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Cross-Species Virus Transmission and the Emergence of New Epidemic Diseases

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INTRODUCTION

Newly emerging viral diseases are major threats to public health. In particular, viruses from wildlife hosts have caused such emerging high-impact diseases as severe acute respiratory syndrome (SARS), Ebola fever, and influenza in humans. The emergence of these and many other human diseases occurred when an established animal virus switched hosts into humans and was subsequently transmitted within human populations, while host transfers between different animal hosts lead to the analogous emergence of epizootic diseases (Table 1). The importance of viral host switching is underscored by the recent avian epizootics of high-pathogenicity strains of H5N1 influenza A, in which hundreds of "spillover" human cases and deaths have been documented. Epidemiological data suggest that the toll on human populations would be enormous if the H5N1 virus acquired efficient human-to-human transmissibility while retaining high human pathogenicity (25, 83). Considered an archetypal host-switching virus for its ability to infect a wide range of avian and mammalian species and for causing frequent zoonotic infections and periodic human pandemic transfers (Fig. 1 and Table 2), the actual or threatened emergence of a new influenza A virus is a cause for alarm. Fortunately for us, most viral host transfers to infect the new hosts cause only single infections or limited outbreaks, and it is rare for a virus to cause an epidemic in a new host.

Three stages of viral disease emergence leading to successful host switching can be identified: (i) initial single infection of a new host with no onward transmission (spillovers into "dead-end" hosts), (ii) spillovers that go on to cause local chains of transmission in the new host population before epidemic fade-out (outbreaks), and (iii) epidemic or sustained endemic host-to-host disease transmission in the new host population (Fig. 2). Variables that affect successful disease emergence influence each of these stages, including the type and intensity of contacts between

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TABLE 1. Examples of viruses that transferred between hosts to gain new host ranges so that they cause outbreaks in those new hosts

Virus(es)	Original host	New host	Mechanism and/or time
Measles virus	Possibly cattle	Humans	Host switching and adaptation? Time not known; after the establishment of populations sufficient to allow transmission
Smallpox virus	Other primates or camels(?)	Humans	Host switching and adaptation? Time >10,000 yr ago?
Influenza virus	Water birds	Humans, pigs, horses	Host switching and adaptation, possible role of intermediate host; many examples. In humans viruses emerged in the period ~1910–1916 and in ~1957 and ~1968. Reassortment involved in 1957 and 1968 emergences. Earlier epidemic viruses not characterized. Changes in several genes required for success in new host
CPV	Cats or similar carnivores	Dogs	Host switching and adaptation; several mutations in the capsid control binding to the canine transferrin receptor. Arose in early 1970s, spread worldwide in 1978
HIV-1	Old World primates, chimpanzees	Humans	Host switching and adaptation; virus entered human population approximately in 1930s and spread widely in 1970s; multiple introductions likely to give the HIV-1 M, N, and O variants
SARS CoV	Bats	Himalayan palm civets or related carnivores; humans	Host switching, adaptation; some adaptation for binding to the ACE2 receptor in humans. 2003–2004
Dengue virus	Old World primates	Humans	<500 yr before present?
Nipah virus	Fruit bats	Humans (via pigs, or direct bat-to-human contact)	Host switching; adaptation may not be necessary: bat and human isolates identical in some outbreaks
Marburg virus and Ebola viruses	Reservoir host not proven (bats?)	Chimpanzees and humans	Host switching; adaptation not certain
Myxoma virus	Brush rabbits and Brazilian rabbits	European rabbits	Existing host range, required contact; spread widely in 1950s by human actions; high virulence, adaptation after host emergence
Hendra virus	Fruit bats	Horses and humans	Host switching; adaptation not reported
Canine influenza virus	Horses	Dogs	Host switching; adaptation to dog may be occurring

the reservoir (donor) host or its viruses and the new (recipient) host, host barriers to infection at the level of the organism and cell, viral factors that allow efficient infections in the new host, and determinants of efficient virus spread within the new host population (Fig. 3).

SOURCES OF NEW EPIDEMIC VIRUSES IN HUMANS AND OTHER ANIMALS

The major sources of new human viral diseases are enzootic and epizootic viruses of animals (149). We likely know only a small fraction of the viruses infecting wild or even domesticated animals (16, 18, 112, 139). The risks of such unrecognized viruses are highlighted by the emergence of SARS coronavirus (CoV), hantaviruses, Ebola and Marburg viruses, Nipah virus, Hendra virus, and human immunodeficiency virus type 1 (HIV-1) and HIV-2, all cross-species host switches of established enzootic viruses that were unknown before their emergences into humans (40, 143, 145).

HIV/AIDS is an important recent example of viral emergence by host switching. Following its emergence into humans from primates an estimated 70 years ago, HIV has infected hundreds of millions of people. Despite our increased understanding of the virus and the development of effective antiviral therapies, an estimated 1.8 to 4.1 million new human HIV infections still occur each year (2, 77). A recent example of viral disease emergence by host switching is the CoV causing SARS, which infected thousands of persons and spread worldwide in 2002 and 2003 (156). Before being controlled by aggressive public health measures, SARS CoV caused hundreds of deaths and economic disruption amounting to $40 billion (66). Other important human viruses (e.g., measles and smallpox) may have originated in wildlife or domesticated animals in prehistoric times (144). It is therefore important that we understand how viruses enter and spread in new hosts, including the demographic factors, host and cellular properties, and the controls of virus transmission.

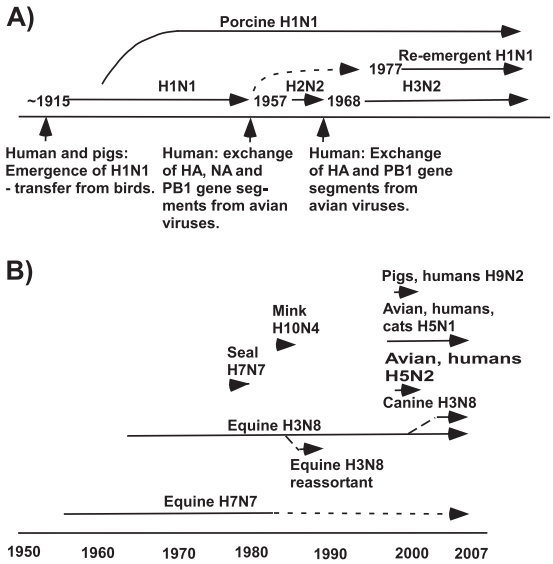

FIG. 1. (A) Known human influenza A pandemics. (B) Animal epidemic and pandemic strains, outbreaks, and human transfers in the past 60 years. Human pandemics of influenza include the related H1N1, H2N2, and H3N2 pandemics, while the transfers to other mammalian or avian hosts that have given rise to epidemic strains or that have resulted in human infection are also shown. More is known about the recent transfers to humans, and it is likely that previous transfers occurred but are not well characterized. Information taken from reference 65.

ENVIRONMENTAL AND DEMOGRAPHIC BARRIERS TO HOST SWITCHING

Cross-host exposures are an important step in transference to new hosts, and some host-switching events are likely prevented because of limited contact between the viruses and the potential new hosts. For example, both HIV-1 and -2 have transferred to humans multiple times since approximately 1920 to create new epidemic virus clades. A major barrier to establishing an epidemic in humans prior to the global emergence of the viruses in recent decades was likely the limited opportunity for primate-to-human exposure that was followed by a level of interhuman encounters sufficient to allow virus transfer and establishment. In most other cases, in particular where the alternative hosts are frequently exposed to new animal viruses,

TABLE 2. Recent outbreaks of influenza A virus where human infection by the virus has been confirmed

Influenza A virus subtype	Location of outbreak	Year of outbreak	No. of human cases	No. dead
H7N7	United Kingdom	1996	1	0
H5N1	Hong Kong	1997	18	6
H9N2	Southeast Asia	1999	>2	0
H5N1	Hong Kong	2003	2(?)	1(?)
H7N7	The Netherlands	2003	89	1
H7N2	United States	2003	1	0
H7N3	Canada	2004	2	0
H5N1	Southeast Asia	2004 and thereafter	>300	>200

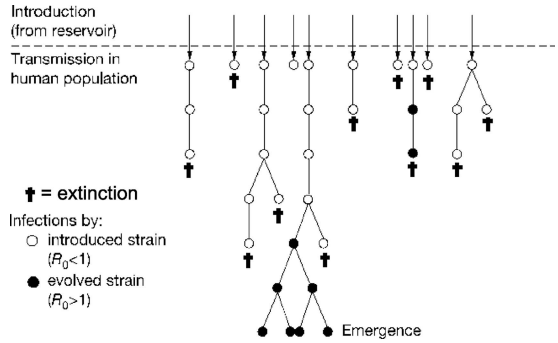

FIG. 2. Diagrammatic representation of the steps involved in the emergence of host-switching viruses, showing the transfer of viruses into the new host (e.g., human) population with little or no transmission. An occasional virus gains the ability to spread in the new host ($R_0 > 1$), and under the right circumstances for transmission those viruses will emerge and create a new epidemic. (Adapted from reference 3 with permission from Macmillan Publishers Ltd.)

transfer is impeded by the requirement for multiple and complex adaptive virus changes.

Ecology and Contact with Alternative Hosts

Contact between donor and recipient hosts is a precondition for virus transfer and is therefore affected by the geographical, ecological, and behavioral separation of the donor and recipient hosts. Factors that affect the geographical distribution of host species (e.g., wildlife trade and the introduction of domestic species) or that decrease their behavioral separation (e.g., bush meat hunting) tend to promote viral emergence (80). Human-induced changes may promote viral host switching from animals to humans, including changes in social and demographic factors (e.g., human population expansion and travel), in human behavior (e.g., intravenous drug use, sexual practices and contacts, and farming practices), or in the environment (e.g., deforestation and agricultural expansion) (88, 140). Various approaches have been used to analyze factors that influence the incidence of zoonotic disease and to predict the global distribution of risk of zoonotic disease emergence (51).

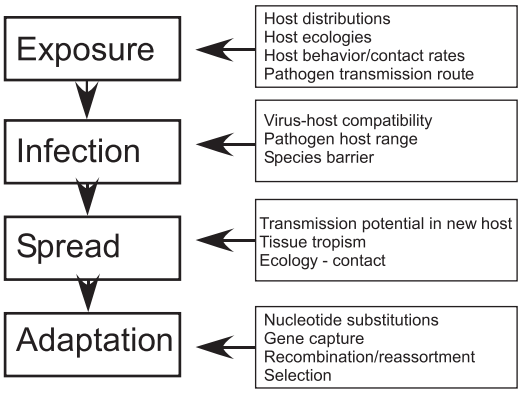

FIG. 3. The steps involved in the emergence of host-switching viruses, showing the host and viral processes that can be involved in the transfer and adaptation process (based on data from reference 149).

The density of the recipient host population is important in the onward transmission and epidemic potential of any transferred virus (16, 18, 21, 143, 149). Human trade and travel patterns have been examined to characterize the spread of important insect vectors of viruses such as *Aedes albopictus* mosquitoes (122) and of viral pathogens such as SARS CoV (47). They have also been examined to predict the likely pathways of the future spread of H5N1 avian influenza through trade and bird migration (57). Patterns of host contact and density may have critical impact on disease emergence. For example, simian immunodeficiency viruses (SIVs) are common in Old World primates and are likely to have caused many dead-end zoonotic infections in the past, but the separation of SIV-infected primates in the jungles of central Africa from major human populations likely limited the spread of spillovers to single infections or to small and isolated human clusters (55, 130, 143). To become fully established, HIV likely required not only genetic changes to confer human adaptation, which was partially accomplished in intermediate (chimpanzee) hosts, but also facilitative changes in human behavior (e.g., travel and sexual behavior patterns) and spread to high-density populations to sustain onward transmission. In contrast, influenza A viruses are carried long distances by migratory birds, allowing them to become widely dispersed geographically (85).

Intermediate and amplifier hosts may play a critical role in disease emergence by bringing animal viruses which would normally have little contact with alternative hosts into close contact with recipient hosts. For example, the emergence of Nipah virus in Malaysia was facilitated by intensive pig farming, which amplified epizootic virus transmission and therefore increased human exposure (27, 63). Fruit bats (genus *Pteropus*) are the reservoirs of Nipah virus, and planting of fruit orchards around piggeries attracted these bats, allowing spillovers of viruses to pigs and a large-scale outbreak (17), showing how ecological changes brought about by humans can impact disease emergence. Similarly, for the SARS CoV, the infection appears to have originated in bats and then infected humans along with civet cats (*Paguma larvata*) and other farmed carnivores. While the exact pathway of transfer is uncertain, it is possible that the infection of the domesticated animals resulted in increased human exposures (131, 134, 156). Human infection with H5N1 influenza viruses most often occurs after the infection of poultry on farms or in live bird markets, allowing viruses of wild birds to gain access to human populations (90, 146).

HOST BARRIERS TO VIRUS TRANSFER

To infect a new host, a virus must be able to efficiently infect the appropriate cells of the new host, and that process can be restricted at many different levels, including receptor binding, entry or fusion, trafficking within the cell, genome replication, and gene expression. The production and shedding of infectious virus may also be host specific. Multiple host barriers to infection would each require one or more corresponding changes in the virus, making the host range barrier increasingly difficult to cross. Other significant impediments to infection can include innate antiviral responses (such as interferon- and cytokine-induced responses) or other cellular barriers or responses that restrict infection by particular viruses, such as apolipoprotein B-editing catalytic polypeptide (APOBEC) proteins and tripartite motif (TRIM5α) protein (see below).

The Role of Host Genetic Separation

Spillover or epidemic infections have occurred between hosts that are closely or distantly related, and no rule appears to predict the susceptibility of a new host. Repeated virus transfers between chimpanzees and humans, who are closely related, resulted in HIV establishment (see above), while the transfer of a feline panleukopenia virus (FPV) to dogs reflected adaptation between hosts from different families in the order Carnivora. A SARS CoV-like virus of bats was apparently transferred to the distantly related humans as well as to civets and other carnivores (49, 64, 71, 49, 145). Avian influenza viruses or their genomic RNA segments may be transferred to humans or other mammals (54, 58, 74, 87, 125). The recent transfers of H3N8 equine influenza virus to dogs (14) and of avian H5N1 to cats were transfers between hosts in different vertebrate orders and classes, respectively.

While the evolutionary relatedness of the hosts may be a factor in host switching, the rate and intensity of contact may be even more critical. Viral host switches between closely related species (e.g., between species within genera) may also be limited by cross-immunity to related pathogens or by innate immune resistance to related viral groups.

Host Tissue Specificity and External Barriers in Alternative Hosts

An initial level of protection of hosts against viruses occurs at the level of viral entry into the skin or mucosal surfaces or within the blood or lymphatic circulation or tissues. Defenses may include mechanical barriers to entry as well as host factors that bind to virion components to prevent infection. For example, glycans or lectins (often called serum or tissue inhibitors) may bind and eliminate incoming viruses. This was seen for human influenza viruses, which may bind to sialylated α-2-macroglobulin in porcine plasma and to alternative sialylated glycoproteins in other animals (78, 97, 98). Viruses which lack efficient neuraminidase or esterase activity for the glycans of the new hosts may be bound and inactivated, requiring that viruses infecting those hosts rapidly adapt. Galactosyl(α1-3)galactose is a glycan that is not found in humans but is present on some intestinal bacteria, so that it elicits an antibody response in humans. Virions produced in hosts which have galactosyl(α1-3)galactose-modified proteins will rapidly be recognized and inactivated by these antibodies when they enter humans, preventing infection (120, 121).

Receptor Binding

The initial viral interaction with cells of a new host is a critical step in determining host specificity, and changes in receptor binding often play a role in host transfer. For example, the SARS CoV was derived from viruses circulating enzootically in a number of bat reservoirs, and the bat-derived viruses interact differently with the angiotensin-converting enzyme 2 (ACE2) receptors of humans and carnivore hosts such as Himalayan palm civets (*Paguma larvata*), which harbor vi-

ruses that are closely related to the human viruses (see also below) (69, 71, 96). FPV changed its host range to infect dogs by binding specifically to the orthologous receptor on the cells of the new host, the canine transferrin receptor (46). Mammalian and avian influenza viruses bind preferentially to different sialic acids or glycan linkages that are associated with particular hosts (109, 117, 150). In addition, avian and mammalian viruses infect cells of different tissues and must recognize sialic acids found on cells of the intestinal tracts of waterfowl or in the respiratory tracts of humans or other mammals (37) so that changes in the binding sites can be selected rapidly as the viruses adapt to new hosts (32, 109, 150). HIV-1 shows some host specificity of binding to the CD4 host receptor and the CCR5 or CXCR4 coreceptors (91, 95).

Gaining the ability to bind the new receptor effectively may be a complex process and require multiple changes in the virus. For SARS CoV, the receptor binding motif includes a short region of the S protein which controls specific ACE2 binding; this motif is largely missing from other group 2 CoVs and from related bat CoVs and may have been acquired from a group 1 CoV by recombination with subsequent mutations (71) (Fig. 4). In the case of canine parvovirus (CPV), the FPV gained at least two mutations that allowed it to bind effectively to the canine transferrin receptor (45, 86). The capsid changes were structurally separate in the assembled capsids but acted together to control receptor binding (34, 86).

Intracellular Host Range Restrictions

After receptor binding, restriction may also occur at other levels in viral infection cycles. For example, several intracellular mechanisms restrict cell infection by retroviruses (6). For HIV-1 and SIV-like viruses in human cells, APOBEC-3G, -3F, and related cytidine deaminases are packaged into virions which lack an appropriate Vif (*v*iral *i*nfectivity *f*actor) protein (30, 99, 153, 157). The APOBEC proteins block infection during the infection of the next cell, although the precise mechanism is not known, as the primary enzymatic activity of the APOBEC, cytidine deamination, is not essential for the antiviral activity (7, 84). The TRIM5α protein binds the incoming capsid protein in the cytoplasm and restricts infection in a host-specific process that depends on the capsid protein structure (72, 116, 152). The adaptation of HIV-1 to humans from chimpanzees was associated with a change in the p17 Gag protein, which may be involved in the specific targeting of the protein within the host cell cytoplasm (133).

Interferon responses protect cells against viruses and are often found to be host specific and to act as host range barriers. For example, murine noroviruses have a broad cell binding ability but are restricted after cell entry by alpha and beta interferons and by STAT-1-dependent responses (53, 141, 142). Interferon responses against influenza viruses can be strain specific. The NS1 protein has been shown to have various effects in infected cells, including regulation of the interferon-induced signaling and effector mechanisms (26). This has been seen for certain NS1 variants of avian H5N1 influenza viruses which show an enhanced virulence for pigs (59, 104).

Other viral proteins involved in the replication of influenza A viruses may also show host-specific activities, and there is often a requirement for particular combinations of proteins.

A)

Predominant S-protein amino acids

S-protein residue #	SARS-CoV from 2003-2004 (e.g. GD03)	SARS-CoV from palm civets (e.g. SZ3)	SARS-CoV from 2002-2003 (e.g. TOR2)
479	N	K	N
487	S	S	T

Most efficient ACE2 association:

S-protein residue #	Reservoir ACE2	Palm civet ACE2	Human ACE2
479	K?	K=N	N
487	S?	T	T

B)

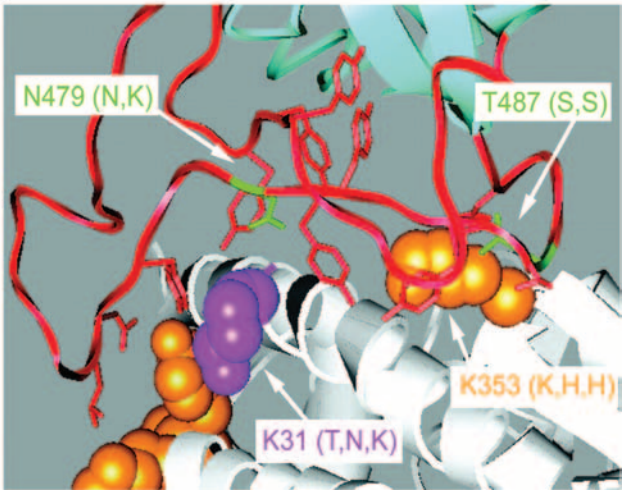

FIG. 4. Some of the virus receptor changes involved in the virus-host interactions of the SARS coronavirus S protein, showing the variation of some residues that affect binding to the receptors (ACE2) from different hosts. (A) The distribution of S protein residues 479 and 487. (Top) The most frequently observed residues from sequences of viruses obtained during the human SARS CoV epidemic of 2002 and 2003, from sporadic infections from 2003 and 2004, and from palm civets in Guangdong, China. One palm civet virus (of >20 sequences examined) had Thr at 487, which is found in all human sequences from the 2002-2003 epidemic (>100 sequences). (Bottom) S-protein residues conferring efficient binding to the ACE2 proteins of the indicated species (the entry for reservoir species [likely bats] is speculative). GD03 and TOR2 are representative human strains of SARS CoV. (B) The contact region between the SARS CoV receptor binding domain and ACE2. Residues that convert rat ACE2 to an efficient receptor for SARS CoV are shown in orange. ACE2 lysine 31, which prevents association with SZ3 S protein, is shown in magenta. Lys (K) 31 and Lys (K) 353 are indicated by arrows, with the amino acids of palm civet, mouse, and rat ACE2 at these positions shown in parentheses. TOR2 S-protein residues Asn (N) 479 and Thr (T) 487 are also indicated, with the GD03 and SZ3 amino acids at these positions shown in parentheses. (Both panels reprinted from reference 71 with permission.)

For example, when single segments of the eight RNA segments of the influenza genome were reassorted into the background of a virus from an alternative host, most reduced the replication rate of the virus (13, 39, 115, 151). The replication of poxviruses may be affected by one or more steps in infection and replication and is influenced by various host-specific factors, including core-uncoating factor; by Hsp90; and by interferon-mediated antiviral signals (79) (Table 3). Other viruses are host restricted at the level of genome replication or gene expression, as is seen for polyomaviruses, where replication

TABLE 3. Genes of various poxviruses that have been found to be associated with the control of viral host range[a]

Gene	Protein type[b]	Cultured cells with defect in virus tropism
Myxoma virus genes		
M-T5	Ankyrin repeats	Rabbit T cells; human tumor cells
M-T2	TNF receptor	Rabbit T cells
M-T4	ER localized	Rabbit T cells
M1 1L	Mitochondrial	Rabbit T cells
Vaccinia virus genes		
E3L	PKR inhibitor	Human HeLa cells, chicken embryo fibroblasts
K3L	dsRNA-binding protein	Hamster (BHK) cells
B22R/SPl-1 genes	Serpin	Human AS49 keratinocytes
C7L	Cytoplasmic	Hamster Dede cells
K1L	Ankyrin-repeats	Pig kidney: PK13 cells
Rabbitpox virus gene		
SPl-1	Serpin	Pig kidney: PK15 A594
Ectromelia virus gene		
p28	E3-ubiquitin ligase	Mouse macrophages
Cowpox virus gene		
C9L/CP77/CHOhr	Ankyrin repeats	Chinese hamster: W-CL9$^+$ grows in CHO cells, W-K1L/C9L$^+$ grows on PRK13 cells

[a] As can be seen, there are many different genes that control infection of cells from different host species through a variety of mechanisms. (Adapted from reference 79 with permission from Macmillan Publishers Ltd.)

[b] TNF, tumor necrosis factor; ER, endoplasmic reticulum; PKR, protein kinase R; dsRNA, double-stranded RNA.

can be determined by the host-specific recognition of sequences surrounding the origin of DNA replication controlled by viral large T antigens (5, 92, 129).

THE EXISTING HOST RANGE OF A VIRUS AS A FACTOR IN HOST SWITCHING

Since the initial infection of individuals of the alternative host is a key step in viral emergence, the preexisting host range of a virus has been thought to influence its ability to become established in a new host. "Generalist" viruses, which infect many different hosts, might be expected to show an increased likelihood of shifting to additional hosts, as they can already use the host cell mechanisms of many hosts to infect and replicate. In contrast, specialist viruses, which naturally infect only one or a few closely related hosts, appear likely to be more strongly restricted by the different receptors and replication mechanisms in newly encountered hosts. However, both generalist and specialist viruses are known to have become established successfully in new hosts, suggesting that there is no generalization that can be made about the likelihood of either type of virus infecting a previously resistant host to create a new epidemic pathogen (Table 1) (148).

VIRAL EVOLUTIONARY MECHANISMS LEADING TO EMERGENCE

Evolutionary changes are not always required for viruses to emerge in new hosts. For example, canine distemper virus has a very wide host range in mammals, naturally infecting marine mammals, lions, black-footed ferrets, and other hosts, and its emergence in these species appears to be limited primarily by contact. However, in other cases emergence requires the evolution of the virus to allow efficient infection and transmission within the new host. The evolution of viruses to allow adaptation to new hosts is still not well understood. The level of genetic variation is important, and most viruses transferred to new hosts are poorly adapted, replicate poorly, and are inefficiently transmitted, so that the greater the rate of variation the more likely a virus is to adapt to the new host. This indicates that cross-species transmission should be more common in rapidly evolving viruses (12, 24, 41, 147, 149). RNA viruses have error-prone replication (23), lack a proofreading mechanism, and have rapid replication, short virus generation times, and large virus populations (22, 82). In contrast, most DNA viruses are less variable and more often associated with virus-host cospeciation (42, 105). However, the distinctions between RNA and DNA viruses in rates of evolutionary change are not straightforward: some retroviruses (e.g., the simian foamy viruses) show temporal rates of nucleotide substitution far lower ($\sim 10^{-8}$ substitutions/site/year) than those seen for other RNA viruses (119). There is also strong evidence that some RNA viruses have coevolved with specific hosts over long periods (including hantaviruses and arenaviruses), developing a high degree of host specialization (9, 19, 56, 76, 111). The rates of variation of some DNA viruses may also be underestimated. In particular, the single-stranded DNA viruses (in animals, the *Parvoviridae* and *Circoviridae*) are more diverse than are other DNA viruses and may evolve at rates similar to those of many RNA viruses (93, 103, 106, 107, 126).

Viral Fitness Trade-Offs

A fundamental challenge for host-switching viruses that require adaptation to their new hosts is that mutations that optimize the ability of a virus to infect a new host will likely reduce its fitness in the donor host (Fig. 2 and 3). The nature of these fitness trade-offs and how they affect cross-species transmission is an important unresolved area of study. Interactions between virus and hosts determine the fitness landscape for the virus, and after a host-switching event combinations of genetic drift and selection will determine the viral genetic variation that remains in the long term. However, only a small proportion of the viral mutational spectrum will exhibit increased fitness, particularly after passing through the population bottlenecks that accompany host switching (15, 24, 81, 101). The advantageous and deleterious mutations often show complex epistatic interactions that likely have major effects on the rate and progress of adaptation. As one example, in the case of vesicular stomatitis virus, regaining full fitness after host transfer is a complex process involving multiple compensatory changes (100).

Mode of Virus Transmission

An important constraint influencing emergence and successful host transfer is the mode of virus transmission. For example, arthropod vectors that feed on a range of mammalian hosts can facilitate cross-species viral exposures. However, both phylogenetic and in vitro studies of arboviruses indicate that their levels of variation are relatively constrained compared to what is observed for viruses transmitted by other mechanisms (62, 128, 136, 154). Those viruses would need to

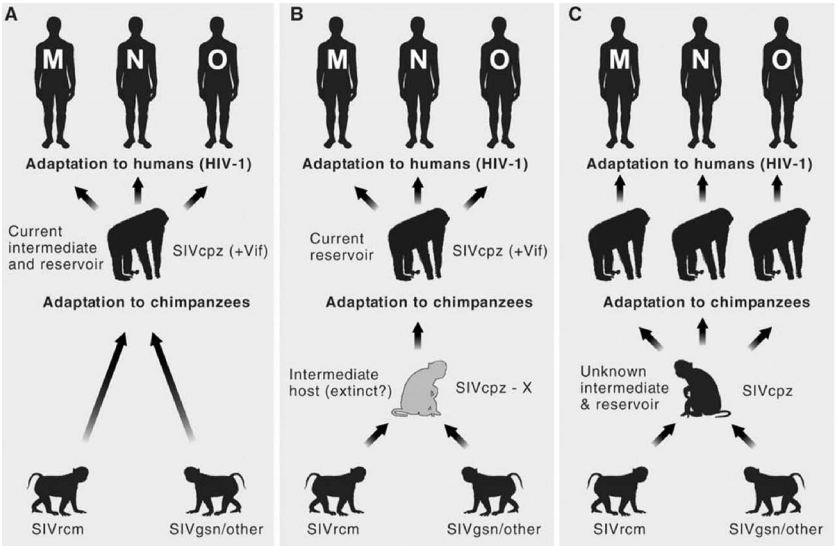

FIG. 5. Origins of HIV-1 in humans from related viruses in chimpanzees, possible pathways of origin from other primates, and the possible roles of recombination. The three major types of HIV (N, M, and O) each derived from a separate transfer event. Cartoons showing three possible alternative routes of cross-species transmissions giving rise to chimpanzee SIV (SIVcpz) as a recombinant of different monkey-derived SIVs illustrate the possible complexity of the steps leading to the introduction of viruses into a new host. +Vif indicates the presence of an HIV-like Vif, which is required to overcome the effects of APOBEC3B. (A) *Pan troglodytes troglodytes* as the intermediate host. Recombination of two or more monkey-derived SIVs (likely SIVs from red-capped mangabeys [SIVrcm] and the greater spot-nosed monkeys [SIVgsn] or related SIVs) and possibly a third lineage requiring coinfection of an individual monkey with one or more SIVs. Chimpanzees have not been found to be infected by these viruses. (B) The SIVcpz recombinant develops and is maintained in a primate host that has yet to be identified, giving rise to the ancestor of the SIVcpz/HIV-1 lineage. *P. t. troglodytes* functions as a reservoir and was responsible for each of the human introductions. (C) Transfer through an intermediate host (yet to be identified) that is the current reservoir of introductions of SIVcpz into current communities of *P. t. troglodytes* and *P. t. schweinfurthii* as a potential source of diverse SIVcpz variants that are each found in limited geographic regions of Africa. (Reprinted from reference 40 with permission of AAAS.)

balance the fitness in at least three hosts during the process of adaptation, i.e., the donor and recipient hosts and the vector(s), presenting a difficult challenge to new emergences. Adaptation to interhost transmission by droplet spread, that by sexual inoculation, and that by fecal-oral transmission each represent different adaptational challenges due to host differences and variation in environmental exposure. However little is known about how shedding and infection are controlled in different hosts. For example, it is not clear why influenza A viruses are enteric viruses in their natural avian hosts but mainly infect the respiratory tract in mammals, but this likely influences the host adaptation of the viruses to mammals and the ability to spread efficiently.

Recombination and Reassortment in Viral Evolution Leading to Host Switching

For many viruses, recombination (and its variation seen for viruses with segmented genomes, reassortment) allow the acquisition of multiple genetic changes in a single step and can combine genetic information to produce advantageous genotypes or remove deleterious mutations. Examples of reassortment in disease emergence include the emergence of the 1957 H2N2 and 1968 H3N2 influenza A pandemic viruses, where new avian genome segments were imported into the backbone of 1918-descended H1N1 viruses (137), as well as the 2003 emergence of the pathogenic Fujian H3N2 influenza strain by interclade reassortment (43).

The potential for recombination varies among different RNA and DNA viruses. Aside from segmental reassortment, recombination is rare among negative-stranded RNA viruses, while retroviruses such as HIV have high rates of recombination (20, 52, 108). Recombination between viruses from different primate hosts was associated with human HIV emergence; the possible donor host origins, recombination events, and intermediate host transfers are depicted in Fig. 5 (55, 67, 102). The SARS CoV appears to have arisen from a recombinant between a bat CoV and another virus (most likely also a bat virus) before infecting humans and carnivore hosts (Fig. 6). As described above, part of the receptor binding sequence of this virus may have been acquired by recombination with a group 1 human CoV, which was then selected for more-efficient use of the human ACE2 receptor (Fig. 4) (71).

Many recombinations or reassortments are likely to be deleterious in that they disrupt optimal protein structures or functional gene combinations. For example, the replication proteins of influenza A virus (PA, PB1, and PB2) work as a complex, and altering the combinations through reassortment of genomic segments can reduce replication efficiency and require subsequent adaptation to the combinations of proteins from different sources (13, 39, 123) (Table 4). The HA and NA proteins of influenza A viruses both act on the cell's sialic acid receptors, and complementarity between virus binding (HA) and cleavage (NA) activities is often required for optimal binding to and release from cells expressing different glycan receptors (109, 118, 132).

Recombination and reassortment may also be important for

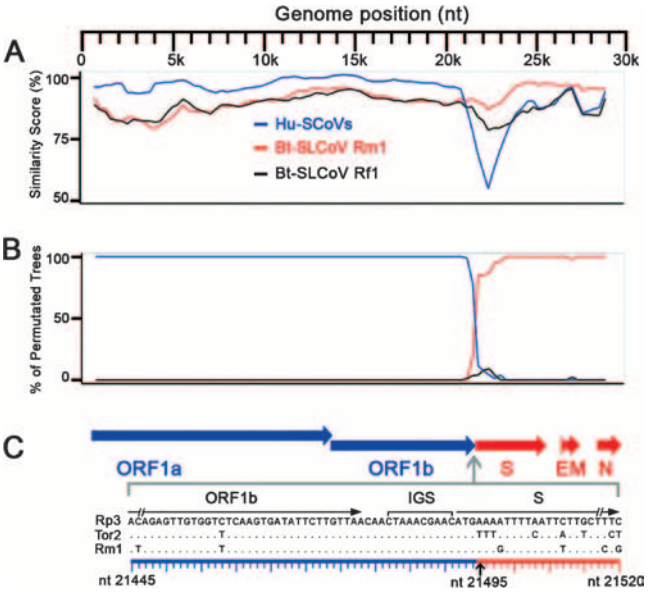

FIG. 6. Detection of recombination and estimation of a breakpoint within the genome of bat SARS-like CoV (Bt-SLCoV) strain Rp3. A similarity plot (A) and a bootscan analysis (B) detected a single recombination breakpoint at around the open reading frame 1b (ORF1b)/S junction. The human SARS-like CoV (Hu-SCoV) group includes strains Tor2 (AY274119), GD01 (AY278489), ZJ01 (AY297028), SZ3 (AY304486), GZ0402 (AY613947), and PC4 (AY613950). (C) Organization of ORFs of the SARS CoV genome and location of the estimated breakpoint. The blue and red horizontal arrows represent the essential ORFs from the major and minor parents, respectively. A sequence alignment of the ORF1b/S junction regions of SARS CoV strains Rp3, Tor2, and Rm1 is shown below. A consensus intergenic sequence (IGS) and the coding regions of ORF1b and S are annotated above the alignment. The black vertical arrow below the alignment indicates the estimated breakpoint located immediately after the start codon of the S coding region. nt, nucleotide. (Reprinted from reference 44 with permission.)

incremental host adaptation after switching to the new host has occurred. For example, after the 1968 emergence of human H3N2 influenza virus, which contained HA and PB1 gene segments imported from avian viruses, extensive secondary reassortments occurred after transfer, which may have facilitated its further adaptation (73).

Are Viral Intermediates with Lower Fitness Involved in Host Switching?

The process of virus transfer to a new host is rarely observed directly but can be inferred by comparing viral ancestors in donor hosts with emergent viruses from recipient hosts. If several changes are required to allow host switching, then intermediate viruses would likely be less fit in either the donor or recipient hosts than the parental or descendant viruses (60) (Fig. 7). As mentioned previously, influenza A reassortant viruses carrying single genomic segments from viruses of alternative hosts showed replication in either of those hosts that was lower than that seen for the parental viruses in their original hosts. The adaptation of FPV to dogs also occurred through at least one lower-fitness intermediate, as the first viruses collected from dogs were both less fit in cats than the FPV from which they were derived and less well adapted in dogs than the CPV variants that replaced them (107, 127).

Crossing any evolutionary "low-fitness valley" for partially adapted viruses can therefore be a key step for virus host switching and may explain the rarity of such transfers: partially adapted viruses would quickly go extinct, as they would be unfit in the donor host and also insufficiently adapted to allow efficient replication and spread in the recipient host (Fig. 7). If the transmission rate in the new host population allows virus maintenance, then the length of the period of lower replication and spread would be a function of the number of genetic changes required to gain high transmissibility. In the new host, the virus may not be competing with similar viruses, and if it spreads with an efficiency with a reproductive number (R_0) of >1, it could increase its fitness by mutation and selection to propagate epidemically.

Early detection of inefficiently spreading viruses in a new host would provide opportunities for epidemic control. In the SARS CoV outbreak, the first virus that emerged was only inefficiently transmitted by most infected people, and early recognition of the outbreak and institution of active control measures (particularly quarantine) allowed the epidemic to be

TABLE 4. Amino acid residues that distinguish human and avian influenza virus polymerases identified by comparison of the genome of the human 1918 virus strain with those of other human, avian, swine, and equine viruses[a]

Gene	Residue no.	Amino acid residue for indicated strain						
		Avian	1918 human H1N1	Later human H1N1	Human H2N2	Human H3N2	Classical swine	Equine
PB2	199	A	S	S	S	S	S	A
PB2	475	L	M	M	M	M	M	L
PB2	567	D	N	N	N	N	D	D
PB2	627	E	K	K	K	K	K	E
PB2	702	K	R	R[c]	R	R	R	K
PB1	375	N/S/T[b]	S	S	S	S	S	S
PA	55	D	N	N	N	N	N	N
PA	100	V	A	A	A	A	V	A
PA	382	E	D	D	D	D	D	E
PA	552	T	S	S	S	S	S	T

[a] Reprinted from reference 123 with permission from Macmillan Publishers Ltd.
[b] Most avian viruses have Asn at position 375 of PB1, but 18% have Ser, and 13% Thr.
[c] All human viruses have Arg, except for two of three A/PR/8/34 sequences, which have a Lys.

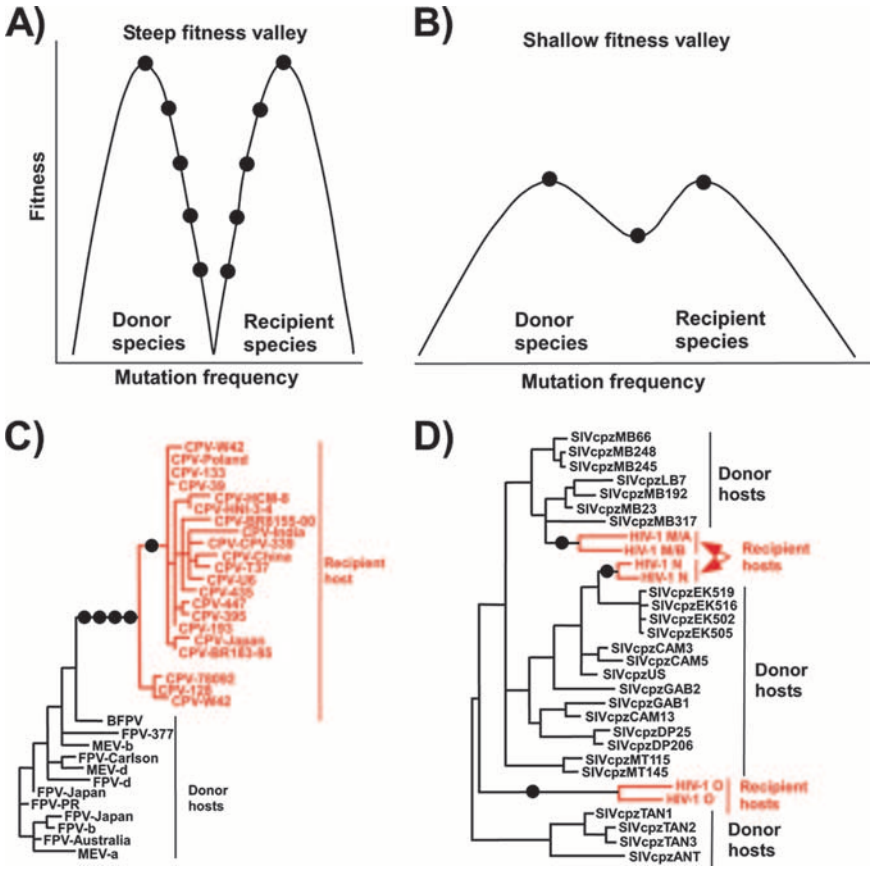

FIG. 7. Evolutionary models and examples of cross-species transmission of viruses. (A) Here the donor and recipient species represent two distinct fitness peaks for the virus which are separated by a steep fitness valley. Multiple adaptive mutations (circles) are therefore required for the virus to successfully replicate and establish onward transmission in the recipient host species. (B) The donor and recipient species are separated by a far shallower fitness valley. This facilitates successful cross-species transmission because only a small number of advantageous mutations are required. (Panels A and B adapted from reference 60 with permission of AAAS.) (C) The emergence of CPV as an example of multiple mutations being required for a virus to adapt to a new host, after which the virus evolves within the recipient species. The phylogeny of the capsid protein gene shows only a single origin of all the CPVs. Viruses in the donor hosts include feline panleukopenia virus (FPV), mink enteritis virus (MEV), and the Arctic (blue) fox parvovirus (BFPV). In this example, there were two known host range adaptation steps where there were multiple mutations (indicated by circles). (D) A second form of host transfer, where there is a lower evolutionary barrier to cross-species transfer, allowed the establishment of the different HIV clades in humans, suggesting a lower barrier to transfer into the new host species. The example shows a phylogenetic analysis of polymerase genes from viruses of chimpanzee (SIVcpz) or human (HIV). Representative strains of HIV-1 groups M, N, and O and SIVcpz from *P. t. schweinfurthii* (SIVcpzTAN1, -TAN2, -TAN3, and -ANT) are shown. (Adapted from reference 55 with permission of AAAS.)

stopped before the virus could become fully established in humans (4, 110, 156) (Fig. 8). How viruses gain the ability to spread efficiently (so that the R_0 is $\gg 1$) is a key question in viral emergence, but the mechanisms involved are poorly understood (68, 124). In addition to optimizing replicative efficiency in cells and tissues, a new virus may have to optimize the intensity of viral shedding from appropriate sites for transmission (e.g., mucosa, respiratory tract, skin, feces, urine, blood, and other tissues), may have to induce sneezing to achieve respiratory shedding, or, for arthropod-transmitted viruses, may have to establish high levels of viremia or replication in vectors (35, 60, 136). As described above, this process likely requires adaptation to allow passage through host-specific passive barriers at the mucosal surfaces and to avoid early elimination by innate immune responses (104, 138).

During the early stages of an outbreak, infected individuals who cause a large number of new infections may play a critical amplifying role. Such "superspreading" individuals were documented during the SARS CoV epidemic and during outbreaks of measles and other aerosolized viruses (75, 89, 135). The determinants of "superspreading" are still poorly understood but may be related to higher levels of virus shedding in some individuals, to host behaviors, and to prolonged times of uncontrolled exposure to susceptible contacts early in the outbreak, before the need for infection control is appreciated (11, 113). Animal-to-animal or person-to-person transmission has been a difficult subject to investigate experimentally, and we know relatively little about the specific factors that control it for most viruses, particularly during transfers into new hosts. Detailed pathogenesis studies in experimental animals will be required to achieve a better understanding of these factors.

FIG. 8. SARS as an example of the global spread of a respiratory virus in humans after transfer from a zoonotic reservoir. The time line is of the SARS coronavirus global outbreak from the initial human infections in China in late 2002 to the global spread of the virus and the subsequent control of the spread of the virus in mid-2003. Numbers indicate the total number of confirmed cases in each country. (Adapted from reference 33 with permission.)

POSTTRANSFER ADAPTATION

For many host-switching viruses, full host adaptation may take months or even years to complete. For example, human H1N1 influenza A viruses preserved in 1918 in pathological specimens or burial in Arctic regions contained many differences from the most closely related avian influenza viruses, probably reflecting either prior adaptation in a mammalian host or adaptation to achieve increased replication and pandemic transmissibility after the initial transfer to humans (Table 4). An analogous process of host adaptation is being suggested for the high-pathogenicity avian H5N1 influenza A virus in various avian hosts, some of which may be gaining mutations associated with mammalian or human adaptation (Table 5) (10, 31, 114, 150). The SARS CoV appeared to gain some host-adaptive changes during its spread among humans, suggesting that it was on the path to full human adaptation (71, 155) (Fig. 4). Isolates of Nipah virus collected at the end of the outbreak also differed significantly from those collected at the beginning, suggesting either adaptation (1) or possibly the occurrence of more than one introduction (94).

The coordination of functions under multiple selections is seen for a number of emerging viruses, as described above for selections of the HA and NA functions or polymerase subunits of influenza viruses in new hosts (36, 48, 132). Some receptor binding sites are also antigenic sites on the viral proteins. For CPV and SARS CoV, changing the binding sites for receptors also altered the antigenic structure of the virus, suggesting that there would be synergistic or competitive effects on the virus in an immune population (45, 70, 71).

TABLE 5. Adaptation of one HA gene during the spread of the avian influenza A viruses among different avian species and populations[a]

Site with ω of >1[b]	Residues[c]	Function	Site ω (± SE)
83	A/D/T/V	Antigenic site E	2.77 ± 0.72
86	A/I/T/V	Antigenic site E	2.77 ± 0.72
129	L/S	Receptor binding	2.71 ± 0.81
138	L/M/Q	Antigenic site A	2.85 ± 0.62
140	E/K/N/Q/R/S/T	Antigenic site A	2.85 ± 0.60
141	P/S	Antigenic site A	2.71 ± 0.80
156	A/S/T	Glycosylation	2.85 ± 0.61
175	L/M	Receptor binding?	2.74 ± 0.77

[a] Positively selected sites of H5N1 influenza viruses (genotype Z) from southern China and Southeast Asia from 2002 to 2005. For the entire data set, ω (the ratio of nonsynonymous mutations to synonymous mutations) is 0.198. (Adapted from reference 114 with permission from Elsevier.)

[b] Sites were included if the posterior probability was ≥0.90 in the CODEML M8 model by use of the BEB method. Sites in boldface had posterior probabilities of ≥0.95. Sites are numbered from the beginning of the mature H5 HA1 protein.

[c] All amino acid residues, given in single-letter code, present at that site in genotype Z viruses.

SUMMARY AND IMPLICATIONS FOR PREDICTION AND CONTROL

Considerable progress has been made in identifying the many factors that control or influence virus host switching. While it is still not possible to identify which among the thousands of viruses in wild or domestic animals will emerge in humans or exactly where and when the next emerging zoonotic viruses will originate, studies point to common pathways and suggest preventive strategies. With better information about the origins of new viruses, it may be possible to identify and control potentially emergent viruses in their natural reservoirs. Conventional infection control procedures (such as health monitoring and quarantine) can substantially reduce contact between reservoir and recipient hosts, preventing outbreaks or terminating them after host transfer but while they are still limited in size (50). For arboviruses, vector control can limit the transmission of viruses from their reservoirs to new hosts. There is arguable evidence that public health measures undertaken in 1918 were effective in controlling the influenza pandemic of that year (8, 38). Other strategies involve reducing anthropogenic change in emerging infectious disease "hot spots," as well as the more expensive and ethically challenging approach of culling reservoir animals or the vaccination of those animals. Vaccination has been used successfully for partial control of rabies in the United States and Europe (by vaccinating raccoons or foxes) and for control of wild dog rabies in Kenya and Tanzania (by vaccinating domestic dogs).

New rapidly spreading viruses can become impossible to control once they cross the threshold of a certain number of infections and/or rate of transmission, for example after spreading in humans into urban populations, where quarantine and/or treatment becomes impractical (4). Therefore, coordinated strategic planning is critical for the rapid responses re-

quired to confront new viruses early after emergence. Such planning must be somewhat generic because we lack the ability to predict which virus will emerge or what its pathogenic or transmission properties will be. National and international planning is also critical, including the harnessing of scientific and diagnostic technologies and establishing methods for rapidly communicating information about outbreaks and for coordinating control measures.

Preemptive strategies should include improved surveillance targeted to regions of high likelihood for disease emergence, improved detection of pathogens in reservoirs or early in outbreaks, broadly based research to clarify the important steps that favor emergence, and modified forms of classical quarantine or other control measures. Human disease surveillance clearly must be associated with enhanced longitudinal veterinary and wild-animal infection surveillance (28, 61). Vaccine strategies could be used in some control programs, but the current rate of development and approval of human vaccines is too low to allow control of most newly emerging virus diseases. Existing vaccines can be used to control the emergence of known viruses when sufficient lead time is available, as might veterinary vaccines which can be developed relatively quickly and used to combat outbreaks, along with the culling or quarantine measures that are now often used. New and improved vaccine technologies include molecularly cloned attenuated viruses that can be rapidly changed into the appropriate antigenic forms with sufficient efficacy and a level of risk low enough for use in the face of some outbreaks. Antiviral drugs may be used where available, although cost, logistic problems, and side effects may make those more difficult to use in a large-scale outbreak, and they would likely work only in the context of other control measures (25, 29).

The emergence of new viral diseases by animal-to-human host switching has been, and will likely continue to be, a major source of new human infectious diseases. A better understanding of the many complex variables that underlie such emergences is of utmost importance to public health.

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