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The global burden of bacterial and viral zoonotic infections

L. Christou

Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece

Abstract

Bacterial and viral zoonotic infections comprise a practically endless, ever-expanding list of pathogens that have the potential to induce human disease of varying severity, with varying means of transmission to humans (including vector-borne and foodborne agents) and of varying epidemiology. Not all theoretically zoonotic pathogens are truly zoonotic in practice, the prime example being influenza viruses; aviann H5N1 influenza remains strictly zoonotic, whereas novel H1N1 influenza displays an anthropocentric cycle that led to a pandemic, despite being of zoonotic origin. The burden of disease induced by zoonotic and viral pathogens is enormous: there are more than ten bacterial zoonoses, each of which affects hundreds of thousands patients annually, often leading to chronic infections and causing significant economic losses of a medical and livestock-related nature. Viral zoonotic agents are constantly emerging or re-emerging, and are associated with outbreaks of limited or expanded geographical spread: the typical trends of viral zoonotic infections, however, is to extend their ecological horizon, sometimes in an unexpected but successful manner, as in the case of West Nile virus, and in other instances less effectively, as was the case, fortunately, in the case of avian influenza. The majority of bacterial and viral zoonotic infections attract disproportionately low scientific and public health interest. Understanding their burden may allow for improved surveillance and prevention measures.

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Corresponding author: L. Christou, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, 45110, Greece
E-mail: lchristu@cc.uoi.gr

Introduction

Zoonotic infections are defined as infections that can be transmitted between vertebrate animals and humans, with either human or the animal as the recipient, either through direct contact, or as foodborne infections, or via intermediate vectors such as ticks and mosquitoes [1]. Infections transmitted from animals to humans are of concern regarding clinical medicine, although diseases transmitted from humans to animals may raise concern about species conservation, as in the case of measles and influenza affecting primates (chimpanzees and mountain gorillas) through human contact [2].

Zoonoses affecting humans can originate in domestic animals or in wildlife; the latter are becoming an increasingly important reservoir for human disease, as recognized in susceptible human groups, including hunters, adventurous tourists camping in forests or cave explorers.

A detailed evaluation of all human pathogens a few years ago demonstrated that the majority of infectious species affecting humans are of a zoonotic nature [3]: of the 1415 species recorded as pathogenic for humans in 2001, 868 (a staggering 61%) could be characterized as zoonotic. Furthermore, the zoonotic nature of a pathogen has been unanimously considered to be an independent factor that increases its potential for emergence or re-emergence: Emergence refers to the appearance of a newly recognized or newly evolved pathogen or the appearance of a known pathogen in a geographical area where it has never been recognized before. Re-emergence similarly refers to known pathogens whose incidence in a given geographical area (ranging from a county to the world in the case of pandemics) is significantly increasing or whose ecology is newly altered, enhancing its potential to cause human disease (e.g. by using novel hosts, jumping from wild animals to domestic ones, exhibiting a wider vector range, and so on) [4]. As the vast majority of novel species pathogenic for humans recognized since 2001 are also of a zoonotic nature, including SARS coronavirus and novel H1N1 influenza virus (pandemic influenza of swine origin), one can presume that the spectrum of human infection attributed to animals is continuing to evolve and remains understudied with regard to its actual burden: The world of infectious diseases is currently dominated by multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* (both technically zoonotic pathogens), or *Acinetobacter* species and novel pan-resistant strains: research and scientific publications are largely targeted towards such pathogens. The world of humanitarian relief and global public health campaigns is dominated by the big three, AIDS, tuberculosis, and malaria. Although the first is strictly a zoonotic infection, jumping species to humans from simians, and although the latter two are, at least in a minority of cases, depending on the species implicated, also zoonotic, it is not their zoonotic nature that has moved these infections to the centre of the Millenium Development Goals, for example [5]. Overshadowed by these scientific and public health targets, millions of people worldwide are susceptible to a wide array of bacterial, viral, parasitic and fungal zoonotic infections that cause millions of new annual cases, exhibit a considerate mortality toll, are often followed by debilitating chronic sequelae, and are directly correlated with a significant burden in terms of veterinary medicine, agriculture, livestock production, and regional and national economies. Zoonoses have been disproportionately neglected until recently, remaining the 'other diseases' of the Millenium Development Goals. Interest in the impact of certain of these neglected diseases, most of them zoonotic, has been slowly resurfacing [6] in terms of science and research funding, but many other zoonoses remain the true neglected 'neglected diseases'.

It is surprising that, apart from the 2001 effort by Taylor *et al.* [3] cited above, there are scarce efforts to actually list the existing zoonotic diseases and evaluate their global effect in terms of actual disease and its socio-economic correlations, particularly as almost all recent outbreaks, pandemic threats, and the single 21st-century pandemic, have been of zoonotic origin.

The present review focuses specifically on outlining in detail the extensive range of zoonotic pathogens affecting humans, and describing their burden in terms of morbidity and mortality, and, where available information exists, the impact of these pathogens on socio-economic parameters, and their dynamics regarding emergence or re-emergence.

Bacterial Zoonoses

The clinically significant bacterial zoonotic pathogens are shown in Table 1, in alphabetical order. Numerous other bacteria can be classified as zoonotic: the reader can refer to the appendix of the review by Taylor *et al.* [3] for a listing of other bacteria. Bacteria that cause a minimal clinical burden of human disease, in terms of cases recorded or geographical extent, have not been included. It should be noted that a zoonotic potential exists for numerous other major pathogens, including *Enterococcus* sp. and *P. aeruginosa*, and also for less frequent ones, such as *Morganella morganii*. However, the vertebrate animal reservoirs of these pathogens, as well as their animal-related life cycles, are of minimal significance for the burden and evolution of human disease, at least at present; this is why such pathogens are not included in Table 1.

Viral Zoonoses

Table 2 shows viral zoonotic infections of clinical significance to humans: this is an ever-expanding list, in terms of both pathogens included and importance, as recent years have shown, with the emergence of novel pathogens of zoonotic origin such as SARS coronavirus and novel H1N1 influenza virus. However, the significance of the diseases caused by both of these viruses was related to their capacity for person-to-person transmission, and not their zoonotic nature, in contrast to, for example, the transmission of avian H5N1 influenza virus, for which animal contact is necessary. Neither of these new diseases would have emerged from the context of zoonotic infection and species jumping from animals to humans. In a historical context, the same could be said about human immunodeficiency virus. Person-to-person transmission is essential for dengue outbreaks and sustaining dengue virus in nature, with animals playing a minor role in this cycle; thus, dengue is not considered to be an essential zoonosis. In order for Table 2 to be more concise, viral pathogens that induce a minimal burden of human disease (in terms of cases recorded or geographical extent), e.g. eastern/western equine and St Louis encephalitis (roughly ten annual cases in the USA each), are not included. The same is true for viral pathogens that have been documented only occasionally in the past as pathogenic for humans.

As shown in Tables 1 and 2, a wide array of pathogens are emerging or re-emerging, and more agents are being introduced into non-endemic areas through the expansion of international travel, in terms of both human travel and global trade. As is also easily seen in Tables 1 and 2, millions of annual cases of human disease are directly attributable to bacterial and viral agents with direct zoonotic correlations. The need for an interdisciplinary approach that extends beyond medical and veterinary specialists cannot be stressed strongly enough. Understanding the enormous economic burden of these diseases might assist international and regional decision-makers in fully evaluating the huge effect of bacterial and viral zoonoses. The implementation of surveillance and prevention measures for these zoonotic infections might

TABLE 1. Clinically significant bacterial zoonoses

Pathogen	Comments
Anaplasma phagocytophilum	Human granulocytic anaplasmosis has been increasing and expanding its incidence: recently recognized in Canada; an ongoing outbreak is reported from China [7]. Exceeding 1000 cases annually in the USA, as of 2008 [8]
Bacillus anthracis	The, fortunately, only case of emergence caused by deliberate release
Bartonella sp.	There are 22 000 new annual cases of cat scratch disease reported annually in the USA [9]; *Bartonellahenselae* and *Bartonella clarridgeiae* implicated. *B. henselae*, *Bartonella elizabethae* and *Bartonella grahamii* are causes of zoonotic endocarditis [10]. *Bartonella vinsonii* and *Bartonella alsatica* are also zoonotic. The spectrum of agents is likely to expand as novel species are recognized
Borrelia sp.	*Borrelia burgdorferi* ecology has resulted in the re-emergence of Lyme disease in the USA: 28 921 confirmed cases were reported in 2008 [8]. All other borreliae are zoonotic, excluding *Borrelia recurrentis*
Brucella sp.	*Brucella melitensis*, *Brucella abortus*, *Brucella canis*, *Brucella suis*, *Brucella pinnipedialis* and *Brucella ceti* cause human disease. It is estimated that there are more than 500 000 new cases annually [11], excluding chronic cases. Repeated outbreaks in former Communist republics of Central Asia, and emergence in Balkan states, previously brucellosis-free. Experimental documentation of *Brucella microti* zoonotic potential. Unknown zoonotic origin of novel non-characterized strains [12]
Burkholderia mallei and *Burkholderia pseudomallei*	The former causes glanders, a typical but very rare zoonosis. Melioidosis annual incidence in northeast Thailand exceeds 12 cases/10^5 [13], with significant mortality. Historical zoonotic outbreak in a Paris zoo in 1973 [14]
Campylobacter sp.	*Campylobacter jejuni* is possibly the commonest zoonotic foodborne pathogen worldwide; almost 200 000 cases are recorded anually in the European Union (EU) [15]. *Campylobacter fetus*, *Campylobacter coli*, *Campylobacter hyointestinalis*, *Campylobacter lari* and *Campylo bacter upsaliensis* are also zoonotic
Capnocytophaga canimorsus and *Capnocytophaga cynodegmi*	Dog-bite related; splenectomy and alcoholism may predispose—a recent review in The Netherlands detected more than ten annual cases [16]
Chlamydophyla psittaci	There are 10–20 cases of psittacosis documented annually by the CDC [8]. Micro-outbreaks are irregularly reported, predominantly from Australia, but also in Japan and The Netherlands
Clostridium sp.	Can be considered to be zoonotic foodborne diseases, although the zoonotic aspect is of limited significance [17]. *Clostridium botulinum* infection is not typically zoonotic, even when foodborne
Corynebacterium ulcerans	*Corynebacterium ulcerans* is increasingly recognized as an important factor in possible diphtheria re-emergence [18]. Other non-diphtheria species are of limited significance
Coxiella burnetii	Massively under-reported worldwide, despite being acknowledged as an important cause of endocarditis. There were 106 acute cases in the USA in 2008 [8]. A recent Netherlands outbreak highlighted limited surveillance issues [19], and increased the number of reported cases in the EU in 2008 to 1594. Germany, Spain, Slovenia and the UK report most other cases [15]
Ehrlichia chaffeensis and *Ehrlichia ewingi*	The number of human monocytotropic ehrlichiosis cases reported in the USA is continuously increasing, exceeding 900 in 2008 [8]. Human ewingii ehrlichiosis is more rare
Escherichia coli	The O157:H7 strain is consistently causing zoonotic foodborne and waterborne outbreaks [20]. Secondary effect through risk of haemolytic–uraemic syndrome development
Francisella tularensis	The tularaemia outbreak in Kosovo underlined the relationship of zoonoses with socio-economic and political factors [21]. Outbreaks of varying intensity have also been reported in Bulgaria, Georgia, and Turkey. Disease is rare (or understudied) in the EU; approximately 100 cases are recorded annually in the USA [8]
Helicobacter sp.	A speculative zoonotic potential for non-*Helicobacter pylori Helicobacter* sp. exists [22], although the role of animals in transmission of these species to humans has not been proven adequately
Leptospira sp.	The annual burden of leptospirosis is largely underestimated (inadequate surveillance; majority of cases mild or subclinical) [23]. The annual number of cases may exceed 500 000, the majority arising from India and Southeast Asia
Listeria sp.	Increasingly recognized in Europe—1300–1500 EU cases annually [15]; declining incidence in the USA that has stabilized below 0.3 cases/10^5 [8]. A recent Canadian outbreak exhibited significant mortality [24]
Mycobacterium sp.	*Mycobacterium bovis* still causes a small percentage of human tuberculosis by transmission from cattle or possums, as also observed less often with *Mycobacterium caprae*. Also included are *Mycobacterium marinum*, *Mycobacterium microti*, *Mycobacterium avium*, *Mycobacteriumgenavense*, possibly *Mycobacterium malmoense*, and *Mycobacteriumfarcinogenes.* There has been a long debate on the potential aetiological relationship between *M. avium paratuberculosis* and Crohn's disease in humans [25]. The mycobacterial life cycle leading to *Mycobacterium ulcerans* human infection and Buruli ulcer, and the significance of animal reservoirs in this cycle, have not yet been clarified adequately enough for it to be classified as zoonotic or non-zoonotic
Orientia tsutsugamushi	The burden of annual scrub typhus cases in Southeast Asia and the Southwest Pacific approaches 1 000 000 [26]
Pasteurella sp.	Pasteurellosis remains a relatively rare human infection,; it has been better understood and studied in animal disease
Rickettsia sp.	The numbers of cases of Rocky Mountain spotted fever reported annually were increasing in the USA in the early 2000s, exceeding 1000 cases in 2002. For rickettsial pox, the mild nature of human disease may contribute to underdiagnosis and under-reporting. The same is partly true for Mediterranean spotted fever, which can, however, be considered to be endemic in the region [27], and for African tick bite fever [26]. The endemicity of North Asian tick typhus remains understudied, whereas Queensland tick typhus and Japanese spotted fever can be considered to be both rare and localized. Murine typhus is generally sporadic and under-reported. Epidemic typhus shows an expanding animal reservoir frame (including flying squirrels in the USA), exhibits the secondary effect of BrillZinsser disease, and, more importantly, exhibits significant outbreak dynamics, which are nowhere better evaluated than in the notorious Burundi outbreak [28]
Salmonella sp.	Excluding *Salmonella typhi*, 51 030 cases of salmonellosis were recorded by the CDC in 2008 [8], the majority of which were caused by *Salmonella enteritidis* and *Salmonella typhimurium*; *S. enteritidis* was responsible for the 2008 US outbreak, with more than 1000 cases, more than 250 hospitalizations, and at least one fatality. More than 100 000 cases are recorded in the EU annually [15]
Shigella sp.	Shigellosis remains a major health issue worldwide, with tens of millions of cases and tens of thousands of deaths annually being attributed to it, particularly in young children, according to the WHO. Twenty-two thousand six hundred and twenty-five cases of shigellosis were reported by the CDC in 2008 [8]. EU data are inadequate on the subject
Staphylococcus aureus	The zoonotic significance of *S. aureus* is predominantly related to the role that animal reservoirs (such as pigs) play in expanding and sustaining the presence of methicillin-resistant *S. aureus* in the community, as demonstrated in The Netherlands [29]
Streptococcus sp.	*Streptococcus suis* is increasingly recognized in East Asia—a Chinese outbreak in 2004 resulted in 38/204 fatalities [30]. An *Streptococcus equi* outbreak associated with goat cheese occurred in Finland in 2003 [31]. The frequency of *Streptococcuscanis* infection may be underestimated. *Streptococcus acidominimus* is also zoonotic. The zoonotic significance of *Streptococcus bovis* is of minor importance concerning its primary manifestations in human disease
Vibrio sp.	Including *Vibrio parahaemolyticus* and *Vibrio vulnificus*, characteristically identified in the USA in the aftermath of Hurricane Katrina [32], but excluding *Vibrio cholerae*. Also with zoonotic potential are *Vibrio alginolyticus*, *Vibrio fluvialis*, *Vibrio furnissii*, *Grimontia hollisae*, and *Vibrio mimicus* [33]
Yersinia sp.	Plague remains, for both historical and purely scientific reasons, a major bacterial threat [34]; the WHO data for 2003 recorded more than 2000 cases, with mortality reaching 8.5%; the vast majority of cases were in Africa. Isolated cases are reported annually in the USA. Yersiniosis annual incidence has been declining in the EU—8346 cases were recorded in 2008, the vast majority of them caused by *Yersinia enterocolitica*

TABLE 2. Clinically significant viral zoonoses

Pathogen	Comments
Borna disease virus	Subject of continuing debate on its potential role in human neuropsychiatric disorders [35]
California serogroup viruses	California encephalitis, Jamestown Canyon, Keystone, La Crosse, Snowshoe hare and Trivittatus viruses—in total causing 60–80 cases annually in the USA [8]
Chikungunya virus	Primates serve as the reservoir in between human outbreaks, when human-to-human vector-mediated transmission occurs. Repeated outbreaks with hundreds of thousands of cases in recent years in the Indian Ocean and Africa, particularly Kenya, Reunion, and India [36]. The situation is similar for Mayaro virus, which has recently re-emerged in South America
Cowpox virus	Of historical significance, illustrating an adverse, beneficial effect of zoonoses. Orf is also a zoonosis
Crimean–Congo haemorrhagic fever virus	Emerging/re-emerging in eastern Europe, the Balkans, and Turkey, with evidence of a spread west, raising concerns for European epidemiology [37]. Still a significant issue in Central Asia and, partly, in sub-Saharan Africa; in the latter, the similar Dugbe virus may account for a few cases
Ebolavirus	Zoonotic in true spirit, as wildlife serves as the virus reservoir between outbreaks and the trigger of outbreaks. Most recent outbreak in Democratic Republic of the Congo in 2008; Ebola Reston variant in Philippines with different behaviour regarding human infection
Hantaviruses	Andes and Laguna Negra viruses cause hantavirus pulmonary syndrome (HPS) in South America. Sin Nombre virus (and, to a lesser extent, Bayou virus) cause HPS in the USA: more than 500 cases have been recorded by the CDC, the majority of them in the southwestern USA, 36% of them fatal. Puumala, Dobrava and Saaremaa viruses cause haemorrhagic fever with renal syndrome (HFRS) in Europe: the vast majority of documented cases arise in Finland [38]. Hantaan virus causes HFRS in Russia and East Asia (where Seoul and Amur viruses are also implicated)
Hendra virus	Limited to Australia and with minimal numbers of cases and fatalities (four), but a novel emerging pathogen with significant environmental correlations. A similar natural history and epidemiology applies to Menangle virus. Also of importance only for Australia are Murray Valley encephalitis and Kunjin viruses, which rarely induce clinical disease
Hepatitis E virus	Zoonotic reservoir of the disease; may not be implicated directly in outbreaks. Isolated cases of direct transmission by ingestion of deer or wild-boar meat [39]
Influenza viruses	The principal zoonotic aspects of influenza are the role of animal hosts as substrates for the development of novel strains, and their role in the introduction of these strains into human pathology. Avian H5N1 influenza is a typical zoonotic infection, requiring close contact with infected animal hosts: at present, after the 2004 outbreak, novel cases with a high fatality ratio are reported randomly from Indonesia, Egypt, Vietnam, and China. The novel H1N1 influenza virus pandemic stopped being zoonotic after human-to-human transmission emerged as the cause of the pandemic. The single non-human host for each of influenza B virus and influenza C virus play a minimal role regarding human disease
Japanese encephalitis virus	Tens of thousands of annual cases reported in East and Southeast Asia. Slow expansion to Western Pacific may highlight risks and significant mortality in future years
Kyasanur forest disease virus	There are 100–500 cases annually in India. Relative of the novel Alkhumra virus in Saudi Arabia
Lassa virus	Other Arenaviridae causing localized viral haemorrhagic fevers are Guanarito virus (Venezuela), Machupo virus (Bolivia), Sabia virus (Brazil), Junin virus (Argentina), and the recently emerging Lujo virus (southern Africa)
Lymphocytic choriomeningitis virus	Extensive seropositivity in studies indicates potential overestimation of morbidity. An emerging infection through pet mice
Marburg virus	The 2004–2005 Angola outbreak resulted in 329/374 fatalities. Two cases, one fatal, were imported into the USA and The Netherlands from Uganda in recent times
Monkeypox virus	Mostly notorious for the multistate outbreak in the USA in 2003, traced back to an imported primate from Africa
Nipah virus	Human-to-human transmission important for outbreaks; however, zoonotic origin (bats) and reservoir (pigs). Limited cases with major mortality ratio reported particularly from Bangladesh
Omsk haemorrhagic fever virus	Localized epidemiology; of interest is its recent switch to direct, non-vector-mediated, transmission from rodents to humans [40]
Oropouche virus	Re-emerging in Brazil in recent years [41]. Sloths are the main hosts; vector-borne, clinically similar to dengue
Rabies and lyssaviruses	Extremely rare in Europe, the few existing cases typically imported, extremely rare in the USA [8,15]. More than 20 000 deaths annually in India [42]. Major mortality foci are also China, Pakistan, Bangladesh, and Myanmar. Lyssaviruses include Duvenhage virus (Africa, bat-related cases), Mokola virus (Africa), and Australian and European bat lyssaviruses
Rift Valley fever virus	Ongoing (2010) outbreak in South Africa, recent outbreaks in Sudan, Kenya, Somalia, and Tanzania, with hundreds of cases and varying mortality ratio (23–45%). Outbreak in Yemen and Saudi Arabia in 2000 with similar morbidity and mortality toll
Ross River virus	Present in Oceania—more than 5600 cases recorded in 2008 [43]. Potential for chronic symptom induction is under investigation. Barmah Forest virus causes similar disease; more than 2000 cases were reported in 2008
SARS coronavirus	Zoonotic in origin, not in subsequent outbreak dynamics
Sindbis virus	Traditionally linked with Egypt, it was nevertheless demonstrated as an outbreak cause in Finland (Pogosta disease) [44]
Tick-borne encephalitis	More than 5000 cases reported in Europe in 2007 [45], the majority from Russia, and central–northern Europe. Incidence on the rise, possibly owing to climate changes
Venezuelan equine encephalitis virus	Outbreaks in Venezuela and Colombia in the mid-1990s with tens of thousands of cases but minimal mortality (<0.2%)
West Nile virus (WNV)	The most characteristic example of a zoonotically sustained massive outbreak, WNV movement through North America in the last decade has resulted in sustained presence in the community: 689 cases were reported in the USA in 2008 [8]. Furthermore, the ongoing WNV outbreak in Greece, with 34/261 deaths [46], demonstrates the trend of the virus to move to Europe, following the previous outbreaks in Romania and Russia
Yellow fever virus	The WHO estimates that there are more than 200 000 annual cases worldwide, with 30 000 deaths—the ongoing vaccination campaign is one of the most ambitious global public health programmes. Both the sylvatic and intermediate cycles of disease transmission are zoonotic in character
Zika virus	Micronesia outbreak of minimal morbidity

also allow for enhanced preparedness regarding the emergence or re-emergence of similar pathogens with the potential to cause epidemics or pandemics.

Transparency Declaration

The author does not have any conflict of interest to declare.

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