

## Micro-hotspots of Risk in Urban Cholera Epidemics

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### Abstract

Targeted interventions have been delivered to neighbors of cholera cases in major epidemic responses globally despite limited evidence for the impact of such targeting. Using data from urban epidemics in Chad and D.R. Congo we estimate the extent of spatiotemporal zones of increased cholera risk around cases. In both cities, we found zones of increased risk of at least 200-meters during the 5-days immediately following case presentation to a clinic.

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Risk was highest for those living closest to cases and diminished in time and space similarly across settings. These results provide a rational basis for rapidly delivering targeting interventions.

**Key Words:** vibrio cholerae; clustering; ring vaccination; cholera; targeted interventions

## **Background**

Cholera epidemics in sub-Saharan Africa produce a large proportion of global cholera-mortality and continue to wreak havoc on already fragile nations(1,2). Targeting cholera interventions to transmission hotspots, or areas of elevated transmission intensity in urban areas may be the best control strategy when resources are constrained(3,4). In recent years, rapid response teams have been proposed as an important way to fight cholera in cholera prone countries. These teams can quickly provide emergency water, sanitation and hygiene interventions (e.g., point-of-use water treatment and basic hygiene educational materials), and sometimes oral cholera vaccine to neighbors of cholera cases(5,6). However, there is limited evidence regarding the impact or optimal spatial scale of these targeted interventions.

Cholera transmission is thought to occur through two modes of exposure:(1) environmentally-mediated exposure, often due to fecal contamination in the broader environment, and (2) “direct” exposure to an infected individual (e.g., being served food directly contaminated by a case)(7). The mix of environmentally-mediated and direct exposure shapes the spatiotemporal distribution of cases within an epidemic. Evidence from Bangladesh and other locations have shown that direct transmission plays an important role in cholera transmission leading to elevated risk when residing close to an incident case(8). Likewise, those living close together will often share risk factors and access shared water sources(9).

Characterizing the small-scale spatiotemporal distribution of cholera cases in epidemics can provide new and useful insight into the mechanisms of transmission ultimately highlighting a path for efficient targeted cholera control. Here we use high-resolution data from epidemics in two African cities separated by thousands of kilometers, N’djamena in Chad and Kalemie in D.R. Congo, to estimate spatiotemporal windows of increased cholera risk among neighbors of incident cholera cases.

## **Methods**

### *Setting*

Chad has experienced cholera outbreaks at least once every 4-years since the 1990’s. Médecins Sans Frontières (MSF) assisted the Chad Ministry of Health (MoH) to respond to a cholera outbreak that started in mid-April 2011 in which most cases occurred in the capital, N’djamena, home to nearly one million people. On 22-June-2011 the

MSF team, with the assistance of other collaborating agencies, began systematically collecting household GPS coordinates through a home visit to each suspected cholera case presenting at one of the official cholera treatment centers/units in N'Djamena(Figs S1,S2). As the number of cases per day began to rapidly increase in early October, MSF modified their protocol to collect household coordinates for one out of every three cases.

Kalemie is located on Lake Tanganyika in eastern D.R. Congo and serves as a large urban trading center for the region. Cholera tends to occur annually in Kalemie with a seasonal peak within the last few months of the year. In Kalemie, MSF has worked with the MoH on comprehensive cholera prevention and control strategies since 2008. From 1-Jan-2013 to 15-Jan-2014, MSF and the MoH collected the household coordinates for each suspected cholera case seeking care at the main diarrhea treatment center in Kalemie, Centre de Traitement de Maladie Diarrhéique(Figs S1,S3).

In both settings, suspected cases were defined using a modified WHO case definition (acute watery diarrhea regardless of age). Teams in both countries were trained in the use of the GPS devices to ensure stable and accurate readings.

### *Statistical Approach*

To characterize the spatiotemporal clustering of cases, we calculated  $\tau$ , a relatively new global clustering statistic estimating the relative risk of the next case occurring at a distance  $d$ , within  $t$  days after a suspected ('primary') case presents at a health facility compared to the risk of the next case occurring anywhere in the population (i.e., the entire city) during the same period. We calculated  $\tau$  using the `IDSpatialStats` package (10), with a 50-meter moving window estimated every 10-meters (except for distances <50m, supplement). This statistic is robust to heterogeneities in how the population is distributed (i.e., differences in population density across a city) and has been shown to be insensitive to dependencies in reporting rates that may vary in space (e.g., distance from health centre) and time (e.g., epidemic phase)(10,11). We calculated 95% confidence intervals as the 2.5<sup>th</sup> and 97.5<sup>th</sup> quantiles from 1,000 bootstrap replicates.

We focused  $\tau$  at distances up to 500m from a 'primary' case and within 5-day windows up to 30-days after a primary case presented to a facility. We considered the zones of increased risk around incident cases to extend until the 95% confidence intervals cross unity for at least two consecutive points (i.e.,  $\geq 20$  consecutive meters). Since this classification may underestimate the extent of the zones of increased risk due to small sample size, we calculated the median distance at which  $\tau$  dropped below 1.2 (e.g., minimum 20% elevated risk) for each bootstrap as an alternative measure. Since it is unlikely that a targeted public health response can be mounted the same day a case seeks care, we also estimated zones of increased risk around incident cases, excluding the day of case presentation(day 0). Code and data from these analyses are at [https://github.com/scottyaz/cholera\\_microhotspots](https://github.com/scottyaz/cholera_microhotspots).

## Results

In Kalemie, DRC, household coordinates were successfully recorded for 1,077 of 1,146 suspected cholera cases reporting to the main diarrhea treatment center from January-2013 through January-2014. In N'djamena, household coordinates were recorded for 1,692 of the 4,359 suspected cases reporting to healthcare facilities within the city. All case households were visited from June-22-2011 and one in three randomly selected case-households visited from August through the end of the outbreak (December) due to logistical constraints.

### *The first five days*

Within the first five days after a suspected cholera case presented for care, the zone of increased cholera risk extended to at least 220m from the home of the suspected cases in Kalemie and 330m in N'Djamena. Zones of increased risk defined using an alternative definition ( $\tau < 1.2$ , Table S1) were similar. Those living within 40m of another case (including those in the same household) had a 121.1-fold (Kalemie; 95%CI 89.7-164.8) higher risk than the general population of becoming a cholera cases within five days of the primary case in Kalemie, and a 32.4-fold (95%CI 25.3-41.0) higher risk in N'Djamena (Figures 2A-B). Those living 75-125m from a case had 2.0 (Kalemie; 95%CI 1.0-3.2) and 3.9 (N'Djamena; 95%CI 2.7-5.4) times the cholera risk in the five days after the initial case compared to those anywhere in the city.

Within these first five days after a case presented for care, the most elevated risk occurred up to one day after case presentation. The zone of elevated risk within one day of a primary case extended to at least 340m in N'Djamena (like the estimate for the first five days), but only 80m in Kalemie. During this time-frame, those within 40m of a primary case had a 189.7-fold (Kalemie; 95%CI 139.7-261.9) and 55.4-fold (N'Djamena; 95%CI 42.3-72.4) increased risk of presenting as a cholera case compared to those anywhere in the cities. From 75-125m from a primary case, this risk decreased to 1.9 (95%CI 0.7-3.6) in Kalemie and 5.9 (95%CI 3.8-8.7) in N'Djamena.

After excluding cases occurring the same day as a primary case (day 0), the zone of increased risk was approximately the same size as estimated when those cases in N'Djamena (310m), however, this reduced to 90m in Kalemie (Figures 1C/1D). During this time-period, those within 40m of a primary case had a 2.7-fold (Kalemie; 95%CI 1.5-4.3) and 3.9-fold (N'Djamena; 95%CI 2.7-5.2) increased risk of presenting as a case compared to those anywhere in the cities. From 75-125m from a primary case, the risk was 1.7 (95%CI 0.8-2.9) in Kalemie and 2.0 (95%CI 1.2-3.0) in N'Djamena.

### *Diminishing risk over time*

In secondary analyses, we explored how the elevated risk changed with time at key distances away from primary cases' households to better illustrate the dynamic increased risk zone. We find that at 20m, a scale likely representative of a household and/or first-degree-neighbours, significant elevated risk disappeared by 3 (Kalemie) and 6 (N'Djamena) days after the presentation of the primary case (Figure 2A), with the relative risk point estimates remaining below 1 in both locations after 7 days. At 50m from the primary case household, risk remains

elevated for slightly longer (~7 days). At 150m from the primary case household the elevated risk period does not start until 2-3 days after case presentation although it still ends by day 5-6 (Figure 2).

## Discussion

These results reveal similar spatiotemporal patterns of cholera cases across epidemics in two African cities. We find clear evidence for zones of increased risk extending at least 200m from the household of a cholera case within the first five days after he/she presents for care, with most elevated risk within the first days after the case and within 100m of the household. While not as dramatic, these zones of risk persist even after excluding those cases that appear on the same day. These suggest that interventions focused within at least 100m around cases' households implemented within one week of case presentation may be an efficient cholera control strategy.

While the similarity in the spatiotemporal structure between two independent settings provides reassurance that these results reflect some shared biological or structural properties of cholera transmission, there are several limitations to these analyses. First, we relied on suspected cases seeking care at health facilities. Analyses of epidemics in similar settings have shown that the true proportion of confirmed cholera cases among suspected cases can vary widely and we expect that this misclassification would often dilute the risk ratios, biasing results towards the null, except in cases with a simultaneous outbreak of a directly transmitted disease. On the other hand, people living near suspected cases might be more likely to seek care due to concerns about cholera, which could create an upward bias. In N'Djamena, we only collected a random subset of cases household locations at the end of the epidemic, however secondary estimates of clustering at different points in the epidemic suggest no major differences (Fig S4-S5). If cases within households (or neighbors) tended to seek care close together in space and time relative to the case sampling fraction in N'Djamena, we may have captured too few pairs 'related cases,' thus biasing our estimates of spatial risk towards unity. While there were likely people who did not seek care with mild and asymptomatic cholera, if they were randomly distributed with respect to their spatiotemporal distance from another case, our estimates would vary little. However, if there was spatiotemporal clustering in non-reported cases, our results could be biased in either direction. While  $\tau$  is related to the more commonly used K-function and pair-correlation functions (11), it allows us to estimate second-order clustering without information on the underlying population structure, but instead with data on the natural history of cholera (e.g., the serial interval) and the overall distribution of cases. Uncertainty in the assumed serial interval was not captured in our estimates. Finally, given that we are dividing our data into spatial and temporal windows, the sample size can get small and we may not have the power to detect low levels of elevated risk. Thus, the true zones of increased risk may be larger than suggested by  $\tau$ 's 95% confidence intervals.

Case-area targeted interventions are not a new concept and have been implemented for diseases like polio and smallpox. In many cholera epidemics, case-area targeted interventions, ranging from hygiene promotion to antibiotic prophylaxis, are part of the standard protocol, although they are rarely documented or evaluated in published literature (12, 13). Careful evaluation of the timing, extent and type of case-area targeted interventions are warranted. These interventions may not be ideal across all settings based on both the available human and other resources (e.g., median 1011 people in 200m rings in N'Djamena, Figure S5) and the epidemic dynamics.

Identifying when (e.g. lull-periods between epidemics(14)) and where case-area targeted interventions may have the biggest impact is key.

These results shed new light on the small-scale spatial structure of cholera transmission and point towards the possibility of conducting effective and efficient targeted interventions in urban cholera epidemics. While the effectiveness of case-area targeted interventions will depend both on the types of interventions and the speed at which they are delivered, this work serves as rationale for their use.

## Footnotes Page

Conflict of Interest: All authors declare that they have no conflict of interest.

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Tables and Figures:

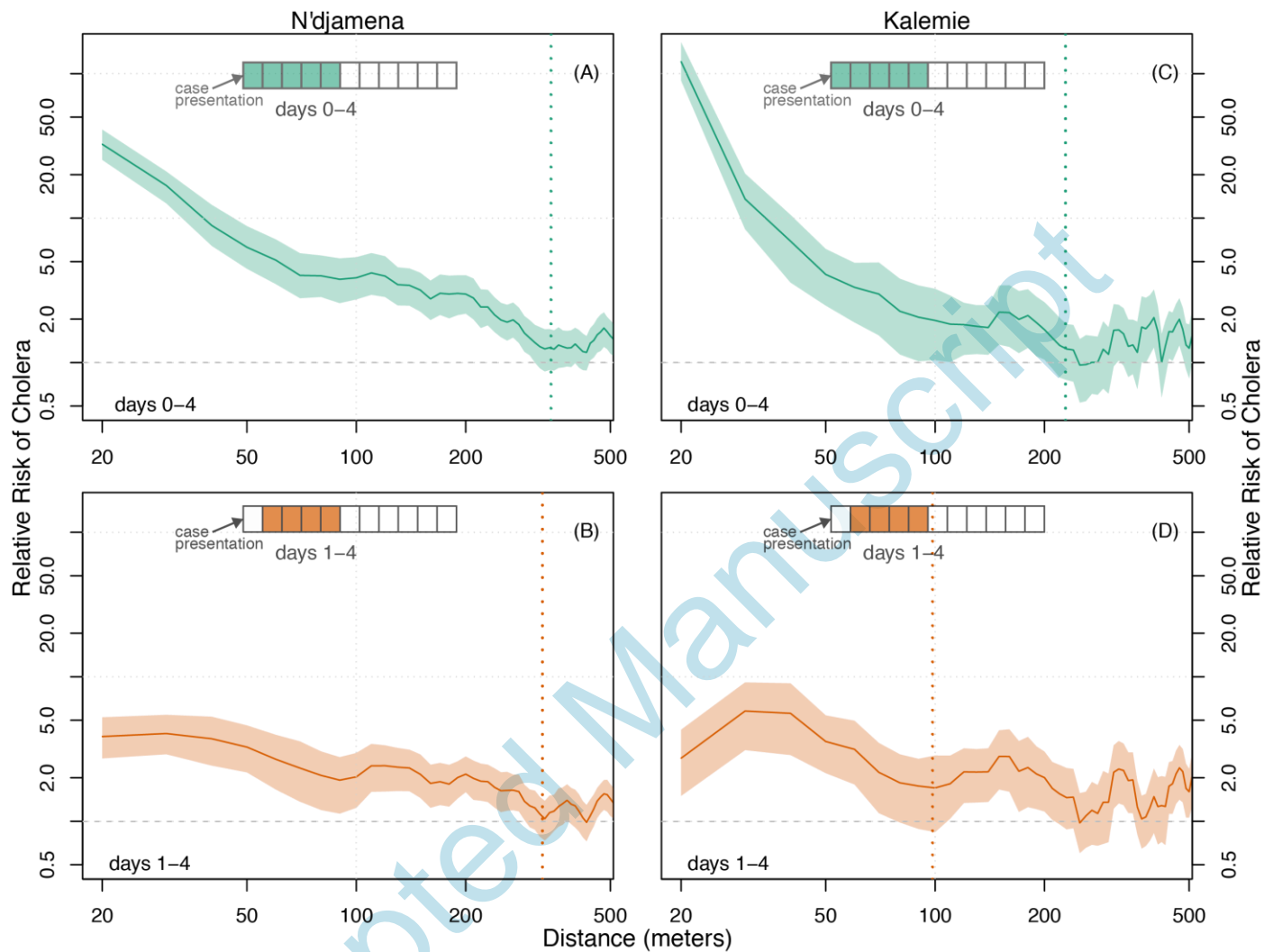


Figure 1. Estimates of the relative risk of the next cholera case being within a specific distance to another case (x-axis) within either days 0-4 (green, A-B) or days 1-4 (orange, C-D) compared to the risk of the case occurring anywhere in the population. Dashed lines represent the spatial extent of the zones of increased risk as defined by the first point at which the 95% confidence intervals cross unity over a 20-meter interval (i.e., over two consecutive 10-meter points).



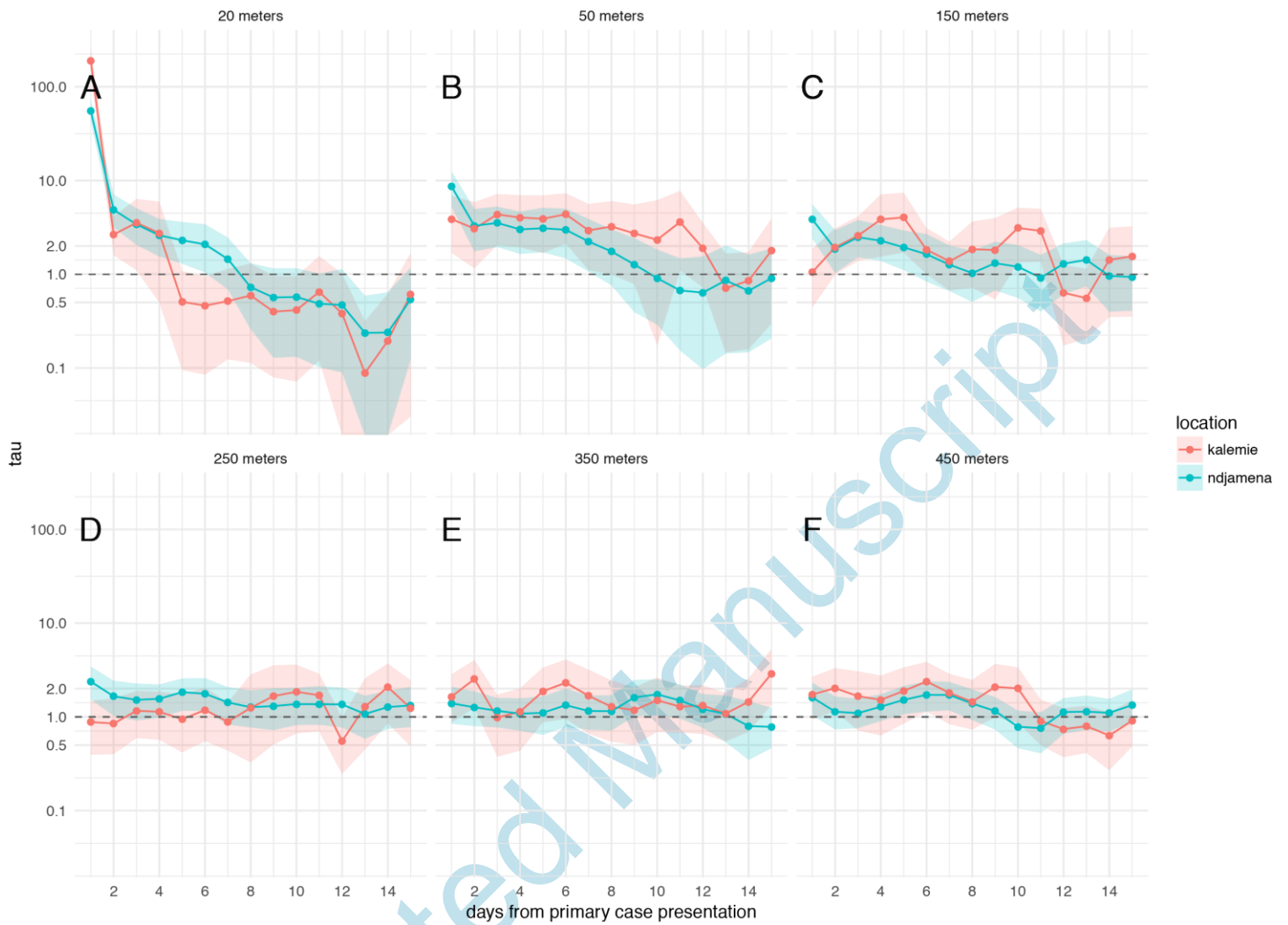


Figure 2. Estimates of the relative risk of the next cholera case occurring at different distances from a primary case (panels illustrate 20-450 meters) compared to the risk of the case occurring anywhere in the population by time from primary case presentation (y-axis). N'Djamena estimates and 95% confidence intervals are shown in green and those from Kalemie are shown in orange.