06

# Improving Health

*A baby receiving a vaccination at a health clinic in Guinea, Africa. © Giacomo Pirozzi – Panos Pictures*

The global health gap remains very large. While life expectancy in industrialised countries is around 78 years it is only 55 years in the developing countries (50 years in Sub-Saharan Africa).[1] Chronic illnesses such as heart and circulatory conditions and cancer cause most morbidity and mortality in the developed countries, in contrast to developing countries where infectious diseases are more significant.[2,3]

Technological advances in controlling infectious diseases have therefore had considerable impact on the poor.

- The yellow fever vaccine, developed in the 1920s, helped eradicate the disease from Central and South America;
- Smallpox was eradicated using a vaccine by 1980;
- Penicillin and other antibiotics in the post World War II years brought down mortality from bacterial infections in both adults and children;
- Oral rehydration therapy, proven to be effective in Bangladesh in 1971, has produced a significant world-wide reduction in mortality from diarrhoeal diseases;
- Anti-retrovirals against HIV, developed in the 1970s, have saved millions of lives.

Recently, scientific research has been more directed at so-called "neglected diseases" largely restricted to the developing countries, and this has resulted in substantial further progress in their control.

Globally these and other technologies embedded in public health programmes, that also include such measures as the provision of clean drinking water and sanitation, have improved the health of many in developing countries.

The MDGs have identified three specific areas for improvement of health – decreasing child mortality, improving maternal health and combating infectious diseases (See Chapter 4). While infectious diseases, particularly HIV/AIDS, TB and malaria, have largely been addressed through campaigns to discover and develop new drugs and vaccines, supported by new funding mechanisms and public-private partnerships (described in Chapter 3), child and maternal health improvements have focused on the improvement of health systems and the extension of conventional technologies. Improving health has also been an element of MDG 7, with its target to improve the supply of clean water and sanitation, and MDG 1, with its commitment to reduce malnutrition.

We begin with this last target, as healthy diets which address malnutrition underpin child and adult health and the resilience to disease. They also underline the critical, but often neglected, link between agricultural and health development targets.

## 1. Improving health by improving diets

Improved diets are fundamental to improving health. They also play a significant role in preventing infection and reducing morbidity and mortality. Thus, advances in agriculture which increase the quantity and quality of food available to the poor can make a major complementary contribution to the direct efforts to improve health. It is difficult, if not impossible, however to identify the relative contribution of infectious disease and malnutrition to ill health – both are important and their interactions are crucial.

Children's health is usually assessed in terms of their weight and height. Low birth weight often stems from a mother's poor health and nutritional status before and during pregnancy. About 16% of infants in developing countries are born weighing less than 2.5kg and are 20 times more likely to die in infancy than heavier babies. Those who survive may be more susceptible to infectious diseases, inhibited growth and cognitive development, and are more likely to suffer from chronic illnesses in later life.[4]



Figure 6.1 – Improving diets is essential for improving health

Stunting, or low height for age, which generally occurs before a child is two, is caused by long-term insufficient nutrient intake and frequent infections. Its effects, which include delayed motor development, impaired cognitive function and poor school performance, are largely irreversible. Nearly one third of children under five in the developing world are stunted. Wasting, or low weight for height, is a strong predictor of mortality among children under five. It is usually the result of acute significant food shortage and/or disease.[4]

**Proteins and other micronutrients**

While carbohydrates, which we derive largely from cereals, are critical to the provision of energy necessary for health and growth, they do not alone constitute a high quality diet. This requires consumption of protein and various micronutrients, particularly in childhood. Insufficient levels of micronutrients in the diet have distinctive effects which are particularly apparent in poor populations. Some of these are illustrated in Box 6.1.

**Box 6.1 The consequences of micronutrient deficiency[4,5]**

| Deficiency | Effects | Incidence |
|---|---|---|
| Iodine | Single greatest cause of preventable mental retardation: severe deficiencies cause cretinism, stillbirth and miscarriage; mild deficiency can significantly affect the learning ability of populations. | 38 million newborns worldwide remain unprotected. |
| Zinc | Increases severity of diarrhoea, pneumonia, and possibly malaria, by one-third and causes stunting. | Over 70% at risk of low zinc intake in south and southeast Asia and Sub-Saharan Africa. |

| Deficiency | Effects | Incidence |
|---|---|---|
| Vitamin A | Results in night blindness and ultimately blindness, growth retardation, damage of mucous membrane tracts, and reproductive disorders. Children are also likely to be anaemic and be at increased risk of severe morbidity from common childhood infections such as diarrhoeal diseases and measles. Pregnant women with vitamin A deficiency have increased risk of mortality. | Some 127 million pre-school children are vitamin A deficient – about one-quarter of all pre-school children in high-risk regions of the developing world. |
| Iron | Deficiency during childhood and adolescence impairs physical growth, mental development, and learning capacity. In adults, it reduces the ability to do physical work. More than 2 billion people worldwide are anaemic and much of it is due to iron-deficiency. Severe anaemia increases the risk of women dying in childbirth. | In developing countries, the most affected population groups are pregnant women (42 %) – although many women aged 15 to 59 years are also affected (30 %) as well as school-age children and pre-school children. |

**Improving dietary intakes**

There are three possible approaches to improving the quality of dietary intakes:

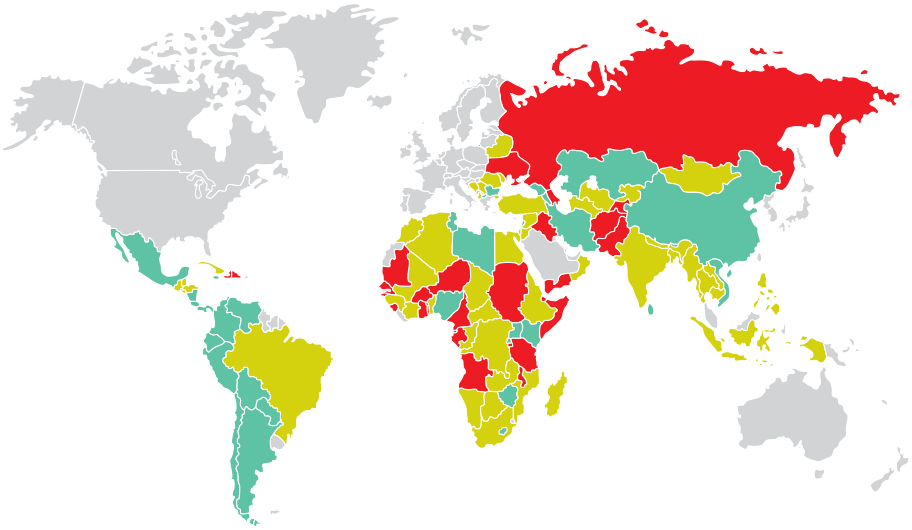
The first is to improve the diversity of the diet. As the FAO points out *'the share of dietary energy from animal foods, vegetable oils, sugar, fruits and vegetables increases with higher per capita income levels, while that from roots, tubers and pulses tends to decrease'*.[6] The poor rely more on staples and consume less meat and fewer dairy products, smaller amounts of oils and fats, and fewer fruits and vegetables that are rich in high-quality proteins and micronutrients, such as iron, zinc and vitamin A. Because such foods cost relatively more than the staples, poor people consume less in times of physical hardship (such as during a major drought) or financial crisis. In urban areas only an increase in income will permit inclusion of animal products, vegetables and fruits in diets. However, in rural areas efforts to encourage the cultivation of a greater diversity of edible foods may be productive, for example through the establishment and improvement of home gardens (see Box 2.7).

The second approach is to provide essential micronutrients in the form of dietary supplements. In the developed world, the science of supplements has long been established and much food, particularly cereals, is fortified with micronutrients. Extending these conventional technologies to developing countries has had some success, for instance in the provision of iodized salt (Figure 6.2) and Vitamin A pills (Figure 6.3).

Nevertheless, for the developing countries as a whole, the provision of good balanced diets, particularly for the poorest, remains a severe challenge. This is partly why recent efforts have focused on a third approach, that of improving the dietary quality of the basic staple crops through biofortification, either through conventional breeding or through recombinant DNA technologies as described in Chapter 5.

**Figure 6.2** – In the developing world most countries have more than 50% of their households consuming adequately iodized salt.[4]



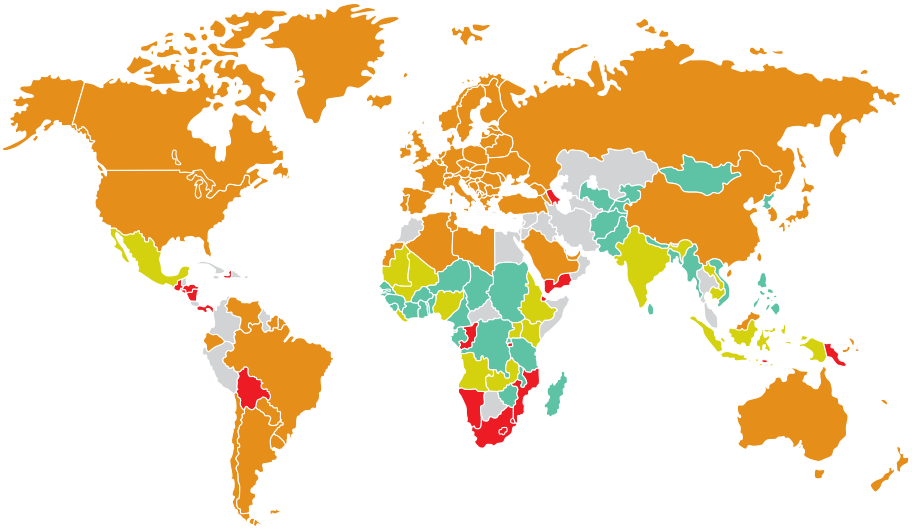


Percentage of households consuming adequately iodized salt (2000-2006)
**Note:** Adequately iodized salt contains 15 parts per million (ppm) or more of iodine.

90% or more | 50–89% | Less than 50% | Data not available

**Figure 6.3** – Provision of two doses of vitamin A (For 103 countries where under five mortality rate or vitamin A deficiency is high).[4]





Vitamin A supplementation coverage levels: two doses (2005)

80% | 50–79% | Less than 50% | Vitamin A priority country; data not reported | Not a vitamin A priority country

## 2. Improving child and maternal health

### Child mortality

As indicated in Chapter 4 considerable progress has been made in reducing the global death rate among under five year olds. To date, the greatest successes in combating child mortality have been in reducing the incidence of measles through vaccination and of malaria through the use of insecticide treated mosquito nets. Nevertheless the mortality rates in developing countries remain unacceptably high.[8] The major causes include neonatal complications, pneumonia and diarrhoea, with undernutrition acting as a significant underlying factor.

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Figure 6.4 – A woman feeds her child as part of a programme which teaches mothers ways to prepare nutritious meals for their children with the resources they have available

The contribution of undernutrition and how it can be tackled has been discussed above and in Chapter 5. Once past the neonatal period, deaths from pneumonia and other acute respiratory infections are currently the biggest concern. As was indicated in Chapter 4, this is largely due to a lack of access to correct diagnosis and antibiotics. Improvements in health system effectiveness are needed to make progress in this area. Diarrhoeal diseases, which cause 16 % of child deaths, will be dealt with first where we look at specific treatments for young children. Later on in this chapter, and in Chapter 7, we will discuss improving hygiene and sanitation for prevention.

Other childhood infections, such as malaria and HIV, will also be discussed later in this chapter.

#### *Childhood treatment of diarrhoea*

Whatever the basic cause, most diarrhoea-related deaths result from starvation or from the dehydration associated with diarrhoea. Acute, watery diarrhoea results in loss of both electrolytes and water; death occurs when the body fluid loss exceeds 10 % . Prior to the 1960s the only effective treatment was intravenous infusions which had to be administered in clinics, by trained personnel. They were costly and only available to a few patients. With the development of oral rehydration therapy (Box 6.2), this situation has changed.

The standard ORT packet consists of common salt, trisodium citrate dehydrate, potassium chloride and glucose, but the recommendations have changed in recent years reflecting a better understanding of what works in the home and community. Research has shown that home-made fluids – particularly those containing sodium and glucose, sucrose or other carbohydrates, like cereal based solutions – can be just as effective.

## Box 6.2 The effectiveness of Oral Rehydration Therapy (ORT)[9]

In 1971 the war for independence in Bangladesh caused the flight of 10 million refugees to overcrowded camps where a deadly cholera outbreak occurred. *'Conditions were squalid and chaotic, intravenous fluid was in scarce supply, treatment facilities and transportation were inadequate, and trained personnel were limited.'*[10]



Figure 6.5 – A woman mixes ORT

Dr Dilip Mahanabilis suggested trying an approach previously proven successful, but on a small scale, in Calcutta and Bangladesh. He and his team produced packets of table salt, baking soda and glucose which were distributed in one of the camps with instructions on how to dissolve the contents of the packets in water. There had been scepticism among health professionals who cautioned that the treatment should only be administered by doctors and other trained personnel.[11] Yet the treatment was given by 'mothers, friends and patients themselves' and proved to be very cheap, highly effective and safe. Mortality fell to 4% compared with 20 to 30% in the camps using intravenous therapy.

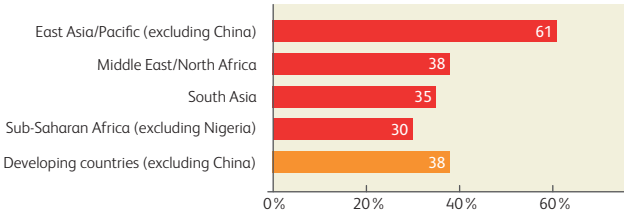
ORT was heralded by the Lancet as '*potentially the most important medical discovery of the 20th century,*'[12] and in 1972 became the WHO's standard treatment. By 2000 deaths from diarrhoea had fallen by 3.1 million/year or 67%.[13]

Recently there have been significant successes in countries such as Bangladesh and Egypt, nevertheless the proportion of affected children treated in this way worldwide still remains low (Figure 6.6).

Part of the problem is that treating a child with ORT does not immediately reduce the diarrhoea. In fact it may even make it worse before it improves. Inevitably, mothers will then resort to purchasing anti-diarrhoeal treatments which may be promoted by the private sector in preference to the much cheaper ORT. One answer, for the more severe and prolonged cases, may lie in developing cheaper, yet safer anti-diarrhoeal treatments for children. The Institute for OneWorld Health in California, with a grant from the Bill and Melinda Gates Foundation, is currently working with the International Centre for Diarrhoeal Disease Research in Bangladesh, Novartis Institutes for BioMedical Research, Roche Pharmaceuticals and others to develop drugs which can be integrated with ORT to reduce

Figure 6.6 – The low proportions of children under five with diarrhoea who receive oral rehydration or increased fluids with continued breast feeding (2000-2006)[4]





fluid and electrolyte loss. They are also pursuing longer-term research and trials to find anti-microbial medications which are safe, effective and affordable for the types of diarrhoea affecting children in developing countries.[14] More generally there has been an emphasis, in recent years, on complementing ORT with a variety of other measures, including continued feeding (breast feeding in infants), clean drinking water, improved personal hygiene, and zinc treatment.[15,16,17]

**Maternal mortality**

Every year more than half a million women die as a result of complications during pregnancy and childbirth, 99 % of them in the developing countries.[18] In addition every year:[19]

- 80 million women face an unwanted or unplanned pregnancy;
- 20 million women risk an unsafe abortion rather than carry their pregnancy to term: 68,000 will die as a result;
- 50 million women suffer from a serious pregnancy related illness;
- 4 million women are disabled as a result of pregnancy or childbirth;
- 15 million adolescents give birth at an age when the risks are particularly high;
- 300 million women worldwide (25 % of the developing world's adult women) currently live with avoidable ill health and disability as a result of pregnancy. Problems include infertility, uterine prolapse (where the womb falls into the vagina) and vesico-vaginal fistula (holes in the birth canal that allow leakage of faeces and/or urine into the vagina). Many women become socially excluded as a result.

Maternal mortality has decreased globally but not at a rate to achieve the MDG and there has been little progress in Sub-Saharan Africa. There, and in South Asia, haemorrhage is the main cause of maternal mortality. Almost all maternal deaths could be prevented if professional care was available during pregnancy and childbirth, and the few weeks following delivery, as well as access to emergency obstetric care in the event of complications.

Experience from Thailand, Bangladesh and Sri Lanka shows that maternal mortality can be reduced in low-income settings – by increasing access to skilled attendants, emergency obstetric care and family planning services.[20] Evidence also indicates that preventing unplanned pregnancies alone could avert at least one quarter of maternal deaths each year. Over 130 million women, who have expressed a desire to space or limit their family size, are not using any form of contraception. A further 64 million rely on less effective traditional methods. Furthermore, when abortion is made legal, safe and accessible, women's health improves rapidly.[21] In South Africa complications resulting from unsafe abortion decreased significantly (from 16.5 % to 9.7 %) between 1994 and 2000, largely due to the legalisation of abortions in 1996.[22]

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Figure 6.7 – Woman giving birth in India

## 3. Preventing and treating infectious diseases

The rest of this chapter is dedicated to the challenge of preventing and treating infectious diseases. This emphasis does not reflect a view that infectious diseases are more important than other health targets in international development. However, infectious diseases are the primary focus of the MDGs and, as a result, are subject to an intensity of science innovation, particularly using new platform technologies.

Following an introduction to infectious disease theory, we will focus on four areas of innovation:

- Environmental and behavioural modification;
- The quest for vaccines;
- The role of treatment and drugs;
- Emerging infectious diseases.

**The nature of infectious diseases**

Infectious diseases spread by transmission between infected individuals and un-infected individuals. Survivors are often immune and not susceptible to further infection. Most infectious diseases persist at low endemic levels; the number of people infected remains fairly constant with occasional short-lived surges in particular regions. However, diseases may explode into major epidemic proportions. This may be due to the virus, bacterium or other disease agent mutating into a form that is more virulent or invasive, or because the environment or human behaviour has changed, increasing transmission or susceptibility to infection. In practice such epidemics die out naturally because the disease agent runs out of susceptible members of the population (many may be naturally immune). The disease may then disappear or return to its previous endemic level. A "pandemic" is when an epidemic of infectious disease spreads through human populations across a large region; for instance a continent, or even worldwide.

The essence of infectious disease control is to achieve a low level of $R_0$ (the number of secondary cases produced by a primary case during its lifetime). At $R_0 = 1.0$ the disease is at a relatively stable endemic level. If $R_0 \leq 1.0$ over a sustainable period, then the disease will ultimately disappear. So far, the latter has only happened globally for smallpox (and for the livestock disease rinderpest see Box 5.19), although polio and Guinea worm are also close to extinction. In other cases it has been possible to eliminate the disease from particular geographic regions (yellow fever from the Americas, malaria from Europe). The more complicated the disease in terms of the structure and dynamics of the disease agent, its relationship with the human immune system and with any non-human host, the more difficult it becomes to reduce to low endemic levels or to eradicate.

We can reduce $R_0$ in one of three ways, through:

- Changing the environment or human behaviour in ways which reduce the risk of infection;
- Using a vaccine or microbicide to kill the disease agent at infection;
- Providing drugs which cure infections early, so reducing illness and mortality, and the risk of further transmission.

These all require appropriate economic and social policies and, in particular, rely on strong political leadership. But they also depend on the use of existing or potential new technologies.

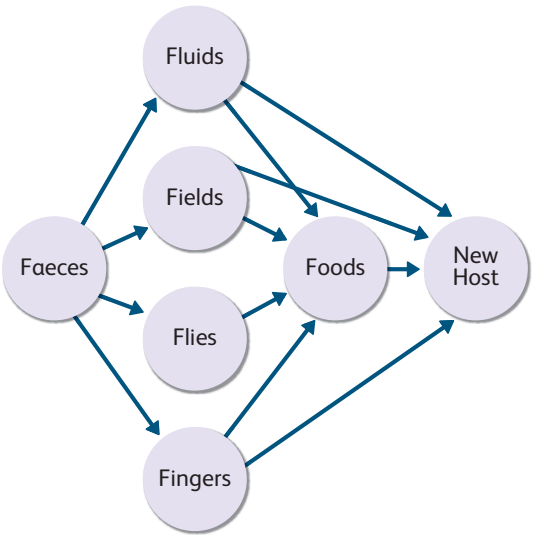
## 4. Environmental and behavioural modification for infectious diseases

### Preventing diarrhoea

Most diarrhoeal causing infections of childhood originate in faecal material which passes through the environment, often via contaminated water, to infect more children (Figure 6.8). In the diagram below the four arrows originating from 'faeces' on the left of the figure represent the primary routes by which infectious organisms get into the environment.

- Primary barriers are the practices that stop this happening – disposal of faeces in latrines, sewers and the removal of traces of faecal material from hands after contact with excreta.
- Secondary barriers are hygiene practices that stop faecal pathogens that have entered the environment in faeces or on the hands, from multiplying and reaching new hosts. For example, washing hands before preparing food or eating, and preparing, cooking, storing and re-heating food in such a way as to avoid pathogen survival and multiplication. Also protecting water supplies from faecal contaminants by treating water through boiling or chlorination. Other secondary barriers include keeping play spaces free of faecal material, preventing children from eating earth and controlling flies.

Figure 6.8 – The multiple pathways through which enteric pathogens pass from one child to another – the so-called F-diagram.[23]




The provision of improved sanitation and clean drinking water is discussed further in the next chapter. However behavioural modification is equally important. A high standard of hygiene – washing hands with soap and water (particularly after defaecation) – is key to reducing transmission (Box 6.3).[24]

**Box 6.3 Hand washing with soap is the most effective intervention against diarrhoea[25]**

| Intervention | Reduction in diarrhoea risk |
|---|---|
| Improved water quality | 16 % |
| Improved water quantity | 20 % |
| Sanitation | 36 % |
| Hygiene education | 35 % |
| Hand washing with soap | 47 % |

### *Improving hand washing*

Various experiments have shown that market-based interventions to promote hand washing can result in persistent uptake of the practice even after a lapse of several years – despite the fact that soap has to be purchased.[26] This suggests that hand washing could be marketed as a consumer product – soap being sold to make hands look, feel, and smell good – rather than to prevent sickness.[25] For this to be a success soaps need to be designed specifically for hand washing in developing countries, as described in Box 6.4 below.

#### Box 6.4 Making hand washing easy and effective

While a wide array of hand washing products are targeted at consumers in the developed world, almost all soaps produced for the developing world market are designed for bathing, washing dishes or doing laundry. Hand washing at key times – such as after using the toilet or before eating – has failed to catch on as a widespread habit and the large soap companies, such as Unilever and Procter and Gamble, have not yet perceived the expansion into hand washing in developing country markets as a profitable opportunity. Yet, according to one estimate, if everyone in India washed their hands with soap at the appropriate moment, the soap market would grow by 40 %.[27]



Figure 6.9 – A hand washing station in Indonesia

Changing behaviour and cultural norms is extremely difficult. The niche here is unique – most households in the target group do not have running water, or any sort of 'sink' area outside their toilet. The soap needs to be conveniently placed, easy and enjoyable to use and effective at removing microbes from hands. Very little work on producing such products has been done, but according to Val Curtis, of the London School of Hygiene and Tropical Medicine (LSHTM), there is 'a big potential for technological innovation in this area.'[27]

First, there is a need to design an effective way to locate soap, and possibly water, outside a toilet. Ideas include putting bars of soap on ropes or bars, or setting up hand washing stations with water barrels fitted with taps. Second, is the formulation of the soap itself, from simple factors such as whether it is a solid or liquid, its size, price, softness or colour, to more creative ideas such as single-serving paper soap squares which dissolve in water.

There is also potential for creating soaps that are more effective at removing and/or killing the microbes that are more prevalent in particular areas. Trials of medicated soaps have been done, but so far no improvements on traditional soap have been discovered.[28] A few companies, such as Hindustan Lever in India, have started work in this area but further work is needed if hand washing is to become a universal habit and for there to be a real impact in preventing diarrhoeal disease.

### The polio environment

The polio virus is also a faecal borne disease agent and spreads in a similar way to diarrhoeal agents. However, once inside the intestines it multiplies and passes into the blood stream where it invades the central nervous system destroying the muscle nerves and, in a small proportion of cases (1 %), causes muscle paralysis (poliomyelitis) in a matter of hours. 50 % of cases occur in children under three.[29]

After initial infection, the virus is shed intermittently in faeces for several weeks, irrespective of whether or not the infected person shows any symptoms. Despite a global vaccination programme to eradicate polio it remains persistent in several pockets, notably in the Indian state of Uttar Pradesh where poor sanitary conditions hinder its elimination (Box 6.5)

**Box 6.5 Ghaziabad is one of the last strongholds for poliovirus.[30]**

*'This impoverished corner of the northern Indian state of Uttar Pradesh offers an almost perfect environment for the virus to survive – even thrive. In urban shanty towns so new they don't even have names, families live in dirt-floored huts, cobbled together out of brick or cardboard secured by grass or plastic; lucky families have a piece of wood instead of burlap for a door. There are no toilets, no running water except for a single standpipe, no electricity. Bare-bottomed kids sit quietly in the mud. Human and animal faeces commingle in drainage ditches.'*

The implication is that it is going to be difficult, if not impossible, to eradicate polio unless the sanitary conditions in places like Ghaziabad are significantly improved.

### Controlling mosquitoes

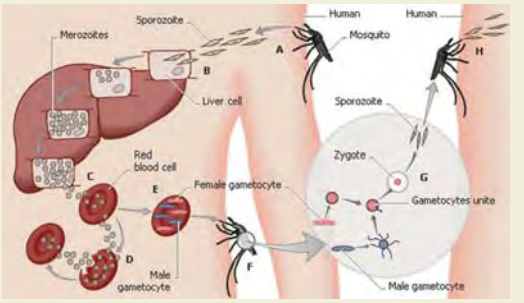
Environmental factors are crucial to malaria control because the infective agent – a *Plasmodium* protozoan – is transmitted from one person to another by anopheline mosquitoes (Figure 6.10). In theory, and to a considerable extent in practice, it is possible to eliminate malaria from large areas by controlling the mosquito carriers. Changing the habitat of the mosquito, in particular the water habitat in which mosquito larvae live, can be enough to bring about local elimination. This was a major factor in eliminating malaria in the UK and western Europe, but it was a slow and complicated process involving a diversity of interventions.[31,32]

In the last century attention focused on directly killing the adult mosquitoes. The rationale for this approach was elegantly presented in a mathematical model by George MacDonald in 1956. Subsequently his model was refined to take into account a wide range of factors. In essence it demonstrates the powerful consequences of reducing the mosquito survival rate. After a malaria parasite is ingested by a female mosquito feeding on human blood, it takes 9 to 10 days for the parasite to complete the cycle described in (G) in Figure 6.10 and for the sporozoites to become available in the salivary glands of the mosquito for transmission at the following feed. Mosquitoes feed every three days, and field estimates suggest that the daily survival rate of the mosquito is about 80 %. Thus only about 10 % of the mosquitoes survive long enough to transmit the disease. Reducing the survival still further will greatly reduce the probability of transmission and $R_0$ will drop below 1.0.[33]

This analysis was the justification for using insecticides, since they reduce both the survival rate and density of the mosquito population. It was soon realised that DDT was a cheap, highly effective

mosquito insecticide. When sprayed on the walls and ceilings of dwellings it was relatively safe and persistent. In the 1950s and 1960s there were very successful malaria control campaigns: a notable example was the near elimination of malaria in Sri Lanka.[35] However, mosquitoes developed resistance to DDT and subsequently there have been resurgences in many parts of the world. DDT was also shown to damage wildlife and the environment and as a result was largely withdrawn from use.

Figure 6.10 – The life cycle of the malaria parasite[34]




**(A)** A mosquito infected with the malaria parasite bites a human, passing cells called sporozoites into the human bloodstream.

**(B)** Sporozoites travel to the liver. Each sporozoite undergoes asexual reproduction, in which its nucleus splits to form two new cells, called merozoites.

**(C)** Merozoites enter the bloodstream and infect red blood cells.

**(D)** In the red blood cells, the merozoites grow and divide to produce more merozoites, eventually causing the red blood cells to rupture. Some of the newly released merozoites proceed to infect other red blood cells.

**(E)** Some merozoites develop into sex cells known as male and female gametocytes.

**(F)** Another mosquito bites the infected human, ingesting the gametocytes.

**(G)** The gametocytes mature in the mosquito's stomach. Male and female gametocytes undergo sexual reproduction, uniting to form a zygote. The zygote multiplies to form sporozoites, which travel to the mosquito's salivary glands.

**(H)** If this mosquito bites another human, the cycle begins again.[33]

### *Indoor residual spraying (IRS)*

IRS has continued but with alternative insecticides such as pyrethroids. These synthetic chemicals are based on natural chemicals derived from the pyrethrum plant. Some of the alternatives are more expensive than DDT; others, such as the pyrethroids, are of comparable cost but are less persistent, requiring two to four sprays a year instead of one. In 2006 the policy was reviewed by WHO. It concluded that IRS using DDT was often appropriate, and more effective, in certain circumstances and its use was once again approved (this was endorsed by the Stockholm Convention on Persistent Organic Pollutants (POPs)), and updated in 2007.[36] Today some 100 million people are protected by IRS, including 70 million in India and 22 million in Africa.[35]

### *Insecticide treated nets (ITNs)*

More recently the development of insecticide treated nets (ITNs), under which people sleep, has become an alternative to residual spraying. The nets are either dipped in insecticidal solution on a regular basis, usually at least once a year, or the insecticide is impregnated in the net fibre, during manufacture providing a long-lasting insecticidal net (LLIN) (see Chapter 1).[37] By long-lasting this means the ability to remain effective for three years or more. ITNs act in a similar way to indoor spraying in that they kill mosquitoes. However, they also provide a protective barrier, and depending on the insecticide, a degree of repellency. ITNs have been shown to avert around 50 % of malaria cases, doubling the protection afforded by untreated nets.[37] Moreover, while ITNs provide personal protection they have a significant effect on the local mosquito population, giving a community-wide reduction in malaria, even if the coverage is only about 50 % of all adults and children.[32,38,39]

The relative value of using IRS or ITNs depends on local ecological, economic and social conditions.[32] IRS is more suitable than ITNs for the rapid protection of a population, but when IRS needs to be continued for many years, there may be an attrition of people's acceptance of spraying. In contrast, ITNs are more suitable for progressive introduction and incorporation into

sustainable population habits. The WHO's guidance is to rapidly scale up the use of ITNs and it recommends that national programmes should only purchase LLINs. However there is now a need for a second-generation of nets that are stronger and longer-lasting, involving more robust polymers and improved treatment technologies in order to cope with the wide range of conditions and cultural preferences encountered.

The most important downside is that IRS and ITNs share the risk of encouraging development of insecticide resistant mosquitoes. For example, pyrethroid resistance has spread very rapidly in Africa. One of the major research challenges is to mitigate this risk (Box 2.3).

***Modifying mosquito behaviour***

One potential solution to overcoming the limitations of control through spraying or mosquito net use is to make changes to the vector population itself. A project funded through the WHO's tropical disease research programme (TDR)[40] called MosqGuide, has been working to explore ways of modifying mosquitoes that carry dengue fever and malaria.

This can be done either through population suppression, where the goal is to reduce the size of the vector population, or population replacement, where the population is converted to a less harmful form. To achieve suppression, researchers can rear the insects in large numbers, sterilise them using irradiation or genetic sterilisation techniques, and then release them to interbreed with the wild population. The progeny of these crosses will inherit the dominant sterile mutation and not reproduce. If enough sterile insects are released, for a sufficient time, the population will decline and collapse. Open field trials, with similar species, have been carried out, as well as contained field trials and laboratory analysis of malaria-specific strains. It is anticipated that the first use of GM mosquitoes will be through a sterile-release suppression strategy.

The other approach is to modify the vector strain so that it is less able, or unable to transmit the malaria parasite. However, modified mosquitoes are likely to have reduced fitness compared to wild types, and natural selection would lead to gradual loss of the gene. Therefore, an additional factor would be required to spread the gene, a so-called 'gene drive system.' The production and release of this combination carries a range of technical challenges, and testing and implementation of this strategy is still some way off.[41]

**Changing human sexual behaviour**

HIV/AIDS does not have a particularly significant environmental context, but since HIV is predominantly transmitted via sexual intercourse, the simplest approach to reducing transmission is to either to stop, or reduce, the frequency of intercourse where the risk of transmission is high. In practice this means adopting safe sexual behaviour:

- Abstinence, which for young people means delaying the age of first sexual intercourse;
- Reducing the number of sexual partners;
- Using a condom correctly and consistently, especially for casual sexual activity and in high-risk situations.[42]

Surveillance indicates that the growth in the AIDS epidemic in Sub-Saharan Africa has started to stabilise or decline in many countries since the late 1990s, although it is still at high levels.[43] The question is how much of this stabilisation is due to the natural course of an epidemic and saturation of disease levels in high-risk populations, or is the result of interventions, including those

aimed at changing sexual behaviour. An increasing number of countries – including Uganda, Thailand, Kenya, Cambodia, Zimbabwe, India, Rwanda, Ethiopia, Dominican Republic, and Haiti – have experienced national or sub-national declines in HIV which may be associated with the widespread adoption of prevention behaviours (Box 6.6).[44,45]

### Box 6.6 Adopting safer sexual behaviour in Eastern Zimbabwe appears to be reducing HIV transmission

Recently the most convincing evidence of a decline in HIV transmission has come from a cohort study in eastern Zimbabwe. Here a decline in HIV prevalence, between 1998 and 2003, was associated with sexual behaviour change in four distinct socioeconomic strata. HIV prevalence fell most steeply at young ages – by 23% and 49%, respectively, among men aged 17 to 29 years and women aged 15 to 24 years – and in more educated groups. Sexually experienced men and women reported reductions in casual sex of 49% and 22%, respectively, whereas recent cohorts reported delayed sexual debut.[46]

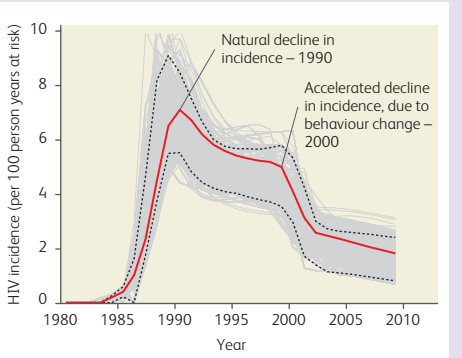



Figure 6.11 – The sharp rate of decline in HIV incidence in urban and semi-urban Zimbabwe[47]

The figure above shows that while the natural evolution of the epidemic was leading to a slow decline in incidence after 1990, a steeper than expected rate was experienced from around 2000. High mortality rates early on in the epidemic contributed to an increased fear of the disease. Word of mouth, and other informal information exchanges, as well as the large variety of formal activities launched at this time have helped to increase understanding of the disease, making it possible for Zimbabweans to make educated changes and for an overall shift in sexual norms.

Formal HIV prevention activities included: early control of sexually transmitted infections; marketing of condoms; voluntary counselling and testing services; television and radio serial dramas and the activities of the Zimbabwe National AIDS Trust Fund.

An important prevention behaviour is the use of condoms. When used correctly and consistently male condoms are *'the single, most efficient, available technology to reduce the sexual transmission of HIV… from both men to women, and also from women to men.'*[48] However, in many societies the power relations are such that it is difficult for a woman to insist that her male partner uses a condom. Even in apparently faithful partnerships transmission from man to woman of HIV (and the reverse) may be a significant risk.

Relatively recently female condoms have become available. Like the male condom, the female condom is intended to prevent HIV transmission by helping avoid exposure to semen or vaginal fluids. While in vitro studies confirm that the female condom provides an effective barrier to organisms smaller than HIV, the necessary clinical studies to confirm its effectiveness are still in progress.[49] A major drawback is that the female condom is more expensive than the male condom and not as readily available.

### Male circumcision

Recent scientific research has identified another important opportunity for preventing HIV infection, through the practice of male circumcision (Box 6.7).

#### Box 6.7 Male circumcision for the prevention of HIV transmission

Three clinical trials in African countries have found that male circumcision can help prevent HIV transmission to HIV-negative men from vaginal intercourse by as much as 60%.[50] The practice is one of the most common surgical procedures, with an estimated 30% of men circumcised worldwide, 2/3rds of whom are Muslim.[51] In the late 1980s scientists noticed that levels of HIV infection seemed to be lower in countries with higher rates of circumcision. This prompted a series of trials between 2002 and 2006 in South Africa, Uganda and Kenya, which showed very similar results, with reduction rates of 60%, 48% and 53% respectively.

The reason for this is still not completely clear. Scientists believe that circumcision may remove key targets for HIV infections, as the foreskin contains a concentration of immune cells, including Langerhans cells that are targeted by HIV during the early stages of infection. Circumcision removes the highly susceptible inner side of the foreskin, and allows quicker drying of the area, reducing the risk of bacterial or other sexual infections. However, circumcision is a surgical operation and also comes with risks, which increase greatly in situations with less-trained medical staff, unhygienic conditions, and when the operation is performed using traditional methods.[50]

While the discovery of this new intervention has significant potential, proponents caution that it must be one of a series of methods integrated in larger prevention programmes. Funding and resources need to be injected to make sure the operation can be offered in a safe and hygienic way. Future programmes will also have to pay close attention to the cultural and religious beliefs relating to circumcision, and work with communities as well as medical staff, to design effective awareness campaigns. Further research is also needed to gain a better understanding of the intervention's effects, including its effect on women (no immediate benefit has yet been observed), and the best means of operationalising it on a larger scale. There is a great potential for the practice to have a positive impact, especially in Southern Africa where circumcision rates are low, and HIV rates high.[50]

## 5. The quest for vaccines for infectious diseases

Vaccines represent a highly efficient and targeted approach to preventing infection. They consist of pharmaceutical products of various forms that establish or improve immunity to one or more diseases. Over time they have had a major impact on the incidence of infectious diseases in both the developed and developing world.

Commonly vaccines stimulate the immune system to kill the infecting organism, usually a virus or bacterium. The human immune system is a highly complex network of interacting proteins, cells, organs, and tissues. Its elements, and the vaccine trial process, are described in Box 6.8.

## Box 6.8 Key elements of the human immune system exploited by vaccines[52]

White blood cells originate from the stem cells of the bone marrow and will identify and eliminate pathogens such as viruses and bacteria. The most important are:

- B cells which are programmed to produce large numbers of antibodies that attack specific antigens (pathogens or elements of pathogens);
- 'Killer' T cells which kill the body's cells that they recognise as being infected by antigens (they express the CD8 glycoprotein on the surface);
- 'Helper' T cells that coordinate the other cells, stimulating B cells and Killer T cells to act (they express the CD4 glycoprotein on the surface).

Antigens are either parts of, or whole, viruses or bacteria which are recognised by the B and T cells. In addition to the immunity that is present at birth, immunity can be acquired by exposure to the appropriate antigen contained in a vaccine. Once exposed B and T cells retain the memory of the antigen, usually for the life of the person.

If a part of a virus or bacterium is used as an antigen it is usually harmless to humans. Otherwise a weakened or killed virus or bacterium may be used as the antigen. Vaccines normally undergo a sequence of three clinical trials (Figure 6.12):

**Phase I –** to assess their safety;

**Phase II –** to assess their efficacy on a small scale;

**Phase III –** to assess large scale efficacy.

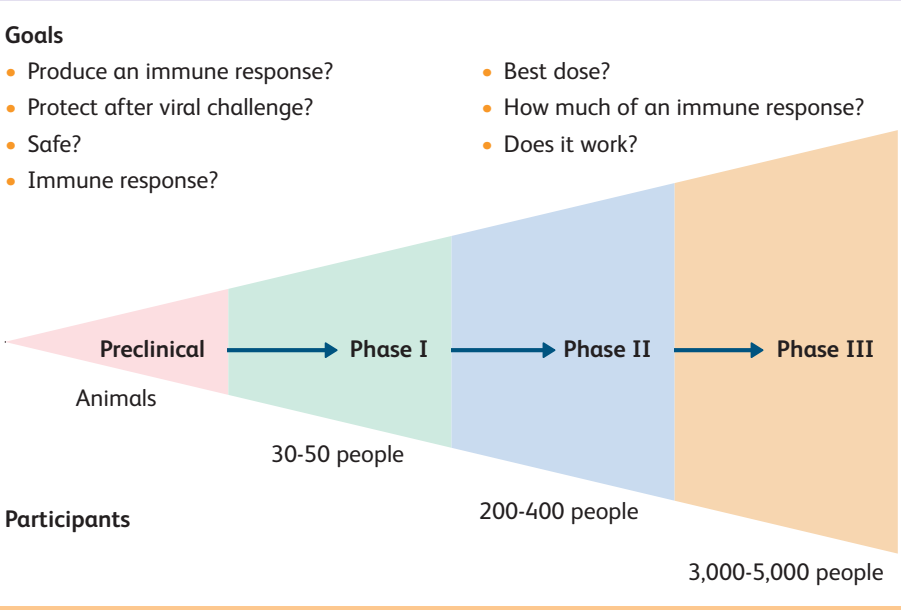



Figure 6.12 – The vaccine clinical trial process (for an HIV vaccine).[53]

Today there are many different forms of vaccine, the latest taking advantage of the revolution in cellular and molecular biology (Box 6.9).

### Box 6.9 The main forms of vaccine[54,55]

**Live, attenuated vaccines as antigens**

- Consists of viruses or mycobacteria weakened (inactivated) through being repeatedly re-grown in a hostile cell culture. They are infectious but relatively benign.
- Targets: measles, mumps, polio, rubella, TB. Elicit strong cellular and antibody responses and often confer lifelong immunity with only one or two doses. Have a good safety record, but can revert to virulent form. There are risks if given to people with weakened immune systems e.g. late-stage AIDS sufferers. Also require cold storage.

**Killed or inactivated vaccines as antigens**

- Composed of previously virulent bacteria or viruses which have been killed with chemicals, such as formaldehyde, heat or radiation.
- Targets: flu, polio, cholera, bubonic plague and hepatitis.
- Simplest and least expensive. Can be freeze-dried and stored and carried in this form. May vary in reproducibility and require careful monitoring to ensure no live organisms are present. Cannot revert to virulent form. They stimulate a weaker immune system response than do live vaccines, so may require several additional doses, or booster shots, to maintain immunity.

**Subunit vaccines as antigens**

- Vaccines based on only the parts of the virus that best stimulate the immune system. They contain anywhere from one to 20 or more antigens. The virus is grown in the laboratory and chemicals are used to break it apart and gather the important antigens, or the antigen molecules are extracted from the virus using recombinant DNA technology (Recombinant Subunit Vaccines).
- Target: Hepatitis B. They are chemically defined, reproducibly prepared and assayed and relatively inexpensive to produce.

**Toxoid vaccines**

- Used when a bacterial toxin is the main cause of illness. Toxins are inactivated by treatment with formalin to render them safe, and then adsorbed onto a compound such as an alum which stimulates the immune system to produce antibodies that lock onto and block the toxin.
- Targets: diphtheria and tetanus.

**Conjugate vaccines**

- Used against bacteria that possess an outer coating of polysaccharides (sugar molecules). These disguise a bacterium's antigens so that immature immune systems of infants and

younger children cannot recognize or respond to them. Conjugate vaccines link antigens or toxoids to the polysaccharides so they can be recognised.

- Target: *Haemophilus influenzae* type B (Hib)

**DNA vaccines**

- Still largely experimental. These use the genes that code for the antigens. When introduced into the body, some cells will take up the gene DNA which then instructs those cells to make the antigen molecules. In effect the body's own cells become vaccine-making factories. Naked DNA vaccines consist of DNA that is administered directly into the body.
- Targets: influenza and herpes.

**Recombinant vector vaccines**

- Also experimental, they use an attenuated virus or bacterium (the vector) to introduce microbial DNA, derived from harmful microbes, to cells of the body. Since they closely mimic a natural infection they are effective in stimulating the immune system.
- Experimental targets: HIV, rabies, and measles.

### Smallpox eradication

The history of smallpox eradication, perhaps the greatest vaccination achievement, illustrates that simply having an effective vaccine is only the first step in a successful programme. Edward Jenner first produced a vaccine against smallpox, inoculating patients with the related, but relatively benign, cowpox virus, in 1798. Yet smallpox was not eradicated until 1980 (Box 6.10).[9] There were a number of features of the disease that made it a suitable candidate for eradication: it had no animal host, it was transmitted through the air, usually by face-to face contact, its rash made it easy to diagnose, survivors gained lifelong immunity and the rate of transmission was relatively slow. Crucial for its success was a very heat-stable vaccine which protected with a single dose. Nevertheless *'eradication was achieved by only the narrowest of margins. Its progress in many parts of the world and at different times wavered between success and disaster, often only to be decided by quixotic circumstance or extraordinary performances by field staff.'*[56]

**Box 6.10 Milestones in the long journey to smallpox eradication**[56,57,58]

**1798** – Jenner developed cowpox virus vaccine.

**1920s** – An improved vaccine was produced.

**1930s** – Elimination was demonstrated to be feasible in the Soviet Union and elsewhere.

**1953** – World Health Assembly (WHA) rejected selecting smallpox for eradication.

**1950s** – A freeze-dried version of the vaccine was developed eliminating the need for refrigeration.

**1958** – Soviet Union donated 25 million doses of vaccine, but the programme was continually short of vehicles, supplies and equipment.

**1967** – Finally WHA approved the launch of the eventually successful Smallpox Eradication Programme.

**1970s** – Increasingly 'military' approach to the campaign.

**1977** – Last endemic case in Somalia.

Continuing scientific research was key to the success of smallpox eradication, *'despite the opposition of senior WHO leadership who insisted that the tools were in hand and the epidemiology was sufficiently well understood and that better management was all that was necessary to eradicate smallpox.'*[56] One important contribution was the development of new innovative vaccination devices, including:

- Vaccine jet injectors – powered by compressed air or gas that deliver a high-pressure narrow jet of the injection liquid to penetrate the skin, instead of a hypodermic needle;
- Bifurcated needles – these were dipped in a vaccine vial and used to make multiple punctures. They were cheap, used less vaccine per person and could be re-used after boiling or flaming. Villagers could be trained in their use in 15 minutes.

Another contribution was field research that revealed the epidemiology of the disease to be different from that described in the textbooks and the discovery that the duration of vaccine efficacy was far longer than that normally stated – both discoveries led to important operational changes in the eradication campaign.

**Childhood vaccines**

The smallpox experience encouraged a belief that it might be possible to globally eradicate a wide range of infectious diseases. This was reinforced by the experience of the developed countries in eliminating (or nearly eliminating) a number of serious diseases. By the 1930s typhoid fever was almost eliminated in the UK (with deaths down from 370 per million a year in the 1870s to 5 per million by the 1930s). This was followed by near elimination of typhus, anthrax and rabies – largely by public health measures – and then diphtheria using a toxoid vaccine.[59]

More recently, the developed countries have brought about significant control over a number of the main childhood infections, using new vaccines (Box 6.11).

Although produced with the developed country market in mind, these vaccines have begun to have a significant effect in the developing countries. In Sub-Saharan Africa, a highly coordinated measles reduction strategy, led by the Measles Initiative,[60] began in 2001. This has brought the number of measles deaths down from an estimated 492,116 in 2001 to 32,278 in 2008 – a 93% reduction. The strategy involves vaccinating all children against measles before their first birthday via routine health services and providing a second opportunity through mass vaccination campaigns.[61]

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Figure 6.13 – Vaccines are an efficient and targeted approach to prevention

**Box 6.11 Vaccines against childhood infections[62]**

| Vaccine | Type | Recommended schedule |
|---|---|---|
| Measles, mumps and rubella (MMR) | Live attenuated | Two doses between the ages of 12 months and 12 years. |
| Rotavirus A | Oral live attenuated | Two to three doses starting at two months. |
| Diphtheria, pertussis, tetanus (DPT) | Diphtheria and tetanus toxoids and inactivated pertussis. | Five doses between two months and 15 years. |
| Maternal/neonatal tetanus | Toxoid | Three dose course of tetanus toxoid (TT) given to mother, protects both mother and baby. |
| Hepatitis B | Subunit | A course of three injections at zero, one and six months. |
| Haemophilus influenza type B (Hib) | Conjugate | Three of four doses to infants, starting after six weeks. |
| Pneumococcal | Conjugate | Four doses, given at two, four, six and 12 months. |
| Inactivated Poliovirus (IPV) | Inactivated | Three doses at two, four and six to 18 months. Booster at four to six years. |
| Influenza | Injected inactivated or spray live attenuated | Annually, with two doses given in the first year. |
| Vericella (chickenpox) | Live attenuated | Can be combined with MMR (MMRV), or given as a separate vaccine in two doses. |
| Hepatitis A | Inactivated | Two doses, starting at one year and then at least six months after. |
| Meningococcal | Conjugate | One dose, after two years. Boosters as necessary. |

Despite successes with vaccination, achieving the larger goal of disease elimination, especially in developing countries, is not straightforward. Campaigns require large scale, sustained funding, and a relatively sophisticated infrastructure including well-trained staff. Eradication is also much more difficult in the 21st century because of the widespread mobility of populations which encourages re-infection and renders even regional elimination difficult. This has led to a more sober assessment of the possibilities of eradication.[56] Some experts actually consider the goal to be an obstacle towards effective disease suppression and control.[59]

### Polio not yet eradicated

Concerns about the feasibility of eradication are underscored by the current global attempt to eradicate polio. It has been a highly successful campaign in many parts of the world, but complete global eradication remains elusive.

The campaign began with the development, by Jonas Salk, of an inactivated (killed) polio vaccine (IPV) in 1955, but took off with the production of a live attenuated (weakened), oral polio vaccine (OPV) developed by Albert Sabin in 1961 (Box 6.12).

Immunization campaigns with OPV in Cuba and in Eastern Europe demonstrated that the poliovirus can be eliminated in large geographic areas. In 1988 when there were some 350,000 cases worldwide, the Global Polio Eradication Initiative was launched. By 1999 the number of cases had dropped to 7,000. Indigenous polio was eradicated in the Americas in 1991 and in China in 1996.[63]

#### Box 6.12 The poliovirus and its vaccines[59]

Poliovirus is one of the simplest of the viruses, consisting of RNA protected by a protein coat or capsid. The virus binds to a receptor on a nerve cell surface and then enters the cell; the RNA is released and instructs the cell to produce more polio viral protein (Figure 6.14).



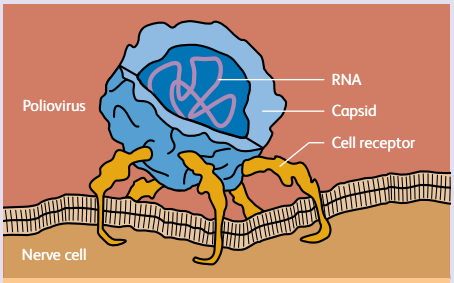



Figure 6.14 – Poliovirus binding to receptors on the surface of a nerve cell.[64]

Typically the virus causes paralysis in only 1 % of those infected, 5-10 % suffer a variety of relatively mild symptoms, the remainder are symptomless but shed the virus in the faeces – and may do for some time.[65] It is for this reason that surveillance is important. A single case with acute paralysis may be an indicator of the presence of a hundred or more infected and infectious children.

#### Polio vaccines

There are three forms of the poliovirus, serotypes 1, 2 and 3, each with a slightly different capsid protein. Type 1 is the most common, 2 was eradicated in 1999 (but see below).

**The Inactivated Polio Virus (IPV)** triggers an excellent response in the immune system of most recipients, producing protective antibodies in the blood – thus preventing the spread of poliovirus to the central nervous system. However, it induces only very low levels of immunity to the poliovirus inside the gut. As a result, it gives protection against polio paralysis but, when a person immunized with IPV is infected with a poliovirus, it can still multiply inside the intestines and be shed in stools – increasing the risk of continued circulation.

A further major disadvantage is that IPV has to be injected by trained health workers, which increases the costs of vaccination.

Since the **Oral Polio Virus (OPV)** is administered by mouth it does not need trained health workers. It is also much cheaper (a fifth of the cost of IPV). Like the IPV it prevents the spread of the poliovirus to the nervous system but it also produces a local immune response in the

lining of the intestines, so preventing the multiplication of the poliovirus in the gut. Thus mass campaigns with OPV can rapidly stop person-to-person transmission of the poliovirus. Moreover, the shedding of vaccine virus in the stools of recently immunized children means that, in areas of poor hygiene and sanitation, immunization with OPV can result in the 'passive' immunization of people in close contact. It is estimated that levels of immunity of 80-85 % are enough to provide sufficient passive immunization to protect those who are susceptible.[66] WHO aims to achieve four doses of OPV in the first year of life.

The trivalent form of OPV contains weakened forms of all three serotypes, but monovalent vaccines are also available which target just one type.

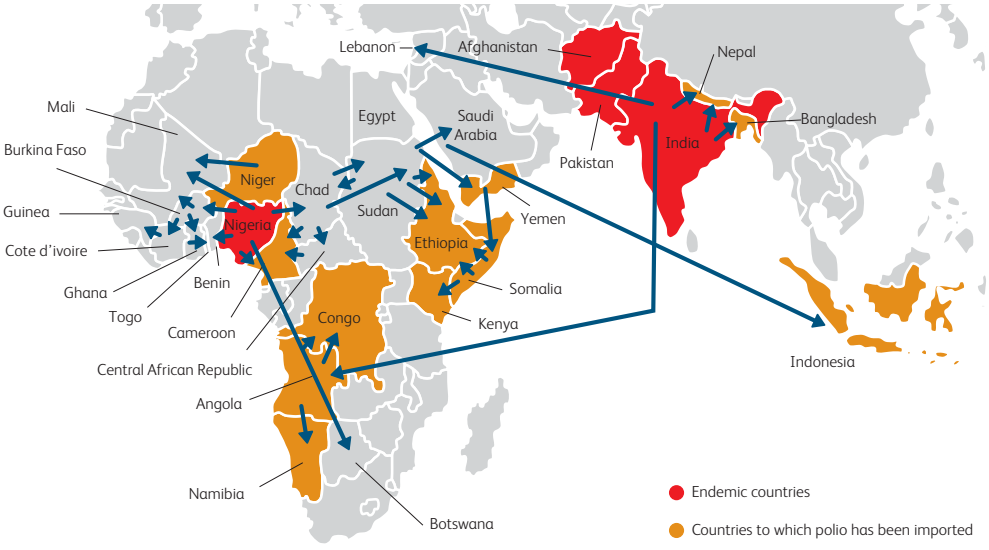
Although OPV is safe and effective, in extremely rare cases (approximately 1 in every 2.5 million doses of the vaccine) the live attenuated vaccine virus in OPV can cause paralysis – either in the vaccinated child, or to a close contact.

***Resurgences and re-emergence***

But in 2002 and 2003 there were severe setbacks. A resurgence occurred in India in 2002 as a result of a major decline in vaccination with OPV against type 3 polio. The following year, because of opposition by religious leaders in the northern states of Nigeria, there was a significant fall in immunisation – 30 % of children went unvaccinated in 10 states in 2005. Following the increase in cases in these two countries, there was a rapid global spread of polio to a dozen other countries (Figure 6.15)

Subsequently, the number of cases in Nigeria has declined but the upsurge in India has continued. In 2008 there were 1,600 polio cases worldwide. The task now is to bring about eradication in the two main endemic areas – in the northern parts of Nigeria and India. Reliance is being placed on OPV vaccination because of its contribution to passive immunization.

**Figure 6.15** – The spread of polio from India and Nigeria between 2002 and 2006[67]



In northern India children are receiving more than 12 doses of vaccine before their second birthday. As indicated earlier (Box 6.5), places such as Ghaziabad in northern India have highly unsanitary conditions that contribute to the spread of poliovirus, but similar places elsewhere in the subcontinent are polio free, so there may be other factors at work.

***Vaccine-derived polio***

Full global eradication is also complicated by the existence of vaccine-derived cases of poliomyelitis. Even if human to human transmission of wild poliovirus is stopped in the endemic countries there may be a lingering problem of circulating vaccine-derived poliovirus (cVDPV) resulting from genetic mutations in the virus strains that make up the OPV. The risk in India is estimated to be 1 in 4 million doses.[64] Such mutations can produce a virulent strain of the virus and trigger an outbreak. Four such outbreaks of cVDPV have occurred since 2000 – in Hispaniola, Philippines, Madagascar and China. Because individuals with these viruses can continue to shed them in their faeces for many years, severe outbreaks in populations with little immunity may suddenly occur. The implication is that as soon as transmission has ceased, OPVs should be discontinued and replaced by IPV.

The case for this strategy is strengthened by the re-emergence of type 2 polio in Nigeria, once thought to have been eradicated.[68] It first appeared in 2005 and began to take off in early 2009. It is the result of a weakened type 2 virus that makes up the trivalent OPV, mutating and regaining its dangerous state. Because monovalent OPVs, against types 1 and 3 (which are more effective), have been used in recent years there is little or no immunity to type 2 in the population. Hopefully, a campaign with trivalent OPV in Nigeria could re-eradicate type 2, but this will not be easy. Alternatively there is a strong case for a switch to the inactivated vaccine, despite its drawbacks.

***Vaccines against TB***

One of the biggest obstacles to reducing the incidence of TB is the lack of an effective vaccine for prevention. The first vaccine for TB, called Bacillus Calmette-Guerin (BCG), after its creators, was discovered in France and administered to humans in 1921. It is a live attenuated form of the bovine TB pathogen. Unfortunately, its efficacy is extremely mixed, being *at most* 80% effective at preventing TB infection. Results vary greatly by geography, patient age and background, with poor protection against pulmonary TB, although it is very effective against non-pulmonary cases (also very effective against leprosy, and may be responsible for its disappearance in Africa).[69] In addition, the vaccine needs refrigeration, which is problematical in the climates of the most highly TB-infected regions. Despite these drawbacks, BCG has been relied on, as the sole form of prevention, for one of the world's most widespread diseases for over 80 years.

There are a number of reasons why decades have passed without a new vaccine. The bacteria are a difficult target. They are able to hide inside cells and avoid normal antibodies; destruction can only be accomplished through the activation of T cells. Furthermore, the bacterium can spend years dormant in the body, so an effective vaccine has to provide long-lasting protection.

A second reason has been a lack of funding, and little research priority. This situation has changed with new attention being drawn to the disease following its inclusion in the MDG targets, work by organisations like Partners in Health, and the formation of the Stop TB partnership.[70] The spotlight has also been put on TB by big funders such as the Bill and Melinda Gates Foundation.[71]

As a consequence there are at least five new types of vaccine in the pipeline, either primary

vaccines, or 'boosters' to complement either BCG or a new primary vaccine. Much of the work focuses on using recombinant viruses or fusion proteins (which combine genes for two different proteins) to improve the way the body recognises TB bacteria and increases the production of T cells. Examples include:[72,73]

1. An attempt to produce an improved version of BCG, using a recombinant strain which over-expresses the most abundant protein produced by the bacterium. Phase I trials began in 2009;
2. A recombinant sub-unit booster, based on a genetically modified vaccinia virus that 'reminds' T cells of the disease and produces a high number of T 'helper' cells when given years after BCG. The most advanced of the current candidates are in Phase IIb trials in South Africa;
3. A dry powder form of the original BCG vaccine using nanotechnology. This does not require refrigeration and avoids problems with dirty needles. It should be relatively cheap and may get through trials faster. Phase I trials are imminent.

While the above vaccine candidates are not expected to be ready for the market for five to 10 years, the fact that such a large number of promising possibilities are in the pipeline after 80 years of near inactivity is good news.

**No HIV vaccines yet available**

We know a great deal about the human immune deficiency virus (HIV), the causative agent of the disease known as Acquired Immunodeficiency Syndrome or AIDS. We have analysed its structure, its behaviour, and how it replicates and is transmitted (Box 6.13). Yet despite over 20 years of research and development we still do not have an effective vaccine.

We know that some people never become infected, despite repeated exposure to HIV, some who are infected never seem to suffer any harm and for others the symptoms do not arise for a decade or more. So there is a form of natural immunity in the human population and the question is whether this can be exploited to provide a significant level of protection.

The challenges are considerable:

- First, HIV infects the helper T cells, the very cells whose purpose is to help combat viruses and other infectious organisms. From the start of the infection HIV directly targets and overcomes 'its enemies.' It does this within the first seven to 10 days after infection, so there is only a brief window of opportunity for a vaccine to be effective.
- Second, the viral DNA becomes hidden away in long-lived cells from where, years later, it may spawn viral particles. If a vaccine is not successful in preventing infection it has to trigger a long-lasting immune response.
- Third, is the extraordinary diversity of the virus, in particular the forms of the glycoprotein spikes. This means that a vaccine effective against one form or clade of the virus e.g. clade B which is predominant in the industrialised countries, may not be as effective against the clades of the developing countries. This diversity is increased by a high mutation rate, creating a 'hypervariability' that renders HIV a moving target (the genetic HIV variability in a single human is equivalent to the global variability in a whole year of the influenza virus A).

As a consequence HIV is one of the most formidable pathogens for which vaccine development has ever been attempted.

## Box 6.13 The HIV structure and replication

The virus is a retrovirus, about 1/10,000 of a millimetre in size and is deceptively simple in structure. Embedded in the lipid envelope are numerous 'spikes' each of which has a cap made of three glycoprotein molecules.

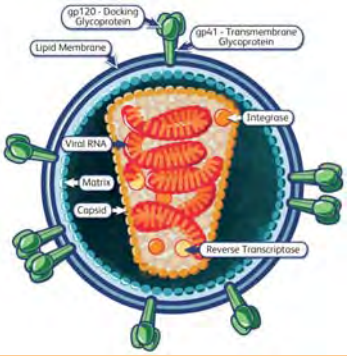



Figure 6.16 – Structure of the Human Immunodeficiency Virus (HIV).[74]

Within the envelope are two single strands of viral RNA, each of which has a copy of the virus's nine genes. They contain the information necessary to produce proteins that control the ability of HIV to infect a cell and to produce new copies of itself.

Infection typically begins when a virus encounters a 'helper T cell.' (CD4+ T cell). The glycoprotein gp120 spikes attach the virus to the cell by binding to CD4 on the cell surface and then the virus binds to a second receptor (CCR5 or CXCR4) which allows the glycoprotein gp41 to fuse with the cell membrane.

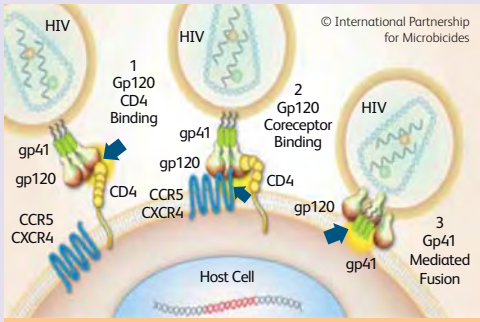



Figure 6.17 – Stages, of the intricate process of HIV attaching and fusing with a human cell.[75]

Once inside the cell, the viral RNA is converted into viral DNA using an enzyme produced by the virus known as reverse transcriptase. The viral DNA moves to the cell's nucleus, where it is spliced into the host's DNA. There it produces more viral particles.

A healthy, uninfected person usually has 800 to 1,200 helper T cells per cubic millimetre ($mm^3$) of blood that orchestrate the activities of the killer T cells and B cells. They may provide a level of immunity to the virus and help ensure a person remains free of the symptoms of AIDS for years.

However, after infection, the numbers of helper T cells progressively decline so reducing their capacity to detect and orchestrate a response to other pathogens. When the count falls below 200/$mm^3$, a person becomes particularly vulnerable to opportunistic infections and cancers. The immune system collapses and full blown AIDS develops that typifies the end stage of the HIV disease.

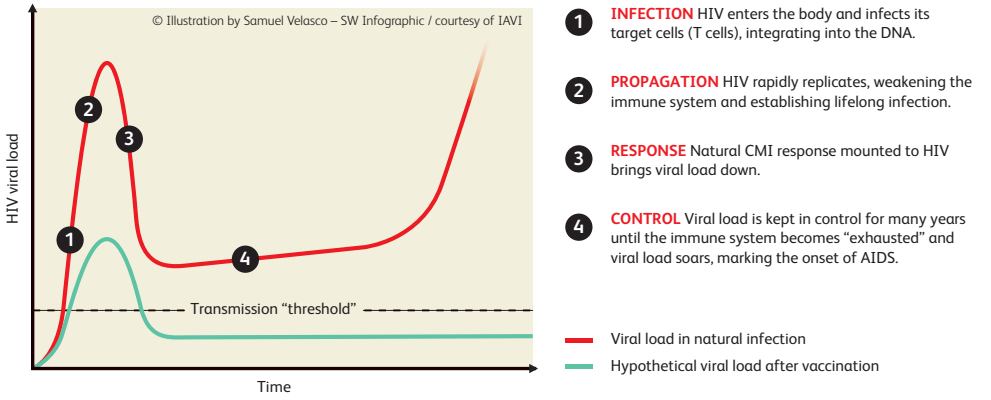
Two approaches to produce a viral vaccine have been tried, based on stimulating production of:

- Antibodies, produced by B cells, that will destroy invading HIV before it can take hold in the body;
- Killer T cells that will destroy helper T cells in the body already infected by the virus.

The first approach used the gp120 glycoprotein spike on the surface of the virus as the antigen. The results however, were disappointing. Gp120 appears to be concealed and shielded from antibodies and also utilises 'decoys.'

The second approach, referred to as cell-mediated immunity (CMI) could, in theory, lower the peak of the viral load and maintain a much lower population of HIV over time (Figure 6.18).

Figure 6.18 – A Cell-Mediated Immunity (CMI) approach can theoretically keep the viral load below the transmission threshold.[76]




Although both approaches have been proved feasible in animal models, neither has individually produced a vaccine that is of significant human benefit. The one partial success is the RV 144, a "prime-boost" combination of two vaccines: ALVAC® HIV vaccine (the prime), and AIDSVAX® B/E vaccine (the boost). The vaccine combination was based on HIV strains that commonly circulate in Thailand and was administered in a Phase III trial involving 16,000 volunteers. The trial demonstrated that the vaccine regimen was safe and modestly effective in preventing HIV infection, reducing it by some 30 %.[77]

What is now clear is that the virus exists in both 'free' and in the helper T cells, so it can only be eliminated by the two approaches working in tandem (antibodies destroying the free viruses and killer T cells destroying the helper T cells containing the virus). Thus the aim is to find a vaccine that does both. The most promising candidates are plasmids (structures outside the chromosome that contain DNA, usually in bacteria) that encode a gene from the virus and live recombinant vaccines, again with genes from the HIV virus, but inserted into harmless viruses such as the adenovirus.[78]

What is needed is an expanded, yet coordinated, research programme aimed at virtually every element along the chain of vaccine development from basic cellular and molecular science to vaccine types and delivery systems.[76,79-81]

**A malaria vaccine in sight?**

An effective human malaria vaccine has been sought for over 70 years, but until recently with little success. This is largely because the infectious agent, *Plasmodium*, is a protozoan, an organism much more complex than a bacterium or virus. The *Plasmodium* has to survive in human cells until it is picked up again by a mosquito and it has developed a very good resistance to the human immune system, based in part on the great diversity of the parasite's protein coats and the variety of signals each coat provides to the antibody. In the words of Professor Kevin Marsh, Director of the KEMRI – Wellcome Collaborative Research Programme in Kenya: *"Not only do different parasites have different protein coats – like humans having different eye or hair colour – but each parasite can also vary the particular signals it displays."*[82]

The approach to a vaccine, similar in some respects to that being adopted against HIV, is to utilise (mostly) sub-unit vaccines, based on a wide range of the antigens presented by the parasite in its different forms. Hopefully this will stimulate both antibodies and cell-mediated immunity. Again, echoing the new HIV vaccine approach, there is a belief that a combination of vaccines will be critical to success.

Because the parasite's life cycle is complicated there are several different broad targets for a vaccine (Box 6.14).

## Box 6.14 The cycle of targets for a malaria vaccine.[83]

After the mosquito bite transfers the parasites to a human, they first invade the liver and replicate there for two weeks, before beginning a cycle of red-blood-cell invasion. Growth, replication and red-cell destruction leads to the disease symptoms.

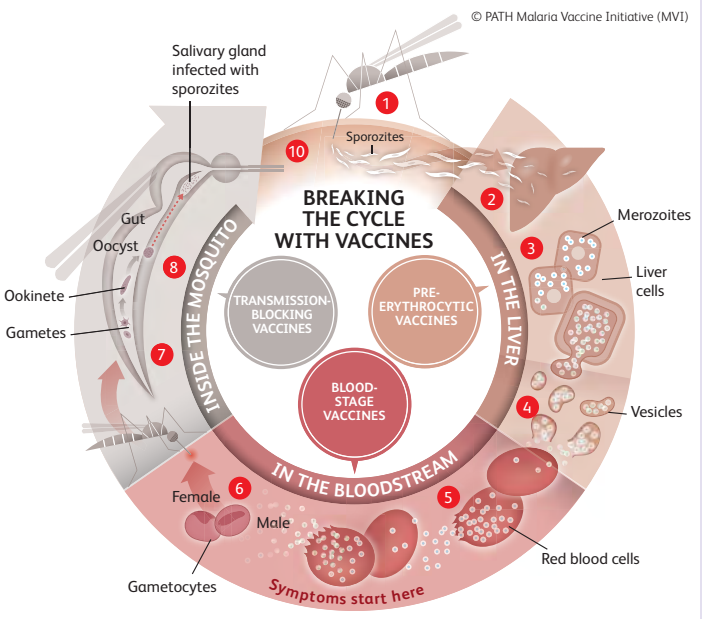



Figure 6.19 – The life cycle of the *Plasmodium* parasite.[83]

**1. Pre-erythrocytic vaccine candidates –** these target the stage at which the parasite enters or matures in an infected person's liver cells. They aim to elicit an immune response that would either prevent infection or attack the infected liver cell if infection does occur. They include:

– Recombinant antigens from the surface of the parasite or from the infected liver cell that induce antibodies, for example against the sporozoite main coat protein (e.g. RTS,S);

– DNA or viral vector vaccines that encode pre-erythrocytic antigens recognised by T cells;

– Live, attenuated vaccines that consist of a weakened form of the sporozoite.

**2. Blood-stage vaccine candidates –** that target the rapid replication of the organism in human red blood cells. These do not aim to block all infection, but to decrease the parasite load, hence reducing the severity of the disease. A vaccine that contains antigens or proteins from the surface of the merozoite could allow the body to develop natural immunity with much less risk of getting ill.

3. **Transmission-blocking vaccine candidates –** these seek to interrupt the parasite's life cycle by inducing antibodies that prevent the parasite from maturing in the mosquito after it takes a blood meal from a vaccinated person. The aim would be to limit the spread of infection by preventing mosquitoes that feed on an infected person from spreading malaria to new hosts.

The most successful candidate to date is the pre-erythrocyte vaccine RTS,S. The latest field trials on children aged five to 17 months have shown promising protection.[84] The vaccine is now recommended to go into Phase III trials and could be submitted to regulatory authorities by 2011.

## 6. The role of treatment for infectious diseases

Treatment of people with infectious diseases serves at least three purposes:

1. To reduce the probability of mortality;
2. To reduce morbidity and help people live normal, productive lives;
3. To prevent further spread of the infection.

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Figure 6.20 – The range of treatments on offer in the small village of M'PeDougou in Mali

### Advancing the treatment of TB

Once infected, a person's immune system if strong will fight to contain the TB bacteria. But, if the immune system is weakened in any way the bacteria will escape, multiply and develop into the active tuberculosis disease. The bacteria then attack the lungs and other organs such as the kidneys, liver, vertebra and brain. They destroy tissue and cartilage, leading to a variety of symptoms including fever, weight loss and a chronic cough producing blood. The disease kills around 60 % of those who are not treated, most commonly through respiratory failure.

No treatment was available for TB for thousands of years and the disease, commonly known as 'consumption', was still killing up to one out of every seven people in the US and Europe in the early 1900s. From the 1850s through to the 1950s, the primary way of dealing with TB patients was to collapse the infected lung or to send patients to 'sanatoriums', where they could get better 'air,' nutrition – and be kept away from the general population.[85] Progress was made in the developed countries largely as a result of the improved social, economic and nutritional status of the population.

In the 1940s medical advances made TB chemotherapy possible. Streptomycin, the first effective antibiotic was discovered in 1944, but it was soon found that it produced resistant mutants within a few months. In the 1950s and 60s other antibiotics were developed, including isoniazid, ethambutol and rifampin, the primary drugs used to treat the disease today. It was also demonstrated that resistance could be overcome by treating the patient with a combination of two or three drugs. Combination therapy has been used to treat TB ever since.[86]

The drugs must be taken over an extended period of time, six to 12 months, in order to completely eliminate the bacteria from the body.[87] Initially, the first patients to be treated in this way were hospitalized for the full course of treatment to ensure compliance. However, in the 1950s, researchers from the British Medical Research Council in Madras, India found that results from those who were treated with TB drugs at home, and monitored by family members, compared equally well with those treated at a sanitarium. While this idea quickly spread, and long-term hospitalization of TB patients ceased, the need for continuing directly supervised care was not widely translated.[85] TB rates in Europe and the US began to dramatically decline, but success has not been seen on the same scale in resource-poor settings with poor health-systems, unreliable transport and unaffordable drugs.

In 1974 Dr Karel Styblo, working in Tanzania, developed a relatively successful model of short-course chemotherapy under direct supervision. It was exported to six other African countries and to Nicaragua.[85] But this was not at first taken up as a large-scale approach. In fact, TB control measures were relaxed, and often neglected.

***Resurgence and the adoption of DOTS***

The emergence of HIV in the 1980s changed everything. The huge increase in the number of immuno-compromised individuals led to a reversal in trends and a steady increase in TB incidence. An increase in migration, urbanization and overcrowding in cities, and the ongoing problems of poverty, malnutrition and poor public health infrastructure served to add to the problem.[88,89]

By 1993, there were seven to eight million new cases occurring each year, and TB was declared a global emergency.[90] In 1994, the WHO, seeking to respond to the problem, adopted a programme based on the work of Dr Styblo, which was renamed DOTS (Directly Observed Therapy, Short-course).[91] DOTS was gradually expanded around the world, and quickly became the standard method of TB control. The five components of DOTS are:

- Government commitment;
- Case detection by sputum smear microscopy;
- Standardized treatment regimen with directly observed treatment for at least the first two months;
- Regular drug supply;
- Standardized recording and reporting system that allows assessment of treatment results.[90]

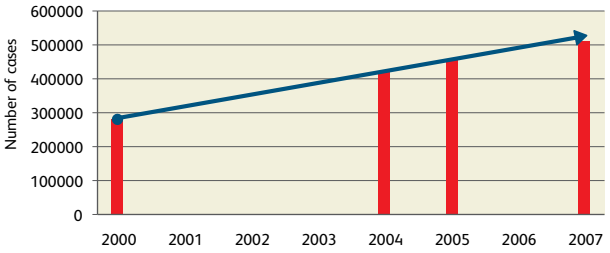
TB prevalence worldwide has declined steadily since 1990, from about 300 cases per 100,000 people, to around 200[92] – and in 1997, the Director General of the WHO termed DOTS the health breakthrough of the 1990s.[85] The strategy has now been adopted by 187 out of 193 WHO member states at high levels of population coverage,[93] and with the 2006 Stop TB strategy continuing to focus on the use of DOTS; it remains '*one of the most widely-implemented and longest-running global health interventions in history*.'[91]

***Remaining challenges***

Despite its widespread uptake, and success in some areas, a large number of challenges remain. Whilst the prevalence of TB has been gradually decreasing globally, it is increasing quite dramatically in both Sub-Saharan Africa and Eastern Europe. A number of factors are combining in these areas to make the successful control of TB through DOTS difficult. These include: poverty, late care-seeking behaviour, lack of transport for repeated treatment, weak health systems, HIV epidemics and, increasingly, the emergence of Multi-Drug Resistant TB (MDR-TB).

MDR-TB is defined as TB that is resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs. It therefore has to be treated with drugs that are more expensive, have more serious side effects, and need to be taken for a longer time – and the success rates go down.

Figure 6.21 – The rise of Multi Drug Resistant TB (MDR-TB)[92,95]




Resistant strains of TB develop through the incorrect treatment of normal TB, either as a result of patients missing doses, doctors prescribing inappropriate drugs, or patients failing to complete the full six plus months treatment programme. While the majority of cases arise in these ways, MDR-TB can also be passed onto new individuals, especially to those with weak immune systems.

The first incidences of MDR-TB were reported in the 1990s, and while exact numbers are difficult to determine[94] and estimates are likely to be low, it is generally agreed to be on the rise. Figure 6.21 above shows global estimates of infected individuals from 2000. The spread of the problem is not evenly distributed. It is estimated that nearly two thirds of the global MDR-TB burden occurs in just three countries – Russia, India and China.[95]

Health officials have tried to respond to the problem, but change has been slow. In the first years of the growing epidemic, there was debate as to whether to use the limited resources of very expensive drugs to treat what was a minority of patients. The WHO only agreed to treat MDR-TB in 2002,[96] but have subsequently put in place extensive guidelines for MDR treatment in their new strategy.

Unfortunately, in the meantime, the TB bacterium has built up further resistance, leading to the evolution of extensively drug-resistant TB, or XDR-TB (TB resistant to three or more of the six classes of second-line drugs). It was first reported in August 2006, out of 52 reported cases, 51 died within a month of being tested. As of 2007 it was estimated that 27,000 new cases were emerging per year, with 80 to 100 % mortality rates being reported.[97]

***Future – new drugs***

New treatment options are urgently needed. Today's first-line anti-TB medicines are *more than 40 years old*. New medications could shorten the treatment time, thus greatly alleviating some of the problems with patient adherence which have led to drug resistance. In addition, drugs are now needed which can attack both multi- and extensively-drug resistant strains, as well as work alongside HIV/AIDS medications.

As with vaccines for TB, there has been a recent increase in attention and funding for the development of new TB medications, and an increase of research and new drugs under trial. The Stop TB Partnership has made new drug discovery one of its key initiatives,[70] and the TB Alliance has been set-up as a public-private partnership to speed-up and facilitate drug discovery and delivery.[98] The objectives set by the 'Stop TB Partnership Task Force on Retooling' for the development of new medicines are:

- To simplify or reduce treatment duration to two months or less;
- To effectively treat multidrug resistance;

- To treat patients with latent TB infection;
- That new medicines should be compatible with antiretroviral therapy for HIV/AIDS patients.[99]

Scientists are working towards these aims by looking at both known and new targets within the bacterium, as well as using novel approaches to target the bacterium as a whole organism. Advances in genomics have proved helpful, especially the recent success in sequencing of the bacterial genome.[100]

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**Figure 6.22** – The development and administration of new drugs for TB will be vitally important

There are currently thousands of potential compounds being screened, synthesized, or optimized in discovery and preclinical studies, with much of the work being done through the TB Alliance and its partners, as well as the private company AstraZeneca. Some of these new drugs may be introduced as new combinations, others as single drugs.[101]

Most advanced in development is the drug Moxifloxacin, which could be substituted for one of current first-line drugs, reducing the time for treatment to four months. Using a mechanism different to existing first-line drugs, it acts by inhibiting an enzyme called DNA gyrase, which is essential for the bacterium's survival. Trials began in 2002 and have now reached the Phase III stage.[99,101]

Another promising candidate is a diarylquinoline TMC207 which provides a new mechanism of action by inhibiting the bacterial ATP synthase. In Phase II trials it has shown effectiveness in patients with multi-drug resistant bacteria.[101]

While we are still some years off from seeing significant changes in the technologies available for TB treatment, the fact that so many new possibilities are now being developed is extremely promising. As stated in a 2007 report: '*For the first time in 40 years, there is a coordinated portfolio of promising new compounds in the pipeline, some of which have the potential to become the cornerstone drugs for the control and possible eventual elimination of TB in the future.*'[99]

**Antiretrovirals (ARV) against HIV**

The first effective drug for the treatment of AIDS had been used to treat cancer patients. In 1985 AZT (known as zidovudine or retrovir) was found to be effective against HIV because of its ability to block the enzyme (reverse transcriptase, see Box 6.13) that translates the viral RNA into DNA. This discovery led to the development of a number of similar nucleoside reverse transcriptase inhibitors (NRTIs). More recently they have been joined by protease inhibitors (PIs) and other drugs that interfere with the replication of the virus (Box 6.15).

Because the virus is capable of rapid mutation, the modern standard of care is a combination of three or four of these drugs (Highly Active Anti-Retroviral Therapy – HAART) to reduce the risk of resistance developing. The widespread introduction of HAART in 1995 transformed the lives of those in the developed world living with AIDS. Although not providing a cure for infected individuals, HAART can greatly reduce the viral load and allow a relatively productive life and better survival prospects.

**Box 6.15 Antiretroviral drugs**

The antiretroviral drugs that are used to treat HIV infected patients adopt various approaches to prevent the virus from replicating:

1. **Nucleoside reverse transcriptase inhibitors –** (NRTIs) target construction of viral DNA;
2. **Protease inhibitors –** (PIs) target viral assembly;
3. **Fusion inhibitors –** block HIV from fusing with a cell's membrane;
4. **Integrase inhibitors –** inhibit the integration of viral DNA into the DNA of the infected cell;
5. **Entry inhibitors –** block HIV from the host cell by binding the co-receptor that HIV normally uses for entry.

Initially HAART was prohibitively expensive for developing countries. However, due to increasing competition, the introduction of a growing number of generic products, new pricing policies from pharmaceutical companies and successful lobbying, the cost has dropped dramatically in the last decade. The most common first treatment for a patient (known as the first line treatment) is Lamivudine plus Stavudine plus Nevirapine. This cost about US$10,000 per patient per year in 2000, but by 2007 had dropped to US$92. Second line treatments, which are needed if resistance develops or if there are serious side effects, cost around US$1,200 per year.[102,103]

Thanks in part to the increasing affordability, access and coverage of ARV therapy has grown rapidly in low-income countries. There were nearly 4 million people receiving treatment in 2008, out of the estimated 1 billion in need. A large gap still exists, with millions of new infections occurring each year and an increasing number of patients requiring second line medicines.[43]

Although more than two dozen different products are now available for the treatment of HIV infection, there is a need for new drugs that:

1 Will combat multi-resistant forms of the virus;

2 Will reduce long-term toxicity;

3 Are easier to take;

4 Are less liable to induce resistance;

5 Are curatives.

***Preventing Mother to Child Transmission (pMTCT)***

One of the most effective uses of anti-retrovirals has been in the treatment of pregnant mothers for their own health and to prevent transmission of HIV to infants. More than 90% of the children living with HIV are infected through MTCT, which can take place during pregnancy, around the time of birth, or through breastfeeding. ARVs for both infected mothers and infants play a key role in reducing MTCT, along with the use of breast milk substitutes or caesarean section delivery when appropriate.

Women who have reached advanced stages of HIV disease will need a combination of ARVs for their own health. Infected pregnant women, who do not yet need treatment can also take a short

course of drugs to help protect the unborn baby. Finally, newborn babies will usually be given a course of treatment for the first days or weeks of life, to further lower the risk.[104] The WHO compiled a set of guidelines for ARV use for pregnant women and infants in 2006, listed in Box 6.16 below. They are currently in the process of reviewing these recommendations based on new experience and evidence, and an update is expected in early 2010.[105]

**Box 6.16 WHO guidelines for pMTCT drug regimens in resource-limited settings[106]**

| | Pregnancy | Labour | After birth: mother | After birth: infant |
|---|---|---|---|---|
| Recommended | Azidothymidine (AZT) after 28 weeks | Single dose nevirapine; AZT+ lamivudine (3TC) | AZT+3TC for seven days | Single dose nevirapine; AZT for seven days |
| Alternative (higher risk of drug resistance) | AZT after 28 weeks | Single dose nevirapine | – | Single dose nevirapine; AZT for seven days |
| Minimum (less effective) | – | Single dose nevirapine; AZT+3TC | AZT+3TC for seven days | Single dose nevirapine |
| Minimum (less effective and higher risk of drug resistance) | – | Single dose nevirapine | – | Single dose nevirapine |

Due to many attempts to scale-up efforts for pMTCT, from groups such as PEPFAR,[107] The Call to Action Project,[108] MTCT-Plus[109] and The Global Fund to Fight AIDS, Tuberculosis and Malaria, ARV use by pregnant women living with HIV in low and middle-income countries is now up to 45 %, up from 10 % in 2004.[43] In addition, experience has enabled health workers to better define the pros and cons of using a simple treatment like single dose nevirapine, versus more effective, yet more expensive and harder to administer combinations of two or three drugs. Since 2006, an increasing number of countries have moved towards combination therapy[43] but there is a clear need for a 'simple, safe and easy-to-use ARV regimen for pregnant women with HIV.'[106]

**The search for a microbicide**

The quest for an effective microbicide is in response to the demand by vulnerable women for protective technologies that are under their control. Microbicides, as the name implies, are chemical compounds that kill micro-organisms. But in the context of HIV a microbicide is '*a woman-controlled method applied before sex that could kill, neutralize or block HIV and other sexually transmitted infections.*' While many compounds attack HIV once it has spread through the body, a topical microbicide, applied as gel, cream, film, suppository or sponge, or contained in a vaginal ring that releases the active ingredient gradually, could be effective in blocking the entry and early multiplication of the virus. To date the concept has not been clinically proven (Box 6.17).

## Box 6.17 The great diversity of potential microbicides against HIV[75]

Several approaches to developing microbicides, underpinned by basic research, are being pursued (Figure 6.23).

**1. Entry inhibitors – that prevent attachment or entry of the virus**

**Polyanions –** electronically charged molecules that create an acid environment in the vagina, attracting HIV and preventing its attachment to a cell. (e.g. Carraguard, PRO2000, BufferGel).

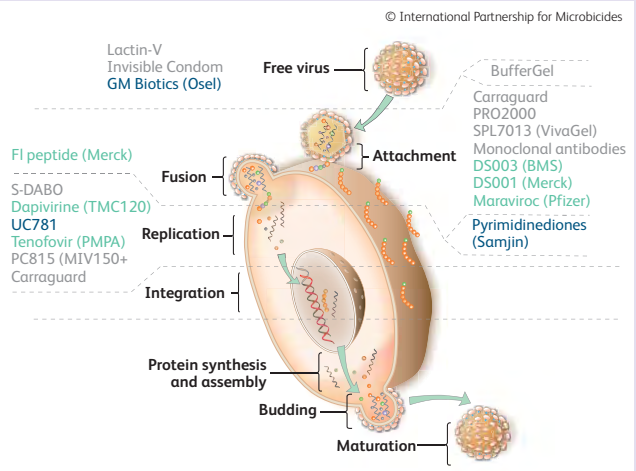



Figure 6.23 – Where the current microbicides in development are targeted.[75]

**Glycoprotein inhibitors –** that bind to gp120 and gp41 preventing attachment and fusion of HIV (e.g. DS003) to the cells.

**CCR5 blockers –** that block the host cell receptors so preventing the virus attaching (e.g. DS001, maraviroc).

**2. Reverse transcriptase inhibitors (RTI) –** that interfere with replication of the virus once it is inside the cell.

**Non-nucleoside reverse transcriptase inhibitors (NNRTIs) –** inhibit replication by binding to the enzyme reverse transcriptase; some may bind permanently. (e.g. dapavrine, MIV 150, UC 781)

**Nucleotide reverse transcriptase inhibitors (NtRTIs) –** once incorporated into the viral DNA they prevent it growing further (e.g. PMPA).

**3. Various combinations of the above.**

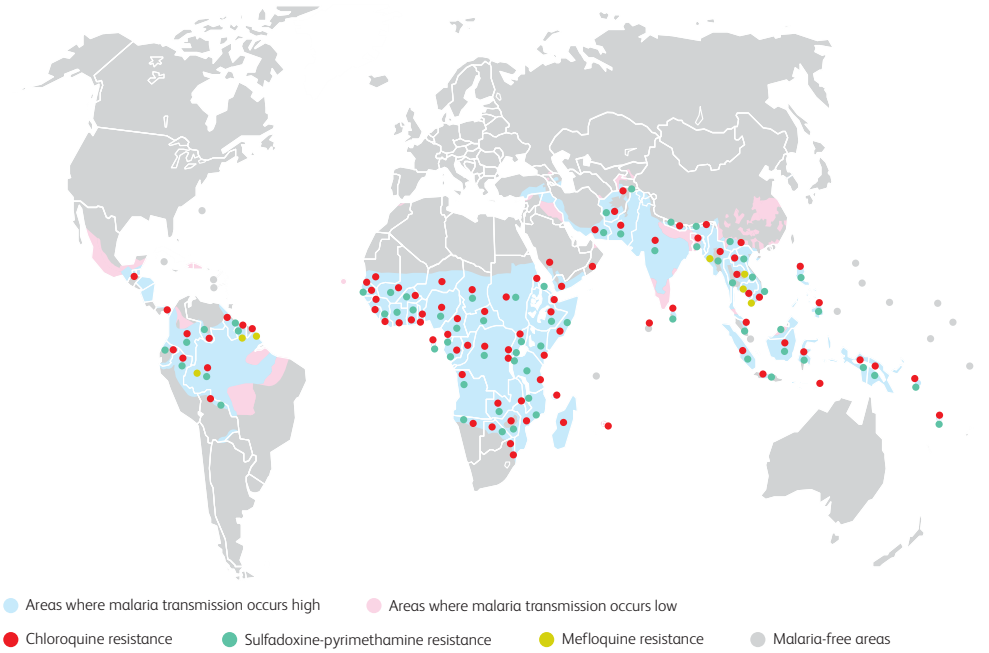
Most of the compounds in clinical trials are polyanions. Carraguard, made from a substance derived from seaweed, completed Phase III trials in 2008. The trials involving 6,000 sexually active South African women, demonstrated that the microbicide was safe and acceptable but did not reduce the risk of women acquiring HIV.[110,111] BufferGel and PRO2000 are currently in Phase III trials. Even although these compounds are not specific to HIV, they are still likely to provide a worthwhile level of protection. Early modelling has shown that even with 60 % effectiveness, if just 20 % of women in the 73 lowest income countries, with access to HIV prevention services, used a microbicide 50 % of the time that a condom is not used, it could avert some 2.5 million infections over 3 years.[112] The next generation of microbicides – those based on ARVs that are specifically designed to be active against HIV – as well as combination therapies, hold the promise of a greater level of protection. But they face the same challenges as the search for a successful vaccine.

**Artemisinin combination therapy against malaria**

Medicines that cure malaria not only reduce illness and save lives; they can greatly reduce the rate of transmission of the disease.

In the past, chloroquine and other drugs were cheap and highly effective treatments, but growing resistance has caused them to be abandoned in many parts of Africa and Asia (Figure 6.25). The timely discovery and development of artemisinin and its derivatives (see Box 2.6 in Chapter 2) promised a new era of effective treatment.

Figure 6.25 – Drug resistance to *P. Falciparum* from studies up to 2004[113]




The mode of action of artemisinin is not fully understood, but it appears to interfere with the cell metabolism of the malaria parasite.[114] It may be less prone to resistance but recognizing the history of resistance to drugs for treatment of malaria, the artemisinin derivatives are being administered in combination with other anti-malarial drugs. The WHO recommendations are:

Artemether + lumefantrine;
Artesunate + amodiaquine;
Artesunate + mefloquine;
Artesunate + sulfadoxine/pyrimethamine.

In the treatment of uncomplicated malaria, artemisinin combination therapies (ACTs) have proven 90% effective, with a recovery from malaria after three days, especially where the parasite is chloroquine-resistant. WHO recommends that a switch to ACT should be made in all countries where the malaria parasite has developed resistance to chloroquine. Artemisinin medicines have minimal adverse side effects.[113] However, they are costly (the most effective ACT treatment is US$2.40 – 10 to 15 times the cost of first line cures) and, because of the need to extract the

compounds from annual plants, they take a long time to produce.[115] One alternative being explored is to genetically engineer yeast to synthesize a precursor called artemisinic acid. The other is to develop a range of drugs to replace artemisinin and to cope with specific situations, namely for:

1. Intermittent preventative treatment (IPT) of women during pregnancy;
2. IPT of infants;
3. Single dose treatment in emergency situations;
4. Intravenous or intramuscular treatment of severe malaria.

At present some 19 drugs or drug combinations are under development through the Medicines for Malaria Venture public-private partnership.

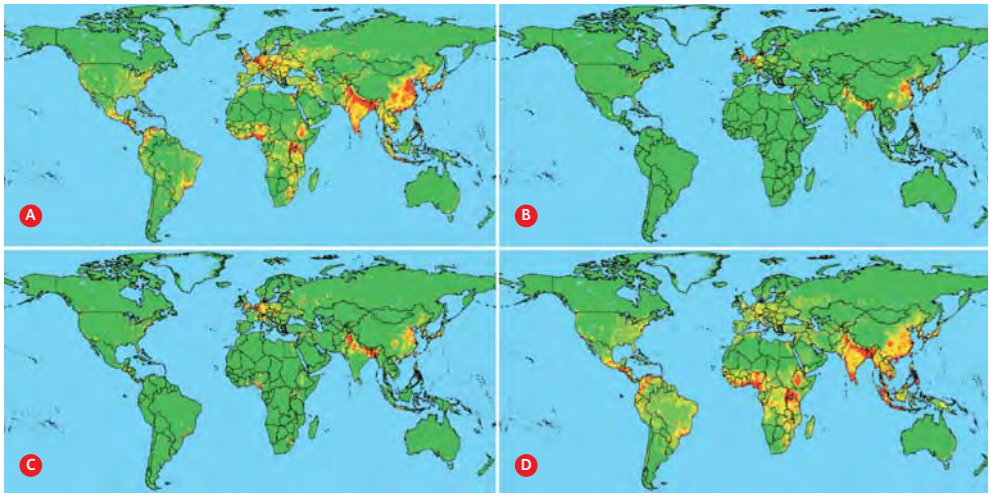
## 7. Emerging infectious diseases

Infectious diseases place an enormous burden on human health but in addition to this chronic burden, sudden outbreaks of new diseases can lead to national and global disasters that are especially devastating for developing countries.

The outbreaks may result from the emergence of a new form of disease, for instance through mutation of a less virulent strain into a more virulent one, or through a switch of a disease from a wild host species to human beings. Alternatively, outbreaks may arise from the movement of an existing disease to a new area where it did not previously occur.

New infectious diseases of these kinds appear regularly (Figure 6.26). In the past 25 years, 38 entirely new diseases have appeared in humans, about two every three years. Over 70 % of new and recently re-emerging diseases are of animal origin.[116]

**Figure 6.26** – Global distribution of the relative risk of emerging infectious diseases[117]




Maps are derived for emerging infectious disease events caused by: Green (lower values) to red (higher values).

A Zoonotic pathogens from wildlife B Zoonotic pathogens from non-wildlife C Drug-resistant pathogens D Vector-borne pathogens

Some of these have evolved from similar diseases in animals, for example HIV/AIDS. The human form of HIV was derived from a Simian Immunodeficiency Virus (SIV) carried by a subspecies of chimpanzee that lives in the forests of Southern Cameroon, Gabon and the Republic of Congo.[118] SIV in chimpanzees developed from successive cross-species transmission and recombinations in the monkeys on which chimpanzees prey.[119] The virus passed to humans sometime early in the 20th century, probably as a result of humans hunting, butchering and eating wild chimpanzees.[120,121] It remained at very low levels until the 1950s and 60s when it took on epidemic form, spreading from Africa around the world.

Other emerging diseases have simply shifted from animal hosts, such as SARS and some influenza viruses. Such diseases, caused by pathogens which infect both humans and animals, are termed zoonotic. Developing countries, where there is close contact between wildlife, livestock and humans, are particularly favourable environments for the emergence of new zoonoses.

**Influenza**

Perhaps the most recurrent of human disease outbreaks is influenza. The influenza virus probably has its origin in wild waterfowl but long ago moved to other animals, in particular swine and domestic poultry, and to humans. '*Epidemics occur in most countries in some years, and in some countries in most years.*'[122] There are also periodic pandemics, the most serious being the so-called 'Spanish' flu of 1918 at the end of World War I when some 50 million people died.

## Box 6.18 Influenza viruses

Only type A influenza viruses are capable of causing pandemics. The virus is distinguished by surface glycoprotein spikes on the viral envelope. The haemagglutinin (H) spike helps the virus attach to the host cell; the neuraminidase (N) spike facilitates the release of newly produced virus particles from the host cell.

Inside the virus are eight strands of RNA carrying a total of 11 genes that code for the glycoproteins and the other proteins that are involved in the replication, transcription and export of the virus.

There are 15 forms of the H spike (H1, H2, H3 etc) and nine of the N spike.[124]



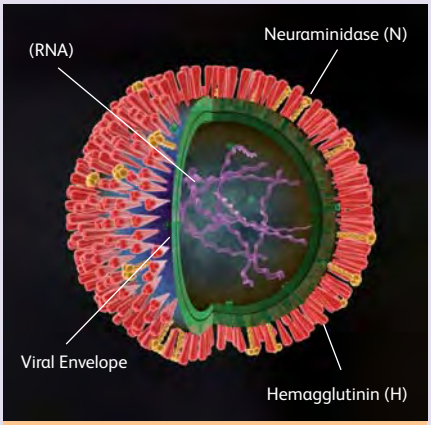



Figure 6.27 – Structure of Influenza virus[123]

H1N1 caused the 1918/19 pandemic and also caused the 2009 Swine flu pandemic;
H2N2 caused Asian flu in 1957;
H3N2 caused Hong Kong flu in 1968;
H5N1 causes the current Avian flu outbreaks which began in 1996.

Immunity to the virus is conferred by antibodies to the glycoprotein and other protein antigens. Viral RNA is subject to very high rates of mutation during replication, causing small changes in the hemagglutinin and neuraminidase antigens on the surface of the virus. This so-called antigenic drift eventually results in a new strain that overcomes much of the immunity.

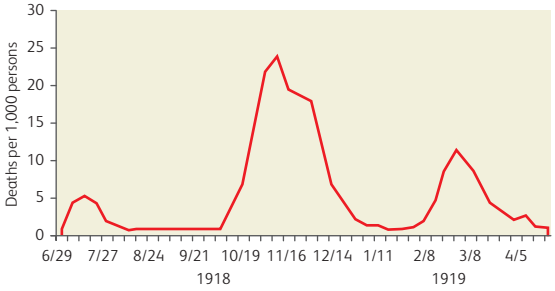
In addition, viral RNA may cross between different viral strains, for example between human and avian strains when both happen to occur in the cells of the same human, bird or pig host. This reassortment, also known as antigenic shift, can result in entirely new antigens (in this way H1N1 evolved into H3N2).[125] The immunity has to be recreated from scratch.

The form of the haemagglutin determines, in part, the ease of transmission between humans. Strains that are easily transmitted have hemagglutinin proteins that bind to receptors in the upper part of the respiratory tract, such as in the nose, throat and mouth. In contrast, strains such as avian flu (H5N1) bind to receptors that are mostly found deep in the lungs.[126]

### *The 1918-19 Spanish flu*

Despite its name this flu did not originate in Spain. There is some evidence that there may have been initial small outbreaks in army barracks in France and the UK in 1916. But the first 1918 outbreaks occurred in February and March in the US, in South Carolina, in Kansas and at St Quentin Prison in California. These were followed by three pandemic waves spread, primarily, by soldiers towards the end of World War I in their barracks and during sea voyages to Europe and beyond (Figures 6.28).[128]

Figure 6.28 – Three pandemic waves of the 1918-1919 influenza outbreak in the UK.[127]




About 50 % of the world's population was eventually infected, half suffering a clinical infection. Fifty million or so deaths occurred, mostly in the second and third waves. The devastating nature of the pandemic has been commentated on by many writers and observers. Isaac Starr, a third year medical student, volunteered to tend the sick in Philadelphia. He commented '*the pandemic ranks with the plague of Justinian and the Black Death as one of the three most destructive human epidemics*.' He and John Barry described in graphic detail the devastation wrought by the infections: '*deaths in the hospital exceeded 25% per night during the peak*.'[129]

Although the pandemic began in the US and travelled to Europe it soon affected Africa and Asia with equal devastation. In India 7 million deaths occurred and there were 1.5 to 2.0 million in Africa. The most extreme consequences were on the Pacific island of Samoa where a quarter of the population died.

After the pandemic ceased, the virus persisted in pigs and in humans causing annual epidemics until the 1950s.[130] With the appearance of a new H2N2 pandemic strain in 1957 ('Asian' flu), the direct H1N1 descendants disappeared from human circulation, although it continued in pigs. However H1N1 're-emerged' from a laboratory in 1977 and has continued to circulate in various forms, including a reassorted H3N2 virus lineage in both pigs and humans. Fortunately none of these, so far, have been as virulent as the 1918 parent. But this could change.

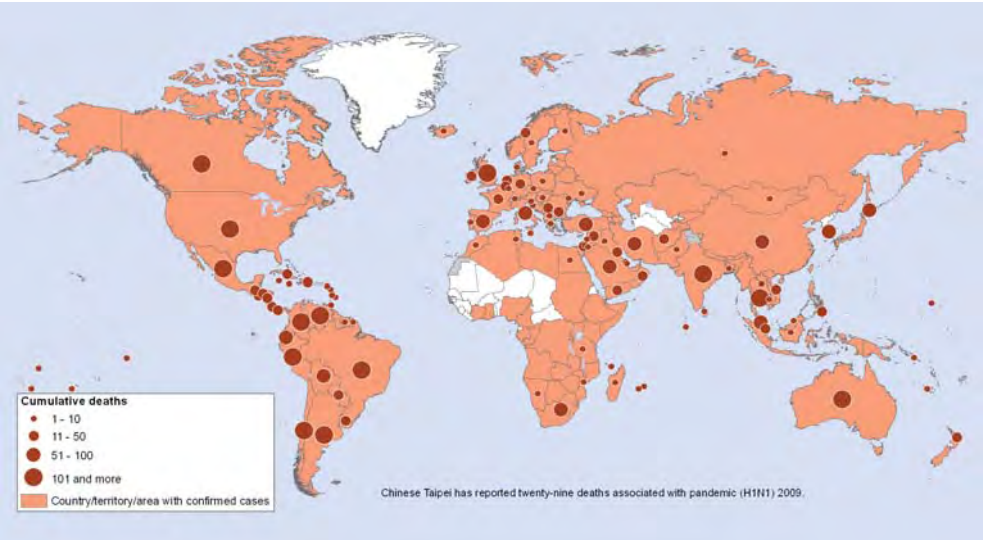
### *The 2009 Swine Flu Pandemic*

In 2009 a new lineage of H1N1 emerged, carrying genes from both bird and swine flu strains, as a result of reassortment (crossing) of North American and Eurasian H1N1 lineages.[124] Not only is it a descendant of the 1918 virus, but there is a worrying similarity in its initial progress.

The first reported case was in Veracruz, Mexico in mid-February 2009, although its origins may have been earlier either in Mexico or the US.

Subsequently it has spread rapidly round the globe driven by global human air travel and very rapid transmission among children in schools. At the time of writing it is in its second pandemic wave, occurring in 208 countries and overseas territories/communities with over 9,500 deaths (Figure 6.29).[131]

Figure 6.29 – Laboratory confirmed cases reported by WHO November 2009[131]




It had an appreciable mortality in the initial phases in Mexico. Most hard hit were the very young, the very old, and young adults as happened in the 1918 pandemic. Yet in its later phases it is, so far, relatively mild in its effects and the lethality is low.[132]

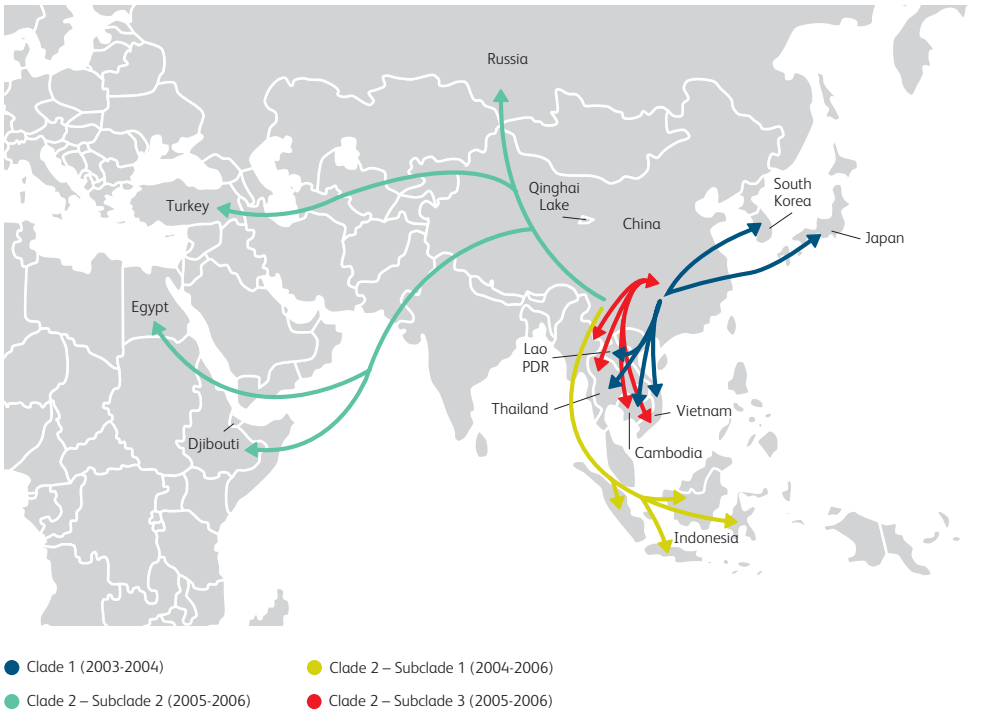
***Avian Flu***

Coincidentally, although originating some time before the swine flu outbreak, there was an outbreak of an A strain avian flu – H5N1 – that was, from the outset, highly virulent. Research into this flu stimulated a re-examination of the 1918 pandemic and served to uncover serious gaps in our knowledge of influenza viral processes and epidemiology. Moreover, the preparations made for a possible new pandemic of this strain have provided a good basis for dealing with the new threat posed by swine flu.

Avian flu was first detected in Guangdong Province, China, in 1996, when it killed some geese, but received little attention until it spread from poultry to humans in Hong Kong in 1997. Six out of 18 infected people died but the outbreak was quickly eliminated by culling all the poultry. Nevertheless, it continued to circulate among ducks in the coastal provinces of China.[133] Subsequently there have been several distinct waves of different forms (clades) of the H5N1 virus in the current outbreak (Figure 6.30).

Today, avian flu is endemic in poultry in various parts of Asia and Africa. What is somewhat surprising is the low transmissibility to humans. Although more than 230 million domestic birds had died or been killed by 2006, only 251 people had become ill. The receptor site for the virus is deep

**Figure 6.30** – Evolution of H5N1variants (clades and subclades) up until 2006.[134]




in the human respiratory tract and it seems that only a few people have these sites in the upper part of the tract. Nevertheless the human death rate is very high; by 2009, 424 human infections have resulted in 261 deaths.[135]

So far there have only been two incidences of apparent human to human transmission – in Thailand in 2004 and Indonesia in 2006. In neither case did it go beyond a single family. However, if the virus mutates to a form where transmission is more readily achieved the consequences could be very serious. Equally worrying is the possibility of H5N1 crossing with swine flu H1N1 so combining lethality with rapid transmission. This is most likely where poultry is widely infected – e.g. in China, Indonesia or Egypt. The viral crossing may occur tomorrow or several years from now (the form of the virus that gave rise to the 1918 pandemic was probably present as early as 1900).

***Influenza prevention and treatment***

Influenza is transmitted among humans through the air by coughs or sneezes that create aerosols containing the virus. Standard surgical facemasks may be effective if placed on infective people, but are unlikely to offer much protection to the uninfected. The virus can also be transmitted by other human secretions. Bird to human transmission often occurs through bird droppings. Sunlight, disinfectants and detergents inactivate the virus. Frequent hand washing is very effective and this is a key public health message.

Vaccination is a well proven preventative measure, but can be defeated by viral mutation and reassortment. Commonly, vaccines are produced by cultivating one or more strains in chicken eggs

and, after purification, killing them to produce an inactivated vaccine. Continued growing of the virus in the eggs can also produce a weakened live vaccine. Because these methods are logistically complicated and relatively time consuming, there is a growing effort to develop alternative vaccine methodologies.[134] These include genetically engineering vaccines that are universal for Influenza A and all its variants, either by targeting those viral proteins that do not mutate very much, or by stimulating 'killer' T cells. Vaccines effective against the current strain of H1N1, using conventional methods, are now (November 2009) available. Most industrialised countries have purchased stocks in advance, but it seems unlikely that there will be adequate supplies for the developing countries.

Vaccines have also been produced to protect poultry against H5N1. In some countries, for example Thailand, such vaccines are illegal, as they may affect the poultry trade but in China the policy is to vaccinate birds in an 8 km radius around the outbreak centre. One risk is that vaccination, which targets certain strains, may enable new more virulent strains to emerge. This may have been the reason for the rapid spread of the new subclade in 2006.[136]

Antivirals can also be effective for prevention and treatment. These target the neuraminidase spikes and reduce the release of the viruses from the host cells. Infected people then have a lower viral burden and are also less infective. Two of the commonly used drugs are oseltamivar (Tamiflu) and zanamivir (Relenza). A major downside of antiviral use is the high probability of developing resistance. Resistance in H5N1 to amantadines (which attack a different target) has occurred in humans in Vietnam, Thailand and Indonesia but there have also been a small number of cases resistant to oseltamivar.[137] H1N1 resistance to oseltamivar has already been reported in Denmark, Japan and Hong Kong.[138]

Mortality from swine flu is likely to be higher in those individuals who already have health conditions. This is evident from the recent mortality cases in the developed world. It is likely to be especially so in Africa and South Asia where many who become infected are likely to be also suffering from HIV/AIDS, malaria and TB. In the 1918 pandemic most influenza deaths resulted from bacterial pneumonia. There was then a lack of antibiotics. The situation is now very different, but it is crucial that sufficient supplies of antibiotics are available in developing countries as the swine flu pandemic progresses.

In summary it is clear that successful approaches to pandemics of both avian and swine flu must rely on a coordinated and multifactorial approach. Planning needs to be made well in advance and be based on a clear sense of priorities.

## 8. Non-communicable diseases

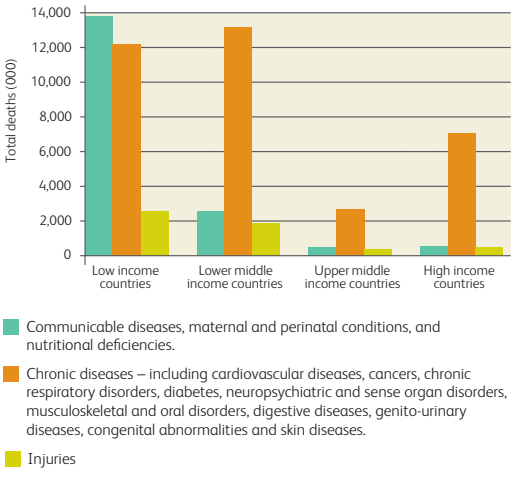
In addition to the burden of infectious diseases, there is a growing mortality from chronic non-communicable diseases (CNCDs) in the developing countries. 60 % of the world's mortality is caused by these diseases. The list includes: cardiovascular conditions (mainly heart diseases and strokes), some cancers, chronic respiratory conditions and type two diabetes. People of all ages, nationalities and classes are affected. Around 80 % of the deaths from chronic diseases occur in the low and middle income countries (Figure 6.31). '*The number of deaths from these diseases is double the number of deaths that result from a combination of infectious diseases (including HIV/AIDS, tuberculosis and malaria), maternal and perinatal conditions, and nutritional deficiencies ).*'[139]

Fortunately, we know the underlying risk factors for CNCDs. They include:

- An unhealthy diet;
- Lack of physical activity;
- The use of tobacco.

Moreover they are largely preventable. For example, up to 80% of premature deaths from heart disease, stroke and diabetes can be prevented with known behavioural and pharmaceutical interventions.[140] What is needed now is to: raise public awareness, enhance economic, legal and environmental policies, modify the risk factors, engage business and the community, mitigate health aspects of poverty and urbanisation and reorientate health systems.[139]

**Figure 6.31** – Projected deaths by major cause and World Bank income group, all ages, 2005[140]




## 9. Conclusion

As we concluded in Chapter 4, progress towards the health MDGs has been mixed. In some cases we have proven technologies and interventions and the challenge is largely one of implementation. In others the technologies are not yet available and progress will continue to be slow.

There are a good range of proven vaccines that can significantly help combat child mortality. They will not, of course, be sufficient on their own. There is still much to be done to improve drinking water quality and sanitation. Similarly the cause of maternal morbidity and mortality are well known as are the required interventions. But creating health systems that will deliver these interventions, where and when they are needed, is a formidable challenge.

The major scientific and technological challenges lie with the 'killer' infectious diseases. Malaria control has seen significant advances. The combination of insecticide treated nets, indoor residual spraying and artemisinin combination therapies are proven interventions which have been shown to work on a large scale. A vaccine, which appears to be just around the corner, could add significantly to this armoury.

The other major diseases – polio, TB, HIV/AIDS and influenza are much more problematic. The situation with polio is very worrying. Even though eradication is tantalisingly close there is a real danger of a breakdown of vaccine control, leading to resurgences which we know can spread globally in a matter of weeks. The current strategies need urgent rethinking. For TB, despite recent efforts, the prospects for improved treatments and vaccines are still disappointing. Even more worrying is the lack of a major step change in the hunt for vaccines and microbicides for HIV. The virus is a fiendish adversary, as trials of new products have revealed. An enormous amount has been learnt and the focus of innovation is now much clearer, but it will be some years before effective compounds are available. By contrast influenza is an easier target for vaccines, but the current pandemic has revealed the dangers of a lack of investment in research into emerging infectious diseases. There are other, as yet unknown, pandemics around the corner.

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