Reverse zoonosis of influenza to swine: new perspectives on the human-animal interface

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Abstract

The origins of the influenza A (H1N1) pandemic of 2009 in swine are unknown, highlighting gaps in our understanding of influenza A virus ecology and evolution. Here we review how recently strengthened influenza virus surveillance in pigs has revealed that influenza virus transmission from humans to swine is far more frequent than swine-to-human zoonosis, and is central in seeding swine globally with new viral diversity. The scale of global human-to-swine transmission represents the largest 'reverse zoonosis' of a pathogen documented to date. Overcoming the bias towards perceiving swine as sources of human viruses, rather than recipients, is key to understanding how the bidirectional nature of the human-animal interface produces influenza threats to both hosts.

Keywords

influenza A virus; swine; pandemic; evolution; human-animal interface

Swine as reservoirs for influenza A virus diversity and pandemic threats

Influenza A viruses (IAVs) are considered to be one of the greatest threats for the next global pandemic due to the abundance of permanent animal reservoirs harboring viruses that occasionally spill over into humans [1]. For decades, swine have been thought to serve as intermediate 'mixing vessel' hosts (see Glossary) for the evolution of pandemic viruses because of their capacity to be infected with both avian and human influenza viruses, which can exchange genome segments via a process termed 'reassortment' to generate new pandemic viruses [2–4]. This threat was borne out in 2009, when the first influenza pandemic of the 21st century was caused by a novel reassortant swine H1N1 virus with genetic segments from both avian-like Eurasian swine viruses and North American swine viruses [5]. Since 2009, the genetic diversity of IAVs in swine populations (swIAVs) has expanded globally, generating additional pandemic threats such as the novel variant H3N2v

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swIAV that infected more than 330 humans in the United States during 2011–2013 [6]. Determining the evolutionary mechanisms that increase IAV diversity in swine is therefore important for human and animal health.

The evolutionary dynamics of IAVs are determined by their complex multi-host ecology, viral structure, and segmented genome. IAVs are single-stranded, negative-sense RNA viruses of the family *Orthomyxoviridae* that infect a wide range of avian and mammalian species. The genome of IAV (total length ~13 kb) is composed of eight single-stranded RNA (ssRNA) segments that encode for at least 12 viral proteins. Two surface glycoproteins, the hemagglutinin (HA) and neuraminidase (NA), are the main viral antigens and are used to describe the diversity of IAV subtypes (e.g., H3N2). Sixteen antigenically distinct HA and nine NA subtypes exist in wild aquatic birds, which are considered to be the reservoir hosts for IAV diversity [7]. Avian influenza viruses occasionally spill over into humans (e.g., H5N1 and H7N9), usually with little onward transmission. On rare occasions, major influenza pandemics occur when an avian influenza virus evolves the capacity to transmit human-to-human, as occurred in 1918, 1957, and 1968 [8,9]. Reassortment was key in generating the novel avian-human reassortant H2N2 and H3N2 viruses associated with the pandemics of 1957 and 1968 [9], respectively, although the proposed role of swine as intermediary mixing vessel hosts remains unclear. Avian influenza viruses also have evolved to be transmissible in non-human mammalian hosts: avian-origin H3N8 viruses have transmitted in horses since the 1960s [10]; avian-origin H3N2 has circulated in dogs in Asia since the mid 2000s [11]; and avian-origin H1N1 has circulated in Eurasian swine since the 1970s [12]. IAVs also can jump between mammalian species, as evidenced by the adaptation of equine H3N8 viruses to canines in the early 2000s [13] and swine H1N1 viruses to humans in 2009 [5]. One determinant of host specificity is the distribution of sialic acid receptors that bind the viral HA glycoproteins on host cells to facilitate viral entry [14]. Understanding what molecular evolutionary changes allow certain IAVs to jump between host species, and the potential role of swine as intermediary hosts, remains a central question in influenza virus research (Box 1).

Box 1

Outstanding questions

- Where did the Eurasian-North American reassortant influenza virus associated with the 2009 H1N1 human influenza pandemic evolve in swine and circulate undetected for approximately one decade?

- Were swine 'mixing vessel' hosts that facilitated the reassortment events between avian and human viruses that generated the pandemic viruses of 1957 and 1968?

- Did humans introduce the 1918 H1N1 'Spanish flu' pandemic virus into pigs, or did the virus circulate and evolve in swine prior to entering the human population?

- What factors make swine so susceptible to human IAVs? What is the relative importance of low immunity in swine, high density of animals facilitating onward transmission, and frequency of exposure to human viruses?

- What is the full extent of human-origin IAV diversity circulating in swine globally, including in under-sampled pig populations in Latin America, Africa, Oceania, and South Asia?

- What are the genetic constraints on the transmission of human viruses to swine? For example, there is no evidence that human H2N2 viruses or influenza B viruses have ever successfully transmitted in swine.

- What are the roles of airborne versus contact in human-to-swine transmission, and do any biosecurity practices on farms reduce transmission between humans and swine?

- Why is reassortment more frequent in swine than in humans?

- How do differences in the intensity of IAV surveillance across different hosts bias our understanding of IAV ecology and inter-species transmission?

- Can we further assess the pandemic threat of human-origin influenza viruses circulating in swine by determining the extent of existing cross-immunity in humans of different age groups?

In the aftermath of the 2009 H1N1 pandemic, there has been great interest in understanding the threat of swIAVs for humans, including (i) estimates of the frequency of human infection with swIAVs [15,16], (ii) assessments of the pandemic potential of various swIAVs in animal models [17,18], and (iii) increased surveillance of global swIAV diversity, including regions and continents that rarely or never previously reported swIAVs, including Africa [19], Latin America [20–23], South Asia [24,25], and Australia [26,27]. Paradoxically, the swIAV sequence data collected to assess the pandemic risk of swine for humans has demonstrated that humans transmit far more IAV diversity to swine than pigs have ever transmitted to humans, at least in terms of viruses that transmit onward in the new host (as opposed to dead-end infections). In this review we describe the central role of human-to-swine transmission events in the evolution of IAV diversity in swine. In particular, since 2009 the continual introduction of pandemic H1N1 (pH1N1) viruses from humans has expanded the genetic diversity of swIAVs globally, introducing new challenges for the control of influenza in swine, pandemic threats for humans, and important research questions related to the human-swine interface.

Humans as major sources of influenza virus diversity in swine

While there is historical evidence for influenza outbreaks in humans, poultry, horses, and even canines dating back several centuries [28], there is evidence of only one possible localized influenza virus outbreak in swine in England prior to the 1918 H1N1 'Spanish flu' pandemic [29]. During early stages of the 1918 pandemic, outbreaks of the virus were identified in both humans and swine in the United States [30], and it remains impossible to determine whether humans first transmitted the virus to pigs, or vice versa, owing to the lack

of data from that time [31]. From 1918 to 1998, this 'classical' swine H1N1 influenza virus, isolated in swine in 1930 [32], exhibited relatively limited antigenic evolution and caused low concern for swine producers. Beginning in the 1970s, the global evolution of swIAVs became much more complex with the introduction of an avian H1N1 virus and a human seasonal H3N2 'Port Chalmers-like' virus into European swine herds, and subsequent reassortment events between them (a detailed historical characterization of global influenza virus diversity in swine has been provided in several recent reviews [33–35]).

Central to the global evolution of genetic diversity of swIAVs is the repeated introduction of IAVs of human seasonal virus origin in swine [21,36–41]. In contrast to major pandemic influenza events that last 1–3 years and occur sporadically, seasonal influenza viruses are associated with annual epidemics in humans that occur in winter in temperate regions. It remains difficult to estimate the full extent of human-to-swine transmission of seasonal viruses historically, owing to large gaps in swIAV surveillance geographically and in past decades (Figure 1). However, a conservative global estimate of 20 discrete human-to-swine transmission events was recently inferred by phylogenetic analysis of whole genome viral sequence data [42] (Figure 2). No clear patterns of geographical distribution or any 'hot zone' of human-to-swine transmission of IAVs is apparent once sampling bias is removed. Instead, these events have occurred multiple times on all four continents that conduct at least minimal swine surveillance: North America, South America, Asia, and Europe. It is highly likely that additional human-to-swine transmission events have gone undetected in countries where surveillance has been low or absent or in cases where the virus transmits in swine for less than five years. Notably, independent human-to-swine introductions are observed in countries where surveillance is not conducted regularly, including Argentina, Thailand, Vietnam, and Japan. In several countries long phylogenetic branch lengths separate the swine viruses from the most closely related seasonal human viruses, signifying circulation in swine for many years prior to recent detection (Figure 3). Notably, the HA and NA segments of human origin have persisted in swine at a higher rate compared to the internal gene segments [42], raising the possibility that reassortment with swine virus internal genes is associated with the adaptation of seasonal human IAVs to new swine hosts.

Large-scale reverse zoonosis of pH1N1 viruses

On May 2, 2009, approximately one month after the pH1N1 virus was detected in humans, pH1N1 was isolated from the first pig on a farm in Alberta, Canada in what was eventually determined to be the first documented case of human-to-swine transmission of pH1N1 [43,44]. Since then, the pH1N1 virus has transmitted repeatedly from humans to swine spanning six continents (Table 1, Figure 4), in what is arguably the largest global occurrence of reverse zoonosis of any infectious disease that has been documented to date [45]. Although the molecular clock suggests that the pH1N1 virus originated in swine approximately one decade prior to its emergence in humans [46], the virus was not detected in the large and relatively routinely sampled swine populations in North America, Europe, or Southern China prior to its emergence in humans, and where the virus originated in swine remains a key outstanding question. The most parsimonious explanation is that pH1N1 evolved in swine in Mexico, where pH1N1 first emerged in humans, or possibly a neighboring country in Central or South America where surveillance in swine is limited

(Figure 1b). Still, there is no evidence that Eurasian and North American swine viruses co-circulate in any part of Latin America, and Asia is the only region to date where viruses have been detected that contain segments from both lineages that resemble pH1N1 [47]. Adding to the mystery of pH1N1's origin, it has been demonstrated that the specific reassortment event required to generate the pH1N1 virus does not occur readily in experimentally infected pigs or cell culture [48].

Since 2009, increases in the intensity and geographic range of surveillance for swIAVs (Figure 1b) have revealed at least 49 introductions of pH1N1 from humans into swine [45]. This estimate is conservative due to reliance on high bootstrap values, low availability of IAV sequence data from swine in many regions, and higher rates of sequencing of the HA and NA segments, which have not transmitted onward in swine as extensively as the internal pH1N1 gene segments due to reassortment. Detection of human-origin pH1N1 in swine herds was reported in many countries where influenza had not previously been documented as an important swine health problem, including Australia [26,27], India [24], Sri Lanka [25], Colombia [23], and Cameroon [19] (Table 1, Figure 4). The introductions of pH1N1 into the large commercial swine herds in Brazil [22] and Nigeria [49] have caused outbreaks that are of particular concern, as these possibly endemic viruses could complicate swine health and production in regions with high hog densities but lacking experience in diagnosing and controlling influenza in swine.

Refining models of influenza A virus ecology

The relatively lower barrier of cross-species transmission of pH1N1 from humans back to swine, compared to other human viruses, may be explained in part by the fact that pH1N1 was originally a swine virus. Still, the human-adapted pH1N1 shows little evidence of transmitting from swine back to humans, at least in terms of stable introductions with onward human-to-human transmission [45]. Direct comparisons of the frequency of human-to-swine versus swine-to-human IAV transmission remains complicated by substantial differences in the intensity of surveillance in humans and swine (Figure 1, Box 1). In general, the lower availability of sequence data from swine means that many human-to-swine transmission events that do not result in substantial onward transmission in swine are likely to go undetected, whereas transient spillovers of swine viruses in humans will be identified due to higher sampling in humans (e.g., the detection of >300 H3N2v spillovers from swine to humans [6]). However, additional swine data is needed to improve our understanding of inter-species transmission dynamics in both directions.

Even excluding the high number of human-to-swine transmission events of the recent pH1N1 virus, a greater number of human influenza viruses have crossed species boundaries to successfully transmit in swine (n = 20) [42] than the number of all other IAV cross-species events with sustained transmission combined. Host jumps of IAV that result in stable transmission in the new host are rare events, at least in recent decades when genetic sequence data is available. Based on genetic data, there have been three avian-to-human transmission events resulting in sustained onward transmission. These avian-to-human transmissions are associated with the 1918, 1957, and 1968 pandemics, although it remains unclear whether a proposed intermediary mammalian host facilitated the adaptation of avian

viruses to humans in any of these cases [9]. Two avian-to-swine transmission events involving sustained onward transmission have been documented (triple reassortant viruses and Eurasian viruses) [12,50], three avian-to-equine transmissions (H7N7 and two H3N8 transmissions) [10,51,52], one avian-to-canine transmission (H3N2) [11], one equine-to-canine transmission (H3N8) [13], and one swine-to-human* (2009 H1N1 pandemic) [5] (*the highly localized outbreak of H1N1 swine influenza in Fort Dix, NJ in 1976 was not considered sustained transmission by our definition[53]) (Figure 5a). For simplicity we adhere to a strict definition of sustained transmission for at least one year in the secondary host, and exclude transmission events between different species of birds, which exhibit extremely low levels of host restriction [54]. Although major outbreaks of IAVs of avian, human, and swine origin also have been observed in other mammalian hosts, including domestic turkeys [55–57] and seals [58–60], at this time there is insufficient evidence of sustained onward transmission.

Notably, the frequency of avian-to-swine transmission is lower than the frequency of human-to-swine transmission, by our definition of viral introductions with onward transmission (Figure 5b). To date, there is evidence of only two full or partial avian influenza viruses successfully adapting to transmit stably in swine: the avian-origin Eurasian H1N1 swine viruses [12] and the avian-origin PB2 and PA segments associated with the triple reassortant viruses that emerged in North American swine in the 1990s [50]. A wide range of avian influenza virus subtypes have transiently infected swine in Asia (H1N1 [61], H3N2 [62], H3N8 [63], H4N1 [64], H4N8 [65], H5N1 [66–68], H5N2 [69], H6N6 [70], H7N2 [71], H9N2 [72–75], H10N5 [76], and H11N6), North America (H1N1 [77], H2N3 [78], H3N3 [77], and H4N6 [79]), and Europe (H1N7 [80]). The detection of avian-swine reassortant H2N3 viruses in swine in 2006 in Missouri, USA raised a particular concern for humans, but also did not sustain viral transmission in swine, and there was no evidence of infection of humans [81]. The higher rate of observed transmission of human viruses to swine could potentially be related to surveillance bias. However, the matrix protein-based primers currently used for IAV diagnostics in swine are able to detect a broad diversity of avian and human viral subtypes. Furthermore, although the relatively low levels of surveillance in swine compared to humans and avian species (Figure 1a) will not identify all transient avian influenza virus spillovers, avian influenza viruses with sustained long-term transmission in swine are far more likely to be detected, suggesting that sustained circulation of avian influenza viruses in swine is indeed a rare event. It is possible that the biological barrier to transmission of avian influenza viruses to swine may be similarly high as for other mammals, such as humans, dogs, and horses. Recent experimental studies indicate that the barriers to avian influenza virus replication and transmission are high in both swine and humans [82,83], and the swine trachea contains a preponderance of α-2,6-linked receptors, similar to humans [84,85]. However, further understanding of the distribution of sialic acid receptors in swine and human hosts and their comparative level of binding with influenza viruses of different host origins is greatly needed.

Questions about the ecology of human-to-swine transmission

Compared to the extensive study of the zoonotic transmission of H3N2v viruses from swine to humans [86,87], including the capacity of swine with asymptomatic influenza infections

to efficiently transmit viruses to humans, mainly children, within the agricultural fair setting [88], relatively little is known about the ecological and immunological circumstances under which human IAVs transmit to swine. This lack of understanding undermines efforts to evaluate potential biosecurity measures, such as vaccination of swine workers. Presumably, human-to-swine transmission is associated with peaks in human influenza activity (pandemic waves or seasonal winter epidemics in temperate regions), but data from swine is not sufficiently resolved at this time to capture such patterns. The higher rate of H3N2 transmission from human to swine compared to seasonal H1N1 viruses since 1968 is consistent with the dominance of the H3N2 subtype in humans. However, at least three introductions of reassortant human H1N2 viruses into swine have been observed [42], despite only circulating in humans from 2001–2003.

Differences in immunity between humans and swine could explain, at least in part, why viruses transmit more frequently from humans to swine than in the reverse direction. Young pigs typically live only six months before going to market. In contrast, adult swine workers are likely to build up immunity over time to swIAVs through exposure, and older humans in general may have at least partial cross-immunity to human-origin swine influenza viruses as a result of previous exposure to the human precursors of the swine viruses. The high density of pigs in commercial settings also may provide an opportunity for human-origin viruses that are imperfectly adapted to swine to continue to transmit between highly connected animals while evolving higher fitness. The co-circulation of multiple swIAVs within herds also may facilitate host jumps by providing more opportunities for reassortment. As our broad understanding of how IAVs successfully jump hosts has been limited to date by the relatively small number of host-switch events observed in nature (Figure 5a), the less constrained human-to-swine interface may provide a useful model system for investigating the interactions between immunity, ecology, and evolution during host switches.

Human-origin viral diversity reduces efficacy of swine influenza vaccines

The repeated introduction of human-origin viral diversity, particularly in the form of multiple antigenically distinct co-circulating HA and NA proteins, has greatly complicated the development of effective vaccines for the control of influenza in swine. In the United States vaccines are used primarily in sows to provide passive antibody to piglets and, to a lesser extent, during the grow/finish phase of production to decrease disease, lung lesions, and transmission [89,90]. One of the commercially available US influenza vaccines is a quadravalent whole inactivated virus (WIV) vaccine that contains four strains: classical H1 (gamma), which has circulated in swine since the 1918 pandemic, and three strains of more recent human origin: H1 delta-1, H1 delta-2, and H3 (cluster 4). Following the introduction of pH1N1 viruses from humans into US swine herds, a monovalent pH1N1 vaccine also was developed. To further complicate the matter, a phenomenon called 'vaccine-associated enhanced respiratory disease' (VAERD) [91] has been observed experimentally in pigs when there is substantial antigenic distance between the vaccine and challenge strains of the same H1 subtype (e.g., any of the classical, delta, and pandemic H1 viruses). Live attenuated influenza virus (LAIV) vaccines administered by the mucosal route mimic natural infection and have the potential to elicit broader cross-protective immunity [92–95] without inducing

VAERD [96], and may present the best strategy for vaccinating against the substantial antigenic variation of human-origin viruses that circulate in US swine.

The future of swIAV surveillance and research

Despite the evidence, it remains counterintuitive to view humans as major sources of disease for swine. This bias is perpetuated by the imbalance in surveillance in humans versus swine (Figure 1), which obscures an accurate understanding of viral ecology in which humans and swine exchange pathogens in both directions. Sample bias continues to be a major impediment to understanding swIAV evolution and diversity, including capturing the full scale of human-to-swine transmission. Major gaps in surveillance of influenza in swine were recently highlighted by the identification of an entirely novel serotype in swine and cattle that are phylogenetically distinct from the diversity of influenza A, B, and C viruses [97]. Characterizing the global diversity of human-origin IAVs in swine will require expanding surveillance, particularly in countries with large swine populations but relatively low surveillance currently (e.g., Brazil, Vietnam, Russia). Substantial temporal and spatial biases in sampling of swine viruses (Figure 1) also make it difficult to infer the geographical origins of human-to-swine transmission events, especially when the virus is first sampled in pigs many years following initial introduction [42]. Globally, swIAVs are rarely sampled in a population-based manner, undermining our understanding of the population dynamics of co-circulating viruses over time.

Recognition of the central role of humans in the evolution of swIAV diversity has important implications for future research and surveillance, including the need for strengthened collaboration between the animal and human health sides. Relations between the human and swine influenza sides have improved considerably since the 2009 'swine flu' pandemic. The regrettable naming of 'swine flu' perpetuated a global misperception that pigs presented an immediate disease risk for humans, which resulted in inhumane conditions and widespread pig culling in several countries [44,98] and cost the US pork industry billions of dollars from unnecessary export bans and reduced pork consumption. Although American and European swine producers regularly collect respiratory samples from sick pigs for diagnostic investigation, many of these samples are sent to private diagnostic companies to inform the design of autogenous influenza vaccines. As a result, only a relatively small number of sequences and/or isolates are made available for public research.

Our knowledge of reverse zoonosis is even lower in other species and wild animal populations that present additional challenges for surveillance [99]. During the 2009 pandemic, pH1N1 viruses of presumed human origin were isolated from a range of species, including felines [100], canines [101], and seals [59]. Human influenza B viruses (IBVs) have a history of causing major outbreaks in seals [102,103], raising the possibility that phocines sustain permanent reservoirs of human-origin IBV diversity. A number of other pathogens of human origin also have been observed in wild and domestic animals [99], although onward transmission of these pathogens is rarely substantiated. Our greater understanding of the human-swine interface for influenza invites further investigation of additional pathogens, for example rotaviruses, that are known to transmit from swine and

other livestock to humans but for which the human-animal interface remains poorly understood, particularly from a bi-directional perspective.

Improving surveillance of swIAVs is also important for understanding how evolutionary processes amplify and disseminate viral diversity in pig populations. Several recent studies have revealed the importance of viral migration via swine movements [104,105] and reassortment with endemic swine viruses [106,107]. Increased whole-genome sequencing of swIAVs in recent years has been particularly important in revealing the frequency of reassortment in swine hosts and the diversity of novel IAV genotypes that are generated, including those such as H3N2v that present threats to humans [106–109] (Figure 5c). The frequency of reassortment between IAVs in swine greatly exceeds the reassortment rate observed in humans. As a case in point, pH1N1 viruses have reassorted extensively with many diverse IAVs in swine hosts [108,110–118] but show no evidence of reassorting with co-circulating seasonal H3N2 viruses in humans. The difference in reassortment rate between humans and swine is still not fully explained, but may relate to higher rates of co-infection in swine due to weaker cross-immunity and differences in fitness. Insights into population dynamics, including patterns of reassortment, require unbiased data that either have been selected randomly from passive surveillance or systematically sampled in swine through active surveillance [119], rather than sequencing ad hoc or selectively for specific genotypes of interest.

Concluding remarks

Recognizing the important role of human-to-swine transmission in the evolution of swIAV diversity requires that we refine our concept of the 'mixing vessel' (Figure 5b), which has perpetuated an over-simplified understanding of IAV ecology. Swine can be considered mixing vessels in the sense that pigs are more capable than humans of harboring a large number of co-circulating IAV lineages that can generate diverse combinations of segments via reassortment. But at this time there is insufficient evidence that swine are more suitable hosts than humans for stable transmission of avian viruses. In theory, humans could be regarded as 'mixing vessel' intermediaries for pigs during the 1968 pandemic, as there is evidence that humans transmitted these reassortant avian-origin H3N2 viruses to swine but no evidence from the field that these viruses circulated in swine prior to emergence in humans. However, as little sequence data from swIAVs are available from the time of the 1968 pandemic, it is possible that future advancements in surveillance and archival sequencing will further revise our understanding of the human-swine interface. At this time, however, it is critical that we employ our improved knowledge of IAV ecology to enhance biosecurity and vaccination strategies in swine workers, learn more about the processes of adaptive evolution involved in host jumps between humans and swine, and further expand swIAV surveillance globally.

Acknowledgments

Glossary

Antigenic drift	the continual evasion of host immunity by the gradual accumulation of mutations in the hemagglutinin and neuraminidase surface glycoproteins that change the antigenic structure of the influenza A virus
Bayesian phylogeography	the inference of viral migration patterns using time-scaled phylogenies inferred in a Bayesian framework in which prior knowledge assesses the probability of model parameters in the presence of new data
Hemagglutinin (HA)	an influenza virus surface glycoprotein, which binds to sialic acid receptors to assist viral entry into host epithelial cells. Eighteen HA serotypes are present in animal species
Mixing vessel	a host species with the capacity to be co-infected with multiple genetically distinct viruses of different animal origins that are able to reassort to generate genetically novel viruses. Swine are considered to be 'mixing vessels' for reassortment between human and avian influenza viruses
Molecular clock	the observation that the rate of molecular evolution is relatively constant for a given lineage, which provides a useful tool for estimating the timing of events in evolutionary history
Pandemic	an influenza outbreak associated with a new viral subtype that occurs over a large geographic area (often globally)
Reassortment	a form of genetic recombination in which two influenza viruses co-infect a single cell and exchange entire RNA segments to form genetically novel viruses
Reverse zoonosis	an infectious disease that can be transmitted from a human to a non-human host (sometimes by a vector)
Zoonosis	an infectious disease that can be transmitted from a non-human host to a human (sometimes by a vector)

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Highlights

- Humans transmit far more influenza viruses to swine than swine transmit to humans.

- Human-to-swine transmission is key to the evolution of influenza diversity in swine.

- In effect, humans sow the seeds of future pandemics by infecting pigs.

- A balanced view of the bi-directional nature of the human-animal interface is needed.
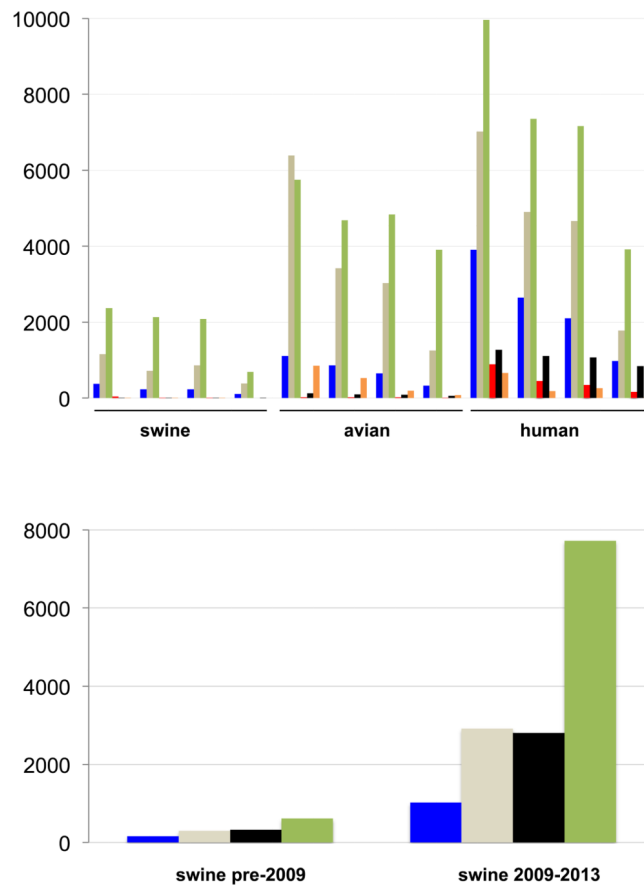
Figure 1. IAV sequence data available for swine, birds, and humans

(a) Number of IAV sequences available at GenBank's Influenza Virus Resource [120] for swine, birds, and humans for the full-length HA segment, full-length NA segment, whole genome, and main antigenic region of the HA (HA1), by region. The bars representing the number of viral sequences from Europe are shaded blue, Asia = light brown, North America = green, South America = red, Pacific region = black, and Africa = orange. (b) Number of swine influenza virus sequences available at GenBank for the full-length HA segment, full-length NA segment, whole genome, and partial HA gene, for the time periods 1931–2008 and 2009–2013.
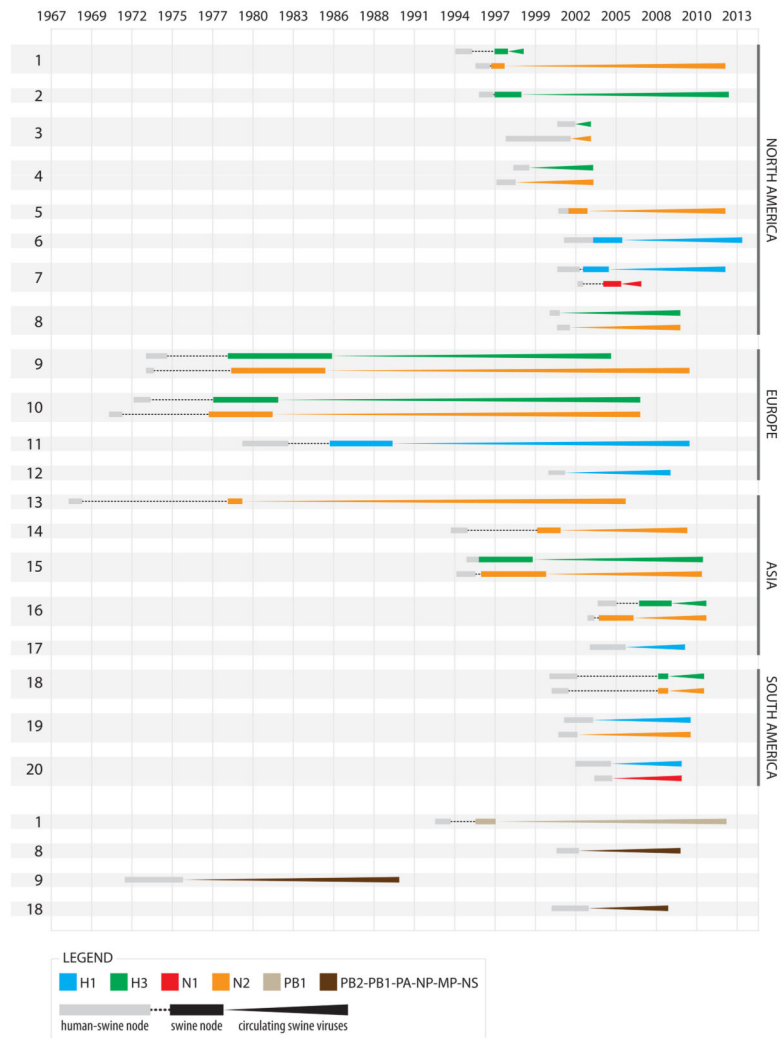
Figure 2. Introductions of human seasonal influenza viruses into swine, 1965–2013
A summary of the 20 introductions of seasonal human IAVs into swine resulting in sustained transmission in swine (for at least one year) by segment and region. Introductions involving the HA and NA segments are depicted in the upper portion of the figure, and the subset involving internal gene segments are presented in the lower portion. Each colored line represents a human-to-swine transmission event of a segment (H1 = blue, H3 = green, N1 = red, N2 = orange, PB1 = light brown, and the full constellation of all six internal gene segments = dark brown). Each introduction is numbered 1–20. Human internal gene segments have persisted in swine for four introductions (introductions 1, 8, 9, and 18), as shown at the bottom of the figure. The timing of each human-to-swine transmission event is estimated from the times to the Most Recent Common Ancestor (tMRCAs) inferred from the maximum clade credibility (MCC) trees, with grey boxes indicating the 95% highest posterior density (HPD) interval between the swine clade and most closely related human viruses, and the black box indicating the 95% HPD interval for the swine clade only. Each line extends forward in time up to the most recently sampled swine virus of that lineage.

Figure 3. Phylogenetic relationships between human and swine N2 segments

Time-scaled Bayesian MCC tree inferred for the NA (N2) sequences of 350 swine influenza viruses identified as of human seasonal virus origin and 325 human H3N2, H2N2, and H1N2 seasonal influenza viruses, collected 1957–2013. Branches of human seasonal H3N2 influenza virus origin are shaded black, while branches associated with viruses from swine are shaded by country of origin: Argentina (ARG) = red; Canada (CAN) = orange; China (CHN, including Hong Kong SAR and Taiwan) = yellow; Europe (EUR) = light green; South Korea (KOR) = teal; JPN = dark green; Mexico (MEX) = light blue; Thailand (THA) = dark blue; USA = purple; Vietnam (VNM) = pink. Posterior probabilities > 0.9 are included for key nodes, and the 13 discrete introductions of the human N2 segment into swine that are supported by high posterior probabilities and long branch lengths are identified with solid black circles. Copyright © American Society for Microbiology, [Journal of Virology, 88, 2014, 10110–10119, doi: 10.1128/JVI.01080-14] [42] reprinted with permission.
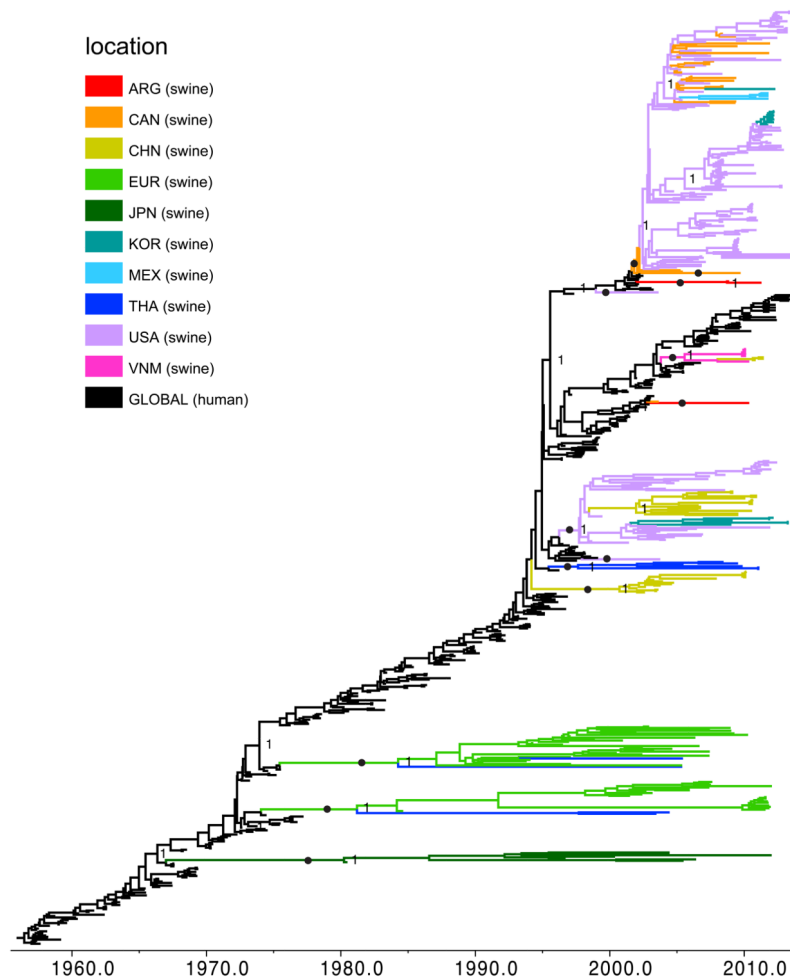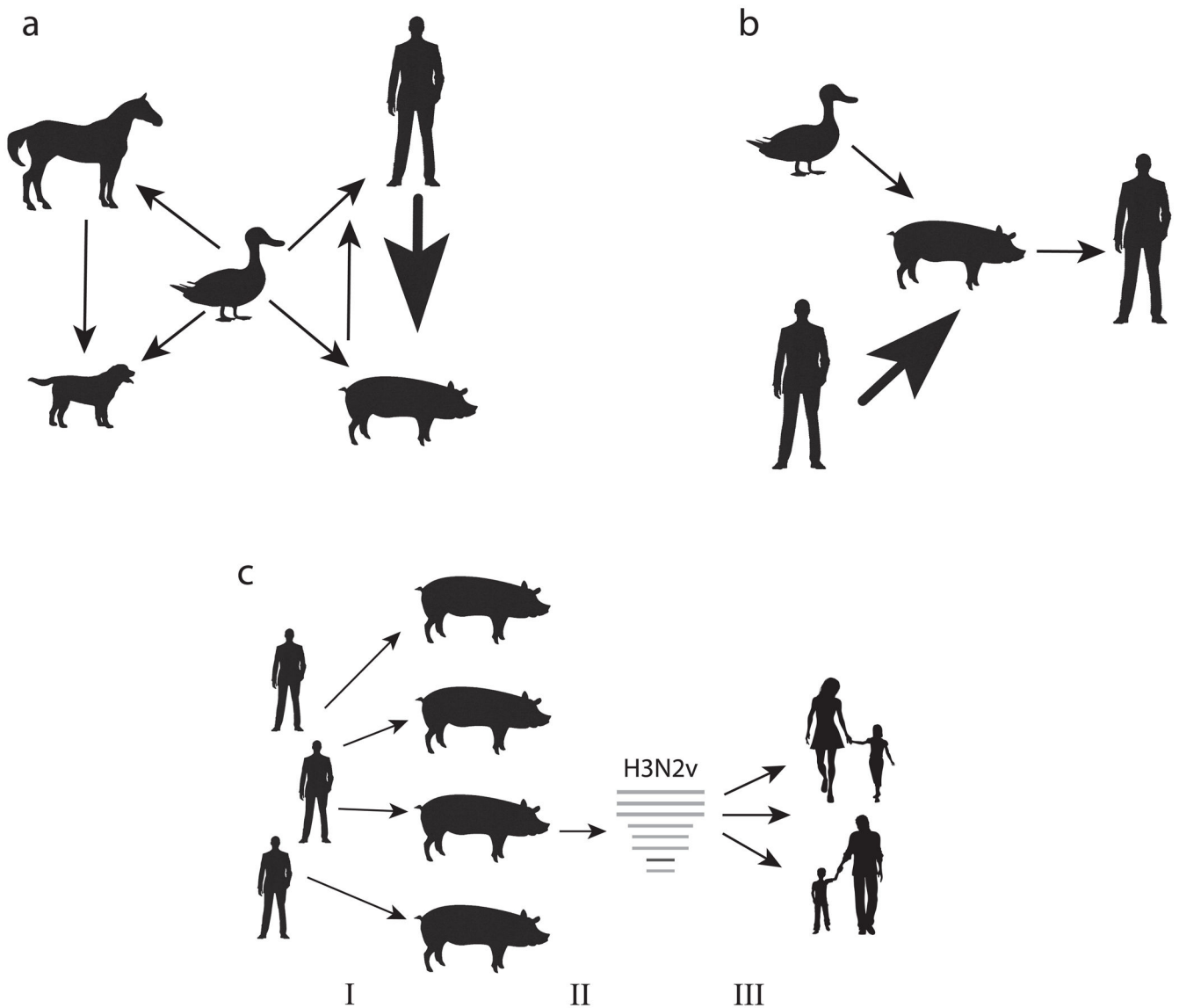
Figure 4. Countries where pH1N1 has been identified in swine
See also Table 1. Countries shaded in purple represent those where pH1N1 viruses of human origin have been detected in swine since 2009.

Figure 5. A model for the ecology of influenza A viruses
(a) Cross-species transmission between avian species (thought to be the main reservoir for IAV diversity) and humans (H1N1, H2N2, and H3N2), equines [H3N8 (2x) and H7N7], canines (H3N2), and swine (H1N1 and triple reassortant PB2/PA), as well as transmission between mammalian species: equine-to-canine (H3N8), swine-to-human (H1N1), and human-to-swine (H1N1, H1N2, and H3N2, at least 20 times). Width of arrows is proportional to the number of IAV transmission events between species that result in endemic circulation of a virus in a new host (transient spillovers not included). (b) Model for the role of swine as 'mixing vessels' for the evolution of pandemic viruses (width of arrows also are proportional to the frequency of transmission). (c) Model for the evolution of H3N2v viruses in swine. Large-scale transmission of pH1N1 viruses from humans to swine seeds pH1N1 in swine populations globally (I); reassortment between pH1N1 viruses and co-circulating triple reassortant H3N2 viruses in the United States, generating novel

reassortant H3N2v variants with seven triple reassortant H3N2 virus segments and the MP segment of pH1N1 origin (II); and transmission of > 300 H3N2v viruses from swine to humans, resulting in one adult fatality, in the United States during 2011–2013 (III).

Table 1

Reports of human-origin pH1N1 viruses in swine during 2009–2014

Location	Year	Pandemic viruses identified	Ref or GenBankaccession
North America			
Canada	2009	pH1N1	[121]
Canada	2009	pH1N1	[43]
Mexico	2009	pH1N1	[122]
United States	2009–2010	pH1N1, pH1N1 reassortants[a]	[112]
	2010	pH1N1 reassortants	[110]
Europe			
France	2010	pH1N1	CCB78518
Finland	2009–2010	pH1N1	[123]
Germany	2009–2010	pH1N1 reassortants	[116]
Germany	2009–2010	pH1N1 reassortants	[114]
Hungary	2010–2011	pH1N1 reassortants	[124]
Italy	2009	pH1N1	[125]
Italy	2013	pH1N1 reassortants	[117]
Norway	2009	pH1N1	[126]
Norway	2009–2010	pH1N1	[127]
Poland	2012	pH1N1	AHJ57400
Russia	2009–2011	pH1N1	AFV31481
Spain	2010–2011	pH1N1	[128]
United Kingdom	2010	pH1N1 reassortants	[115]
United Kingdom	2013	pH1N1	[129]
Asia			
China	2009–2010	pH1N1 reassortants	[118]
China	2010–2011	pH1N1 reassortants	[113]
Japan	2009–2010	pH1N1	[130]
India	2009	pH1N1	[24]
Singapore	2009	pH1N1	ACY82404
South Korea	2009	pH1N1	[131]

Location	Year	Pandemic viruses identified	Ref or GenBankaccession
South Korea	2009	pH1N1	[132]
Sri Lanka	2009–2012	pH1N1	[25]
Thailand	2009–2010	pH1N1	[133]
Thailand	2010–2012	pH1N1, pH1N1 reassortants	[111]
Vietnam	2010–2011	pH1N1	[130]
Vietnam			[134]
South/Central America and Caribbean			
Argentina	2009	pH1N1	[20]
Brazil	2009–2010	pH1N1	[22]
Colombia	2009–2011	pH1N1	[23]
Costa Rica	2010	pH1N1	ADW93781
Cuba	2010	pH1N1	[135]
Africa			
Cameroon	2010	pH1N1	[19]
Nigeria	2011	pH1N1	[49]
Togo	2013	pH1N1	AIO11674
Pacific			
Australia	2009	pH1N1	[27]
Australia	2009	pH1N1	[26]

[a] pH1N1 reassortants refers to influenza viruses that were generated by reassortment between pH1N1 and other co-circulating swine viruses, and therefore have some, but not all, segments of pH1N1 origin