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(v)   Summary and keywords:

Highly Pathogenic Avian Influenza (HPAI) is of major importance for human and animal health because of high morbidity and mortality in poultry and the potential for transmission of this zoonotic pathogen to humans. Knowledge of HPAI epidemiology in avian populations and practical information on the temporal and spatial spread of the disease after introduction into a country is important in order to enhance the capacity of predicting and managing epidemics to minimize the negative impacts on human and animal health. Using data reported to the World Organisation for Animal Health between 2005 and 2017 by 199 countries for 14,129 outbreaks in poultry, we used a spatial and time-series analysis to determine that: 1) During the last 12 years, there were two major global peaks in the number of countries affected by HPAI with 23% and 26% of countries affected in 2006 and 2016. 2) Based on the seasonality analysis, spread is the lowest in September, begins to rise in October, and peaks in February. 3) The median distance HPAI outbreaks spread from the index outbreak was 111 km, while the median apparent rate of spread of outbreaks was 1.9 km/day. 4) In 39% of HPAI events, the disease did not spread beyond the index outbreak and the median maximum spread from the index outbreak per event was 45 km. 5) The distance HPAI outbreaks spread from the index outbreak was significantly negatively correlated with the number of outbreaks during the same time period, indicating that the spread of HPAI was lower during global panzootics than during periods of low transmission. These findings are of major importance for veterinary services to design and implement surveillance measures for improving preparedness to minimize the impacts of this disease.

KEYWORDS:

(vi) **Main text:**

1. Introduction

Highly pathogenic avian influenza (HPAI), caused by influenza A viruses in the family *Orthomyxoviridae*, is a major global health challenge due to heavy morbidity and mortality in poultry, as well as the necessity for implementation of strict disease control measures to prevent transmission of this potentially zoonotic virus to humans (Katz et al., 2009; Kilpatrick et al., 2006; Paarlberg et al., 2007). Prevention and control of avian influenza is particularly challenging due to its complex biology and epidemiology. As a segmented RNA virus, the genome can undergo rapid and substantial changes that lead to shifts in viral traits such as transmissibility, virulence, and host range. Additionally, multiple species of waterfowl are the primary natural reservoir for this pathogen providing wide variation in selection pressure and spread via long distance migration (Webster et al., 1992). Consequently, the threat of significant transmission between poultry and humans and the emergence of virulent viral subtypes that are readily transmissible between humans is ongoing.

Historically, HPAI outbreaks were readily controlled with mass culling. In 1997, the epidemiology of the virus changed with the emergence in China of the ancestor of the currently circulating H5N1 subtype (Xu et al., 1999) and interventions failed to control the disease (Cox and Subbarao, 2000; Subbarao et al., 1998). Since then, the virus has demonstrated an impressive ability to spread nationally and internationally. During late 2003 and 2004, HPAI spread extensively in Asia. Despite destruction of large numbers of birds and trade restrictions, the disease spread into Kazakhstan and Russia in the summer of 2005 and into many European and African countries by the autumn and winter of 2005-2006 (Paarlberg et al., 2007). Between 2003 and 2011, HPAI viruses caused outbreaks in over 60 countries distributed across Asia, Europe, and Africa. Additionally, the global burden of HPAI on public health is significant, with more than 850 human cases and 450 deaths between 2003 and 2016 (World Health Organization, 2016).

This ongoing global spread of avian influenza in birds and humans indicates current surveillance and control measures are insufficient. A better understanding of the epidemiology of HPAI through time will help identify strengths as well as areas for improvement in the approach of veterinary services to controlling HPAI. Toward this end, the primary objective of the paper is to contribute to the understanding of the global epidemiology of HPAI in poultry since 2005, and to provide practical information on the extent of disease spread after its introduction into a given area, taking as reference the index outbreak. To accomplish this, we use 12 years of avian influenza data analyzed both globally and at the country level to determine: 1) changes in the percent of countries affected over time; 2) changes in the number of outbreaks over time; 3) the seasonality of HPAI outbreaks; 4) the distance and apparent rate of spread of HPAI after introduction into a new area; 5) if either the distance or apparent rate of spread of HPAI from the index outbreak is higher during periods of high international spread. The findings are discussed in the context of HPAI control efforts.

2. Materials and Methods

2.1. Databases used

All data were from the World Organisation for Animal Health (OIE), whose mandate is to ensure transparency in the global animal disease situation. These data are submitted to the OIE by the national authorities of 181 Member Countries that have the legal obligation to report data concerning high impact animal diseases, including HPAI, and more than 20 additional countries and territories that provide information to the OIE on a voluntary basis. The data used in this study were derived from two related data streams: the OIE monitoring system and the OIE early warning system. HPAI is notifiable in poultry and wild birds through both systems, though only data from poultry was included in this study.

The OIE monitoring system includes data sent every six months by each country and includes absence or presence, changes in the occurrence of all listed diseases, and information of epidemiological significance to the international community.

The OIE early warning system includes data sent by each country to inform the international community of introductions or reoccurrences of potentially high impact diseases as they occur. These disease introductions or reoccurrences are defined by the OIE in terms of outbreaks and events (World Organisation for Animal Health, 2017). Specifically, an event includes all epidemiologically connected outbreaks within a country. Each outbreak is defined as the occurrence of one or more cases of disease in an epidemiological unit, which could include a farm, village, or backyard. Multiple outbreaks comprise a single event if the outbreaks are epidemiologically connected, are caused by the same pathogen, and have the same source of introduction, as assessed by national authorities. Importantly, this data stream includes weekly updates providing information on the progression of each event. For example, new epidemiologically linked outbreaks may be detected within an event, while other outbreaks end, as disease control measures are implemented. Reporting continues until the disease is eradicated or the situation becomes stable.

2.2.   Methods

2.2.1.   Percent of countries with HPAI through time

The yearly percentage of countries with HPAI over time was based on information provided by 199 countries from January 1, 2005 to May 11, 2017 through OIE early warning and monitoring systems. The dataset used for this analysis contained information about presence or absence (binary variable) of HPAI in poultry in countries per year. The number of countries which submitted information on the presence or absence of HPAI to the OIE increased from 170 in 2005 to 186 in 2012 due, in large part, to the increasing number of countries reporting

to the OIE during the period. The number of countries, which submitted information on HPAI to the OIE remained stable at 186 between 2012 and 2016. If for any given year, a country did not provide information, it was excluded from the analysis. Consequently, not all countries are included in all years.

Among the countries which submitted information on HPAI to the OIE through their reports, the percent of countries which notified HPAI as present in poultry during each year was calculated.

2.2.2. Computation of global long-term trend and seasonality of HPAI outbreaks in poultry

The dataset used for this analysis was derived from OIE's early warning and monitoring systems and included information about the numbers of HPAI outbreaks aggregated by calendar month based on the start date of each outbreak. This dataset includes 14,129 outbreaks and corresponds to all outbreaks identified by countries during epidemics. The number of outbreaks by calendar month were formatted into time-series and a seasonal-trend decomposition based on loess (STL) was applied using the "stl" function in the R software 3.2.1 (Cleveland et al., 1990) (R Core Team, 2015). STL is a filtering procedure for decomposing a time-series into trend, seasonal, and irregular components. The loess window for seasonal extraction was assigned to 13, as it is recommended to use the next odd number following the number of observations in each seasonal cycle (i.e., 12 months, Cleveland et al., 1990). Raw data were log-transformed to correspond to multiplicative decomposition, given that, in the raw data, variability increased with increasing incidence. The decomposition was evaluated utilizing normal quantile plots of the residuals, ensuring its distribution was well approximated by the normal distribution. Additionally, scale bars were included in the plots to describe the range of each component of the decomposition. Marginal remainder plots were investigated to identify any pattern that could be of concern. Next, the

interquartile range of each component of the decomposition compared to the interquartile range of the raw data (relative IQR) was used to measure the relative magnitude of the variability in the data explained by each component, excluding the extreme values, which means values lower than the first quartile or greater than the third quartile.

2.2.3. Computation of distance and apparent rate of spread of HPAI outbreaks in poultry

For each outbreak within each event, the distance from the index outbreak and corresponding apparent rate of spread were calculated using data from the early warning system for outbreaks occurring between January 1, 2005 and December 31, 2016.

A total of 247 events, corresponding to 6,359 outbreaks, in 64 countries were included in the analysis (Fig. 1). For each event, the outbreak with the earliest start date was defined as the index outbreak. The distance between the index outbreak and each subsequent outbreak within an event was calculated using the Haversine formula (Robusto, 1957), based on geocoordinates (latitude and longitude) provided by national authorities, with a resolution between 2 and 6 decimals. This measure was then used to estimate the distance each HPAI outbreak spread in kilometers (km) from the index outbreak. If the first outbreaks in an event started on the same date, the location of the index outbreak was calculated as the centroid among the initial outbreaks. Next, to define the maximum distance each of the 247 events spread within a country, the maximum distance within each event from the index outbreak to an associated outbreak within the country was determined.

In addition, the apparent rate of spread from the index outbreak to each subsequent outbreak, in km per day, was calculated for 156 events, which corresponds to 6,042 outbreaks in 56 countries. The calculation was not applicable to the remaining events because they were comprised of a single outbreak. The apparent rate of spread of HPAI

from the index outbreak was determined by dividing the distance (km) from the index outbreak by the number of days between the start of the index outbreak and the start of the subsequent outbreak.

2.2.4. Computation of the correlation between number of outbreaks, distance, and apparent rate of spread of HPAI outbreaks in poultry

Rather than using a calendar year, which inaccurately reflects HPAI seasonal transmission, the HPAI outbreaks were categorized according to HPAI seasonal spread period as determined by the seasonal decomposition method on the time series. The identified transmission season was used to calculate correlations between the number of outbreaks, distance, and apparent rate of spread. For each outbreak, the distance and the apparent rate of spread were associated with the outbreak start date. Spearman's rank correlation test was used to test the correlations between the global number of HPAI outbreaks during the HPAI seasonal spread periods and the median distance and rate of spread from index outbreaks.

In addition, two possible biases were tested. First, for the size of countries, the correlation test mentioned above was repeated, standardizing median distance from index outbreaks by a proxy for country size.

Second, for the size of events, Spearman's rank correlation test was used to test the correlations between the global number of HPAI outbreaks during the HPAI seasonal spread periods and the median number of outbreaks per event.

3. Results

3.1. Percent of countries with HPAI in poultry over time

From 2005 to 2016, of the countries reporting information about HPAI, 14% on average (range: 7%-26%) were affected each year. Variations were observed in the trend over these 12 years (Fig. 2). Between 2005 and 2006 the percent of affected countries increased from 7% to 23%. It declined to 8% in 2009, remained stable until 2013 and then increased again to 26% in 2016.

3.2. Global long-term trend and seasonality of HPAI outbreaks in poultry

In the STL decomposition applied on HPAI outbreaks, the scale bars included in the plots show that the remainder component of the decomposition had the highest range (Fig. 3a), mainly because of marginal remainder plots in 2005 and end of 2016. The range of the seasonal component and the trend component were comparable.

However, the relative IQR measures, which exclude extreme values, were 50% for the seasonal component, 49% for the trend component and 42% for the random component. The quantile plots of the residuals showed that the distribution approximated a normal distribution.

STL decomposition of HPAI outbreaks show a consistent seasonality pattern over the period of analysis, increasing from October of a given year to a peak in February and a decrease until September of the following year. Only very small variations of this seasonal pattern were observed across the period of analysis (Fig. 3b). Eleven complete HPAI seasonal spread periods (October to September) were therefore identified within the period of analysis (Fig. 3a). Based on the raw data, the HPAI seasonal spread periods with the highest number of outbreaks were October 2014 to September 2015 with 2,469 outbreaks, October 2005 to September 2006 with 2,249 outbreaks, and October 2007 to September 2008 with 2,008 outbreaks.

The trend component of HPAI outbreaks (Fig. 3a) indicates an increase in HPAI outbreaks from 2005 to 2006, followed by a period of stability until 2009. The number of HPAI outbreaks decreased from 2009 to 2012, and then increased again from 2012 to 2016. Multiple modes are observed in the trend component in 2006, 2008, 2009, 2011, 2013 and 2015.

3.3. Distance and apparent rate of spread of HPAI outbreaks in poultry

The median distance from the index outbreak to each subsequent outbreak was 111 km across all outbreaks (Table 1). Considering the 247 events within a country, the median value of the maximum distance events spread from the index was 45 km. The majority of outbreaks (1,733) spread between 0 and 50 km from the index outbreak (Fig. 4a).

Countries reported that for 39% of the 247 events included in the analysis, there was no spread beyond the index outbreak (Fig. 4b). Among the 64 countries included in the analysis, 41 reported events that included only 1 outbreak.

Focusing on the events in which HPAI spread beyond the index outbreak, the median apparent rate of spread from the index outbreak to each subsequent outbreak was 1.9 km/day (Table 1). For 17 outbreaks, HPAI spread from the index outbreak to a contiguous farm and the rate of spread was considered null. The most frequent rate of spread was between 0 and 1.0 km/day (2,246 records in this class) (Fig. 5a).

For most events, the maximum apparent rate of spread was less than 13.5 km/day (median). However, some maximum apparent rates of spread were much higher, particularly in certain Asian and African countries, up to 756.6 km/day (Fig. 5b).

3.4. Correlation between number of outbreaks, spread distance and apparent rate of spread of HPAI outbreaks in poultry

The median spread distance from the index outbreak was significantly negatively correlated with the number of outbreaks reported for the same HPAI seasonal spread period, as shown by the Spearman's rank correlation test (rho = -0.6; p-value=0.05) (Fig.6, Fig. S1).

The standardization of median distance from index outbreaks by a proxy for country size affected neither the rho coefficient of the correlation nor the significance of the test. The median number of outbreaks per event was not significantly correlated with the number of outbreaks reported for the same HPAI seasonal spread period, as shown by the Spearman's rank correlation test (rho=0.2; p-value=0.45). Finally, there was no significant correlation between the median apparent rate of spread and the global number of HPAI outbreaks reported for the same seasonal spread period (rho=0.3; p-value=0.21) (Fig. S2).

4. Discussion

The spatial dynamics of influenza have been well-studied in humans (e.g., Cliff et al., 1989; Viboud et al., 2006), but in animals, quantitative information is often lacking (Verhagen et al., 2015; Gilbert et al., 2006a; Gilbert et al., 2006b). The epidemiology of the disease is complex and affected by many factors including the composition of animal populations, production systems, viral diversity, and the capacity of each country to rapidly identify and respond to outbreaks. Consequently, these factors preclude generalization of the epidemiology of HPAI between regions and countries. The main objective of this study was to bolster the foundation of disease control strategies by providing an extensive and practical analysis of the temporal and spatial behavior of HPAI after its introduction into a new area using data from over 14,000 HPAI outbreaks worldwide.

In this context, the main conclusions of this study are: 1) Two major global peaks in the number of countries affected by HPAI occurred in 2006 and 2016. Between these two peaks, there was a period of stability. 2) Based on the seasonality analysis, spread in poultry is the lowest in September, begins to rise in October and peaks in February. 3) The median distance HPAI outbreaks spread from the index outbreak to subsequent outbreaks was 111 km, while the median apparent rate of spread of outbreaks was 1.9 km/day. 4) In 39% of HPAI events, the disease did not spread beyond the index outbreak and, within a country, the median maximum spread within events was 45 km. 5) The distance HPAI outbreaks spread from the index outbreak to subsequent outbreaks was significantly negatively correlated with the number of outbreaks during the same time period, indicating that the spread of HPAI in poultry was lower during global panzootics than during periods of low transmission.

The data used in this study are based on mandatory reporting to the OIE. Reporting of each listed disease to the OIE has been evaluated based on comparison with other sources of information. HPAI was one of the diseases with the highest reporting probability (Awada, 2012; Caceres, 2016; World Organisation for Animal Health, 2016). A high reporting probability is logical because HPAI causes high mortality in poultry populations, which is readily recognized through surveillance. Importantly, robust diagnostic tools are available leading to accurate diagnosis.

Despite these factors, disease data reported from national authorities has limitations due to the variability among countries in animal disease surveillance systems, which, in general, can lead to underreporting. Consequently, the percentage of countries affected by HPAI over time represents the minimum values.

Furthermore, outbreaks are considered included in one event if they are caused by the same pathogenic agent and have the same source of introduction, as assessed by national authorities. However, not all countries have sufficient capacities to determine these

parameters with accuracy, and therefore the identification of the index outbreak may be inaccurate and detection of all subsequent outbreaks may be incomplete. Misidentification of the index outbreak could lead to either underestimation or overestimation of the distance and apparent rate of spread of HPAI. Over 150 events and more than 6,000 outbreaks were used in these analyses. The large sample size helps to improve estimates of central tendency and, as discussed below, the outliers may be due to misidentification of index outbreaks.

Due to the well-known seasonality of HPAI spread, we used a seasonal-trend decomposition analysis to identify October-September as the biologically relevant seasonal spread period. In the decomposition, the relative IQRs of the seasonal, trend and remainder components were nearly equal, showing that these three components contribute equally to the variability in the raw data. The relative IQR allows this evaluation excluding the extreme values. This is why the relative IQR results are not aligned with the size of the scale bars on the plot (Fig. 3a), which include the extreme values.

Identifying the transmission periods provides useful information for preparedness, highlighting periods of both high and low risk. The seasonal-trend decomposition method based on loess was preferred to other methods such as decomposition by moving average, as the seasonal component might not have been constant through time. Little variation was expected due to environmental changes and the occurrence of festivals that involve high poultry consumption, and the method allowed capturing these variations. The results indicate that these variations were small and did not preclude consistency in the periods of high and low activity of HPAI in poultry across the years included in the analysis. In addition, the relative IQR of the seasonal component of the decomposition is high, and this shows that the seasonal pattern across years is well supported by the data. The February peak is consistent with findings described in other studies (Park and Glass, 2007; Si et al., 2009; Zhang et al., 2012), in which peak spread occurs from October to March in the northern hemisphere. In part, this may be linked to temperature as lower ambient temperatures can lead to decreased immune function in poultry and increased influenza outbreaks among poultry (Chaichoune et

al., 2009; Tiensin et al., 2007; Thanawat et al., 2005; Aly et al., 2008; Durand et al., 2015; Wang et al., 2008; Chen et al., 2012). Additionally, the February spread peak mirrors the higher number of cases detected in humans at a global level, indicating that monitoring of the disease in animals during high risk periods is important for risk assessment in public health (Lai et al., 2016). Finally, festivities taking place in the winter increase the number of avian influenza outbreaks, due to increased production, marketing and slaughter of local poultry during this period (Soares Magalhães et al., 2012; Hanh et al., 2007). The potential role of wild birds in the global spread of avian influenza has been highlighted for several strains (The Global Consortium for H5N8 and Related Influenza Viruses, 2016; Tian et al., 2015) but the ecology of influenza viruses in wild birds still presents significant gaps of knowledge, including their seasonal patterns of transmission at a global level. The available studies suggest that the prevalence of avian influenza viruses is higher during the fall migration than the spring migration (Munster et al., 2007; Verhagen et al., 2017). In our study, the period at higher risk in poultry begins after the fall migration peak for long-distance migratory birds in the northern hemisphere (Newton and Brockie, 2008). Verhagen et al. demonstrated a variable time interval between the isolation of related viruses in wild birds and poultry. Despite intensive surveillance programs in wild birds, the link between the occurrence of the viruses in wild birds and poultry requires further investigation (Verhagen et al., 2017).

Periods of low spread are also important from a resource management perspective. The period of lowest activity in poultry occurs in September, and importantly, this corresponds with a low disease burden of HPAI in humans (Lai et al., 2016). It is important to highlight that the seasonality patterns described in this paper are mostly applicable in countries in the northern hemisphere, with peak of activity of the virus in the cooler months (Forrest and Webster, 2010; Monto, 2008). A total of 99% of the outbreaks considered in the analysis were reported in northern hemisphere, while HPAI remained absent from most of the southern hemisphere during the period of analysis.

The trend component of HPAI outbreaks is consistent with the trend of countries affected during each year. The modes observed in the trend component in 2006, 2008, 2009, 2011, 2013 and 2015 correspond to sudden increases in HPAI incidence in certain countries. The 2006, 2011 and 2015 modes are within the peak season. The 2006 mode is due to a very high increase in HPAI incidence in Egypt, where the disease reoccurred after 51 years of absence (World Organisation for Animal Health, 2006). Similarly, the 2011 mode is due to a sudden increase in HPAI incidence in Bangladesh and the 2015 mode corresponds to a HPAI event in the United States of America. Conversely, the 2008, 2009 and 2011 modes are outside the peak season. The 2008 and 2009 modes are due to increases in HPAI incidence in Indonesia, where veterinary services faced significant challenges in disease control (Food and Agriculture Organization of the United Nations, 2008) and the 2011 mode is due to an increase in HPAI incidence in Nepal.

In addition, the range of the remainder component is higher than the ranges of the trend and seasonal components, showing that there is much unexplained variation contained in the remainder. However, by excluding the extreme values using the relative IQR, the amplitude of the remainder component is comparable to the seasonal and trend components amplitudes. The marginal remainder values in the year 2005 may be due to poorer reporting quality at the beginning of the first HPAI global panzootics. For this period, four countries in South-East Asia reported HPAI outbreaks to the OIE, and the quality of the information provided may be sub-optimal. The 2016 marginal remainder values correspond to the HPAI H5N8 wave in Europe, where wild birds played a role in the introduction of the virus in the region (Napp et al., 2018), ahead of the usual January/February peak. The high range of the remainder component in the decomposition shows the importance of unexpected occurrence of HPAI outbreaks outside the trend and seasonal patterns. This is not surprising, given the variety of parameters that can influence the occurrence of HPAI outbreaks at the local level in addition to the global trends.

Optimal country prepardness for HPAI control requires analysis of the temporal and spatial spread of the disease after introduction into a country. The estimation of the distance HPAI spreads from the index outbreak to the subsequent outbreaks allows prediction of the potentially at risk areas, and therefore the target area for surveillance and control activities during outbreak response. The estimation of the apparent rate of spread of HPAI outbreaks informs the time within which control measures must be implemented as well as the appropriate areas for heightened surveillance to avoid the dissemination of disease. Many factors, such as trade, movement of poultry and wild birds as well as environmental factors can all contribute to local spread (Henning et al., 2016; Kilpatrick et al., 2006; Fang et al., 2008; Tuncer and Martcheva, 2013). Identifying and understanding the contribution of these factors requires in-depth knowledge of local environments and disease events.

Surveillance and reporting efforts of national animal disease surveillance systems most commonly target poultry, consequently HPAI in wild birds may go undetected. Therefore, this study did not include outbreaks in wild birds, which can modify the dynamics of the disease (Tian et al., 2015; Bahl et al., 2016; Hesterberg et al., 2009) not only at the international level, which is well recognized (Feare, 2010; The Global Consortium for H5N8 and Related Influenza Viruses, 2016), but also at the country level (Keawcharoen et al., 2011; Rappole and Hubálek, 2006). Applying the methods used in this paper for HPAI outbreaks in wild birds would require preliminary modeling to correct for the effects of significant reporting gaps.

The results obtained for the spread of HPAI outbreaks from the index outbreak suggest that in most cases, the implemented control measures limit disease spread within a "risk buffer zone", but in some cases the viruses are able to spread several hundred kilometers beyond the index outbreak (Gilbert et al., 2006b; Kilpatrick et al., 2006; Loth et al., 2010; Henning et al., 2016). In contrast, the apparent rate of spread of HPAI shows one main peak, indicating that HPAI dissemination was homogeneous in most affected countries. To the best of our knowledge, no paper published on HPAI dynamics has taken the rate of spread into account.

For both the distance and apparent rate of spread, sporadic outliers possibly indicate spread mechanisms that are rare and difficult to control, but create a significant challenge for control efforts. Alternatively, it is possible the index outbreaks in these cases were misidentified.

Across the entire time frame of the study, the distance outbreaks spread was negatively correlated with the number of outbreaks, indicating that HPAI spread over a shorter distance during panzootics than during periods of low spread. However, the limited number of years including possible outliers may affect precision. In addition, possible bias due to the size of events and the size of countries were tested and these two parameters did not influence the significance of results. One of the possible explanations of these results is that control of HPAI events is more efficient during periods of global panzootics, likely due to improved preparedness within countries. This might also indicate that control measures are reactive rather than proactive (Capua and Catolli, 2013) and a more proactive approach may reduce or prevent future panzootics. These hypotheses might be further explored by extending the time frame of the study.

Overall, these results provide information on the global trends in HPAI outbreak control. Considerable efforts at controlling and preventing HPAI have been implemented at the global level since the 2005/2006 panzootic, but these efforts have not prevented the re-emergence of HPAI in recent years, suggesting knowledge gaps in the epidemiology of HPAI remain and improvements in prevention and control measures are still necessary. Information provided in this paper will support national veterinary services in improving the design of HPAI surveillance and control strategies.

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Table 1. Distance (km) and rate of spread (km/day) of HPAI from the index outbreaks to the subsequent outbreaks in poultry observed worldwide between 2005 and 2016.

	Number of outbreaks	Minimum	Lower quartile	Median	Upper quartile	Maximum
Distance from index outbreak (km)	6,133	0	40	111	229	6,875
Rate of spread from index outbreak (km/day)	6,042	0	0.5	1.9	4.7	756.6

○ HPAI outbreak location

No. reporting countries / % reporting countries

- ■ Countries reporting presence of the disease during each year
- ▨ Countries reporting absence of the disease during each year
- ☐ Countries not reporting information on the disease each year
- — % of countries affected during each year