Seasonality of influenza and coseasonality with avian influenza in Bangladesh, 2010–19: a retrospective, time-series analysis

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Summary

Background Seasonal and avian influenza viruses circulate among human and poultry populations in Bangladesh. However, the epidemiology of influenza is not well defined in this setting. We aimed to characterise influenza seasonality, examine regional heterogeneity in transmission, and evaluate coseasonality between circulating influenza viruses in Bangladesh.

Methods In this retrospective, time-series study, we used data collected between January, 2010, and December, 2019, from 32 hospital-based influenza surveillance sites across Bangladesh. We estimated influenza peak timing and intensity in ten regions using negative binomial harmonic regression models, and applied meta-analytic methods to determine whether seasonality differed across regions. Using live bird market surveillance data in Dhaka, Bangladesh, we estimated avian influenza seasonality and examined coseasonality between human and avian influenza viruses.

Findings Over the 10-year study period, we included 8790 human influenza cases and identified a distinct influenza season, with an annual peak in June to July each year (peak calendar week 27·6, 95% CI 26·7–28·6). Epidemic timing varied by region (I^2=93·9%; p<0·0001), with metropolitan regions peaking earlier and epidemic spread following a spatial diffusion pattern based on geographical proximity. Comparatively, avian influenza displayed weak seasonality, with moderate year-round transmission and a small peak in April (peak calendar week 14·9, 95% CI 13·2–17·0), which was out of phase with influenza peaks in humans.

Interpretation In Bangladesh, influenza prevention and control activities could be timed with annual seasonality, and regional heterogeneity should be considered in health resource planning. Year-round avian influenza transmission poses a risk for viral spillover, and targeted efforts will be crucial for mitigating potential reassortment and future pandemic threats.

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Introduction

The epidemiology of influenza is well defined in many temperate regions, with annual seasonal epidemics occurring during the winter months.[1] However, influenza seasonality is not as well characterised in tropical and subtropical climate regions globally. Key parameters of interest include periodicity (ie, epidemic frequency), phase angle (ie, epidemic peak timing), and amplitude (ie, seasonal strength), which can be used to measure the peak timing and intensity of annual or semi-annual influenza seasons.[2] Robust data on influenza seasonality are also crucial for supporting guidance on prevention and control efforts, such as optimal vaccine timing, particularly since treatment for influenza infection remains suboptimal and is costly to national health-care systems.[3]

In Bangladesh, the burden of influenza is moderately high, with an estimated annual incidence of 458 cases per 100 000 people and six to 11 influenza-associated deaths per 100 000 people across all age groups.[4,5] Bangladesh does not have a national influenza immunisation policy and vaccine uptake remains low;[6] however, vaccine campaigns have been recommended for specific high-risk subgroups including Hajj pilgrims.[7] Previous studies have reported a distinct seasonal influenza pattern in Bangladesh,[8,9] but long-term trends and subnational heterogeneity in seasonality have not been examined. A better understanding of regional influenza transmission patterns in Bangladesh could be used to bolster the development of immunisation policies, direct appropriate health resource planning and facility preparedness, and support diagnostic and treatment approaches.

Examining influenza seasonality not only in humans, but also in animals such as poultry and swine, is important for understanding zoonotic risk.[10] In Bangladesh, sporadic avian influenza outbreaks in poultry have been reported since 2007 and avian influenzas are endemic in live bird markets.[11] In Bangladesh, more than 90% of poultry products are marketed through live bird markets and

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Research in context

Evidence before this study

We searched PubMed with no language restrictions for studies published from database inception to Dec 7, 2021, that reported on the seasonality of influenza or avian influenza in humans or poultry in Bangladesh. Using the search terms "(influenza OR avian influenza OR bird flu) AND (seasonality OR coseasonality) AND (Bangladesh)", we identified 63 studies, of which 27 contained information on influenza seasonality or burden in Bangladesh. Several studies reported on the burden of human influenza and cocirculation with other respiratory viruses in Bangladesh, including COVID-19 and respiratory syncytial virus. Five studies examined human influenza seasonality across multiple countries in south and southeast Asia, and three were single-site studies in Bangladesh. In general, these studies noted diversity in national influenza epidemic timing across south Asia, with epidemic peaks in Bangladesh occurring broadly between May and September. In addition to seasonality, two studies reported on correlation or associations between environmental factors and influenza epidemics. Six studies reported on avian influenza burden and seasonality in domestic and wild poultry. Only one study examined influenza seasonality in humans in Bangladesh at the subnational level and coseasonality with avian influenza, but this study covered a short time span and relied on passive avian influenza surveillance. All studies used descriptive statistics to examine seasonality, which do not robustly account for non-stationarity over time and cannot capture multiyear trends. To our knowledge, no robust long-term studies of influenza and avian influenza seasonality and coseasonality exist for Bangladesh.

Added value of this study

This 10-year, retrospective, time-series study characterised influenza seasonality and timing at the subnational level in Bangladesh. Using robust time-series methods, we modelled seasonality in ten regions spanning all of Bangladesh, and identified heterogeneity in influenza epidemic timing and season intensity. Although at the national level influenza peaked in early July, we found that subnational influenza epidemics are spatially structured and peak earlier in metropolitan areas. We also characterised seasonality of avian influenza based on active environmental surveillance efforts in live bird markets in Dhaka, Bangladesh. Avian influenza did not display a strong seasonal trend and instead had moderate year-round transmission, with a small peak in April. We note that although influenza peaks in humans and poultry do not coincide, year-round avian influenza transmission continues to pose a substantial risk for viral reassortment and novel influenza strain emergence in Bangladesh.

Implications of all the available evidence

Characterising influenza seasonality is crucial to inform prevention and control efforts, including optimal vaccine timing and health resource planning. The national and subnational peak timings estimated in our study could be used by clinical and public health officials to direct resources for health facility preparedness in accordance with local influenza epidemics, which is particularly important in Bangladesh as there is currently no national vaccination policy. Examining coseasonality between human and avian influenza viruses is also important and can support risk assessments for viral reassortment and pandemic influenza threats.

surveys have reported that over 50% of the urban population regularly visit these markets.[12] Therefore, live bird markets are an important source of exposure to avian influenzas and for potential influenza viral reassortment if seasonal influenza is concurrently circulating in humans. Comparing influenza and avian influenza seasonal transmission dynamics in humans and poultry and identifying whether there is overlap in epidemic peak timings can help characterise risks for novel strain emergence and direct targeted prevention measures.[10]

Using time-series methods, we aimed to characterise the timing and intensity of influenza seasonality in humans, examine regional heterogeneity in seasonal influenza transmission patterns, and evaluate coseasonality with avian influenzas in Bangladesh over the 10-year period comprising January, 2010 to December, 2019.

Methods

Influenza surveillance datasets

Human influenza data were obtained from two sentinel surveillance systems: the hospital-based influenza surveillance (HBIS) and the national influenza surveillance Bangladesh (NISB), which span the country's eight divisions. Standardised surveillance protocols for case recruitment and testing have been described elsewhere.[5,8] Briefly, on one or two randomly selected days each week, surveillance physicians enrolled patients with influenza-like illness (defined as measured fever ≥38°C and cough with onset in the previous 10 days) from hospital outpatient departments. Additionally, patients with severe acute respiratory infection (SARI; defined as subjective or measured fever ≥38°C and cough with onset in the previous 10 days and requiring hospitalisation) were enrolled from inpatient departments. Nasopharyngeal and oropharyngeal swabs were collected from each patient. Samples were tested at the laboratories of the Institute of Epidemiology, Disease Control and Research and the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) by real-time RT-PCR to identify influenza and, if positive, types and subtypes. Over the study period, 32 hospitals across the country contributed to the influenza surveillance network; however, the number of hospitals participating and the testing efforts varied over time (appendix pp 2–3).

See Online for appendix

Avian influenza data were obtained from environmental surveillance operated by the UN Food and Agriculture Organization and the Bangladesh Department of Livestock Services in live bird markets in North and South Dhaka City Corporations (DCC). Routine, active, market-level avian influenza surveillance commenced in January, 2016, and here we report on data available from January, 2016, to December, 2019. Detailed live bird market sampling and surveillance protocols have been described previously.[13] Briefly, each month, environmental surveillance officers collected samples from around 110 live bird markets across DCC. Within each live bird market, three work areas were sampled—poultry arrival, poultry slaughtering and processing, and consumer exposure and sales—and area-specific swabs were pooled. All pooled samples were tested for influenza at the Bangladesh Livestock Research Institute by RT-PCR; if a sample pool was positive, it was further subtyped.

Our analyses focus on the study period January, 2010, to December, 2019 (inclusive), for seasonal influenza and January, 2016, to December, 2019 (inclusive), for avian influenza, given the improvement in surveillance quality after the A(H1N1)pdm09 influenza pandemic in 2009 and before the large-scale impacts of the COVID-19 pandemic in 2020.[14]

This study received ethics approval from the University of Toronto (protocol number 38902), the Institute of Epidemiology Disease Control and Research (IRB/2019/11), and the London School of Hygiene & Tropical Medicine (reference 17661). At the time of surveillance enrolment, participants or legal guardians provided written informed consent for data collection; the present study used deidentified data obtained from these surveillance databases.

Statistical analysis

Influenza data across all regions were aggregated by month and year, and the number of samples tested (or live bird markets sampled), number of positive results, and the influenza types and subtypes were described. To examine regional variation in human influenza seasonal characteristics, we grouped the HBIS and NISB surveillance sites into ten regions by geography, as follows: the eight administrative divisions of Bangladesh with Chattogram divided into north and south regions, and DCC as its own region (appendix p 2). Avian influenza surveillance data were missing for six consecutive months in DCC, and human influenza data were missing for three consecutive months in Mymensingh and Chattogram North regions (appendix p 4). A Poisson regression imputation method accounting for monthly and annual trends was used to impute data for missing months in each region; imputed datasets were used for all harmonic regression analyses.

We used harmonic regression models[15] to estimate the timing and strength of the influenza peak in each region. In each a priori specified model, we adjusted for linear and quadratic terms and included an offset term for the number of monthly samples tested to control for temporal trends and surveillance changes over time (eg, changes in surveillance effort or size of population under surveillance [which was unknown]). We examined both Poisson and negative binomial models; mean and variance estimates and model goodness-of-fit statistics suggested over-dispersion of influenza case counts (appendix p 7). Therefore, we fitted negative binomial generalised linear models with harmonic terms to time series from each region separately, as follows:

$$Y(t) \sim nbinomial(\lambda_t)$$

$$\ln(\lambda_t) = \beta_0 + \beta_1 sin\left(\frac{2\pi t}{12}\right) + \beta_2 cos\left(\frac{2\pi t}{12}\right) + \beta_3 t + \beta_4 t^2 + ln(n_t) + \varepsilon$$

where Y(t) is the monthly count of combined influenza A and B positive samples, t is the running index for month beginning January, 2010, and $ln(n_t)$ is the log-transformed monthly number of samples tested (ie, offset term). The harmonic sine and cosine terms correspond to a 12-month period of oscillation, as supported by preliminary examination using wavelet analysis and autocorrelation functions (appendix pp 5–6).[16] The coefficients from each regional harmonic regression model were used to calculate the amplitude and phase angle of the influenza season. The amplitude was calculated as $sqrt(\beta_1^2 + \beta_2^2)$. We present exponentiated amplitude estimates, which reflect the ratio between the annual influenza peak and mean, where smaller values indicate weaker seasonality and larger values indicate stronger seasonality. The phase angle was calculated as $-atan(\beta_1/\beta_2)$, which was then converted from radians to weeks using standardised methods as described by Naumova and colleagues.[15] We calculated 95% CIs for seasonal estimates using a seasonal block bootstrap with 1000 replicates, to preserve the autocorrelation structure of the time series.[17]

Subsequently, we pooled region-specific estimates of amplitude and peak timing using a random-effects meta-analytic model to calculate national estimates. Between-region heterogeneity of seasonal estimates were examined using Cochran's Q and I^2 statistics.[18] Given evidence of heterogeneity, we constructed a meta-regression model to examine whether spatial variability in seasonal characteristics was explained by distance from DCC (distance in km; calculated as the regional mean of the distances from the centroids of each hospital's district to the centroid of DCC). Meta-regression models were weighted by the inverse of the variance of region-specific seasonal estimates. As a sensitivity analysis, pooled estimates were also calculated using a negative binomial generalised linear mixed model with trend and harmonic terms as fixed effects and random intercepts for region to jointly fit to all ten regions. In addition to seasonal parameters, we also estimated indicators of seasonal onset and end for each

	Seasonal influenza in humans						Avian influenza in live bird markets			
	Tested, n	Influenza positive, n (%)*	Influenza subtype				Tested, n	Influenza positive, n (%)*	Influenza subtype	
			Total A, n (%)†	A(H1N1), n (%)†‡	A (H3), n (%)†	Total B, n (%)†‡			A (H5), n (%)†	A (H9), n (%)†
Overall	60 906	8790 (14·4%)	5478 (62·3%)	2671 (30·4%)	2788 (31·7%)	3332 (37·9%)	4359	2274 (52·2%)	1411 (62·0%)	1191 (52·4%)
2010	4367	696 (15·9%)	355 (51·0%)	253 (36·4%)	101 (14·5%)	342 (49·1%)	..	..	..	..
2011	4694	547 (11·7%)	287 (52·5%)	16 (2·9%)	268 (49·0%)	261 (47·7%)	..	..	..	..
2012	5328	810 (15·2%)	434 (53·6%)	369 (45·6%)	64 (7·9%)	376 (46·4%)	..	..	..	..
2013	3863	637 (16·5%)	509 (79·9%)	156 (24·5%)	354 (55·6%)	128 (20·1%)	..	..	..	..
2014	5440	762 (14·0%)	394 (51·7%)	6 (0·8%)	386 (50·7%)	373 (49·0%)	..	..	..	..
2015	6018	722 (12·0%)	678 (93·9%)	522 (72·3%)	154 (21·3%)	45 (6·2%)	..	..	..	..
2016	7086	957 (13·5%)	414 (43·3%)	14 (1·5%)	398 (41·6%)	549 (57·4%)	1251	818 (65·4%)	493 (60·3%)	385 (47·1%)
2017§	7193	1164 (16·2%)	855 (73·5%)	507 (43·6%)	346 (29·7%)	311 (26·7%)	620	405 (65·3%)	303 (74·8%)	225 (55·6%)
2018	7117	685 (9·6%)	571 (83·4%)	462 (67·5%)	115 (16·8%)	114 (16·6%)	1250	654 (52·3%)	480 (73·4%)	428 (65·4%)
2019	9800	1810 (18·5%)	981 (54·2%)	366 (20·2%)	602 (33·3%)	833 (46·0%)	1238	397 (32·1%)	135 (34·0%)	153 (38·5%)

*Proportion of total tested. †Proportion of total influenza-positive cases. ‡Includes 20 samples co-infected with influenza A and B. §2017 is missing 3 months of human influenza data in two regions, and 6 months of avian influenza live bird market data.

Table 1: **Influenza cases detected through hospital-based sentinel surveillance in Bangladesh, 2010–19, and avian influenza detected through live bird market surveillance in Dhaka City Corporation, 2016–19**

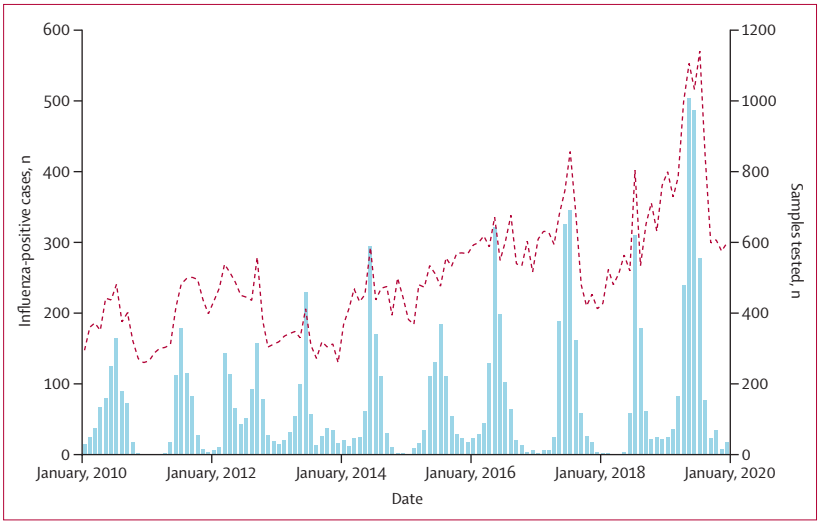


Figure 1: **Monthly time series of influenza cases and samples tested from hospital-based sentinel surveillance in Bangladesh, 2010–19**
Bars indicate the monthly number of positive influenza cases. The dashed line indicates the monthly number of samples tested.

region, defined as the first month in which model-based estimates of influenza activity exceed (ie, onset) and fall below (ie, end) the mean annual influenza positivity.

To examine coseasonality between human and avian influenza, we restricted the HBIS and NISB surveillance sites to the DCC region for the period 2016–19 to align with the live bird market surveillance. Correlation between monthly counts of avian influenza-positive live bird markets and influenza-positive patients was assessed visually using wavelet coherence analysis, which displays correlation between non-stationary time series.[19] Negative binomial harmonic regression models were then used to estimate the peak timing and amplitude of influenza in humans and avian infleunza in live bird markets in DCC for this period, with 95% CIs calculated for each using seasonal block bootstrapping.[17] Coseasonality in epidemic peak timing was examined by calculating the difference in phase angle between the human and avian influenza estimates.

In sensitivity analyses, we used the original surveillance datasets with missing values and conducted zero-inflated negative binomial harmonic regression models to account for the excess zeros. All analyses were done in Stata version 16.0 and R version 4.1.0; spatial analyses were done in QGIS version 3.12.

Results

Between January, 2010, and December, 2019, 60 906 samples were tested, with 8790 (14·4%) positive for influenza (table 1). Most positive cases were influenza A (62·3%), and influenza B accounted for about a third of cases (37·9%). The largest proportion of influenza A cases were the pandemic A(H1N1)pdm09 strain, followed by A(H3) strains. The proportion of influenza-positive cases remained fairly consistent over time (ie, 2010–19), but there were differences in circulating influenza types by year, with 2015 being influenza A dominant (93·9%) and 2016 being influenza B dominant (57·4%; table 1). Despite changes in surveillance sites within the study period (appendix p 3), testing generally increased over time. There was a consistent annual peak in influenza positivity each year (figure 1), and wavelet analysis and autocorrelation functions indicated a significant 12-month oscillatory period (appendix pp 5–6).

The number of surveillance sites varied by region, as did the sampling intensity, with the greatest mean annual number of tests done in the Rajshahi region

	Distance from DCC, km	Hospital sites, n	Mean annual tests, n	Mean annual influenza positive, n (%)	Peak timing*, calendar week		Amplitude*	
					Estimate	95% CI	Estimate	95% CI
Bangladesh† overall	..	32	6090·6	879·0 (14·4%)	27·6‡	26·7–28·6	3·74§	3·25–4·30
Barisal	136	3	724·9	98·2 (13·5%)	28·4	27·9–29·1	4·69	4·14–5·63
Chattogram (north districts)	110	2	454·9	59·8 (13·1%)	27·3	26·4–28·4	2·75	2·46–3·25
Chattogram (south districts)	239	4	565·7	84·2 (14·9%)	26·3	25·6–27·1	4·82	3·99–5·93
Dhaka	50	4	890·0	142·7 (16·0%)	27·2	26·6–28·0	2·85	2·58–3·19
DCC	0	2	368·8	37·3 (10·1%)	24·3	23·5–25·3	4·42	3·84–5·72
Khulna	146	4	794·9	128·3 (16·1%)	29·3	28·7–29·9	4·40	3·91–5·13
Mymensingh	118	2	238·3	37·4 (15·7%)	27·3	25·8–28·8	2·66	2·29–3·33
Rajshahi	168	5	1037·7	141·1 (13·6%)	29·4	28·9–30·0	3·97	3·55–4·54
Rangpur	256	4	478·8	74·9 (15·6%)	28·9	28·1–29·7	3·94	3·35–4·72
Sylhet	159	2	584·3	82·6 (14·1%)	27·9	27·1–28·6	3·83	3·31–4·54

DCC=Dhaka City Corporation. *Jurisdiction-specific estimates were calculated using negative binomial regression models with harmonic terms adjusted for linear and quadratic trend, and an offset for samples tested. 95% CIs were estimated using 1000 block-bootstrapped samples. A Poisson regression imputation method was used to impute data for jurisdictions with missing monthly data. †Pooled estimate for Bangladesh calculated using random-effects meta-analytic model of jurisdiction-specific estimates. ‡Heterogeneity for pooled peak timing, I^2=93·9%; p<0·0001. §Heterogeneity for pooled amplitude, I^2=88·4%; p<0·0001.

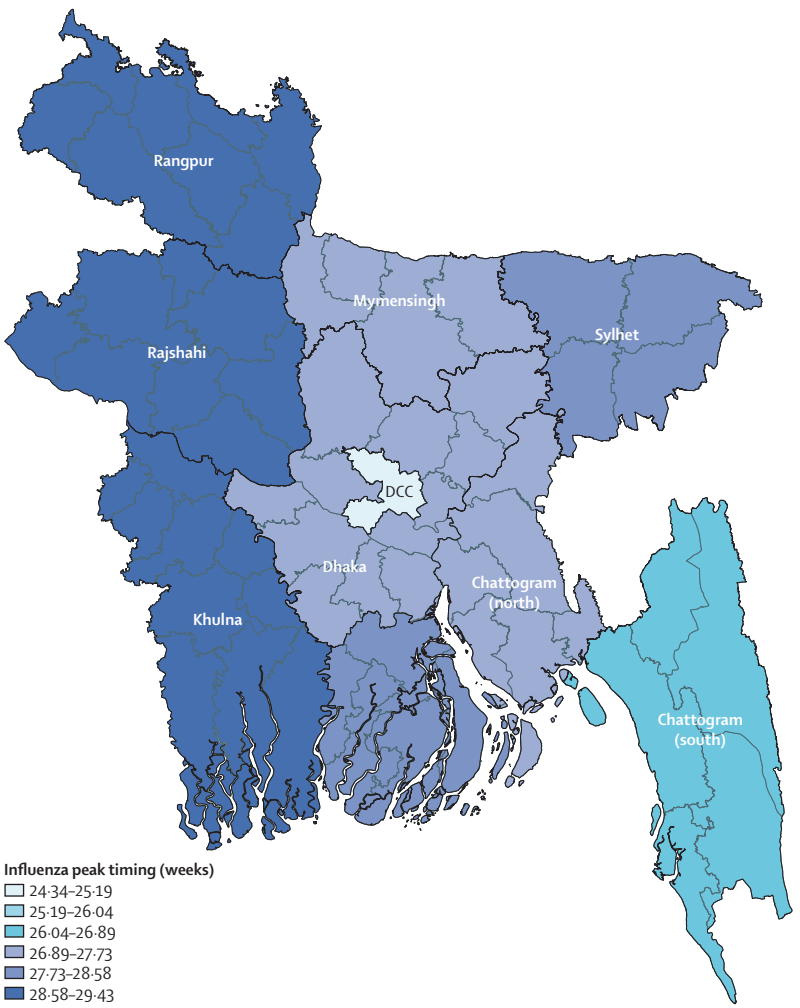
Table 2: **Influenza surveillance characteristics, sampling intensity, and seasonality estimates across ten regions in Bangladesh, 2010–19**

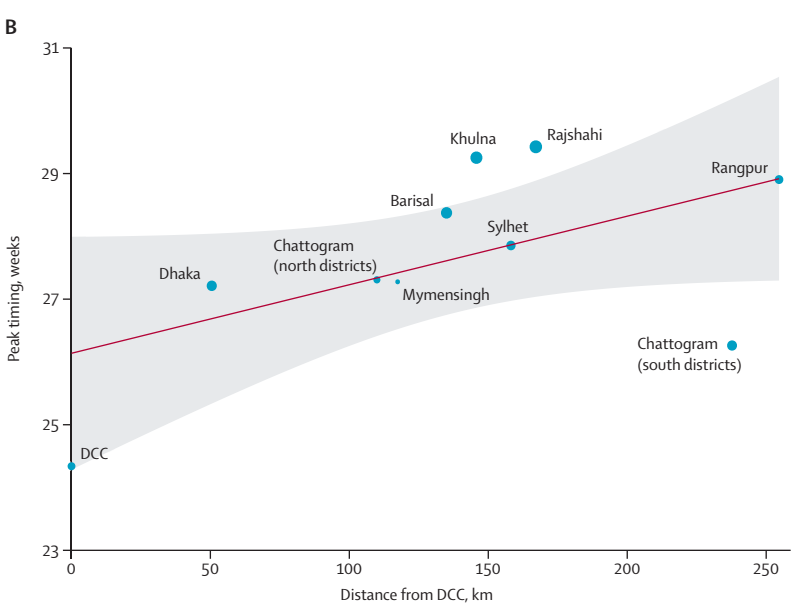
(n=1037·7 tests per year; table 2) and the least in Mymensingh (238·3 tests per year). The mean annual influenza positive proportion was similar across regions (table 2). Seasonal estimates indicated that influenza was concentrated in the monsoon season in all regions, with influenza peaking in mid-June in DCC (peak calendar week 24·3, 95% CI 23·5–25·3) to late-July in Rajshahi (29·4, 28·9–30·0; table 2). Influenza showed strong annual periodicity across regions, with the strongest seasonality (ie, greatest amplitude) in Chattogram south districts (amplitude 4·82, 95% CI 3·99–5·93) and moderate seasonality in Mymensingh (2·66, 2·29–3·33; table 2). When pooled across the region-specific estimates, there was significant heterogeneity in both influenza peak timing (pooled peak calendar week 27·6, 95% CI 26·7–28·6; I^2=93·9%; p<0·0001) and seasonality (pooled amplitude 3·74, 95% CI 3·25–4·30; I^2=88·4%; p<0·0001; table 2). Across Bangladesh, DCC had the earliest epidemic timing, with epidemic spread generally following a spatial diffusion pattern based on geographical proximity and peaking latest in the western part of the country (figure 2A). In exploratory meta-regression, greater distance from DCC, measured in km, was associated with later epidemic peak timing, although this was not statistically significant (coefficient 0·01, 95% CI 0·00–0·02; p=0·071; figure 2B). We found no association between influenza amplitude and distance from DCC (p=0·299). Estimates of seasonal onset and end, as well as the proportion of influenza activity during seasonal, interseasonal, and peak periods are included in the appendix (p 8).

In terms of avian influenza, 4359 live bird market samples were tested between January, 2016, and December, 2019. 2274 (52·2%) live bird market samples were positive for avian influenza, but the proportion of positive markets decreased over time with 818 (65·4%) positive in 2016 down to 397 (32·1%) positive in 2019 (table 1). Subtypes identified in live bird markets included A(H5) and A(H9), with A(H5) being predominant but both subtypes circulating each year (table 1). There was moderate year-round avian influenza circulation (figure 3; appendix p 5), which contrasts with the distinct annual peak observed in human influenza positivity in DCC. Seasonal estimates for DCC indicated a small avian influenza peak in early April (peak calendar week 14·9, 95% CI 13·2–17·0); however, there was very weak seasonality (amplitude 1·17, 95% CI 1·13–1·22; table 3). The corresponding epidemic peak timing for human influenza in DCC during this period was mid June (peak calendar week 24·4, 95% CI 23·4–25·5), with intense seasonality (amplitude 7·64, 95% CI 5·75–13·1; table 3). Peak timing of avian influenza in live bird markets was out of phase with peak timing of influenza in humans, with a phase difference of 9·4 weeks (95% CI 8·6–10·2; table 3). Correlation between avian influenza in live bird markets and influenza cases in humans was not significant over time (appendix p 7). Results for peak timing and amplitude from region-specific zero-inflated models and pooled estimates from mixed-effects models remained robust in sensitivity analyses (appendix p 9).

Discussion

In this study, we applied time-series methods to multi-year laboratory-confirmed influenza surveillance data to examine regional epidemic timing and intensity in Bangladesh. We identified a distinct annual seasonal pattern, with influenza activity peaking between June and July each year. Our results suggest that influenza epidemics are spatially structured, beginning earlier in central Bangladesh and spreading radially to neighbouring





regions over the following months. We also characterised avian influenza seasonality in live bird markets and found a weak seasonal pattern, with a small peak in April. Although seasonal influenza and avian influenza peaks do not coincide, evidence of year-round avian influenza circulation increases the possibilities for co-circulation of influenza viruses, co-infections in a population that is known to have high exposure to live poultry on a regular basis,[12] and viral reassortments, which could generate novel influenza strains with pandemic potential.[10]

The strong, annual seasonality of human influenza epidemics identified in our 10-year study aligns with results from shorter-term studies in Bangladesh.[8,9] Unlike some tropical and subtropical regions in Asia, which report biannual peaks,[1] we identified a single, consistent epidemic influenza peak during the summer monsoon season. This contrasts with seasonality in neighbouring countries, including India, which reports semi-annual peaks in January to February and June to July,[20] and Thailand, which reports peaks in February and June to August.[21] Compared with winter-time environmental drivers of influenza activity reported in temperate settings (eg, low absolute humidity and low temperature),[22] the correlation between annual influenza peaks and the monsoon season in this subtropical setting suggests that distinct drivers are at play. Although not examined here, further work could explore whether these differences are due to other environmental factors (eg, precipitation) or reflect changes in population behaviour during the monsoon season that mirror the behaviours of populations in temperate settings during winter months. Additionally, despite being geographically located in the northern hemisphere, influenza epidemic timing in Bangladesh aligns with calendar peaks of southern hemisphere countries.[23] These geographical differences in influenza seasonality have implications for not only vaccine timing but also potentially for vaccine composition.[6] Furthermore, studies have noted changes in influenza seasonality during the COVID-19 pandemic both in Bangladesh and in general;[14] however, continued surveillance is needed to examine whether these changes will result in sustained seasonal shifts in the post-pandemic years. Analyses using phase–phase and phase–amplitude synchronisation could also be done to provide more nuanced understanding of disease synchronisation over time, including by influenza strain.

A novel finding in our study was the significant heterogeneity in influenza epidemic peak timing by

Figure 2: **Regional variation in annual influenza epidemic peak timing in Bangladesh, 2010–19**
(A) Regional variation in influenza epidemic peak calendar week. Darker shades indicate later influenza peak calendar week. (B) The distance from DCC is plotted against influenza epidemic calendar week for each region. Marker size is proportional to the inverse variance of the region-specific estimate. The solid line represents a weighted regression line estimated from a meta-regression model. The shaded area represents the 95% CI for the weighted regression estimate. DCC=Dhaka City Corporation.

region within Bangladesh. Similar regional heterogeneity in influenza seasonality has been reported in countries such as Brazil, China, and the USA.[2,24,25] We identified a spatial diffusion pattern, with regions further from DCC reporting later influenza epidemic peaks. The exception was the region we defined as Chattogram south districts, which also peaked in June despite being a greater distance away from DCC. This finding could be due to Chattogram having the second most populous metropolitan centre (Chittagong City Corporation) in Bangladesh and strong travel links between these two densely populated urban centres.[8] Further work examining epidemic timing by regional demographic factors, such as population size and density, could help explain these patterns. The epidemiology of influenza and other respiratory viruses, such as respiratory syncytial virus, in the USA displays similar trends with highly synchronised epidemics beginning in large population centres and spreading radially to other regions.[25,26] Transmission dynamic modelling studies have also identified that population mobility (eg, due to religious festivals such as Eid al-Fitr) plays an important role in the epidemic spread of influenza in Bangladesh,[27] as well as for other seasonal diseases such as malaria and chikungunya.[28,29] Therefore, regional heterogeneity could be an important consideration in the future development of national immunisation policies (eg, permitting staggered vaccine delivery), and might be a useful assessment in other subtropical global regions.

In contrast to influenza seasonality in humans, we found that avian influenza in live bird markets showed weak seasonality, with moderate year-round transmission. Although our findings suggest that avian influenza has a modest yearly peak in April, which does not coincide with the June influenza epidemic peak in humans, there does continue to be transmission throughout the year, with over 40% of markets reporting avian influenza positive samples in June. This finding contrasts with previous studies, which have reported distinct avian influenza seasons out of phase with human influenza.[8] One reason for this difference could be that previous studies have reported seasonality based on passively reported poultry outbreaks,[8,10] whereas we measured seasonal characteristics using active surveillance in live bird markets. Although not the focus of our study, this work highlights the importance of active surveillance in live bird markets[13] to better understand avian influenza transmission dynamics. We observed a reduction in avian influenza positive markets over the study period, which could be due to ongoing intervention efforts. Avian influenza circulation continues to have important implications for viral reassortment and pandemic risk, particularly given that research has shown that in DCC over 50% of the population visits live bird markets, and almost 75% of people have regular exposure to live poultry.[12]

Our study has some limitations. Although the availability and robustness of human influenza surveillance data has

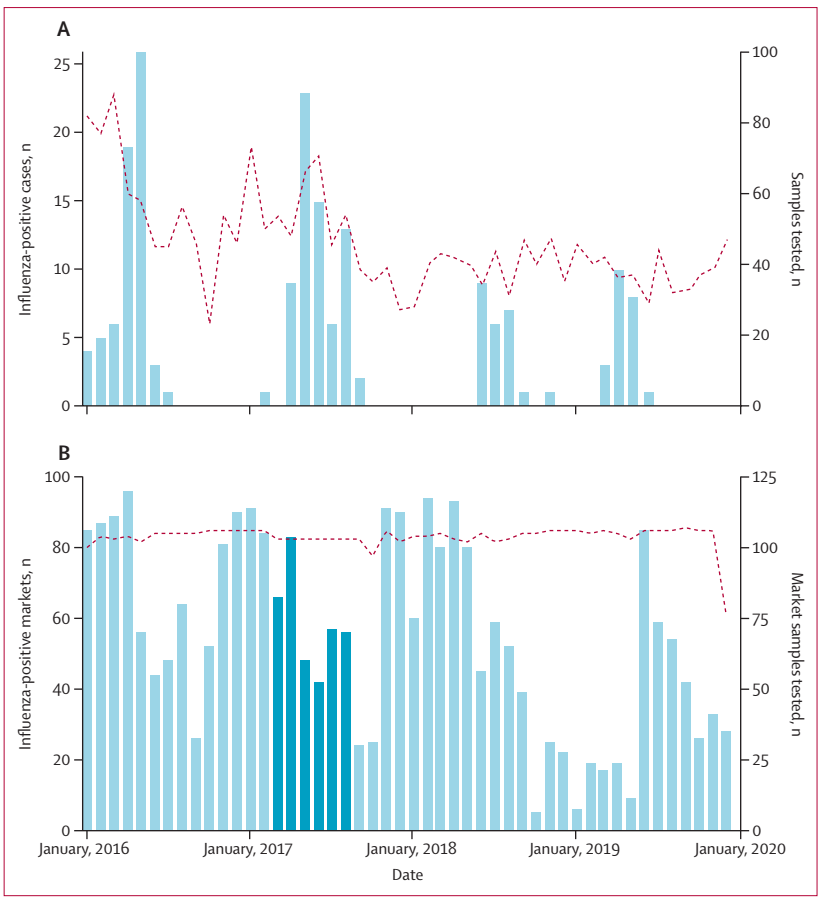


Figure 3: **Seasonal influenza in humans and avian influenza in poultry in Dhaka City Corporation, 2016–19**
(A) Monthly time series of influenza cases and samples tested from hospital-based sentinel surveillance. (B) Monthly time series of avian influenza positive markets sampled from live bird market surveillance. Bars indicate the monthly number of positive influenza cases. The dashed line indicates the monthly number of samples tested. A Poisson regression imputation method was used to impute data for months with missing avian influenza data (dark blue bars).

	Estimate*	95% CI
Seasonal influenza in humans		
Peak timing, calendar week	24·4	23·4–25·5
Amplitude	7·64	5·75–13·1
Avian influenza in live bird markets		
Peak timing, calendar week	14·9	13·2–17·0
Amplitude	1·17	1·13–1·22
Interval difference		
Peak timing, weeks	9·4	8·6–10·2

*Estimates were calculated using negative binomial regression models with harmonic terms adjusted for linear and quadratic trend, and an offset for samples tested (humans) or markets sampled (poultry). 95% CIs were estimated using 1000 block-bootstrapped samples. A Poisson regression imputation method was used to impute data for missing monthly data.

Table 3: **Seasonality and coseasonality estimates for influenza from hospital-based sentinel surveillance and avian influenza from live bird market surveillance in Dhaka City Corporation, 2016–19**

improved since the A(H1N1)pdm09 influenza pandemic in 2009,[23] there was inconsistent reporting over time within the HBIS and NISB surveillance network. The number of regional surveillance sites varied from year to year during the study period, which impacted the number of samples tested. However, we used the monthly number of samples tested in each region as an offset in our harmonic regression models to account for these changes in surveillance efforts. There were also missing data from avian influenza time series for 6 months due to data collection and storage issues. Although we imputed data for missing periods using a Poisson process, the true influenza trends in this period are unknown; however, our results were robust to sensitivity analyses using zero-inflated negative binomial regression models. Longer-term time series would be useful to have more power to detect and verify avian influenza trends. Given variability in human surveillance sampling protocols, we aggregated data to the monthly level in all analyses, which might hide granular variability that could occur at the weekly level. However, fine-scale temporal surveillance data are not usually available and previous studies have found that these are not essential to capture temporal disease transmission patterns.[26] Hospital-based influenza-like illness and SARI surveillance is likely to capture more severe influenza cases, and patients might present later in their course of illness. Although this fact could result in delayed estimates of epidemic peak timing, the effect is probably non-differential across regions given the use of standard case definitions. Additionally, sentinel surveillance only captures a fraction of cases, and can therefore not be used to estimate the burden of disease. Finally, we did not have data to formally explore factors associated with the heterogeneous radial spread of seasonal human influenza from central Bangladesh outwards. There are a wide range of regional, climatic, and environmental (eg, precipitation, temperature, and humidity), and population level (eg, population density) factors that could be examined in meta-regression models to better understand drivers of spatial diffusion. Future work could also include the use of transmission dynamic models and phylogenetic data to further evaluate regional differences and influenza evolutionary dynamics.[30]

Despite these limitations, our study provides robust quantitative estimates for influenza in a subtropical region over a 10-year period at the subnational level. Our findings suggest that influenza epidemics in humans are highly seasonal and peak earlier in metropolitan areas. By contrast, we found that avian influenza in poultry does not show a strong seasonal trend in Bangladesh. Although influenza peaks do not coincide, year-round avian influenza transmission continues to pose a risk for viral reassortment, which suggests that Bangladesh could be a hotspot for emergence of novel influenza strains with pandemic potential. Our results support the need for more quantitative risk assessments of viral reassortment in urban Bangladesh and could be used to inform future timing of sequencing-based surveillance. Additional strategies could also include enhanced SARI surveillance throughout the year for early avian influenza detection or enhanced surveillance for mild infections among humans during periods of higher circulation in poultry.

Contributors

IB, PM, SKM, ALG, MSF, and DNF conceived and designed the study. MR, ASMA, MHK, RA, ML, TS, MAI, FC, SD, EB, MGO, MSF, and IB implemented the study and collected, collated, and verified the data. IB analysed the data and wrote the first draft of the manuscript. IB, MR, PM, SKM, ALG, MSF, and DNF contributed to writing subsequent versions of the manuscript. All authors had access to the data and critically reviewed the manuscript for important intellectual content and approved the final version. IB and DNF had final responsibility for the decision to submit for publication.

Declaration of interests

DNF has received support by a grant from the Canadian Institutes for Health Research (2019 COVID-19 rapid researching funding OV4-170360). DNF has served as a legal expert on issues related to COVID-19 epidemiology for the Elementary Teachers Federation of Ontario and the Registered Nurses Association of Ontario. DNF has served on advisory boards related to influenza and SARS-CoV-2 vaccines for Seqirus, Pfizer, AstraZeneca, and Sanofi-Pasteur vaccines. All other authors declare no competing interests.

Data sharing

According to the data policies of the contributing institutions, to protect intellectual property rights, the primary data cannot be made publicly available by the authors. The data can be made available upon reasonable request to the Institutional Data Access Committees of the contributing institutions. Requests for data can be forwarded to Research Administration at icddr,b, Dhaka, Bangladesh (aahmed@icddrb.org).

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References

1 Hirve S, Newman LP, Paget J, et al. Influenza seasonality in the tropics and subtropics—when to vaccinate? *PLoS One* 2016; **11:** e0153003.

2 Alonso WJ, Viboud C, Simonsen L, Hirano EW, Daufenbach LZ, Miller MA. Seasonality of influenza in Brazil: a traveling wave from the Amazon to the subtropics. *Am J Epidemiol* 2007; **165:** 1434–42.

3 Bhuiyan MU, Luby SP, Alamgir NI, et al. Economic burden of influenza-associated hospitalizations and outpatient visits in Bangladesh during 2010. *Influenza Other Respir Viruses* 2014; **8:** 406–13.

4 Troeger CE, Blacker BF, Khalil IA, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2019; **7:** 69–89.

5 Ahmed M, Aleem MA, Roguski K, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010–2012. *Influenza Other Respir Viruses* 2018; **12:** 65–71.

6 Hirve S, Lambach P, Paget J, Vandemaele K, Fitzner J, Zhang W. Seasonal influenza vaccine policy, use and effectiveness in the tropics and subtropics—a systematic literature review. *Influenza Other Respir Viruses* 2016; **10:** 254–67.

7 Mathai D, Shamsuzzaman AK, Feroz AA, et al. Consensus recommendation for India and Bangladesh for the use of pneumococcal vaccine in mass gatherings with special reference to Hajj pilgrims. *J Glob Infect Dis* 2016; **8:** 129–38.

8 Zaman RU, Alamgir AS, Rahman M, et al. Influenza in outpatient ILI case-patients in national hospital-based surveillance, Bangladesh, 2007–2008. *PLoS One* 2009; **4:** e8452.

9 Saha S, Chadha M, Al Mamun A, et al. Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. *Bull World Health Organ* 2014; **92:** 318–30.

10 Durand LO, Glew P, Gross D, et al. Timing of influenza A(H5N1) in poultry and humans and seasonal influenza activity worldwide, 2004–2013. *Emerg Infect Dis* 2015; **21:** 202–08.

11 Rimi NA, Hassan MZ, Chowdhury S, et al. A decade of avian influenza in Bangladesh: where are we now? *Trop Med Infect Dis* 2019; **4:** E119.

12 Berry I, Rahman M, Flora MS, et al. Frequency and patterns of exposure to live poultry and the potential risk of avian influenza transmission to humans in urban Bangladesh. *Sci Rep* 2021; **11:** 21880.

13 Chakma S, Osmani MG, Akwar H, et al. Risk areas for influenza A(H5) environmental contamination in live bird markets, Dhaka, Bangladesh. *Emerg Infect Dis* 2021; **27:** 2399–408.

14 Akhtar Z, Chowdhury F, Rahman M, et al. Seasonal influenza during the COVID-19 pandemic in Bangladesh. *PLoS One* 2021; **16:** e0255646.

15 Naumova EN, MacNeill IB. Seasonality assessment for biosurveillance systems. In: Auget J-L, Balakrishnan N, Mesbah M, Molenberghs G, eds. Advances in statistical methods for the health sciences. Boston: Birkhäuser, 2007: 437–50.

16 Johansson MA, Cummings DA, Glass GE. Multiyear climate variability and dengue--El Niño southern oscillation, weather, and dengue incidence in Puerto Rico, Mexico, and Thailand: a longitudinal data analysis. *PLoS Med* 2009; **6:** e1000168.

17 Politis DN. Resampling time series with seasonal components. Frontiers in data mining and bioinformatics: proceedings of the 33rd symposium on the interface of computing science and statistics; Orange County, California, June 13–17, 2001.

18 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327:** 557–60.

19 Cazelles B, Chavez M, Berteaux D, et al. Wavelet analysis of ecological time series. *Oecologia* 2008; **156:** 287–304.

20 Chadha MS, Potdar VA, Saha S, et al. Dynamics of influenza seasonality at sub-regional levels in India and implications for vaccination timing. *PLoS One* 2015; **10:** e0124122.

21 Suntronwong N, Vichaiwattana P, Klinfueng S, et al. Climate factors influence seasonal influenza activity in Bangkok, Thailand. *PLoS One* 2020; **15:** e0239729.

22 Shaman J, Pitzer V, Viboud C, Lipsitch M, Grenfell B. Absolute humidity and the seasonal onset of influenza in the continental US. *PLoS Curr* 2009; **2:** RRN1138.

23 Alonso WJ, Yu C, Viboud C, et al. A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation. *Sci Rep* 2015; **5:** 17214.

24 Yu H, Alonso WJ, Feng L, et al. Characterization of regional influenza seasonality patterns in China and implications for vaccination strategies: spatio-temporal modeling of surveillance data. *PLoS Med* 2013; **10:** e1001552.

25 Viboud C, Bjørnstad ON, Smith DL, Simonsen L, Miller MA, Grenfell BT. Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science* 2006; **312:** 447–51.

26 Zheng Z, Pitzer VE, Warren JL, Weinberger DM. Community factors associated with local epidemic timing of respiratory syncytial virus: a spatiotemporal modeling study. *Sci Adv* 2021; **7:** eabd6421.

27 Engebretsen S, Engø-Monsen K, Aleem MA, Gurley ES, Frigessi A, de Blasio BF. Time-aggregated mobile phone mobility data are sufficient for modelling influenza spread: the case of Bangladesh. *J R Soc Interface* 2020; **17:** 20190809.

28 Chang HH, Wesolowski A, Sinha I, et al. Mapping imported malaria in Bangladesh using parasite genetic and human mobility data. *eLife* 2019; **8:** e43481.

29 Mahmud AS, Kabir MI, Engø-Monsen K, et al. Megacities as drivers of national outbreaks: the 2017 chikungunya outbreak in Dhaka, Bangladesh. *PLoS Negl Trop Dis* 2021; **15:** e0009106.

30 Rejmanek D, Hosseini PR, Mazet JA, Daszak P, Goldstein T. Evolutionary dynamics and global diversity of influenza A virus. *J Virol* 2015; **89:** 10 993–1001.