Unravelling the drivers of MERS-CoV transmission

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With more than 1,700 laboratory-confirmed infections, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) remains a significant threat for public health. However, the lack of detailed data on modes of transmission from the animal reservoir and between humans means that the drivers of MERS-CoV epidemics remain poorly characterized. Here, we develop a statistical framework to provide a comprehensive analysis of the transmission patterns underlying the 681 MERS-CoV cases detected in the Kingdom of Saudi Arabia (KSA) between January 2013 to July 2014. We assess how infections from the animal reservoir, the different levels of mixing and heterogeneities in transmission have contributed to the build-up of MERS-CoV epidemics in KSA. We estimate that 12% (95% Credible Interval CI: 9%, 15%) of cases were infected from the reservoir, the rest via human-to-human transmission in clusters (60%; CI: 57%, 63%), within (23%; CI: 20%, 27%) or between (5%; CI: 2%, 8%) regions. The reproduction number at the start of a cluster was 0.45 (CI: 0.33, 0.58) on average, but with large standard deviation (0.53; CI: 0.35, 0.78). It was >1 in 12% (CI: 6%, 18%) of clusters but fell by approximately half (47% CI: 34%, 63%) its original value after 10 cases on average. The ongoing exposure of humans to MERS-CoV from the reservoir is of major concern, given the continued risk of substantial outbreaks in health care systems. The approach we present allows the study of infectious disease transmission when data linking cases to each other remain limited and uncertain.

Epidemic dynamics | Mathematical modelling | Zoonotic virus | Animal reservoir | Outbreaks

Introduction

Despite the occurrence of 1728 laboratory-confirmed cases and 624 deaths (1) since the virus was first isolated in 2012, transmission of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) remains poorly understood. Dromedary camels play a role in transmission (2) but the nature and extent of human exposure to camels is not well defined. Despite multiple reintroductions from the reservoir, there has been no sign of the continuous exponential growth in human case numbers that is the typical signature of the start of a pandemic. Furthermore, most infections have occurred in Middle Eastern countries on the Arabian Peninsula, with approximately 75% of cases reported by the Kingdom of Saudi Arabia (KSA). Spatial expansion to other areas has been limited. While these simple observations suggest that MERS-CoV is not presently capable of self-sustaining transmission in humans (at least in the Middle East), large clusters of human cases, typically in health care settings, have been documented (3). Notably, in March-May 2014, KSA experienced a large, rapidly growing outbreak affecting many hospitals and which spanned multiple regions of the country (Figure 1) (4, 5).

A number of studies have attempted to characterize the human-to-human transmission of MERS-CoV and the contribution of the reservoir from the analysis of specific features of the epidemic - for example cluster sizes (6), epidemic time series in clusters (7), transmission trees in few large clusters (8, 9) or the proportion of MERS-CoV cases with no known human source of infection (5, 10) – sometimes restricted to one or more large outbreaks (5, 8, 9). Such an approach simplifies inference but comes with a number of limitations. First, by restricting analysis to simple features of the epidemic, strong assumptions about the underlying transmission process are often required, such as assuming that cases with no known source of infection are infected by the reservoir (5-7, 10), that clusters are closed epidemics independent of each other (6, 7, 10) or that transmission rates are constant over time (6). In addition, analysis restricted to large outbreaks may bias estimates of human-to-human transmission upwards. A coherent and holistic picture of MERS-CoV epidemic dynamics therefore remains elusive, reflected, for instance, in published estimates of the proportion of infections due to the animal reservoir varying from a few percent (5) to 55% (10).

Here, to obtain a comprehensive picture of MERS-CoV transmission dynamics, we developed a general framework to analyze detailed epidemiological records of all MERS-CoV cases reported between 1 January 2013 and 31 July 2014 in KSA, a timeframe that included the largest outbreaks of MERS-CoV reported to date. The framework makes it possible to relax the simplifying assumptions often made in past work about the epidemic process (e.g. independence of clusters, unknown sources of infection being interpreted as infections from the reservoir). It builds on methods used to reconstruct transmission trees from case data (11, 12) but greatly expands them by allowing estimation of the generation time distribution, multiple and heterogeneous

Significance

Since it was discovered in 2012, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has infected more than 1,700 persons, a third of whom died, essentially in the Middle East. People can get infected by direct or indirect contact with dromedary camels and although human-to-human transmission is not self-sustaining in the Middle East, it can nonetheless generate large outbreaks, particular in hospital settings. Overall, we still poorly understand how infections from the animal reservoir, the different levels of mixing and heterogeneities in transmission have contributed to the build-up of MERS-CoV epidemics. Here, we quantify the contribution of each of these factors from detailed records of MERS-CoV cases from the Kingdom of Saudi Arabia, which has been the most affected country.

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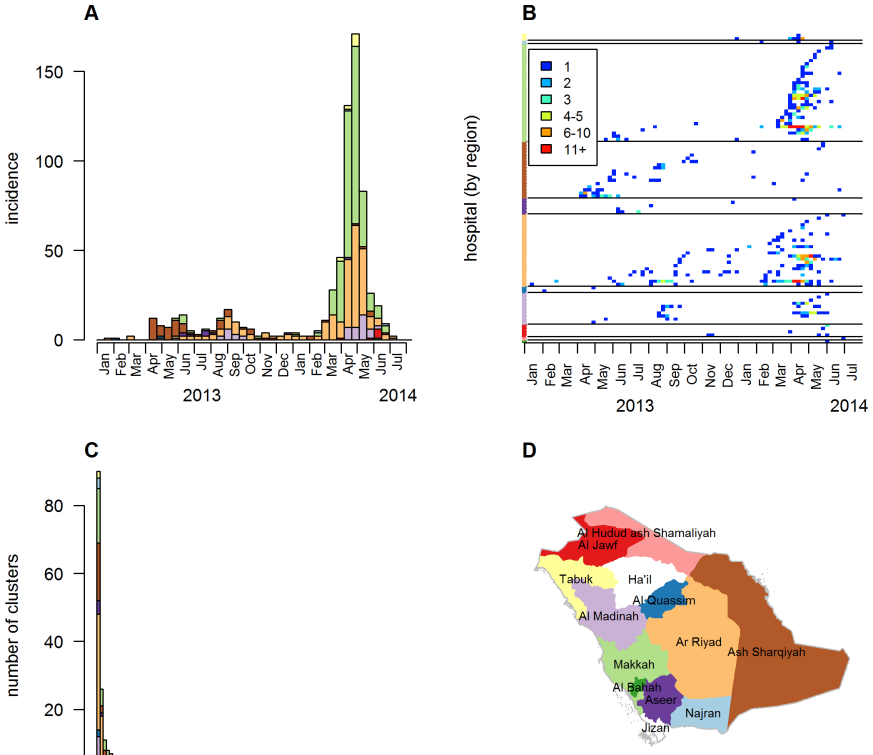

Fig. 1. The epidemic of MERS-CoV in KSA between 1 January 2013 and 31 July 2014. A. Biweekly number of MERS-CoV laboratory-confirmed infections per region. **B.** Weekly number of cases in the different hospitals and over time. The color of dots indicates the weekly number of cases. Colors on the y-axis indicate the region of the hospital. **C.** Distribution of the number of cases per cluster. **D.** Map of the Kingdom of Saudi Arabia. Colors in panels A, B and C match the color of regions in panel D.

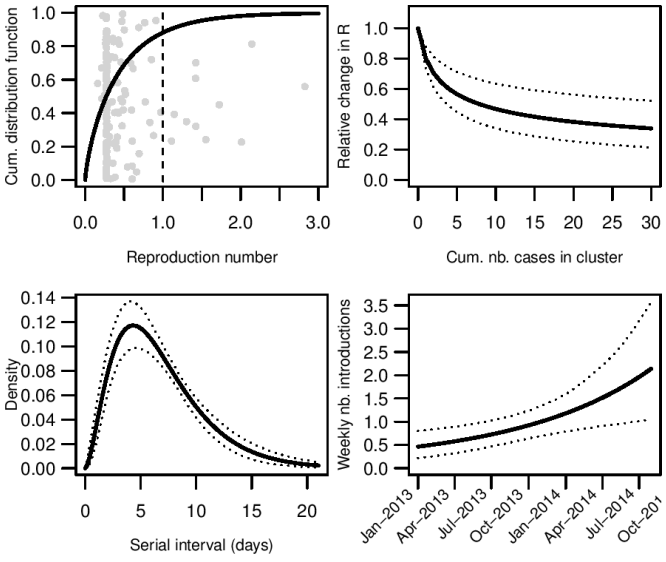

Fig. 2. Transmission characteristics of MERS-CoV in KSA. A. Cumulative distribution function of the within-cluster reproduction number at the start of a new cluster (black line). Grey dots show the posterior mean for each cluster. **B.** Variations in the within-cluster reproduction number as a function of the cumulated number of cases in the cluster (solid line: posterior mean; dotted lines: 95% CI) **C.** Distribution of the serial interval of MERS-CoV. **D.** Weekly number of introductions from the reservoir during the study period (solid line: posterior mean; dotted lines: 95% CI).

levels of transmission, and changing risks of infection from a zoonotic reservoir.

Results

Between 1 January 2013 and 31 July 2014, 681 MERS-CoV patients were identified in KSA. The first outbreak was reported in the region of Ash Sharqiyah in April-May 2013 followed by an outbreak in Riyadh in July-September 2013 (Figure 1). The largest outbreak in March-May 2014 principally affected Makkah region (mostly Jeddah) and Riyadh. Combined, these two regions accounted for 78% (N=294 in Makkah region and 235 in Riyadh) of cases. Figure 1B shows how cases clustered over space, time and according to the hospital (N=98) in which they were treated, diagnosed and/or tested. We identify 162 clusters, where a cluster is defined as a group of cases who were treated, diagnosed and/or tested in the same hospital, with a time lag between two consecutive cases of at most 21 days. The distribution of cluster sizes is highly skewed (Figure 1C).

We were able to characterize the overall pattern of transmission by estimating the within-cluster reproduction numbers (i.e. average number of secondary cases generated by a case in their cluster), the within-region reproduction number (i.e. average number of secondary cases in other clusters of the region) and the between-region reproduction number (i.e. average number of secondary cases in other regions) (see Methods). Figure 2A shows the distribution of the initial within-cluster reproduction number, R_c. It has a mean of 0.45 (95% CI: 0.33, 0.58) but with substantial heterogeneity between clusters (standard deviation: 0.53; 95% CI: 0.35, 0.78). The initial within-cluster reproduction number is over 1 in 12% (95% CI: 6%, 18%) of clusters. We can also assess where each cluster falls within this distribution (Figure 2A). We find that the within-cluster reproduction number at a point in time is a declining function of the cumulative number of cases that have accrued in the cluster by that time (Figure 2B). We estimate that after 10 cases, the within-cluster reproduction

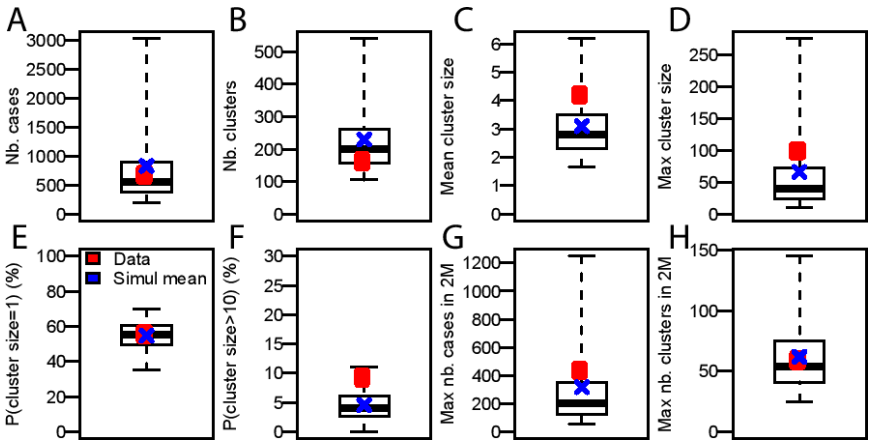

Fig. 3. Model adequacy. Observed values (red dot) and values predicted by the model from 10,000 simulations (blue cross: mean; black boxplot gives quantiles 2.5%, 25%, 50%, 75%, 97.5%) **A.** Number of cases **B.** Number of clusters **C.** Mean cluster size. **D.** Maximum cluster size. **E.** Probability that a cluster is of size 1. **F.** Probability that the size of a cluster is larger than 10. **G.** Maximum number of cases over a two-month period. **H.** Maximum number of clusters over a two-month period.

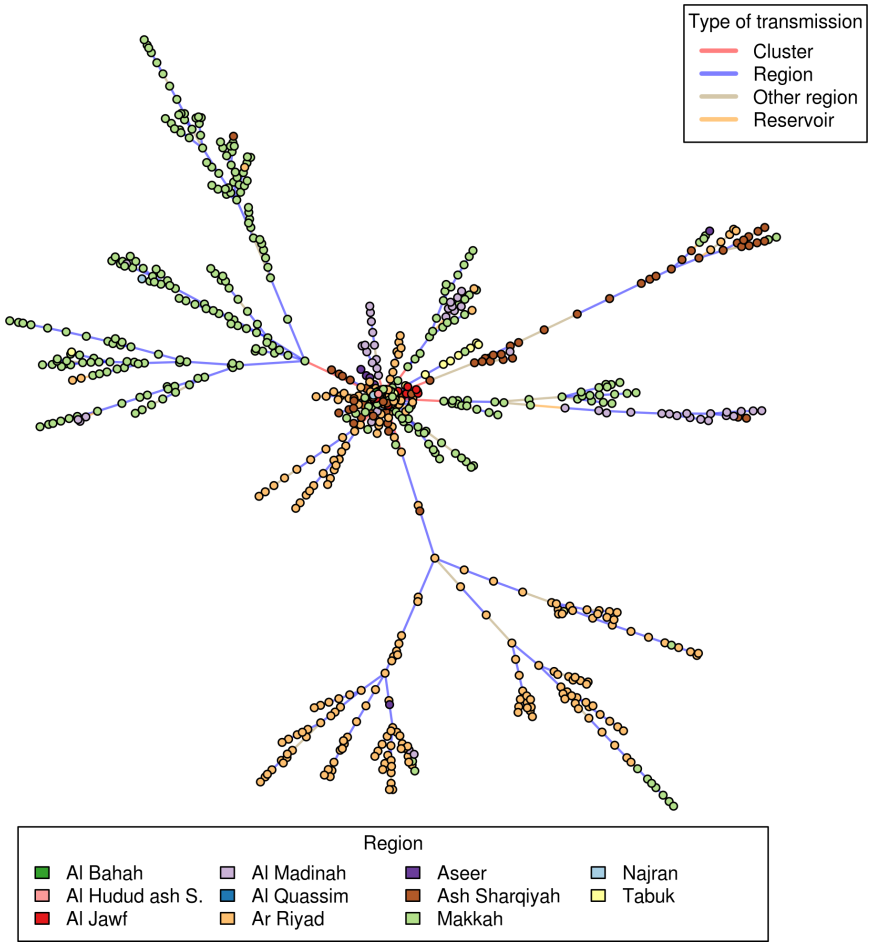

Fig. 4. A reconstructed transmission tree consistent with the data. Each dot represents a case. The large central dot represents the animal reservoir.

number is on average 47% (95% CI: 34%, 63%) of its initial value (Figure 2B).

The within-region reproduction number R_g is estimated at 0.24 (95% CI: 0.19, 0.29). This suggests that clusters of the same region are not necessarily closed epidemics independent of each other but that there can be substantial transmission between them. In contrast, clusters from different regions appear to be largely independent of each other (between-region reproduction number R_o: 0.05, 95% CI 0.02, 0.09).

We estimate that the serial interval (delay between symptom onset in a case and symptom onset in the persons they infect) of MERS-CoV has a mean of 6.8 (95% CI: 6.0, 7.8) days and a standard deviation of 4.1 (95% CI: 3.4, 5.0) days (Figure 2C).

We estimate that the weekly number of introductions from the reservoir grew by approximately four-fold during the study period: from 0.5 (95% CI: 0.2, 0.8) reported cases per week infected by the reservoir in early 2013 to 2.1 (95% CI: 1.0, 3.6) in mid-2014.

We explore the ability of our model to reproduce MERS-CoV epidemic dynamics in KSA by using the model to simulate epi-

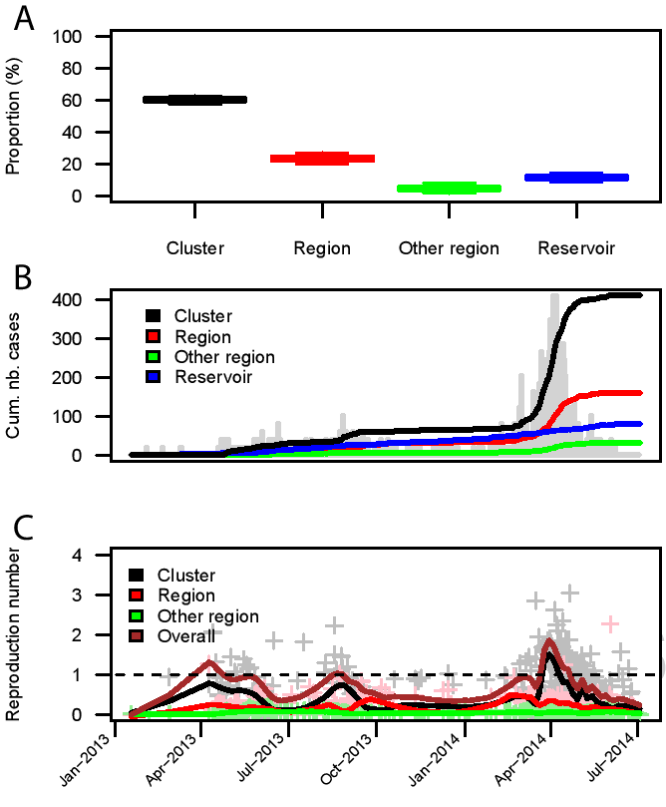

Fig. 5. Relative contributions of the different routes of transmission. A. Proportion of cases by inferred route of transmission. **B.** Temporal trend in the cumulated number of cases by inferred route of transmission. Trends in the daily number of cases appear in grey. **C.** Temporal trend in the estimated reproduction number for the different routes of transmission. Grey, pink and green crosses give estimates of within-cluster, within-region and between-region reproduction numbers for individual cases, respectively. These summary statistics were derived from the probabilistic reconstruction of 500 transmission trees consistent with the data like the one plotted in Figure 4.

demics from 1 January 2013. We find that the model satisfyingly reproduces the distribution of the number of cases (Figure 3A), of the number of clusters (Figure 3B) and of the size of these clusters (Figures 3C-F). The model can also generate explosive outbreaks over short time periods similar to what was observed in spring 2014 (Figures 3G-H).

We can also use the model to reconstruct the transmission tree and probabilistically determine the likely source of infection of each case. Figure 4 shows an example of an inferred transmission tree. Figure 5 presents summary statistics calculated from a sample of 500 such trees. We estimate that 12% (95% CI: 9%, 15%) of the cases were infected via exposure to the animal reservoir, 60% (95% CI: 57%, 63%) were infected in their cluster, 23% (95% CI: 20%, 27%) were infected by cases from other clusters in their region and only 5% (95% CI: 2%, 8%) from cases of other regions (Figure 5A). This finding is illustrated in Figure 4 where the different regional outbreaks appear to be largely independent. In particular there is very little transmission between Riyadh and Makkah regions. Figure 5B shows the time series of the reconstructed cumulative number of cases by source of infection. It suggests that infections from the reservoir have occurred repeatedly over the study period. In contrast, within-cluster infections are concentrated in time during 3 three substantial outbreaks that occurred in May 2013, September 2013 and March-May 2014. The last of these outbreaks involved by far the largest contribution of within-cluster and within-region transmission. These three peaks of transmission are apparent in Figure 5C, which presents reconstructed trends in individual reproduction numbers. The smoothed overall reproduction number peaked at 1.9 in March-April 2014. Figure 4 also shows that while most introductions generated few secondary infections, a small number of them had a disproportionate contribution to the epidemic. We estimate that three zoonotic infections were responsible for 464 (95% CI: 376, 532) MERS-CoV cases during this time period, indicating large heterogeneity in the length of chains of human-to-human transmission.

Discussion

In this paper, we studied the spatiotemporal clustering of MERS-CoV cases in KSA, the country that has been the most affected by MERS-CoV. The framework we developed made it possible to analyze all surveillance data in a coherent and integrated manner, in contrast to previous studies that have examined individual aspects of the observed epidemiology (for example cluster sizes). Our analysis has resulted in a more holistic characterization of MERS-CoV epidemiology in KSA.

Surveillance data for zoonotic infections such as MERS-CoV or avian influenza are often challenging to interpret because it is rarely possible to reliably identify the source of infection of each case. If multiple clusters of cases are detected in the same area and time period, it is unclear whether we should assume that they are independent introductions of the virus from the reservoir or that they belong to the same chain of transmission. If no human source of infection has been identified, does it mean that the case was infected by the reservoir? The answer depends on the quality of the epidemiological investigation, which may vary geographically and over time. A strength of our approach is that we do not need to assume that clusters are completely independent of each other. Instead we can estimate the degree of epidemiological linkage between clusters and assess how that linkage varies by the geographic separation of clusters (within- vs between- region). Our algorithm for identifying clusters was deliberately designed to be liberal in linking cases, to match the way surveillance data are collected. However, we found that the clusters thus identified were highly relevant epidemiological units in that we estimate that two thirds of human-to-human transmissions occurred within clusters. The clusters we identified also stratified observed heterogeneity in transmission intensity well. We estimated that there was substantial transmission between clusters within the same region, validating our prior belief that clusters cannot be treated as independent, but little transmission between regions. Another strength of our approach is that it does not require that the source of infection of a case (human or animal) to be known to ascertain the contribution of the animal reservoir in the overall epidemic.

We found that a majority of MERS-CoV cases (88%) reported during this time period were due to human-to-human transmission. Different strategies may be considered to evaluate the relative contribution of the animal-to-human and human-to-human transmission First, one can perform thorough epidemiological investigations of MERS-CoV patients to ascertain their likely source of infection. Second, viral genetic sequences can be used to assess the number of independent introductions of the virus in an area. Third, analysis and modelling of the spatiotemporal clustering of MERS-CoV patients as performed here can be used to better characterize the dynamics of spread. Each of these approaches has limitations. Epidemiological investigation may struggle to identify sources of infection when modes of zoonotic exposure remain poorly characterized and when multiple exposures are possible. Although the number of concurrent viral lineages may be inferred from sequence data, the origin of these lineages (e.g. animal reservoir vs. humans from other regions) may be harder to ascertain. Last, modelling relies on spatiotemporal locality to link cases and may be sensitive

to assumptions about the mechanisms of spread. Given these limitations, substantial insights may be gained by running these analyses independently and then carefully comparing their findings (7, 13). In that respect, the large Jeddah outbreak in March-May 2014 offers an interesting opportunity. A thorough field investigation of MERS-CoV patients in the outbreak concluded that the proportion of cases infected by the reservoir was likely to be very small (3 out of 112 of MERS-CoV patients who were not health care workers and had exploitable data) (5). This is largely consistent with our analysis that estimates that 5 (95% CI: 2-11) cases in this outbreak were infected by the reservoir. These results are also corroborated by the analysis of seven sequences isolated during the Jeddah outbreak that were found to be largely homogeneous, all falling within a single clade (4). For the 2014 Riyadh outbreak, concurrently circulating viruses were found to be distributed across at least 6 different clades (4), which is roughly consistent with our estimate of 4 (95% CI: 1, 8) introductions from the reservoir in that outbreak. Compared with epidemiological investigations that are thorough but limited in time and space (5), the analysis of surveillance data presented here makes it possible to get a more comprehensive picture of MERS-CoV transmission across KSA for an 19-month time period. Although transmission was relatively quickly controlled in most clusters, our study highlights that few clusters acted as major amplifiers of the epidemic. Ensuring a consistent response is quickly implemented in all clusters is essential to reduce the burden of MERS-CoV.

In the absence of detailed data documenting infection control measures implemented during MERS-CoV outbreaks, it is not possible to estimate the intrinsic transmissibility of MERS-CoV in the absence of interventions (the basic reproduction number R_0). We can only estimate the reproduction number seen in individual outbreaks, an estimate that implicitly incorporates the effects of the interventions in place. Our study shows that for the level of control implemented in KSA, MERS-CoV epidemics are not self-sustaining in that country. However, one needs to be cautious when extrapolating from this study to countries with more limited health care resources. Analogies exist with the recent Ebola epidemic in West Africa; previous Ebola outbreaks were contained after at most few hundred cases, arguably leading to a false sense of security that all future outbreaks would also be readily contained. Like Ebola, MERS-CoV also exhibits high levels of heterogeneity in onward infection rates from case to case and hospital to hospital. Indeed, given MERS-CoV infections are not as consistently clinically severe as Ebola, case finding and effective contact tracing might be more challenging in a large scale outbreak in a resource-poor setting. Furthermore, evolutionary theory suggests that pathogens that are most at risk of evolving high levels of transmissibility are those that are already moderately transmissible; predicted probabilities of major epidemics increase non-linearly as reproduction numbers approach one and case numbers increase (14). Our approach, like other methods that reconstruct the transmission tree from case data (11, 12), can quantify trends in the effective reproduction number. However, more detailed models and data are needed to decipher the mechanisms explaining these trends. For example, is the declining trend in the within-cluster reproduction number (Figure 2B) due to control measures or to other mechanisms such as depletion of susceptibles? Answering this question will require detailed data on control measures but also on the structure of hospitals (number of wards and number of beds per ward, bed occupancy etc).

This study has a number of limitations. Like for most emerging infectious diseases, reporting of MERS-CoV cases is imperfect and has changed over time. For example, the case definition changed on 13 May 2014 to allow for wider testing of suspect cases (15). Under-reporting and variations in testing protocols can potentially bias estimates. To evaluate the robustness of our findings to these issues, in a sensitivity analysis, we restricted the study to 495 cases (73%) which were detected through passive surveillance (SI Text, Table S1), i.e. the surveillance type that was most stable over time. Even though a third of cases were removed, results remained roughly unchanged with the proportion of infections from the reservoir increasing slightly from 12% (95% CI: 9%, 15%) to 17% (95% CI: 13%, 20%). In particular, exponential growth in the risk of spillover was robust to the surveillance subset (SI Text, Table S1). This suggests that the quantified increase was not a mere surveillance artefact and that there was indeed a growing MERS-CoV epidemic in the reservoir at the time of the study. We also explored sensitivity of our findings to the presence of atypically large clusters and found that our estimates changed little when we removed 102 cases from the most affected hospital from the analysis (SI Text, Table S2). We modeled temporal variations in introductions from the reservoir with a Poisson distribution that had a time-varying mean. However, introductions may occur in clumps. To explore this possibility, we considered an alternative scenario in which the daily number of introductions was modeled with a Negative Binomial distribution characterized by high overdispersion. We found this had little impact on our estimates (SI Text, Table S3). We cannot rule out the possibility that some of the human-to-human transmission events we inferred could actually be animal-to-human transmission events even though our population level estimates are consistent with other data sources.

While healthcare facilities can amplify transmission of MERS-CoV, we still poorly understand the factors that facilitate human-to-human transmission in health care settings and in the community, and which may therefore explain the heterogeneity in transmission intensity we have characterized. In a number of nosocomial outbreaks, a large proportion of cases had comorbidities (3, 5) which have been suggested to increase susceptibility to infection or disease severity. Another possibility is that certain aerosolizing medical procedures in hospitals facilitate spread. Unfortunately, we were unable to test these hypotheses here as information on comorbidities and hospital practices was unavailable. It is important that we address such knowledge gaps to strengthen outbreak control in the future.

The ongoing exposure of the humans to MERS-CoV is of major concern, with the risk of a major epidemic growing larger the longer exposure remains unchecked. Understanding the medical, healthcare and social factors that facilitate high levels of human-to-human transmission and lead to large outbreaks is critical to continued containment of the ongoing threat posed by MERS-CoV.

Material and Methods

Data

The KSA Ministry of Health routinely collects detailed information on all patients with laboratory-confirmed MERS-CoV infection through multiple sources that include MERS-CoV case report forms, laboratory report forms, and clinical records. The database contains for each case: the reason for testing, whether the case had symptoms meeting the MERS-CoV case definition at the time of testing, clinical status (hospitalized, home isolation, discharged, or deceased), demographic information, date of symptom onset, hospital where treated, diagnosed and/or tested. The study period is 1 January 2013 to 31 July 2014.

We partition MERS-CoV cases into clusters. A cluster is defined as a group of cases who were treated, diagnosed and/or tested in the same hospital, with a time lag between two consecutive cases of at most 21 days. These clusters thus encompass not just nosocomial infections that occurred within the hospital, but also infections that may have occurred in the catchment area of the hospital (either from another person in the community or from the animal reservoir).

The data are available as Supplementary Material (dataset S1).

Modelling the risk of MERS-CoV infection

The reproduction number R (*i.e* the mean number of secondary cases generated by a human case) is decomposed into mutually exclusive categories arising from within-cluster transmission (R_C), from within-region transmission (R_R, i.e. transmission to other clusters of the region) and from between-region transmission (R_O, i.e. transmission to clusters of other regions). To capture the dynamics of transmission and control within clusters, we assume that when a new cluster c starts, the within-cluster reproduction number $R_C^c(0)$ in that cluster is drawn from a Gamma distribution with mean R_C and standard deviation σ_C. After C_t cases, the within-cluster reproduction number is $R_C^c(C_t) = R_C^c(0)(1+C_t)^{-\gamma}$ *(16, 17)*. Decline in the within-cluster reproduction number could be due to control measures and/or to other factors such as the natural depletion of susceptible individuals.

We explore scenarios where the risk of infection from the reservoir could be constant or increase exponentially over time.

Statistical inference

In a Bayesian setting, we develop a data augmentation strategy to estimate parameters of the model (18-21). The source of infection of each case (reservoir or another human case of the dataset) is considered as augmented data. Markov chain Monte Carlo sampling is used to explore the joint posterior distribution of parameters and augmented data (18-22).

Technical details are given in SI Text.

Acknowledgments.

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