A spatiotemporal simulation study on the transmission of harmful microorganisms through connected healthcare workers in a hospital ward setting

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Abstract

Background: Transmission of harmful microorganisms may lead to infections and poses a major threat to patients and healthcare workers in healthcare settings. The most effective countermeasure against the transmission and spread of harmful microorganisms is the adherence to spatiotemporal hand hygiene policies, but adherence rates are relatively low and vary over space and time. The spatiotemporal effects on the transmission and spread of harmful microorganisms for varying levels of hand hygiene compliance are unknown. The objectives of this study are to (1) identify a healthcare worker occupancy group of potential super-spreaders and (2) quantify spatiotemporal effects on the transmission and spread of harmful microorganisms for varying levels of hand hygiene compliance caused by this group.

Methods: Spatiotemporal data were collected in a ward of an academic hospital using radio frequency identification technology over a period of seven days. A potential super-spreader healthcare worker occupation group was identified using the contact data derived from the frequency identification sensors. The effects of five probability distributions of hand hygiene compliance and three rates of harmful microorganism transmission were simulated using a dynamic agent-based simulation model. The effects of initial simulation assumptions on the simulation results were quantified using five risk factors.

Results: Nurses, doctors and patients are together responsible for 78.8% of all contacts. Nurses made up 57% of all contacts, which is more than five times that of doctors (11.1%). This identifies nurses as the potential super-spreader healthcare worker occupation group. For initial simulation conditions of extreme lack of hand hygiene compliance (5%) and high transmission rates (5% per contact moment), a colonized nurse can transfer microbes to three of the 17 healthcare worker or patients encountered during the 87 minutes of visiting 22 rooms while colonized. The harmful microorganism transmission potential for nurses is higher during weeknights (5pm – 7am) and weekends as compared to weekdays (7am – 5pm).

Conclusion: Spatiotemporal behaviour and social mixing patterns of healthcare can change the expected number of transmissions and spread of harmful microorganism by super-spreaders in a closed healthcare setting. These insights can be used to develop better informed infection prevention and control strategies.

Keywords

Spatiotemporal risk factors; RFID; Wearable proximity sensors; Spatiotemporal simulation; Healthcare-associated infections; Transmission; Hand hygiene compliance

Background

Vancomycin-resistant enterococci (VRE) is one of the important harmful microorganisms (HMO) which may cause healthcare associated infections which estimated to affect more than four million European patients every year. It results in an additional 16 million days patients spent in hospital, translating into a direct cost of €7 billion annually [1]. The ease of transmission of HMO depends upon the features of the microorganism, patient characteristics and the behaviour of healthcare workers (HCW), whereas the damage caused by the infection that follows ranges from none to potentially fatal. [2]

The most effective precautionary measure to combat the mass transmission and spread of harmful microorganisms in closed healthcare settings is the adherence to well established and effective hand hygiene policies also known as hand hygiene compliance (HHC). Unfortunately, HHC is often unsatisfactory with highly variable levels within and between hospitals. Rates of hand hygiene compliance range from 5% to 81%, with an average compliance of approximately 40%. With a level of 85% adherence seen as high levels of HHC and 95% as very high, it is not surprising that the spread of HMO in closed healthcare settings remains a major dilemma [3]. Reasons for hand hygiene non-compliance include increased work intensity, lack of education and ineffective placement or defective alcohol dispensers. For instance, one hour of overtime worked by an HCW can lead to a 3% decrease in the level of HHC. [4,5] The result is a highly variable level of HHC within closed healthcare settings. Compounding the non-adherence to hand hygiene policies is that the medium and method used for hand hygiene are not 100% efficient. With an estimated efficacy rate of 83%, some HMO may remain, even if HCWs perform hand hygiene with alcoholic rub. This can lead to further transmission. [6]

The combination of colonized and non-colonized HCWs or patients, who are potentially immunocompromised and in a confined space, makes healthcare facilities a high-risk environment for the spread of HMO. The term super-spreader is used to categorise an individual with a disproportionately high potential to spread HMO. Super-spreaders were the cause of several super-spreading events (SSE) in the past with devastating consequences [7]. Highly connected HCWs can

increase the risk of SSE in closed healthcare environments. The amount of contact between HCWs or patients as well as HHC are critical factors that contribute to the extent and severity of an SSE. [8]

For these reasons, the SSE is affected by the joint spatiotemporal behaviour, i.e. where and when, and social mixing patterns, i.e. with whom of the HCW or patients inside a hospital ward as well as the level of HHC, including its variability. It is therefore necessary to understand the spatiotemporal effect on the transmission and spread of HMO for varying levels of HHC for potential super-spreader in a closed healthcare setting.

Automatic contact tracking methods like Radio Frequency IDentification (RFID) technology are now being adopted by healthcare institutes by tagging healthcare equipment, HCWs and patients in order to improve logistics and patient safety. There is still reluctance to fully adopt this technology, mainly driven by security and privacy concerns. [9] Real contact data between patient and HCWs became more prevalent since 2002 when data were collected by means of shadowing. Medical records, surveys and more recently, sensors became more important for data and contact detection. Assab et al. (2017) showed that studies using empirical contact data within closed healthcare settings lead to a better understanding of the transmission and spread of HMO. Such data can result in the development of improved control interventions. Using real-time RFID tracking data it is possible to model the spread of HMO at an individual level rather than using a compartmental-based model [2,10]. RFID data have been used to model the spread of HMO in different closed healthcare settings and at different proximities using a temporal proximity network at schools [9],[10], conferences [13], households [14], hospitals [15–21] and other healthcare facilities [22]. In addition to the research that has recently been done, innovations in data collection and modelling are clearly needed in order to implement better control strategies. [23] Studies based on contact data only are unable to determine the effect of spatiotemporal healthcare policies like HHC. A few hours of RFID tracking can be sufficient to produce a statistical model that shows the heterogeneity of spatiotemporal social contact patterns, which represents how people socially interact in space and time. [24]

The spatiotemporal effects of varying levels HHC on the transmission and spread of HMO in a closed healthcare setting must still be quantified, based upon empirical spatiotemporal tracking data. HCWs and policymakers may benefit from understanding the impact of spatiotemporal infection control interventions and healthcare policies on the transmission and spread of HMO.

The main objectives of this study were to (1) identify an HCW occupancy group of potential super-spreaders and (2) quantify the spatiotemporal effects on the transmission and spread of HMO for varying levels of hand hygiene compliance caused by this group.

Methods

We used spatiotemporal data from the University Medical Center Groningen (UMCG), being one of the largest hospitals in the Netherlands with more than 10 000 employees and almost 1 400 beds. Between 2 April 2018 and 8 April 2018, data were collected in a 32-bed general hospital ward, for stomach, gut and liver patients (Figure 1). The dates were chosen such that they cover a whole calendar week from Monday to Sunday and all shifts to increase the representativeness of the estimates obtained. The floor plan of the ward was divided into 33 rooms of which 14 were patient rooms, with between one and four beds, nine medical storage rooms and ten rooms ranging from a doctor's office to a staff kitchen.

Data were collected using RFID sensors worn by the HCWs working in the ward during the study period. Sensors were grouped by HCW occupation groups. Each HCW chose a sensor at the start of a shift at random belonging to his/her respective occupation group. The RFID tags (Figure 1: A) emit radio signals with a unique identifying information and RFID readers (Figure 1: B), on the ceiling of the rooms, register those signals. The range of the RFID readers was set to the size of the rooms and they continuously monitored the uniquely identifiable RFID tags in their range. HCWs moving in and out of the rooms were registered and the data were generated and stored. The data consist of a room ID, a RFID sensor ID and a datetime stamp corresponding to the movement of the RFID tag into and out of

a room (Figure 1: C). The spatial resolution is at the room level and defined by the set of rooms inside the ward. The temporal resolution equals the second at which the observation signal was received.

Figure 1: Floorplan of the 32-bed general hospital ward, for stomach, gut and liver patients.

B C

A = Floorplan of the 32-bed general hospital ward, for stomach, gut and liver patients where sample data were collected using **B** = RFID tags worn by HCWs during data collection using **C** = RFID readers placed on the ceiling of the ward rooms.

During the seven days of data collection, a total of 2 631 observations were recorded of which 58 had to be removed because of spurious measurements detected using outlier detection and identifying aberrant movement patterns in the collected data (Table 1). The sampled data were divided into two

subsets. Data in subset 1 contain the sampled data collected during weekdays (7am – 5pm) and subset 2 the sampled data collected during the evenings (5pm – 7am) and over the weekend.

Table 1: Example of data collected using the RFID sensors and readers.

Room	From	To	Sensor
54.3.35A	03/04/2018 16:49	03/04/2018 16:50	58007
54.3.45	03/04/2018 16:51	03/04/2018 17:00	58007
54.3.14	03/04/2018 17:00	03/04/2018 17:37	58007
54.3.17	03/04/2018 17:37	03/04/2018 17:41	58007

Contact data were extracted from the empirical spatiotemporal data. They are generated by the underlying contact network between HCWs and determines the possible pathways over which the spread of HMO occurs over space and time [25,26]. Since the spatial resolution of the collected data were at the room level and not at the face-to-face level, an assumption was needed for the contact definition. We define a contact as the physical co-occurrence of two HCWs or patients in a single room and a contact moment as contact over a 30 second period of time. This contact definition is used in computational epidemiology as a proxy for face-to-face contacts [27]. For example, if a HCW enters a patient's room, then the HCW and the patient are assumed to be in contact with each other for the time over which they co-occur in that room. Using the sampled data and the contact definition, potential super-spreaders can be identified by occupation group.

We investigate different HCW occupation groups as potential super-spreaders. A general guideline to identify super-spreaders is to identify the 20% of the people contributing at least 80% of the transmission potential [28]. Seven HCW occupation groups were identified, namely doctor (DOC), nurse (NUR), cleaner (CLN), department assistant (DAS), department co-assistant (DCA), consultant (CON) and feeding assistant (FAS). Each HCW occupation group's potential to transmit an HMO was evaluated based upon the number of times contact was made (contact moment) and time spent with other HCWs or patients. The estimated transmission potential is obtained for each HCW occupation group and compared to identify disproportionality and thus potential super-spreaders.

For objective 1, i.e. the identification of a potential super-spreader HCW occupation group (G) we performed the following steps:

Step 1.1: Obtain the total time spent in minutes (ψ) and the number of contacts (M) between all groups of HCW occupations or patients.

Step 1.2: Rank order HCW occupation groups by ψ and M.

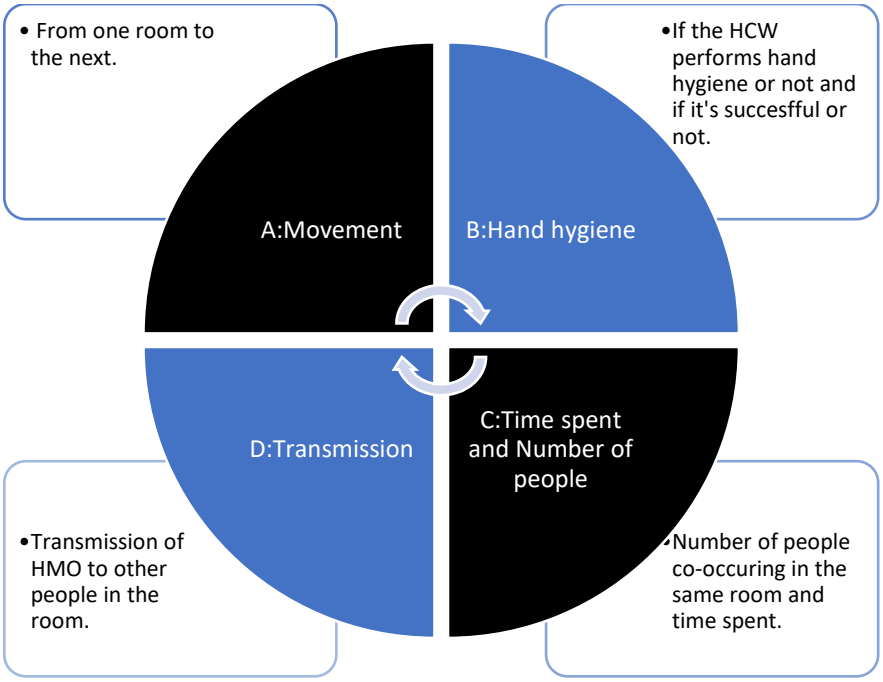
Step 1.3: Identify the HCW occupation group with the highest ψ and M and in this sense differs the most from the other HCW occupation group as G.

Once G is identified, we estimated the effect of the transmission and spread of an HMO by a colonized HCW from occupation group G for varying levels of HHC using five risk factors while colonized (RF1 – RF5). The risk factors are defined as follows for a member of G while colonized: the amount of time (minutes) spent colonized (RF1), the amount of time (minutes) spent with HCWs or patients (RF2), the number of HCWs or patients encountered (RF3), the number of transitions made from one room to another (RF4) and the expected number of HMO transmissions to other HCWs or patients before successfully performing hand hygiene (RF5).

To simulate the underlying distribution from the sampled data, we estimated the underlying distribution, followed by resampling to generate more samples. This simulation process aids us to explore the consequences of initial simulation assumptions.

To estimate RF1 – RF5, we construct a dynamic agent-based transition simulation model [29]. The simulation follows a four-part (A-D) workflow (Figure 2). We assumed that RF1 – RF5 are dependent upon the order in which an HCW moves between the different rooms in the hospital ward (A), the likelihood of the HCW performing hand hygiene and the efficacy of doing so (B), the amount of time an HCW spends in each room with a number of other HCWs or patients (C) and the transmission dynamics of the HMO (D). Parts A and C are based on statistics from the sampled data while parts B and D are based on assumptions from the literature.

Figure 2: The four-part of the simulation workflow.



A and C are dependent of the sampled data and B and D on initial assumptions from literature.

For part A in the simulation workflow (Figure 2), we used continuous Markov chains. They allowed us to model the movement of HCWs from one of n rooms to the next [30]. If R is the set of n rooms, i.e. $R = \{R_1, R_2, \dots, R_n\}$, then the transition probability p_{ij} (Formula 1) in row i and column j of the $n \times n$ transition probability matrix $\boldsymbol{P}$ (Formula 2) is the probability that an HCW will transition from room R_i to room R_j during the next transition. Since an HCW will either be in the same room or in another room after the next transition, the rows of the matrix $\boldsymbol{P}$ must add up to 1 i.e. $\sum_{j=1}^{n} p_{ij} = 1$ for $i = 1, \dots, n$. Each element p_{ij} is between 0 and 1 inclusively i.e. $0 \leq p_{ij} \leq 1$ for $i, j \in (1, \dots, n)$. An estimate for p_{ij} is obtained by dividing the number of transitions to R_j from R_i by the total number of transitions from R_i. Using only the transition data of G we obtain a transition probability matrix $\boldsymbol{P}$ for G.

$$p_{ij} = P\left(\text{Next room} = R_j \middle| \text{Current room} = R_i\right) \text{ for i, j } \in (1, \dots, \text{n}) \qquad \text{Formula 1}$$

$$\boldsymbol{P} = \begin{array}{c} \\ R_1 \\ \vdots \\ R_n \end{array} \begin{array}{c} \begin{array}{ccc} R_1 & \dots & R_n \end{array} \\ \begin{bmatrix} p_{11} & \cdots & p_{1n} \\ \vdots & \ddots & \vdots \\ p_{n1} & \cdots & p_{nn} \end{bmatrix} \end{array} \qquad \text{Formula 2}$$

We assume that the length of time spent in each room (ψ_{R_i}) is exponentially distributed with parameter η with mean $1/\eta$ and variance $1/\eta^2$ [30]. The estimated values of η and the average number of HCWs or patients co-occurring inside each room, together with the corresponding estimated variance, are obtained at room level from the sampled data. We assumed that the number of HCWs or patients co-occurring within each room follows either a normal distribution or Poisson distribution with mean and standard deviation equal to the estimates obtained from the sampled data.

The performance and efficacy of hand hygiene (B) compliance and the transmission of a HMO (C) are simulated using agent-based modelling and the corresponding model assumptions in Table 2, based on [7].

Table 2: Agent-based model parameters (Thomas Hornbeck et al.).

Symbol	Definition	Range
P	Probability of transmission per 30 s of contact	$0.0005, 0.005$ and 0.05
λ	Hand hygiene efficacy using alcohol rub	0.83
γ	Hand hygiene compliance level	$\mu = 0.05,0.25,0.5,0.75,0.95$ and $\sigma = 0.1$

The simulation starts with one colonized HCW $g \in G$ in a random room inside the hospital ward and ends when g successfully performed hand hygiene. We assume that all patient rooms are occupied. The simulation procedure is performed as follows:

Objective 2

2.1 Obtain sample statistics

Step 2.1.1: Use the sampled data generated by the sensors carried by G to construct a 1-step transition probability matrix ($\boldsymbol{P}$) for the transitions between rooms $R = \{R_1, R_2, \dots, R_n\}$.

Step 2.1.2: Obtain the average and standard deviation of the number of HCWs or patients co-occurring with $g \in G$ in each room R_i as ω_{R_i}.

Step 2.1.3: Obtain the average and standard deviation of the number of minutes spent by G in each room as ψ_{R_i}.

2.2 Simulation

Step 2.2.1 (Workflow A): Select at random a room R_i for $i = 1, \dots, n$ as the initial room where g will start the simulation.

Step 2.2.2: Select five equally probable values from a random univariate distribution between 0 and 1 with assigned variables names $u_1, \dots, u_5$.

Step 2.2.3:

1. (Workflow B): Determine if g successfully performed hand hygiene after entering the room:
   $PH = P(Successful\ handhygiene) = \lambda \times \gamma$, where we make the assumption that $H \sim N(\mu, \sigma)$ where μ and σ are as in Table 2 and γ is sampled from H. Sample a random number γ from H until $u_1 \leq (\gamma * \lambda)$ when the simulation has converged as hand hygiene was performed successfully and the HCW is no longer contagious. Record the number of transitions as T.

2. (Workflow C): Simulate the number of HCWs or patients co-occurring in room R_i:
   We assume $\omega_{R_i} \sim N(\nu, \varphi^2)$ or $\omega_{R_i} \sim Poisson(\nu)$, where ν and φ^2 are estimated using the average and variance of ω_{R_i} from the sampled data respectively. Select a random number from ω_{R_i}, using the value u_2, and round up the results to the nearest integer.

3. (Workflow C): Simulate the number of minutes spent in room R_i:

We assume that $\psi_{R_i} \sim Exp\left(\frac{1}{\eta}\right)$, where η is the sample average of ψ_{R_i}, estimated from the sampled data. Select a random number from ψ_{R_i}, using the value u_3, and round up the results to the nearest integer. Let m be the number of contact moments of 30 s i.e. $m = \psi_{R_i} \times 2$.

4. (Workflow D): Simulate the number of ω_{R_i} colonized by g with the HMO:

   We assumed each person co-occurring in a room has an independent binomial distribution given by $I \sim Bin(m, P)$ to get colonized by g over m contact moments with and transmission probability P. We assume that the successful transmission during at least 1 of the m contact moments for each of the ω_{R_i} co-occurring HCWs or patients are independent, which is why the expected number of HCWs or colonized during a the co-occurrence in room R_i (IN) can be estimated as $E[IN] = \sum_{j=1}^{\omega_{R_i}} \{1 - P(I = 0)\} = \omega_{R_i} \times (1 - (1 - P)^m)$.

5. (Workflow A): Determine the next room after the following transition:

   Use u_5 as input for the inverse cumulative probability distribution of the transition probability matrix $\boldsymbol{P}$ found by taking the cumulative sum on the row of $\boldsymbol{P}$ corresponding to current room R_i.

6. Three cumulative measures during simulation while g is colonized are collected: the time spent in minutes (ψ_c), ω_{R_i} co-occurring with g (ω_c) and the expected number of HCWs or patients colonized by g (IN_c).

7. Repeat Step 2.2.3

One thousand simulations were performed for three different rates of transmission (P) between 0.0005 and 0.05 for each of the five HHC distributions. The result of the simulation is 15 (3×5) scenarios with outputs ψ_c, M, ω_c, T and IN_c corresponding to RF1 – RF5 respectively. The simulations were repeated for the subsets 1 and 2 separately and combined.

We summarise the simulation assumptions made by workflow section as follows:

Workflow A: Movement

1. Contact definition is based on HCWs or patients co-occurring at a room level.
2. Patient rooms are always occupied by at least 1 patient which is the reasons for the HCW to visit the room.

Workflow B: Hand hygiene

1. A colonized NUR can perform hand hygiene once during every transition between rooms.
2. For a colonized NUR to be decolonized, hand hygiene needs to be performed and it needs to be successful. The former depends on the action of the NUR with probability γ and the latter on the efficacy of the solution used to perform hand hygiene with probability λ.

Workflow C: Time spent and Number of people

1. The number of minutes an infected NUR spends in a room R_i is given by $\psi_{R_i} \sim Exp\left(\frac{1}{\eta}\right)$, where η is the sample average of ψ_{R_i}.
2. The number of HCWs or patients co-occurring in room R_i with the infected NUR is given by $\omega_{R_i} \sim N(\nu, \varphi^2)$ or $\omega_{R_i} \sim Poisson(\nu)$, where ν and φ^2 are estimated using the average and variance of ω_{R_i} from the sampled data respectively.

Workflow D: Transmission

1. Only colonized nurse can transmit an HMO.
2. HCW and patients only have two states: susceptible and colonized.
3. Number of colonized HCW or patients after co-occurring with a colonized NUR for m contact moments with probability of transmission P for each 30 s of co-occurrence is distributed as $I \sim Bin(m, P)$.

There are two key moments in the model. The first is when g enters a room – that is when an opportunity is given to perform hand hygiene with probability γ and corresponds to part B of the

simulation workflow. Five probability distributions are used to simulate HHC for simulation. A normal distribution with mean 0.05 represents very low HHC, 0.25 and 0.5 shows the effect of low to average HHC and 0.75 to 0.95 for high to near perfect HHC levels. Should g perform hand hygiene, then the probability that the hand hygiene was successfully performed, meaning that all traces of the HMO were eradicated, is given by λ. The probability of successful use of hand hygiene is based on Girou et al [6] and the difference compliance levels (low, medium and high) are based on Temime et al [8].

The second key moment is when more than one HCW or patient co-occurs with g in the same room. The colonized HCW has a probability of transferring microbes to all HCWs or patients in the room every 30 s with probability P. The probability of transmitting a HMO from one person to another results in a 1.5% - 13.5% probability of infection for each 15 minutes spent together, which is similar to [8]. We assume that transmissions between all HCWs and patients are equally likely for each 30 s spent together in the same room. For example, HCWs or patients in contact with an g will be subject to the probability stated in Formula 3 during the first 30 s of contact. The last two terms in Formula 1 decrease the probability of transmission because of the chance that g will effectively perform hand hygiene and not carry the HMO anymore. Only the parameter P remains for subsequent 30 s interval because g only performs hand hygiene when entering the room.

$$P[Susceptible \rightarrow Infected|n = 1] = P \times \gamma \times (1 - \lambda) \quad \text{Formula 3}$$

For successive 30 s contact moments, we assume that the probability that a colonized HCW contaminates an uncontaminated transfers microbes to an uncolonized HCW or patient follows a binomial distribution with parameter m indicating the number of 30 s intervals and parameter P indicating the probability of transmission. In order to model this as a binomial distribution, we assume that there are only two outcomes, i.e. colonized and decolonized, that each 30 s interval is independent from the other and that the probability of transmission stays constant.

The effect of P is positively correlated with the number of transmissions, meaning that more transmissions should take place if the rate of infection increases. Model parameters λ and γ however

have an inverse relationship with the expected number of transmissions. Some simulation parameters are positively correlated and some with a negatively correlated with the expected number of transmissions. The linear nature of the transmission formula makes it possible to create scenarios where two parameters, with opposite correlation with the expected number of transmissions, can mitigate and even completely off-set effect of the other on the expected number of transmissions. This provides further insight into the effects of the initial simulation assumptions propagated through the sampled spatiotemporal data.

Results

During the seven-day period, 2 215 contact moments were derived from the 2 573 sampled observations which equates to 412 hours (24 719 minutes) of contact data. NUR, DOC and patients (PAT) were together responsible for 78.8% and 77.1% of all contacts and time spent in contact respectively (Table 3). NUR made up 57.0% and 56.8% of these percentages which is five times more than the second higher HCW occupation group, DOC (11.1% and 12.6%). Therefore, a colonized NUR has a disproportionately high potential of transmitting and HMO based on the amount of contact and time spent with HCWs or patients. For these reasons, we investigate the NUR HCW occupation group as potential super-spreaders in this study.

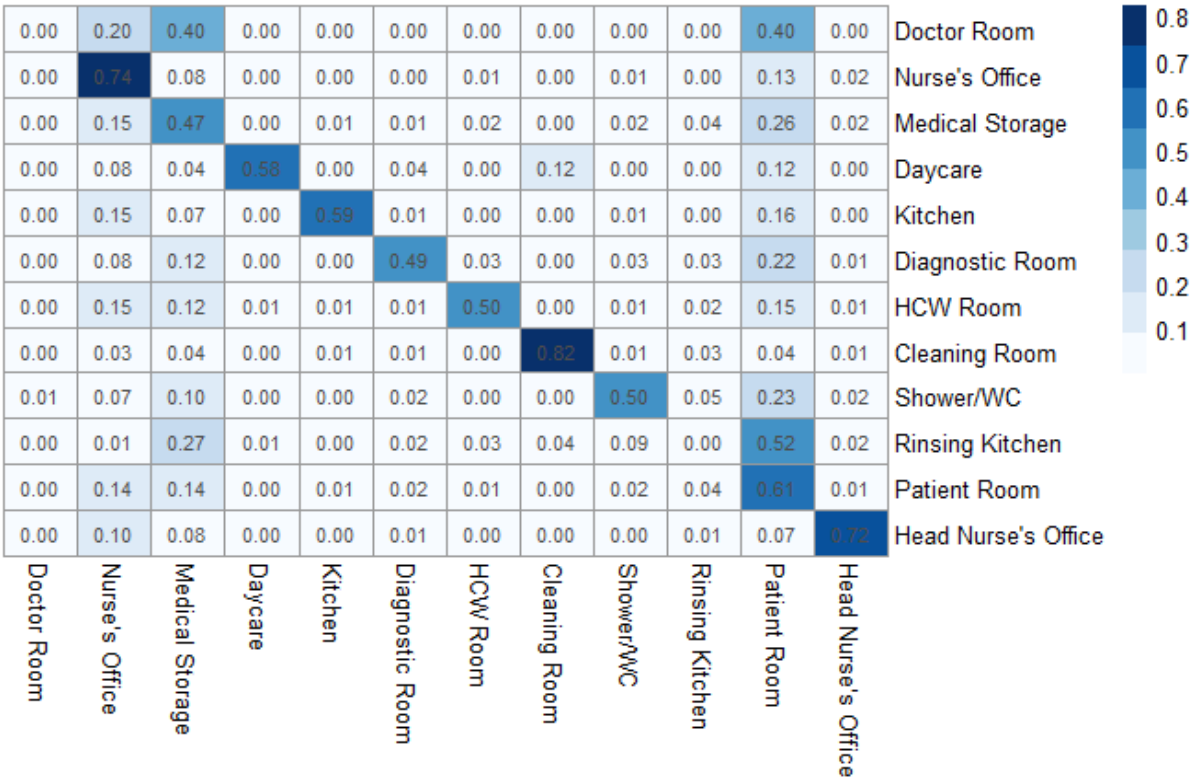
Table 3: Summary of number of contact and duration of contacts by individual category.

(Occupation) Group	Average Contact Minutes (SD)	Number of Contacts (% of total)	Contact Minutes (% of total)
NUR	11.13 (20.05)	1262 (57.0%)	14 040 (56.8%)
DOC	12.56 (20.65)	248 (11.2%)	3 116 (12.6%)
PAT	8.04 (12.23)	234 (10.6%)	1 882 (7.6%)
DAS	13.63 (16.16)	192 (8.7%)	2 616 (10.6%)
CON	145.98 (23.27)	143 (6.5%)	2 097 (8.5%)
CLN	6.06 (10.35)	83 (3.7%)	503 (2.0%)
CAS	10.47 (12.88)	36 (1.6%)	377 (1.5%)
FAS	5.18 (8.27)	17 (0.8%)	88 (0.4%)
Total	11.16 (19.75)	2215 (100.0%)	24719 (100.0%)

NUR = Nurse, DOC = Doctor, PAT = Patient, DAS = Department assistant, CON = Consultant, CLN = Cleaner, CAS = Co-assistant, FAS = Feeding assistant

The estimated transition probability matrix ($\boldsymbol{P}$) for NUR summarises the transitions of NUR between rooms observed in the sampled data (Figure 3). According to $\boldsymbol{P}$, NUR are most likely to transition to either a patient room, a medical storage area or the nurse's office.

Figure 3: Transition probability matrix $\boldsymbol{P}$ for movement of NUR between rooms.



The transmission probabilities are given as p_{ij} in the i^{th} row and j^{th} column for the movement of NUR between rooms. Each element is the estimated probability that a nurse will transition from room i to room j after the next transition.

The time weighted average number of HCWs or patients co-occurring with a NUR (Table 4) shows that the nurse's office has both the highest estimated ω_{R_i} and ψ_{R_i}. For this reason, the relatively high estimated probability that a NUR will transition to the nurse's office, implies that an HCW of the occupation group NUR spends a large portion of their time here while co-occurring with a relatively large number of people. Patient rooms have a lower expected ψ_{R_i}, relative to the nurse's office, but the ω_{R_i} is almost the same. Since we assumed that there is at least one patient in the patient room, the expected ω_{R_i} for the patient rooms is more than 2.

Table 4: Number of HCWs or patients and the time they co-occurred in each room.

Room (R_i)	ω_{R_i} (SD)	ψ_{R_i} (SD)
Cleaning Room	1.45 (0.37)	8.05 (12.50)
Daycare	1.10 (0.30)	8.55 (11.07)
Diagnostic Room	1.11 (0.59)	27.57 (45.01)
Doctor Room	1.00 (0.00)	4.82 (5.25)
HCW Room	1.04 (0.32)	18.17 (22.75)
Head Nurse's Office	1.82 (1.59)	18.64 (33.09)
Kitchen	1.15 (0.46)	9.51 (9.96)
Medical Storage	1.12 (0.49)	8.90 (14.70)
Nurse's Office	2.16 (1.59)	19.39 (26.70)
Patient Room	2.09 (0.40)	11.55 (19.01)
Rinsing Kitchen	1.00 (0.14)	0.08 (0.19)
Shower/WC	1.10 (0.40)	10.74 (20.94)

ω_{R_i} = average number of people co-occurring in room R_i, ψ_{R_i} = average amount of time (minutes) spent in room R_i

Simulation results

The ($P = 0.05$; $\lambda = 0.05$) scenario in Table 5 corresponds to the highest probability of transmission (P) and the lowest HHC level (λ). For this scenario, a colonized NUR can transition through 22 wardrooms ($T = 22.32$) for almost one and a half hours ($\psi_c = 87.39$) while making contact with 13 HCWs or patients ($\omega_c = 17.10$) which results in 76 30 s opportunities to transmit HMO ($M = 76.34$). This scenario also resulted in the highest amount of expected transmissions ($IN_c = 3.13$). Reducing the transmission rate results into an exponential decrease of the number of expected transmissions as expected.

In the ($P = 0.005$; $\lambda = 0.75$) scenario, where the level of HHC is highest and the transmission probability is lowest, the expected time that a colonized NUR would spend carrying an HMO is just under 6 minutes even though the assumed effectiveness of the alcohol rub used is only 83%. Note that the (P = 0.005; $\lambda = 0.05$) scenario results in a similar amount of expected number of infections as the scenario where $P = 0.05$ and $\lambda = 0.5$ (0.37 vs. 0.43) even though differs by a factor of ten.

Table 5: Results of all the 1 000 simulations performed.

P	λ	RF1: ψ_c (SD)	RF2: M (SD)	RF3: ω_c (SD)	RF4: T (SD)	RF5: IN_c
0.05	0.05	87.39 (72.01)	76.34 (67.87)	17.10 (13.54)	22.32 (21.37)	3.13 (2.70)
0.005	0.05	88.00 (71.25)	76.62 (68.24)	16.90 (13.57)	22.42 (21.58)	0.37 (0.33)
0.0005	0.05	92.97 (72.14)	81.21 (71.41)	17.84 (13.76)	23.94 (22.33)	0.04 (0.04)
0.05	0.25	19.21 (22.78)	18.77 (25.43)	4.10 (4.51)	4.56 (4.21)	0.75 (0.98)
0.005	0.25	19.99 (22.68)	19.26 (25.00)	4.38 (4.68)	4.84 (4.30)	0.09 (0.12)
0.0005	0.25	19.79 (22.92)	18.93 (24.56)	4.31 (4.61)	4.76 (4.40)	0.01 (0.01)
0.05	0.5	9.48 (9.15)	11.13 (16.15)	2.26 (2.25)	2.39 (1.78)	0.43 (0.59)
0.005	0.5	9.44 (10.72)	9.96 (14.72)	2.32 (2.43)	2.48 (1.89)	0.05 (0.07)
0.0005	0.5	9.59 (10.90)	10.24 (16.82)	2.10 (2.20)	2.36 (1.84)	0.01 (0.01)
0.05	0.75	6.63 (5.91)	7.80 (11.50)	1.61 (1.64)	1.61 (0.97)	0.30 (0.43)
0.005	0.75	6.94 (6.86)	8.07 (13.19)	1.64 (1.66)	1.72 (1.03)	0.04 (0.06)
0.0005	0.75	6.65 (6.59)	7.92 (13.89)	1.59 (1.68)	1.59 (0.99)	0.00 (0.01)
0.05	0.95	5.81 (5.37)	6.80 (12.15)	1.31 (1.41)	1.31 (0.64)	0.25 (0.41)
0.005	0.95	6.02 (5.35)	7.27 (11.60)	1.35 (1.38)	1.26 (0.61)	0.03 (0.05)
0.0005	0.95	5.85 (5.70)	7.24 (11.89)	1.38 (1.40)	1.27 (0.61)	0.00 (0.01)

Sampled data for three different transmission assumptions and five distributions of HHC for one colonized NUR starting in a random room in the hospital ward, a hand hygiene efficacy (γ) of 0.83 and that ω_{R_i} follows a Poisson distribution. $P =$ probability of transmission, $\lambda =$ HHC level, $\psi_c =$ amount of time spent colonized, $M =$ number of contact moments, $\omega_c =$ number of HCWs or patients made contact with, $T =$ number of transition between hospital ward rooms, $IN_c =$ expected number of HMO transmissions

The simulation results based upon subset 1 (Table 6) show that, for the ($P = 0.05;\ \lambda = 0.05$) scenario, a colonized NUR is expected to spend less time colonized while transitioning through the wardrooms during weekdays than during weeknights or weekends (72.93 vs. 101.54 minutes) even though more HCWs or patients are expected to be encountered (19.07 vs. 15.96) by the colonized NUR. From Table 6 and Table 7 we see that the difference between the expected number of transitions (T) by a colonized NUR for subset 1 and 2 is less than 10% for all scenarios. The difference in the expected number of transmissions caused by a colonized NUR between subset 1 and 2 equals 20% for the ($P = 0.05, \lambda = 0.05$) scenario and equals 52% for the ($P = 0.05, \lambda = 0.95$) scenario. These differences are the result of the change of spatiotemporal and social mixing patterns of the HCW observed during the weekdays and weeknights or weekends.

Table 6: Results of 1 000 simulations performed on weekday (7am-5pm)

P	λ	RF1: ψ_c (SD)	RF2: M (SD)	RF3: ω_c (SD)	RF4: T (SD)	RF5: IN_c

0.05	0.05	72.93 (58.37)	68.47 (61.71)	19.07 (15.52)	22.74 (21.82)	2.94 (2.60)
0.005	0.05	74.76 (58.11)	72.06 (62.66)	19.86 (15.72)	23.50 (21.82)	0.35 (0.31)
0.0005	0.05	72.00 (58.79)	66.90 (58.71)	18.68 (14.95)	21.73 (20.37)	0.03 (0.03)
0.05	0.25	16.57 (19.43)	16.76 (22.35)	4.65 (5.41)	4.77 (4.61)	0.70 (0.92)
0.005	0.25	15.96 (17.74)	16.76 (21.60)	4.43 (4.79)	4.61 (4.13)	0.08 (0.11)
0.0005	0.25	17.74 (19.32)	18.24 (22.23)	4.72 (5.15)	4.95 (4.48)	0.01 (0.01)
0.05	0.5	7.30 (7.84)	8.24 (12.37)	2.10 (2.28)	2.25 (1.75)	0.33 (0.48)
0.005	0.5	7.86 (8.33)	9.48 (13.48)	2.38 (2.45)	2.43 (1.85)	0.04 (0.06)
0.0005	0.5	8.09 (8.32)	9.09 (12.66)	2.26 (2.43)	2.41 (1.84)	0.00 (0.01)
0.05	0.75	5.63 (5.45)	6.83 (10.63)	1.63 (1.68)	1.62 (0.99)	0.27 (0.40)
0.005	0.75	5.52 (5.11)	6.58 (10.37)	1.63 (1.75)	1.59 (1.00)	0.03 (0.05)
0.0005	0.75	5.38 (5.06)	6.97 (10.47)	1.71 (1.80)	1.62 (1.03)	0.00 (0.01)
0.05	0.95	4.81 (4.48)	5.96 (9.07)	1.38 (1.40)	1.31 (0.65)	0.23 (0.33)
0.005	0.95	4.91 (4.45)	6.06 (9.54)	1.38 (1.44)	1.29 (0.62)	0.03 (0.04)
0.0005	0.95	4.95 (4.31)	5.79 (8.86)	1.35 (1.38)	1.29 (0.64)	0.00 (0.00)

Sampled data for three different transmission assumptions and five distributions of HHC for one colonized NUR starting in a random room in the hospital ward, a hand hygiene efficacy (γ) of 0.83 and that ω_{R_i} follows a Poisson distribution. $P =$ probability of transmission, $\lambda =$ HHC level, $\psi_c =$ amount of time spent colonized, $M =$ number of contact moments, $\omega_c =$ number of HCWs or patients made contact with, $T =$ number of transition between hospital ward rooms, $IN_c =$ expected number of HMO transmissions

Table 7: Results of 1 000 simulations performed on weeknights (6pm – 6am) and weekend

P	λ	RF1: ψ_c (SD)	RF2: M (SD)	RF3: ω_c (SD)	RF4: T (SD)	RF5: IN_c
0.05	0.05	101.54 (81.75)	95.75 (89.27)	15.96 (12.45)	23.44 (22.09)	3.61 (3.19)
0.005	0.05	103.02 (81.06)	99.07 (89.73)	16.13 (12.87)	23.66 (22.60)	0.48 (0.43)
0.0005	0.05	101.34 (79.78)	97.56 (89.70)	16.02 (12.68)	23.23 (22.27)	0.05 (0.04)
0.05	0.25	24.36 (25.15)	24.20 (32.35)	4.18 (4.31)	4.91 (4.26)	0.90 (1.13)
0.005	0.25	23.92 (24.96)	24.17 (32.03)	4.10 (4.36)	4.87 (4.41)	0.11 (0.15)
0.0005	0.25	23.39 (24.56)	24.11 (34.26)	3.93 (4.18)	4.62 (4.14)	0.01 (0.02)

0.05	0.5	12.04 (12.21)	12.82 (19.68)	2.04 (2.26)	2.44 (1.86)	0.46 (0.64)
0.005	0.5	11.66 (12.37)	13.19 (19.25)	2.14 (2.28)	2.32 (1.80)	0.06 (0.09)
0.0005	0.5	12.24 (12.23)	12.85 (19.69)	2.14 (2.32)	2.41 (1.83)	0.01 (0.01)
0.05	0.75	9.04 (8.55)	10.50 (16.98)	1.52 (1.52)	1.62 (0.93)	0.37 (0.54)
0.005	0.75	8.84 (8.07)	10.81 (16.75)	1.62 (1.63)	1.62 (0.98)	0.05 (0.08)
0.0005	0.75	9.18 (9.02)	10.61 (17.50)	1.51 (1.56)	1.61 (0.96)	0.01 (0.01)
0.05	0.95	8.39 (7.69)	9.97 (16.45)	1.33 (1.36)	1.30 (0.64)	0.35 (0.52)
0.005	0.95	8.25 (7.65)	10.81 (19.30)	1.37 (1.44)	1.28 (0.64)	0.05 (0.09)
0.0005	0.95	8.87 (8.45)	10.46 (18.37)	1.40 (1.44)	1.31 (0.68)	0.01 (0.01)

Sampled data for three different transmission assumptions and five distributions of HHC for one colonized NUR starting in a random room in the hospital ward, a hand hygiene efficacy (γ) of 0.83 and that ω_{R_i} follows a Poisson distribution. $P =$ probability of transmission, $\lambda =$ HHC level, $\psi_c =$ amount of time spent colonized, $M =$ number of contact moments, $\omega_c =$ number of HCWs or patient made contact with, $T =$ number of transition between hospital ward rooms, $IN_c =$ expected number of HMO transmissions

Discussion

This study identified nurses as a potential super-spreader healthcare worker (HCW) occupation group. Nurses have a disproportionately high potential to transmit harmful microorganisms (HMO) to other HCWs or patients as compared to the other HCW occupation groups. In this study we showed that the expected number of transmissions caused by a colonized nurse increases exponentially as the level of hand hygiene compliance (HHC) deteriorates or the transmission probability increases. This is due to the spatiotemporal behaviour and social mixing patterns of HCWs.

Five risk factors were defined to quantify the spatiotemporal effects of varying levels of HHC on the transmission and spread of HMO in a healthcare setting. These were: 1) the time that a colonized super-spreader is expected to be colonized; 2) the number of contact moments with other HCWs or patients; 3) the number of HCWs or patients encountered; 4) the number of ward rooms frequented while colonized and 5) the expected number of HCWs or patients a super-spreader will transfer microbes to before performing proper hand hygiene. These risk factors were quantified for various levels of hand hygiene compliance and probabilities of transmission. We quantified the decrease in

the expected number of transmissions for different levels of HHC. This may encourage approval for healthcare interventions such as increased education and awareness about HHC and strategic accessibility to alcohol dispensers in healthcare settings. The simulation results are based on empirical social mixing patterns of HCWs and highlight the impact of one colonized nurse as the super-spreader. Such a simulation can be used in educational materials to emphasize personal control and responsibility to perform HHC. Normal HHC levels of 50% may deteriorate to 25% during busy periods in a healthcare setting because of reduced healthcare worker capacity or time pressure. The simulation results allow for “what if?” questions to be answered under different assumed levels of HHC and transmission probabilities in terms of the five risk factors. HCWs are then able to simulate the impact of the initial assumptions on the expected number of transmissions caused by a super-spreader based on empirical spatiotemporal behaviour and social mixing patterns of HCWs in a real healthcare setting.

The results are consistent with other work done on super-spreaders in healthcare facilities [18]. Our contribution is that we quantified potential consequences of the spatiotemporal behaviour of HCWs for varying levels of hand hygiene compliance and different transmission probabilities. The simulation results showed that, for the same transmission rates and HHC levels, the number of transmissions is higher during weeknights and weekends. An explanation is that during weeknights and weekends, HCWs spent more time with fewer HCWs or patients but had more contact moments for every minute spent colonized. An increase in the time that a super-spreader navigates through the hospital ward results in an increase in the number of encountered HCWs or patients, allowing for more opportunity to transmit the HMO. HHC may vary over time because of varying ward occupancy levels or different days of the week: the simulation results show that for a HMO with a transmission rate of 0.05 and with the average level of HHC of 50% during the week and 25% over the weekend, that the expected number of HCWs and patients to whom a colonized nurse transfers microbes will almost double. Simulation scenarios were identified with equal risk factors for different initial conditions. They

illustrate that infection prevention and control interventions can use combinations of strategies and bundles of interventions to fight the transmission and spread of HMO to achieve the same results.

The expected number of HCWs or patients a super-spreader will transfer microbes to before performing proper hand hygiene (risk factor 5) is the ultimate consequence which should be controlled by managing spatiotemporal behaviour (risk factors 1 – 4) and the level of HHC. A possible intervention based on these results is to limit the amount of movement/contact during periods of low expected levels of HHC. For example, if Friday evenings are very busy and affecting the levels of HHC, a possible preventative intervention might be to optimise HCW routes and logistics according to an algorithm based on sampled spatiotemporal movement data. This should then specifically be designed to minimise the potential transmission and spread of harmful microorganisms. Risk factors can thus be monitored over time, for instance allowing one to determine any seasonal trends or the effects of spatiotemporal interventions or policy changes. The five risk factors may then be used in combination to compare hospital wards or in the formulation of healthcare policy.

Limitations

Our sample is taken over a period of seven days giving a unique sample with a good coverage for a single week. Differences may exist, however, with other weeks throughout the year and even between years. The data used in this study may further be biased towards HCWs who were diligent in wearing the RFID badges. The data were carefully checked for any inconsistencies; some loss in data quality caused by incorrect room classification because of overlapping RFID reader areas could still be present in the data. The hospital ward in our study is similar to wards found in most healthcare facilities in most aspects. Our results are based upon the sampled RFID tracking data for one specific ward. It is a future challenge to generalise these results to other wards in other hospitals. These data, together with the knowledge of typical spatiotemporal HHC levels, can be used to estimate the five risk factors. The spatial resolution of our data is the room level and made assumptions on the proximity and interaction between people, thus adding uncertainty in the simulation results. Future opportunities

include the collection of data of a higher spatial resolution that will allow us to identify the proximity between people, within room locations in the hospital and interaction with objects like alcohol dispensers and mobile (diagnostic) equipment like computers on wheels. An increase in spatial resolution will enable a more accurate event classification and may result in more accurate simulation results. For instance, interaction with a hand hygiene dispenser does not require any assumption about the level of HHC, but only on its efficacy. Interaction of an HCW with objects and equipment inside a room, allows one to refine the transmission models thus improving the transmission scenarios.

Conclusion

This study contributes to infection prevention and control by highlighting five risk factors which are essential for interventions the describe the possible spread of an HMO both on a temporal and individual level, as well as on the spatial level in a closed healthcare setting. These insights can be used to develop better informed preventative strategies, for heterogeneous hand hygiene education, feedback, work-place reminders and other interventions. The risk factors defined in this study enable the quantification of geospatial behaviour which may result in the increase in transmission and spread of harmful microorganisms. The simulations increase our insight into the consequences of varying levels of adherence to spatiotemporal-dependent healthcare policies such as hand hygiene compliance. Spatiotemporal behaviour and social mixing patterns of HCWs can change the expected number of transmissions in a closed healthcare setting and should be better understood to inform better policy making and further educating HCWs about the risks of their actions. In this sense, the differences between weekdays and weekend days is very illustrative.

List of abbreviations

CLN	CLeaNer
CON	CONsultant
DAS	Department ASsistant
DCA	Department Co-Assistant
DOC	DOCtor
FAS	Feeding ASsistant
HCW	Healthcare Worker
HHC	Hand Hygiene Compliance
HMO	Harmful Microorganisms
MRSA	Methicillin-Resistant Staphylococcus Aureus
NUR	NURse
PAT	PATient
RFID	Radio Frequency IDentification
SD	Standard Deviation
SSE	Super-Spreading Events
UMCG	University Medical Center Groningen
WC	Water Closet

Ethics approval and consent to participate

Ethics approval was not required under Dutch law (WMO) according to the medical ethical technical committee of UMCG (METc UMC Groningen: 201600818). Verbal informed consent was given by all participants and deemed sufficient given the anonymised nature of the data.

Consent for publication

All authors read and approved the manuscript.

Availability of data and material

The data that support the findings of this study are available from UMCG but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of UMCG.

Competing interests

None

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Author's contributions

JM, JEWC, A contributed to the conceptualization of the research and commenting on the draft and final version of the paper. JM, JEWC, A, MHED, ML and LMA contributed in editing and writing the draft and final version of the paper. JM performed the data analysis, statistical analysis and wrote the draft and final version of the paper. . MHED and ML introduced the Radio Frequency IDentification (RFID) technology developed by RePoint (https://repoint.nl/nl/) on the ward and motivated HCWs to wear batches to generate data.

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References

1. van Kleef E, Robotham J V., Jit M, Deeny SR, Edmunds WJ. Modelling the transmission of healthcare associated infections: A systematic review. BMC Infect Dis [Internet]. 2013 [cited 2017 Oct 9];13(1). Available from: https://bmcinfectdis.biomedcentral.com/track/pdf/10.1186/1471-2334-13-294?site=bmcinfectdis.biomedcentral.com

2. Cheng CH, Kuo YH, Zhou Z. Tracking Nosocomial Diseases at Individual Level with a Real-Time Indoor Positioning System. J Med Syst. 2018;42(11).

3. Sickbert-Bennett EE, Dibiase LM, Schade Willis TM, Wolak ES, Weber DJ, Rutala WA. Reduction of healthcare-associated infections by exceeding high compliance with hand hygiene practices. Emerg Infect Dis. 2016;22(9):1628–30.

4. Chassin MR, Mayer C, Nether K. Improving hand hygiene at eight hospitals in the United States by targeting specific causes of noncompliance. Jt Comm J Qual Patient Saf [Internet]. 2015;41(1):4–12. Available from: http://dx.doi.org/10.1016/S1553-7250(15)41002-5

5. Hofmann DA, Staats BR, Dai H, Milkman KL. The Impact of Time at Work and Time off from Work on Rule Compliance: The Case of Hand Hygiene in Healthcare. J Appl Psychol. 2015;100(3):846–62.

6. Girou E, Loyeau S, Legrand P, Oppein F, Brun-Buisson C. Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. BMJ [Internet]. 2002;325(7360):362. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12183307%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC117885

7. Hornbeck T, Naylor D, Segre AM, Thomas G, Herman T, Polgreen PM. Using sensor networks to study the effect of peripatetic healthcare workers on the spread of hospital-associated infections. J Infect Dis. 2012;206(10):1549–57.

8. Temime L, Opatowski L, Pannet Y, Brun-Buisson C, Boelle PY, Guillemot D. Peripatetic health-care workers as potential superspreaders. Proc Natl Acad Sci [Internet]. 2009;106(43):18420–5. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0900974106

9. Haddara M, Staaby A. RFID applications and adoptions in healthcare: A review on patient safety. Procedia Comput Sci [Internet]. 2018;138:80–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1877050918316430

10. Lopez-Garcia M, Aruru M, Pyne S. Health analytics and disease modeling for better

understanding of healthcare-associated infections. BLDE Univ J Heal Sci [Internet]. 2018;3(2):69–74. Available from: http://www.bldeujournalhs.in/article.asp?issn=2468-838X%0Ayear=2018%0Avolume=3%0Aissue=2%0Aspage=69%0Aepage=74%0Aaulast=Lopez-Garcia

11. Ciavarella C, Fumanelli L, Merler S, Cattuto C, Ajelli M. School closure policies at municipality level for mitigating influenza spread: A model-based evaluation. BMC Infect Dis [Internet]. 2016;16(1):1–11. Available from: http://dx.doi.org/10.1186/s12879-016-1918-z

12. Salathe M, Kazandjieva M, Lee JW, Levis P, Feldman MW, Jones JH. A high-resolution human contact network for infectious disease transmission. Proc Natl Acad Sci. 2010;107(51):22020–5.

13. Smieszek T, Castell S, Barrat A, Cattuto C, White PJ, Krause G. Contact diaries versus wearable proximity sensors in measuring contact patterns at a conference: Method comparison and participants' attitudes. BMC Infect Dis [Internet]. 2016;16(1):1–14. Available from: http://dx.doi.org/10.1186/s12879-016-1676-y

14. Ozella L, Gesualdo F, Tizzoni M, Rizzo C, Pandolfi E, Campagna I, et al. Close encounters between infants and household members measured through wearable proximity sensors. PLoS One. 2018;13(6):1–16.

15. Voirin N, Payet C, Barrat A, Cattuto C, Khanafer N, Régis C, et al. Combining high-resolution contact data with virological data to investigate influenza transmission in a tertiary care hospital. Infect Control Hosp Epidemiol. 2015;36(3):254–60.

16. English KM, Langley JM, McGeer A, Hupert N, Tellier R, Henry B, et al. Contact among healthcare workers in the hospital setting: Developing the evidence base for innovative approaches to infection control. BMC Infect Dis. 2018;18(1):1–12.

17. Mastrandrea R, Soto-Aladro A, Brouqui P, Barrat A. Enhancing the evaluation of pathogen transmission risk in a hospital by merging hand-hygiene compliance and contact data: A proof-of-concept study Public Health. BMC Res Notes [Internet]. 2015;8(1):426. Available from: http://www.biomedcentral.com/1756-0500/8/426

18. Vanhems P, Barrat A, Cattuto C, Pinton JF, Khanafer N, Régis C, et al. Estimating potential infection transmission routes in hospital wards using wearable proximity sensors. PLoS One [Internet]. 2013 [cited 2017 Jul 18];8(9):e73970. Available from: http://dx.plos.org/10.1371/journal.pone.0073970

19. Ozella L, Gauvin L, Carenzo L, Quaggiotto M, Ingrassia PL, Tizzoni M, et al. Wearable Proximity Sensors for Monitoring a Mass Casualty Incident Exercise: Feasibility Study. J Med Internet Res. 2019;21(4):e12251.

20. Machens A, Gesualdo F, Rizzo C, Tozzi AE, Barrat A, Cattuto C. An infectious disease model on empirical networks of human contact: bridging the gap between dynamic network data and contact matrices. BMC Infect Dis [Internet]. 2013 Apr;13(1):185. Available from: http://bmcinfectdis.biomedcentral.com/articles/10.1186/1471-2334-13-185

21. Isella L, Romano M, Barrat A, Cattuto C, Colizza V, van den Broeck W, et al. Close encounters in a pediatric ward: Measuring face-to-face proximity and mixing patterns with wearable sensors. PLoS One. 2011 Feb;6(2).

22. Najafi M, Laskowski M, De Boer PT, Williams E, Chit A, Moghadas SM. The Effect of Individual Movements and Interventions on the Spread of Influenza in Long-Term Care Facilities. Med Decis Mak [Internet]. 2017 May 24 [cited 2017 Jul 18];37(8):871–81. Available from:

http://journals.sagepub.com/doi/10.1177/0272989X17708564

23. Assab R, Nekkab N, Crépey P, Astagneau P, Guillemot D, Opatowski L, et al. Mathematical models of infection transmission in healthcare settings: Recent advances from the use of network structured data. Curr Opin Infect Dis. 2017;30(4):410–8.

24. Kim B, Barrat A, Khanafer N, Cattuto C, Régis C, Vanhems P, et al. Estimating Potential Infection Transmission Routes in Hospital Wards Using Wearable Proximity Sensors. PLoS One [Internet]. 2013;8(9):e73970. Available from: http://dx.plos.org/10.1371/journal.pone.0073970

25. Chen H, Yang B, Pei H, Liu J. Next Generation Technology for Epidemic Prevention and Control: Data-Driven Contact Tracking. IEEE Access. 2019;7:2633–42.

26. Iozzi F, Trusiano F, Chinazzi M, Billari FC, Zagheni E, Merler S, et al. Little italy: An agent-based approach to the estimation of contact patterns- fitting predicted matrices to serological data. PLoS Comput Biol. 2010;6(12).

27. Génois M, Barrat A. Can co-location be used as a proxy for face-to-face contacts? EPJ Data Sci [Internet]. 2018 May;7(1):11. Available from: https://doi.org/10.1140/epjds/s13688-018-0140-1

28. Woolhouse MEJ, Dye C, Etard J-F, Smith T, Charlwood JD, Garnett GP, et al. Heterogeneities in the transmission of infectious agents: Implications for the design of control programs. Proc Natl Acad Sci. 2002;94(1):338–42.

29. Jit M, Brisson M. Modelling the epidemiology of infectious diseases for decision analysis. Pharmacoeconomics. 2011;29(5):371–86.

30. Banks HT, Broido A, Canter B, Gayvert K, Hu S, Joyner M, et al. Simulation algorithms for continuous time Markov chain models. Stud Appl Electromagn Mech. 2012;37:3–18.