

Original Research

Cite this article: Salem-Bango L, Hasan Md. A, Agbogan JA, Miah L, Antoine C, Tonon B, Spiegel P and Altare C (2024). COVID-19 Epidemiology in Fragile Contexts:

A Descriptive Analysis of COVID-19 in Host Communities in Cox's Bazar, Bangladesh During the First Year of the Pandemic. *Disaster Medicine and Public Health Preparedness*, **18**, e318, 1–8
<https://doi.org/10.1017/dmp.2024.304>

Received: 27 July 2023

Revised: 13 May 2024

Accepted: 26 September 2024

Keywords:

COVID-19; pandemics; epidemiology; disease outbreaks; fragile settings

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COVID-19 Epidemiology in Fragile Contexts: A Descriptive Analysis of COVID-19 in Host Communities in Cox's Bazar, Bangladesh During the First Year of the Pandemic

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Abstract

Objectives: In 2020, COVID-19 modeling studies predicted rapid epidemic growth and quickly overwhelmed health systems in humanitarian and fragile settings due to preexisting vulnerabilities and limited resources. Despite the growing evidence from Bangladesh, no study has examined the epidemiology of COVID-19 in out-of-camp settings in Cox's Bazar during the first year of the pandemic (March 2020–March 2021). This paper aims to fill this gap.

Methods: Secondary data analyses were conducted on case and testing data from the World Health Organization and the national health information system via the District Health Information Software 2.

Results: COVID-19 in Cox's Bazar was characterized by a large peak in June 2020, followed by a smaller wave in August/September and a new wave from March 2021. Males were more likely to be tested than females (68% vs. 32%, $P < 0.001$) and had higher incidence rates (305.29/100 000 males vs. 114.90/100 000 female, $P < 0.001$). Mortality was significantly associated with age (OR: 87.3; 95% CI: 21.03–350.16, $P < 0.001$) but not sex. Disparities existed in testing and incidence rates among upazilas.

Conclusions: Incidence was lower than expected, with indicators comparable to national-level data. These findings are likely influenced by the younger population age, high isolation rates, and low testing capacity. With testing extremely limited, true incidence and mortality rates are likely higher, highlighting the importance of improving disease surveillance in fragile settings. Data incompleteness and fragmentation were the main study limitations.

Research has shown that COVID-19 has differential impacts on communities depending on individual factors like age and health status as well as structural factors like population density, access to resources, and ability to quarantine and isolate.^{1,2} In early 2020, the worsening COVID-19 pandemic spurred growing concerns among the humanitarian community regarding its potential impact in fragile settings. Facing significant political, economic, environmental, and/or social vulnerabilities, these communities faced compounded risks that potentially exacerbate their likelihood of severe morbidity and mortality from a respiratory disease.³

Cox's Bazar (CXB), a district within the Chattogram Division of Bangladesh, is one such fragile context. One of the poorest districts in Bangladesh, CXB had long faced environmental, social, and economic vulnerabilities.⁴ Of the almost 3 million people in the district in 2020, approximately 33% lived below the poverty line.⁴ Furthermore, the district has hosted one of the largest refugee populations in the world since 2017, when over 900 000 Forcibly Displaced Myanmar Nationals (FDMN) crossed the border into CXB to seek safety.⁵ While international aid organizations provided significant resources and services over the years to support the sudden, significant influx of people in need,^{6,7} the institutional capacity of CXB was still limited and underprepared for an emergency of its own.⁴ For example, at the beginning of the pandemic, the health system in CXB had 1 10-bed intensive care unit (ICU)⁸ and 1 machine conducting Polymerase Chain Reaction (PCR) tests.⁹ Faced with an increasingly fragile system, the host community of CXB was considered as not well-positioned to contain the spread of COVID-19.

With the first COVID-19 case reported in CXB on March 23, 2020 (2 weeks after the country's first case on March 8),¹⁰ alarm bells rang within the humanitarian community for the possible spread in refugee camps and the district.^{11,12,13} Epidemiological models predicted dire morbidity and mortality in refugee camps,¹³ leading to intense public health measures and resource allocation by the government and international aid organizations.

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More than 4 years into the pandemic, a plethora of research has been conducted on COVID-19 in Bangladesh. Epidemiological analyses highlight national-level disease dynamics, including trends in epidemic curves and age- and sex-specific rates.^{10,14,15,16} Researchers have also investigated COVID-19 knowledge, attitudes, and practices in Bangladesh, identifying differences by sex, education level, and other demographic factors.^{17,18,19,20} Several studies also investigated interruptions in routine health services at the national level, providing a variety of estimates including a 40% decrease in outpatient consultations and a 3.5% decrease in Bacillus Calmette-Guérin (BCG) child vaccination,²¹ a 71.3% reduction in the provision of antibiotics, and a 36% decrease in diphtheria, tetanus, and pertussis (DPT3) vaccination.²²

A handful of studies have been conducted in CXB, mostly among the refugee communities and only a few including the host communities as well. These include studies investigating knowledge, practices, and attitudes about preventive measures in camps²³ and infection prevention and control best practices,²⁴ risk factors for severe COVID-19 in the inpatient department of a field hospital,²⁵ changes in health care utilization,²⁶ and drivers of vulnerability.²⁷ One serosurvey was conducted in the camps, revealing that almost half of the camp dwellers had been infected by COVID-19 by December 2020.²⁸ Despite this extensive literature, there remains limited evidence on the epidemiology of COVID-19 in CXB's vulnerable host community. As growing conflict, natural disasters, and other crises increase the number of humanitarian emergencies worldwide, it is critical to understand how epidemics and pandemics have impacted vulnerable groups in fragile settings to better inform future public health strategies. This paper aims to address this research gap, providing a descriptive epidemiological analysis of the morbidity and mortality of COVID-19 in the host population of CXB during the first year of the COVID-19 pandemic.

Methods

Study Setting

Cox's Bazar district falls within the Chattogram Division of Bangladesh and has an estimated total population of 3 million, excluding FDMN. 53% of the host population is aged 19 years and under. Only 5.1% of the population is over age 60.²⁹ CXB is broken up into 8 *upazilas*, or sub-districts: Cox's Bazar Sadar (the economic hub of the district), Chakaria, Kutubdia, Moheshkhali, Pekua, Ramu, Teknaf, and Ukhia. This analysis focuses on the out-of-camp host population within the district.

Data Sources

Secondary anonymized data was compiled from several sources and included

- 1) Individual-Level Case Data – A line list of confirmed COVID-19 cases from the host community was obtained from the World Health Organization (WHO). These data included testing date, *upazila*, and outcome for each reported confirmed case in Cox's Bazar.
- 2) Individual-Level Testing Data – A line list of COVID-19 tests conducted in Cox's Bazar was obtained from WHO. These data included testing data and location, patient address, and test result. Patient addresses were provided at various levels including ward, village, and *upazila* and were aggregated at the *upazila* level for consistency of analysis.

- 3) Case Management Data – Hospitalization data was obtained from the District Health Information Software 2 (DHIS2). Data included the number of new cases, hospitalized patients, recovered patients, and deaths per day at the district-level.
- 4) National Morbidity and Mortality Data – Data on cases and deaths at national level was obtained from the Johns Hopkins COVID-19 Dashboard.³⁰
- 5) National Testing Data – National-level data on COVID-19 testing in Bangladesh was obtained from Our World in Data.³¹
- 6) Population Data – Population data were obtained from the 2011 Population and Housing Census and the 2011 growth rate applied to the adjusted 2011 population sizes by *upazila*.²⁹

Additional information on data sources and management can be found in Supplemental Material.

Statistical Analysis

Descriptive statistics were conducted in RStudio (version 2021.09.2-382; R version 4.2.1)³² to analyze the epidemiology of COVID-19 within CXB. Chi square tests were conducted to compare observed versus expected counts of cases and deaths between different binary characteristics. Expected counts were calculated by applying a select incidence rate to the applicable population data. Two-sample *t* tests were conducted to compare average ages of cases from the confirmed case line list. Lastly, logistic regressions were run to identify demographic characteristics associated with higher odds of death from COVID-19.

Ethical Considerations

Ethical approval was obtained from the Johns Hopkins Bloomberg School of Public Health's Institutional Review Board (IRB) under IRB determination notice 14719 for non-human subject research as all data were aggregated and anonymized. National ethical and administrative approvals were received by the Bangladesh Medical Research Council (registration number 36610122020 dated 04/03/2021).

Results

Incidence, Testing, and Positivity Rates

CXB district recorded 6072 confirmed cases of COVID-19 between March 23, 2020-March 31, 2021 (Table 1). At the district level, the incidence rate began rising in April, peaked in June 2020, and began to quickly decline in July. A smaller wave occurred in August and September, but overall, the incidence rate declined gradually over time before starting to increase again in March 2021. *Upazila*-level epidemic curves followed similar patterns. Figure 1 shows the rolling 2-week average incidence rates over the study period.

The 2-week rolling average testing rate varied considerably throughout the period; 4 main waves occurred in June 2020, September 2020, November 2020, and March 2021. Often these waves aligned with those of incidence rates, with testing and incidence rates starting to increase in the same week (see Figures 1 and 2). CXB Sadar and Teknaf *upazilas* had the greatest proportion of their populations tested, while Ramu, Pekua, and Kutubdia had the lowest testing rates. People who were tested ranged from 7 days of age to 99 years of age. Males were more likely to get tested, making up 68% of the tests ($P < 0.001$).

Positivity rates spiked in May and June 2020 and trended downward the rest of the study period before rising again in March

Table 1. Morbidity, mortality, and testing capacity, Cox's Bazar vs. Bangladesh, March 2020-March 2021

	No. cases	Incidence rate (per 100,000)	No. deaths	CFR (%)	Testing rate (per 100,000)	Positivity rate (%)
Bangladesh	611 295	371.18	9046	1.48	2835.73	13.09
Cox's Bazar district	6,072	202.65	76	1.30	2867.1	9.31
Chakaria	564	120.4	8	1.40	1564.99	7.87
Cox's Bazar Sadar	3180	517.74	47	1.50	4894.64	14.06
Kutubdia	106	70.93	2	1.90	754.76	11.81
Moheshkhali	394	96.48	2	0.50	2861.43	4.14
Pekua	221	63.45	2	0.90	1074.45	7.56
Ramu	458	130.21	5	1.10	1322.44	12.27
Teknaf	512	224.2	8	1.60	6065.06	5.03
Ukhia	637	227.87	2	0.30	3316.72	8.49

Note: Incidence rates were calculated using the Case line list, while testing and positivity rates were calculated based on the testing data. Discrepancies cannot be excluded and are due to data incompleteness and secondary upazila classification.

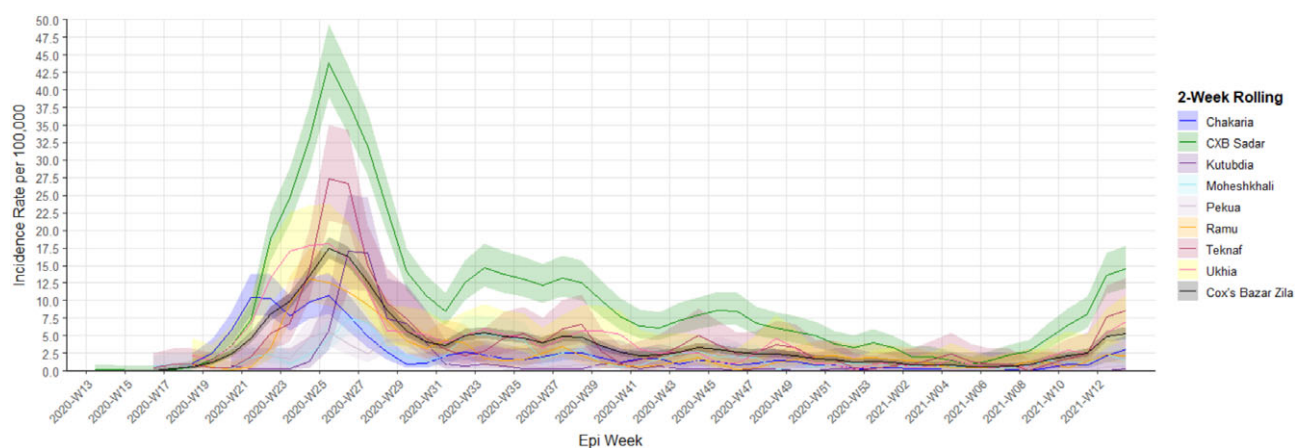


Figure 1. Epidemic curve of incidence rates for all upazilas, March 2020-March 2021. Two-week rolling incidence rates per 100 000 people were calculated for each upazila from March 2020-March 2021. All upazilas followed similar trends.

2021. The cumulative positivity rate for CXB district was 9%, with a range of 1-20%. Kutubdia, which had the lowest testing rate, had the third highest cumulative positivity rate. Compared to Bangladesh nationally, CXB district had a 45% lower incidence rate (IRR 0.55; only CXB Sadar upazila had a 39% higher incidence rate) and a comparable testing rate (testing rate ratio 1.01). The district's positivity rate was 28.9% lower. Table 1 provides key epidemiological figures at national, district, and upazila level.

Epidemic curves for each upazila can be found in Supplementary Figures 1-9; monthly rates by upazila can be found in Supplementary Table 1; maps of the incidence, testing, and positivity rates by upazila can be found in Supplementary Figures 9-12.

Morbidity and Mortality Risk Factors

Incidence rates differed by age and sex. Across all upazilas, incident cases were higher among males than females (Table 2). At the district level, the incidence rate among men was twice as high as that among women ($P < 0.001$). Within upazilas, the incidence rate for men ranged from 2 times higher in Ukhia to 8 times higher in Moheshkhali. The median age of cases ranged from 29-36 years,

with an overall median age of 32 for the district. Overall, the highest incidence rates occurred among people aged 50-59 while the age group 60+ recorded the lowest incidence rate among adults. Age-specific incidence rates (along with histograms of cases and deaths by age) can be found in Supplementary Table 2 and Supplementary Figures 13 and 14. CXB recorded 76 total deaths from March 2020-March 2021. Table 3 shows case fatality rates (CFR) for the entire population, the elderly, and males by upazila. Kutubdia had the highest case-fatality rate (1.9%), while Ukhia the lowest (0.3%). Difference in CFR between males and females was statistically significant only in Ramu ($P < 0.01$) where females had a higher case-fatality rate. Case-fatality rates were higher among cases aged 60 years and above (ranging from 10-16.7%).

Odds of mortality (Table 4) were significantly higher among people aged 60+ than adults under 60 (OR: 87.03, 95% CI 21.03-350.16, $P < 0.001$). Sex was not significantly associated with increased mortality and did not appear to confound the relationship between mortality and age. The odds of death among individuals under age 18 was zero, as no deaths occurred in this age group. The lowest age group included in the regression was adjusted to include at least 1 death.

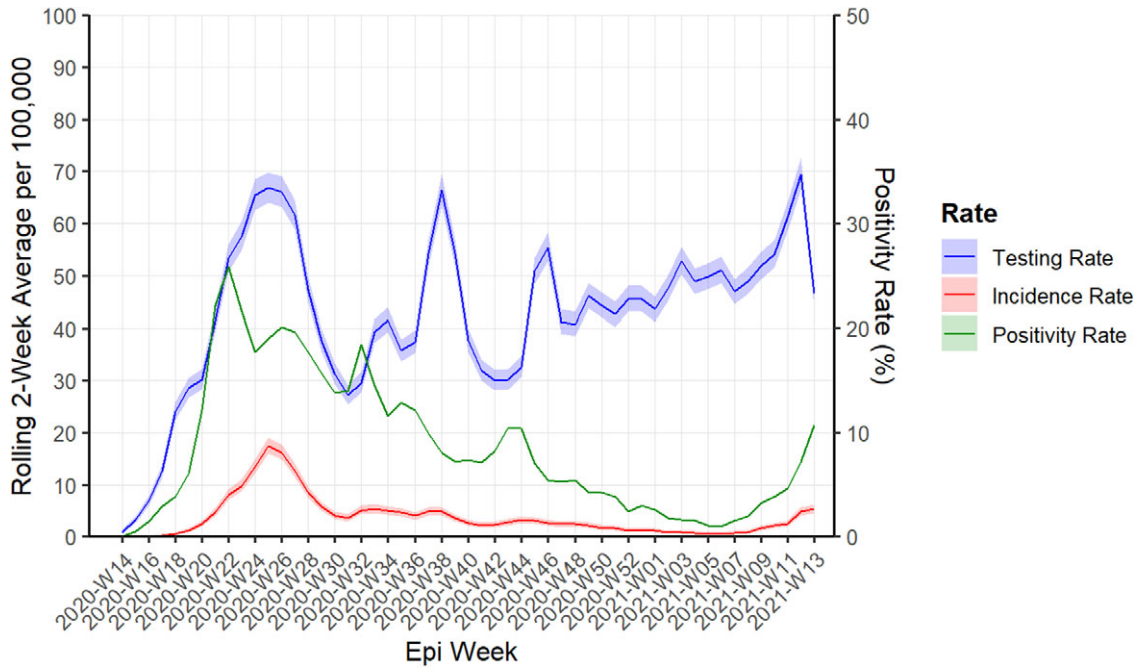


Figure 2. Incidence, testing, and positivity rates for Cox’s Bazar District. Incidence, testing, and positivity rates were calculated for Cox’s Bazar District from March 2020-March 2021. Incidence and testing rates are a rolling 2-week average while positivity rate is a percentage.

Case Management

In April 2020, 86.1% of cases were isolated, either at home, in hospitals, or in specialized isolation facilities. By June 2020, 100% of cases were reportedly isolated. In total, 63.81% of recorded cases were reported as hospitalized, representing approximately 0.14% of the entire population. From March to August 2020, 100% of reported cases were hospitalized. Reported hospitalization rates rapidly dropped to 19% in September 2020 and remained at 0% for the rest of the time period. However, data from hospitals indicate that they were still admitting COVID-19 patients throughout the time period, suggesting hospitalizations continued.

Table 2. Incidence by sex, COVID-19 cases in Cox’s Bazar District, Bangladesh, March 2020-March 2021

	Incidence (no. cases)		Incidence rates (per 100 000)	
	Male	Female	Male	Female
CXB District	4445	1600***	305.29	114.90
Chakaria	437	127***	185.03	54.68
CXB Sadar	2273	885***	702.84	304.32
Kutubdia	76	30***	99.4	41.1
Moheshkhali	352	41***	167.1	20.74
Pekua	177	44***	100.37	25.59
Ramu	338	120***	190.86	68.71
Teknaf	369	142***	321.14	125.15
Ukhia	423	211***	300.09	152.25

Chi square tests on observed versus expected cases found statistically significant differences in the incidence of COVID-19 between males and females. To calculate expected cases for males and females, the total incidence rate was applied to sex-specific population counts for each upazila. Only cases with known sex (99.56%, n = 6045) are included. ***P < 0.001

Limitations

Data completeness is the largest limitation of this study, as data availability restricted the analyses that could be run (Supplementary Tables 3-5). In-country capacity was quickly overwhelmed when case counts began rising at a faster pace, leading to only core data – date of detection, age, sex, and upazila – being consistently collected. Underreporting can therefore not be excluded. Furthermore, utilizing data from different sources is often subject to discrepancies in data collection and management, leading to incongruencies such as the number of reported cases (6450 as per DHIS2 and 6072 as per WHO) and reported deaths (82 per DHIS2 and 76 per WHO). Overall, however, datasets were largely similar, giving confidence to the analysis. Data from routine health services are known to only capture people seeking care, with the risk of underreporting cases. Another limitation relates to underlying

Table 3. Case-fatality rates (CFR; %) of COVID-19 in Cox’s Bazar district, Bangladesh, March 2020-March 2021

	CFR	CFR male	CFR age 60+
Cox’s Bazar District	1.3	1.2	10.1
Chakaria	1.4	1.4	10
CXB Sadar	1.5	1.7	10.9
Kutubdia	1.9	1.3	16.7
Moheshkhali	0.5	0	10
Pekua	0.9	1.1	15.4
Ramu	1.1	0.3	13.8
Teknaf	1.6	1.4	13.8
Ukhia	0.3	0.2	0

Case-fatality rates (CFR) in percentages.

Table 4. Odds of mortality by age and sex, COVID-19 cases in Cox's Bazar District, Bangladesh, March 2020-March 2021

Characteristics	Univariate analyses		Multivariate analysis	
	OR	(95% CI)	OR	(95% CI)
Age				
<=25 years	1.0	(Reference)	1.0	(Reference)
26–39 years	2.57	(0.54–12.12)	2.62	(0.56–12.39)
40–59 years	9.2**	(2.14–39.6)	9.42**	(2.19–40.6)
60+ years	85.42***	(20.66–353.11)	87.03***	(21.03–350.16)
Sex				
Male	1.0	(Reference)	1.0	(Reference)
Female	1.13	(0.69–1.87)	1.2	(0.72–2.02)

P values:

*<0.05

**<0.01

***<0.001

OR = odds ratio; CI = confidence interval.

population data which were based on the last available census (2011) and updated using the 2011 annual growth rate. This may influence the incidence and testing rates. Furthermore, this study only examines the first year of the pandemic. Other research has suggested that the epidemic size significantly increased during the rest of 2021. Additional research should be conducted to examine the impact of more transmissible variants like Delta and Omicron, and the role of vaccination. While COVID-19 vaccines officially became available in Bangladesh in January 2021, in practice, roll-out was delayed and by June 2021 less than 4% of the country was fully vaccinated.³³ Thus, vaccination was not included in this analysis. Lastly, the impact of COVID-19 on a community goes beyond incidence and mortality to affect livelihoods, food security, education, and gender-based violence, as highlighted in several studies.^{34,35}

Discussion

We present an overview of the epidemiology of COVID-19 in CXB, triangulating a variety of existing data. The epidemiological dynamics and the epidemic curve of COVID-19 in CXB from March 2020 to March 2021 aligned to those found at national level. They correlated with several events that led to mass movements within the region, including the return of factory workers from Dhaka to their home communities at the start of the lock down (followed by the first increase in cases in the second half of April 2020); the end of the national lockdown at the end of May 2020, allowing factories and mass transportation to renew operation; and the subsequent permitted Eid al-Fitr celebrations (May 23–24, 2020), which contributed to widespread travel and large gatherings.^{15,16} The link between societal events and epidemic curves highlights how effective public health measures can be in delaying or slowing down infections, when in place. Yet, governments across the world faced important challenges and pressure in enforcing such measures, as other political, economic, and societal factors have at times prevailed given the complexity of managing a crisis affecting entire societies, low level of preparedness, and different levels of institutional capacity. Critics did not spare the government of Bangladesh, which was criticized for delayed action, contradicting policies, and corruption.^{36,37}

The main peak in June further coincided with an increase in testing capacity in the district, as the Cox's Bazar Medical College received its second PCR machine.⁹ Following this rapid peak (which occurred nationwide), the Government of Bangladesh initiated a fee for PCR testing.³⁸ This spurred a significant decline in testing in July.³⁸ While not to the same degree as in June, the epidemic curve experienced another wave in August and September 2020. This wave correlated with nationwide mass gatherings, with incidence rates rising 1–2 weeks after Eid-ul-Adha on July 25, 2020. While testing capacity in the district had further improved by August (increasing from 200 to 1000 tests/day),³⁹ the rise in testing rates was delayed compared to the rise in incidence rates, suggesting that the increase in cases was not solely due to an increase in testing rates. An increase in cases may have in fact spurred more people to get tested despite the testing fee. These overall trends in the epidemic curve of the host population further mirror those found among Rohingya refugees in the district. Positivity rates among Rohingya refugees in CXB peaked in June 2020, and an epidemic wave was recorded in September and October 2020.⁴⁰

When comparing upazilas, CXB Sadar had the second highest testing rate and highest incidence rate. Its high testing rate is likely due to its increased access to health facilities, including the CXB 250 Bed District Sadar Hospital and the Cox's Bazar Medical College. Meanwhile, its high incidence rate is likely a factor of both the increased testing and its position as the economic hub of the district. Teknaf and Ukhia had the highest and third highest testing rates in the district. This increased access to testing could be an artifact of the resources poured into preventing large outbreaks within the refugee camps and could partially explain why these 2 sub-districts had the second and third highest incidence rates, after CXB Sadar. However, while these 2 upazilas had similar incidence rates, Teknaf had a case-fatality rate 5 times greater than that of Ukhia, which had the lowest case-fatality rate of the 8. The higher CFR could be influenced by the age-specific incidence rates; Teknaf had higher incidence rates among people older than 50 than did Ukhia.

Similar to national trends (with men in Bangladesh making up 72% of cases),¹⁰ incidence in CXB was also higher among men than women. This could have been influenced by numerous factors, such as greater knowledge of COVID-19 and higher practice of preventative behaviors among women than men;^{17,18,20} disparate exposures;^{41,42} as well as higher testing rates among men, possibly linked to the lower autonomy and access to care of women compared to men.⁴³ For example, some women in camps have reported requiring their husband's approval to get tested for COVID-19,¹⁹ while women in Bangladesh have lower health care seeking behavior than men.^{44,45} Yet, and unlike data from Bangladesh nationally and from other countries, reported data from CXB did not reveal differential case-fatality rate.^{10,46,18} The lack of a higher case-fatality rate among men in CXB could be influenced by the lower testing and incidence rates among women. If women were less likely to be tested, identified cases may have been of greater severity, artificially raising the CFR of women and masking the possible difference. This is further supported by the fact that Ramu (the only upazila with a disparate CFR) had a higher CFR among women than men.

One potential contributor to the lower-than-expected morbidity and mortality in CXB is the age-distribution of the population. International data has highlighted how big a role a population's age-distribution can play in morbidity and mortality levels from COVID-19, with younger cases more likely to have milder symptoms and lower risk of death.^{10,47,48,49} In CXB, most cases occurred in younger age groups; the 60+ age group had the lowest incidence

rate among adults. Yet, mortality was significantly higher with increased age. If a larger proportion of cases had been among this more vulnerable population, overall mortality and case-fatality rates may have been significantly higher. The overall effect of the pandemic has likely been underestimated in similar fragile settings where low institutional capacity and milder symptoms due to a younger age structure may have contributed to lower proportion of true cases being identified via testing.⁵⁰ Increased effort in risk communication targeted for youth are warranted in future epidemic/pandemic responses to ensure higher awareness and engagement of the younger population.

Isolation strategies may also partially explain the unexpectedly low reported morbidity and mortality. The first lockdown after the initial cases (from March-May 2020) may have influenced the 27-day lag before the district recorded another case. Clinically, 99.8% of the cases in CXB were reportedly isolated, which may have helped reduce transmission. Additional severe acute respiratory infection isolation and treatment facilities were also established so that even mild cases could be treated and isolated if they could not adequately isolate at home.⁵¹ However, these isolation measures were likely stronger on paper than in reality. WHO reported challenges in getting cases to present to isolation facilities.⁵² Data were also unavailable as to where, how, and for how long each case isolated, reducing confidence in this single measure.

While the reported data suggest that morbidity and mortality were not as severe as expected, it is important to highlight that with testing capacity so limited, the reported case counts are likely significantly underreported. Upazilas with higher testing rates tended to have higher incidence rates, while upazilas with lower testing rates had lower incidence rates. The true incidence and mortality rates in CXB are likely much higher than what is reported in this paper.⁴⁰ To our knowledge, no seroprevalence survey has been conducted among the non-refugee community in CXB district which could provide a better estimate of previous infections. Published seroprevalence results from Bangladesh during or close to the study period range from 54.2% in Chattogram (October 2020-February 2021),⁵³ to 28.7% in rural areas outside of Dhaka (April-October 2020), and to 48.3% among FDMN in the camps (December 2020).^{53,54} While just an approximation, this would correspond to 859 926 (28.7%)-1 623 971 (54.2%) cases, i.e., 141-268 times the reported number. An accurate understanding of the disease spreading is crucial for an adequate response and relies on a stronger surveillance system with decentralized testing capacity. Rapid scaling up of testing capacity remains a cornerstone of future pandemic responses.

Conclusion

This study analyzed the epidemiological dynamics of COVID-19 during the first year of the pandemic in Cox's Bazar, Bangladesh. The district's epidemic curve corresponded with sociological factors including intranational movement, large religious celebrations, and changes in testing. Incidence and case-fatality rates were comparable if not better than national rates. Overall, this study highlights the importance of improving disease surveillance systems in fragile settings. Incidence rates were likely significantly artificially lowered by low testing capacity. Incomplete data reduced the ability to identify disparities, gaps, and barriers, which limits strategic interventions and advocacy efforts. Future research should be conducted on the dynamics of the following years of the pandemic as well as the indirect impacts of the pandemic on other health outcomes.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1017/dmp.2024.304>.

Data availability. Data from Our World in Data, Johns Hopkins COVID-19 Dashboard, and the 2011 Bangladesh census are publicly available at the sources provided in the references in the manuscript. WHO and the MoH of Bangladesh require the data used in this analysis to be accessed through them via formal requests after receiving clearance from the national IRB.

Acknowledgements. We would like to thank the USAID's Bureau for Humanitarian Assistance for funding this work under funding agreement 720FDA20GR00228.

We would also like to thank the Bangladesh Ministry of Health for granting access to secondary data, specifically Cox's Bazar's Civil Surgeon for overall local level data access and WHO Country office for sharing COVID-19 data.

Author contribution. Lindsay Salem-Bango: Data curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft preparation, Writing – review and editing; Abul Hasan: Investigation, Writing – review and editing; Jogie Abujejo Agbogan: Project administration, Supervision, Writing – review and editing; Lalan Miah: Investigation, Writing – review and editing; Caroline Antoine: Project administration, Writing – review and editing; Brigitte Tonon: Project administration, Supervision, Writing – review and editing; Paul Spiegel: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review and editing; Chiara Altare: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review and editing.

Funding statement. Funds for this research were provided by the Bureau for Humanitarian Assistance, US Agency for International Development (<https://www.usaid.gov/>) Grant number 720FDA20GR00228). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interest. The authors have declared that no competing interests exist.

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