Great strides have been made over the past quarter of a century in the prevention and control of viral diseases, largely through a combination of measures to minimize transmission and vaccination of populations at risk. More recently, the third pillar of a control strategy, the use of specific antiviral drugs, has also begun to be significant in reducing the dissemination and impact of a number of viral diseases, most notably for viral hepatitis and HIV (see Chapter 12: Antiviral Chemotherapy). Improved socioeconomic living conditions also play an important general role: less overcrowding leads to reduced disease transmission, and improved nutrition and physical well-being lessen the clinical impact of many infections. However, the ultimate step for the control of any infectious disease is global eradication, as was achieved for smallpox in 1977 and is hoped soon for poliomyelitis.

Control measures are applied at many different levels (Table 14.1). Government public health authorities have national responsibility for the control of infectious disease threats, although they are often constrained by a lack of scientific knowledge, inadequate budgets, expediency and political will. International bodies such as the World Health Organization (WHO) provide expert guidelines, trained personnel, and disease surveillance, but practical constraints often limit what can be achieved. At a local level, hospital infection control committees and workplace health and safety units promote policies for protecting patients and staff from infectious diseases. Exotic diseases may be excluded by quarantine, and different levels of barrier isolation are practiced for individuals who may present different degrees of risk as sources of infection. Hygiene and sanitation are important methods of controlling enteric infections, and vector control is clearly important for the control of arbovirus diseases. However, the most generally useful control measure is vaccination.

Outbreaks of severe diseases such as Ebola hemorrhagic fever and Lassa fever can be inflamed by delayed and/or inadequate control procedures. The outbreak of Ebola hemorrhagic fever in Zaire (now DRC) and the Sudan in 1976 was controlled largely by closing the hospitals at the center of the outbreaks combined with the meticulous tracking and isolation of contacts and family members. Recent experience with SARS has shown vividly both how applying classical infection control measures can stop outbreaks, and that nosocomial outbreaks of disease may still occur even in the best-equipped and staffed hospital settings. Traditional isolation methods consisted of barrier nursing, use of disposables, and quarantine, in the early hours of containing a disease outbreak. Recent experience has shown these need to be supplemented by additional disease-specific measures.

To the above could be added the necessity to involve veterinarians, especially where zoonotic disease is suspected. The 1999 West Nile outbreak in the United States showed how valuable time was lost when the first signs of disease incursion were seen in wild and domestic animals, but these observations were not communicated efficiently to the relevant local public health authorities. Traditionally there has been little integration of human and veterinary public health, yet the principles and practice of disease control are broadly the same regardless of the target species. Just how important this can be is shown by new pathogens that have come to light almost annually since the early 1990s, almost all of which are pathogens with animal reservoirs.

**SURVEILLANCE AND MODELING OF VIRUS DISEASES**

Epidemiological surveillance is the foundation for immediate and long-term strategies for combating infectious diseases. Such monitoring is usually the responsibility of national authorities and includes assessing individual cases, identifying the causative organisms, and compiling population-based data that inform public health policy (see also Chapter 13: Epidemiology of Viral Infections).

Infections know no boundaries and thus rapid communication at an international level is essential. The SARS outbreak of 2003 and new pandemics of influenza in particular have done much to strengthen international efforts to ensure better integration of national and international reporting systems. The focus must be on collecting background data and discerning trends, with the lead being taken by international agencies such as WHO and others. The
difficulty is that outbreaks of emerging diseases frequently arise in regions lacking both clinical and epidemiological expertise in infectious disease. Many national laboratories—especially in Africa—are often poorly equipped and lack adequately trained personnel for recognizing the unusual and being able to react appropriately.

In the longer term, disease monitoring should also be correlated with data and data interpretation of climatic variation and other determinants of disease activity, particularly if use is to be made of the data in predicting the emergence of zoonoses and vector-borne diseases in regions free of these diseases. Satellite surveillance of vegetation growth can give an early warning of escalating vector numbers.

Passive surveillance. Historically this has often been achieved by a system of “notifiable” diseases. These are specified clinical conditions that must be reported to health authorities by attending clinicians and pathologists. This provides a window into the understanding of infections with clinical impact; importantly, notification allows detection in the community of any new or more frequent occurrence of disease. It is, however, notoriously inefficient as typically only a minority of infections are reported. It also fails to detect the size of any disease occurrence where most infections are asymptomatic, for example, as in the spread of poliovirus infection through a community which is only recognized after sporadic cases of paralysis become apparent.

Laboratory data add an important dimension, through routine reporting of positive diagnoses to local and national health authorities. These data will include some asymptomatic infections and thus add value to any incidence estimate; furthermore, laboratory information about particular viral strains may be crucial. However, most systems suffer from the drawback that often only a minority of clinical cases are actually tested for markers of infection.

Active surveillance. Specific policies are in place for the reporting of certain human infectious diseases. For example, influenza surveillance is a coordinated international effort that aims to recognize as rapidly as possible the emergence of virus strains exhibiting new antigenic profiles or increased virulence. Local surveillance may include use of sentinel clinical practices that report numbers of influenza-like illnesses in real time; hospital emergency departments and large employers also report trends in numbers of respiratory infections. New virus isolates are sent by local laboratories to a member of an international network of WHO influenza reference laboratories, where analyses are to antigenic composition and sensitivity to common antiviral drugs are tested.

Surveillance of HIV/AIDS is an example of a successful international operation coordinated by WHO; test data arising from the surveillance programs of most countries are assembled and analyzed to give a remarkable picture of the global prevalence, pattern of spread, and demographics of HIV/AIDS.

In some specific situations, active case identification and contact tracing are important to track the spread of infection, for example, following identification of a case of measles in a measles-free community, contacts may be followed up and offered prophylaxis, advice, and diagnostic testing. Persons suspected of having rabbies or exotic infections such as Ebola hemorrhagic fever or Lassa fever, suspected because of their clinical presentation and travel history, may be isolated and contacts managed appropriately. Cases of acute flaccid paralysis are reported and investigated virologically wherever poliovirus infection is a possibility.

Much surveillance information is easily and rapidly available on excellent websites; for example, from the WHO (www.who.int/csr) and the US Centers for Disease Control and Prevention (www.cdc.gov/mmwr), and in specialist publications and reports.

Role of Modeling in Control of Virus Infections. Mathematical modeling can provide important guidance about the likely progression of an infection and the impact of proposed control measures. It is based on certain assumptions, for example that the host population is homogeneous with respect to the epidemiology of infection and the consequences of vaccination. All hosts are considered to be equally exposed and equally susceptible (unless vaccinated) to infection, the assumption being that the populations of infectious and susceptible hosts are perfectly mixed. While these assumptions are rarely satisfied in practice, the approach has proven sound for many vaccination programs.

The predicted consequences of vaccination at the population level, to the interpretation of the results of vaccine trials, all contribute to the design of optimal vaccination programs.

Mathematical theory can integrate this information to address such questions as to whether it is possible to eliminate an infection; what proportion of individuals must be vaccinated to achieve this; at what age should individuals first be vaccinated; and at what interval, if at all, should individuals be revaccinated. As one might expect for diseases that are transmitted directly by contact or aerosol, vaccination has advantages not only for the vaccinated

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**TABLE 14.1 Four Essential Components for Successful Surveillance and Control of Viral Diseases**

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alerting clinicians to recognize the unusual; ensuring they have easy access to local laboratories and specialist expertise</td>
<td></td>
</tr>
<tr>
<td>High-standard local diagnostic facilities, backed by national reference laboratories with experienced staff</td>
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</tr>
<tr>
<td>Involving epidemiologists and communicable disease specialists early whenever unusual events are suspected</td>
<td></td>
</tr>
<tr>
<td>The authority and resources to deliver effective and prompt control measures</td>
<td></td>
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</tbody>
</table>
individuals, who are directly protected, but also for unvaccinated individuals. The latter are indirectly protected because the opportunities for the transmission of the virus in the population as a whole are reduced.

Computer modeling has also provided useful insights into the effects of different vaccination regimens and different levels of acceptance of vaccination. One effect of vaccination programs is to increase the average age at which unimmunized individuals contract the infections against which that particular vaccine protects. Up to a certain level, increasing herd immunity may actually increase the risk of disease if older individuals are more vulnerable, by increasing the age of first exposure to the virus. A second conclusion from such modeling is that because of the cyclic incidence of the viral rash diseases, with intervals between peaks that increase as vaccination coverage improves, the evaluation of vaccination programs that stop short of countrywide elimination must be carried out over a prolonged period of time.

MEASURES TO MINIMIZE TRANSMISSION

Quarantine and Isolation

Quarantine is a measure first used by the Venetian Republic in the 14th century for the control of plague. Literally meaning “40 days” (quaranta giorni), the quarantine of shipping was also used by the English colonists in North America in 1647 to try to prevent the entry of yellow fever and smallpox. Quarantine proved very effective in keeping Australia free of endemic smallpox, and in delaying the entry of pandemic influenza into that country in 1919. However, with the onset of air travel and the consequent arrival of passengers before the end of most incubation periods, quarantine as a sole measure of control has become less effective. It was replaced, for smallpox, by the widespread requirement that international travelers were required to have a valid certificate of smallpox vaccination, a requirement that is no longer necessary since eradication of the virus. Currently, a similar provision operates for travelers who come from or pass through countries where yellow fever is endemic. Attempts were made during the recent H1N1 swine flu pandemic to quarantine new or suspected cases on arrival into a new country: thermal scanners became commonplace within hospitals; the measures adopted, for example, “enteric” or “blood” precautions, and the stringency of the isolation, are governed by the characteristics of the virus involved. The recent Ebola hemorrhagic fever epidemic in West Africa has demonstrated that much more stringent precautions, special training, and personal protective equipment (PPE) may be required in some instances.

Measures to Reduce Enteric Spread

Hygiene and sanitation have had a profound effect on the incidence of enteric infections, both viral and bacterial. Viruses that infect the intestinal tract are shed in feces, and in many human communities the recycling of fecal material back into humans through the oral route following fecal contamination of food or water is common. A more voluminous and more fluid output (diarrhea) increases environmental contamination. Hands contaminated at the time of defecation and inadequately washed may transfer viruses directly or indirectly to food, a particular problem among those responsible for the preparation of meals to be eaten by others. Education about adequate hand washing, and provision of running water for toilet purposes, are vitally important measures.

In many densely populated parts of the world there are no reticulated sewerage systems, and sewage may seep into wells, streams, or other drinking water supplies, particularly after heavy rain. Explosive outbreaks of many different gastroenteritis viruses occur from time to time when sewerage mains burst or overflow and contaminate drinking water supplies.

Raw sewage contains $10^3$ to $10^6$ infectious virus particles per liter, mostly enteroviruses, caliciviruses, adenoviruses, and rotaviruses. Titters drop 100-fold, typically to 10 to 100 pfu per liter, following treatment in modern activated sludge plants, because virions adsorb to the solid waste and this sediments as sludge. The primary sludge is generally subjected to anaerobic digestion, leading to a significant reduction of virus titer. Some countries require that treated sludge be inactivated by pasteurization prior to being discharged into rivers and lakes or prior to use as landfill or fertilizer in agriculture.

In countries where wastewater is recycled for drinking and other domestic purposes, the treated effluent is further treated by coagulation with alum or ferric chloride, adsorption with activated carbon, and finally chlorination. Evidence that by-products of chlorination are toxic to fish and may be carcinogenic for humans has encouraged several countries to turn instead to ozonation. Ozone is a very effective oxidative disinfectant, for viruses as well as bacteria, provided that most of the organic matter containing adsorbed viruses is first removed.

There is also a good case for the chemical disinfection of recycled wastewater not used for drinking purposes, such as agricultural irrigation by sprinklers, public decorative fountains, and industrial cooling towers, as such procedures disseminate viruses in aerosols. However, the liability of
viruses to heat, desiccation, and ultraviolet light ensures that the virions remaining in wastewater from which most of the solids have been removed will be inactivated within a few weeks or months, depending on environmental conditions, without further intervention. Even during a cold northern winter, the number of viable enteroviruses in standing water drops by about 10-fold per month; during a hot dry summer the rate of decay is as high as 100-fold per week. Hence storage of the final effluent in an oxidative lagoon for one to two months is an inexpensive and effective way of inactivating viruses.

**Measures to Reduce Respiratory Spread**

Increased understanding about how respiratory viruses are transmitted via both aerosol droplets and contaminated fomites (Chapter 13: Epidemiology of Viral Infections) has led to improved guidelines to reduce respiratory virus transmission, both between hospital patients and staff and in the community. These guidelines include advice about hand washing after contacting respiratory secretions, care in disposal of used tissues, and advice to minimize transfer of contaminated objects (including stethoscopes!) between individuals. Commercially available facemasks have varying grades of performance specifications with respect to fluid resistance, breathability, and efficiency in filtering microparticles. Masks should be chosen appropriate to the degree of risk, the purpose required, and closeness of fit. Attempts to achieve “air sanitation” by filtration and/or ultraviolet irradiation in public buildings have proved to have only a marginal effect, although these measures are an important feature of the biosafety cabinets widely used in virus laboratories.

Respiratory viral infections remain very common, and the congregation of large numbers of people in crowded public places and the frequency of air travel enhance the rapid spread of respiratory viruses to non-immune populations. This is seen most clearly with newly emerging infections such as SARS and the 2009 H1N1 pandemic influenza. The population of the world now constitutes a single ecosystem for human respiratory viruses, although seasonal and climatic differences between the northern and southern hemispheres affect the incidence of particular diseases, like influenza, at any particular time.

**Measures to Reduce Spread of Sexually Transmitted Infections**

The emergence of HIV/AIDS, together with increases in genital warts and chlamydial infections, led in the 1980s to major efforts to understand sexual behavior and factors affecting sexual transmission of viruses. This was assisted in many Western countries by increased acceptance of homosexuality and frankness in discussing sexuality. Psychologists and behavioral scientists have provided notable guidance to public health campaigns regarding motivation, cultural barriers, and other reasons why particular target groups may or may not accept advice about the risks of sexually transmitted infections (STIs). This has led to increased understanding and promotion of “safe sex” principles in many societies (see Box 14.1), and increased acceptance of testing for STIs, including HIV, as a normal part of routine health care. Another fundamental aspect of public health education is the understanding of the importance of individuals’ rights over their own sexuality and sexual choices, and the awareness that health messages may have little effect unless they also address the cultural, religious, and educational context of those receiving the messages. For example, the guidelines in Box 14.1 are targeted to a developed Western community, and very different language and specific advice may be more appropriate in other cultures.

Campaigns based on the above have had different degrees of impact in many parts of the world. In a number of developed countries, HIV remains largely confined to more promiscuous or risk-taking groups. In many other countries HIV is more widespread among the general community, despite vigorous control campaigns that include blood transfusion screening, improved access to HIV testing and antivirals, marketing of condoms, self-treatment kits for STIs, and safe-sex education programs. HIV prevention campaigns can be impeded by “AIDS-fatigue” among carers, complacency, and/or less practice of safe sex following on from greater antiviral drug use, new laws against homosexual practices, and condemnation of condoms by religious bodies. On the other hand, individuals with successful suppression of viral replication by antiviral therapy now pose a very low risk of transmitting infection to others (“Treatment as Prevention”), and post-exposure

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**BOX 14.1 Principles of Safer Sex—Example of Guidelines for Teenagers**

- Seriously consider whether you want to have sex
- Get tested. Be sure you know your and your partner’s HIV status
- Prevent exposure to blood, semen, vaginal and other bodily fluids
- Cover up body parts that could be infectious
- Always use a condom, and use a new one every time
- Be in a monogamous relationship, or limit your number of sexual partners
- Get screened for other STDs
- If you or your partner have/has contracted an STD, receive treatment immediately and do not have sex until your doctor says it’s okay
- Don’t abuse alcohol or drugs, which are linked to sexual risk-taking
- Talk openly with your partner. Remember these discussions are easier with your clothes on
prophylaxis and pre-exposure prophylaxis with antiviral drugs are becoming more widely used to restrict transmission (see Chapter 23: Retroviruses). This demonstrates the complex and unpredictable outcomes in the interaction between health advice, human behavior, government policy, and health funding, against a background of cultural and religious issues. There is an enormous challenge to apply medical and social advances, in an appropriate manner, more widely to affected populations in a global context.

**Measures to Reduce the Spread of Blood-Borne Infections**

In the past three decades there has been major recognition of the importance of blood-borne infections including HIV and hepatitis B and C, and far greater understanding of the mechanisms and social settings for transmission of these agents. This has led to widely adopted guidelines and public health policies in order to reduce the risks of transmission of these infections. Within health and treatment settings, the risks of transmission can be considerably reduced, if not eliminated, by sterilization of all invasive medical instruments, treating all blood and secretions as potentially infective, avoiding the reusage of equipment, for example needles, wherever possible, the screening of donated blood, blood products and organs, the management of needle-stick injuries by established protocols, and by adopting strict protocols for acupuncturists and tattooists. The more difficult goal of reducing transmission between injecting drug users involves the promotion of needle exchange programs, safe injecting rooms, education, and drug rehabilitation centers. Establishing such measures and gaining co-operation amongst intravenous drug abusers can be challenging and sometimes can meet with political and legal opposition. However a significant restriction of the spread of infection, for example, of HIV among intravenous drug abusers, has been achieved where such measures are promoted (Box 14.2).

**Vector Control**

Because the control of non-human vertebrate reservoir hosts is usually difficult to achieve, control of arboviruses may be approached both (1) by directly reducing the numbers of arthropod vectors, and (2) by minimizing human exposure to these vectors. Guidelines and advice are available from many government public health authorities, environmental protection agencies, international bodies such as WHO, and local councils. The philosophy of an “Integrated Pest Management” is widely used: it consists of a combination of approaches selected for the particular problem and with concern for the full environmental, health, and economic context.

The targeting of vectors includes the elimination of breeding sites and the direct destruction of adult mosquitoes or larvae. The flight range of many vector mosquitoes is so limited that much can be achieved by concentrating on the immediate vicinity of human settlements, particularly in the case of species attracted to human habitation such as *Aedes aegypti*. Any still water constitutes a potential breeding site. Swamps and ditches should be drained, and water-collecting refuse such as discarded tires, tin cans, and plastic containers destroyed. Domestic pot-plants, wet shower floors, toilet water tanks, and rainwater tanks pose special problems. Larvicidal chemicals can be placed in domestic water jars, and kerosene or diesel oil layered on the surface of non-potable water.

The biological control of mosquito larvae is an alternative, albeit less developed, control strategy. Approaches include the introduction of fish species that ingest mosquito larvae and the introduction of sterilized male mosquitoes in order to reduce insect breeding. The use of *Bacillus thuringiensis*, which releases crystals toxic to mosquito larvae, has also been attempted. The introduction of the bacterium *Wolbachia* has also been found to reduce the capacity of *Aedes aegypti* mosquitoes to transmit dengue, chikungunya, and yellow fever viruses. However, the growth of cities in developing countries, largely by the growth of urban slums, has greatly accentuated the difficulties of control of domesticated *Aedes* mosquitoes. The “Asian tiger” mosquito *Aedes albopictus*, an aggressive daytime biting species and important vector of dengue and chikungunya viruses, has spread widely since the 1950s and now covers large areas of the world. Once established it is difficult to eradicate. For most arbovirus infections other than urban dengue and yellow fever, the vectors breed over too wide a geographical

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**BOX 14.2 Control of Blood-Borne Infections**

1. **Mechanisms of transmission**
   - transfusion of infected, unscreened blood, or blood products, organs
   - use or reuse of unsterilized medical equipment
   - needlestick injury to health care or laboratory worker
   - sharing injecting equipment by IVDUs
   - tattooing, body piercing, acupuncture, initiation rites
   - contact sport with bleeding

2. **Control measures to prevent transmission**
   - screening of donated blood and blood products
   - strict guidelines for medical procedures, instrument sterilization
   - single use for needles and other equipment
   - protocol for management of needlestick injuries
   - strict guidelines and regulation of tattooists, body piercing, acupuncture
   - IVDUs—needle exchange, drug rehabilitation centers, education
   - safe injecting rooms (NB effect of legality, needle policy in prisons)
The use of insecticides is a controversial issue, because there are frequent objections from environmentalists and mosquitoes eventually develop resistance. Any policy should be decided on the basis of a risk–benefit analysis on a situation-by-situation basis. Some countries have based their arbovirus control programs on aerial insecticide spraying, but most retain this approach only for emergency control in the event of an epidemic, specifically aimed at the rapid reduction of the adult female mosquito population. Organophosphorus insecticides such as malathion or fenitrothion are delivered as an ultra-low-volume (short-acting) aerosol generated by spray machines mounted on backpacks, trucks, or low-flying aircraft. Spraying of the luggage bays and passenger cabins of aircraft with insecticides may reduce the chances of intercontinental transfer of exotic arthropods, whether infected or not. Whether this is effective is questionable, however. Some experts believe the introduction of West Nile virus into North America in 1999 occurred as a result of infected insects being carried into the United States on a commercial flight from the Middle East.

Avoidance of exposure to the bite of arthropods is the other mainstay of control. Personal protection against mosquito bites can be achieved by the use of screens on doors and windows, nets over beds, long-sleeved protective clothing, especially at dusk, and repellents. In developed countries the major barrier has been whole-house air conditioning. Insect repellents containing the chemical N,N-diethyl-meta-toluamide (DEET) are particularly effective and do not present a health concern when used as directed. However, in many economically disadvantaged parts of the world, many of such measures are beyond reach and infections like dengue continue to thrive.

**IMMUNIZATION**

Each of the foregoing methods of control of viral diseases is focused on reducing the transmission of the causative virus. The second major method of control, immunization, is directed primarily at making the individual resistant to infection, and in many cases by reducing the incidence of new cases it can also substantially reduce the source of further spread. Immunization may be active, that is, induction of an immune response by administration of antigen (vaccine), or passive, that is, by administration of antibody (immune serum or immunoglobulin).

As outlined in Chapter 11: Vaccines and Vaccination, and discussed at length in the chapters of Part II, there are effective vaccines for many common viral diseases. These vaccines are especially effective in diseases with a viremic phase, such as poliomyelitis, yellow fever, and the acute exanthems. The dramatic success of vaccination programs in reducing the incidence in the United States of measles, mumps, and rubella is illustrated in Fig. 14.1. Similar declines have occurred in the incidence of poliomyelitis. In the United States, endemic circulation of polio ceased in 1979 and of measles around 2000.

**Active Immunization Policy**

Although the principal aim of vaccination is to protect the vaccinated individual, vaccination on a sufficiently wide enough scale will also enhance herd immunity to such an extent that transmission can be restricted, or even arrested altogether, within a given community or country. In different examples, vaccines may be used with different goals in mind, for example, to protect individuals at risk, to protect particular groups within a community or in specific parts of the world, to manage outbreaks, or to eradicate the causative virus.

The optimal design of a vaccination program varies according to the characteristics of the vaccine and the epidemiology of the virus infection. Relevant vaccine characteristics are the proportion of those vaccinated that achieve protection after vaccination, the duration of protection, and the coverage achieved by the vaccination program.

Many important aspects need to be considered in developing an effective strategy for a particular vaccine (see Box 14.3). For example, vaccination against hepatitis A is most needed for protection against clinical hepatitis A among older children and adults, at an age when clinical cases are more likely. In economically developing countries where hepatitis A infection is endemic and occurs in childhood, many see little clinical disease and therefore may choose to fund alternative health priorities. Many of the currently used vaccines, both bacterial and viral, are aimed at preventing diseases the risks of which are greatest in infancy. Live vaccines, for example, measles, are less reliable if given while maternal antibody is present but need to take effect before the typical age at which natural infection occurs; thus the recommended age of vaccination needs to fit a window that matches the dynamics of infection within each community.

Even in the case of a disease as feared as poliomyelitis, it has been difficult to maintain enthusiasm for a program of universal immunization after the disease has become rare, localized to only a few remote sites in Asia and Africa. Measles quickly reemerges when immunization programs wane. With many virus diseases it is essential to continue routine vaccination after the threat of epidemic has declined. The short-term absence of wild virus in the population leaves any unvaccinated people uniquely susceptible to further introductions of virus as the protective effect of herd immunity wanes. For these reasons it is essential that all countries continue to maintain highly organized and robust health services, paying particular attention to unimmunized cohorts, such as those living in urban ghettos, immigrants, and certain religious minorities.
FIGURE 14.1 (Continued)
Acceptability of a vaccine by a community is affected by many issues: balancing vaccine efficacy against safety, balancing fear of disease against fear of needles and side effects, balancing trust of public health authorities and the medical profession against trust in misinformed anti-vaccine activist groups, and balancing personal complacency and inertia against the usual deep-seated understanding as to what is correct for protecting the health of communities.

If the disease is lethal or debilitating, both the public and vaccine-licensing authorities will accept a risk of even moderately serious consequences of vaccination in a tiny minority of recipients. If, on the other hand, the disease is perceived as trivial, no side effects will be countenanced. Where more than one satisfactory vaccine is available, considerations such as cost and ease of administration tip the balance. Many other mechanisms are used to help improve compliance, including minimizing the number of clinic visits using polyvalent vaccines such as that available for measles–mumps–rubella (MMR vaccine), simplified vaccine schedules, in some instances promoting “national immunization days,” and requiring proof of vaccination before allowing enrollment in school.

In designing and implementing vaccination campaigns other issues also need to be considered: these include religious sensitivities (e.g., use of the terms “live” or “dead” to characterize a vaccine may discourage its acceptance) and
political sensitivities such as the country where the vaccine was manufactured. In recent years, vocal anti-vaccination lobbies have become prominent, and in some cases have seriously undermined vaccine uptake rates leading to localized disease outbreaks. Arguments raised by these groups are often ill-informed or based on misinterpretations of data, and not based on any quantitative risk assessment. For example, the introduction of a human papillomavirus vaccine was opposed by some groups on the grounds it would encourage promiscuity. Health professionals have a responsibility to provide accurate, balanced information.

Table 14.2 shows schedules for the use of the major human viral vaccines in common use. The vaccines used in particular diseases are discussed in the relevant chapters of Part II.

Passive Immunization

It is possible to confer short-term protection through the intramuscular or intravenous inoculation of preformed antibody, either using immune serum or immune (serum) globulin. Human immunoglobulin has replaced animal-derived (e.g., horse) preparations, because heterologous protein may provoke serum sickness or anaphylaxis. Pooled normal human immunoglobulin contains sufficiently high titer of antibody to protect against measles and hepatitis A. Specific high-titer immunoglobulin collected from individuals who have been recently immunized or have recovered from a particular infection is available to protect against hepatitis B, varicella-zoster, respiratory syncytial virus, human cytomegalovirus, and vaccinia. Specific high-titer immunoglobulin collected from paid donors who are vaccinated, revaccinated, and tested for high antibody titer is used for post-exposure rabies treatment. Humanized monoclonal antibodies against particular viruses, for example, respiratory syncytial virus (Palivizumab), can be used to prevent infection in high-risk infants (Chapter 26: Paramyxoviruses).

These preparations give immediate passive protection that then diminishes over the next two to four months, and can also confer “passive–active” immunity if a partially protected individual subsequently undergoes a subclinical infection with wild-type virus. Passive immunization should be regarded as an emergency procedure to achieve immediate protection of unimmunized individuals exposed to special risk. It can be used as a pre-exposure measure to give short-term protection against hepatitis A for travelers to developing countries. It is also important for post-exposure management of close contacts of a hepatitis A index case, for hepatitis B in new-born babies of infected mothers, or in unimmunized laboratory or health workers following a needle stick or comparable accident, for measles in unimmunized close contacts of a patient, and for varicella to protect new-born babies of mothers suffering from chickenpox at the time of delivery, or to protect non-immune contacts who are immunosuppressed.

### Table 14.2 Schedules for Immunization against Human Viral Diseases

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Primary Course</th>
<th>Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poliomyelitis</td>
<td>2, 4, 6 months&lt;sup&gt;b&lt;/sup&gt;</td>
<td>School entry (5 years)</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>2, 4, (6) months</td>
<td>4–6 years</td>
</tr>
<tr>
<td>Measles</td>
<td>12, 18 months&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>4–6 years</td>
</tr>
<tr>
<td>Rubella</td>
<td>12, 18 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4–6 years</td>
</tr>
<tr>
<td>Mumps</td>
<td>12, 18 months&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4–6 years</td>
</tr>
<tr>
<td>Varicella</td>
<td>18 months</td>
<td>10–15 years</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Before travel to endemic area</td>
<td>Booster after 10 years</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>&gt;9 months, in endemic regions</td>
<td>1–2 years later</td>
</tr>
<tr>
<td>Inactivated vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>Autumn annually&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Annual booster</td>
</tr>
<tr>
<td>Rabies</td>
<td>Pre-exposure: 0, 7, 28 days&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Every 2 years&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Post-exposure: 0, 3, 7, 14, 28, 90 days&lt;sup&gt;h&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>For routine infant vaccination—2 doses at least 6 months apart, commencing after 12 months of age</td>
<td>Booster after 10 years</td>
</tr>
<tr>
<td></td>
<td>If living in or traveling to endemic area—2 doses at least 6 months apart</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Birth&lt;sup&gt;i&lt;/sup&gt;, 2, 4, 6 months</td>
<td>Booster 10–15 years</td>
</tr>
<tr>
<td></td>
<td>When at risk, then 1 and 6 months later</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>12–13 years (girls and/or boys)—3 doses at 0, 1 and 6 months</td>
<td></td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>2 doses 28 days apart, in endemic regions or for travellers</td>
<td></td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>2–3 doses (see local schedules)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Schedules vary from country to country. This table is to be taken only as a guide.

<sup>b</sup>Two or three doses spaced 2 months apart, commencing between 2 and 6 months of age, conveniently timed to coincide with diphtheria–pertussis–tetanus (DPT) vaccine. The third dose can be delayed to 15 months, at the time of MMR vaccine.

<sup>c</sup>Given shortly after first birthday in most developed countries, but at 9 months in developing countries where measles death rate is high in the second 6 months of life.

<sup>d</sup>Usually as combined measles–mumps–rubella (MMR) vaccine.

<sup>e</sup>Vulnerable groups only, especially the aged and chronic cardiopulmonary invalids.

<sup>f</sup>Veterinarians, animal handlers, etc.

<sup>g</sup>Of rabies immune globulin.

<sup>i</sup>Ideal within 24 hours.
Specific antibody can also occasionally be used as therapy for an established viral disease, for example, among immunocompromised individuals with disseminated herpes zoster or vaccinia. Immune plasma together with ribavirin has been shown to reduce the mortality of Lassa fever in monkeys and has been used in exposed humans, but lack of availability in target areas is unresolved. Immune plasma is also effective in the treatment of Argentine hemorrhagic fever caused by Junin virus—its use has largely been replaced by vaccination of at-risk populations using the live attenuated vaccine Candid #1.

The WHO Expanded Program on Immunization and Other Initiatives

In developed countries both public health agencies and private medical practitioners carry out immunization. However, many developing countries lack adequate health services, political will, and funds to provide for the majority of the population. To capitalize on the health infrastructure that had been developed to support the Intensified Smallpox Eradication Program, the WHO in 1974 established the Expanded Programme on Immunization (EPI), with the specific goal of immunizing the world’s children against six diseases: Bacillus Calmette-Guérin (BCG) for tuberculosis, diphtheria–tetanus–pertussis (DTP), oral polio, and measles. In 1985 the WHO program was greatly strengthened by the participation of the United Nations Children’s Fund (UNICEF) as a provider of vaccines and augmented funding. Most countries have now added hepatitis B, Haemophilus influenzae type b (Hib) and meningococcal group A vaccines, and an increasing number are adding pneumococcal conjugate vaccine and rotavirus vaccines. By 2010 it was estimated that 85% of children under 1 year of age globally had received at least three doses of DPT vaccine. Between 2000 and 2008, measles deaths dropped worldwide by over 78%, and maternal and neonatal tetanus had been eliminated in 20 of 58 high-risk countries. Other vaccines, for example, yellow fever, hepatitis A, tick-borne encephalitis, and Japanese encephalitis, are offered in areas where these diseases are prevalent.

Other recent international initiatives include the Global Alliance for Vaccines and Immunization (GAVI), a consortium founded in 2000 that aims to deliver new vaccines to all children of the developing world. GAVI initially focused on vaccines against yellow fever and hepatitis B, but more recently has also included measles, rubella, HPV, rotavirus, and Japanese encephalitis. The Bill and Melinda Gates Foundation has also provided substantial support for vaccine research and delivery.

The adoption of vaccines into regional and national childhood immunization programs requires effective integration of vaccine delivery into primary healthcare systems, and long-term commitment to ensure sustainability coupled with effective monitoring for disease. Long-term planning is often hindered by a lack of data about the burden of disease in any particular region and effective communication to those groups most at risk.

ERADICATION

So far, global eradication has been achieved for only two viral diseases, the human disease smallpox and the animal disease rinderpest. The last naturally occurring case of smallpox was reported in Somalia in October 1977. Smallpox eradication was achieved by an intensive effort that involved a high level of international co-operation and used a potent, inexpensive, and easily administered stable vaccine. However, mass vaccination alone could not have achieved eradication of the disease from the densely populated tropical countries where it remained endemic in the 1970s, as it was impossible to achieve the necessary very high level of vaccine coverage. The effective approach was to combine vaccination with surveillance and containment in a strategy of ring vaccination; individual cases and pockets of infection were actively sought out (health workers were financially rewarded for finding new cases), isolated, and their contacts vaccinated, initially in the household and then at increasing distances from the index case.

The global smallpox eradication campaign was a highly cost-effective operation. The expenditure by the WHO between 1967 and 1979 was US$81 million, to which could be added about US$32 million in bilateral aid contributions and some US$200 million in expenditures by the endemic countries involved in the campaign. Against this expenditure of about US$313 million over the 11 years of the campaign could be set an annual global expenditure of about US$1000 million for vaccination, airport inspections, etc., made necessary by the existence of smallpox. This equation takes no account of the deaths, misery, and costs of smallpox in afflicted people, or of the medical complications of untoward reactions to vaccine.

In the years since smallpox eradication, most laboratory stocks of the virus have been destroyed, except for those held in two designated, tightly regulated laboratories, one in Russia, and the other in the United States. Research on smallpox has been discontinued except in these laboratories, and arguments for and against the total destruction of all virus stocks are regularly discussed. Nevertheless, the possibility of a related zoonotic poxvirus becoming a new human problem, or of smallpox virus being obtained for bioterrorism purposes, has led to the maintenance of large supplies of smallpox vaccine (vaccinia virus) under the auspices of the WHO and some national governments.

The achievement of smallpox eradication gave rise to discussions as to whether other diseases could also be eradicated, in particular measles and poliomyelitis. The
biological characteristics of the three diseases that affect the ease of eradication are set out in Table 14.3. These diseases share several essential characteristics:

1. The absence of an animal reservoir;
2. No long-term persistent infectivity in the human host;
3. One or few stable serotypes; and
4. The availability of an effective vaccine.

However, other characteristics of smallpox are not typical of measles or poliomyelitis: smallpox cases present with such a typical clinical picture that rather accurate diagnosis was made in the field by physical examination (the most common confounder being chickenpox). The absence of virus transmission during the prodromal stage of infection made surveillance and isolation/containment feasible. This strategy was very important in the eradication of smallpox from tropical countries. The natural history of poliomyelitis and measles is quite different and eradication concepts and strategies must therefore also be different.

There are three antigenically distinct polioviruses requiring three vaccines, there is a preponderance of subclinical infections (from around 100 to 1000 to 1), there can be rather long-term shedding by infected people and virus may survive in sewerage systems for some time. Despite these concerns, in 1988 WHO, UNICEF, and other international organizations agreed on a plan for global eradication. Good progress was made in the early years, utilizing novel techniques for surveillance (flaccid paralysis notification) and for vaccination (national vaccination days, mopping up vaccination around recognized cases). As a result, paralytic poliomyelitis due to wild poliovirus was eliminated from the Americas in August 1991 (see Chapter 32: Picornaviruses).

Measles presents different problems. Because cases become infectious before the subject becomes ill, it is not possible to control measles by vaccination supplemented by surveillance and containment, but rather only by attaining very high levels of herd immunity, estimated at 96% of the population. Such a level is very difficult to achieve, because it is almost impossible to reach this proportion of the population with a reliably potent vaccine. In addition, maternal antibody inhibits replication of the standard Schwarz vaccine until some time between 9 and 12 months after birth; hence, vaccination is not recommended before the infant is 12 months old. However, in developing countries where measles is still a common disease, many infections occur in children aged 9 to 12 months. It has also become apparent that once the circulation of virus becomes rare and the basic immunity provided by vaccination is not being boosted by later subclinical infections, vaccination in infancy does not provide a certainty of protection throughout life. It is therefore recommended that there should be a booster inoculation of vaccine at school entry.

Three actions were recommended: (1) a one-time national campaign to bring children between 1 and 14 years of age up to date with measles vaccination, (2) the strengthening of routine vaccination to reach a minimum of 95 per cent of children every year, and (3) to undertake massive follow-up campaigns every 4 years, to reach a minimum of 95 per cent of children aged 1 to 4 with a 2nd dose of vaccine.

Following this strategy, the last indigenous measles outbreak was registered in Venezuela in 2002. However, some countries in the Americas still notified imported cases. Between 2003 and 2014, 5077 imported measles cases were registered in the region.

After declaring the elimination from the Western Hemisphere of rubella and congenital rubella syndrome in
2015, an International Expert Committee sought evidence for the interruption of a measles outbreak in Brazil, which had begun in 2013 and lasted for more than a year. After a year of targeted actions and enhanced surveillance, the last case of measles in Brazil was registered in July 2015.

With this achievement the elimination of measles from the Americas was declared.

BIOTERRORISM

Several viruses have been identified as having the potential as biological weapons. The former Soviet Union, the United States, and other countries have had bioweapon programs in past years. The Russian research and production program ran from 1926 to 1992 and was massive in scale. The production program of the United States ended in 1943 and its offensive research program ended in 1969. In 1975, 22 countries ratified the Biological and Toxins Weapons Convention that outlawed offensive biological weapons, and by 2013, 170 countries had ratified or acceded to the Convention. Research aimed at defensive capability (infectious agent detection, identification, diagnosis, and potentially dual-use research and development of vaccines and drugs) is carried out in many countries. Such research is mindful of the potential to make biological threat agents more dangerous by genetic engineering technologies.

Biological weapons share along with nuclear and chemical weapons the label of weapons of mass destruction. The Biological and Toxins Weapons Convention stipulated that all biological threat agent stockpiles were to be destroyed and new work on offensive biological and chemical weapons abandoned. Unfortunately, it became clear in the 1990s that a number of countries—including Russia—had continued such programs after having ratified the terms of the Convention. One ominous sign of this was the sudden announcement by Russian president Boris Yeltsin in 1992 that an anthrax outbreak, which occurred in 1979 in Sverdlovsk (Yekaterinburg), was the result of an accidental release of spores from a factory producing large amounts of anthrax spores for use in warfare. In the following years many international inspections and agreements have led to the shutdown of known facilities, but there are still countries where bioweapon research, development, and production facilities are operational and protected from view by strict security measures.

FURTHER READING

Fenner, F., Henderson, D.A., Arita, L., Ježek, Z., Ladnyi, I.D. (1988) Smallpox and its Eradication. World Health Organisation, Geneva, Switzerland. ISBN 92-4-156110-6. This is the definitive account of the WHO Smallpox Eradication Programme, detailing both the background of the disease, early efforts at its control, and a region by region account of how the virus was eliminated.