The Threat from Emerging Virus Infections: Today and Tomorrow

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47.1 Introduction

The title may have changed, but the situation is fundamentally the same as it was in 1960, as shown by the quotation above. Emerging viral infections continue to infect humans, some threaten human life today, but what about in the future? (Fig. 47.1).

47.2 Upper Respiratory Tract Infections

By its very nature as the passage by which air can enter the body, the upper respiratory tract is exposed to all manner of pathogens as well as polluting agents. Acute upper respiratory tract infection (URTI) refers to a transmissible infection of the upper respiratory tract, consisting of the nose, nasopharynx, pharynx, hypopharynx and larynx, and is a universal experience, despite decades of research.

The range of pathogens covers many viruses and bacteria. The common cold, caused by multiple different viruses, is the most familiar acute infective disorder affecting the upper airway, although other infections can also produce sinusitis, pharyngitis, epiglottitis and tracheobronchitis [2, 3].
Viruses

The term “virus” derives from Latin, where it refers to a poison [4]. It describes an infective agent, too small to be visible on light microscopy, able to multiply only within the living cells of a host. A virus typically consists of a nucleic acid molecule (DNA or RNA) in a protein coat. It is estimated that the biosphere contains $10^{31}$ viruses and for every single human cell, 100 viruses exist [5]. It has been known for around a century that they exist [6], with the first documented references to viruses occurring in the very late 1800s. Viruses themselves are thought to have existed as long as there has been life on the planet [7, 8].

Viruses are the pathogens responsible for many acute infective episodes. They can affect virtually all organ systems and are frequently noted clinically. Up to 1939, a mere 36 distinct viruses had been noted and separated on immunological grounds, of which 22 could be cultured routinely in laboratories [1]. During the 1940s, a further 26 viruses responsible for human diseases were categorised on serological grounds. Then, in the 1950s, major advances were achieved in instrumentation and other novel techniques, which permitted a further 90 plus viruses to be added to the list of known pathogens. At present, the laboratory detection of viruses has developed to the point where diagnostic tests are highly sensitive and virology is no longer the preserve of academic research [1].

Epidemiology

In both men and women, irrespective of age, acute respiratory infections are the most prevalent of all diseases. Epidemiological and community-focused research conducted since the early 1900s have ascertained the frequency of these diseases and identified the pathogens responsible. It has been demonstrated that by far the...
most common pathogen causing respiratory infections and asthma exacerbations is rhinoviruses. The transmissibility has also been investigated. Recent developments in diagnostic methods have meant that the viral pathogens responsible for respiratory infections can be more precisely identified, with benefits in tailoring antiviral therapy to suit the type of infection [3].

47.5 Aetiology and Pathogenesis

The group of bacteria known to be responsible for upper respiratory tract infections is well-established, and, despite the wide variety of organisms that can infect the sinuses and tonsils, currently all known bacterial pathogens have a degree of sensitivity to existing antimicrobial agents. The same cannot, unfortunately, be said of viruses. Since researchers first became aware of their existence, viruses have been studied intensively. Yet much remains obscure about this class of pathogen, even to the extent of deciding how they evolved and whether they should be classified as living or nonliving. This general ignorance about many aspects of viruses is reflected in the clinical challenges faced when attempting to treat and manage viral infections [9].

47.6 Clinical Characteristics

Whilst there are numerous viruses which can cause infection, the clinical presentation of URTIs tends to be broadly similar for a range of pathogens. More severe symptoms are experienced when viral pneumonia occurs.

47.6.1 Nasal Discharge and Stuffiness

Virtually all upper respiratory viral infections initially present with nasal discharge and stuffiness. Initially the nasal discharge is clear. It may subsequently gain a purulent character with the involvement of bacteria. Nasal stuffiness may accompany nasal hypersecretion as a result of swelling of the conchae. The new coronavirus SARS-CoV-2 can cause a range of effects, the major ones being cough and fever, rather than URT symptoms. However early anosmia has been reported by some patients.

47.6.2 Sneezing

Irritation of the nasal mucosal lining provokes sneezing, a protective reflex that serves to expel pathogens from the nasal cavity. Despite its actually beneficial nature, sneezing is a frequent patient complaint.
47.6.3 Pyrexia

Viral infections can provoke an increase in body temperature that ranges from mild to severe. In the past, it was assumed that a severe elevation in body temperature was indicative of bacterial pathogenic involvement, but it now appears that viruses have evolved which are capable of provoking severe pyrexia, and this sign therefore no longer reliably indicates a bacterial origin to a fever. Pyrexia associated with influenza ranges in temperature from 37.8 °C (100 °F) to a maximum of 40 °C (104 °F). Parents of young children are often extremely alarmed by a marked temperature increase, but children often experience a greater degree of temperature elevation than adults. Pyrexia is also associated with a subjective sensation of feverishness, which may comprise chills, sweating or the sensation of being cold in spite of actual body temperature rises. Pyrexial duration is typically less than 7 days, with the majority of episodes persisting for 3 or 4 days.

47.6.4 Cough

A dry, persistent cough may accompany upper respiratory infections. Some upper respiratory virus infections also involve the lungs. The cough may worsen, becoming uncomfortable and painful. Patients may also experience shortness of breath or chest discomfort during this time. The usual duration of an influenza-related cough is approximately 2 weeks.

47.6.5 Headache

A severe headache may herald the onset of a viral URTI. On occasion, ocular or auditory symptoms, such as photophobia or phonophobia, may accompany the headache.

47.6.6 Muscular Ache

Muscular ache is a frequent occurrence, particularly the neck, back and limbs. The pain is frequently of sufficient severity to render movement distressing, even routine basic activities. Lethargy and apathy are extremely frequent symptoms in URTI but are also common in other conditions, too. Malaise is common to multiple conditions, including URTI. These symptoms may have a very rapid onset and can prove challenging to manage.

47.6.7 Diarrhoea and Vomiting

Although it is not especially characteristic of respiratory viral infections, diarrhoea and vomiting have also been reported amongst non-respiratory symptoms of coronavirus (COVID-19) infections in China.
47.6.8 Hyposmia and Anosmia

Loss of the sense of smell can follow a viral cold and is sometimes permanent. Anosmia has been reported as an early symptom of COVID-19, with inflammation confined to the olfactory area seen in a CT scan from one Chinese patient. This needs confirmation.

47.7 Diagnosis

The majority of patients suffering from a URTI are aware of the cause and do not seek medical care other than visiting a pharmacy. They are generally looking for symptomatic relief, rather than a diagnosis. If a physician is consulted, the majority of URTIs can be identified from an appropriate patient account and by routine otorhinolaryngological physical examination. The pharynx may be swabbed to identify a bacterial pathogen. Group A β-haemolytic streptococci may be identified using rapid antigen detection techniques. If URTI increases in severity, it may presage pneumonia or bronchitis, in which case radiological confirmation by plain x-ray or CT may be required.

47.7.1 Detection of Virus

Accurate diagnosis of infections of coronavirus disease 2019 (COVID-19), Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV) is of paramount importance in mapping outbreaks and for efficient measures to prevent further spread. Given the current lack of efficacious pharmacotherapy for coronavirus infection, diagnostic confirmatory tests are of limited use in clinical management, other than randomised trials of therapy.

Techniques which can swiftly and accurately detect all of the recognised strains of coronavirus in humans have only recently become available. Such methods include reverse-transcriptase polymerase chain reaction (RT-PCR) and immunofluorescence antigen detection assays [10, 11].

Since the polymerase technique is capable of identifying each of the four coronavirus variants found in humans, it has now mainly replaced other ways of detecting the presence of the virus. There are PCR primers available suitable for all types of coronavirus, but they lack the specificity of primers tailored for each individual quasi-species [11–13]. The method is more sensitive when used in a real-time fashion [14]. Tissue culture is challenging for viruses of the wild type found in the community.
47.8 Treatment

The management of severe viral RTIs is currently focused on preservation of respiration and alleviation of life-threatening conditions such as renal failure, myocarditis and disseminated intravascular coagulation.

For URTIs nasal decongestants make it easier to breathe. Headaches are treated with pain killers. Paracetamol and the NSAIDs are effective in reducing pyrexia and myalgia. It is recommended to inhale steam and gargle with salt water. Antitussives and expectorants may be required in particular cases.

For certain serious URTIs, antiviral medication is indicated as these agents can mitigate the symptoms and lessen the duration of illness. However, there are numerous causative pathogens involved, few of which are affected by currently available antiviral drugs. The search for effective therapy demands rapidly organised controlled trials.

47.9 Prevention

47.9.1 What Can Be Done to Prevent Acute Upper Respiratory Infections?

Regular use of intranasal saline reduced the frequency of URTIs in an open study by Tano and Tano [15]. Sixty-nine recruits found daily physiological saline significantly ($p = 0.027$) reduced the number of days with nasal secretion and/or blocked nose (mean 6.4 days) compared to the observation period (mean 11 days). Furthermore, the participants had a mean of 0.7 episodes of upper respiratory tract infection during the spray period, compared with 1.0 episodes during the observation period ($p = 0.05$).

Professor Ron Eccles, former director of the Common Cold Centre in Cardiff, advocates keeping the nose warm with a protective scarf in cold weather to prevent nasal drying which reduces mucociliary clearance. There is a nasal spray (Vicks First Defence) that claims to prevent colds, reducing the chance of a full-blown cold by up to 50% if taken at the first sign of symptoms and cutting symptom severity by 40%. The treatment, which is not a drug, works by trapping the virus in a viscous gel, disarming it and allowing eradication by mucociliary clearance.

For COVID-19 washing hands regularly with soap and water has the greatest protective effect as it removes the lipids in the outer wall of the coronavirus [16–18]. Some other ways to reduce transmission are:

- Avoidance of contact with sick individuals [19]. Persons caring for them need adequate protective equipment.
- Social distancing, since asymptomatic individuals can transmit the infection.
- Use of wipes on objects that may be touched by more than one person, including the infected individual. Such objects may include remote control devices, telephones and door handles. Wearing disposable gloves can help.
- The affected individual should cover his or her mouth and nose.
47.9.2 Recent Measures to Prevent 2019-nCoV (See Also Sect. 47.9.3)

Recently, the strategy to contain COVID-19 has involved case detection and identifying the contact network, as well as screening individuals travelling between different countries, particularly those coming from areas where outbreaks have occurred. Whilst these actions have proven insufficient to stop COVID-19 becoming a pandemic, the aims are to:

1. Lessen the rate at which transmission occurs.
2. Allow a longer period for people in general, and healthcare personnel in particular, to be prepared for the disease burden from the disease affecting very large numbers of people.
3. Allow a fuller appreciation of the nature of 2019-nCoV on which to base public health strategy and clinical response, namely, detection methods, possible drug treatments and vaccination [17].

47.9.3 Coronavirus 2019

Coronaviruses (CoV) consist of numerous viruses capable of producing a variety of diseases, from coryza to conditions of greater severity such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV). A novel coronavirus (nCoV) refers to a previously unknown virus type capable of infecting human beings. Coronavirus infections are zoonoses, in other words, diseases which pass from an animal to a human. Intensive research has uncovered the transmission from civet cats of SARS-CoV and of MERS-CoV from dromedary camels. There exist a number of coronavirus strains which currently infect animals but have not yet been transmitted to human beings [18].

47.10 What May Happen in the Near Future During an Outbreak?

During an outbreak, cases generally increase on a daily basis. If it is possible, human-to-human transmission becomes the dominant mode of viral transmission. This places a high burden on medical facilities, which experience a surge in demand. Schools, daycare facilities, workplaces and other settings in which people collect together may be less crowded than usual or may need to be closed for some time, together with other places such as nonessential shops, restaurants, theatres, cinemas, churches and mosques, i.e. anywhere people congregate. The public healthcare infrastructure may be overstretched, if admissions to hospital and fatalities increase beyond a certain level. This may also produce a detrimental effect on other public services, e.g. the police, accident and emergency and public transport systems. Collapse of such services is a potential risk, as is collapse of the economy. In the case of COVID-19, the lack of suitable
pharmacotherapy and a vaccine mean that management needs to rely on nondrug interventions [19].

47.11 What Is the Longer-Term Outlook for Emerging Viral Infections?

Disturbances within ecosystems that have led to the emergence of novel human pathogens within the last decades seem set to persist for the foreseeable future. Such disturbances include deforestation to increase available agricultural land, more intensive cattle farming, globalisation, the sale of bush meat and the continued growth of cities. On that basis, it seems probable that novel pathogens will keep emerging as these trends continue [20].

A review of every novel pathogen identified from 1980 onwards reveals patterns in the type of pathogen involved. There are four features anticipated to be present in most newly emergent infections:

- Viral pathogens are likely to be RNA-based, as the majority have been so far.
- The majority are zoonoses, with animal (especially mammalian) reservoirs.
- Viruses will usually already infect a variety of different animal hosts before becoming transmissible to humans.
- The virus should be at least partially capable of human-to-human transmission, even if initially this transmission is not very efficient. As the virus evolves and the pattern of human exposure changes, a limited number of cases may become an epidemic [20, 21].

These four characteristics are broad general trends, but there are historical examples that appear to buck the trend, such as the apparently sudden emergence of syphilis in Europe in the late 1400s. It is still not certain where the pathogen originated, but it is known to be a bacterium without an animal reservoir of infection. Despite such counterexamples, the four characteristics still have use as a general indicator of the type of novel pathogen to expect in the future [20, 21].

47.12 Surveillance

Swiftly detecting cases and identifying the pathogen is the vital first step in containing emergent infections. The experience gained in the BSE (bovine spongiform encephalopathy) and SARS crises has provided valuable real-world insights into how swift detection and case confirmation can be used to put prophylactic measures in place in a timely fashion [22, 23]. Virtual modelling of potential pandemic influenza appears to show that unless detection is very rapid and prophylactic measures are adopted without delay, stopping the spread of an epidemic becomes less and less likely [24].
Nonetheless, obtaining a clear overview of emergent infections is not without difficulty. In the first instance, surveillance will probably rely on reported observations made by clinicians, e.g. a case series with atypical features in common. It is also feasible to use the Internet to collate reports of novel pathological features. In the more distant future, diagnostic equipment capable of detecting all recognised human viral pathogens should be in use. An example is the so-called lab-on-a-chip [25].

As it is clearly indicated, emergent pathogens arise right across the globe, and spread in an age of ever-increasing international travel and cross-border trade is likely to be global. This was the case with the SARS epidemic. The emergence of viral pathogens is a global problem calling for a global response.

47.13 Multidisciplinary Aspects

Looking at the catalogue of emergent viral infections so far, we can perceive the fundamental significance of animal reservoirs. A corollary of this is that monitoring of the reservoir of infection in animals helps guide risk management in human beings [26]. A novel pathogenic agent in humans is likely to be better known initially to veterinary science [27]. Some examples of this zoonotic basis include neoplasia linked to infection, retroviral and lentiviral infections, transmissible spongiform encephalopathies, rotaviruses and papillomaviruses, with the potential addition of coronaviruses and ehrlichiosis. It is becoming increasingly accepted that pathogens in humans are mostly identical with those found in other animal species [28].

Schwabe argued in 1969 that veterinary and human medicine should be seen as “one medicine”, a theory that resonates powerfully with virology researchers who have an interest in emerging pathogens.

Whilst the biological science underlying the host-pathogen interaction in humans and emerging pathogens is undoubtedly central to an appreciation of the phenomenon of disease emergence, the concept of ecological disturbance plays an equally important part. Ecological refers to a wide variety of elements that can drive disease emergence, in particular, environmental alteration, changes in agriculture, arthropod vectors (including insects), human population changes, specific behaviours, culture, the economy and sociological factors. To give some specific examples, one might note the role of bush meat trading in fostering HIV and SARS, agricultural feeding practices in BSE and vCJD (variant Creutzfeldt-Jakob disease) and different methods in pig raising, which inadvertently promoted Nipah virus. What these examples reveal is that many academic disciplines can contribute to knowledge of novel pathogens and explanations need to be multilayered. Researchers will need to build working relationships with colleagues both veterinary and medical, as well as in a broad spread of academic departments.
47.14 Conclusions

Understanding previous outbreaks is the only way we can predict what may happen in the future. Studying the four levels which comprise the pathogen pyramid helps to guide thinking about how epidemics by new pathogens can occur. It needs to be admitted, however, that the individual levels are themselves often incompletely understood.

The bottom layer of the pyramid concerns exposure, an area in which current knowledge is particularly deficient. The full range of potential pathogens is largely unknown, but systematically evaluating each environment where exposure can occur, particularly to mammalian zoonoses, is one way forward. Shotgun sequencing may be of value here.

Then there is the problem of working out in advance which pathogens possess the ability to cross the species barrier. At present, receptors by which they can enter human cells have been identified in only 50% of the 189 known human viral pathogens. Discovering the receptor for all cases will assist the predictive process.

The pyramid’s third level relates to transmissibility between humans, and the efficacy of this process is only knowable by detailed evaluation of the earliest outbreaks. These evaluations may provide vital clues as to the population most at risk. Analysing the figures on affected individuals as they become available gives an indication of how transmissible the pathogen has become. Such data are frequently lacking for pathogens which rarely infect humans, and it may be unknown whether human-to-human transmission occurs. Viral mutation may also alter the transmission potential.

The probability of novel pathogens emerging in the near future is close to 1. The scientific and logistical resources need to be in place to manage such outbreaks as and when they occur.

The experience of SARS, H1N1 influenza and Ebola to date gives some grounds for a cautious optimism about our ability to contain outbreaks. However, much remains to be done to ensure the current COVID-19 pandemic does not kill as many as the Spanish influenza one of a century earlier. Surely we have learnt enough in the interim to improve our performance?

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