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The role of vaccination and environmental factors on outbreaks of high pathogenicity avian influenza H5N1 in Bangladesh

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ABSTRACT

High Pathogenicity Avian Influenza (HPAI) H5N1 outbreaks continue to wreak havoc on the global poultry industry and threaten the health of wild bird populations, with sporadic spillover in humans and other mammals, resulting in widespread calls to vaccinate poultry. Bangladesh has been vaccinating poultry since 2012, presenting a prime opportunity to study the effects of vaccination on HPAI H5N1circulation in both poultry and wild birds. We investigated the efficacy of vaccinating commercial poultry against HPAI H5N1 along with climatic and socio-economic factors considered potential drivers of HPAI H5N1 outbreak risk in Bangladesh. Using a multivariate modeling approach, we estimated that the rate of outbreaks was 18 times higher before compared to after vaccination, with winter months having a three times higher chance of outbreaks than summer months. Variables resulting in small but significant increases in outbreak rate were relatively low ambient temperatures for the time of year, literacy rate, chicken and duck density, crop density, and presence of highways; this may be attributable to low temperatures supporting viral survival outside the host, higher literacy driving reporting rate, density of the host reservoir, and spread of the virus through increased connectivity. Despite the substantial impact of vaccination on outbreaks, we note that HPAI H5N1 is still enzootic in Bangladesh; vaccinated poultry flocks have high rates of H5N1 prevalence, and spillover to wild birds has increased. Vaccination in Bangladesh thus bears the risk of supporting "silent spread," where the vaccine only provides protection against disease and not also infection. Our findings underscore that poultry vaccination can be part of holistic HPAI mitigation strategies when accompanied by monitoring to avoid silent spread.

1. Introduction

Until 1995, the avian influenza virus (AIV) mostly occurred in a low pathogenic form with only occasional emergences of high pathogenicity avian influenza (HPAI) [1]. From 1996 to the present, we have witnessed a progressively more rapid and wider spreading of HPAI caused by virus from the H5N1 A/goose/Guangdong/1996 lineage evolving into several distinct and diverse clades [2,3]. Notably, viruses belonging to H5Nx Clade 2 have caused significant socio-economic damage and health concerns for livestock, wildlife, and humans. Since October 2021, viruses belonging to Clade 2.3.4.4b have caused a panzootic of unprecedented magnitude, spreading to all continents except Australia and Antarctica, thus far leading to the loss of more than half a billion poultry and high mortality across a great variety of species of wild birds [4–6]. Furthermore, HPAI H5N1, including the present panzootic clade 2.3.4.4b H5N1 viruses, have demonstrated the ability to cross the barrier between birds and mammals, resulting in infections in humans and other mammalian species [6–8], including a range of marine mammal species (such as south American sea lions, harbor seals, porpoises and dolphins) [9,10]. Since its emergence, the virus has led to at least 878 laboratory-confirmed human cases in 23 different countries [8,11]. This event has increased calls to implement poultry vaccination against HPAI more widely [5,12]. While vaccination against some HPAI lineages has proven successful in significantly reducing casualties amongst poultry [13,14], vaccination alone has thus far not resulted in eradication of those lineages [15].

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Moreover, when vaccination merely reduces disease symptoms and does not adequately prevent infection, as is currently the case, it may result in “silent spread” and promote further virus evolution [16]. Therefore, improved vaccination practices alone may not be sufficient to contain the current panzootic, and it is of crucial importance to learn about additional factors that may drive the spread of HPAI, including climatic, socio-economic, ecological, and biosecurity factors. In Bangladesh, vaccination of the national poultry stock against HPAI H5N1 commenced in 2012 [17,18]. Detailed accounts of Bangladesh’s outbreak history, specifically preceding and following this intervention from 2007 to 2018, offer a valuable opportunity to identify factors that influence outbreaks in poultry in both the presence and the absence of a large-scale vaccination program. Such analysis is an opportunity to yield insights that may be crucial in developing adequate mitigation strategies for current and future epizootics.

It is well known that meteorological factors may affect disease emergence, including cross-species viral spillover risk [19,20], and that an improved understanding of climate implications on viral ecology is crucial in developing mitigation strategies to reduce adverse health impacts on humans and animals [21]. For instance, in humans, weather conditions such as low temperature, high relative humidity, and high frequency of rainfall were found to contribute to the transmission of Influenza A [22–24]. Low temperatures and high wind speed were also associated with seasonal influenza A outbreaks in China [25]. Table 1 summarizes the effects of weather and climate on both HPAI and low pathogenicity avian influenza (LPAI) prevalence and outbreaks globally.

Socio-economic factors may also significantly influence avian influenza outbreaks [26,27]. Sufficiently large populations of poultry farms may become maintenance reservoirs for HPAI [28]. Previous studies have also demonstrated that higher human population density increased the risks of avian influenza outbreaks in Hong Kong and Thailand [29,30]. Other socioeconomic components, such as literacy and poverty rates, were also related to avian influenza outbreak risk [31]. Additionally, several studies have identified a number of ecological factors, such as the presence of migratory bird staging areas and wetland habitats for key reservoir species such as waterfowl and shorebirds [32], that may significantly increase the likelihood of HPAI-H5N1 outbreaks in poultry [33,34]. Thus, we further collated socio-economic and ecological variables from the literature for inclusion in Table 1, as well as the suggested pathways through which they might act. Many of the variables associated with AIV outbreaks and prevalence vary seasonally. This is true for a number of the meteorological and ecological variables highlighted in Table 1, e.g., wildlife host abundance, like waterfowl. Likewise, many influenza studies, be it in humans [35,36], poultry [37,38], or wild birds [32,39], have found clear seasonality in AIV prevalence/outbreaks. Thus, when analyzing time series of outbreaks, seasonality must be accounted for to isolate the true effects of other explanatory variables.

Bangladesh is a low-income developing country with one of the highest population densities worldwide, estimated at 1115 humans/km^2 [40]. Since 2007, Bangladesh has been badly impacted by HPAI H5N1 outbreaks in commercial poultry, specifically those belonging to clade 2.2 and descendant lineages commercial poultry [41]. The poultry industry is an important part of the economy of Bangladesh, generating 4.12 billion USD annually (1.17% of the GDP) and creating employment for >6.0 million people, primarily females and young people [42,43]. As a result, HPAI has been a source of significant economic losses for the industry and, in turn, the country. In the 2008 HPAI H5N1 wave of outbreaks, about 50% of poultry farms were closed, and >1.8 million chickens were culled at an economic cost of around 40 million USD, with 2.5 million people made jobless [44,45]. In response, in 2012, two vaccines against H5 were authorized for importation from China and USA for use in Bangladesh [46]. Here, we provide a detailed analysis of how this vaccination campaign has impacted the rate of HPAI H5N1 outbreaks in Bangladesh, in combination with a range of climatic, socio-economic, and ecological factors hypothesized to be of importance in driving AIV outbreak risk, to inform future mitigation strategies against the ongoing HPAI threat.

Table 1
Factors observed to have an effect on HPAI H5N1 outbreaks in poultry and the suggested underlying mechanisms.

Category	Variables	Observed effect on HPAI H5N1 outbreaks	Suggested mechanism	Supporting literature
Meteorological	Relative humidity (%)	+	Virus survival outside host	Lowen, Mubareka [47], Peci, Winter [48]
	Maximum temperature (°C)	–	Virus survival outside host	Lowen, Mubareka [47], Peci, Winter [48]
	Minimum temperature (°C)	–	Virus survival outside host	Lowen, Mubareka [47], Peci, Winter [48]
	Wind speed (knots)	+	Promoting virus dispersal while outside host	Ssematimba, Hagenaars [49], Lau, Wang [50]
	Cloud cover (octa)	+	Virus survival outside host	Guo, Xue [51], Biswas, Islam [52]
Socio-economic and ecological	Adult literacy rate (%)	+	Reporting bias	Mahendri, Saptati [53], Roy, Singh [54]
	Chicken density (number km^2)	+	Host reservoir size and increased connectivity promoting dispersal	Gilbert, Chaitaweesub [55], Henning, Pfeiffer [56]
	Domestic duck density (number km^2)	+	Host reservoir size and increased connectivity promoting dispersal	Gilbert, Chaitaweesub [55], Gilbert, Newman [57]
	Crop density (acres per km^2)	+	Driver of host reservoir size	Loth, Gilbert [41], Paul, Tavornpanich [58]
	Number of markets (number per district	+	Increased connectivity promoting dispersal	Indriani, Samaan [59]
	Presence of wetland (no/yes)	+	Driver of host reservoir size	Yupiana, de Vlas [60], Martin, Pfeiffer [61]
	Presence of national highway (no/yes)	+	Increased connectivity promoting dispersal	Loth, Gilbert [41], Paul, Tavornpanich [58]
	Presence of migratory birds staging areas (no/yes)	+	Driver of host reservoir size	Ward, Maftei [62], Ward, Maftei [63]

2. Methodology

2.1. HPAI H5N1 outbreak data

We used all HPAI H5N1 outbreaks in Bangladesh collated in the Global Animal Disease Information System (EMPRES-i) database available at the Food and Agriculture Organization between January 2007 and December 2018 [64]. For a total of 585 outbreaks, we extracted information on the date of the outbreak, the species affected, and the latitude and longitude of the outbreak epicenter. With these data, we compiled one data set containing the monthly outbreak counts for the country and another data set containing the total outbreak counts from March 2007 to December 2018 for each of the 64 districts in Bangladesh. The national data set containing the monthly counts was used to investigate the role of vaccination and climatic factors. The district data set containing the overall outbreak counts between 2007 and 2018 was used to investigate the role of socio-economic and ecological factors as drivers of HPAI outbreaks.

2.2. *Meteorological data*

We accessed meteorological data from the Bangladesh Meteorological Department (BMD) (https://www.bmd.gov.bd/) [65]. BMD keeps daily records of maximum temperature (°C), minimum temperature (°C), relative humidity (%), wind speed (knot), and cloud cover (octa) at 35 meteorological observatories across the nation. Any occasional missing data points were linearly interpolated. We calculated the monthly mean of each meteorological variable for each station and then took the average across all 35 stations to obtain a national monthly average for that variable. Lastly, we calculated the monthly anomaly for each variable (i.e., the difference between the monthly average and the mean of the monthly average across all years) for inclusion in our analyses.

2.3. *Socio-economic and ecological data*

We used district-level adult literacy rate (%) from the Bangladesh Population and Housing Census 2011 [66]. We extracted chicken density (number km^{-2}), duck density (number km^{-2}), and crop density (acres km^{-2}) for each district from the Bangladesh Agriculture Census 2008 conducted by the Bangladesh Bureau of Statistics [67]. We also collected data on migratory bird staging areas that were classified as of “international importance” in the literature [31,68], as well as data on the presence of wetlands in that district from the FAO GeoNetwork [69]. For each district, we recorded the presence of national highways facilitating connectivity and the number of live bird markets from the Local Government Engineering Department Bangladesh [70].

2.4. *Statistical analyses*

Using the national level monthly outbreak data, we investigated the effect of season, weather, and vaccination on monthly outbreak numbers using generalized linear models in R version 4.2.0 within Rstudio version 2022.02.2. We calculated the Pearson’s correlation coefficients between all-weather anomalies to assess multicollinearity (Figure SM1), after which we decided to remove the monthly anomalies for cloud cover and minimum temperature, yielding a maximum absolute correlation coefficient of 0.543 between any of the weather anomalies retained. To test the effect of season, we included month as a categorical variable. Vaccination was entered as a binary variable and set to “no” prior to 2012 and “yes” thereafter. The anomalies for maximum temperature, relative humidity, and windspeed were included as covariates to estimate the effects of weather conditions adjusted for the season.

Using the district data set with the overall outbreak counts, we investigated the effects of literacy rate, chicken density, duck density, crop density, number of live bird markets, presence of highways (yes/no), presence of migratory bird staging areas (yes/no), and presence of wetlands (yes/no) through generalized linear models. One of the 64 districts, Mymensingh, contained extreme outliers, notably an extraordinarily high number of live-bird markets (829), and was omitted from analyses. In the reduced data set, Pearson’s correlation coefficients and Cramer Vs were used to examine relationships between the explanatory variables prior to analysis. We identified a very high correlation between chicken and duck density of 0.804 (Fig. SM2); therefore, duck density was removed from the data set.

We fitted generalized linear models (GLM) to the monthly number of outbreaks that assumed Poisson, negative binomial, zero-inflated Poisson, zero-inflated Poisson with regression zero-inflation correction, zero-inflated negative binomial, zero-inflated negative-binomial with regression zero-inflation correction and a quasi-Poisson distribution. The best-fitted model was determined to be the negative binomial model based on the dispersion statistic and Akaike information criteria (AIC), aiming for a dispersion statistic value as close to 1 as possible [71,72]. All models were run twice: once with all continuous explanatory variables untransformed and once with all continuous explanatory variables scaled. The latter was done to allow a better comparison of effect sizes across explanatory variables. For month, the only categorical variable in the analyses with more than two levels, we conducted post-hoc pairwise comparisons using the emmeans package [73].

3. Results

HPAI H5N1 outbreaks were recorded exclusively in commercial and backyard chickens and wild, free-roaming house crows (*Corvus splendens*). The number of outbreaks in Bangladesh between March 2007 and December 2018 showed considerable temporal variation with peaks in early 2008 and 2011 (Fig. 1A). There was a distinct decline in poultry outbreaks after the national vaccination campaign began in 2012, with only occasional outbreaks reported afterward. Conversely, there was an increase in outbreaks detected in house crows post-vaccination. The total number of outbreaks detected from 2007 to 2018 was non-uniformly distributed across the 64 districts, with some strong spatial clustering in the center of the country (Fig. 1B).

As expected, the meteorological parameters represented in the study demonstrated a distinct seasonality, be it with a low amplitude (Fig. 2). Maximum and minimum monthly average temperature, relative humidity, cloud cover, and wind speed all follow a unimodal distribution, with high values prevailing in summer and low values prevailing in winter.

When modeling the number of monthly HPAI H5N1 outbreaks across Bangladesh, we found that the incidence was significantly lower between the months of May-November, after vaccination and during relatively high maximum temperatures. (Fig. 3, Table Supplementary (SM1).

To illustrate these effects in more detail, marginal means for these three explanatory variables are plotted in Fig. 4. Of the significant variables, vaccination had the strongest effect on monthly outbreak incidence, where the estimated incident rate of outbreaks for unvaccinated months (prior to national vaccination) was 18 times the rate of outbreaks for vaccinated months (post vaccination) (IRR = 0.055; Fig. 3). On average, the warmer months of the year, notably May–November, had a lower rate of outbreaks compared to the colder months, specifically January–March (Fig. 3, Fig. 4A; pairwise post-hoc testing identified significant, differences in outbreak frequency between February and July, and March and May through to November). The maximum temperature anomaly had a slightly negative, yet significant, effect on the rate of outbreaks (Fig. 3, Fig. 4 C), further illustrating the effect of temperate on outbreak incidence.

The GLM for the total number of outbreaks by district from 2007 to 2018 showed that adult literacy rate, chicken density, crop density, and the presence of national highways significantly increased the rate of HPAI H5N1 outbreaks (Fig. 5, Table SM2). To illustrate these effects in more detail, marginal means for these three significant explanatory variables are also plotted in Fig. 6. The presence of highways had the strongest effect of the three explanatory variables, resulting in a 3-fold increase in the number of outbreaks (Fig. 5, Fig. 6D). Following highway presence, an increase in adult literacy is expected to correspond to an increase in district outbreak incidence, such that a single unit

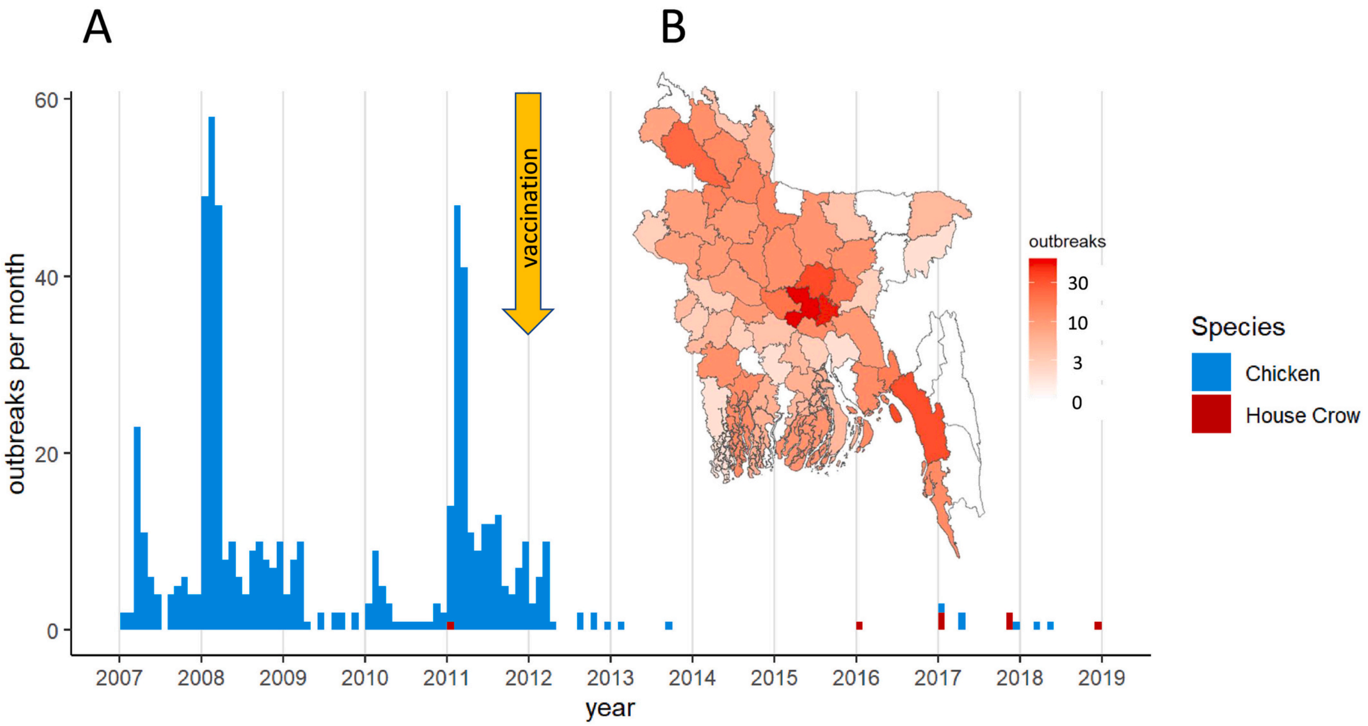

Fig. 1. Temporal (A) and spatial (B) patterns in HPAI H5N1 outbreaks in poultry and wild birds. In panel A, the monthly number of HPAIV outbreaks summed across all 64 districts in Bangladesh is depicted as a function of time, and the start of the national AIV vaccination campaign is indicated with an arrow. In panel B, the cumulative number of outbreaks per district over the period of 2007–2018 is depicted with a colour gradient corresponding to the number of outbreaks.

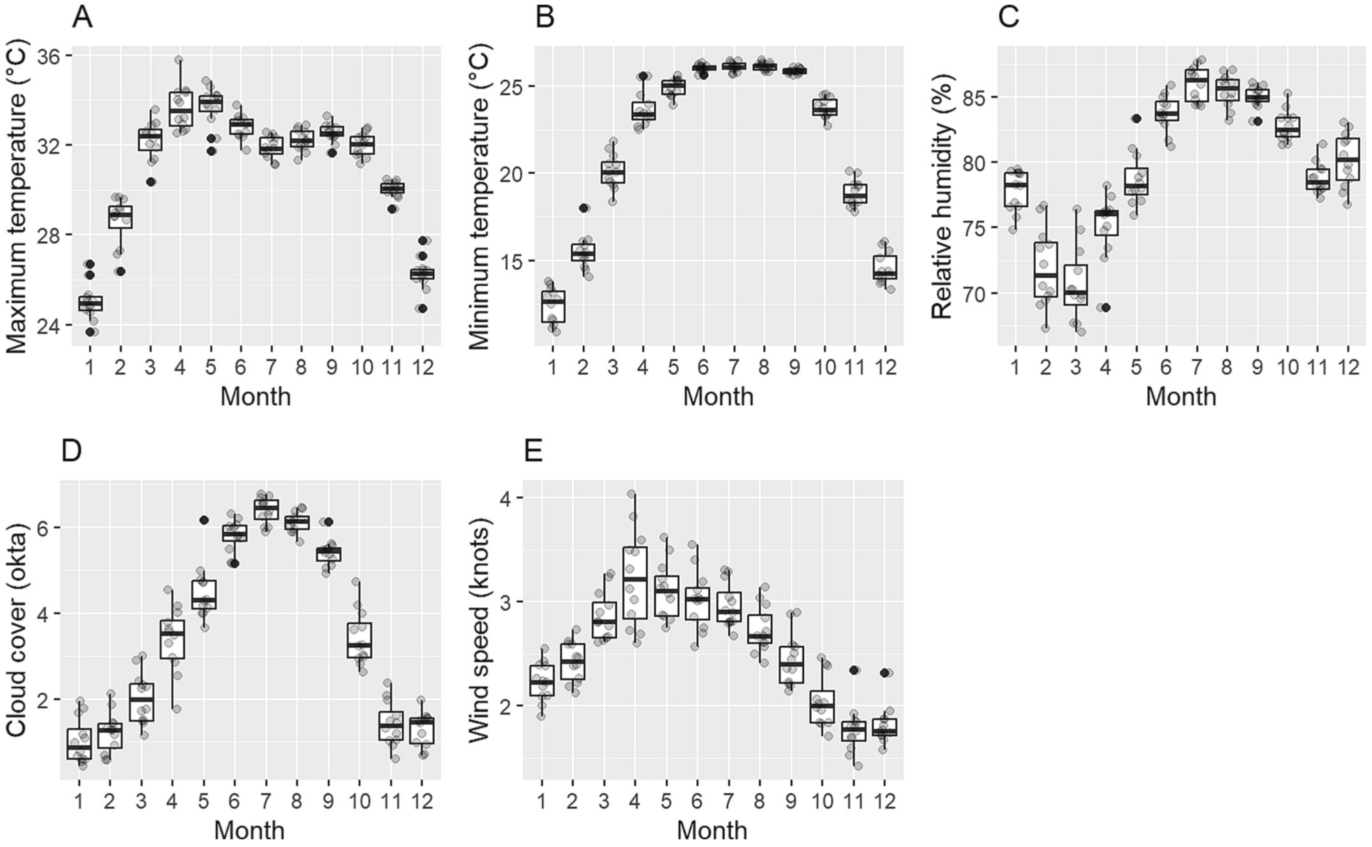

Fig. 2. In panel A-E, boxplots of monthly maximum temperature, minimum temperature, relative humidity, cloud cover, and wind speed averaged across 35 stations across Bangladesh recorded between March 2007 and December 2018 are plotted as a function of the month. The original data for each boxplot are also plotted (grey dots).

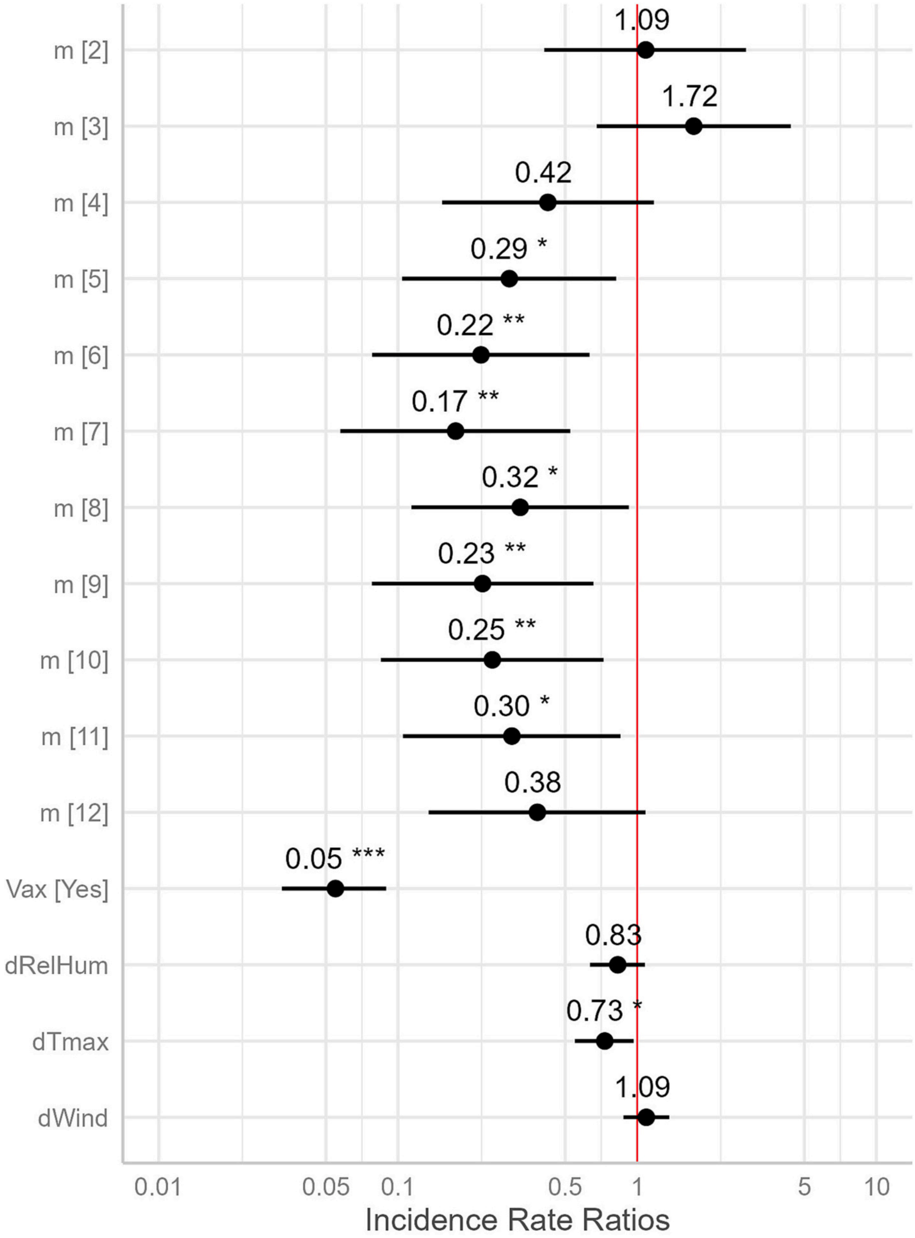

Fig. 3. Incidence Rate Ratios (± 95% confidence interval) of HPAI H5N1 outbreaks as a function of the month (m [1]-m [12]), vaccination (Vax), and the (scaled) anomalies of relative humidity (dRelHum), maximum temperature (dTmax) and wind speed (dWind). January (i.e. m [1]), no vaccination and zero anomalies form the reference (red vertical line), indicating that vaccination, the months May–November, and relatively high maximum temperatures were significantly associated with (* $P < 0.05$, **$P < 0.01$, ***$P < 0.001$) lower numbers of monthly outbreaks. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

increase in literacy (1%) at the district level is expected to increase the outbreak rate ratio by a factor of 1.53 (Fig. 5, Fig. 6A).

While more limited than the previous effects, increases in chicken and crop densities are expected to result in an increase in outbreak incidence at the district level (Fig. 5, Fig. 6B, Fig. 6C)). Given the effect of chicken density, it should be noted that domestic duck density, which was not used as an explanatory variable in the analysis, was strongly correlated with chicken density ($r = 0.799$).

4. Discussion

4.1. The impact of vaccination

We conducted a comprehensive study on the role of vaccination, climatic, socio-economic, and ecological factors on H5N1 outbreaks in poultry and wild birds using a 12-year dataset representing all 64 districts in Bangladesh. We demonstrated that poultry vaccination resulted in a substantial reduction in the rate of H5N1 outbreaks, by a factor of 18, which was higher than any other variables included in our study. While poultry vaccination against some HPAI lineages has proven successful in reducing morbidity and mortality amongst poultry [13,14], there are, to the best of our knowledge, no studies that have quantified this effect, let alone in combination with other environmental factors. Furthermore, adult literacy rate, chicken density, crop density, and presence of national highways were all associated with small but significant increases in outbreak incidence.

Our study, in addition to others, has demonstrated the significant protective effect of poultry vaccination against HPAI H5N1 outbreaks [14,74–76]. Although the vaccination campaign in Bangladesh has successfully reduced the recorded number of outbreaks, it has not

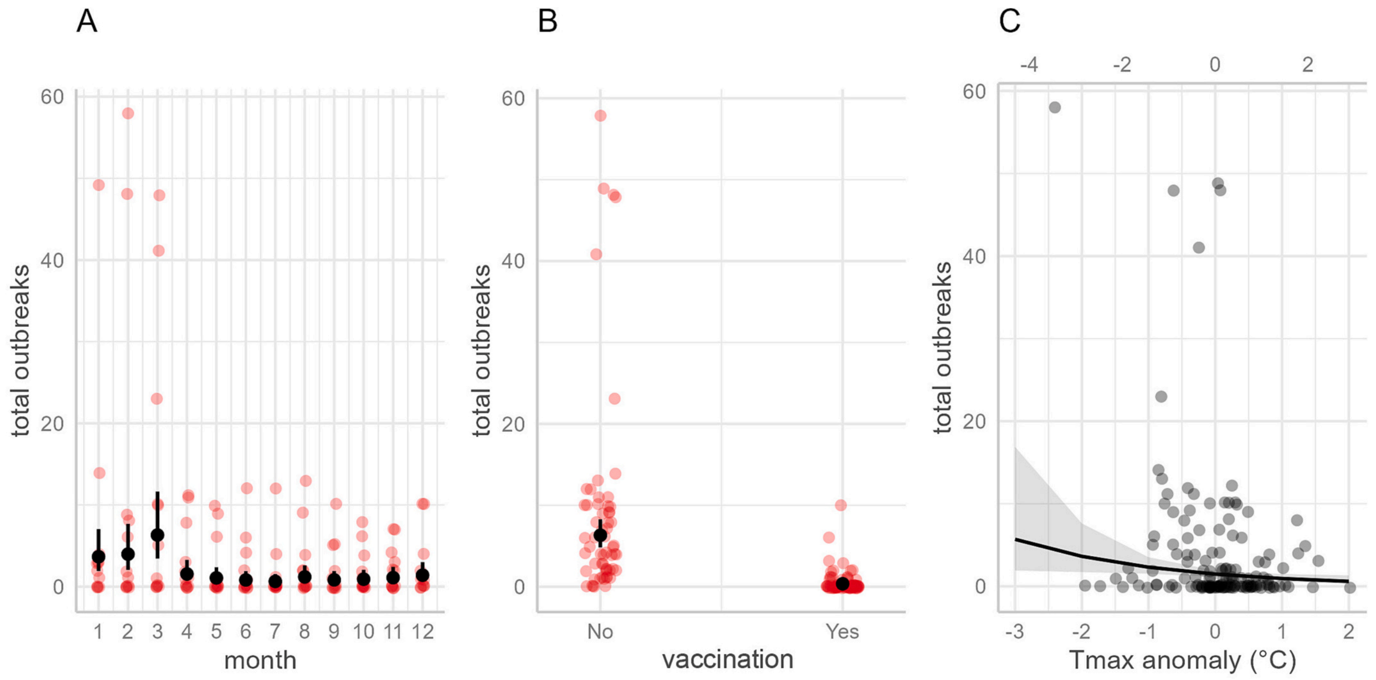

Fig. 4. Marginal means for explanatory variables that significantly explain variation in the number of monthly HPAI H5N1 outbreaks across Bangladesh. In panels A and B, the average marginal means (black dots) and their 95% confidence intervals (black bars) are plotted for month and vaccination, respectively, with the original data corrected for all other effects plotted for reference (pink dots). In panel C, the regression line (in black) and its 95% confidence interval (grey shading) are plotted for the anomaly of the maximum temperature (bottom axis in °C and scaled top axis). The original data corrected for all other effects are plotted for reference (grey dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

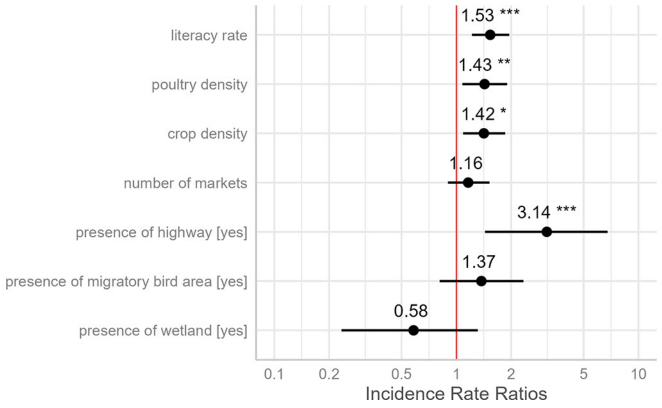

Fig. 5. Incidence Rate Ratios (± 95% CI) of HPAI H5N1 outbreaks as a function of four scaled co-variates (literacy rate, chicken density, crop density number of markets) and three binary, categorical explanatory variables (presence of highway, presence of migratory bird staging area and presence of significant wetland). The reference for the estimated probabilities is formed by the absence of the last three features and the averages of the four covariates (i.e., red vertical line). Literacy rate, chicken density, crop density, and the presence of highways are significantly associated with an increase in outbreaks at the district level (* < 0.05, ** < 0.01, *** < 0.001). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

sufficiently controlled the circulation of H5N1, considering that year-round detection of the virus is still observed in both poultry and wild birds around the country [77,78]. Even in farms with adequate biosecurity practices, vaccinated commercial poultry are still frequently shown to be shedding HPAI H5N1 virus [77]. Similar circumstances have been observed in Egypt and Mexico, where the H5N1 virus has developed into multiple antigenically distinct subclades and has become enzootic following the rollout of vaccination against HPAI H5N1 [79,80]. These unintended effects of vaccination are due to the vaccine providing inadequate protection against infection, in such cases when the vaccination leads to a reduction in disease symptoms only. This phenomenon may result in "silent spread" and promote further virus evolution [16]. Unvaccinated birds, notably wild birds, may become the victims of such a process, which may explain the observed increase in outbreaks amongst house crows in Bangladesh after 2012 (Fig. 1A) [81,82].

Despite the risk of silent spread, vaccination of poultry can still be a very important component of comprehensive HPAI mitigation strategies, provided it is accompanied by monitoring to verify that vaccination results in sufficient protection against infection and not only protection against disease. In case flocks are found infected, the virus should be stamped out to stop the spread. This means that vaccination should also be accompanied by improved farm and LBM biosecurity practices to reduce the chance of infection, even in vaccinated populations [8,83]. Additionally, vaccination against H5N1 in Bangladesh is currently focused on commercial chicken farms, while 9.7% of HPAI outbreaks are reported in backyard chickens [8]. Furthermore, domestic ducks appear to be an important host reservoir and may play a central role in the maintenance, amplification, and spread of HPAI viruses in Bangladesh [84,85]. Extending the vaccination campaign to domestic ducks and backyard chickens may therefore be essential for controlling AIV in Bangladesh.

Spillover from poultry into wild mammals, which has been observed in the current H5N1 clade 2.3.4.4b outbreaks in the United States, is of particular concern as it may facilitate viral adaptation to mammalian hosts – a necessary step towards causing a human epidemic [86,87]. Although the urgency for action to fight the current HPAI panzootic and limit the risks of spillovers into humans is high, the associated risk of silent spread explains why vaccination of chickens against HPAI H5N1 is the subject of global controversy. This is also one of the key reasons why the EU, while increasingly being open to adequate and safe vaccination of poultry as a complementary intervention by its member states, is only allowing for doing so in combination with biosecurity measures and

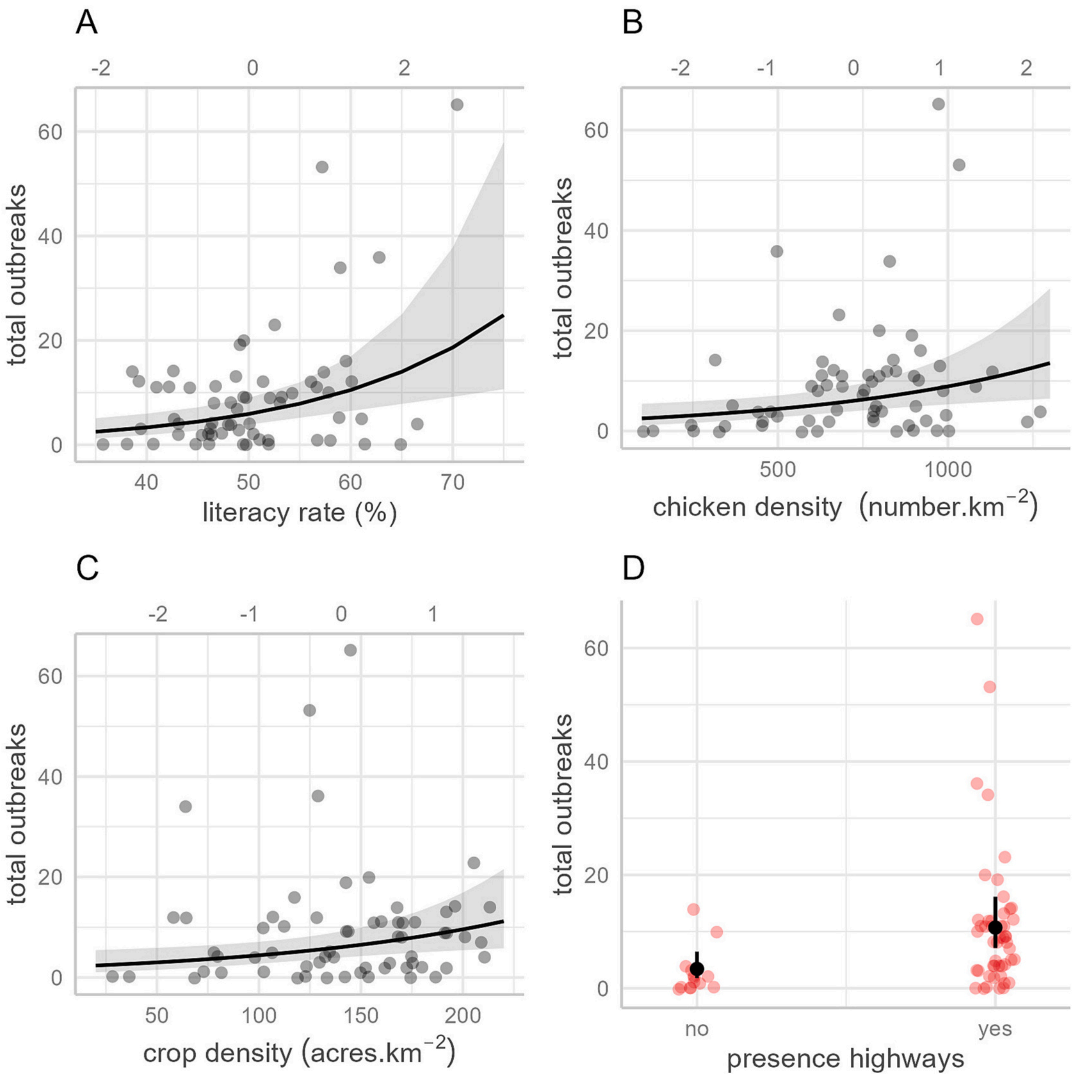

Fig. 6. Marginal means for explanatory variables that significantly explain variation in the number of HPAI H5N1 outbreaks in each of the districts across Bangladesh. In panels A, B, and C, the regression line (in black) and its 95% confidence interval (grey shading) are plotted for the literacy rate (bottom axis in % and scaled top axis), chicken density (bottom axis in km^{-2} and scaled top axis) and crop density (bottom axis in km^{-2} and scaled top axis). The original data corrected for all other effects are plotted for reference (grey dots). In panel D, the average marginal means (black dots) and their 95% confidence intervals (black bars) are plotted for the presence of highways, respectively, with the original data corrected for all other effects are plotted for reference (pink dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

appropriate monitoring of the vaccinated poultry flocks [88], which will avoid silent spread.

4.2. Meteorological and seasonal effects

Of the environmental factors investigated, the season had the strongest significant effect on outbreak risk, with the summer months (May–November) having a lower rate of outbreaks than most winter months. This may be partly explained by the purported role of temperature in influenza transmission. Although studies on environmental drivers of HPAI outbreak risk have been conducted in Bangladesh previously, these were limited in longitudinal scope, representing two to five years of data, and were conducted prior to the start of the vaccination campaign [31,52]. Consistent with findings from the literature [89,90], we detected a protective effect of temperature on outbreak risk, where a higher maximum temperature anomaly was associated with a reduction in outbreak incidence. We identified a distinct yearly seasonal trend, with a single peak of H5N1 occurring from November to March. Similar annual peaks in HPAI outbreaks have been observed in other tropical and subtropical regions of Asia, like Indonesia, Egypt, and Vietnam [38,91]. However, biannual influenza prevalence peaks have also been reported in countries such as India [92] and Thailand [23]. Our finding of summer months having a 2–3 times lower incidence rate than most winter months supports the finding that spillover of HPAI H5N1 into humans is more than three times higher during the winter and spring months than during the autumn and summer months [93].

In Bangladesh, the months between November and March coincide with the lowest ambient temperatures, relative humidity, cloud cover, and wind speed (Fig. 2). While all these factors have previously been considered to have an impact on HPAI prevalence (Table 1), only lower temperatures were thought to promote HPAI prevalence, while the inverse has been predicted for relative humidity, cloud cover, and wind speed. By demonstrating that the maximum temperature anomaly had a protective effect on HPAI H5N1 outbreak rate (i.e., relatively low temperatures for the time of year had a positive effect on outbreak risk), our findings suggests that the seasonal effect on HPAI outbreaks in Bangladesh may indeed be causally linked to temperature. Many studies have similarly shown that lower temperatures increase the probability of outbreak occurrence [94–98]. The mechanisms behind this effect may include higher replication rates [99] and survival [35,99,100] of AIV at lower ambient temperatures. The seasonal patterns that we detected in HPAI H5N1 outbreak risk did not correspond to the effects of relative humidity, cloud cover, and wind speed that we collated from the literature. The anomalies for relative humidity (which itself was highly correlated with cloud cover) and wind speed had no significant effect on outbreak risk (Fig. 3). The discrepancy between our findings and those in other studies that did find an effect of humidity [101,102] and wind speed [103] may be due to the strong effects of vaccination and temperature within our data set. However, it should also be noted that previous studies occasionally found contrasting effects on AIV prevalence for both humidity [47,48] and wind speed [103], suggesting that these effects may either vary in interaction with other drivers or are due to spurious correlations (see for Fig. SM1 for examples of high correlations between various weather factors).

4.3. Socio-economic and ecological effects

As many as four of the seven socio-economic and ecological factors tested for significantly explained the variation in HPAI H5N1 outbreak rate across the districts in Bangladesh. To our surprise, we noted that districts with a higher literacy rate had a significantly higher rate of outbreaks. The veterinary authority in Bangladesh primarily relies on farmers to report high morbidity and mortality in their flocks. What might serve as an explanation for this finding is that increased literacy may be associated with public awareness of the disease and facilitate the reporting of suspected outbreaks.

Our study also revealed that an increase in chicken density was associated with an increase in the rate of HPAI H5N1 outbreaks at the district level, which aligns with findings in Vietnam [104]. However, we should note that we observed a high correlation ($r = 0.799$) between chicken and domestic duck densities across the districts (Fig. SM2), meaning that this effect may be due to either chicken density, duck density, or both. Given that domestic ducks may act as an important reservoir for HPAI H5N1 [105,106], it is conceivable that high duck densities are associated with an increased outbreak rate. As an alternative explanation for the effect of chicken density on outbreak risk, Table 1 indicates that greater densities of poultry increase the risk of contact with potentially infected poultry due to a more elaborate network of trading and other farming-related activities. In this, it should be considered that the spread of disease is not only due to the movement of sick birds but also contaminated chicken products and equipment [107]. It would be valuable to investigate these variables further to isolate the true relationship, considering that these two drivers would inform different control strategies.

Road infrastructure may also promote the spread of HPAI H5N1 by facilitating the movement of infected birds or contaminated equipment and feed between farms within a district. We found that the presence of major highways was significantly associated with the rate of HPAI H5N1 outbreaks at the district level. Importantly, these highways also promote traffic to distant farms (in other districts) and trading facilities, boosting the size of the network and increasing connectivity. Previous studies also confirmed the role that road infrastructure might play in HPAI H5N1 dispersal, both in Bangladesh ([41] and elsewhere in Southeast Asia [58,62]. Connectivity, coupled with poor biosecurity and disease surveillance, would plausibly account for within-district and between-district spread of H5N1.

Finally, we found crop density to significantly correlate with HPAI H5N1 outbreak risk. The production of backyard poultry in rural areas, whether chicken or free-ranging ducks, is closely associated with rice cultivation in Bangladesh and other parts of Southeast Asia [31,108]. Crop density may thus be considered a proxy for densities of backyard poultry, which are typically not vaccinated. Previous studies in Thailand, Vietnam, and Taiwan [33,108,109] acknowledged the potential significance of free-ranging ducks and rice agriculture in contributing to HPAI epidemiology. The number of live bird markets in a district and the presence/absence of wetlands and migratory bird staging areas all had a non-significant effect on the rate of outbreaks within districts. These findings are seemingly in contrast with the literature. For instance, it has been confirmed in many studies that live bird markets are of profound significance in the maintenance and spread of HPAI [110–112]. However, LBMs are omnipresent in all districts, and it is only the variation in the number of markets and not their presence/absence that we investigated here. Similarly, in many previous studies, wild waterbirds, and migratory bird staging areas in particular, have been assigned an important role in the maintenance and dissemination of HPAI [63]. Our results do not necessarily refute that the proximity of wild bird habitats and the birds themselves play a role in the epidemiology of HPAI. Rather, our results may suggest that if wild birds have a role, that role is likely relatively limited compared to the other factors we investigated. One of the limitations of this study is the dependence on passive surveillance in Bangladesh, wherein the identification of potential outbreaks of HPAI H5N1 mostly relies on the reporting of chicken mortality by poultry farmers to the local veterinary hospital [113]. The potential for underreporting of clinical cases cannot be ruled out due to concerns regarding culling and the absence or insufficiency of compensating measures for poultry farmers.

5. Conclusions

Here we presented a comprehensive analysis of the role of vaccination and a set of meteorological, socio-economic, and ecological factors on the incidence of HPAI H5N1 outbreaks in Bangladesh. The study revealed significant and strong impacts of vaccination and season on outbreak incidence, with slightly lesser but still significant effects of temperature and a range of socioeconomic factors. These factors are important in developing and implementing HPAI mitigation strategies in Bangladesh and possibly other regional countries. For instance, our study highlights the importance of designing surveillance strategies for HPAI H5N1 outbreaks as a climate-sensitive disease and increasing biosecurity awareness during winter. The role of highway networks as a contributing factor to the spread of HPAI justifies the significance of tracking poultry transports and setting transportation limits to curb the spread, as earlier suggested by Rivas, Chowell [114]. Although not explicitly researched here, our findings suggest that supporting increased literacy, public education, and awareness campaigns aimed at farmers might also improve early detection and shorten response times to contain HPAI-H5N1 outbreaks. While vaccination resulted in a dramatic decrease in HPAI H5N1 outbreaks in poultry, we highlighted that the virus might continue to circulate in vaccinated flocks with few signs of sickness [115], resulting in further evolution, increased spillover risk into wild birds and mammals, and ultimately, endemicity [116]. This considerable threat as a result of inadequate vaccination warrants a reassessment of the vaccination policy in Bangladesh and calls for great scrutiny when planning on implementing it elsewhere in the world. It is imperative that any implementation of vaccination should, at a minimum, be accompanied by careful monitoring to guarantee that vaccination results in a decrease in infection rate and not (only) a decrease in disease symptoms.

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Ethical approval

No ethical consideration was required as the study uses open-source datasets.

CRediT authorship contribution statement

Ariful Islam: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Validation, Software, Writing – original draft. **Sarah Munro:** Methodology, Validation, Writing – review & editing. **Mohammad Mahmudul Hassan:** Methodology, Writing – review & editing, Supervision. **Jonathan H. Epstein:** Methodology, Resources, Funding acquisition, Supervision, Project administration, Writing – review & editing. **Marcel Klaassen:** Conceptualization, Formal analysis, Visualization, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors assert that they have no commercial or financial connections that could be seen as a conflict of interest with the research.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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