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Dispersal of antibiotic-resistant high-risk clones by hospital networks: changing the patient direction can make all the difference

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SUMMARY

Background: Patients who seek treatment in hospitals can introduce high-risk clones of hospital-acquired, antibiotic-resistant pathogens from previous admissions. In this manner, different healthcare institutions become linked epidemiologically. All links combined form the national patient referral network, through which high-risk clones can propagate.

Aim: To assess the influence of changes in referral patterns and network structure on the dispersal of these pathogens.

Methods: Hospital admission data were mapped to reconstruct the English patient referral network, and 12 geographically distinct healthcare collectives were identified. The number of patients admitted and referred to hospitals outside their collective was measured. Simulation models were used to assess the influence of changing network structure on the spread of hospital-acquired pathogens.

Findings: Simulation models showed that decreasing the number of between-collective referrals by redirecting, on average, just 1.5 patients/hospital/day had a strong effect on dispersal. By decreasing the number of between-collective referrals, the spread of high-risk clones through the network can be reduced by 36%. Conversely, by creating supra-regional specialist centres that provide specialist care at national level, the rate of dispersal can increase by 48%.

Conclusion: The structure of the patient referral network has a profound effect on the epidemic behaviour of high-risk clones. Any changes that affect the number of referrals between healthcare collectives, inevitably affect the national dispersal of these pathogens. These effects should be taken into account when creating national specialist centres, which may jeopardize control efforts.

Introduction

Hospital-acquired pathogens such as *Clostridium difficile*, vancomycin-resistant *Enterococci*, meticillin-resistant *Staphylococcus aureus* and carbapenemase-producing enterobacteriaceae are a menace to patients and hospitals. They are a frequent cause of hospital-acquired infections, and are

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difficult to treat due to their combined resistance against many antibiotic drugs, leading to outbreaks and disruption of services. Moreover, most of these infections are caused by high-risk clones that can be transmitted easily between hospitals by referred patients.[1–3] In this manner, hospitals become linked epidemiologically through the patients they share by referral, each becoming a connection within a hospital referral network.[4,5] National data on acute care admission and referral have shown that all hospitals within a country become connected over the course of a single year.[6] However, national patient referral networks do not show the properties of so-called 'small world networks', whereby the average degree of separation would be so small that these clones would easily spread nationwide within a matter of weeks. In contrast, patient referral networks show a community structure (i.e. they are largely modular).[7]

The structure of the patient referral network influences both the chance of introduction and the prevalence of high-risk clones in any single hospital.[7] Furthermore, closely connected hospitals share similar clones,[8] demonstrating the local influence of the community structure. The explicit geographical signature of all national patient referral networks investigated to date supports a concept tentatively called the 'healthcare collective'. These collectives consist of regional primary, secondary and tertiary healthcare institutions that exchange more patients between each other than with other institutions. As the hospitals within these collectives serve defined catchment populations, influence each other's infection rates, and clones remain rather homogenous, the collectives have also been referred to as 'germ sheds', in analogy to water sheds.[9]

Despite the modular structure of the patient referral network, the dissemination of high-risk clones is not regionally confined. Instead, they have often been mapped over larger geographical scales.[10] A well-known example is the dispersal of EMRSA-15 and 16 in the UK, which spread through the UK in a matter of 10 years.[11,12] This is evidence that the healthcare collectives are not hermetic, but hierarchically interconnected. Like all other links in the hospital referral network, these interconnections are maintained by patients moving between hospitals of different collectives.

However, patient flows change over time because healthcare systems are not static. Notably, referral networks will be influenced by re-organization, centralization and regionalization[13,14] in the wake of economic streamlining,[15] new policy directives and changes in reimbursement systems.

This study investigated the extent to which patient referral destinations influence the ability of national healthcare networks to decelerate the dissemination of high-risk clones through hospital networks. Furthermore, the evolution of nationwide outbreaks under different scenarios of hospital utilization were simulated, and possible intervention strategies likely to reduce the epidemic potential of high-risk clones through modification of patient referral patterns were explored.

Methods

Healthcare utilization patterns, such as the effect of the patient's place of residence on the referral destination, were mapped using admission data from the UK National Health Service (NHS) Hospital Episode Statistics (HES) between April 2006 and March 2007. The catchment areas of NHS hospital trusts were described by mapping the observed distribution of patients' residences (electoral ward of home addresses) in relation to admitting hospital for all hospital admissions in England between April 2006 and March 2007.

First, the healthcare collectives were identified by reconstructing the hospital referral network for England, and assigning hospital trusts to collectives using a network community structure algorithm.[16] This algorithm searches for the partition of hospitals with the highest modularity, reflecting the difference between the number of patients referred within and between collectives. A bootstrapping method was used to test if the partitions were robust by varying the number of exchanged patients at random, as described previously.[7] Subsequently, the catchment areas of the healthcare collectives were reconstructed. This was done by assigning each electoral ward to the healthcare collective with hospitals that received the largest proportion of the ward's admitted patients, comparable to a 'first past the post' electoral system.

The distance from the centroid of each electoral ward to the nearest border of another healthcare collective's catchment area was calculated to assess the effect of geographical location of patients on their healthcare utilization. Two proportions were calculated for each electoral ward: the proportion of admissions of patient residing in the ward to hospitals outside the catchment area, and the proportion of re-admissions that included a switch between catchment areas. Furthermore, the average proportion of admissions outside the collective was calculated as a function of the distance to the border. This was used to determine the patient exchange baseline, which was defined as the lowest proportion of outside collective admissions or transfers.

Simulations

All admission records per patient were aligned from the NHS-HES data. Subsequently, a 14-year-long dataset was created by sampling patients from the NHS-HES data. Each sampled patient was assigned a random day of first admission between −100 and 5110, and all re-admissions were adjusted according to the true admission histories. The period before $t = 0$ was used as 'burn-in' to ensure that the daily number of admissions was at equilibrium from $t = 0$ onwards. Any admissions before $t = 0$ or after $t = 5110$ were discarded.

In the simulated dataset, the locations of the patients (i.e. which patients were admitted to each of the hospitals on a given day) were tracked. Patients can be either susceptible (S) or infected (I), with no distinction between colonized or infected. Each patient has a probability of $p(S \rightarrow I) = \beta\, I_i/N_i$ of becoming infected, where I_i is the number of infected individuals in hospital i and N_i is the total number of patients in that hospital. Patients become free of, and susceptible to, infection with rate γ, where $1/\gamma$ is the mean duration of colonization. An average duration of colonization of 365 days ($\gamma = 1/365$) was assumed, and β was set at 0.085/patient-day. To simulate onset of an epidemic, 5% of the patients in a given index hospital were infected on a random day during the first year of the simulated dataset. Each of the 146 hospitals was used 10 times as the index hospital, resulting in 1460 runs of the model.

Furthermore, three theoretical scenarios that affect the referral patterns between hospitals or between healthcare