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Does community-wide water chlorination reduce hepatitis E virus infections during an outbreak? A geospatial analysis of data from an outbreak in Am Timan, Chad (2016–2017)

Annick Lenglet, Lutz Ehlkes, Dawn Taylor, Jean-Francois Fesselet, Jean Noel Nassariman, Abdelkhadir Ahamat, Alexandra Chen, Idriss Noh, Abakar Moustapha and Alexander Spina

ABSTRACT

Hepatitis E Virus (HEV) genotype 1 and 2 infect an estimated 20 million people each year, via the faecal-oral transmission route. An urban outbreak of HEV occurred in Am Timan, Chad, between September 2016 and April 2017. As part of the outbreak response, Médecins Sans Frontières and the Ministry of Health implemented water and hygiene interventions, including the chlorination of town water sources. We aimed to understand whether these water treatment activities had any impact on the number of HEV infections, using geospatial analysis of epidemiological and water treatment monitoring data. By conducting cluster analysis we investigated whether there were areas of particularly high and low infection risk during the outbreak and explored the reasons for this. We observed two high-risk spatial clusters of suspected cases and one high-risk cluster of confirmed cases. Our main finding was that confirmed HEV cases had a higher median number of days of exposure to unsafe water compared to suspected and non-confirmed cases (Kruskal-Wallis Chi Square: 15.5; $p < 0.001$). Our study confirms the mixed, but shifting, transmission routes during this outbreak. It also highlights the spatial and temporal analytical methods, which can be employed in future outbreaks to improve understanding of HEV transmission.

Key words | community water treatment, disease transmission, geospatial analysis, Hepatitis E Virus, outbreak

HIGHLIGHTS

- Use of spatial and temporal analytical methods to explore the impact of water treatment interventions in a hepatitis E outbreak.
- Geo-spatial analysis of epidemiological and water treatment monitoring data.

Annick Lenglet†
Lutz Ehlkes†
Dawn Taylor (corresponding author)
Jean-Francois Fesselet
Médecins Sans Frontières,
Plantage Middenlaan 14, 1018 DD, Amsterdam,
The Netherlands
E-mail: *dawn.taylor@amsterdam.msf.org*

Annick Lenglet†
Department of Clinical Microbiology,
Radboud UMC,
Geert Grooteplein Zuid 10, Nijmegen,
The Netherlands

Lutz Ehlkes†
Gesundheitsamt,
Kölner Str. 180, Düsseldorf,
Germany

Jean Noel Nassariman
Abdelkhadir Ahamat
Alexandra Chen
Idriss Noh
Abakar Moustapha
Médecins Sans Frontières,
Quartier Klemat, Rue 3211, Porte 429, N'Djamena,
Chad

Alexander Spina
College of Medicine and Health,
St Luke's Campus, Exeter University, Heavitree Road, Exeter,
United Kingdom

†These first authors contributed equally to the work.

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BACKGROUND

It is estimated that Hepatitis E Virus (HEV) infection from genotypes 1 and 2 infect 20 million people globally each year (Rein *et al.* 2012). As such, HEV infection is a common form of acute hepatitis (Goel & Aggarwal 2016). HEV infection of genotype 1 is increasingly recognised as an important cause of acute hepatitis (presenting clinically as acute jaundice syndrome [AJS]) in outbreaks in lower resource and humanitarian settings in sub-Saharan Africa (Guthmann *et al.* 2006; Teshale *et al.* 2010b; Elduma *et al.* 2016; Leung *et al.* 2017; Spina *et al.* 2017). Even though the transmission dynamics of outbreaks of genotype 1 are currently not fully understood, contaminated water is considered to be the most common source of infection (World Health Organization 2014). However, evidence from outbreaks in Kenya, Uganda and Chad suggests that other routes of faecal-oral contamination through person-to-person transmission at the household level (presence of small children, limited handwashing etc.) are also associated with recent HEV infections (Mast *et al.* 1994; Teshale *et al.* 2010a; Vernier *et al.* 2018).

During large-scale outbreaks in humanitarian settings, public health interventions have primarily relied on the following components: (1) early detection of symptomatic cases (especially pregnant women, who are at risk of serious clinical disease); (2) clinical management and laboratory diagnosis of identified AJS cases; (3) community engagement and health promotion (early detection and improved hygiene practices); and (4) point-of-use water treatment and safe water storage (World Health Organization 2014). In 2015, the World Health Organization (WHO) also issued a position paper on the use of a HEV vaccine 'to mitigate or prevent outbreaks' particularly in high risk groups such as pregnant women (World Health Organization 2015).

It is difficult to evaluate the impact of implemented public health interventions on reducing the magnitude, duration and severity of HEV outbreaks in humanitarian settings. Information regarding the underlying sero-epidemiology for HEV infection (and its associated immunity) in affected populations is usually absent and transmission dynamics of HEV are poorly understood. Furthermore, the incubation period of the disease can be up to six weeks, which means any impact of control measures can only be observed at the earliest, six weeks post-intervention.

Understanding the impact of safe water interventions is crucial for responding to future HEV outbreaks. Whilst these interventions are frequently implemented at population level and sustained for the duration of an outbreak response (possibly several months), they are labour intensive and there is limited evidence of their effectiveness (Yates *et al.* 2018).

Between September 2016 and April 2017, a large urban outbreak of HEV occurred in Am Timan, located in the eastern part of Chad (Spina *et al.* 2017). Active case finding led to the detection of 1,443 cases of AJS of which 274 cases underwent laboratory diagnosis for HEV and 127 (46.4%) were confirmed as having HEV infection (Spina *et al.* 2017). The genotype circulating during this outbreak was identified as genotype 1e (Spina *et al.* 2017). According to seroprevalence studies conducted at the end of this outbreak, 59.6% of the town's population had antibodies against HEV and models suggest that 45.2% were susceptible to infection when it started in September 2016 (Vernier *et al.* 2018). We have previously demonstrated that the likely transmission route for this outbreak was linked to household transmission factors (Spina *et al.* 2017), but we were unable to document any specific impact of public health interventions implemented for the duration of the outbreak.

The outbreak response implemented by Médecins Sans Frontières (MSF) in collaboration with the Ministry of Health included active case finding, hygiene promotion and clinical management of suspected cases. Also, to encourage the use of safe water, a town-wide distribution of hygiene kits took place as well as implementation of wide-scale chlorination of the small water network and numerous community water sources (Spina *et al.* 2018). In this study, we aimed to understand whether these water treatment activities had a notable impact on the number of HEV infections, using geospatial analysis of epidemiological and water treatment monitoring data. We also investigated whether there were areas of particularly high

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and low infection risk during the outbreak and explored the reasons for this.

METHODS

Study population

This study focused on the town of Am Timan, which is located in eastern Chad. We restricted the study area to the geographical limits of the town as this was where the water chlorination activities were targeted for the duration of the outbreak. At this point in time, the study area had a population of approximately 61,930 inhabitants (MSF estimate, 2016). As part of the outbreak response, MSF teams had subdivided the town into 648 approximately equally sized neighbourhood blocks in order to facilitate population based distribution of hygiene kits. Each block contained a mean household number of 16.6 houses (standard deviation (SD): 10.9), 96.2 people (SD: 63.5) and a median of 15 households (interquartile range (IQR): 9–23) and 87 people (IQR: 52–133).

Data sources

For this study, we used three separate data sources: community based surveillance, clinically assessed AJS cases at the hospital, and water treatment monitoring records. The first included all cases of AJS identified during active community case finding. The operational methods associated with this have previously been described in detail (Spina *et al.* 2017). Briefly, trained community health workers (CHWs) visited all households within the town every two weeks. During these household visits, CHWs identified any symptomatic AJS cases and referred them to the hospital for clinical assessment. The CHWs also conducted hygiene and health promotion to encourage households to improve their use of safe drinking water and to practice handwashing with soap and water. All AJS cases identified at household level were entered into a database. The information collected included date of detection, sex, age, location of residence (by GPS coordinates), and pregnancy status. We only included persons whose area of residence was within the study area.

The second data source included all AJS cases that were clinically assessed at the hospital in Am Timan – some through referral by the CHWs and some through self-reporting. This dataset included information on clinically observed and self-reported symptoms, detailed pregnancy status of female patients and results of any HEV rapid diagnostic testing (RDT). It should be noted that referral to the hospital and subsequent testing with the HEV RDT was restricted to AJS cases with a severe clinical presentation and all pregnant women with AJS, as these were at increased risk of severe manifestations of disease.

The third data source described the monitoring and reporting of the community water treatment activities, between September 2016 and April 2017. This dataset provided the location of the operational drinking water sources in the study area, which were part of the MSF chlorination programme ($n = 85$). The dataset also detailed the type of water source (open reservoir, hand pump, motorised borehole), as well as daily data on the free residual chlorine (FRC) level in the water.

Case definition

Suspected cases of HEV infection were all persons presenting with AJS (yellowing of the eyes). Suspected cases (AJS cases) that underwent confirmatory testing were defined as confirmed HEV cases (RDT-positive) or non-HEV cases (RDT-negative).

Study design

We conducted two separate analyses in this study. We first conducted an HEV and suspected cases cluster analysis on spatial and temporal level. Secondly, we conducted an exposure analysis, in which we investigated whether exposure to unsafe water during an incubation period of six weeks was a determinant for confirmed HEV infection. We used a significance level of $\alpha \leq 5\%$ in all analyses.

Cluster analysis

For this cluster analysis and its visualisation, we employed the Kulldorff's Spatial Scan Statistic (SaTScan^{TM}) and QGIS 2.18.16. We performed a cluster analysis in order to test the impact of water treatment interventions on the magnitude of the outbreak. We assumed that in town blocks of

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Am Timan that had functional and correctly chlorinated water points, AJS and HEV incidence would be lower. We also expected that AJS and HEV incidence would decrease in areas as soon as the water and hygiene activities commenced during the outbreak response. Thus, we tested whether there was an area of the town that was particularly at risk for high AJS and HEV incidence between September 2016 and April 2017. For both the spatial and temporal cluster analysis, we calculated estimates for the relative risk of AJS and HEV on the block level (spatial analysis) or within a specified time-period (temporal analysis).

For the spatial cluster analysis we restricted the reporting of clusters to the most likely clusters. Thus, no identified cluster could be located within a more likely larger cluster. Due to the range of the standard incubation period for HEV (5–6 weeks) and the assumption that detection of AJS/HEV infection would be delayed in comparison to the time of infection (due to bi-weekly household visits as part of the surveillance activities), we set the time aggregation to 14 days. This meant that there was a moving window of 14 days for which the cases were aggregated. We also mapped the results for better visualisation.

We aggregated all AJS and HEV cases on the block level of their household and used the block population as the underlying population at risk. Population information by block was available from surveillance data. We defined the block's location as the centroid of each block. Base maps for the study area were retrieved from OpenStreetMap (see: www.openstreetmap.org/copyright). For both the spatial and temporal cluster analysis we ran two separate scans, one for confirmed HEV cases and one for AJS cases.

For the spatial cluster analysis, we performed a retrospective purely spatial analysis scanning for clusters of high and low incidence rates, using the Poisson model. As the outbreak occurred in a small study area (ca. 12 km^2), we set the maximum cluster size of all scans to 1 km radius and 50% of the population at risk (default setting). For the temporal cluster analysis, we used a retrospective, purely temporal model, using a Poisson distribution and a maximum temporal cluster size of 50% of the period at risk (default setting).

Association of disease and water source and water quality

We examined whether the exposure to unsafe drinking water was a determinant for developing HEV within the incubation period of 5–6 weeks (29–42 days). We classified cases as: confirmed HEV cases, suspected cases (AJS cases) and non-HEV cases. For each of these cases, we calculated the distance from their household to the closest water point based on line of flight from the household. We did not include the shortest path from each household as the quality of data were insufficient for this part of Chad. Water points in the study area were categorised into open reservoirs (concrete tanks) and pump-operated (manual hand/foot pumps, motorised boreholes).

We defined a day of 'unsafe' water as any day for which the measurement of free residual chlorine (FRC) fell below 0.5 mg/l at each respective water point. This cut-off was used, as the current WHO guidelines consider an FRC level of 0.5 mg/l to be effective at disinfecting water and thus making it safe for consumption (World Health Organization 2014). Chlorination at water points was performed daily during the course of the outbreak, but FRC testing was generally only performed on weekdays as a monitoring tool. Thus for Saturdays and Sundays (when FRC measurements were not conducted), we classified water points as having 'safe' water if they were covered water points (pump-operated) and having 'unsafe' water if they were not covered (open reservoirs). This is based on our assumption that these uncovered water points would be at higher risk for recontamination, as people collected water by dipping in their containers into the reservoirs.

For each affected individual (confirmed, suspected, and non-cases) we calculated the total number of days they were exposed to unsafe water (FRC < 0.5 mg/l) from the water point closest to their household during the most likely incubation period of 5–6 weeks (i.e. day 29–42) before the onset of symptoms.

We compared the proportion of safe water sources by case classification and estimated the association between water source and case status by calculating odds ratios (OR) and their respective 95% confidence intervals (95%CI).

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This analysis was performed using QGIS 2.18.16, R version 3.6.0 and Stata 13.

RESULTS

Study population

The outbreak characteristics and population groups most at risk during the Am Timan HEV outbreak are described in previous work (Spina *et al.* 2017; Vernier *et al.* 2018). For the 1,443 suspected cases identified during the outbreak, the household location was available for 1,052 people (72.9%). Of these, 860 (81.7%) people were living in 623 different households located within the defined study area and thus met the inclusion criteria for this study. Of those included in the study, 42 individuals were confirmed HEV cases, 72 were non-HEV cases and 746 remained suspected cases (AJS cases).

Spatial cluster analysis

Acute jaundice syndrome

The AJS risk estimates were highest in the blocks in the north and lowest in the south of the town. The scan detected two high risk clusters: one in the north-west with an area of 1.1 km^2, with 75 observed AJS cases compared to 26.2 that would have been expected assuming a homogenous case distribution (relative risk: 3.06, p-value <0.001), and one in the north, spanning 3.1 km^2, counting 350 observed AJS cases compared to 182.5 expected cases (relative risk: 2.65, p-value <0.001). Two low-risk clusters were also detected in the south, one with an area of 3.1 km^2 and counting 140 AJS cases compared to 301.9 that would have been expected (relative risk: 0.35, p-value <0.001), and one with an area of 2.1 km^2 and counting 3 observed AJS cases compared to 41.7 expected cases (relative risk: 0.068, p-value <0.001) (Figure 1).

Hepatitis E Virus

We observed 42 confirmed HEV cases in the study area. The HEV risk estimates of each block showed a heterogeneous distribution, with the highest risk estimates in the north-west and central areas. The cluster scan detected one significant high-risk HEV cluster in the center of the study area, spanning 0.3 km^2. This cluster included 11 HEV cases, compared to 2.4 expected cases, resulting in a relative risk of 5.99 (p-value: 0.038) (Figure 2).

Temporal cluster analysis

We detected one high-risk temporal AJS cluster between December 12th 2016 and February 4th 2017. This cluster included 608 AJS cases, compared to 323 expected cases, assuming a homogenous case distribution during this period (relative risk 4.9, p-value: 0.001). Hence, more than 75% of observed suspected cases were reported in this 2-month period. No low-risk cluster was observed (Figure 3).

We detected one high-risk temporal HEV cluster between September 19th and October 30th 2016, which coincided with the start of the outbreak. During this period, 20 HEV cases were observed compared to the 6.5 cases expected, resulting in a relative risk of 5.0 (p-value: 0.002). No low-risk cluster was observed (Figure 3).

Association of disease to water source and quality

Out of 85 operational water points identified by MSF, 74 water points were located within the study area and were the closest water source to at least one study participant. Out of these, 34 were open reservoirs (45.9%) and 40 were pump-operated (54.1%). Forty percent of confirmed cases had a pump (foot or hand pump) as their closest water source (12/30; 40%). Almost half of suspected cases (356/754, 47.2%) had a pump as their closest water source. Comparatively, 31.5% of non-HEV cases had pumps as their closest water source (24/76). Cases were more likely than non-HEV cases to have pumps as their closest water source, but this finding was not statistically significant (OR: 1.4, CI95%: 0.6–3.5; $p = 0.4$).

Association of disease and water quality

Confirmed HEV cases had a higher median number of days of exposure to unsafe water compared to non-HEV cases and suspected cases (Kruskal-Wallis Chi Square:

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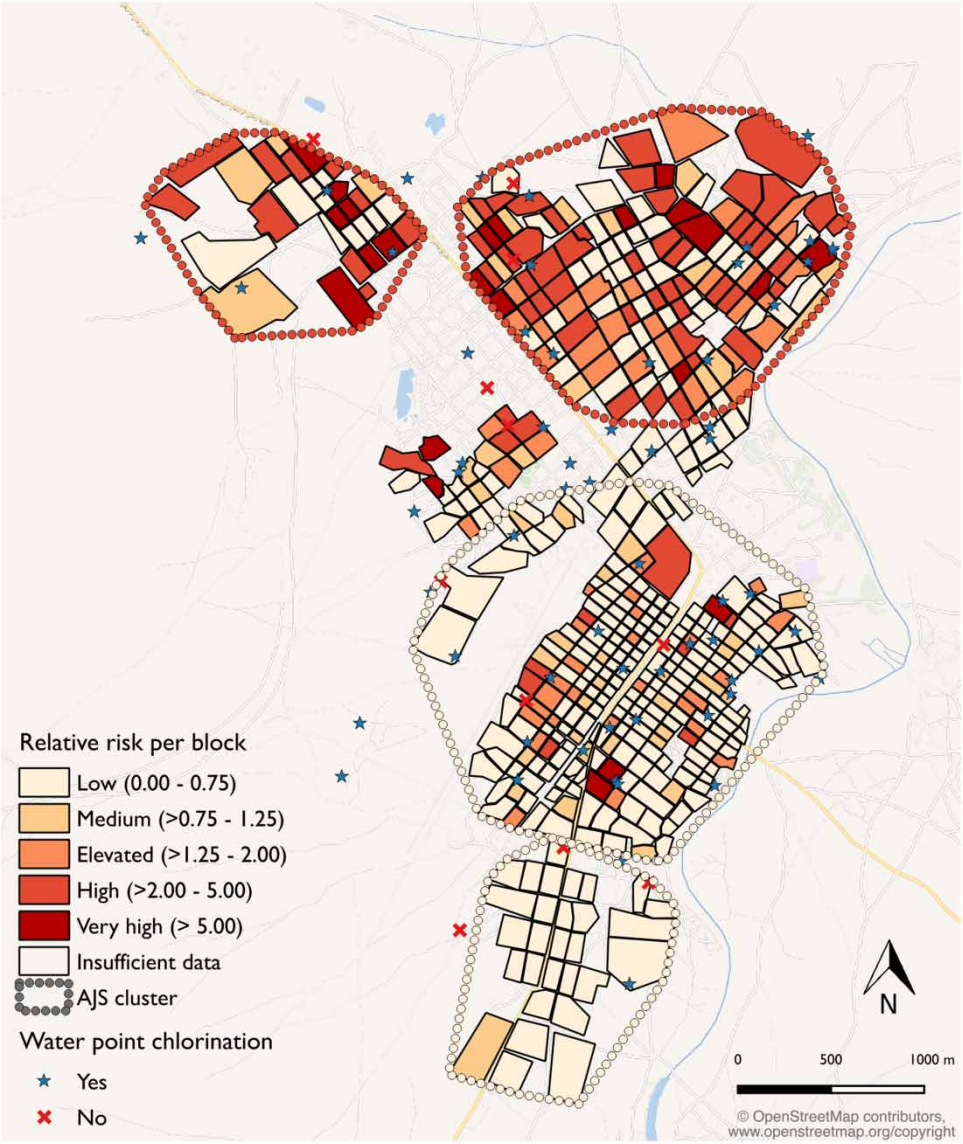

Figure 1 | Relative risk for developing acute jaundice syndrome (AJS), stratified by town block. Clusters are outlined according to their risk category. Water points are classified according to their chlorination status.

15.5; $p < 0.001$). The median exposure time to unsafe water was 14 days for confirmed HEV cases (IQR: 1–14; mean: 8.3), 4.5 days for non-HEV cases (IQR: 0–14; mean: 6.5 days), and 2 days for suspected cases (IQR: 0–12; mean: 4.9).

DISCUSSION

Our results indicate that transmission of HEV in outbreak settings is most likely through mixed routes. First, we showed that confirmed HEV cases were more likely to have consumed unsafe water for more days compared to those without confirmed HEV infection. As data on confirmed cases were more restricted to the start of the outbreak when most of the diagnostic activities were ongoing, this finding suggests that contaminated water played a role in the early days of the outbreak. The finding that non-HEV cases had more days of exposure to unsafe water compared to suspected cases is probably due to the fact that suspected cases may have had mixed aetiologies

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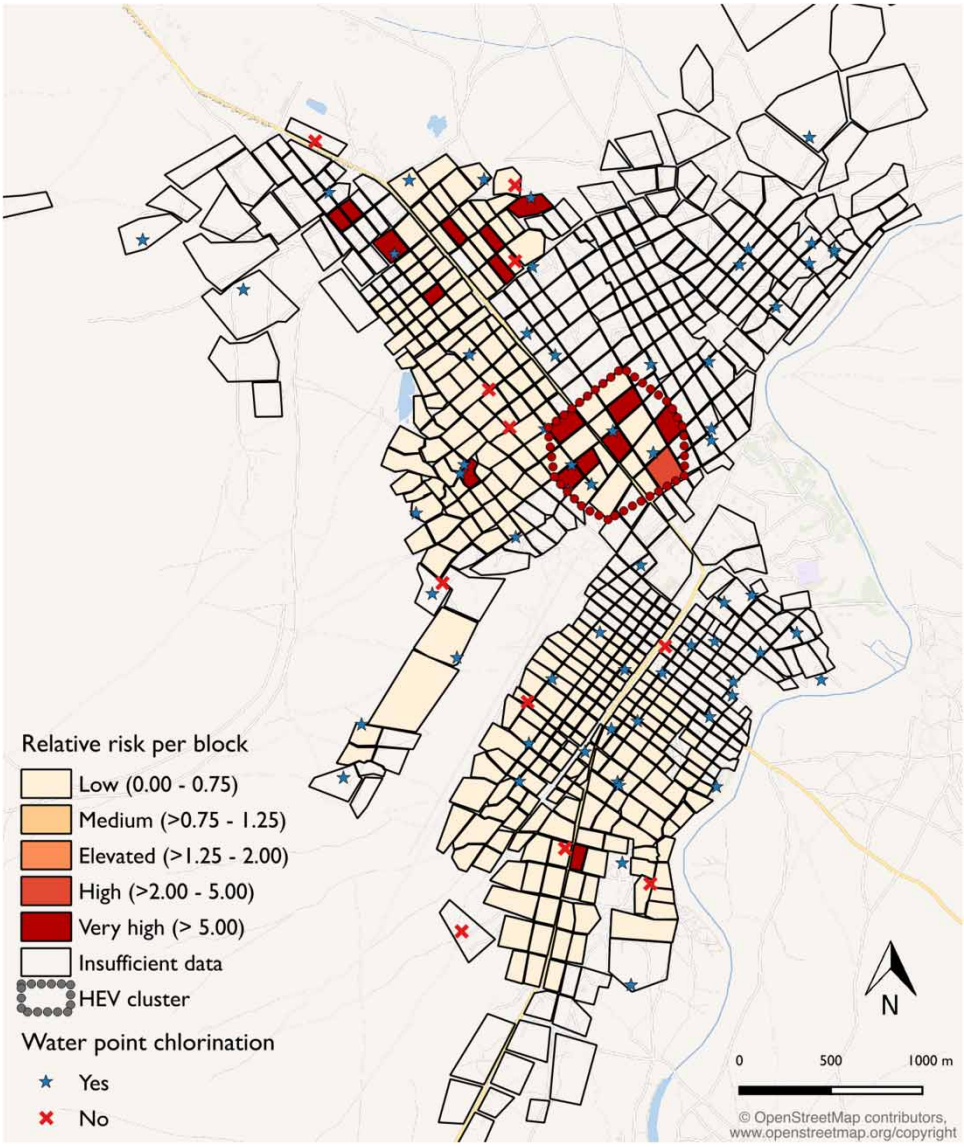

Figure 2 | Relative risk for confirmed hepatitis E (HEV), stratified by town block. The cluster is outlined according to its risk category. Water points are classified according to their chlorination status.

responsible for their symptoms. However, the spatial and temporal cluster analysis showed that confirmed and suspected cases clustered in specific, but non-linked areas of the city and different time periods. These findings confirm the understanding that a single and continuous contaminated source was not the main vehicle of transmission for the duration of the outbreak.

Other descriptions of HEV outbreaks, and other epidemiological studies also conducted in Am Timan, show that large-scale HEV outbreaks cannot be linked to a single source of transmission (Guthmann *et al.* 2006; Teshale *et al.* 2010a, 2010b; Elduma *et al.* 2016; Leung *et al.* 2017; Spina *et al.* 2017). Our findings corroborate these results. A combination of consumption of unsafe (untreated) water and a non-negligible degree of person-to-person transmission of HEV, mostly through exposure to poor hygiene facilities and practices, best explains the outbreak dynamics of this current outbreak. We think that a 'seeding event' of consumption of unsafe water happened before the outbreak was detected and possibly continued to be the driving factor

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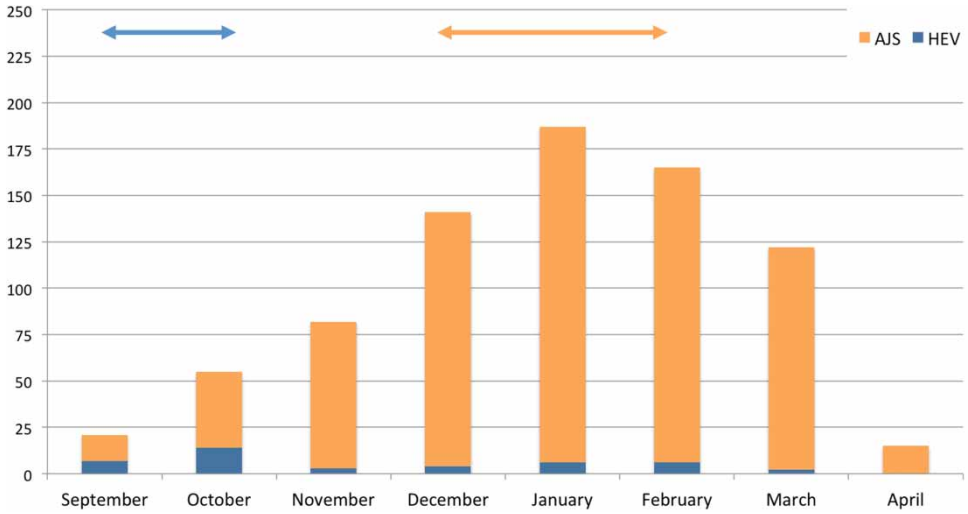

Figure 3 | Temporal distribution of acute jaundice syndrome (AJS) cases and confirmed hepatitis E (HEV) cases from September 2016 to April 2017, by month of onset. Arrows indicate duration of temporal high-risk clusters.

in the early days of the outbreak. In response to the outbreak, water treatment, hygiene and surveillance activities were implemented, and the predominant transmission dynamic subsequently shifted from water-based to the person-to-person route. This would explain the inability to match spatial and temporal clusters of confirmed and suspected cases in the current study.

The high-risk spatial cluster of confirmed HEV cases identified in the centre of the city may be a surveillance bias due to its close vicinity to the hospital where diagnostic testing was performed. Thus, persons with AJS who were referred to the hospital would have had easier access to testing services. Also, anecdotal evidence suggested that the water and sanitation conditions in this part of Am Timan were poorer than in other parts of the city (e.g. inadequate safe water, inadequate sanitation facilities and poor access to these).

It is accepted that the current guideline value for chlorination of water (FRC 0.5 mg/l) is effective in inactivating HEV (Guerrero-Latorre *et al.* 2011; Girones *et al.* 2014), however, in this outbreak we were unable to demonstrate that the use of treated water from protected water sources measurably reduced the risk of developing AJS or HEV infection. This either suggests that the chlorination activities were equally ineffective at all types of water points during the outbreak, or that we did not have enough (reliable) data to be able to make a more refined analysis. We accept that demonstrating any health impact is an ongoing challenge for the water and sanitation research community, particularly when dealing with outbreaks in humanitarian settings. This is confirmed in other published research, where the treatment of water at the point of use has appeared to reduce the risk of water related diseases (mainly cholera and diarrhoeal diseases), however the quality of this evidence remains very limited (Ramesh *et al.* 2015; Yates *et al.* 2018).

As the data were collected in a humanitarian setting, this study did face severe limitations that we were unable to mitigate with the current design. Even though the water treatment activities targeted 74 operational water points throughout the town, we know that there were several other water points in use that we were not able to account for. In addition, despite a broken chlorine dosing pump, one of the town's two water supply networks (notably, the one located in the north of the town), continued to distribute water throughout the outbreak, to a limited but unknown number of households. These aspects could have increased the exposure of people to unsafe water. We were unable to quantify the impact of this or control for it in the present study. Only 13% of the total AJS case numbers within the study area were confirmed HEV cases. Thus, our analysis around safe water sources and their association with developing HEV infection was based on a small and (due to the RDT inclusion criteria) biased dataset of confirmed HEV

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cases. Equating our findings for HEV cases with those for AJS cases is therefore not appropriate. Furthermore, apart from hygiene promotion focussing on promoting use of latrines and handwashing with soap after defecation, no intervention targeting sanitation was implemented in this outbreak. Therefore, we are unable to ascertain if poor sanitation practices exacerbated the outbreak or negated the effectiveness of those interventions implemented for safe water supplies and hygiene promotion.

Furthermore, as previously noted, the data used in this study were collected under operational conditions during an active large-scale outbreak response. As such we acknowledge that the design and planning of the data collection was notably less rigorous than could be expected in a controlled scientific study. All previously highlighted limitations and conditions are intrinsically linked to the humanitarian setting, and are shared by any post-outbreak evaluation such as the one presented in this study. Hence we consider our findings not only to be important as they contribute to the existing evidence of safe water interventions during HEV outbreaks, but also to encourage other researchers and health-care workers to publish important findings based on data collected during large-scale outbreaks.

CONCLUSIONS

The outbreak in Am Timan is one of the better-described HEV outbreaks of genotype 1e. It has long been suspected that the propagation of large HEV outbreaks is not solely due to the consumption of contaminated water, but also other modes of transmission. Our study suggests that there was not a single contaminated source during this outbreak, as high risk and low risk clusters did not coincide with specific water sources. Thus it confirms that this outbreak was likely propagated by mixed, but shifting, modes of transmission. While water treatment activities remain indispensable in the control of HEV and other water-borne disease outbreaks, we urge emergency responders to broaden their scope to a more multidisciplinary approach that also targets other modes of transmission. This particularly holds true for prolonged outbreaks, as the potential for person-to-person transmission increases with time. We also recommend that in future outbreaks when water treatment interventions are implemented, every effort is made to ensure the supply of safe water is uninterrupted. Where resources are limited, this might require a much more targeted strategy.

HEV should be considered a neglected tropical disease (Azman *et al.* 2019) and any evidence from real outbreak settings should be used to improve our understanding of how to respond to these situations. We have highlighted the spatial and temporal analytical methods, which could be employed in future outbreaks to improve the understanding of HEV transmission and hence the public health response. Only by trialing new methods, continuing to improve data collection, and sharing results of these efforts can a solid evidence base for water and sanitation interventions and their impact on outbreak dynamics be built.

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