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Research Article

Spatio-Temporal Analysis of High Pathogenic Avian Influenza outbreaks reveal persistent and emerging subtypes

Muhammad Harris Rashid [1], Rajaa Haamid[1], Ahmed Riaz Khan [2]*

[1] Kauser Abdulla Malik School of Life Sciences, Forman Christian College University, Lahore
[2] School of Engineering, Ulster University, Belfast, Northern Ireland, United Kingdom

*Corresponding author:
Ahmed Riaz Khan
(e-mail: Khan-ar1@ulster.ac.uk)

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ABSTRACT Avian Influenza (AI) is a significant global concern due to its impact on animal health, agriculture, and public health. High pathogenic avian influenza (HPAI) viruses, particularly H5 and H7 subtypes, are known for causing severe outbreaks in poultry. This study aims to analyze the spatio-temporal distribution and subtype dynamics of HPAI outbreaks globally. Data from the World Organization for Animal Health (WOAH) spanning 2005 to May 2024 were analyzed. A total of 19,216 reports documented 20,093 outbreaks and 93.9 million cases involving 159 species, including domestic and wild birds. Temporal density analysis revealed H5N1 as the most persistent and problematic subtype, with other subtypes like H5N6 and H5N8 causing outbreaks in recent years. Seasonal patterns highlighted recurring outbreaks, particularly during late winter and early spring, with variations in outbreak intensity across years. Spatial analysis showed a high concentration of cases in countries like the USA, China, and Russia reporting the largest caseloads. HPAI subtype diversity was highest in Asia and Europe, with reporting unique subtypes such as H5N9 in Europe and H7N9 in Asia. Spatio-temporal clustering using the ST-DBSCAN algorithm identified persistent clusters in specific regions and emergence of new clusters in subsequent years. It suggests that there is shift in geographic impact and introduction of new subtypes. Domestic birds accounted for more than 75% of cases, with significant differences in infection duration and subtype susceptibility compared to wild birds. Statistical analyses highlighted regional variations in subtype prevalence and outbreak dynamics. The study underscores the need for continuous monitoring and tailored biosecurity measures to address the evolving HPAI threat. Identifying spatio-temporal trends and high-risk regions can guide targeted interventions and improve global readiness for future outbreaks.

KEYWORDS Avian Influenza, Spatio-Temporal, STDBSCAN, Global Surveillance, Epidemics

Introduction

Avian Influenza (AI) viruses primarily infect birds and are classified into two groups such as low pathogenic AI (LPAI) and high pathogenic AI (HPAI) (Thiermann, 2015). As the name implies, this classification is based on levels of mortality and morbidity in birds (Szablewski *et al*, 2023). Apart from importance in veterinary medicine, HPAI is threat to food safety, agricultural economics, and public health because of their zoonotic potential (Carnegie *et al*, 2023). WHO and WOAH have declared HPAI as a notifiable disease for all the member countries (Thiermann, 2015; Chatziprodromidou *et al*, 2018). It has caused approximately 316 million deaths of both domestic and wild birds between 2005 and 2021 as per animal health control agencies reports (Simancas-Racines *et al*, 2023). Identified HPAI subtypes belong to H5 and H7 subtypes that can cause more than 90% mortality in less than 48 hours after onset of outbreak (To *et al*, 2013; Kanaujia *et al*, 2022). Therefore, HPAI remains relevant for top-priority concern by veterinarians and human health departments globally.

Apart from the health impact, HPAI has a significant economic effect on agriculture and trade internationally especially in low and low middle income countries (LMIC) (Parvin *et al*, 2020; Leight *et al*, 2022). Alongside the farmers, loss of poultry business also impacts the related businesses i.e. feed industry and food processing industry (Pramuwidyatama *et al*, 2023). HPAI outbreaks can compel other nations to impose trade barriers that enhance these

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losses due to ban on exportation of poultry and related commodities from the affected regions (Zhou *et al*, 2019). Furthermore, infection control measures can essentially burden upon struggling economies (Keogh-Brown *et al*, 2020).

To tackle the HPAI outbreaks, systematic monitoring of its spread is imperative. To better understand the disease spread, surveillance initiatives have been started at both global and local levels (Sharan *et al*, 2023). These programs include those coordinated by WHO i.e. Global Influenza Surveillance and Response System (GISRS), World Organization for Animal Health (WOAH) i.e. World Animal Health Information System (WAHIS), the Food and Agriculture Organization (FAO), U.S. Department of Agriculture (USDA) i.e. the Animal and Plant Health Inspection Service (APHIS), the Public Health Agency of Canada, and China's Centres for Disease Control (Wang *et al*, 2021). Additionally, the passive surveillance system established in European Union member states serves as an early warning mechanism. Such surveillance programs help to determine the spatial and temporal dynamics of HPAI subtypes and geographically important factors. Control efforts emphasize the importance of transparency, advancing knowledge of phylodynamic methods, and implementing robust biosecurity measures to safeguard poultry and mitigate potential human infections (Carnegie *et al*, 2023).

Given the continuous evolution of HPAI, it is critical to review recent control strategies to address HPAI effectively. It is important to conduct long-term population specific tendency analyses of HPAI to understand changes happening to the virus. Furthermore, current and future patterns of HPAI distribution is also important to develop more effective prevention measures and preparedness plans. Spatio-temporal analysis can determine the change in HPAI outbreak patterns over a specific period and regions. The purpose of this study therefore is to analyze the temporal and geographical distribution of HPAI outbreaks together with their viral subtype type and location. Hence, this research aims at explaining these patterns to develop better strategies towards disease control and to improve the readiness of the world in case of the subsequent HPAI epidemic.

Materials and Methods

Data Collection

AI is a declared notifiable disease by WOAH, formerly known as OIE. WOAH maintains records of avian influenza outbreaks. All HPAI occurrence reports from 2005 up to May 5, 2024 were obtained along with their corresponding date of occurrence. Data obtained included outbreak reports dates, the subtypes involved, the bird population impacted, its geographical coordinates and domestic or wild birds' categories infected. Total number of outbreak reports and total number of affected birds were also included in this data.

Temporal density

Temporal analyses were performed based on date of outbreak started. Temporal density was conducted to determine temporal changes in the emergence of various subtypes of HPAI. This temporal density also includes the total number of cases caused by the subtypes. Additionally, temporal analyses were conducted to review the annual outbreak numbers and combined reports of the total number of cases to gauge the difference in the virus's effects per year.

Spatial density

Spatial density was estimated using HPAI cumulative caseload across the world which was useful as a quick gauge for total caseload in each country. Countries with no reports of cases during the time duration between 2005 and 2024 were also determined. Moreover, HPAI subtype distribution and the subtypes in continents were also analysed for comparing the geographical distribution of subtypes.

Spatio-Temporal Clustering

The Spatio-temporal density-based clustering was performed using the ST-DBSCAN algorithm. This algorithm clusters the outbreaks according to space and time density. Data obtained were separated based on year and subtypes followed by application of the algorithm separately. These clusters were then visualized on world maps of several years and regions with repeated epidemic flashes and potentially endangered areas were revealed.

Statistical analysis

Data were analysed using R-statistical language version 4.2.2. Qualitative data were represented using percentage while quantitative data were analysed using Inter-quartile range (IQR) and median using gtsummary package. To identify the significance of the differences in reaction of different bird types to HPAI, Fisher's Exact Test and Kruskal-Wallis rank sum test were used for several variables. Bird types were divided into the domestic and wild birds as well as both. Data wrangling was performed using reshape2 and dplyr packages. Spot maps and choropleth map were visualized using ggmaps, ggplot2, and worldmap packages.

Results

A total of 19,216 reports were retrieved from the WOAH database till May 5, 2024. These reports contained information related to 20,093 total numbers of outbreaks while total number of cases reported were 93,926,226. There were various species of animals found infected including domestic, wild and both animals (17318, 1879, 16, respectively). A total of 159 species were found infected. Domesticated species found were domesticated birds, Equidae, cats, sheep/goats, and cattle. While other 154 species were found that belonged 97 genus groups. A total of 18 HPAI subtypes were identified which included H5, H7 untyped and HPAI uncategorized.

Temporal density and subtypes

Temporal density reveals the relative occurrence and similarity of various variants of HPAI across various time segments ranging from 2005 to 2024 (Fig. 1). Analysis revealed that since 2005, H5 and H7 subtypes including H5N1, H5N2, H5N6, and H5N8 have been dominant in terms of total cases. H5N1 has remained relatively problematic throughout most of the period which highlights their continuous incidence in HPAI. Certain subtypes seem to be periodic or have cropped up at some periods of development. For example, density of H5N8 is higher beginning mid 2010’s while density of H7N3 gradually increases and density of which also varies year wise. Temporal density analyses also revealed that there are some subtypes reported with low density in terms of total number of cases and outbreaks. Several subtypes such as H5N3, H5N4, H5N9, H7N1, H7N2, H7N5, and H7N6 are present at very low densities and therefore reflect low incidence of recorded case involvement with these subtypes in the past years.

Towards the end of the period (year 2020 and beyond), huge densities of H5 subtypes are still present and this affirms that Hierarchy 5 or H5 is still a strong sub-type of HPAI. H5N6 and H5N8 have also appeared of recent year, which could be due to some reoccurrence or continued circulation of the two subtypes. Whereas constant detection of subtypes as is H5N1 further portrays globally and probable reinfection subtypes as well as occasional detection of other subtypes might be seen as a localized or contained flu.

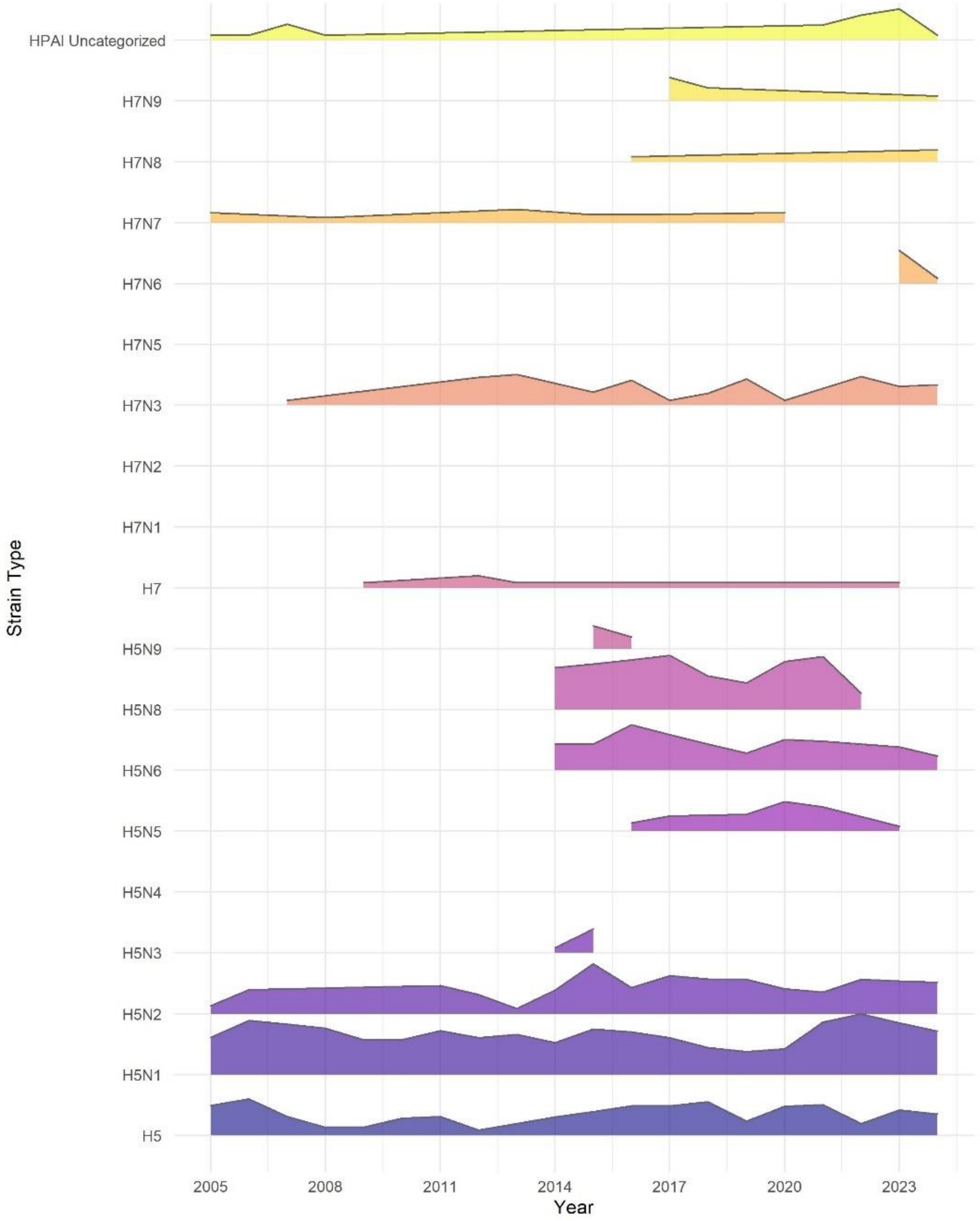

Fig. 1: Temporal Density of Avian Influenza Subtype Patterns (Log Scale). Colored areas denote the different subtypes and black lines represent the different years for each subtype as the thickness of the colored area is proportional to density or number of cases reported each year for that particular subtype.

Seasonal patterns and HPAI outbreaks

Temporal analysis also determines the timelines of outbreak of HPAI on monthly bases for the duration between 2015 and 2024 (Fig. 2). There is some indication of the fluctuations periodically spiking in previous years, especially in the first quarter of the year (January to March). This indicates a favorable cycle for epidemics particularly during the month of March so there is a high possibility for recurrent late winter early spring epidemics like avian influenza shifted by bird movements based on environmental conditions concerning virus diffusion.

During 2020-2022, this occurrence pattern contrasts with the relative cycle of outbreak reports. In 2022, the relative cycle of outbreak reports is again at its lowest in January and then rising again in February and quite prominently, thus implying that outbreak reports could positively correspond to the increased activity of a particular subtype in this month. it is possible to identify months of varying magnitudes of contagion instead of just one season, for instance; 2020, 2021, and, partially, 2022, show that the contagion was not at a high in one season but rather in different seasons of the year. This may suggest successive waves or occasions of virus transmission across diverse locations.

During 2018-2019 and 2023-2024, reduced outbreak reports have been recorded. In these durations, the number of outbreaks seems to be less volatile with slight differences. This may be due to periods of low transmission or strict compliance with containment measures.

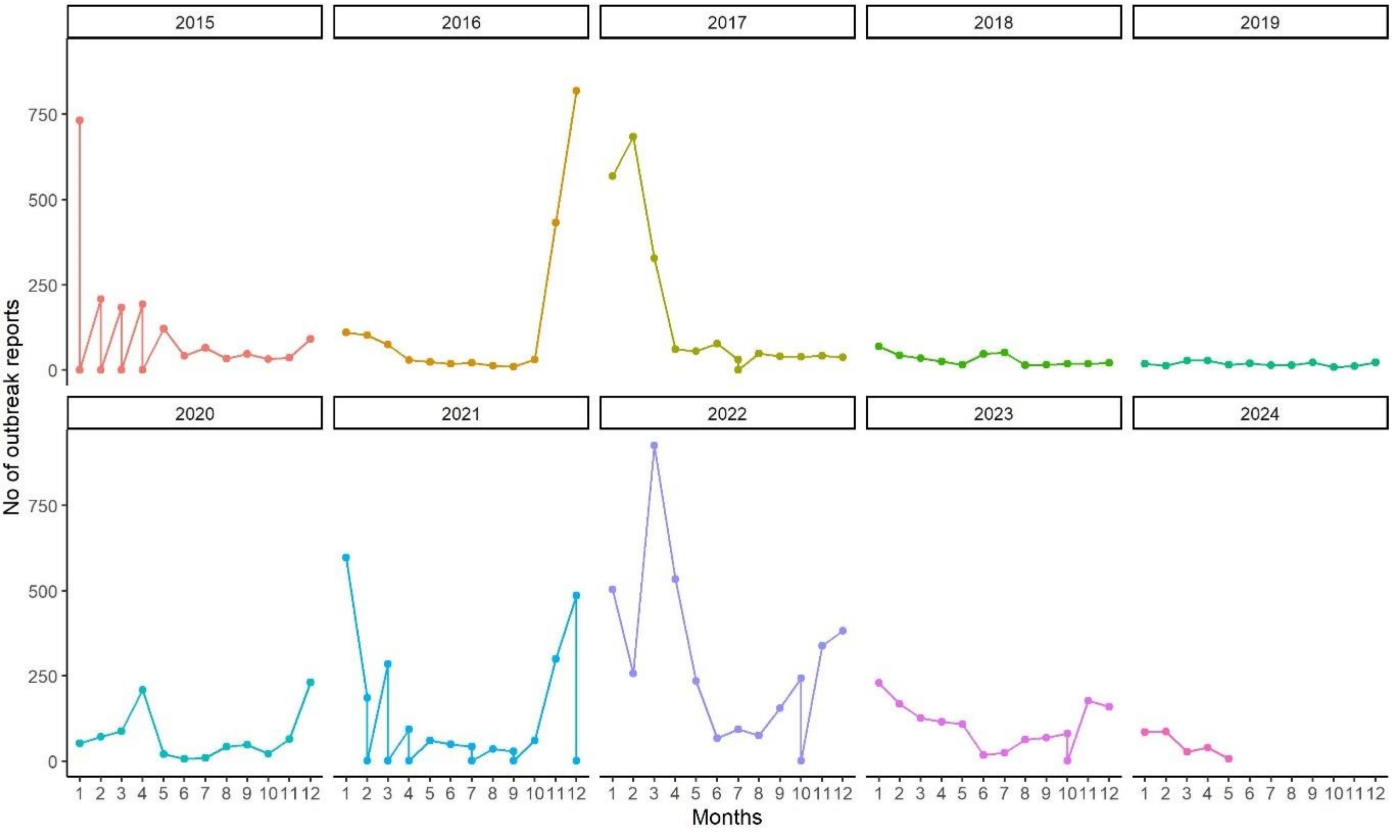

Fig. 2: Temporal analysis and timelines of HPAI outbreak reports in the decade (2015-2024). All the panels display single year on the horizontal axis, which is further divided into the 12 months of the year, vertical axis indicates the number of outbreak reports. To get better visibility, only data of last ten years (2015-2024) is shown here.

Distribution of Subtypes, Continents, Total Cases, Duration

Comparison among types of birds revealed that there is relationship of distribution of different variables with types of birds. The “Domestic” group had more overall cases with 13,283 (75%) and the “Wild” birds account for 1,879 (11%) cases showing significant variation in the total cases across the described bird types (p-value <0.05). Subtypes of HPAI and the frequency also revealed a difference among groups (Table 1). For instance, H5N1 is seen more severely in the domestic birds (10,085, 58%) and is also found in enough numbers in the wild birds (766, 41 %). Among the Continents, it was determined that a regional distribution of HPAI cases exists Europe has the largest number of positive cases in domesticate species (7,032, 41%) and wild birds (1,441,77%) followed by Asia with positive cases 6,030 (35%). In domesticated species. Total Cases contrasts the rate of occurrence for all the different species of birds. Among the types of birds, total number of cases also showed variations such as wild birds mostly found with low number of infections as compared to domestic species and both wild and domestic. Domestic birds have a median duration of 51 days (IQR: 10–151 days of infection and 42 days (IQR: 0–116) days old for the wild birds. There was also a highly significant difference in duration for the different bird types as estimated from the P-value <0.001.

Table 1: Difference among the distribution of subtypes, continents, duration, and total cases. This table summarizes the distribution of various avian influenza virus (AIV) subtypes, continents, total cases, clustering information, and duration in days, comparing these variables across bird types: These where; "Both" (birds found in both domestic and wild settings), "Domestic", and "Wild". Statistical tests such as Fisher's Exact Test and Kruskal-Wallis rank sum test were applied to assess differences.

Variables	**Levels**	**Both** (n = 16)	**Domestic** (n = 17,321)	**Wild** (n = 1,879)	**P-value**
Subtype	H5	1 (6.2%)	568 (3.3%)	44 (2.3%)	<0.001
	H5N1	8 (50%)	10,085 (58%)	766 (41%)	
	H5N2	0 (0%)	1,598 (9.2%)	34 (1.8%)	
	H5N3	0 (0%)	25 (0.1%)	1 (<0.1%)	
	H5N4	0 (0%)	1 (<0.1%)	0 (0%)	
	H5N5	0 (0%)	95 (0.5%)	2 (0.1%)	
	H5N6	0 (0%)	654 (3.8%)	176 (9.4%)	
	H5N8	7 (44%)	3,772 (22%)	849 (45%)	
	H5N9	0 (0%)	25 (0.1%)	0 (0%)	
	H7	0 (0%)	8 (<0.1%)	0 (0%)	
	H7N1	0 (0%)	0 (0%)	1 (<0.1%)	
	H7N2	0 (0%)	2 (<0.1%)	0 (0%)	
	H7N3	0 (0%)	242 (1.4%)	4 (0.2%)	
	H7N6	0 (0%)	87 (0.5%)	0 (0%)	
	H7N7	0 (0%)	16 (<0.1%)	0 (0%)	
	H7N8	0 (0%)	1 (<0.1%)	0 (0%)	
	H7N9	0 (0%)	28 (0.2%)	0 (0%)	
	HPAI Uncategorized	0 (0%)	114 (0.7%)	2 (0.1%)	
Continent	Africa	2 (12%)	2,744 (16%)	8 (0.4%)	<0.001
	Asia	5 (31%)	6,030 (35%)	374 (20%)	
	Europe	9 (56%)	7,032 (41%)	1,441 (77%)	
	North America	0 (0%)	1,416 (8.2%)	56 (3.0%)	
	Oceania	0 (0%)	6 (<0.1%)	0 (0%)	
	South America	0 (0%)	93 (0.5%)	0 (0%)	
Total Cases		12 (3, 36)	317 (33, 2,805)	1 (1, 2)	<0.001
Duration in days		51 (34, 113)	51 (10, 151)	42 (0, 116)	<0.001

Amount of total reported cases per country

Spatial distribution describes the total reported cases across the countries of the world (Fig. 3). High incidence of HPAI cases were reported in USA, Brazil, Russia and China. On the other hand, France, Russia, and some parts of Asia are in the middle to high numbers of the respective cases. On the other hand, Middle level and low prevalence territories which include Canada, a part of South America and the parts of Eastern European countries and some parts of Southeast Asia. Several African and Europe countries, some part of Middle East and South American countries are described as least affected countries. On the other hand, a few regions are free or nearly free of such diseases mainly in Africa and the Middle East. This least or nearly free status could be explained by low reporting, low surveillance, or low incidence. There are certain regions showing no information or cases reported like in some part of Africa, Central Asia, some other corners of the world. All Levels of HPAI prevalence are evident in Europe, Asia, and North America, implying the virile nature spreading of AIV to diverse locations.

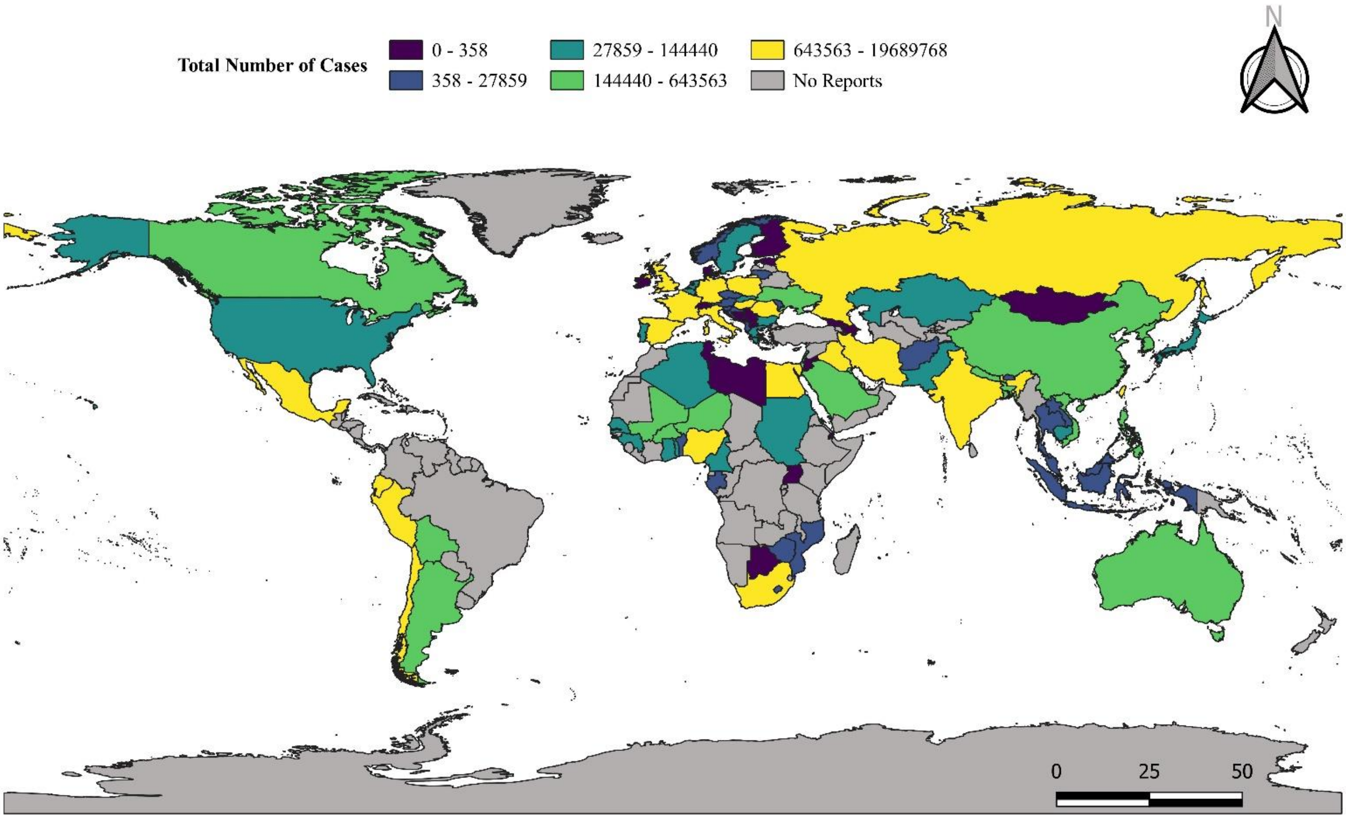

Fig. 3: Choropleth map showing total cases across the globe. Colors indicate the amount of total reported cases per country within this timeframe, giving the overview of HPAI distribution across the globe

Distribution of subtypes across continents

Distribution of HPAI subtypes across various continents were determined in spatial analysis (Fig. 4). Among the Continents, Asian and European continent showed diverse HPAI subtypes. Asia presented other subtypes such as H5N3, H7N7, H7N9 and HPAI uncategorized subtypes showing there are multiple subtypes of HPAI. European continent also showed high diversity of subtypes especially for H5N9 which is not reported anywhere in other continents. Europe also confirmed H7N7, H7N1 and HPAI uncategorized subtypes and shows both high diversity and frequency of subtypes. On the other hand, African continent contain variation of subtypes, about 33 reported H5 and H5N1 subtypes were prevalent. Other inclusions include H7N1 and H7N7 although in smaller numbers in comparison to the aforementioned (H5N1) virus.

On other hand, in North America, high reportage of H5, H5N8 and H5N4 populations was found though H5N8 is indicating something unique. There are also certain mentioned subtypes like H7N9 and H7N8.Oceania continent mainly Australia reported fewer subtypes compared to other continents, in total. It has three subtypes; H7, H7N2, and H7N7. This region seems to have relatively few incidences especially of the H5 or H5N1 sub types which are more prevalent in other regions of the world. Like Oceania, South America also showed reports of very few subtypes. H5, H5N1 and HPAI uncategorized are reported in this continent. Africa and South America also testify to the uniqueness but the number of reports in these two continents is considerably less compared to Asian and European countries.

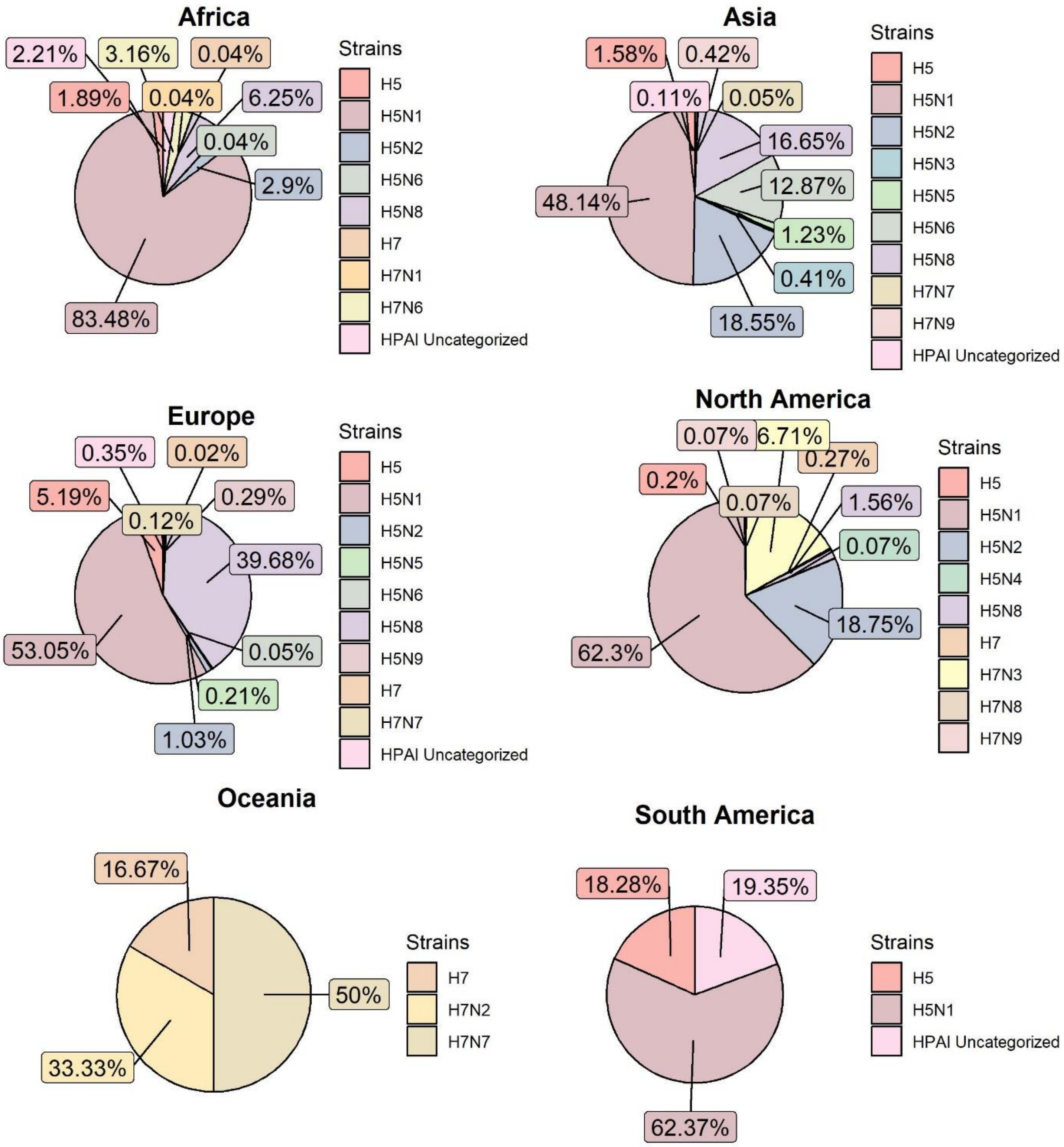

Fig. 4: Pie chart shows the classification of AIV based on the subtypes and their distribution by continents. The size of pie denotes the number of reports on the specific subtype in the given continent. The arrangement of the chart is based on the continent to enable the distinction of the various subtypes of AIV that is prevalent all over the globe

Spatio-temporal density-based clustering (STDBSCAN)

STDBSCAN determined the Cluster Consistency Over Time, Geographical Spread of Clusters, Emergence of New Clusters and Cluster Overlap and Interaction (Fig. 5). A few clusters consistently persist or appear across the years in similar geographic areas. It suggests a sustained presence or recurring outbreaks of that subtype in those areas. On other hand, some clusters appear in multiple geographic locations within a single year, indicating subtypes that are dispersed

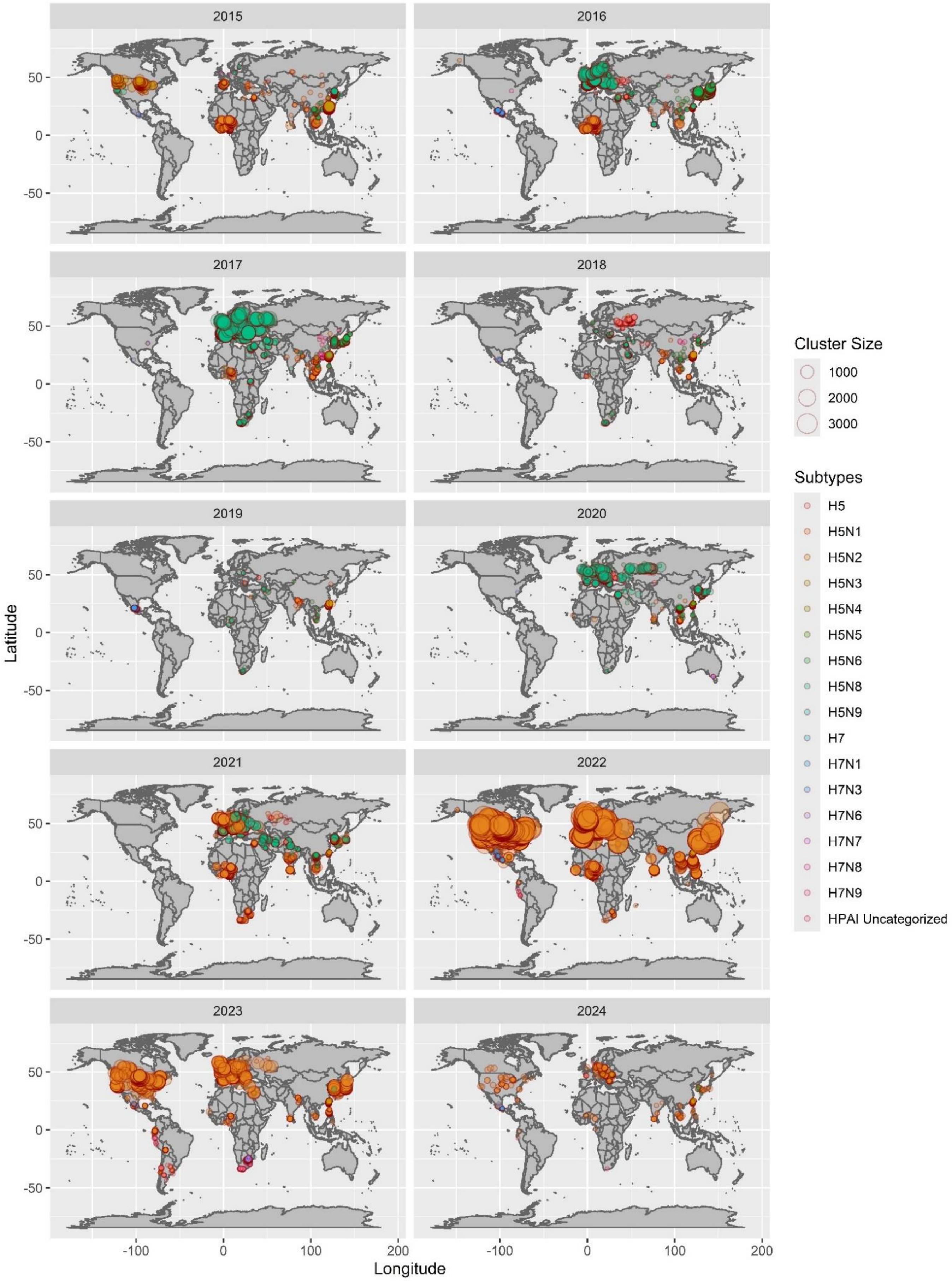

Fig. 5: Point map chart plotted year-wise with world map depicting the results of Spatio-Temporal Density-Based Spatial Clustering of Applications with Noise (ST-DBSCAN) applied to the HPAI outbreak dataset. Each subplot corresponds to one year (2015–2024), and outbreaks are grouped into clusters.

across different regions. For instance, subtypes H5N6 and H5N8 in 2016-2017 and 2020-2021 might be having higher density in both Eastern Asia and Europe, showing that this subtype has spread or appeared simultaneously in distant locations. On the other hand, subtypes H5N1 and H5N2 were found persistently present with varying density during this 10-year analysis. During year 2022 and 2023, their density was overwhelmingly high. Geographically, few H7 subtypes such as H7N3 are being consistently reported from North America (Mexico) with low density sizes.

As far as emergence of new clusters is concerned, new clusters appearing in subsequent years suggesting the introduction of new subtypes or shifts in geographic areas impacted by certain subtypes. For example, HPAI subtypes such as H7N6, H5N9, and H5N3 appears only in certain years, it might represent a unique subtype that was only present or detected during that year. In some years, multiple clusters with different colors overlap geographically, suggesting regions with subtype diversity as discussed earlier. These regions could be of particular interest for studying interactions between clusters and potential cross-subtype influences.

Discussion

Spatio-temporal analysis is a powerful tool to study the events over time and across different locations. It is useful for identifying hotspots, emerging patterns, and changes in outbreak trends over the years (Sharan *et al*, 2023). In case of HPAI, this approach can determine seasonality, recurring outbreaks, and HPAI spread geographically (Duan *et al*, 2023). By understanding these patterns, resources can be allocated more effectively leading to targeted interventions (Chatziprodromidou *et al*, 2018). It also helps explore links between outbreaks and factors like climate, trade, or farming practices. Overall, spatio-temporal analysis provides valuable insights for predicting future outbreaks and designing strategies to control diseases.

Temporal density performed in this study highlights the temporal patterns of HPAI outbreaks from 2005 to 2024. The temporal analysis revealed that H5 and H7 subtypes, especially H5N1, remain dominant, underscoring their sustained impact on avian populations. The periodic emergence of subtypes like H5N8 in the mid-2010s and H7N3 in later years reflects the dynamic nature of HPAI evolution. Notably, H5N1's consistent presence and high densities in recent years suggest its resilience and potential for continued outbreaks (Lai *et al*, 2016; Charostad *et al*, 2023). Previous studies have suggested the better vaccination and monitoring strategies to handle H5N1 subtype (Claes *et al*, 2016). These findings emphasize the need for ongoing monitoring and preparedness, as well as targeted interventions for the most persistent subtypes.

Temporal analysis revealed that seasonal fluctuations exist in outbreak intensity, with peaks often occurring in the first quarter of the year, particularly in March. This seasonal pattern likely correlates with bird migration cycles and environmental conditions that favor viral transmission (Tian *et al*, 2015). However, deviations in outbreak patterns during certain years indicate additional factors, such as human intervention, biosecurity measures, or viral adaptations (Morin *et al*, 2018). These findings support the hypothesis that HPAI outbreaks are influenced by both biological and external factors. Furthermore, low outbreak activity in some years may reflect effective containment measures or natural decreases in viral spread.

Spatial distribution analysis showed that certain regions, including Europe, Asia, and North America, have the highest burden of HPAI cases. Europe, for instance, recorded significant outbreaks in both domestic and wild birds. It highlights its vulnerability due to dense poultry farming and extensive migratory bird pathways (Velkers *et al*, 2021). Asia's high diversity of subtypes, including H5N1, H7N9, and others, highlights the importance of regional surveillance systems to track emerging subtypes. Conversely, regions like Oceania and South America reported fewer outbreaks and subtype diversity, potentially reflecting limited surveillance or lower poultry density. These geographical differences show the need for tailored surveillance and control programs across continents.

The spatio-temporal clustering analysis provided deeper insights into the spread and persistence of HPAI. Persistent clusters in specific regions suggest recurring outbreaks due to sustained viral circulation, while geographically dispersed clusters within a single year indicate rapid subtype transmission. For instance, the concurrent appearance of H5N6 and H5N8 in Eastern Asia and Europe suggests the movement of these subtypes via migratory birds or trade. The emergence of new clusters, such as H5N9 and H7N6 in specific years, highlights the evolving nature of HPAI and the importance of continuous genetic and epidemiological studies (Dhingra *et al*, 2018).

In conclusion, this study highlights the HPAI dynamic spread, persistent subtypes, and economic impact. The findings highlight the critical role of global surveillance networks like WHO's GISRS and WOAH's WAHIS in tracking outbreaks and informing policy. Future efforts should focus on integrating advanced spatio-temporal modeling with genetic analysis to predict outbreak patterns and identify hotspots. Collaborative efforts between countries, particularly in regions with shared migratory bird pathways, are essential to mitigate HPAI's impact on poultry, wildlife, and human health

Declaration of Competing Interest

The authors declare that they have no competing or conflict of interests.

Author Contributions:

Muhammad Harris Rashid: Conceptualization, Methodology, formal analysis, Writing—original draft preparation. **Rajaa Haamid:** Conceptualization, Methodology, formal analysis, **Ahmed Riaz Khan:** Formal analysis, Writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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