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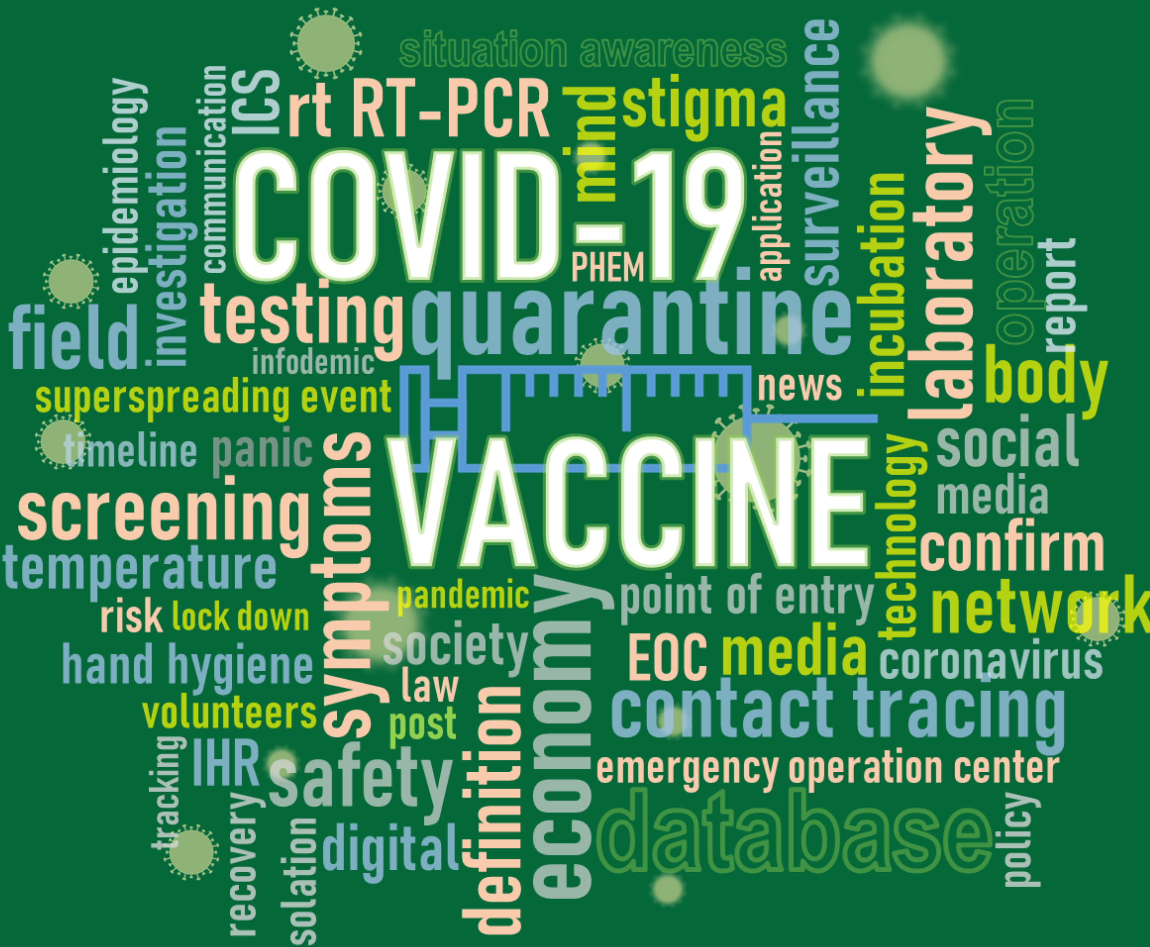

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Editorial

The Coronavirus Disease 2019 (COID-19) Sandbox is Working amidst the Continued Local Transmission of the Virus

Wiwat Rojanapithayakorn, Chief Editor

For the past 100 years, there has not been any single disease that has caused huge socioeconomic and health impacts as the coronavirus disease 2019 (COVID-19). Not to mention the health consequences which have caused over 230 million cases and 4.7 million deaths so far. The disease has brought about massive and widespread social impact, affecting wellbeing of people in almost all countries around the world. The high magnitude of undesirable outcomes includes interference or interruption on population mobility, closure of various social functions including airports, educational institutions, hotels, markets, business centers, factories and many other settings, which result in severe negative impact on economy but, in the same time, cause huge investment for the control of the outbreaks. Most governmental bodies are facing a dilemma between the strict epidemic control and some relaxation to allow the return of various economic movements such as the tourism business and international travelling.

Among all the alleviation efforts, the Government of Thailand has operated a “Sandbox” approach to revitalize tourism in the country. On 30 Mar 2021, the Cabinet endorsed an operation on “Phuket Sandbox” to welcome foreign tourists into the country. The starting date was 1 Jul 2021. The detailed mechanism is that any tourist who has fully vaccinated and shows negative COVID-19 screening result will be allowed to go to Phuket and can travel freely within the province.

The brief operational criteria are as follow:

1. The program welcomes all foreigners who received full dosage of COVID-19 vaccine at least 2 weeks before the travel date;
2. Each tourist must show evidence of health insurance against COVID-19 with the coverage of at least US$ 100,000;
3. Children under 6 are eligible if travelling with vaccinated parents;
4. Any person aged 6-18 who is not vaccinated is required to obtain COVID-19 screening on arrival;
5. Traveler must carry a vaccination certificate from original country; and the type of vaccine should be in line with the vaccine registrations in Thailand or that endorsed by the World Health Organization;
6. The accommodation in Phuket has to be any hotel that passes the Safety & Health Administration (SHA) plus criteria;
7. Travel to other provinces is allowed after a 14-day of stay in Phuket;
8. Tourists need to comply with the public safety requirements which include the use of masks, frequent hand washing, and social distancing.

This Phuket Sandbox is planned to be evaluated after 3 months. If it is effective, the model will be applied in other tourist provinces. Thus, it could be a key for open-up tourism which is a main income generation for Thailand.

After nearly 3 months of the operation, very positive outcomes were observed and reported to Thailand's Ministry of Public Health. As of 21 Sep 2021, there were 35,169 tourists (compared with the expected target of 129,000) from 397 flights. A total of 101 COVID-19 cases were subsequently identified. Majority of them (74 cases or 73.3%) were asymptomatic and 27 cases or 26.7% were with mild symptoms. Most of the infected cases (85.2%) were detected during the first week of their arrival. The findings suggested that the Phuket Sandbox model is feasible and safe. It can revitalize economy of the country and ensure effective control of COVID-19 spreading. In addition, the epidemiological findings can provide evidence for modification of the disease control measures. For example, 14-day observation can be reduced to 7 days for any tourist with vaccination certificate indicating the vaccination date over 2 weeks before the date of entry; or 10-day observation for person with no certificate after 2 negative screening tests upon arrival and again on day 8-9. Detailed report on the findings and recommendations for modifications should be available after the end of the 3-month test run.

Although the initial findings are quite promising, there are some risks involved in the model. It is well-known that fully vaccinated persons are not completely immune from infection; and mortality can occur in those with high-risk conditions such as ageing or having chronic illnesses like diabetes, hypertension or cardiovascular disease. Foreign tourists may not be willing to go to high prevalence countries; and this is the case for Thailand where the current high level of spreading has caused significant reduction of the number of tourists during the first three months of the sandbox operation. Moreover, misconception of the security issue in the sandbox may facilitate un-control spreading of the virus leading to reemerging of generalized epidemic in the province. Thus, the active involvement of epidemiologists is needed both at the local and the national levels.

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A Cluster of Thyrotoxicosis, Presenting with Muscle Weakness, at a Prison in Sakon Nakhon Province, Thailand, 2019

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Abstract

In April 2019, a cluster of prisoners with muscle weakness and palpitation was detected at Prison A in Sakon Nakhon Province, Thailand. An investigation was conducted to describe epidemiological characteristics, and to provide appropriate control measures. A descriptive cross-sectional study was done. Suspected cases were prisoners or prison officers who had at least one of the following manifestations: muscle weakness, palpitation, fatigue, increased perspiration, weight loss, or tachycardia during 1 Jan to 30 Sep 2019. Confirmed cases were suspected cases who had low thyroid-stimulating hormone (TSH) levels. We interviewed food suppliers and examined the food ingredients. Food samples were collected to test for thyroid hormone. Thirty confirmed cases and 61 suspected cases were found. The overall attack rate was 4.6%. Only male prisoners were affected. The majority of the cases had low TSH and low serum potassium levels. All cases had a history of eating pork offals. Pork offal was suspected as the cause of elevated tri-iodothyronine (T_3) and levothyroxine (T_4) levels. Establishing standard of food quality for food supplier and evaluation of food material could prevent future outbreaks.

Keywords: outbreak, thyrotoxicosis, thyroid hormone, pork offal, prison

Introduction

Thyrotoxicosis is a condition that occurs due to excessive thyroid hormone from any cause such as autoimmune disease, and excess iodine intake.[1] Specifically, thyrotoxicosis factitia refers to a condition of thyrotoxicosis caused by the ingestion of exogenous thyroid hormone.[2] It can be the result of excess drug, such as levothyroxine or as a thyroid tissue inadvertently removed from meat; which has resulted in two community outbreaks of thyrotoxicosis in the United States.[3,4] Moreover, there have been case reports that have described similar findings after consumption of beef sausage contaminated with thyroid tissue.[5,6] Classic symptoms of thyrotoxicosis include palpitations, muscle weakness, fatigue, weight loss, tachycardia and hand tremor. In relation to laboratory findings, patients with thyrotoxicosis factitia have low serum thyroid-stimulating hormone (TSH) levels. Serum tri-iodothyronine (T_3) and/or levothyroxine (T_4) may be elevated or normal, depending upon the degree of thyrotoxicosis while serum thyroglobulin (Tg) is suppressed.[7] Additionally, thyroid hormones also increase $3Na^+/2K^+$ ATPase activity leading to hypokalemia.[8] Discontinuation of thyroid hormone ingestion is usually the only treatment needed. When patients discontinue exposure to exogenous T_4, serum T_4 levels fall approximately 50 percent in seven days. T_3 is cleared more rapidly (serum half-life is approximately one day).[7]

In April 2019, the Department of Disease Control (DDC) in Thailand received a notification that there were 28 cases with muscle weakness, palpitation and fatigue at Prison A in Sakon Nakhon Province who received treatment at Hospital B. From all 8 specimens of blood collected from the cases, 7 specimens revealed hypokalemia and 1 out of 5 patients had low serum TSH levels. Then, after thyrotoxicosis had already been diagnosed, the DDC, the Office of Disease Prevention and Control Region 8 Udon Thani, the Sakon Nakhon Provincial Health Office and Hospital B conducted an investigation beginning May 2019. The objectives were to confirm the diagnosis among those cases and outbreak, to describe epidemiological characteristics, and to provide recommendations and control measures.

Methods

We undertook a descriptive cross-sectional study of the thyrotoxicosis outbreak. The study population was both prisoners and prison officers in Prison A within the period 1 Jan to 30 Sep 2019. An active case finding was conducted using definition of patient under investigation (PUI). A PUI was defined as a prisoner or a prison officer at Prison A who had abnormal screening test: had a hand tremor or was unable to stand after squatting 3 times, or had muscle weakness during 1 Jan to 30 Sep 2019. A suspected case was defined as a prisoner or a prison officer at Prison A who had at least one of the following signs or symptoms during 1 Jan to 30 Sep 2019: muscle weakness, palpitation, fatigue, increased perspiration, weight loss, or resting pulse rate faster than 100 beats per minute (bpm). A confirmed case was defined as a suspected case who had low TSH levels (<0.3 µIU/mL).

All prisoners were screened by physicians using PUI definition. Then, prisoners and prison officers were interviewed and physically examined by physicians (Figure 1). Medical records of index cases were reviewed. A semi-structured questionnaire was used to collect information of demographic data, signs and symptoms, duration of imprisonment and history of food consumption.

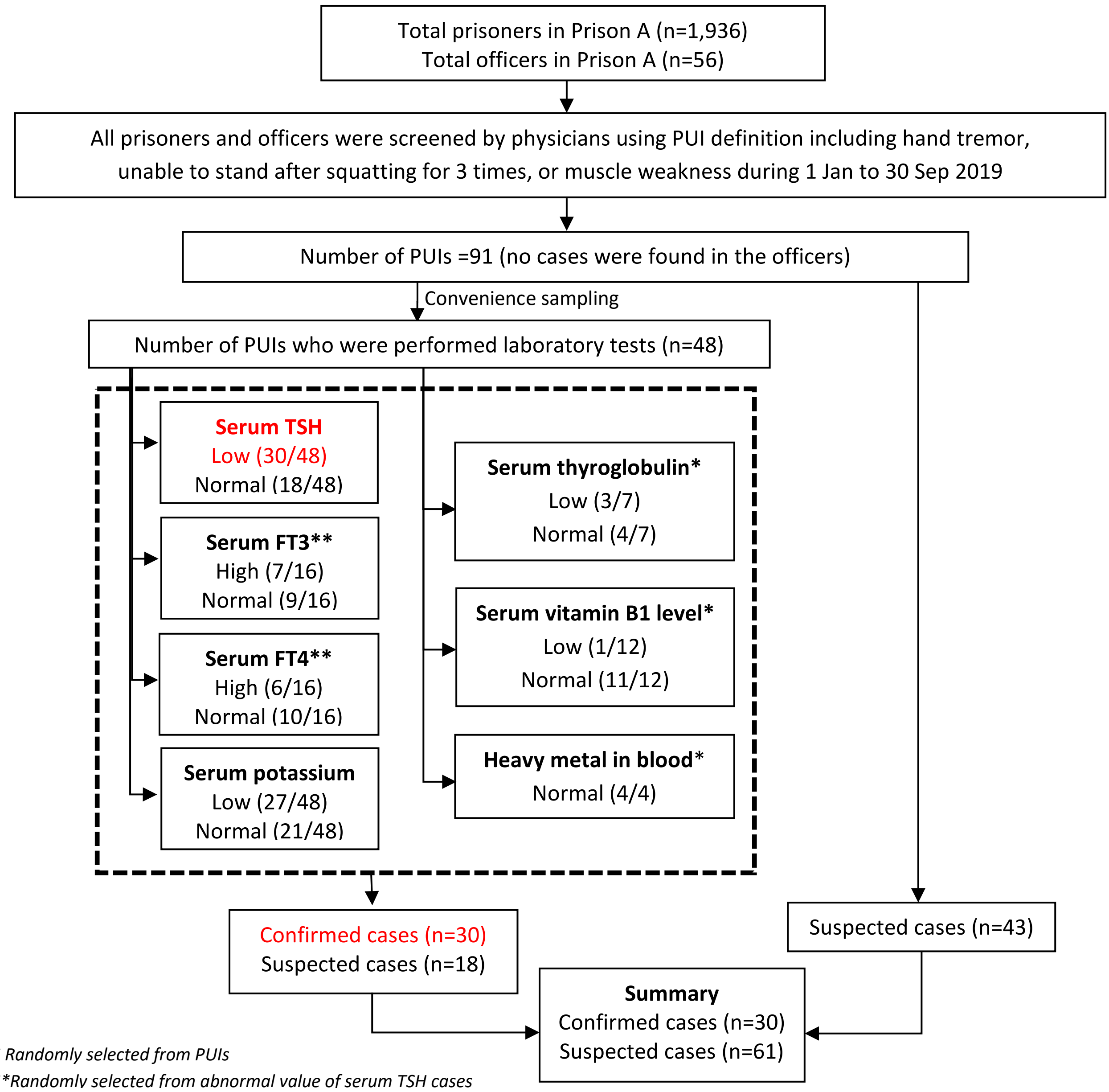

Figure 1. Diagram of active case finding in Prison A, Sakon Nakhon Province during 1 Jan–30 Sep 2019

Serum TSH and serum potassium were tested in suspected cases. Only cases who had abnormal TSH were tested for free T_3 and free T_4. Thyroid function test was performed at Hospital B. Suspected cases were randomly selected to test for serum vitamin B1, heavy metal in blood (Cadmium, Lead, Manganese), and serum thyroglobulin by convenience sampling. Vitamin B1, heavy metal in blood, and serum thyroglobulin were tested at the Center for Medical Diagnostic Laboratories, Faculty of Medicine, Chulalongkorn University, National Institute of Health (NIH) of Thailand, and BANGKOK R.I.A. LAB, respectively (Table 1).

Table 1. Normal values of laboratory testing

Test name	Specimen	Normal value	Unit
Thyroid-stimulating hormone (TSH)	Serum	0.3-3.6	µIU/mL
Free tri-iodothyronine (FT_3)	Serum	2.2-4.2	pg/mL
Free levothyroxine (FT_4)	Serum	0.8-1.7	ng/dL
Thyroglobulin (Tg)	Serum	3.5-77	ng/mL
Potassium	Serum	3.5-5.1	mmol/L
Vitamin B1	Serum	28-85	µg/L
Cadmium (Cd)	Blood	≤2	µg/L
Lead (Pb)	Blood	≤10	µg/dL
Manganese (Mn)	Blood	≤15	µg/L
Iodine level in table salt	Salt	2.0-3.0	mg/kg
Iodine level in fish sauce	Fish sauce	2.0-3.0	mg/kg
Iodine level in drinking water	Water	≤0.02	mg/L

For an environmental study, prisoners, prison officers, and food suppliers were interviewed. The suspected source of the outbreak was identified as follows: pork, pork offal and chickens supplied to Prison A during 2 Jul to 17 Sep 2019 which were randomly tested for T_3 and T_4 levels (measured as µg/g protein) by Division of Clinical Chemistry, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University. Because there was no standard laboratory values in food, food items including pork, pork offal and chickens from a registered market in Chiang Mai Province were collected by a veterinarian to be the best possible items for the control. Tissue lysates were prepared by extracting 20 mg of tissue samples with Radioimmunoprecipitation assay (RIPA) buffer. Protein concentration from the lysate supernatants were determined by Bicinchoninic acid (BCA) protein assay kit (Thermo Scientific). Total T_3 and T_4 in lysate supernatants were determined by Cobas e411 autoanalyzer (Roche) based on the principle of electrochemiluminescence immunoassay (ECLIA). Iodine levels of table salt, fish sauce and drinking water were measured at the Department of Medical Sciences.

Statistical Analysis

Continuous data were represented using median with inter-quartile range (IQR). Categorical data were presented using proportions and attack rate (AR). The data were analyzed using STATA® version 14.2 and Microsoft® Excel® 365. EpiData version 3.1 was used for data collection.

Ethics

Ethical clearance was omitted as this investigation was conducted as part of a response to a disease outbreak.

Results

Setting and General Description

Prison A located in Sakon Nakhon Province. There were 1,936 prisoners (1,769 males and 167 females) and 56 officers (54 prison officers and 2 nurses).

A Cluster of Thyrotoxicosis Description

There were 30 confirmed cases and 61 suspected cases; all were identified among prisoners. There was no case among prison officers. All cases were male. Overall attack rate was 4.6% (91/1,992) while specific attack rate among male prisoners was 5.1%. The median (IQR) age was 38 years (32-43 years). The epidemic curve indicated intermittent common source pattern. The indexes were reported in April, but retrospective investigation found that cases had begun in January. After cessation of pork offal purchasing, the number of cases declined (Figure 2). Median (IQR) duration of imprisonment of cases was 9 months (IQR: 6-22 months). In addition, suspected and confirmed cases had muscle weakness (93.8%). Fatigue and numbness were 70.8% and 64.6%, respectively. Other reported symptoms were increased perspiration (56.3%), weight loss (45.8%) and palpitations (43.8%). From the physical examination, we found hand tremor (29.2%), thyroid enlargement (10.4%), thyroid tenderness (8.3%), pulse rate >100 bpm (8.3%) and exophthalmos (4.2%) (Figure 3). From prisoner interviews, all prisoners ate only the food provided by Prison A and had a history of consuming pork offal during 2018–2019. Additionally, in the monthly food menu, it was found that there was pork offal menu about 3 percent of food items per month (Figure 4).

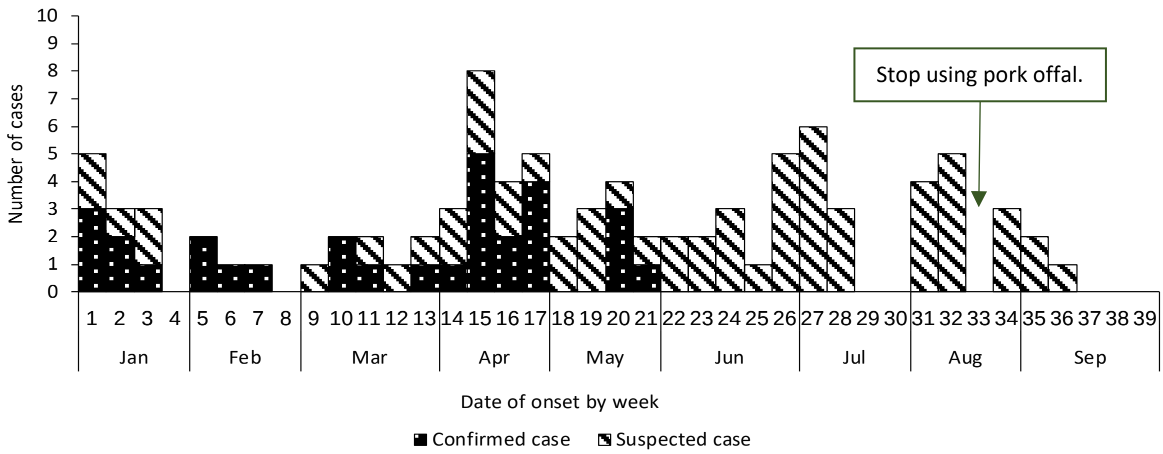

Figure 2. Number of thyrotoxicosis cases in Prison A, Sakon Nakhon Province during 1 Jan–30 Sep 2019 (n=91: confirmed=30, suspected=61)

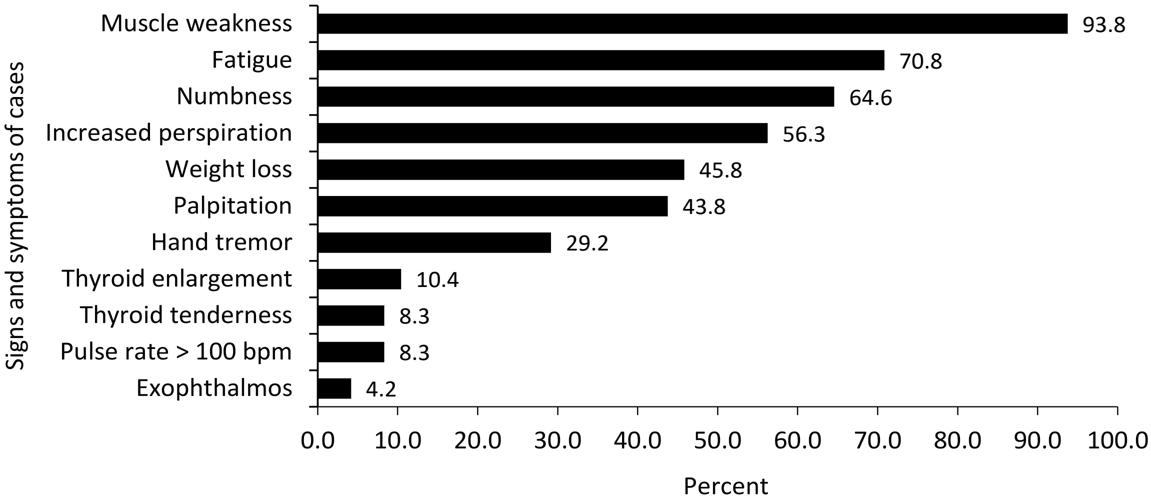

Figure 3. Signs and symptoms of thyrotoxicosis cases in Prison A, Sakon Nakhon Province during 1 Jan–30 Sep 2019 (n=48)

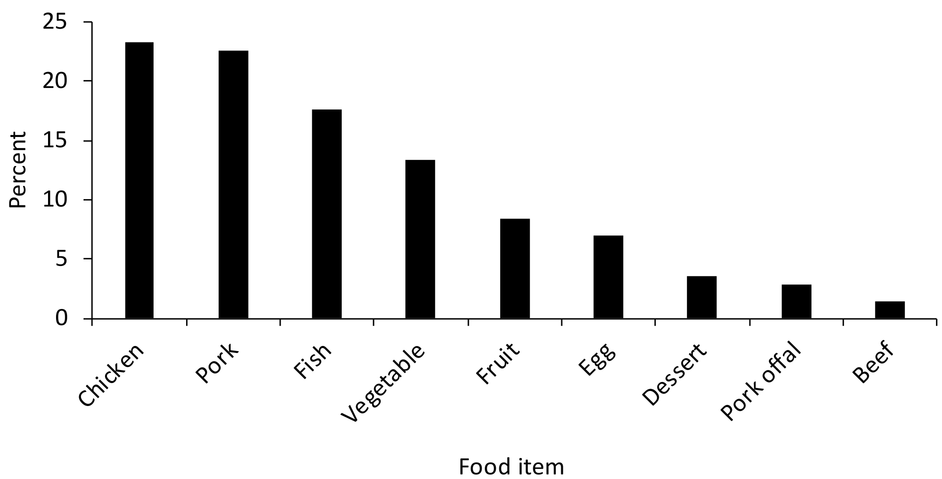

Figure 4. Percentage of food items consumed per month in Prison A, 2019 (n=142 food items)

Laboratory Study

We tested serum TSH levels by convenience sampling in 48 suspected cases showing 30 cases had low serum TSH (<0.3 µIU/mL). Free T_3 and free T_4 levels were elevated (>4.2 pg/mL and >1.7 ng/dL) in 7 of 16 cases (44%) and 6 of 16 cases (38%), respectively. Serum thyroglobulin levels were depressed (<3.5 ng/mL) in 3 of 7 cases (43%). Serum potassium levels were low (<3.5 mmol/L) in 27 of 48 cases (56%). Only 1 of 12 cases had low serum vitamin B1. Heavy metal in blood (Cadmium, Lead, Manganese) were normal in 4 cases measured.

Environmental Study

There were 9 zones in this prison; 8 male prisoner zones including kitchen, fieldwork, carpenters, cleaning, discipline training, education zone, outside working and nursing room and 1 female prisoner zone. Common food provided for the prisoners per month composed of chicken (23.2%), pork (22.5%), and fish (17.6%). Pork offal was 2.8% (Table 2). We sent the specimens by convenience sampling from Prison A including 8 pork samples, 7 chicken samples and 8 pork offal samples for T_3 and T_4 levels testing. In addition, pork (2 samples), chicken (1 sample) and pork offal (11 samples) from a registered market in Chiang Mai Province were tested as controls. We found that the median T_3 and T_4 levels in pork offal from Prison A including lung, bronchus, liver, spleen and intestine were 2 to 7 times higher than controls. In comparison, the median T_3 and T_4 levels in prison pork and chicken were nearly the same as controls (Table 2). Iodine levels in samples of table salt, fish sauce and drinking water from Prison A were within normal limit (Table 3).

Table 2. Laboratory of average T_3 and T_4 levels in pork, chicken, and pork offal

Specimen	Prison A			Control		
	Number of specimens	T_3 (µg/g protein)	T_4 (µg/g protein)	Number of specimens	T_3 (µg/g protein)	T_4 (µg/g protein)
Pork	8	1.92	4.34	2	1.32	3.08
Chicken	7	2.55	6.19	1	2.03	4.17
Pork offal	8			11		
• Lung	1	10.80	26.53	2	2.15	5.07
• Bronchus	1	10.70	24.84	2	2.14	5.36
• Liver	3	5.04	11.92	2	1.91	4.43
• Spleen	1	8.80	21.70	2	1.48	3.48
• Intestine	2	5.74	14.40	3	2.06	4.86

Table 3. Laboratory tests of iodine levels in table salt, fish sauce, and drinking water

Specimen	Iodine level	Expected level
Table salt	<3.0 mg/kg	2.0-3.0 mg/kg
Fish sauce	2.53 mg/kg	2.0-3.0 mg/kg
Drinking water	0.02 mg/L	≤0.02 mg/L

Discussion

Confirm Diagnosis

A cluster of thyrotoxicosis occurred in Prison A. Signs and symptoms among cases were compatible with thyrotoxicosis factitia that showed hyperthyroid manifestation. Decreased TSH, increased T_3 and T_4 with low serum thyroglobulin were also correlated with thyrotoxicosis factitia. Nonetheless, low vitamin B1 level was found in only one case. The magnitude of B1 deficiency was likely imprecise as symptoms were subjective and confirmatory physical examination had not been performed.

Characterize Outbreak

The number of cases had increased since January 2019. The overall attack rate in this outbreak was 4.6%. It was considered low extension when compared to previous outbreaks which occurred in Mae Hong Son and Sri Sa Ket Provinces during 2016 to 2017 in which the overall attack rate was 51.1% and 12.6%, respectively.[9] Furthermore, if laboratory had been tested for all prisoners, more cases might be found. The reason that the outbreak involved only male prisoners was the female prisoner's kitchen received food ingredients from a different source.

Identify Cause

We found high thyroid hormone levels in pork offal collected from the kitchen in Prison A that might be due to contamination which occurred during slaughtering process.[3] Consumption of food that is contaminated with thyroid hormone can cause thyrotoxicosis because the hormone is absorbed–similar to the drug used in treatment of hypothyroidism. Thyroid hormone is heat stable, so it is not degraded by cooking.[3] Consumption of thyroid contaminated pork and chicken were the causes of the previous outbreaks.[10]

Actions Taken and Follow Up

Active case finding, laboratory testing and environmental evaluation were done. We advised the officers for observing abnormal appearance of the meat as well as advised the officers to stop importing pork offal since 13 Aug 2019. Since then, there has been no further case after stopping purchase of pork offal for 2 weeks.

Limitations

Due to restrictions and authority in the prison setting, we could not implement the good sampling method for laboratory testing. Asymptomatic cases may be lost from this study. Besides, it was difficult to determine the amount eaten among cases. Thyroid contamination was not included in the food safety guideline in Thailand. We had no authority to obtain some important information such as pork offal source from the food suppliers. Due to limited resources, the preventive and control measures were not fully implemented. The supplier continued providing the pork offal leading to the prolonged outbreak.

Recommendations

The Department of Correction should set up the food quality standard for food suppliers and food ingredients inspection. Prisons should continue surveillance for thyrotoxicosis that was announced and performed simple case finding followed the PUI definition at least one month after the onset of the last case. Furthermore, thyroid hormone contamination as a food safety issue should be considered by Bureau of Food Safety Extension and Support, Ministry of Public Health. The Department of Livestock Development should also set up a slaughterhouse quality standard for thyroid contaminated prevention procedure. In addition, thyroid laboratory testing of food should be developed by the National Institute of Health of Thailand.

Conclusion

During January to September 2019, a thyrotoxicosis outbreak occurred in Prison A, Sakon Nakhon Province, Thailand. The outbreak affected only male prisoners with the overall attack rate of 4.6%. Pork offal was suspected because thyroid hormone levels in pork offal were higher than control. High thyroid hormone levels were found in pork offal which was collected from the kitchen in the prison. The contamination might occur during the slaughtering process. Establishing a standard of food quality for food suppliers and evaluation of food material could prevent future outbreaks.

Acknowledgements

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Suggested Citation

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Investigation of a Highly Pathogenic Avian Influenza Outbreak in a Poultry Farm, Dhamrai, Bangladesh, 2017: a One Health Approach

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Abstract

In January 2017, a highly pathogenic avian influenza (HPAI) A virus killed 732 chickens in a farm in Dhamrai, Bangladesh. An investigation assessed transmission of the virus from chickens to farmworkers. Contacts were farmworkers with direct exposure to affected chickens. We interviewed all suspected cases, conducted an active case finding for human cases at the implicated farm and local clinics, and actively searched for carcasses of wild and domestic birds within two kilometers of the implicated farm. All contacts were asymptomatic and had buried dead poultry; 70% touched dead poultry and 29% used protective gloves while working. Nasal and throat swabs were negative for influenza A and B viruses (subtyped for M-gene positive influenza A viruses by PCR and seasonal H3, H1N1 pdm09, and avian H5/H7/H9). The virus was probably introduced to the farm when ducks from the farm were taken to a live bird market and unsold ducks were returned to the farm. While farmworkers were exposed to the infected chickens, there was no evidence of the virus being transmitted to workers. We recommend starting H5N1 surveillance in live bird markets to monitor HPAI.

Keywords: HPAI, outbreak investigation, biosecurity

Introduction

Highly pathogenic avian influenza (HPAI) viruses have a high mortality in poultry. The H5N1 strain was first isolated from geese in China in 1996.[1,2] The first outbreak in a poultry farm occurred in Hong Kong in 1997.[3] The first documented avian H5N1 in poultry in Bangladesh occurred in 2007 and by December 2012, 556 outbreaks were reported; 89.8% in commercial farms and 10.2% in private farms.[4,5]

The first human case of HPAI (H5N1) was reported in Hong Kong in 2007 with the source identified as a goose.[2,4,6] From 2007 to 2020, the World Health Organization (WHO) reported 861 human H5N1 cases and 455 fatalities.[7] In Bangladesh, the first human case occurred in 2008 and by 2020, there were eight cases with one death.[7,8] In a study of live bird markets (LBMs) in Dhaka, samples were collected from over 2,000 suspected human avian influenza cases and 61 had detectable avian influenza virus in their RNA (12 H5, 26 H9 and 6 H6/H9 co-detection and 17 A/unsub-typable) from direct contact with infected poultry.[9]

To reduce transmission of HPAI, poultry farms follow the World Organisation for Animal Health (OIE), the Food and Agriculture Organization (FAO), and the WHO recommendation for vaccinating poultry and other control methods such as wearing personal protective equipment while handling poultry, controlling rodents with fencing, and using foot baths at entry points of poultry sheds.[10-13]

On 16 Jan 2017, an outbreak due to the H5N1 virus in a commercial chicken farm in Dhamarai, Dhaka, was reported (Figure 1). This investigation aimed to identify poultry to human transmission of H5N1 and determine the possible source of this outbreak.

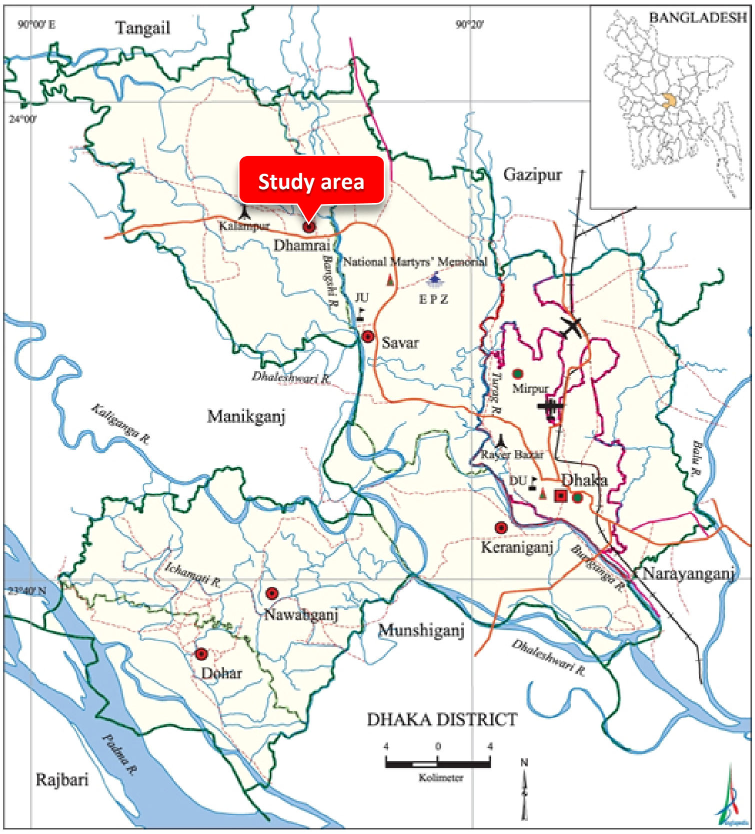

Figure 1. Location of the infected poultry farm, Dhamrai, Bangladesh

Methods

The investigation was conducted from 17 to 31 Jan 2017 in Dhamarai, Dhaka and used a mixed method concurrent triangulation strategy. Qualitative methods consisted of field observations and interviews of cases, their contacts, and veterinarians. Quantitative methods consisted of descriptive epidemiology of cases and laboratory tests.

Our multi-sector investigative team included a veterinarian, entomologist, and physician. We expanded the scope of the investigation to include observations of operations in a LBM, walk-through surveys in the implicated and nearby farms, visiting clinics to identify additional cases, and a search for dead birds in the surrounding area.

Definitions

Suspected human case was any person residing within 500 meters of the affected farm with fever (>37 °C), cough, and difficulty breathing between 14 and 31 Jan 2017.

Human contact with poultry was any person who touched sick or dead poultry or visited the affected farm during the outbreak and participated in the culling of birds between 14 and 17 Jan 2017.

Data Collection

A questionnaire was developed to collect information on the affected farm. The questionnaire for contacts included socio-demographic characteristics, exposure and contact history, symptoms, and farm working activities before and after the outbreak. The farm owner and poultry workers were interviewed face-to-face. Farm biosecurity practices were examined against the guideline of the Department of Livestock (DLS) and the FAO.[14]

We interviewed community residents to ascertain if they noticed any unusual deaths of poultry or wild birds. We also interviewed other key informants such as poultry supply dealers, livestock service providers, and veterinary field assistants. We actively searched for dead birds within a 2-kilometer radius.

During the visits to the farms, we looked for the presence and use of personal protective equipment by poultry workers.

Active Case Finding for Infected and Dead Birds and Humans Who were Sick

We asked the farm manager of the implicated farm to list all farms within a two-kilometer radius, and provide us with the names and telephone numbers of the managers in order to inquire about the health conditions of the poultry and workers. We searched for patients with influenza-like symptoms at the Upazila Health Complex at Dhamrai. We followed up every poultry worker daily for two weeks by telephone and inquired about their symptoms.

Laboratory Investigation of Exposed Poultry Workers

We collected nasopharyngeal and oropharyngeal swabs and blood samples from all contacts. Samples were tested at the National Influenza Center, Institute of Epidemiology Disease Control and Research (IEDCR) for influenza A and B viruses with subtyping of M-gene for seasonal H3, H1N1 pdm09, and avian H5/H7/H9 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay.[15] Antigen detection was carried out at the National Influenza Center, IEDCR by immunofluorescence or enzyme immunoassay methods.[15]

Statistical Analysis

The data were entered into a spreadsheet and imported into Stata (version 14, College Station, Texas) for analysis. The mean number and percentage of dead birds were recorded and the morbidity and mortality rates were calculated.

Ethical Approval

As the investigation was performed under the government order by the IEDCR, Ministry of Health and Family Welfare (MoHFW) and Department of Livestock Services, Bangladesh, ethical approval was waived.

Results

Case Finding for Farmworkers and Sick or Dead Birds

The field investigation team arrived in Dhamrai on 16 Jan 2017 and met with the farmworkers and veterinarian. They reported that 56 chickens had died on 14 Jan, and by 17 Jan, 732 (24.4%) had died. The veterinarian collected nasal and oropharyngeal swabs and blood from the dead and live chickens. Testing by the Bangladesh Livestock Research Institute (BLRI) confirmed H5N1.[16] All dead chickens lived in two sheds, which housed a total of 3,000 Sonali chickens. A third shed housed 100 ducks. The chickens were kept in their sheds 24 hours/day while the ducks were allowed to roam around the farm during the day but were kept in their shed at night.

There were 43 people who worked on poultry farms, including the implicated farm, within a two-kilometer radius from the implicated farm. Of these, only seven workers, all from the implicated farm, had had contact with chickens, which were later confirmed to be infected with H5N1. None of the ducks on the implicated farm were symptomatic. The farm managers in this area reported that they had seen no sick birds, that they had not noticed an increase in the number of dead birds, and that none of their workers felt ill in January 2017.

Characteristics of the Contacts

The seven workers from the implicated farm were classified as contacts. Six were male and the median age was 30 (range: 21-45) years. Most worked on the farm for 1-2 years (Table 1). The farm owner visited the farm during the outbreak and was also classified as a contact. However, the investigation team was not able to get detailed information of the farm owner.

Table 1. Socio-economic characteristics of the human contacts exposed to a H5N1 outbreak in a poultry farm in Dhamrai, Dhaka, 2017 (n=7)

Characteristics of contacts	n (%)
Age (years)	
21-25	2 (29)
26-30	1 (14)
31-35	1 (14)
36-40	1 (14)
41-45	2 (29)
Gender	
Male	6 (86)
Female	1 (14)
Education	
Below secondary	3 (42)
Secondary	2 (29)
Higher secondary	2 (29)
Working Experience (years)	
1-2	4 (58)
3-4	3 (42)
Monthly Income (in Bangladeshi Taka (BDT) and US dollars)	
<20,000 BDT (<$235.29)	3 (42)
20,000-25,000 BDT ($235-$294)	2 (29)
>25,000 BDT (>$294)	2 (29)

Exposure of Contacts to Poultry

The eight contacts were two veterinarians, five poultry workers, and the farm owner. The veterinarians conducted a post-mortem of the 56 dead chickens who died on day 14 and provided ciprofloxacin or azithromycin and oral rehydration to the remaining birds. The poultry workers performed daily activities related to poultry husbandry such as feeding and watering the poultry and cleaning the floor and cages.

All five workers lived on the farm and worked eight hours per day, seven days per week. The two veterinarians rotate their time at the farm and collected the dead chickens from the shed during the outbreak. The workers and veterinarians used thin plastic gloves, rubber boots and aprons while performing their duties. The workers did not wear masks or hoods nor were they trained in poultry husbandry. The veterinarians reported that they had farm biosecurity training but the team did not observe that biosecurity measures were practiced (Table 2). The most significant observations of poor biosecurity were that feces were present on the floor and cages of the sheds. Litter was moist and foot baths lacked potassium permanganate. Food and water was mixed with feces and bedding materials, and large cracks appeared in walls, allowing rodents to easily enter.

Table 2. Distribution of biosecurity measures practiced by contacts, HPAI outbreak, Dhamrai, Dhaka, 2017 (n=7)

Measure	n
Activities done by poultry workers on the farm	
Contact with dead poultry	7
Contact with sick poultry	7
Feed poultry	5
Clean floors	5
Clean cages	5
Clean the feeding tray	5
Slaughter the poultry	3
Expose the post-mortem of dead poultry	2
Expose during culling	7
Mean working hours/day (hour)	8
Medicate sick poultry	5
Use of protective measures during dead poultry handling and culling	
Mask	0
Plastic gloves	7
Apron	2

Clinical Features and Laboratory Results of Contacts

The average body temperature of the contacts was 36.7±0.21°C. None reported influenza-like symptoms either during the outbreak or at any time over the next 14 days. All nasopharyngeal and oropharyngeal swabs of the seven contacts were negative for H5N1. We did not collect any sample from the farm owner.

Possible Epidemiological Link of the Outbreak

There were no migratory birds in a nearby lake and no history of any deaths in chickens previously on the farm. However, on 7 Jan 2017, the farm manager took the ducks to a nearby LBM for sale. Some unsold ducks were brought back to the farm and were housed close to the poultry shed. All of the ducks appeared to be asymptomatic.

The investigation team interviewed residents who lived near the poultry farm and all said that they had observed no unusual death of poultry or wild bird in the local community or in ponds, rivers, or wetlands. The team also actively searched for birds and poultry carcasses surrounding a 2-kilometer radius of the outbreak farm and followed up the surrounding community for the next 14 days. No dead birds were observed.

Discussion

This study presented evidence that an H5N1 outbreak occurred among chickens but not in humans despite their direct contact with the birds and despite poor biosecurity measures on the farm. The source of H5N1 was probably a live bird market. This premise is based on the fact that ducks from the farm were taken to the market and when the unsold ducks were returned to the farm, some of the chickens died seven days later. Additionally, there was no evidence of other deaths of birds near the farm and no deaths on the farm before the ducks were taken to the market.

Despite direct contact with the infected chickens, no farmworker developed any symptoms. In Bangladesh, unusual deaths of chickens in commercial poultry farms have been previously reported. Until 2019, 556 avian influenza A outbreaks occurred among chickens resulting in eight human cases.[17] In Thailand, a nationwide surveillance in 2004 revealed 610 H5N1 outbreaks with 12 confirmed human cases, of which eight reported having direct contact with dead chickens.[18] Similar reports have been seen in Vietnamand Hong Kong.[3,19] In all of these outbreaks, there was no human-to-human transmission. However, human-to-human transmission of H5N1 occurred in a Hong Kong health facility and a family cluster in Northern Sumatra, Indonesia and Eastern Turkey.[20,21]

Live bird markets in many developing countries are considered a hotspot of avian influenza virus transmission.[22] These markets can also sell other goods. People shopping in mixed markets can become infected with avian influenza if they have close contact with infected birds. Avian influenza virus has an incubation period of 3-5 days in chickens, during which time infected birds may unknowingly be traded before they show signs or symptoms of an illness.[23] The HPAI H5N1 viruses can propagate silently among domestic and wild ducks.[24] From a surveillance program conducted from July 2006 to August 2007 in LBMs in central Thailand, H5N1 was isolated from two healthy ducks.[25] According to the Food and Agricultural Organization, LBMs play an important role in the spread of viruses in poultry workers or susceptible hosts in South Asian countries because of poor biosecurity practices.[10] The FAO has been promoting the improvement of biosecurity measures in LBMs in Bangladesh since June 2009.[26] Despite not being able to identify any other birds, domestic or wild, that died before the outbreak, we assume that the H5N1 strain was transmitted to the ducks at the LBM and carried by the unsold ducks to the poultry farm thereby infecting the chickens. A follow-up study in the implicated LBM and others nearby isolated the H5N1 virus from waterfowl, dead crows, and environmental samples from the markets and concluded that HPAI viruses circulated in these markets.[27]

Public Health Action and Recommendations

Every H5N1 outbreak in poultry is an opportunity to examine the bird-to-human and human-to-human transmission of a potentially deadly respiratory pathogen. The Bangladesh Government has made great efforts to control avian influenza over the last decade. However, the virus has persistently prevailed and caused sporadic infections and continues to be a public health problem. The biosecurity status of large commercial-scale poultry farms should be strictly maintained. Live bird markets are a likely source of HPAI. As such, proper isolation, containment, and quarantine should be practiced with poultry in and around the market. The Upazila Livestock Office should conduct an active H5N1 surveillance in all LBMs at Dhamrai to screen for sick or dead poultry species, confirm the agent, and enforce biosecurity related to the market.

Although all of the workers wore inadequate personal protective equipment, none developed avian influenza infection. Nevertheless, proper protective equipment is necessary to prevent the transmission of many infectious diseases. Improving biosecurity practices in a commercial poultry farm and wearing personal protective equipment is necessary to prevent poultry-to-human transmission.

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Dengue Outbreaks in Abidjan: Seroprevalence and Cocirculating of Three Serotypes in 2017

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Abstract

Dengue fever is a major public health problem in the world, because it is especially endemic in the tropical and subtropical areas. Arbovirus infection is less well documented in African countries. We aimed to assess the distribution of patients in the dengue epidemic and the seroprevalence of different serotypes of the circulating dengue virus. A retrospective study included analyses of human blood samples sent to the National Reference Laboratory for diagnosis during dengue infection outbreak. Samples were screened by IgM capture ELISA (MAC-ELISA) or by RT-PCR. Of the 2,849 serum samples from suspected dengue cases, 2,297 (80.6%) were from Abidjan. The seroprevalence of dengue was (15.1%) during this epidemic. The seroprevalence of dengue virus serotypes in cocirculation was predominated by DENV-2 with 189 cases (6.6%), followed by DENV-3 77 cases (2.7%), and DENV-1 14 cases (0.5%). The seroprevalence in children was 8.7% compared to 19.0% in adults. The age group of 16 to less than 45 years accounted for 54.0% of total positive cases. In addition, positive peak was observed in July (28.3%) and Abidjan East was the most affected locality. The increasing trend of serotypes of the dengue virus cocirculation suggests that Abidjan is becoming a hyperendemic state from an endemic one.

Keywords: dengue virus, outbreaks, surveillance, National Reference Laboratory, epidemiology, Abidjan

Background

Among arboviruses, dengue fever is a major public health problem in the world, especially in the tropical and subtropical areas.[1] As proof, several studies have reported on its distribution.[2–5] They show that more than 3.97 billion people in 128 countries are currently exposed to this infection.[6] Dengue viruses (genus *Flavivirus*, family *Flaviviridae*) are mosquito borne and the principal vector (*Aedes aegypti*) is a day-biting domestic mosquito of public importance that breeds in stagnant water.[3,7] Dengue illnesses are caused by any of the five serologically related viruses designated as dengue virus (DENV), DENV-1-5.[8–10] Infection with any one of these serotypes mostly causes a mild, self-limiting febrile illness (classical dengue fever), although a few cases develop severe life-threatening, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). However, this classification can be summarized as dengue with warning signs versus severe dengue. Severe dengue known as DHF or DSS has become a major public health problem.[11] The estimated number of 50–100 million infections per year, results in 250,000–500,000 cases of DHF and 25,000–50,000 deaths each year.[1,12] The routine laboratory diagnosis of dengue virus infection is primarily achieved by serodiagnosis, detection of IgM/IgG antibodies, and/or molecular detection by the demonstration of viral ribonucleic acid (RNA) by reverse transcription–polymerase chain reaction (RT-PCR).[13–15]

Arbovirus infections were less well documented in coastal African countries.[16,17] Dengue seroprevalence rates reported were lower than those in Asia or America.[18] From Bhatt et al., the burden of dengue fever in Africa may be similar to that of the Americas.[19] Brady et al. has published a summary of evidence of dengue fever in West Africa.[2] That was the case for countries experiencing recurrent epidemics of dengue fever of various serotypes. In Burkina Faso, serotype 3 has been detected in 2003, 2004, 2007, 2013 and 2016.[20] In Guinea 2007, a study reported several arbovirus infections.[21] In Mali, a study found a seroprevalence of 93% anti-dengue IgG and serotype 1 and 3 circulation by Sang R.C.[1,16] Serotype 3 was responsible for the epidemics that occurred simultaneously in 2009 in Senegal and for the first time in Cape Verde.[22,23]

Dengue fever is endemic in Ivory Coast. However, since 2008, we have had epidemic peaks of dengue fever, with cocirculation of yellow fever and dengue fever.[24] In 2010, an epidemic of dengue fever syndromes was reported in Ivory Coast.[25] Unfortunately, every year sporadic cases of dengue fever are detected. That was the case in 2015, where three cases were confirmed, and in 2016, six cases were detected (Unpublished). The year 2017 was marked by the biggest epidemic in Ivory Coast. Ivory Coast and other West African countries are increasingly equipped with national reference laboratories and qualified personnel. These countries are now able to detect epidemics through their epidemiological surveillance system. These different tools have better documented the circulation of all dengue serotypes in West Africa.[16,17,26–32] The role of support to the health system is meaningful and reflected in the information and alerts provided to health authorities during the epidemic outbreak.

Unfortunately, in this context, little is known about the distribution of the profile of patients affected by the dengue virus during the Abidjan epidemics in Ivory Coast and especially on the serotypes of the virus circulating in that country. The objective of this study was to draw up a map of the distribution of the patient population of this dengue epidemic and the seroprevalence of different serotypes of the dengue virus circulating in Abidjan.

Materials and Methods

Study Setting and Design

This retrospective study included analyses of human blood samples sent to the National Reference Laboratory (NRL) of the Epidemic Virus Department of the Institut Pasteur de Côte d'Ivoire (IPCI) between January to December 2017 for diagnosis during the dengue infection outbreak in Ivory Coast.

Since its creation in 1972, the IPCI through the Epidemic Virus Department had missions in addition to research, to ensure thorough collection of the virologic component of the epidemiological surveillance of arbovirus and viral hemorrhagic fevers through the NRL. The NRL for arboviruses and viral hemorrhagic fevers participated in the management of epidemics by confirming suspected cases: diagnosis (serological and molecular biology: typing and genomic sequencing), then virus identification by virus isolation and tissue culture (if possible) and finally by validating new diagnostic techniques.

The arboviruses and hemorrhagic fever virus unit dedicated the study of viruses transmissible to humans by arthropods, *Flaviviridae* (yellow fever virus, dengue virus), *Alphaviridae* (Chikungunya virus), and *Arenaviridae* (Lassa virus), for the alert and investigation of epidemics and the seroprevalence study.

Sample Collection and Processing

Blood samples were collected from patients with fever presenting to outpatient departments of 83 health districts in the country. These blood samples were packed with ice to the laboratory of virus transmitted by vectors in the Epidemic Virus Department for detection of dengue viruses. The clinical basis for diagnosing the patients as having dengue virus infection was based on World Health Organization (WHO) definitions.[23] In the NRL of hemorrhagic viral fevers, samples were received in triple packs. Red cap sampling tubes were used for collection of whole blood. They were all accompanied by a standard survey form for collecting epidemiological and biological information from the patient. Three aliquots were prepared on each sample after centrifuging. One aliquot was transferred to the biobank for long-term conservation in the liquid nitrogen. The other two remained in the laboratory: one in a dedicated freezer at -70°C and the other was screened for the presence of dengue specific IgM antibodies by IgM capture ELISA (MAC-ELISA) or by RT-PCR, using a commercial kit, following the manufacturer's protocol.

Serological Tests

The dengue tests were performed in accordance with the WHO diagnostic guidelines for Africa.[33] These tests have been made available to the NRL for viral hemorrhogic fevers by WHO through the Institut Pasteur de Dakar (IPD). The sera diagnosed as positive are then sent to the WHO Collaborating Center for Arboviruses and Hemorrhagic Fever Viruses (CRORA) at IPD for confirmation.

All samples received during the outbreak period were tested by IgM antibody capture ELISA. Transparent clear Flat-Bottom Immuno-nonsterile 96-well Plates (Thermo Scientific™) were sensitized with an anti-IgM capture antibody and incubated overnight at 4°C (Kirkegaard and Perry Laboratories, with Affinity Purified Antibody to Human IgM (µ), F(ab')). Samples were diluted to 1:100 and tested in duplicate. A mixture of Pasteur institute of Dakar 1-4 DENV antigen was diluted and incubated for one hour at 37°C. A 6B6C-1 peroxidase-labelled antibody (IgM/IgG conjugate peroxidase fraction of anti-body foam) specific to the flavivirus group was added. After 10 minutes' incubation in a darkroom at room temperature with a 3.3' and 5.5'-tetramethylbenzidine (SIGMA) substrate, the plate was read at 620 nm. The samples were interpreted by dividing the mean optical density (OD) of the samples by the mean OD of the negative control (positive/negative ratio). 2.0 values were considered positive.

Polymerase Chain Reaction Detection

This study selected the manual viral RNA extraction system commonly available in public health laboratories. For the manual viral RNA extraction from serum specimens, the silica-based filter column systems QIAamp Viral RNA Mini kit (Qiagen) was selected. After elution the extraction product was stored at -70°C or used for RT-PCR immediately.

To investigate the presence of dengue virus in patients, the Trioplex real-time RT-PCR Assay Primer and Probe Set (CDC; catalog #KT0166) developed by the CDC was used, but with some modifications regarding the enzyme kit.

Briefly, the reaction mix for the one step RT-PCR was performed in total of 25 µL including: 12.50 µL of 2X RT-PCR Buffer (AgPath-ID™ One-Step RT-PCR Reagents-Applied Biosystems™), 9.50 µL of nuclease-free water, 1.25 µL of forward and reverse primers, 0.5 µL of TaqMan® probes, 0.25 µL of 25X RT-PCR Enzyme Mix and 1 µL extracted RNA.

The cycling profile performed by StepOnePlus™ Real Time PCR system (Applied Biosystems™) involved reverse transcription at 50°C for 10 min and initial denaturation at 95°C for 15 min followed by 40 cycles with 95°C for 15 min and 1 min at 60°C. The fluorescence acquisition was made in the cycling step.

The dengue positive sera by Trioplex real-time RT-PCR were re-run in another PCR to determine the type. Dengue typing was performed by real-time RT-PCR using primers and probes. The reaction mix contained 12.5 µL of 2X reaction buffer (Ambion Kit), 8.25 µL of miliQ 1 water, 25 µL of each primer (FP, RP at 10 µM), 0.5 µL of the probe (P at 10 µM) and 0.25 µL of enzyme. The amplification of the viral genome was carried out with a 7500 PCR machine (Applied Biosystems) under the following conditions: Reverse transcription: 5°C, 5 min, initial denaturation: 95°C, 15 min: (45 cycles) 95°C, 5 sec, 60°C, and 15 sec. Positive controls were RNA from Dengue positive strains and negative controls were performed by RNase-free water in each amplification cycle.

The positive dengue case was defined as the one with positive RT-PCR or the ELISA positive for dengue IgM. The algorithm shown in Figure 1 allows better understanding of which tests were employed.

Statistical Analysis

Descriptive statistics for the study population characteristics and laboratory findings were performed by using EPI-Info 6 version 3.3.2. The seroprevalences of dengue serotype (DENV-1, DENV-2, DENV-3 and DENV-4) were expressed for the entire study group. Qualitative variables were characterized by numbers and percentages. Quantitative variables were described by mean and standard deviation. The chi-square test was applied in the analysis of the qualitative variables to establish a link, and *p*-values below 0.05 were considered statistically significant.

Results

A total of 2,849 samples were received for cases of suspected dengue infection and screened. There were no deaths in that outbreak. Of all the serum samples, 552 (19.4%) were from the interior of the country versus 2,297 (80.6%) from the economic capital of Ivory Coast (Abidjan).

At the national level, table 1 presented the overall seroprevalence of dengue (15.1%) among the suspected population during this epidemic. Our data showed that the seroprevalence of different dengue virus serotypes in cocirculation was predominated by DENV-2 with 189 cases (6.6%); followed by DENV-3 with 77 cases (2.7%), and DENV-1 14 cases (0.5%).

Table 1. Distribution of diagnostic and seroprevalence of dengue cases during the 2017 outbreak

Diagnostic dengue	n (%)
Negative	2,420 (84.9)
Positive	429 (15.1)
DENV-1	14 (0.5)
DENV-2	189 (6.6)
DENV-3	77 (2.7)
DENV IgM positive	149 (5.2)
Total	**2,849 (100)**

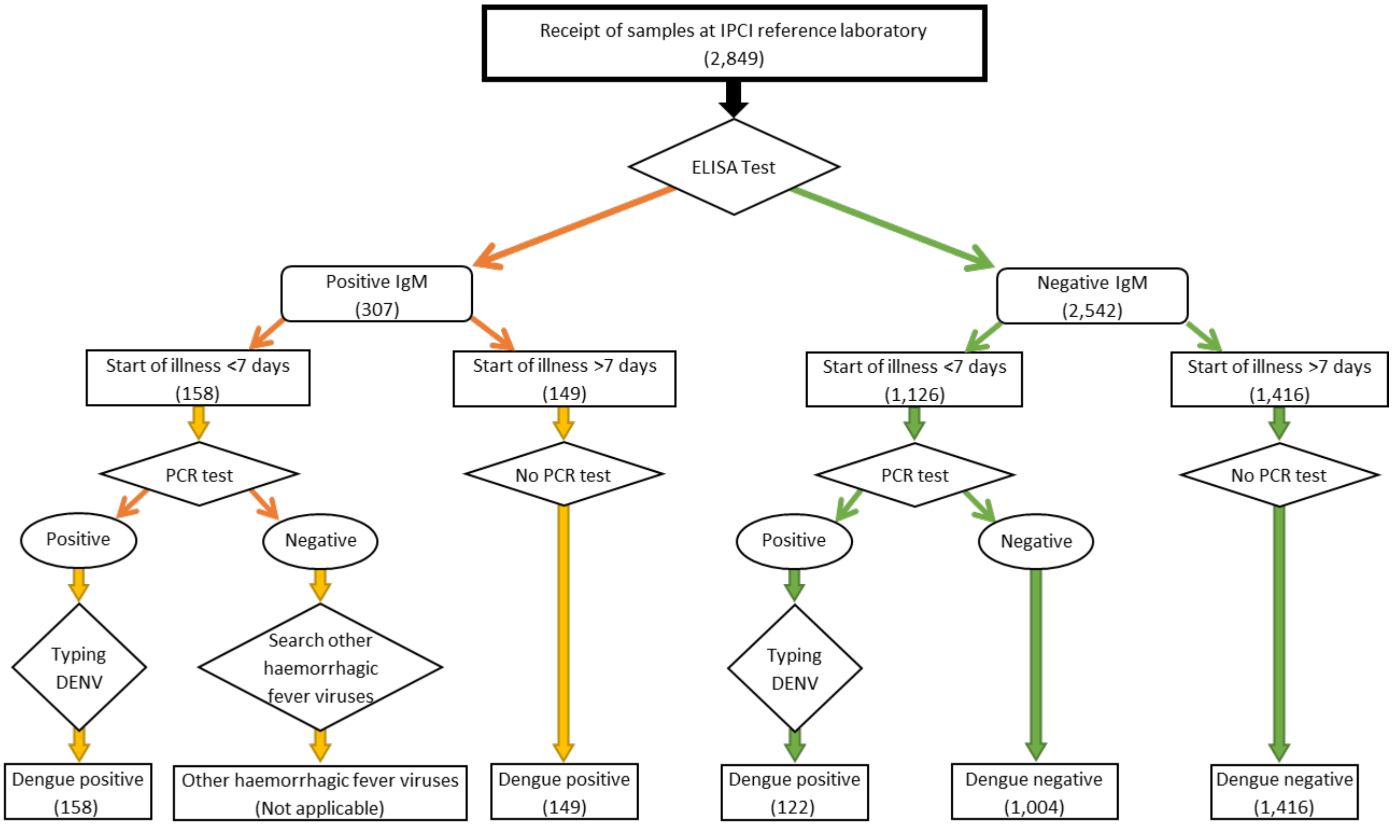


Figure 1. Algorithm for the analysis of suspected dengue patient samples at the IPCI reference laboratory

Table 2 showed the socio-demographic distribution of suspected dengue cases during the outbreaks and that only gender was not associated with the dengue diagnoses. Males were 1,519 (53.3%). The male to female ratio was 1.1:1. The mean and standard deviation of population age was 36.1±19.0 years. The seroprevalence in children (0-16 years) was 8.7% compared to 19.0% in adults. The largest number of positive samples was from the age group of 16 to less than 45 years, which accounted for 54.0% of total positive cases.

Table 2. Socio-demographic distribution of dengue cases during the 2017 outbreak among 2,849 suspected dengue cases

	Diagnostic of dengue cases			
	Negative n (%)	**Positive n (%)**	**Total tested n (%)**	***p*-value**
Gender (n=2,849)				0.2598
Male	1,301 (85.6)	218 (14.4)	1,519 (53.3)	
Female	1,119 (84.1)	211 (15.9)	1,330 (46.7)	
Age group (years) (n=2,699*)				<0.001
<16	868 (91.3)	83 (8.7)	951 (35.2)	
16 to <30	528 (81.5)	120 (18.5)	648 (24.0)	
30 to <45	517 (83.3)	104 (16.7)	621 (23.0)	
45 to <60	255 (75.9)	81 (24.1)	336 (12.5)	
≥60	116 (81.1)	27 (18.9)	143 (5.3)	
Place of residence (n=2,849)				<0.001
Country Interior	552 (100.0)	0 (0.0)	552 (19.4)	
Abidjan (capital)	1,868 (81.3)	429 (18.7)	2,297 (80.6)	
Abidjan North (abobo; anyama)	71 (95.9)	3 (4.1)	74 (3.2)	
Abidjan Center (adjame-plateau)	27 (84.4)	5 (15.6)	32 (1.4)	
Abidjan East (cocody-bingerville)	1,591 (79.7)	405 (20.3)	1,996 (86.9)	
Abidjan South (grand-bassam; koumassi; marcory, treichville)	146 (92.4)	12 (7.6)	158 (6.9)	
Abidjan West (yopougon, songon)	33 (89.2)	4 (10.8)	37 (1.6)	

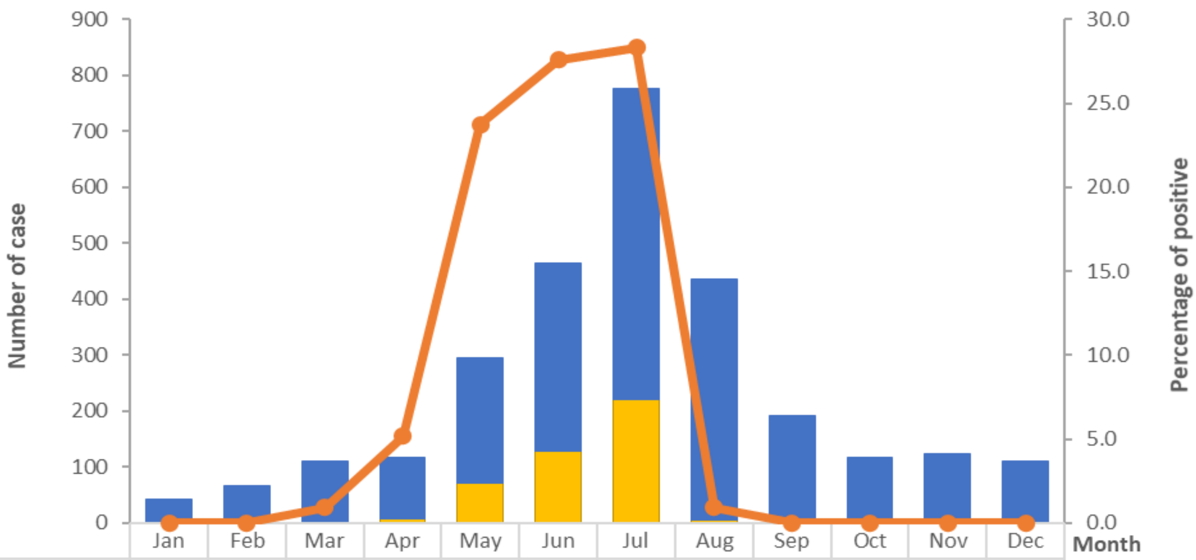
*Missing data at the age level

In Abidjan among the 2,297 suspect cases the seroprevalence was 18.7% (429/2,297). The geographical repartition of seroprevalence of positive cases reported showed that this prevalence was distributed as follows: 20.3% (405/2,297) was seroprevalence for Abidjan East and followed by Abidjan Center, Abidjan West, Abidjan South and Abidjan North (Table 2). The seroprevalence of different dengue virus serotypes in the cocirculation in the capital was 0.6% (14/2,297) for DENV-1; 8.2% (189/2,297) for DENV-2; and 3.4% (77/2,297) for DENV-3.

The distribution of dengue patients by time of year in figure 2 showed that the prevalence increased rapidly from 0.9% in March to 5.2% in April; 23.6% in May and 27.6% in June. The peak was observed in July at 28.3% with a rapid decline in August.

Table 3. Distribution of dengue virus serotypes by socio-demographic characteristics during the 2017 dengue outbreak

	DENV-1 n (%)	DENV-2 n (%)	DENV-3 n (%)	PCR positive n (%)	IgM positive n (%)	Total positive n (%)
Gender (n=429)						
Male	8 (5.9)	86 (63.7)	41 (30.4)	135 (61.9)	83 (38.1)	218 (50.8)
Female	6 (4.1)	103 (71.0)	36 (24.8)	145 (68.7)	66 (31.3)	211 (49.2)
Age (years) (n=415)						
<16	0 (0.0)	39 (72.2)	15 (27.8)	54 (65.1)	29 (34.9)	83 (20.0)
16 to <30	5 (5.4)	64 (69.6)	23 (25.0)	92 (76.7)	28 (23.3)	120 (28.9)
30 to <45	8 (11.6)	42 (60.9)	19 (27.5)	69 (66.3)	35 (33.7)	104 (25.1)
45 to <60	0 (0.0)	30 (69.8)	13 (30.2)	43 (53.1)	38 (46.9)	81 (19.5)
≥60	1 (7.1)	10 (71.4)	3 (21.4)	14 (51.9)	13 (48.1)	27 (6.5)
Period (n=429)						
March	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (0.2)
April	0 (0.0)	3 (60.0)	2 (40.0)	5 (83.3)	1 (16.7)	6 (1.4)
May	1 (0.7)	30 (75.0)	9 (22.5)	40 (57.1)	30 (42.9)	70 (16.3)
June	7 (5.2)	62 (72.9)	16 (18.8)	85 (66.4)	43 (33.6)	128 (29.8)
July	6 (4.4)	91 (62.3)	49 (33.6)	146 (66.4)	74 (33.6)	220 (51.3)
August	0 (0.0)	3 (100)	0 (0.0)	3 (75.0)	1 (25.0)	4 (0.9)



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Negative	42	67	109	110	225	336	557	432	191	118	123	110
Positive	0	0	1	6	70	128	220	4	0	0	0	0

Figure 2. Seasonal distribution of diagnosed dengue cases during the 2017 outbreak

Discussion

To the best of our knowledge, this was the first study to employ socio demographical-based and laboratory reporting data to investigate the dengue outbreak in Ivory Coast country. Our study found that the corresponding rate for dengue seroprevalence was 15.1% and 3 serotypes of dengue viruses cocirculate in the country, which were consistent with previous studies in West African countries.[1,34-36] With reports of dengue outbreaks in other parts of Africa and importation of dengue into Europe from West Africa.[37,38] It is noteworthy that the incidence of dengue in this part of West Africa is very high. During the studied outbreak, the seroprevalence appeared high even if it remained lower than those found in other studies. Gupta in India found 52.3%, Gregianini et al. in Brazil obtained a prevalence of 29.3% and Onoja et al. in Nigeria revealed 23.4%.[5,35,39] The seroprevalence that we found could be explained by the location of the epidemic in Abidjan, but there were also logistical issues related to the management of reagents and laboratory input.

This study found no difference in seroprevalence of dengue virus infection between men and women in the period analyzed. Other authors have made the same observation.[38] Dengue affects humans of all age groups worldwide, even though in some parts of the world it is mainly the pediatric public health problem.[8,12,40] Our study also showed that a fare proportion of dengue fever cases were children. Studies in Latin America where current reports of adolescents with recent dengue infections have been established lends credence to the conclusions of our current study.[19,41-43] The mean of age of our participants was close to that of Yeh 45.6±21.2 years.[44] Older individuals (those ≥20 years of age) in this study is an indication that they are more commonly affected. Therefore, the active population of our studied country is seriously threatened.

Larger proportions of serologically positive cases were observed among adults.[45] This has confirmed the economic importance of dengue fever in developing countries.[3] The difference between numbers of serologically positive cases among adult and pediatric groups was significant ($p < 0.05$). Studies have shown that during dengue outbreaks, several serotypes cocirculate with a predominant serotype.[8,34,35,39,46] This finding was confirmed by our study in which the DENV-1 to 3 serotypes cocirculated with the predominance of DENV-2. RT-PCR offers accuracy and speed along with serotype specific diagnosis of various circulating dengue viruses and information about cocirculation of different subtypes.[7] The high seroprevalence of IgM positive (undetermined serotype) could be explained by the delay in the consultation of patients and their therapeutic course. This result is exceeding the viraemia period, which is seven days.

More dengue virus exposure occurred during the rainy season.[34,35,47] This is due to abundant vegetation cover that is available in tropical rain forests region and the high relative humidity.[35] This present study found monthly peaks in dengue seroprevalence during the rainy season from April to July. Positive correlation was found between dengue outbreak and rainfall pattern from increase in number of breeding sites.[48] Our observation was similar to that made by Li in his study in Selangor, Malaysia. Dengue in the tropical rain forest region has increased due to uncontrolled urbanization, and lack of effective and sustainable vector control programs.[49]

In Nigeria, in the study by Onoja et al., it was found that transmission of the dengue virus in several urban areas indicated that it is maintained in both urban and human populations.[35] A Taiwanese study also reported that 74.1% of patients affected by the dengue epidemic lived in urban areas.[40] Many of these areas are forested, with stagnant water and indiscriminate hollow containers, throwing garbage everywhere, providing excellent breeding sites for increased vector activity. Mosquito-DENV-Human cycle has been reportedly found in nearly all urban and peri-urban environments throughout the tropics.[50] All these assertions were corroborated in our study. The Trioplex real-time RT-PCR tests enabled a differential diagnosis of Zika and Chikungunya simultaneously.[51] This test whose performance has been demonstrated by Santiago et al. allows simultaneous detection of dengue (DENV), Chikungunya virus (CHIKV) and Zika (ZIKV) on the same well plate in RT-PCR multiplex.[52] The genome screens for dengue virus types 1–4 by fluorogenic RT-PCR using the technique described by Ito et al.[53]

There are some limitations in this study. First, this was a retrospective study and without predictive assessment that was conducted using reported data. Second, the limitation that concerns most clinical studies on dengue fever is that for molecular analysis based on PCR, which gives high specificity of viral serotype and sensitivity, the sample must be collected within 5 days of onset of symptoms. However, dengue symptoms can be mild, so most samples are collected after this time window, thus requiring other assays to diagnose the case that do not allow identification of DENV serotype. Third, the limitation found in the present study was the lack of information in the epidemiological records about the symptoms, co-morbidities and chronic diseases presented by the patients, and information about previous vaccination against yellow fever was missing.

Conclusion

This study has revealed that DENV-2 has dominated this outbreak even though all three serotypes were found to be cocirculating as detected by RT-PCR. The increasing trend of cocirculation dengue virus serotypes suggests that Abidjan is becoming a hyperendemic state from an endemic one. The study has highlighted a high percentage of concurrent infections by different dengue virus serotypes for the first time from Ivory Coast. It is unrealistic to consider dengue fever as one of the less serious acute febrile diseases (like malaria). This consideration requires early detection and appropriate treatment of cases before they progress to the severe form. To do this, regular communication campaigns are essential to help prevent dengue and other arboviruses.

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Ethical

Since the diagnostic samples were received during an outbreak, no prior ethical clearance was required. However, the patient information was de-linked from sample information to protect the privacy of the patients.

Competing Interests

The author(s) declare that they have no competing interests.

Authors' Contributions

SY carried out all the RT-PCR experiments, RNA extraction, helped in careful collection of case history and analyzed them. DKM and SY were responsible for collection and storage of clinical samples and carried out the clinical sample processing and drafted and reviewed the manuscript. AVE and KH supervised the Virology diagnostic laboratory. DKM and SY conceived the study and all the research was carried out in the Virology Diagnostic Laboratory. DM reviewed the manuscript. All authors read and approved the final manuscript.

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An Outbreak of Guillain-Barre Syndrome with Respiratory Failure in Joypurhat, Bangladesh, 2018

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Abstract

We describe an investigation to identify the causative agent and risk factors for a cluster of Guillain-Barre Syndrome (GBS) reported in northern Bangladesh, November 2018. Medical record review and verbal autopsies were conducted. We actively searched for and interviewed other GBS cases in the hospital to gather demographic and clinical information. Blood samples were collected for serological testing for campylobacter and molecular testing for dengue, Zika, and Chikungunya and stool samples for poliovirus. We identified 13 GBS patients of which eight were males. The case fatality rate was 23%. We found development of respiratory muscle paralysis in 10 patients; three had rapid involvement within 48 hours and eventually died in the acute progressive phase without mechanical ventilation support. Serological tests confirmed the presence of antibodies against *Campylobacter jejuni* in three of seven patients. All other tests were negative. The high case fatality rate was due to rapid onset of respiratory muscle paralysis. We recommend establishing a surveillance system to timely capture and report GBS patients and to enhance investigation capacity. We also recommend that sufficient quantity of mechanical ventilators be present in peripheral tertiary hospitals.

Keywords: Guillain-Barre Syndrome, GBS, respiratory muscle paralysis, mechanical ventilation, Bangladesh, fatality

Introduction

Guillain-Barre Syndrome (GBS) is an autoimmune disease of the peripheral nerves that typically presents as acute, relatively symmetric, flaccid limb weakness.[1,2] The global incidence is estimated at 1–2 cases/100,000 population per year.[3] The rate in Bangladesh is less than 5/100,000 population per year.[4–6]

GBS has three phases: a progressive phase lasting from days to 4 weeks and peaks at 7–14 days, a plateau phase with little clinical change lasting from days to months, and a recovery phase lasting months to years.[7] Patients may develop autonomic instability, cranial nerve dysfunction and neuromuscular respiratory failure, which are the most common causes of death in GBS.[8-10] Deaths associated with GBS predominantly occur during the recovery phase.[11] Mortality from GBS is also associated with the need for mechanical ventilation resulting from respiratory failure in 14% of cases. It usually takes 10–14 days from development of first symptoms to peak weakness.[12] The median duration of mechanical ventilation is 28 days, interquartile range (IQR) 12–60 days. Tetraparesis or tetraplegia can develop within 24 hours. The reported mortality rates range from 3–7% in North America and Europe to 13% in Asia.[3,13]

In Guillain-Barre Syndrome, the immune system mistakenly attacks healthy nerves, the exact cause of this being unknown. Therefore, there is no known prevention. However, the disease's occurrence can be decreased by combating common triggering infected agents, such as *Campylobacter jejuni*, certain arboviruses (e.g., dengue, Chikungunya, and Zika viruses), *Mycoplasma pneumoniae*, cytomegalovirus, Epstein-Barr virus, *Haemophilus influenzae*, and *Leptospira*.[14,15]

On 8 Nov 2018, the Civil Surgeon of Joypurhat District, in northern Bangladesh, notified the Institute of Epidemiology, Disease Control and Research (IEDCR) about the deaths of three hospitalized patients with GBS in several hospitals. The IEDCR immediately deployed an outbreak investigation team, including three medical doctors, two medical technologists, one logistician, and one driver. The objectives of the investigation were to verify the event, identify the etiologic agent, determine associated factors of death due to GBS, and to contain the outbreak.

Methods

We investigated the outbreak from 8 to 17 Nov 2018 in Joypurhat District Hospital where GBS cases-patients were reported and in the communities of the case-patients. We conducted a descriptive study using mixed methods and field investigations. We also searched hospital records in the Joypurhat District Hospital for case-patients diagnosed with GBS and for previous records of GBS outbreaks at the local, regional, and national levels.

A suspected case was a resident of Joypurhat District with clinically diagnosed GBS from 1 Sep to 15 Nov 2018. A probable case was a suspected case with albuminocytologic dissociation in cerebrospinal fluid with or without electrophysiologic findings. The clinical diagnosis of GBS consisted of symmetrical ascending paralysis or weakness, reduction or loss of deep tendon reflex, autonomic neuropathy, and cranial nerve palsy. In this investigation, there were only suspected and probable cases because laboratory testing for GBS was not available.

We reviewed the medical records of all inpatients in the medicine, pediatric, and neurology departments of Sadar Hospital and all sub-district hospitals, Rajshashi Medical College and Shohid Ziaur Rahman Medical College to identify suspected and probable GBS cases. We abstracted the patient's clinical information and traveled to the patient's home to interview the case-patients and relatives of dead case-patients. We modified questionnaire, developed by the World Health Organization for verbal autopsies.[16] We collected cerebrospinal fluid (CSF) from the case-patients and performed nerve conduction studies.

Blood, urine and nasal swab samples were collected from the patients and tested for *Campylobacter jejuni (C. jejuni)*, Zika, dengue, and Chikungunya. The *C. jejuni* test determines the presence of lipo-oligosaccharides by ELISA and was done at the International Center for Diarrheal Disease Research, Bangladesh. Zika, dengue, and Chikungunya were tested by RT-PCR and ELISA for IgG and IgM and influenza by RT-PCR. A serological test was used to identify cytomegalovirus. Urine samples were tested at IEDCR lab for *Leptospira*. We also collected stool samples from children aged less than 18 years to test for poliovirus at the National Polio and Measles Laboratory in the Institute of Public Health.

Descriptive statistics, such as frequency, percentage, mean and standard deviation were used to summarize and describe the data. Analyzed data were presented in the form of tables and charts, including an epidemic curve and spot map.

Ethical Consideration

This investigation was exempt from Human Subjects Review Board because it was a response to an acute health event. Verbal consent was obtained from all case-patients and their relatives before they were interviewed.

Results

There were eight probable and five suspected GBS cases. The first case occurred on 28 Sep 2018. Cases increased gradually from September to mid-November 2018 with the highest number of cases reported during the first week of November. The last case was reported on 15 Nov 2018 (Figure 1). We continued surveillance until 13 Dec 2018 with no further GBS cases identified.

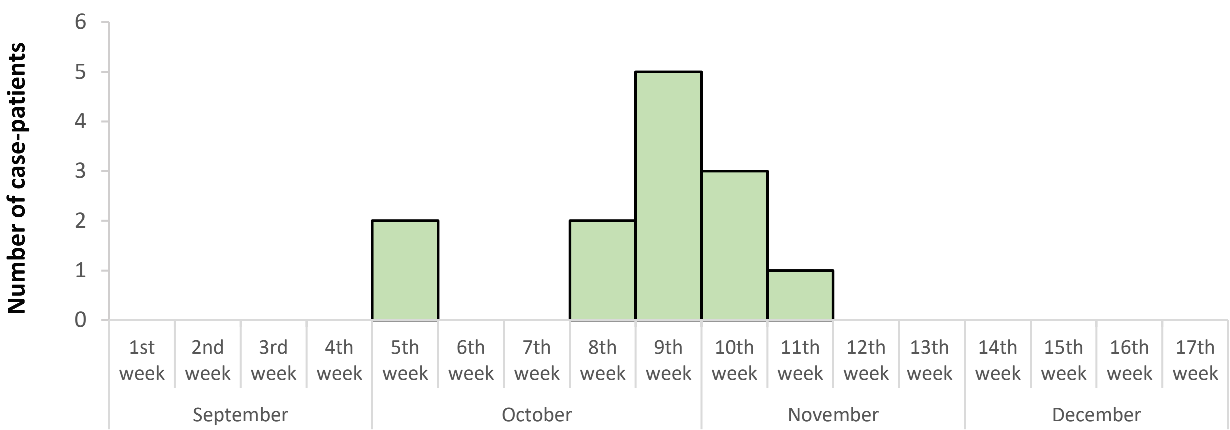

Figure 1: Distribution of GBS case-patients by week of illness onset, Joypurhat District, Bangladesh, 2018

We reviewed the medical records from January to September 2018, prior to the outbreak, at the district hospitals and found no more GBS cases.

The median age of the 13 GBS patients was 30 years (IQR: 18–51 years); eight were males; seven had attended higher than secondary school; 10 were from an urban area. The cases had a mixture of occupations. Five cases had a history of gastroenteritis or fever before onset of GBS (Table 1). Four cases resided within a half-kilometer radius and formed a time-place cluster (Figure 2).

Table 1. Socio-demographic status and epidemiological findings among GBS case-patients in Joypurhat District outbreak, Bangladesh, 2018 (n=13)

Characteristics of case-patients	n (%)
Age group	
<20 years	3 (23.1)
20 to <40 years	3 (23.1)
≥40 years	7 (53.8)
Gender	
Male	8 (61.5)
Female	5 (38.5)
Education	
Primary	2 (15.4)
Secondary	3 (23.1)
Higher than secondary	7 (53.8)
Occupation	
Student	3 (23.1)
Housewife	3 (23.1)
Farmer	2 (15.4)
Small business	2 (15.4)
Service	3 (23.1)
Location	
Within municipality (urban)	10 (76.9)
Outside municipality (rural)	3 (23.1)
Epidemiological findings	
History of gastroenteritis within 4-6 weeks	5 (38.5)
History of fever within 2-5 days	3 (23.1)
History of travel within 6 weeks	3 (23.1)
Relevant food history within 2-5 days	3 (23.1)

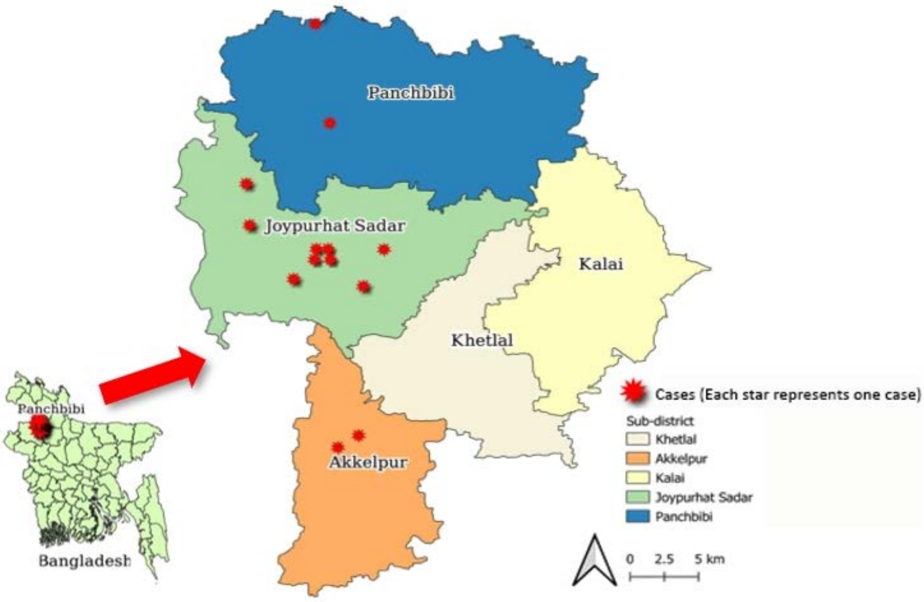

Figure 2. Map of Joypurhat District with residence of GBS cases and time space cluster of GBS cases in Joypurhat Sadar, November 2018

Clinical Profile and Laboratory Findings

Most of the cases had clinical signs and symptoms typical of GBS: symmetrical ascending paralysis (7/13), bulbar palsy (10/13), acute motor axonal neuropathy (4/13), autonomic neuropathy (5/13) and albuminocytologic dissociation in cerebrospinal fluid (8/13).

In this GBS cluster, tetraparesis occurred within 53.7 hours on average. Respiratory muscle involvement that resulted in paralysis was present among 10 case-patients and paralysis occurred within 48 hours (mean of 37.3 hours) in three cases. Five cases died in the acute progressive phase for a case fatality rate of 38.5% (Table 2 and Table 3). *C. jejuni* was isolated in three of seven blood samples. All other tests were negative.

Table 2. Clinical findings among Guillain Barre Syndrome case-patients in Joypurhat District, Bangladesh, 2018 (n=13)

Characteristics of case-patients	n (%)
Limb muscle involvement	
Areflexia (absent all deep tendon reflex)	13 (100.0)
Typical symmetrical ascending paralysis	7 (53.8)
Tetraparesis affecting upper limb first	6 (46.2)
Respiratory muscle involvement	
Respiratory muscle weakness	10 (76.9)
Mechanical ventilation needed	6 (46.2)
Rapid involvement of respiratory muscles (within 48 hours)	3 (23.1)
Cranial nerve involvement	
Bulbar palsy	10 (76.9)
Facial nerve palsy	0 (0.0)
Autonomic neuropathy	5 (38.5)
Time from onset of 1st symptoms to tetraparesis	
<24 hours	3 (23.1)
24 to <48 hours	4 (30.8)
48 to <72 hours	2 (15.4)
≥72 hours	4 (30.8)
Time from onset of tetraparesis to respiratory muscle paralysis (n=10)	
<12 hours	1 (7.7)
12 to <24 hours	5 (38.5)
≥24 hours	4 (30.8)
Clinical course (n=10)	
Use of mechanical ventilation	6 (46.2)
No use of mechanical ventilation	4 (30.8)
Duration between tetraparesis to ventilator dependency (n=5)	
<12 hours	2 (15.4)
12 to <24 hours	2 (15.4)
≥24 hours	1 (7.7)

Table 3. Laboratory findings among Guillain Barre Syndrome case-patients in Joypurhat District, Bangladesh, 2018

Laboratory findings	n (%)
Cerebrospinal fluid (CSF) profile (n=8)	
CSF protein (15-45 mg/dl)	
46-100 mg/dl	1 (12.5)
101-150 mg/dl	2 (25.0)
151-200 mg/dl	3 (37.5)
>200 mg/dl	2 (25.0)
CSF cell count ≤20 mm^3	
0-10 mm^3	6 (75.0)
11-20 mm^3	2 (25.0)
Lymphocytes (%)	
90-100 (%)	8 (100.0)
Nerve conduction studies (NCS) profile (n=5)	
Acute Motor Axonal Neuropathy (AMAN)	4 (80.0)
Mixed variety, both axonal and demyelinating	1 (20.0)
Serology (n=7)	
Campylobacter LOS (Lipo-oligosaccharide) ELISA	3 (23.1)
RT-PCR & Antibody IgG, IgM for dengue	0 (0.0)
RT-PCR & Antibody IgG, IgM for Zika	0 (0.0)
RT-PCR & Antibody IgG, IgM for Chikungunya	0 (0.0)
Stool sample (n=3)	
Test for poliovirus	0 (0.0)
Urine samples (n=7)	
Test for *Leptospira*	0 (0.0)

Clinical Description of Three Deaths that Occurred in the Early Progressive Phase

On 31 Oct 2018, an 18-year-old male presented with gradual development of weakness of fingers for two days (Table 4). On 1 Nov, he developed sudden paralysis of the upper limbs and then lower limbs within eight hours. From 2 to 3 Nov, he developed respiratory difficulty with respiratory failure within a few hours. He was transferred immediately to the intensive care unit and intubated. All deep tendon reflexes were absent and autonomic dysfunction and bulbar palsy developed. Cerebrospinal fluid and nerve conduction study results in implicated GBS with axonal and demyelinating neuropathy. He developed severe respiratory failure on 3 Nov and died. He had a history of gastroenteritis one month before onset of GBS.

On 1 Nov 2018, a 15-year-old male presented with weakness of both lower limbs. Rapid progression of weakness and muscle paralysis developed within 8-9 hours. Respiratory distress started rapidly and within 48 hours respiratory paralysis occurred. He was diagnosed clinically as GBS by a neurologist. He did not receive medical treatment and was referred to the National Institute of Neuroscience in Dhaka. He died from respiratory failure on route to Dhaka. He had a history of loose stool in the previous few months.

On 3 Nov 2018, a 55-year-old male presented with sudden development of weakness of both lower limbs. On 4 Nov, he developed tetraparesis followed by quadriplegia within 24–30 hours. On 5 Nov, he developed respiratory distress and was given oxygen and referred to a hospital with a higher level of treatment. On 5 Nov 2018, he was diagnosed with GBS based on results from cerebrospinal fluid. His oxygen saturation gradually decreased but he was not intubated. No bed in the intensive care unit was available at that time and he was referred to the National Institute of Neuroscience in Dhaka. He died on route.

Table 4. History of Guillain Barre Syndrome (GBS) case-patients in Joypurhat Outbreak, Bangladesh, 2018 (n=13)

Case Id	JH001	JH002	JH003
Gender	F	M	M
Symptoms	Weakness starts from finger to upper limbs, involves lower limbs within few hours; rapid progression of paralysis; respiratory involvement within 48 hours; history of fever 2 weeks back	Weakness starts from finger to upper limbs, involves lower limbs; rapid progression; no respiratory involvement	Weakness starts from finger to upper limbs, involves lower limbs within 72 hours; difficulty in deglutition; rapid progression of respiratory distress by day 4; tracheostomy in situ
Date of first symptom	27 Oct	31 Oct	30 Sep
Time of first symptom	6:00 PM	11:00 AM	5:30 AM
Date of first limb involvement	Upper limb, 27 Oct	Upper limb, October	Upper limb, 30 Sep
Onset of tetraparesis	28 Oct	4 Nov	3 Nov
Time from onset of 1st symptoms to tetraparesis (hours)	21	96	70
Time from tetraparesis to respiratory muscle paralysis (hours)	21	-	96
Time from onset to respiratory failure (hours)	46	-	166
Bulbar palsy	Yes	Yes	Yes
Autonomic neuropathy	Yes	No	Yes
Outcome	ICU	Under treatment	Under treatment

Case Id	JH004	JH005	JH006
Gender	F	F	M
Symptoms	Weakness starts from lower limbs, involves upper limbs; rapid progression of paralysis; respiratory distress	Weakness starts from lower limbs; rapid progression of ascending paralysis within 72 hours; no respiratory involvement	Problem in standing from knee bending position; weakness of both lower limbs; rapid progression of weakness; paralysis affects all limbs within 8-9 hours; respiratory involvement within 48 hours; history of loose motion 3 days back
Date of first symptom	6 Nov	25 Oct	1 Nov
Time of first symptom	7:00 AM	4:30 PM	4:00 PM
Date of first limb involvement	Lower limb, 6 Nov	Lower limb, 27 Oct	Standing from knee bending with weakness of both lower limbs
Onset of tetraparesis	7 Nov	28 Oct	22 Nov
Time from onset of 1st symptoms to Tetraparesis (hours)	35	72	9
Time from Tetraparesis to respiratory muscle paralysis (hours)	17	-	11
Time from onset to respiratory failure (hours)	72	-	20
Bulbar palsy	Yes	No	No
Autonomic neuropathy	Yes	No	No
Outcome	ICU	Under treatment	Death

Table 4. History of Guillain Barre Syndrome (GBS) case-patients in Joypurhat Outbreak, Bangladesh, 2018 (n=13) (cont.)

Case Id	JH007	JH008	JH009
Gender	M	F	M
Symptoms	Problem in swallowing solid food; rapid progression of ascending type of paralysis; all limbs affected by 24 hours; respiratory involvement within 48 hours; history of chronic loose motion	Difficulty in swallowing food; Problem in standing from knee bending position; rapid progression of ascending type of paralysis; all limbs affected by 72 hours; respiratory involvement after 5 days	Weakness of the finger first, followed by whole upper limb; rapid progression of paralysis within 8-10 hours; urinary retention; respiratory involvement after 2 days
Date of first symptom	20 Oct	4 Oct	31 Oct
Time of first symptom	7:00 AM	12:30 PM	3:00 PM
Date of first limb involvement	Lower limb, 21 Oct	Lower limb, 7 Oct	Upper limb, 1 Nov
Onset of tetraparesis	22 Oct	7 Oct	3 Nov
Time from onset of 1st symptoms to tetraparesis (hours)	39	54	10
Time from tetraparesis to respiratory muscle paralysis (hours)	72	66	22
Time from onset to respiratory failure (hours)	111	120	42
Bulbar palsy	Yes	Yes	Yes
Autonomic neuropathy	Yes	No	Yes
Outcome	Death	Death	Death

Case Id	JH010	JH011	JH012	JH013
Gender	M	M	M	M
Symptoms	Weakness of lower limb; rapid progression of paralysis within 6-8 hours; abdominal distention; vomiting; respiratory involvement after 12 hours	Difficulty in swallowing; ascending type of paralysis, both limbs affected after 4 days; respiratory involvement after 6 days	Problem in swallowing food; progression of lower limb paralysis within 24 hours, not affect all limbs; respiratory involvement within 72 hours; history of gastroenteritis 2 weeks back	Problem in swallowing food; both upper and lower limb weakness
Date of first symptom	3 Nov	29 Oct	9 Nov	3 Nov
Time of first symptom	7:30 PM	11:30 PM	8:45 AM	5:40 PM
Date of first limb involvement	Both lower limb, 3 Nov	Lower limb, 30 Nov	Lower limb, 10 Nov	Both lower limbs
Onset of tetraparesis	4 Nov	2 Nov	10 Nov	8 Nov
Time from onset of 1st symptoms to tetraparesis (hours)	24	82	39	144
Time from tetraparesis to respiratory muscle paralysis (hours)	23	43	33	-
Time from onset to respiratory failure (hours)	47	125	72	-
Bulbar palsy	Yes	Yes	Yes	No
Autonomic neuropathy	No	No	No	No
Outcome	Death	ICU	Under treatment	Under treatment

Discussion

In this outbreak, most of the suspected and probable cases had typical signs and symptoms of Guillain-Barre Syndrome. However, in many cases, weaknesses started from the arms and typical symmetrical ascending paralysis was not evident. Several studies found that in 10–15% of cases, symmetrical ascending paralysis was not present, rather the weakness started from the arms, and was not symmetrical.[17] Moreover, common facial palsy in case of cranial nerve involvement was not present, rather bulbar palsy was evident among most cases. Autonomic disturbance with typical sinus tachycardia, orthostatic hypotension, and changes in sweat affected five case-patients. Most of these case-patients developed limb muscle weakness and respiratory paralysis within three days and needed mechanical ventilation. This was unusual because, in most cases of GBS, respiratory failure occurs within 10–12 days.[12,18] Limb muscle weakness and respiratory failure reach a nadir at 2 to 4 weeks after symptoms onset.[19–22] Typically, mechanical ventilation resulting from respiratory failure occurs in about 14–30% of case-patients.[12]

Mechanical ventilation for GBS case-patients with acute respiratory failure is the most common risk factor for death.[9,12,23] In our investigation, six (46.2%) case-patients required mechanical ventilation and five died. The rapid progression of respiratory muscle paralysis required mechanical ventilation support with an increased risk for mortality. Moreover, three case-patients died due to the unavailability of mechanical ventilation.

Outbreaks of GBS have occurred after epidemics of dengue or Zika viral infections.[24–27] During this GBS outbreak, there was an unusual increase in dengue cases in Dhaka. Some of the cases traveled to Dhaka during the dengue outbreak. While no cases reported having dengue, asymptomatic dengue infections can occur in 20–30% of the cases.[28] A search of medical records in Joypurhat Sadar Hospital from July to October 2018 showed no evidence of the increased frequency of dengue cases or microsomia cases.

In this GBS outbreak, five cases had a history of gastroenteritis and three had blood cultures that isolated *C. jejuni*. In Bangladesh, many patients diagnosed with GBS have been reported after campylobacter infection following gastroenteritis.[1,29,30] Campylobacteriosis is the most commonly identified antecedent infection for GBS (20%–50%) cases.[6,30–32] In addition, annual rates of hospitalization for GBS were significantly correlated with campylobacteriosis.[33] Several studies have also suggested that campylobacter is associated with the acute motor axonal neuropathy subtype.[5,30,32,34,35] However, neurologic symptoms are more severe and more likely to be irreversible when GBS is preceded by *C. jejuni* infection.[36]

Other risk factors for death included bulbar nerve involvement, longer progressive phase, autonomic dysfunction, and older age.[23] In this study, most of the cases had bulbar palsy rather than facial palsy, autonomic dysfunction, and age more than or equal 40 years which is similar to the findings of other studies. A study in Bangladesh reported higher mortality when the progressive phase lasted more than eight days.[23]

In our study, most of the GBS deaths occurred in the acute progressive phase, while case-patients in high-income countries more frequently die in the recovery phase due to pulmonary infection and cardiovascular complications.[11,23] In one study in Bangladesh, 12% of GBS case-patients died within 6 months of disease onset.[6,13,15,26] The interval between the onset of weakness and death varied, but most of the deaths occurred within a month.

Most countries do not have a surveillance system for GBS or other neurological disorders. Physicians can notify health authorities when a cluster of unusual cases occurs. GBS may be reported as part of the acute flaccid paralysis surveillance system that is used by countries to identify polio. In addition, the United States and New Zealand, in their influenza vaccination programs, include the occurrence of GBS in their "Adverse Event Following Immunization" report.[33,37]

This investigation had several limitations. We could not use the Medical Research Council Score for measuring muscle strength among cases, because this indicator, which can help diagnose GBS, was not included in the patient's medical records. There was limited data on the cases that died, thus we were unable to compare those cases with cases that survived to determine risk factors. There was limited laboratory testing capacity for microbial agents associated with GBS and no samples were available from the decedents.

Conclusion and Recommendations

We confirmed an outbreak of GBS in Joypurhat District. The mortality rate was unexpectedly high due to rapid involvement of respiratory muscle paralysis and unavailability of mechanical ventilation in the hospitals. We suspect a *Campylobacter jejuni* infection may have been a contributing factor because five cases had a history of gastroenteritis one month before their onset of GBS.

Despite not having a surveillance system for GBS and other neurological diseases, this incident was reported to the District Civil Surgeon. However, the reporting was late, and these conditions are probably under-reported. Consequently, the burden of GBS and other neurological diseases is unknown.

We recommend increasing support for mechanical ventilation in intensive care units in tertiary hospitals, so people diagnosed with GBS can receive appropriate and timely care, which can reduce morbidity and mortality.

We also recommend establishing a surveillance system for neurological diseases that will describe the burden of these diseases and encourage timely diagnosis and reporting of neurological diseases. To increase awareness, we recommend educating people at risk for developing GBS and physicians about symptoms and risk factors of GBS.

Suggested Citation

Raman S, Billah MM, Monalisa, Jony MHK, Shirin T, Flora MS. An outbreak of Guillain–barre syndrome with respiratory failure in Joypurhat, Bangladesh, 2018. OSIR. 2021 Sep;14(3):104-14.

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Analysis of Oxygen Supply and Demand amid the Coronavirus Disease 2019 (COVID-19) Pandemic in Thailand, 2021

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Abstract

The need for medical oxygen in Thailand tends to be increasing due to rising coronavirus disease 2019 (COVID-19) cases. An analysis of oxygen supply and demand can provide a useful insight into the demand for oxygen therapy during the pandemic. To overcome the oxygen supply crisis, the government needs to address the shortage of related equipment, such as oxygen cylinders, generators and concentrators, which are mostly used for home and community isolations and also in field hospitals. We recommend that the government should dramatically increase the capacity for oxygen production as well as the production of related equipment. Furthermore, mechanisms to ensure adequate and equitable distribution of oxygen therapy should be in place. A promotion of domestic research and development to increase the capacity of oxygen production and ensure equitable oxygen distribution is urgently needed.

Keywords: oxygen supply, demand, COVID-19, Thailand

Introduction

Coronavirus disease 2019 (COVID-19) is now considered a major health crisis with more than 212 million people infected.[1] Recent research has indicated that 14% of patients face severe signs and symptoms.[2] The most common symptoms are associated with respiratory failure and 5% of patients need intensive care.[3,4] Oxygen therapy is a critical component of treatment and is included in the list of essential medicines recommended by the World Health Organization. It is used for the treatment of hypoxemic conditions, which are commonly found in COVID-19 patients. Delayed treatment with oxygen for more than 2 days after the onset of hypoxia may almost double the risk of death.[5] Therefore, hospitals and health care facilities need a robust supply of oxygen as part of the management.[6]

The COVID-19 situation in Thailand was under control and manageable since the first case was discovered in January 2020. Until December 2020, the accumulated cases were 6,900, and more than 2,500 patients were hospitalized.[7] However, the number of cases has sharply increased since March 2021, leading to more than 1 million cases with approximately 5,000 severe cases currently hospitalized.[8] Hospital beds in Bangkok and in other big cities have been occupied entirely by COVID-19 patients. In the past, the Ministry of Public Health (MOPH) stipulated that all COVID-19 patients must be hospitalized. However, due to the skyrocketing of cases in mid-2021, the MOPH has set a new treatment policy to prevent the healthcare system from being overwhelmed. The new treatment guidelines categorize patients according to the severity of their symptoms. Asymptomatic and those with mild symptoms are classified as 'green' and are encouraged to isolate at home (Home Isolation—HI) or at designated areas in the community (Community Isolation—CI). Patients with moderate symptoms or at risk of developing a severe condition are classified as 'yellow'. This group is required to stay in a field hospital or a 'hospitel' (a hotel transformed into a small hospital under the supervision of health personnel). Patients with pneumonia or any other severe complications are classified as 'red'. This group needs to be hospitalized and some require close monitoring and aggressive treatment in an intensive care unit (ICU).

The new treatment guidelines came in parallel with the supply of medicines and self-monitoring kits such as pulse oximetry provided by the National Health Security Office for green and yellow classified patients. However, there is debate among health practitioners and policymakers that there should be an adequate supply of oxygen in addition to medicines and monitoring kits, especially for the yellow patients whose conditions might turn red any time. In addition, experiences from other regions such as India and sub-Saharan Africa showed that during the peak of the pandemic, it is critical to have a clear plan on oxygen supply in response to COVID-19.[9-11]

This article thus investigated the situation of medical oxygen supply for COVID-19 patients in Thailand based on both supply and demand perspectives, and aimed to provide optimal recommendations for a better management of oxygen supply in Thailand in response to the COVID-19 pandemic.

Analysis on the Demands for Oxygen Therapy

The Department of Disease Control and the International Health Policy Program of the Ministry of Public Health estimated the prevalence of COVID-19 patients stratified by severity level. The model employed the compartmental (susceptible-exposed-infectious-recovered) model in combination with the system dynamics concept. Table 1 describes the key parameters of the model.

Table 1. Essential parameters of the model

Area	Reproduction number (R0)	Population (millions)	Percentage of initial infectees
Bangkok and vicinity (n=5)	1.43	12.2	50.0
Provinces with high degree of epidemics (n=7)	1.45	6.6	25.0
Other provinces (n=65)	1.35	49.3	15.0

The model also relied on the following assumptions. First, the model estimated the number of COVID-19 cases based on different scenarios: no lockdown measures, lockdown measures with 20% effectiveness in a reduction of the basic reproduction number, and lockdown measures with 25% effectiveness. Second, the model calculated the likely number of actual cases, not reported cases, based on a hypothesis that the actual (unobserved) cases were about 3-6 times greater than daily reported cases. Third, the model was based on an assumption that each type of patient (green, yellow, red) required a different amount of oxygen. For green patients, we assumed that 20% of cases required oxygen at a maximum of 5 litres per minute. The patients in the red group would need, via ventilator, 50 litres of oxygen per minute. Yellow patients would require different amounts of oxygen as follows: 30% of the patients would require, via oxygen cannula, 5 litres of oxygen per minute, 50% of patients would require, via oxygen mask, 10 litres of oxygen per minute, and the remaining 20% would require, via high-flow cannula, 20 litres of oxygen per minute.

Our analysis shows that the highest demand of oxygen would be observed if the prevalence rose to 140,842 patients (most in the yellow group). Such a situation would cause a demand for 2.15 million liters of oxygen per day. The peak of oxygen demand would occur during the end of August 2021 (Figure 1).

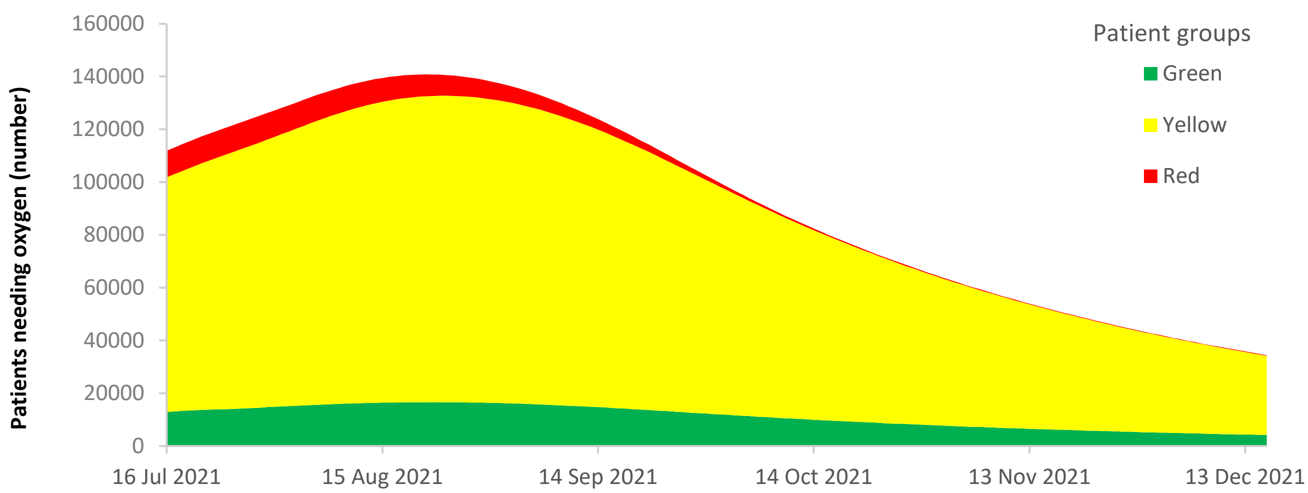

Figure 1. An estimation of the number of COVID-19 patients from July to December 2021

Figure 2 estimates the need for oxygen in each epidemic scenario. In theory, if no lockdown policy had been implemented, the demand for oxygen nationwide would have exceeded 2,000 million litres per day by mid-August 2021 then declined to below 1,500 million litres by mid-September 2021. However, a lockdown policy was a more likely scenario as Thailand had undergone lockdown measures since mid-July 2021. In the two lockdown scenarios, the peak of demand was observed between mid-July and early August 2021 then dropped to below 1,000 million litres a day by approximately the first and the second weeks of September 2021.

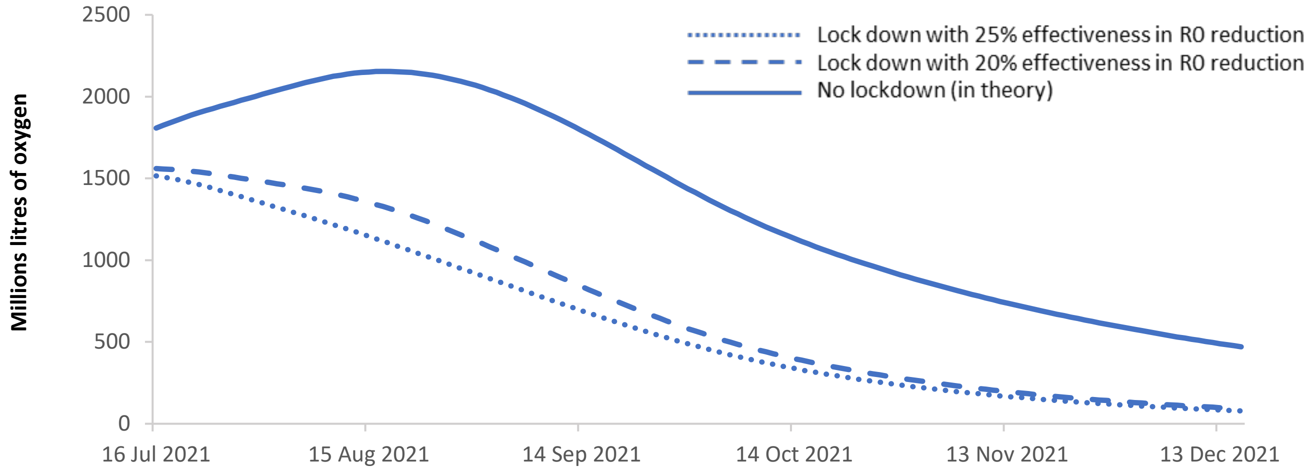

Figure 2. Estimated demand for oxygen (all patient codes combined) in different scenarios

Analysis of Supply for Oxygen Therapy

National Production Capacity

The national production capacity of oxygen in Thailand currently amounts to 1,750 million liters per day. Production capacity could be increased by approximately 20%, leading to a total of 2,100 million liters per day. Until now, only one-fifth to one-third of the national oxygen production has been dedicated to medical use, whereas the rest was effectively destined for industrial use.[12] However, an internal consultation with representatives in the industrial sector found that, in practice, the property of oxygen produced for industrial use was indistinguishable from the property of oxygen for medical use; meaning that the oxygen from both strands of production could be used interchangeably. Regarding this situation, the supply of medical oxygen was not in serious shortage.

Modalities of Oxygen Supply

Oxygen supplies used for the care for COVID-19 patients can be delivered through various means as follows.

Liquid Oxygen Tank

A liquid oxygen tank contains about 3,000 liters of oxygen, which can treat about 30 patients requiring 5 litres per minute of oxygen for at least 11 consecutive days (Figure 3). The establishment of a liquid oxygen tank needs about a week and requires an operating area of approximately 4 m^2. Then oxygen is transferred from the tank to the patients via a pipeline. Such liquid oxygen tanks are commonly used in well-established health facilities. The cost of establishment is about 200,000 baht (US$ 6,100) per unit. The tank can be rented at a cost of 20,000 baht (US$ 610) per month.

(a)

(b)

Figure 3. Example of (a) oxygen tanks and (b) oxygen cylinders

Oxygen Cylinders

An oxygen cylinder is a metal tank filled with liquid oxygen under high pressure (Figure 3).[13] Normally, Thailand imports the cylinders from China as there are no domestic manufacturers. Currently, the number of cylinders is estimated to be about 100,000. During April 2021, before Thailand faced the big wave of COVID-19 cases, there was a high demand of oxygen cylinders from neighbouring countries such as Myanmar, India and Indonesia.[14-16] Numerous cylinders in Thailand were exported to those countries. Thailand is now planning to produce its own cylinders to meet the surge in demand during the COVID-19 pandemic. The cylinders can produce a flow of oxygen, via oxygen cannula or oxygen mask, of up to 15 litres per minute.

Oxygen Generator and Oxygen Concentrator

An oxygen generator is an alternative source of oxygen therapy (Figure 4). However, they are generally set up in healthcare facilities as they require the on-site establishment of oxygen cylinders and, in parallel, a central oxygen supply. Within this process, one to two months are needed for a standard test of setting up the system.

Another option is an oxygen concentrator. This is a device that uses nitrogen to remove oxygen from a gas supply. It is commonly used to provide enriched air in a household area. The cost varies from about 10,000 to 40,000 baht (US$ 308-1230). It is easily movable and can be operated in a household context. However, the flow of oxygen is limited (normally about 1-10 litres per minute) compared with that of oxygen cylinders. Therefore, the use of oxygen concentrators is likely to be limited to green and yellow patients. The majority of oxygen generators and oxygen concentrators were imported from China. Other necessary equipment includes oxygen valves and pipes, of which existing stock is now able to meet the national demand.

(a) (b)

Figure 4. Example of (a) oxygen generators and (b) oxygen concentrators

Which Choice is Suitable and in Which Setting?

Overall, the supply of medical oxygen is considered adequate to meet the demand of the lockdown policy. However, the demand may be far greater than at present if the lockdown policy is relaxed and the pandemic worsens. In such circumstances, current oxygen supplies are likely to be insufficient. Thus, an increase in production capacity is still needed.

A more challenging situation involves the supply of related equipment needed for oxygen therapy. Under current market conditions, there is still a shortage of oxygen cylinders, generators, and concentrators as this equipment is mostly produced abroad. In this scenario, green and yellow patients, who are supposed to be treated at home, may suffer most from the shortage.

Oxygen generators may be a suitable option for a small field hospital or a hospitel. A central bank of oxygen cylinders should be created in communities with a high number of cases in order to ensure adequate delivery for patients undergoing home and community isolation.[9] However, any community oxygen bank must be implemented in parallel with strong safety measures of setting up the system. Table 2 summaries the advantages and limitations of each oxygen modality based on the capacity of oxygen equipment and its use in diverse health care settings.

Table 2. Summary of oxygen modalities

Option	Advantages	Limitations	Suitable setting
Liquid oxygen tank system	• Suitable for high demand for care • Needs a well-established engineering system	• Needs a pipeline system in tandem	• Well-established health facilities (such as hospitals or large field hospitals)
Oxygen cylinder	• Easy to use • Have surge capacity from using nitrogen cylinders	• Needs intensive exchange for a new cylinder, therefore it is a risk for disease transmission • Shortage of cylinders • Needs high levels of precaution for setting up the system	• Suitable for home and community isolation, and field hospital or hospitel (if necessary) • Option for supplementing oxygen supplies
Oxygen generator	• Closed system • Low cost • Relatively mobile	• May take a long time to set up • Shortage of domestic supply • Oxygen needs to be filled on site.	• Field hospital • Hospitel • Community isolation
Oxygen concentrator	• Easy to use and relatively safe • Low cost compared to other modalities • Very mobile	• Shortage of domestic supply • Need to be imported from abroad • Low productivity of oxygen • Suitable for only patients with mild conditions	• Home isolation • Community isolation

Conclusion and Policy Recommendations

Our analysis shows that oxygen production is likely to catch up with demand for oxygen under the status quo. The crucial point is related to the supply of related equipment. To address this, the following recommendations are proposed.

1. The Ministry of Public Health should work closely with the Ministry of Industry to carefully monitor the oxygen supply situation in parallel with the monitoring of COVID-19 cases.
2. Additional authorization from the Ministry of Commerce regarding, for example, the export of oxygen cylinders, should be authorized under the Central Committee on the Price of Goods and Services under the Act on Goods and Services Prices B.E. 2542 (1999), since this will support the effectiveness of existing legislation.
3. Oxygen supplies in large hospitals should be kept in reserve. A model of a hospital-chain system to provide oxygen supplies from a large hospital to smaller hospitals under its network is recommended.
4. The industrial sector should rapidly increase oxygen production capacity before the lockdown policy is relaxed and before the COVID-19 cases begin to rise again.
5. Liquid oxygen tanks should be set up in large hospitals and field hospitals with authorized standards and quality checks.
6. Procurement of oxygen generators and concentrators should be negotiated between the government and providers. Rapid response for products at affordable prices is urgently needed. Additionally, domestic production should be increased in order to alleviate the reliance on imported products.
7. Domestic research and development on the production and distribution of oxygen in response to the public health crisis should be promoted. This needs mutual collaboration among all parties, including government authorities, academics, and the private sector.

Suggested Citation

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