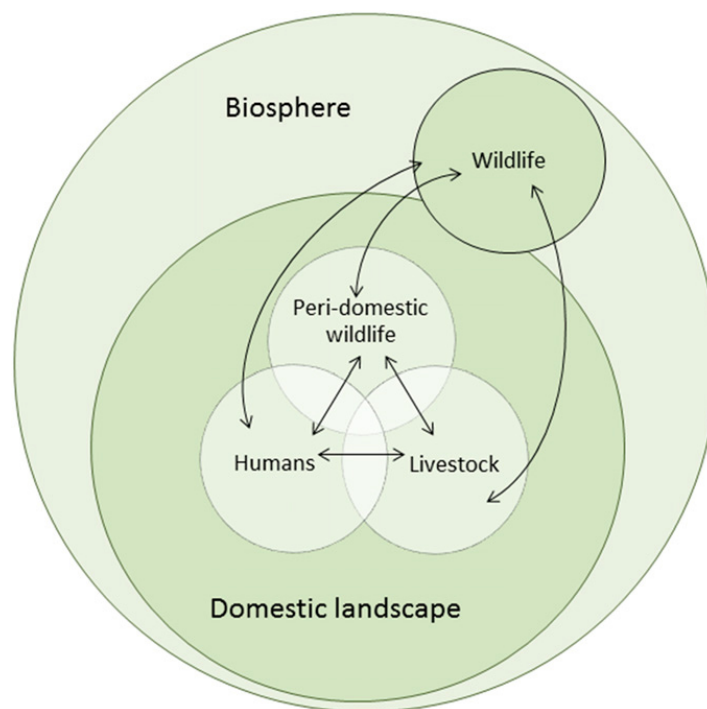


Emerging zoonotic viruses: What characterizes them and what are the risk factors for their emergence?

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Zoonotiska virus - Ett framtida hot. Vad karakteriserar dem och vad driver deras uppkomst?

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SAMMANFATTNING

Infektiösa patogener som påvisats i en population för första gången, alternativt uppvisar en ökning i incidens eller geografisk spridning, utgör ett allvarligt framtida hot för såväl människor som djur. Majoriteten av dessa patogener orsakar endast mindre hälsoproblem, men risken att nästa stora pandemi kan vara nära i antågande får ej försummas. Detta illustreras tydligt av HIV, som på relativt kort tid har etablerat sig som en av världens mest fruktade infektiösa agens. Patogenerna av denna typ antas sällan vara nyutvecklade, utan förmodas oftast ha förekommit tidigare i naturen. De allra flesta är zoonotiska och därmed kapabla att infektera andra arter utöver människa. Virus är överrepresenterade, vilket dels antas bero på svårigheterna i att behandla och kontrollera virala sjukdomar, såväl som den enorma genetiska mångfald som virus uppvisar. Än så länge har ingen tydlig association kunnat påvisas mellan ett virus zoonotiska status och dess benägenhet att nyinfektera människor. Men eftersom en betydande andel trots allt innehar förmågan att infektera djur utöver människa, eller har haft historiskt, är det sannolikt att zoonotiska virus är en av de patogengrupper som utgör störst risk för framtiden.

Eftersom många av de patogener som påvisats i humana populationer för första gången, alternativt uppvisar en ökning i incidens eller geografisk spridning, är sprungna ur djurpopulationer, kan överföringen av mikroorganismer från djur till människa antas spela en central roll. Troligen exponeras människan ständigt för främmande patogener, men endast ett mindre antal av dessa kommer att inneha de rätta genetiska förutsättningarna för att kunna orsaka mänsklig infektion. Av dessa är det troligen bara ett fåtal som kommer att utveckla förmågan att spridas mellan människor, varav endast en fraktion lyckas förfina detta till den grad att de kan skapa humana pandemier. Denna övergång från djurinfektion till human pandemi sker anmärkningsvärt ofta i områden som står under antropogen påverkan. Vissa av dessa aktiviteter förmodas verka genom att utöka exponeringen av människor för nya patogener, dess reservoarer eller vektorer, andra genom att underlätta spridning i populationen. För att mänskligheten i framtiden ska kunna förhålla sig till hotet som dessa infektiösa patogener utgör, finns det stora behov av forskning inom flera områden. Eftersom processen är komplex och multifaktoriell är en multidisciplinär och internationellt samordnad angreppsmetod ofta att rekommendera.

SUMMARY

Emerging infectious diseases poses a great future threat, not only to humans but also to domestic animals and wildlife. Even though the majority of these infections only cause minor health problems, the relatively recent emergence of HIV clearly illustrates that the next major human pandemic may surface at any time. Regardless of what the name indicates, most emerging human pathogens are not believed to be recently evolved, but to have existed previously in the natural environment. Most emerging pathogens are zoonotic, i.e. able to infect animals besides humans. Viruses are significantly overrepresented, which is thought to be due to the general difficulties in treating and controlling viral diseases, as well as the substantial amount of genetic diversity that viruses exhibits. Even though there is no clear association between the classification of a virus as zoonotic and its' risk of emergence, many emerging viruses have been shown to be zoonotic or have a zoonotic history. Therefore it is probably accurate to conclude that zoonotic viruses constitute a significant risk for future emergence events.

Since the majority of emerging pathogens are zoonotic, the process of cross-species transmission of a microbe from its reservoir to humans is likely to play a central role. It is probable that humans are exposed to unfamiliar pathogens regularly, but that only a few of them will possess the required genetic features to successfully cause human infection. A fraction of these pathogens may go on to acquire the ability to transmit between humans, whereof an additional few may evolve to transmit at a rate that enables major epidemics. When emergence occurs, it appears to disproportionately often happen in areas that are affected by anthropogenic activities. Some of these activities are believed to act by augmenting exposure of humans to novel pathogens, reservoirs or vectors, others by enhancing disease transmission. In order to be prepared for future emergence events, there is a great need for additional research on numerous aspects of the emergence process. Also, given the complexity and multifactorial nature of disease emergence, a multidisciplinary and internationally conjunctive approach is often advised.

INTRODUCTION

Infectious diseases have a long history of being one of mankind's greatest nemeses. Today, infectious diseases are the second biggest contributor to worldwide mortality, only surpassed by ischemic heart disease (WHO, 2004). While plagues from the past continue to tantalize human populations, and despite improvements in diagnostics and treatment methods, new infections appear to be emerging at an unprecedented rate (Jones et al., 2008). Also, it is becoming increasingly obvious that anthropogenic activities, such as deforestation, intensive agriculture and encroachment on previously unoccupied habitats, play a central role in the emergence process (Antia et al., 2003; Institute of Medicine, 1992; Morse et al., 2012; Parrish et al., 2008; Schrag et al., 1995; Wolfe et al., 2005; Woolhouse et al., 2007).

The majority of emerging pathogens have been shown to be of viral origin, and characteristics such as having broad host ranges seem to facilitate the process (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2005a). The purpose of this paper is to briefly analyze why viruses are more likely to emerge than other taxonomic groups, as well as review how different characteristics, such as zoonotic status and routes of transmission, influences the process. Also, since many emerging viruses are zoonotic or have a zoonotic history (Woolhouse et al., 2005b), the process of viral transition from solely infecting animals to causing human pandemics, will be analyzed. Last but not least, risk factors for viral emergence will briefly be summarized. Although the focus is set on zoonotic viruses, a substantial proportion of presented facts are also applicable to other categories of emerging pathogens.

METHODS

By using the search words *emerging*, *zoono** and *virus** in the databases Scopus and Web of Science, original articles and reviews were accessed. Moreover, the reference lists were used to further extend the search.

LITERATURE REVIEW

Background

An emerging disease is caused by a pathogen that has appeared in a population for the first time, or that has existed previously but is increasing in incidence or in geographic range (WHO, 2014). Sometimes reemerging diseases are included in this concept, which are those that previously showed decreased incidence but now again is experiencing an upsurge (Morse, 1995), often due to failing public health measures (Institute of Medicine, 1992; Morse et al., 2005) or antimicrobial resistance (Jones et al., 2008). Despite what the name may indicate, emerging infectious pathogens are usually not believed to be recently evolved, but to have existed previously in nonhuman reservoirs (Morse et al., 1990). The majority of research is concentrated on emerging human diseases, but the concept of pathogen emergence is also becoming increasingly recognized as threats to domestic animals and wildlife (Cleaveland et al., 2001; Woolhouse, 2002).

Approximately one eighth of the currently known human pathogens are classified as emerging, whereof about $\frac{3}{4}$ are considered to be zoonotic. Overall, zoonotic pathogens have been shown to be approximately twice as likely to emerge as non-zoonotic pathogens (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2005a). About 40% of the emerging pathogens are of viral origin, which makes viruses the biggest contributor of all the pathogenic groups. Viruses have also been shown to be significantly more probable to emerge than other taxonomic orders (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2005a). Also, viruses are significantly overrepresented in the group of pathogens that were discovered after the 1980s, constituting approximately $\frac{2}{3}$ of the total number. This is a significant overrepresentation, since viruses still only make up about 14% of human pathogens. Approximately three new viral species are discovered each year (Woolhouse et al., 2007), and extrapolating of the discovery curve indicates that there is still a substantial pool of undiscovered viruses out there (Woolhouse et al., 2012).

So far there has yet to be demonstrated a connection between the classification of a virus as zoonotic, and its' risk of emergence (Taylor et al., 2001; Woolhouse et al., 2005a). However, approximately $\frac{3}{4}$ of human viruses are zoonotic (Taylor et al., 2001) and many have a zoonotic history (Parrish et al., 2008). Famous examples of human viruses that either has a nonhuman reservoir or are believed to have originated in animals, include HIV-1 (chimpanzees), HIV-2 (sooty mangabees), Influenza A (wildfowl), SARS (bats) and Measles and Smallpox (livestock) (Woolhouse et al., 2012). When taking this into consideration, it seems likely that the zoonotic pool is important for emerging viruses as well.

Why are viruses especially prone to emerge?

There are a few plausible explanations as to why an emerging pathogen is particularly likely to be of viral origin. One is that today there are few effective antivirals, making viral diseases more difficult to control and therefore also more likely to spread within a population (Cleaveland et al., 2001). Another possible explanation is the substantial amount of genetic diversity exhibited by viruses. This diversity is likely to be especially high in RNA-viruses,

due to their exceptional mutation rate, which in turn is because of the lack of proofreading ability of the RNA-polymerase (Quinn et al., 2011). This big genetic diversity enables viruses in general, and RNA-viruses in particular, to generate greater amounts of genetic diversity, and are thereby more likely to adapt to a new host (Woolhouse et al., 2001).

If studied numerically, RNA-viruses appear to be more probable to emerge than DNA-viruses. RNA-viruses constitute approximately 37% of all emerging pathogens, which makes them the biggest contributor (Cleaveland et al., 2001; Woolhouse et al., 2005a). Also, the fraction of RNA-viruses among emerging disease agents appear to be increasing. Since the 1980s, RNA-viruses have been shown to account for more than 56% of newly discovered pathogens (Woolhouse et al., 2007). However, so far the importance of RNA-viruses has not been shown to be of statistical significance (Cleaveland et al., 2001; Woolhouse et al., 2005a). Also, no significant difference has been detected regarding different viral families and risks of emergence (Woolhouse et al., 2005a).

In addition to mutations, viruses are also able to generate genetic change through recombination, or reassortment in viruses with segmented genomes. These processes enable the acquirement of multiple genetic changes in a short amount of time, as well as the combining of genomic sequences from different viruses (Parrish et al., 2008; Quinn et al., 2011). Reassortment is thought to have played a vital role in the generation of the 1957 and 1968 pandemic influenza strains (Ma et al., 2009).

Viral transition from infecting animals to causing human pandemics

The emergence of novel viruses can be described with the so called “pathogen pyramid”, containing four different levels. Some pathogens are prevented from transcending to the next stage by different barriers, for instance genetic maladaptation, lack of sufficient pathogen-host interaction etc. (Woolhouse et al., 2007). The number of transcending events between levels is believed to decrease further up the pyramid, while the consequences of events are believed to increase (Morse et al., 2012).

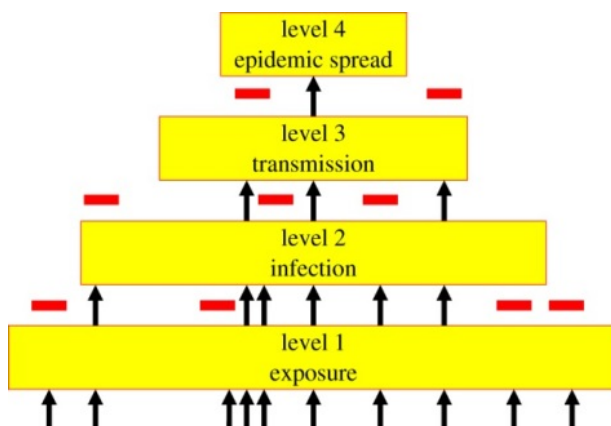


Figure 1: The pathogen pyramid, containing four different levels. These levels get progressively smaller higher up the pyramid, which illustrates a decreasing number of transcending events. Arrows illustrate the possibility for some pathogens to transcend from one level to the next. Bars illustrate transience barriers for others. (From Woolhouse et al., 2012)

Level 1: Exposure of humans to the virus, either through direct contact, indirect contact or via vector. Exposure at this stage is often due to changes in human, animal or vector ecology, which affects the interaction frequency between man and virus. The only possible impediment at this stage is insufficient geographical overlap of reservoir, vector and human habitats (Woolhouse et al., 2007). Exposure of this kind is thought to be a frequent occurrence (Woolhouse et al., 2012).

Level 2: The viruses at this level have successfully completed cross-over transmission to humans and are capable of causing infection. The ability to reach this level is partly determined by viral genetics, and/or partly by the physiology of the infected host, most notably immune status (Woolhouse et al., 2012). Some pathogens have an innate ability to infect humans, and can therefore enter the pyramid at level 2, without the need of preceding exposure (Morse et al., 2012).

Level 3: These viruses can maintain shorter chains of transmission between humans. One critical requirement for this to occur is that the virus can access tissues from which it can exit the host, such as the urogenital tract, lower gut, skin, blood and the upper respiratory tract (Woolhouse et al., 2012).

Level 4: The viruses that have reached this level are sufficiently transmissible to cause pandemics and/or become endemic in the human population, without the need for reintroductions from nonhuman reservoirs. The ability of a virus to transcend to this stage is not only related to viral genetics, but also to human demography and behavior, and its influence on transmission (Woolhouse et al., 2012). Pandemic spread is often aided by global travel of infected humans and the international movement of vectors and reservoir species (Morse et al., 2012).

Out of the 219 viruses that are infective to humans, approximately 50% have reached stage 3, whereof about half have managed to reach level 4. Interestingly, this makes the shape of the pathogen pyramid remarkably different for viruses compared to other groups of pathogens, where much smaller fractions have reached level 4 and pandemic spread. One possible explanation is the quicker genetic evolution of viruses which gives them a greater ability to adapt to new hosts (Woolhouse et al., 2012).

The correlation between R_0 and outbreak size

The extent of an outbreak of a zoonotic virus, or any other infectious pathogen, is dependent on the size of the susceptible population, the number of primary introductions, and R_0 , also known as the basic reproduction number (Woolhouse, 2002). R_0 can be defined as the mean number of secondary cases of infection associated with every primary case, and is the sum of the products of the average contact rate between infectious and susceptible individuals, the probability of infection of a susceptible host, as well as the mean longevity of infection-time (Calisher et al., 2006). In order for a virus to successfully cause human pandemics, R_0 needs to exceed one (Woolhouse et al., 2005b). For these pathogens, the final size of an outbreak is

chiefly determined by the size of the susceptible population (Woolhouse et al., 2005a). This category is likely to constitute the biggest threat for future emergence events (Woolhouse et al., 2005b). For viruses with a R_0 of less than one, the size of an outbreak is primarily dependent on the number of successful introductions from the reservoir species (Woolhouse et al., 2005a). These viruses will probably only experience limited spread, e.g. only reach the third level of the pathogen pyramid (Woolhouse et al., 2007).

Between these two, there is a transition state where viruses have an R_0 -value of around 1. These viruses are believed to constitute a possible source of future emerging diseases. The final size of an outbreak of these pathogens is extremely sensitive to even the smallest changes in R_0 (Woolhouse et al., 2005a). An increased R_0 -value can be achieved through for example increased proximity of the old and new host, increased host density, behavioral changes or genetic adaptation of the pathogen (Antia et al., 2003; Wolfe et al., 2005; Woolhouse et al., 2005b; Woolhouse et al., 2007). Risk factors are more extensively reviewed further down.

The species jump

Cross-species transmission is dependent on an intricate balance between viral genetics (i.e. ability to infect) and ecology (i.e. frequency of exposure) (Morse et al., 2012). It is likely that many animal viruses at some point will spill-over into humans, but then fail to establish itself due to an inadequate transmission potential. This process has been termed “viral chatter”, where pathogens are repeatedly spread from animals to humans, often without further transmission. This process have been hypothesized to be of great importance in the emergence of viruses, since it is believed to increase viral diversity and thereby also the probability of a virus evolving that is able to infect and spread within the human population (Wolfe et al., 2005). The frequency of spill-over events is likely to depend predominantly on the frequency of contact between humans and reservoir, which in turn is largely regulated by geographic overlap of habitats and behavioral factors of the hosts (Parrish et al., 2008).

In order for some viruses to successfully jump species, they are in need of an amplifier host, i.e. a species that increases transmission of the pathogen in question. They act by establishing a contact between pathogen and recipient host that otherwise would not occur, or by providing an opportunity for the microbe to adapt to humans. In the emergence of SARS it is believed that the virus spilled-over from fruit bats to civet cats in wild animal markets in Asia, followed by the establishment of a market cycle of infection. This is believed to have amplified virus load (Calisher et al., 2005) as well as enabled the virus to adapt to humans (Song et al., 2005).

For Influenza A viruses, it is often hypothesized that domestic pigs serve as mixing vessels in which new infectious variants may be generated. This is due to the fact that avian, swine and human strains are all capable of infecting and replicating in cells of the respiratory tract of pigs, which permits reassortment and the possible generation of new virulent strains. If few or

none in the population previously have acquired immunity to the new strain, extensive pandemic spread and global disease may follow (Ma et al., 2009).

Factors influencing viral emergence

When studying the relative importance of taxonomy, transmission route and host range regarding its' contribution to the risk of emergence, multifactorial analyses indicates that taxonomic division is the most important, and that broadness of host range also has great impact (Cleaveland et al., 2001).

Multi host vs. single host pathogens

Approximately 75% of emerging pathogens are zoonotic, and overall, multi host pathogens are about twice as likely to emerge as single host pathogens (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2005a). Also, the capability of infecting more than one taxonomic order has been shown to constitute another risk factor (Cleaveland et al., 2001). About 80% of the human pathogens that were discovered after the 1980s are zoonotic, and these microbes have been shown to be significantly more likely to be zoonotic compared to species detected earlier (Woolhouse et al., 2007). Also, human RNA-viruses have been shown to be zoonotic to a higher degree than human DNA-viruses (84% vs 36%) (Woolhouse, 2002). This may to some extent explain why RNA-viruses numerically are a bigger contributor to emerging pathogens than DNA-viruses.

Determinants of host range are poorly mapped, but for viruses there is a significant association between breadth of host range and the usage of phylogenetically conserved cell receptors. According to Woolhouse et al. (2012), there are no human viruses with broad host ranges that do not recognize and bind to phylogenetically conserved receptors.

Importance of transmission route

No clear association between different transmission routes and risk of emergence has been discovered. Numerically, the majority of the emerging viruses are transmitted by direct contact, followed by vector-borne transmission and indirect contact (Taylor et al., 2001). However, if the proportion of the number of emerging species is studied, the results look somewhat different (see table 1 below).

<i>Taxonomic division</i>	<i>Zoonotic status</i>	<i>Transmission route</i>	<i>Proportion of emerging species</i>
Virus	Zoonotic	Indirect	0,459
Virus	Zoonotic	Direct	0,413
Virus	Non-zoonotic	Indirect	0,308
Virus	Non-zoonotic	Direct	0,298
Virus	Zoonotic	Vector-borne	0,293

Table 1: Modified from Taylor et al. (2001)

Human vector-borne pathogens have been shown to be more likely to be zoonotic than pathogens transmitted by indirect contact. Pathogens transmitted by direct contact are the least likely to be zoonotic. This is hardly surprising, given the fact that generalist vectors often feed on numerous different species and are thereby producing an evolutionary incentive for pathogens to acquire the ability to infect multiple hosts. In comparison, direct transmission that requires close physical contact provides fewer opportunities for interspecies spread (Woolhouse et al., 2001). However, vector borne transmission may also cause additional constraints on the adaptability of a pathogen to new host-species. This is due to the need to balance fitness in three or more different species, i.e. the reservoir, the vector and the recipient host (Parrish et al., 2008). This hypothesis is supported by the findings of Taylor et al. (2008) where vector-borne pathogens in general were proven to be more likely to emerge than pathogens transmitted by other routes, while zoonotic pathogens transmitted via vector were shown to be less inclined to emerge (Taylor et al., 2001). Despite this, a significant increase has been observed in the number of emerging pathogens transmitted by vectors. Since the 1940s, vector-borne diseases have been responsible for 22,8% of emerging pathogens, and for 28,8% from 1990-2000 (Jones et al., 2008).

Reservoir species

There are no clear correlations between the usage of different reservoir species and risk of emergence. Overall, mammals are associated with about 80% of emerging pathogens, birds with less than 20% and very few with other vertebrates (Woolhouse et al., 2012). If studied numerically, the most important reservoir hosts for emerging viruses are rodents, followed by ungulates, non-mammals (i.e. birds and invertebrates), primates and carnivores (Woolhouse et al., 2005a). For emerging pathogens in general, ungulates are the most important, followed by carnivores, rodents, primates and non-mammals (Cleaveland et al., 2001). In order for an animal to become an important reservoir of human infections, it either needs to be closely related phylogenetically to humans, i.e. primates, or experience frequent encounters with humans, i.e. rodents. Notably, primates appear to be the source of approximately one fifth of the major human pathogens, despite their infrequent contact with man (Wolfe et al., 2007).

Pathogens with reservoirs in wildlife have been shown to be especially likely to emerge, compared to the usage of reservoirs in domestic animals (Cleaveland et al., 2001). Since the 1940s, almost 72% of zoonotic emerging pathogens appear to have originated in wildlife, and this trend shows signs of steadily increasing over time (Jones et al., 2008).

The importance of bats as reservoirs is becoming increasingly recognized (Calisher et al., 2006; Drexler et al., 2011; Drexler et al., 2012; Smith et al., 2013). In the last two decades, bat borne viruses such as Nipah, Hendra, SARS and Ebola, have caused significant health burdens globally (Smith et al., 2013). Bats comprise more than one fifth, as well as some of the most ancient, mammalian species. This raises the hypothesis that viruses that have co-evolved with bats may use cell receptors that subsequently have been conserved in other mammals, which in turn would enhance their transmission (Calisher et al., 2006). Additionally, bats live long lives, are widely dispersed globally and live at great population

densities. Also, bats are the only mammals capable of powered flight. These factors are all likely to enhance transmission of bat borne viruses (Calisher et al., 2006; Smith et al., 2013).

Risk factors associated with the emergence of viruses

Emergence of an infectious pathogen is usually precluded by one or several changes. These changes can crudely be subdivided into: changes in the ecology of host, pathogen or vector, genetic change of the pathogen, or genotypic or phenotypic change of the host, most notably immunosuppression. Ecologic changes act by altering the opportunity for transmission of a pathogen, for example through changed distribution or behavior of pathogen, vector or host (Woolhouse, 2002). Different risk factors operate on different parts of the emergence process. Some facilitates interaction between human and pathogen; others affect the disease-agents transmission within a population. Often a combination of drivers is needed for emergence to occur (Institute of Medicine, 1992; Woolhouse et al., 2012).

Below in Table 2 follows risk factors commonly recognized in processes of disease emergence. Sometimes the term “drivers of emergence” is also used. Some of them are further explained in text below.

<i>Risk factor</i>	<i>Specific examples</i>	<i>Examples of viruses</i>
Changes of ecosystems and global warming	Deforestation, agriculture, damming etc.	Influenza A, Hantavirus, Rift Valley Fever virus, Nipah virus ² etc.
Human demography	Population growth, increased population density, urbanization, immunosuppression etc.	Lassa fever virus, Yellow fever virus, Dengue fever virus etc.
Human behavior	Sexual activity, intravenous drug abuse, international travel, bushmeat consumption ¹ etc.	Simian foamy virus ¹ Ebola virus ¹ , HIV ^{1,3} , SARS ⁴ etc.
Technology and industry	Nosocomial infections, antimicrobial resistance, international trade, food and water processing etc.	Hepatitis B and C, Reston Ebola and Marburg Virus etc.
Societal change	Overcrowding in cities, inadequate hygiene, breakdown of public health measures etc.	Dengue fever, measles etc.

Table 2: Risk factors associated with pathogen emergence, along with more specific examples of activities as well as examples of associated viruses.

Adapted from the Institute of Medicine (1992) unless specified otherwise

¹ Wolfe et al. (2005)

² Chua et al. (2002)

³ Bengis et al. (2004)

⁴ Song et al. (2005)

Another factor that is believed to affect emergence of infectious diseases is genetic adaptation of the pathogen. This has been discussed previously in the text and is therefore not included in the table above. Also, genetic change of the host is another plausible explanation for disease emergence. However, this is more likely to constitute a problem in inbred populations of endangered species or domestic animals (Woolhouse et al., 2005b), and is therefore not included in the table above.

There has been some debate regarding the relative importance of ecologic changes and genetic adaptation. The most common conclusion seems to be to assign ecologic factors, i.e. changes that affect how humans interact with their immediate surroundings, a leading role (Institute of Medicine, 1992; Morse, 1995; Schrag et al., 1995; Woolhouse et al., 2005b)

Change of ecosystems and global warming

Change of ecosystems is a wide concept that includes many different drivers, whereof one of the most frequently mentioned is changed land use. It has been shown that since the 1940s, almost 50% of the events of zoonotic pathogen emergence have resulted from changes in land use (Keesing et al., 2010). This concept includes for example deforestation, agriculture, modification of wetlands, dam construction etc. (Institute of Medicine, 1992). These drivers are believed to act by placing humans, reservoirs and vectors in increased proximity to one another (Institute of Medicine, 1992; Patz et al., 2004). Some may also affect wildlife habitats, which in turn will increase contact frequency between humans and wildlife pathogens (Patz et al., 1994). The fact that since the 1940s almost 75% of emerging zoonotic pathogens originated in wildlife, and that this trend appears to be significantly increasing over time, supports the hypothesis that human activities that increases contact with pathogens of wildlife, are substantial risk factors for disease emergence (Jones et al., 2008). Processes such as damming and irrigation water in agriculture, are likely to promote vector-borne disease agents since many vectors breed in standing water (Morse, 1995). Also, recent information suggests that activities that contribute to reducing biodiversity in flora and fauna also may increase transmission of infectious pathogens via different mechanisms (Keesing et al., 2010).

The influences of global warming on the emergence of infectious diseases have yet to be fully elucidated. The survival of pathogens outside their hosts, as well as the seasonality of viruses such as Influenza A, is likely to be affected by climate change. Pathogens transmitted by vectors are also expected to be affected in different ways. First of all, higher global temperatures may increase the areas of habitats suitable for breeding. Secondly, an increased precipitation and a subsequent rise in sea level may positively affect vectors that are dependent on water to complete their life cycles (Institute of Medicine, 1992). The fact that a significant increase in the importance of vector borne transmission has been observed, and that it has been correlated to climate anomalies, may be regarded as supports to this hypothesis (Jones et al., 2008).

Human demographic changes

Increased population size and density is often hypothesized to play an important role in the emergence of many infectious diseases (Institute of Medicine, 1992). This hypothesis is supported by a study performed by Jones et al. (2008) where human population density was found to be a significant predictor for disease emergence. Urbanization is another important factor, which acts by allowing isolated pathogens to gain foothold in larger population. This is thought to have played a vital role in the emergence of HIV/AIDS (Morse, 1995).

There are also reasons to believe that opportunistic infections in an increasingly immunocompromised population, may threaten future human populations. Life expectancy in most notably the western world is steadily rising, while malnutrition continues to impair immune defenses in the developing world. The HIV-pandemic as well as hospital treatments in association with cancer or organ transplantation, are also important factors to take into consideration (Institute of Medicine, 1992). Immunocompromised hosts living at high density may enable ill-adapted human pathogens to evolve into transmissible agents, first to the immunodeficient host and then to immunocompetent humans (Weiss et al., 2004).

Human behavior

Human behavior is a vital component for emergence of many infectious diseases, and therefore changing patterns of human activities is often important to halt epidemics (Institute of Medicine, 1992; Morse et al., 2012). Human consumption of bushmeat is believed to constitute an important factor in the emergence of several infectious diseases. It places humans in close contact with not only live animals and vectors, but also with body fluids during butchering of the carcasses (Karesh et al., 2009)(Wolfe et al., 2005). Also, transportation, sale and consumption may put humans at additional risk. HIV/AIDS is believed to initially have spilled-over to humans via this route (Wolfe et al., 2005).

International travel and trade are two other key components in disease emergence, enabling pathogens to spread globally and thereby reach level 4 on the pathogen pyramid (Morse et al., 2012).

DISCUSSION

According to the findings of this review, the typical emerging pathogen is of viral origin and infects multiple host species, often in different taxonomic groups (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2002). No clear association has been found between the risk of emergence and different routes of transmission, or usage of specific reservoir species, but the importance of vector-borne transmission and reservoirs in wildlife appear to be increasing (Jones et al., 2008). Also, emergence seems to disproportionately often occur in areas afflicted by human activities (Antia et al., 2003; Institute of Medicine, 1992; Morse et al., 2012; Parrish et al., 2008; Schrag et al., 1995; Wolfe et al., 2005; Woolhouse et al., 2007). So far no association has been found between the ability of a virus to infect multiple species and the risk of emergence, even though this is a common characteristic for emerging pathogens overall (Taylor et al., 2001; Woolhouse et al., 2005a). However, this may be due to lack of data on viral host ranges, since we in general know less about viruses than other types of pathogens (Morse et al., 2012).

The fact that the majority of emerging pathogens are zoonotic, i.e. infects multiple hosts, is a cause of concern. Single host pathogens tend to evolve to an optimum level of virulence, determined by the trade-off between virulence and transmissibility (Woolhouse et al., 2001). For example, a virus may evolve towards a state of fewer health implications in order to increase the time when the host is infective to others. Unfortunately, this may not be the case for multi host pathogens. Here, virulence is likely to vary between different host species, and the addition of a new species can both increase and decrease virulence in previous hosts. Also, if the new host does not contribute to the overall fitness of the pathogen, there will be no constraints on virulence in that host (Woolhouse et al., 2001). This may explain the high virulence of for example Ebola virus, Nipah virus and SARS in humans (Woolhouse et al., 2007). An additional cause of concern regarding emerging pathogens is the possible lack of evolutionary time for a specific pathogen to evolve optimal virulence in humans (Woolhouse et al., 2001).

Research on pathogen emergence may be affected by biases at numerous stages. First of all, when analyzing traits such as taxonomic grouping, broadness of host range and transmission route, it is important to remember that these factors are non-independent and therefore also likely to be confounded. For example, the highest proportion of emerging species has been found in viruses that are classified as zoonotic and transmitted indirectly (Taylor et al., 2001). However, it has also been shown that zoonotic pathogens are relatively likely to be spread by indirect contact (Woolhouse et al., 2001). This makes it more difficult to draw clear conclusion on the importance of indirect transmission for emerging viruses. Biases may also affect studies of risk factors for emergence. This is because the process of identifying drivers is inevitably subjective (Woolhouse et al., 2005a), and there are very few ways to test the accuracy of proposed hypotheses. Also, the emergence of a pathogen is often due to the conjoint efforts of several drivers, many of whom are facilitating emergence indirectly (Institute of Medicine, 1992; Woolhouse et al., 2012). This makes it difficult to not only draw conclusions regarding individual drivers, but also to test their relative importance.

The classification of a pathogen as emerging may also be subjectively affected, reflecting the specific interests of the researcher. Also, the number of emergence events may be affected by improved diagnostics, as well as recent discoveries of the aetiological agents of old diseases (Woolhouse, 2002). Moreover, the studies presented here that analyzes how different characteristics affect the probability of pathogen emergence (Cleaveland et al., 2001; Taylor et al., 2001; Woolhouse et al., 2005a) are all basing their studies at species level. This means that diversity at subspecies level, which for some pathogen families is substantial, is overlooked (Woolhouse et al., 2007). However, if subspecies are included in the analysis, there is a risk of biases due to phylogenetic relatedness of subspecies rich organisms (Taylor et al., 2001).

There is a great need of additional research on the subject of emerging infectious pathogens. Considerable progress has been made, but we still lack crucial knowledge on several steps in the emergence process. For example, we are in need of additional knowledge on the diversity of pathogens that humans are currently exposed to, or risk exposure to in the future. This makes surveys of the pathogen burden of most notably mammalian species, a future necessity (Woolhouse et al., 2007). Also, there is a need for additional research on genetic markers that are associated with an increased risk of emergence. For viruses, the usage of different cell receptors and how it affects the probability of emergence is something that needs further illuminating (Woolhouse et al., 2007). We also need to increase our understanding of how pathogen virulence is determined in different hosts. Today we know very little about why some pathogens are benign in their natural host but causes fatal diseases in other species (Morse et al., 2012). To get a better understanding of the complex, multifactorial process of pathogen emergence, a lot of knowledge can be gained through studying previous successful emergence events, and attempt to dissect its' epidemiological and evolutionary patterns (Morse et al., 2012).

Emergence of pathogens is not a straight forward process, as it often involves several different drivers (Institute of Medicine, 1992; Woolhouse et al., 2012). Therefore, in order to properly take on the problem of emerging infectious pathogens, a multidisciplinary approach is often advised (Morse et al., 2012; Wolfe et al., 2005; Woolhouse, 2002; Woolhouse et al., 2007). Microbiologists are needed to monitor genetic diversity, research on genetic markers and find common attributes that characterizes pathogens with potential to cause major epidemics. Medical doctors and veterinarians are required to oversee general population health of humans and animals, as well as contribute to research with a medical viewpoint. Also, a wide range of other professions are needed to further delineate crucial processes. Since emergence can be driven by a wide range of changes in demography, behavior, land use, public health etc., competence and knowledge in these areas are of great importance.

Some may argue that it is foolish to focus on diseases that have yet to emerge, given the enormous health burdens caused by already established infections such as malaria and tuberculosis. However, if the relatively recent emergence of HIV is taken into consideration, a virus that in less than a generation has established itself as one of the world's biggest killers, the magnitude of the risks imposed are highlighted. HIV proves that even though the vast

majority of emerging pathogens so far only causes minor health problems, there is an always present risk for new fatal diseases with extensive global spread, to develop (Woolhouse et al., 2007). It is an issue of global, not regional, importance, since the rapid international movement of both humans and animals today enables swift spread of disease agents (Woolhouse et al., 2012). Given the fact that anthropogenic activities that are associated with disease emergence, for example deforestation and bushmeat consumption, continues to occur at an un-halted rate, it is likely that the emergence of infectious pathogens will trouble mankind also in the future (Woolhouse, 2002; Woolhouse et al., 2007).

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