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Title: SARS-CoV-2 and Influenza Virus Co-infection among Patients with Severe Acute Respiratory Infection During COVID-19 Pandemic in Bangladesh

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Abstract: (254/300 words)

Background: Recent evidences reported that co-infection with SARS-CoV-2 and Influenza virus is common. We explored hospital-based influenza surveillance (HBIS) data during the COVID-19 pandemic.

Methods: We analyzed data from March to December 2020 among patients admitted with severe acute respiratory infections (SARI), defined as subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days. Physicians recorded patients' demographic, clinical, and laboratory information

and obtained nasopharyngeal and oropharyngeal swabs to test for influenza virus and SARS-CoV-2 by rRT-PCR.

Results: We enrolled 1,986 SARI case-patients with a median age of 28 years (IQR: 1.2 - 53 years), and 67.6% were male. Among SARI case patients, 285 (14.3%) were infected with SARS-CoV-2 and 175 (8.8%) infected with the influenza virus. Only five (0.3%) SARI patients were co-infected with SARS-CoV-2 and influenza virus. Difficulty breathing (83% vs. 77%, p=0.024) and sore throat (26% vs. 17%, p<0.001) were more likely to be present in SARS-CoV-2-infected SARI patients. SARI case-patients with diabetes and hypertension were more likely (14% vs. 6%, p<0.001 and 27% vs. 12%, p<0.001 respectively) to be infected with SARS-CoV-2 virus than those without comorbidities. Influenza virus remained undetectable during the first 14 weeks of the 20 weeks (May to September) of peak influenza circulation period in Bangladesh.

Conclusions: Our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common together with the nonappearance of the influenza virus during most of the peak influenza period in Bangladesh during the COVID-19 pandemic. Future studies are warranted for further exploration.

Article Summary

Strengths and Limitations of the study

- The study adds baseline data about the prevalence, clinical features, and mortality following of SARS-CoV-2 and Influenza virus infection among the general population during the first wave of the COVID-19 pandemic period in 2020 in Bangladesh.
- The study also reported the disappearance of the influenza virus circulation for the first 14 weeks out of the 20 weeks of the peak season in 2020.
- The study did not screen and test for Influenza-like illnesses (ILI) in the out-patient departments whose illness was not severe enough to require hospitalization.
- The virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all.
- The study also did not document the treatment provided, health-seeking behaviors, and access to health care of the study participants, which may have confounded the estimates of in-hospital deaths and post-discharge mortality.

Introduction:

Seasonal influenza epidemics in temperate zones of the northern and southern hemispheres occur during their respective winters, November to March in the northern hemisphere and April to September in the southern hemisphere (1-4). Bangladesh is a tropical country of the northern hemisphere, but the annual seasonal influenza epidemic occurs typically during the monsoon period, i.e., from May to September (5), with influenza peak activity during July and August every year (4).

Influenza season during 2019-2020 ended very early in China compared to previous years (6), and there was a sharp decline of influenza circulation in the USA and several Asian countries (7-10) of the Northern Hemisphere. Similar observations were also reported in the Southern Hemisphere countries of Australia, Chile, South Africa, and New Zealand (11, 12). This decline in influenza virus activity might be attributed to many factors, including the substantial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a global pandemic and public health efforts to control this virus (7, 11, 12). Both Influenza and SARS-CoV-2 produce similar clinical manifestations like- fever, cough, headache, muscle and joint pain, severe malaise, sore throat, runny nose, anosmia, and ageusia (13). Furthermore, SARS-CoV-2 and influenza viruses share the common route of human-to-human transmission through aerosolized or respiratory droplets (14). Researchers have speculated about the possibilities of co-infection by both viruses since the beginning of the COVID-19 pandemic (13). Furthermore, there have been reports of co-infections during the early pandemic period (15). Yue et al. reported a high rate of co-infection of SARS-CoV-2 and influenza viruses; 49.8% for Influenza A and 7.5% for Influenza B at the initial stage of pandemic (16).

Influenza remains a major public health concern, and there is a high prevalence of comorbid conditions such as chronic respiratory or cardiovascular conditions and malnutrition, leading to an excess influenza burden (17-19) in resource-poor settings like Bangladesh. Estimates of 2011-2012 data

indicated seasonal influenza strains contributed to substantial mortality (6,097 [95% CI: 2,604-14,199] deaths in 2010-2011 and 16,804 [95% CI: 8,588- 2,5019] deaths in 2011-2012) with 60% to 80% of deaths among elderly aged >60 year (20). Together with a significant burden of Influenza in Bangladesh, on March 8, 2020, the first three laboratory-confirmed cases of SARS-CoV-2 were detected, and the SARS-CoV-2 has been circulating since then (21).

The World Health Organization (WHO) encouraged the detection of SARS-CoV-2, particularly using the Global Influenza Surveillance and Response System (GISRS) as the laboratories, sentinel sites, and reporting platforms are the same for both influenza virus and SARS-CoV-2 (22). In Bangladesh, hospital-based influenza surveillance (HBIS) has been operating as one of the components of the National Influenza Center (NIC), detecting both Influenza and SARS-CoV-2 and, among severe acute respiratory infection (SARI) case-patients and reporting to GISRS even during challenging situations of the COVID-19 pandemic. We explored this HBIS data based on SARI case patients to describe rates, clinical features, and outcomes following SARS-CoV-2, influenza virus infections, and co-infections by both viruses during the COVID-19 pandemic period in 2020.

Methods:

Surveillance sites and population: The hospital-based influenza surveillance (HBIS) system in Bangladesh was initiated in 2007 as a part of NIC and during 2020 operated in nine sites (seven public and two private) tertiary level hospitals across Bangladesh through a collaboration between the Institute of Epidemiology, Disease Control and Research (IEDCR) of the Government of Bangladesh, the International Centre for Diarrheal Diseases Research, Bangladesh (icddr,b) and the United States Centers for Disease Control and Prevention (US CDC) (23). Detailed descriptions of surveillance systems have been described elsewhere (23-26). Despite pandemic control efforts, the surveillance remained operational in inpatient departments of medicine and pediatrics wards, coronary care units, and

specialized isolation wards established during the COVID-19 pandemic. In this paper, we report findings based on the patients enrolled between March to December 2020 only.

Case identification: Since the inception of the surveillance platform, six days a week during work hours (8.30 am to 5.00 pm), study support staff and study physicians screen inpatients of medicine and the pediatric departments and coronary care units to identify case-patients with SARI, defined as subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days and requiring hospital admission. This case definition was adopted from WHO (27) and used in this surveillance to screen participants since May 2016. During the COVID-19 pandemic period from March 2020, study staff also screened for SARI case patients in specialized isolation wards where suspected and probable COVID-19 patients were admitted.

Specimen collection and laboratory analysis: Study physicians, upon written consent, collected nasopharyngeal (NP) and oropharyngeal (OP) swabs from the enrolled patients under all aseptic precautions using full personal protective equipment. Collected swabs were then stored in Nitrogen dry shippers on-site and transported to icddr,b virology lab based in Dhaka every two weeks. Viral nucleic acid was extracted from 200 µl of pooled nasopharyngeal and oropharyngeal swab samples using InviMag Virus DNA/RNA Mini Kit (Invitek, STRATEC Molecular, Berlin-Buch, Germany) on Kingfisher Flex 96 (Thermo Fisher Scientific Inc.) automated nucleic acid extraction system according to the manufacturer's instructions. NP and OP swabs undergoing laboratory analysis were tested for seasonal influenza virus A, subtypes: A(H1N1)pdm09, A (H3N2), A(H5N1), and influenza virus B, lineages: Yamagata lineage and Victoria lineage by real-time reverse transcription-polymerase chain reaction (rRT-PCR) using primers and probes supplied by the US CDC. RNA was tested for SARS-CoV-2 by rRT-PCR targeting ORF1ab- and N-gene-specific primers and probes following the protocol recommended by the Chinese Center for Disease Control and Prevention (briefly as China CDC). Amplification was carried out

using the iTaq universal probes one-step Kit (Bio-Rad Laboratories, Inc. California, USA) in a Bio-Rad CFX96TM Real-Time PCR Detection System (Bio-Rad Laboratories, Inc. California, USA).

Data Collection: The surveillance physicians performed a physical examination of enrolled patients and collected data on a standardized surveillance report form on demographics, clinical presentations, and diagnostics tests if available. Detailed information on demographic, clinical, and diagnostic variables is described in our earlier published article describing HBIS (23). We also registered the status (full recovery, partial recovery, referral to another facility, and in-hospital death) of the enrolled participant at discharge and again (alive/deceased) after 30 days of discharge. Study staff made phone calls to patient/or family members to enquire about the patient's well-being after the SARI episodes. If a participant died within 30 days post-discharge, we registered the date, place of death, and the family members' reported causes of death.

Data Analysis: We conducted descriptive analyses to describe the frequencies of SARI, influenza virus, influenza virus types, and subtypes and SARS-CoV-2 virus infection. We have analyzed through bivariate comparisons using Pearson's χ^2 tests and logistic regression to study the association of the proportion of laboratory-confirmed SARS-CoV-2 infection and Influenza with different variables. For the time between illness onset and treatment-seeking variable, we performed the Mann-Whitney U non-parametric test to determine the differences between laboratory-confirmed influenza-positive and negative cases and also SARS-CoV-2-positive and negative cases. We plotted epidemiological curves describing the monthly SARS-CoV-2 and Influenza virus circulation in Bangladesh.

Patient public involvement: We developed research questions related to influenza virus and SARS-CoV-2 detection according to the public health needs of Bangladesh. COVID-19 test results were immediately and confidentially shared with the Directorate General Health Services, Government of

Bangladesh, they in term shared them with the individual patients. Anonymized Influenza test results are regularly uploaded on WHO's GISRS platform, on IEDCR, and icddr,b websites.

Results:

Demographic and clinical characteristics: We enrolled in 1,986 SARI case-patients with a median age of 28 years (IQR: 1.2 - 53); 67.6% were males. Demographic and clinical information concerning the SARS-CoV-2 virus and influenza virus and co-infection are reported in Table 1. There were 285 (14.3%) SARI case-patients infected with SARS-CoV-2 and 175 (8.8%) SARI case-patients infected with the influenza virus. Only five (0.3%) SARI patients were co-infected with SARS-CoV-2 and influenza viruses. SARI patients of age group >60 (24% vs. 11%, p<0.001) were more likely to be infected with SARS-CoV-2 than ≤60 years of age. Alternatively, those aged >60 years (5% vs. 14%, p<0.001) were less likely to be infected with the influenza virus than those aged between ≤60 years. Males were more likely to be infected with the SARS-CoV-2 (75% vs. 66%, p=0.004) than SARS-Cov-2 noninfected cases but less likely to be infected with the influenza virus (58% vs. 69%, p=0.003) compared to influenza negative SARI cases. Median duration (± standard deviation) from illness onset to hospital visit was longer (6.0, ±2.1 days vs. 5.0, ±2.0 days, p<0.001) for SARS-Cov-2-infected SARI patients but shorter (4.0, ±1.6 days vs. 5.0, ±2.0 days, p<0.001) for Influenza virus-infected patients, compared with SARI cases without any SARS-CoV-2 and Influenza virus infection respectively. Fever and cough were present in all patients as we followed WHO SARI case definition; however, difficulty breathing (83% vs. 76%, p=0.016) and sore throat (26% vs. 17%, p<0.001) were more likely to be present in SARS-CoV-2-infected SARI patients. Difficulty breathing was less likely (66% vs. 78%, p<0.001) among Influenza virus-infected SARI cases. Runny nose was more likely (63% vs. 45%, p<0.001) to be present among Influenza virus-infected SARI cases but was less likely (28% vs. 50%, p<0.001) for SARS-CoV-2-infected ones. SARI case-patients with diabetes and hypertension were more likely (14% vs. 6%, p<0.001 and 27% vs. 12%, p<0.001

respectively) to be infected with SARS-CoV-2 virus compared to non-diabetic and non-hypertensive patients. In contrast, SARI case-patients with diabetes and hypertension were less likely (4% vs. 7%, p=0.047 and 6% vs. 14%, p<0.001 respectively) to be infected with influenza virus than those without diabetes and hypertension.

Influenza virus and SARS-CoV-2 detection: Only Influenza A(H1N1)pdm09 was detected through the surveillance system in March 2020 (epi weeks 10-14). Then from epi week-15 onwards to epi week-32 (first week of April to the second week of August), no influenza virus was detected in the surveillance system in a range of 100—300 samples tested per month during the period. Later, only Influenza A/H3N2 was detected again from epi week-33 onwards, ranging from 2% to 34% proportion positive till epi week-44 (end of October 2020). Influenza/B lineages were not detected at all in Bangladesh during the COVID-19 pandemic in 2020 (figure 1). Six weeks after SARS-CoV-2 was first detected in Bangladesh, the first case in this surveillance system was detected on epi week- 17 (April 23, 2020).

Patient status at discharge and after 30 days post-discharge: There were 31 in-hospital deaths (10%) registered among laboratory-confirmed SARS-CoV-2 cases, and in-hospital death was more likely (11% vs. 4%, p<0.001) among SARS-CoV-2 infected patients. However, for Influenza virus-infected SARI case-patients, in-hospital death was lower (3% vs. 8%, p=0.009) than Influenza negative patients. SARS-CoV-2 and influenza virus-infected case patients were more likely (33% vs. 3%, p<0.001; 68% vs. 61%, p=0.012 respectively) to be referred to other healthcare facilities than SARS-CoV-2 and Influenza virus-negative case patients, respectively. At one month post-discharge, we registered another 25 deaths (9%) in SARS-CoV-2-infected case-patients, which was significantly higher (p<0.001) compared to SARI cases without SARS-CoV-2 infection (4%). No in-hospital mortality or post-discharge mortality was registered among the five SARS-CoV-2 and Influenza virus co-infected SARI cases-patients.

Discussion

We found a very low proportion of SARS-CoV-2 and influenza virus co-infection among SARI case patients. Early studies reported a similarly low proportion of co-infection with influenza virus in the US (0.9%) and China (0.4%) (15, 28, 29). However, later studies from larger cohorts reported a higher proportion (52%) of influenza virus infection among laboratory-confirmed SARS-CoV-2 infected cases and 20% co-infection with other respiratory pathogens in China and the USA, respectively. However, they did not report the clinical prognosis among the co-infected cases (28, 30). Following the clinical course of SARI patients was beyond the scope of our study, and furthermore, with only the five cases of SARS-CoV-2 and influenza virus co-infection, our findings were inadequate to draw inference whether co-infected cases had worse off clinical prognosis or not. Future studies on larger cohort and clinical prognosis of co-infected patients are warranted.

During the 20 weeks (May to September) of peak influenza circulation time in Bangladesh, we did not detect any circulating influenza for the first 14 weeks of the peak season. Several public health control efforts in Bangladesh were undertaken from mid-March epi (week -13) to control the COVID-19 pandemic (31). Notable ones included: closure of educational institutes, suspension of any political, religious, social, and cultural gathering including state public program and events, closure of transport services including domestic and international flights, and finally closure of all public and private offices except for hospitals, kitchen markets, drug stores, and emergency services. A general holiday was issued from March 26 and extended a number of times till May 30 with mass communications regarding social distancing, wearing face masks, and frequent hand washing messages (31). With the emergence of the SARS-CoV-2 virus in Bangladesh in the first week of March 2020, the Influenza virus seemed to have disappeared and was not detected from the first week of April. The first reported case of Influenza was from another study in Bangladesh on epi-week 29 of 2020(32), which was detected four weeks ahead of

this surveillance platform. In Bangladesh, there is no routine vaccination for Influenza (33, 34). Since both SARS-CoV-2 and Influenza viruses have similar modes of transmission through respiratory and contact routes (35), these public health pandemic control efforts may have completely limited the transmission of influenza virus circulation in Bangladesh during its peak season. Similar marked influenza circulation reductions were also reported in Singapore, Thailand, China and Taiwan, and New Zealand during the COVID-19 pandemic citing as a collateral effect of pandemic control measures as the predominant cause (7-10, 12).

Since we enrolled all SARI cases, fever and cough were common in all SARS-CoV-2 infected patients, together with difficulty breathing and sore throat as significant clinical features. During the early pandemic period, Chinese researchers reported fever and cough to be the most prevalent symptoms (36). Also, a meta-analysis during the early pandemic period reported difficulty breathing (46%) as the most prevalent symptom after fever (89%) and cough (58%) (37). Our findings were consistent with these reported findings. Regarding demographics, elderly aged >60 years were likely to get infected with SARS-CoV-2 infection. Older age has been considered a significant risk factor for COVID-19 disease in early reports from China (38). In our study, males were also more likely to be infected. Our findings are consistent with findings from Italy (39) and also from National level data of Bangladesh (21), where more males being infected were reported than females. We found diabetes and hypertension as significant comorbid conditions among SARS-CoV-2 infected patients. Comorbid conditions with diabetes and hypertension are the most frequently reported comorbidities for COVID-19 in reports from China(38, 40) and the US (41). Therefore, it is highly recommended that elderly people with diabetes and hypertension take necessary precautions to protect against SARS-CoV-2 infection (42).

Our in-hospital mortality proportion was much lower than in other parts of the world during the start of the pandemic. Early retrospective studies among three cohorts from China reported 12%, 17%,

and 28% in-hospital mortality (43-45) while another study from the USA reported 24% in-hospital mortality among laboratory-confirmed SARS-CoV-2 infection cases (43). We could not find any literature comparing our 30 days' post-discharge mortality, which was 9% of the laboratory-confirmed SARS-CoV-2 infection cases. Considering the low number of deaths (in hospital n=31 and post-discharge n=25), we were unable to identify any demographic or clinical characteristics that are likely to play a significant role in determining mortality both in-hospital or during post-discharge. More extensive formative studies are recommended to better understand context-specific factors that may influence survival status following SARS-CoV-2 infection in Bangladesh.

Limitations to acknowledge were not screening and testing for Influenza-like illnesses (ILI) in the out-patient departments whose illness was not severe enough to require hospitalization. Secondly, using a specific WHO case definition of SARI probably made it more likely to miss actual COVID-19 cases, which might have had either fever or cough as the only presenting symptom. Thirdly, the virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all. All the above may be accountable for having minimal estimates of influenza/SARS-CoV-2 detections. Our study did not document the treatment provided, health-seeking behaviors, and access to health care of the study participants, which may have confounded the estimates of in-hospital deaths and post-discharge mortality. Furthermore, associating these deaths to SARS-CoV-2/influenza virus infection alone was not possible as verbal autopsies were not performed.

In conclusion, our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common in Bangladesh and had less disease severity considering mortality. There was an apparent reduction of influenza virus circulation during most of the peak influenza season in Bangladesh. Studies exploring possible causes of the marked decrease of influenza virus infections during the COVID-19

pandemic are warranted to better understand the association of COVID-19 pandemic and reduction of influenza virus infection.

Author's contributions:

ZA was the lead in implementing this study, wrote the paper and performed data analysis. The protocol was drafted by FC, ZA, MAI, SMM, MuR, MZR and MaR. MAI and SMM also contributed in implementing the study and writing this paper. MKA contributed for project implementation and managed data. PKG developed data visualization and was responsible for statistical analyses. MuR, MZR, MKS and MMR performed laboratory analysis. TS, AA, SB and MaR provided critical feedback in implementing and writing this paper. FC provided overall guidance in implementing this study and in writing this paper.

Data availability:

Data generated during the study are subject to a data access policy of icddr,b and are available from icddrb's research administration on reasonable request through the corresponding author.

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Conflict of interest disclosure:

The authors have disclosed that no competing interests exist.

Ethics approval and consent to participate

The study was approved by the icddr,b institutional review board prior to enrolling participants, US CDC's Human Research Protection Office approved a continuing reliance on the icddr,b IRB. Informed written consent to participate in the study was obtained.

References

1. Hampson AW. Vaccines for pandemic influenza. The history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. Annals Academy of Medicine Singapore. 2008;37(6):510.
2. Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environmental health perspectives. 2011;119(4):439-45.
3. Azziz Baumgartner E, Dao CN, Nasreen S, Bhuiyan MU, Mah-E-Muneer S, Mamun AA, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. The Journal of infectious diseases. 2012;206(6):838-46.
4. Saha S, Chadha M, Al Mamun A, Rahman M, Sturm-Ramirez K, Chittaganpitch M, et al. Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. Bulletin of the World Health Organization. 2014;92:318-30.
5. Zaman R, Alamgir ASM, Rahman M, Azziz-Baumgartner E, Gurley E, Sharker Y, et al. Influenza in Outpatient ILI Case-Patients in National Hospital-Based Surveillance, Bangladesh, 2007–2008. PloS one. 2009;4:e8452.
6. Liu M, Deng L, Wang D, Jiang T. Influenza activity during the outbreak of coronavirus disease 2019 in mainland China. Biosafety and Health. 2020.
7. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerging infectious diseases. 2020;26(8):1933.
8. Suntronwong N, Thongpan I, Chuchaona W, Budi Lestari F, Vichaiwattana P, Yorsaeng R, et al. Impact of COVID-19 public health interventions on influenza incidence in Thailand. Pathogens and Global Health. 2020:1-3.
9. Lei H, Xu M, Wang X, Xie Y, Du X, Chen T, et al. Nonpharmaceutical interventions used to control COVID-19 reduced seasonal influenza transmission in China. The Journal of infectious diseases. 2020;222(11):1780-3.
10. Kuo S-C, Shih S-M, Chien L-H, Hsiung CA. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. Emerging infectious diseases. 2020;26(8):1928.

11. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, et al. Decreased influenza activity during the covid-19 pandemic—United States, Australia, Chile, and South Africa, 2020. Morbidity and Mortality Weekly Report. 2020;69(37):1305.
12. Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nature communications. 2021;12(1):1-7.
13. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet. 2020;395(10236):e84.
14. Antony SJ, Almaghlouth NK, Heydemann EL. Are coinfections with COVID-19 and influenza low or underreported? An observational study examining current published literature including three new unpublished cases. Journal of medical virology. 2020;92(11):2489-97.
15. Zheng X, Wang H, Su Z, Li W, Yang D, Deng F, et al. Co-infection of SARS-CoV-2 and Influenza virus in Early Stage of the COVID-19 Epidemic in Wuhan, China. The Journal of Infection. 2020.
16. Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. J Med Virol. 2020;92(11):2870-3.
17. Nicholson KG WJ, Zambon M. Influenza. Lancet. 2003;362(9397):1733-45.
18. Nair M, Prabhakaran D. Why do South Asians have high risk for CAD? Global Heart. 2012;7(4):307-14.
19. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. The Lancet. 2007;368(9554):2211-8.
20. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and Other Respiratory Viruses. 2017.
21. Organization WH. COVID-19 Bangladesh situation reports: World Health Organization; 2020 [Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who_covid-19-update_41_20201207.pdf?sfvrsn=d21baace_7.
22. Organization WH. GISRS sentinel surveillance for COVID-19: frequently asked questions (FAQ), 31 July 2020. World Health Organization; 2020.
23. Zaman RU, Alamgir A, Rahman M, Azziz-Baumgartner E, Gurley ES, Sharker MAY, et al. Influenza in outpatient ILI case-patients in national hospital-based surveillance, Bangladesh, 2007–2008. PloS one. 2009;4(12):e8452.
24. Azziz-Baumgartner E, Alamgir A, Rahman M, Homaira N, Sohel BM, Sharker M, et al. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008-2010. Bulletin of the World Health Organization. 2012;90:12-9.
25. Homaira N, Luby SP, Alamgir A, Islam K, Paul R, Abedin J, et al. Influenza-associated mortality in 2009 in four sentinel sites in Bangladesh. Bulletin of the World Health Organization. 2012;90:272-8.
26. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and other respiratory viruses. 2018;12(1):65-71.
27. Organization WH. Global epidemiological surveillance standards for influenza. Edited by Influenza WHOWGESSf Geneva, Switzerland: World Health Organization. 2013.
28. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. Jama. 2020;323(20):2085-6.
29. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza: a report from Iran. 2020.

30. Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China. Int J Infect Dis. 2020;96:683-7.
31. Organization WH. Coronavirus disease (COVID-2019) Bangladesh situation report # 4 2020 [updated 24-03-2020. Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who-ban-covid-19-sitrep-04.pdf?sfvrsn=69b6d931_8.
32. Akhtar Z, Chowdhury F, Aleem MA, Ghosh PK, Rahman M, Rahman M, et al. Undiagnosed SARS-CoV-2 infection and outcome in patients with acute MI and no COVID-19 symptoms. Open Heart. 2021;8(1).
33. Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M. Seasonal influenza vaccine dose distribution in 195 countries (2004–2013): little progress in estimated global vaccination coverage. Vaccine. 2015;33(42):5598-605.
34. 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 and other respiratory viruses. 2016;10(4):254-67.
35. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet (London, England). 2020;395(10236):e84.
36. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-93.
37. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
38. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8.
39. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. Jama. 2020;323(14):1335-.
40. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
41. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. Morbidity and mortality weekly report. 2020;69(15):458.
42. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN comprehensive clinical medicine. 2020:1-8.
43. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.

Table 1: Demographic and Clinical Characteristics of SARI case-patients with SARS-CoV-2 and influenza virus infection in Bangladesh during March-December 2020

	SARS-CoV-2 virus infection			*Influenza virus infection*			*Co-infection with Influenza and SARS-CoV-2*		
Characteristics	**positive, N = 285 n (%)**	**negative, N = 1,701 n (%)**	**p value**	**positive, N = 175 n (%)**	**negative, N = 1,811 n (%)**	**p value**	**positive, N = 5 n (%)**	**negative, N=1,981 n (%)**	**p value**
Age									
0-60 Years	218 (76.5)	1,510 (88.8)	Ref.	166 (94.9)	1562 (86.3)	Ref.	5 (100)	1723 (87.0)	Ref.
>60 Years	67 (23.5)	191 (11.2)	**<0.001**	9 (5.1)	249 (13.7)	**0.001**	0	258 (13.0)	0.387
Median age (IQR), years	50 (38-60)	20 (09-50)	**<0.001**	11 (1.0-35)	30 (1.3-55)	**<0.001**	33.4 (14-58)	29.2 (1.2-53)	0.763
Sex									
Male	214 (75.1)	1,129 (66.4)	**0.004**	101 (57.7)	1,242 (68.6)	**0.003**	3 (60.0)	1,340 (67.6)	0.715
Mean temperature (range), ℃ Celsius	39.1 (38.3 -40.6)	39.0 (37.9 - 41.1)	0.260	39.0 (38.3-40.0)	39.0 (37.9-41.1)	0.331	38.9 (38.3-39.4)	39.0 (37.9-41.1)	0.683
Median days from illness onset to hospital visit, (±SD)	6.0 (±2.1)	5.0 (±2.0)	**<0.001**	4 (±1.6)	5 (±2.1)	**<0.001**	4.0 (±1.9)	5.0 (±2.0)	0.937
Clinical features (symptoms)									
Runny nose	81 (28.4)	849 (49.9)	**<0.001**	110 (62.9)	820 (45.3)	**<0.001**	2 (40.0)	928 (46.8)	0.759
Headache	141 (49.5)	562 (33.0)	0.575	51 (29.1)	652 (36.0)	0.490	2 (40.0)	701 (35.4)	0.911
Sore throat	75 (26.3)	282 (16.6)	**<0.001**	38 (21.7)	319 (17.6)	0.177	0	357 (18.0)	0.295
Difficulty breathing	235 (82.5)	1292 (76)	**0.016**	115 (65.7)	1412 (78.0)	**<0.001**	4 (80.0)	1523 (76.9)	0.869
Underlying chronic conditions									
One or more	138 (48.4)	445 (26.2)	0.246	37 (21.1)	546 (30.1)	0.535	2 (40.0)	581 (26.1)	0.842
Asthma	12 (4.2)	71 (4.2)	0.300	10 (5.7)	73 (4.0)	0.507	1 (20.0)	82 (4.1)	0.080
COPD	3 (1.1)	31 (1.8)	0.788	3 (1.7)	31 (1.7)	0.822	0	34 (1.7)	0.806
Diabetes	40 (14.0)	101 (5.9)	**<0.001**	7 (4.0)	134 (7.4)	**0.047**	0	141 (7.1)	0.629
Hypertension	76 (26.7)	195 (11.5)	**<0.001**	10 (5.7)	261 (14.4)	**0.001**	1 (20.0)	270 (13.6)	0.642
Others	8 (2.8)	49 (2.9)	0.438	6 (3.4)	51 (2.8)	0.876	0	57 (2.9)	0.752

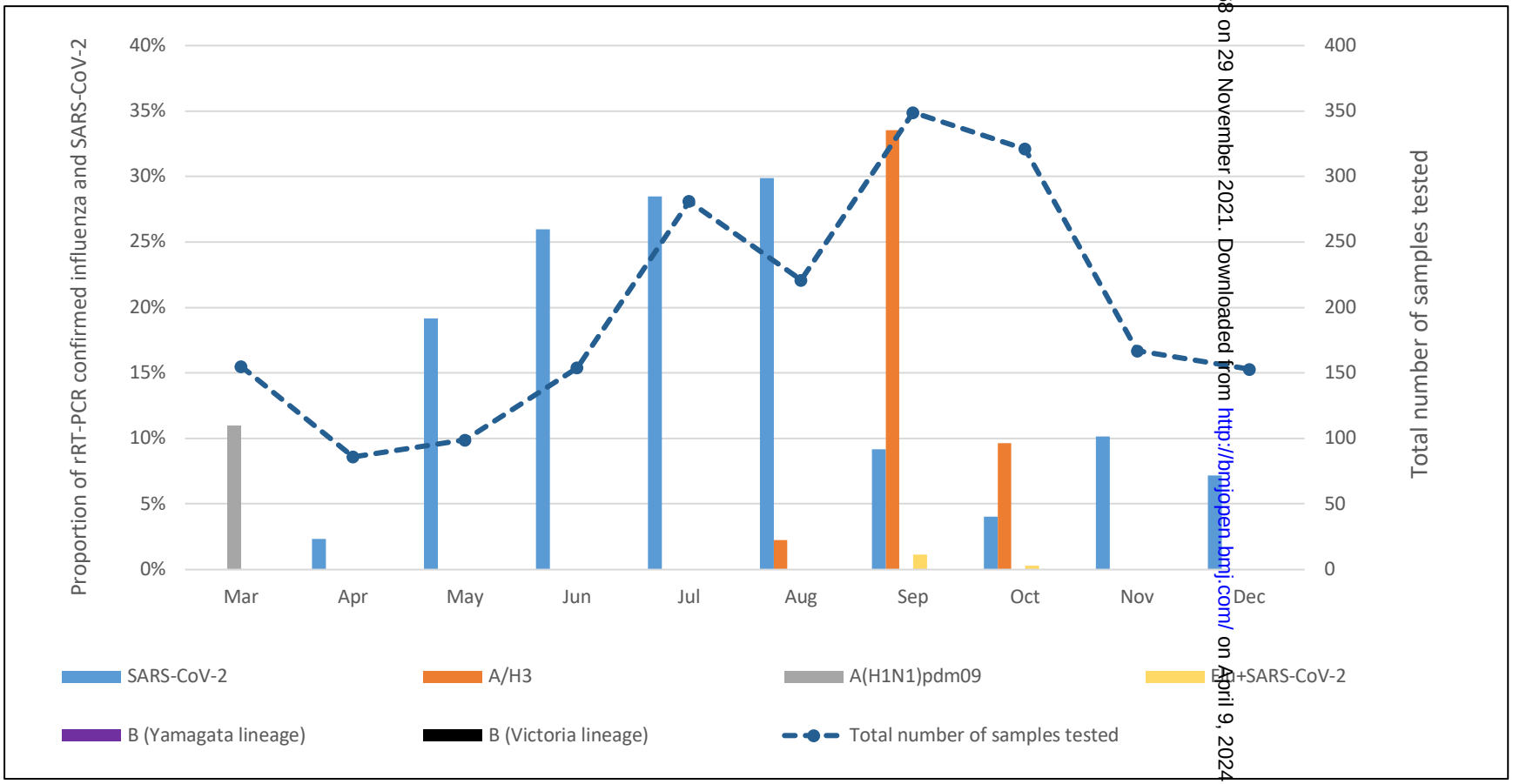
*Bold fonts are statistically significant <0.05

Table 2: Discharge and one-month post-discharge outcomes among SARI case-patients with SARS-CoV-2 and Influenza Virus infection during March – December 2020 in Bangladesh

	SARS-CoV-2 virus infection			Influenza virus infection			Co-infected with Influenza and SARS-CoV-2		
	positive, N = 285 n (%)	negative, N =1,701 n (%)	p value	positive, N = 175 n (%)	negative, N=1,811 n (%)	p value	positive, N = 5 n (%)	negative, N=1,981 n (%)	p value
Condition during Discharge									
Fully recovered	13 (4.6)	487 (28.6)	Ref.	49 (28.0)	454 (25.1)	Ref.	1 (20.0)	499 (25.2)	Ref.
Partially recovered	146 (51.2)	1081 (63.6)	**<0.001**	49 (28.0)	451 (24.9)	0.946	3 (60.0)	1224 (61.8)	0.867
Referred	95 (33.3)	58 (3.4)	**<0.001**	119 (68.0)	1108 (61.2)	**0.012**	1 (20.0)	152 (7.7)	0.328
In–hospital Death	31 (10.9)	75 (4.4)	**<0.001**	5 (2.9)	148 (8.2)	**0.009**	0	106 (5.4)	0.709
Post discharge mortality after one month									
Death	25 (8.8)	74 (4.4)	**0.001**	4 (2.3)	95 (5.2)	0.069	0	99 (5.0)	0.586

*Bold fonts are statistically significant <0.05

Figure 1: SARS-CoV-2, Influenza virus and Co-infection during March - December 2020 among SARI case patients in Bangladesh



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Title: SARS-CoV-2 and Influenza Virus Co-infection among Patients with Severe Acute Respiratory Infection During the First Wave of COVID-19 Pandemic in Bangladesh: a hospital-based descriptive study

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Abstract: (297/300 words)

Objective: To estimate the proportion of SARS-CoV-2 and influenza virus co-infection among severe acute respiratory infection (SARI) cases-patients during the first wave of COVID-19 pandemic in Bangladesh.

Design: Descriptive study.

Setting: Nine tertiary level hospitals across Bangladesh.

Participants: Patients admitted as SARI (defined as cases with subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days and requiring hospital admission) case-patients.

Primary and secondary outcomes: Proportion of SARS-CoV-2 and influenza virus co-infection and proportion of mortality among SARI case-patients.

Results: We enrolled 1,986 SARI case-patients with a median age: 28 years (IQR: 1.2 - 53 years), and 67.6% were male. Among them, 285 (14.3%) were infected with SARS-CoV-2; 175 (8.8%) were infected with the influenza virus, and five (0.3%) were co-infected with both viruses. There was a nonappearance of influenza during the usual peak season (May to July) in Bangladesh. SARS-CoV-2 infection was significantly more associated with diabetes (14.0% vs. 5.9%, p<0.001) and hypertension (26.7% vs. 11.5%, p<0.001). But influenza among SARI case-patients was significantly less associated with diabetes (4.0% vs. 7.4%, p=0.047) and hypertension (5.7% vs. 14.4%, p=0.001). The proportion of in-hospital deaths among SARS-CoV-2 infected SARI case-patients were higher [10.9% (n=31) vs. 4.4% (n=75), p<0.001] than those without SARS-CoV-2 infection; the proportion of post-discharge deaths within 30 days was also higher [9.1% (n=25) vs. 4.6% (n=74), p=0.001] among SARS-CoV-2 infected SARI case-patients than those without infection. No in-hospital mortality or post-discharge mortality was registered among the five co-infected SARI case-patients.

Conclusions: Our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common and had less disease severity considering mortality in Bangladesh. There was no circulating influenza virus during the influenza peak season during the COVID-19 pandemic in 2020. Future studies are warranted for further exploration.

Article Summary

Strengths and Limitations of the study

- The study used data from a robust national surveillance system that follows the WHO recent recommended methodology and has been operational since 2007 as a part of the national influenza center of Bangladesh.
- The study adds baseline data about the prevalence, clinical features, and mortality following SARS-CoV-2 and Influenza virus co-infection among the general population during the first wave of the COVID-19 pandemic during 2020 in Bangladesh.
- SARS-CoV-2 and Influenza virus detection tests were carried out in virology laboratory of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).
- The study did not screen and test for Influenza-like illnesses (ILI) in the out-patient departments whose illnesses were not severe enough to require hospitalization.
- The virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all.

Introduction:

Seasonal influenza epidemics in temperate zones of the northern and southern hemispheres occur during their respective winters, from November to March in the northern hemisphere and April to September in the southern hemisphere (1-4). Bangladesh is a tropical country in the northern hemisphere, but the annual seasonal influenza epidemic occurs typically during the monsoon period, i.e., from May to September (5), with influenza peak activity for 12.5 weeks on average spanning from May (epi-weeks 18) and July (epi-weeks 30.5) every year (6).

Influenza season during 2019-2020 ended very early in China compared to previous years (7), and there was a sharp decline of influenza circulation in the USA and several Asian countries (8-11) of the Northern Hemisphere, including in Bangladesh (6). Similar observations were also reported in the Southern Hemisphere countries of Australia, Chile, South Africa, and New Zealand (12, 13). This decline in influenza virus activity might be attributed to many factors, including the substantial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a global pandemic and public health efforts to control this virus (6, 8, 12, 13). Both Influenza and SARS-CoV-2 produce similar clinical manifestations like- fever, cough, headache, muscle and joint pain, severe malaise, sore throat, runny nose, anosmia, and ageusia (14). Furthermore, SARS-CoV-2 and influenza viruses share the common route of human-to-human transmission through aerosolized or respiratory droplets (15). Researchers have speculated about the possibilities of co-infection by both viruses since the beginning of the COVID-19 pandemic (14). Furthermore, there have been reports of co-infections during the early pandemic period (16). Yue et al. reported a high rate of co-infection of SARS-CoV-2 and influenza viruses; 49.8% for Influenza A and 7.5% for Influenza B at the initial stage of pandemic (17).

Influenza remains a major public health concern, and there is a high prevalence of comorbid conditions such as chronic respiratory or cardiovascular conditions and malnutrition, leading to an excess influenza burden (18-20) in resource-poor settings like Bangladesh. Estimates of 2011-2012 data indicated seasonal influenza strains contributed to substantial mortality [6,097 (95% CI: 2,604-14,199] deaths in 2010-2011 and 16,804 (95% CI: 8,588- 2,5019) deaths in 2011-2012] with 60% to 80% of deaths among elderly aged >60 year (21). Together with a significant burden of Influenza in Bangladesh, on March 8, 2020, the first three laboratory-confirmed cases of SARS-CoV-2 were detected, and the SARS-CoV-2 has been circulating since then (22).

The World Health Organization (WHO) encouraged the detection of SARS-CoV-2, mainly using the Global Influenza Surveillance and Response System (GISRS) as the laboratories, sentinel sites, and reporting platforms are the same for both influenza virus and SARS-CoV-2 (23). In Bangladesh, hospital-based influenza surveillance (HBIS) has been operating as one of the components of the National Influenza Center (NIC), detecting both Influenza and SARS-CoV-2 and, among severe acute respiratory infection (SARI) case-patients and reporting to GISRS even during challenging situations of the COVID-19 pandemic. We explored this HBIS data based on SARI case-patients to describe rates, clinical features, and outcomes following SARS-CoV-2, influenza virus infections, and co-infections by both viruses during the COVID-19 pandemic in 2020.

Methods:

Surveillance sites and population: The hospital-based influenza surveillance (HBIS) system in Bangladesh was initiated in 2007 as a part of NIC and during 2020 operated in nine sites (seven public and two private) tertiary level hospitals (Figure-1) across Bangladesh through a collaboration between the Institute of Epidemiology, Disease Control and Research (IEDCR) of the Government of Bangladesh, the International Centre for Diarrheal Diseases Research, Bangladesh (icddr,b) and the United States

Centers for Disease Control and Prevention (US CDC) (24). The surveillance remained operational six days a week (Saturday to Thursday) but is suspended during the weekend (Friday) and any national holidays. Detailed descriptions of surveillance systems have been described elsewhere (24-27). Despite pandemic control efforts, the surveillance remained operational in inpatient departments of medicine and pediatrics wards, coronary care units, and specialized isolation wards established during the COVID-19 pandemic. This paper reports findings based on the patients enrolled during the COVID-19 pandemic between March to December 2020 only.

Case identification: Since the inception of the surveillance platform, six days a week during work hours (8.30 am to 5.00 pm), study support staff and study physicians screen inpatients of medicine and the pediatric departments, coronary care units, and specialized isolation wards to identify case-patients with SARI, defined as subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days and requiring hospital admission. This case definition was adopted from WHO (28) and used in this surveillance to screen participants since May 2016. During the COVID-19 pandemic from March 2020, study staff also screened for SARI case-patients in specialized isolation wards where suspected and probable COVID-19 patients were admitted.

Specimen collection and laboratory analysis: Study physicians, upon written informed consent, collected nasopharyngeal (NP) and oropharyngeal (OP) swabs from all the enrolled SARI patients under all aseptic precautions using full personal protective equipment. Collected swabs were then stored in Nitrogen dry shippers on-site and transported to icddr,b virology lab based in Dhaka every two weeks. Viral nucleic acid was extracted from 200 µl of pooled nasopharyngeal and oropharyngeal swab samples using InviMag Virus DNA/RNA Mini Kit (Invitek, STRATEC Molecular, Berlin-Buch, Germany) on Kingfisher Flex 96 (Thermo Fisher Scientific Inc.) automated nucleic acid extraction system according to the manufacturer's instructions. NP and OP swabs undergoing laboratory analysis were tested for seasonal

influenza virus A, subtypes: A(H1N1)pdm09, A (H3N2), A(H5N1), and influenza virus B, lineages: Yamagata lineage and Victoria lineage by real-time reverse transcription-polymerase chain reaction (rRT-PCR) using primers and probes supplied by the US CDC. RNA was tested for SARS-CoV-2 by rRT-PCR targeting ORF1ab- and N-gene-specific primers and probes following the protocol recommended by the Chinese Center for Disease Control and Prevention (briefly as China CDC). Amplification was performed using the iTaq universal probes one-step Kit (Bio-Rad Laboratories, Inc. California, USA) in a Bio-Rad CFX96TM Real-Time PCR Detection System (Bio-Rad Laboratories, Inc. California, USA).

Data Collection: The surveillance physicians performed a physical examination of all enrolled SARI patients and collected data on a standardized surveillance report form on demographics, clinical presentations, and diagnostics tests if available. Detailed information on demographic, clinical, and diagnostic variables is described in our earlier published article describing HBIS (24). We also registered the status (full recovery, partial recovery, referral to another facility, and in-hospital death) of the enrolled participant at discharge and again (alive/deceased) after 30 days of discharge. Study staff made phone calls to patient/or family members to enquire about the patient's well-being after the SARI episodes. If a participant died within 30 days post-discharge, we registered the date, place of death, and the family members' reported causes of death. Data collected were transferred in real time to our central server and have algorithms developed to report primary missing variables and/or values in variables that concern data quality (e.g., age 115 years). Finally, during the later part of the workday, a data manager skimmed through the data, made a final check, followed up with the field team, and ensured correction of wrong entries to maintain a robust data management system.

Data Analysis: We conducted descriptive analyses to describe the frequencies of SARI, influenza virus, influenza virus types, and subtypes and SARS-CoV-2 virus infection. We have analyzed through bivariate comparisons between proportion of laboratory-confirmed SARS-CoV-2 and Influenza infections

and non-infected case-patients using Pearson's χ^2 tests. For the time between illness onset and treatment-seeking variable, we performed the Mann-Whitney U non-parametric test to determine the differences between laboratory-confirmed influenza-positive and negative case-patients and also SARS-CoV-2-positive and negative case-patients. We plotted epidemiological curves describing the monthly SARS-CoV-2 and Influenza virus circulation in Bangladesh. We also used Python 3.6 to develop graphical illustration of study sites.

Patient public involvement: We developed research questions related to the influenza virus and SARS-CoV-2 detection according to the public health needs of Bangladesh. COVID-19 test results were immediately and confidentially shared with the Directorate General Health Services, Government of Bangladesh, they in term shared them with the individual patients. Anonymized Influenza test results are regularly uploaded on the WHO's GISRS platform, on IEDCR, and icddr,b websites.

Results:

Demographic and clinical characteristics: We enrolled in 1,986 SARI case-patients with a median age of 28 years (IQR: 1.2 - 53); 67.6% were males. Demographic and clinical information concerning the SARS-CoV-2 virus and influenza virus and co-infection are reported in Table 1. There were 285 (14.3%) SARI case-patients infected with SARS-CoV-2 and 175 (8.8%) SARI case-patients infected with the influenza virus. Only five (0.3%) SARI patients were co-infected with SARS-CoV-2 and influenza viruses. SARI patients of age group >60 were more likely to be infected with SARS-CoV-2 [23.5% (n=67) vs. 11.2% (n=191), p<0.001)] but less likely if age is <60 years [76.5 (n=218)% vs. 88.8% (n=1510), p<0.001). Alternatively, those aged >60 years were more likely to be infected with the influenza virus than non-influenza case-patients [5.1% (n=9) vs. 13.7% (n=249), p<0.001)]. Males were more likely to be infected with the SARS-CoV-2 than SARS-CoV-2 non-infected case-patients [75.1%

(n=214) vs. 66.4% (n=1,129), p=0.004] but less likely to be infected with the influenza virus compared to influenza negative SARI case-patients (57.7% (101) vs. 68.6% (1,242), p=0.003). Median duration (± standard deviation) from illness onset to hospital visit was longer (6.0, ±2.1 days vs. 5.0, ±2.0 days, p<0.001) for SARS-Cov-2-infected SARI patients but shorter (4.0, ±1.6 days vs. 5.0, ±2.0 days, p<0.001) for Influenza virus-infected patients, compared with those without any SARS-CoV-2 and Influenza virus infections respectively. Fever and cough were present in all patients as we followed WHO SARI case definition; however, clinical symptoms were more likely to be present among SARS-CoV-2-infected SARI patients compared to those without any SARS-CoV-2; difficulty breathing [82.5% (n=235)vs. 76.0% (n=1,292), p=0.016] and sore throat [26.3% (n=75)vs. 16.6% (n=282), p<0.001]. Difficulty breathing was less likely among Influenza virus-infected SARI case-patients than those without [65.7% (n=115) vs. 78.0% (n=1,412), p<0.001]. Runny nose was more likely to be present among Influenza virus-infected SARI case-patients compared to those without [62.9% (n=110) vs. 45.3% (n=820), p<0.001] but was less likely for SARS-CoV-2-infected ones than those without any SARS-CoV-2 [28.4% (n=81) vs. 49.9% (n=849), p<0.001]. SARI case-patients with underlying chronic conditions were more likely to be infected with SARS-CoV-2 virus compared to those without any SARS-CoV-2 infection: diabetes [14.0% (n=40) vs. 5.9% (n=101), p<0.001] and hypertension [26.7% (n=76), vs. 11.5% (n=195), p<0.001]. In contrast, SARI case-patients with with underlying chronic conditions were less likely to be infected with influenza virus than without Influenza virus infection: diabetes [4.0% (n=7), vs. 7.4% (n=134), p=0.047] and hypertension [5.7% (n=10), vs. 14.4% (n=261), p<0.001)].

Influenza virus and SARS-CoV-2 detection: Only Influenza A(H1N1)pdm09 was detected through the surveillance system in March 2020 (epi weeks 10-14). Then from epi week-15 onwards to epi week-32 (first week of April to the second week of August), no influenza virus was detected in the surveillance system in a range of 100—300 samples tested per month during the period. Later, only Influenza A/H3N2 was detected again from epi week-33 onwards (mid-August), ranging from 2% to 34%

proportion positive till epi week-44 (end of October 2020). Influenza/B lineages were not detected at all in Bangladesh during the COVID-19 pandemic in 2020 (figure 2). Six weeks after the first detection of SARS-CoV-2 in Bangladesh, the first SARS-CoV-2 case-patient was detected in this surveillance system on epi week- 17 (April 23, 2020). According to different surveillance sites, the proportion of SARS-CoV-2 and influenza virus infection with co-infection of SARS-CoV-2 and influenza virus are reported in supplementary table-1.

Patient status at discharge and after 30 days post-discharge: There were 31 (10%) in-hospital deaths registered among laboratory-confirmed SARS-CoV-2 case-patients, and in-hospital death was more likely among SARS-CoV-2 infected patients than non infected patients [10.9% (n=31) vs. 4% (n=75), p<0.001]. However, for Influenza virus-infected SARI case-patients, in-hospital death was lower than Influenza negative patients [1.1% (n=2) vs. 5.7% (n=104), p=0.009]. SARS-CoV-2 and influenza virus-infected case-patients were more likely to be referred to other healthcare facilities than SARS-CoV-2 and Influenza virus-negative case-patients, respectively [33.3% (n=95) vs. 3.4% (n=58), p<0.001; 2.9% (n=5) vs. 8.2% (n=148), p=0.012 respectively). At one month post-discharge there were 114 (5.7%) case-patients lost to follow up. We registered another 25 deaths (9.1%) in SARS-CoV-2-infected case-patients, which was significantly higher compared to SARI case-patients without SARS-CoV-2 infection [9.1% (n=25) vs. 4.6% (n=74), <0.001]. No in-hospital mortality or post-discharge mortality was registered among the five SARS-CoV-2 and Influenza virus co-infected SARI cases-patients (Table 2).

Discussion

We found a very low proportion of SARS-CoV-2 and influenza virus co-infection among SARI case-patients. Early studies reported a similarly low proportion of co-infection with influenza virus in the US (0.9%) and China (0.4%) (16, 29, 30). However, later studies from larger cohorts reported a higher proportion (52%) of influenza virus infection among laboratory-confirmed SARS-CoV-2 infected cases

and 20% co-infection with other respiratory pathogens in China and the USA respectively. They did not report the clinical prognosis among the co-infected cases (29, 31). Following the clinical course of SARI patients was beyond the scope of our study. Furthermore, with only the five cases of SARS-CoV-2 and influenza virus co-infection, our findings were inadequate to draw inference whether co-infected cases had a worse off clinical prognosis or not. Future studies on larger cohorts and the clinical prognosis of co-infected patients are warranted.

During the 12.5 weeks (May to July) of peak influenza circulation time in Bangladesh (6), we did not detect any circulating influenza till 14 weeks from the start of the peak influenza season. Several public health control efforts in Bangladesh were undertaken from the mid-March epi (week -13) to control the COVID-19 pandemic (32). Notable ones included: closure of educational institutes, suspension of any political, religious, social, and cultural gathering including state public program and events, closure of transport services including domestic and international flights, and finally closure of all public and private offices except for hospitals, kitchen markets, drug stores, and emergency services. A general holiday was issued from March 26 and extended several times till May 30 with mass communications regarding social distancing, wearing face masks, and frequent hand washing messages (32). With the emergence of the SARS-CoV-2 virus in Bangladesh in the first week of March 2020, the Influenza virus seemed to have disappeared and was not detected from the first week of April. The first reported case of Influenza was from another study in Bangladesh on epi-week 29 of 2020 (33), which was detected four weeks ahead of this surveillance platform. In Bangladesh, there is no routine vaccination for Influenza (34, 35). Since both SARS-CoV-2 and Influenza viruses have similar modes of transmission through respiratory and contact routes (36), these public health pandemic control efforts may have completely limited the transmission of influenza virus circulation in Bangladesh during its peak season (6). Similar marked influenza circulation reductions were also reported in Singapore, Thailand,

China, Taiwan, and New Zealand during the COVID-19 pandemic citing as a collateral effect of pandemic control measures as the predominant cause (8-11, 13).

Since we enrolled all SARI case-patients, fever and cough were common in all SARS-CoV-2 infected patients, with difficulty breathing and sore throat as significant clinical features. During the early pandemic period, Chinese researchers reported fever and cough to be the most prevalent symptoms (37). Also, a meta-analysis during the early pandemic period reported difficulty breathing (46%) as the most pervasive symptom after fever (89%) and cough (58%) (38). Our findings were consistent with these reported findings. Regarding demographics, the elderly aged >60 years were more likely to get infected with SARS-CoV-2 infection. In early reports from China, older age has been considered a significant risk factor for COVID-19 disease (39). In our study, males were also more likely to be infected. Our findings are consistent with findings from Italy (40) and also from national-level data of Bangladesh (22), where more males being infected were reported than females. We found diabetes and hypertension as significant comorbid conditions among SARS-CoV-2 infected patients. Co-morbid conditions with diabetes and hypertension are the most frequently reported comorbidities for COVID-19 in reports from China(39, 41) and the US (42). Therefore, it is highly recommended that older people with diabetes and hypertension take necessary precautions to protect themselves against SARS-CoV-2 infection (43).

Our in-hospital mortality proportion was much lower than in other parts of the world during the start of the pandemic. Early retrospective studies among three cohorts from China reported 12%, 17%, and 28% in-hospital mortality (43-45), while another study from the USA reported 24% in-hospital mortality among laboratory-confirmed SARS-CoV-2 infection cases (44). We could not find any literature comparing our 30 days' post-discharge mortality, which was 9.1% of the laboratory-confirmed SARS-CoV-2 infection cases. Considering the low number of deaths (in hospital n=31 and post-discharge n=25),

we could not identify any demographic or clinical characteristics that are likely to play a significant role in determining mortality both in-hospital or post-discharge. More extensive formative studies are recommended to better understand context-specific factors that may influence survival status following SARS-CoV-2 infection in Bangladesh.

Limitations to acknowledge firstly were not screening and testing for Influenza-like illnesses (ILI) in the out-patient departments whose illness was not severe enough to require hospitalization. Secondly, using a specific WHO case definition of SARI probably made it more likely to miss actual COVID-19 case-patients, which might have had either fever or cough as the only presenting symptom. Thirdly, the virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all. Lastly, six workdays a week, and this surveillance platform was subjected to under-reporting of cases (45). All the above may be accountable for having minimal estimates of influenza/SARS-CoV-2 detections. Our study did not document the treatment provided, health-seeking behaviors, and access to health care of the study participants, which may have confounded the estimates of in-hospital deaths and post-discharge mortality. Furthermore, associating these deaths to SARS-CoV-2/influenza virus infection alone was impossible as verbal autopsies were not performed.

In conclusion, our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common in Bangladesh and had less disease severity considering mortality. There was an apparent absence of influenza virus circulation during the peak influenza season in Bangladesh. Studies exploring possible causes of the marked decrease of influenza virus infections during the COVID-19 pandemic are warranted to better understand the association of the COVID-19 pandemic and reduction of influenza virus infection.

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Author's contributions:

ZA was the lead in implementing this study, wrote the paper, and performed data analysis. The protocol was drafted by FC, ZA, MAI, SMM, MuR, MZR, and MaR. MAI, MAA and SMM also contributed to implementing the study and writing this paper. MKA contributed to project implementation and managed data. PKG developed data visualization and was responsible for statistical analyses. MuR, MZR, MKS, and MMR performed laboratory analysis. MAA, TS, AA, SB, and MaR provided critical feedback in implementing and writing this paper. FC provided overall guidance in implementing this study and in writing this paper.

Data availability:

Data generated during the study are subject to a data access policy of icddr,b and are available from icddrb's research administration on reasonable request through the corresponding author.

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Conflict of interest disclosure:

The authors have disclosed that no competing interests exist.

Ethics approval and consent to participate

The study was approved by the icddr,b institutional review board prior to enrolling participants; US CDC's Human Research Protection Office approved a continuing reliance on the icddr,b IRB. Informed written consent to participate in the study was obtained.

References

1. Hampson AW. Vaccines for pandemic influenza. The history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. Annals Academy of Medicine Singapore. 2008;37(6):510.
2. Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environmental health perspectives. 2011;119(4):439-45.
3. Azziz Baumgartner E, Dao CN, Nasreen S, Bhuiyan MU, Mah-E-Muneer S, Mamun AA, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. The Journal of infectious diseases. 2012;206(6):838-46.
4. Saha S, Chadha M, Al Mamun A, Rahman M, Sturm-Ramirez K, Chittaganpitch M, et al. Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. Bulletin of the World Health Organization. 2014;92:318-30.

5. Zaman R, Alamgir ASM, Rahman M, Azziz-Baumgartner E, Gurley E, Sharker Y, et al. Influenza in Outpatient ILI Case-Patients in National Hospital-Based Surveillance, Bangladesh, 2007–2008. PloS one. 2009;4:e8452.
6. Akhtar Z, Chowdhury F, Rahman M, Ghosh PK, Ahmmed MK, Islam MA, et al. Seasonal influenza during the COVID-19 pandemic in Bangladesh. PLoS One. 2021;16(8):e0255646.
7. Liu M, Deng L, Wang D, Jiang T. Influenza activity during the outbreak of coronavirus disease 2019 in mainland China. Biosafety and Health. 2020.
8. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerging infectious diseases. 2020;26(8):1933.
9. Suntronwong N, Thongpan I, Chuchaona W, Budi Lestari F, Vichaiwattana P, Yorsaeng R, et al. Impact of COVID-19 public health interventions on influenza incidence in Thailand. Pathogens and Global Health. 2020:1-3.
10. Lei H, Xu M, Wang X, Xie Y, Du X, Chen T, et al. Nonpharmaceutical interventions used to control COVID-19 reduced seasonal influenza transmission in China. The Journal of infectious diseases. 2020;222(11):1780-3.
11. Kuo S-C, Shih S-M, Chien L-H, Hsiung CA. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. Emerging infectious diseases. 2020;26(8):1928.
12. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, et al. Decreased influenza activity during the covid-19 pandemic—United States, Australia, Chile, and South Africa, 2020. Morbidity and Mortality Weekly Report. 2020;69(37):1305.
13. Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nature communications. 2021;12(1):1-7.
14. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet. 2020;395(10236):e84.
15. Antony SJ, Almaghlouth NK, Heydemann EL. Are coinfections with COVID-19 and influenza low or underreported? An observational study examining current published literature including three new unpublished cases. J Med Virol. 2020;92(11):2489-97.
16. Zheng X, Wang H, Su Z, Li W, Yang D, Deng F, et al. Co-infection of SARS-CoV-2 and Influenza virus in Early Stage of the COVID-19 Epidemic in Wuhan, China. The Journal of Infection. 2020.
17. Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. J Med Virol. 2020;92(11):2870-3.
18. Nicholson KG WJ, Zambon M. Influenza. Lancet. 2003;362(9397):1733-45.
19. Nair M, Prabhakaran D. Why do South Asians have high risk for CAD? Global Heart. 2012;7(4):307-14.
20. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. The Lancet. 2007;368(9554):2211-8.
21. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and Other Respiratory Viruses. 2017.
22. Organization WH. COVID-19 Bangladesh situation reports: World Health Organization; 2020 [Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-

who-bangladesh-situation-reports/who_covid-19-update_41_20201207.pdf?sfvrsn=d21baace_7.

23. Organization WH. GISRS sentinel surveillance for COVID-19: frequently asked questions (FAQ), 31 July 2020. World Health Organization; 2020.
24. Zaman RU, Alamgir A, Rahman M, Azziz-Baumgartner E, Gurley ES, Sharker MAY, et al. Influenza in outpatient ILI case-patients in national hospital-based surveillance, Bangladesh, 2007–2008. PloS one. 2009;4(12):e8452.
25. Azziz-Baumgartner E, Alamgir A, Rahman M, Homaira N, Sohel BM, Sharker M, et al. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008-2010. Bulletin of the World Health Organization. 2012;90:12-9.
26. Homaira N, Luby SP, Alamgir A, Islam K, Paul R, Abedin J, et al. Influenza-associated mortality in 2009 in four sentinel sites in Bangladesh. Bulletin of the World Health Organization. 2012;90:272-8.
27. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and other respiratory viruses. 2018;12(1):65-71.
28. Organization WH. Global epidemiological surveillance standards for influenza. Edited by Influenza WHOWGESSf Geneva, Switzerland: World Health Organization. 2013.
29. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. Jama. 2020;323(20):2085-6.
30. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza: a report from Iran. 2020.
31. Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020;96:683-7.
32. Organization WH. Coronavirus disease (COVID-2019) Bangladesh situation report # 4 2020 [updated 24-03-2020. Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who-ban-covid-19-sitrep-04.pdf?sfvrsn=69b6d931_8.
33. Akhtar Z, Chowdhury F, Aleem MA, Ghosh PK, Rahman M, Rahman M, et al. Undiagnosed SARS-CoV-2 infection and outcome in patients with acute MI and no COVID-19 symptoms. Open Heart. 2021;8(1).
34. Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M. Seasonal influenza vaccine dose distribution in 195 countries (2004–2013): little progress in estimated global vaccination coverage. Vaccine. 2015;33(42):5598-605.
35. 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 and other respiratory viruses. 2016;10(4):254-67.
36. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet (London, England). 2020;395(10236):e84.
37. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-93.

38. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
39. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8.
40. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA. 2020;323(14):1335-.
41. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
42. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. Morbidity and mortality weekly report. 2020;69(15):458.
43. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN comprehensive clinical medicine. 2020:1-8.
44. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.
45. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. Emerging infectious diseases. 1999;5(5):607.

Table 1: Demographic and Clinical Characteristics of SARI case-patients with SARS-CoV-2 and influenza virus infection in Bangladesh during March-December 2020

	SARS-CoV-2 virus infection			*Influenza virus infection*			*Co-infection with Influenza and SARS-CoV-2*		
Characteristics	**positive, N = 285 n (%)**	**negative, N = 1,701 n (%)**	**p value**	**positive, N = 175 n (%)**	**negative, N = 1,811 n (%)**	**p value**	**positive, N = 5 n (%)**	**negative, N=1,981 n (%)**	**p value**
Age									
0-60 Years	218 (76.5)	1,510 (88.8)	<0.001*	166 (94.9)	1,562 (86.3)	0.001*	5 (100)	1,723 (87.0)	0.387
>60 Years	67 (23.5)	191 (11.2)	<0.001*	9 (5.1)	249 (13.7)	0.001*	0	258 (13.0)	0.387
Median age (IQR), years	50 (38-60)	20 (09-50)	<0.001*	11 (1.0-35)	30 (1.3-55)	<0.001*	33.4 (14-58)	29.2 (1.2-53)	0.763
Sex									
Male	214 (75.1)	1,129 (66.4)	0.004*	101 (57.7)	1,242 (68.6)	0.003*	3 (60.0)	1,340 (67.6)	0.715
Mean temperature (range), ℉ Celsius	39.1 (38.3 -40.6)	39.0 (37.9 - 41.1)	0.260	39.0 (38.3-40.0)	39.0 (37.9-41.1)	0.331	38.9 (38.3-39.4)	39.0 (37.9-41.1)	0.683
Median days from illness onset to hospital visit, (±SD)	6.0 (±2.1)	5.0 (±2.0)	<0.001*	4 (±1.6)	5 (±2.1)	<0.001*	4.0 (±1.9)	5.0 (±2.0)	0.937
Clinical features (symptoms)									
Runny nose	81 (28.4)	849 (49.9)	<0.001*	110 (62.9)	820 (45.3)	<0.001*	2 (40.0)	928 (46.8)	0.759
Headache	141 (49.5)	562 (33.0)	0.575	51 (29.1)	652 (36.0)	0.490	2 (40.0)	701 (35.4)	0.911
Sore throat	75 (26.3)	282 (16.6)	<0.001*	38 (21.7)	319 (17.6)	0.177	0	357 (18.0)	0.295
Difficulty breathing	235 (82.5)	1,292 (76)	0.016*	115 (65.7)	1412 (78.0)	<0.001*	4 (80.0)	1,523 (76.9)	0.869
Underlying chronic conditions									
One or more	138 (48.4)	445 (26.2)	0.246	37 (21.1)	546 (30.1)	0.535	2 (40.0)	581 (26.1)	0.842
Asthma	12 (4.2)	71 (4.2)	0.300	10 (5.7)	73 (4.0)	0.507	1 (20.0)	82 (4.1)	0.080
COPD	3 (1.1)	31 (1.8)	0.788	3 (1.7)	31 (1.7)	0.822	0	34 (1.7)	0.806
Diabetes	40 (14.0)	101 (5.9)	<0.001*	7 (4.0)	134 (7.4)	0.047*	0	141 (7.1)	0.629
Hypertension	76 (26.7)	195 (11.5)	<0.001*	10 (5.7)	261 (14.4)	0.001*	1 (20.0)	270 (13.6)	0.642
Others	8 (2.8)	49 (2.9)	0.438	6 (3.4)	51 (2.8)	0.876	0	57 (2.9)	0.752

* statistically significant <0.05

Table 2: Discharge and one-month post-discharge outcomes among SARI case-patients with SARS-CoV-2 and Influenza Virus infection during March – December 2020 in Bangladesh

	SARS-CoV-2 virus infection			Influenza virus infection				
	positive, N = 285 n (%)	**negative, N =1,701 n (%)**	**p value**	**positive, N = 175 n (%)**	**negative, N=1,811 n (%)**	**p value**	**positive, N = 5 n (%)**	**negative, N=1,981 n (%)**
Fully recovered	13 (4.6)	487 (28.6)	<0.001*	49 (28.0)	451 (24.9)	0.367	1 (20.0)	499 (25.2)
Partially recovered	146 (51.2)	1081 (63.6)	<0.001*	119 (68.0)	1108 (61.2)	0.076	3 (60.0)	1224 (61.8)
Referred	95 (33.3)	58 (3.4)	<0.001*	5 (2.9)	148 (8.2)	0.012*	1 (20.0)	152 (7.7)
In–hospital Death	31 (10.9)	75 (4.4)	<0.001*	2 (1.1)	104 (5.7)	0.010*	0	106 (5.4)
	positive, N = 276 n (%)	**negative, N =1,596 n (%)**	**p value**	**positive, N = 164 n (%)**	**negative, N=1,708 n (%)**	**p value**	**positive, N = 5 n (%)**	**negative, N=1,867 n (%)**
Death	25 (9.1)	74 (4.6)	<0.001*	4 (2.4)	95 (5.6)	0.006*	0	99 (5.0)

Figure 1: Study sites of the hospital-based influenza surveillance system: **Public hospitals** (1. RMCH: Rajshahi Medical College Hospital, Rajshahi; 2. CuMCH: Cumilla Medical College Hospital, Cumilla; 3. KMCH: Khulna Medical College Hospital, Khulna; 4. SBMCH: Sher-e-Bangla Medical College Hospital, Barishal; 5. CMCH: Chattogram Medical College Hospital, Chattogram; 6. MARMCH: M Abdur Rahim Medical College Hospital, Dinajpur; 7. JGH Jashore 250 bed General Hospital, Jashore) **Private hospitals*** (8. JIMCH: Jahurul Islam Medical College Hospital, Kishoregonj; 9. JRRMCH: Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet)

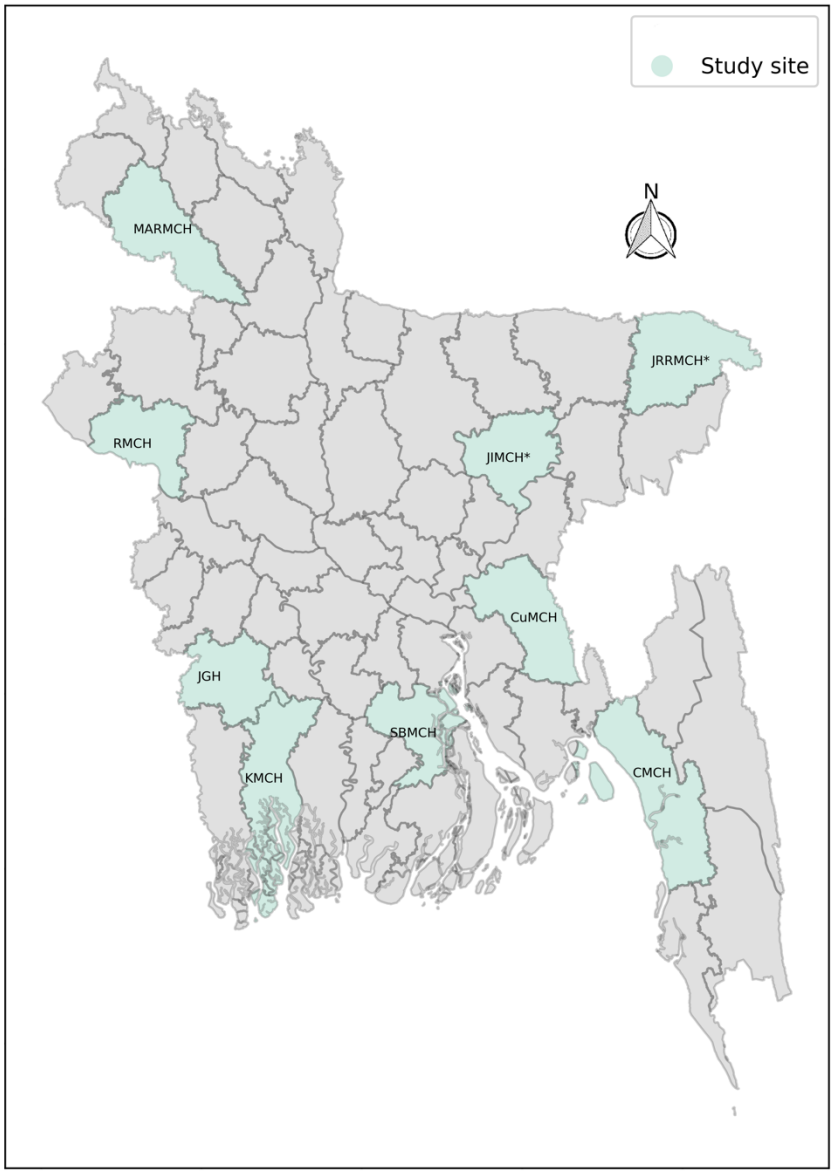
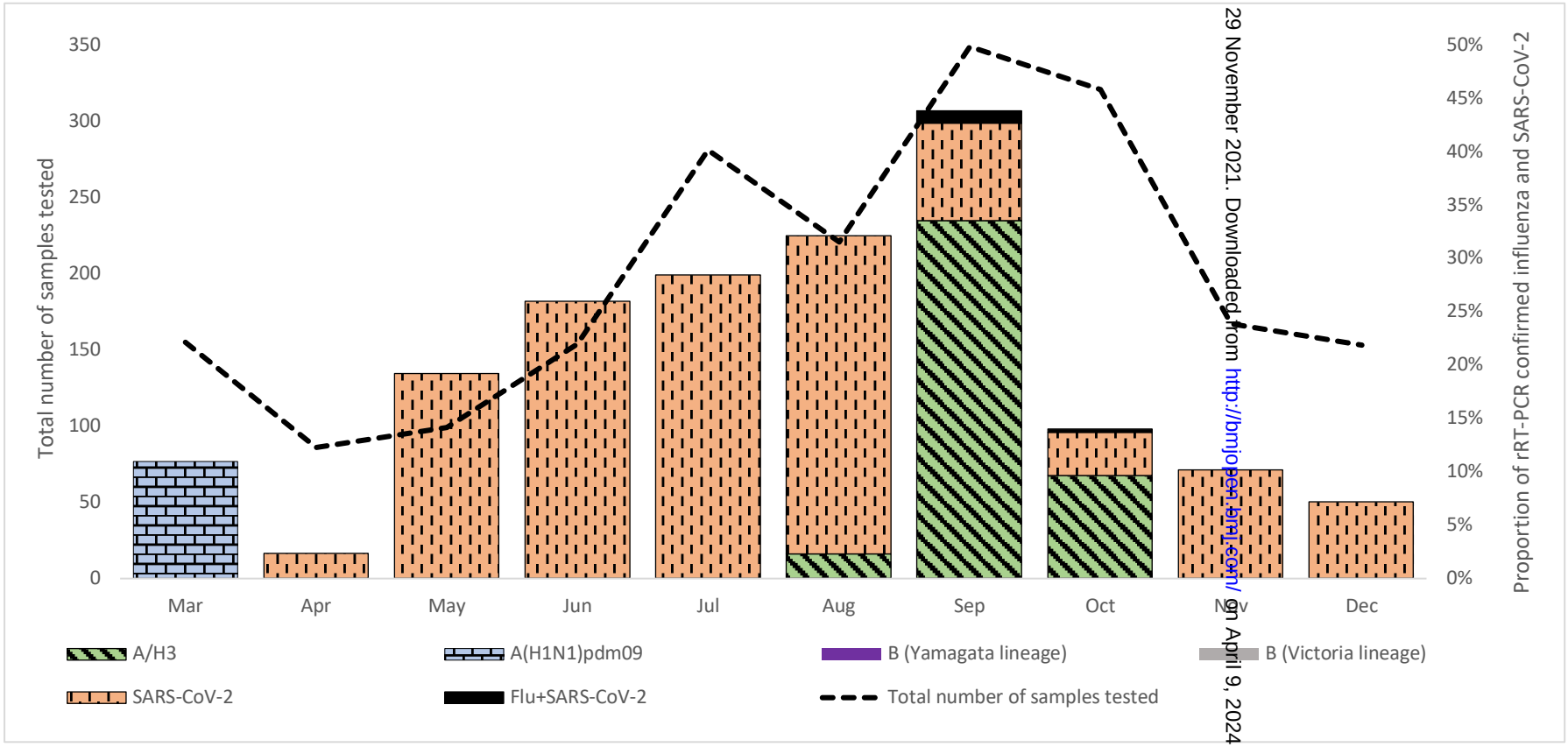


Figure 2: SARS-CoV-2, Influenza virus and Co-infection during March - December 2020 among SARI case-patients in Bangladesh



Supplemental Table-1: Proportion of SARS-CoV-2, Influenza virus infection and co-infection with SARS-CoV-2 and influenza virus, March -December 2020

Hospital	District	Sample tested N=1,986	Influenza, (%) N=175	SARS-CoV-2, (%) N=285	Co-infection with influenza and SARS-CoV-2, (%) N=5	SARS-CoV-2 and Influenza negative N =1,531
JIMCH	Kishoregonj	243	23 (9)	21 (9)	1 (0)	200 (82)
RMCH	Rajshahi	253	16 (6)	18 (7)	0 (0)	219 (87)
CuMCH	Cumilla	169	11 (7)	21 (12)	0 (0)	137 (81)
KMCH	Khulna	245	9 (4)	74 (30)	1 (0)	163 (67)
JGH	Jashore	180	20 (11)	39 (22)	1 (1)	122 (68)
JRRMCH	Sylhet	209	26 (12)	21 (10)	1 (0)	163 (78)
SBMCH	Barishal	239	35 (15)	22 (9)	0 (0)	182 (76)
CMCH	Chattogram	277	23 (8)	51 (18)	1 (0)	204 (73)
MARMCH	Dinajpur	171	12 (7)	18 (11)	0 (0)	141 (82)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Page # 1, Line # 1 (b) Page # 1, Line # 21	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page # 1, Line # 22 Page # 1, Line # 25
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page # 4, Line # 62		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page # 5, Line # 97		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page # 5, Line # 101		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page # 5, Line # 101		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page # 6, Line # 113	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page # 6, Line # 113
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page # 7, Line # 136	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page # 7, Line # 145
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page # 6, Line # 121		

Bias	9	Describe any efforts to address potential sources of bias			
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page # 7, Line # 145		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page # 7, Line # 145		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page # 7, Line # 136

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page # 7, Line # 144
Linkage		..	Page # 7, Line # 149	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page # 7, Line # 144
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 8, Line # 164	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 8, Line # 164
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page # 8, Line #164		

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page # 8, Line # 166 Page # 10, Line # 204		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page # 8, Line # 164	-	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page # 10, Line # 204		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page #10, Line #217		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page #13, Line #271	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page #13, Line #271
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page #13, Line #283		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page #13, Line #283		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page #14, Line#307		
Accessibility of protocol, raw data, and programming code		..	Page #14, Line# 304	RECORD 22.1: Authors should provide information on how to access any supplemental information, such as the study protocol, raw data, or programming code.	Page #14, Line# 304

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

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SARS-CoV-2 and Influenza Virus Co-infection among Patients with Severe Acute Respiratory Infection During the First Wave of COVID-19 Pandemic in Bangladesh: a hospital-based descriptive study

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Title: SARS-CoV-2 and Influenza Virus Co-infection among Patients with Severe Acute Respiratory Infection During the First Wave of COVID-19 Pandemic in Bangladesh: a hospital-based descriptive study

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Abstract: (297/300 words)

Objective: To estimate the proportion of SARS-CoV-2 and influenza virus co-infection among severe acute respiratory infection (SARI) cases-patients during the first wave of COVID-19 pandemic in Bangladesh.

Design: Descriptive study.

Setting: Nine tertiary level hospitals across Bangladesh.

Participants: Patients admitted as SARI (defined as cases with subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days and requiring hospital admission) case-patients.

Primary and secondary outcomes: Proportion of SARS-CoV-2 and influenza virus co-infection and proportion of mortality among SARI case-patients.

Results: We enrolled 1,986 SARI case-patients with a median age: 28 years (IQR: 1.2 - 53 years), and 67.6% were male. Among them, 285 (14.3%) were infected with SARS-CoV-2; 175 (8.8%) were infected with the influenza virus, and five (0.3%) were co-infected with both viruses. There was a nonappearance of influenza during the usual peak season (May to July) in Bangladesh. SARS-CoV-2 infection was significantly more associated with diabetes (14.0% vs. 5.9%, p<0.001) and hypertension (26.7% vs. 11.5%, p<0.001). But influenza among SARI case-patients was significantly less associated with diabetes (4.0% vs. 7.4%, p=0.047) and hypertension (5.7% vs. 14.4%, p=0.001). The proportion of in-hospital deaths among SARS-CoV-2 infected SARI case-patients were higher [10.9% (n=31) vs. 4.4% (n=75), p<0.001] than those without SARS-CoV-2 infection; the proportion of post-discharge deaths within 30 days was also higher [9.1% (n=25) vs. 4.6% (n=74), p=0.001] among SARS-CoV-2 infected SARI case-patients than those without infection. No in-hospital mortality or post-discharge mortality was registered among the five co-infected SARI case-patients.

Conclusions: Our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common and had less disease severity considering mortality in Bangladesh. There was no circulating influenza virus during the influenza peak season during the COVID-19 pandemic in 2020. Future studies are warranted for further exploration.

Article Summary

Strengths and Limitations of the study

- The study used data from a robust national surveillance system that follows the WHO recent recommended methodology and has been operational since 2007 as a part of the national influenza center of Bangladesh.
- The study adds baseline data about the prevalence, clinical features, and mortality following SARS-CoV-2 and Influenza virus co-infection among the general population during the first wave of the COVID-19 pandemic during 2020 in Bangladesh.
- SARS-CoV-2 and Influenza virus detection tests were carried out in virology laboratory of International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b).
- The study did not screen and test for Influenza-like illnesses (ILI) in the out-patient departments whose illnesses were not severe enough to require hospitalization.
- The virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all.
- The surveillance activities to enrol SARI case-patients were conducted six days a week excluding the weekend.

Introduction:

Seasonal influenza epidemics in temperate zones of the northern and southern hemispheres occur during their respective winters, from November to March in the northern hemisphere and April to September in the southern hemisphere (1-4). Bangladesh is a tropical country in the northern hemisphere, but the annual seasonal influenza epidemic occurs typically during the monsoon period, i.e., from May to September (5), with influenza peak activity for 12.5 weeks on average spanning from May (epi-weeks 18) and July (epi-weeks 30.5) every year (6).

Influenza season during 2019-2020 ended very early in China compared to previous years (7), and there was a sharp decline of influenza circulation in the USA and several Asian countries (8-11) of the Northern Hemisphere, including in Bangladesh (6). Similar observations were also reported in the Southern Hemisphere countries of Australia, Chile, South Africa, and New Zealand (12, 13). This decline in influenza virus activity might be attributed to many factors, including the substantial outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a global pandemic and public health efforts to control this virus (6, 8, 12, 13). Both Influenza and SARS-CoV-2 produce similar clinical manifestations like- fever, cough, headache, muscle and joint pain, severe malaise, sore throat, runny nose, anosmia, and ageusia (14). Furthermore, SARS-CoV-2 and influenza viruses share the common route of human-to-human transmission through aerosolized or respiratory droplets (15). Researchers have speculated about the possibilities of co-infection by both viruses since the beginning of the COVID-19 pandemic (14). Furthermore, there have been reports of co-infections during the early pandemic period (16). Yue et al. reported a high rate of co-infection of SARS-CoV-2 and influenza viruses; 49.8% for Influenza A and 7.5% for Influenza B at the initial stage of pandemic (17).

Influenza remains a major public health concern, and there is a high prevalence of comorbid conditions such as chronic respiratory or cardiovascular conditions and malnutrition, leading to an excess influenza burden (18-20) in resource-poor settings like Bangladesh. Estimates of 2011-2012 data indicated seasonal influenza strains contributed to substantial mortality [6,097 (95% CI: 2,604-14,199] deaths in 2010-2011 and 16,804 (95% CI: 8,588- 2,5019) deaths in 2011-2012] with 60% to 80% of deaths among elderly aged >60 year (21). Together with a significant burden of Influenza in Bangladesh, on March 8, 2020, the first three laboratory-confirmed cases of SARS-CoV-2 were detected, and the SARS-CoV-2 has been circulating since then (22).

The World Health Organization (WHO) encouraged the detection of SARS-CoV-2, mainly using the Global Influenza Surveillance and Response System (GISRS) as the laboratories, sentinel sites, and reporting platforms are the same for both influenza virus and SARS-CoV-2 (23). In Bangladesh, hospital-based influenza surveillance (HBIS) has been operating as one of the components of the National Influenza Center (NIC), detecting both Influenza and SARS-CoV-2 and, among severe acute respiratory infection (SARI) case-patients and reporting to GISRS even during challenging situations of the COVID-19 pandemic. We explored this HBIS data based on SARI case-patients to describe rates, clinical features, and outcomes following SARS-CoV-2, influenza virus infections, and co-infections by both viruses during the COVID-19 pandemic in 2020.

Methods:

Surveillance sites and population: The hospital-based influenza surveillance (HBIS) system in Bangladesh was initiated in 2007 as a part of NIC and during 2020 operated in nine sites (seven public and two private to have representation of case-patients from a socioeconomic perspective) tertiary level hospitals (Figure-1) across Bangladesh through a collaboration between the Institute of Epidemiology, Disease Control and Research (IEDCR) of the Government of Bangladesh, the International Centre for

Diarrheal Diseases Research, Bangladesh (icddr,b) and the United States Centers for Disease Control and Prevention (US CDC) (24). The surveillance remained operational six days a week (Saturday to Thursday) but is suspended during the weekend (Friday) and any national holidays. Detailed descriptions of surveillance systems have been described elsewhere (24-27). Despite pandemic control efforts, the surveillance remained operational in inpatient departments of medicine and pediatrics wards, coronary care units, and specialized isolation wards established during the COVID-19 pandemic. This paper reports findings based on the patients enrolled during the COVID-19 pandemic between March to December 2020 only.

Case identification: Since the inception of the surveillance platform, six days a week during work hours (8.30 am to 5.00 pm), study support staff and study physicians screen inpatients of medicine and the pediatric departments, coronary care units, and specialized isolation wards to identify case-patients with SARI, defined as subjective or measured fever of ≥ 38 C° and cough with onset within the last ten days and requiring hospital admission. This case definition was adopted from WHO (28) and used in this surveillance to screen participants since May 2016. During the COVID-19 pandemic from March 2020, study staff also screened for SARI case-patients in specialized isolation wards where suspected and probable COVID-19 patients were admitted.

Specimen collection and laboratory analysis: Study physicians, upon written informed consent, collected nasopharyngeal (NP) and oropharyngeal (OP) swabs from all the enrolled SARI patients under all aseptic precautions using full personal protective equipment. Collected swabs were then stored in Nitrogen dry shippers on-site and transported to icddr,b virology lab based in Dhaka every two weeks. Viral nucleic acid was extracted from 200 µl of pooled nasopharyngeal and oropharyngeal swab samples using InviMag Virus DNA/RNA Mini Kit (Invitek, STRATEC Molecular, Berlin-Buch, Germany) on Kingfisher Flex 96 (Thermo Fisher Scientific Inc.) automated nucleic acid extraction system according to the

manufacturer's instructions. NP and OP swabs undergoing laboratory analysis were tested for seasonal influenza virus A, subtypes: A(H1N1)pdm09, A (H3N2), A(H5N1), and influenza virus B, lineages: Yamagata lineage and Victoria lineage by real-time reverse transcription-polymerase chain reaction (rRT-PCR) using primers and probes supplied by the US CDC. RNA was tested for SARS-CoV-2 by rRT-PCR targeting ORF1ab- and N-gene-specific primers and probes following the protocol recommended by the Chinese Center for Disease Control and Prevention (briefly as China CDC). Amplification was performed using the iTaq universal probes one-step Kit (Bio-Rad Laboratories, Inc. California, USA) in a Bio-Rad CFX96TM Real-Time PCR Detection System (Bio-Rad Laboratories, Inc. California, USA).

Data Collection: The surveillance physicians performed a physical examination of all enrolled SARI patients and collected data on a standardized surveillance report form on demographics, clinical presentations, and diagnostics tests if available. Detailed information on demographic, clinical, and diagnostic variables is described in our earlier published article describing HBIS (24). We also registered the status (full recovery, partial recovery, referral to another facility, and in-hospital death) of the enrolled participant at discharge and again (alive/deceased) after 30 days of discharge. Study staff made phone calls to patient/or family members to enquire about the patient's well-being after the SARI episodes. If a participant died within 30 days post-discharge, we registered the date, place of death, and the family members' reported causes of death. Data collected were transferred in real time to our central server and have algorithms developed to report primary missing variables and/or values in variables that concern data quality (e.g., age 115 years). Finally, during the later part of the workday, a data manager skimmed through the data, made a final check, followed up with the field team, and ensured correction of wrong entries to maintain a robust data management system.

Data Analysis: We conducted descriptive analyses to describe the frequencies of SARI, influenza virus, influenza virus types, and subtypes and SARS-CoV-2 virus infection. We have analyzed through

bivariate comparisons between proportion of laboratory-confirmed SARS-CoV-2 and Influenza infections and non-infected case-patients using Pearson's χ^2 tests. For the time between illness onset and treatment-seeking variable, we performed the Mann-Whitney U non-parametric test to determine the differences between laboratory-confirmed influenza-positive and negative case-patients and also SARS-CoV-2-positive and negative case-patients. We plotted epidemiological curves describing the monthly SARS-CoV-2 and Influenza virus circulation in Bangladesh. We also used Python 3.6 to develop graphical illustration of study sites.

Patient public involvement: We developed research questions related to the influenza virus and SARS-CoV-2 detection according to the public health needs of Bangladesh. COVID-19 test results were immediately and confidentially shared with the Directorate General Health Services, Government of Bangladesh, they in term shared them with the individual patients. Anonymized Influenza test results are regularly uploaded on the WHO's GISRS platform, on IEDCR, and icddr,b websites.

Results:

Demographic and clinical characteristics: We identified a total of 2,015 SARI case-patients; among the SARI case-patients, 11 (0.5%) refused to provide consent, and 18 (0.9%) were not enrolled due to other causes: absconded, discharged or referred to other facilities before sample collection. Finally, we enrolled in 1,986 SARI case-patients with a median age of 28 years (IQR: 1.2 - 53); 67.6% were males. Demographic and clinical information concerning the SARS-CoV-2 virus and influenza virus and co-infection are reported in Table 1. There were 285 (14.3%) SARI case-patients infected with SARS-CoV-2 and 175 (8.8%) SARI case-patients infected with the influenza virus. Only five (0.3%) SARI patients were co-infected with SARS-CoV-2 and influenza viruses. SARI patients of age group >60 were more likely to be infected with SARS-CoV-2 [23.5% (n=67) vs. 11.2% (n=191), p<0.001)] but less likely if age is

<60 years [76.5 (n=218)% vs. 88.8% (n=1510), p<0.001). Alternatively, those aged >60 years were more likely to be infected with the influenza virus than non-influenza case-patients [5.1% (n=9) vs. 13.7% (n=249), p<0.001)]. Males were more likely to be infected with the SARS-CoV-2 than SARS-CoV-2 non-infected case-patients [75.1% (n=214) vs. 66.4% (n=1,129), p=0.004] but less likely to be infected with the influenza virus compared to influenza negative SARI case-patients (57.7% (101) vs. 68.6% (1,242), p=0.003). Median duration (± standard deviation) from illness onset to hospital visit was longer (6.0, ±2.1 days vs. 5.0, ±2.0 days, p<0.001) for SARS-Cov-2-infected SARI patients but shorter (4.0, ±1.6 days vs. 5.0, ±2.0 days, p<0.001) for Influenza virus-infected patients, compared with those without any SARS-CoV-2 and Influenza virus infections respectively. Fever and cough were present in all patients as we followed WHO SARI case definition; however, clinical symptoms were more likely to be present among SARS-CoV-2-infected SARI patients compared to those without any SARS-CoV-2; difficulty breathing [82.5% (n=235)vs. 76.0% (n=1,292), p=0.016] and sore throat [26.3% (n=75)vs. 16.6% (n=282), p<0.001]. Difficulty breathing was less likely among Influenza virus-infected SARI case-patients than those without [65.7% (n=115) vs. 78.0% (n=1,412), p<0.001]. Runny nose was more likely to be present among Influenza virus-infected SARI case-patients compared to those without [62.9% (n=110) vs. 45.3% (n=820), p<0.001] but was less likely for SARS-CoV-2-infected ones than those without any SARS-CoV-2 [28.4% (n=81) vs. 49.9% (n=849), p<0.001]. SARI case-patients with underlying chronic conditions were more likely to be infected with SARS-CoV-2 virus compared to those without any SARS-CoV-2 infection: diabetes [14.0% (n=40) vs. 5.9% (n=101), p<0.001] and hypertension [26.7% (n=76), vs. 11.5% (n=195), p<0.001]. In contrast, SARI case-patients with with underlying chronic conditions were less likely to be infected with influenza virus than without Influenza virus infection: diabetes [4.0% (n=7), vs. 7.4% (n=134), p=0.047] and hypertension [5.7% (n=10), vs. 14.4% (n=261), p<0.001)].

Influenza virus and SARS-CoV-2 detection: Only Influenza A(H1N1)pdm09 was detected through the surveillance system in March 2020 (epi weeks 10-14). Then from epi week-15 onwards to epi week-

32 (first week of April to the second week of August), no influenza virus was detected in the surveillance system in a range of 100—300 samples tested per month during the period. Later, only Influenza A/H3N2 was detected again from epi week-33 onwards (mid-August), ranging from 2% to 34% proportion positive till epi week-44 (end of October 2020). Influenza/B lineages were not detected at all in Bangladesh during the COVID-19 pandemic in 2020 (figure 2). Six weeks after the first detection of SARS-CoV-2 in Bangladesh, the first SARS-CoV-2 case-patient was detected in this surveillance system on epi week- 17 (April 23, 2020). According to different surveillance sites, the proportion of SARS-CoV-2 and influenza virus infection with co-infection of SARS-CoV-2 and influenza virus are reported in supplementary table-1.

Patient status at discharge and after 30 days post-discharge: There were 31 (10%) in-hospital deaths registered among laboratory-confirmed SARS-CoV-2 case-patients, and in-hospital death was more likely among SARS-CoV-2 infected patients than non infected patients [10.9% (n=31) vs. 4.4% (n=75), p<0.001]. However, for Influenza virus-infected SARI case-patients, in-hospital death was lower than Influenza negative patients [1.1% (n=2) vs. 5.7% (n=104), p=0.010]. SARS-CoV-2 and influenza virus-infected case-patients were more likely to be referred to other healthcare facilities than SARS-CoV-2 and Influenza virus-negative case-patients, respectively [33.3% (n=95) vs. 3.4% (n=58), p<0.001; 2.9% (n=5) vs. 8.2% (n=148), p=0.012 respectively). At one month post-discharge there were 114 (5.7%) case-patients lost to follow up. We registered another 25 deaths (9.1%) in SARS-CoV-2-infected case-patients, which was significantly higher compared to SARI case-patients without SARS-CoV-2 infection [9.1% (n=25) vs. 4.6% (n=74), <0.001]. No in-hospital mortality or post-discharge mortality was registered among the five SARS-CoV-2 and Influenza virus co-infected SARI cases-patients (Table 2).

Discussion

We found a very low proportion of SARS-CoV-2 and influenza virus co-infection among SARI case-patients. Early studies reported a similarly low proportion of co-infection with influenza virus in the US (0.9%) and China (0.4%) (16, 29, 30). However, later studies from larger cohorts reported a higher proportion (52%) of influenza virus infection among laboratory-confirmed SARS-CoV-2 infected cases and 20% co-infection with other respiratory pathogens in China and the USA respectively. They did not report the clinical prognosis among the co-infected cases (29, 31). Following the clinical course of SARI patients was beyond the scope of our study. Furthermore, with only the five cases of SARS-CoV-2 and influenza virus co-infection, our findings were inadequate to draw inference whether co-infected cases had a worse off clinical prognosis or not. Future studies on larger cohorts and the clinical prognosis of co-infected patients are warranted.

During the 12.5 weeks (May to July) of peak influenza circulation time in Bangladesh (6), we did not detect any circulating influenza till 14 weeks from the start of the peak influenza season. Several public health control efforts in Bangladesh were undertaken from the mid-March epi (week -13) to control the COVID-19 pandemic (32). Notable ones included: closure of educational institutes, suspension of any political, religious, social, and cultural gathering including state public program and events, closure of transport services including domestic and international flights, and finally closure of all public and private offices except for hospitals, kitchen markets, drug stores, and emergency services. A general holiday was issued from March 26 and extended several times till May 30 with mass communications regarding social distancing, wearing face masks, and frequent hand washing messages (32). With the emergence of the SARS-CoV-2 virus in Bangladesh in the first week of March 2020, the Influenza virus seemed to have disappeared and was not detected from the first week of April. The first reported case of Influenza was from another study in Bangladesh on epi-week 29 of 2020 (33), which

was detected four weeks ahead of this surveillance platform. In Bangladesh, there is no routine vaccination for Influenza (34, 35). Since both SARS-CoV-2 and Influenza viruses have similar modes of transmission through respiratory and contact routes (36), these public health pandemic control efforts may have completely limited the transmission of influenza virus circulation in Bangladesh during its peak season (6). Similar marked influenza circulation reductions were also reported in Singapore, Thailand, China, Taiwan, and New Zealand during the COVID-19 pandemic citing as a collateral effect of pandemic control measures as the predominant cause (8-11, 13).

Since we enrolled all SARI case-patients, fever and cough were common in all SARS-CoV-2 infected patients, with difficulty breathing and sore throat as significant clinical features. During the early pandemic period, Chinese researchers reported fever and cough to be the most prevalent symptoms (37). Also, a meta-analysis during the early pandemic period reported difficulty breathing (46%) as the most pervasive symptom after fever (89%) and cough (58%) (38). Our findings were consistent with these reported findings. Regarding demographics, the elderly aged >60 years were more likely to get infected with SARS-CoV-2 infection. In early reports from China, older age has been considered a significant risk factor for COVID-19 disease (39). In our study, males were also more likely to be infected. Our findings are consistent with findings from Italy (40) and also from national-level data of Bangladesh (22), where more males being infected were reported than females. We found diabetes and hypertension as significant comorbid conditions among SARS-CoV-2 infected patients. Co-morbid conditions with diabetes and hypertension are the most frequently reported comorbidities for COVID-19 in reports from China(39, 41) and the US (42). Therefore, it is highly recommended that older people with diabetes and hypertension take necessary precautions to protect themselves against SARS-CoV-2 infection (43).

Our in-hospital mortality proportion was much lower than in other parts of the world during the start of the pandemic. Early retrospective studies among three cohorts from China reported 12%, 17%, and 28% in-hospital mortality (43-45), while another study from the USA reported 24% in-hospital mortality among laboratory-confirmed SARS-CoV-2 infection cases (44). We could not find any literature comparing our 30 days' post-discharge mortality, which was 9.1% of the laboratory-confirmed SARS-CoV-2 infection cases. Considering the low number of deaths (in hospital n=31 and post-discharge n=25), we could not identify any demographic or clinical characteristics that are likely to play a significant role in determining mortality both in-hospital or post-discharge. More extensive formative studies are recommended to better understand context-specific factors that may influence survival status following SARS-CoV-2 infection in Bangladesh.

Limitations to acknowledge firstly were not screening and testing for Influenza-like illnesses (ILI) in the out-patient departments whose illness was not severe enough to require hospitalization. Secondly, using a specific WHO case definition of SARI probably made it more likely to miss actual COVID-19 case-patients, which might have had either fever or cough as the only presenting symptom. Thirdly, the virus detection estimates are based on only those who came to seek care in surveillance hospital sites and not those who did not seek care at all. Lastly, six workdays a week, and this surveillance platform was subjected to under-reporting of cases (45). All the above may be accountable for having minimal estimates of influenza/SARS-CoV-2 detections. Our study did not document the treatment provided, health-seeking behaviors, and access to health care of the study participants, which may have confounded the estimates of in-hospital deaths and post-discharge mortality. Furthermore, associating these deaths to SARS-CoV-2/influenza virus infection alone was impossible as verbal autopsies were not performed.

In conclusion, our findings suggest that co-infection with SARS-CoV-2 and influenza virus was not very common in Bangladesh and had less disease severity considering mortality. There was an apparent absence of influenza virus circulation during the peak influenza season in Bangladesh. Studies exploring possible causes of the marked decrease of influenza virus infections during the COVID-19 pandemic are warranted to better understand the association of the COVID-19 pandemic and reduction of influenza virus infection.

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Author's contributions:

ZA was the lead in implementing this study, wrote the paper, and performed data analysis. The protocol was drafted by FC, ZA, MAI, SMM, MuR, MZR, and MaR. MAI, MAA and SMM also contributed to implementing the study and writing this paper. MKA contributed to project implementation and managed data. PKG developed data visualization and was responsible for statistical analyses. MuR, MZR, MKS, and MMR performed laboratory analysis. MAA, TS, AA, SB, and MaR provided critical feedback in implementing and writing this paper. FC provided overall guidance in implementing this study and in writing this paper.

Data availability:

Data generated during the study are subject to a data access policy of icddr,b and are available from icddrb's research administration on reasonable request through the corresponding author.

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Conflict of interest disclosure:

The authors have disclosed that no competing interests exist.

Ethics approval and consent to participate

The study was approved by the icddr,b institutional review board prior to enrolling participants; US CDC's Human Research Protection Office approved a continuing reliance on the icddr,b IRB. Informed written consent to participate in the study was obtained.

References

1. Hampson AW. Vaccines for pandemic influenza. The history of our current vaccines, their limitations and the requirements to deal with a pandemic threat. Annals Academy of Medicine Singapore. 2008;37(6):510.
2. Tamerius J, Nelson MI, Zhou SZ, Viboud C, Miller MA, Alonso WJ. Global influenza seasonality: reconciling patterns across temperate and tropical regions. Environmental health perspectives. 2011;119(4):439-45.
3. Azziz Baumgartner E, Dao CN, Nasreen S, Bhuiyan MU, Mah-E-Muneer S, Mamun AA, et al. Seasonality, timing, and climate drivers of influenza activity worldwide. The Journal of infectious diseases. 2012;206(6):838-46.
4. Saha S, Chadha M, Al Mamun A, Rahman M, Sturm-Ramirez K, Chittaganpitch M, et al. Influenza seasonality and vaccination timing in tropical and subtropical areas of southern and south-eastern Asia. Bulletin of the World Health Organization. 2014;92:318-30.
5. Zaman R, Alamgir ASM, Rahman M, Azziz-Baumgartner E, Gurley E, Sharker Y, et al. Influenza in Outpatient ILI Case-Patients in National Hospital-Based Surveillance, Bangladesh, 2007–2008. PloS one. 2009;4:e8452.
6. Akhtar Z, Chowdhury F, Rahman M, Ghosh PK, Ahmmed MK, Islam MA, et al. Seasonal influenza during the COVID-19 pandemic in Bangladesh. PLoS One. 2021;16(8):e0255646.
7. Liu M, Deng L, Wang D, Jiang T. Influenza activity during the outbreak of coronavirus disease 2019 in mainland China. Biosafety and Health. 2020.
8. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerging infectious diseases. 2020;26(8):1933.
9. Suntronwong N, Thongpan I, Chuchaona W, Budi Lestari F, Vichaiwattana P, Yorsaeng R, et al. Impact of COVID-19 public health interventions on influenza incidence in Thailand. Pathogens and Global Health. 2020:1-3.
10. Lei H, Xu M, Wang X, Xie Y, Du X, Chen T, et al. Nonpharmaceutical interventions used to control COVID-19 reduced seasonal influenza transmission in China. The Journal of infectious diseases. 2020;222(11):1780-3.
11. Kuo S-C, Shih S-M, Chien L-H, Hsiung CA. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. Emerging infectious diseases. 2020;26(8):1928.
12. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, et al. Decreased influenza activity during the covid-19 pandemic—United States, Australia, Chile, and South Africa, 2020. Morbidity and Mortality Weekly Report. 2020;69(37):1305.
13. Huang QS, Wood T, Jelley L, Jennings T, Jefferies S, Daniells K, et al. Impact of the COVID-19 nonpharmaceutical interventions on influenza and other respiratory viral infections in New Zealand. Nature communications. 2021;12(1):1-7.
14. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet. 2020;395(10236):e84.
15. Antony SJ, Almaghlouth NK, Heydemann EL. Are coinfections with COVID-19 and influenza low or underreported? An observational study examining current published literature including three new unpublished cases. J Med Virol. 2020;92(11):2489-97.
16. Zheng X, Wang H, Su Z, Li W, Yang D, Deng F, et al. Co-infection of SARS-CoV-2 and Influenza virus in Early Stage of the COVID-19 Epidemic in Wuhan, China. The Journal of Infection. 2020.
17. Yue H, Zhang M, Xing L, Wang K, Rao X, Liu H, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. J Med Virol. 2020;92(11):2870-3.

18. Nicholson KG WJ, Zambon M. Influenza. Lancet. 2003;362(9397):1733-45.
19. Nair M, Prabhakaran D. Why do South Asians have high risk for CAD? Global Heart. 2012;7(4):307-14.
20. Murray CJ, Lopez AD, Chin B, Feehan D, Hill KH. Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis. The Lancet. 2007;368(9554):2211-8.
21. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and Other Respiratory Viruses. 2017.
22. Organization WH. COVID-19 Bangladesh situation reports: World Health Organization; 2020 [Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who_covid-19-update_41_20201207.pdf?sfvrsn=d21baace_7.
23. Organization WH. GISRS sentinel surveillance for COVID-19: frequently asked questions (FAQ), 31 July 2020. World Health Organization; 2020.
24. Zaman RU, Alamgir A, Rahman M, Azziz-Baumgartner E, Gurley ES, Sharker MAY, et al. Influenza in outpatient ILI case-patients in national hospital-based surveillance, Bangladesh, 2007–2008. PloS one. 2009;4(12):e8452.
25. Azziz-Baumgartner E, Alamgir A, Rahman M, Homaira N, Sohel BM, Sharker M, et al. Incidence of influenza-like illness and severe acute respiratory infection during three influenza seasons in Bangladesh, 2008-2010. Bulletin of the World Health Organization. 2012;90:12-9.
26. Homaira N, Luby SP, Alamgir A, Islam K, Paul R, Abedin J, et al. Influenza-associated mortality in 2009 in four sentinel sites in Bangladesh. Bulletin of the World Health Organization. 2012;90:272-8.
27. Ahmed M, Aleem MA, Roguski K, Abedin J, Islam A, Alam KF, et al. Estimates of seasonal influenza-associated mortality in Bangladesh, 2010-2012. Influenza and other respiratory viruses. 2018;12(1):65-71.
28. Organization WH. Global epidemiological surveillance standards for influenza. Edited by Influenza WHOWGESSf Geneva, Switzerland: World Health Organization. 2013.
29. Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens. Jama. 2020;323(20):2085-6.
30. Khodamoradi Z, Moghadami M, Lotfi M. Co-infection of coronavirus disease 2019 and influenza: a report from Iran. 2020.
31. Ma S, Lai X, Chen Z, Tu S, Qin K. Clinical characteristics of critically ill patients co-infected with SARS-CoV-2 and the influenza virus in Wuhan, China. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2020;96:683-7.
32. Organization WH. Coronavirus disease (COVID-2019) Bangladesh situation report # 4 2020 [updated 24-03-2020. Available from: https://www.who.int/docs/default-source/searo/bangladesh/covid-19-who-bangladesh-situation-reports/who-ban-covid-19-sitrep-04.pdf?sfvrsn=69b6d931_8.
33. Akhtar Z, Chowdhury F, Aleem MA, Ghosh PK, Rahman M, Rahman M, et al. Undiagnosed SARS-CoV-2 infection and outcome in patients with acute MI and no COVID-19 symptoms. Open Heart. 2021;8(1).

34. Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M. Seasonal influenza vaccine dose distribution in 195 countries (2004–2013): little progress in estimated global vaccination coverage. Vaccine. 2015;33(42):5598-605.
35. 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 and other respiratory viruses. 2016;10(4):254-67.
36. Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, Blasco M, Poch E, et al. SARS-CoV-2 and influenza virus co-infection. Lancet (London, England). 2020;395(10236):e84.
37. Yang W, Cao Q, Qin L, Wang X, Cheng Z, Pan A, et al. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. J Infect. 2020;80(4):388-93.
38. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.
39. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-8.
40. Livingston E, Bucher K. Coronavirus Disease 2019 (COVID-19) in Italy. JAMA. 2020;323(14):1335-.
41. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
42. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. Morbidity and mortality weekly report. 2020;69(15):458.
43. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. Comorbidity and its Impact on Patients with COVID-19. SN comprehensive clinical medicine. 2020:1-8.
44. Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020;108:154262.
45. Mead PS, Slutsker L, Dietz V, McCaig LF, Bresee JS, Shapiro C, et al. Food-related illness and death in the United States. Emerging infectious diseases. 1999;5(5):607.

Table 1: Demographic and Clinical Characteristics of SARI case-patients with SARS-CoV-2 and influenza virus infection in Bangladesh during March-December 2020

	SARS-CoV-2 virus infection			*Influenza virus infection*			*Co-infection with Influenza and SARS-CoV-2*		
Characteristics	**positive, N = 285 n (%)**	**negative, N = 1,701 n (%)**	**p value**	**positive, N = 175 n (%)**	**negative, N = 1,811 n (%)**	**p value**	**positive, N = 5 n (%)**	**negative, N=1,981 n (%)**	**p value**
Age									
0-60 Years	218 (76.5)	1,510 (88.8)	<0.001*	166 (94.9)	1,562 (86.3)	0.001*	5 (100)	1,723 (87.0)	0.387
>60 Years	67 (23.5)	191 (11.2)	<0.001*	9 (5.1)	249 (13.7)	0.001*	0	258 (13.0)	0.387
Median age (IQR), years	50 (38-60)	20 (09-50)	<0.001*	11 (1.0-35)	30 (1.3-55)	<0.001*	33.4 (14-58)	29.2 (1.2-53)	0.763
Sex									
Male	214 (75.1)	1,129 (66.4)	0.004*	101 (57.7)	1,242 (68.6)	0.003*	3 (60.0)	1,340 (67.6)	0.715
Mean temperature (range), ℉ Celsius	39.1 (38.3 -40.6)	39.0 (37.9 - 41.1)	0.260	39.0 (38.3-40.0)	39.0 (37.9-41.1)	0.331	38.9 (38.3-39.4)	39.0 (37.9-41.1)	0.683
Median days from illness onset to hospital visit, (±SD)	6.0 (±2.1)	5.0 (±2.0)	<0.001*	4 (±1.6)	5 (±2.1)	<0.001*	4.0 (±1.9)	5.0 (±2.0)	0.937
Clinical features (symptoms)									
Runny nose	81 (28.4)	849 (49.9)	<0.001*	110 (62.9)	820 (45.3)	<0.001*	2 (40.0)	928 (46.8)	0.759
Headache	141 (49.5)	562 (33.0)	0.575	51 (29.1)	652 (36.0)	0.490	2 (40.0)	701 (35.4)	0.911
Sore throat	75 (26.3)	282 (16.6)	<0.001*	38 (21.7)	319 (17.6)	0.177	0	357 (18.0)	0.295
Difficulty breathing	235 (82.5)	1,292 (76)	0.016*	115 (65.7)	1412 (78.0)	<0.001*	4 (80.0)	1,523 (76.9)	0.869
Underlying chronic conditions									
One or more	138 (48.4)	445 (26.2)	0.246	37 (21.1)	546 (30.1)	0.535	2 (40.0)	581 (26.1)	0.842
Asthma	12 (4.2)	71 (4.2)	0.300	10 (5.7)	73 (4.0)	0.507	1 (20.0)	82 (4.1)	0.080
COPD	3 (1.1)	31 (1.8)	0.788	3 (1.7)	31 (1.7)	0.822	0	34 (1.7)	0.806
Diabetes	40 (14.0)	101 (5.9)	<0.001*	7 (4.0)	134 (7.4)	0.047*	0	141 (7.1)	0.629
Hypertension	76 (26.7)	195 (11.5)	<0.001*	10 (5.7)	261 (14.4)	0.001*	1 (20.0)	270 (13.6)	0.642
Others	8 (2.8)	49 (2.9)	0.438	6 (3.4)	51 (2.8)	0.876	0	57 (2.9)	0.752

* statistically significant <0.05

Table 2: Discharge and one-month post-discharge outcomes among SARI case-patients with SARS-CoV-2 and Influenza Virus infection during March – December 2020 in Bangladesh

	SARS-CoV-2 virus infection			Influenza virus infection			Co-infected with Influenza and SARS-CoV-2		
	positive, N = 285 n (%)	negative, N =1,701 n (%)	p value	positive, N = 175 n (%)	negative, N=1,811 n (%)	p value	positive, N = 5 n (%)	negative, N=1,981 n (%)	p value
Condition during discharge									
Fully recovered	13 (4.6)	487 (28.6)	<0.001*	49 (28.0)	451 (24.9)	0.367	1 (20.0)	499 (25.2)	0.789
Partially recovered	146 (51.2)	1081 (63.6)	<0.001*	119 (68.0)	1108 (61.2)	0.076	3 (60.0)	1224 (61.8)	0.935
Referred	95 (33.3)	58 (3.4)	<0.001*	5 (2.9)	148 (8.2)	0.012*	1 (20.0)	152 (7.7)	0.302
In–hospital Death	31 (10.9)	75 (4.4)	<0.001*	2 (1.1)	104 (5.7)	0.010*	0	106 (5.4)	0.595
Post-discharge mortality after one month (114 case-patients lost to follow-up)									
	positive, N = 276 n (%)	negative, N =1,596 n (%)	p value	positive, N = 164 n (%)	negative, N=1,708 n (%)	p value	positive, N = 5 n (%)	negative, N=1,867 n (%)	p value
Death	25 (9.1)	74 (4.6)	<0.001*	4 (2.4)	95 (5.6)	0.006*	0	99 (5.0)	0.735

* statistically significant <0.05

Figure 1: Study sites of the hospital-based influenza surveillance system: **Public hospitals** (1. RMCH: Rajshahi Medical College Hospital, Rajshahi; 2. CuMCH: Cumilla Medical College Hospital, Cumilla; 3. KMCH: Khulna Medical College Hospital, Khulna; 4. SBMCH: Sher-e-Bangla Medical College Hospital, Barishal; 5. CMCH: Chattogram Medical College Hospital, Chattogram; 6. MARMCH: M Abdur Rahim Medical College Hospital, Dinajpur; 7. JGH Jashore 250 bed General Hospital, Jashore) **Private hospitals*** (8. JIMCH: Jahurul Islam Medical College Hospital, Kishoregonj; 9. JRRMCH: Jalalabad Ragib-Rabeya Medical College Hospital, Sylhet)

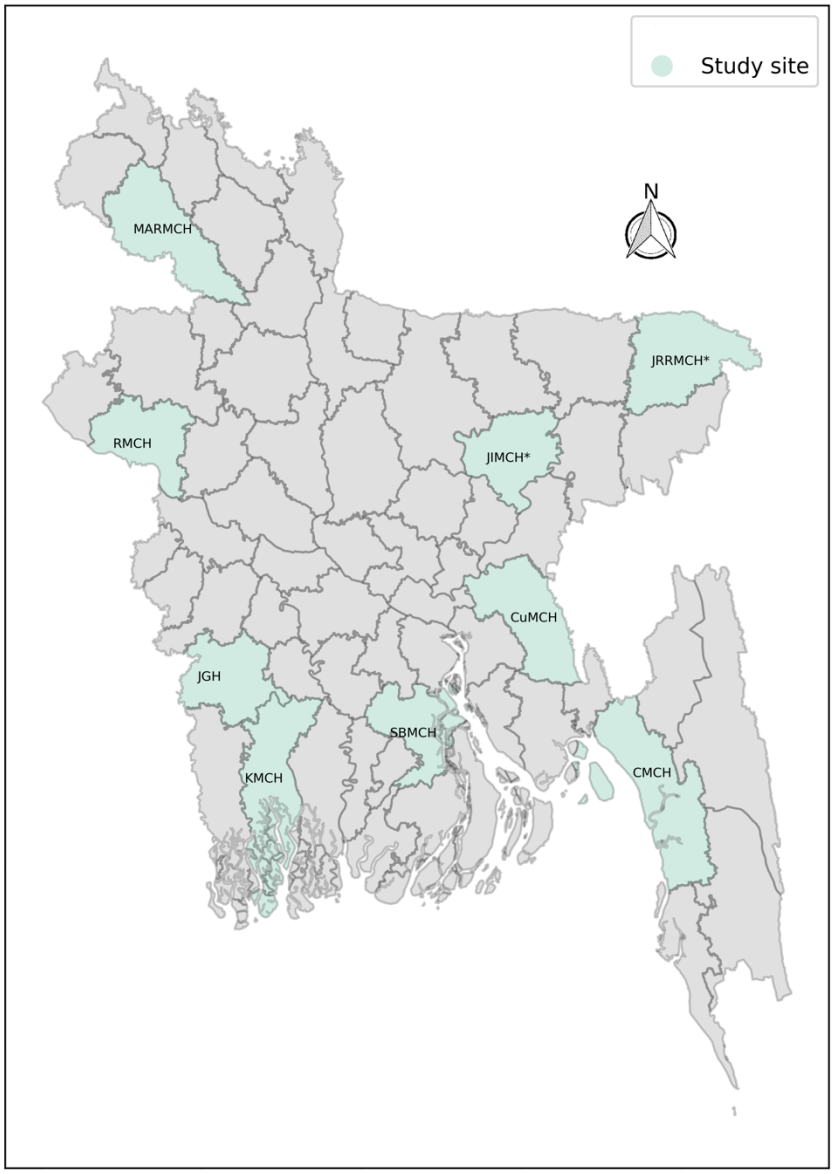
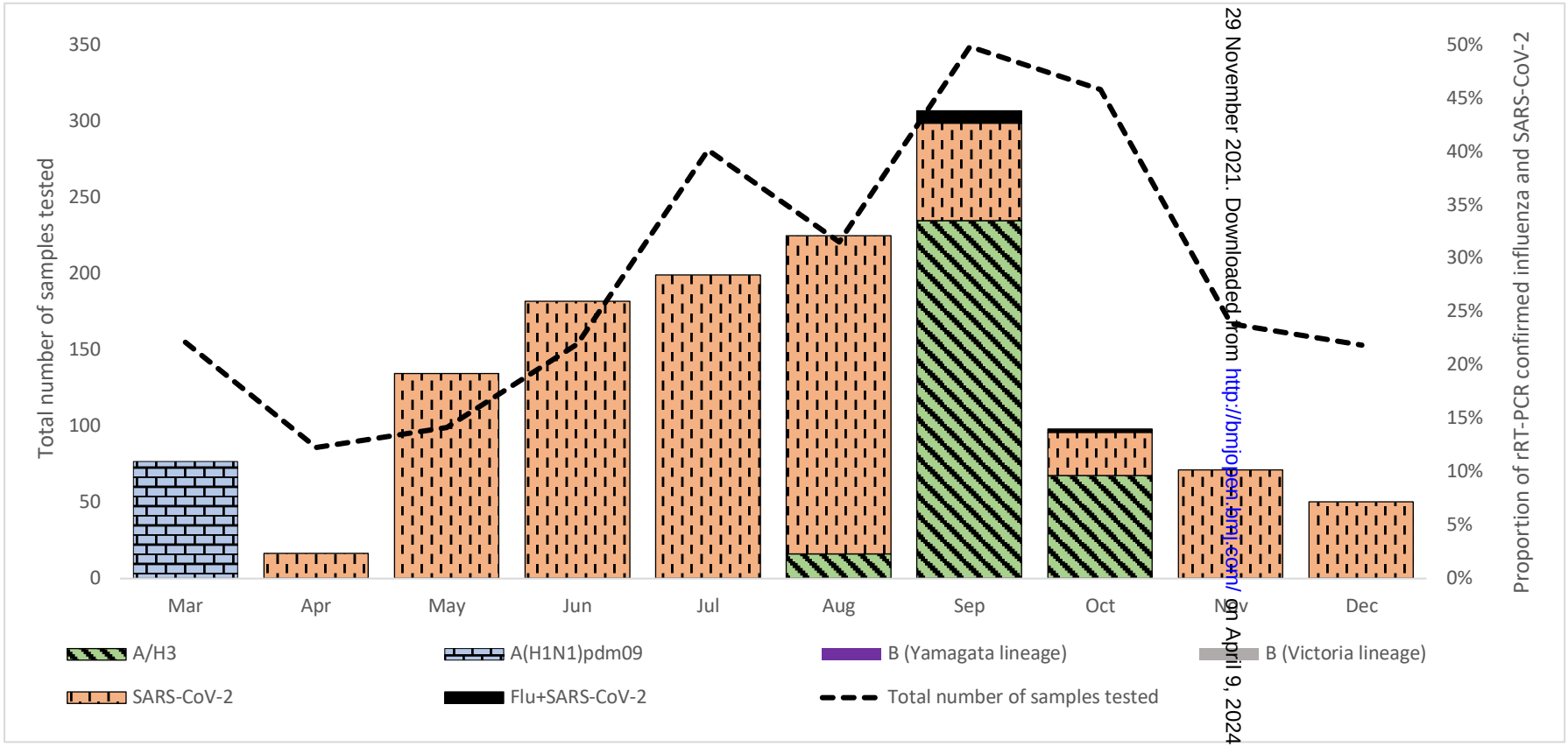


Figure 2: SARS-CoV-2, Influenza virus and Co-infection during March - December 2020 among SARI case-patients in Bangladesh



Supplemental Table-1: Proportion of SARS-CoV-2, Influenza virus infection and co-infection with SARS-CoV-2 and influenza virus, March -December 2020

Hospital	District	Sample tested N=1,986	Influenza, (%) N=175	SARS-CoV-2, (%) N=285	Co-infection with influenza and SARS-CoV-2, (%) N=5	SARS-CoV-2 and Influenza negative N =1,531
JIMCH	Kishoregonj	243	23 (9)	21 (9)	1 (0)	200 (82)
RMCH	Rajshahi	253	16 (6)	18 (7)	0 (0)	219 (87)
CuMCH	Cumilla	169	11 (7)	21 (12)	0 (0)	137 (81)
KMCH	Khulna	245	9 (4)	74 (30)	1 (0)	163 (67)
JGH	Jashore	180	20 (11)	39 (22)	1 (1)	122 (68)
JRRMCH	Sylhet	209	26 (12)	21 (10)	1 (0)	163 (78)
SBMCH	Barishal	239	35 (15)	22 (9)	0 (0)	182 (76)
CMCH	Chattogram	277	23 (8)	51 (18)	1 (0)	204 (73)
MARMCH	Dinajpur	171	12 (7)	18 (11)	0 (0)	141 (82)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(a) Page # 1, Line # 1 (b) Page # 1, Line # 26	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Page # 1, Line # 23 Page # 1, Line # 25
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Page # 4, Line # 64		
Objectives	3	State specific objectives, including any prespecified hypotheses	Page # 5, Line # 100		
Methods					
Study Design	4	Present key elements of study design early in the paper	Page # 5, Line # 104		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page # 5, Line # 104		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Page # 6, Line # 117	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Page # 6, Line # 117
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Page # 7, Line # 140	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Page # 7, Line # 142
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page # 6, Line # 122		

Bias	9	Describe any efforts to address potential sources of bias	Page # 5, Line # 106		
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Page # 7, Line # 153		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Page # 7, Line # 153		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Page # 7, Line # 150

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Page # 7, Line # 150
Linkage		..	Page # 7, Line # 143	RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page # 7, Line # 144
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Page 8, Line # 169	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Page 8, Line # 169
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Page # 8, Line #171		

Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	Page # 8, Line # 174 Page # 10, Line # 211		
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page # 9, Line # 182	-	
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page # 10, Line # 211		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Page #10, Line #224		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page #13, Line #278	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page #13, Line #284
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page #13, Line #290		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page #13, Line #282		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page #14, Line#315		
Accessibility of protocol, raw data, and programming code		..	Page #14, Line# 311	RECORD 22.1: Authors should provide information on how to access any supplemental information, such as the study protocol, raw data, or programming code.	Page #14, Line# 311

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.