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Lessons learned from research and surveillance directed at highly pathogenic influenza A viruses in wild birds inhabiting North America

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ABSTRACT

Following detections of highly pathogenic (HP) influenza A viruses (IAVs) in wild birds inhabiting East Asia after the turn of the millennium, the intensity of sampling of wild birds for IAVs increased throughout much of North America. The objectives for many research and surveillance efforts were directed towards detecting Eurasian origin HP IAVs and understanding the potential of such viruses to be maintained and dispersed by wild birds. In this review, we highlight five important lessons learned from research and surveillance directed at HP IAVs in wild birds inhabiting North America: (1) Wild birds may disperse IAVs between North America and adjacent regions via migration, (2) HP IAVs can be introduced to wild birds in North America, (3) HP IAVs may cross the wild bird-poultry interface in North America, (4) The probability of encountering and detecting a specific virus may be low, and (5) Population immunity of wild birds may influence HP IAV outbreaks in North America. We review empirical support derived from research and surveillance efforts for each lesson learned and, furthermore, identify implications for future surveillance efforts, biosecurity, and population health. We conclude our review by identifying five additional areas in which we think future mechanistic research relative to IAVs in wild birds in North America are likely to lead to other important lessons learned in the years ahead.

1. Introduction

The importance of wild birds as a reservoir for influenza A viruses (IAVs) has been recognized since the 1960s (Easterday et al., 1968), in part, through research and surveillance efforts targeting wild birds in North America (defined in this review as Canada and the United States of America; USA). However, the nature of research and surveillance efforts directed towards IAVs in wild birds in North America has evolved considerably over the past 50 years, and particularly, since the repeated detection of highly pathogenic (HP) IAVs of Goose/Guangdong (Gs/GD) lineage in wild birds inhabiting Asia, Europe, and Africa beginning shortly after the start of the new millennium. In 2002, an outbreak of H5N1 Gs/GD lineage HP IAV in a zoological collection and sympatric free-ranging birds in Hong Kong marked the first mortality of wild aquatic birds attributed to a HP IAV since 1961 (Ellis et al., 2004; Sturm-Ramirez et al., 2004). A subsequent outbreak of H5N1 HP IAV in wild birds at Qinghai Lake, China in 2005 (Chen et al., 2005) raised concerns about the role of migratory birds in the dispersal of Gs/GD lineage HP IAVs, including the potential for the introduction of such viruses into North America via intercontinental migratory bird movements. Thus, following detections of HP IAVs in wild birds inhabiting East Asia after the turn of the millennium, the intensity of sampling of wild birds for IAVs increased throughout much of North America and the objectives for many research and surveillance efforts were directed towards detecting foreign origin HP IAVs and understanding the potential of such viruses to be maintained and dispersed by wild birds. In this review, we highlight five important lessons we feel have been learned from research and surveillance directed at HP IAVs in wild birds inhabiting North America.

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1.1. Wild birds may disperse IAVs between North America and adjacent regions via migration

Following the 2005 outbreak of H5N1 HP IAV at Qinghai Lake, China, considerable research was conducted in North America to assess the evidence for dispersal of IAVs by wild birds between East Asia and North America via Alaska, a pathway by which large numbers of waterbirds make interhemispheric migratory movements (Winker and Gibson, 2010). Although previous research efforts had not identified an entirely foreign-origin IAV genomic constellation in North America (including Alaska; Winker et al., 2007), and Eurasian lineage gene segments had been found to be relatively rare in IAV isolates derived from samples collected in Alberta, Canada and Delaware Bay, USA (Krauss et al., 2007), the infrequent detection of Eurasian lineage gene segments in IAVs isolated from wild birds sampled in North America suggested at least low levels of intercontinental viral dispersal via Alaska or another unidentified pathway. Thus, a series of targeted investigations were conducted to assess the dispersal of IAVs between East Asia and North America via Alaska where the East Asian-Austral Asian, Central Pacific, and Pacific Americas flyways overlap.

Through the genetic characterization of IAVs derived from northern pintails (*Anas acuta*) sampled in Alaska during a single year, Koehler et al. (2008) found evidence for a higher proportion of isolates with Eurasian lineage gene segments as compared to previous reports for waterfowl sampled at Alberta, Canada (Krauss et al., 2007). Follow-up studies confirmed this observation (Ramey et al., 2010a) and, furthermore, provided support for the dilution by distance of Eurasian lineage gene segments within North America (Pearce et al., 2009; Ramey et al., 2010a, 2010b). That is, sampling of waterbirds in western Alaska, near the Asian-North American interface, has consistently provided a high probability of encounter of Eurasian lineage gene segments as compared to elsewhere in North America, which supports this region as a probable location for viral introductions via migratory birds (Ramey et al., 2010a, 2010b, 2011; Reeves et al., 2013). Indeed, through additional sampling of wild birds in western Alaska in 2011, H9N2 IAVs were isolated from swabs collected from a northern pintail duck and an emperor goose (*Chen canagica*), two waterfowl species with intercontinental migratory tendencies (Miller et al., 2005; Hupp et al., 2007, 2011), that shared > 99% genomic identity to viruses previously identified in wild birds inhabiting China and South Korea (Ramey et al., 2015). Furthermore, IAVs sharing similarly high genetic identity to these H9N2 viruses detected in wild birds sampled in Alaska, China, and South Korea have not been identified in domestic poultry and the South Korean H9N2 strain, A/bean goose/Korea/220/2011, did not replicate in experimentally inoculated three week-old chickens (Lee et al., 2016a), providing further evidence that this genomic constellation was most likely dispersed intercontinentally by wild birds.

In November 2014, a clade 2.3.4.4 HP IAV of the H5N8 subtype comprised of eight Eurasian lineage gene segments was detected in the Pacific Americas Flyway of North America and it was widely speculated that this HP IAV was dispersed between East Asia and North America by wild birds (Lee et al., 2015; Verhagen et al., 2015; Lycett et al., 2016). While the introduction of a clade 2.3.4.4 IAV from East Asia to North America via Alaska is consistent with: (1) previous evidence for viral dispersal via this pathway, (2) intercontinental migratory pathways of wild birds, (3) the timing of arrival for migrants from Alaska to the region where clade 2.3.4.4 IAVs were first detected in North America (Hill et al., 2017), and (4) proposed evolutionary pathways of reassortant clade 2.3.4.4 HP IAVs in wild birds in the Pacific Northwest of the USA and Canada (Lee et al., 2016b; Ramey et al., 2016a, 2017; Hill et al., 2017), definitive support for the hypothesis that migratory birds introduced H5N8 clade 2.3.4.4 HP IAV into North America from East Asia remains elusive. None-the-less, it is reasonable to conclude that the circulation of economically costly poultry pathogens or IAVs of concern to public health in wild birds inhabiting East Asia poses some degree of risk to the biosecurity of Canada and the USA.

In addition to targeted investigations in Alaska to assess evidence for the intercontinental exchange of IAVs between North America and East Asia, research efforts conducted since 2005 have also examined the potential for wild birds to disperse viruses between North America and adjacent regions via other migratory routes identified through ornithological investigations. For example, research conducted in Newfoundland, Canada has provided evidence that seabirds, including gulls (*Larus* spp.) and murres (*Uria* spp.), may facilitate the exchange of viruses between Western Europe and North America via a trans-North Atlantic pathway (Wille et al., 2011; Huang et al., 2014a, 2014b). This includes the purported first detection of a wholly Eurasian lineage virus in North America (Huang et al., 2014a). Additionally, research conducted in Texas and Louisiana (USA), Barbados, Guatemala, and Columbia, collectively provide support for the hypothesis that Neotropical migrants, such as blue-winged teal (*Anas discors*), may disperse IAVs among locations in North America, Central America, the Caribbean Islands, and northern South America (Douglas et al., 2007; González-Reiche et al., 2012; Karlsson et al., 2013; Ramey et al., 2016b). Thus, surveillance for the early detection of foreign-origin IAVs in wild birds inhabiting North America may be optimized by targeted sampling at geographical regions where genetic data for IAVs and ornithological information collectively support an increased probability for viral introductions into the USA and Canada from adjacent regions.

1.2. HP IAVs can be introduced to wild birds in North America

The first confirmed outbreak of HP influenza A in North American birds per the current Office International des Epizooties (OIE) definition (i.e., characterized by a polybasic hemagglutinin [HA] cleavage site), affected domestic poultry in Ontario, Canada in 1966 (Swayne, 2008; Ping et al., 2012). Subsequent outbreaks of HP IAVs in North America during the period of 1983–2014 affected domestic gallinaceous birds in Pennsylvania, Maryland, New Jersey, and Virginia, USA in 1983 (Buisch et al., 1984); Texas, USA in 2004 (Lee et al., 2005; Pelzel et al., 2006); British Columbia, Canada in 2004 (Hirst et al., 2004); and Saskatchewan, Canada in 2007 (Berhane et al., 2009). In each of these outbreaks, it also appears that a low pathogenic (LP) IAV precursor circulated, at least briefly, among domestic gallinaceous birds before developing high pathogenicity in poultry (Suarez and Senne, 2000; Lee et al., 2005; Pasick et al., 2005; Berhane et al., 2009; Ping et al., 2012). No poultry-adapted LP IAVs epidemiologically connected to HP outbreaks or HP IAVs causing disease in domestic poultry were detected in wild birds in North America prior to 2014. Thus, prior to autumn 2014, there was no evidence for spill-over of HP IAVs into wild birds inhabiting the USA or Canada, or even for the re-introduction of LP IAVs into the wild bird reservoir following poultry adaptation.

In late November 2014, increased mortality was observed among domestic turkeys and chickens in British Columbia, Canada leading to the identification of a HP IAV of the H5N2 subtype (Pasick et al., 2015). Through genetic sequencing, this HP H5N2 IAV was identified as an intercontinental reassortant virus descended from the H5 Gs/GD lineage clade 2.3.4.4 HP IAVs that were concurrently circulating in Eurasia and one or more IAVs circulating among waterfowl inhabiting North America (Pasick et al., 2015). In early December 2014, H5N2 and H5N8 clade 2.3.4.4 HP IAVs were isolated from samples collected from a wild northern pintail (*Anas acuta*) and a captive-reared gyrfalcon (*Falco rusticolus*) that had recently fed upon a wild American wigeon (*Anas americana*), respectively, in Washington, USA (Ip et al., 2015). The H5N2 clade 2.3.4.4 HP isolates recovered from poultry in British Columbia, Canada and a wild northern pintail in Washington, USA were genomically highly similar (i.e., > 99% shared nucleotide identity), closely related to HP IAVs circulating in East Asia at the HA gene, and the apparent product of reassortment between a clade 2.3.4.4 HP IAV and one or more IAVs circulating in North America (Ip et al., 2015). In contrast, the H5N8 clade 2.3.4.4 HP IAV isolated from a captive-reared gyrfalcon was genomically highly similar (i.e., > 99% shared