RNA Viruses: A Case Study of the Biology of Emerging Infectious Diseases

MARK E. J. WOOLHOUSE, KYLE ADAIR, and LIAM BRIERLEY
Centre for Immunity, Infection & Evolution, University of Edinburgh, Edinburgh EH9 3JT, United Kingdom

ABSTRACT There are 180 currently recognized species of RNA virus that can infect humans, and on average, 2 new species are added every year. RNA viruses are routinely exchanged between humans and other hosts (particularly other mammals and sometimes birds) over both epidemiological and evolutionary time: 89% of human-infective species are considered zoonotic and many of the remainder have zoonotic origins. Some viruses that have crossed the species barrier into humans have persisted and become human-adapted viruses, as exemplified by the emergence of HIV-1. Most, however, have remained as zoonoses, and a substantial number have apparently disappeared again. We still know relatively little about what determines whether a virus is able to infect, transmit from, and cause disease in humans, but there is evidence that factors such as host range, cell receptor usage, tissue tropisms, and transmission route all play a role. Although systematic surveillance for potential new human viruses in nonhuman hosts would be enormously challenging, we can reasonably aspire to much better knowledge of the diversity of mammalian and avian RNA viruses than exists at present.

INTRODUCTION
Viruses account for only a small fraction of the 1400 or more different species of pathogen that plague humans—the great majority are bacteria, fungi, or helminths (1). However, as both the continuing toll of childhood infections such as measles and recent experience of AIDS and influenza pandemics illustrate, viruses are rightly high on the list of global public health concerns (2). Moreover, the great majority of newly recognized human pathogens over the past few decades have been viruses (3) and a large fraction of emerging infectious disease “events” have involved viruses (4).

There are two kinds of viruses: RNA viruses and DNA viruses. The latter largely consist, with the exception of a handful of pox- and herpesviruses, of viruses that have probably been present in and coevolved with humans for long periods of time. RNA viruses are very different. The majority of RNA viruses that infect humans are zoonotic, meaning that they can infect vertebrate hosts other than humans. Many of those that are not regarded as zoonotic are believed to have had recent (in evolutionary terms) zoonotic origins. So it is the RNA viruses that are of greatest interest in the context of One Health.

In this chapter, we review current knowledge of how RNA viruses in humans and other vertebrates are related, in terms of both their evolution and their ecology, with the intention of trying to understand where human RNA viruses came from in the past and where new ones might emerge in the future. Until recently, research on these topics was essentially a series of case studies. Extraordinary work has been done detailing events such as the historical emergence of HIV-1 in Central Africa (5) and the more recent emergence of Nipah virus in Southeast Asia (6). But while every emergence event is a fascinating story in its own right, our aim here is to look beyond the specifics and to try to...
identify any underlying generalities that tell us something useful about the emergence of RNA viruses as a biological process.

We begin by comparing the RNA viruses reported to infect humans with RNA virus diversity as a whole and exploring the overlap between viruses in humans and viruses in other kinds of hosts. Next, we refine the analysis by distinguishing among viruses according to their ability not just to infect humans but also to transmit from one human to another, which is a prerequisite for a virus being able to cause major epidemics and/or become an established, endemic human pathogen. We then consider in more detail the subset of human RNA viruses that can persist in human populations without the need for a nonhuman reservoir. Next, we attempt to identify characteristics of RNA viruses that allow them to cross the species barrier and those that predispose them to cause severe disease, as such viruses are of particular public health concern. We go on to discuss how new human RNA viruses arise (sometimes to subsequently disappear again). From the information assembled we construct a conceptual model of the relationship between RNA viruses in humans and other hosts. We consider how this model might be of practical value, concentrating on risk assessments for newly discovered viruses and also the much discussed topic of the design of surveillance programs for emerging infectious diseases.

**DIVERSITY OF HUMAN RNA VIRUSES**

The diversity of human RNA viruses was recently surveyed using a formal methodology (3), and we update that information here. All RNA viruses known to infect humans were included, with the exception of those only known to do so as the result of deliberate laboratory exposures.

In this chapter, we use virus species as designated by the Ninth Report of the International Committee for the Taxonomy of Viruses (ICTV) (7) (noting that this differs from earlier ICTV reports used in previous work and that it will doubtless change again in the not-too-distant future). ICTV designations may not always accurately reflect the biological meaning of a “species,” i.e., reproductive isolation. The operational criteria used for RNA viruses may include any or all of (i) phylogenetic relatedness based on sequence data, (ii) serological cross-reactivity, (iii) host range, and (iv) transmission route. It is also important to note that any analysis at the level of a virus species implicitly ignores a great deal of biomedically relevant diversity. This point is best illustrated by the influenza A viruses: the epidemiology and public health importance of seasonal influenza A and the H5N1 or H7N9 “bird flu” variants are very different, but all are included within a single species. Less variable virus species than influenza A may still contain multiple serotypes and other functionally distinct subtypes. Despite these limitations, the species remains the most useful unit for studying virus diversity currently available.

Updating the earlier survey (3) with new taxonomic information (7) reveals 180 recognized species of RNA viruses that have been reported to infect humans. These viruses represent 50 genera and 17 families (with one genus, *Deltavirus*, currently unassigned to a family). It is not immediately obvious what we should make of this. Is 180 a large number or a small one? Should we be surprised that it is not much higher or that it is not much lower? We consider such questions further below. We can, at least, be sure that 180 is an underestimate. New human RNA virus species are still being discovered or recognized at a rate of approximately 2 per year, although recent work (8) has suggested that the pool of undiscovered species could be much smaller than previously proposed (3). Even if we still have very little idea of the number of species “out there,” it is, as we will consider in detail later on, possible to say something about where “out there” is.

The possibility of large numbers of as yet unrecognized viruses also raises the specter of ascertainment bias. Certain kinds of RNA viruses may be underrepresented, perhaps dramatically so, among those currently recognized. These might be viruses from particular taxonomic groups, those associated with less severe disease or certain kinds of symptoms, or simply those that are rare and/or occur in less studied regions of the world. While this is clearly an issue, it is worth pointing out that both the rates and kinds of RNA viruses being discovered or recognized have been remarkably consistent for the past half century, despite massive changes in the technologies for virus detection and identification and considerable variability in the effort put into virus discovery in different places and at different times (3).

**RNA VIRUSES OF HUMANS AND NONHUMANS**

One striking observation is that 160 species of human-infective RNA virus species (89% of the total) are regarded as zoonotic; i.e., they can also infect other kinds of vertebrate hosts. (The definition of “zoonotic” ignores arthropod vectors; these are regarded as specialized transmission routes rather than alternative host
species.) The nonhuman hosts usually (>90% of all zoonotic RNA virus species) include other mammals and less commonly (<40%) birds. Humans rarely, if ever, share their RNA viruses with anything else. Although the bias toward sharing viruses with other mammals is obvious, it is less clear whether we preferentially share viruses with particular kinds of mammals. Many human viruses (both RNA and DNA) are shared with ungulates, carnivores, rodents, primates, or bats (3), but our knowledge of the host range of most viruses is too incomplete for us to be confident about any underlying patterns. The remaining 20 RNA viruses are not known to naturally infect nonhuman hosts. However, most of these have close relatives that can infect other mammals. The only exceptions are hepatitis C, hepatitis delta, and rubella virus.

The overlap between the ability to infect humans and the ability to infect other mammals can be illustrated in other ways, too. Of the 62 recognized RNA virus genera containing species that can infect at least one kind of mammal, 50 (81%) contain species that can infect humans. And of the 19 recognized RNA virus families that contain species reported to infect mammals, all but 2 include species found in humans. The exceptions are the Nodaviridae, which are essentially insect viruses, and the Arteriviridae, which include species infecting a range of different mammals, notably including simian hemorrhagic fever virus.

The fact that human-infective species are distributed so widely among the RNA viruses of mammals strongly suggests that, in evolutionary terms, the ability to infect humans is very easily acquired by these viruses. It also implies that many, perhaps most, human RNA viruses need not have arisen by evolving from other human RNA viruses. This idea is supported by a recent analysis of the relationship between phylogeny and host range for three RNA virus families—Paramyxoviridae, Caliciviridae, and Rhabdoviridae—and two genera—Alphavirus and Flavivirus—which concluded that the majority of speciation events were associated with host species jumps (9). Note that this pattern contrasts markedly with the human DNA viruses, among which taxa such as the Papillomaviridae and the Anelloviridae appear to have undergone extensive diversification within humans.

**THE PATHOGEN PYRAMID**

The categorization of viruses based simply on their ability to infect humans fails to distinguish between a vast range of epidemiologies, from occasional very mild cases of Newcastle disease virus infection to pandemics of influenza A or HIV-1. A useful conceptual framework for thinking about this issue is the pathogen pyramid (10). The version of pyramid used here has four levels (Fig. 1).

Level 1 corresponds to human exposure, whether via ingestion, inhalation, the bite of an arthropod vector, or any other route. As discussed in the previous section, the most important sources of exposure are other mammals and, to a lesser degree, birds. There are no good estimates of the total diversity of mammal and bird viruses, but it seems likely that the human population is exposed to hundreds, perhaps thousands, of species on a regular basis. The major determinants of the rate of exposure to new viruses are the ecology and behavior of humans, the nonhuman virus reservoir(s), and (in some cases) arthropod vectors.

Level 2 corresponds to human infection, which we take to mean the ability to enter and replicate in human cells in vivo. For all (known) RNA viruses there are associated host responses, although not all infections necessarily lead to clinical symptoms of disease. Key determinants of the ability to infect humans include the route of entry (e.g., needle sharing has created a new entry route for blood-borne viruses) and the molecular biology of the human-virus interaction (discussed in more detail below). Of the 180 recognized species of RNA viruses that can infect humans, almost 60% (107 species) are restricted to level 2 (Fig. 2).

Level 3 corresponds to the ability both to infect humans and to transmit from one human to another. The ability to transmit refers to all kinds of transmission routes, including vectors. Less than half of human-infective RNA viruses (73 species in all) are able to transmit between humans. A minority of these (26 species) are restricted to level 3 (Fig. 2).

Level 4 corresponds to the ability to transmit sufficiently well that the virus can invade human populations, causing epidemics and/or establishing itself as an endemic human pathogen. In epidemiological parlance, this corresponds to the condition that \( R_0 > 1 \) within the human population, where \( R_0 \) is the basic reproduction number, defined as the number of secondary cases generated by a single primary case introduced into a large population of naïve hosts. In contrast, level 3 viruses have an \( R_0 < 1 \) in humans, which implies that although self-limiting outbreaks are possible, the infection cannot “take off” and cause a major epidemic. Although \( R_0 \) is partly determined by the transmissibility of the virus, it is also a function of the behavior and demography of the human host population; for example,
changes in living conditions, travel patterns, and sexual behavior (for sexually transmitted viruses) can all greatly influence $R_0$. More generally, the term “crowd diseases” implies that certain human viruses (and other pathogens) can only become established once critical host population densities have been reached (10). Our best estimate is that there are 47 level 4 RNA virus species in humans (Fig. 2).

A useful exercise is to consider what kinds of viruses are found at levels 2, 3, and 4 in the pyramid. There appear to be three major determinants of this: (i) taxonomy (at the level of both family and genus), (ii) transmission route (especially the distinction between vector-borne transmission and other routes), and (iii) host range (expressed here as the ability to infect different mammalian orders). These three factors are not independent (1); in particular, there are very few vector-borne viruses with narrow host ranges (11).

Nonetheless, several patterns can be identified. First, only two vector-borne viruses are found at the top of the pyramid (level 4): yellow fever and dengue (Fig. 2). It is not immediately apparent why this should be so; we will consider this point further later on. Second, viruses with a host range that is, as far as we know, restricted to primates are rarely found lower down on the pyramid (levels 2 and 3), with a few exceptions such as the simian foamy viruses. The obvious implication is that if a virus is capable of infecting and transmitting from our closest relatives, then it is very likely to have the same capabilities in us. Patterns are also apparent in the taxonomy of human-infective viruses: for example, the Bunyaviridae, Rhabdoviridae, Arenaviridae, and Togaviridae (with the exception of rubella, which is atypical of that group) are not represented at level 4 at all. This reflects the fact that these four families are made up of viruses that are vector borne and/or are not primate specialists.

**FIGURE 1** A representation of the pathogen pyramid. Each level of the pyramid represents a different degree of interaction between a virus and a human host. Level 1 corresponds to exposure of humans, level 2 to the ability to infect humans, level 3 to the ability to transmit from one human to another, and level 4 to the ability to cause epidemics or persist as an endemic infection. Arrows indicate pathways that viruses may take to reach each level. For example, a level 4 virus may arrive at that state directly, simply by exposure to the virus from a nonhuman reservoir. This is known as an “off-the-shelf” virus. Alternatively, it may initially enter the population as a level 2 or 3 virus—not capable of sustained transmission—but evolve the ability to transmit between humans at a sufficiently high rate to persist within a human population. This is known as a “tailor-made” virus. Adapted from reference 25. doi:10.1128/microbiolspec.OH-0001-2012.f1
Finally, it is worth noting that the “shape” of the pathogen pyramid for RNA viruses differs from that for nonviral human pathogens. Most strikingly, much smaller fractions of recognized species of bacteria, fungi, protozoa, or helminths are capable of extensive spread in human populations (i.e., are found at level 4). On the other hand, human DNA viruses are even more concentrated at the top of the pyramid, with almost 90% of species at level 4. These patterns could simply be an artifact of our incomplete knowledge of virus diversity at lower levels of the pyramid, but they could also reflect real biological differences between viruses and other kinds of pathogens: viruses (especially DNA viruses) may be more likely to speciate within humans, or viruses (especially RNA viruses) that jump the species barrier into humans may be more capable of spreading in human populations or of rapidly evolving that capability (see below).

HUMAN-ADAPTED RNA VIRUSES

There is a semantic argument that only those viruses that are capable of persisting in human populations in the absence of a nonhuman reservoir should be described as...
“human” viruses. In our terminology these are, by definition, the level 4 viruses, comprising 47 species, 20 of which are not known to have any natural hosts other than humans. These 47 viruses—referred to here as “human adapted”—represent 12 families and 29 genera. Their most striking common characteristic is that almost all of them are transmitted by ingestion, inhalation, or direct contact; just 2 are transmitted by vectors.

There are several possible routes for a virus to reach level 4 on the pathogen pyramid (indicated by the arrows in Fig. 1). One possibility is that humans are exposed to a virus that is already capable of effective transmission between humans; i.e., the virus is preadapted to humans (noting that this does not preclude further adaptation once the virus has entered the human population). These have been termed “off-the-shelf” viruses. Such viruses may be rare, perhaps extremely rare, variants of the population in the nonhuman reservoir, in which case the main determinants of the rate at which such viruses enter the human population is the amount of genetic variability within the reservoir and the rate at which humans are exposed to the preadapted variants.

Another possibility is that the virus first enters the human population with limited ability to transmit between humans (i.e., level 3) but that it is able to evolve that ability before the otherwise self-limiting chain of infections dies out (12). These have been termed “tailor-made” viruses. Key determinants of the rate at which such viruses invade the human population are the frequency of primary infections and the virus mutation rate. We note that for a level 2 virus to evolve human transmissibility, this would have to happen during the course of a primary infection. Such infections presumably give evolution relatively little material to work with, and it may be that level 2 viruses are “dead ends” in an evolutionary sense as well as an epidemiological sense. For example, rabies infections are relatively common in humans and are likely to have been so for thousands of years, but human-transmissible variants have failed to materialize (with the proviso that rabies is technically a level 3 pathogen because of rare instances of human-to-human transmission via organ transplants).

The origins of the human-adapted RNA viruses are of considerable interest, not least as a possible pointer to the likely sources of future viral threats to human health. It has previously been noted (10) that we have information on the origins of only a small minority of human pathogens, including RNA viruses. However, as stated above, it seems likely that many of them arose by species jumps from other mammals or (less often) birds, perhaps followed by some diversification within humans (e.g., human enteroviruses or parainfluenza viruses). The direct transmission routes used by most of these viruses are consistent with their being crowd diseases; that is, in contrast to vector-borne viruses, the basic reproduction number increases with human population density.

MECHANISMS
As explained above, whether a virus is found at level 2, 3, or 4 of the pyramid reflects its ability to transmit from one human to another. Human demography and behavior play a key role in this, but of course, intrinsic properties of the virus are also crucial.

The first consideration is the ability of the virus to infect humans at all. Given the importance of this topic, we know surprisingly little about it. In effect, the question comes down to factors that restrict host range. Empirically, it does seem that the species barriers between different mammals, including humans, are very leaky: the majority of known mammal RNA viruses are capable of infecting multiple species. Only two studies (3, 13), however, have looked systematically at mechanisms, showing that use of a phylogenetically conserved receptor to gain entry to host cells is a necessary but not sufficient condition for a virus to be able to infect both humans and nonprimates. This result appears robust, but the data are incomplete because the cell receptor has yet to be identified for the majority of human viruses.

Gaining entry to host cells is only the first step in initiating an infection. The virus must also be capable of replicating in host cells, being released from host cells, evading the innate immune response, and perhaps becoming systemic. All of these processes depend on the specifics of the molecular interplay between virus and host, and all can contribute to the species barrier and host range restriction (14). The species barrier may be quantitative rather than qualitative, perhaps expressed by the need for a higher infective dose. In one of very few experimental studies of the species barrier (15), it was found that the 50% lethal dose for rabies virus obtained from foxes was up to a million times lower for foxes than it was for cats and dogs. Similarly, there is evidence that human influenza A viruses can replicate in chimpanzees but do so at a much lower rate (14).

The ability to get into (i.e., infect) a host does not equate with the ability to get out of (i.e., transmit from) that host. A key determinant of the ability to transmit is the virus’s capacity to invade and replicate in cells of
particular tissues, notably the lower gastrointestinal tract, the upper respiratory tract, the urogenital tract, or possibly the blood or skin. In a few cases, the determinants of tissue tropisms are well understood. For example, H5N1 influenza A transmits well from ducks and poultry but not from humans. This is because it utilizes a variant of the sialic acid receptor in the host cell membrane that occurs in the upper respiratory tract of ducks and poultry but is confined to the lower respiratory tract of humans (14).

Tissue tropisms inevitably play a key role in determining the route of virus transmission (e.g., respiratory, Enterobacteriaceae, or arthropod vector). It has been suggested that altering tissue tropism is harder for a virus to achieve than switching host species (9). This idea is borne out by the observation that transmission route tends to be a relatively deep-rooted trait in virus phylogenies, often to the level of family, in marked contrast to host range, which tends to be far more labile.

These few mechanistic and ecological insights fall well short of a proper understanding of why some kinds of viruses tend to occur at higher or lower levels of the pathogen pyramid. Host relatedness seems to play a role; hence, viruses from other primates do seem more likely to be transmissible in humans than those acquired from nonprimates, an idea supported by other studies of host relatedness and pathogen transmissibility (16). But not all highly transmissible human viruses have been acquired from other primates. Transmission route is also important; vector-borne viruses in particular seem to be relatively good at infecting humans but relatively poor at being transmitted by humans (17). It is possible that although humans are frequently exposed to vector-borne viruses, some of which are capable of setting up an infection, these viruses are not easily able to adapt to a new host (perhaps because any adaptation to a new vertebrate host must not compromise their interaction with the invertebrate vector [14]). Those that have adapted to humans—dengue and yellow fever—are ones that probably originated in other primates.

**VIRULENCE**

In public health terms the ability of a virus to spread through human populations is, of course, only part of the story; human RNA viruses also vary enormously in the degree of harm they cause, a characteristic referred to as virulence. In the context of human infections we generally regard a pathogen as virulent if it has a high case-fatality ratio or if infection routinely results in severe clinical disease. On this basis, HIV-1, severe acute respiratory syndrome coronavirus (SARS-CoV), and rabies would be regarded as virulent, whereas parainfluenza and rhinoviruses would not.

Pathogen virulence is a very complex phenomenon, reflecting properties of the pathogen, the host, and the interaction between them. It has been variously proposed that virulence is influenced by transmission route, host range, level of the pathogen pyramid, and the time that the pathogen and the host have had to coevolve (see reference 18 for an introduction to a large body of literature). These characteristics are not independent, so hypothesis testing is not straightforward, although some theories do look promising. For example, the only two recent instances of newly emerging level 4 pathogens—HIV-1 and SARS-CoV—are/were both spectacularly virulent, in line with ideas that the virulence of novel host-pathogen combinations need not be near any evolutionary optimum. The only two level 4 RNA viruses that are vector borne—dengue and yellow fever—are also relatively virulent, in line with ideas that vector-borne diseases can be more virulent because an ambulant host is not needed for transmission. There are also good examples of very virulent RNA viruses, such as rabies, for which humans are effectively dead-end hosts, in line with ideas that such infections are not subject to any evolutionary constraints because they do not contribute to the next generation of infections. On the other hand, many level 2 viruses, such as Newcastle disease virus, Sindbis virus, and others, result in only mild infections, so rabies may just lie at one end of a broad spectrum.

Another idea is that viruses acquired from particular kinds of reservoirs, primates versus nonprimates or mammals versus birds, might be especially virulent. The evidence, however, is inconsistent in this regard. It is true that some highly virulent human viruses, such as HIV-1 and dengue, were acquired from or are shared with other primates, our closest relatives. On the other hand, some highly virulent viruses are ultimately acquired from hosts much more distantly related to humans, such as H5N1 influenza A from birds or SARS and Nipah viruses from bats.

This important topic would clearly benefit from a systematic survey of the virulence of human RNA viruses (none has been published to date), which could be used to construct formal tests of the various hypotheses about pathogen virulence to be found in the evolutionary biology literature.
EMERGENCE AND THE CHANGING CAST OF RNA VIRUSES

New RNA virus species continue to be discovered, identified, or recognized in humans. Recent examples include Nelson Bay orthoreovirus, Irkt virus, primate T-lymphotropic virus 3, human coronavirus HKU1, and human rhinovirus C. Moreover, there is usually a backlog of reports of new human viruses that have yet to be formally recognized as species. Not all of these viruses will have recently invaded human populations; many will turn out to be long-standing human pathogens that have only recently been recognized or accepted as “species.”

It is therefore important to understand that the continued accumulation of recognized human RNA virus species may reflect less the possibility that genuinely new viruses are continually emerging, most likely acquired from nonhuman reservoirs, than the fact that we are still getting to grips with the taxonomic diversity of viruses that have been with us for some time. This distinction between viruses that we have only just discovered and viruses that have only just discovered us is, of course, crucial in the context of emerging infectious diseases. If most of the so-called new viruses are not new at all, then this implies that events such as the advent of HIV/AIDS in the early 1980s or the curtailed SARS epidemic in 2003 may be just unusual, one-off occurrences with their own specific causes. If, on the other hand, genuinely new viruses are appearing all the time, then the HIVs and SARS-CoVs are more accurately regarded as just the highly visible tip of a much larger iceberg. Without a much more detailed and thorough understanding of the phylogenies and origins of all human viruses, not just those with high public health profiles, we cannot resolve this question.

Perhaps the most striking feature of recently discovered RNA viruses is that they tend to be much like the RNA viruses that we already knew about. They are members of the same virus families, have the same transmission routes, and share the same kinds of nonhuman hosts. If these newly recognized viruses are indeed emerging, then it seems as though there is nothing special about emergence, at least from a biologist’s perspective. Even if this is correct, it is still often suggested that the rate, if not the biology, of pathogen emergence is higher in the early 21st century than it has been in the past. This reflects the notion that a variety of so-called drivers of emergence, ranging from human population growth to changes in farming methods, are combining to create a “perfect storm.” This idea is difficult to evaluate critically. Arguably there have been only a handful of global emergence events in the past century, notably those involving HIV-1, variants of influenza A, and SARS-CoV. This is not a strikingly large number given that many of the other 40 or so human-adapted RNA viruses may have emerged only in the past few millennia. Of course, it could be argued that less dramatic events such as the geographical spread of West Nile virus or outbreaks of Ebola are more frequent now than they have been in the past, but that claim is even harder to test with any rigor.

Another side to this issue is rarely discussed. One recent study [8] reports that while the number of virus species accumulates, at the same time many of those recognized in past years or decades seem to have disappeared, these making up about one-third of the total. There is, of course, one well-known example of the eradication of a human RNA virus through human intervention, SARS-CoV, accompanying the even more impressive story of the eradication of smallpox, a DNA virus. However, there are many more examples of viruses that seem to have disappeared of their own accord, an unexpected observation worthy of careful consideration. There are several possibilities. First of all, rare infections, especially those with mild or common clinical presentations, may simply have been missed or no one has bothered to report them. Another possibility is that reports from earlier times are unreliable; for example, it is striking that no human cases of foot-and-mouth disease have been noticed since a handful of reports in the mid-1960s. But it seems likely that many of the missing viruses have indeed disappeared, at least temporarily, from humans, even if they are still present in nonhuman reservoirs. Some, of course, could reappear in humans at some point in the future: this has happened for the bat lyssaviruses, for example, and is a worrying possibility for SARS-CoV.

The implication of these missing viruses is that the extant diversity of human RNA viruses is perhaps closer to 100 species than the figure of 180 given earlier. The number of missing species corresponds, very roughly, to an average loss rate of 1 per year [8]. Another way of expressing this is that there would have to be one new or rediscovered species of human RNA virus reported every year just to maintain the level of diversity that we are aware of at present.

A CONCEPTUAL MODEL

All of the above is consistent with the following conceptualization of the relationship between RNA viruses that can infect humans and those found in other kinds of
hosts, particularly other mammals. Rather than being distinct groups, viruses of humans and viruses of other mammals are readily interchanged over evolutionary time. Some of the viruses that cross the species barrier into humans persist and may become human-adapted viruses, though this seems to be a relatively rare occurrence. Many of the others remain as zoonoses, and yet others disappear again. The repertoire of human viruses is therefore not fixed but is dynamic, over time scales measured in decades (8). However, this process is far from random. Although humans share their RNA viruses with many different mammalian taxa, those from other primates appear most likely to be capable of spreading through human populations. Similarly, although almost every family of viruses found in mammals contains species found in humans, some virus families seem to be capable of, at best, limited spread in human populations. This conceptual model is illustrated diagrammatically in Fig. 3.

**SURVEILLANCE AND RISK ASSESSMENT**

Our conceptual model has practical implications for both disease surveillance and risk assessment, especially in the context of newly emerging infectious diseases.

The importance of early detection of potential epidemics or pandemics cannot be overstressed, a point made by several major studies (2). The early detection through clinical surveillance of SARS, coupled with effective intervention based on case isolation and quarantine, prevented a potentially catastrophic pandemic (19). A matter of some debate is whether or not surveillance should be extended into the nonhuman reservoirs of infection from which novel human pathogens are most likely to emerge—a concept sometimes referred to as “getting ahead of the curve.”

It helps, of course, if we know what we are looking for and where best to look for it (20). We currently have only the beginnings of answers to these questions. Viruses, especially respiratory viruses, are often picked out as the most obvious threat to global public health (2). New viruses are very likely to have a zoonotic origin, almost certainly acquired from mammals or birds. Emergence events are most likely to occur in regions—so-called hot spots—that combine high human population densities with high densities of domestic animals and/or a high diversity of wildlife (4). All of this information is useful but falls well short of a recipe for designing a feasible global surveillance system (20).

One strategy to increase the likelihood of early detection is to implement sentinel surveillance in people in close, high-risk contact with animal populations, such as bush meat hunters or slaughterhouse workers. In tandem with recent advances in the technologies available for virus detection—especially those based on high-throughput nucleic acid sequencing—such programs should at least improve our knowledge of the diversity of viruses “out there” that humans are exposed to, a process sometimes referred to as “chatter” (10). Pathogen discovery programs, particularly in understudied taxa such as wild rodents and bats (21), should also add greatly to our knowledge of potential threats to human health.

Once a novel or previously unknown virus is identified, it is obviously important to assess any potential risk to public health. Initial assessments are generally based on the kind of comparative biology approach discussed here. A recent example of this is Schmallenberg virus, a novel virus first detected in sheep and cattle in northern Europe in 2011. Schmallenberg is a member of Orthobunyavirus, a diverse genus of vector-borne bunyaviruses that are found in a variety of...
hosts but especially in ungulates. Given these characteristics, and despite the fact that some distantly related orthobunyaviruses—notably Oropouche virus—do cause disease in and may even be transmitted by humans, Schmallenberg was provisionally designated low risk to humans and no human cases have yet been found. The even more recently reported Middle East respiratory syndrome (MERS) coronavirus has rightly caused much more concern.

CONCLUDING REMARKS
Emerging diseases caused by RNA viruses are a One Health issue. There is a continuous interchange, over both epidemiological and evolutionary time scales, between viruses in humans and viruses in other animals that we cannot ignore. RNA viruses that pose serious threats to global public health have arisen repeatedly by jumping into humans from other animals. This has been going on for millennia and it continues today, as fast as ever and perhaps even faster. We have to anticipate that new viral threats will emerge in coming years or decades and we need to be prepared to rise to these new challenges as they appear.

It is worth pointing out that the first virus was discovered in nonhuman animals (foot-and-mouth disease virus at the very end of the 19th century) before they were identified in humans. The same is true for several important kinds of viruses, such as retroviruses (and lentiviruses specifically), rotaviruses, papillomaviruses, and coronaviruses. A corollary of this is that veterinary rather than medical expertise may, at least initially, be our best source of knowledge about newly discovered viruses.

We have discussed the need for more effective surveillance for novel viruses but concluded that although attempts to characterize the kinds of viruses most likely to emerge are useful, precise prediction is not a realistic objective, for now at least. On the other hand, there could be considerable benefit from a better understanding of RNA virus diversity in the most important host species. At present we do not even have a complete inventory of the viruses in humans, and while we have some knowledge of the viruses in major livestock species, we know very little about the viruses present in wild mammals or birds. These gaps can and should be filled: we need to know what is out there now, and what might be waiting around the corner.

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