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An outbreak of H3N2 from Ernakulam district, Central Kerala during the post COVID period

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Abstract: Influenza virus infection in humans is a zoonotic disease having high economic and public health impacts. Outbreaks of overlapping respiratory viral infections have been reported in the past. Here we describe the characteristics of a similar viral outbreak that occurred among students in a University campus in Kerala, India, during May, 2022. We conducted an epidemiologic investigation to describe the outbreak and elucidate the dynamics of viral transmission. Nasal swabs were collected randomly from suspected patients. Real-time reverse transcription polymerase chain reaction (RT-PCR)-based diagnosis was performed to detect influenza A and B viruses followed by sequencing and phylogenetic analysis. COVID 19 was tested using rapid antigen detection kits. Of the 185 affected students included in the outbreak investigation, 87% reported either respiratory or gastrointestinal symptoms or both. The median time taken for the onset of symptoms was 3 days. Out of 16, 11 sampleswere laboratory confirmed for Influenza A (H3N2) while 18 samples were positive for COVID 19. The phylogenetic analysis showed that the Influenza virus is close to the current, Darwin 2021 vaccine strain. The only stool sample collected, turned positive for Noro Virus. Risk factors for infection included close proximity and exposure to droplet infection. The public health response included isolation of cases, contact tracing, temporary shutdown of college and hostels and enforcement of COVID appropriate behaviour in the campus. Early laboratory confirmation and an immediate public health response contained the outbreak.

Keywords: Covid19, H3n2, Norovirus, Co-Infection, Outbreak

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INTRODUCTION

Influenza and other respiratory viruses' cases dropped worldwide to unprecedented lows. The impact on circulation of respiratory viruses during the COVID-19 pandemic is due to non-pharmaceutical interventions to mitigate the COVID-19 such as social distancing, mask-wearing, hand washing, restricted international travel, closure of schools etc. Past flu seasons have followed no pattern and were unpredictable (Huang *et al*., 2021). Herd immunity to certain disease can diminish due to absence of circulating pathogens, leading to the emergence of more serious epidemics (Sanz-Muñoz *et al*., 2021).

Despite being one of the most researched pathogens, Influenza continues to pose a major threat to public health. Even though it can be as mild as a common cold, it is continuously changing and evolving to defy the immune system (Webster & Govorkova, 2014). This enables the virus to cause recurrent outbreaks worldwide, affecting 5 -15% of the population each year(Petrova & Russell, 2018). The WHO estimates that approximately 2,90,000-6,50,000 people die each year from influenza, with LMICs such as India accounting for more than one-third of all cases (Narayan *et al*.,

2020). Influenza and COVID-19 have similar clinical symptoms and transmission routes. Influenza activity is monitored in India through laboratory-based surveillance systems.

The influenza virus is a single-stranded negative-sense RNA virus belonging to the Orthomyxoviridae family, with four primary types: A, B, C, and D. Among the four, Influenza A and B cause most human diseases (Te Velthuis & Fodor, 2016)[6]. Influenza A virus which caused the great influenza pandemic of 1918, and 2009 pandemic is always a potential threat to public health (Gaitonde *et al*., 2019). The influenza A virus which emerges from zoonotic reservoirs is highly susceptible to antigenic variations and exists as a quasi-species (Webster & Govorkova, 2014). According to the hemagglutinin and neuraminidase types, many subtypes of Influenza A have been identified. H1N1 and H3N3 are the currently circulating subtypes (Park & Ryu, 2018).

Starting from the Spanish Influenza of 1918, India has always been one of the worst-hit countries by the influenza-related mortality and morbidity (Chandra & Kassens-Noor, 2014). H1N1 and H3N3 are being reported from various parts of India annually (Peter *et al*., 2015), (Mudhigeti *et al*., 2018). Considering the nature of the Influenza virus and its potential to cause pandemics, a constant vigil is essential, especially in countries like India (Bresee *et al*., 2018). India is one of the countries that report data to FluNet, a global influenza surveillance platform. India struggles to maintain influenza surveillance in the face of the COVID-19 pandemic, with prioritization of COVID-19 testing and diversion of flu staff for COVID-19 work. The Kerala unit of National Institute of Virology(NIV) is a part of the networked surveillance system for Influenza. Influenza cases reported during the COVID 19 pandemic was comparatively less compared to the previous years, the main reason being the COVID-19 restrictions in place. The restrictions were relaxed after the second wave of COVID-19 leading to several outbreaks of influenza throughout Kerala. The reason for current outbreaks could be the loss of population immunity in the last two years. Here, we report an outbreak of Influenza from a university campus in Kerala in May 2022, following a cultural festival among the students.

METHODOLOGY

Study Setting

The study was carried out in the light of an ILI outbreak that was reported from a university campus in Kochi, Ernakulam district of Kerala. Ernakulam district, situated in the central part of Kerala is the third most populous district and is the only metro city in Kerala. It is also an educational hub of the state.

The current outbreak occurred in a university campus with a total strength of over 1300 students. Students from across India and foreign students pursue various science courses in the campus. Residential students which constitute the majority share of students stay in 13 different hostels spread across the sprawling campus. Three students are accommodated per room in all the hostels. Each room has a surface area of over 200 Square feet, with adequate ventilation and no overcrowding.

Description of the outbreak

Following a weeklong arts and cultural festival among the students in a university campus in central Kerala, many students started reporting to the casualty of a Government Medical College in the district, with symptoms which includes fever, cough, sore throat, headache, and myalgia. More than 40 students reported to the hospital casualty with these symptoms on the first day following the conclusion of the festival. Over the next three days more than 150 students with various symptoms reported to the casualty. Due to suspicion of an outbreak, a detailed investigation and a medical camp was carried out by the Department of Community Medicine of the Medical College along with the Directorate of Health Services, Ernakulam District. Nasopharyngeal swabs were randomly collected from the students who had respiratory symptoms and sent to the National Institute of Virology, Alappuzha for viral study.

Statistical analysis

Data regarding baseline characteristics and details including food intake in the past 72 hours prior to the onset of symptoms and details on the presenting symptoms of the students who reported in the medical camps conducted at the hostels were collected after getting their consent, using Google forms and further analysis was done using SPSS v26.0. The date of onset of symptoms was collected from which median time taken for onset of symptoms was calculated and

an epidemic curve showing the trend in onset of symptoms by date was also plotted. Pattern of symptomatology was tabulated and expressed in proportions. Pattern of food intake by the students over the past 72 hours was too detailed and cumbersome to be summarized and it did not show any pattern.

Ethical Clearance

The study was conducted as a part of a routine outbreak investigation. All the information and samples were collected with prior consent from the participants. Expedited Institutional ethics committee clearance was obtained simultaneously from the Institutional Ethics Committee, Govt. Medical College, Ernakulam. The confidentiality of the data was maintained throughout the process. Ethical clearance for the study was also obtained from National Institute of Virology, Pune.

Laboratory diagnosis

The students presenting with the symptoms were tested for COVID-19 using rapid antigen tests. Further, nasopharyngeal swabs were randomly collected from 16 students who presented with respiratory symptoms. The samples were transported in a screw-capped container with VTM to NIV Alappuzha for virological testing. The RNA was extracted and stored at -80 degrees. Stool sample of a student with GI symptom was send to the state public health laboratory at Trivandrum for testing. Liver Function Tests, Renal Function tests and routine blood tests were performed at the medical college hospital laboratory. Specific serological tests for Dengue and Leptospirosis were also done at the medical college laboratory.

RNA extraction, RT-PCR, and sequencing:

RNA extraction was done using the MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit according to the manufacturer's protocol. The extracted RNA was tested by real-time RT-PCR using SuperScript III One-Step RT-PCR System (Invitrogen, Carlsbad, USA) with PlatinumTaq reagents. The targets tested were universal influenza A (InfA), and Influenza B. All the specimens that gave a positive result for universal influenza A, were then tested for H1N1 and H3N2.

Sequencing and phylogenetic analysis:

Haemagglutinin-1 gene was amplified from the selected samples. The amplicons were purified by using Qiagen PCR purification kit. The purified amplicons were sequenced using BigDye Terminator v3.1 cycle sequencing kit (ABI). The sequencing was done on an ABI 3730 DNA analyser. The obtained sequences were aligned with related sequences available from GenBank including the sequences from India using ClustalW programme available in MEGA software version 11. The phylogenetic tree was constructed using Neighbor-Joining method and the robustness of tree was assessed with 1000 bootstrap replicates.

RESULTS

On the first day after the festival, 47 students reported ILI symptoms. The predominant symptoms were fever (61.7%), headache (34%) and cough (31.9%).The other minor symptoms included sore throat, vomiting, running nose, myalgia, giddiness, and stomachache. They were tested for COVID-19 using the Rapid Antigen Test (RAT) kit available in the hospital and out of the 47 tested, 5 turned out to be positive (10.6%). All the tested students were vaccinated with at least 2 doses of the COVID vaccine.

In the detailed investigation and the medical camp conducted in the University campus in the following days, 185 students with symptoms who participated in the medical camp were included as cases in our outbreak investigation. The mean age of the students in the outbreak was 21.5(±1.32) years. Sixty six percent of the affected students were females. Out of 185 participants, 168(90.8%) stayed in hostels inside or outside the campus, 17 (9.2%) were day scholars. The reported symptomatology of the participants is as shown in Table 1. The median time taken for the onset of symptoms was 3 days with IQR of 2 days to 3.5 days. Based on the date of onset of symptoms as reported by the students, trend diagram was drawn as shown in the Figure 1.

Details regarding food consumption were collected from the students to get any information on the chances of food poisoning as over 40% of the affected students had reported one or the other abdominal symptom. Among the 185 participants, 87 (47.0%) had at least one meal from outside (other than hostel or home) in the preceding three days. The food consumption pattern and the onset of symptoms did not show any pattern. All the 13 university hostels in which the students resided had reported cases with no specific preponderance to the hostel of stay or food intake either from the hostel or outside.

***Table** 1: Symptomatology pattern in the Participants of the medical camp*

Symptoms (n=185)	**Frequency (%)**
Headache	129 (69.7%)
Fever	122 (65.9%)
Myalgia	110 (59.5%)
Nausea	42 (22.7%)
Abdominal Pain	33 (17.8%)
Vomiting	27 (14.6%)
Loose stools	25 (13.5%)
Cough	19 (10.3%)
Sore throat	18 (9.7%)
Running/ Stuffy nose	17 (9.2%)
Dizziness	2 (0.1%)
Difficulty in breathing	2 (0.1%)

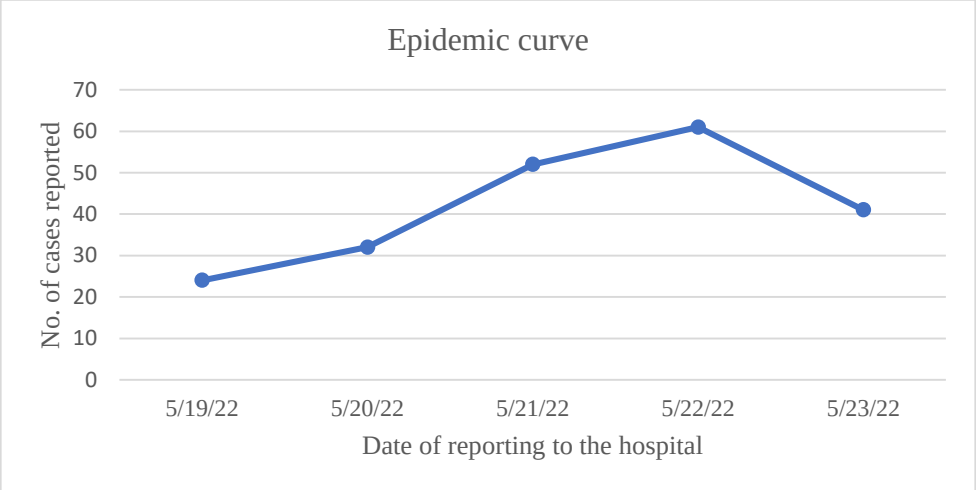

***Figure 1:** Trend diagram showing the epidemic curve based on the date of onset of symptoms*

Results of Routine Investigations

Routine blood tests, Liver Function Tests, and Renal Function tests were inconclusive. Specific serological tests for Dengue and Leptospirosis turned out to be negative in all the cases.

Results of Virological Investigations

All the cases were tested for COVID 19 by rapid antigen testing, of which 18 of them turned out to be positive. Out of the 16 samples randomly tested for viruses at NIV, 11 of them turned out to be positive for H3N2. The stool sample turned out to be positive for Norovirus G2.

Sequence analysis of H3N2:

The phylogenetic analysis showed that the influenza virus is close to the current vaccine strain (Darwin 2021 strain). According to unpublished data, the virus belongs to the same branch as the 2021 Pune, Indian strain

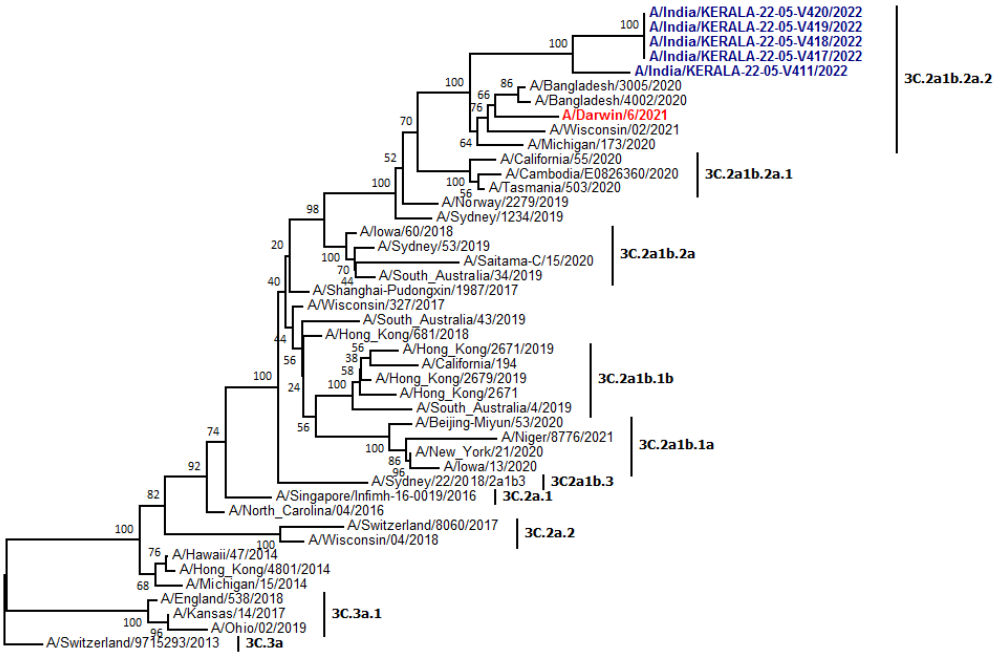

Figure 2. *Phylogenetic tree constructed based on HA gene of H3N2*

DISCUSSION

In the medical camp conducted on the university campus during the outbreak, details were obtained from 185 participants who had reported having any symptom at the time of data collection. The analysis of data collected from the medical camp showed that the major symptoms were fever, myalgia and headache followed by nausea or vomiting and abdominal pain. Around 40% of patients had respiratory symptoms like sore throat, cough, and nasal symptoms. As COVID is the first differential diagnosis in the current scenario, all the cases were tested for COVID 19 Rapid antigen testing kits, and 18 turned out to be positive and among the16 samples randomly collected for influenza testing, 11 tested positive for H3N2. The co-existence ofCOVID 19 and Influenza has already been documented (Chotpitayasunondh *et al*., 2021).

The initial symptoms of COVID 19 and Influenza are similar as both can present as influenza-like illnesses, though the progress of the diseases can be different (Zayet *et al*., 2020). However, the studies have described certain symptoms like sore throat, sneezing and vomiting are less frequent in COVID 19 compared to Influenza (Pormohammad *et al*., 2021). COVID-19 pandemic has influenced the incidence and trends of other respiratory viruses including Influenza. The circulating levels of Influenza have been at their all-time low during the pandemic. The various control measures including social distancing and face masks might have led to this decline (Olsen *et al*., 2021). As the world is trying to get back to normalcy these trends may also change; studies have predicted the possibility of an influenza pandemic following COVID-19 (Laurie & Rockman, 2021). The influenza virus is highly unpredictable as it is prone to antigenic

variations, so it is practically difficult to predict the strain and nature of infection in the coming years (Dos Santos *et al*., 2016). So, careful evaluation and surveillance of Influenza infections are the need of the hour.

India has also witnessed a decline in reported cases of influenza in recent times, but studies related to these aspects are limited. One study from temperate region of northern India in 2020-21, has reported a decline in Influenza cases which is attributed to the COVID-19 mitigation measures (Mir & Koul, 2021). Another study conducted in three states of India (Kerala, Karnataka, and Goa) also reported a decline in testing and diagnosis of Influenza compared to pre COVID times, however, the study also reported that there were no significant changes in positivity rate (Jayaram *et al*., 2022). This, in contrast to the assumptions of decreased transmission of Influenza cases indicates a decreased reporting amidst the pandemic. As a part of surveillance, the Kerala unit of NIV was monitoring the influenza outbreaks in the state and the cases were less during the COVID times. Since the COVID restrictions loosen, the cases reporting positive for influenza is also increasing and the outbreak detailed here is the first to be reported in Kerala, which occurred in a cohort of students in a university after a large gathering. This possibly indicates that the COVID 19 mitigation measures had a positive impact on the spread of Influenza also.

Since the affected students had gastrointestinal (GI) symptoms as well, a detailed investigation to rule out ADD or food poisoning was also carried out, but no significant association or pattern could be identified. GI symptoms are reported in Influenza also, but data is inconclusive (Minodier *et al*., 2015). Though one of the patients with gastrointestinal symptoms was tested positive for Norovirus (G1), the coexistence of Influenza and Norovirus could not be confirmed due to the non-availability of more stool samples for testing. Due to hesitancy from the students and due to the outpatient nature of management of the affected students at the medical camp venue, only one stool sample from a patient with GI symptoms could be collected. So far, no case reports are available on the coexistence of Influenza and Noro virus.

The prevalence of infections like acute respiratory infections, acute diarrheal diseases, etc. is seen to be high during summer and monsoon seasons in India. Though influenza has been reported throughout the year the number of cases reported during rainy seasons is comparatively higher. Various other factors including latitude, humidity and temperature are known to affect the seasonality of the virus (Chadha *et al*., 2015), (Waghmode *et al*., 2021). As per studies, the peaks of Influenza in places below 30-degree latitudes are expected during monsoon (Chadha *et al*., 2015). A similar pattern is observed in Kerala too, as is evident from the data available from the reporting portal for infectious diseases of the Integrated Disease Surveillance Project (IDSP, MoHFW, GoI)(25). The current outbreak occurred in May, the summer season in Kerala during which influenza outbreaks are not much expected. But as per the IMD report, Ernakulam district had received excess rain during May compared to past years. Climate change has a great influence on Influenza (Lane *et al*., 2022). Kerala is having a very unpredictable climate for the past few years with off-season rains; hence it will be difficult to predict the seasonality of Influenza in the state. So, a constant vigil for the disease throughout the year is recommended.

Air pollution has been studied as a risk factor for acquiring Influenza. Various researchers have identified air pollutants such as ozone, sulfur dioxide, nitrogen dioxide, nitric oxide, PM 2.5 etc. can increase the risk of Influenza transmission (Domingo & Rovira, 2020), (Sooryanarain & Elankumaran, 2015). The average air quality index of Kochi a few weeks before the outbreak was 110 (moderate) as per the published data on air quality of various cities in India (NAQI 2022) [29] and might have influenced the influenza transmission.

Phylogenetic analysis of HA gene showed that the viruses involved in the outbreak belong to the genetic subclade 3C.2a1b.2a.2 (Bangladesh like), predominantlycirculating worldwide. Also, the virus is in the same branch with 2021 Pune, Indian strain as per an unpublished data. The virus is close to the vaccine strain A/Darwin/6/2021 which is a component of vaccines recommended for use in Northern hemisphere for the year 2022-23 by WHO (Melidou *et al*., 2022), (Organization, 2022)

CONCLUSION

This would be the first study to report the simultaneous occurrence of Influenza, COVID-19, and Norovirus in the same cohort. Viral infections might have overlapping symptoms, so it's imperative to have a high degree of suspicion for every potential diagnosis.

LIMITATIONS

Owing to the outpatient nature of management at the medical camps conducted in the university campus for the sick students and the consequent reluctance of the students in providing stool samples for viral testing, our Noro virus testing was limited to a single sample, which turned out to be positive for the same. Also, a limited number of nasopharyngeal samples could be collected and tested for Influenza, from the larger affected student population.

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