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Introduction

The viral haemorrhagic fevers—often included in the wider category of emerging viruses—constantly surprise, both in terms of where they emerge and the sudden severity with which they may strike. Traditionally, viral haemorrhagic fevers were associated with severe human outbreaks that afflicted comparatively few individuals despite causing widespread alarm and the diversion of scarce public health resources. Marburg virus, for example, was first discovered in 1967 and nearly 40 years on the cumulative number of cases has yet to exceed a thousand. Otherwise viral haemorrhagic fevers remained the preserve of those infectious disease specialists with a particular interest in tropical diseases, rarely emerging into the consciousness of clinicians in North America and Europe apart from occasional imported cases. All this changed with the growing awareness that agents of viral haemorrhagic disease along with other geographically restricted agents of severe human disease were evolving into new ecological niches, particularly in periods of abnormal weather and climatic change. A perfect example is the hantaviruses. Although known for many years, interest in the prototype, Hantaan virus, was largely restricted to those with a somewhat esoteric interest in Korean haemorrhagic fever and occasional cases of nephropathia epidemica in Northern Europe, The Balkans and Scandinavia. Then in 1993, with the sudden emergence of an acute respiratory syndrome\(^1\) in the Four Corners region\(^2\) of the United States caused by what is now referred to as the Sin Nombre Virus, these agents were no longer obscure pathogens in the eyes of western clinicians, but major threats to public health. Mobilisation of resources and a refocusing of effort have shown hantaviruses as widespread throughout the Americas. A particularly severe strain was isolated from Argentina by scientists more familiar with identifying and treating Argentine haemorrhagic fever (AHF), a discovery almost certainly dependent upon the heightened awareness of emerging disease among the clinicians involved.

Interest in these agents has been heightened still further by concern among Western governments that at least some of these viruses have the potential to be used as agents of bioterrorism. Although an international consensus had been achieved in the 1960s as to the anathema of biological weapons and the threat they could pose to mankind outside of any theatre of war, we know that clandestine attempts to weaponise haemorrhagic fever viruses continued until the collapse of the Soviet Union. It is debatable whether such efforts continue in regions where political extremism abounds, but the eventuality is taken seriously by those responsible for securing societies from such threats. This in turn

\(^1\) Now known as Hantavirus pulmonary syndrome (HPS).
\(^2\) The region bordering the US states of New Mexico, Arizona, Colorado and Utah.
has meant an upsurge of interest in these viruses, with research and development into the causes and prevention of haemorrhagic fevers undergoing somewhat of a renaissance as part of the wider context of monitoring for abnormal disease patterns among societies of the economically developed world. This follows several decades where research into these viruses has been at low ebb. A cursory examination of papers listed in the National Library of Medicine PubMed database shows a steady increase in the volume of dengue research since the mid-1990s (Table 1), a reflection of the growing importance of this virus as a cause of morbidity in ever increasing number of countries, especially in Asia and the tropics. Despite the uplift in research on viral haemorrhagic fevers, the research capacity is still low as judged on research reported in the international literature. For example, despite the growing awareness of hantavirus infections as causing severe respiratory disease in the Americas, the number of papers is barely above 100 per year. This contrasts with, for example, around 780 papers per year on herpes simplex virus (Fig. 1).

Table 1
Viral haemorrhagic fevers: overview and global distribution

| Family      | Disease                      | Virus                          | Vector       | Distribution                        |
|-------------|-------------------------------|--------------------------------|--------------|-------------------------------------|
| Flaviviridae| Yellow fever                  | Yellow fever virus              | Mosquitoes   | Africa, Caribbean, South America    |
|             | Dengue                        | Dengue virus serotypes 1-4     | Mosquitoes   | Americas, Asia, Oceania             |
| Arenaviridae| Lassa fever                   | Lassa fever virus              | None         | West Africa                         |
|             | Argentine haemorrhagic fever | Junin virus                    | None         | Argentina                           |
|             | Bolivian haemorrhagic fever   | Machupio virus                 | None         | Bolivia                             |
|             | Venezuelan haemorrhagic fever | Guaranito virus                | None         | Venezuela                           |
|             | Brazilian haemorrhagic fever  | Sabia virus                    | None         | Brazil                              |
| Bunyaviridae| Rift Valley fever             | Rift Valley fever virus        | Mosquitoes   | East Africa, Arabian Peninsula      |
|             | Congo-Crimean haemorrhagic fever | Congo-Crimean haemorrhagic fever virus | Ticks | East Africa, Eastern Europe, Asia |
|             | Haemorrhagic fever with renal syndrome | Hantaan, Seoul | None | Asia |
|             | Nephropathia endemica         | Dobrava viruses, Puumala virus | None         | Eastern Europe, Scandinavia, former Soviet Union |
|             | Hantavirus pulmonary syndrome | Sin Nombre and Andes viruses   | None         | North and South America             |
| Filoviridae | Marburg disease               | Marburg                        | None         | Africa                              |
|             | Ebola                         | Ebola virus (Zaire, Sudan and Côte d'Ivoire variants) | None | Africa |
|             | Ebola haemorrhagic fever      |                               |              |                                     |
The causative agents of viral haemorrhagic fevers are distributed across four widely different RNA virus families (Table 1). These agents differ markedly in size, morphology, method of replication and interactions with the host. Yet all are capable of causing severe human disease manifested by a catastrophic failure of the vascular network and haematopoiesis. Interestingly, only a few viruses within each of these four families have such a capacity. Thus, there are several conundrums—what property or properties unite these virologically diverse agents to cause these similar clinical manifestations? And why do closely related viruses within the same family do not share the same propensity to cause severe clinical illness, if indeed they cause human disease at all?

What surely must be of concern is the all too likely scenario that other viruses with equal capacity to cause a serious outbreak of human disease may be misdiagnosed and thus go unrecognised in the critical early stages of an epidemic. Rapid air travel means that virus from a single index case can be spread in a matter of hours across three continents. The matter of laboratory diagnosis and confirmation of exotic infections have not been taken seriously by those responsible for public health and control. Development of new tests for early detection of viral haemorrhagic fevers and other emerging diseases is unfashionable with those administering peer review research funding and the commercial sector is reluctant to invest in developing assays for what it sees as a very restricted market opportunity in an era of increasingly heavy product regulation.

The burden of disease

The extent and scale of the prevalence, morbidity and mortality associated with viral haemorrhagic fevers are not well understood. Even in the developed world such assessments are often incomplete, and even when available often conflict with
the short-term aspirations of politicians lacking the vision to appreciate the benefits afforded in the longer term by the planning and support of public health programmes. The perception of the general public at large is that infectious diseases are preventable and something more akin to the social ills of times past rather than a menace that threatens a technologically advanced modern society. This mentality drives political policy to the extent that surveillance becomes starved of resources and in turn basic epidemiological information is at best unreliable and at worst lacking. It is against this backdrop of more needing to be done in terms of quantifying both the social and economic impact of these diseases especially in those countries where healthcare resources are scarce. WHO estimates that countries such as many small and impoverished nations in West Africa spend less than $20 per person on all aspects of medical care, a pitifully small sum considering the need for extensive childhood immunisation programmes and ignores the constant drain on resources presented by persisting disease. A case in point is Lassa fever, once thought to be a comparatively rare disease. Now recognised as surprisingly common in West Africa, McCormick et al. (1987a) have shown that Lassa fever is responsible for over 40% of all febrile adult admissions to hospitals in Sierra Leone and Liberia, and the most important cause of (medical) deaths in as many as 30%.

In the wider context of infectious disease research, infections that give rise to high morbidity and significant mortality in the developed world are priority candidates for public resources—the HIV epidemic is a clear example. In contrast, infections that are both rare and produce only mild illness and low mortality among the populations of the world’s richest countries fall at the opposite end of the spectrum as far as funding agencies are concerned. The direct costs of treatment and control, together with the indirect costs associated with morbidity and loss of productive life, are quantifiable with an output that can be directly compared between diseases, both infectious and non-infectious. There have been moves to re-assess the likely economic impact and presumed economic benefits to be gained as a result of preventing infectious diseases, most notably by the United States’ Institute of Medicine (Committee to Study Priorities for Vaccine Development, 2000). These studies show just how difficult it is to make the economic argument in support of disease prevention in developing countries where reliable estimates of direct and indirect costs are that much more difficult to obtain.

There is often a conflict between the priorities of international organisations such as the World Health Organisation and national needs. Globally, attention is often drawn to diseases that can spread easily, particularly by arthropods. Dengue fever is the prime example, representing as it does the most widespread of the viral haemorrhagic fevers, present on all major continents and affecting or threatening over 50 countries. In contrast, national and local health authorities may be more concerned with diseases of local importance, particularly zoonoses that are restricted to an animal reservoir limited in its distribution. Junin virus, the causative agent of AHF, is such an agent, being of considerable public health importance in Argentina but largely irrelevant elsewhere.

To an epidemiologist, it is the incidence of disease that determines its impact on a population, a parameter notoriously difficult to measure. Effective measurement of incidence requires good techniques for measuring antibody and virus detection, an infrastructure to ensure surveillance, and above all knowledgeable clinicians capable of
differentiating viral haemorrhagic fevers from other febrile illnesses. Considerable data exists for disease caused by dengue and hantaviruses in the more economically developed regions, but as with all measurements of disease incidence, the only certainty is that there is extensive under-reporting. The question is: by how much? The official annual incidence of yellow fever in Central and South America is less than 1000 cases per year, but this number almost exclusively represents those fatal cases identified and detected by viscerotomy. Given a case fatality rate of 20%, the actual number of clinical cases is most likely to be far greater, most probably nearer 20 times the reported incidence (Monath, 2001). Data collected from Africa suggests that the degree of under-reporting is substantial, with up to 250 cases occurring for each officially reported case. For these reasons there has, until recently, been a mistaken perception that yellow fever is a comparatively rare disease. There is now an awakening realisation of yellow fever as a significant cause of morbidity, especially in Africa and South America. Only in the last decade has yellow fever vaccine been incorporated into childhood immunisation programmes in any meaningful way.

The economic impact of disease burden is almost impossible to assess in many regions where viral haemorrhagic fevers occur, particularly in terms of wage loss and a reduction in productivity. The duration of any temporary disability and the impact of social norms regarding the care of sick relatives are also difficult to quantify in fiscal terms, but are likely to be significant among the poorer nations. In terms of impact, the haemorrhagic fevers are intermediate between the flavivirus encephalitides, such as Japanese encephalitis, and self-limiting febrile illness. Monath (1985) some years ago attempted to estimate the socio-economic burden of yellow fever in West Africa, using a comparative analysis of “days of healthy life” previously applied in Ghana. This West African country suffers yellow fever outbreaks at regular intervals. One such epidemic occurred between 1977 and 1980, characterised by an attack rate of 20 per 100,000 of population. Monath estimated the total burden to be roughly that of cholera, venereal diseases or trypanosomiasis. If the undoubtedly high level of under-reporting were taken into account, yellow fever would rank as one of the most important cause of disease in West Africa. Although this analysis is somewhat dated, it shows that the socio-economic cost of yellow fever in the developing world is considerable. These conclusions can easily be applied to other infections, for example dengue, the most widespread of all the viral haemorrhagic fevers. Indeed, Monath makes the point that the case fatality ratio of dengue approaches cholera and polio. Lassa fever is a further example as to the difficulties in estimating the total burden of infection. McCormick et al. (1987b) found a surprisingly high proportion of febrile admissions to hospitals in Sierra Leone associated with Lassa fever. In this setting, the cost of keeping a patient in hospital for a week exceeds four times the average salary.

Despite the overwhelming case for investing adequately in public health infrastructure, there is an extreme reluctance on the part of governments to recognise the long-term value of such investment. The problem is exacerbated by incomplete data resulting from poor surveillance, adding fuel to the politician’s argument that investment is not warranted owing to a lack of evidence. Political indifference in turn leads to a further decline in the very infrastructure needed to monitor infectious disease.
The changing environment

The environment in which we live is changing on an unprecedented scale. Approximately 25% of the Earth's rain forest has been cleared in the last 50 years, and greenhouse gases such as CO$_2$ have increased by 20% over the last two centuries. The net result of the greenhouse effect is to increase the surface temperature by around half a degree Celsius. This apparently trivial increase is an indicator of profound climatic change: global warming is linked with the melting of the polar caps and a continuous shift in weather patterns leading to sustained droughts and floods. Global warming is reshaping the environment and habitats of humans and wildlife. Mosquito vectors and rodent reservoirs are affected as a direct result of such swings in climatic conditions. Outbreaks of viral haemorrhagic fevers have been unequivocally associated with abnormal periods of drought, leading to unusually rapid increases in rodent numbers. This upsurge in turn increases considerably the risk of human exposure to the pathogens they carry and furthers the opportunity that viral genomes vary as the ecology of their hosts changes. This can lead to altered patterns of disease. To some extent, the emergence of viral diseases—particularly the viral haemorrhagic fevers—are warning signs that serious perturbations of our ecosystems are happening. It is sobering that there has been at least one new disease coming to our attention every year for the last decade (Table 2).

The relentless change inflicted by humans on habitats in the name of progress has had a marked effect on rodent habitats. Over the last 50 years, nearly a quarter of the world's forests have disappeared to make way for intensive agriculture, mining, roads and other artefacts of human existence. Murine species are more resistant and adaptable than most. Whilst other rodent genera have declined, murine rodents have expanded in population size, especially in peri-urban areas. This resilience is immediately evident by casual observation from the platforms of any subway system in a major capital city. What this means is that, although species diversity has become less with fewer genera represented, those remaining have thrived; in most instances these are murine rodents, the species most likely to harbour zoonoses.

Table 2

| Year | Virus               | Country          | Features                                      |
|------|---------------------|------------------|-----------------------------------------------|
| 1990 | Guanarito virus     | Venezuela        | Haemorrhagic disease, first thought to be dengue |
| 1993 | Sin Nombre virus    | USA              | Hantavirus Pulmonary Ssyndrome (HPS)          |
| 1994 | Sabia virus         | Brazil           | Laboratory infection                          |
|      | Alkhurma virus      | Saudi Arabia     | Outbreak in butchers                          |
| 1995 | Hendra virus        | Australia        | New paramyxovirus discovered in flying foxes  |
|      | Whitewater Arroyo virus | USA          | Severe human disease                          |
| 1996 | Andes virus         | Argentina        | New pathogenic hantavirus                     |
| 1997 | Nipah virus         | Malaysian peninsula | New paramyxovirus discovered in pigs         |
| 2002 | SARS coronavirus    | China, SE Asia  | Acute respiratory disease                     |
Of all the member species of the mammalian order Rodentia, it is members of the family Muridae that has been most successful and are to be found in almost all habitats. This family has species that are the natural hosts of almost all arenaviruses and hantaviruses. Importantly, these species are susceptible to climate and ecological change, resulting in variable population numbers. Rodents belonging to the family Muridae appear to have undergone most of their evolutionary history in the Old World, arriving in the New World comparatively recently via the Bering land isthmus some 20–30 million years ago. It is these more recent arrivals into South America that represent the reservoirs of arenaviruses and hantaviruses.

The influence of climate changes on wild rodent populations can be considerable. Fluctuations in population sizes occur in regular cycles, particularly in arid and semi-arid zones where small climate changes can bring about significant fluctuations in food quality and quantity. The extent of such variations is magnified when there are abnormal weather patterns. The most potent climatic driver of environmental change is the so-called “El Niño—Southern Oscillation (ENSO)” centred on an irregular pattern of atmospheric and oceanic current conditions along the Pacific seaboard of South America. These trigger aberrant weather patterns ranging from extreme arid periods to abnormal rainfall, the latter resulting in floods and explosive increases in arthropod and rodent populations. The sudden expansion in number of deer mice that immediately preceded the 1993 Four Corners emergence of HPS has been blamed on abnormal rainfall resulting from changes in the El Nino system. Thus, the risk of vector borne disease and zoonoses are exacerbated, often in areas where the medical infrastructure is fragile even in times of stability. The emergence of Machupo virus (Bolivian haemorrhagic fever) in the Beni region of North East Bolivia in the 1960s was linked to a sudden rise in the numbers of *Calomys callosus* that followed an abnormally dry period, this exacerbated by a drop in the number of feral cats as a result of the widespread use of DDT.

Those diseases requiring an arthropod vector for transmission between reservoir and humans can emerge suddenly after heavy rainfall, especially if transovarial transmission maintains the virus in the environment during dry periods. The relationship between a virus and its arthropod vector is more than just regarding the insect acting as a mechanical vehicle for transferring virus from one host to another. A well-established biological relationship evolves in a way that the vector plays a major role in the evolution of the virus and adaptation of the virus to a changing ecology. Present thinking is that viruses evolve to the point where there is a steady-state relationship between virus and vector, and virus and host. Any perturbation in the vector, host or genome thus would imbalance these equilibria, leading to the emergence or re-emergence of disease.

**The importance of surveillance**

The monitoring of infectious disease outbreaks normally rests with national authorities charged with assessing individual cases for cause, and compiling population-based epidemiological data. The move to centralise diagnostic facilities mitigates against sustaining a competence in recognising those unusual clinical cases that may herald an outbreak of something new and more dangerous than the normal run of febrile illness.
All experts in the control of infectious diseases agree that effective control requires the engagement of multidisciplinary teams spearheaded by alert clinicians. Experience from many outbreaks shows clearly the need for veterinarians, epidemiologists and ecologists to work in concert with microbiologists. This has been amply shown by the experience of agencies in the USA in controlling the West Nile incursion into North America in 1999. Failure to integrate these disciplines can have disastrous consequences.

The four cornerstones for controlling viral haemorrhagic fevers, and indeed any emerging disease, are:

1. **Alert clinicians with easy access to local laboratories and pathology services:** Training in infectious disease control has suffered in many regions over the last two decades, with continuing professional development often neglecting the more traditional approach of sharpening clinical skills backed by a sound knowledge of pathogen diagnosis, pathology and epidemiology. Rationalisation of laboratories in developed countries has continued unabated, with the result that all too often microbiologists at a local level are poorly equipped to recognise the first signs of disease outbreaks and react accordingly.

2. **Good serology provided by national reference laboratories:** Keeping stocks of characterised and standardised reagents is crucial. Almost all of the viral haemorrhagic fever outbreaks recorded in recent years have been diagnosed rapidly and accurately by antibody detection assays for which remain the most relevant of all the presently available methods. Although genome-specific assays employing PCR technology are increasingly used as soon as is practicable, such assays are fraught with difficulties relating to specificity and sensitivity. Sample collection is frequently not performed with the degree of rigour necessary to avoid the confusion that can result from sample contamination.

3. **Involvement of epidemiologists and communicable disease specialists at the earliest possible opportunity:** Increasingly sophisticated mathematical modelling of disease outbreaks brings insight into the transmissibility kinetics and offers time-saving pointers to effective containment and control. In the case of vector borne disease, the use of satellite images to detect climate-induced changes in vegetation patterns also enhances the accuracy of these models. If vaccines are available, the application of sound epidemiological principles is essential in order that an adequate level of herd immunity is attained as quickly as possible.

4. **The ability to deliver effective and prompt control measures:** Time and time again outbreaks of severe diseases such as Ebola and Lassa fever have been inflamed by inadequate control procedures and, when implemented, often too late in the day for effective containment. The outbreak of Ebola in the Sudan in 1996 was controlled largely by closing the hospitals at the centre of the outbreak combined with the meticulous tracking and isolation of contacts and family members. Recent experience with SARS has shown vividly how nosocomial outbreaks of disease may occur even in the best equipped and staffed hospital settings.
To the above could be added the necessity of engaging veterinarians, especially where zoonotic disease is suspected. The 1999 West Nile outbreak in the USA showed how valuable time can be lost when the first signs of disease incursion are seen in wild and domestic animals. Traditionally, there has been little effort to integrate human and veterinary public health, yet the principles and practice of disease control are broadly the same regardless of the target species. New pathogens have come to light almost annually since the early 1990s, many associated with domesticated species and livestock.

Although outside the brief of most microbiologists, the handling of the press and other media can take a heavy toll on those directly involved in controlling an outbreak. Specialists in media relations can be of considerable help, not only in controlling news flow but also in communicating to the public at large the degree of risk individual circumstances may present, and the tracing of potential contacts. News media are often badly informed as is graphically illustrated by the continued use by British tabloid journalists of the term Green Monkey Disease for filovirus infections; despite the fact that such monkeys are not known to be susceptible to either Ebola or Marburg viruses. Yet a fully informed and briefed press can play an important role in containing the spread of disease in the community. As with many aspects of science, there is a reluctance of microbiologists and medical personnel alike to engage the media. Experts in infectious disease control frequently lack the skills and motivation to ensure journalists understand the issues of the moment. Failure to do so invites the misinterpretation of events and ignores a vital channel of communicating essential information to the public at large. Media training as an essential element of infectious disease education is long overdue.

The use of the web has transformed communications between professionals and the public alike. Used responsibly, secure websites dedicated to the recording and dissemination of data can do much to alert clinicians, microbiologists and public health officials with responsibility for containing an outbreak. Health care professionals in the developing world frequently are in a position that, for them, access to the Internet is easier than obtaining printed journals and reports. To this end, the World Health Organisation, the Food and Agricultural Organisation, and Centers for Disease Control maintain excellent portals for accessing disease control protocols and information.

A further issue is the preparedness of government agencies to maintain isolation facilities and disease control capability in prolonged periods between outbreaks. Governments become lulled into a sense of false security and come reluctant to sustain expensive facilities. An example was the decision of the Victorian State Government in Australia to close the isolation facilities at the Fairfield Hospital in Melbourne, despite vigorous advice to the contrary from infectious disease experts worldwide. Just a few years later, new morbilliviruses were isolated in Queensland that could have easily presented a new public health threat to much of Australia. Governments are traditionally myopic as to the true costs of disease. For example, WHO estimates that the actual cost of the BSE crisis in the UK to exceed around $32 billion.
Viral haemorrhagic fevers at a glance

All of the viral haemorrhagic fevers possess certain common features (Table 3). With the exception of hantavirus infections, clinical disease correlates with the period of virus circulation in the blood. This has implications both for diagnosis and for the handling of samples as well as for the isolation of infected individuals. All begin with an insidious acute febrile phase. Patients present with myalgia and malaise, progressing to prostration. The challenge for the attending physician is distinguishing the early stages of viral haemorrhagic fevers from the onset of other, invariably more common, causes of febrile illness such as influenza and malaria. Individuals themselves may delay seeking medical attention thus increasing the risk of spread to family and close contacts, as occurred during the outbreak of Ebola haemorrhagic fever in the Sudan in 1977. It is only towards the end of the 3–4 day acute phase that signs of any vascular disturbance become apparent.

Vascular permeability due to damage of the vascular endothelium is accompanied by a precipitate drop in platelet count and often a marked reduction in leucocytes. A thrombocytopenia is particularly indicative of viral haemorrhagic fever. The disease process is poorly understood although we are now beginning to understand more concerning the interactions between viral proteins and the cells they infect. Vascular endothelium is particularly susceptible to a surge in chemokine and cytokine levels triggered by virus replication. Most viral haemorrhagic fevers are directly cytolitic for the cells they infect, leading to rapid loss of organ function. The exceptions are the hantaviruses and dengue where the immune response plays a major role in the pathological process. In general, viral haemorrhagic fevers are multi-organ diseases and pantropic in their effects.

It is critical that a presumptive diagnosis is arrived at as early as possible. Thus, a complete patient history is essential to aid the differential diagnosis from other causes of febrile illness (Table 4). An accurate travel history recording countries visited and whether the patient has visited rural areas. Vaccination status for yellow fever needs to be checked in the traveller who has returned from South or Central America, or West Africa.

Table 3

| Similarities and differences among the viral haemorrhagic fevers |
|---------------------------------------------------------------|
| **Similarities**                                        | **Differences**                                             |
| Virology                                                 |                                                            |
| Enveloped viruses                                        | Virion structure                                             |
| Small single stranded RNA genomes                        | Distinct mechanisms of gene expression and replication       |
|                                                            | Inhibition by ribavirin                                      |
| Epidemiology                                             | Vectors and animal hosts                                     |
| Aerosol infectivity                                      | Geographical distribution                                   |
| Persist in the environment                               |                                                            |
| Pathology                                                | Pathogenesis                                                 |
| Causes vascular dysfunction                              | Host immune responses                                        |
| Sensitivity to interferon                                | Cytopathic effects on mammalian cells                        |
Table 4
Factors to be considered in the early stages of diagnosis

| Clinical history: factors to be considered |
|------------------------------------------|
| Travel to tropical/endemic areas? If so, time of arrival and departure |
| Has the patient visited sick relatives, family or friends whilst away? |
| Did the visit include excursions into rural areas? |
| Has there been a known exposure to ticks, wild animals or rodents? |
| Has the patient been vaccinated against yellow fever? |

Detailed information on current outbreaks can be found on many national and international websites (see Appendix 1 for further details). Travellers restricting their visits to major cities are unlikely to encounter the pathogens described in this book, most of which are essentially confined to rural areas. The exception is those who visit family and friends in hospitals within endemic areas: as many viral haemorrhagic fever outbreaks have been associated with inadequate isolation of infected patients, the true nature of the infection having escaped recognition on admission.

Patients with a history of contact with wild animals and peridomestic rodents are particularly at risk. Those with evidence of tick bite could have been exposed to agents such as Congo-Crimean haemorrhagic fever or Omsk haemorrhagic fever. Unfortunately exposure to mosquitoes is so common to make the patient recounting of mosquito bites unhelpful, although the season of travel is relevant as many of the viral haemorrhagic fevers cause epidemics during or immediately after heavy rainfall.

The recording of arrival and departure dates is important to establish the likelihood of a patient being within the incubation period of a particular infection. Patients presenting more than 3 weeks after returning from an endemic area are most unlikely to have contracted a viral haemorrhagic fever and other causes should be suspected. Even an individual having visited a rural area and presenting with an acute febrile illness within a few days of return may not necessarily be incubating a viral haemorrhagic fever if they have spent some time within a major city before their return flight. Many patients have not received prompt attention for malaria owing to delays in preparing and examining a blood smear.

The rapid adoption of rigorous barrier nursing procedures coupled with the handling of clinical specimens under containment conditions can do much to alleviate the heightened risks that are present before a definitive diagnosis is made. Viral haemorrhagic fevers are extremely dangerous and, wherever there is doubt, immediate advice should be sought from national and international authorities.

Scope of the book

Each of the following chapters contains self-contained descriptions of the major causes of viral haemorrhagic fevers, grouped according to families. The properties of each virus are outlined in relation to epidemiology, clinical presentation and treatment. Each is
preceded by an overview of the molecular properties and replication. This is a rapidly expanding area, however, thus the virology of each infection is presented more in a manner intended to provide the reader with an overview prior to delving more fully into the original references. Where appropriate, a brief historical backdrop can be found as many early pioneers in this field have done much to inform and shape our present thinking as to how best these infections can be controlled and treated.

The final chapter attempts to place the viral haemorrhagic fevers in the broader context of infectious disease control and prevention. In particular, the potential threat from the use of these viruses as agents of terror is commented upon with some suggestions as to how best this threat may be countered. The emphasis throughout is to develop an understanding as to the nature of this rather disparate collection of human pathogens, through an integrated approach of clinical diagnosis, pathology, epidemiology and virology.

The number of references has been kept to a minimum in order to ease the reader through the chapters as ready access to web-based literature databases now permits more exhaustive literature reviews than can possibly be presented in a single monograph. A guide to obtaining further information on the worldwide web is given in Appendix 1. Appendix 2 summarises various sources of further reading, including more populist works that have been written for the general public, many of which contain useful sources of information for the specialist and thus should not be ignored. Finally Appendix 3 offers a brief description as to the different containment levels as applied to laboratories and associated facilities.