Quantifying the transmission dynamics of MRSA in the community and healthcare settings in a low-prevalence country

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Methicillin-resistant Staphylococcus aureus (MRSA) is a primarily nosocomial pathogen that, in recent years, has increasingly spread to the general population. The rising prevalence of MRSA in the community implies more frequent introductions in healthcare settings that could jeopardize the effectiveness of infection-control procedures. To investigate the epidemiological dynamics of MRSA in a low-prevalence country, we developed an individual-based model (IBM) reproducing the population’s sociodemography, explicitly representing households, hospitals, and nursing homes. The model was calibrated to surveillance data from the Norwegian national registry (2008–2015) and to published household prevalence data. We estimated an effective reproductive number of 0.68 (95% CI 0.47–0.90), suggesting that the observed rise in MRSA infections is due not to an ongoing epidemic but driven by more frequent acquisitions abroad. As a result of MRSA importations, an almost twofold increase in the prevalence of carriage was estimated over the study period, in 2015 reaching a value of 0.37% (0.25–0.54%) in the community and 1.11% (0.79–1.59%) in hospitalized patients. Household transmission accounted for half of new MRSA acquisitions, indicating this setting as a potential target for preventive strategies. However, nosocomial acquisition was still the primary source of symptomatic disease, which reinforces the importance of hospital-based transmission control. Although our results indicate little reason for concern about MRSA transmission dynamics in the immediate future, the increases in importation and global circulation highlight the need for coordinated initiatives to reduce the spread of antibiotic resistance worldwide.

Significance
Methicillin-resistant Staphylococcus aureus (MRSA), traditionally associated with hospitals, is increasingly circulating in the community. This imposes, in turn, a potential burden on hospital infection control due to a more frequent hospitalization of colonized patients. We developed an individual-based model, reproducing community and healthcare settings, to understand the epidemiological drivers of MRSA and the connections between the society and the healthcare institutions. We show that in Norway, a low-prevalence country, the rise of infections is driven by an increasing inflow of cases from abroad rather than by an ongoing epidemic. We demonstrate the major role played by households in transmitting MRSA and show that the burden on hospitals from the growing community circulation is still limited thanks to aggressive infection-control protocols.
the individual characteristics of the members of a population (e.g., age, sex, and occupation), compared with the more traditional equation-based approach, which aims to capture the average characteristics of a limited number of population subgroups. IBMs are particularly suitable to investigate infections with a high degree of heterogeneity in infection dynamics as is the case for MRSA, but they are more complex and computationally burdensome. IBMs developed for the transmission of MRSA have predominantly focused on studying transmission within hospital wards, entire hospitals, or hospital networks (11, 12, 16, 18), and few included other settings (15, 18); due to computational constraints, many consider small populations (up to a few thousands), and none has yet been built at a national scale for MRSA.

In this study, we present an IBM of MRSA transmission in healthcare environments and community settings in Norway, distinguishing between MRSA colonizations and infections and including importation of cases from abroad. We calibrated the model to national surveillance data from the period 2008–2015 and to published household prevalence data (19) to identify the main routes of transmission, quantify transmissibility in the general population and the impact of MRSA importations, and to elucidate the interaction between community circulation and healthcare settings.

Results

Despite the implementation of strict measures for infection prevention and control, the number of notified MRSA infections in Norway has increased in the period 2008–2015 by almost a factor of 3. The model reproduced well the rise of MRSA infections observed in Norway between 2008 and 2015 in both community and healthcare settings (Fig. L4). The age-specific incidence of MRSA infection in different settings, which was not used during calibration, was also correctly predicted by the model thereby validating its robustness (Fig. 1B).

The observed growth of MRSA infections over time is worrying as it may be interpreted as a signal of containment failure. However, model results were not suggestive of this possibility as the estimated effective reproduction number for MRSA colonization was \( R_e = 0.68 \) (95% CI 0.47–0.90), remaining stable over time. In a fully closed population, an effective reproduction number below one would result in a gradual disappearance of the pathogen; therefore, the increasing trend in domestic infections is explained as the result of a growing inflow of individuals acquiring MRSA abroad rather than as an ongoing epidemic. At the same time, the value of \( R_e \) is sufficiently close to the epidemic threshold to allow for the occurrence of sporadic outbreaks of considerable size, which are indeed observed in Norway (10). Defining a cluster as the group of colonized persons directly or indirectly generated by a single index case, the model estimated that about 2% of all index cases resulted into a cluster involving more than 50 individuals (Fig. 2). On the other hand, about 60% of imported cases in the model were singletons, i.e., did not transmit MRSA to other persons; this finding is corroborated by genotype analyses on MRSA isolates collected in Norway, showing that about 50% of them have unique spa types (20). The estimated reproduction number per hospital admission was also below the epidemic threshold \( R_e = 0.25 \) (95% CI 0.21–0.29).

The model is able to provide surrogate estimates by setting of transmission for the prevalence of MRSA carriage in Norway in the absence of large-scale population studies. We determined that the growth of imported MRSA over time resulted in an increase in the prevalence of carriage in the general population from 0.18% (95% CI: 0.13–0.22%) in 2008 to 0.37% (95% CI: 0.25–0.54%) in 2015 (Fig. 3 A and B). These numbers are compatible with results from a cross-sectional study suggesting a prevalence around 0.2% (range: 0–0.4%) in Sweden and the Netherlands in 2009–2010 (21). The prevalence of MRSA carriage among individuals with immigrant backgrounds was twice as high than among Norwegians (0.64% vs. 0.31% at the end of 2015), a consequence of the differential influx of MRSA carriers from abroad in the two subpopulations. Prevalence in the community
setting was estimated to be higher among the elderly compared with other age groups (Fig. 3C). The model predicted a slight increase in the prevalence of carriage with household size (Fig. 3D). The circulation of MRSA in the community was found to affect hospital settings: The prevalence of carriage among inpatients was estimated to rise from 0.65% (95% CI: 0.45–0.89%) to 1.11% (95% CI: 0.79–1.59%) over the study period. For what concerns nursing homes, the prevalence remained stable at about 1.7% [a value that compares well to the 1–24% range estimated for European countries (22)]. The constant level in nursing homes contrasts with the rise in other settings and may be attributed to the revision of control guidelines introduced since 2010. This change in the infection-control measures, implemented as a reaction to the rising frequency of MRSA outbreaks in nursing homes during previous years, was included in the model.

Model results also provide statistics about the place of carriage acquisition, which are very challenging to obtain through the analysis of the data collected by experimental studies. The model suggests that, despite a much higher transmission rate in the nosocomial setting with respect to households and nursing homes, household contacts accounted for the largest share (49%, 95% CI: 33–65%) of all colonization events (Fig. 4A). Hospitals followed with 34% (95% CI: 22–46%) and nursing homes with about 5%; the remaining 12% (95% CI: 8–15%) were acquired abroad. This result can be attributed to the intensive control interventions that are in place within healthcare settings and suggests the possibility of further reducing MRSA prevalence by acting on household contacts of colonized individuals. However, although community transmission represented the main route of MRSA acquisition, the largest proportion of all symptomatic infections (44%, 95% CI: 32–56%, see Fig. 4B) was developed after nosocomial transmission, followed by acquisition in the community (39%, 95% CI: 26–52%). This can be explained with the much lower rate of progression to infection estimated for the general population compared with inpatients (about 40:1, see SI Appendix, Supplementary Material), justified by increased risk factors for infection among hospitalized individuals, such as the presence of surgical wounds, pressure ulcers, or the use of catheters and other invasive devices (23).

In addition, we found that nosocomial transmissions were responsible for 34% of all infections occurring in the community. This finding highlights an important interaction between the two settings and confirms recent observations that document the dissemination of hospital-associated lineages throughout the community (24). Nosocomial acquisitions were also responsible for the vast majority of infections developed in hospitals (83%) and for 16% of those developed in nursing homes (Fig. 5 and SI Appendix, Supplementary Material). On the other hand, community transmission was only directly responsible for 12% of nosocomial infections, presumably thanks to control measures which successfully identify the majority of carriers at hospital admission and prevent infection development through decolonization therapies. However, even in the context of a search and destroy policy, introduction of MRSA in hospitals may occasionally occur unnoticed; when this happens, the outbreak size can be substantial due to the large transmission rate in hospitals. Healthcare workers play an important role in the spread of MRSA, often acting as vectors for transmission (25). This dynamic is reflected in the high incidence of infections observed in healthcare workers (80 per 100,000 person years, compared with 3.5 in the general population). By estimating a high prevalence of MRSA carriage among nurses directly interacting with patients (between 2.2 and 3.8%), the model was able to correctly predict the number of infections observed in this category (SI Appendix, Supplementary Material).

The model-estimated age-specific transmission matrices are presented in Fig. 6. The overall matrix derives from the superposition of the transmission matrix in the community, hospitals, and nursing homes. The community transmission matrix shows the characteristic diagonals due to contacts between spouses and siblings, and between parents and children within households (26, 27). Transmission in the hospital matrix is mainly concentrated in very young and older age groups (50–85 y old) where hospitalization rates are high.

Discussion

We have studied the transmission of MRSA in Norway within and between the community and the healthcare facilities using a
stochastic IBM with a realistic representation of the community, hospitals, and nursing homes. To our knowledge, this paper represents a comprehensive modeling effort to understand the interplay between importations and transmission in community, hospitals, and nursing homes on the national scale. As a country with one of the lowest MRSA prevalence levels, high-quality national registry data, and aggressive control policies, Norway represents an optimal setting for studying the effect of increasing epidemiological pressure from abroad.

The model estimated an effective reproductive number of about 0.7, suggesting that circulation of MRSA in Norway was not self-sustained but maintained by the rising import of carriers from abroad. By identifying importations as a primary driver of MRSA epidemiology in a low-prevalence country, our study confirms the critical role of travel in spreading resistance (9, 28, 29). We estimated that the rise in importation has fueled an almost twofold increase in the prevalence of carriage in the general community from 2008 to 2015 up to a value of 0.57%. The reproduction number $R_e$ reflects nationwide average transmission in the community since $\sim 97\%$ of the transmission events generated by imported cases occurred outside healthcare settings. The reproduction number per hospital admission was estimated to be smaller ($R_a = 0.25$) in the range of previous values reported in low-endemic countries, such as the Netherlands and Denmark, also found to be below the epidemic regime (30, 31). This lower value is likely a consequence of the fact that patients have a much shorter length of stay in hospitals, typically a few days, compared with the average duration of MRSA colonization (32).

Household transmissions accounted for about half of all colonizations acquired within the Norwegian territory. This result is likely an effect of the aggressive infection control policies in the healthcare setting as well as of the high prevalence of MRSA carriage (around 40%) detected among household members during contact tracing studies in low-prevalence countries (19, 24, 33). The proportion of community transmission may even be underestimated due to our assumption of a negligible impact of other community settings in MRSA transmission. This assumption, however, was substantiated by preliminary analyses on an extended version of the model, including school, workplace, and distance-dependent random contacts (SI Appendix, Supplementary Material). Although some transmission events, including occasional MRSA outbreaks, can be traced to specific contexts, such as contact sports associations (8), an evaluation of their contribution was not possible given the lack of information at this level of granularity. Nonetheless, it is unlikely that these settings play a major role in the overall epidemiology of MRSA in Norway.

Among persons carrying MRSA, symptoms may arise several months after the acquisition of MRSA carriage. The model was helpful in discriminating between the settings where transmissions occur from the setting where clinical infections develop. Disentangling the place of infection development vs. the place of carriage acquisition, we estimated that the largest proportion of the burden of clinical disease was attributed to nosocomial acquisitions because of the increased risk factors for infection characterizing inpatients. Importantly, about one-third of symptomatic infections developed in the community where they were acquired in the hospital; in contrast, only 12% of nosocomial infections originated from community acquisition, thanks to the screening and decolonization protocols at the admission of patients. However, the occasional admission of asymptomatic carriers may still result in widespread transmission in hospital wards. For example, this may happen when colonized patients with no record of MRSA in their family and no history of travel abroad in the previous year are hospitalized since these patients are not subject to screening at admission (34).

Several assumptions and simplifications were taken in this study. An important limitation is that we did not include a hospital referral network representing the movements of patients between hospital institutions. Consequently, our model may overestimate within-hospital transmission. Findings from a study in the United Kingdom have shown that MRSA transmissions related to patients’ movements between hospitals was mainly associated with a noneffective communication between the source and the destination institutions (35). The national MRSA guidelines in Norway require the notification of MRSA carriage when patients are transferred between institutions. In addition, patient movements between Norwegian hospitals is overall very limited and mostly related to short-term ambulatory visits. Thus, the impact of patient transfer on transmission may be limited. The model also does not incorporate patient movements between wards, based on Norwegian hospitalization data showing that over 90% of patients visit only one ward and less than 0.2% more than three wards during the same hospitalization.

We assumed complete adherence to national MRSA guidelines across all hospitals. The actual effort put into the control measures has likely changed over time within and across different
We considered data from the national infection registry (the Norwegian Surveillance System for Communicable Diseases [MSIS]) that contains all laboratory-confirmed MRSA cases reported to the Norwegian Infectious Disease Control Authority. This is a common choice adopted by the majority of mathematical models developed to investigate MRSA epidemiology. The study of MRSA as a specific pathogen, independent from MSSA, is justified by its evolutionary history, characterized by a successful diffusion in hospital settings and more recently, in community settings, and by its capacity to become endemic in many areas of the world. Furthermore, previous analyses in Norway have shown that model conclusions are robust with respect to assumptions about the number of imports. The inclusion of this additional level of complexity in modeling studies might help to refine our understanding of transmission of antibiotic-resistant pathogens.

Finally, we did not consider the emergence of resistance in patients caused by antimicrobial therapies. These cases would behave in a way that is indistinguishable from importation since they appear in the population independent of transmission. We have shown that model conclusions are robust with respect to assumptions about the number of imports. Furthermore, the low consumption of antibiotics and the decreasing use reported in recent years in Norway suggest that the emergence of resistance after antimicrobial therapies likely has a minor effect on the epidemiology of MRSA.

Conclusion
The transmission dynamics of MRSA worldwide is changing with the community playing an increasingly central role in its spread. Data-driven modeling studies that include community environments in addition to healthcare settings can help frame this complex epidemiology, and it is necessary to support evidence-based planning and adaptation of integrated control measures. On one hand, our findings highlight the primary role of community transmission, pinpointing households as a potential target of preventive measures for the transmission control in the general population; on the other hand, they reemphasize the critical role of hospitals in controlling disease burden and the importance of stringent infection control measures in healthcare settings to keep the epidemiological pressure from the community at bay. Reassuringly, the model excluded the possibility of an ongoing MRSA epidemic, highlighting the drive exerted by the inflow of carriers from other countries. In Norway, a low-incidence country with below-threshold transmission, the movement of pathogens across borders represents a primary cause of the increasing number of observed MRSA infections. This result underscores the importance of coordinated global actions to tackle the rising burden of antibiotic resistance worldwide.

Materials and Methods
Data. We considered data from the national infection registry (the Norwegian Surveillance System for Communicable Diseases [MSIS]) that contains all of the laboratory-confirmed MRSA cases reported to the Norwegian Institute of Public Health (66) between January 2008 and December 2015. The dataset reports various individual-level information, such as age, ethnic background, place of detection, and information about the hospitalization status of the patient at the time of testing. The number of symptomatic infections over time was used to calibrate the model, considering the place of MRSA detection to separate the infections in the community, hospital, or nursing home. Individual-level data from the Norwegian Patient Registry (NPR) on episodes of hospital care within 2012 in the South-Eastern Norway health region

![Fig. 6. Average number of transmission events by age of the infectors and of the infected (transmission matrix). (A) Overall. (B) Within the community. (C) Within hospitals. (D) Within nursing homes.](image-url)
were used to define age-specific hospitalization rates and length of stay distributions. The study of the NPR data was approved by the Regional Committees for Medical and Health Research Ethics—South-East Norway (project number 2013/1004).

Census data from the Statistical Office of the European Commission (Eurostat) were used to inform the sociodemographic structure of the model (household size distribution, typology of household, and age profile of the population). Public data from Statistics Norway (SSB) were used to define the hospitals and their size and to profile the number of people with an immigrant background.

Data on population density were obtained from the Gridded Population of the World version 3 (47) produced by the Center for International Earth Science Information Network of the Earth Institute at Columbia University.

**Model Structure.** We developed a stochastic IBM to study the transmission of MRSA in the community and the healthcare setting (Fig. 7A), building on a previously published sociodemographic model (27). A grid of 4978 geo-located cells represents the Norwegian territory. The model consists of a synthetic population, whose characteristics are based on census sociodemographic data of Norway. Individuals are assigned to households distributed on the grid in accordance with the Norwegian population density (48) and age distribution. Except for unemployed, retired, and infants, persons are associated with workplaces or schools, depending on their age. The assignment to specific places is performed through a random process based on the commuting distance distribution, modeled on observed human mobility patterns (48). In this paper, we expanded the model by adding hospitals, structured into wards, and nursing homes with long-term patients. Large hospitals also include ICUs. Individuals can become hospitalized with age-dependent probabilities according to NPR data and assigned to hospital wards with a length of stay sampled from a distribution matching available data, also from NPR. Control measures recommended in healthcare institutions by the national MRSA guidelines (34) are implemented in the model, including: risk-based screening at hospital admission; screening of hospital wards and healthcare workers in case of unexpected discovery of MRSA carriers; isolation of carriers and infected patients; work restrictions for MRSA-wards and healthcare workers in case of unexpected discovery of MRSA carriers; following preliminary analyses excluding a role for schools and workplaces, we only considered transmission within households in the community. MRSA carriers can become infected with a rate depending on whether they are currently not hospitalized, hospitalized in a general ward, hospitalized in an ICU, or living in a nursing home. Colonized and infected persons may return to the susceptible state after decolonization treatments; asymptomatic carriers may also undergo natural decolonization.

**Epidemiological Model.** The epidemiological model adopted in this study has three disease states: susceptible, colonized (i.e., asymptomatic carriers), or infected (individuals with symptoms) (Fig. 7B). Susceptible individuals can acquire MRSA and become colonized by contact with other colonized or infected persons. Within each setting (e.g., a household or a hospital ward), we assumed homogeneous mixing of individuals. Colonization with MRSA is acquired from close contact with carriers; following preliminary analyses excluding a role for schools and workplaces, we only considered transmission within households in the community. MRSA carriers can become infected with a rate depending on whether they are currently not hospitalized, hospitalized in a general ward, hospitalized in an ICU, or living in a nursing home. Colonized and infected persons may return to the susceptible state after decolonization treatments; asymptomatic carriers may also undergo natural decolonization.

**Model Calibration.** The model comprises the following set of free parameters: the rates of colonization in households, hospitals, and nursing homes, the rate of infection in the community (i.e., for individuals currently not hospitalized), and the three initial values of MRSA prevalence in the community, nursing homes, and hospital healthcare workers. We calibrated the model to the yearly MRSA infections reported to the Norwegian national registry between 2008 and 2015 and to the prevalence of colonization in household contacts of MRSA carriers (19). We explored the parameter space with Latin Hypercube Sampling, computed a likelihood score for each sampled parameter set, and selected the optimal parameter values via a multistep calibration procedure fully described in the SI Appendix, Supplementary Materials. Model results presented in this paper are based on simulations performed by running 50 stochastic realizations of the model for each of the 100 most likely parameters sets.

**Key Estimated Epidemiological Indicators.** The calibrated model was used to estimate a number of measures relevant for MRSA epidemiology. Taking advantage of the individual-based structure of the model, which enabled to track the infector in each single transmission event, we computed the effective reproductive number $R_0$ as the average number of MRSA transmissions directly generated by a new imported carrier. Similarly, we computed the reproduction number associated with nosocomial transmissions linked to hospital admissions of colonized patients $R_e$. We defined a transmission cluster as the set of primary transmissions generated by the index case and all of the transmissions generated by his offspring; the size of the cluster is given by the number of persons being part of the cluster. The prevalence of MRSA was defined as the proportion of carriers in a given population at a specified point in time. The age-specific transmission matrix was estimated by reporting the mean number of colonization events, disaggregated by the ages of the infector and of the infected (ages were grouped by 5 y).

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