



Review

Animal influenza virus infections in humans: A commentary

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ABSTRACT

Here we review evidence for influenza A viruses (IAVs) moving from swine, avian, feline, equine, and canine species to infect humans. We review case reports, sero-epidemiological, archeo-epidemiological, environmental, and historical studies and consider trends in livestock farming. Although this focused review is not systematic, the aggregated data point to industrialized swine farming as the most likely source of future pandemic viruses, yet IAV surveillance on such farms is remarkably sparse. We recommend increased biosafety and biosecurity training for farm administrators and swine workers with One Health-oriented virus surveillance throughout industrialized farming and meat production lines. Collaborative partnerships with human medical researchers could aid in efforts to mitigate emerging virus threats by offering new surveillance and diagnostic technologies to livestock farming industries. © 2019 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Brief review of human and animal influenza viruses

There are four recognized types of influenza viruses (A, B, C, and D), with influenza D virus (IDV) the most recently discovered (2011) (Hause et al., 2013). Influenza A viruses (IAVs) cause the most morbidity in both humans and animals. There are 18 recognized hemagglutinin (HA) and 11 neuraminidase (NA)

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glycoproteins by which IAVs are subtyped. IAVs change through mutation, recombination, and reassortment, frequently challenging the immune systems of their human and animal hosts (Table 1).

Swine and poultry are two key reservoirs of IAVs and are notably two rapidly growing livestock industries (Figure 1). As livestock industry farms are often home to several thousand birds or pigs, sometimes harboring multiple subtypes of IAVs, they are often considered high-risk areas for novel IAV generation. Large livestock populations often have frequent introductions of immunologically naïve animals, which helps maintain IAVs within livestock. Animal workers and other animal species may introduce new IAV strains to the flocks or herds (Rajao et al., 2018). These same animal workers may serve as a bridging population in moving IAVs circulating among livestock to other humans (Ma et al., 2017). In this review, we examine the risks of human infections with IAVs that normally circulate among swine, poultry, and other domesticated animals and offer recommendations to mitigate these zoonotic risks.

Zoonotic transmission of influenza A viruses

Swine influenza

Swine production is rapidly undergoing change with small and medium-sized farms being supplanted by more efficient industrial swine farms. This is particularly true in China, the world leader in pork production, where the aim of production growth is to not only expand to meet China's consumption, but also to eventually become an exporter of pork. In modern farming, swine influenza viruses (SIVs), often of multiple subtypes, are frequently enzootic within these modern swine production facilities. While SIV infections cause significant economic losses to the agricultural industry, especially in combination with other respiratory pathogens, surveillance for novel SIVs is generally sparse and normally conducted only when there is unusually high morbidity in pigs. Vaccination against IAVs is common in some countries like the United States but rare in most developing countries.

Although a matter of some debate, SIVs have been associated with, if not considered the source of, the 1918 (H1N1), 1957 (H2N2), 1968 (H3N2), and 2009 (H1N1) pandemics in humans (Easterday, 2003; Crosby, 2003; Krueger and Gray, 2012; Scholtissek et al., 1978; Mena et al., 2016). Moreover, there is considerable evidence that swine workers are at increased risk of SIV infection. Our 2004 study conducted in Iowa indicated that individuals with occupational exposure to pigs had significantly increased odds (OR 54.9; 95% CI 13.0, 232.6) of elevated antibody levels against classical swine H1N1 and H1N2 viruses (OR 13.5; 95% CI 6.1, 29.7) when compared to non-swine-exposed individuals (Gray et al., 2007).

Table 1
Types of influenza A virus which have moved from animals to infect humans.^a

Host animal	Virus types detected in humans
Porcine	H1N1 (Novel Swine-Origin Influenza A Virus Investigation Team, 2009), H1N2 (Centers for Disease Control and Prevention, 2012a), H3N2 (Bowman et al., 2017)
Avian	H5N1 (Writing Committee of the World Health Organization Consultation on Human Influenza A/H5, 2005), H5N6 (Pan et al., 2016), H7N2 (Peiris, 2009), H7N3 (Centers for Disease Control and Prevention, 2012b), H7N7 (Fouchier et al., 2004), H7N9 (Parry, 2013), H9N2 (Cheng et al., 2011), H10N7 (Arzey et al., 2012), H10N8 (Liu et al., 2015)
Feline	H7N2 (Lee et al., 2016)
Equine	None reported
Canine	None reported

^a This list is not necessarily all-inclusive.

Even spouses of swine-exposed individuals, who had no direct contact with pigs, had elevated antibody levels against swine H1N1 virus (OR 28.2; 95% CI 6.1, 130.1) as well as swine H1N2 virus (OR 6.9; 95% CI 2.8, 17.2) (Gray et al., 2007). This finding suggests considerable SIV transmission between pigs and humans and provides evidence that the virus is being carried from the farms to the workers' homes or towns either via fomites or respiratory infection. In addition, modern farming practices where live pigs are often transported across national borders contribute to the rapid international dissemination of novel SIVs (Nelson et al., 2011; Nelson et al., 2014). Our recent epidemiological studies of IAVs in swine environments have shown that IAVs are ubiquitous in these environments and there are considerable opportunities for cross-species transmission and reassortment or recombination events between IAVs that may be present in pigs, chickens, ducks, geese, and dogs (Ma et al., 2015, 2017). This greatly enhances virus transmission across species particularly if personal protective equipment is lacking.

Beyond swine farms, numerous studies have found evidence that IAVs move between pigs and humans at US agricultural fairs (Bowman et al., 2014, 2017; Duwell et al., 2018; Schicker, 2016; Gray et al., 2012). The first detection of influenza A (H1N1)pdm09 in pigs was at the 2009 Minnesota State Fair five months after the first detection of this virus in humans (Gray et al., 2012), suggesting a low threshold for cross-species infection. Similar detections of influenza A (H1N1)pdm09 virus in pigs across multiple countries soon corroborated this finding and led to the detection of reassortant influenza A (H1N1)pdm09 virus progeny detections in pigs (Starick et al., 2011; Vijaykrishna et al., 2010; Moreno et al., 2011; Ducatez et al., 2011). Later, Bowman and colleagues sampled 161 pigs at seven agricultural fairs and found an overall IAV molecular prevalence of 77.5% at the end of fairs with marked evidence by sequence studies of pig-to-pig transmission (Bowman et al., 2017). Taken together, these findings of humans developing SIV infections after visiting agricultural fairs suggest considerable opportunity for amplification of IAV and transmission to humans at swine agricultural fairs.

In 2018, Walia et al. reviewed the genetic diversity of SIVs, reporting more than ten unique subtypes of viruses circulating in U.S. pigs (Walia et al., 2018). Subsequent reports have found even more variants (Chamba Pardo et al., 2017; Watson et al., 2015), including research in China where more than 60 unique SIV genotypes were detected among pigs (Zhu et al., 2018). This increasing variety of unique SIV subtypes maintained in large industrial farm systems logically increases the probability that a novel virus that is harmful to humans may emerge from modern farming enterprises.

Despite the available data regarding the potential role of swine in generating pandemic IAV strains, evidence of IAV cross-species transmission to both pigs and humans, and the numerous unique genotypes of SIVs, there is still not a clear understanding of IAV ecology in pigs. Epidemiological studies of IAVs among pigs are sparse and frequently limited to passive surveillance. It seems unfortunate that it may take an alarming number of humans or pigs to experience severe SIV disease before routine surveillance for novel IAVs among pigs becomes a public health or veterinary health priority (Gray and Baker, 2011; Gray and Cao, 2013).

Avian influenza

Similar to SIVs, there is considerable evidence of zoonotic transmission of avian influenza viruses (AIVs) from birds to humans. Several H7 and H5 strains are the most common AIVs among humans, often causing severe disease (Food and Agriculture Organization of the United Nations, 2019a), but in some cases causing mild and asymptomatic infections (Khuntirat et al., 2011).

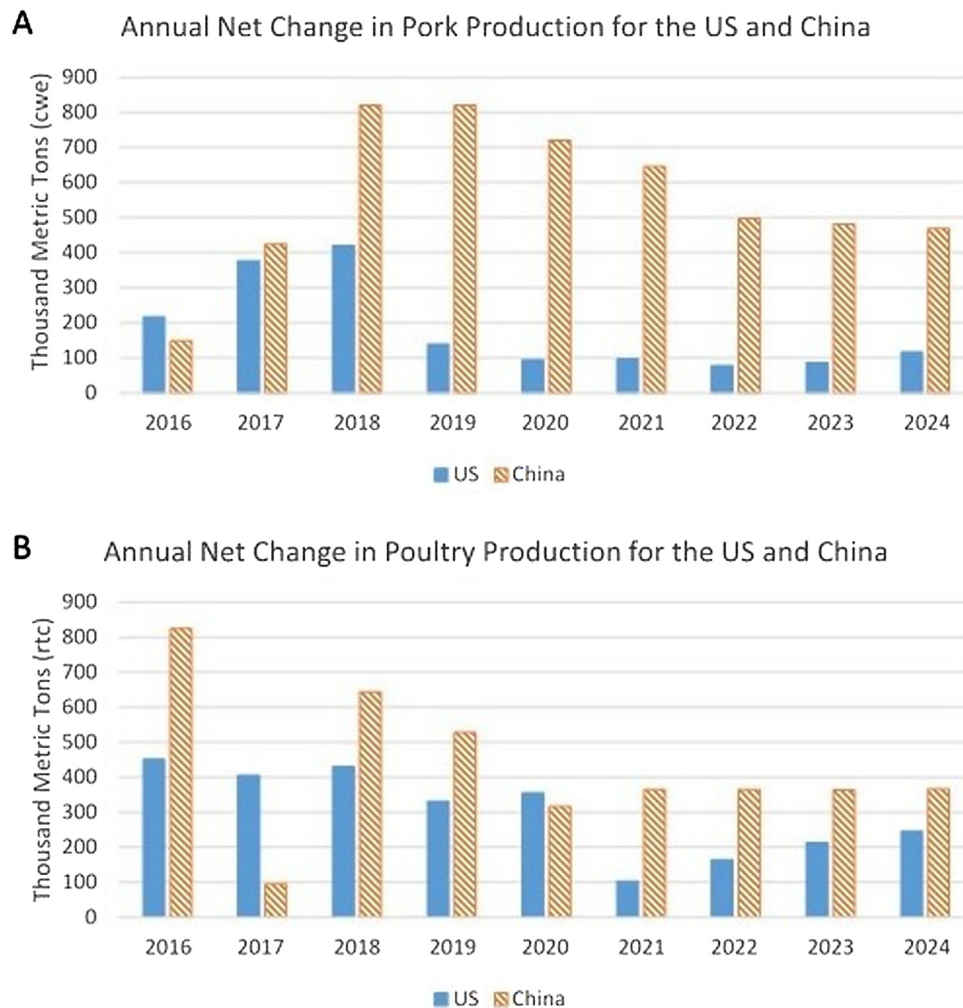


Figure 1. These graphs show the estimated net change year-to-year in (A) pork production (carcass weight equivalent; cwe), and (B) poultry production (ready to cook; rtc) in the United States and China from the years 2015 to 2024. The United States and China are the world's largest producers for both pork and poultry. Baseline 2014 production figures for pork in thousands of metric tons: China = 54,608 cwe; United States = 10,210 cwe. Baseline 2014 production figures for poultry in thousands of metric tons: United States = 19,910 rtc; China = 17,508 rtc. These data were abstracted from OECD/FAO (2019), "OECD-FAO Agricultural Outlook (Edition 2018)" OECD Agriculture Statistics (database), <https://doi.org/10.1787/d4bae583-en> (accessed on 08 February 2019) (OECD Food Agriculture Organization of the United Nations, 2018).

AIV infections in humans most often occur after exposure to infected or dead birds, as evidenced by periodic serological surveillance for H5 and H7 in humans (Sikkema et al., 2016). In the United States, the world leader in poultry production, as the prevalence of AIVs among poultry is low (save for H5 incursions in 2014/15 which led to the culling ~50M birds) (United States Department of Agriculture, 2016), the risk of human infections is thought to be very low (United States Department of Agriculture, 2019). In contrast, this risk is higher in China where highly pathogenic H7N9 and H5N1 viruses have been more prevalent in poultry (Su et al., 2015).

Live animal markets, which have high concentrations of avian species often with exposure to other animals including humans, are a source of increased risk of novel AIV generation (Su et al., 2015). Ma et al. cohort study of 468 poultry vendors at live bird markets in China monitored from 2013–16 found that, despite very intense exposure to birds, seroconversion against AIVs was less than 3% for each of the H7N9, H9N2, and H5N1 subtypes (Ma et al., 2018). There have, however, been instances of severe cases of H7N9 AIVs in humans occurring in five waves since 2013 with live bird markets implicated as a likely source (Food and Agriculture Organization of the United Nations, 2019a). Since the first observed

human infections with H7N9 AIV, there have been 1,568 confirmed cases, with a nearly 40% case fatality rate (Food and Agriculture Organization of the United Nations, 2019a). Introduction of a compulsory bivalent H5/H7 vaccination for poultry in China has reduced this H7N9 infection risk to humans (Wu et al., 2019). While these cases are severe, they are also sporadic and relatively few considering the high number of people in China with intense exposure to infected poultry.

While AIVs are known to infect humans with intense exposure to poultry on occasion, human influenza viruses are not known to infect avian species. There is still, however, considerable potential for AIVs to play a role in generating pandemic IAV strains (Peiris et al., 2016).

Feline influenza

Reports of feline influenza virus infections are relatively recent, with the first cases documented in 2004 (Keawcharoen et al., 2004). Interspecies transmission events with avian (Keawcharoen et al., 2004; Zhang et al., 2013), canine (Song et al., 2011; Jeoung et al., 2013), human (Knight et al., 2016), and equine (Su et al., 2014) influenza viruses have been shown to infect cats, but naturally

occurring cases are sporadic. One such outbreak of influenza A (H7N2) (an avian-lineage virus) in felines occurred in a New York city animal shelter in 2016 (Lee et al., 2017). Approximately 500 cats were infected during this outbreak, and no other shelter animals (dogs, chickens, or rabbits) tested positive for an IAV. One veterinarian with intense exposure to the infected cats at this shelter developed symptoms and confirmed infection with influenza A(H7N2) (Lee et al., 2017). A follow-up serological survey was performed among 121 shelter workers, and one additional employee with serological evidence of influenza A (H7N2) infection was identified (Poirot et al., 2018). This suggests that influenza viruses circulating in felines have potential to play a role in generating pandemic IAV strains and may infect humans.

Equine influenza

Equine influenza viruses (EIVs) are an important cause of respiratory tract disease in horses, chiefly caused by the H3N8 influenza A subtype (Singh et al., 2018). Before vaccines were developed, EIV outbreaks in equine populations were very common and had a case fatality as high as 20% (Sack et al., 2017). These outbreaks have been most common in countries with large equine populations and sparse EIV vaccination programs, such as Mongolia and Australia (Cowled et al., 2009; Yondon et al., 2013). One 1983–84 outbreak in Mongolia infected an estimated 760,000 horses (40% of the total horse population) in the country with nearly a third of those infections resulting in death (Yondon et al., 2013). Epizootics such as these lead to great economic losses for horse farming, meat production, as well as leisure and racing industries (Sack et al., 2017; Cowled et al., 2009).

There are certain historical reports that may provide evidence of EIV infections in humans and perhaps even in dogs and in cats before influenza viruses had been identified (Law, 1874). This includes one archeo-immunological study where neutralizing antibodies against influenza A/Equine-2/63 virus were found among humans born between 1870 and 1900 (Minuse et al., 1965). There have also been studies of experimental infections where IAVs were passed through ponies to humans and back demonstrating subclinical and clinical infections in both hosts (Alford et al., 1967). More recently, our study of individuals with horse exposure in Iowa showed evidence of previous EIV infection compared to controls with no equine exposure (Larson et al., 2015). Since EIV infection in humans causing severe disease has not been recently observed (Xie et al., 2016), our review of these available data regarding zoonotic transmission of EIVs suggests that while EIVs have the potential to infect humans, the risk is low.

Canine influenza

An influenza H3N8 variant virus with similarities to EIV was first detected in canines in Florida racing greyhounds in 2004 (Crawford et al., 2005). It is now thought that canines can be infected with a number of different strains of IAVs. Sustained canine influenza virus (CIV) infections are more often observed where there are dense populations of dogs, such as animal shelters, races, and dog farming (Voorhees et al., 2018). In the last five years, there have been several reports of canine species infected with IAVs of at least six different subtypes (H1N1, H3N2, H3N8, H5N1, H6N1, H9N2) (Jang et al., 2017; Sun et al., 2013; Songserm et al., 2006; Lin et al., 2015). In recent years, more serious influenza infections in dogs with AIVs have been observed, some of which have caused sustained IAV transmission of virus among dogs (Giese et al., 2008; Song et al., 2008). Looking at zoonotic transmission, mild infection among dogs challenged with certain human influenza viruses have been demonstrated (Todd and Cohen, 1968), and one study from China found a case of transmission of

human influenza viruses to dogs (Chen et al., 2018). Our study of persons with occupational exposure to dogs found no statistically significant increased risk of CIV infection compared to unexposed persons (Krueger et al., 2014). Currently, there are no well-documented cases of CIV infections in humans.

Where should our priorities lie?

When considering the height of the “barrier” between the animals studied and humans, we conclude that the pig-human interface is the most important (Figure 2), followed by avian species. The large, dense populations of these two animal species with their affinity IAV infection is a major contributor to this high risk. There is a significant barrier for feline, equine, and canine IAVs to move to humans, supported by the limited number of sporadic cross-species infections that have been detected from these animals to humans. Additionally, there are not the same large dense populations of cats, horses, and dogs necessary to sustain viral endemicity in a single geographical area; hence, IAV outbreaks in these animals move around geographically and the animals seldom are observed to harbor multiple unique IAV strains, lessening the risk of pandemic virus generation.

In contrast, commercial farming has brought large populations of pigs and poultry near metropolitan centers where IAVs may be exchanged between species and sustained. Such large animal farms may harbor a variety of IAV subtypes. In this review, we have found that, at least in recent years, this variety of novel IAV subtypes is greatest and more sustained among pigs than among poultry. Additionally, SIV infections among swine workers are detected more often than AIV infections are detected among poultry workers. In general, AIVs are rarely transmissible between humans. On the other hand, SIV infections in humans are commonly reported, even after brief exposure to pigs (Schicker, 2016), and were associated with four major influenza pandemics (Smith et al., 2009). The importance of the pig-human nexus is not only true for IAVs but also for influenza B, C, and D, where among all animal hosts for influenza viruses only pigs and humans can be infected with all four viruses (Bailey et al., 2018). The aforementioned SIV risks including the frequency of spillovers of SIVs to humans, susceptibility of both humans and pigs to strains among all four types of influenza viruses, and the staggering growth the swine industry has undergone increasing transmission risk of novel influenza virus emergence, all provide compelling evidence

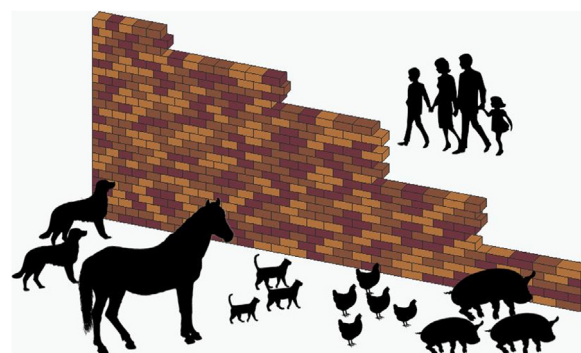


Figure 2. This is a qualitative, graphical depiction of the authors' assessment of the current risk of influenza A viruses crossing from various domestic animals to infect humans. The graphic is composite or gestalt of case reports, sero-epidemiological studies, archeo-epidemiological studies, environmental studies, and historical observations. The authors' intent with this graphic is to illustrate the high relative probability of continued movement of influenza A viruses between pigs and humans, contrasting that with the knowledge that swine viruses have been associated with at least four recent pandemics, yet worldwide we continue to have relatively sparse surveillance for novel influenza A virus detections among pigs.

that pigs and SIVs need to be considered a higher priority when conducting surveillance for pandemic threats.

How do we mitigate zoonotic influenza virus threats to humans?

While most industrial farms in the United States and Europe have comprehensive biosecurity and biosafety measures in place, this is not true worldwide. We have observed that while countries in Asia are rapidly intensifying their swine operations, it is often done with scant biosecurity and biosafety measures. The recent African Swine fever (ASF), a nonzoonotic infection, outbreaks in China and other countries in Asia, illustrate the problems with low level of biosecurity as a significant factor in the spread of this virus. Since August 2018 when first ASF report was made in China, the July 2019 FAO reports have documented ASF spread to most provinces in China, as well as to Cambodia, The Democratic People's Republic of Korea, Laos, Mongolia, and Vietnam ([Food and Agriculture Organization of the United Nations, 2019b](#)). Much of this spread has been attributed to the role a low level of biosecurity can play on national agricultural economies and food security.

Hence, training programs with international quality standards to build reliable biosecurity including biosafety procedures are needed. In such training programs, both farm management and animal workers need intensive biosecurity and biosafety training that includes demonstrations of facility biosecurity enhancements, as well as the importance of using personal protective equipment in reducing pathogen incursions on the farms and to workers ([Ramirez et al., 2006](#)). Furthermore, we posit that biosecurity and biosafety training should extend beyond the farm to livestock wholesale markets, and abattoirs. Finally, we argue that workers in contact with live animals would also benefit from annual receipt of seasonal human influenza vaccine.

While there have been important efforts on behalf of organizations such as USDA-APHIS to conduct surveillance for IAVs on US swine farms, this is often contingent upon pigs developing unusual clinical evidence of IAV infection, overlooking the sustained infections and patterns in the emergence and transmission of SIVs. These surveillance efforts pale in comparison to AIV surveillance in the United States, where routine testing of every flock is mandated. While we need to continue to conduct IAV surveillance among poultry, we need to do a markedly better job among swine. Hence, there remains a great need to broker One Health-oriented, novel virus surveillance within large swine farms and other pork production points worldwide.

While the large animal production industries often avail themselves of the scientific talent at agricultural academic institutions, seldom do these same industries engage the often better-resourced human public health and medical academic centers. The disparity in federal resources between agricultural institutions and human medical institutions is not trivial, with human medical institutions often receiving many more fold funding. Yet we observe a reticence for animal industries to engage the human health sector lest occupational health or other problems be discovered that damage business bottom lines, as was the case for example when public misunderstanding of the role of pigs in the 2009 H1N1 pandemic led to decreases in pork sales globally ([Gray and Baker, 2011](#)). With One Health partnerships in mind, we need to find ways for animal production industries to partner in non-threatening ways with human public health and medical care facilities so as to benefit from their deeper resources and novel technologies.

One way to approach this challenging undertaking would be to continue to develop simple, robust virus sampling that could take place at the farm through non-invasive surveillance techniques. Bioaerosol samplers coupled with rapid diagnostics, for example,

have proven to be a powerful screening tool with great potential ([Anderson et al., 2017](#); [Alonso et al., 2017](#); [Bui et al., 2018](#)). New diagnostic tools for potential use both pen-side and in human healthcare settings are in development and offer easy to use, rapid characterization of endemic animal pathogens. Several companies are currently working on such pen-side and rapid tests, for this virus as well as others, that can satisfy this required tool for a One Health surveillance. For example, InDevR Inc. has developed a platform called the FluChip-8G that aims to identify and characterize specific influenza A or B subtypes in less than ten hours. Similarly promising, the sequencing platforms (e.g. Oxford's MinION™ nanopore sequencer and Illumina Iseq 100 sequencing system) are becoming more portable and powerful. Coupled with cloud-based data storage, and remote access to bioinformatics software pipelines, (e.g. Chan Zuckerberg Biohub's IDseq – San Francisco, CA) such sequencing approaches are promising as future tools to rapidly detect the presence of many infectious disease pathogens and to characterize them via their partial or whole genome.

Conclusion

In summary, in this review we find the risk of zoonotic IAV infections to humans to be greatest from swine viruses ([Figure 2](#)), yet swine-human IAV transmission seems neglected as a surveillance focus. We argue that while surveillance for novel IAVs among poultry, horses, dogs, and cats is still necessary, this swine-human interface surveillance gap desperately needs to be addressed. We need to conduct such surveillance using a One Health approach that includes monitoring swine, swine workers, and swine production environments. Swine farm management teams and swine workers worldwide need comprehensive biosecurity and biosafety training. We also need to bring rapid and accurate diagnostics to swine farms such that swine industries might benefit from early warning should a novel IAV be detected. These interventions might be addressed in additional ways that engage modern microbiological tools and funding that are often resident in large human medical academic centers. Such new partnerships could yield field studies that would benefit human, animal, and industry sectors. However, such partnerships will require new strategies to protect the business interest of the intensive animal farming institutions.

Contributors

GCG conceived this review which was based upon a webinar he gave for the American College of Veterinary Preventive Medicine on Nov 15th, 2018. LKB and GCG drafted much of the text. MDS and M-JM added their critical review, comments, and suggestions for changes. All authors have participated in preparing the manuscript and approve of its publication.

Conflict of interests

Gregory Gray is collaborating in contract research with InDevR, Inc (Boulder, CO). He is also collaborating (no funding support) in research with Chan Zuckerberg's IDseq team (San Francisco, CA).

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Ethical approval

This work does not involve the use of animal or human subjects.

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