Heterogeneity in social and epidemiological factors determines the risk of measles outbreaks

Paolo Bosetti[a,b,1], Piero Poletti[a,1,2], Massimo Stella[a], Bruno Lepri[a], Stefano Merler[a,3], and Manlio De Domenico[a,3]

[a]Center for Information and Communications Technology, Fondazione Bruno Kessler, 38123 Povo (Trento), Italy; and [b]Mathematical Modelling of Infectious Diseases Unit, Institut Pasteur, UMR2000, CNRS, 75015 Paris, France

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Political and environmental factors—e.g., regional conflicts and global warming—increase large-scale migrations, posing extraordinary societal challenges to policymakers of destination countries. A common concern is that such a massive arrival of people—often from a country with a disrupted healthcare system—can increase the risk of vaccine-preventable disease outbreaks like measles. We analyze human flows of 3.5 million (M) Syrian refugees in Turkey inferred from massive mobile-phone data to verify this concern. We use multilayer modeling of interdependent social and epidemic dynamics to demonstrate that the risk of disease reemergence in Turkey, the main host country, can be dramatically reduced by 75 to 90% when the mixing of Turkish and Syrian populations is high. Our results suggest that maximizing the dispersal of refugees in the recipient population contributes to impede the spread of sustained measles epidemics, rather than favoring it. Targeted vaccination campaigns and policies enhancing social integration of refugees are the most effective strategies to reduce epidemic risks for all citizens.

multiplex networks | human mobility | infectious diseases | population dynamics

Human migration represents a complex phenomenon influencing in several interconnected ways the economy, the healthcare, and the social cohesion of whole countries (1–7). However, it is only recently that the availability of massive datasets opened to new advancements in modeling and understanding such complexity (8–16), addressing the urgent need for effective, large-scale intervention policies toward managing the consequences of massive migration flows (5).

Here, we focus our attention on Turkey, a country facing a humanitarian emergency of unprecedented levels (17). In the last decade, more than 3.5 million (M) Syrians, displaced by the war, have sought refuge in Turkey. The arrival of a huge amount of people with different economic, health, and living conditions, and from a country where the healthcare system has been almost completely disrupted, may raise serious concerns about the risks of the Turkish health system being overburdened.

Turkish infectious-disease specialists are concerned that the crisis of Syrian refugees may impose serious risks to Turkey by bringing back infectious diseases previously eliminated or in the process of being eliminated (18, 19). According to the latest reports from the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) (20), immunization coverage in Syria dropped from more than 80% before the war to a worrying 41% in 2015 for the most basic vaccines, resulting in millions of unvaccinated children. Direct consequences of this alarming situation are a high risk of epidemic outbreaks [e.g., evidence for polio (21) and measles (22–24) has been reported] and a potential increase of mortality due to diseases which could be prevented with vaccines (25). Countries, such as Turkey, Lebanon, and Jordan, hosting a great concentration of Syrians perceive the lack of an appropriate immunization coverage as a potential risk of epidemic outbreaks for the local population (18).

The aim of this study is to investigate the risk of observing widespread measles epidemics in Turkey and how this risk is affected by the level of mixing between refugees and the local populations. After the influx of Syrian refugees, an increase of measles cases has been observed (24), and two measles outbreaks in 2013 and 2018 have been reported (24, 26, 27). In order to reduce the risk of vaccine-preventable diseases, the Ministry of Health of Turkey—in collaboration with UNICEF—conducted several vaccination campaigns between 2013 and 2014. Syrian children living in and out of temporary shelters have been vaccinated free of charge and are now included in the Turkish National Childhood Vaccination Program. Refugees have been receptive to vaccination, and recent estimates suggest that a 95% vaccine uptake was reached in the temporary shelters. However, in this country, more than 90% of the Syrian population lives in communities where immunity levels might be significantly lower, and seeking vaccination services remains a problem because of high mobility and lack of knowledge about refugee health centers (23).

The contribution of our work is twofold. On the one hand, we quantify the epidemic risks associated with measles in Turkey and how appropriate policies devised to enhance social integration between refugees and local populations may significantly reduce the risk of observing widespread epidemics. On the other hand, we highlight crucial epidemiological and socio-demographic components shaping these risks, identifying

Significance

The recent increase in large-scale migration trends generates several concerns about public health in destination countries, especially in the presence of massive incoming human flows from countries with a disrupted healthcare system. Here, we analyze the flow of 3.5 M Syrian refugees toward Turkey to quantify the risk of measles outbreaks. Our results suggest that heterogeneity in immunity, population distribution, and human-mobility flows is mostly responsible for such a risk: In fact, adequate policies of social integration and vaccine campaigns provide the most effective strategies to reduce measles disease risks for both migrant and hosting populations.

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[1]P.B. and P.P. contributed equally to this work.

[2]To whom correspondence may be addressed. Email: poletti@fbk.eu.

[3]S.M. and M.D.D. contributed equally to this work.

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high-risk areas in the country that should be prioritized by public health interventions aimed at reducing current immunity gaps.

Results

The risk of measles reemergence in Turkey was analyzed by using a multilayer transmission model, explicitly taking into account potential infectious contacts occurring between individuals moving across the country. In the model, Turkey was divided into 1,021 patches corresponding to Turkish prefectures, which are spatial subunits of provinces and of the largest cities, reflecting administrative districts and metropolitan municipalities. The absolute number of Syrian and Turkish individuals in each prefecture and moving between patches was inferred from available mobile-phone data (28), following an approach similar to one used in previous studies (29–33). Measles immunity across different Turkish provinces for the two populations was estimated by combining epidemiological records available from different sources (4, 20, 24, 26, 27, 34) and taking into account possible geographical heterogeneity in measles-vaccine uptake (13–15). Measles transmission was modeled by considering a tunable parameter that accounted for a variety of scenarios on how much refugees interact with Turkish citizens, ranging from full segregation to full integration.

A schematic representation of the model is shown in Fig. 1, along with spatial mobility patterns inferred by the analysis of call detailed records (CDRs) associated with the usage of mobile phones in the country. An overview of the model structure and of the proposed methodological approach is reported in *Materials and Methods*. Technical details can be found in *SI Appendix*.

Measles Immunity Levels in Turkey. To overcome the lack of serological data, we inferred the fraction of susceptible individuals in the two populations by analyzing the epidemic growth rate of cases reported for Syria in 2017, the spatial heterogeneity in the proportion of children vaccinated in Turkey between 2006 and 2016, and the age distribution of cases reported during recent measles outbreaks (2013–2018).

The dynamics of infectious diseases are strongly determined by the infection-transmission potential, which can be measured through the basic reproduction number (R_0), defined as the average number of secondary infections generated by a typical case in a fully susceptible population (35–40). When considering diseases with preexisting levels of immunity (e.g., childhood diseases like measles), a measure of the actual transmission potential is provided by the effective reproduction number (R_e) (36, 40, 41).

We found that R_e associated with a measles epidemic that recently occurred in Syria was 1.27 (95% CI 1.19 to 1.37). Consequently, we estimated that the percentage of susceptible individuals in this country at the beginning of 2017 was 8.62% (95% CI 6.96 to 10.71%), while the percentage of susceptible individuals among Syrian refugees in Turkey was estimated to be 9.5% (95% CI 7.7 to 11.8%; Fig. 2). The spatial displacement of Syrian refugees in Turkey as inferred by CDRs (Fig. 1) clearly suggests that the current amount of refugees among different provinces is neither homogeneous over space nor proportional to local population sizes (Fig. 3).

Estimates obtained for Turkish citizens suggest that the percentage of susceptible Turkish citizens is lower than 5% in 92% of the Turkish prefectures. At the national level, only 2.3% of Turkish people might be currently susceptible to measles infection. However, this percentage ranges between 1.78% and 10.0% across prefectures, and worryingly high levels of susceptibility among Turkish citizens were found in some provinces

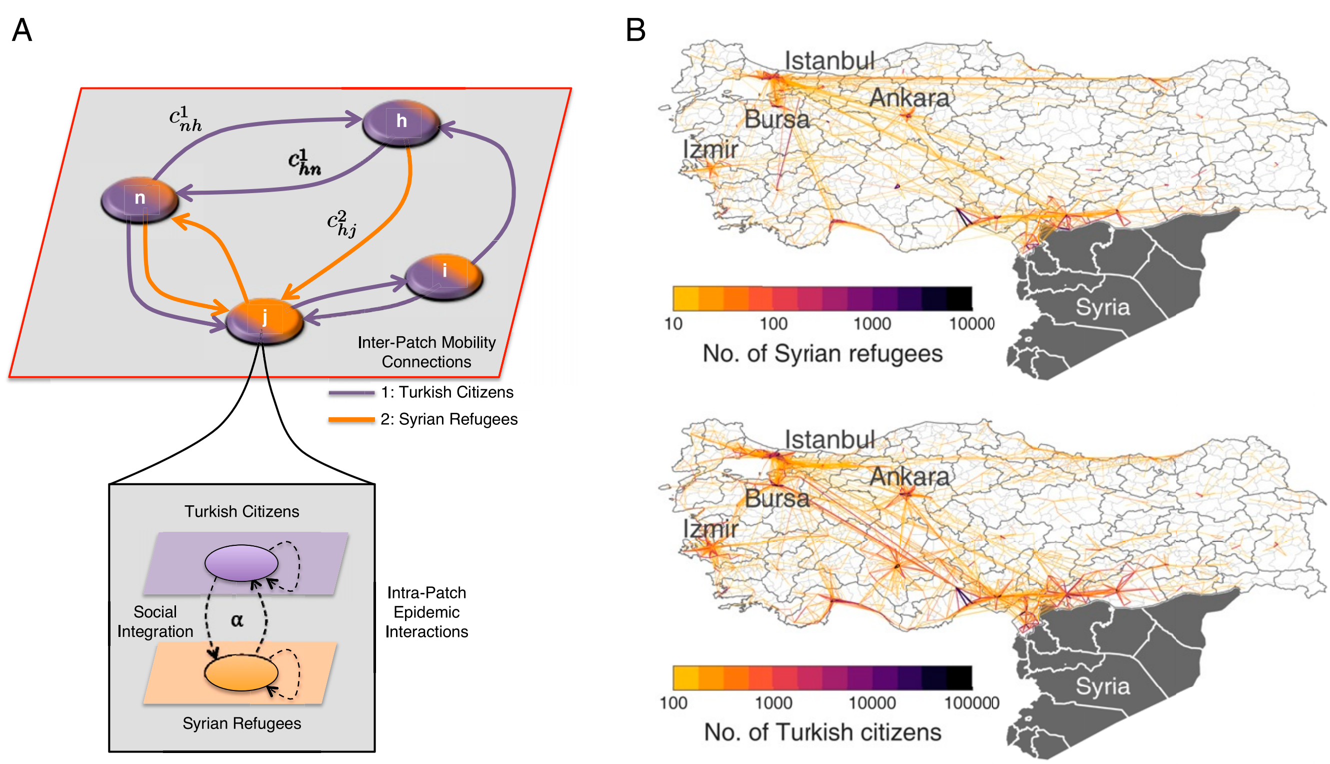

Fig. 1. Model structure and human mobility. (*A*) Schematic illustration of the model considered in this work. Each prefecture of Turkey is considered as a node of a metapopulation network of geographic patches. Two populations, namely, Turkish and Syrians, are encoded by different colors and move between patches following the inferred interpatch mobility pathways. Turkish and Syrian populations encode two different layers of a multilayer system (31–33), where social dynamics and epidemics spreading happen simultaneously. (*B*) Mobility of Syrian refugees (*Upper*) and Turkish citizens (*Lower*) between the prefectures of Turkey as inferred from CDRs. Different colors are used to indicate the number of individuals moving from a prefecture to another.

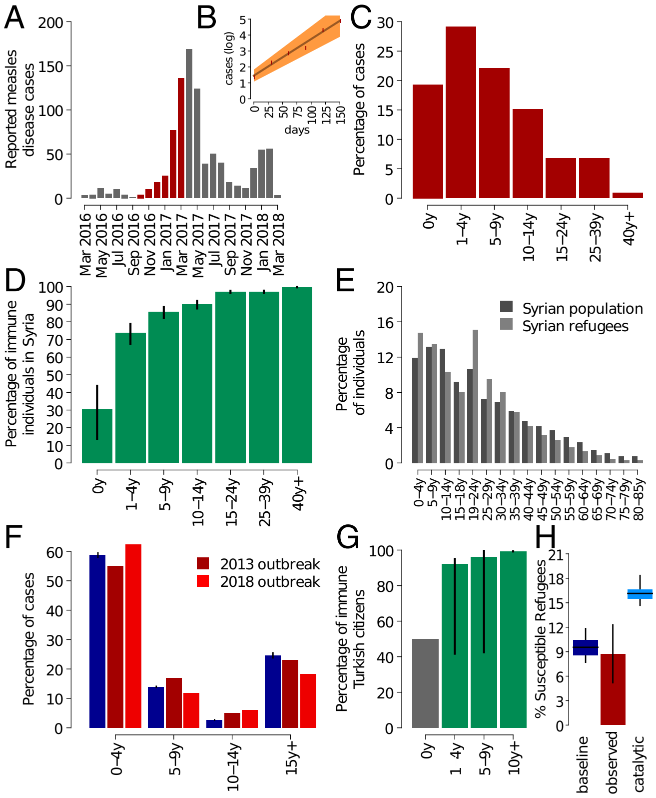

Fig. 2. Measles immunity levels. (*A*) Reported number of measles disease cases over time, during the 2016–2018 measles epidemics in Syria, as recently reported by the WHO (27); red bars correspond to data points used to derive the R_e as a function of the exponential growth rate of the observed epidemic. (*B*) Obtained fit of the epidemic exponential growth between September 2016 and February 2017 in Syria: The red solid line represents the mean estimate; the orange shaded area represents 95% CI. (*C*) Observed distribution of measles cases across different ages during the 2016–2018 measles epidemics in Syria, as recently reported by the WHO (27). (*D*) Model estimates of the age-specific immunity profile in Syria at the beginning of 2018: Green bars represents mean values; vertical black lines represent 95% CI. (*E*) Observed age distribution of Syrian refugees in Turkey (light gray) (42) compared with the population age distribution in Syria (dark gray). (*F*) Estimated (blue) and observed (red) distribution of measles cases across different ages during the 2013 and 2018 measles epidemics in Turkey. (*G*) Model estimates of the age-specific immunity profile in Turkey at the beginning of 2018. The gray bar represents the level of measles immunity in infants, here assumed to be 50%, as a consequence of maternal antibodies. Vertical bars in the age bands 1 to 4 y and 5 to 9 y show the variability (minimum and maximum) across different Turkish provinces in the immunity level of these age segments. The vertical bar shown for individuals older than 10 y of age represents the 95% CI of the immunity level in this age segment, as obtained by fitting the model on the age distributions of cases shown in *F*. (*H*) Estimated percentage of susceptible individuals among Syrian refugees in Turkey. Blue and light blue boxplots represent the immunity estimates obtained with the baseline model and by using the catalytic method, respectively. The red bar shows the observed immunity level among Syrian refugees reported in ref. 43 in a refugee cohort in Germany in 2015. Black lines represent the 95% CI.

in the southeast of the country, close to the borders with Georgia, Armenia, Iran, Iraq, and Syria (Fig. 3). These regions should be considered at risk for measles epidemics, regardless of the presence and the level of integration of Syrian refugees.

For endemic diseases like measles, a rough estimate of the proportion p of immune population (either due to vaccination or natural infection) required to prevent large outbreaks can be inferred by using the widely accepted equation $p = 1 - 1/R_0$ (38–40, 44). In our simulations, we explored values of R_0 ranging from 12 to 18, which are typical values of R_0 estimated for measles in other countries (38–40). For these values of R_0, areas with a proportion of susceptible individuals larger than 5 to 8% are potentially at risk for sustained local transmissions.

Obtained results suggest that, nowadays, in Turkey, 270,000 to 410,000 out of 3.5 M Syrian refugees and about 1.8 M out of 80 M Turkish people are measles-susceptible. The resulting fraction of susceptible population across different Turkish prefectures (*SI Appendix*) suggests that provinces located on the border with Syria are those at a major risk of local measles transmission because of low local immunity levels among Turkish citizens and of a high concentration of susceptible refugees in the resident population.

In the extreme and rather unrealistic case of no mixing between the two populations, the infection would separately spread within each population, registering few cases in the highly immune Turkish population and causing way larger outbreaks in the highly susceptible population of Syrian refugees.

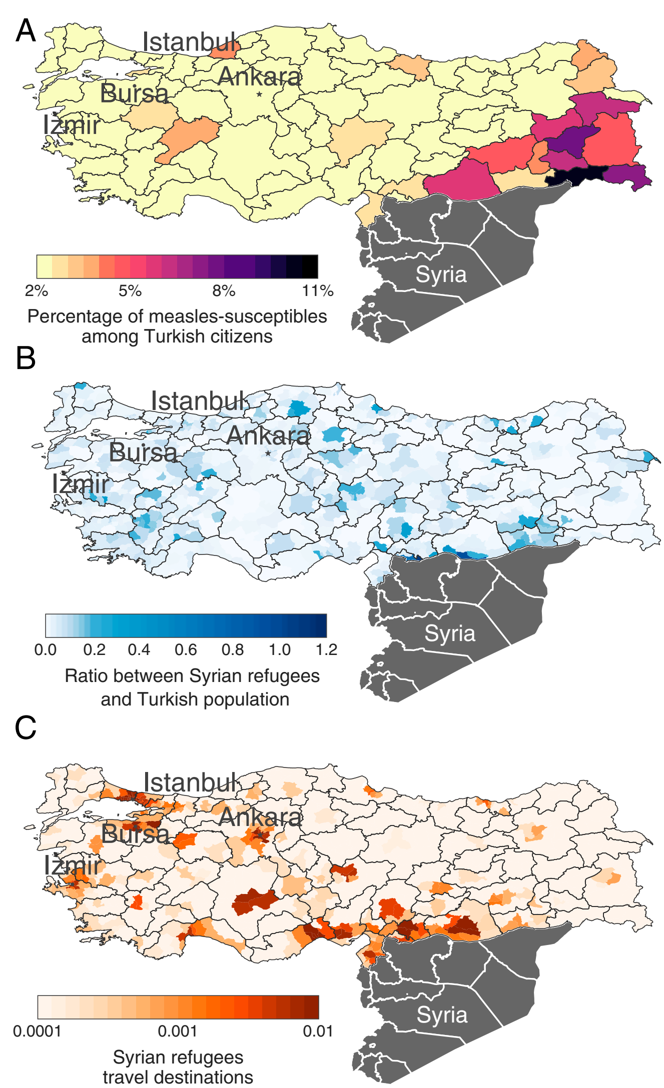

Fig. 3. Risk factors. (*A*) Percentage of measles-susceptible Turkish citizens as estimated across different prefectures (34). (*B*) Ratio between Syrian refugees and Turkish population—i.e., $N_k^{(R)}/N_k^{(T)}$—as inferred from CDRs. (*C*) Proportion of traveling refugees visiting the different Turkish prefectures.

Social Integration and Measles-Epidemic Risks in Turkey. We simulated measles transmission in Turkey, under different hypothetical scenarios on the level of mixing of refugees with local populations, taking into account mobility patterns inferred from CDRs. Our results show that the risk of observing large epidemics and the consequent number of cases increase with the basic reproduction number and the proportion of susceptible among the refugees and decrease with the increasing level of social integration between Syrian and Turkish citizens (Fig. 4 and *SI Appendix*).

High levels of mixing between refugees and Turkish citizens have the potential of preventing the spread of measles in many prefectures and can reduce by 75 to 90% the overall number of measles cases of potential epidemics (Fig. 4–6). In fact, when refugees mix well with the Turkish, potentially infectious contacts would more probably occur with Turkish immune individuals, who represent about 90% of people currently living in Turkey. On the contrary, in the case of low mixing between the two populations, measles transmission is sustained by the lack of adequate immunity levels among refugees. In particular, we found that if only 20% of Syrian contacts occur with Turkish citizens, the risk of observing sustained transmission in the country is large for any value of R_0 larger than 15, but also for lower values of R_0 (e.g., $R_0 = 12$) if the proportion of refugees susceptible is 9.5% or more (*SI Appendix*). In this case, measles epidemics could produce nonnegligible spillover of cases among local residents as well, causing thousands of Turkish cases all over the country (Fig. 4). Regardless of the level of integration considered, significant spillover of cases among Turkish citizens is expected to mainly arise when the onset of measles epidemics occurs on the eastern border with Syria and Iraq, where local measles transmission is possible, even in the absence of Syrian refugees, as a consequence of local low immunity among Turkish citizens.

We found that if 9.5% of refugees are measles-susceptible, the probability of observing an epidemic that causes at least 20 cases among Syrian refugees and Turkish citizens decreases from 100% (high segregation) to less than 10% (high integration), and, in the case of outbreak, when refugees mix well with Turkish citizens, the expected overall number of cases becomes no larger than a few hundred (*SI Appendix*).

Spatial Diffusion of Potential Epidemics. We analyzed simulations' results to identify the potential spatiotemporal spread of measles epidemics in Turkey and highlight how high segregation levels are also expected to promote the spatial invasion of the epidemic across the whole country. Figs. 5 and 6 show the impact of measles epidemics randomly started in one of 100 prefectures more at risk for local transmission, under a worst-case scenario, where $R_0 = 18$ and the percentage of susceptible Syrian refugees is 11.8%. In this case, when more than 90% of Syrian contacts occur within the Syrian population, measles epidemics are expected to affect more than 300 of 1,021 prefectures of Turkey (Fig. 6*A*). On the contrary, for the majority of considered epidemiological scenarios, if more than 70% of contacts of refugees occur with Turkish people, as a consequence of refugees' good integration with Turkish citizens, measles epidemics are expected to remain geographically bounded in less than 10 prefectures of the country (Fig. 6 and *SI Appendix*). Apparently, beyond local levels of immunity, frequent destinations for both Turkish and Syrian people represent areas that are most at risk for being affected by large epidemics (Figs. 1, 3*C*, and 6).

Our results suggest that the level of social integration between refugees and the Turkish population can strongly affect the spatiotemporal spread of potential epidemics. Fig. 6 *E–H* show for each prefecture the expected cumulative measles incidence over time for different levels of social integration under the worst-case scenario. Obtained estimates indicate that, in the case of full segregation, 43% of Turkish prefectures are expected to experience more than 10 measles cases after 30 weeks since the beginning of an epidemic. Such percentage decreases to 16%, 4%, and 1% when refugee contacts with Turkish citizens increase to 20%, 40%, and 60%, respectively. Interestingly, in the case of full segregation, prefectures where cases of infections are registered at earlier stages are mainly located in regions associated with the four largest cities of Turkey (62%; Fig. 6*E*). In contrast, when 60% of refugees' contacts occur with Turkish citizens, a remarkable fraction of prefectures that would be affected in the

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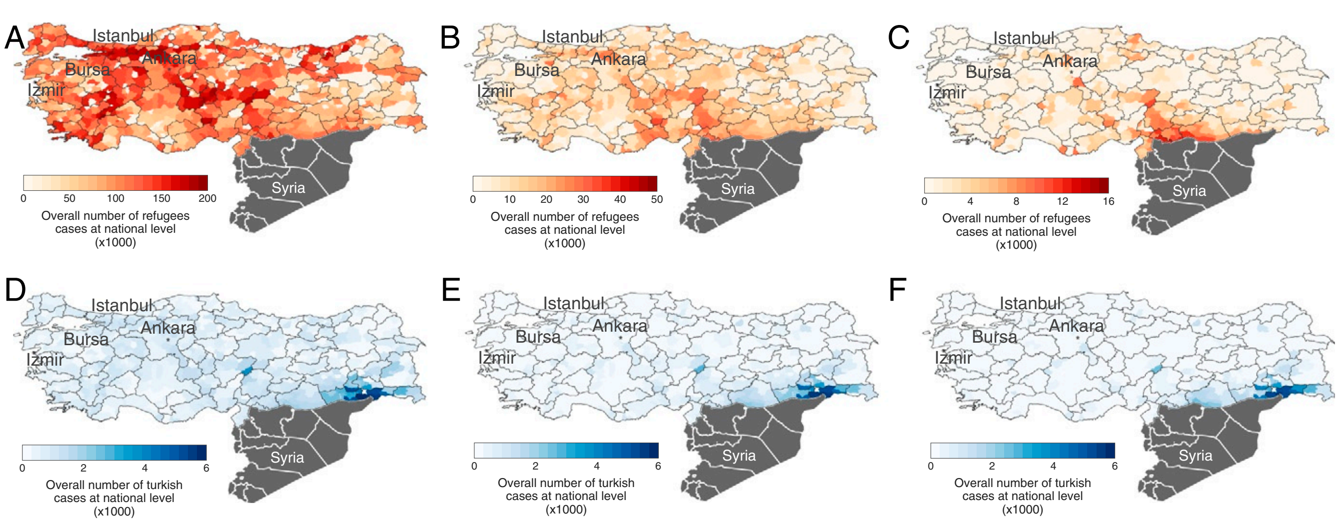

Fig. 4. The potential of widespread measles epidemics. (*A*) Cumulative number of cases among refugees at the national level as expected by considering scenarios where the measles epidemics start from different patches by assuming 20% of Syrian contacts with Turkish citizens, $R_0 = 18$ and that the percentage of susceptible refugees is 11.8%. For each patch, the color encodes the estimated incidence in the total population due to epidemics starting in that prefecture: This choice allows one to appreciate how each geographic area can potentially affect the whole country. (*B*) As in *A*, but for 40% of Syrian contacts with Turkish citizens. (*C*) As in *B*, but for 60% of Syrian contacts with Turkish citizens. (*D*) As in *A*, but considering cases among Turkish citizens. (*E*) As in *D*, but for 40% of Syrian contacts with Turkish citizens. (*F*) As in *D*, but for 60% of Syrian contacts with Turkish citizens.