were seen in Peru. Cases in South America numbered about 10–20% of the cases in African countries, but the percentage of undetected cases is probably high, since inapparent infections or subclinical infections cannot be readily distinguished from other febrile infections. A specific therapy of yellow fever is not available, and therefore the case fatality rate is high. Immunization of populations at risk with yellow fever vaccine can help reduce the number of cases.

Vaccination is required by law upon entry to certain countries: in some endemic countries irrespective of the country of origin, and in other countries when arriving from endemic areas (Figure 7). In some cases, vaccination against yellow fever is recommended, even though it is not required by law; if for example, yellow fever has been reported in the country of destination. In some Asian and other tropical countries, where yellow fever does not exist but the transmitting mosquito is present, yellow fever vaccination is required for arrivals from an endemic country to prevent importation of yellow fever.

Yellow fever is a live, attenuated viral vaccine (17D) produced in chick embryos. It is extremely safe and effective. One singular subcutaneous injection with 0.5 ml of the vaccine is supposed to induce life-long immunity, but the yellow fever vaccination certificate is valid for only ten years, and therefore booster injections must be administered at ten- year intervals. At present, vaccination is usually not required for children under 1 year of age, but according to a new recommendation of WHO (EPI), yellow fever vaccine should be routinely administered to children under 1 year of age in all endemic areas by 1993 [22].

Meningococcal Meningitis

Neisseria meningitidis is pathogenic exclusively in humans. The natural reservoir for meningococci is the human nasopharynx, and transmission is facilitated by airborne droplets (coughing, sneezing) or close contact. Nasopharyngeal carriage rates vary widely with age and the population under study. During endemic periods, nasopharyngeal carriage usually persists for weeks to months. In closed populations (e.g. military camps) carriage rates range from 20 to 60%. Spread of disease is usually mediated by carriers, not by case-to-case contacts. Overcrowding, lower socioeconomic status, climatic conditions and poor general health have all been considered predisposing factors. Not all individuals exposed to a meningococcal carrier will acquire the infection.

Meningococcal disease is a significant cause of mortality and morbidity in many parts of the world (Figure 8), despite the introduction of new antimicrobial agents. The

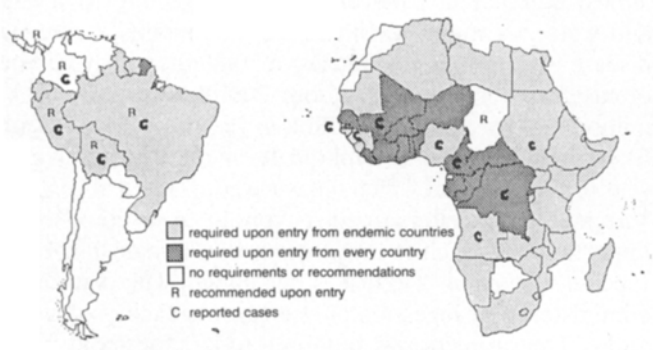


Figure 7: Yellow fever vaccination requirements for individuals travelling to Africa and South America.

Figure 8: Areas in which meningococcal meningitis is endemic (■ = "meningitis belt").

Infection 21 (1993) No. 1

disease is noteworthy for causing major periodic epidemics with attack rates exceeding 500/100,000 [23]. Epidemics of meningococcal meningitis [24] have been reported in New Delhi, Nepal, sub-Saharan Africa ("meningitis belt"), Mecca and Medina (Saudi Arabia), Brazil and other South American countries, and recently in Canada. A marked increase was recorded in African countries in 1988 and 1989 [25]. With increased international travel, global dissemination of an outbreak-associated virulent strain may become more common. In the summer of 1987, group A meningococcal disease, imported into Saudi Arabia by pilgrims to Mecca, resulted in several thousand cases of invasive disease amongst the gathered religious congregation. In the future, outbreaks are to be prevented by requiring vaccination of pilgrims to Mecca [26]. Cases in travellers returning from the areas mentioned are infrequent; however, prolonged contact with the local population may increase the risk of infection and make vaccination a reasonable precaution.

Depending on the immunological specificity of their capsular polysaccharides, different meningococcus serogroups can cause invasive disease. The most common cause of epidemics in the countries mentioned above is serogroup A; serogroup C has also been associated with epidemics. The most recent epidemic occurred in Canada in winter 1991/92. In Germany serogroup B is prevalent.

Morbidity and mortality from meningococcal disease can be significantly reduced by administering currently available vaccines to groups at high risk for the disease, particularly during epidemics. The A + C and ACYW-135 polysaccharide vaccines are currently licensed in Germany and are recommended for immunization of adults as a single 0.5 ml injection of vaccine containing 50 µg of each polysaccharide. Unfortunately, a vaccine against serogroup B is not yet available. Routine immunization of the population against meningococcal disease is not recommended, as the risk of disease is low in the absence of an outbreak. Immunization is recommended for travellers to hyperendemic areas and to those countries experiencing outbreaks as mentioned above [27]. The immunization is effective 10–12 days after administration, and protective immunity is estimated to last for three to five years.

The vaccines are effective in protecting against invasive disease, but infants respond only poorly to polysaccharide antigens. Since attack rates are highest in children 3 months to 1 year of age and then decrease with age, the vaccination has limited efficacy in preventing disease among those at highest risk.

Japanese Encephalitis

Japanese encephalitis is caused by a flavivirus and transmitted by mosquitos. In many countries of Asia, the disease is a serious public health problem in rural areas, with significant mortality in children and the elderly, who are its main victims (Figure 9). The incidence of disease appears to be subsiding in China, Japan and the Republic of Korea, but at the same time it has been increasing and spreading over parts of Bangladesh, Burma, India, Nepal, northern Thailand and Vietnam. Sporadic cases have been reported from southern Thailand, Sri Lanka, Indonesia, Malaysia and Singapore [28]. The proximity of pigs and/or water fowl to human beings increases the chance of transmission. Those travellers visiting rural areas for a longer period of time are at greatest risk. The disease is very rare in travellers from overseas.

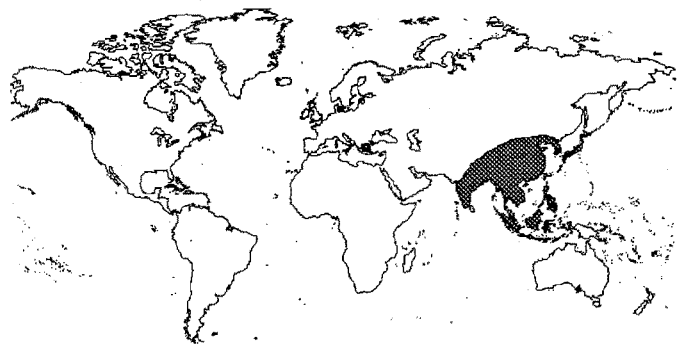


Figure 9: Areas in which Japanese encephalitis is endemic.

An active immunization against Japanese encephalitis is possible, and nationwide vaccinations have decreased the annual incidence of Japanese encephalitis in Japan. The vaccine ("Biken") is produced in intracerebrally inoculated mice with the "Nakayama-NIH" strain. After homogenization of the infected mice brains, the supernatant is inactivated with formalin, further purified and lyophilized. Two doses of 1 ml each are administered subcutaneously at an interval of one to two weeks. To maintain immunity, booster immunization is necessary every year or at least every four years. The vaccine is not licensed in Germany, but some vaccination centers in Germany administer this vaccine upon request. Side effects include local (induration, redness, tenderness) as well as systemic (chills, headache, fever) reactions. Reported hypersensitivity to this vaccine has previously been rare and non life-threatening. Recently, however, an increase of serious adverse reactions following the use of Japanese encephalitis vaccine was reported [29]. After vaccination of about 4,000 individuals against Japanese encephalitis in Australia, adverse reactions (including oedema and rash) were reported in 30 persons. The increase of adverse reactions in Australia remained unexplained. Approval for Japanese encephalitis vaccine has since been suspended in Australia. Serious side effects were also reported after vaccination in Denmark after 1989 [30].

Vaccination is recommended for travellers during the summer monsoon season in endemic areas, especially for visitors to rural areas and for visitors staying longer than one month [31]. Others, however, recommend that vaccination be reserved for those individuals at high risk who remain in endemic areas for one year or more, due to the reported serious side effects of the vaccine [28].

Rabies

In the tropics, rabies is a major human viral disease [32]. The course is fatal; only three cases in the world have been reported to have survived. The virus is transmitted to humans by the bite of dogs and cats or, in some places, by the bite of wild animals, especially carnivores and bats. The virus can also be spread by aerosols from dung, especially in caves. Travellers to areas where rabies is endemic should be cautioned about the risk of infection related to contact with wild or domestic animals. Although dogs are the main reservoir for infection in developing countries, the epidemiology of infection in animals differs significantly worldwide. Any animal bite or scratch should prompt thorough local treatment, and postexposure prophylaxis should be considered. The high mortality from rabies can be prevented by modern postexposure vaccination. Because of the long incubation period, active postexposure vaccination is possible and should be administered immediately after the bite or scratch. Postexposure prophylaxis is most likely to be effective if it can be instituted within the first 24 hours after exposure. Wound cleaning, however, remains the first priority in all cases of animal bites.

In unvaccinated people exposed to rabies, administration of rabies-specific immunoglobulin, simultaneous with active postexposure prophylaxis, is indicated to neutralize the rabies virus before the appearance of vaccine-induced antibodies. Passive immunization should be given at the same time as the first dose of vaccine, but at a different site. Approximately half the dose of hyperimmune serum is infiltrated around the bite wound, and the rest is given intramuscularly at a site distant from the vaccination (but not in the gluteal region, because antibody resorption may be poor).

A preexposure vaccination is recommended for people at high risk in rabies-endemic areas, such as veterinarians, most health care personnel, public health laboratory workers and dog catchers. Travellers at particular risk of exposure to rabies include zoologists and other fieldworkers, forest rangers, cave explorers (bats) and those whose work involves walking and cycling in urban and rural areas of India, Southeast Asia and Latin America. However, preexposure vaccination, including booster injections, does not eliminate the need for additional therapy after rabies exposure.

Two different vaccines are licensed in Germany, the primary chicken embryo cell culture (PCEC) vaccine and the human diploid cell culture (HDC) vaccine. Vaccination schedules are the same for both vaccines. PCEC vaccine is less expensive than HDC vaccine but should not be given to people with a history of allergy to eggs. Two different vaccination schedules for preexposure prophylaxis have been established. Three basic intramuscular injections are necessary for sufficient protection: booster injections should be administered every two to five years. Vaccines used in preexposure and postexposure prophylaxis are the same.

Figure 10: Areas in which cholera is endemic.

Cholera

Cholera is an acute non-inflammatory bacterial diarrheal disease caused by the enterotoxins of *Vibrio cholerae* O group 1, acquired through the ingestion of contaminated food or water [33]. At present, the practice of careful eating and drinking habits remains the most important strategy in preventing cholera. Although cholera is spreading not only in Asia and Africa but since 1991 also in Latin America, the risk to travellers is exceedingly low, because cholera is mainly a disease of poverty, prevailing in areas not frequented by the touristic mainstream (Figure 10).

The currently available vaccine against cholera provides only about 50% protection. The resulting immunity lasts only three to six months. Vaccination does not reduce the rate of asymptomatic infections but reduces the rate of symptomatic infections. Local and systemic adverse reactions are frequent with the killed bacterial vaccine in use. Vaccination can produce a false feeling of safety so that more efficacious measures are neglected [34]. Countries are reminded by the WHO that cholera vaccination is not recommended as a measure for prevention or control and that it should not be required for persons entering or leaving endemic countries. On no account should the travel of people across borders be restricted because of cholera [35]. Nevertheless, vaccinations will sometimes be required for travel between certain countries, particularly in Africa. A single dose is sufficient to satisfy these unjustified health regulations. Vaccination is recommended only for people living and working under epidemic circumstances or less than adequate sanitary conditions and those with compromised gastric defense mechanisms in endemic areas.

Hepatitis B

Hepatitis B virus (HBV) can cause acute and chronic liver disease. The virus is transmitted mainly by the blood of HBV carriers. Therefore, vaccination is recommended for all hospital personnel who have close contact with patients or their blood, as well as cleaning personnel in hospitals who come into contact with blood-soiled material.

Infection 21 (1993) No. 1

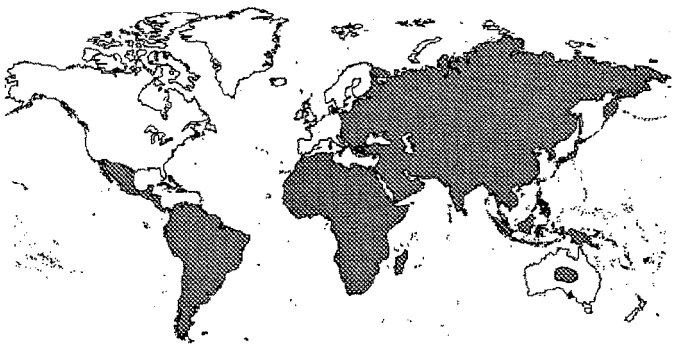


Figure 11: Areas in which hepatitis B is endemic (HBsAg-carrier rates > 1%).

The rate of HBV carriage is low in Germany but high in many tropical and subtropical countries, where carriers constitute a serious public health problem (Figure 11). The disease and its consequences, namely liver failure and hepatocellular carcinoma, can be effectively prevented by vaccination. Nationwide hepatitis B vaccination programs have already been launched in several tropical and subtropical countries [36].

Apart from the above-mentioned risk groups, immunization is also recommended for adults at increased risk of occupational, social, family, environmental or illness-related exposure to HBV. As HBV is also transmitted through sexual contact, vaccination should also be considered for travellers likely to have unprotected sexual contact with the members of the local population in areas with high rates of endemic disease. Sexual contact not only bears the risk of hepatitis B and other sexually transmitted diseases but also the risk of life-threatening HIV infection. This form of transmission can be prevented only by proper avoidance behaviour.

The available hepatitis B vaccine is the first genetically engineered (recombinant) vaccine that has been licensed. It induces good protection but is too expensive for vaccination of the entire population. Therefore, recommendations are still restricted to people at high risk as mentioned above. Attempts have been made to reduce the cost by intradermal vaccination with a dose smaller than that used for intramuscular injection, but antibody responses were lower [37]. Therefore, intramuscular injection, preferably into the deltoideus muscle, remains the recommended route of administration [38]. The response to vaccination should be controlled by serological examination of antibodies to hepatitis B surface antigen (anti-HBs) after basic immunization with three injections. The effectiveness of booster injections is dependent on the anti-HBs level in serum.

Measles

Measles is a highly contagious viral infection that is transmitted very effectively by droplets or aerosol from the respiratory tract. Thus, infections occur mainly in childhood. The severity of the disease is higher in developing than in industrialized countries; case fatality rates are 10–1,000 times higher in the former. Worldwide, measles causes more than 2,000,000 preventable childhood deaths per year [39]. Complications affect virtually all organ systems of the body.

The widespread use of measles vaccine in several industrialized countries has led to a significant reduction in disease incidence, but also to neglect of immunization. Nonimmune individuals with no history of measles or vaccination are at high risk when travelling to developing countries. Vaccination with the currently available attenuated live virus vaccine is recommended from the 15th month of life in Germany, but for infants travelling to developing countries it is recommended from the 9th month of life. Formerly, a single dose of 0.5 ml of the vaccine was administered subcutaneously, but at present a second dose administered between 6 and 10 years of age is recommended to minimize the vaccine failure rate and to achieve eradication of the disease.

Studies in the USA have shown an increase in measles in the last few years [40,41], not only in children but in nonimmune adults as well, especially health care workers [42]. Seroprevalence in health care workers was about 86%. Measles vaccination is recommended for all adults susceptible and likely to be exposed to measles [43].

Special Groups of Travellers

Pregnant Women

Touristic travel to tropical countries should be avoided by pregnant women because of certain increased risks, one of which is the increased chance of acquiring infections. Certain vaccines should be avoided in pregnancy because they may damage the fetus and because of the reduced immunological defence mechanisms during pregnancy.

Of the vaccinations mentioned in this report, measles, yellow fever and oral typhoid fever vaccine (all live vaccines) should be avoided. In cases of absolute necessity to travel, only yellow fever vaccine should be administered. No adverse reactions to this vaccination have been described in the fetus.

Vaccinations that can be administered during pregnancy are oral polio vaccine (OPV), inactivated polio vaccine (IPV), toxoid vaccines such as tetanus, and the genetically engineered recombinant hepatitis B vaccine. Only in cases of unavoidable risk should diphtheria, rabies and cholera vaccines be administered.

HIV-Infected Individuals

HIV-infected individuals should be advised about the ways to lower the adverse effects of travel, especially international travel, on their health. The potential for infectious complications of sexual activity and illicit drug use should be stressed, and recommendations for reducing the risk should be discussed [44]. Vaccines are currently available for only a few of the pathogens that are

potentially important for HIV-infected individuals; these include influenza virus, *Streptococcus pneumoniae* and HBV. However, antibody responses to these vaccines may be unsatisfactory in immunocompromised persons [45]. The immune response of symptomatic HIV patients to toxoid and polysaccharide vaccines is significantly lower than that of non-immunocompromised patients [46]. Vaccinations possible in infected and symptomatic HIV patients are shown in Table 1.

New Approaches in Vaccines for Travellers

With the exception of hepatitis B vaccine, the vaccines currently used are produced from the infectious agents themselves, either by attenuation (live vaccines) or inactivation (dead vaccines). Although these products have been successful in controlling many diseases, efforts are being made to improve their quality. In addition, there are some infectious diseases for which vaccines are not yet available, because the causal agents cannot be grown in sufficient quantities. Thus, a new field of vaccine production by methods of molecular biology and biotechnology has emerged. Genetic engineering is the basis of a new generation of vaccines aimed at eradicating of a number of diseases throughout the world [47].

New Approaches with Currently Available Vaccines

There have been no recent attempts to improve the very good and highly effective tetanus and diphtheria-toxoid vaccine, but in the past few years tetanus- [48] and diphtheria- [49]toxoid have been introduced as carrier molecules for other covalently bound antigens (conjugate vaccines). Such combinations have been described between *S. pneumoniae* polysaccharide, *N. meningitidis* group C polysaccharide or *Haemophilus influenzae* type b and tetanus- or diphtheria-toxoid [50]. Humoral immunity is induced against the covalently attached antigen, but not against the carrier molecules.

Experimentally, certain epitopes of poliovirus and other viruses, such as HBV, were expressed as genetic inserts in outer membrane proteins, for example, those of *Escherichia coli* or *S. typhimurium*, which were administered to animals parenterally or orally [51]. Conversely, poliovirus is being used as an expression vector for other foreign genes [52].

Efforts have also been made to express HAV epitopes in recombinant vaccinia virus [53]. Furthermore, a live attenuated vaccine produced from tissue culture will be available in China for human use in the near future [54]. The attenuated strains of *S. typhi* now available in some countries not only function as live oral vaccine against typhoid fever but also serve as experimental carrier vaccines for expressing foreign antigens of other pathogens and presenting them to the immune system [52,55]. Parenterally applied purified Vi polysaccharide is another new approach to a typhoid fever vaccine [56].

An infectious complementary DNA of yellow fever virus (17D strain) has now been produced, opening the way for developing the 17D strain as a recombinant vaccine [57]. Polysaccharide vaccines, like the currently available meningococcal vaccine, elicit only a poor immune response in young children. Immunogenicity can be improved when polysaccharides are conjugated to protein carriers or other carrier molecules such as tetanus-toxoid [47]. A very promising approach to the development of an effective group B meningococcal vaccine is the use of lipopolysaccharide-depleted outer membrane proteins (OMP) as vaccine. Clinical studies indicate that these vaccines are safe and immunogenic but often evoke local reactions, systemic reactions being minimal.

A live attenuated vaccine against Japanese encephalitis is under development. Recently, a recombinant vaccinia virus engineered to express different epitopes of the Japanese encephalitis virus representing the most important antigens for protective immunity (E-proteins = envelope glycoproteins) has been produced [58]. Thus, a new type of vaccine against Japanese encephalitis virus may become available in the future [59].

Vaccinia recombinant vaccines have been constructed to induce protective immunity against rabies [60]. Animals were orally vaccinated by dropping baits containing this recombinant rabies vaccine [61] from aircraft into woods [62]. This method is highly valuable for prophylaxis of rabies in animals. Another approach is immunization with synthetic viral peptides, which evoke a solid immune response [59]. Neither type of vaccine is available yet for human use.

More effective vaccines against cholera are currently under development, including live oral vaccines, hybrid vaccines [63] and oral cholera toxin B subunit vaccines [55].

Attempts have been made to express HBV antigens in, for example, attenuated salmonellae for use as live oral vaccine [64] to elicit a protective immune response. Other research has included efforts to recombine HBV with another live viral vaccine, such as varicella zoster-virus vaccine [52].

New Approaches in Vaccine Development

There are a number of important infectious diseases for which it has not been possible to develop vaccines by conventional methods. Increased knowledge of the molecular structure of infectious agents and the requirements for a protective immune response have led to novel approaches. At present, in vaccine development four main approaches exist: recombinant vaccines, synthetic peptide vaccines, immunostimulating complexes (ISCOMs) and anti-idiotypic vaccines.

Recombinant Vaccines

The ability to construct genetically engineered recombinant viral vaccines by the use of a vaccinia vector

Infection 21 (1993) No. 1

Die Forschungs-

arbeit von

SmithKline Beecham

hat sich gelohnt:

Havrix, der aktive

Hepatitis-A-

Impfstoff ist da!

Havrix*

aktiver Impfschutz gegen Hepatitis A

Ein Produkt von SmithKline Beecham

*Havrix ist ein Warenzeichen

Havrix*
Wirkstoff: Hepatitis-A-Impfstoff. **Zusammensetzung:** 1 Impfdosis (1 ml Suspension) enthält: 720 Antigeneinheiten inaktiviertes Hepatitis-A-Virus, gezüchtet in Kulturen menschlicher diploider Zellen, 0,95 mg Aluminiumhydroxid-Gel (entspr. 0,5 mg Aluminium), 5,0 mg 2-Phenoxyethanol, max. 0,05 mg Polysorbat 20, max. 0,1 mg Formaldehyd. **Anwendungsgebiete:** Aktive Immunisierung gegen Hepatitis A; insbesondere für Reisende in Endemiegebiete, beruflich Exponierte wie z. B. Kanal- und Klärwerksarbeiter, Personen, die mit der Herstellung und der Verteilung von Lebensmitteln beschäftigt sind, Mitarbeiter pädiatrischer Einrichtungen und Kliniken, Angehörige von Entwicklungsdiensten, Schutz- und Streitkräften bei Einsätzen in Endemiegebieten sowie andere Risikogruppen. **Gegenanzeigen:** Bekannte Überempfindlichkeit gegen Bestandteile des Impfstoffes. Akute, insbesondere fieberhafte Infekte. Zur aktiven Immunisierung bei Kindern aufgrund begrenzter Erfahrung nicht empfohlen. Hinweis: In der Schwangerschaft und Stillzeit nur nach sorgfältiger Abwägung der Indikation und des Risikos impfen. **Nebenwirkungen:** Lokale vorübergehende Reaktionen wie Rötung, Schwellung, Induration oder leichte Schmerzen. Gelegentlich Allgemeinreaktionen leichter Art: Kopfschmerzen, Unwohlsein, Mattigkeit, Fieber, Appetitlosigkeit, Übelkeit. Bei unter 1% der Geimpften Schmerzen im Oberarm, Infektion der oberen Luftwege, Erbrechen, Durchfall oder vorübergehend leicht erhöhte Leberenzymwerte. In Einzelfällen allergische Reaktionen möglich. Im Falle des Auftretens eines Schocks übliche Behandlungsmaßnahmen einleiten. Hinweis: Havrix schützt nicht vor durch andere Erreger als HAV hervorgerufene Hepatitiden. Die Impfung verhindert nicht die klinische Manifestation einer bereits bestehenden HAV-Infektion. **Wechselwirkungen:** Die gleichzeitige passive Immunisierung mit anti-HAV-haltigem Immunglobulin kann zu niedrigeren Antikörpertitern als nach Havrix allein führen. Bei immungeschwächten Personen kann der Impferfolg eingeschränkt sein. **Wirkungsweise:** Der Impfstoff bewirkt die Bildung spezifischer Antikörper und damit Schutz vor Hepatitis A. **Dosierung:** Gebrauchsfertige Impfstoffsuspension zur i. m. Injektion. Empfohlenes Impfschema: 2 Impfungen mit je 1 Dosis (1 ml Havrix) im Abstand von 4 Wochen oder mind. 2 Wochen (für schnelleren Impfschutz) i. m., vorzugsweise intradeltoidal, verabreichen. 3. Impfung nach 6–12 Monaten durchführen. Nicht i.v. injizieren! Nicht mit anderen Impfstoffen oder Arzneimitteln mischen! Bei gleichzeitiger Gabe mit anderen Impfstoffen 2 verschiedene Injektionsorte für die i.m. Gaben wählen! In Ausnahmefällen (z. B. Hämophilie-Patienten) subkutane Injektion mit anschließender Titerkontrolle. Bei immungeschwächten Patienten siehe Gebrauchsinformation. **Packungsgrößen und Preise** (AVP inkl. MwSt): Originalpackungen als **Flasche:** 1 Impfdosis Havrix mit 1 ml Suspension DM 72,55; 2 x 1 Impfdosis Havrix mit je 1 ml Suspension DM 137,68; 10 x 1 Impfdosis Havrix mit je 1 ml Suspension DM 670,46. *Havrix ist ein Warenzeichen. Stand: Dezember 1992

SB SmithKline Beecham Pharma

HAV0007

for the presentation of antigens was first described in 1982. A large number of different types of viruses and other infectious agents, such as *E. coli*, *S. typhimurium*, BCG, poxviruses other than vaccinia virus, adenovirus, herpesviruses and poliovirus [65], can now be adapted to serve as efficient and effective vectors for specific antigens (epitopes).

The most common vector system is vaccinia virus. An advantage of vaccinia virus is its large viral genome, which enables the insertion of a large amount of foreign genetic information and the use of the derived recombinants as a live vaccine. Most of these recombinants are highly effective at inducing both humoral and cellular immunity. A large number of recombinant vaccines against many infectious agents have been constructed. Eventually, it will become possible to construct polyvalent vaccines containing antigens from several different pathogens or perhaps antigens from several different serotypes of the same pathogen.

Such vaccines could be of particular value in developing countries because they would be inexpensive, easy to administer, and would provide long-lasting immunity [65]. Nevertheless, despite the many advantages of the vaccinia virus vectors, the system does have some inherent limitations. Although rare, postvaccinal encephalitis and progressive vaccinia virus complications are known to occur after vaccination with vaccinia virus, especially in individuals whose cell-mediated immune mechanisms are impaired. Before these vaccinia vector systems can be applied, their safety must be secured. Recombinant vaccinia-rabies vaccine is currently in use in animals [60].

Synthetic Peptides

This approach is to define sites on an infectious agent responsible for eliciting protective immunity and to use chemically or biologically synthesized short chains of amino acids (peptides) representing these sites as potential vaccines [66].

Synthetic peptides play a major role in malaria vaccine development. Peptides, representing a protective sequence from the sporozoite stage of *Plasmodium falciparum*, have been conjugated to tetanus-toxoid, resulting in some degree of protection after application [67–69].

Coupled and uncoupled synthetic peptides, for example those of foot-and-mouth disease virus and rabies virus [70], have been shown to induce an antibody response in different animals. Induction of antibodies is obviously influenced by the length of the peptide as well as by the kind of carrier and coupling [71]. Even an uncoupled synthetic peptide of only nine amino acids in length has been shown to protect against lethal murine cytomegalovirus infection [72].

Immunostimulating Complexes

To make purified antigens highly immunogenic, they must be presented in several copies in the form of a microscopic or submicroscopic particle, regardless of whether the antigens are obtained by isolation from conventional microorganisms, isolation from gene-manipulated cells, or by synthesis. Immunostimulating complexes (ISCOMs) are spherical structures presenting immunogens as multimers in a matrix. The antigens in ISCOMs are rapidly transported from the injection site to the draining lymphatic organ. ISCOMs have been shown to enhance the immunogenicity of several antigens that are important for the development of human as well as veterinary vaccines [73]. In animals, protective immunity has been induced against several infectious agents, such as influenza virus, measles virus, Epstein-Barr virus, HIV [74], *Trypanosoma cruzi* [75] and *Plasmodium falciparum* [73].

Anti-Idiotypic Antibodies

Anti-idiotypic antibodies, which are directed against the antigenic characteristic of the variable region of an antibody, have recently been suggested as candidates for potential vaccines against numerous infectious organisms [76] as well as against different kinds of tumors [77,78].

In the case of biological toxins such as mycotoxin, tetrodotoxin and saxitoxin, whose toxic nature precludes their use as immunogens in the induction of protective immunity, anti-idiotypic antibodies can be used to elicit an antigen-specific immune response [79].

Unfortunately, to date it is not possible to vaccinate against diarrheal disease and malaria, two of the main health problems in travellers and in tropical and subtropical countries.

Malaria

One of the main health problems of tropical countries is malaria. At present, mechanical prophylaxis and chemoprophylaxis are the only measures to prevent malaria, but increasing resistance to antimalarial agents makes it more difficult to prevent and to treat the disease. Attempts to develop an effective vaccine against malaria have been ongoing for years, but the development of a vaccine against a parasitic disease is more complicated than against a viral disease, because of antigenic changes in each developmental stage. Three approaches are currently under investigation:

- a vaccine against sporozoites, the parasitic forms transmitted by mosquitos to humans;
- a vaccine against merozoites, the parasitic forms that multiply in human erythrocytes; and
- a vaccine against the gametocytes, the sexual parasitic forms that are transmitted when a mosquito feeds on a malaria patient.

All malaria parasites have certain epitopes that can be inserted in a vaccinia or other vector. These combinations can now be produced in large amounts. The resulting

Infection 21 (1993) No. 1

(synthetic) peptides can be coupled to carrier molecules, like tetanus-toxoid, as mentioned above. Optimal results will be obtained by combining antigens of the different parasitic stages.
Thus far no malaria vaccine has been licensed, but clinical testing has been undertaken, especially with synthetic peptide vaccines representing a protective sequence from sporozoite stages of *P. falciparum* coupled to tetanus-toxoid or other carrier molecules. However, antiparasitic antibody responses were generally low [66,68,80]. An effective vaccine against malaria for travellers will not be licensed in the near future.

Diarrhea

Considerable progress has been made in the past decade in developing vaccines against the most important bacterial and viral infections of the gastrointestinal tract. A genetically engineered live oral cholera vaccine is under investigation in clinical trials in cholera-endemic areas. Other approaches include investigation of hybrid vaccines [61] and oral cholera toxin B subunit vaccines [62]. Salmonella recombinant vectors have been used because they offer the advantage of oral administration, thus providing a mucosal immunity that is clearly required for many enteric infections. Various vaccine candidates against *Shigella*, enterotoxigenic *E. coli* and rotavirus are being investigated in clinical trials in some countries [81–83]. Vaccines that would be easier to distribute than most previous vaccines may soon be produced at low cost [84]. This would be of great help in reducing the enormous problems caused by enteric diseases in the developing world.

Other Vaccines

Dengue

Dengue, a viral infection transmitted by mosquitos, has become an increasing health problem in Southeast Asia, Central America and the South Pacific region. Immunization against dengue may become an important tool in the prevention of dengue infection in the future. Live attenuated dengue candidate vaccines against types 1, 2 and 4 are being evaluated in Thailand, and investigators are attempting to develop a genetically engineered dengue vaccine [85]. Nevertheless, it may take several years until an efficacious dengue vaccine is available for general use. In some infections pathological effects can be mediated by immune response. Thus, with dengue virus, repeated infection can take a worse course than the first, due to immune enhancement by residual antibody. Vaccines may carry the same hazard. Meanwhile, vector control measurements remain the principal tool for the prevention of dengue infection in populations at risk. At present travellers still have to rely mainly on primary prevention (mosquito nets, clothing) to avoid dengue.

HIV

Despite intense efforts worldwide using state-of-the-art methods and techniques, and despite ever-increasing knowledge about the molecular and structural make-up of HIV, a practicable vaccine against this virus has yet to be developed. Using recombinant DNA techniques and synthetic peptide technology, many groups have been able to identify at the epitope level the regions of HIV proteins which act as targets for (and stimulate) the immune response. However, it still is not clear which of the different immune responses (or combinations thereof) must be stimulated in order to protect from infection. Infected humans develop neutralizing antibodies, antibody-dependent cellular cytotoxicity inducing antibodies, and cytotoxic T-lymphotoxic responses against a variety of viral proteins, but it is not known which of these can control or prevent infection *in vivo*. The very nature of HIV makes vaccine development very difficult, if possible at all [86].

Conclusions

Travellers to tropical or subtropical countries can acquire various infectious diseases. The risk is mainly dependent on the hygienic conditions prevailing at the place of destination or on the distribution of arthropods acting as vectors for the infectious agents. Many infectious diseases still cause health problems for the local population in developing countries. The aim of the WHO is to eradicate some of the most important infectious diseases by the year 2000, by means of vaccination.
For travellers, the risk of acquiring a serious infectious disease is today quite low due to expanded vaccination programs in developing countries and vaccination of travellers before their departure. Most of the available vaccines are very effective, and rates of adverse reactions are low. Travellers should be vaccinated against infectious diseases as stated above, not only for their own protection but also to avoid importation of infectious diseases which could infect nonimmune persons on return.
Many attempts are being made to develop new vaccines, but not only for the protection of travellers, who from a global point of view represent only a minority of those in need of vaccination. More important is the development of affordable, heat-resistant, polyvalent vaccines against the infectious diseases threatening the populations of developing countries. For important infectious diseases in tropical and subtropical countries such as parasitoses like trypanosomiasis, or helminthoses like schistosomiasis or filariasis, no vaccines will be available in the near future.

Acknowledgements

Maps were drawn by PC Globe 4.0 software. Copyright for the unmodified maps 1990: PC Globe, Inc. Modifications of the maps were mainly according to *D. Stürchler*, Endemic Areas of Tropical Infections. Hans Huber Publishers, Toronto 1988. I thank Dr. *Harald Kretschmer*, Dr. *Aart van Soest*, Dr. *Gabriele Döller*, and *Joy Ann McDougall* for their critical comments and careful review of the manuscript.

References

1. **Bockemühl, J.:** Reisediarrhoe. Dtsch. Ärztebl. 88 (1991) 1437–1440.
2. **Pöhn, H. P., Zastrow, K. D., Großmann, R.:** Infektionskrankheiten: Epidemiologische Situation 1989 in der Bundesrepublik Deutschland. Bundesgesundhbl. 34 (1991) 199–202.
3. **Pietsch, M.:** Lücken in der Impfimmunität der Deutschen Bevölkerung. Hyg. und Med. 16 (1991) 158–163.
4. **Werner, G. T., Berdel, W. E., Frühwein, N., Ulm, K.:** Untersuchungen zur Tetanusimmunität der Münchner Bevölkerung. Münch. Med. Wochenschr. 129 (1987) 157–159.
5. **Korger, G., Quast, U., Decnert, G.:** Tetanusimpfung – Verträglichkeit und Vermeidung von Nebenreaktionen. Klin. Wochenschr. 64 (1986) 767–775.
6. **Halsey, N. A., Smith, M. H. D.:** Diphtheria. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 860–867.
7. **Korzenkova, M. P., Ivanov, V. A., Platonova, T. V., Doljikova, M. A.:** Routine screening for *Corynebacterium diphtheriae*. Lancet 338 (1991) 577–578.
8. **Anonymous:** Expanded programme on immunization. Outbreak of diphtheria. Wkly. Epidemiol. Rec. 66 (1991) 181–185.
9. **Höfler, W., Heizmann, W., Höring, E., Junga, C., von Gaisberg, U., Kusch, G., Weidner, F.:** Drei Fälle von Hautdiphtherie bei Afrikareisenden. Dtsch. Ärztebl. 86 (1989) 221–223.
10. **Melnick, J. L.:** Poliomyelitis. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 559–576.
11. **Anonymous:** Expanded programme of immunization. Wkly. Epidemiol. Rec. 65 (1990) 34–35.
12. **Sutter, R. W., Patriarca, P. A., Brogan, S., Malankar, P. G., Pallansch, M. A., Kew, O. M., Bass, A. G., Cocji, S. L., Alexander, J. P., Hall, D. B., Suleiman, A. J. M., Al-Ghassany, A. A. K., El-Bualy, M. S.:** Outbreak of paralytic poliomyelitis in Oman: evidence for widespread transmission among fully vaccinated children. Lancet 338 (1991) 715–720.
13. **Beale, A. J.:** Polio vaccines: time for a change in immunization policy. Lancet 335 (1990) 839–842.
14. **Schwick, H. G.:** Poliomyelitis, in der Zeit von Landsteiner und heute. Wien. Klin. Wochenschr. 103 (1991) 136–140.
15. **Minor, P. D., Macadam, A., Cammack, N., Dunn, G., Almond, J. W.:** Molecular biology and the control of viral vaccines. FEMS Microbiol. Immunol. 2 (1990) 207–213.
16. **Flehmig, B., Heinricy, U., Pfister, M.:** Immunogenicity of a killed hepatitis A vaccine in seronegative volunteers. Lancet 334 (1989) 1039–1041.
17. **Chriske, H. W., Abdo, R., Rickrath, R., Braumann, S.:** Hepatitis-A-Infektionsgefährdung bei Kanal- und Klärwerksarbeiten. In: *Zerlett, G., Chriske, H. W.* (eds.): Arbeitsmedizin im Öffentlichen Dienst. Tagungsbericht 1990. Gentner Verlag, Stuttgart 1990, pp. 159–163.
18. **Andre, F. E., Hepburn, A., D'Hondt, E.:** Inactivated candidate vaccines for hepatitis A. Prog. Med. Virol. 37 (1990) 72–95.
19. **Salata, R. A., Olds, G. R.:** Infectious diseases in travellers and immigrants. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 228–242.
20. **Butler, T.:** Typhoid fever. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 753–757.
21. **Anonymous:** Yellow fever in 1988. Wkly. Epidemiol. Rec. 65 (1990) 213–220.
22. **Anonymous:** Expanded programme on immunization. Part I. Wkly. Epidemiol. Rec. 67 (1992) 11–15.
23. **Schwartz, B., Moore, P. S., Broome, C. V.:** Global epidemiology of meningococcal disease. Clin. Microbiol. Rev. 2 (1989) (Suppl.) S118–S124.
24. **Scheld, W. M.:** Meningococcal diseases. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 798–814.
25. **Anonymous:** Meningococcal meningitis in Africa. Wkly. Epidemiol. Rec. 65 (1990) 120–122.
26. **Anonymous:** Vaccination requirements. Pilgrimage to Mecca (Hajj). Wkly. Epidemiol. Rec. 66 (1991) 99.
27. **Frasch, C. E.:** Vaccines for prevention of meningococcal disease. Clin. Microbiol. Rev. 2 (1989) (Suppl.) S134–S138.
28. **Umenai, T., Krzysko, R., Bektimirov, T. A., Assaad, F. A.:** Japanese encephalitis: current worldwide status. Bull. World Health Organ. 63 (1985) 625–631.
29. **Ruff, T. A., Eisen, D., Fuller, A., Kass, R.:** Adverse reactions to Japanese encephalitis vaccine. Lancet 338 (1991) 881–882.
30. **Andersen, M. M., Ronne, T.:** Side effects with Japanese encephalitis vaccination. Lancet 337 (1991) 1044.
31. **Denning, D. W., Kaneko, Y.:** Should travellers to Asia be vaccinated against Japanese encephalitis? Lancet i (1987) 853–854.
32. **Warrel, D. A., Shope, R. E.:** Rabies. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 635–644.
33. **Butler, T., Sack, D.:** Cholera. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 745–753.
34. **Exner, M., Böllert, F.:** Hygienische Aspekte der Cholera unter besonderer Berücksichtigung der Epidemie in Südamerika. Bundesgesundhbl. 34 (1991) 401–414.
35. **Anonymous:** Vaccination requirements. Wkly. Epidemiol. Rec. 66 (1991) 56.
36. **Tsen, Y. J., Chang, M. H., Hsu, H. Y., Lee, C. Y., Sung, J. L., Chen, D. S.:** Seroprevalence of hepatitis B virus infection in children in Taipei, 1989: five years after a mass hepatitis B vaccination program. J. Med. Virol. 34 (1991) 96–99.
37. **Ronish, R. H., Diniega, B. M., Kelley, P. W., Sjogren, M. H., Arday, D. R., Aronson, N. E., Hoke, C. H., Petruccelli, B. P.:** Immunogenicity achieved by the intradermal hepatitis B vaccination programme for US Army soldiers in Korea. Vaccine 9 (1991) 364–368.
38. **Anonymous:** Inadequate immune response among public safety workers receiving intradermal vaccination against hepatitis B--United States, 1990–1991. MMWR 40 (1991) 569–572.
39. **Halsey, N. A., Job, J. S.:** Measles. In: *Warren, K. S., Mahmoud, A. A. F.* (eds.): Tropical and geographical medicine. McGraw-Hill Information Service Co., New York 1990, pp. 607–619.
40. **Anonymous:** The measles epidemic. The problems, barriers, and recommendations. The National Vaccine Advisory Committee. JAMA 266 (1991) 1547–1552.
41. **Campos Outcalt, D.:** Measles update. Am. Fam. Physician 42 (1990) 1274–1283.
42. **Atkinson, W. L., Markowitz, L. E., Adams, N. C., Seastrom, G. R.:** Transmission of measles in medical settings--United States, 1985–1989. Am. J. Med. 91 (1991) 320.
43. **LaForce, F. M.:** Adult immunizations: are they worth the trouble? J. Gen. Intern. Med. 5 (1990) (Suppl.) S57–S61.
44. **Filice, G. A., Pomeroy, C.:** Preventing secondary infections among HIV- positive persons. Public Health Rep. 106 (1991) 503–517.
45. **Weber, R., Lüthy, R.:** Sekundärprophylaxe bei HIV-Infektion. Ther. Umsch. 48 (1991) 258–263.
46. **Opravil, M., Fierz, W., Matter, L., Blaser, J., Lüthy, R.:** Poor antibody response after tetanus and pneumococcal vaccination in immunocompromised, HIV-infected patients. Clin. Exp. Immunol. 84 (1991) 185–189.
47. **Péret, R.:** Biotechnologies et vaccinations. Actual Odontostomatol. Paris (1990) 663–674.
48. **Peeters, C. C., Tenbergen-Meekes, A. M., Poolman, J. T., Beurret, M., Zegers, B. J., Rijkers, G. T.:** Effect of carrier priming on immunogenicity of saccharide-protein conjugate vaccines. Infect. Immun. 59 (1991) 3504–3510.
49. **Robbins, J. B., Schneerson, R.:** Evaluating the *Haemophilus influenzae* type b conjugate vaccine PRP-D. N. Engl. J. Med. 323 (1990) 1415–1416.
50. **Parke, J. C. Jr., Schneerson, R., Reimer, C., Black, C., Welfare, S., Bryla, D., Levi, L., Pavliakova, D., Cramton, T., Schulz, D., Cadoz, M., Robbins, J. B.:** Clinical and immunologic responses to

Infection 21 (1993) No. 1 © MMV Medizin Verlag GmbH München, München 1993

Haemophilus influenzae type b-tetanus toxoid conjugate vaccine in infants injected at 3, 5, 7 and 18 months of age. J. Pediatr. 118 (1991) 184–190.

51. **O'Callaghan, D., Charbit, A., Martineau, P., Leclerc, C., van der Werf, S., Nauciel, C., Hofnung, M.:** Immunogenicity of foreign peptide epitopes expressed in bacterial envelope proteins. Res. Microbiol. 141 (1990) 963–969.
52. **Shiraki, K., Hayakawa, Y., Mori, H., Namazue, J., Takamizawa, A., Yoshida, I., Yamanishi, K., Takahashi, M.:** Development of immunogenic recombinant Oka varicella vaccine expressing hepatitis B virus surface antigen. J. Gen. Virol. 72 (1991) 1393–1399.
53. **Karayiannis, P., O'Rourke, S., McGarvey, M. J., Luther, S., Waters, J., Goldin, R., Thomas, H. C.:** A recombinant vaccinia virus expressing hepatitis A virus structural polypeptides: characterization and demonstration of protective immunogenicity. J. Gen. Virol. 72 (1991) 2167–2172.
54. **Mao, J. S.:** Development of live, attenuated hepatitis A vaccine (H2-strain). Vaccine 8 (1990) 523–524.
55. **Lewis, D. J., Novotny, P., Dougan, G., Griffin, G. E.:** The early cellular and humoral immune response to primary and booster oral immunization with cholera toxin B subunit. Eur. J. Immunol. 21 (1991) 2087–2094.
56. **Rao, N.:** Protecting travelers from typhoid fever. Infect. Control. Hosp. Epidemiol. 12 (1991) 168–172.
57. **Putnak, J. R., Schlesinger, J. J.:** Protection of mice against yellow fever virus encephalitis by immunization with a vaccinia virus recombinant encoding the yellow fever virus non-structural proteins, NS1, NS2a and NS2b. J. Gen. Virol. 71 (1990) 1697–1702.
58. **Mason, P. W., Pincus, S., Fournier, M. J., Mason, T. L., Shope, R. E., Paoletti, E.:** Japanese encephalitis virus-vaccinia recombinants produce particulate forms of the structural membrane proteins and induce high levels of protection against lethal JEV infection. Virology 180 (1991) 294–305.
59. **Yasui, K., Miyamoto, M., Kimura Kuroda, J., Yasuda, A., Matsuura, Y., Sato, T., Kojima, A., Kubonoya, H.:** Analysis of Japanese encephalitis (JE) virus genome and implications for recombinant JE vaccine. Southeast Asian J. Trop. Med. Public Health 21 (1990) 663–669.
60. **Fu, Z. F., Dietzschold, B., Schumacher, C. L., Wunner, W. H., Ertl, H. C., Koprowski, H.:** Rabies virus nucleoprotein expressed in and purified from insect cells is efficacious as a vaccine. Proc. Natl. Acad. Sci. USA 88 (1991) 2001–2005.
61. **Linhart, S. B., Blom, F. S., Dasch, G. J., Roberts, J. D., Engeman, R. M., Esposito, J. J., Shaddock, J. H., Baer, G. M.:** Formulation and evaluation of baits for oral rabies vaccination of raccoons (Procyon lotor). J. Wildl. Dis. 27 (1991) 21–33.
62. **Bachmann, P., Bramwell, R. N., Fraser, S. J., Gilmore, D. A., Johnston, D. H., Lawson, K. F., MacInnes, C. D., Matejka, F. O., Miles, H. E., Pedde, M. A., Webster, W. A.:** Wild carnivore acceptance of baits for delivery of liquid rabies vaccine. J. Wildl. Dis. 26 (1990) 486–501.
63. **Forrest, B. D., LaBrooy, J. T.:** *In vivo* evidence of immunological masking of the *Vibrio cholerae* O antigen of a hybrid *Salmonella typhi* Ty21a-*Vibrio cholerae* oral vaccine in humans. Vaccine 9 (1991) 515–520.
64. **Schodel, F., Will, H.:** Expression of hepatitis B virus antigens in attenuated salmonellae for oral immunization. Res. Microbiol. 141 (1990) 831–837.
65. **Anonymous:** Potential use of live viral and bacterial vectors for vaccines. WHO meeting, Geneva, 19–22 June, 1989. Vaccine 8 (1990) 425–437.
66. **Francis, M. J.:** Peptide vaccines for viral diseases. Sci. Prog. 74 (1990) 115–130.
67. **Etlinger, H. M., Renia, L., Matile, H., Manneberg, M., Mazier, D., Trzeciak, A., Gillessen, D.:** Antibody responses to a synthetic peptide-based malaria vaccine candidate: influence of sequence variants of the peptide. Eur. J. Immunol. 21 (1991) 1505–1511.
68. **Stürchler, D., Zimmer, G., Berger, R., Etlinger, H., Fernex, M., Matile, H., Just, M.:** Interferon-alpha and synthetic peptide malaria sporozoite vaccine in non-immune adults: antibody response after 40 weeks. Bull. World Health Organ. 68 (1990) 38–41.
69. **Herrington, D. A., Clyde, D. F., Davis, J. R., Baqar, S., Murphy, J. R., Cortese, J. F., Bank, R. S., Nardin, E., DiJohn, D., Nussenzweig, R. S., Nussenzweig, V., Torres, J. R., Murillo, J., Cortesia, M., Stürchler, D.:** Human studies with synthetic peptide sporozoite vaccine (NAN)3-TT and immunization with irradiated sporozoites. Bull. World Health Organ. 68 (1990) 33–37.
70. **Dietzschold, B., Ertl, H. C.:** New developments in the pre- and post-exposure treatment of rabies. Crit. Rev. Immunol. 10 (1991) 427–439.
71. **Liebermann, H., Holl, U., Reimann, I., Nockler, A., Schafer, D., Thalmann, G., Dolling, R.:** Synthetic peptides against foot-and-mouth disease – immunization with VP1-peptides of type O1-Kaufbeuren. Arch. Exp. Veterinärmed. 44 (1990) 883–890.
72. **Del Val, M., Schlicht, H. J., Volkmer, H., Messerle, M., Reddehase, M. J., Koszinowski, U. H.:** Protection against lethal cytomegalovirus infection by a recombinant vaccine containing a single nonameric T-cell epitope. J. Virol. 65 (1991) 3641–3646.
73. **Sjolander, A., Lovgren, K., Stahl, S., Aslund, L., Hansson, M., Nygren, P. A., Larsson, M., Hagstedt, M., Wahlin, B., Berzins, K., Uhlén, M., Morein, B., Perlmann, P.:** High antibody responses in rabbits immunized with influenza virus ISCOMs containing a repeated sequence of the *Plasmodium falciparum* antigen Pf155/RESA. Vaccine 9 (1991) 443–450.
74. **Hoglund, S., Akerblom, L., Ozel, M., Villacres, M., Eriksson, M., Gelderblom, H. R., Arthur, L., Morein, B.:** Characterization of immunostimulating complexes (ISCOMS) of HIV-1. Viral Immunol. 3 (1990) 195–206.
75. **Morein, B.:** The iscom: an immunostimulating system. Immunol. Lett. 25 (1990) 281–283.
76. **Zhou, E. M., Dreesman, G. R., Kennedy, R. C.:** Anti-idiotypic antibodies: a new generation of vaccines against infectious agents. Microbiol. Sci. 4 (1987) 36–40.
77. **Robins, R. A., Denton, G. W., Hardcastle, J. D., Austin, E. B., Baldwin, R. W., Durrant, L. G.:** Antitumor immune response and interleukin 2 production induced in colorectal cancer patients by immunization with human monoclonal anti-idiotypic antibody. Cancer Res. 51 (1991) 5425–5429.
78. **Pohl, C., Sieber, M., Diehl, V., Pfreundschuh, M.:** Idiotype vaccine against Hodgkin's lymphoma: generation and characterization of an anti- idiotypic monoclonal antibody against the Hodgkin-associated (anti-CD 30) monoclonal antibody HRS-3. Anticancer Res. 11 (1991) 1115–1124.
79. **Chanh, T. C., Siwak, E. B., Hewetson, J. F.:** Anti-idiotype-based vaccines against biological toxins. Toxicol. Appl. Pharmacol. 108 (1991) 183–193.
80. **Guiguemde, T. R., Stürchler, D., Ouedraogo, J. B., Drabo, M., Etlinger, H., Douchet, C., Gbary, A. R., Haller, L., Kambou, S., Fernex, M.:** Vaccination contre le paludisme: premier essai avec un vaccin antisporozoite, le (NANP)3-TT (RO 40-2361) en Afrique (Bobo-Dioulasso, Burkina-Faso). Bull. Soc. Pathol. Exot. Filiales 83 (1990) 217–227.
81. **Edelman, R., Levine, M. M.:** Enteric vaccines. Md. Med. J. 40 (1991) 199–203.
82. **Levine, M. M.:** Vaccines and milk immunoglobulin concentrates for prevention of infectious diarrhea. J. Pediatr. 118 (1991) (Suppl.) S129–S136.
83. **Holmgren, J., Svennerholm, A. M.:** New vaccines against bacterial enteric infections. Scand. J. Infect. Dis. 70 (1990) (Suppl.) 149–156.
84. **Sack, D. A., Freij, L., Holmgren, J.:** Swedish Agency for Research Cooperation with Developing Countries. Prospects for public health benefits in developing countries from new vaccines against enteric infections. J. Infect. Dis. 163 (1991) 503–506.
85. **Anonymous:** Dengue haemorrhagic fever (DHF). Wkly. Epidemiol. Rec. 65 (1990) 13–15.
86. **Kurth, R., Binninger, D., Ennen, J., Denner, J., Hartung, S., Norley, S.:** The quest for an AIDS vaccine: the state of the art and current challenges. AIDS Res. Hum. Retroviruses 7 (1991) 425–433.