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Examining unmet needs in infectious disease

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In the past 30 years, more than 30 new aetiological agents of infectious disease have been identified. Some of these are responsible for entirely novel and life-threatening disorders, such as AIDS, Ebola fever, hantavirus pulmonary syndrome and Nipah virus encephalitis. During the same period, some longstanding infectious diseases (such as tuberculosis) have became resurgent, as a result of a combination of complacency, increased travel and social dislocation, and also increasing drug resistance. This review looks at some of the key unmet needs in this therapeutic area and discusses strategies to address them.

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▼ Thirty years ago infectious diseases were regarded as all but conquered; the successful eradication of smallpox and the control of infections such as tuberculosis (TB) and poliomyelitis had led to the complacent assumption that vaccination programmes and a regular supply of new antibiotics would reduce infectious diseases to a minor problem, even on a global scale. Isolation hospitals and sanatoria were closed down, and few training posts in infectious disease, considered a dying discipline, were available. In 1967, the Surgeon-General of the USA went on record stating 'We can close the book on infectious disease'. However, this situation has changed radically over the past quarter-century, for two main reasons:

- There has been an upsurge of 'new' (or at least newly-recognized) infectious disorders (see Table 1), including AIDS, a variety of viral haemorrhagic fevers, and several novel viral hepatitides and herpesvirus infections [1,2]. There is increasing awareness of the potential for novel or established infections of animals to cross the species barrier and affect man [3].
- Many 'old' infectious diseases, such as TB, have become resurgent owing to relaxation of control measures as a result of complacency, increasing resistance to antimicrobial agents, and social factors that include increased travel, social displacement and poverty. Some long-established infections have expanded to previously unaffected regions, for example, West Nile virus in North America. There is now some evidence that global climate change might be contributing to the spread of infectious disease [4]. The threat of bioterrorism has raised the spectre of new outbreaks of highly infectious and deadly diseases, such as smallpox, anthrax and plague [5].

In addition, there has been the recognition that we still possess inadequate prophylaxis or therapy for many common infectious disorders, including the common cold, influenza and hepatitis B and C viruses.

As a result of all these factors there is now heightened interest in (and increased funding for) basic and clinical research into infectious diseases and their management. Indeed, rather than 'closing the book on infectious disease' the question has recently been posed, 'Are all diseases infectious?' [6]. Included in this discussion article were the causative role of *Helicobacter pylori* in peptic ulcer disease, the association of *Chlamydia pneumoniae* with atherosclerosis [7], and the intriguing possibility that Borna disease virus (a pathogen of horses) has a role in human neuropsychiatric disorders [8]. Other suggested links include that of retroviral infection with schizophrenia [9], and of various organisms in the pathogenesis of autoimmune disorders; for example, Coxsackie B virus and insulin-dependent diabetes mellitus [10], and *Borrelia burgdorferi* and multiple sclerosis [11].

Strategies to meet the unfulfilled needs in infectious disease include:

- Development and validation of diagnostic tests and control measures for novel

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Table 1. Major new pathogens identified in the past 30 years

Year	Agent	Disease
1973	Rotaviruses	Infantile diarrhoea
1976	Ebola virus	Ebola fever
	Cryptosporidium parvum	Enterocolitis
1977	*Legionella pneumophila*	Legionnaire's disease
	Hepatitis D virus	Hepatitis D
	Hantaan virus	Haemorrhagic fever with renal syndrome
1982	*Borrelia burgdorferi*	Lyme disease
1983	HIV1, HIV2	AIDS
	Helicobacter pylori	Peptic ulcers
1989	Hepatitis C virus	Hepatitis C
1990	Hepatitis E virus	Hepatitis E
1993	Sin Nombre virus	Hantavirus pulmonary syndrome
1994	Human Herpes virus 8	Kaposi's sarcoma
1995	Hendravirus	Meningoencephalitis
1996	BSE prion	New variant CJD
1998	Nipah virus	Meningoencephalitis
2001	Metapneumovirus	Bronchiolitis

infections, with identification of targets for vaccine and drug development.

- Sociological interventions and improved local healthcare delivery, with proper case-finding and treatment programmes, for resurgent and inadequately controlled diseases.
- Measures to monitor the development of antimicrobial drug resistance and enhance prescriber education and patient compliance: the reduction of inappropriate antibiotic usage, for example in animal feeds.

Many of the major infectious diseases (e.g. TB, AIDS, hepatitis B, malaria) predominantly affect the poorer nations of the world, and the development of new vaccines and medicines might not be seen as commercially attractive by the pharmaceutical industry. Therefore, it might be necessary for national governments and global agencies to provide incentives for research and development in these areas [12].

Emerging infectious diseases – strategies for control

AIDS

The AIDS epidemic was first recognized in 1981 and the causative organism, HIV, was identified in 1984. It is now clear that HIV type 1 (HIV1) evolved with the *Pan troglodytes troglodytes* chimpanzee subspecies, and it is probable that sporadic transmission to man has occurred intermittently over the centuries before circumstances (including rural–urban migration, sexual promiscuity and increased intercontinental travel) set the scene for epidemic spread. The HIV2 subtype is also pathogenic for man, although it is less virulent, and shows a marked degree of homology with the simian immunodeficiency virus (SIV), which is endemic in sooty mangabeys [13].

This novel disease, which appeared to single out males and females in the prime of life, stimulated an unprecedented research effort that saw the first effective anti-HIV agent (zidovudine) being tested clinically within 6 months of publication of the sequence of the causative virus.

Unfortunately, as happened 35 years earlier when streptomycin monotherapy of TB led to the rapid development of resistance, zidovudine-resistant strains of HIV were soon isolated. Fortunately, many new anti-HIV agents were soon identified, including additional nucleoside inhibitors of viral reverse transcriptase, non-nucleoside reverse transcriptase inhibitors [14], and HIV1 protease inhibitors [15]. It was confirmed that combination chemotherapy with agents from at least two drug classes could reduce the emergence of drug resistance, suppress viral replication and delay the onset of overt disease, perhaps indefinitely [16]. However, at present it appears to be impossible to achieve viral eradication, suggesting that lifelong therapy could be necessary. Data presented recently showed that 78% of a sample of HIV-infected patients in the USA carried virus that was resistant to at least one current anti-HIV agent [17], and it has been shown that selection of anti-HIV therapy on the basis of genotypic-resistance testing could have a significant benefit on the therapeutic response [18].

Currently approved anti-HIV agents are all targeted at one of the two viral enzymes, reverse transcriptase or protease; novel agents under development are targeted at blocking viral entry to the cell (fusion inhibitors and inhibitors of the HIV co-receptor CCR5) [19], or inhibiting HIV integrase, the enzyme responsible for inserting the proviral DNA of HIV into the host cell chromosome [20]. Antiviral CD8+ T cells in chronic infection have impaired cytotoxicity, which can be restored *in vitro* by interleukin-2 (IL2) and other co-stimulatory signals [21]. Clinical trials of IL2 in HIV infected patients are ongoing. Concurrently, work is also in progress on the development of topical (vaginal) microbicides [22] and membrane-modifying agents [23], to try to reduce the risk of transmission.

Two interesting recent observations that could lead to new therapeutic approaches are: (1) HIV1 (and also Ebola

virus) make use of the human cellular protein Tsg101 to permit exit of virions from the cell [24]; and (2) for reasons as yet unexplained, co-infection with GB virus type C is associated with delayed progression of HIV disease and prolonged survival [25].

Clearly, lifelong therapy with multiple, expensive antiviral agents is impracticable as a control measure for HIV infection in most, if not all, of the developing world, where the greatest burden of diseases exists [26]. Although barrier methods have their place, the greatest hope for controlling the disease must lie in the development of an effective vaccine. Unfortunately, it has proved difficult to stimulate effective immunity to HIV. Current candidate vaccines elicit poor antibody responses. However, there is now some hope that the stimulation of an effective cellular (cytotoxic T-cell) response might control viral replication and this could lead to the development of an effective therapeutic vaccine [27].

Highly pathogenic RNA viruses – viral haemorrhagic fevers

This group of diseases consists of a variety of viral infections with rodent reservoirs, which can cause serious illness in man, particularly haemorrhagic fevers.

Lassa virus, the cause of Lassa fever, was first isolated in 1969. Lassa fever is endemic in West Africa but the incubation period can be as long as 21 days and occasional cases have occurred in travellers returning from endemic areas. Mortality from the disease is high, but is reduced by treatment with high-titre immune plasma, or with the broad-spectrum nucleoside antiviral ribavirin [28]. There is no vaccine available. Related South American arenaviruses (Junin, Machupo, Guanarito and Sabia viruses) are responsible for Argentine, Bolivian, Venezuelan and Brazilian haemorrhagic fevers, respectively [29].

Ebola virus, a filovirus, was first identified in 1976 during the course of two simultaneous outbreaks of highly deadly (53–88% mortality) haemorrhagic fever in Zaire and the Sudan. Subsequent outbreaks have occurred in Gabon and Uganda. A related virus (Marburg virus) also causes a lethal haemorrhagic fever (~80% mortality) in central Africa, and caused fatalities (from infected laboratory monkeys) in Germany in 1967. Both diseases are highly contagious. Interestingly, asymptomatic human carriers of Ebola virus have been identified [30]. There is no effective treatment for Ebola or Marburg virus infection, but some progress has been made towards developing an effective vaccine [31], and the recent finding that Ebola virus enters and exits host cells using lipid rafts on the cell membrane [32] could assist in the development of antiviral strategies. A calcium-dependent lectin (DC-SIGN) expressed on dendritic cells efficiently promotes the attachment of Ebola virus (and also HIV) to cell membranes, facilitating infection of susceptible cells; therefore, this could be a potential therapeutic target [33].

The hantaviruses (members of the family Bunyaviridae) are the causative agents of haemorrhagic fever with renal syndrome (HFRS) in Eurasia; this varies from a mild, endemic form in Scandinavia to a much more serious disease in the Far East. A novel hantavirus (Sin Nombre virus) has recently been identified as the cause of hantavirus pulmonary syndrome (HPS), a life-threatening condition first noted in the Southwestern USA in 1993, but subsequently found to be widespread throughout the Americas [34]. Intravenous ribavirin has been shown to be beneficial in HFRS in the Far East [35], but seems to be ineffective in HPS, although large doses of corticosteroids appear to be helpful [34]. A group from the US Army Medical Research Institute of Infectious Diseases (USAMRIID; http://www.usamriid.army.mil/) have recently announced the discovery of an animal model (Syrian hamster) of hantavirus disease [36], which might expedite the development of a vaccine or novel therapies.

Novel paramyxovirus infections

In 1994, a novel paramyxovirus (Hendra virus) was identified as the cause of two outbreaks of respiratory disease in horses, in Queensland, Australia. Three humans also developed infections, and two of the cases proved fatal. It seems likely that flying foxes (fruitbats) might have acted as the vector of transmission [37]. In 1998–1999 there was an outbreak of severe febrile encephalitis with a high mortality rate among pig farmers in Malaysia and Singapore. The causative virus (Nipah virus) was isolated and found to be closely related to Hendra virus, the two representing a unique genus within the family Paramyxoviridae. Antibodies to Nipah virus have been identified in local flying foxes, which probably form the natural disease reservoir [38]. Currently, no effective therapy for either disease has been identified.

New hepatitis viruses

Thirty years ago, two hepatotropic viral pathogens were recognized; Hepatitis A virus (HAV), which causes a usually benign acute hepatitis without residual sequelae, and Hepatitis B virus (HBV), which could cause chronic infection with an increased risk of progression to liver cirrhosis and cancer. It was appreciated that cases of hepatitis (commonly post-transfusion) occurred that were not caused by either virus, and these were designated 'Non-A, Non-B hepatitis'. The major cause of post-transfusion hepatitis was identified in 1989 as a flavivirus, and designated Hepatitis C virus (HCV). Subsequently D, E and G viruses

have been identified [39]. Hepatitis D, or the Delta virus, is unusual in that it requires the presence of HBV to establish an infection, when it can cause fulminant hepatitis and lead to aggressive chronic hepatitis. Hepatitis E virus is similar to HAV because it is spread by faecal–oral transmission and causes a self-limiting acute hepatitis; however, for reasons unknown, in pregnant women it causes a fulminant hepatitis with high mortality. Hepatitis G (HGV or GBVC) was identified in 1995–1996 by two separate groups from patients with hepatitis. It is prevalent (2–5% of the general population) and can be spread by blood transfusion and probably sexually; however, there is little evidence that it is actually pathogenic in man. Similarly, another virus (transfusion transmissible virus, TTV) has recently been identified but again there is no firm evidence that it has a pathogenic role. Thus, the major problems (and unmet needs) relate to HBV and HCV infection.

There are estimated to be up to 400 million HBV carriers worldwide. Effective vaccines were introduced in the early 1980s, which will eventually reduce the prevalence of infection [40]. However, treatment for those currently infected is less than adequate; interferon-α increases the conversion rate from high to low level viral replication from the spontaneous level of ~5% per year to 15–20%, but is associated with side effects at the dose necessary to achieve this. A nucleoside antiviral agent, lamivudine (a viral polymerase inhibitor), was introduced in 1999 and is a potent inhibitor of viral replication; however, resistance develops with prolonged treatment [41]. Fortunately, several other active agents are under investigation; one (adefovir, a nucleotide analogue) is awaiting approval. It has shown promising results in clinical trials and the development of resistance appears to be much lower. Combination therapies are under investigation [42].

Hepatitis C is thought to affect 170 million people worldwide. Like HBV, it commonly causes a chronic infection, with ongoing liver inflammation and an increased risk of cirrhosis and hepatocellular carcinoma [43]. It is spread almost exclusively by exposure to blood or untreated blood products (most commonly now associated with intravenous drug abuse and 'needle-sharing') but there is probably some inefficient sexual transmission [39]. Development of a vaccine against HCV is hampered by wide genetic and antigenic diversity between viral strains; HCV infection itself does not confer good immunity against re-infection [40]. Current therapy is inadequate; interferon-α monotherapy gives sustained response rates of ~25%, which can be increased using combination therapy with interferon and ribavirin. The use of pegylated interferon-α (which has a prolonged half-life) with ribavirin can increase the response rate above 50% [44]. Response to therapy is affected by the viral genotype, treatment being less effective in patients with genotype 1 (the most common strain in the USA). In patients who fail to respond to interferon monotherapy, retreatment combination therapy with ribavirin gives sustained responses of ~15% [45]. Basic research with HCV has been hampered in the past by an inability to achieve viral replication in *in vitro* systems and the lack of a usable animal models (chimpanzees appear to be the only susceptible animal); however, a cell culture system has now been reported, although it has so far failed to produce intact viral particles, and recently a mouse model has been described using immunodeficient animals transplanted with human hepatocytes [43]. Potential therapeutic targets (including the key replicative enzymes NS3 protease, NS3 helicase and NS5B polymerase) have been identified and work on candidate drugs is ongoing [46].

Newly recognized herpesvirus infections

In the past 15 years, three new herpesviruses (designated HHV6, 7 and 8) have been discovered [47]. HHV6 causes roseola in children and can cause a non-specific febrile illness and a glandular fever-like syndrome in adults. It is neurotopic, and has been associated with febrile seizures in infants; it has also been detected in the brains of multiple sclerosis patients. It is reactivated in immunosuppressed patients and is considered a potential pathogen.

Like HHV6, HHV 7 is ubiquitous, and can be isolated from the majority of healthy adults. It shows a considerable degree of homology with HHV6. No clear pathogenic role for it has been identified, although it has been associated with a similar spectrum of disorders to HHV6; however, this might be explained by the ability of HHV7 to reactivate HHV6 from latency.

HHV8 can be isolated from virtually all cases of Kaposi's sarcoma, whether HIV-related or not. It has also been found in body cavity lymphomas and in multicentric Castleman disease [47], and in biopsy samples from patients with sarcoidosis [48].

The role of iatrogenesis in the spread of infection

It is worth pointing out that several 'new' human infections have been generated, or disseminated, as a result of efforts to improve health. Infusion or injection of infected blood products (particularly those derived from pooled plasma) were responsible for the transmission of HIV and HCV, affecting the haemophilia community in particular. The risk of transfusion-related infection is now small, but there is still concern about the possibility of transmission of novel hepatotropic viruses, transmissible spongiform

encephalopathies [e.g. new variant Creutzfeldt Jakob disease (nvCJD)], and some bacteria and parasites [49]. The prevalence of HCV in Egypt is exceptionally high, ~25%, and this is probably a result of the use of reusable syringes and needles for injectable treatment of schistosomiasis before the introduction of oral therapy in the 1970s [50]. In 1961, it was discovered that some batches of the Salk parenteral polio vaccine were contaminated with a monkey virus (simian virus 40, or SV40) originating from the rhesus monkey kidney cells used to culture the poliovirus. The extent of this contamination is unknown although it is estimated that up to 30% of the batches could have been affected. Epidemiological surveillance of immunized cohorts was initially reassuring, but it has eventually become apparent that SV40 infection is linked to the occurrence of certain tumours, including childhood ependymomas and choroid plexus tumours, osteosarcomas, malignant mesotheliomas and non-Hodgkin lymphoma [51,52].

Resurgent infections

Tuberculosis

A vaccine against TB (admittedly of variable efficacy) has been available since 1921, and effective drugs and treatment regimens were developed during the 1950s. Nonetheless, the steady decline in incidence of the disease in the West was halted and to some extent reversed in the late 1980s/early 1990s, and in 1993 the World Health Organization (WHO; http://www.who.org) declared TB to be a global public emergency. The reasons for the resurgence of the disease are multifactorial, including failure to implement and monitor effective case-funding and treatment programmes, movement of immigrants and refugees, widespread development of drug resistance, and an increase in disease susceptibility resulting from the global HIV epidemic and (in the West) an ageing population. The HIV–TB relationship forms a vicious circle: HIV-induced depletion of CD4+ T cells increases the patient's susceptibility to TB, but concurrently TB stimulates HIV replication via induction of tumour necrosis factor-α and other cytokines [53].

The threat of multi-drug resistant (MDR) TB is enormous. The cost of treating an MDR TB patient with reserve drugs can be orders of magnitude higher than the cost of curing a patient with fully sensitive organisms [54]. However, the development of new anti-TB drugs virtually ceased for quarter-of-a-century with the last new specific anti-TB agent, rifampicin, being introduced nearly 40 years ago. There are several antibiotics originally developed for other indications, which have been shown to have potentially useful anti-TB properties: these include the fluoroquinolones ofloxacin, ciprofloxacin and moxifloxacin; amoxicillin plus clavulanic acid; and the oxazolidinones [55]. Joint ventures by national governments, global non-governmental organisations, and industry (such as the Global Fund to fight AIDS, TB and Malaria; http://www.globalfundatm.org) are beginning to promote basic and clinical research. Key objectives in anti-TB drug design are to develop more rapidly acting drugs to shorten the duration of chemotherapy, and to target dormant intracellular bacilli. Several new drug targets have been identified and most are involved with the synthesis or integrity of the mycobacterial cell wall [56]. One particularly interesting approach involves the use of a non-pathogenic mycobacterium to ferry a lytic bacteriophage into TB-infected macrophages [57]. Recent advances in our understanding of the immune response against TB, particularly the role of key cytokines such as interferon-γ and the importance of CD4+ and CD8+ T cells [58], provide rational strategies for developing and testing new candidate vaccines [59].

West Nile Virus

West Nile virus (WNV) is a flavivirus that causes an acute febrile syndrome, which can be complicated by meningoencephalitis and is associated with severe neurological disease in 1% of cases. Rare fatalities have occurred, usually in older patients. It is not a 'new' disease (the virus was identified in 1937) but is of interest because of its occurrence in North America for the first time in 1999; previously, its range had been confined to Africa, the Middles East, Western Asia, and occasional outbreaks in Southern and Central Europe [60]. During the 1999 outbreak a total of 62 cases were identified in New York City and the surrounding area. During the same period, large numbers of dead birds in the area were found to be infected (wild birds serve as the principal hosts of WNV, which is spread by mosquitoes). Subsequent surveillance has shown that the virus has become endemic in avian populations in the Eastern USA and Southern Canada. It is still not known how the virus reached N. America; an infected human could have travelled to the USA and infected a mosquito, an infected migratory or captive bird could have introduced the virus into the native mosquito population, or an infected mosquito could have been transported to the USA in an aeroplane [60]. The international trade in used car tyres is also a risk for transport of mosquito eggs or larvae [61]. There is currently no effective therapy for WNV (although the combination of ribavirin and interferon-α is efficacious *in vitro*) but recently a candidate vaccine has been produced by chimerization of WNV with dengue virus type 4, yielding a highly attenuated chimera with preserved immunogenicity [62].

Dengue fever

Dengue is caused by a mosquito-borne RNA virus of the Flaviviridae family. It is a familiar and common cause of fever in the tropics, which is unpleasant but rarely severe. Occasionally, a life-threatening haemorrhagic fever develops, more commonly after a secondary Dengue virus infection. The incidence, distribution and severity of Dengue have all increased dramatically in the past 60 years, as a result of population growth, urbanization, inadequate vector control measures and increased travel [63]. No specific treatment exists, although several potential vaccines are in clinical development [64].

Herpesviruses

Two relatively benign members of the herpesvirus family have become of greater pathogenic importance in immunosuppressed patients, particularly post-transplant patients on immunosuppressive therapy and late-stage HIV-infected subjects: these are cytomegalovirus (CMV), which usually causes asymptomatic infection or a 'glandular fever' syndrome, and herpes simplex viruses type 1 and 2 (HSV1 and HSV2), which are usually associated with 'cold-sores' and genital herpes. CMV can cause severe and potentially fatal disease, including pneumonia, in transplant patients, and in AIDS patients it is particularly associated with a progressive retinitis, which can lead to blindness. Prophylactic or pre-emptive treatment of transplant patients with the antiviral agent ganciclovir reduces the incidence of CMV disease; combination therapy of established disease with ganciclovir and immune globulin gives better survival than monotherapy with either agent. Nonetheless, infection continues to cause significant morbidity and mortality, and the treatment itself can be associated with severe side effects [65]. Acyclovir and its prodrug, valaciclovir, (which exhibits better oral bioavailability) cause fewer side effects but are less effective. The nucleotide analogue cidofovir is used in the treatment of CMV retinitis, but also causes severe side effects including nephrotoxicity. An interesting approach for CMV retinitis is the intravitreal injection of an antisense oligonucleotide, formivirsen, which inhibits antiviral synthesis; however, this agent can cause intra-ocular toxicity. A promising new therapeutic target is the viral terminase responsible for DNA cleavage and packaging into capsids. Inhibitors of one or other terminase subunit are attractive potential agents because mammalian DNA replication does not involve cleavage, hence such drugs should be safe and highly selective [66].

Acyclovir and its derivatives are active against HSV1 and HSV2 and are well tolerated but viral resistance develops after prolonged or repeated therapy. Once triphosphorylated these agents act by inhibiting viral DNA polymerase. Recently, a new generation of anti-HSV agents has been reported, which act by targeting the viral helicase–primase complex that generates the primers for DNA synthesis. Two new classes of drug that target this complex are orally active and show impressive anti-HSV activity in a mouse model [67].

Influenza

Until recently, the only agents available for the treatment of influenza were amantadine and its analogue rimantadine, which target the viral M_2 membrane protein and hence are only active against influenza A virus (influenza B lacks the M_2 protein). Recently, a new class of drugs has been introduced that inhibit the viral neuraminidase (sialidase), which facilitates release of new virions from the host cell. Two of these agents, zanamivir and oseltamivir, show modest efficacy in clinical practice against influenza A and B [68]. However, the influenza virus undergoes periodic major antigenic shifts, which can result in global pandemics of severe and potentially fatal disease, and currently it is not known if these agents would prove effective in this situation [69]. Much effort is going into the development of more effective vaccines, including cold-adapted live-virus vaccines and vaccines based on novel adjuvants and recombinant DNA techniques [70].

Potential bioterrorism agents

The Centers for Disease Control (CDC; http://www.cdc.gov) have recently updated their list of infectious agents that could potentially be used in acts of biowarfare or bioterrorism. These include smallpox, anthrax, plague and viral haemorrhagic fevers, such as Ebola. Although smallpox has been eradicated in the wild, it is feared that various 'rogue states' and terrorist groups could have obtained supplies of the virus. This is because routine vaccination was discontinued in the 1970s and so there is little residual herd immunity and, therefore, potential for a serious epidemic [5]. Thus, supplies of vaccine are being upgraded. Several compounds, including idoxuridine, fialuridine and methisazone, have shown activity against poxviruses [71], although only methisazone has been reported to confer some degree of clinical benefit in smallpox. Recently, the antiviral agent cidofovir has been shown to be a potent inhibitor of poxvirus replication *in vitro*, and alkoxyalky esters of cidofovir, which have enhanced oral bioavailability, have been synthesized, [71] and show potential for mass administration under epidemic circumstances. An accelerated programme to develop improved vaccines against anthrax is under way in the USA [72].

Antimicrobial resistance and the development of new antibiotics

Antimicrobial resistance is increasing and constitutes a global problem [73]. Resistance is a problem not only with antibacterial and antiviral agents but also with antifungals [74] and even with antiseptics and disinfectants [75]. The development of resistance is promoted by inappropriate prescribing and by lack of patient compliance, both of which can result in too low a dose being taken, for too short a duration. Prolonged monotherapy of chronic infections (e.g. TB, HIV) commonly leads to the emergence of resistant strains, which can be prevented or at least reduced by the use of combination chemotherapy. However, even with optimal treatment regimens resistance can eventually develop. Simplistically, antimicrobials will select for the growth of pre-existing but otherwise rare resistant organisms. In addition, most resistance genes are mobile and can be transmitted between organisms in several different ways [76]. Widespread use of antibiotics in animal feeds has almost certainly contributed to the dissemination of resistance. Resistance mechanisms include the production of drug-inactivating enzymes, modification of the drug target, acquisition of a target bypass mechanism, reduced cell permeability to the antimicrobial and enhanced drug removal from the cell (the 'efflux pump') [76].

Some examples, of clinical relevance include: the resistance of *Stapholococcus aureus* isolates to methicillin increased from nearly zero 15 years ago to 28% in the USA and 30% in the UK by 1998; MDR *Streptococcus pneumoniae* have increased from zero to over 50% in some countries; nearly 10% of *M. tuberculosis* isolates from previously untreated patients are resistant to one of the four main anti-TB drugs, and 0.2% are resistant to all four; among many parts of the world penicillin-resistant *N. gonorrhoeae* (the cause of gonorrhoea) is now endemic, and resistance to fluoroquinolones is increasing; there is increasing antibiotic resistance in common organisms causing gastrointestinal infections, including salmonella and shigella species [3,76]; and in parts of East Africa chloroquine is no longer used as first-line treatment for malaria, because of increasing resistance [77].

What can be done to combat this increasing problem?

Education of prescribers and patients is important. Banning the use of antibiotics as routine additives to animal feedstuffs has been reported to reduce the development of clinically important drug resistance [78]. Temporary or partial withdrawal of an antibiotic from clinical use could result in a decline in resistance because of removal of selective pressure, and there has recently been a call for worldwide adoption of antibiotic rotation schemes [79]. There is an ongoing search for agents that can be used to reverse acquired antibiotic resistance [80]. Finally, molecular strategies for the development of novel antimicrobials are being developed [81]. Novel agents in pre-clinical or clinical development include the ketolides, glycylcyclines, glycopeptides, oxazolidinones [82] and the streptogramins (an association of two chemically distinct compounds that act in synergy) [83].

Conclusion

In the past 30 years, more than 30 new causative infective agents of human disease have been identified [2]. Among others not discussed elsewhere in this review are *Legionella pneumophila* (the cause of Legionnaire's disease), Ehrlichia (tick-borne ehrlichioses), Parvovirus B19, Enterovirus 71, Campylobacter spp. (the cause of acute diarrhoeal diseases), *Borrelia burgdorferi* (the cause of Lyme disease), BSE prion (the cause of nvCJD), and metapneumovirus (a cause of infant bronchiolitis).

The only infectious disease ever to have been eradicated in the wild is smallpox. Poliomyelitis is now endemic in only 10 countries but eradication has not been attained [84]. Despite effective drugs and a vaccine, TB still infects one-third of the global population and more than 700,000 new leprosy patients were registered worldwide in 2000 [85]. An outbreak of cryptosporidiosis in Milwaukee (WI, USA) in 1993, affected more than 400,000 people [86] and malaria is still a major cause of mortality and morbidity in the developing world. Demographic and climatic changes have contributed to the spread of 'old' infectious diseases, and the emergence of new diseases: encroachment into the tropical rainforests has probably been responsible for the recognition and spread of HIV and several potentially lethal viral haemorrhagic fevers. Bioterrorism and biowarfare using existing or 'weaponized' organisms constitute a new threat.

However, it is not all gloom: the problems have been recognized and are being addressed. Development of new antibiotics is keeping us ahead (just) of the emergence of drug-resistant organisms and novel prophylactic and therapeutic [87] vaccines are under development. Nonetheless, the unfilled needs in this therapeutic area are still enormous.

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