The emergence of novel influenza viruses among pigs in North America due to interspecies transmission and reassortment

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Abstract. In 1997–1998, H3N2 influenza viruses of different genotypes emerged among North American pigs. Triple reassortant H3N2 viruses containing human, classical swine and avian virus genes spread widely within the swine population and gave rise subsequently to reassortant H1N2 and H1N1 viruses. Together with wholly avian viruses recovered from North American pigs since 1999, these viruses emphasize that influenza virus interspecies transmission and reassortment in pigs can occur throughout world. They provide important research tools with which the genetic factors that control interspecies transmission can be investigated. © 2003 Elsevier B.V. All rights reserved.

Keywords: Influenza; Swine; Reassortment; Interspecies transmission; Pandemic

1. Introduction

Influenza virus infection in pigs is a cause of economically important respiratory disease in the animals and a human public health concern. Influenza viruses are transmitted from pigs to people as zoonotic agents (reviewed in Ref. [1]) and pigs can serve as hosts for influenza virus reassortment, thus potentially contributing to the creation of pandemic viruses (reviewed in Refs. [2,3]). Southeast Asia has historically been described as an “epicenter” for pandemic viruses (reviewed in Refs. [4,5]), but the viruses that have appeared recently within the swine population of North America (reviewed in Refs. [6,7]) demonstrate that interspecies transmission and reassortment of influenza viruses in pigs can occur anywhere in the world.

2. Emergence of H3N2 influenza viruses among North American pigs

Swine influenza in the United States was caused almost exclusively by the “classical” H1N1 swine viruses from the time of their first isolation in 1930 through the mid-1990s.
In 1997–1998, however, H3N2 viruses appeared among North American pigs [10–12]. Genetic analyses of an initial group of nine isolates revealed that 3 different genotypes of H3N2 viruses had emerged independent of one another: a wholly human virus [12]; a reassortant virus containing human and classical swine virus genes [11]; and “triple reassortant” viruses containing genes from human, classical swine and avian viruses [11,12]. Of these, only the triple reassortant viruses have been maintained in the population (Table 1). These are now endemic throughout the American swine population [13] (Olsen et al., unpublished surveillance data). In fact, the wholly human isolate has been shown experimentally to be inherently restricted in its ability to infect pigs [14] and primary swine respiratory epithelial cells (Landolt et al., in preparation), compared with a prototypical triple reassortant virus.

### 3. Emergence of second generation reassortant H1N2 and H1N1 viruses

After 1998, both the triple reassortant H3N2 and classical swine H1N1 viruses co-circulated among American pigs, and both subtypes have been isolated from single swine samples (Olsen et al., unpublished data). Therefore, it is not surprising that additional reassortant genotypes of viruses have also appeared. The first to be recognized were H1N2 viruses that had the “genetic backbone” of the triple reassortant H3N2 viruses, but had acquired an H1 HA gene from a classical swine virus (Table 1) [15]. These H1N2 viruses have become endemic throughout the American swine population [16–18], and have also been isolated from wild waterfowl [19] and domestic turkeys [20].

Reassortment between the triple reassortant H3N2 (or H1N2) viruses and classical swine H1N1 viruses also created H1N1 viruses containing the human/swine/avian genetic backbone of the reassortant H3N2 and H1N2 viruses, but with both H1 HA and N1 neuraminidase genes from a classical swine virus (Table 1). Interestingly, these reassortant H1N1 viruses were first recognized in a human being [21], but were isolated subsequently from pigs [22]. Our surveillance data (Olsen et al., unpublished data) indicate that they are becoming the predominant form of H1N1 virus isolated from American pigs.

### 4. Isolation of wholly avian viruses from North American pigs

Wholly avian viruses have been isolated from pigs in Canada on three occasions since 1999. These include H1N1 and H3N3 viruses (Olsen et al., in preparation), as well as

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H4N6 viruses [23]. Of these, the H4N6 viruses isolated from pigs on a farm in Ontario in 1999 are of particular interest because this is a subtype to which the human population is immunologically naïve and, in the course of moving from waterfowl to pigs, this virus had already acquired signature sequences consistent with an ability to utilize the α2,6-linked sialic acid receptors expressed by human respiratory airway cells [23].

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