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A Typhus and Typhoid Fever Outbreak: A Diagnostic Dilemma in Joypurhat District, North-western Bangladesh, 2021

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Abstract

Typhoid (enteric) and typhus (*Rickettsia*) fevers are endemic in Bangladesh. This study describes an outbreak initially thought to be typhoid fever, but upon several patients' non-response to treatment, further evaluation discovered that these patients had typhus. One typhoid case did not respond to ceftriaxone (although sensitive in blood culture) and, due to empirical knowledge of the physician, was diagnosed as typhus by a significant Weil–Felix test and responded to doxycycline. A total of 241 cases were identified: 158 (65.6%) cases of typhoid fever, 44 (18.2%) with typhus, and 39 (16.2%) with typhoid and typhus co-infections. In this outbreak, cases in the spotted fever group rickettsia (SFGR) constituted the largest proportion, followed by the typhus group (TG), while the scrub typhus group (STG) had the smallest proportion. This finding was different from the typical subgroup pattern seen in Bangladesh of TG>STG>SFGR. Typhus may be misdiagnosed as typhoid fever due to similar clinical presentation, so it is essential for physicians to distinguish between the diseases because of different treatment and intervention modalities. Epidemiologists should be aware that both diseases can occur simultaneously in outbreaks. This study recommends enhanced training of physicians on the differential diagnosis of typhus and typhoid fever to reduce the misdiagnosis. In addition, laboratories need to upgrade their diagnostic protocols and capacity to use blood cultures to diagnose typhoid fever.

Keywords: typhoid fever, typhus, *Rickettsia*, typhus subgroups, Bangladesh

Introduction

Typhoid and typhus fever (*Rickettsia*) are endemic in tropical and subtropical countries worldwide, along with Bangladesh and neighbouring countries.[1–3] The three rickettsia subgroups are typhus group (TG), scrub typhus group (STG), and spotted fever group rickettsia (SFGR).[4] All typhus subgroups are evident throughout Bangladesh year-round, with the highest prevalence of SFGR in Rangpur and Rajshashi Divisions.[5,6] Rickettsial infections are a frequent, yet under-recognized cause of febrile illness in Bangladesh.[7]

Co-infection of typhoid fever with diseases such as dengue, malaria, leptospirosis, and hepatitis A or E has been documented.[7–10] There have been reports of typhoid and typhus co-infection in Bangladesh, other tropical and sub-tropical nations, and in South and East Asia. Both epidemic and endemic (murine) typhus can be misdiagnosed as typhoid fever due to overlapping clinical presentations and similar laboratory findings.[3,8–10]

A specific typhoid or typhus diagnosis is essential because the transmission and treatment is different. The mode of typhoid diseases transmission is mainly waterborne, followed by food-borne and direct contact. Multiple intervention strategies can be taken including provision of adequate chlorination and health education enhancement.[11–13] However, the mode of typhus transmission is mainly through vectors such as lice, fleas, or mites, or fecal droppings from rodents. Control and containment of typhus outbreak includes improving sanitation, controlling fleas, and reducing populations

of rats, mice, and other animals.[11–14] Typhoid fever responds more effectively to fluoroquinolones or ceftriaxone; typhus with doxycycline treatment.[15]

On 17 Oct 2021, the pediatric consultant at Joypurhat Sadar Hospital (JSH) in Joypurhat District reported an increase in pediatric cases of suspected enteric fever to the Institute of Epidemiology, Disease Control and Research. The cases showed no improvement after two weeks of intravenous antibiotic treatment. The National Rapid Response team (NRRT), conducted an outbreak investigation to verify the outbreak, identify sources, determine the scope and magnitude, and described the misdiagnosis and mistreatment of a typhus fever case.

Methods

This study investigated the outbreak from 18 to 28 Oct 2021 at JSH, Joypurhat Municipality, Joypurhat Sadar Upazilla. A descriptive study following the One Health approach by describing the cases (by case definition, case finding) and field investigation (by case investigation with laboratory testing) followed by environmental sample testing.[15]

Operational Definitions

In this investigation, the term *typhus* was used to encompass all rickettsial infections detectable by the Weil–Felix test. Based on antigen reactivity, cases were categorized into typhus group (TG; OX19), spotted fever group rickettsiae (SFGR; OX2) scrub typhus group (STG; OXK), or mixed patterns involving more than one antigen.

This study defined suspected, probable and confirmed cases as follows:

- A suspected case (both for typhoid and typhus) was any person, irrespective of age and gender, in JSH presenting with fever associated with any of the following symptoms: headache, abdominal pain, nausea, vomiting, diarrhea/constipation for seven days from 4 Sep to 25 Oct 2021.
- A probable typhoid case was a suspected case with a fourfold or higher rise in Widal test titers. However, in this study, probable cases study were classified based on single high titers rather than a fourfold rise.
- A confirmed typhoid case had *Salmonella typhi* identified in a blood or stool culture.
- A probable typhus case was a suspected case with a fourfold or higher rise in Weil–Felix test.
- A confirmed case of typhus had a positive polymerase chain reaction (PCR) test for *Rickettsia*.

Data Collection

The NRRT reviewed medical records from the pediatrics and medicine departments at JSH and municipality health centers to compile a line list of cases, describing them by time and person. Clinical information and laboratory results (complete blood count, Widal test, Weil–Felix test, blood and stool cultures with drug sensitivity) were abstracted from these records.

Interviews were conducted with patients or their guardians using a semi-structured questionnaire (adapted from U.S. Centers for Disease Control and Prevention) to collect demographic information and symptoms.

Laboratory Investigation

The study team collected 5 mL whole blood and stool samples from patients with no prior history of antibiotic consumption. Serum was separated from blood cells, collected, stored refrigerated, and sent in a cold box to Rajshashi Medical College for serological testing. Stool samples were sent to Rajshashi Medical College microbiology laboratory for culture and antibiotic sensitivity test. Cold chain was maintained during storage and transfer of blood and stool samples within 72 hours.

The Widal test (Labkit, SPINREACT, S.A.U., Genoa, Spain) was used for typhoid and the Weil-Felix test for typhus (Tulip Diagnostics/PROGEN (India) and Sclavo Diagnostics (Italy), respectively. The Widal test measures agglutinating antibodies against the O and H antigens of *S. typhi* in sera of people with suspected typhoid. In Bangladesh, an antibody titer of greater than 1:160 and greater than 1:80 for anti-H antigen and anti-O antigen is the cutoff level to detect typhoid. However, the Weil–Felix test primarily checks for antibodies against certain Proteus bacteria strains (OX2, OX19, and OXK). High OX2 titer indicates “spotted fever group rickettsia”, high OX19 indicates “endemic/epidemic typhus group”, and high OXK titer suggests “scrub typhus”.

Environmental Investigation

This study collected surface and municipal water samples from seven sites where there were increased reported cases of typhoid fever and typhus and tested for salmonella and faecal coliforms. Samples were sent to the International Centre for Diarrhoeal Disease Research, Bangladesh laboratory, an international, non-profit health research organization based in Bangladesh, and the Public Health Engineering Department laboratory.

Data Analysis

The demographic characteristics of the study sample and detailed results were expressed as percentages. Descriptive statistics such as frequency, percentage, mean and standard deviation were used primarily to summarize and describe the data. Analyzed data were presented in the form of epidemic curve, and a Venn-diagram.

Case Study

After non-response to drug treatment was reported in a few cases in this typhoid outbreak, typhus was suspected because other cases had been diagnosed with typhus. Then key informants were interviewed, medical records were reviewed, and diagnostic laboratory tests for typhus were ordered. This study described two cases, one a misdiagnosis of typhus and another with concomitant typhoid fever and typhus.

Results

This study identified 241 probable cases in Joypurhat District; 158 (65.6%) were typhoid fever, 44 (18.2%) were typhus and 39 (16.2%) had typhoid and typhus co-infections. The epidemic curve represented a simultaneous outbreak of typhoid fever and typhus. The first case of typhoid fever started on 8 Sep 2021, peaked on 13 Oct 2021 and the last reported case was on 27 Oct 2021. The first typhus case was detected on 11 Sep 2021 which peaked on 21 Oct 2021, and the last case was on 31 Oct 2021 (Figure 1).

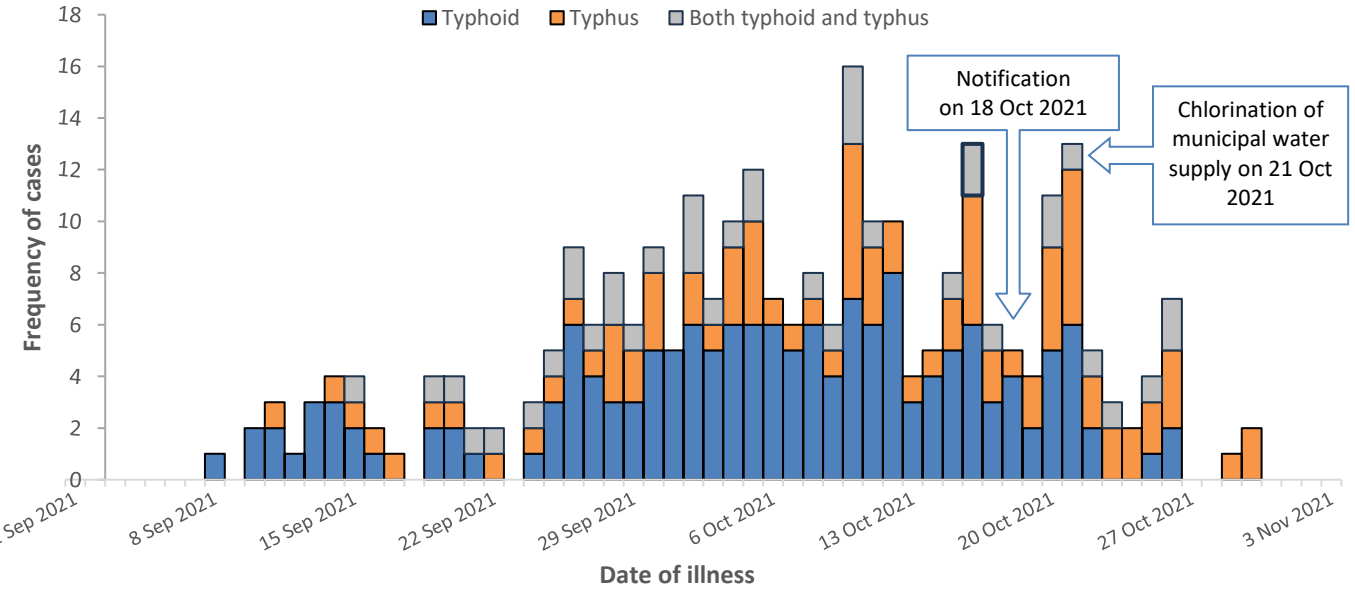


Figure 1. Frequency of cases by date of illness onset in the typhoid fever and typhus outbreak, Joypurhat District, Bangladesh 2021 (n=241)

Males accounted for 135 (56%) of the cases and children <15 years were mostly affected in the community. The most cases identified were in the 5–14 years age group. The fewest cases were in the ≥44 years age group (Figure 2). Clinical presentations of 241 typhoid and typhus fever cases were recorded as: fever (100%), headache (70%), nausea/vomiting (40%), abdominal cramps (36%), and hepatomegaly/hepatosplenomegaly (17%). Rash and lymphadenopathy were only reported in 5% of the cases. Thrombocytopenia occurred among 10% of the cases and mild to moderate anemia among 40% of the cases. The characteristic step-ladder rise in temperature in typhoid fever was reported in 38% of the patients. However, 9% of the cases developed pneumonitis, which is a common complication of typhus, but not common with typhoid fever. In addition, for all cases, the hospitalization rate was 54%, which was higher than 11–14% in previous months. The duration of hospital stay of 14 days, was longer than the 4–7 days duration in previous months.

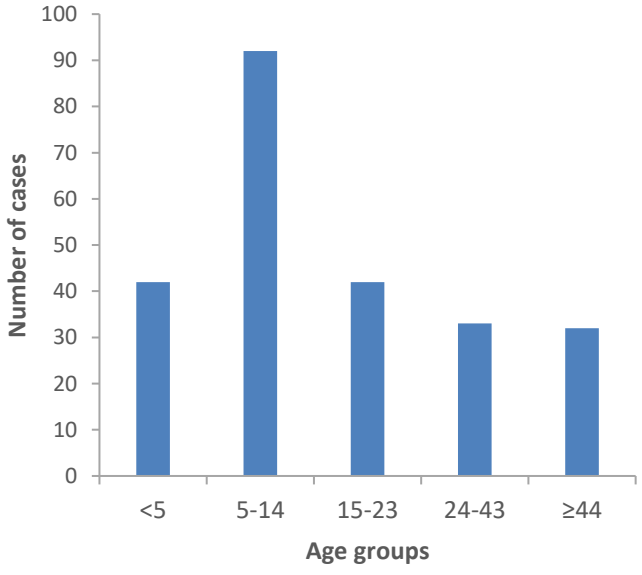


Figure 2. Distribution of cases by age groups in the typhoid fever and typhus outbreak, Joypurhat District, Bangladesh 2021 (n=241)

Case Study

The case study included information from case interviews conducted on 19–20 Oct 2021, when suspicion of typhus arose. A 7-month-old male with five days of fever, vomiting, abdominal pain, and nausea visited a doctor on 17 Oct 2021 and was admitted to JSH on 19 Oct 2021 with a diagnosis of typhoid fever, and a Widal test (average sensitivity 64–88%, average specificity 56–98%) was non-significant. The child was treated with ceftriaxone, but after four days, his fever did not subside. The physician suspected it could be typhus fever and a Weil–Felix test (average sensitivity 40–50%, average specificity 70–80%) was significant. The patient was given doxycycline and discharged on 27 Oct 2021 with complete recovery. Another case demonstrated co-infection with typhoid fever and typhus. On 6 Oct 2021, a 6-year-old male presented with three days of high fever, loss of appetite, no rash, and mild cough. He was given ciprofloxacin, paracetamol, and antihistamine and sent home. There was no response for ten days and the child returned to the doctor who advised a Widal test and blood culture, and both were positive for typhoid fever. The child was given ceftriaxone, but his fever did not subside after four days. The child returned to the doctor again and had a positive result for Weil–Felix test. The child was given doxycycline on 22 Oct 2021 and his fever subsided within three days.

Laboratory Investigation

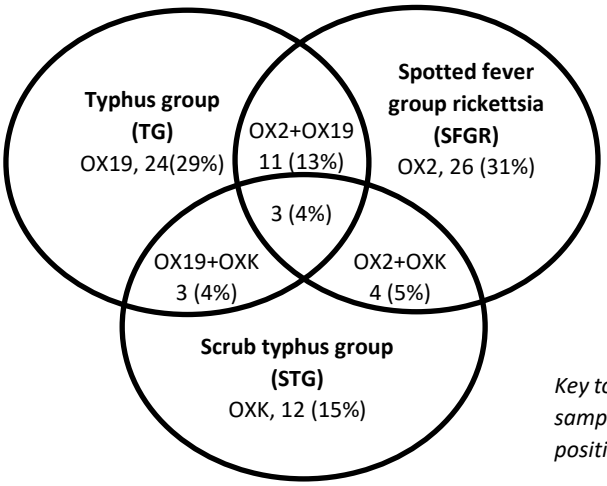
S. typhi was identified in four out of nine blood cultures and three out of seven stool cultures (Table 1). The Widal test was significant in 76% (158/241) cases, with 4% (12/241) anamnestic reaction based upon a fourfold increase of titers above standard. Among confirmed cases of typhoid fever, only one case was positive for both Widal test and Weil–Felix test. Culture sensitivity revealed that *Salmonella spp*. (antibiogram) showed resistance to cefuroxime, cefoxitin, cefixime, and ceftriaxone and intermediate to ciprofloxacin for most cases and sensitive to amoxicillin–clavulanate, meropenem, ofloxacin and 7–10 other antibiotics.

However, 83 cases had a positive reaction to antigens OX2, OX19, and OXK in the Weil–Felix test of typhus fever. No confirmation by PCR was feasible. Among 83 probable cases of typhus in this outbreak, the predominant subgroups were SFGR (31%) and TG (29%), followed by mixed subgroup (26%), and SFGR>TG>mixed>STG (15%). This study also observed the presence of multiple subgroups with OX2+OX19 (13%), OX19+OXK (4%), OX2+OXK (5%), and all three antigens at 4% (referred as mixed subgroup) (Figure 3).

Table 1. Distribution of cases by test: Widal test, Weil–Felix test, and confirmatory culture/PCR test for Typhoid and Typhus, Joypurhat District, Bangladesh 2021

Disease	Weil–Felix test positive	Widal test positive	Blood/stool culture positive for typhoid	PCR positive for typhus	Probable cases	Confirmed cases
Typhoid	39	158	7/16	NA	**151**	**7**
Typhus	44	39	NA	Nil	**44**	-
Typhoid and typhus	39	39	1/16	-	**38**	**1 (typhoid)**

Total number of people tested is unknown. NA: not applicable, Nil: not done, -: no cases in this cell.



Key to numbers: typhus subgroup, number of samples positive by Weil–Felix test, percent positive by Weil–Felix test.

Figure 3. Distribution of positive reaction with different antigens (OX2, OX19, OXK) in Weil–Felix test of Rickettsia fever, in typhoid and typhus fever outbreak, Joypurhat District, Bangladesh 2021 (n=83)

Environmental Investigation

Informal interviews of household members of the patients regarding their food habits, sanitation, water supply, hygiene and household environment revealed no specific clue, other than most of them consumed drinking water from the municipality water tank supply.

The source of the typhoid outbreak was suspected to be the municipal water supply because faecal coliform was detected in three out of seven municipal water samples. No *S. typhi* was recovered in these samples.

Actions Taken

On 21 Oct 2021, chlorination of the municipal water supply was done as immediate action. Moreover, awareness raising among community people and health workers was done for future prevention by providing information education and communication materials and training.

Discussion

Initially, this outbreak was classified as a typhoid fever outbreak, because patients presented with high fever, headache, vomiting/nausea, abdominal cramp and a positive Widal test for *S. typhi*. However, one physician suspected a rickettsial disease which was confirmed when a Weil–Felix test was positive, and patients had a rapid response to doxycycline. Thus, typhoid fever and typhus occurred simultaneously in this outbreak.

Typhus and typhoid fever have overlapping signs and symptoms. Diagnostic laboratory tests aid physicians to differentiate between the two. For typhoid fever, the diagnostic test is blood culture, but in Joypurhat District, the site of this outbreak, only the Weil–Felix and Widal tests were available. Physicians treated their patients for typhoid fever based on clinical suspicion. However, differentiation between typhoid fever and typhus is important because of different treatments and different public health responses.[16]

This outbreak did not have the typical distribution of typhus subgroups (TG>STG>SFGR) as previously seen in Bangladesh.[5,7] In this outbreak, the predominant subgroups were SFGR, followed by TG and STG. SFGR typhus is not common in Bangladesh due to vector unavailability. The *Rickettsia felis*, a variety of SFGR, is emerging in Bangladesh with a nationwide prevalence of 19.6%.[17,18] Higher detection rates of *R. felis* were observed in neighboring northwest regions of Rangpur and Rajshashi and central regions.[19]

Identifying the rickettsial subgroup is important because subgroups have different vectors and thus prevention strategies are different. The current typhus prevention strategy is based on control of ticks and mites. However, with the emergence of spotted fever group rickettsial, prevention needs to include control of cat fleas and mosquitoes, both regionally and nationally.

Reliance on clinical diagnosis of typhoid fever and typhus presents a diagnostic dilemma, because they have similar symptoms. Laboratory tests commonly used to test for typhoid fever and typhus, Widal and Weil–Felix tests, respectively, are widespread and inexpensive and need few sophisticated instruments. However, these tests are non-specific and have false negatives and positives.

In this study, spotted fever group rickettsioses were included within the broader *Rickettsia* group for analytical purposes, reflecting their shared epidemiologic and clinical characteristics with typhus group rickettsioses. However, cases identified through laboratory testing were reported separately as spotted fever where applicable. The case definitions used followed standard field epidemiology and surveillance practices suitable for resource-limited settings. Suspected cases were defined clinically by prolonged fever with associated systemic symptoms, while probable cases required a fourfold or higher rise in Widal or Weil–Felix test titers for typhoid and typhus, respectively. Confirmed cases were based on pathogen identification by culture for *S. Typhi* or by PCR for *Rickettsia*. This tiered diagnostic framework balances sensitivity for case detection with specificity for laboratory confirmation and enables meaningful interpretation of disease burden where diagnostic resources are limited.

In Bangladesh, other tropical infections such as dengue fever and malaria are also endemic and may present with overlapping clinical features, complicating the diagnosis of febrile illnesses. However, certain clinical distinctions can assist in differentiation. Dengue fever typically presents with very high fever, severe joint and muscle pain, and sometimes a rash. In contrast, typhoid fever and typhus generally cause continuous high fever with gastroenteritis and rash without joint pain. Malaria is characterized by intermittent fever and frequently leads to anemia due to hemolysis. Recognizing these characteristic fever patterns and associated symptoms, in combination with appropriate laboratory testing for malaria and dengue, is essential for accurate diagnosis and effective management in endemic settings.

Prevalence of typhoid fever in Bangladesh is high and Rajshashi with Rangpur are an endemic zone for typhoid. Therefore, a high-prevalence area, with a Widal test of moderate sensitivity and variable specificity, has very high positive predictive value (PPV) meaning a positive test strongly confirms disease. Bangladesh is considered endemic for several rickettsial infections, including scrub typhus and flea-borne spotted fever (especially *R. felis*). Using a Weil–Felix test of low sensitivity (many missed cases) and moderate specificity (many false positives) severely limits its reliability to confirm disease.

Limitations

All typhus cases were probable because confirmatory PCR test was not available. For confirmation of typhoid fever, only blood samples were collected from the 16 patients who did not start their antibiotic treatment. Despite universal health care in Bangladesh, people who have symptoms of fever may not seek health care and so selection bias might have been present in this study. The Widal and Weil–Felix tests have low specificity which weakens their diagnostic rigor. The low sensitivity (40–50%) and specificity (70–80%) of the Weil–Felix test can lead to misdiagnosis of patients.[21] In this outbreak, there were patients with a positive Weil–Felix test and diagnosed as typhus, but who had typhoid fever. The absence of paired sera resulted in probable cases being classified based upon single high titers rather than a four-fold rise. Reporting of demographic variables of the cases were limited to age and sex, because of the limited collection of demographic and clinical outcome data.

Conclusion and Recommendations

This was a unique outbreak of two different diseases with similar presentations: typhoid and typhus fever. The municipality water supply was the probable source of infection for typhoid fever, but the source of typhus remains unknown. These diseases must be differentiated because of different treatment and intervention modalities. Therefore, it is essential for physicians to recognize the importance of differentiating between typhoid and typhus fever, and for epidemiologists to be aware that both diseases can occur simultaneously in outbreaks.

Consequently, diagnostic accuracy should be improved for good patient outcomes. It is essential to screen patients diagnosed with typhoid fever for rickettsial diseases, especially when patients do not respond to standard typhoid treatment. Screening the patients with suspected typhoid fever by triple antigen test, so that concomitant/co-infection by typhus can be detected in earlier stage of disease progression, would mean that morbidity and mortality resulting from rickettsial fever could be prevented. Moreover, correct identification of the rickettsial subtypes could lead to effective prevention strategies. Initiating active rickettsial disease surveillance is recommended, using a One Health approach, incorporating vector assessments such as cat, dog and rat fleas to identify areas vulnerable to rickettsial transmission.

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Author Contributions

Sohel Rahman: Conceptualization, methodology, investigation, project administration, data curation, formal analysis, visualization, writing—original draft, writing—review & editing. **Alden Henderson:** Visualization, writing—review & editing. **Md. Yousuf Ali:** Investigation, writing—original draft. **Mallick Masum Billah:** Writing—review & editing. **Ishrat Jahan:** Investigation, conceptualization, project administration, visualization. **Nawsher Alam:** Formal analysis, writing—review & editing. **Zakir Hossain Habib:** Writing—review & editing. **Murshida Khanum:** Investigation, conceptualization, project administration, visualization. **Tahmina Shirin:** Project administration, resources, supervision.

Ethical Approval

This response was exempt from institutional review because it was a response to an emergency situation.

Informed Consent

Informed consent was obtained from all participants involved in the study.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

Conflicts of Interest

No conflicts of interest.

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Declaration of Generative AI and AI-assisted Technologies in the Writing Process

No generative AI or AI assisted technologies were used in writing.

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