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Review

Avian influenza viruses in pigs: An overview

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ABSTRACT

This paper reviews important aspects of infection of pigs with avian influenza viruses. Wild waterfowl are the main reservoir for influenza A viruses; other species, such as pigs, can be infected, but most avian strains are imperfectly adapted to replication and transmission in such new hosts. However, some avian-to-porcine host jumps have resulted in the emergence of stable swine influenza virus lineages, with major consequences for both animal and human health. Different categories of factors are involved in these cross-species adaptations, both epidemiological (relating to host–host interactions) and virological (relating to host–virus interactions). An understanding of the adaptation of avian influenza viruses to pigs has benefited from a number of recent studies, but more research is warranted to fully appreciate the key molecular and epidemiological factors involved in this intriguing viral host jump.

Introduction

Waterfowl are the main epidemiological reservoir of influenza A viruses (Slemons et al., 1974; Hinshaw et al., 1982; Fouchier et al., 2005; Obenauer et al., 2006; Olsen et al., 2006). Most of these avian strains have a relatively restricted host range, whereas some can also infect non-avian species, including human beings and domestic animals. The epidemiological consequences of such host jumps are unpredictable and potentially catastrophic. Most occurrences are unsuccessful in the sense that they do not result in the establishment of a new lineage in the recipient species, although they can be consequential in terms of individual case mortality. Conversely, some instances of cross-species adaptation have resulted in the emergence of new strains and suspected strain displacement at a continental scale. With the possible exception of bats (Chan et al., 2013; Mehle, 2014), the current mammalian strains of influenza virus probably originated from a host jump from the waterfowl reservoir to a new species.

Pigs are one such candidate new host for viruses of avian origin. The avian-to-porcine host jump is a topic of special concern in influenza epidemiology because: (1) infection of pigs with influenza viruses has direct consequences for pig health (Van Reeth, 2007; Kuntz-Simon et al., 2010); and (2) pigs are potential intermediate hosts for the adaptation of avian viruses to human beings.

In this context, the aim of this paper is to provide an overview of some epidemiological and virological aspects of porcine infections with avian influenza viruses. It will discuss evidence for cross-species infections and imperfect adaptation, the most successful host jumps to pigs and the downstream consequences of swine influenza virus (SIV) infections for public health, notably in terms of documented zoonotic transmissions. Two sections will then provide a brief theoretical discussion of the different categories of factors involved in host range restriction and possible links between molecular adaptation studies and epidemiological approaches. Finally, some recent developments shedding light on specific avian-to-porcine molecular adaptation routes are presented.

Evidence for cross-species infection and imperfect adaptation

Pigs have been infected with low pathogenicity avian influenza (LPAI) virus strains on different occasions, either experimentally or naturally; for instance, Kida et al. (1994) found that 29/38 strains of LPAI viruses of a variety of subtypes (mainly isolated from ducks) were detected in nasal swabs 3 and 4 days after intranasal inoculation to pigs and thus were already able to replicate in pigs and to induce a serological response. However, the potential for transmission of these viruses between pigs was not examined. Karasin et al. (2000a) reported an outbreak of H4N6 subtype swine influenza clinically affecting 5% of 2600 pigs on a farm in Canada. Every gene segment of the virus involved was most similar to a segment of avian origin, with nucleotide identities of 90.6–98.2%. Since this farm did not import pigs from unrelated herds, it is supposed that this virus was transmitted from neighbouring wild birds. The virus did not maintain itself in pigs; thus, the extent to which viral segments evolved within the pig herd after an initial cross-species transmission event is unknown.

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Nonetheless, experimental data suggest that only a minority of such cross-species transmission events are likely to result in the establishment of a stable porcine lineage; for example, de Vleeschauwer et al. (2009a) could infect pigs experimentally with an avian influenza virus strain (A/chicken/Belgium/150/99 H5N2 LPAI), but the virus grew to lower titres in much of the respiratory tract compared to a control SIV. de Vleeschauwer et al. (2009b) also showed that pigs infected with two different SIVs could transmit the infection to in-contact pigs and ferrets, while pigs infected with a panel of 10 avian viruses could not. Such observations are consistent with the hypothesis that, in general, avian strains are imperfectly adapted to new (non-avian) hosts and must undergo further adaptation before they can establish a stable new lineage.

Successful establishment of influenza virus lineages in pigs

SIVs are widely distributed in pigs. However, the most prevalent strains differ greatly between locations (Van Reeth et al., 2012), suggesting different possible molecular and epidemiological pathways for lineage establishment in pigs as a new host. The influenza virus genome consists of eight segments, numbered 1–8 (Palese, 1977), that individually encode the major viral proteins, PB2, PB1, PA, HA, NP, NA, M and NS, respectively. Coinfection of a single cell with two different parental strains of influenza virus may give rise to progeny viruses bearing combinations of eight segments derived from either parent (a highly efficient form of modular evolution known as 'reassortment'). The history of successful establishment of influenza virus lineages in pigs is complex and has involved a number of such reassortment events. This results in an intricate epidemiology for current SIV lineages, with continuing virus introductions from one country to another, largely as a result of trade in pigs (Nelson et al., 2015b). The paragraphs below do not aim to provide an exhaustive description of all lineages circulating in pigs worldwide, but rather illustrate some features of the establishment of influenza A virus lineages in pigs in different regions.

Establishment of influenza virus lineages in American pigs

Influenza in pigs was suspected as early as 1918 in the USA and soon was believed to be closely related to the cocirculating human influenza virus strain (Shope, 1931) that had emerged (possibly from birds) as the 'Spanish Flu' pandemic. This porcine lineage was later named the 'classical' swine influenza H1N1 lineage and remained the most common lineage in pigs in the USA for several decades, with an estimated seroprevalence of 21% in 1976–1977. Seroreactivity to the human A/Victoria/3/75 H3N2 virus started to be detected in pigs during the 1970s, with an estimated seroprevalence of 1.4% during this decade (Hinshaw et al., 1978). Antibodies to both classical porcine and 'human' H3N2 viruses continued to be detected in pigs in the USA over the following decade, with estimated prevalences of 30% and 1.1%, respectively, in 1988–1989 (Chambers et al., 1991).

The prevalence of seroreactivity to H3 viruses increased from 1997 to 1999 and several H3N2 viruses isolated at that time were associated with disease outbreaks in pigs. Phylogenetic analyses have shown that, while a 1997 H3N2 Ontario porcine virus was wholly of human origin, the 1998–1999 H3N2 USA viruses were 'triple reassortants' (Karasin et al., 2000b). These viruses had HA, NA and PB1 genes of human origin, NP, M and NS genes of the classical SIV lineage, and PB2 and PA genes of avian lineages. These triple reassortants went on to be highly successful, circulating and causing disease in North American pigs, and undergoing further reassortment on different occasions, including with H1N1 'classical' viruses (Van Reeth et al., 2012). The 2009 pandemic H1N1 virus notably was generated through reassortment of a triple reassortant descendant with the European avian-like porcine virus (see the paragraph on European swine influenza lineages below) (Smith et al., 2009b). Thereafter, numerous spillover events from human beings to pigs established the 2009 pandemic lineage more firmly in pigs on a global scale (Nelson et al., 2015a; Nelson and Vincent, 2015). These events also contributed to the evolution and diversity of SIVs through extensive reassortment with other established porcine lineages. This was well illustrated in the USA, in which, for example, 69% of 368 unique H3N2 SIV genomes collected from 2009 to 2016 contained at least one (and up to six) genes from the 2009 pandemic lineage (Rajão et al., 2017).

Reverse genetics experiments have investigated the in vivo consequences of reassortment of the six 2009 pandemic strain internal genes with the two surface protein genes (HA and NA) of a highly pathogenic avian influenza (HPAI) virus strain (Abente et al., 2017). This study showed that, in challenge pigs, such reassortants caused higher lung virus titres at 5 days post-infection compared to the wholly HPAI strain. Furthermore, in a transmission experiment, the reassortant was transmitted to 5/5 in-contact pigs, as opposed to 3/5 in-contact pigs for the wholly HPAI strain. This suggests that reassortment with 2009 pandemic strains in pigs could cause increased pig-to-pig transmission of other strains of concern (including avian strains), and that further investigations into this issue could be useful. Of note, exhibition pigs at agricultural fairs in the USA appear to have played an important role in SIV evolution and transmission (Nelson et al., 2016; Lauterbach et al., 2017).

Establishment of influenza virus lineages in European pigs

The classical porcine H1N1 influenza virus lineage also circulated in Europe in the 20th century. However, a new H1 influenza A strain was isolated from sick pigs in Belgium in 1979. Hæmagglutination inhibition (HI) tests showed that these isolates were easily neutralised by sera raised against duck H1 strains isolated in 1976 and 1977, while being largely insensitive to sera raised against classical H1 SIV strains from 1930, 1939 and 1967 (Pensaert et al., 1981). This suggested that these new isolates could represent a new European H1 porcine lineage recently emerged from the waterfowl reservoir, designated 'avian-like'. These distinct antigenic properties mirror genetic analyses showing that avian-like strains form a largely monophyletic group included within an avian cluster in an H1 haemagglutinin phylogeny (Bourret et al., 2017); classical porcine strains form another, separate, cluster. The classical porcine lineage has gone largely undetected for a number of years in Europe (last detected on the European mainland in 1976) where it may have been displaced by the avian-like lineage (Brown, 2000, 2013; Simon et al., 2014).

Various SIVs isolated from 1985 to 1989 were reassortants bearing the HA and NA genes from human H3N2 viruses and the internal genes from the avian-like lineage (Castrucci et al., 1993). Avian-like porcine viruses also reassorted with human influenza viruses to cause the emergence of H1N2 viruses in pigs (Brown et al., 1998).

Swine influenza virus lineages in Asia

In East and South-East Asia, the majority of porcine infections with influenza viruses currently are caused by H1N1 viruses. These are believed to have emerged on successive occasions since at least 1991 and include strains descended from the 'classical' and 'avian-like' lineages, amongst others, along with reassortants (Trévennec et al., 2011). Influenza viruses closely related to the human 1968