Using Modelling to Disentangle the Relative Contributions of Zoonotic and Anthroponotic Transmission: The Case of Lassa Fever

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Abstract

Background: Zoonotic infections, which transmit from animals to humans, form the majority of new human pathogens. Following zoonotic transmission, the pathogen may already have, or may acquire, the ability to transmit from human to human. With infections such as Lassa fever (LF), an often fatal, rodent-borne, hemorrhagic fever common in areas of West Africa, rodent-to-rodent, rodent-to-human, human-to-human and even human-to-rodent transmission patterns are possible. Indeed, large hospital-related outbreaks have been reported. Estimating the proportion of transmission due to human-to-human routes and related patterns (*e.g.* existence of super-spreaders), in these scenarios is challenging, but essential for planned interventions.

Methodology/Principal Findings: Here, we make use of an innovative modeling approach to analyze data from published outbreaks and the number of LF hospitalized patients to Kenema Government Hospital in Sierra Leone to estimate the likely contribution of human-to-human transmission. The analyses show that almost 20% of the cases at KGH are secondary cases arising from human-to-human transmission. However, we found much of this transmission is associated with a disproportionally large impact of a few individuals ('super-spreaders'), as we found only 5% of human cases result in an effective reproduction number (*i.e.* the average number of secondary cases per infectious case) >1, with a maximum value up to 12.

Conclusions/Significance: This work explains the discrepancy between the sizes of reported LF outbreaks and a clinical perception that human-to-human transmission is low. Future assessment of risks of LF and infection control guidelines should take into account the potentially large impact of super-spreaders in human-to-human transmission. Our work highlights several neglected topics in LF research, the occurrence and nature of super-spreading events and aspects of social behavior in transmission and detection.

Introduction

Diseases at the animal-human interface are in general subjected to different modes of cross-species transmission: animal-to-animal, animal-to-human, human-to-human and even human-to-animal. Estimating the relative contribution of each is of fundamental importance for the planning and implementation of appropriate infection control and preventive measures. This can be an extremely difficult task if humans and animals share the same physical space, and/or if experimentation (*e.g.* to quantify the probability of animal-to-animal transmission) is subjected to serious limitations. This is the case of Lassa fever (LF), a rodent-borne disease endemic in West Africa. Despite its clear zoonotic origin, there are strong arguments, listed below, to hypothesize that a significant proportion of the burden of LF in humans arises from human-to-human transmission. The aim of this work is to test whether or not patterns in the epidemic curve describing the cases of LF observed in Sierra Leone [1], are compatible with patterns observed in chains of pure human-to-human transmission recorded in nosocomial and extra-nosocomial outbreaks [2,3].

Lassa fever is an acute, viral hemorrhagic disease caused by Lassa fever virus (LASV), an enveloped RNA virus of the Arenaviridae. The disease was first recognized in the village of Lassa, Nigeria in 1969, which caused the death of two missionary-nurses and the grave illness of a third [4]. However, cases consistent with LF from the eastern part of Sierra Leone can be traced back to 1956 [5]. Since the identification of LASV, human-to-human transmission has been documented in several nosocomial outbreaks (*e.g.* [2,3] and also [6] for a review), leading to an initial perception that the virus was both highly contagious and virulent [4]; this resulted in stringent requirements for containment of the patients [7]. Soon after, its zoonotic origin was recognized and *Mastomys natalensis*, one of the most common African rodents, was identified as the reservoir of the virus [8]. The risk of nosocomial transmission was shown to be dramatically reduced by using simple barrier nursing method [7,9–11], suggesting that the risk of human-to-human transmission might be negligible.

These findings support an apparent, modern-day consensus that in the epidemiology of the disease, human-to-human transmission plays a less important role compared to zoonotic transmission. Accordingly, it has been suggested that patients with LF in non-endemic countries should not be confined to biosafety level 4 containment [10], and patient containment guidelines issued by the Centers for Disease Control (CDC) and the UK Department of Health and Social Security, in the past have been amended to be less restrictive (see [11,12], also [13] and its previous versions).

This narrative concerning the relative importance of human-to-human transmission for LASV, however, requires re-evaluation as there are important indications of human-to-human transmission. More precisely, one of the early nosocomial outbreaks, in Jos, Nigeria (see [2], Fig. 1 and also the Supporting Information, S2 Text) was triggered by an index case that transmitted to possibly 15−23 others in the hospital, with no indication of iatrogenic transfer. Further cases of extra-hospital transmission within a single family (five from the same family, *EE*, *EE*2, *SE*, *TI*, and *FT* who likely initiated the chain) were reported, here and

throughout we refer to this chain as an 'extra-nosocomial' chain. Haas *et al.* [14] investigated secondary transmission after an imported case of LF into Europe and found that one of 149 contacts that were tested serologically, a physician who examined the patient on day 9 of illness, had become infected. The authors concluded that, during the initial phase of symptomatic LF the risk of transmission is low, but it may increase with progression of disease and increasing viral excretion. Emond *et al.* [15] described a case of LF in the UK in which the virus was isolated from urine 16 days after the acute phase had ended, despite not being detected earlier. The virus may also be found in pharyngeal secretions for 3−4 weeks after the onset of clinical signs [16]. In an experimental model, Stephenson *et al.* [17] showed the ability to infect guinea pigs and cynomolgus monkeys with LASV via the respiratory route and Peters *et al.* [18] demonstrated fatal LASV transmission to monkeys through being held in the same room for 12 days with inoculated rodents. Sagripanti *et al.* [19], in a dark room at ambient laboratory temperatures controlled between $20°C$ and $25°C$ and $30−40\%$ relative humidity, showed that the time required for a 90% reduction in viral load of LASV in glass containers was >58 hours and was 9.7 days for a 99.99% relative humidity. Also, Kernéis *et al.* [20] identified that risk factors for positive seroconversion to LASV included either having received a medical injection, or having lived with someone displaying a haemorrhage, in the previous twelve months. No factors related to contact with rodents were identified. Similarly, McCormick *et al.* [21] reported a lack of correlation between human LASV-specific IgG prevalence and either the level of domestic infestation by *Mastomys*, or the presence of LASV infection in *Mastomys*. These observations, taken together, suggest that a significant (if perhaps variable) proportion of the burden of LF might be associated with human-to-human transmission.

Estimating the contribution of human-to-human transmission of LASV and related patterns of transmission (*e.g.* existence of super-spreaders) is of fundamental importance when considering risk assessment and control of LF and related diseases such as the one caused by the arenavirus, Lujo virus [22], not least because LF is one of the more common haemorrhagic fevers exported from endemic areas [23–28]. In addition, perceiving LF as essentially a zoonotic disease only acquired from rodents with little or no infection arising from human beings, may have prevented investigations of the role, if any, of human-to-rodent transmission (i.e. spillback) in the epidemiology of LF.

Understanding routes of transmission and the proportion of LF cases resulting from human-to-human transmission is critical for developing and prioritizing effective prevention and control interventions, especially in the presence of large variation among subjects in their capability of infecting. The current Ebola outbreak has emphasised further the need for targeted biosecure measures which distinguish managing hemorrhagic fever cases and outbreaks from preventing spillover from reservoirs. This issue has not previously been fully addressed for Lassa Fever. Traditional approaches, such as cluster analysis, to distinguish human-to-human transmission from pure zoonotic transmission cannot be employed here due to the potential of clustering of infection in households from common exposure to infected rodents in addition to clustering arising from infected people. We overcome this

Author Summary

Many pathogens have the ability to infect different species. Lassa fever virus is an important example; this virus infects a species of rodent in West Africa, and can cause a severe disease in people. Lassa fever virus is transmitted from rodent-to-rodent, rodent-to-human, human-to-human and perhaps human-to-rodent. So far, the relative importance of these routes has not been assessed. Here we focus on the risk for humans; undoubtedly, most human infections are acquired by contact with rodents or their urine, but the relative risk of rodent-to-human and human-to-human transmission is unknown. We use mathematical modeling to address this. First, we identified Lassa fever outbreaks known to be due to human-to-human chains of transmission. Then, we looked at people hospitalized with the disease in Kenema Government Hospital, Sierra Leone (KGH), who could have been infected either by rodents or humans. We asked, what should the proportion of patients be who get infected by humans, assuming the statistical patterns observed in the human-to-human chains are the same in both instances? We found that around 20% of patients with Lassa fever in KGH probably acquired the disease from another person. In addition, the patterns of disease in people suggest that these 20% of cases are probably initiated by only a small number of infected people (who could be thought of as super-spreaders).

problem by adapting other approaches [29,30], and using data from nosocomial and extra-nosocomial outbreaks and hospitalized patients in Kenema Governmental Hospital (KGH), Sierra Leone [1]. We use these data to provide an estimation of the contribution of human-to-human transmission to the Lassa fever occurrence in endemic areas and to provide a more-robust assessment of the risk of secondary spread from index cases.

Materials and Methods

Ethics statement

The Tulane University Institutional Review Board and the Sierra Leone Ethics Committee approved the research [1]. Patients either approached KGH directly or were referred to the KGH Lassa Ward from regional health centers or the hospital's general ward on the basis of suspicion of LF. All adult subjects provided written informed consent for the analysis and publication of anonymized laboratory and clinical data. A parent or guardian of any child participant provided written informed consent on their behalf. All data were anonymized prior to analysis.

Structure and rationale of the modeling approach

- Carey, Monath and co-workers [2,3] provided evidence of nosocomial and extra-nosocomial chains that are examples of human-to-human transmission of LASV. Based on these early works[2,3] and on the arguments listed in the introduction, it is reasonable to hypothesize that a proportion Q of hospitalized patients in KGH (Fig. 2) contracted the disease from a human source (see section "Available data and evidence of human-to-human transmission").
- The next step was to estimate this proportion Q ensuring that aspects of (e.g. the effective reproduction number) the epidemic curve from KGH are compatible with those in the observed chains [2,3].

- To this end, we employed and re-adapted the method of Wallinga and Teunis [29], who developed a method to calculate the effective reproduction number (which takes into account depletion of susceptibles) for an epidemic curve. If the network of transmission is known, no further information is required (see section "The effective reproduction number in the nosocomial and extra-nosocomial outbreaks"). Otherwise the distribution of the generation time, i.e. the time between a primary case and a secondary case, needs to be ascertained (see section "The effective reproduction number for cases of hospitalised patients in KGH").
- An important feature of the approach of [29] is the option to consider a fraction of cases in the curve as externally imported, i.e. people being infected outside the community. In the context of hospitalized patients in KGH, the cases from animal-to-human transmission are interpreted as externally imported cases, whose proportion is $1 - Q$. As we don't know which cases arises from zoonotic or human origin, we randomly selected a fraction Q of the number of hospitalized patients at the Lassa ward and considered this subset of the epidemic curve as a pure human-to-human chain of transmission. This random sampling was repeated many times to ensure the findings are based on a reliable statistics.
- We calculated i) a daily mean effective reproduction numbers, $\overline{R}^{Nos}$ and $\overline{R}^{ExtrdNos}$ (definition below and in the glossary in S1 Text), associated with the nosocomial and extra-nosocomial chains of pure human-to-human transmission [2,3] as well as the corresponding distributions of the generation times; ii) based on these distributions of the generation times we then estimated a daily mean effective reproduction numbers, $\overline{R}(Q)$, associated to each subset, consisting of a fraction Q of patients, of the epidemic curve from KGH; iii) finally, by imposing equality of the two reproduction numbers: either $\overline{R}^{Nos} = \overline{R}(Q)$ or $\overline{R}^{ExtraNos} = \overline{R}(Q)$, we estimated the proportion of cases arising from human-to-human transmission, Q.

Appropriateness of comparing data from Sierra Leone with the Jos/Zorzor outbreaks. Like Kenema in Sierra Leone, Jos and Zorzor are at the heart of the Nigerian and Liberian endemic areas of LF occurrence and, as in Sierra Leone, it is assumed that LASV has been circulating in these areas historically [5,31,32]. This is supported by molecular evidence that the Nigerian LASV strain is ancestral to the Sierra Leonean one [33]. In addition, although studies in human prevalence of antibodies to LASV exhibit variation amongst regions (e.g. low values in coastal areas), in general human seroprevalence appears to be similar in Nigeria and in the Mano River region (Guinea, Sierra Leone, Liberia) [20,34–40].

Furthermore in recent decades, infection control has focused essentially in minimizing nosocomial transmission, albeit with partial success [41–43]. In particular, a study by Tobin et al. [42] revealed a general lack of knowledge of barrier nursing among health workers in rural areas. This problem is expected to be even more persistent among non-professionals, suggesting that control measures have not significantly changed since LF was discovered. Hence despite these data sets being collected at quite different points in time, health-care practices have not changed meaningfully over this time period.

Finally, the Jos/Zorzor outbreaks were exceptionally severe disease outbreaks, therefore by analyzing only hospitalized patients in KGH, we ensured that we are comparing equivalent situations.
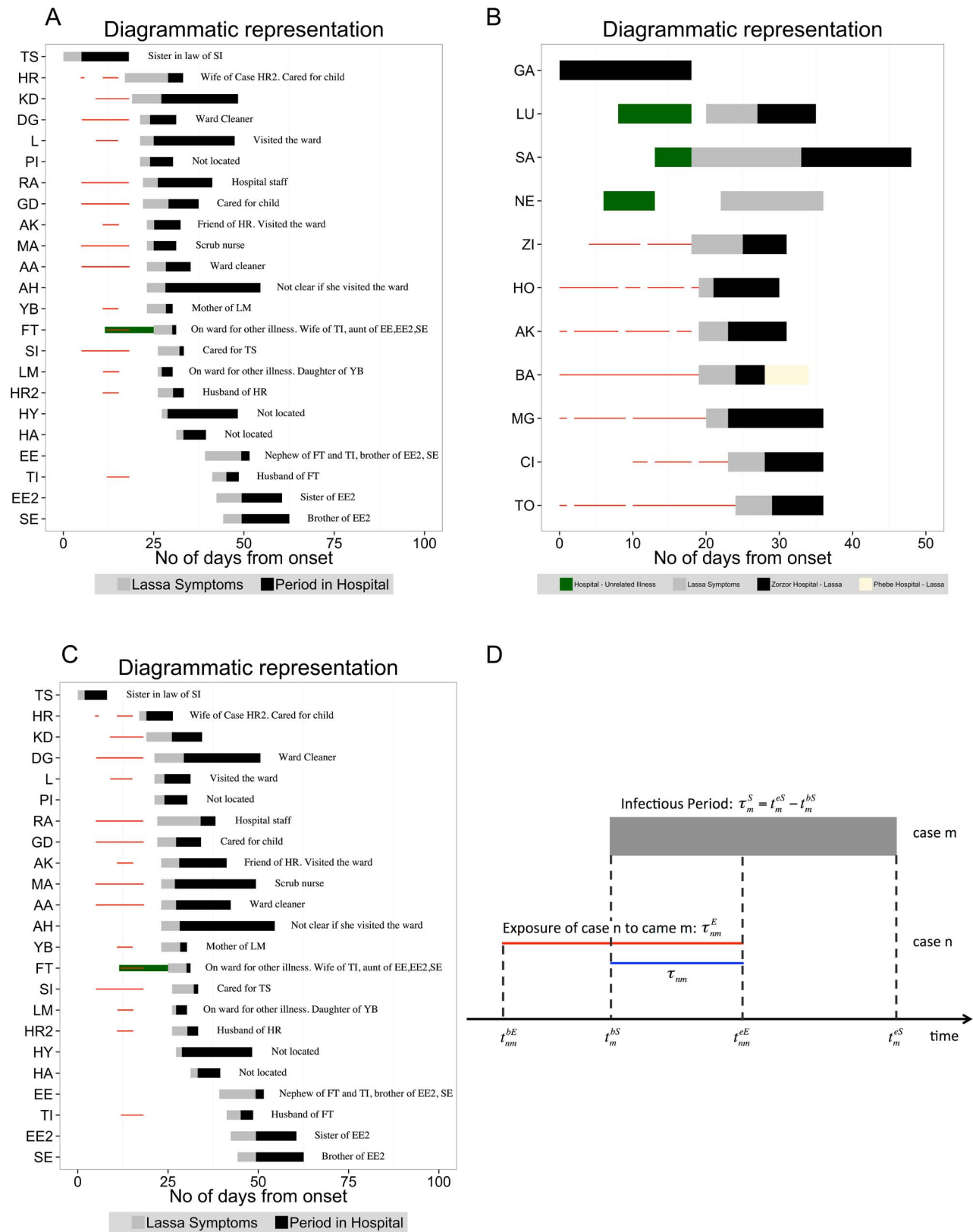
Fig. 1. Nosocomial outbreaks. A: Diagrammatic representation of LF cases admitted at Jos Hospital, Nigeria (total duration of the outbreak 62 days), showing period of illness and interrelation among patients [2]. The horizontal bars represent each patient. The x-axis is the time expressed in days from the start of the outbreak, when TS developed the illness (thus time 0 in the calculation corresponds to 25 December 1969). The grey portion of the bars are the period between the onset of the symptoms and admission to hospital; the black portion of the bars are the period between admission to hospital and discharge/death of the patients; the red thin lines are the period of exposure to the index case TS. The green bar

represent the time when the patient was at the ward for unrelated illness. Note, the same diagram in [2] present an extra case, JT, which is not included here. This case refers to Dr. Jeanette M. Troup one of the first scientists working on Lassa Fever Virus, who contracted the disease from an autopsy accident incurred during examination of one of the fatal cases. B: Diagrammatic representation of LF cases admitted at Zorzor Hospital (total duration of the outbreak 35 days), Liberia, showing period of illness and interrelation among patients [3]. C: As in Fig. 1.A, but the periods of illness (symptoms plus time at hospital) are randomly permuted. The contact network is kept the same. D: An example of how the time τ_{nm} was calculated. In this particular case $\tau_{nm} = t_{nm}^{eE} - t_m^{bS}$ if $t_{nm}^{eE} \le t \le t_m^{bS}$ and 0 otherwise, where t_{nm}^{eE} is the time when case n is no longer exposed to case m.

These considerations justify the choice of comparing the data from KGH with the extra-nosocomial outbreak that occurred in Jos, while the appropriateness of comparing the KGH data with the nosocomial cases in the Jos outbreak is one of the hypothesis being tested in the current work.

Available data and evidence of human-to-human transmission. We analyzed the data from two nosocomial LF outbreaks: Jos, Nigeria in 1970 (23 cases) [2] and Zorzor, Liberia in 1972 (11 cases) [3]. In the Jos outbreak, extra hospital infections with no contact with the index case were observed (a single family *EE*, *EE2*, *SE*, *TI*, and *FT* with the three children *EE*, *EE2* and *SE* who never visited the ward). These appear to be human-to-human chains; sampling and testing of rodents near the homes of LF patients in Jos, as well as in the larger geographic area, showed no evidence of LASV in rodents [2], further supporting human-to-human transmission maintaining these epidemics. Further details of the two outbreaks and the full networks of contacts are presented in the Supporting Information, S2 Text.

In contrast with many emerging zoonoses, the reported incidence of LF in people is high in endemic areas, as reflected in data from KGH in Sierra Leone [1] (Fig. 2), thus allowing a more robust analysis of the transmission dynamics. KGH is the only health facility in Sierra Leone where people can be diagnosed and treated for suspected LF. The hospital facilities include an isolation ward specifically for LF patients with a highly trained clinical staff equipped with appropriate personal protective equipment. KGH records provide hospitalized patient data (day of admission, day of discharge, etc.) for suspected and confirmed cases of LF, divided by age, gender, ethnic group, location and other factors [1].

We used data abstracted from patient medical charts and LF diagnostic tests for 1002 suspected Lassa cases presenting to the KGH Lassa Ward from 27th of April 2010 to the 31st of January 2012. Among these subjects, 295 (Fig. 2) were confirmed as LF cases, *i.e.* either subjects with acute infection (tested positive LF using an antigen-based ELISA approach) or with recent LF (tested positive to IgM antibodies) [1]. These data correspond to the most accurate and complete set of patient records available at KGH. April 2010 was chosen as the lower endpoint for our study sample due to significant improvements in data quality. These improvements are largely attributed to several NIH-funded research projects to develop and improve the diagnostic tests for LF. Improvements in clinical data quality can be attributed to more comprehensive questionnaire forms and increased community outreach and surveillance activities.

The effective reproduction number in the nosocomial and extra-nosocomial outbreaks. We calculated the effective reproduction number based on the observed dates of onset of symptoms, start and duration of exposure to the index cases and start and duration of exposure to all other cases. This information was directly obtained from the literature [2,3], which provided detailed descriptions of the network of contacts (Fig. 1 and S1 table in S2 Text). Inspired by the work of Wallinga and Teunis [29], the relative likelihood q_{ij} that case i has been infected by case j was calculated as:

$$q_{ij} = \frac{\tau_{ij}}{\sum_{k \ne i} \tau_{ik}} \qquad (1)$$

here τ_{nm} is the time of exposure of case n to case m while case m is infectious, *i.e.* the interval τ_{nm} is given by the intersection $\tau_{nm} = \tau_m^S \bigcap_\tau nm^E$, where $\tau_m^S = [t_m^{bS}, t_m^{eS}]$ is the infectious period of case m, calculated as the difference between the time t_m^{eS}, when the symptoms end (either because the patient recovers or dies) and the time t_m^{bS}, when the symptoms begin; τ_{nm}^E is the duration of exposure of case n to case m provided by the literature [2,3]. It is important to note that τ_{nm}, and thus q_{ij}, is explicitly time-dependent, (Fig. 1.D). The index k represents all possible cases within a nosocomial outbreak. Important underlying assumptions are: each event can independently start a new chain of human-to-human transmission, beginning of infectiousness coincides with the onset of symptoms, and infections occur with equal probability at any time during the interval τ_{nm}. Accordingly, the sum $R_j^{Nos}(t_j) = \sum_i q_{ij}$ over all cases i, represents the *individual* effective reproduction number for case j at the time t_j when the case arises. If multiple cases are observed at the same time t_j, then $R_j^{Nos}(t_j)$ is averaged appropriately. To increase the sample size and improve the estimation, the duration of the symptoms of LF and the period spent at the hospital associated with each patient were randomly rearranged among the 23 cases (Fig. 1.C), then the *ensemble* average individual effective reproduction number was calculated based on 100 of these permutations. The network of contacts was kept the same. The identical approach was used to calculate the effective reproduction number, $R_j^{ExtraNos}(t_j)$, for the extra-nosocomial situation, with the network of contacts restricted to the family *TI*, *EE*, *EE2*, *SE* and *FT* who presumably initiated the chain. We use the notation R_{Ind}^{Nos} and $R_{Ind}^{ExtraNos}$ to indicate the set of all individual effective reproduction numbers for the nosocomial and extra-nosocomial cases respectively, while the total effective reproduction numbers R^{Nos} and $R^{ExtraNos}$ represent the corresponding average number of cases during the entire outbreak, *i.e.* $R^{Nos} = \sum_j R_j^{Nos}(t_j)$ and $R^{Extra\,Nos} = \sum_j R_j^{Extra\,Nos}(t_j)$ respectively. To adjust for the different duration expected in different outbreaks, we calculate a *daily mean* effective reproduction number as $\overline{R}^{Nos} = \sum_j R_j^{Nos} / T^{Nos}$ and $\overline{R}^{ExtraNos} = \sum_j R_j^{ExtraNos} / T^{ExtraNos}$ where T^{Nos} and $T^{ExtraNos}$ are the typical duration of the nosocomial and extra-nosocomial outbreaks.

The correctness of the approach was corroborated by performing the same analysis but by imposing that each case is exposed only to the index case. For the situation in Jos, the individual reproduction numbers were zero for all cases except for *TS* which results in 15, *i.e.* the only cases exposed to *TS* and marked with a thin red line in Fig. 1.

The distribution of the quantity τ_{nm} is interpreted as the distribution of the generation time, *i.e.* the time between a primary case and a secondary case, and it is presented in Figs. 3.C and 3.D (see also Figures S2, S3, S4 and S5 in S2 Text).

The effective reproduction number for cases of hospitalised patients in KGH. Following the approach of Wallinga and Teunis (see [29,30] and their appendix for validation of the procedure), the relative likelihood that case i has been infected by case j, given their difference in time of symptom onset $\tilde{\tau}_{ij}$,
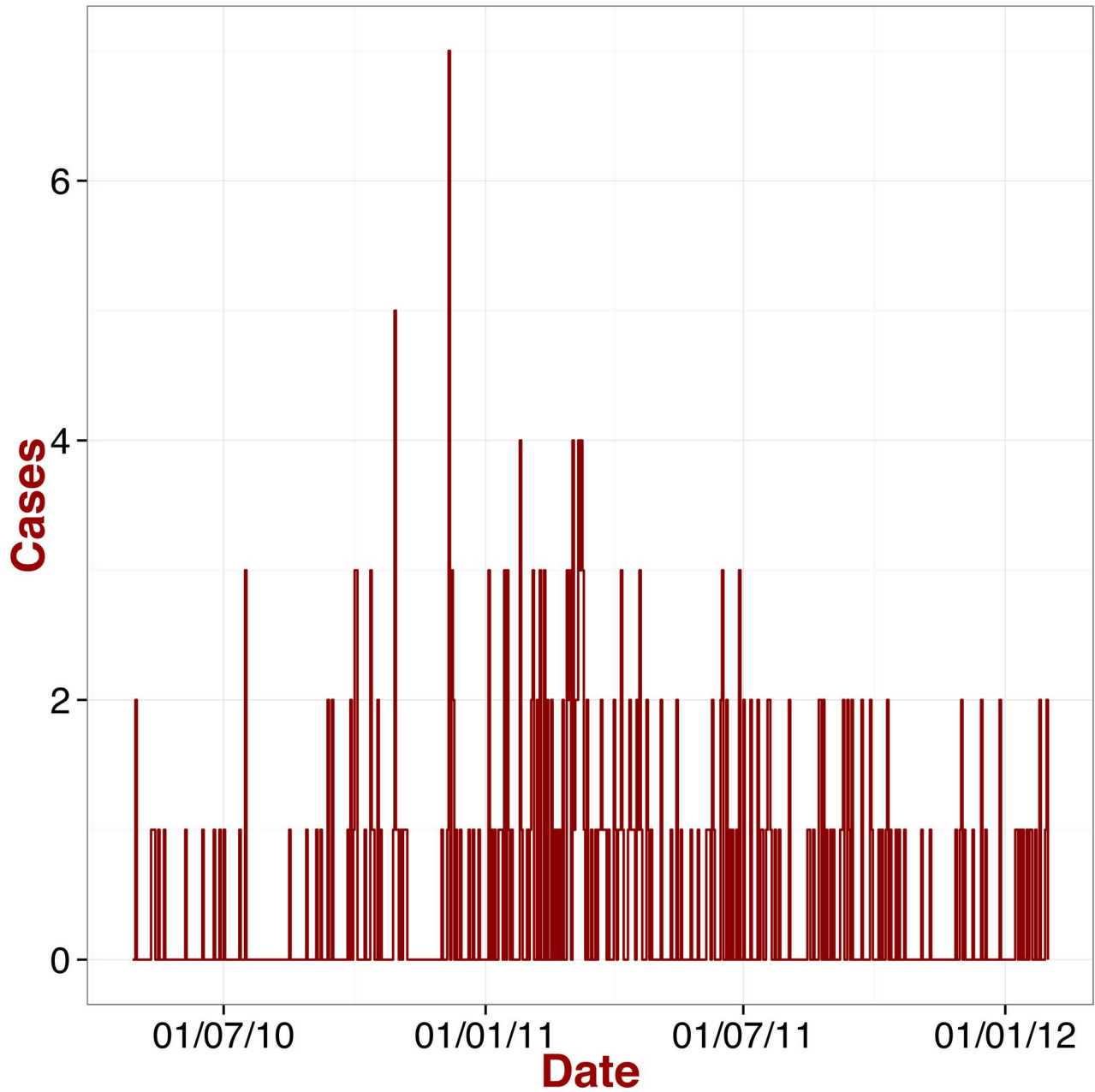
Fig. 2. Epidemic curve. Daily number of referred/visiting patients at KGH (confirmed cases only) from the 27th of April 2010 to the 31st of January 2012, [1].
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approximated here as the difference in time of admission to hospital, is then the likelihood that case i has been infected by case j, normalized by the likelihood that case i has been infected by any other case k

$$p_{ij} = \frac{w(\tilde{\tau}_{ij})}{\sum_{i \neq k} w(\tilde{\tau}_{ik})} \qquad (2)$$

where $\tilde{w}(\tilde{\tau}_{ij})$ is the distribution for the generation interval and it is assumed to be the empirical distribution obtained from the nosocomial and extra-nosocomial outbreaks (shown in Figs. 3.C and 3.D). The effective reproduction number for case j is the sum over all cases i, weighted by the relative likelihood that case i has been infected by case j

$$R_j(t_j) = \sum_{i=1}^{n} p_{ij} \qquad (3)$$

This quantity depends on the time t_j when case j occurs. The set of all i cases are obtained by the epidemic curve, describing the daily number of reported cases by date of symptom onset (Fig. 2), n is the total number of reported cases. Underlying this calculation is the assumption that the spread of the disease occurs through human-to-human transmission only, however, a substantial proportion of cases, $1 - Q$, is expected to be due to
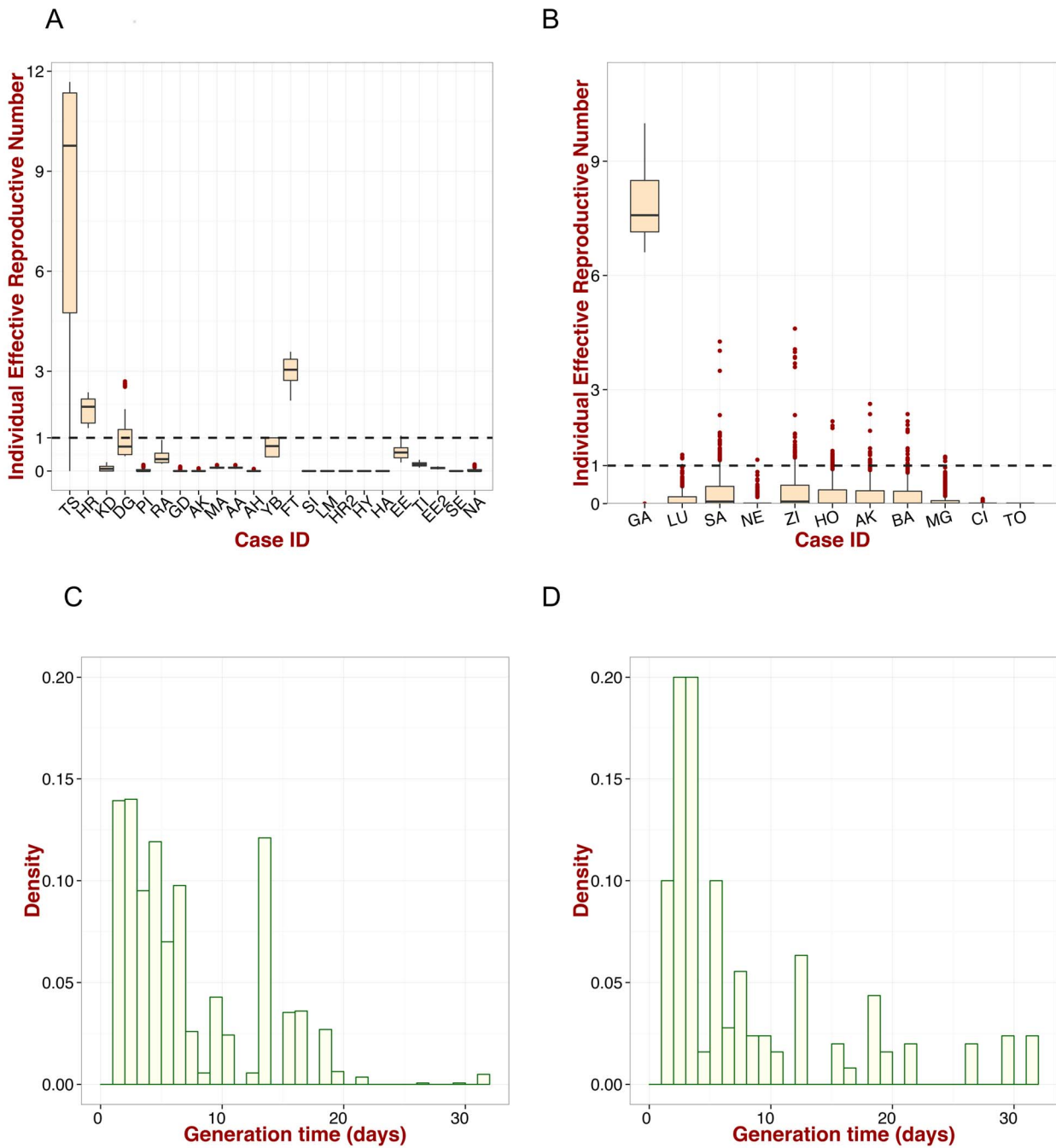
Fig. 3. Individual effective reproduction number and generation time. Box-plot for the individual R_j^{Nos} for the nosocomial outbreak described in [2] based on the 100 permutations of the duration of illness. It shows the first and third percentiles, the minimum and maximum values, the median, and outliers (red dots). The dashed line represents the case when the effective reproduction number is equal to 1. A: nosocomial outbreak in Jos [2]. B: nosocomial outbreak in Zorzor [3]. C: Distribution of generation time for the two nosocomial outbreaks. The statistics are based on the 100 permutations of the duration of illness. D: Distribution of generation time for extra-nosocomial cases. The statistics are based on the 100 permutations of the duration of illness.
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zoonotic transmission, *i.e.* only through contacts with the rodent population, which can be considered as cases that have contracted infection from outside the population. These, therefore, cannot be regarded as secondary-tertiary etc. cases,

although they can initiate a human-to-human chain. Under these circumstances, the effective reproduction number in equation (3) must be calculated by removing these $n(1-Q)$ imported cases, *i.e.*

$$R_j(Q) = \sum_{i=1}^{nQ} p_{ij} \qquad (4)$$

The set of all individual effective reproduction numbers is indicated by R_{Ind}, while $R(Q)$ is the *total* effective reproduction number, *i.e.* $R(Q) = \sum_j R_j(Q)$, where to simplify the notation we dropped the dependency on t_j. This value represents the average number of cases during the entire epidemic compatible with the particular generation time. As above, we averaged to obtain the *daily mean* effective reproduction number $\overline{R}(Q) = \sum_j R_j(Q)/T$ where T is the duration of the epidemics. The calculations were carried out by using the R package R0, provided by Obadia and co-authors [30,44].

We compared two published outbreaks to illustrate the likely bounds of human to human transmission. Initially, we assumed that the extent of human-to-human transmission in nosocomial outbreaks in Jos and Zorzor [2,3] represent the general situation in an endemic area. Alternatively, we rejected this assumption and considered only the out of hospital human-to-human transmission in Jos (five from the same family, *TI*, *EE*, *EE2*, *SE* and *FT* who initiated the chain), as being representative of the general endemic situation. We estimated the generation number and the mean nosocomial reproduction numbers for these two alternatives. By imposing equality with the mean nosocomial reproduction numbers (either $\overline{R}(Q) = \overline{R}^{Nos}$ or $\overline{R}(Q) = \overline{R}^{ExtraNos}$), we inferred the proportion Q.

To allow comparison with the effective reproduction number for the Kenema data, which by definition is based only on outbreaks where the primary case is assumed to be among those reported [29], the index patients *TS* and *GA* from the Jos and Zorzor outbreaks were assumed to be secondary cases to unreported human cases. On the grounds of realism, and also computational economy, the epidemic curve from KGH (Fig. 2) is assumed to be a collection of multiple chains of mean duration T, rather than a 2-year long un-interrupted epidemic. The starting times of each human-to-human chain were randomly chosen within the $2-$ year period of the KGH epidemic curve. Similarly, as humans and rodents share the same physical space, cross-species transmission can occur at any time, thus the $n(1-Q)$ imported cases were randomly chosen from the network of contacts. For each value of Q, the ensemble sample of the simulations was 300.

Results

Effective reproduction number for nosocomial outbreaks

Figs. 3.A and 3.B show the effective reproduction number for each patient for the two nosocomial outbreaks respectively. As expected, the largest values are associated with the index case *TS* and *GA* for the Jos and Zorzor outbreaks, respectively. In several cases, however, the effective reproduction number >1; particularly important is case *FT* in the Jos outbreak with an effective reproduction number ≈ 3, who most likely initiated extra-nosocomial transmission in her family.

Estimating the contribution of human-to-human transmission

Fig. 4 shows the total effective reproduction number $R(Q)$ and its daily mean $\overline{R}(Q)$ for the cases in KGH, *vs* the estimated proportion Q of cases due to human-to-human transmission. The shaded grey area covers the range between 25th and 75th percentiles arising from the 300 simulations for each value of Q. The predictions were then compared with the total effective reproduction number (or with the equivalent daily mean), in the nosocomial outbreaks R^{Nos} (or $\overline{R}^{Nos}$) based on the full network of cases and with the extra-nosocomial cases in Jos alone $R^{ExtraNos}$ (or $\overline{R}^{ExtraNos}$). For the full network of cases, the mean nosocomial reproduction number was higher than the mean KGH one, implying that the severe hospital outbreaks ought to be seen as exceptional circumstances. In contrast, the daily mean effective reproduction number arising from the Jos extra-hospital cases (due only to human-to-human transmission) was entirely compatible with the daily mean KGH effective reproduction number if we allow a proportion of cases to be due to human-to-human transmission $Q \approx 20\%$. Based on the 25th and 75th percentiles in the predictions for the reproduction number $R(Q)$, the lower and upper estimates for the proportion of human-to-human transmission are $\approx 15\%$ and $\approx 30\%$ respectively.

Quantifying the impact of the super-spreaders

Super-spreaders are individuals who can infect a disproportionately large pool of susceptibles [45]. Here, super-spreading events are identified and quantified by analyzing how the effective reproduction number is distributed. The distribution of the individual effective reproduction numbers for the Jos and Zorzor outbreaks, based on the 100 permutations of the duration of illness, is shown in Fig. 5.A. Although 85% of the predictions for individual $R_{Ind}^{Nos} < 1$, there is a fat tailed distribution, with extreme values of $R_{Ind}^{Nos} < 12$. Similar patterns are observed for KGH cases for the individual effective reproduction number R_{Ind}. As shown in Fig. 5.B and 5.C, the distribution of the individual and total, effective reproduction numbers, R_{Ind} and R appears to have a fat-tailed distribution, especially for larger values of Q.

A simple approach to evaluate the risk of super-spreaders is to invoke the so-called '20/80 rule' (whereby 20% of cases cause 80% of transmission, see [45,46]). To this end, for different values of the contribution of human-to-human transmission, Q, we calculated i) the proportion of cases when $R_{Ind} > 1$ (Fig. 6.A), and ii) its proportional impact, given by the expected, relative number of secondary cases generated by this proportion (see Fig. 6.B for further explanations); the maximum R_{Ind} in the simulations was also recorded. For a contribution of human-to-human transmission in the region of 20%, only 1% of realizations gave $R_{Ind} > 1$, but they are, on average, responsible for 20% of secondary cases, with a maximum $R_{Ind} \geq 5$. In an extreme situation, when the disease is transmitted only by humans, $\approx 14\%$ of cases are responsible for the $\approx 77\%$ of secondary cases with a maximum R up to ≈ 10, which resembles the '20/80 rule'.

More sophisticated ways to assess the risk of super-spreaders are presented in the S2 Text. In particular, we fitted the distribution for the individual effective reproduction number R_{Ind} from KGH with an exponential and a log-normal distribution. The observed KGH distribution is 'fatter' than the corresponding exponential fit, although not as heavy as the log-normal. Furthermore we fitted two standard discrete distributions, the Poisson, representative of thin-tailed distributions, and the negative-binomial, representative of fat-tailed distributions, with the distribution for the integer part (as we are considering discrete distributions) of R, *i.e.* the average number of cases during the entire epidemic. As can be seen, the last distribution is better fitted by a negative-binomial distribution, especially for the tail (S6 Figure in S2 Text).

Sensitivity of the predictions

Effect of the duration of epidemics. Different values for the typical duration of a human-to-human chain, T, were explored. As expected, the longer the duration, T, the larger the availability of susceptibles and the higher the effective reproduction number. However, when the effective reproduction number is rescaled by the duration of the epidemics, *i.e.* the daily mean effective reproduction number $\overline{R}(Q)$, all the predictions are similar. This can be seen by comparing the plots $\overline{R}(Q) = R(Q)/T$ in Figs. 4.B ($T = 33.5$ days), 4.D ($T = 62$ days) and S1 Figure in S2 Text ($T = 124$ days).

Based on this invariance, we can infer the proportion Q, irrespective of the choice of the mean duration T, provided that we know the typical duration of the nosocomial and extra-nosocomial chains T^{Nos} and $T^{ExtraNos}$. For the nosocomial case, a reasonable choice is $T^{Nos} = 33.5$ days, which is the average duration of nosocomial outbreaks observed in Jos and Zorzor hospitals (44 and 23 days respectively, the last days correspond to when the last person developed symptoms). For the extra-nosocomial chains the choice is less clear, as the member of the family were already in contact with the index case FT before she developed symptoms, and shedding of the virus could happen any time before symptom onset. Therefore we made a conservative choice of $T = 62$ days which corresponds to the maximum duration of the Jos outbreak (here the last day corresponds to when case SE recovered). Any shorter choice of the duration $T^{ExtraNos}$, will result in a larger value of the proportion Q (for instance if the typical duration of the outbreak is 50 days, *i.e.* including while TS was at the hospital, we found that $Q \approx 26\%$ instead of $\approx 20\%$ while the estimates based on the intersection with the 25th-percentile and 75th-percentile were $\approx 19\%$ and $\approx 38\%$ respectively rather than $\approx 15\%$ and $\approx 30\%$), which reinforces the key message of this current work that a significant proportion of cases of LF arises from human-to-human transmission.

Effect of the distribution of the generation times. The robustness of the approach was tested by considering different distributions for the generation time. We considered i) the distribution of generation time arising from the entire network, ii) the distribution arising from the particular subset of the data corresponding to the extra-nosocomial cases TI, EE, $EE2$, SE and FT, iii) a gamma distribution with the same empirical mean and variance, iv) the empirical distribution by removing part of the tail, v) a 'stretched' distribution by multiplying the empirical generation times by a factor 2 to allow for a longer shedding of the virus, and vi) a 'shrunk' distribution by multiplying the empirical generation times by a factor 0.5. In general, each of these methods had limited effects on the predictions (see S2 Figure in S2 Text, S3 Figure in S2 Text, S4 Figure in S2 Text, and S5 Figure in S2 Text).

Discussion

Disentangling the contribution of different hosts in spreading a zoonotic, emerging disease is a key challenge for determining effective, proportionate public health and safety measures. Such a conundrum has steered a scientific debate on LF, which appears to fluctuate around whether or not human-to-human transmission plays a major role compared to rodent-to-human transmission. The current work reconciles these two opposing paradigms. Here, we adopted a relatively simple mathematical approach to analyze data of hospitalized patients in KGH, Sierra Leone. The daily mean effective reproduction numbers, $\overline{R}$, observed in the nosocomial outbreaks (only human-to-human transmission) are

much larger, and thus incompatible, with the ones estimated from the data from KGH, even if we assume 100% human-to-human transmission. If we regard the extra-nosocomial cases observed in the Jos outbreak as representative of disease transmission in an endemic area, then a significant proportion of LF cases ($\approx 20\%$) arise from human-to-human transmission. A significant proportion of these secondary cases, however, are attributable to a few events with disproportionately large effective reproduction numbers: super-spreading events. In general, the distributions of the individual reproductive number, R_{Ind}, and the average number of cases during an epidemic, R, exhibits a tail heavier than the exponential or Poisson distributions, here used as benchmarks for thin-tailed distributions. This reveal over-dispersion indicating the presence of super-spreading events.

These results have implications for clinical practice and policy. Super-spreading occurrences appear not to be exceptional for infectious diseases [46,47]. According to this perspective, the lack of recorded secondary cases in Britain after the importation of confirmed cases of LF [7,12] should not be regarded as proof of absence of human-to-human transmission. Any future assessment of the associated risk of LF and formulation of patient containment guidelines [13], therefore, should take into account the fat-tail nature of the underlying distribution of individual reproduction number.

Super-spreading events have been documented for many infectious diseases [45,46], including tuberculosis [48], measles [49] and SARS [50–52]. The underlying reasons for super-spreading are not fully understood, but include amount of pathogen excreted, length of the infectious period, social behavior and environmental factors. Understanding the mechanisms of super-spreaders in LF requires an understanding of all of these factors, but transmission of LASV is not well characterized. In the Jos outbreak, Carey et al. [2] speculated that the severe pulmonary involvement of the index case and the location of her bed could cause airborne spread of virus to the rest of the ward. The long persistence of viruria, even during the recovery period, could facilitate transmission of LASV to other people or to the rodent reservoir host, especially in rural settlements in areas of West Africa where sanitary facilities are limited. Participatory modeling and ethnographic research [53] would be an invaluable tool to assess the variety of practices and settings in which people come into contact with each other's urine and other body fluids, perceptions of risk, and approaches to hygiene. Apart the work of Stephenson et al. [17] and Peter et al. [18], we are not aware of specific experiments aimed to test routes of LASV transmission. Studies on environmental contamination are also required to explore if human-to-rodent transmission is important for the maintenance or spread of LASV infection [6].

Limitations of this study and future work

The current model is based on the assumption that the distribution of the generation times observed in the extra-nosocomial outbreak is representative of the generation times in the Sierra Leonean situations. This is probably reasonable, but public health measures may impact on this in the future. The predictions are based on the assumption of uniform mixing, *i.e.* each case from KGH is potentially in contact with each other case. Although this is a reasonable assumption, considering the large human mobility in Sierra Leone, for livelihoods, work and trade, social visits and events [54], it will overestimate $\overline{R}$. In addition, there is likely to be incomplete reporting which will underestimate $\overline{R}$. Although the two factors might compensate for each other, if KGH could reduce reporting bias and increase information on
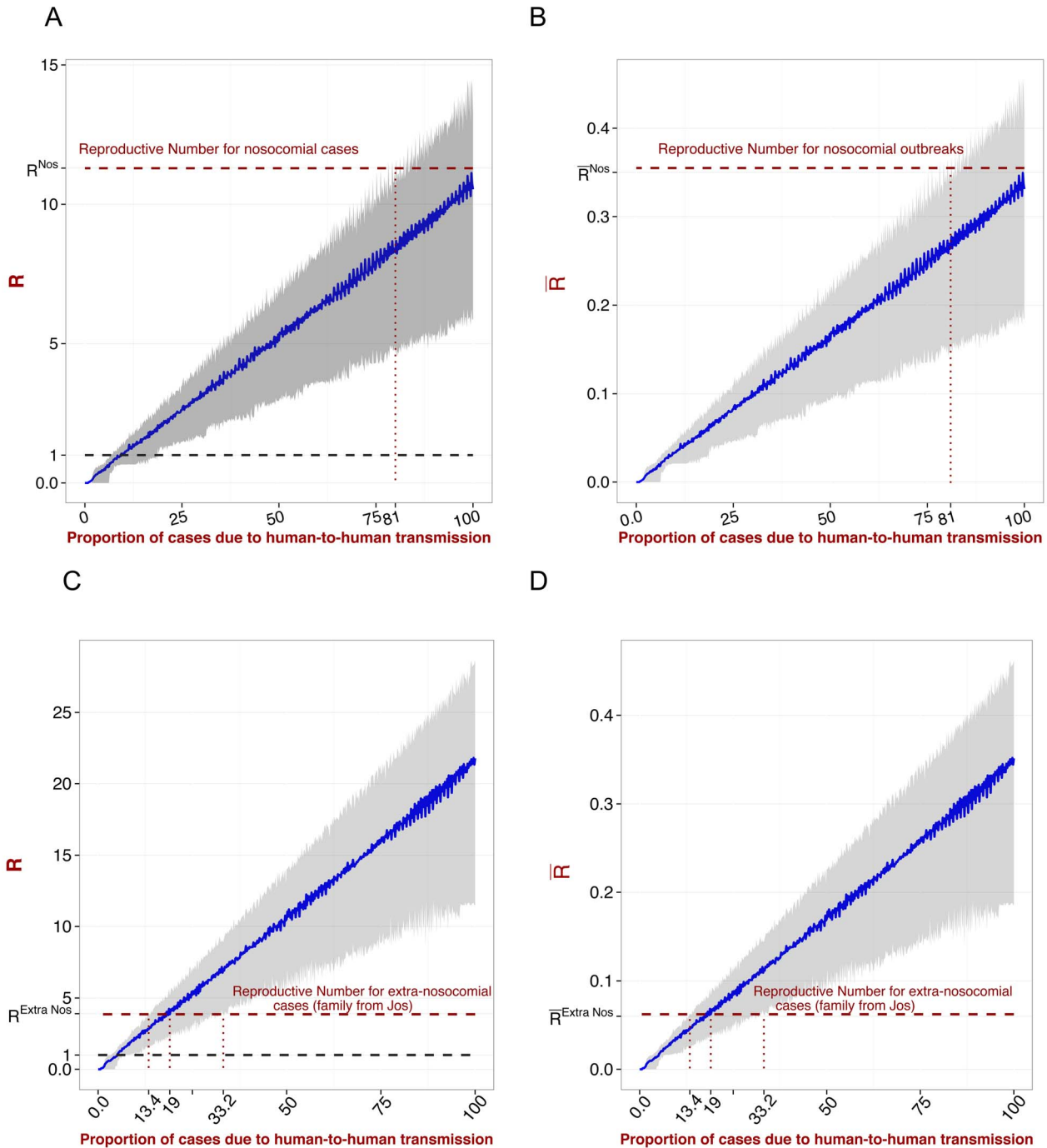
Fig. 4. Contribution of human-to-human transmission. Mean value of the total effective reproduction number, R and its daily mean, $\overline{R}$, for the KGH epidemic curve *vs* the proportion Q of cases due to human-to-human transmission (blue line). The shaded grey area covers the range between the 25th and 75th percentiles in R and/or $\overline{R}$; the dashed red line represents the mean, nosocomial, effective reproduction number. A and B: R^{Nos} and $\overline{R}^{Nos}$ based on the full networks (in Jos and in Zorzor) of nosocomial cases; $T = 33.5$ days. C and D: $R^{ExtraNos}$ and $\overline{R}^{ExtraNos}$ based on the extra-nosocomial cases in Jos; $T = 62$ days.

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network contacts, it would be highly beneficial to studies such as this, especially as human mobility and overcrowding has been associated with an amplification of LF [31]. This represents a further area where participatory modeling/ethnographic research is much needed to gather information on actual patterns of mobility and social networking, and hence potential contact patterns.

Other methods are possible, for example cluster-based inference of the reproduction number (see *e.g.* [55,56]) is a promising approach. In the current context, Kernéis *et al.* [20] provided detailed information on prevalence and risk factors of Lassa (*e.g.* history of collecting, cutting and eating rats) stratified by age. In addition, the age distribution from KGH is also available. These
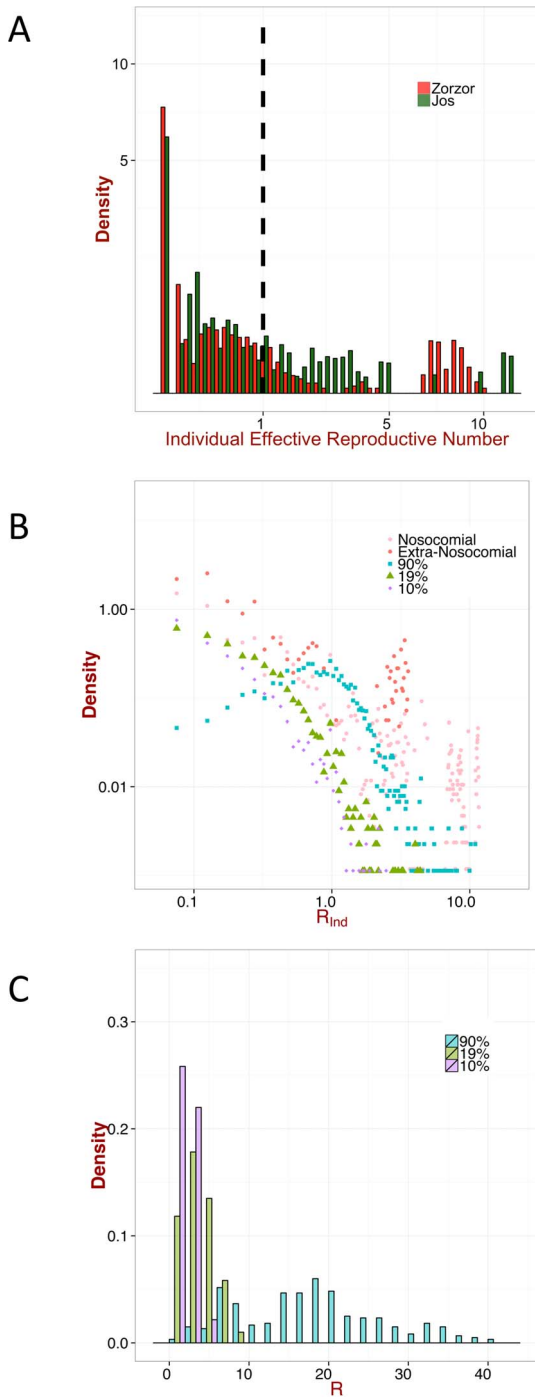
Fig. 6. Impact of super-spreaders II. A: proportion of cases when the individual effective reproduction number R_{Ind} is greater than one. (*i.e.* the ratio of the cardinalities of $\mathcal{S}_\mathcal{O}$ and $\mathcal{S}$, where $\mathcal{S}$ is set of all simulated R_{Ind} and $\mathcal{S}_\mathcal{O}$ the subset of cases when R_{Ind} is greater than one). B: the expected, relative number of cases generated by this proportion. (*i.e.* the fraction of the areas of $\sum_{\mathcal{S}_\mathcal{O}} R_{Ind} / \sum_{\mathcal{S}} R_{Ind}$)
doi:10.1371/journal.pntd.0003398.g006

Fig. 5. Impact of super-spreaders I. A: Distribution of all individual R^{Nos} for both nosocomial outbreaks, based on the 100 permutations of the duration of illness. Mean value of the joint data: 0.73, median: 0.04, maximum: 11.7, proportion of cases when $R^{Nos} > 5$: 4.2%, proportion of cases when $R^{Nos} > 10$: 1.2%. B: Distribution of the effective reproduction number for cases of hospitalized patients in KGH for different values of the contribution of human-to-human transmission, Q, the corresponding data for the extra-nosocomial (100 permutation based on *FT, TI, EE, EE2, SE* cases in Jos) and all nosocomial outbreaks (based on all Jos and Zorzor cases) are also shown. C: Distribution of the total effective reproduction number, *i.e.* the average number of cases during the entire duration of the epidemic for different values the contribution of human-to-human transmission, Q.
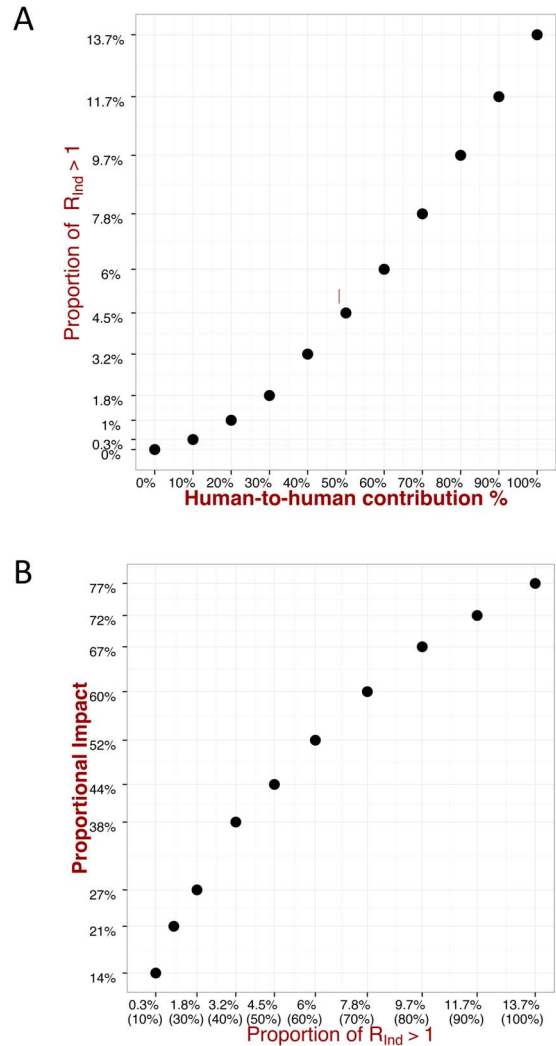doi:10.1371/journal.pntd.0003398.g005

data could be combined together to build a matrix of transmission rates among age-groups (as done in [55,56]) and between rodents and each age-group with values based on the findings of Kernéis *et al.* [20].

For the KGH data, the difference in time of onset of symptoms was approximated here with the difference in time of visit/referral to the hospital following disease onset. This assumption can be an important source of error as patterns of health seeking behavior might vary largely among the Sierra Leonean population. For example, a particular group of the population might favor traditional medicine and approach institutional health care only at a late stage of the disease. Patients from rural areas might be subjected to further delay due to poor infrastructure. Health seeking behavior is perhaps one the most fruitful areas where participatory modeling and ethnographic research have been successfully employed and should be considered in the present context.

The estimations here are based on the assumption that probability of cross-species transmission occurs at random throughout outbreaks, although these events are expected to be strongly driven by a multitude of interacting causes, including ecological (*e.g.* seasonality in the abundance of the reservoir), epidemiological (*e.g.* seasonality in the prevalence of the pathogen), genetic variation (*e.g.* broad set of pathogen life histories) and socio-economic (*e.g.* the practice of burning the fields after harvesting affecting the ecology and dispersal patterns of *M. natalensis*) factors.

The estimation of the proportion of human-to-human transmission was based on the assumption that the typical duration of a chain of transmission is equal to the duration of the extra-nosocomial outbreak. As this information was only approximately known, we made the prudent choice that the duration of the extra-nosocomial outbreak was the entire extent of the outbreak in Jos, which was the maximum value from the data available. This led to a conservative estimation of $Q \approx 20\%$. Despite some inevitable inaccuracies, all of our alternative/additional tests confirm that a significant proportion (in the region of 20% or greater) of the burden of LF is due to human-to-human transmission.

The basis of our work is that, to the best of our knowledge, the nosocomial and extra-nosocomial outbreaks in Jos and Zorzor were instances of pure human-to-human chains. This is a message too important to be neglected. Despite some improvement in the implementation of barrier nursing in hospital structures, there is no evidence that in the last decades prophylactic measures have significantly changed in ordinary situations as in households and villages, and this issue has been abundantly clear during the current Ebola outbreak in West Africa. It is therefore reasonable that chains of human-to-human transmission, like the extra-nosocomial outbreak that occurred in Jos more than 40 years ago are much more common than expected.

This study highlights the need for integrated One Health approaches to model zoonoses more effectively in order to better-inform disease control and prevention. Zoonoses remain a neglected group of diseases, under-prioritised in national and international health systems.

Supporting Information

S1 Text List of symbols and glossary.
(PDF)

S2 Text Details on the nosocomial outbreaks and further tests.
(PDF)

S1 Data The file provides the daily number of referred/visiting patients at KGH (confirmed cases only) from the 27th of April 2010 to the 31st of January 2012 [1], as displayed in Fig. 2.
(TXT)

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Author Contributions

Conceived and designed the experiments: GLI AAC EFC ML CTW JLNW. Performed the experiments: GLI CTW. Analyzed the data: GLI CTW. Wrote the paper: GL AAC EFC LMM ML CTW JLNW. Provided and processed the data from Kenema Government Hospital: RFG DSG SHK LMM JSS JGS.

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