Urbanization prolongs hantavirus epidemics in cities

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Urbanization and rural–urban migration are two factors driving global patterns of disease and mortality. There is significant concern about their potential impact on disease burden and the effectiveness of current control approaches. Few attempts have been made to increase our understanding of the relationship between urbanization and disease dynamics, although it is generally believed that urban living has contributed to reductions in communicable disease burden in industrialized countries. To investigate this relationship, we carried out spatiotemporal analyses using a 48-year-long dataset of hemorrhagic fever with renal syndrome incidence (HFRS; mainly caused by two serotypes of hantavirus in China: Hantaan virus and Seoul virus) and population movements in an important endemic area of south China during the period 1963–2010. Our findings indicate that epidemics coincide with urbanization, geographic expansion, and migrant movement over time. We found a biphasic inverted U-shaped relationship between HFRS incidence and urbanization, with various endemic turning points associated with economic growth rates in cities. Our results revealed the interrelatedness of urbanization, migration, and hantavirus epidemiology, potentially explaining why urbanizing cities with high economic growth exhibit extended epidemics. Our results also highlight contrasting effects of urbanization on zoonotic disease outbreaks during periods of economic development in China.

Significance

Urbanization reduces exposure risk to many wildlife parasites and in general, improves overall health. However, our study importantly shows the complicated relationship between the diffusion of zoonotic pathogens and urbanization. Here, we reveal an unexpected relationship between hemorrhagic fever with renal syndrome incidence caused by a severe rodent-borne zoonotic pathogen worldwide and the process of urbanization in developing China. Our findings show that the number of urban immigrants is highly correlated with human incidence over time and also explain how the endemic turning points are associated with economic growth during the urbanization process. Our study shows that urbanizing regions of the developing world should focus their attention on zoonotic diseases.

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HFRS, China accounts for 90% of total HFRS cases worldwide (23, 24), mainly caused by two strains of hantavirus: Hantaan virus (HTNV; carried by Apodemus agrarius) and Seoul virus (SEOV; carried by Rattus norvegicus) (25, 26). More than 1.2 billion people live in provinces of China where HFRS has been reported (27).

An increasing number of studies point to links between the urbanization process and the spread of zoonotic diseases (28–31). Previous studies have shown that HFRS incidence is linked to land use change (32–34), especially along the urban–rural gradient (35, 36). However, studies that address the dynamics of zoonotic spillover, with particular focus on the role of urbanization over long timescales, are lacking. We set out to disentangle the complex relationship between urbanization and infectious disease dynamics at the human–wildlife interface using an unprecedented amount of data covering 48 y (1963–2010). These data date back to the first HFRS case reported in Hunan Province, China.

Results
Dynamics and Spatial Clustering. More than 110,000 HFRS cases were reported in Hunan Province from 1963 to 2010 in a province with more than 60 million people, covering an area of 211,800 km² in southern China. The incidence curve over the 48-y period is reasonably characterized by two phases: phase I spanning from 1963 to 1990 and phase II covering the period between 1991 and 2010 (Fig. 1A). The time series of incidence highlights the geographic pattern of the epidemic, which spread from western cities to eastern ones throughout the 1980s and 1990s (Fig. 1B and SI Appendix, Fig. S1). During phase I, the main endemic areas of HFRS were located in western Hunan Province (Fig. 1C), while in phase II, newly established endemic areas emerged in the east (Fig. 1D). It is worth noting that the spatial and temporal patterns of HFRS incidence coincide with trends in urbanization and immigration patterns across Hunan (Fig. 1 D and E) rather than native population growth or the balance between immigration and emigration (SI Appendix, Figs. S2 and S3). A second notable feature is the synchronized pattern of the urbanization process and immigration across the cities.

Urbanization and Immigration. We compared patterns of urbanization and number of immigrants at both provincial and city scales with those of HFRS incidence from 1963 to 2010. HFRS incidence and urbanization followed an inverted U-shaped relationship at the provincial scale (Fig. 2A). In phase I, the primary stage of urbanization, HFRS incidence and urbanization were strongly positively correlated, whereas in phase II, they were negatively correlated. We propose the existence of an endemic turning point (ETP) between urbanization and zoonotic trends as a result of interventions reducing incidence during phase II (Fig. 2A). The HFRS incidence and number of immigrants are strongly positively correlated for both phases (1963–2010) (Fig. 2B). This result indicates that the effect of urbanization on HFRS epidemics changed, while the effect of immigration remained constant (SI Appendix, Fig. S4).

We used the city level to parameterize the spatiotemporal model. Fig. 3 shows the incidence of HFRS and pattern of urbanization for each city. The patterns are conspicuously different between locations—most, although not all, eastern cities experienced more prolonged epidemic buildup than western cities. This difference may be associated with specific socioeconomic profiles, a point to which we return later. To account for uncertainty in the ETPs, we used a Bayesian approach (Materials and Methods). Posterior medians and 95% credible intervals for the model parameters are provided in SI Appendix, Table S3. Our final results focus on the posterior median values. HFRS incidence exhibits a first-order autoregressive signature, indicating that the occurrence of HFRS in a given year is related to the numbers in the preceding year. In addition, we found that cities with a large immigrant population have a higher incidence of HFRS than cities with a small immigrant population. The predicted incidence from the spatiotemporal model fit well with the observations over the 1992–2010 period, including peak values (Fig. 4) (the average R² train and R² test of cross-validation are 0.89 and 0.71, respectively). Trace plots (SI Appendix, Fig. S5) and

![Fig. 1. Time series dynamics of HFRS outbreaks in Hunan Province. (A) Temporal distribution patterns of HFRS incidence (black bars), urbanization (blue line), and number of immigrants (gray bars) in Hunan Province, 1963–2010. The number of immigrants in Hunan is not available for the years 1967–1969, 1990–1991, and 1995. (B) HFRS incidence in the 14 cities of Hunan by longitudes. (C) The spatial distribution of HFRS incidence and urbanization in each city for phase I (1963–1990). (D) Urbanization (blue circles) and (E) percentage of immigrants (gray circles) in each city for phase II (1991–2010). In C and D, the background maps with color gradient present the incidence of HFRS for phase II (1991–2010). Urbanization of cities in our study is defined as the percentage of the nonagricultural population (which is recorded in China’s Hukou household registration system) to the total population.](www.pnas.org/cgi/doi/10.1073/pnas.1712767115)
We studied the variation in ETPs among cities by examining the correlation between urbanization growth and per capita economic growth. The results reveal strong correlations between the ETPs, economic growth, and immigration (Fig. 5A). It is important to note that ETP is positively associated with per capita gross domestic product growth ($r = 0.80, P < 0.01$). Urbanization growth correlated with per capita gross domestic product growth as well ($r = 0.69, P < 0.01$). Note that all of these quantities are significantly negatively correlated with elevation of city (unit: meters). Overall, the duration of HFRS epidemics (represented by the time to peak of HFRS incidence since the end point of the epidemic, which may be influenced by vaccination campaigns that started after 2010; note that the epidemic is still ongoing) was prolonged in cities with higher ETPs ($r = 0.70, P < 0.01$) (Fig. 5B) and relatively high levels of urbanization. These results suggest that cities with faster economic growth during the urbanization process may reach their ETPs later (i.e., experienced more prolonged epidemics) due to the large number of immigrants prolonging the epidemic duration, while economic growth contributes toward improvements in the living conditions and general health of a population. These contrasting effects may influence the dynamics of the epidemics (e.g., epidemic duration and ETP). A structural equation model analysis consistently supported our hypothesis and previous analysis and indicated the following pathways (Fig. 6). Urbanization growth correlated with per capita gross domestic product growth followed by a direct positive effect of per capita gross domestic product growth on immigration. This result is consistent with previous studies, which found evidence of long-run causality from per capita economic growth to immigration but not vice versa (38). Additionally, a long-term balanced relationship exists between urbanization and economic growth in China (39). The urbanization process seems to have a positive indirect effect on the ETP via gross domestic product growth rate, and immigration has a positive direct effect on the ETP.

**Discussion**

The transition of populations from rural to urban environments has resulted in changing global patterns of disease and mortality (40, 41). Our study of hantavirus spillover raises a number of issues. We clearly show the important roles of urbanization and population migration in epidemic spread using historical datasets of time series comprising half a century of records. In particular, the long-term data from Hunan Province allow us a unique opportunity to study the relationship between urbanization and zoonotic diseases. In our study area, HFRS was first reported in 1963; a relatively low prevalence of hantavirus infections among both rodent and human cases would be expected to be seen in the early years (accompanying a relatively low level of urbanization). Then, during the period of eastward spread, the virus spread among rodents from endemic to nonendemic areas. This was followed by an increase in incidence of HFRS until urbanization finally resulted in an ETP.

In industrialized nations, urban living has generally contributed to an overall improvement of health (8). During the last 50 y, we find a biphasev inverted U-shaped relationship between urbanization and HFRS rates in Chinese cities. We use the ETP to quantify the difference in peak between cities. Our results show that cities with a higher economic growth rate experienced
more rapid urbanization and prolonged HFRS epidemics. We infer that the process of urbanization and associated economic growth may delay zoonotic disease decline, possibly due to a higher volume of immigrants and the specific living conditions of recent immigrants (SI Appendix, Fig. S8). The statistical relationship between HFRS, urbanization, and immigration plausibly results from a chain effect from economic growth, which drives the urbanization process and regulates/encourages immigrant movement, thereby influencing overall epidemic situations. The number of immigrants is also affected by many factors, such as urbanization, economic growth, increased demand for labor, and other socioeconomic factors. Therefore, the relationships between immigration and zoonotic spillover and between immigration and urban growth may be complex and may not be linear for every case (SI Appendix, Figs. S4 and S8). In addition to the urbanization process, there is evidence that elevation is also an important factor with regards to immigration. Higher-elevation areas tend to have lower economic growth rates and in turn, attract fewer immigrants (Fig. 5A and SI Appendix, Fig. S9). Perhaps this is not a surprising result: lower average elevation contributes positively to economic growth in China (42). Thus, the complexity of zoonotic spillover is likely to be a result of a combination of environmental, biological, and anthropogenic dimensions to the interactions at the human–wildlife interface (7, 16). The detailed interrelatedness of urbanization rates, immigration, and economic growth is an important area for future work.

Urban environments have proven to be favorable for rat (Rattus spp.) population growth and associated zoonoses (43), with a notable increase in SEOV-related HFRS in cities of China due to the increased contact between rats and humans (44). The early stage of urbanization is characterized by mass rural–urban immigration alongside rapid urban expansion with poorly developed infrastructure (45). New immigrants usually enter urban regions with poor housing and health care conditions, which are factors contributing toward a high risk of human infection. Moreover, owing to farmland conversion, deforestation, and other land use changes induced by urban expansion, habitat loss and fragmentation could drive rodent movement and thereby, increase human exposure to rodents (46, 47).

Finally, we show that epidemic levels of HFRS generally decline when the urbanization process (SI Appendix, Figs. S10 and S11 and Table S1) results in an ETP. Urbanized settings are driven by economic growth, and economic growth contributes to improvements in the general health of a population. Increased development generally improves living conditions, thereby reducing rat populations. The key to HFRS control is to both reduce peri-domestic rodent abundance and enhance vaccination coverage. Vaccination programs need to take into account the particular challenge of human migration from rural to urban settings. In particular, our analysis shows that immigration influences spatiotemporal patterns of HFRS incidence during the urbanization process, with resulting health implications. On the
Materials and Methods

Data. We used official reports and associated socioeconomic data for Hunan Province. Records of HFRS cases from 1963 to 2010 were obtained from the Hunan Provincial Center for Disease Control and Prevention. As HFRS is a severe viral disease in China, strict criteria are applied to both clinical diagnosis and reporting procedures, and the surveillance strategies for HFRS in Hunan remained constant during the study period. Since the 1980s, cases were also confirmed by detecting antibodies against hantavirus in patients’ serum samples. We also conducted the analysis using the dataset from 1980 to 2010. The results consistently supported our analysis (SI Appendix, Figs. S14 and S15). In 2008, the HFRS-targeted Expanded Program on Immunization was implemented to reduce the incidence of HFRS, and a vaccination campaign was conducted in our study area since 2009 (50). Therefore, the incidence of HFRS after 2010 was not included in our analysis.

Demographic data, including the total population size and number of immigrants (from 1963 to 2010), were obtained from Hunan Province’s statistical yearbook, China’s statistical yearbook of cities, and the Hunan Public Security Bureau. Here, immigration is defined as the movement of people into a destination city to settle or to take up employment as migrant workers. In our study, the urbanization at the provincial level is defined as the percentage of the total population living in urban areas (Fig. 1), while the urbanization at the city level is defined as the percentage of the non-agricultural population (which is recorded in China’s Hukou household registration system) to the total population. Due to changes in the official statistical category of “urban population” at the city level, these data span a shorter period. The data were grouped by city according to the administrative boundaries for 14 cities. There is high concordance between the urban population (SI Appendix, Fig. S12) and the nonagricultural population at both the provincial and city levels (SI Appendix, Fig. S13). Remotely sensed data were acquired using Landsat Thematic Mapper and Enhanced Thematic Mapper Plus as the base images used to extract coverage of urban areas and to quantify urban area expansion.

Urbanization and HFRS Dynamics. The relationship between urbanization and HFRS incidence is explored as a function of the urbanization and the number of immigrants. Early urbanization information was incomplete for some cities; these were, therefore, replaced through linear extrapolation. We note that it is difficult to accurately reconstruct the missing number of annual immigrants for the early study period (details are in SI Appendix, Table S2).

Estimating the ETP. At some time point during the course of the urbanization process, all cities exhibit an ETP defined as the inflection point along the epidemic curve at which incidence changes from increasing to decreasing. This point is likely a complex function of improved sanitation, health care access, and shifts in peridomestic abundance of the rodent reservoir host. To investigate HFRS dynamics across cities, we used a flexible Bayesian estimation method, which links observed HFRS incidence in city s and year t, Y(st), to immigration (N), urbanization (U), and the city-specific empirical ETPs. The spatiotemporal Poisson regression model considered is given by

\[
Y(s, t) \sim \text{Poisson}(\mu(s, t))
\]

\[
\log(\mu(s, t)) = g(s, t) + E_t + E + \eta(s)
\]

\[
E_t = \varphi \exp \left( -\frac{U(s, t) - \text{ETP}(s, t)}{\tau} \right)
\]

where \(\varphi\) denotes the fitted model, \(E_t\) is the overall urbanization effect, and \(E\) is the overall immigration effect on HFRS epidemics, with the coefficients \(\beta, \gamma, \text{and } \varphi\) representing regression parameters. Temporal random effects were modeled by a first-order autoregressive process: \(g(s, t) = \rho g(s, t - 1) + \epsilon\). The parameter \(\rho\) is the temporal correlation between consecutive years. The spatial random effect used a spatial process \(\rho(s)\), which was assumed to have a conditionally autoregressive (CAR) structure (51). The CAR structure incorporates spatial dependence by specifying the distribution of the random effect for a city as being dependent on the collection of random effects for all geographically adjacent cities. \(\| \rho(s) \| = \mathcal{N}(\rho(s), c(s))\); \(c(s)\) is the number of neighbors corresponding to city \(s\), \(\| \cdot \|\) denotes the mean of neighboring random effects for city \(s\), and \(t\) is a scaling variance parameter. Hence, cities that border many other cities have a smaller variance.

We fitted the epidemic model (Eqs. 1–4) to the reported incidence for each city using a subset of data from 1992 to 2010 (due to the missing covariate information) (SI Appendix, Table S2) using hierarchical Bayesian
modeling with sampling-based methods. To assess the accuracy of the model, we used the dataset (1992–2005) for training runs (in-sample prediction) and the remaining data (2006–2010) to test the model (out-of-sample prediction). Metropolis–Hastings Markov Chain Monte Carlo was used for sampling the posterior distributions (52). Model fitting and model convergence were conducted using MATLAB (r2009b) tool box Delayed Rejection Adaptive Metropolis (53). Three chains with different initial conditions were used to check for convergence of posterior distribution estimates. Priors for all parameters were defined as Gaussian distributions, with a mean of 0 and a variance of 100. Each chain was run for 5 million iterations, with a burn-in of 500,000 iterations.

Structural Equation Model. Urbanization has a complex effect on the incidence of zoonotic disease; hence, we used structural equation models as an integrated approach to estimate the structural correlation between variables by using the R package lavaan (54) with maximum likelihood estimation procedures.

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