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Review

Avian influenza virus: Of virus and bird ecology

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ABSTRACT

The recent introductions of highly pathogenic avian influenza (HPAI) H5N1 virus in wild birds and its subsequent spread throughout Asia, the Middle East, Africa and Europe has put a focus on the role of wild birds in the geographical spread of HPAI H5N1 virus. Large-scale surveillance programs are ongoing to determine a potential role of wild birds in H5N1 virus spread and to serve as sentinel systems for introductions into new geographical regions. The unprecedented scale and coverage of these surveillance programs offer a unique opportunity to expand our current knowledge on the ecology of LPAI in wild migratory birds. We provide an update on the current knowledge on the relation between host and virus ecology.

Contents

1. Introduction

Wildfowl and shorebirds form the primary influenza A virus reservoir [1]. Avian influenza A viruses may, on occasion, be transmitted directly or indirectly to other host species such as domestic birds, pigs, horses, mink, marine mammals, and humans and either cause transient or endemic circulation of influenza A viruses in these new host populations [1]. Influenza A viruses are classified on the basis of antigenic properties of two surface glycoproteins expressed on virus particles; the hemagglutinin (HA) and neuraminidase (NA). In wild birds, influenza A viruses representing 16 HA (H1–H16) and 9 NA (N1–N9) antigenic subtypes have been detected [2]. These subtypes can be found in numerous possible combinations (e.g., H5N1, H16N3) [3]. Besides classification based on HA and NA, avian influenza A viruses are also classified by their pathogenic properties in chickens. Influenza A viruses of subtypes H5 and H7, but not other subtypes, may become highly pathogenic after introduction into poultry and can cause outbreaks of highly pathogenic avian influenza (HPAI). The transition from a low pathogenic avian influenza (LPAI) phenotype to the HPAI phenotype is achieved by the introduction of basic amino acids into the hemagglutinin cleavage site, which facilitates systemic virus replication, causing an acute generalized disease in poultry in which mortality may be as high as 100% [4,5]. Other avian influenza strains, including the H5 and H7 influenza A viruses without basic cleavage site, are LPAI. The last decade has seen a marked increase in HPAI outbreaks [6,7]. While most HPAI outbreaks have been controlled relatively quickly, HPAI H5N1 virus has been circulating in poultry

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continuously since 1997. In addition to this continued circulation, HPAI H5N1 virus is also unusual in the unprecedented scale and geographical spread of the outbreak, the transmission to a wide variety of mammalian species including humans and the introductions of HPAI H5N1 in wild birds [8–13]. These recent introductions of HPAI H5N1 virus in wild birds and the subsequent spread of the virus throughout Asia, the Middle East, Africa and Europe has put a focus on the role of wild birds in the geographical spread of HPAI H5N1 virus. Large scale surveillance programs have been implemented in several parts of the world to determine the role of wild birds in the spread of HPAI H5N1 and to serve as sentinel system for the introduction of HPAI H5N1 virus into new geographical regions [14–16].

Most of our current understanding of the ecology of LPAI viruses is derived from long-term surveillance studies, that analyzed over 100,000 samples obtained from wild birds in various parts of the world over a period of 40 years [1,17–25]. The large-scale influenza A virus surveillance programs directed at HPAI H5N1 detection currently analyze an estimated 300,000 samples on a yearly basis. Therefore, these surveillance activities will not only provide data on the extent of the circulation of HPAI H5N1 virus in wild birds but will additionally offer a unique opportunity to expand our current knowledge on the ecology of LPAI in wild migratory birds. The ecology of influenza A viruses is inseparable from the ecology of their respective hosts. The epidemiology of influenza A viruses is closely related to behavior of the potential host species, such as diet and foraging behavior; habitat use; migratory patterns and behavior; population size; group size and frequency of aggregation. Here, we provide an overview of our current understanding of the relation between host ecology and influenza A virus ecology.

2. Virus ecology and host populations

Large-scale surveillance studies have identified a predominant role for dabbling ducks, i.e., ducks which feed mainly on vegetable matter by upending on the water surface, in the perpetuation of most HA subtypes [1,6,15,25–27]. Factors contributing to this role of dabbling duck populations as influenza A virus host species include population size and mode of transmission. The importance of population size, age structure and herd-immunity on the epidemiology of infectious diseases has been described for human pathogens like measles [28]. Large populations are probably more capable of sustaining a large variety of different influenza A virus subtypes, as observed in dabbling ducks. The dabbling duck populations are estimated 10,000,000 birds in Europe alone, with mallards (*Anas platyrhynchos*) being the most abundant species (∼5,000,000 in Europe and ∼27,000,000 worldwide) [29]. The estimated yearly turnover rate of Mallards in Northern Europe is roughly 1/3 [30]. A large part of the population is therefore rejuvenated every year, potentially allowing simultaneous co-circulation of multiple genetic lineages and subtypes within one meta-population of potential hosts for influenza A virus. In contrast, the population estimates for the different goose species in Europe are significantly lower compared to the dabbling ducks with a total population size of ∼1.2 million geese [29]. Smaller population sizes would likely limit the perpetuation and maintenance of multiple influenza A virus subtypes and allow only a limited number of influenza A virus subtypes to co-circulate within these populations. The global populations of Laridae (gulls and terns) species appears to be large enough to allow co-circulation of two distinct influenza A virus lineages the H13 and H16 influenza A viruses. Although other avian influenza virus subtypes are also occasionally detected in terns and gulls, the H13 and H16 influenza A viruses appear to circulate exclusively in Laridae species [23,25,26,31,32].

3. Virus ecology and host species

In general there is little available information on host factors in relation to the differences in LPAI virus prevalence and circulation. Although LPAI viruses have been isolated from at least 105 different host species of 26 different families the respective contribution of most of these species to the ecology of avian influenza viruses is less clear. Large differences of LPAI virus prevalence exist between different wild bird species. Whereas these differences could be accounted for on the level of host ecology, another accompanying explanation could be intrinsic differences between these wild bird species in their ability to function as host for influenza A viruses. For instance, differences in permissiveness for infection with LPAI viruses between species might be accounted for by differences in receptor distribution on one side and the recognition of such receptors by different avian influenza viruses on the other [33,34]. One example of species differences, is the inability of gull H13 influenza viruses to efficiently replicate in the intestinal and respiratory tract of ducks [35]. Analyses of the HA receptor-binding sites of avian influenza viruses isolated from Laridae and Anatidae revealed differences between the ability of these viruses to bind to different receptor moieties [34]. In addition, the composition of receptors present on the epithelium of the intestinal tract of different bird species was examined by lectin histochemistry revealing differences in sialic acid distribution which could account for differences in LPAI virus prevalence [36]. Infection experiments conducted with HPAI H5N1 viruses conducted in various wild bird species such as ducks, geese, swans and gulls displayed large differences in susceptibility, tissue tropism, mortality and virus shedding [37–41]. Whereas it is impossible to extrapolate data obtained on HPAI H5N1 viruses to the situation of LPAI viruses in wild birds, similar differences between species and between different LPAI viruses might be present and need further investigation.

4. Temporal and spatial variation in influenza virus prevalence in relation to host ecology

The prevalence of avian influenza A viruses in their hosts depends on geographical location, seasonality and species. The prevalence of avian influenza A viruses in dabbling ducks in North America and Europe varies from less than 1% during their spring migration to up to 30% prior to and during fall migration [1,25]. Surveillance of Mallards at two different geographical locations within the same flyway, showed that influenza A virus prevalence during fall migration (roughly north–south migration) varied between the two locations at the same time point. The prevalence in Mallards at the northern sampling site was ∼3-fold higher as compared to the prevalence in Mallards at the wintering grounds [25]. This suggests that timing relative to migration is the determinant of influenza A virus prevalence. High virus prevalence early in fall migration likely gradually declines as the migration proceeds, thus forming a North–South gradient of influenza A virus prevalence. This explains geographical differences in influenza A virus prevalence between Northern and more Southern latitudes observed in different surveillance studies [25,42]. The peak in prevalence during fall migration is believed to be related to the large numbers of young immunologically naive birds of that breeding season that aggregate prior to and during their southbound migration.

The complexity of the ecology of avian influenza viruses is reflected by the temporal, spatial and species variation observed the circulation of influenza A viruses in wader species. Waders in the Charadriidae and Scolopacidae families, including species such as turnstones, sandpipers, knots, redshanks, bar-tailed godwits, are adapted to marine or freshwater habitats. In general, the annual cycle of wader species consists of breeding in the arctic regions,