Emergence of New Epidemic Viruses through Host Switching

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EMERGENCE OF NEW EPIDEMIC VIRUSES THROUGH HOST SWITCHING.

Report of the Workshop.

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Sponsors: The National Institutes of Allergy and Infectious Disease and the Office of Rare Diseases.

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Workshop focus: The over-all goal of the workshop was to consider the topic of viruses that could emerge and become widespread in the human population through host switching, and the special issues that are raised by that type of viral emergence.

Specific objectives were:
(1) To consider how such emergences have occurred in the past, and the principles that can be learned from those examples.

(2) To understand the sources of new viruses and, for zoonoses, the nature of their reservoirs. Consider the changes in reservoir-human interactions and how those impact on the emergence of new viruses in humans.

(3) Examine the molecular controls of viral host range, the number of separate molecular barriers involved, and to consider how viruses cross such barriers.

(4) Define the evolutionary mechanisms and pathways that allow viruses to gain the necessary changes, under the right circumstances, to transfer and infect new hosts.

(5) Consider how viruses might enter human populations in the future, and whether those types of emergences can be predicted.

(6) Consider how those might be prevented, or if they do occur, how they might be controlled. Control strategies to be considered include those implemented early in the outbreak or others that would minimize the harm done if a virus does get away.

These are clearly big topics, and the idea of the meeting was to define the broad principles of these topics in a way that would help the virological and public health community to understand these types of emergence and to use the information to make practical plans for the future.

Outcomes, goals, and publication strategies: Identification of common and underlying themes, identification of gaps in our understanding, recommendations for future research directions and planning.

A review manuscript that reports the findings and conclusions of the workshop is being written for publication, most likely in the Journal of Infectious Diseases where the editors have agreed to consider such a report. That is in the form of a review of the material covered – summarizing both the identified knowledge and the apparent gaps in that knowledge.

Summary Conclusions and Recommendations:

Overall: The emergence of new epidemic viruses is likely to happen, but we lack much of the information required to predict and counteract such events. There are certain features of the emergence of new epidemic viruses that we can use to prepare for such events, even if we cannot describe the exact virus and the time of its emergence.

1) Lack of knowledge about the ecology of potentially zoonotic viruses in their reservoirs. The emergence of epidemic viruses is a multidimensional problem that requires us to understand how viruses work at several different levels – from the landscape to the atomic level. The problem can be thought of as a series of spaces that describe some of the topics that were covered in the workshop. Those include the physical space that the virus occupies in the environment and in the context of its various hosts (ecology, epidemiology, and transmission), the host and host cell space (pathogenesis in the animal and replication in the cell), and the genome sequence space (the population genetics and evolution of the virus).

Recommendation: We need to gain a more complete understanding of the natural history of potentially emerging viruses. Studying viruses in their reservoirs and understanding their natural means of variation, transmission and pathogenesis should give us more predictive tools to anticipate the emergence of new viruses in humans.

2) We lack knowledge about the factors that control host-host transmission. Some aspects of the emergence of epidemic viruses are very poorly understood, the viral or host controls on host-host spread in particular. This lack of understanding likely represents an incomplete understanding of the pathogenesis of the viruses and of the viral and host interactions that lead to efficient shedding of the infected host and efficient infection of the host being exposed.

Recommendation: That more carefully designed pathogenesis studies be conducted to address this important issue in the spreading of viruses and to define the viral and host controls of viral shedding and infection.

3) We have a poor understanding of the evolutionary events that lead to new virus emergence. The evolutionary events that surround the transfer of viruses to new hosts are poorly understood, particularly those that lead to the emergence of variant viruses in the donor host, the transfer event itself, and the post-transfer adaptation (if present).

Recommendation: A more comprehensive analysis of the sequences of viruses before and after the transfer event is required, along with a more detailed analysis post transfer adaptation. That should be coupled with a good understanding of the molecular controls of host range and of the host barriers restricting infection so that the sequence variation can be interpreted in the context of known properties of the virus and the host.

4) A more complete epidemiological model of the initiation of outbreaks of different diseases and the best means of control.

5) The use of new technologies for the more rapid development of effective vaccines. New technologies are available that allow the preparation of safe attenuated vaccines of many viruses based on a good understanding of viral virulence and attenuation and of the effective host immune responses. These should be made ready to counteract any newly emerging virus.

Viral reservoirs in animals - the effects of human behavior and interactions with other animals or effects on the environment that can potentially result in new viral emergences.

Which animals are the potential sources of viruses that might emerge in humans or other animals?

It is clear that there are many different viruses of all types of viral families in all species of vertebrates and invertebrates that are potential sources of new infections in humans or that could emerge in other domestic or wild animals.

It is likely that we know very little about this vast array of different viruses – it appears likely that we know the identity of fewer than 1% of the potential sources of future host jumping viruses. As cases in point, the emergence of SARS, Hantavirus, Nipah and HIV-1 and HIV-2 were all due to the transfer into humans of viruses of other hosts that had not been previous identified. Another source of new pandemic viruses would be a change in the properties of an existing mild human virus to acquire an increased pathogenic or epidemiological advantage. This may have been the source of the enterovirus 70 which spread through much of the world during the 1970s.

What do we know about the evolutionary or epidemiological dynamics of viruses in their reservoirs?

The evolutionary dynamics of the viruses in their reservoirs may vary. In many cases the viruses appear to be well adapted to their reservoir hosts. In the case of influenza viruses, those that are endemic in the reservoirs (water birds) do not show the same degree of genetic variation compared to those which enter other populations and spread in epidemics. It is not clear whether this is due to the particular circumstances of the epidemiology of the virus in the water bird populations or to some other differences in the natural history of the virus.

What is the role (if any) of intermediate hosts between the reservoir and the final host.

The role(s) of intermediate hosts are not clear, but they may be involved in one or more ways to facilitate the emergence of new viruses: allowing the co-infection of more than one virus, allowing recombination or re assortment of the viral genomes to occur (the so-called mixing vessel

hypothesis). While this has been invoked for the influenza viruses in humans (pigs or terrestrial birds), the evidence is now suggesting that the human influenza was just as (or even more) likely to emerge directly or after re assortment in humans.

Another possible role of intermediate hosts would be in allowing the emergence of viruses with host range changes that allowed the virus to evolve more efficiently to infect humans or other animals – possibly this was seen in the emergence of SARS or Nipah viruses, although this has not been formally proven.

A third possible function would be in bringing a virus from wild life, which would normally have little contact with humans, into close contact where infection could occur. This is seen in the emergence of Nipah virus in Malaysia where infection of pigs by a bat virus allowed an increased exposure to humans, while the emergence of the SARS virus apparently involved the transfer of a bat virus to civet cats and then the infection of humans from the civets.

What is the potential for control of emerging viruses in their reservoirs or reduction in the possibility of spread to humans?

The control of the viruses in their reservoirs appears to be potentially very difficult for the reasons spelled out above, as it appears to be difficult to identify the emerging virus ahead of time among the many viruses in wildlife and domestic animals. Control of the animals that could be acting as reservoirs may be possible, as is the reduction of contact between the reservoir and the possible recipient host, or the control of invertebrate vectors that might act to transmit the virus from the reservoir to the new host.

What do we know about the importance of certain reservoir animals versus others - is there anything in common about the reservoirs that have given rise to emerged viruses in humans or other animals that would allow us to evaluate relative risks?

There appear to be a number of forms of introduction – including those that involve the transfer of a virus from a closely related host and the transfer of a virus from a relatively distant host. The first case is exemplified by the emergence of HIV in humans from chimpanzees or of canine parvovirus in dogs after transfer from cats. The second case appears to be seen in the emergence of SARS or influenza in humans, where the viruses transfer from distantly related hosts. We can certainly survey the viruses in closely related primates to determine those that might cause the first type of transfer into humans. The second type is harder to predict unless there is a subset of hosts that might be the sources of viruses (waterfowl, bats?). The recent emergence of a canine influenza virus through transfer of an equine H3N8 virus falls somewhere in the middle: there is no clear biological similarity between horses and dogs that would suggest this was the most obvious transfer route; and the absence of influenza viruses in dogs previously would suggest that they are not a natural recipient host.

Host-virus interactions at cellular, molecular and/or receptor levels and the control of host range.

How do viruses change their basic host ranges in order to infect a new host species?

Host range itself is a difficult property to define and depends on the system under consideration. Here we refer to host range as the ability to naturally infect animals. In many cases there is only a very loose connection between the viral host range seen in tissue cultured cells or after artificial inoculation of neonatal animals and the natural host ranges seen by in animal hosts in nature. Some

viruses are generalists and can infect many different hosts with relative success, while others are more specialists and infect only 1 or a small number of hosts. The generalists have methods for solving the problems of cell infection and replication using a variety of different proteins or using common mechanisms found in a number of hosts. The specialists have a narrower ability to use the mechanisms of one cell. Whether either is more likely to become a new epidemic pathogen in another host is unclear.

The molecular problems that are solved by each type of virus are likely different in scope and number, but it is not clear which type of virus carriers is the greater risk of making a host transfer to create a new epidemic virus. The known examples appear to be mostly those viruses that have fairly narrow natural host ranges.

What molecular events allow viruses to become successfully adapted to a new host species?
At the cellular level, it is clear that there can be many levels of restriction of viruses in a different host and that a particular virus may be blocked at 1 or more of those levels. The steps that can be restrictive include (but are probably not limited to): differences in the ability to bind the cell surface receptor, to engage the entry or fusion machinery correctly, to overcome or avoid the host interferon responses, to interact appropriately with the replication machinery, and to be assembled into new viruses. The assembly of new and active virus particles may also be cell specific. Each restrictive step likely requires a number of adaptive changes in the virus.

The stages of transfer – does interhost adaptation occur through a low fitness valley, and is that followed by a period of adaptation?
The process of transfer into a new host is generally not observed directly but must be inferred retrospectively by comparing the properties of the known ancestors in the donor host and the earliest emergent viruses in the recipient host and then by comparing those to the later viruses. It appears likely that an intermediate virus between the two would less fit in either host than the parental or descendent virus. This was observed (perhaps indirectly) for the influenzas where the viruses with reassortant genomes containing segments from the different hosts were less able to replicate in either the potential donor host (water birds) or in primates. Bridging this low fitness valley between the two peaks is a key step in transferring to a new host and may explain the rarity of such transfers. In the case of canine parvovirus in dogs, the first strain of virus that was detected appeared less fit in a number of characteristics compared to the later, apparently, more adapted viruses.

After the initial infection of the new host, there is likely a period of low efficiency spread before the virus gains the ability to spread rapidly. It is not known what determines the length of this period, but clearly, if identified, this presents a window of opportunity that can be exploited to control viruses shortly after they emerge.

What are the host barriers that are overcome?
There are many potential barriers, which differ for different viruses. For a number of examples, the specificity of receptor binding was a critical step that determined the host range of the virus (SARS virus interacting with the ACE2 receptor, parvovirus with the transferrin receptors, some influenza viruses with sialic acids), while other viruses where the receptor(s) did not determine the restriction, but the restriction occurs intracellularly as part of the interferon induced or other antiviral immune responses (as seen for the poxviruses), or to inhibition in other steps. For influenza viruses, the replication of avian viruses in human cells or humans is restricted or reduced at several steps of the viral replication cycle. For DNA viruses such as the polyomaviruses, there is a strong restriction at the level of the DNA replication that determines the ability to replicate in the cells of specific hosts.

How many changes (in how many genes) are required in the virus to allow the successful replication and spread?
The number of changes required appears to vary and most likely related to the host barriers that need to be overcome. If only one property of the new host has to be overcome, then only a small number of changes may be required. Where more barriers are overcome, then more changes will be required. This is seen for HIV where it appears that the barriers to transfer are low, and few or no changes are required to allow the emergence of the virus in humans. For SARS, the number of changes appears to be quite modest and related to the process of adaptation to the human receptor. In both cases, it is possible that a large part of the barrier to the host switching to humans was an ecological or epidemiological one (lack of extensive contacts between humans and the reservoir hosts or of transmission from the initially infected people) rather than at the level of the virus host restriction. In other cases such as influenza virus, changes in most or perhaps all of the viral genes appear to be required to allow the adaptation to humans, suggesting that there are several barriers to successful transfer and establishment.

What is the effect on replication in the presumed original (donor) host – did this decrease as the virus adapted to the new (recipient) host? Where this has been examined, the fitness of the virus for the original (donor) host appears to decrease after transfer to the new host. This was seen for influenza viruses where most mutations that allow human adaptation make the virus replicate less well in primates. For the canine parvoviruses, although the virus later regained the ability to infect cats, back adaptation to the original host did not appear to involve a reversion to any of the original (feline virus) sequences.

This implies at least two things about the process of transfer. First, that the acquisition of host range switching mutations in a virus in the donor host will generally make it less fit in that host; therefore, those mutants will be lost unless they pass through a bottleneck that preserves that sequence. Alternatively, they could be carried by transcomplementation by another virus. Second, the transfer to the new host is a one way jump.

<u>Adaptation to and pathogenesis in the new host; innate and adaptive host responses to viruses.</u>

How do the host responses to viruses affect their susceptibility to infection or disease? Host responses are a key to the control of an emerging infection. As host range barriers the innate responses are a key to controlling infection and host-host transmission, and the adaptive immune responses are the basis of any successful vaccination program. We are beginning to understand the level of complexity involved in the interactions of the viruses with the various host responses.

What is the role of innate immune responses to viruses – can they distinguish between viruses from different hosts to determine the viral host ranges? Viral anti-immune response genes in determining host specificity and adaptation and in allowing the virus to replicate in the face of innate and adaptive immune responses from the original and the new hosts. For many viruses the innate responses appear to determine host susceptibility as seen in STAT and other knock out or deficient animals which show a much broader range of pathogens than are the wild type animals. It is also likely that innate immune responses suppress the infection of dead end infections where the virus clearly has the ability to infect and replicate in the cells but do not reach levels in the correct tissues to allow transmission. The low efficiency of transmission of those viruses is also likely to be due to immediate responses in the new host that block the virus very early in the infection process. Responses can include the RNA, DNA, glycan or other motif detecting TLRs, as well as the

interferon responses and the apoptotic responses of the cell. A successful virus must overcome or avoid all these responses, often using active mechanisms, and the particular interplay between the virus and the host can be a result of a long term adaptive processes of both the virus and the host.

Host tissue specificity and the pathogenesis of the virus in the donor and recipient hosts – is there adaptation to new host tissues? The pathogenesis of the disease often involves not just interactions at the cellular level but also interactions at the level of the blood and lymph circulatory systems and within the tissues and barriers to tissue invasion.

Avoidance of inhibition by host tissues and plasma components (e.g. serum inhibitors that are bound by viral proteins or lectins that recognize the glycosylation of the viral proteins). More passive defenses include the mucosal and other barriers to entry, as well as the presence of non-specific viral binding factors, often glycans such as sialic acids that are different in the donor and the recipient hosts. These factors can non-specifically bind and eliminate the incoming viruses which may have to rapidly adapt to avoid such interactions or to cleave the ligand to allow the virus to be released.

<u>Viral evolution and the process of transfer and adaptation to new hosts.</u>

Fundamental principles of virus evolution, particularly as they apply to the emergence of viruses that across the host species barrier. The fundamental principles of virus evolution are at many levels similar to those that apply to many organisms. However, there are some special features that are unique. Although haploid, viruses can exchange information by recombination and in some cases reassortment. The high error rates can create a diverse population of polymorphic sequences, but in some cases a wide variety of different sequences created can transcomplement to compensate for each others' reduced fitness.

The generation of diversity in viral genomes including genomic sequence error rates and conservation or selection of viral sequences.
Error rates of viral genome replication can be very high, close to the rate that leads to error catastrophe. This is particularly true for the RNA viruses and retroviruses but may also be true for some of the DNA viruses. Despite this, some RNA viruses show highly conserved sequences suggesting that they are subjected to strong selective pressures to conserve not only the coding sequence but also the nucleotide sequences. Other RNA viruses show a large amount of variation and are appear to have large parts of their genomes, and often their protein sequence, to accommodate large amounts of sequence diversity while still maintaining their relative fitness.

Comparison of large and small genome viruses, as well as RNA, DNA and retroviruses. Common themes and differences among virus families--implications for potential host transfers. From an evolutionary standpoint, the role of genome type and epidemic emergence is not directly obvious, but the high error rates seen for many RNA viruses and for many retroviruses during reverse transcription suggest that those would be more likely to gain new properties that might allow emergence of new host rang variants. However, beyond that, other factors such as having fewer replication or host infection barriers may be more important. The examples of host switching viruses examined do not obviously favor a type of virus over another.

Short term acute infections vs. long term persistent/latent infections and the comparison of epidemic and endemic virus populations.

Short term acute infections with rapid transmission and slow infections with persistence may differ in many properties. Persistent infections could have specific effects – perhaps allowing viruses to generate more variants allowing for the production of variants that are able to transfer to new hosts. Alternatively, some persistently infecting viruses could be in more highly refined relationships with their hosts, which do not allow much variation and would therefore result in fewer opportunities for host-host transfers. The issue of the evolution of transmissibility is one poorly defined for most viral systems examined; however, this is likely to be a critical step in the adaptation of any virus to a new host becoming a highly transmissible virus. We still don't understand the mechanisms that control host-host transmissibility of most viruses (see below).

The special problem of transfer to new hosts – acquisition of variation in the donor host: transfer and founder effects and post-transfer adaptation.

The transfer to a new host involves a bottleneck event which likely involves a single virus infecting one individual of the new host and then propagating in the new host before transferring to further hosts to start the new epidemic. This requires the generation of the new virus genotype and followed by creating the opportunity for transfer. This involves ecological factors including the proximity of the donor and recipient hosts, and the size and density of their relative populations, as well as the adaptive constraints that apply to the virus in the two hosts.

<u>Acquiring high transmissibility among new hosts by viruses, and epidemic spread, also insect vector adaptation of arboviruses.</u>

Many viruses can replicate in new or alternative hosts without being able to spread efficiently to new host animals (dead end infections) - what changes in the viruses permit efficient host-host spread?

This is a relatively poorly understood aspect of the virus cell spread, and details depend on the virus. For acutely infecting viruses which must spread rapidly to the next host, the kinetics of replication and the level of virus titers and the sites of shedding (mucosal, respiratory, fecal) are likely critically important, as are the initial infection processes. Even for a virus that is shed at a high level and able to replicate once it enters a host cells, an infection becomes established in a host animal only once the passive and active innate immune responses are overcome; therefore, these factors need to be better understood. For viruses that establish persistent infections, the opportunities for spread can occur over a longer time period, so there must be a persistence of shedding which involves the continual production of new infectious virus as well as the susceptibility of the new host. For arthropod transmitted viruses, an important factor is the availability of the vector and its access to new susceptible hosts. Another issue is the potential role of a small number of infected individuals who, for poorly understood reasons, cause a large number of new infections – the so called "super spreaders". These individuals appear to have been well documented in the SARS epidemic, but their role in initiating new epidemics is still not clear.

However, this is a difficult subject to investigate experimentally, and for most viruses, we appear to know little about the specific molecular or other factors that control host-transmission.

How many steps are involved in this stage of host adaptation, and how much is known about the processes involved?

Beyond the changes required for simple infection in the cells of a particular host, further changes may be required for high transmissibility. As mentioned, the specific molecular steps involved in generating a highly transmissible virus are not well understood, but for many viruses this is a key step in the emergence of new epidemic variant rather than a simple dead-end infection. Some

viruses may always have had the intrinsic ability to infect and spread in another host but required the right epidemiological circumstances to initiate the epidemic – this may be the case for HIV-1. For the influenza viruses, the ability to cause limited infections is common, but the ability to spread efficiently within the new host is very limited. This is a key issue in the emergence of new viruses. For the human influenza viruses, changes in several genes were required to allow rapid spread among new hosts; for the canine influenza virus, a few amino acid changes were present compared to the parental equine influenza.

The role of virus and host specificity of invertebrate vectors in allowing the efficient spread of arboviruses between different hosts.

Invertebrate vectors are very important for the transmission of many viruses, and their feeding habits can determine their relative ability to infect different hosts. However, vector born viruses appear to be underrepresented among the known emerging viruses suggesting that they are subjected to more selective constraints than the non-vectored viruses. The differences in host range of the arboviruses are not well understood expect that, even within the same virus family, some have very broad natural host ranges (West Nile virus) while others have very narrow host ranges (e.g. Dengue viruses).

The process of post-transfer adaptation – how do viruses become optimized for replication in and transmission between the new host?

Once a virus transfers to the new host and gains the ability to spread efficiently, a second stage of adaptation likely optimizes the virus for its new host – what do we know about this process?

This may be an underappreciated process which could represent an opportunity for better viral control. For many of the viruses examined, post transfer adaptation clearly occurred, and this took a reasonable amount of time to complete (months to years). For example, for the influenza viruses during the emergence of the H3N2 viruses, the emergence and replacement of secondary reassortants appears to be particularly prominent during the fist few years of spread in humans. The earlier stages of the disease before the first isolate were made are difficult to define in retrospect. However, an earlier stage is being predicted to be occurring for the H5N1 virus in Asia and other parts of the world where H5N1 virus is gaining mutations required for mammalian or human adaptation while spreading in birds.

Viral factors involved in the host optimization process and how do they (in some cases) work together. For example, the co-adaptation of two (or more) different viral proteins.

These issues are related to the evolution and adaptation of the virus, and it is clear that, for most viral emergences, changes are required in more than one gene or that multiple changes are required in the same gene. Those changes may be interrelated or independent, but again, the requirement for the simultaneous or sequential occurrence of multiple changes makes the final emergence of the virus incrementally less likely. As described previously, understanding how this works requires a detailed understanding of the virus and its pathogenesis in the host.

Role of multiple selections on the same gene/function – e.g. selection for antigenic variation and receptor binding on the same protein.

The coordination of the functions of a single protein for multiple selections is seen for a number of emerging viruses. For influenza virus, the post-transfer adaptation clearly has both antigenic and receptor binding adaptations of the HA occurring at the same time; and for canine parvovirus, there appears to be overlap of the receptor and neutralizing antibody binding sites on the viral capsid. It is not clear exactly how these interact, but they are likely to result in synergistic or competitive effects on the fitness of the virus.

The epidemiology of new pathogens at different stages of the adaptation process. Infectious disease prevention and control strategies and their use in the cases of emerging epidemic viruses.

What are the most effective rapid methods for detecting new emerging viruses? What infrastructure, people, or processes would allow earliest detection of new agents? What are the most effective control strategies: consider the earliest stages of outbreak while still localized and also the most effective strategy once the spread has started. How does the adaptation process of the virus play into the control strategies – early less adapted versus later better adapted viruses? The roles of vaccinations, drugs, emergency responses? International coordination and planning – strategic considerations?

These topics are keys to controlling a newly emerged epidemic virus. A rapidly spreading acutely infecting virus may be difficult to stop after it has crossed a threshold of numbers and rates of transmission, and once it has spread into urban populations where quarantine and/or treatment are difficult to maintain. The development of preemptive strategies should be considered. New vaccine strategies appear to be important, and the development and use of new and improved vaccine technologies, particularly those based on well attenuated viruses, should be encouraged. The use of antiviral drugs is now possible for some viruses (particularly influenza) but with a caveat that we do not know how those will hold up in the face of an epidemic and the rate of resistance emergence in a situation of widespread virus infection with drug use.

The development of coordinated plans in advance of outbreaks is critical for the rapid responses that would be required to confront a new epidemic virus. Both national and international planning are critical, and are the harnessing of both scientific and diagnostic technologies, methods for rapidly communicating about the outbreak, and coordinating control measures.

These issues were largely outside the scope of the meeting but are clearly of foremost importance. National and international agencies should take the lead on these preparations.