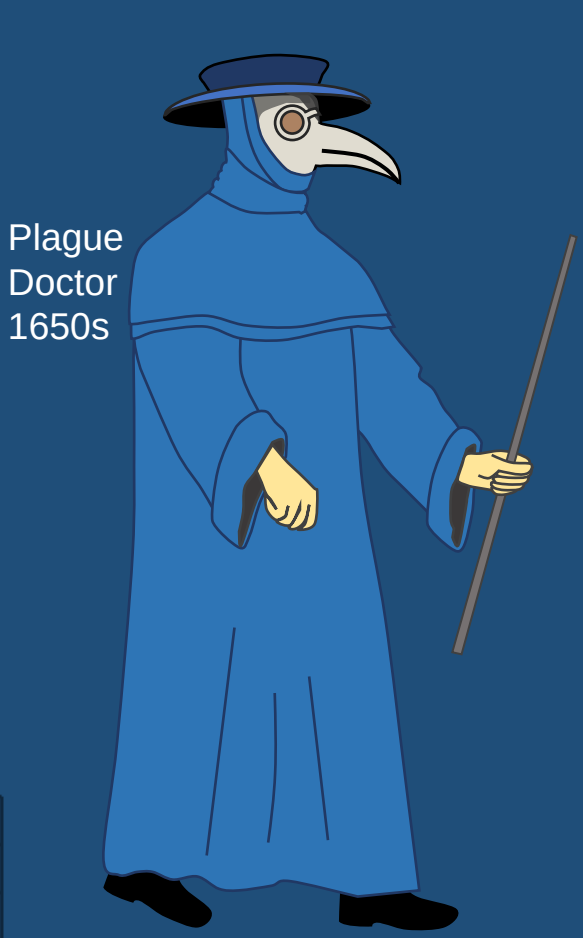
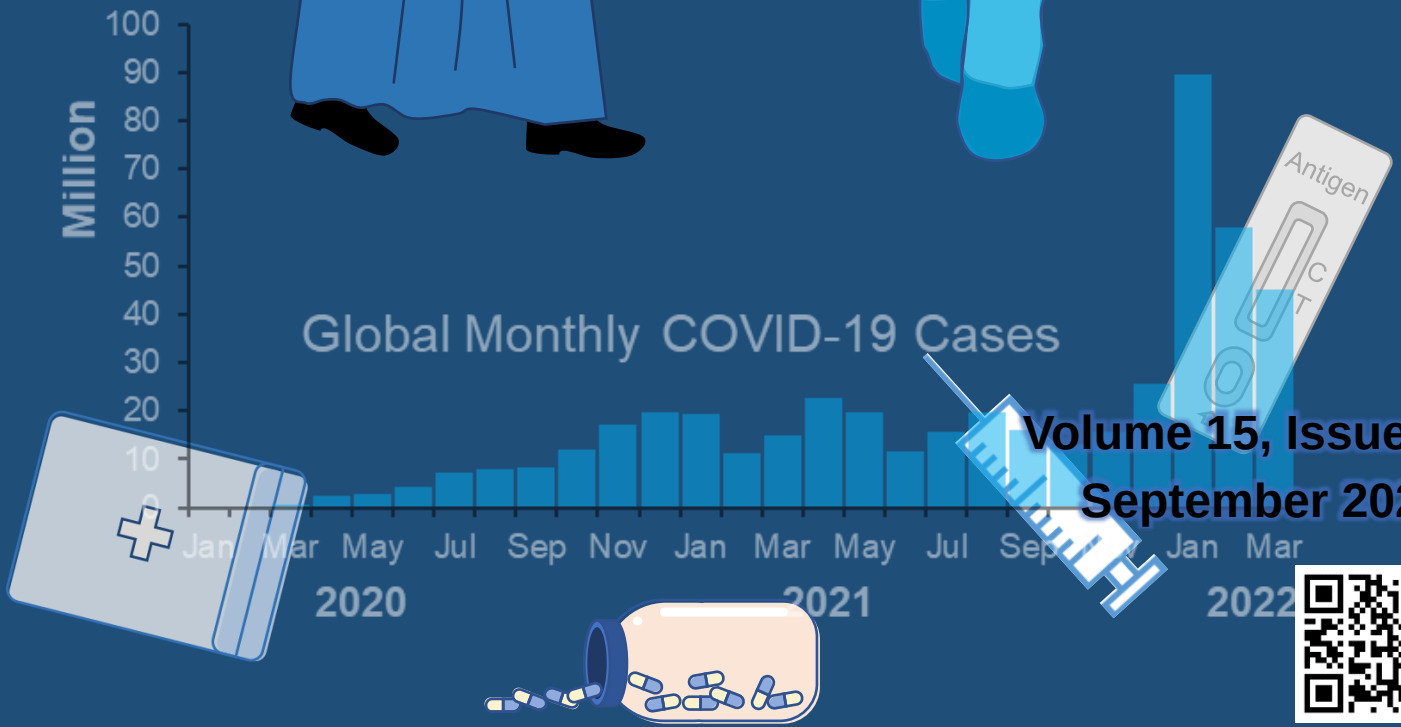
OSIR

Outbreak, Surveillance, Investigation and Response



Plague Doctor 1650s

COVID-19 Healthcare Worker 2020s



Volume 15, Issue 3

September 2022

www.osirjournal.net

ISSN: 2651-1061

The Outbreak, Surveillance and Investigation Reports (OSIR) Journal was established in 2008 as a free online publication in order to encourage and facilitate communication of health information and disease reporting across Asia and the Pacific. In September 2018, the journal is retitled as the "Outbreak, Surveillance, Investigation & Response" while maintaining the same abbreviation as OSIR.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Tiwanond Road, Talad Kwan Subdistrict, Muang District, Nonthaburi 11000, Thailand

Tel: +662-5901734, Fax: +662-5918581, Email: osireditor@osirjournal.net

Website: <**http://www.osirjournal.net**>

Volume 15, Issue 3, September 2022

Contents

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Editorial

Disease Reemergence as Non-pharmaceutical Interventions End

Angela Song-En Huang, Chief Editor

Before vaccines against coronavirus disease 2019 (COVID-19) were widely available, to control the spread of the disease, non-pharmaceutical interventions (NPIs) were promoted and implemented. People used hand hygiene products, practiced respiratory etiquette, and kept their distance when interacting with others. Governments closed schools, or shifted children and adolescents to online learning, imposed stay-at-home policies, and mandated mask use. These were all aimed to slow down the spread of COVID-19, a new disease, which most people had no immunity against.

With these interventions in place, in addition to limiting the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, other diseases, such as influenza, the common cold, and enterovirus infections, also stopped spreading. The decrease in these diseases, at first glance, seems to add value to NPIs practiced in the past two and a half years. However, without the exposure to multiple viruses throughout the years, we have created a cohort of young children who had had limited exposure to common viruses to build up strong immunity, and older adults who lacked the continued immune stimulation.

With good coverage of COVID-19 vaccination and the availability of effective medication against COVID-19, healthcare systems can now manage the number of COVID-19 cases. Therefore, nearly all countries have lifted policies originally placed to control the COVID-19 pandemic. As countries eased social restrictions, people dropped their masks and emerged from isolation. Having populations which had had limited exposure to common viral illnesses, lifting social restrictions had been associated with increases in, not only respiratory diseases, but also gastrointestinal diseases. Furthermore, it is not yet clear if these diseases will occur in the same seasonal pattern or cause the same disease as was seen in the pre-pandemic era.

In May 2022, cases of acute hepatitis of unknown etiology in children under the age of 10 years were first reported by the United Kingdom. In the following months, cases were reported from countries in Europe, the Americas, and Asia. Some children had disease so severe. They required liver transplant, and a few died. Studies during the past six months had put forth hypotheses including atypical response by children to their first adenovirus infection and immune phenomenon following SARS-CoV-2 infection. This is an example demonstrating that there are still much we do not know about the effects of prolonged large-scale implementation of NPIs and the consequences of the COVID-19 infection in the population.

Therefore, in the post-COVID-19 pandemic period, we must continue surveillance to identify possible deviations from expected disease occurrence patterns, maintain good vaccine coverage of vaccine preventable diseases, and prepare our healthcare systems to face possible surges of diseases other than COVID-19.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

An Acute Gastroenteritis Outbreak from Rice, Bangladesh, January 2021

Jafrin Jahed Jiti[1]*, Mallick Masum Billah[1], Mahbubur Rahman[1], Rashedul Hassan[1], Zakir Hossain Habib[1], A.S.M. Alamgir[1], Alden Henderson[2], Tahmina Shirin[1]

1 Institute of Epidemiology, Disease Control and Research, Bangladesh

2 Centers for Disease Control and Prevention, USA

*Corresponding author email: jafrinjahed@yahoo.com

Abstract

On 7 Jan 2021, the health manager at Bheramara, Bangladesh, notified the Institute of Epidemiology, Disease Control, and Research that 18 people were hospitalized for acute gastrointestinal illness. We conducted a retrospective cohort study to describe the outbreak and identify its source and took actions to contain it. Cases ate lunch after a funeral service on 5 January in Bheramara and had three or more loose stools in 24 hours, and vomiting or abdominal cramps after 5 January. We interviewed attendees with a semi-structured questionnaire. A Food Safety Inspector examined the food preparation areas. Stool and water samples were tested for enteric pathogens. Food-specific-attack rates, risk ratios, and 95% confidence interval (CI) were calculated. Common symptoms were diarrhea (94%) and vomiting (42%). The median incubation period was 16 hours (range 7–23). The attack rate of lunch attendees was 62% (72/117) with one death. Attendees who ate the second serving of rice had significantly higher risk of having acute gastrointestinal illness than those who did not (risk ratio 2.59, 95% CI 1.06–6.34). No pathogenic organism was isolated from stool and water samples. We suspected inadequately stored cooked rice was the source of the outbreak. We recommend proper cooking and storage of rice in a clean environment to prevent future outbreaks.

Keywords: acute gastroenteritis, bacillus cereus, reheated rice, outbreak, Bangladesh

Introduction

A foodborne disease outbreak occurs when two or more people develop acute gastroenteritis symptoms such as diarrhea, vomiting, or abdominal cramps from eating a common food.[1] Every year thirty million people in Bangladesh develop foodborne illness.[2] The common risk factors are improper food processing, inappropriate food storage conditions, contamination of food with infective microorganisms, cross-contamination from the environment, and insufficient knowledge on food preservation.[3]

In Bangladesh, foodborne outbreaks are reported by the Event-Based Surveillance and other foodborne and waterborne disease surveillance systems.[4] When a foodborne outbreak is reported, Ministry of Health staffs investigate to determine the source of those outbreaks so that future outbreaks can be stopped or prevented. In those investigations, *Vibrio cholerae* (8%), *Enterotoxigenic Escherichia coli* (3%), *Shigella* (2%), and *Salmonella* (1%) were identified.[5] However, no etiologic organism was identified in 86% of the samples.[5] When the etiologic agent cannot be identified, environmental findings, clinical symptoms, incubation period, epidemiological studies, and biological plausibility help to identify the source of the outbreak.[2]

On 7 Jan 2021, the health manager of Bheramara Upazila of Kushtia District in Bangladesh reported to the Institute of Epidemiology, Disease Control and Research (IEDCR) that several people with acute gastroenteritis were admitted to Bheramara Upazila Health Complex after attending a funeral service on 5 Jan 2021. A national rapid response team from IEDCR investigated the event, as it is the focal institution for investigation and response to outbreaks on behalf of the Ministry of Health and Family Welfare.[6] The objectives of the investigation were to identify the source and risk factors and to suggest measures for preventing future outbreaks.

Material and Methods

Study Design

We used a retrospective cohort study and described the demographics of all people who attended the lunch and calculated risk ratios to identify the food item that caused the outbreak. We also collected stools and water samples for laboratory investigation and conducted assessment of food preparation. Our investigation team consisted of three field epidemiologists, one Food Safety Inspector (FSI), and a medical technologist. The field investigation occurred from 7–12 Jan 2021.

Location and Timeframe

The foodborne outbreak occurred in Bheramara, Kushtia, Bangladesh. The affected people attended a funeral service on 5 Jan 2021.

Study Population

We obtained the guest list of the funeral service and interviewed them. The list consisted of people from the rural community, neighboring villages, and districts. Of those, people who attended the funeral and ate the lunch on 5 Jan 2021 at the host house in Bheramara, Kushtia were included in the cohort study. A suspected case was someone who ate food served at the lunch and had three or more loose stools in 24 hours or vomiting from 5 January to the date of interview, 7–12 Jan 2021.

Data Collection

The team first visited the hospital and interviewed the patients to collect details on the event and the food items served. That information was used to finalize the food items on the questionnaire. For the decedent, we conducted a verbal autopsy with her family and medical providers using the International Standard Verbal Autopsy Questionnaire 3.[7] Record reviews at local and referral hospitals were done.

Using a semi-structured questionnaire, we collected data on age, gender, signs and symptoms, time of the meal, onset of illness, hospitalization, time of recovery, specific food items, and about recovery or death for the cohort study.

Stools from patients and water that was used for drinking and cooking at the lunch were collected for laboratory testing.

We interviewed the cooks regarding the food ingredients and preparation. The FSI inspected the cooking and preparation areas for any breach in the food processing chain.

Data Analysis

The distributions of the demographics, clinical symptoms, incubation period, hospitalization, and outcomes of the study participants were summarized using frequencies and proportions. Attack rates (AR) were calculated by age, gender, food items, type of lunch attendees, and food servings. To measure the association between different food items and illness among the exposed and non-exposed groups, risk ratios (RR) were calculated. The statistical significance was set at a 95% confidence interval (CI) and the *p*-value was set at <0.05. Analysis was done using the statistical software STATA (version 14.2, Texas, USA).

Ethical Approval

The investigation was an emergency public health response and was not considered research subject to institutional review board approval. However, before interview and sample collection, verbal informed consent was requested and obtained from participants and guardians of the minors. Data security and confidentiality were ensured by a password-protected device.

Results

Demographic Information

There were 117 people who attended a funeral service in Bheramara, Bangladesh on 5 Jan 2021 (Figure 1). All those attendees ate food from the lunch were interviewed. Of them, 63% (74/117) were older than 18 years and 55% (64/117) were male (Table 1).

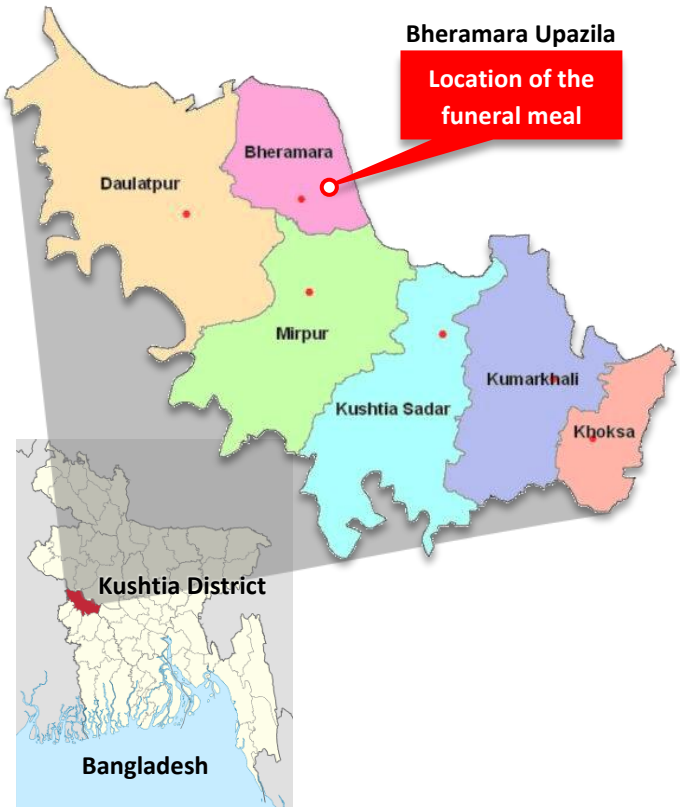


Figure 1. Upazilas of Kushtia District and location of the funeral service on 5 Jan 2021, Bheramara Upazila, Bangladesh

Epidemic Curve

The lunch started at 12:30 PM and ended at 5:00 PM on 5 Jan 2021. The median time from eating lunch to symptom onset was 16 hours (range 7–24 hours). The number of cases peaked in 10 hours after the first reported case. The epidemic curve suggested a point-source outbreak (Figure 2).

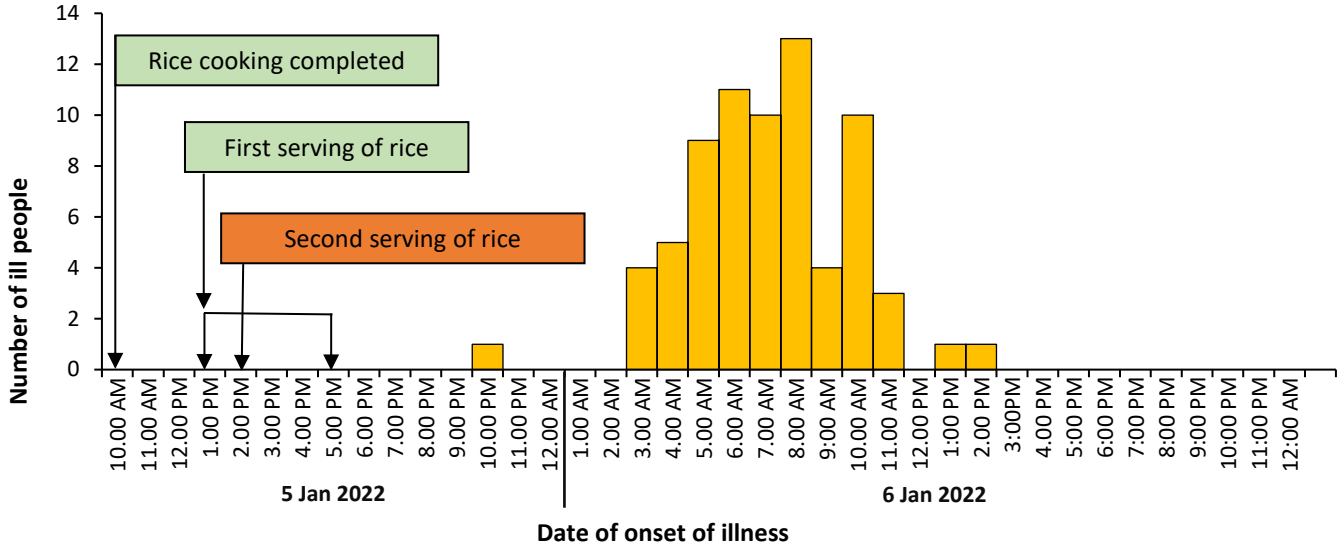


Figure 2. Epidemic curve showing total number of ill people who attended the funeral on 5 Jan 2021 by time of onset in Bheramara, Bangladesh (n=72)

Characteristics of Cases from the Lunch Cohort

Of the 117 people who ate lunch, 62% (72/117) presented with GI illness. The common symptoms were diarrhea 94% (68/72) and vomiting 42% (30/72). Among them, 38% (27/72) needed hospitalization and 85% (61/72) recovered within 24 hours of illness (Table 2). One elderly, co-morbid woman died from hypovolemic shock following uncorrected fluid loss and delayed hospitalization. The highest attack rates occurred among people aged 5–34 years (AR 72%, 41/57), females (AR 74%, 39/53) and people who ate the second serving of rice (AR 91%, 71/78) (Table 1–2).

Table 1. General characteristics and attack rate of the people who attended the lunch after the funeral service, Bheramara, Bangladesh, 5 Jan 2021 (n=117)

General characteristics	Total cohort (n=117)		Ill (n=72)		Attack rate (%)
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	
Age range					
<5	7	6.0	4	5.6	57.1
5-14	28	23.9	23	31.9	82.1
15-24	16	13.7	9	12.5	56.3
25-34	13	11.1	9	12.5	69.2
35-44	17	14.5	10	13.9	58.8
45-54	16	13.7	9	12.5	56.3
55-64	11	9.4	4	5.6	36.4
>64	9	7.7	4	5.6	44.4
Gender					
Male	64	54.7	33	45.8	51.6
Female	53	45.3	39	54.2	73.6
Types of funeral service attendees					
Relative	70	59.8	43	59.7	61.4
Neighbor	42	35.9	24	33.3	57.1
Host family	5	4.3	5	6.9	100.0
People attended lunch during two servings of rice					
First serving	39	33.3	1	1.4	2.6
Second serving	78	66.7	71	98.6	91.0

Table 2. Clinical profile of the funeral service attendees who developed illness after taking food at lunch, Bheramara, Bangladesh, 5 Jan 2021 (n=72)

Clinical status	Frequency (n)	Percentage (%)
Symptoms[a]		
Diarrhea[b]	68	94.4
Vomit	30	41.7
Abdominal cramp	29	40.3
Feverishness	27	37.5
Dehydration	25	34.7
Weakness	19	26.4
Fever with rigor	5	6.9
Headache	5	6.9
limb cramp	2	2.8
Incubation period (in hours)		
<8	1	1.4
8-16	42	58.3
>16	29	40.3
Hospitalization		
Yes	27	37.5
No	45	62.5
Recovery (within hours)		
<24	61	84.7
>24	11	15.3

Note: [a]Multiple responses. [b]Three or more loose stools within 24 hours

Source of the Foodborne Illness

Eating rice had the highest risk (RR 2.15, 95% CI 0.83–5.60) among the seven food items at the lunch (Table 3). Between 12:30 and 2:00 PM, 37 people ate the first serving of rice and 2.7% (1/37) got ill (Table 4). The 70 people who ate the second serving of rice had significantly higher risk of developing illness (RR 2.59, 95% CI 1.06–6.34). All members of the host family (5/5) ate the second serving of rice and got ill (Table 1). The cooks took rice home from the first serving for family and neighbors. None of the cooks or family members (0/28) developed illness. All three people who did not eat rice at lunch and ate the second serving of rice at home were ill. No commercial foods were served at the lunch.

Table 3. Food specific attack rate among the funeral service attendees, Bheramara, Bangladesh, 5 Jan 2021 (n= 117)

Food items consumed	Among exposed[a]				Among unexposed[b]				Relative risk	95% CI	*P*-value
	Ill	Not ill	Total	Attack rate (%)	Ill	Not ill	Total	Attack rate (%)			
Rice	69	38	107	64.5	3	7	10	30.0	2.15	0.83–5.60	0.03
Lentils	61	40	101	60.4	11	5	16	68.8	0.87	0.61–1.27	0.52
Water	64	40	104	61.5	8	5	13	61.5	1.00	0.63–1.58	1.00
Chicken	2	2	4	50.0	70	43	113	61.5	0.81	0.30–2.17	0.63
Beef	67	42	109	61.5	5	3	8	62.5	0.98	0.56–1.72	0.95
Vegetables	54	39	93	58.1	18	6	24	75.0	0.77	0.58–1.03	0.13
Rice pudding	50	37	87	57.5	22	8	30	73.3	0.78	0.59–1.04	0.12

Note: CI: confidence interval. [a]Exposed refers to an individual who consumed specific food items during the lunch. [b]Unexposed refers to individual who did not consume specific food items during the lunch

Table 4. Rice specific attack rate by time of intake among the funeral service attendees, Bheramara, 5 Jan 2021 (n=117)

Rice servings[a]	People who ate rice				People who did not eat rice				Relative risk	95% CI	*P*-value
	Ill	Not ill	Total	Attack rate (%)	Ill	Not ill	Total	Attack rate (%)			
Second serving (n=78)	68	2	70	97.1	3	5	8	37.5	2.59	1.06–6.34	<0.001
First serving (n=39)	1	36	37	2.7	0	2	2	0.0	-	-	0.81

Note: CI: confidence interval. [a]None among the people who attended the funeral and ate lunch took rice from both servings during the lunch

Laboratory Investigation

Bacteriological tests on eight stool samples and three water samples did not isolate any pathogens after 48 hours of culture. Food samples were not tested because leftover food was discarded on soil and was unsuitable for laboratory testing due to the possibility of contamination.

Assessment of Rice Preparation

None of the three cooks who prepared rice reported gastrointestinal symptoms before or after cooking the rice. The raw rice was stored in a cool, humid place. Thirty-eight kilograms of rice was washed in a large pan (Figure 3) beside a cowshed (Figure 4) and then cooked on a temporary wood-burning-stove outside the kitchen (Figure 5). The FSI inspected the area and noted that there was a possibility of environmental and soil contamination of the rice. Cooking of the rice ended at 10:00 AM and was separated into two non-equal parts and stored at room temperature. The first serving was stored inside the house and served at 12:30 PM. At 2:00 PM, the remaining rice which was kept beside the cowshed with half-open lid was reheated for 1–2 minutes and served to lunch attendees.

Note: Photo taken on 8 Jan 2021

Figure 3. The utensils in which rice were processed. These were kept beside the cowshed when the FSI inspected the area, Bheramara, Bangladesh

Note: Picture taken on 8 Jan 2021 and represents typical situation

Figure 4. The cowshed beside which rice was washed and cooked at the funeral service, Bheramara, Bangladesh

Note: Photo taken on the fourth day of the event during inspection of the cooking area by the FSI, Bheramara, 8 Jan 2021, which may not represent the situation on 5 Jan 2021

Figure 5. Parts of temporary stove where cooking of the main rice meal was done after the funeral-service, Bheramara, Bangladesh

Discussion

A foodborne outbreak occurred in Bheramara, Bangladesh due to eating rice. Laboratory testing could not identify any enteric pathogen. However, we suspected that an enterotoxin-producing organism caused the outbreak based on environmental findings, incubation period, and clinical symptoms.

Among the pathogens could cause this outbreak, *Bacillus cereus* seems the most likely cause. *B. cereus* produces a toxin mediated emetic or diarrheal gastro-intestinal illness.[8] The incubation period, symptoms and outcome of this outbreak are compatible to the form of toxin producing *B. cereus* which causes diarrheal form of illness.[9] Of the two rice servings, the second batch stored beside the cowshed and served two hours after the first batch was the probable source. The second batch had the highest attack rate and the later serving may allow *B. cereus* to multiply and contamination may have occurred after cooking and during storage beside the shed. Several studies in Bangladesh have shown the presence of *B. cereus* in contaminated food items and the environment.[10,11]

The outbreak may have been avoided if the rice was stored properly. Outbreaks in Canada, Netherland, Finland, United Kingdom, United States of America, China, Belgium, Japan and Malta have been associated with consumption of rice.[12–20]

In most instances, foodborne outbreaks are under-reported and fail to identify an etiologic agent in developing countries like Bangladesh. The reasons may be due to mild signs-symptoms, misdiagnosis, initiation of antibiotic intake before collection of samples and a lack of laboratory capacity to identify the organisms.[21] Most outbreaks that are reported occur in institutions such as schools and after large gatherings such as weddings. However, this outbreak was reported by the health manager of Bheramara who attended a training on public health rapid response that encouraged reporting of foodborne illnesses.

Death can occur following acute gastrointestinal illness due to ingestion of a high dose of exotoxin or complications of dehydration.[22,23] Moreover, people with compromised immune systems are likely to suffer serious consequences after consuming food containing enterotoxin.[24] The fatality in this outbreak was left alone at home after she ate the rice. She was a diabetic patient on insulin. As her family members were at work, she was unattended and taken to the hospital after more than 24 hours of fluid loss due to diarrhea and vomiting which caused hypovolemic shock and death.

Limitations

The etiology of the outbreak could not be confirmed due to limited laboratory capacity to detect enteric pathogens or measure enterotoxin in stools, vomitus, or contaminated food samples. The environmental assessment of the cooking area was done on the third day of the exposure event, which might not represent the actual conditions available during the food storage and preparation.

Public Health Actions and Recommendations

The leftover food items were discarded on 7 January. Local health authorities distributed leaflets on safe food processing and proper behavioral practices regarding food safety. Community members were encouraged to seek early hospitalization and proper intake of oral rehydration fluid in case of diarrhea. The local health authority at Bheramara Upazila was advised during a meeting to strengthen the emergency hotline services for acute cases.

We recommended proper storage and processing of food from preparation to consumption. Raw food should be stored in a clean and dry environment to avoid contamination. Food like rice should be boiled in small quantities in several pots and kept at 140°F (60°C) or above and served hot.[25] If reheating is required, the rice should be heated for at least 5 minutes at 133°F (56.1°C).[26]

Increasing food safety education in the community would encourage health-related behavioral practices such as proper handling, processing, and storage of food. Moreover, people should be encouraged to seek physicians' advice following any rapid onset gastrointestinal illness after eating meals at a social event. Laboratory capacity needs to be strengthened to identify suspected pathogens with biochemical and serological characteristics, toxin gene profiling and toxin quantification, which will assist in investigating the cause of future outbreaks.

Acknowledgements

We acknowledge the Field Epidemiology Training Program, Bangladesh; Centers for Disease Control and Prevention, United States of America; Upazila Health and Family Planning Officer of Bheramara Sub-district; Institute of Epidemiology, Disease Control and Research; Laboratory of Environmental Health, Laboratory Sciences and Services Division, International Center for Diarrheal Disease Research, Bangladesh, and the people who participated in the study.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

Suggested Citation

Jiti JJ, Billah MM, Rahman M, Hassan R, Habib ZH, Alamgir ASM, et al. An acute gastroenteritis outbreak from rice, Bangladesh, January 2021. OSIR. 2022 Sep;15(3):68–75.

References

1. World Health Organization. Foodborne disease outbreaks: Guidelines for investigation and control. Geneva: WHO Press, World Health Organization; 2008. 162 p.
2. Khairuzzaman M, Chowdhury FM, Zaman S, Al Mamun A, Bari ML. Food safety challenges towards safe, healthy, and nutritious street foods in Bangladesh. Int J Food Sci. 2014;2014:483519.
3. Noor R, Feroz F. Food safety in Bangladesh: A microbiological perspective. S.J. Microbiol. 2017 Aug 10;6(1):1–6.
4. Foodborne Illness Surveillance System In Bangladesh [Internet]. Dhaka: Institute of Epidemiology, Disease Control and Research; c2018 [cited 2021 Sep 25]. <https://old.iedcr.gov.bd/ index.php/surveillance/133-food-borne-illness>
5. Afzalur Rahman M, Flora M, Rahman M, Billah M. Food-borne Illness Surveillance and Etiology of Diarrhea in Bangladesh. Iproc. 2018;4(1):e10605.
6. Husain M, Rahman M, Alamgir A, Uzzaman MS, Flora MS. Disease Surveillance System of Bangladesh: Combating Public Health Emergencies. Online J Public Health Inform. 2019 May 30;11(1):e334.
7. World Health Organization. Verbal autopsy standards: ascertaining and attributing causes of death [Internet]. Geneva: WHO Press, World Health Organization; 2007. Part 2, International Standard Verbal Autopsy Questionnaires; [cited 2021 Sep 26]; p. 5–51. <https://apps.who.int/iris/handle/10665/43764>
8. May FJ, Polkinghorne BG, Fearnley EJ. Epidemiology of bacterial toxin-mediated foodborne gastroenteritis outbreaks in Australia, 2001 to 2013. Commun Dis Intell Q Rep. 2016 Dec 24;40(4):E460–9.
9. Parihar HS. Bacillus cereus. In: Wexler P, editor. Encyclopedia of Toxicology. 3rd ed. Amsterdam: Acedemic Press; 2014. p. 353–4.
10. Choi W, Kim SS. Outbreaks, germination, and inactivation of bacillus cereus in food products: A review. J Food Prot. 2020 Sep 1;83(9):1480–7.
11. Veysseyre F, Fourcade C, Lavigne JP, Sotto A. Bacillus cereus infection: 57 case patients and a literature review. Med Mal Infect. 2015 Nov–Dec;45(11–12):436–40. <http://dx.doi.org/10.1016/j.medmal.2015.09.011>

12. Todd E, Park C, Clecner B, Fabricius A, Edwards D, Ewan P. Two outbreaks of Bacillus cereus food poisoning in Canada. Can J Public Health. 1974 Mar–Apr;65(2):109–13.

13. Dirnhofer R, Sonnabend O, Sonnabend W. Eine todlich verlaufene Lebensmittelvergiftung durch Bacillus cereus [A fatal food poisoning caused by bacillus cereus]. Z Rechtsm. 1977 Aug 26;80(2):139–51. German.

14. Raevuori M, Kiutamo T, Niskanen A, Salminen K. An outbreak of Bacillus cereus food-poisoning in Finland associated with boiled rice. J Hyg (Lond). 1976;76(3):319–27.

15. Nichols GL, Little CL, Mithani V, De Louvois J. The microbiological quality of cooked rice from restaurants and take-away premises in the United Kingdom. J Food Prot. 1999 Aug;62(8):877–82.

16. Bennett SD, Walsh KA, Gould LH. Foodborne disease outbreaks caused by Bacillus cereus, Clostridium perfringens, and Staphylococcus aureus - United States, 1998-2008. Clin Infect Dis. 2013 Aug;57(3):425–33.

17. Chen D, Li Y, Lv J, Liu X, Gao P, Zhen G, et al. A foodborne outbreak of gastroenteritis caused by Norovirus and Bacillus cereus at a university in the Shunyi District of Beijing, China 2018: A retrospective cohort study. BMC Infect Dis. 2019 Oct 29;19(1):910.

18. Dierick K, Van Coillie E, Swiecicka I, Meyfroidt G, Devlieger H, Meulemans A, et al. Fatal family outbreak of Bacillus cereus-associated food poisoning. J Clin Microbiol. 2005 Aug;43(8):4277–9.

19. Shiota M, Saitou K, Mizumoto H, Matsusaka M, Agata N, Nakayama M, et al. Rapid detoxification of cereulide in bacillus cereus food poisoning. Pediatrics. 2010 Apr;125(4);e951–5.

20. Vella KA. A case-control study investigating an outbreak of Bacillus cereus food poisoning in a hotel in Malta. Maltese Medical Journal. 1997;9(1):23–7.

21. Jessberger N, Dietrich R, Granum PE, Martlbauer E. The Bacillus cereus Food Infection as Multifactorial Process. Toxins. 2020 Nov 5;12(11):701.

22. Hernandez-Cortez C, Palma-Martinez I, Gonzalez-Avila LU, Guerrero-Mandujano A, Solis RC, Castro-Escarpulli G. Food Poisoning Caused by Bacteria (Food Toxins). In: Malangu, N, editor. Poisoning-From Specific Toxic Agents to Novel Rapid and Simplified Techniques for Analysis [Internet]. London: IntechOpen; 2017 [cited 2021 Sep 25]. <https://www.intechopen.com/chapters/56521 doi: 10.5772/intechopen.69953>

23. World Health Organization. WHOo estimates of the global burden of foodborne diseases: foodborne disease burden epicemiology reference group 2007–2015 [Internet]. Geneva: WHO Press; World Health Organization; 2015 [cited 2021 Sep 25] 265 p. <https://apps.who.int/iris/bitstream/handle/10665/199350/9789241565165_eng.pdf>

24. Food and Drug Administration. Bad Bug Book, Foodborne Pathogenic Microorganisms and Natural Toxins. 2nd ed. College Park (MD): Center for Food Safety and Applied Nutrition, Food and Drug Administration; 2012 [cited 2021 Sep 25]. <https://www.fda.gov/food/foodborne-pathogens/bad-bug-book-second-edition>

25. Division of Foodborne, Waterborne, and Environmental Diseases, National Center for Emerging and Zoonotic Infectious. 10 Dangerous Food Safety Mistakes [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2021 Sep 25]. <https://www.cdc.gov/foodsafety/ten-dangerous-mistakes.html>

26. Islam MN. Fried rice syndrome, a disease of fast world: scientific analysis. Am J Biomed Sci Res. 2019;5(6):512–4.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Social Determinants and Leprosy in High Endemic Regions of Myanmar: an Ecological Study between 2016 and 2019

Sein Hlyan Bo[1,2]*, Rapeepong Suphanchaimat[1,3]

1 International Field Epidemiology Training Programme, Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

2 National Leprosy Control Program, Disease Control Unit, Department of Public Health, Ministry of Health, Myanmar

3 International Health Policy Program, Ministry of Public Health, Thailand

*Corresponding author email: seinhlyanbo@mohs.gov.mm, seinhlyanbo@gmail.com

Abstract

Leprosy has been a public health problem in Myanmar for many centuries. This study aims to explore the situation of leprosy and the association between leprosy and social determinants at the township level in seven endemic regions in Myanmar. The objectives of the study are to (i) describe the incidence and severity of leprosy and the disability due to leprosy in Myanmar between 2016 and 2019, and (ii) determine the correlation between leprosy incidence and social determinants in Myanmar in 2019. We used annual surveillance data of leprosy cases between 2016 and 2019 from the National Leprosy Control Program, Myanmar, and social determinant variables from the 2019 General Administration Department Census Report of Myanmar. An ecological cross-sectional study was conducted. Univariable and multivariable analyses applying zero-inflated negative binomial regression models were used. A geographic information system mapping was used to visualize leprosy cases, disease severity, and disability due to leprosy between 2016 and 2019. The number of all leprosy indicators changing pattern was seen obvious between regions. The eastern region showed relatively an increase in detection of new cases in 2019 compared with years 2017 and 2018. The increase in the detection of multibacillary leprosy cases was also observed in the eastern region during this period. Yet, the detection of Grade-II disability cases across regions remained relatively stable throughout study years. The number of tuberculosis cases per 1,000 population was significantly correlated with leprosy incidence at the township level (risk ratio 1.27, 95% confidence interval 1.04–1.55). These findings highlight the importance of enhancing active case finding campaigns in high-endemic regions, especially the eastern states of Myanmar. Integration of leprosy and tuberculosis case-finding programmes is likely to help leverage resources and maximize efforts to cope with leprosy problems in Myanmar.

Keywords: leprosy, township, social determinants, Myanmar

Introduction

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae*.[1] The disease mainly affects the skin, peripheral nerves, mucosal surfaces of the upper respiratory tract, and eyes of an infected person. People of all ages are at risk of the disease. Leprosy is curable and early treatment is recommended to avert potential disabilities. Prolonged and close contact with untreated leprosy cases is a key risk factor.[2]

Leprosy is classified based on skin smear results and the degree of disability. In the classification of skin smears, the disease is categorized into paucibacillary leprosy and multibacillary leprosy (MB), a more severe form of the disease. The World Health Organization proposes a grading system for leprosy-related disabilities.[3] Grade-II disability (G2D) is related to late diagnosis and complications, including deformities. MB leprosy is reported to have a positive association with G2D.[4] Bangladesh, India, Indonesia, Myanmar, Nepal, and Sri Lanka are the leading nations with high leprosy incidence in Asia.[4,5]

Myanmar launched a policy to eliminate leprosy in 2003. By late 2019, there were 2,287 previously registered leprosy cases in the country and the national prevalence rate was 0.4 per 10,000 population. High endemic areas of leprosy in Myanmar in 2019 were Ayeyarwady, Bago, Magway, Mandalay, Nay Pyi Taw, Shan, Sagaing, and Yangon. Nay Pyi Taw was just union territory under Mandalay Region. In total, seven regions consisting of 210 townships, (making up about 63.6% of the 330 townships nationally) were considered high endemic areas.

Despite some existing knowledge about the leprosy situation in Myanmar, little is known about the relationship between various social determinants and leprosy in Myanmar. Social determinants of health are conditions in the places where people live, learn, work, and play that affect a wide range of health risks and outcomes.[6,7]

Previous ecological studies in leprosy endemic countries, such as Brazil, have found significant relationships between leprosy and social determinants, including employment status, income, race, health quality, comorbid diseases (especially tuberculosis) and education.[8–10,20] However, a similar analysis has not yet been conducted in Myanmar. To reach the goal of strategic direction, it is necessary to identify individual and community determinants; this will support the planning and implementation of appropriate public health interventions. The interventions should also be tailored to specific priority subgroups in the population, for example, the unemployed, people in rural areas, and people in endemic areas where there is a high prevalence of MB leprosy.

The objectives of this study are (1) to describe the epidemiological situation of leprosy in terms of incidence, severity and disability at the township level in the seven high endemic regions in Myanmar between 2016 and 2019, and (2) to determine the association between leprosy incidence and social determinants of health in 2019.

Methods

An ecological cross-sectional study was conducted and the unit of analysis was township. The study areas included 210 townships in the seven high burden leprosy endemic areas in Myanmar. The period of study was 2016–2019 for objective 1, and 2019 for objective 2. The analysis was limited to 2019 for the second objective due to the lack of social determinant data from the national census before 2019.

For objective 1, we analysed three main variables at the township level over time: (i) annual incidence proportion of leprosy, (ii) multibacillary proportion, and (iii) proportion of new G2D cases. These leprosy indicators were obtained from the National Leprosy Control Program, Department of Disease Control, Ministry of Health. For objective 2, we included social determinant variables, which were selected based on expert consultation and a literature review. The social determinant data were obtained from the General Administration Department, Ministry of Internal Affairs. The operational definitions of the outcome variables are shown in Table 1 while those of selected social determinants are shown in Table 2.

Table 1. Operational definitions of the outcome variables at township level (leprosy indicators)

Variables	Definitions
Incidence proportion of leprosy (new case detection rate)	Number of newly detected cases per 100,000 population in a year
Multibacillary proportion (severity based on smear result)	Number of new MB cases per total number of newly detected cases each year
G2D proportion (severity based on disability level)	Number of new cases with G2D per total number of newly detected cases each year

Table 2. Operational definitions of selected social determinant variables at the township level

Variables	Definitions
Literacy rate	Percentage of literate people per total population
Unemployment rate	Percentage of unemployed labor per all labor force
Ethnic group proportion	Percentage of ethnic groups per total population (e.g., Shan, Karen, and Rakhine)
Tuberculosis prevalence	Total number of existing tuberculosis cases in the area per 1,000 population
Rural population proportion	Percentage of rural residents per total population

Note: The variables reflect socioeconomic status of the population

Data analysis was carried out using Stata (version 16) and Microsoft Excel® (2013). Descriptive statistics, including percentage, mean and standard deviation were used. Median and interquartile range were also presented for data validity. Choropleth maps were created to visualize leprosy indicators at the township level over time. Pearson's correlation was used to examine the relationship between leprosy indicators in 2019 and social determinant variables (univariable analysis). Then all social determinant variables were included in the multivariable model. Zero-inflated negative binomial regression model was used because more than twenty percent of townships reported zero cases. Adjusted rate ratios and 95% confidence intervals were calculated. Zero-inflated negative binomial was selected instead of conventional regression models because (i) the outcomes are frequency counts where the population volume in a township was considered the offset, (ii) some townships reported the absence of cases (zero values), and (iii) overdispersion of data.

As this study involved secondary data analysis and did not include an analysis of individual-level data, ethics approval was not required.

Results

Based on the National Leprosy Control Program, the annual leprosy indicators during 2016–2019 are presented in Table 3. The mean incidence proportion across four study years was 9.96 new cases per 100,000 population, while MB cases accounted for 80% and G2D constituted approximately 10% of total new cases. Increasing trends in leprosy incidence and MB proportion were observed between 2016 and 2019. The proportion of G2D cases decreased in 2017, then rebounded in 2018–2019. In 2019, MB cases accounted for about 84.0% of all new cases. Additional data from National Leprosy Control Program revealed that the fraction of child cases constituted about 4.2% of all new cases in 2019.

Table 3. Mean value of annual leprosy indicators (%) in Myanmar during 2016–2019

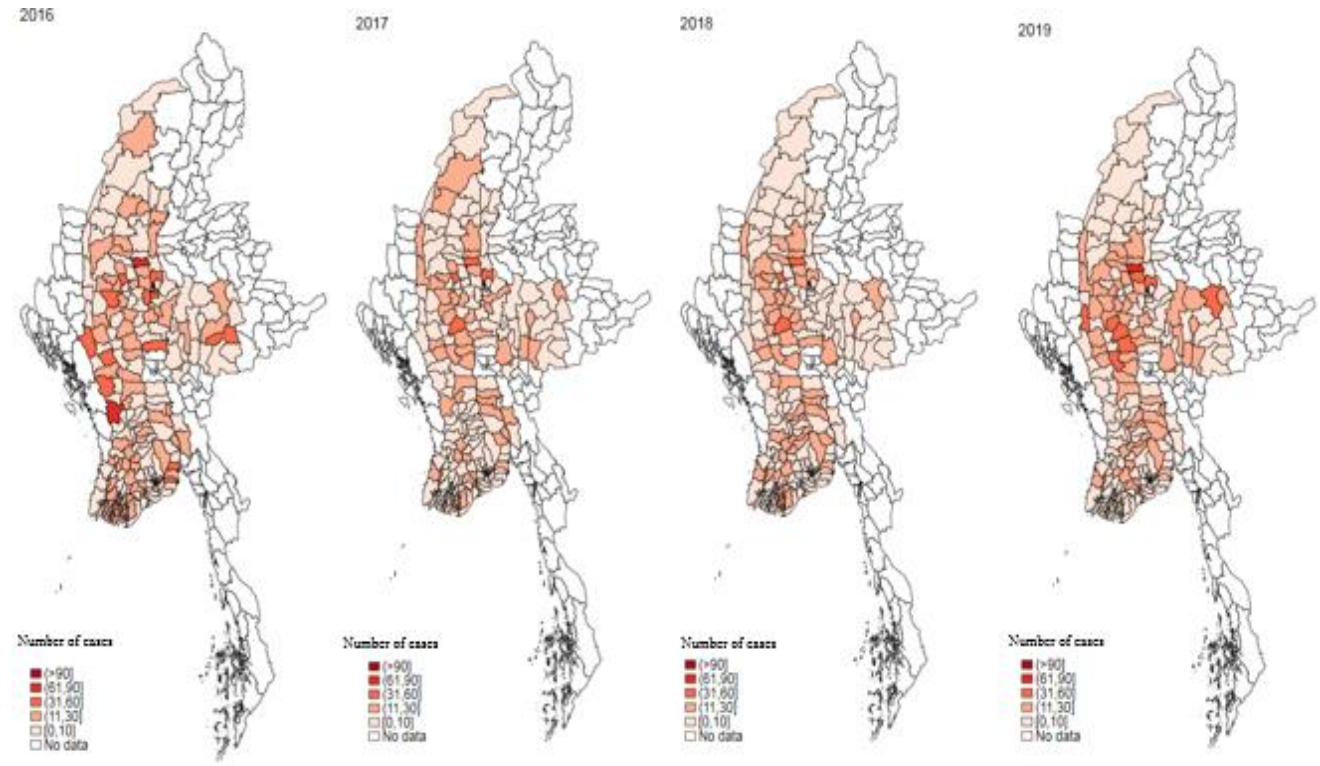
Leprosy indicators	Years mean (standard deviation)				
	2016	2017	2018	2019	Total
Incidence per 100,000 population	10.02 (63.51)	8.42 (67.36)	9.73 (84.81)	11.66 (82.51)	9.96 (74.99)
Multibacillary proportion (%)	77.64 (19.59)	77.95 (20.27)	82.15 (20.72)	84.03 (17.00)	80.48 (90.58)
G2D proportion (%)	10.75 (17.10)	7.96 (13.65)	12.99 (22.23)	11.85 (19.07)	10.86 (18.23)

The median leprosy incidence proportions during 2016–2019 are shown in Table 4. The indicators varied between 2.52 and 3.56 cases per 100,000 population during the study years. This implied the data had a right-skewed distribution. In contrast, the median proportion of MB cases among new cases was close to the corresponding mean. The median G2D proportion was zero in most years.

Table 4. Median value of annual leprosy indicators (%) in Myanmar during 2016–2019

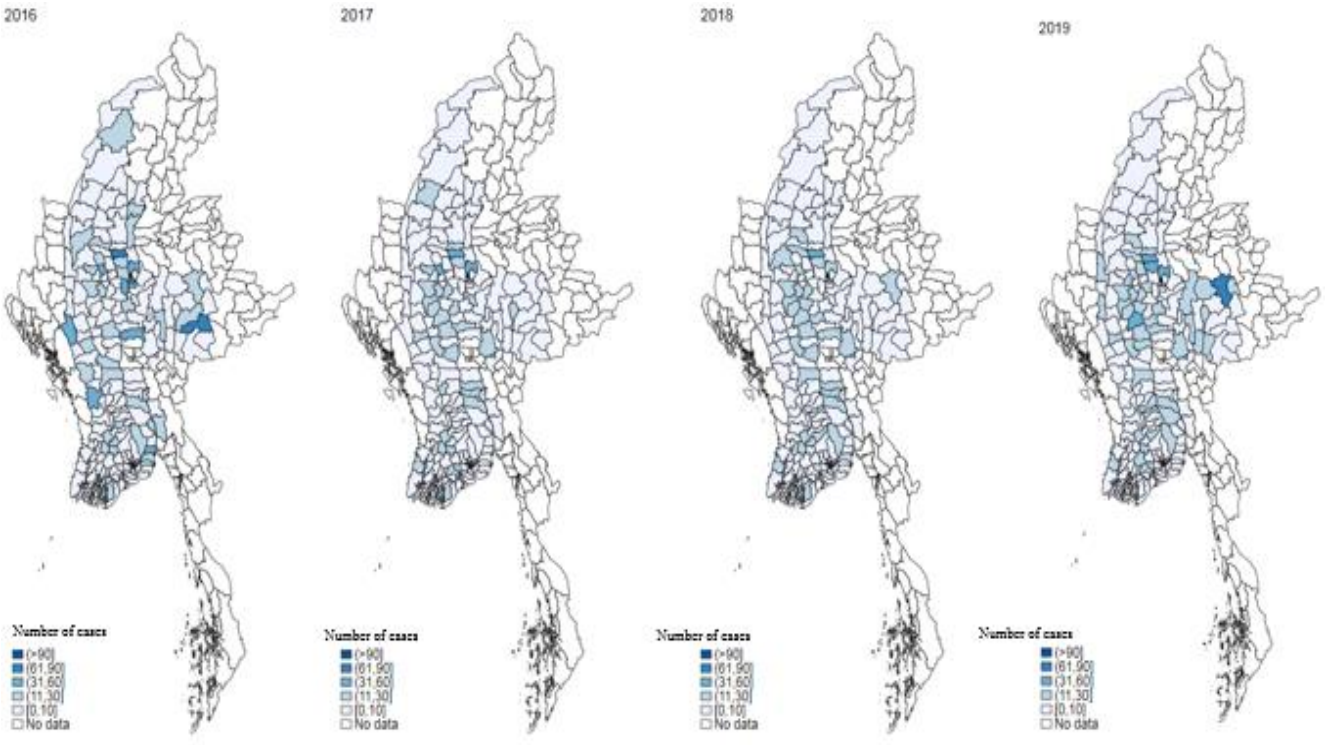
Median leprosy indicators	Years median (interquartile range)				
	2016	2017	2018	2019	Total
Incidence proportion of leprosy	3.09 (5.54)	2.52 (5.17)	2.73 (4.69)	3.56 (6.21)	2.81 (5.29)
Multibacillary proportion (%)	80.00 (25.00)	80.90 (33.34)	85.71 (27.27)	88.89 (27.18)	83.34 (33.34)
G2D proportion (%)	3.28 (16.67)	0.00 (10.53)	0.00 (17.65)	0.00(19.58)	0.00(16.66)

Figures 1–3 show the geographical distribution of cases in Myanmar townships, with darker color shades reflecting higher numbers of leprosy cases. Only hyper endemic regions were included in study. Townships in the central regions (Ayeyarwaddy, Mandalay, and Yangon) presented with a relatively higher number of new leprosy cases. In 2016, most of the new and MB cases were detected in the central region compared with other regions. The detection rate of new cases in 2017 and 2018 appeared to be lower in all regions, relative to year 2016. However, higher detection of new cases was observed in 2019, especially in the eastern region. The same change pattern was also found in MB cases. Yet there were no obvious differences in the geographical concentration of G2D cases across years.



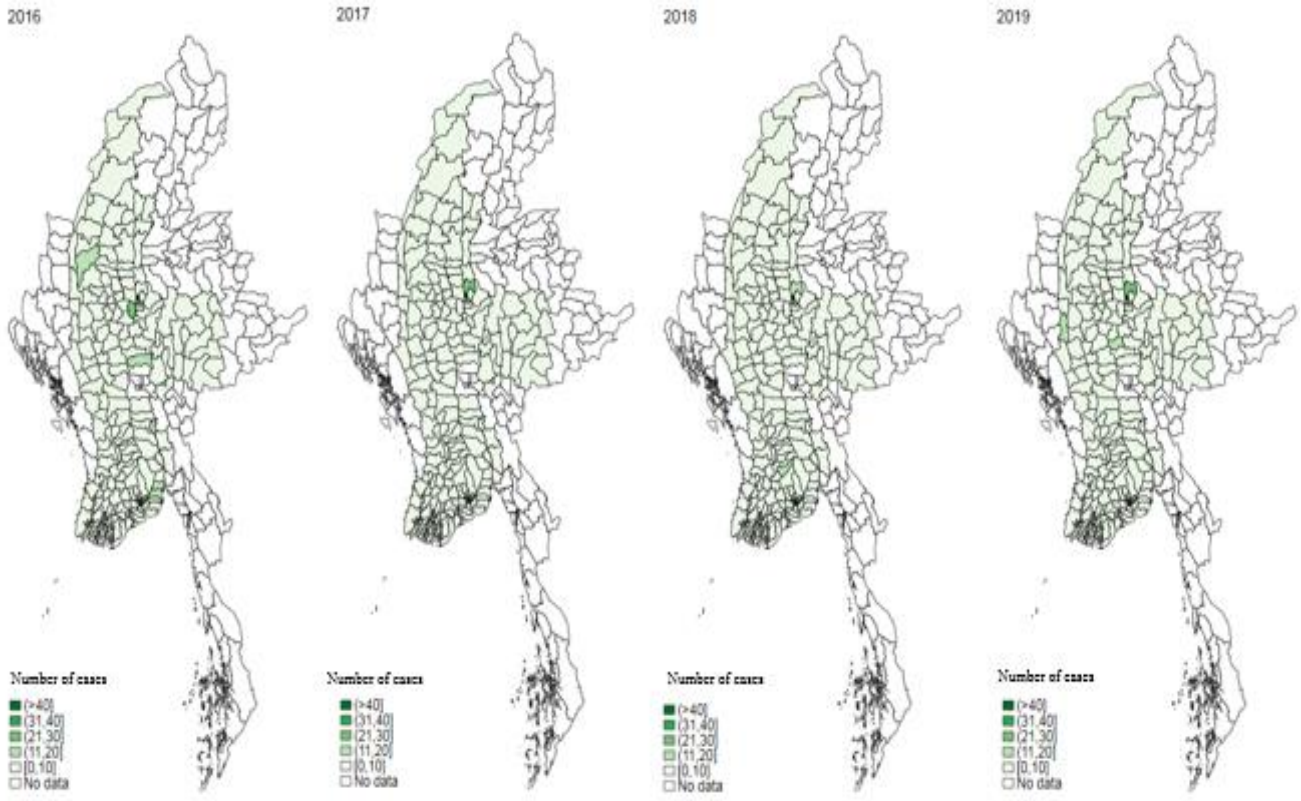
Note: White areas in map ("no data" in legend) were not included as study sites

Figure 1. Geographical distribution of all new leprosy cases in seven high endemic regions in Myanmar, 2016–2019



Note: White areas in map ("no data" in legend) were not included as study sites

Figure 2. Geographical distribution of multibacillary leprosy cases in seven high endemic regions in Myanmar, 2016–2019



Note: White areas in map ("no data" in legend) were not included as study sites

Figure 3. Geographical distribution of grade-II disability leprosy cases in seven high endemic regions in Myanmar, 2016–2019

Social determinant variables in 2019 are shown in Table 5. About 96.9% of the population was literate, and 8.3% were unemployed. The ethnic groups comprised 17.1% of the total population. About two-third of the population lived in rural areas. The mean prevalence of tuberculosis cases per 1,000 population was 1.5.

Table 5. Social determinants of health in the seven high endemic regions of leprosy in Myanmar, 2019 (n=210 townships)

Variables	Mean (standard deviation)
Literacy rate (%)	96.9[a] (9.2)
Unemployment rate (%)	8.3 (8.9)
Ethnic group percent (%)	17.1 (28.7)
Percentage of people living in rural areas (%)	62.3 (38.1)
Number of tuberculosis cases per 1,000 population	1.5 (1.1)

Note: [a]Some townships reported a literacy rate of more than 100%

In the univariable analysis shown in Table 6, a positive correlation coefficient implied that the value of social determinants went along with the value of leprosy indicators, and negative if otherwise. There was a significant positive correlation between tuberculosis prevalence and new leprosy cases. There was also a significant positive correlation between tuberculosis prevalence and G2D proportion. However, no significant correlations were found between the MB proportion and any social determinant variable.

Table 6. Univariable analysis between leprosy indicators and social determinants

Social determinant variables	Leprosy incidence		MB proportion		G2D proportion	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Literacy rate	-0.002	0.98	-0.05	0.51	0.03	0.65
Unemployment rate	-0.06	0.37	-0.03	0.72	-0.01	0.87
Prevalent tuberculosis cases per 1,000 population	0.21	<0.01	0.12	0.09	0.16	0.02
Percentage of ethnic population	-0.003	0.97	0.01	0.87	-0.06	0.41
Percentage of rural population	-0.12	0.09	-0.07	0.35	-0.11	0.10

Results of the multivariable analysis are shown in Table 7. After controlling for other variables, we found that for each unit increase in the tuberculosis prevalence, the incidence of leprosy increased by about 27% (*p*-value 0.02). A one-percentage-point increase in the rural population was associated with a 2.2-fold increase in leprosy incidence, although the significance was only marginal (*p*-value 0.06). Both multivariable analysis of MB leprosy and G2D with social determinants showed no significant result.

Table 7. Multivariable analysis of leprosy incidence and social determinants

Independent variables	Risk ratio	95% confidence interval	*P*-value
Literacy rate	0.24	0.02–2.79	0.25
Unemployment rate	0.22	0.03–1.92	0.17
Prevalent number of tuberculosis cases	1.27	1.04–1.55	0.02
Ethnic group percentage	1.30	0.58–2.90	0.52
Rural population percentage	2.18	0.97–4.93	0.06

Discussion

This study revealed a slight rising trend of leprosy indicators from 2016 to 2019 in seven leprosy endemic regions of Myanmar.[4] Moreover, a high proportion of MB cases among new cases was observed. MB leprosy mostly occurs in people with a weakened immune response against *M. leprae*, with a high bacillary load, and MB cases are likely to be important sources of disease transmission.[14] Therefore, active case detection and active surveillance among contacts are critical for early detection of new cases and breaking the transmission chain.[14] Local strategies to diagnose and treat MB cases should be prioritized in townships with high leprosy burden.

About 10% of new cases presented with G2D during 2016–2019. The large proportion of G2D partly reflects a deficit in the country's health system to perform early case detection and partly reflects delayed health-seeking of the patients.[15]

There are a few differences between the findings of this study and a report by World Health Organization. Globally and in South-East Asia, the number of reported new cases of leprosy and cases with G2D declined during 2011–2019.[5] These differences can be explained by the fact that the leprosy profile at the township level, particularly in endemic regions, differs from the profile at the national level. Additionally, a high level of case detection is not just a reflection of the disease burden but it also involved reflects the operation of the system or the intensity of programmatic activities (including case-finding campaigns). We found that townships with a higher number of G2D cases were concentrated in the central region. In addition, MB cases were accumulated more in the eastern region.[16] This phenomenon is partly due to a shift in case findings campaigns from the central and western parts of the country during 2016 to the eastern region in 2019.

We did not find a significant association between literacy rates and leprosy indicators. This is in contrast with the findings from other countries.[17] However, we identified a positive correlation between rural population percentage and leprosy detection, although the significance was marginal. This result is consistent with a study in Bangladesh which highlights the importance of active case finding campaigns for leprosy in rural areas.[18] People living in a rural setting are likely to face barriers that hamper access to healthcare, such as large distances between residences and the nearest health facility and communication hurdles, compared with those living in urban settings.[18]

The prevalence of tuberculosis was positively correlated with leprosy incidence in the multivariable analysis. A study from the Netherlands found that leprosy and tuberculosis have significant cross-reactivity at the T-cell level.[11] This finding coincides with studies from the United Kingdom and the United States of America, suggesting that leprosy and tuberculosis have similar geographic endemicity and tend to present with coinfection in a patient.[19,20] This result reaffirms the idea that active case finding strategies for leprosy should be conducted in tandem with tuberculosis active case finding campaigns.

Limitations

This study has some limitations which are worth mentioning. First, the nature of an ecological study is prone to the ecological fallacy. Therefore, results of this study should be interpreted with caution, particularly when applying them to individual-level phenomena. Second, not all social determinant variables were collected in the routine data collection system of the Ministry of Internal Affairs. Thus, some important variables, such as household economic status and healthcare resources, were not included in the analysis. Third, this study was not free from reporting bias. Although the choropleth maps showed some potential

spatial relationships, a spatial effect analysis was not formally conducted. Some townships might over-represent the cases because they have referral centers where many cases were transferred. In contrast, townships with a small number of cases or those containing only low-level health facilities which are not able to handle leprosy care might be prone to zero-case reporting. Finally, the nature of a cross-sectional study prevents claiming a strong causal inference. Further study that explores the change of social determinants and leprosy indicators in a longitudinal fashion is warranted to identify a more solid causal inference.

Conclusion

An increasing trend of leprosy incidence and proportion of MB leprosy cases were observed in endemic regions of Myanmar. Most cases were localized in the central region, and a rising trend was seen in the eastern region. A positive relationship between leprosy incidence and tuberculosis cases suggests a need to integrate the disease control programmes of both diseases. A strong correlation was also found between leprosy incidence and percentage of rural population. Further studies that collect social determinant variables at the household and individual levels are recommended.

Recommendations

The authorities should enhance and prioritize active case finding programmes in townships exhibiting rising trends in leprosy incidence. In addition, a leprosy active case finding programme should be performed in parallel with those for tuberculosis cases. Rural areas should be considered target sites for active case finding. Barriers to healthcare access in rural settings should be promptly addressed. Future studies that employ primary data collection and incorporate more social determinants that represent the socioeconomic status of the observations rather than a reliance on surrogate variables is recommended. Further studies exploring the leprosy incidence and social determinants at the individual or household level will help extend the academic value in the field of leprosy epidemiology.

Acknowledgements

The authors would like to thank the National Leprosy Control Program, Myanmar, for permission to access and use their data. We would like to thank Dr. Emily Bloss for her valuable advice during the development of this manuscript.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for this research study and for subsidizing the publication fee of this article.

Suggested Citation

Bo SH, Suphanchaimat R. Social determinants and leprosy in high endemic regions of Myanmar: an ecological study between 2016 and 2019. OSIR. 2022 Sep;15(3):76–83.

References

1. World Health Organization. Leprosy in SEARO: What is leprosy? [Internet]. Geneva: World Health Organization; [cited 2021 Dec 26]. <https://www.who.int/southeastasia/health-topics/leprosy>
2. Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention. Hansen's Disease (Leprosy) [Internet]. Atlanta: Centers for Disease Control and Prevention; [updated 2017 Feb 10, cited 2021 Dec 26] <https://www.cdc.gov/leprosy/about/about.html>
3. Regional Office for South-East Asia, World Health Organization. Global Leprosy Strategy 2016–2020 : Accelerating towards a leprosy-free world [Internet]. New Delhi: WHO Regional Office for South-East Asia; 2016 [cited 2021 Dec 26] <https://apps.who.int/iris/handle/10665/208824>
4. National Leprosy Control Program, Department of public Health, Ministry of Health and Sports. National Leprosy Control Strategy 2019–2023 [Internet]. Nay Pyi Taw: Myanmar Health Sector Coordinating Committee; 2018 [cited 2021 Dec 26]. 34 p. <https://www.myanmarhscc.org/wp-content/uploads/2019/09/National-Leprosy-Control-Strategy-2019-2023-Myanmar.pdf>
5. World Health Organization. Global leprosy (Hansen disease) update, 2020: impact of COVID-19 on global leprosy control. Wkly Epidemiol Rec [Internet]. 2021 Sep 10 [cited 2021 Dec 26];96(36):421–44. 24 p. <https://www.who.int/publications-detail-redirect/who-wer9636-421-444>
6. World Health Organization. Social determinants of health. Geneva: World Health Organization; [cited 2021 Dec 26]. <https://www.who.int/teams/social-determinants-of-health>

7. Social Determinants of Health, Centers for Disease Control and Prevention. Social Determinants of Health: About Social Determinants of Health (SDOH) [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2021 Dec 26]. <https://www.cdc.gov/socialdeterminants/about.html>

8. Cury MR, Paschoal VD, Nardi SM, Chierotti AP, Rodrigues Junior AL, Chiaravalloti-Neto F. Spatial analysis of leprosy incidence and associated socioeconomic factors. Rev Saude Publica. 2012 Feb;46(1):110–8.

9. Freitas LR, Duarte EC, Garcia LP. Leprosy in Brazil and its association with characteristics of municipalities: ecological study, 2009–2011. Trop Med Int Health. 2014 Oct;19(10):1216–25.

10. Kerr-Pontes LR, Montenegro AC, Barreto ML, Werneck GL, Feldmeier H. Inequality and leprosy in Northeast Brazil: an ecological study. Int J Epidemiol. 2004 Apr;33(2):262–9.

11. Mangum L, Kilpatrick D, Stryjewska B, Sampath R. Tuberculosis and leprosy coinfection: A perspective on diagnosis and treatment. Open Forum Infect Dis. 2018 Jun 5;5(7):ofy133.

12. Ministry of Health and Sports. Myanmar Demographic and Health Survey 2015-2016. Nay Pyi Taw: Ministry of Health and Sports; 2017 Mar [cited 2021 Dec 26]. <https://dhsprogram.com/pubs/pdf/FR324/FR324.pdf>

13. World Health Organization. Number of new leprosy cases:2020 [Internet]. Geneva: World Health Organization; [cited 2021 Dec 26]. <https://apps.who.int/neglected_diseases/ntddata/leprosy/leprosy.html>

14. Nobre ML, Illarramendi X, Dupnik KM, Hacker MA, Nery JA, Jeronimo SM, et al. Multibacillary leprosy by population groups in Brazil: Lessons from an observational study. PLoS Negl Trop Dis. 2017 Feb 13;11(2):e0005364.

15. Sales AM, Ponce de Leon A, Duppre NC, Hacker MA, Nery JA, Sarno EN, et al. Leprosy among Patient Contacts: A Multilevel Study of Risk Factors. PLoS Negl Trop Dis. 2011 Mar 15;5(3):e1013.

16. Dharmawan Y, Fuady A, Korfage I, Richardus JH. Individual and community factors determining delayed leprosy case detection: A systematic review. PLoS Negl Trop Dis. 2021 Aug 12;15(8):e0009651. <https://doi.org/10.1371/journal.pntd.0009651>

17. Li YY, Shakya S, Long H, Shen LF, Kuang YQ. Factors Influencing Leprosy Incidence: A Comprehensive Analysis of Observations in Wenshan of China, Nepal, and Other Global Epidemic Areas. Front Public Health. 2021 May 31;9:666307.

18. Fischer E, Pahan D, Chowdhury S, Richardus J. The spatial distribution of leprosy cases during 15 years of a leprosy control program in Bangladesh: an observational study. BMC Infect Dis. 2008 Sep 23;8:126.

19. Donoghue HD. Tuberculosis and leprosy associated with historical human population movements in Europe and beyond–an overview based on mycobacterial ancient DNA. Ann Hum Biol. 2019 Mar;46(2):120–8.

20. Geluk A, van Meijgaarden KE, Franken KL, Subronto YW, Wieles B, Arend SM, et al. Identification and characterization of the ESAT-6 homologue of Mycobacterium leprae and T-cell cross-reactivity with Mycobacterium tuberculosis. Infect Immun. 2002 May;70(5):2544–8.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

Secondary Human-to-human Transmission of Nipah Virus in an Ambulance, Northwestern Bangladesh, February 2019

Mohammad Gazi Shah Alam[1]*, Mallick Masum Billah[2], Ahmad Raihan Sharif[1], Sharmin Sultana[1], Shahanaj Shano[1], Md Kaisar Rahman[3], Ariful Islam[3], A.S.M. Alamgir[1], Tahmina Shirin[1], Meerjady Sabrina Flora[1]

1 Institute of Epidemiology, Disease Control and Research, Bangladesh

2 Training Programs in Epidemiology and Public Health Interventions Network Secretariat, a Program of the Task Force for Global Health, USA

3 EcoHealth Alliance, USA

*Corresponding author email: gazi84vet@gmail.com

Abstract

Nipah virus (NiV) infection is a zoonotic disease with epidemic potential due to its human-to-human transmission. In Bangladesh, where NiV infection is frequent, NiV spillover from fruit bats to humans usually occurs in winter. This study aimed to describe the magnitude and scope of a NiV outbreak in February 2019, identify the source of infection, and contain the spread of disease. We interviewed the cases' family members, conducted verbal autopsies, and collected samples for laboratory tests. Five family members reported died from, at the time, an unknown disease. All had fever, altered mental status, vomiting and diarrhea. Reverse transcription polymerase chain reaction confirmed NiV in one person. We suspected secondary transmission occurred when the family traveled with the primary case from their house to the hospital by ambulance. The trip took 8.5 hours and no one wore a face mask or gloves. The secondary attack rate among ambulance travelers was 67%. In this outbreak, NiV was transmitted human-to-human among riders in the ambulance. We recommend that everyone should use protective measures while traveling with suspected NiV infected patients to reduce the risk of transmission. Strengthening the existing Nipah virus surveillance system may generate earlier notification and response to contain further transmission.

Keywords: Nipah virus, outbreak, Bangladesh, zoonoses, transmission

Introduction

The World Health Organization categorizes Nipah virus (NiV) infection as an emerging infectious disease with epidemic potential.[1] Epidemics have occurred in Malaysia, India, and the Philippines.[2–4] In Bangladesh, NiV disease first appeared in 2001 and since then, 319 NiV cases and 225 deaths have been reported.[5,6] The northwestern and central parts of Bangladesh are known as the 'Nipah belt'.[7] In Thakurgaon District in Rangpur Division, a previous outbreak of NiV disease occurred in February 2007.[8]

Nipah virus is a paramyxovirus. Its most frequent transmission route in humans in Bangladesh is drinking raw date palm sap contaminated with bat excreta.[9,10] NiV spillover from bats to humans occurs mostly from December to May.[11] Human-to-human transmission among close contacts has been previously reported in two NiV disease outbreaks in Bangladesh and Kerala, India.[8,9,11–13] Approximately 3% of people exposed to NiV infected patients could develop the disease after 12–24 hours of exposure.[14] Elderly NiV infected patients with respiratory symptoms are more likely to transmit human-to-human NiV infection.[14] Adequate barrier control measures such as wearing a face mask and gloves can reduce NiV infection among close contacts and healthcare professionals.[8,9,13]

The Bangladesh Ministry of Health and Family Welfare started an Acute Meningo-Encephalitis Syndrome (AMES) surveillance system in 2007 with the objective to detect early meningo-encephalitis diseases.[15] There are sentinel sites in Rajshahi,

Rangpur, Faridpur, Chittagong and Khulna Medical College Hospitals that conduct active NiV disease surveillance. On 24 Feb 2019, the AMES surveillance system at Rangpur Medical College Hospital (RMCH) was alerted of the death of four people and one critically ill patient due to an unknown cause in a northwestern district of Bangladesh. We investigated this outbreak to describe its magnitude and scope, to identify the infection source, and to contain its spread.

Methods

A suspected case was defined as a person who lived in Thakurgaon District and had a fever and one of the following symptoms: vomiting, diarrhea, cough, respiratory distress, myalgia, severe weakness, or altered mental condition from 15 Jan to 17 Mar 2019. A probable case was a suspected case who had contact with another suspected or confirmed case. A confirmed case was a suspected or probable case with positive reverse transcription polymerase chain reaction (RT-PCR) or immunoglobulin M (IgM) for NiV. The primary case was defined as the suspected case who spread the disease to others. The index case was identified as the infected person who was first reported by the AMES surveillance authorities of RMCH.[16] A contact was a person who came into direct contact or stayed in the same room or vehicle for at least 15 minutes with a probable, suspected, or confirmed case, and who touched the body, nursed, fed, or cleaned body secretions or vomitus, or participated in funeral practices of any suspected case.[5]

We identified contacts among health workers in Baliadangi Upazila Health Complex, Thakurgaon Modern Sadar Hospital, and RMCH hospitals (Figure 1). We reviewed medical records from December 2018 to February 2019 of patients with NiV disease, Japanese encephalitis, measles, rabies, dengue encephalitis, cerebral malaria and bacterial meningitis.

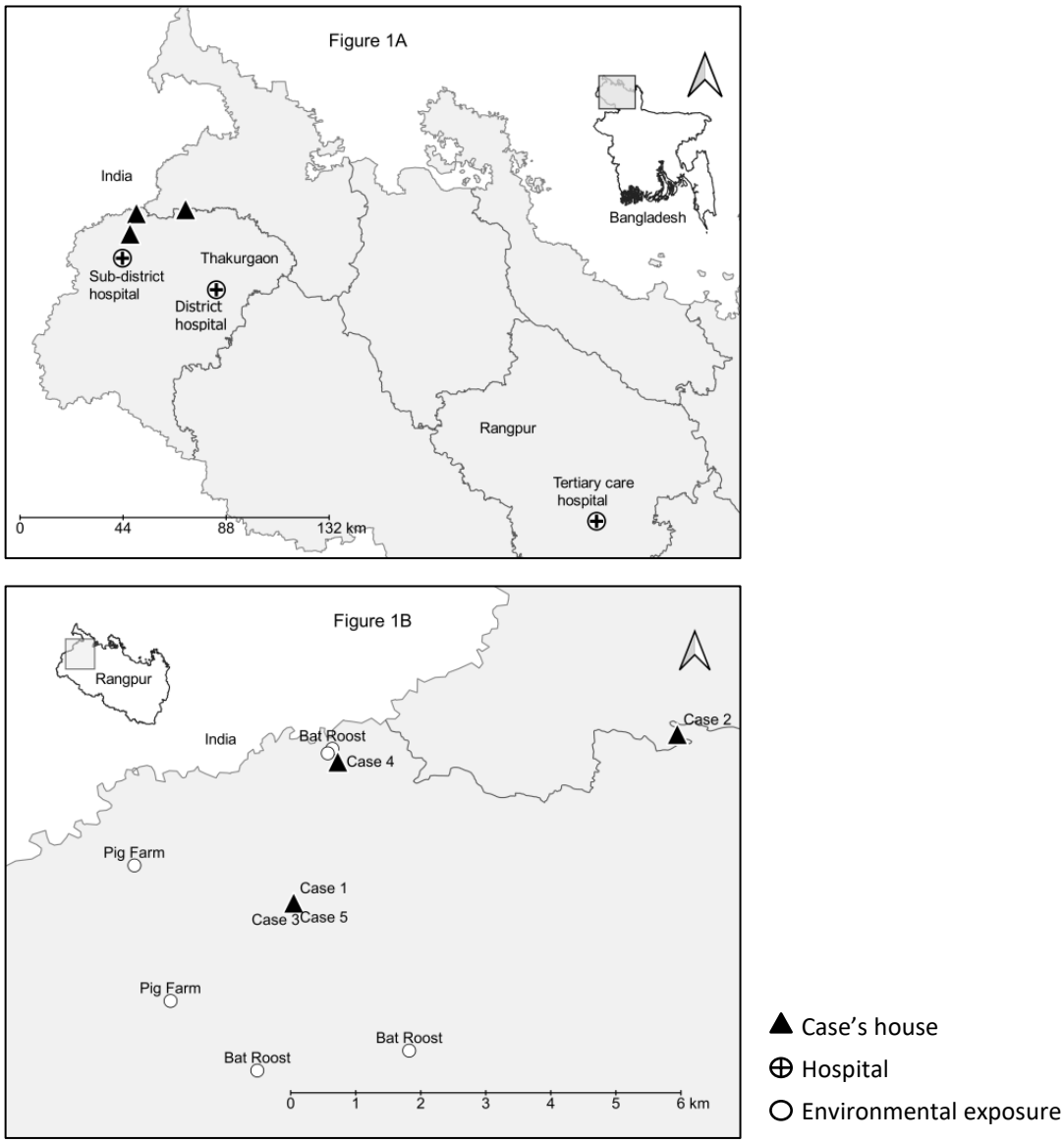


Figure 1. Map of NiV outbreak, showing residences of the cases, hospitals where patients were taken (A), and nearby environmental exposure from the case's houses (B) in a northwestern district of Bangladesh, 2019

The investigation team traveled to the cases' homes to identify contacts among family members, relatives, neighbors, friends, transporters, and people who participated in the funeral practice. We went door-to-door to the neighboring homes of cases with local health authorities and community members to identify other cases. Contacts were identified by snowball sampling. We continued active surveillance for two incubation periods (42 days) of NiV disease.

We collected blood and nasal and throat swabs from three people that rode in the ambulance and from some of the contacts. Nasal and throat swabs samples were tested for NiV by RT-PCR. Serum samples were tested for anti-NiV IgM antibodies by enzyme-linked immunosorbent assay (ELISA) following the NiV detection protocol of the U.S. Centers for Disease Control and Prevention. All samples were tested at the Virology Laboratory at Institute of Epidemiology, Disease Control and Research (IEDCR).

An anthropologist conducted interviews and held discussions with family members, relatives, friends, neighbors, and community members to identify the source of the outbreak.

We collected clinical and demographic information from hospital records. We interviewed contacts and conducted informal group discussions with healthcare professionals regarding personal protection. Data were collected through electronic forms on tablets and forms built using Epi-Info7 software (version 7.2.3.1). Descriptive data were analyzed in Epi-Info7 and Microsoft Excel to calculate frequencies and percentages. We used QGIS (version 3.12.1) to create a map of the cases and environmental links.

Ethics Considerations

This outbreak was investigated under the directive and approval from the Office of the Director of the IEDCR. Activities of this outbreak investigation were in response to a public health emergency. All respondents were older than 18 years of age. We took verbal informed consent from all respondents who were older than 18 years of age. We maintained confidentiality of the information obtained from this outbreak investigation.

Results

Descriptive Data and Clinical Features

We identified five cases; one suspected case, three probable cases and one confirmed case from 5 to 24 Feb 2019. The median age of the cases was 38 years and four were male. The median incubation period was 10 days (range 8–13 days). All suspected, probable and confirmed cases died and all had a history of fever, altered mental status, headache, vomiting, diarrhea, respiratory distress, and severe weakness, while four cases developed cough and two myalgia (Table 1).

Table 1. Demographic and clinical findings of cases during a Nipah virus outbreak in a northwestern district of Bangladesh, February 2019

Case number	Age (years)	Gender	Date of exposure	Date of onset of symptoms	Date of sample collection	Date of death	Incubation period (days)	Duration of illness (days)	Clinical symptoms
1	55	Male	Not applicable	5 February	Not done	9 February	Not applicable	4	F, A, M, H, C, V, D, R, S
2	35	Male	9 February	17 February	Not done	21 February	8	4	F, A, H, C, V, D, R, S
3	50	Female	9 February	20 February	Not done	21 February	11	1	F, A, H, V, D, R, S
4	28	Male	9 February	22 February	Not done	24 February	13	2	F, A, H, C, V, D, R, S
5	26	Male	9 February	18 February	24 February	24 February	9	6	F, A, M, H, C, V, D, R, S

Note: Clinical symptoms; F: Fever, A: Altered mental status, M: Myalgia, H: Headache, C: Cough, V: Vomiting, D: Diarrhea, R: Respiratory syndrome, S: Severe weakness

The primary case (case-1) was a 55-year-old male who died 15 days before the outbreak was reported. On 5 February, he developed a low-grade fever. On 8 February, he visited a village doctor, complaining of fever, myalgia, headache, and cough and was treated with anxiolytic and antibiotics. His condition deteriorated and he died in the hospital the next day (Figure 2).

At 8:00 AM on 9 February, six persons (case-2, -3, -4, -5, the daughter of case-1, and an ambulance driver) traveled with case-1 to hospital-2 and then hospital-3.

The ambulance took 8.5 hours to reach hospital-3. During that time, none of them wore face masks or gloves. Later, all passengers became infected except the daughter of case-1 and the ambulance driver. Case-2 became ill on 17 February, case-5 on 18 February, case-3 on 20 February and case-4 on 22 February. Case-2 and -3 died on 21 February and cases-4 and -5 died on 24 February. The mortality rate was 67% (4/6) among those who traveled with case-1 in the ambulance.

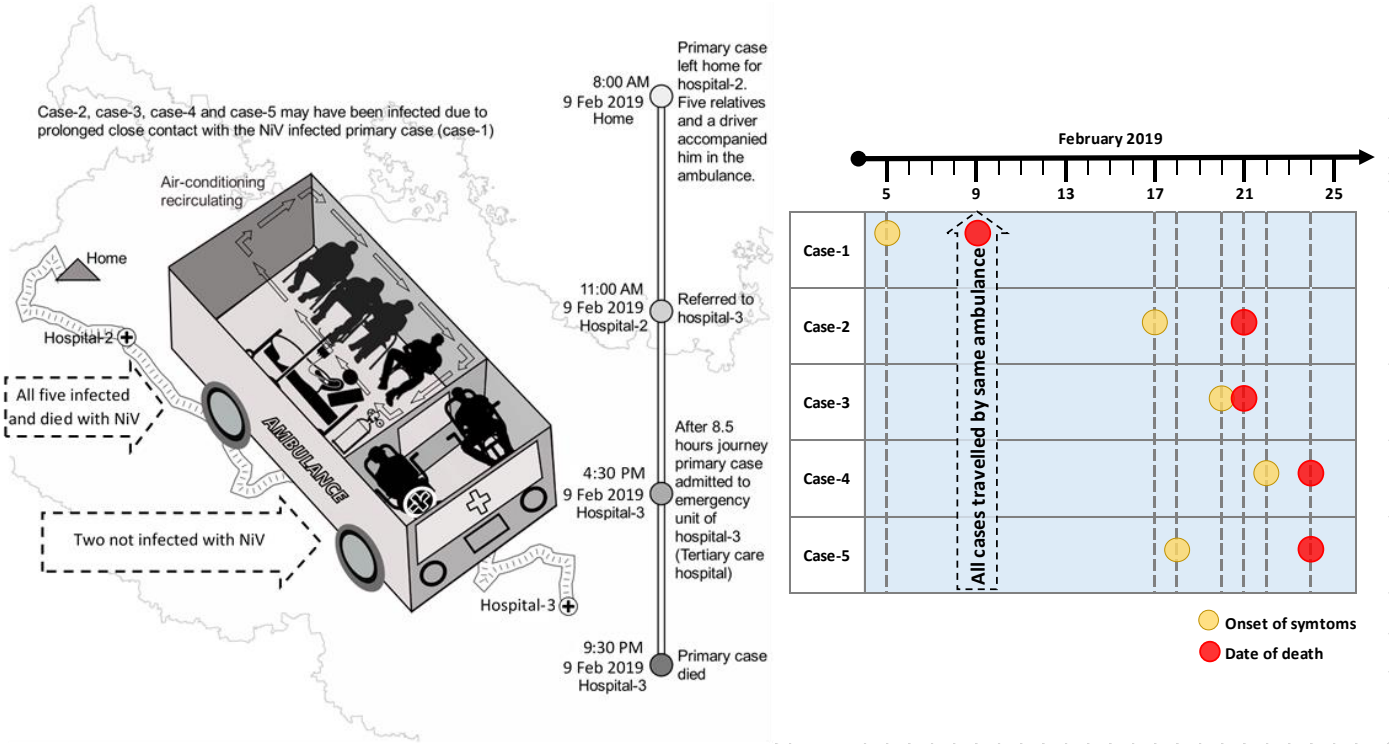


Figure 2. Human-to-human transmission of NiV in an ambulance, Nipah outbreak in a northwestern district of Bangladesh, February 2019

Identification of contacts

We identified 64 contacts; 8 from the primary case and 56 from secondary cases. Some contacts (contacts 30, 31, 37, 45, 58, 50 and 62) were exposed to more than one case. Most of the contacts were caregivers (55%) (Figure 3). The first- and second-generation attack rate was 50% (4/8) and 0% (0/56), respectively.

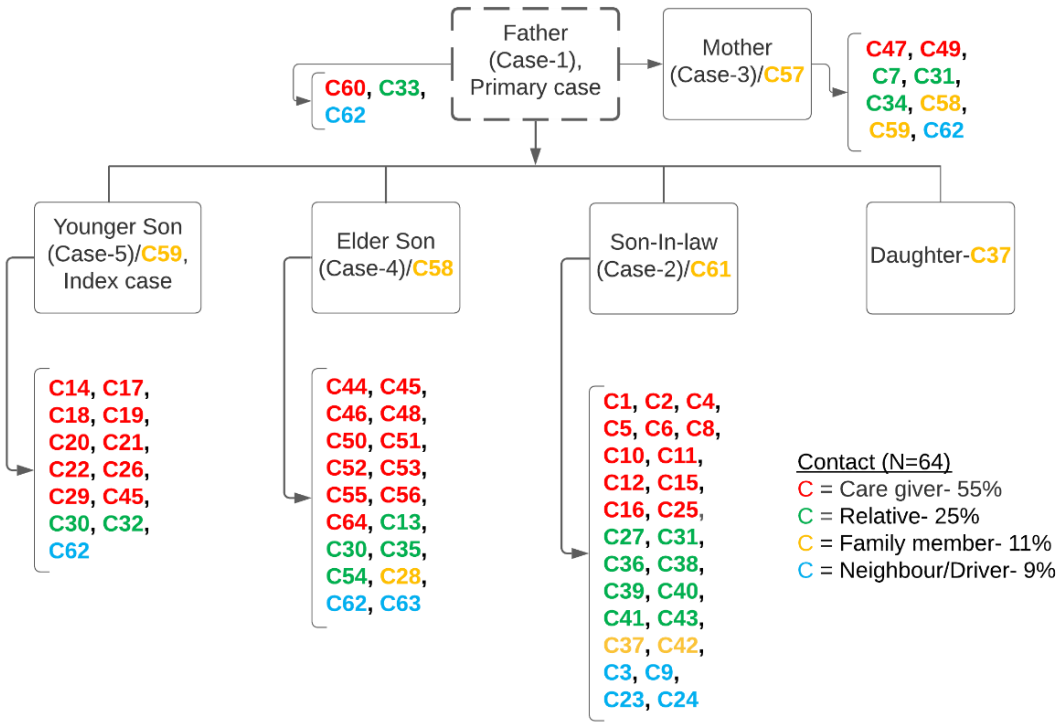


Figure 3. Sociogram of contacts in Nipah virus outbreak in a northwestern district of Bangladesh, February 2019

Laboratory Results

We collected and tested 45 blood, nasal swab, and throat swab samples from one case (case-5) and 44 contacts. They all tested negative for NiV by PCR and ELISA, except case-5 who had positive IgM and RT-PCR tests (Table 2) on 26 February. Among the 64 contacts, six were compatible with the suspected case definition. The suspected cases were three family members, one nurse, one doctor, and the ambulance driver. They were investigated and some were discarded from the list of cases.

Table 2. Contact exposures and laboratory findings of cases that traveled in an ambulance during a Nipah virus outbreak in a northwestern district of Bangladesh, February 2019

Case number	Type of contact	Nature of exposure	Epidemiological link	NiV real-time RT-PCR	NiV IgM ELISA
1	Primary case	Not applicable	Not identified	No sample collected	No sample collected
2	Companion to primary case in ambulance	Touched the patient during transportation	Contact with primary case	No sample collected	No sample collected
3	Family contact and companion to primary case in ambulance	Touched the patient at home and during transportation	Contact with primary case	No sample collected	No sample collected
4	Companion to primary case in ambulance	Touch the patient during transportation	Contact with primary case	No sample collected	No sample collected
5	Companion to primary case in ambulance	Stayed in the same room and touched the patient during transportation	Contact with primary case	Sample collected on 24 February and results were positive	Positive

Anthropological Investigation of the Primary Case

The primary case was a traditional healer and collected herbs and animals in the forest before he became ill. His neighbors reported that he used herbs and some animals to prepare medicines. Therefore, he might have used various parts of a bat's body for preparation of traditional medicine. No person who was interviewed reported that the primary case consumed raw date palm sap.

Public Health Response

The investigation team quarantined four of the six suspected cases in RMCH but were unable to quarantine the other two. We continued active monitoring of all contacts up to 17 Mar 2019. We contacted several government stakeholders about the current situation and requested them to prepare for an emergency. IEDCR distributed NiV disease prevention-related messages and guidelines through person-to-person contacts, official letters, and print and electronic media. The local health authority disseminated NiV disease prevention and control-related messages to the community. All members of our team used personal protective equipment (PPE) during the investigation and incinerated all used PPE and equipment used for sample collection.

Discussion

We verified this episode as a NiV disease outbreak based on the laboratory findings, clinical information, and epidemiological data. Of the five cases, one had a positive laboratory test and all had clinical signs and symptoms consistent with NiV disease. The outbreak area was located in the 'Nipah belt' where NiV spillovers frequently occur.[7] The primary case infected four other people in the back of the ambulance; all were symptomatic and all died. We identified sixty more contacts who were all asymptomatic and there were no new NiV cases until 17 Mar 2019.

The evidence for human-to-human transmission of NiV in this outbreak consists of an incubation period compatible with secondary spread. In the ambulance, people were in close contact in a confined and poorly ventilated space, did not wear PPE, and traveled for eight and a half hours.[3,8,13,17] Lastly, older adults can transmit NiV person-to-person, and coughing at the terminal stage of life can increase the infection rate.[8,9,12,14] The primary case was 55 years old and experienced respiratory distress while in the ambulance.

A few outbreak investigations have reported human-to-human transmission from close contact, such as caregivers of NiV disease patients.[3,8,12,13] NiV can also be transmitted from human-to-human contact during burial practices, by contact with the bodily secretion of deceased persons infected with NiV.[9] In this outbreak, we suspected that the enclosed environment of an air-conditioned ambulance was a risk factor for human-to-human transmission of NiV.

The source of this outbreak was not identified because the primary case died on 9 February, before the notification of this event to public health authorities on

24 February, thus he was not interviewed. A verbal autopsy on the primary case could also not identify the source of this outbreak because the case was an introverted person who isolated himself and his family from his neighbors and relatives. The most likely source of NiV infection for the primary case was direct contact with bats or bat excreta when he harvested herbs in the forest.

Surveillance is an essential tool to prevent future NiV disease outbreaks. In this outbreak, over half of the NiV infected patient contacts were healthcare professionals and family members. This outbreak is similar to other NiV disease outbreaks in Bangladesh and India.[8,9,18,19] Early detection is crucial to the early isolation of cases and quarantining of contacts to prevent secondary spread. In this incident, the AMES surveillance of RMCH did not capture the two earlier cases, including the primary case, that had been admitted to RMCH. Although this active surveillance system did capture the third admitted cases, it might not have been able to detect the outbreak earlier due to the large spillover event distance from the surveillance hospital (132 kilometers). A previous study found a 0.78 reduction in the odds of NiV spillover event detection by a surveillance hospital with every increase in 10 kilometers.[20] Tracing of contacts is essential because there are no vaccines and specific treatments to prevent NiV infection.

Public Health Action and Recommendations

The source of NiV infection for the primary case was likely from contact with bat excreta during forest visits or from making traditional medicine. The investigation found evidence of human-to-human transmission of NiV in the enclosed environment of an ambulance. We recommend that visiting forests, especially around bat habitats, should be discouraged to prevent further NiV spillover from bats to humans. All ambulance attendees should use protective measures while transporting suspected NiV infected patients, and other patients with infectious diseases, to prevent human-to-human transmission. To promote this behavior, an informatic should be developed and displayed in a prominent position in the ambulance office or garage. Increasing the number of sentinel sites in the Nipah belt of Bangladesh may increase the chance of detecting NiV spillover events. Increased surveillance could prevent future NiV disease outbreaks.

Acknowledgments

We thank all local health authorities, health workers, and community members, including families of the cases and the contacts, for their support in this investigation.

Funding Source

The Bangladesh Ministry of Health and Family Welfare (MoHFW), the Institute of Epidemiology, Disease Control and Research (IEDCR)

Conflict of Interest

There are no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Footnotes

An abstract written from this work has been published in the online supplement to the International Journal of Infectious Diseases, Volume 101, Supplement 1, 252, 1 Dec 2020 (https://doi.org/10.1016/j.ijid.2020.11.095).

Suggested Citation

Alam MGS, Billah MM, Sharif AR, Sultana S, Shano S, Rahman MK, et al. Secondary human-to-human transmission of Nipah virus in an ambulance, Northwestern Bangladesh, February 2019. OSIR. 2022 Sep;15(3):84–90.

References

1. World Health Organization. WHO publishes list of top emerging diseases likely to cause major epidemics [Internet]. Geneva: World Health Organization; 2015 Dec 10 [cited 2020 Aug 16]. <https://www.who.int/news/item/10-12-2015-who-publishes-list-of-top-emerging-diseases-likely-to-cause-major-epidemics>
2. Lam SK, Chua KB. Nipah virus encephalitis outbreak in Malaysia. Clin Infect Dis. 2002 May 1;34 Suppl 2:S48–51.
3. Chadha MS, Comer JA, Lowe L, Rota PA, Rollin PE, Bellini WJ, et al. Nipah virus-associated encephalitis outbreak, Siliguri, India. Emerg Infect Dis. 2006 Feb;12(2):235–40.
4. Ching PKG, de los Reyes VC, Sucaldito MN, Tayag E, Columna-Vingno AB, Malbas FF, et al. Outbreak of Henipavirus Infection, Philippines, 2014. Emerg Infect Dis. 2015 Feb;21(2):328–31.
5. Flora MS, Salimuzzaman M, Alamgir ASM, Sultana S, Muraduzzaman AKM, editors. National guideline for management, prevention and control of Nipah virus infection including encephalitis [Internet]. 2nd ed. Dhaka (BD): Institute of Epidemiology, Disease Control and Research; 2016 Nov [cited 2020 Nov 13]. <https://iedcr.gov.bd/publication/guidelines/10adb7d5-b36b-4e87-a37c-7fc981f4f888>

6. Institute of Epidemiology, Disease Control and Research. Nipah virus transmission in Bangladesh [Internet]. Dhaka: Institute of Epidemiology, Disease Control and Research; [cited 2020 Nov 14]. <https://iedcr.gov.bd/surveillances/93c87e70-9c22-4f21-9506-a1161ecf404f>

7. Luby SP, Hossain MJ, Gurley ES, Ahmed BN, Banu S, Khan SU, et al. Recurrent Zoonotic Transmission of Nipah Virus into Humans, Bangladesh, 2001–2007. Emerg Infect Dis. 2009 Aug;15(8):1229–35.

8. Homaira N, Rahman M, Hossain MJ, Epstein JH, Sultana R, Khan MSU, et al. Nipah virus outbreak with person-to-person transmission in a district of Bangladesh, 2007. Epidemiol Infect. 2010 Nov;138(11):1630–6.

9. Sazzad HMS, Hossain MJ, Gurley ES, Ameen KMH, Parveen S, Islam MS, et al. Nipah virus infection outbreak with nosocomial and corpse-to-human transmission, Bangladesh. Emerg Infect Dis. 2013 Feb;19(2):210–7.

10. Islam M, Sazzad H, Satter S, Sultana S, Hossain M, Hasan M, et al. Nipah virus transmission from bats to humans associated with drinking traditional liquor made from date palm sap, Bangladesh, 2011–2014. Emerg Infect Dis. 2016 Apr [cited 2018 Mar 21];22(4):664–70. <https://wwwnc.cdc.gov/eid/article/22/4/15-1747_article>

11. Rahman M, Chakraborty A. Nipah virus outbreaks in Bangladesh: a deadly infectious disease. WHO South East Asia J Public Health. 2012 Apr–Jun;1(2):208–12.

12. Gurley ES, Montgomery JM, Hossain MJ, Bell M, Azad AK, Islam MR, et al. Person-to-person transmission of Nipah virus in a Bangladeshi community. Emerg Infect Dis. 2007 Jul;13(7):1031–7.

13. Arunkumar G, Chandni R, Mourya DT, Singh SK, Sadanandan R, Sudan P, et al. Outbreak investigation of Nipah virus disease in Kerala, India, 2018. J Infect Dis [Internet]. 2019 Jun 15 [cited 2019 Feb 17];219(12):1867–78. <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiy612/5144922>

14. Nikolay B, Salje H, Hossain MJ, Khan AKMD, Sazzad HMS, Rahman M, et al. Transmission of Nipah virus — 14 years of investigations in Bangladesh. N Engl J Med. 2019 May 9;380(19):1804–14.

15. Institute of Epidemiology, Disease Control and Research. Surveillance [Internet]. Dhaka: Institute of Epidemiology, Disease Control and Research; [cited 2020 Sep 21]. Available from: <https://www.iedcr.org/index.php?option=com_content&view=article&id=42&Itemid=99>

16. Giesecke J. Primary and index cases. Lancet. 2014 Dec 6;384(9959):2024.

17. Homaira N, Rahman M, Hossain MJ, Nahar N, Khan R, Rahman M, et al. Cluster of Nipah Virus Infection, Kushtia District, Bangladesh, 2007. PLoS ONE [Internet]. 2010 Oct 21 [cited 2020 Jan 26];5(10):e13570. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2958840/>

18. Lo MK, Lowe L, Hummel KB, Sazzad HMS, Gurley ES, Hossain MJ, et al. Characterization of Nipah virus from outbreaks in Bangladesh, 2008–2010. Emerg Infect Dis. 2012 Feb;18(2):248–55.

19. Thomas B, Chandran P, Lilabi MP, George B, Sivakumar CP, Jayadev VK, et al. Nipah virus infection in Kozhikode, Kerala, South India, in 2018: epidemiology of an outbreak of an emerging disease. Indian J Community Med. 2019 Oct–Dec;44(4):383–7.

20. Cortes MC, Cauchemez S, Lefrancq N, Luby SP, Jahangir Hossain M, Sazzad HMS, et al. Characterization of the Spatial and Temporal Distribution of Nipah Virus Spillover Events in Bangladesh, 2007–2013. J Infect Dis. 2018 May 1;217(9):1390–4.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

An Investigation of Extensively Drug-resistant Tuberculosis: Revealing Potential Improvements for Tuberculosis Control Program

Suphanat Wongsanuphat[1]*, Charuttaporn Jitpeera[1], Orathai Suwanchairob[1], Wannisa, Theprongthong[2], Patcharin Tantiworrawit[3], Panithee Thammavijaya[1]

1 Division of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand

2 Division of Tuberculosis, Department of Disease Control, Ministry of Public Health, Thailand

3 Division of Innovation and Research, Ministry of Public Health, Thailand

*Corresponding author email: suphanat.wong@gmail.com

Abstract

On 31 May 2019, the Division of Epidemiology (DoE) was notified of a confirmed extensively drug-resistant tuberculosis (XDR-TB) case in Bangkok. The DoE and local teams conducted a joint investigation to describe the epidemiological characteristics of the case, identify possible source cases and contacts, and implement control measures. A descriptive study was performed among cases and close contacts by interviewing and reviewing the medical records using a standard case definition. An environmental study was performed at the case's house, workplaces, and tuberculosis (TB) clinic. The TB drugs were tested to analyze the content of active ingredients and dissolution. The case was a 36-year-old Thai male. In 2011, he was diagnosed with pulmonary tuberculosis and had received inappropriate treatment. He developed multidrug-resistant tuberculosis (MDR-TB) eight months later and XDR-TB in May 2019 with delayed hospital admission. Two possible source cases, both co-workers of the index case, were identified. Of 21 contacts, 13 were screened with a chest x-ray and found to have no abnormality. At the TB-clinic, drugs were stored in a room with inappropriate levels of temperature and humidity; however, the content of active ingredients and dissolution of TB drugs were within normal limits. Early hospital admission and monitoring of drug stockpile environments according to standard guidelines are recommended.

Keywords: extensively drug-resistant tuberculosis, XDR-TB, health insurance, drug quality

Background

The emergence of drug-resistant tuberculosis (DR-TB), a form of tuberculosis (TB) which is resistant to at least one first-line anti-TB drug, is a recent and major threat to global TB control. The treatment duration is substantially longer and more expensive and, compared with drug-susceptible TB (DS-TB), side-effects are more harmful.[1–6] DR-TB can be categorized into three groups, mono-resistant (rifampicin-resistant tuberculosis; RR-TB), multidrug-resistant tuberculosis (MDR-TB), which means resistant to isoniazid and rifampicin, and extensively drug-resistant tuberculosis (XDR-TB) which means MDR-TB with additional resistance to fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin).[7]

In Thailand, 106,000 new TB cases were identified in 2018, which is approximately 153 cases per 100,000 population.[8] Of these, around 26% consisted of MDR/RR-TB, which caused various outbreaks in both the community and health care facility settings.[8–10] In addition, XDR-TB was decided as a dangerous communicable disease in Thailand.[11]

On 31 May 2019, the Department of Disease Control (DDC) received notification of a newly identified confirmed XDR-TB case in Bangkok. The DDC and the Public Health Nurse Division conducted a joint investigation during 31 May to 6 Jun 2019. The objectives of the investigation were to verify the diagnosis, describe clinical and epidemiological characteristics of the case, identify possible source cases and secondary cases, and provide recommendations for disease control.

Methods

Descriptive Study

A descriptive study was conducted among the index case, contacts and possible source case(s) by interviewing and reviewing medical records. The case and contact definition followed National Tuberculosis (NTB) Control Programme guidelines, which are shown in Table 1.[12] A possible source case is a contact who had been diagnosed with TB within two years prior to the index case's symptoms onset.

Table 1. Definition of tuberculosis cases and contacts

Type	Definition
Tuberculosis case	
Presumptive case	A person who met at least one of the following criteria: (i) cough ≥2 weeks (ii) hemoptysis (iii) cough <2 weeks plus fever or unexplained weight loss
Probable case	A person diagnosed with tuberculosis and treated with tuberculosis drugs but with no bacteriologically confirmed laboratory results.
Confirmed case	A person with bacteriologically confirmed tuberculosis based on laboratory results.
Contact	
Contact	All persons with a history of contact with the index case during 3 months before the index case developed symptoms to 2 weeks after adequate treatment
Household contact	A person living with the index case within the same place of residence.
Close contact	A person who associated, socialized or interacted with the index case for more than 8 hours per day or 120 hours per month but did not live in the same house

Face-to-face interviews were conducted using a semi-structured questionnaire of Thailand's tuberculosis case investigation form-02 and -03 for TB cases and contacts, respectively.[13] For the case, data collected included demographic characteristics, past and present illnesses and a list of possible source cases and contacts. In addition, the risk of developing DR-TB and potential strategies to combat this risk was evaluated using a patient-centered approach (PCA), which is a method for quality improvement of TB treatment recommended by World Health Organization and the Thai Division of Tuberculosis.[12,14] PCA can be defined as "providing care that is respectful of, and responsive to, individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions".[14] For contacts, data collected included demographic characteristics, contact category (household or non-household), and underlying diseases and symptoms.

Environmental Study

We conducted an environmental study at the index case's house, workplaces and affected TB-clinics using face-to-face interviews and direct observation. For the index case's house, we directly observed the type of building and physical structure, sputum disposal locations, and presence of air ventilation. For workplaces, we interviewed personnel concerning the type of activity, duration of employment, health screening, and number of co-workers and position, and observed the index case's working zone and presence of air ventilation. For TB-clinic, we interviewed personnel concerning clinic workflow, type, and number of health care providers. The temperature and relative humidity of all TB stockpiles were recorded using a standard thermohydrometer, three times per day, at 9:00 AM, 12:00 AM and 3:00 PM during 6 to 10 Oct 2019.

Laboratory Study

Chest radiography was done among all contacts. If any abnormality of chest imaging was detected, sputum for TB and DR-TB using GeneXpert MTB/RIF was performed.[15] In order to assess the active ingredients and dissolution of tuberculosis drugs in the TB clinic, we purposively collected the oldest batch of first-line TB drugs from a selected stockpile and sent it to the Bureau of Drug and Narcotic, Department of Medical Sciences for processing.[16]

Results

Descriptive Study

Index case description

The index case was diagnosed with XDR-TB in Bangkok and reported to the DDC on 31 May 2019. The case was a 36-year-old Thai male living in Bangkok with a history of MDR-TB. He had health insurance under the Universal Coverage Scheme and was registered at his home town (400 kilometers from Bangkok).[17]

In July 2011, he visited a private hospital after experiencing unexplained weight loss and was diagnosed with TB based on chest imaging without an acid fast bacilli (AFB) test or drug susceptibility test (DST). After two months of medication prescription, he was lost to follow up.

In April 2012, his symptoms worsened and, after visiting a general practitioner, he was referred to a TB clinic. He reported that at the TB clinic, the multidisciplinary team, which used a patient-centered approach, could support him by increasing his awareness and improving his understanding on the importance of treatment.

In May 2012, based on his first DST, his disease was found to be resistant to first-line drugs. He was diagnosed with MDR-TB and was prescribed five TB drugs of which only two, namely kanamycin and ethionamide, were active. One year later, he obtained culture conversion and was treated monthly for another six months. At the end of this treatment, he had had treatment for a total of 45 months, meaning that his final status was "completed treatment".

On 16 May 2019, he re-visited the same TB clinic due to chronic cough and was diagnosed with relapsed TB by positive sputum AFB results.

On 31 May 2019, he was diagnosed with XDR-TB. However, he was not hospitalized until 5 June due to problems with his health insurance. During the admission period, patient-centered approaches were not performed.

Results of the DST, diagnosis, drug regimens received and critical points at each treatment place are shown in Table 2.

Table 2. Timeline of index case from medical record review showing place of treatment, drug sensitivity test, diagnosis, drug regimen and critical points

	July 2011	April 2012	May 2012	October 2014	May 2019
Place of Treatment	Private Hospital D	TB-clinic	TB-clinic	TB-clinic	TB-clinic
DST (Resistant to)	No initial AFB No DST	I, R, Z, Ofx, PAS	I, R, Z, Ofx, PAS, Lfx	Sputum negative for 6 months	I, R, FQs, AG/CP (Genotypic DST)
Diagnosis	New TB	MDR-TB	MDR-TB	Improved	XDR-TB
Treatment	I, R, Z, E	Km, Eto, Ofx[a], PAS[a], Z[a]	Km, Eto, Ofx[a], PAS[a], Z[a]	Discontinue drug	Start XDR regimen
Critical points	No initial AFB and DST No PCA -> poor compliance	Inappropriate diagnosis Inadequate drug regimen	Inadequate drug regimen		Delayed hospital admission process due to health insurance problem

Note: [a]TB drugs that the patient received while already being resistant to them. I: Isoniacid, R: Rifampicin, Z: Pyrazinamide, E: Ethambutal, PAS: Para-aminosalicyclic acid, Ofx: Ofloxacin, Lfx: Levefloxacin, Eto: Ethionamide, Km: Kanamycin (Km), PCA: Patient-centered approach, FQs: Fluoroquinolones, AG/CP: Aminoglycosides/Cyclic polypeptide

Identification of contacts and possible source case

There were 21 reported contacts, as shown in Table 3. We screened 13 of these, all three household contacts and 10 of the 18 close contacts. Only one of his four close friends were screened because he preferred not to tell them all due to fear of stigmatization and some of his old contacts during his first episode of TB were not contactable. However, no additional case among the screened contacts was detected. All had normal chest imaging and no abnormal symptoms. Therefore, sputum GeneXpert MTB/RIF was not performed.

Table 3. Contact screening of index case and demographic characteristics of contacts

Type of contact (number)	No. of contacts screened (%)	Median age (range)
Household contacts (3)	**3 (100%)**	**11 (4–34)**
Close contacts (18)	**10 (56%)**	**34 (22–44)**
• 2009–2014 colleagues (10)	6 (60%)	32 (26–44)
• 2015–2019 employees (4)	3 (75%)	26 (22–30)
• 2009–2019 friends (4)	1 (25%)	35

For possible source case, two suspected persons were identified, both from a restaurant where the index case worked. The first case was a 26-year-old male co-worker, treated at the TB clinic. He was diagnosed

with DS-TB in 2005 and MDR-TB in late 2005. His illness persisted during 2005–2013. While working at the restaurant in 2009, his sputum culture remained positive with a high concentration of the Mycobacterium organism. He worked in the kitchen with the index case for almost two years, spending more than eight hours per day together in close proximity.

The second case was a male co-worker who the index case reported having a chronic cough during 2009–2011. He died from TB (presumptive) in 2011. However, we could not identify the hospital or clinic where he was diagnosed or treated and therefore could not review his medical record.

Environmental Study

Index case house

The house of the index case was a two-story townhouse consisting of two bedrooms and two bathrooms, one bedroom had an air-conditioner, and each had two windows which were rarely opened. The index case reported that he usually disposed of his sputum in the toilet bowl.

Previous workplace (2009–2015)

From 2009 to 2015, the index case worked at a restaurant where his major duties involved preparing and cooking food in the kitchen, which had an air-conditioner. His workspace was located next to an MDR-TB patient's workspace (approximately two meters away). From an interview with the restaurant owner, health screening was not provided for restaurant employees until 2012.

Current workplace (2015–2019)

The index case's main work activities involve preparation of ingredients at his house and distribution of ingredients to vendors under his employment.

TB-clinic

This clinic was a major public TB clinic located in Bangkok. It consisted of two outpatient department (OPD) rooms and one directly observed treatment (DOT) room. All three rooms had adequate natural air ventilation. More than 20 multidisciplinary health care providers were employed. The clinic serviced approximately 50 TB cases per day.

Three medication stockpiles were identified: a main stockpile, an OPD stockpile and a DOT stockpile. The main stockpile was kept in a room with adequate temperature (<30°C) and humidity control (<60%). It contained most of the TB drugs including second-line drugs which were transferred to the OPD stockpile once a month. The OPD stockpile was stored in a room with an air-conditioner which was turned on only during working hours. It stocked TB drugs for six months without temperature or humidity control. The DOT stockpile was a medication stockpile for DOT which was transferred from the OPD stockpile once a week. It was stored in a room without temperature and humidity control. Relative humidity and temperature ranged from 36–55% and 24.4–27.0°C, 44–54% and 25.0–29.4°C, and 45–64% and 27.2–33.5°C in main, OPD and DOT stockpile, respectively. For drug quality, samples of active ingredients and dissolution were all within normal levels (Table 4).

Table 4. Environmental and Laboratory study of quality of four different drugs from OPD stockpile

Drug	Environmental Study			Laboratory Study	
	Detail of samples / storage duration at OPD stockpile (suggested duration)	Storage at OPD stockpile		Standard Identification[2]	
		Temp (Standard Level)	Humidity (Standard Level)	Concentration (Normal range)	Dissolution
Rifampin	In Packages / 3 months (<1 month)	During 6–10 October, Working hour 25.0–29.4°C (<30°C)	During 6–10 October, Working hour 44–54% (<60%)	97.4 (90.0–110.0% la.)	Passed
Isoniazid	In Bottles / 3 months (<1 month)			98.6 (90.0–110.0% la.)	Passed
Ethambutol	In Packages / 3 months (<1 month)			96.5 (95.0–105.0% la.)	Passed
Pyrazinamide	In Packages / 5 months (<1 month)			99.7 (93.0–107.0%% la.)	Passed

Note: % la.: % label claim

Action Taken

Five days after confirmation of XDR-TB, the index case was admitted to a hospital and started on a regimen two days later. He remained in hospital for two months until sputum conversion. After discharge, he attended the TB clinic and opted for DOT at a healthcare service near his home. We suggested to his wife to clean the entire house thoroughly, change the bedding set regularly, open the windows every day to improve air ventilation, and identify a proper sputum disposal area. We planned to follow up the contacts every six

months for the next two years and encouraged them to see a doctor if suspicious symptoms developed. At the TB clinic, we advised health personnel to monitor the temperature and humidity levels of all stockpile rooms.

Discussion

This DR-TB investigation illustrated several gaps in TB control in Thailand. Here, we discuss the TB control gaps in four perspectives including; patient perspective (risk of developing DR-TB), healthcare provider perspective (lack of DST during first period of treatment and inadequate treatment), TB clinic and health system (inadequate drug storage and problem with health insurance), and employer perspectives (pre-working health screening and sick leave).

From the patient perspective, the index case had a history of working with a confirmed DR-TB case which was a risk factor for DR-TB.[18] Infection with MDR-TB had a direct impact on the poor end-of-treatment outcome.[19] Another contributing factor was that he was a relapsed case who had a history of having taken TB drugs in the past.[20] Moreover, his poor drug adherence during the initial treatment period could be one of the factors associated with DR-TB.[21–23] In Bangkok, the rates of lost to follow-up and relapse were higher than the national level during 2016–2019.[24] Lost to follow-up might be the result of associated factors such as remoteness of an accommodation to the nearest healthcare facility, living in an urban area and having a regular occupation, which were factors found in this case.[25,26] Moreover, lost to follow up is known to be associated with poor drug adherence and relapse, which are known key risk factors for developing secondary DR-TB.[21] PCA performed by a multidisciplinary team at the TB clinic appeared to improve his drug compliance and adherence to follow up. However, the PCA approach can only be well-organized in TB clinics which have a large number of healthcare providers and is not isolated from a medicine dispensary and family medicine unit.[27,28]

From the health care provider perspective, we could not determine whether the index case was a primary or secondary DR-TB case due to a lack of DST during the first period of treatment. This issue was also mentioned in a previous case investigation.[29] DST can provide a definitive diagnosis and proper treatment of DR-TB, which can improve the treatment success rate.[30] In addition, the index case received the adequate dosage and duration of TB drugs, but his disease was resistant to two drugs during the MDR-TB treatment period. According to NTB and the U.S. Centers for Disease Control and Prevention recommendations, patients should receive at least four different drugs that are active against tuberculosis.[31,32] Therefore, the index case received an inadequate drug regimen during his MDR-TB treatment period. Inadequate drug treatment for MDR-TB could amplify XDR strains (secondary XDR-TB), which could eventually be transmitted to contacts, who then develop primary XDR-TB.[22,23,29,33]

From the health system perspective, drug quality is another risk factor explored in this study. In the TB clinic the room containing the DOT stockpile during the day-time had inadequate temperature and humidity levels, which could affect the quality of drugs leading to treatment failure.[34–39] Nevertheless, the concentration and dissolution of all drugs tested among the standard TB regimen were within normal ranges based on independent laboratory tests. Despite the fact that XDR-TB patients are designated by law to be isolated with compulsory hospitalization, the identification process of the hospital in isolating the index case and providing timely treatment was delayed due to a health insurance issue.[2] This can lead to further problems including treatment failure and disease spreading.[18,21,27,40]

From the employer perspective, of the two possible source cases, one co-worker did not leave his job during the period when the index case was still working at the restaurant. His sputum culture remained positive which could increase the risk of transmission to the index case.[18] According to NTB guidelines, patients should leave their job until sputum conversion occurs in order to prevent disease transmission.[13] Furthermore, the co-worker did not have chest imaging performed before beginning their employment in the restaurant. All employees should have adequate health checks before starting employment.[41]

Limitations

Firstly, we could not interview the first of the two possible sources. However, a two-year period of daily and prolonged contact with the index case and the high concentration of Mycobacterium organism meant that he was the most likely source of infection. Secondly, we could not interview all contacts of the index case due to insufficient contact information. Thirdly, we did not have information why the first doctor did not take DST during his first visit and the other doctor prescribed four drugs that only two drugs were active during his treatment for MDR-TB. And lastly, we could not perform any tests on MDR-TB or XDR-TB drugs, which are known to degenerate more quickly than the standard TB drugs and evaluate the temperature and humidity of the stockpile rooms during the night-time.[42]

Recommendations

For National TB Control Agency

A number of recommendations can be made from the results of our investigation. Firstly, identification and clarification of the health insurance status of TB cases, especially DR-TB cases, and an additional consensus on the healthcare facilities available for admission of index cases who lack health insurance, are needed. Secondly, sputum specimens, especially among DR-TB cases, should be kept until completion of treatment. Thirdly, encouraging an annual health check-up policy, including chest imaging, among employees and workers should be reemphasized. Strengthening the patient-centered approach, not only to DR-TB patients but also to those with DS-TB, is suggested, contingent on the availability of human resources. Lastly, enhancing the co-operation between TB clinics and family medicine units is recommended.[14,28]

For Tuberculosis Clinics

Appropriate diagnostic methods, including a requirement to perform AFB testing and DST, and the prescription of appropriate drug regimens, especially among DR-TB patients, should be reemphasized to attending physicians.[12,13] Establishing a protocol to reassure physicians of the appropriate diagnosis and drug regimen is also suggested. Additionally, the humidity and temperature of stockpile rooms should be checked regularly. Lastly, an adequate sick leave period for all new TB cases should be reemphasized to attending physicians.

Conclusion

We identified a TB outbreak involving three cases, including one confirmed XDR-TB (index case) and two possible source cases who were co-workers of the index case. No TB was detected among any of the index case's contacts. Close and prolonged contact with a confirmed DR-TB case, poor drug compliance, and prescription of an inappropriate drug regimen were factors related to XDR-TB development. Early clarification of health insurance status, provision of an adequate sick leave period, use of a patient-centered approach, and regular monitoring of standard TB drug stockpiles are strongly recommended.

Acknowledgements

We would like to acknowledge the support from Dr. Petchawan Pungrassami, Senior Expert in Preventive Medicine from the Department of Disease Control, Division of Tuberculosis, the Institute of Urban Disease Control and Prevention, Bamrasnaradura Infectious Disease Institute, the Drug and Narcotic Division in the Department of Medical Sciences, and the Public Health Nurse Division, Bangkok.

Suggested Citation

Wongsanuphat S, Jitpeera C, Suwanchairob O, Theprongthong W, Tantiworrawit P, Thammavijaya P. An investigation of extensively drug-resistant tuberculosis: revealing potential improvements for tuberculosis control program. OSIR. 2022 Sep;15(3):91–8.

References

1. World Health Organization. Tuberculosis (TB) [Internet]. World Health Organization; [cited 2019 Nov 8]. <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
2. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, et al. Worldwide emergence of extensively drug-resistant tuberculosis. Emerg Infect Dis. 2007;13(3):380–7.
3. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: The new XDR-TB threat. Is "science" enough to tackle the epidemic? Eur Respir J. 2007;29(3):423–7.
4. Zignol M, Hosseini MS, Wright A, Weezenbeek CL, Nunn P, Watt CJ, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis. 2006 Aug 15;194(4):479–85.
5. Matteelli A, Migliori GB, Cirillo DM, Centis R, Girardi E, Raviglione MC. Multidrug-resistant and extensively drug-resistant Mycobacterium tuberculosis: epidemiology and control. Expert Rev Anti Infect Ther. 2007 Oct;5(5):857–71.
6. World Health Organization. Drug-resistant TB: XDR-TB FAQ [Internet]. Geneva: World Health Organization; 2018 [cited 2019 Nov 8]. <https://www.who.int/tb/areas-of-work/drug-resistant-tb/XDR-TB-faq/en/>
7. World Health Organization. TB drug resistance types [Internet]. Geneva: World Health Organization; 2015 [cited 2019 Nov 8]. <https://www.who.int/tb/areas-of-work/drug-resistant-tb/types/en/>
8. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018. 231 p.

9. Jiraphongsa C, Wangteeraprasert T, Henpraserttae N, Sanguanwongse N, Panya L, Sukkasitvanichkul J, et al. Community outbreak of multiple drug resistance tuberculosis, Kanchanaburi province, Thailand on 2002–June 2010. Journal of Preventive Medicine Association of Thailand. 2011 Sep–Dec;1(3):261–71. Thai.

10. Oeltmann JE, Varma JK, Ortega L, Liu Y, O'Rourke T, Cano M, et al. Multidrug-resistant tuberculosis outbreak among US-bound Hmong refugees, Thailand, 2005. Emerg Infect Dis. 2008 Nov;14(11):1715–21.

11. Communicable disease act B.E. 2558 (2015), Royal Thai Government Gazette [English version on the Internet], Volume 132, part 86 Kor (Dated 2015 Sep 8) [cited 2019 Nov 8]:26–44. <https://ddc.moph.go.th/uploads/ckeditor/c74d97b01eae257e44aa9d5bade97baf/files/001_2gcd.pdf>

12. National Tuberculosis control programme guidelines, Thailand, 2018. Bangkok: Division of Tuberculosis, Department of Disease Control; 2018. 120 p.

13. Tuberculosis investigation and control guidelines, Thailand, 2018. Bangkok: Division of Tuberculosis, Department of Disease Control; 2018. 80 p.

14. World Health Organization. A patient-centred approach to TB care [Internet]. Geneva: World Health Organization; 2018 [cited 2019 Nov 17]. 2 p. <https://apps.who.int/iris/bitstream/handle/10665/272467/WHO-CDS-TB-2018.13-eng.pdf?ua=1>

15. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. A new tool to diagnose tuberculosis: the Xpert MTB/RIF assay [Internet]. Atlanta: Centers for Disease Control and Prevention; [cited 2020 Apr 11]. 2 p. <https://www.cdc.gov/tb/publications/factsheets/pdf/xpertmtb-rifassayfactsheet_final.pdf>

16. Pharmapproch. Quality control tests for tablets [Internet]. [place unknown]: Pharmapproach.com; 2019 [cited 2019 Oct 23]. <https://www.pharmapproach.com/quality-control-tests-for-tablets/>

17. Sumriddetchkajorn K, Shimazaki K, Ono T, Kusaba T, Sato K, Kobayashi N. Universal health coverage and primary care, Thailand. Bull World Health Organ. 2019 Jun 1;97(6):415–22.

18. Division of Tuberculosis Elimination, National Center for HIV, Viral Hepatitis, STD, and TB Prevention. Tuberculosis: Drug-resistant TB [Internet]. Atlanta: Centers for Disease Control and Prevention; 2017 [cited 2018 Jun 10]. <https://www.cdc.gov/tb/topic/drtb/default.htm>

19. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, et al. Tuberculosis recurrence and mortality after successful treatment: Impact of drug resistance. PLoS Med. 2006 Oct;3(10):e384. doi:10.1371/journal.pmed.0030384.

20. Bestrashniy JRBM, Nguyen VN, Nguyen TL, Pham TL, Nguyen TA, Pham DC, et al. Recurrence of tuberculosis among patients following treatment completion in eight provinces of Vietnam: A nested case-control study. Int J Infect Dis. 2018 Sep [cited 2020 Apr 11];74:31–7. <https://www.sciencedirect.com/science/article/pii/S1201971218344485>

21. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaout I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. BMC Pulic Health. 2011 Feb 28;11:140.

22. Raviglione MC, Smith IM. XDR tuberculosis—implications for global public health. N Engl J Med. 2007 Feb 15;356(7):656–9.

23. Ebrahim GJ. Drug resistance in tuberculosis. J Trop Pediatr. 2007 Jun;53(3):147–9.

24. Division of Tuberculosis. Tuberculosis Case Management [Internet]. Bangkok: Division of Tuberculosis, Department of Disease Control; [cited 2019 Dec 15]. <https://tbcmthailand.ddc.moph.go.th/uiform/>

25. Santos E, Felgueiras O, Oliveira O, Duarte R. Factors associated with loss to follow-up in Tuberculosis treatment in the Huambo Province, Angola. Pulmonology. 2019 May–Jun;25(3);190–2.

26. Abubakar I, Lipman M. Reducing loss to follow-up during treatment for drug-resistant tuberculosis Ibrahim. Eur Respir J. 2019 Jan 10;53(1):1802268.

27. McMullen CK, Safford MM, Bosworth HB, Phansalkar S, Leong A, Fagan MB, et al. Patient-centered priorities for improving medication management and adherence. Patient Educ Couns. 2015 Jan;98(1):102–10.

28. Gargioni, G. Role of communities in tuberculosis care and Prevention [Internet]. [place unknown]: Z-Library; 2009 [cited 2019 Nov 19]. p. 660–7. doi:10.1016/b978-1-4160-3988-4.00064-0.

29. Araujo-Filho JA, Vasconcelos AC Jr, Sousa EM, Silveira Cd, Ribeiro E, Kipnis A, et al. Extensively drug-resistant tuberculosis: a case report and literature review. Braz J Infect Dis. 2008;12(5):447–52. doi:10.1590/s1413-86702008000500019.

30. World Health Organization. Implementing tuberculosis diagnostics: a policy framework [Internet]. Geneva: World Health Organization; 2015 [cited 2020 Jan 3]. <https://apps.who.int/iris/handle/10665/162712>

31. Reechaipichitkul W, Netniyom S, Pungrassami P, editors. Guideline for programmatic management of drug-resistant tuberculosis. Bangkok (TH): Division of Tuberculosis, Department of Disease Control; 2015 May. 97 p. Thai.

32. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. MMWR Recomm Rep. 1998 Oct 30;47(RR-20):1–58.

33. Lawn SD, Wilkinson R. Extensively drug resistant tuberculosis. BMJ. 2006 Sep 16;333(7568):559–60.

34. Cao K, Yang K, Wang C, Guo J, Tao L, Liu Q, et al. Spatial-temporal epidemiology of tuberculosis in Mainland China: An analysis based on bayesian theory. Int J Environ Res Public Health. 2016 May 5;13(5):469.

35. Onozuka D, Hagihara A. The association of extreme temperatures and the incidence of tuberculosis in Japan. Int J Biometeorol. 2015 Aug;59(8):1107–14.

36. Rao HX, Zhang X, Zhao L, Yu J, Ren W, Zhang XL, et al. Spatial transmission and meteorological determinants of tuberculosis incidence in Qinghai province, China: A spatial clustering panel analysis. Infect Dis Poverty. 2016 Jun 2;5(1):45.

37. Yanagawa H, Hara N, Hashimoto T, Yokoyama H, Tachibana K. Geographical pattern of tuberculosis and related factors in Japan. Soc Sci Med Med Geogr. 1981 Feb;15(1):141–8.

38. World Health Organization. Survey of the quality of anti-tuberculosis medicines circulating in selected newly independent states of the former Soviet Union [Internet]. Geneva: World Health Organization; 2012 Feb 4 [cited 2019 Nov 11]. <https://www.who.int/news/item/04-02-2012-survey-of-the-quality-of-anti-tuberculosis-medicines-circulating-in-selected-newly-independent-states-of-the-former-soviet-union>

39. Burugina Nagaraja S, Satyanarayana S, Chadha SS, Kalemane S, Jaju J, Achanta S, et al. How do patients who fail first-line TB treatment but who are not placed on an MDR-TB regimen fare in South India? PLoS ONE. 2011 Oct 11;6(10):e25698. doi:10.1371/journal.pone.0025698.

40. Reid MJA, Goosby E. Patient-centered tuberculosis programs are necessary to end the epidemic. J Infect Dis. 2017 Nov 6;216(Suppl 7):S673–4.

41. Ministerial regulations: the criteria and procedure for medical examination of employees, and submission of examination result to Labor Official, B.E. 2547 (2004), Royal Thai Government Gazette Volume 122, part 4 Kor (Dated 2005 Jan 13):19–22. <http://www3.mol.go.th/sites/default/files/laws/th/00151640.pdf>

42. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014. 403 p.

Outbreak, Surveillance, Investigation & Response (OSIR) Journal

Field Epidemiology Training Program, Division of Epidemiology
Department of Disease Control, Ministry of Public Health, Thailand
Tel: +6625903894, Fax: +6625903845, Email: osireditor@osirjournal.net, http://www.osirjournal.net

The Grammar of Science: How do We Count Time?

Jaranit Kaewkungwal

Mahidol University, Thailand

Corresponding author email: jaranitk@biophics.org

Some people say that time cannot be counted as time has no physical properties to measure. What we are really measuring is time intervals, the duration separating two events.[1] In history, people counted time as day and night between sunrise to sunset. Time shown on sundials, pendulum clock, and analog or digital watch tells us loosely about the passage of time. People in different cultures created and use different methods for keeping track of days and larger divisions of time. The Gregorian calendar is the calendar used in most of the world.[2] As introduced in October 1582 by Pope Gregory XIII, the average calendar year is approximately 365.2425 days long according to the Earth's revolution around the Sun.

Cambridge dictionary notes that "Time" is a noun with a number of meanings while it could be countable or uncountable.[3] We may use time as countable to refer to what is measured in seconds, minutes, hours, days, weeks, months and years—*"I was diagnosed and treated for cancer for 6 years since 25 Jul 2016."* On the other hand, we may use time as uncountable—*"He is out of sight for a long time."* However, when we talk about time we usually have a "Reference Time Point" —the point in time that acts as a fixed reference point to an event— *"She has been waiting since 8:00 AM"*. Some people count time from their own loose referential point—*"I have been in this position for only 6 years counting from when I started to work here."* So how do we actually count time in "Time-to-event" analysis?

Time-to-event Analysis

Time-to-event or survival analysis is a statistical procedure that considers amount of time until an event occurs.[4] The event, also called endpoint or outcome, of interest can be good (e.g., cure/recover after treatment) or bad (e.g., death, tumor recurrence). Why do we need to take time into consideration? The answer is that time will give you "rate" (or speed) of the event; it will tell you how fast an event can occur in a certain time period. Figure 1 depicts a scenario of a clinical trial which 10 patients were randomly allocated to either Drug A or Drug B. Without time effect, 3 of 5 patients who received Drug A were cured (incidence proportion=0.6). Similarly, 3 of 5 patients who received Drug B were cured (incidence proportion=0.6). The two groups were not different in terms of disease cure proportion. When considering time each patient was in the study, 3 of 9 months of follow-up among all patients who received Drug A were cured (incidence rate=0.33) while 3 of 20 months of follow-up among all patients who received Drug B were cured (incidence rate=0.15). This informs us that the cure rate per month of Drug A is better than that of Drug B.

In performing time-to-event analysis, we need two pieces of information for every study participant: (1) the time to the event and (2) the event status (whether or not the event occurs).[5] The effect of time to reach the event typically characterizes as "survival function". The function represents the probability of an individual surviving or still not reaching the event beyond time X.[4] In reality, we cannot observe events for all of the study participants as the study may end before the events of some participants occur or the participants may be lost to follow-up, drop out, death from other causes or leave the study. This leads to a concept of censoring; i.e., each participant either has the event (so-called failure case) or have not yet experienced the event (so-called censored case).[4,5] As shown in Figure 2, the time-to-event analysis is applicable to two types of study designs, cohort and experimental studies.

Figure 2 (a) shows time-to-event which could be in a prospective cohort (study starts at present and follow 3 years onward) or retrospective cohort (study starts by reviewing medical records 3 years ago until the closing date of the study). Time counts from date of diagnosis with cancer to date of dead as the endpoint event. For the patient who was not dead, he/she was

censored at date of lost to follow-up (LFU) or date of study closure. Some textbooks call a censored case that his/her time is cut off at the study closure as a "truncated" case. The case with the endpoint as dead due to suicide could be either a failure case or a censored case depending on the definition of the event. If the endpoint is defined as "all causes of death", the case is considered as a failure case; on the contrary, if the endpoint is defined as "death of cancer", the case is a censored case.

Figure 2 (b) shows time-to-event of a clinical trial which study participants were allocated to Drug A or Drug B. The outcome of the study is time from date of treatment initiation to date of cure as the endpoint event. For patient who was not cured, he/she was censored at date of lost to follow-up, date of consent withdrawal or date of study closure. Again, a censored case that his/her time is cut off at the study closure may be called a truncated case.

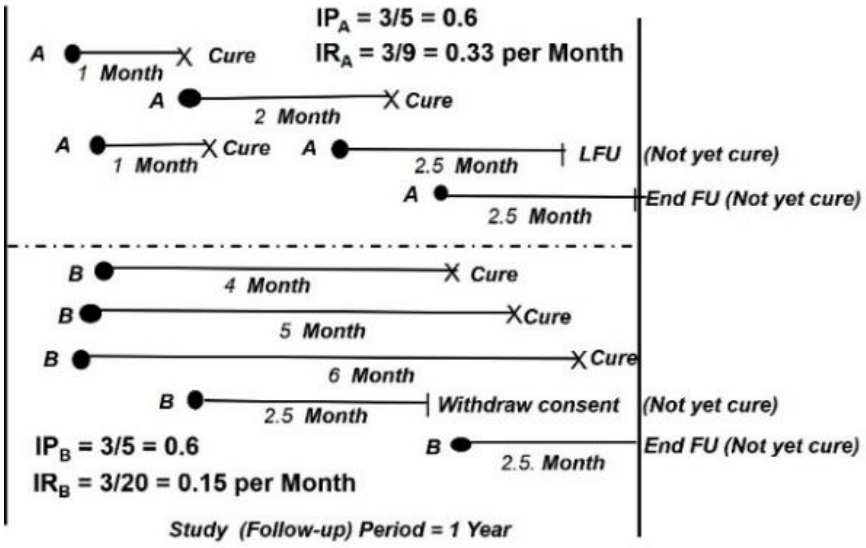
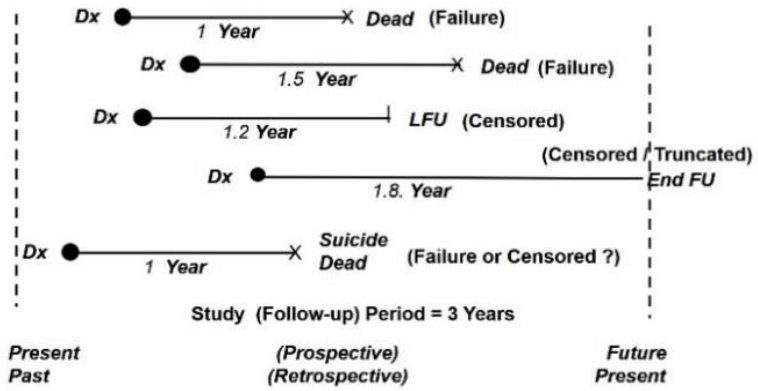
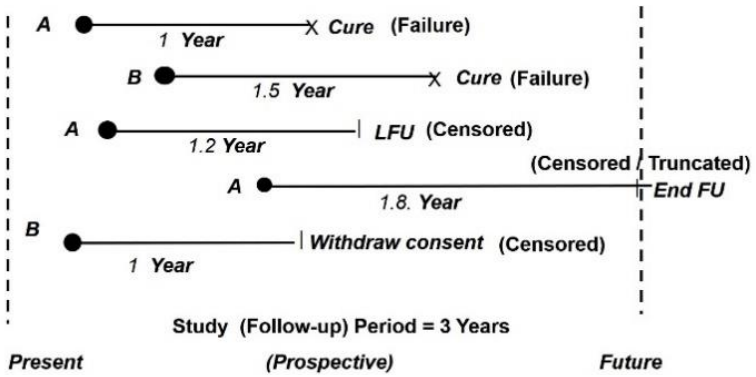


Figure 1. Examples of incidence proportion vs. incidence rate of disease cure



(a) Time to event in cohort study (time from diagnosis to dead)



(b) Time to event in experimental study (time from treatment initiation to cure)

Figure 2. Examples of time-to-event in cohort study and experimental study

Censoring & Truncating Time

When collecting time-to-event data the researchers must consider the study-specific details of recruitment and inclusion criteria.[6] When making predictions with time-to-event data, it is critical to define the risk set appropriately.[7] The study participants in the risk set include those who reach the event (failure) and those who do not have the event (censored) at the particular time point. In general, there are three types of censoring mechanisms: right censoring, left censoring, and interval censoring.[8,9]

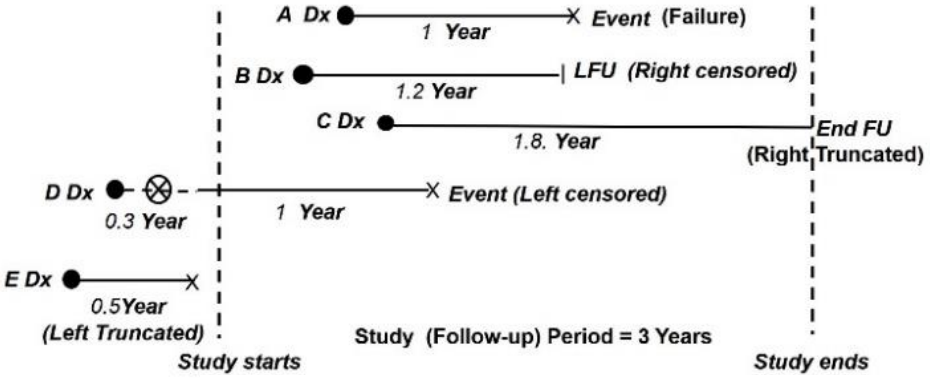
Right-censoring

The most common type of censoring is right-censoring. As previously discussed, right censoring occurs when a study participant drops out or leaves the study before the event occurs, or the study ends before the event has occurred. Right censoring might be imposed due to a competing risk, i.e., the event of interest cannot be observed because of the occurrence of a competing event (e.g., death from other causes).[9] It should be noted that the right-censored case is assumed to follow the same survival distribution after withdrawal as the non-censored cases.[8]

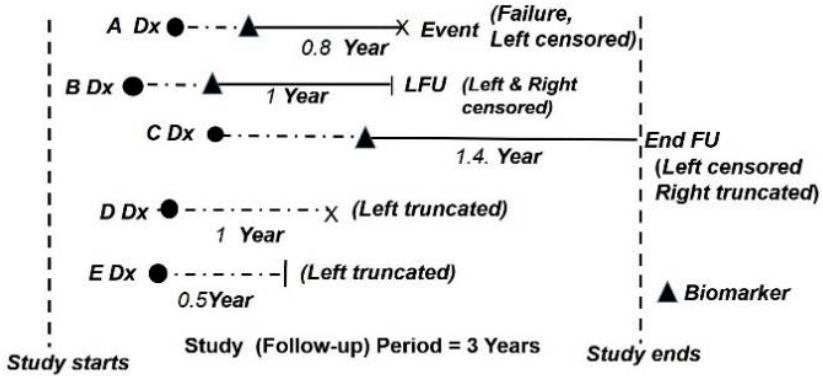
Left Censoring

This is the opposite of right censoring, when the time of a study participant is cut on the left-hand side rather than the right-hand side. There are several situations for a study participant to be considered as a left-censored case. Figure 3 shows different scenarios of left censoring. As shown in Figure 3 (a), a study participant is left censored when his/her event has already occurred prior to enrollment or before the study starts. Such case is sometimes called left truncated case. Patients E reached the event prior to the study starts and thus he is not included in the study. This scenario is very rarely encountered in most study. Patient D was diagnosed prior to the study starts but had been followed until the event occurred within the study time period. In some study, such case may be included as a study participant but the time prior to the study starts is cuff off (censored on the left-hand side).

Another left censoring example is shown in Figure 3 (b) when the time-to-event starts from a certain milestone marker. Study participants who reached the milestone marker (i.e., biomarker in this example) are included in the study (Patients A, B, C) while those who did not are excluded (Patient D, E). Patients A, B, C could be handled in different ways depending on the objective of the study; the time prior to milestone marker can be cut off (as left-hand side censoring) or can be split and treated as a case with 2 time periods (before and after milestone marker) in the analysis model.



(a) Right & left censoring / truncating from initial time point



(b) Right & left censoring / truncating from milestone marker

Figure 3. Examples of right and left censoring cases

Interval Censoring

The censoring occurs when the failure event of interest cannot be observed directly but is known to have occurred during a time interval. Interval censoring is a generalization of left and right censoring.[9] This censoring is common and natural in a clinical trial or longitudinal study in which there is periodic follow-up.[8] Patients have different visit times and durations between visits; the outcome event is measured at each visit. The exact time of event is not observed and is known to fall in an interval between visits.[10] Figure 4 shows 2 classic scenarios of interval censoring cases. Patient A missed a few visits and thus was considered as a LFU case but later on he decided to resume to the study; he reported that he had the event but forgot when the event happened during the missing time period. Patient B had regular visits throughout the study period and he had an event at Visit 6. In a typical time-to-event analysis, it can be simply assumed that he had an event at Visit 6. But in some study, the researchers may decide to model that he had an event some times between Visit 5 and Visit 6, i.e., considering interval censoring between Visit 5 and Visit 6.

In handling interval censoring data by interpolating the event time as the midpoint of the censored interval, it must be cautious that doing so depends strongly on the underlying distributions and the width of the intervals. The survival function based on midpoint event may be biased and the variability of the estimates may be underestimated.[10]

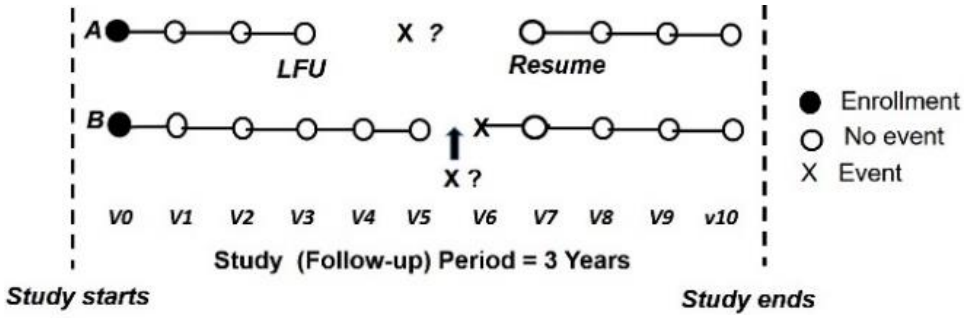


Figure 4. Examples of interval censoring cases

Biases Related to Time-to-Event

There are several biases that should be considered in time-to-event analysis. The researchers should have plan to mitigate such biases that could occur in the study.

Drop-out Bias (Selection Bias)

When a study participant drops out from the study, his/her time is censored at the drop out date. In a typical time-to-event analysis, the distribution of censoring time is assumed to be independent of the distribution of the survival time.[8] In other words, censoring should be random.[4] As an example, in a clinical trial, if there is a certain subgroup (say, younger males) drops out more than the rest of the study participants, the study sample will become biased. Moreover, the reasons for the drop out study participants should not be related to the purpose of the study.[8] Such assumption cannot be met in many studies. For example, in a cancer study, censored cases may be found more among patients who are at a higher risk of progression/death, or among patients who discontinue treatment due to toxicity and have to be shifted to start some other therapy.[8]

If such censoring bias is ignored, there would be selection bias in the data and the survival probability might be overestimated.[4] The researchers should monitor the study whether such bias occurs or not. If so, the researchers should select appropriate methods including, for example, stratification-based techniques, regression adjustment, joint modeling, or censoring weighted estimation.[8]

Length-time Bias

It is also called length-biased sampling or survivorship bias; such bias occurs when time is truncated at a certain cut off point.[4] Analysis at the time cut-off point may affect assessment of survival function among incomplete risk set, not including the number of people who still have not experienced the event. As an example shown in Figure 5, when the researchers want to estimate survival function at 1.5 years (at Month 18) within the study period (3 years), they would assess information from only 3 of 4 patients (Patients A, B, C) while cut off 1 patient (Patient D) who would be diagnosed and experience the event at later time. Incomplete risk set at Month 18 may yield underestimated survival function. Analysis based on complete risk set during the entire 3 years study period, accounting for Patient D, might result in a more precise and correct conclusion.

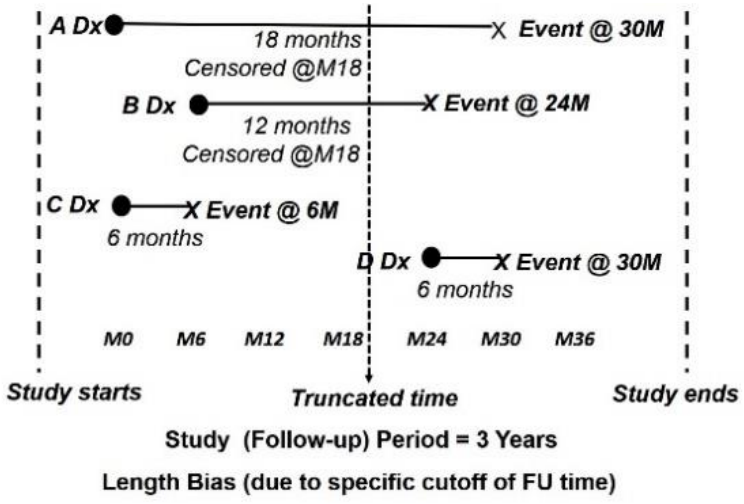


Figure 5. Example for length-time bias

Time-dependent Bias

There are many kinds of time-dependent bias. This bias is also known as immortal time bias or survivor treatment selection bias.[4] Figure 6 shows an example of time-dependent bias in terms of "time-dependent exposure", when an exposure (treatment) varies at different time points among study participants. As shown in Figure 6, treatment was only dispensed when the patient has reached a certain level of biomarker, not at enrollment. There are some patients who had never reached the set level of biomarker and thus they did not get the treatment however, they were followed up/monitored for the endpoint event (Patient A). Patients who reached the set level would receive treatment and followed up for the endpoint events (Patients B, C, D). If the researchers want to compare survival functions between those who received and did not receive the treatment, they must consider time-dependent bias. The researchers cannot simply compare time from diagnosis to the endpoint event between those who received vs. not received treatment (e.g., Patient A vs. Patient B). While those who did not receive treatment had 1 time count (Patient A), those who received treatment did actually have 2 time counts, time before and after treatment (Patient B). To correctly classify the treatment cases, their time should be split into 2 time-to-event periods: time before treatment and no event, and time after treatment and with endpoint event (as shown in Patient C, D). The appropriate time-to-event analytic model must be assessed by taking into consideration of this split time-dependent exposures.

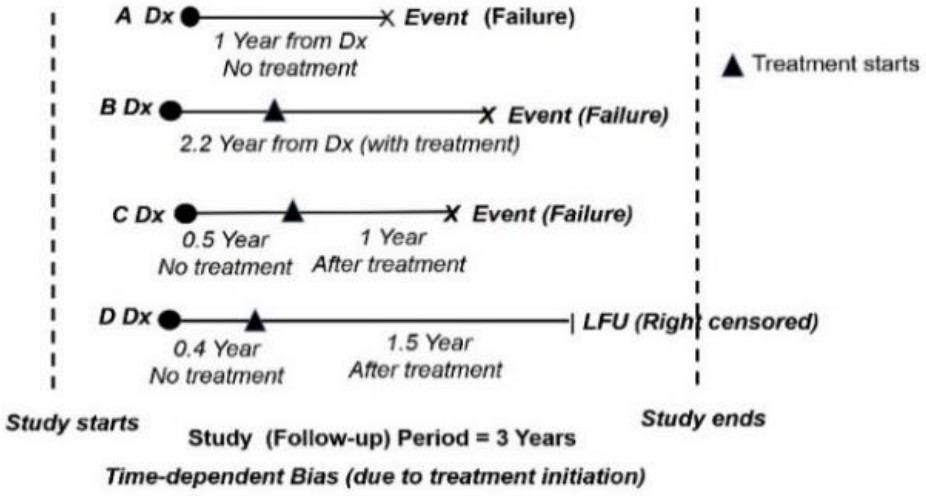


Figure 6. Example of time-dependent bias

Lead Time Bias and Stage Migration

Lead time bias occurs due to the early detection of disease is made before the usual diagnosis based on symptoms, and consequently leads to a fallacious increase in a patient's time to event.[8] As shown in Figure 7, compared to the survival time after usual diagnosis of Patient A, the survival time after early diagnosis of Patient B is longer due to lead time, time gap between early diagnosis and usual diagnosis. In fact, this increase in survival dues only to the lead time and has nothing to do with the survival of the patient.

Particularly in cancer study, another related bias, i.e., stage migration, could occur. Patients at the boundary of cancer stages might be reclassified into the higher stage and thus results in a misleading increase in survival estimation due to earlier detection before the symptoms become evident.[8] As shown in Figure 7, Patient C has much longer survival time due to lead time and gain time as he might get earlier and therefore better treatment outcome than Patient A whose survive time is based on routine practice. When early diagnosis is part of the study procedure, the researchers should acknowledge these potential biases and conclude the estimated survival time by accounting for such lead and/or gain times.

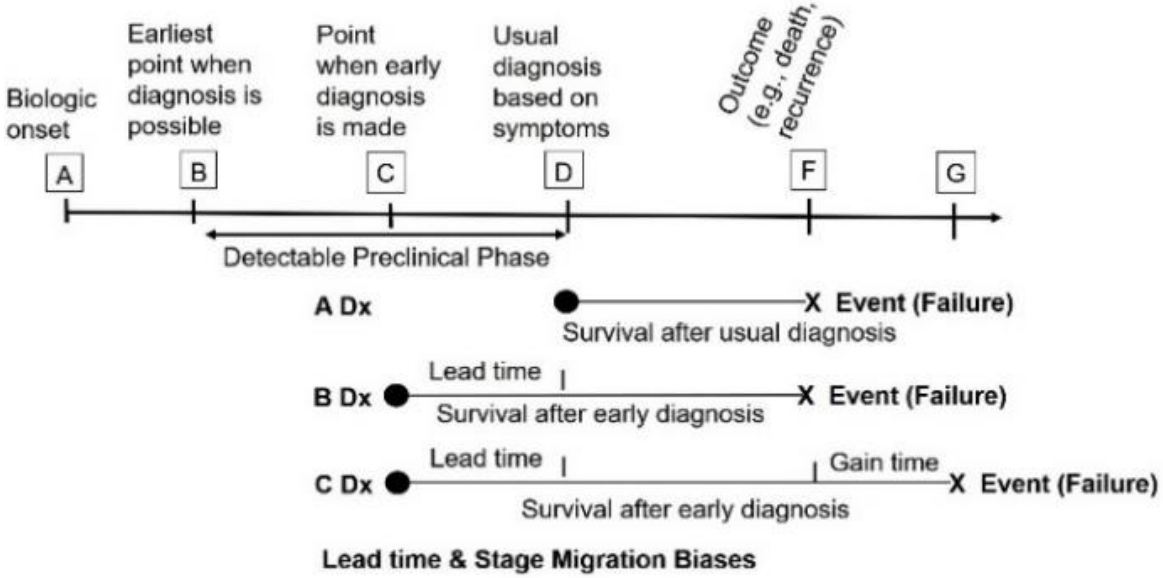


Figure 7. Example of lead time bias

In handling biases, besides procedures within Cox's proportional hazard model, there are several other methods and models that could provide precise survival function including, for examples, interval-censored data models, imputation-based methods, parametric regression models, nonparametric maximum-likelihood estimation, semiparametric regression models, and Bayesian analysis.[10,11]

Conclusion

Time-to-event is not simply counting from the time you start observing the event until the event actually occurs or does not occur. There are situations when time counting is quite complicated due to case censoring and truncating as well as several potential biases related to assessment of time effect. Incomplete information regarding time-to-event of subjects should not be simply discarded as they may reflect certain relevant information for final results of the study. The researchers must understand the concept of time in survival analysis and select the appropriate statistical procedures. Time management for time-to-event analysis need to be predetermined to avoid erroneous conclusion.

Suggested Citation

Kaewkungwal J. The grammar of science: how do we count time? OSIR. 2022 Sep;15(3):99–105.

References

1. National Institute of Standards and Technology, U.S. Department of Commerce. How Do We Measure Time? [Internet]. Gaithersburg (MD): National Institute of Standards and Technology, U.S. Department of Commerce; 2021 Oct 26 [updated 2022 Apr 8, cited 2022 Sep 15]. <https://www.nist.gov/how-do-you-measure-it/how-do-we-measure-time>
2. Wikipedia contributors. History of calendars [Internet]. San Francisco: Wikimedia Foundation; 2022 Aug 11 [cited 2022 Sep 15] <https://en.wikipedia.org/wiki/History_of_calendars>
3. English Grammar Today. Time [Internet]. Cambridge: Cambridge University Press; c2022 [cited 2022 Sep 15]. <https://dictionary.cambridge.org/grammar/british-grammar/time>
4. Liou L. How well do you "really" know survival analysis? [Internet]. Ontario (CA): Towards Data Science; 2021 Feb 5 [cited 2022 Sep 15]. <https://towardsdatascience.com/how-well-do-you-really-know-survival-analysis-221885b89a8e>

5. Quantics Biostatistics. An introduction to survival analysis for clinical trials [Internet]. Edinburgh (GB): Quantics Biostatistics; 2017 Nov 9 [cited 2022 Sep 15]. <https://www.quantics.co.uk/blog/introduction-survival-analysis-clinical-trials/>

6. Cain KC, Harlow SD, Little RJ, Nan B, Yosef M, Taffe JR, et al. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. Am J Epidemiol. 2011 May 1;173(9):1078–84.

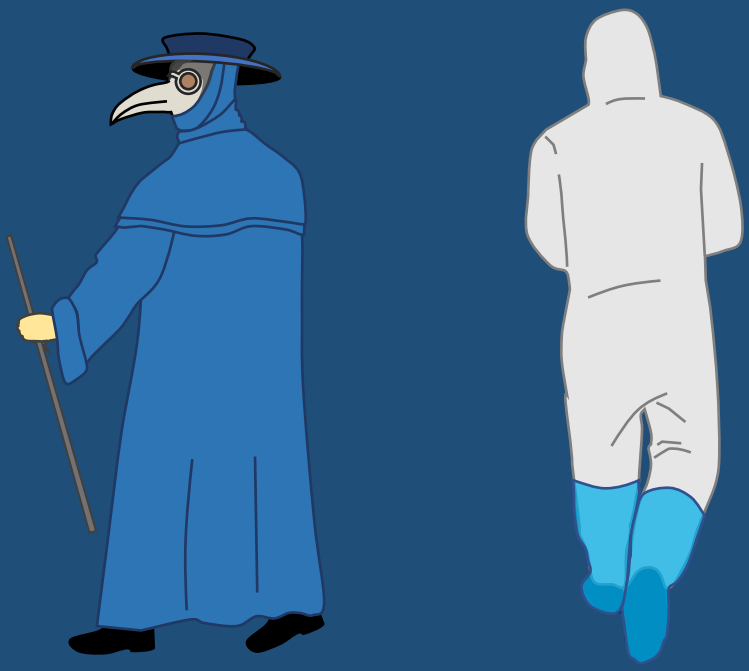
7. McGough SF, Incerti D, Lyalina S, Copping R, Narasimhan B, Tibshirani R. Penalized regression for left-truncated and right-censored survival data. Stat Med. 2021 Nov 10;40(25):5487–500.

8. Dey T, Mukherjee A, Chakraborty S. A Practical Overview and Reporting Strategies for Statistical Analysis of Survival Studies. Chest. 2020 Jul;158(1 Suppl):S38–42.

9. Rodrigues AS, Calsavara VF, Silva FIB, Alves FA, Vivas APM. Use of interval-censored survival data as an alternative to Kaplan-Meier survival curves: studies of oral lesion occurrence in liver transplants and cancer recurrence. Applied Cancer Research. 2018 Nov 26;38:16.

10. Yang X. Analyzing interval-censored survival-time data in Stata [PowerPoint presentation]. Proceedings of the 2017 Stata Conference; 2017 Jul 27–28; Baltimore (MD). Texus: StataCorp LLC; 2017 Jul 29 [cited 2022 Sep 15]. 35 p. <https://www.stata.com/meeting/baltimore17/slides/Baltimore17_Yang.pdf>

11. Turkson AJ, Ayiah-Mensah F, Nimoh V. Handling censoring and censored data in survival analysis: a standalone systematic literature review. International Journal of Mathematics and Mathematical Sciences. 2021 Sep 24; 2021: Article ID 9307475 [16 p]. <https://doi.org/10.1155/2021/9307475>



OSIR

Outbreak, Surveillance,
Investigation and Response