ORIGINAL ARTICLE

Interindividual Contacts and Carriage of Methicillin-Resistant *Staphylococcus aureus*: A Nested Case-Control Study

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BACKGROUND. Reducing the spread of multidrug-resistant bacteria in hospitals remains a challenge. Current methods are screening of patients, isolation, and adherence to hygiene measures among healthcare workers (HCWs). More specific measures could rely on a better characterization of the contacts at risk of dissemination.

OBJECTIVE. To quantify how close-proximity interactions (CPIs) affected *Staphylococcus aureus* dissemination.

DESIGN. Nested case-control study.

SETTING. French long-term care facility in 2009.

PARTICIPANTS. Patients (n = 329) and HCWs (n = 261).

METHODS. We recorded CPIs using electronic devices together with *S. aureus* nasal carriage during 4 months in all participants. Cases consisted of patients showing incident *S. aureus* colonization and were paired to 8 control patients who did not exhibit incident colonization at the same date. Conditional logistic regression was used to quantify associations between incidence and exposure to demographic, network, and carriage covariables.

RESULTS. The local structure of contacts informed on methicillin-resistant *S. aureus* (MRSA) carriage acquisition: CPIs with more HCWs were associated with incident MRSA colonization in patients (odds ratio [OR], 1.10 [95% CI, 1.04–1.17] for 1 more HCW), as well as longer CPI durations (1.03 [1.01–1.06] for a 1-hour increase). Joint analysis of carriage and contacts showed increased carriage acquisition in case of CPI with another colonized individual (OR, 1.55 [1.14–2.11] for 1 more HCW). Global network measurements did not capture associations between contacts and carriage.

CONCLUSIONS. Electronically recorded CPIs inform on the risk of MRSA carriage, warranting more study of in-hospital contact networks to design targeted intervention strategies.

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Nosocomial transmission of germs is a major public health issue.[1] Because most germs may be transmitted by direct contact, reducing the per-contact risk by improving hygiene has been at the heart of prevention strategies.[2,3] To further reduce risk, it may be necessary to alter the structure of contacts itself, as proposed in theoretical studies.[4–6]

Yet, contacts leading to nosocomial transmission are poorly characterized in hospitals: they are often assumed to occur at random within the wards,[7] or, at best, equated with attendance of the same ward at the same date among carriers of the same strains.[8,9] Indeed, no convenient way to record contacts existed before advances in communication technologies made it possible to record high-resolution close-proximity interaction (CPI) networks.[10] CPIs correlate with contacts measured in more traditional ways[11] and are not affected by the reporting bias inherent to self-reporting.[12] They may therefore

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provide a good proxy for between-humans contacts and inform on interactions leading to transmission.[13]

Here, we report on a longitudinal, observational study, in which all participants were monitored for 4 months to continuously record CPIs and weekly detect *Staphylococcus aureus* carriage. The study took place in a long-term care facility (LTCF) in France. LTCFs, where patients usually stay for extended periods, present a large prevalence of carriage. As such, they have long been identified as a potential reservoir of antibiotic-resistant bacteria such as *S. aureus*.[14–17]

We conducted a nested case-control analysis to identify CPI-related risk factors associated with *S. aureus* transmission. Our objective was to identify CPI patterns that were associated with colonization. To that aim, we studied both local features of the CPI network (restricted to an individual of interest and his direct contacts) and global network measures. We also investigated whether the joint analysis of CPIs and bacterial carriage provided more information on the risk of colonization than mere CPI patterns.

METHODS

Study Organization and Setting

The I-Bird (Individual-Based Investigation of Resistance Dissemination) study took place from May 1 through November 1, 2009, in a 200-bed follow-up care and rehabilitation hospital in Berck-sur-Mer, France. During the study, 329 distinct patients stayed in the hospital and the total hospital staff comprised 261 healthcare workers (HCWs). They were all informed of the study and could refuse to participate or cease participation at any time. All participants (patients and HCWs) agreed to wear a small wireless sensor that recorded their CPIs and to undergo weekly nasal swabs to monitor *S. aureus* carriage. Usual hygiene procedures in France rely mostly on hand hygiene (alcohol-based hand rub, hand washing, and gloving for nursing cares) and do not implement routine screening for bacterial carriage. The complete i-Bird study protocol is detailed in the online supplementary text.

S. aureus Carriage and Incident Colonization Episodes

S. aureus isolates were *spa*-typed[18] and tested for resistance to 20 antibiotics (see online supplementary text). Methicillin was used to distinguish between methicillin-sensitive (MSSA) and methicillin-resistant *S. aureus* (MRSA). Two strains were considered identical if they had the same *spa*-type and antibiotic resistance profile.

Incident colonization in a patient was defined when a strain was present that had not been carried the preceding week or, in case of multiple carriage, that had not been carried in the 2 preceding weeks.

Recording CPIs Within the Hospital

Patients and staff wore a small wireless sensor at all times while in the hospital, recording the identity of others in a 1.5-m range, front-facing for at least 30 s. The radio signal propagated in all directions but could sometimes be shielded by the body of participants. Patients wore the sensors on the wrist or ankle to limit positioning effects in the recordings. The sensor design is detailed in the online supplementary text. Recording was discontinued for 2 days on 3 occasions to replace sensor batteries.

There were 2,740,728 distinct CPIs recorded over the 4 months. These defined a dynamic (time-varying) network of interactions between participants, where individuals (nodes) were linked (edge) if a CPI had been recorded between them. This "full CPI network" was pruned of all CPIs lasting less than d min, varying d systematically between 0 and 15 min. In the text, we report the results for the network of all CPIs at least 5 min long.

The 1-hop CPI neighborhood of an individual included all his direct CPI contacts in the network; the 2-hop neighborhood included his 1-hop neighborhood and all the CPI contacts of his direct CPI contacts.

Case and Controls Definition

The case-control study was nested in the longitudinal follow-up of the LTCF patients. A case was defined as a patient with incident colonization. Eight matched controls were selected as patients present in the LTCF at the date of the case's incident colonization but who were neither colonized with *S. aureus* at this date nor the week before.

Statistical Analysis

We used conditional logistic regression to analyze factors associated with incident MRSA colonization. Our primary aim was the investigation of individual and CPI-related factors, including the following:

- Age, sex, Functional Independence Measure score,[19] history of MRSA carriage detected during the study,
- Number and occupation of CPI neighbors, duration of CPIs, density of links, centrality, number of neighbors-of-neighbors,
- Combination of network topology as above with carriage status: same MRSA strain or any MRSA strain carriage.

Time at risk was defined as the time between inclusion and date of incident colonization episodes (cases) or date of selection (controls). Functional Independence Measure scores were recoded as quartiles. For all network measures, the networks were aggregated over 1 week (the time interval between swabs) by pairs of participants. The betweenness centrality (the fraction of all shortest paths connecting pairs of participants passing through the person of interest) was computed using the whole network. We analyzed CPI durations directly (hours) and apportioned according to occupation of the contacts (patients or HCWs in contact with the case). As a sensitivity analysis, all analyses were repeated with various pruned CPI networks. The

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Jaccard index,[20] a measure of the percentage of common edges in 2 networks, was used for comparisons.

Ethics

Authorizations were obtained in accordance with French regulations regarding medical research and information processing. All French institutional review board–equivalent agencies accorded the i-Bird program official approval (CPP 08061; Afssaps 2008-A01284-51; CCTIRS 08.533; CNIL AT/YPA/SV/SN/GDP/AR091118 N°909036). Signed consent was not required by the French ethics committees to which the project was submitted.

RESULTS

The median (range) age of patients was 58.5 (24.5–102.8) years, with a median (range) length of stay of 33 (1–158) days. The median (range) number of swabs collected in patients was 5 (1–16) and in HCWs was 8 (1–13). The full CPI network was dense, linking 20% of all possible pairs of individuals and clustered according to wards. Most CPIs were short (Table 1). As the CPI network was pruned of short CPIs, the Jaccard index decreased less quickly than the number of links, showing that most short CPIs doubled with a longer interaction with the same person. The CPI network based on CPIs longer than 5 min included a quarter of all CPIs (26%) but still had 38% edges in common with the full CPI network.

Incident Colonization Episodes

Overall, 4,175 swabs were obtained from the participants. *S. aureus* prevalence of carriage was 37.1% (1,550 swabs in 363 participants) with few instances of multiple carriage (90 swabs from 65 participants showed 2 strains). Various strains (n = 114) were isolated multiple times in different participants, indicating that transmission occurred. There were 237 incident colonization episodes in patients: 144 involved MRSA and 93 MSSA. Only MRSA episodes were investigated. After excluding episodes for which sensor data was not available at the time of sampling, 106 MRSA episodes were left for analysis. Eight controls were matched to each case unless too few were available (those cases were matched to 7 [n = 1], 6 [n = 1], 5 [n = 6], 2 [n = 4], and 1 [n = 2] controls). Five cases were discarded because they could not be matched to any control. Fig. 1 illustrates the selection of cases and matching controls and the comparison of their neighborhoods.

Individual Risk Factors for MRSA Colonization

Age or sex did not affect the risk of MRSA colonization (Table 2). Cases had been at risk for a longer time than controls (53.6 d vs 61 d, $P = .002$), with a 5% (95% CI, 2%–9%) increase per additional week ($P = .003$). Patients with lower functional ability scores were more prone to MRSA colonization. A history of previous MRSA carriage was more frequent in cases (OR, 24.53 [95% CI, 12.47–48.27], $P < .0001$). Antibiotic exposure was associated with increased incidence (OR, 3.01 [95% CI, 1.63–5.59], $P = .0005$).

Network-Level Risk Factors for MRSA Colonization

Having more distinct neighbors during the preceding week was associated with an increased colonization risk (OR, 1.05 [95% CI, 1.01–1.09) for 1 additional neighbor, $P = .009$; Table 3), more so with HCW neighbors than with patient neighbors. The risk was larger with neighbors in the same ward (OR, 1.09 [95% CI, 1.04–1.14], $P = .0009$) and with night shift staff (OR, 1.29 [95% CI, 1.04–1.59], $P = .019$).

Increased cumulated CPI duration with HCWs was associated with increased incidence (3% more per hour) as well as a higher share of one's CPIs spent with HCWs (OR, 1.15 [95% CI, 1.06–1.25] for a 10% increase, $P = .001$). The betweenness centrality was not associated with the risk of colonization and neither was the density of the 1-hop neighborhood.

Interestingly, having CPI with contacts who themselves had many CPIs was associated with an increased colonization risk.

Associations were found at all levels of pruning of the full CPI network, with increasing ORs as shorter CPIs were discarded (Fig. 2).

TABLE 1. Characteristics of Complete and Thinned Close-Proximity Interaction (CPI) Networks

Network threshold, min	0	1	2	5	10	15
Network size, n (patients; HCWs)	590 (329; 261)	589 (329; 260)	588 (329; 259)	581 (328; 253)	567 (322; 245)	552 (317; 235)
Jaccard index[1]	1.0	0.86	0.68	0.38	0.17	0.11
CPIs, n (before aggregation)	85,025 (1,320,364)	62,993 (699,524)	46,459 (398,338)	22,347 (143,318)	11,315 (61,692)	8,382 (38,728)
CPIs/pers/day	10 (6–16)	7 (4–12)	6 (3–9)	3 (2–5)	2 (1–3)	2 (1–2)
Cumulative CPI duration, h	72,634	67,478	61,362	49,342	40,382	35,868
CPI duration/pers/day	8.6 (6.4–12.2)	8.1 (6.2–11.6)	7.7 (5.7–10.9)	7.5 (5.2–9.6)	7.8 (5.4–9.8)	8.2 (5.2–10.4)

NOTE. Values are median (interquartile range) unless stated otherwise. HCW, healthcare worker.

[1]The Jaccard index (a measure of similarity between networks) corresponds to the percentage of edges in common between 2 networks G_1 and G_2. Here, we show Jaccard(G_d, G_0), that is, the fraction of edges in common between a (pruned) network G_d and the full CPI network G_0.

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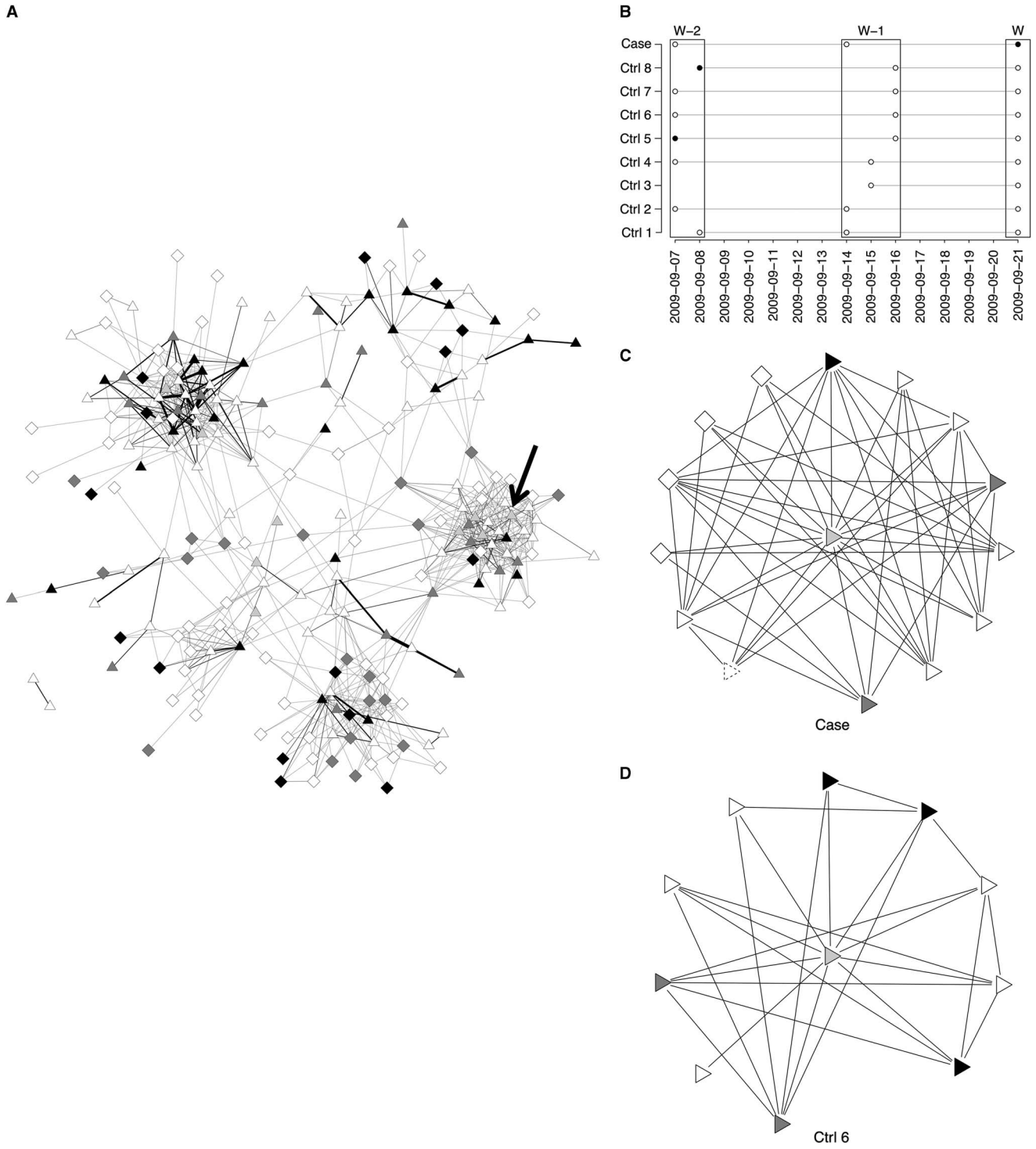


FIGURE 1. **Case-control matching in the reference close-proximity interaction network.** ***A***, An example close-proximity interaction (CPI) network in the week preceding a positive swab specimen in a case (identified by the arrow). Patients are shown as triangles and healthcare workers as diamonds and are colored according to their colonization status (white: noncolonized; dark gray: methicillin-sensitive *Staphylococcus aureus*; black: methicillin-resistant *S. aureus* [MRSA]). Two individuals are linked with an edge when a CPI exists between them. Thicker edges correspond to larger cumulated times of interaction. The case and matched controls are shown in light gray. ***B***, Longitudinal swab specimen results in the case and matched controls at the date of case incidence (week W) and 2 preceding weeks (W-1 and W-2), colored according to colonization status (white: noncolonized; black: MRSA). ***C***, Subnetwork centered on the case (from panel B) and restricted to his direct contacts (1-hop neighborhood). ***D***, Subnetwork centered on a matched control (from panel B) and restricted to his direct contacts (1-hop neighborhood).

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Joint Use of Individual Status and Carriage Data

We analyzed jointly the characteristics of CPIs with carriage status for the risk of colonization (Table 4). The associations were generally stronger than above for CPIs with a neighbor carrying the same MRSA strain (OR, 2.13 [95% CI, 1.40–3.26]), and larger for patients' contacts than for HCWs' contacts. Such associations were also found when considering carriage of any MRSA strain, although smaller (OR, 1.4 [95% CI, 1.2–1.6]). Longer CPIs with colonized patients led to an increased risk (OR, 1.03 [95% CI, 1.01–1.05], $P = .006$).

A strong association was found with the number of carriers at 2-hops (OR for same strain, 6.1; OR for any strain, 1.7). Connection to such carriers via an HCW was associated with a larger risk than via another patient.

Here again, keeping only longer CPIs in the network generally led to stronger associations (Fig. 2). In HCWs, the strongest association was found when considering the network of all CPIs longer than 1 min—that is, keeping a large portion of short CPIs.

TABLE 2. Individual Risk Factors of MRSA Colonization in Patients

Covariable	OR [95% CI]	*P* value
Male sex	1.18 [0.78–1.79]	.427
Age	1.00 [0.99–1.02]	.866
Time at risk (weeks)	1.05 [1.02–1.09]	.003
Antibiotic exposure	3.01 [1.63–5.59]	.0005
Past carriage (case)		
any MRSA strain	10.88 [6.74–15.57]	<.0001
same MRSA strain	24.53 [12.47–48.27]	<.0001
FIM Score		.006
Q1	2.90 [1.46–5.77]	
Q2	2.67 [1.35–5.30]	
Q3	1.81 [0.88–3.70]	
Q4	1.0	

NOTE. FIM, Functional Independence Measure; MRSA, methicillin-resistant *Staphylococcus aureus*; OR, odds ratio.

Investigating Confusion Factors for Contacts and MRSA Incidence

Patients with higher dependence or a history of incident MRSA colonization had CPI with more neighbors in the preceding

TABLE 3. Network-Level Risk Factors of MRSA Colonization in Patients

Network characteristics	OR [95% CI]	*P* value
Case/control		
Betweenness centrality (%)	1.09 [0.94–1.27]	.231
Number of CPIs per day	1.54 [1.03–2.30]	.034
Number of distinct neighbors	1.05 [1.01–1.09]	.009
by occupation		
Patients	1.03 [0.97–1.09]	.259
HCWs	1.10 [1.04–1.17]	.001
by location		
Same ward	1.09 [1.04–1.14]	.0009
Other ward	1.01 [0.96–1.06]	.633
Cumulative CPI duration, h	1.00 [1.00–1.00]	.069
by occupation		
with patients	1.00 [1.00–1.00]	.106
with HCWs	1.03 [1.01–1.06]	.008
Time repartition (% with HCWs)	1.15 [1.06–1.25]	.001
Contacts		
Betweenness centrality (%)	0.95 [0.73–1.23]	.700
Number of CPIs per day	1.41 [1.00–1.99]	.052
Number of distinct neighbors	1.08 [1.02–1.15]	.012
by occupation		
Patients	1.05 [0.96–1.15]	.213
HCWs	1.15 [1.05–1.26]	.004
Cumulative CPI duration, h	1.01 [1.00–1.01]	.003
by occupation		
with patients	1.01 [1.00–1.01]	.005
with HCWs	1.10 [1.01–1.20]	.029
Overall		
Network density (%)	0.98 [0.88–1.09]	.681

NOTE. Depending on the characteristic, odds ratios (ORs) were computed for 1 more neighbor, 1 more hour cumulative close-proximity interaction (CPI) duration, or a 10% increase. HCW, healthcare worker; MRSA, methicillin-resistant *Staphylococcus aureus*.

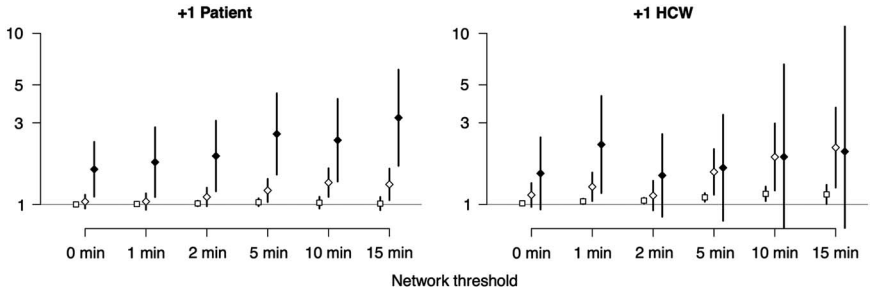


FIGURE 2. **Close-proximity interaction (CPI) network topology and methicillin-resistant *Staphylococcus aureus* (MRSA) colonization.** The odds ratios are for the number of contacts for incidence of MRSA colonization, according to occupation. White squares correspond to CPI network topology-only measures. Diamonds correspond to the joint analysis of carriage and CPI network topology when neighbors carry any MRSA strain (white) or the same MRSA strain as the case (black).

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TABLE 4. Joint Microbiological and Network-Based Risk Factors of MRSA Colonization in Patients

Network characteristics	OR [95%CI]	*P* value
Distinct neighbors carrying		
Any MRSA strain	1.39 [1.21–1.60]	<.0001
Same MRSA strain	2.13 [1.40–3.26]	.0005
Distinct patient neighbors carrying		
Any MRSA strain	1.21 [1.03–1.41]	.017
Same MRSA strain	2.58 [1.49–4.46]	.0007
Distinct HCW neighbors carrying		
Any MRSA strain	1.55 [1.14–2.11]	.005
Same MRSA strain	1.64 [0.80–3.35]	.174
Distinct 2-hop neighbors carrying		
Any MRSA strain	1.66 [1.31–2.10]	<.0001
Same MRSA strain	6.05 [2.82–12.98]	<.0001
Any MRSA strain via patients	1.07 [0.81–1.40]	.649
Same MRSA strain via patients	4.30 [1.61–11.51]	.004
Any MRSA strain via HCWs	1.98 [1.50–2.61]	<.0001
Same MRSA strain via HCWs	19.77 [5.60–69.81]	<.0001
Cumulative CPI duration (h) with colonized neighbors		
Any MRSA strain	1.01 [1.00–1.02]	.0002
Patients	1.01 [1.00–1.02]	.0003
HCWs	1.56 [1.18–2.06]	.002
Same MRSA strain	1.03 [1.01–1.05]	.006
Patients	1.03 [1.01–1.05]	.006
HCWs	0.96 [0.28–3.23]	.942
Time repartition (% with carriers of any MRSA)	1.16 [1.09–1.23]	<.0001
with MRSA-carrying patients	1.13 [1.06–1.21]	.0002
with MRSA-carrying HCWs	2.00 [1.29–3.09]	.002

NOTE. Depending on the characteristic, odds ratios (ORs) were computed for 1 more neighbor, 1 more hour cumulative close-proximity interaction (CPI) duration, or a 10% increase. HCW, healthcare worker; MRSA, methicillin-resistant *Staphylococcus aureus*.

week (analysis of variance, $P = .005$). These 2 characteristics were also associated with an increased colonization risk. After adjustment on the Functional Independence Measure score, the association of colonization with the number of distinct HCWs and longer CPIs with HCWs remained with similar odds ratios. Likewise, accounting for previous MRSA carriage did not change the associations. Cases still had had more CPIs during the week (OR, 1.02 [95% CI, 1.00–1.03] for 1 more neighbor; $P = .02$).

DISCUSSION

The characteristics of CPIs between individuals, especially between patients and HCWs, were associated with the risk of incident MRSA colonization in patients. Given our understanding of MRSA transmission,[2] these associations are expected and provide indication that CPIs capture contacts relevant to the spread of MRSA. However, summary characteristics of the overall network such as density did not correlate with MRSA incidence because they remained approximately constant over time. Centrality was not associated with incidence either, although theoretical studies suggest a major role in transmission.[4]

Whether CPIs provide a good proxy for contacts leading to transmission is debated. Indeed, interactions with little risk of transmission (talking) and those at higher risk (nursing care) may lead to the same CPI records. However, this lack of specificity should lead to no association of CPIs with incidence because the same patterns would be found in case and in controls. Here, we found an association and it was the strongest for CPIs of longer duration. Yet, contacts alone cannot explain MRSA incidence unless contacts are carriers. The increased associations when considering CPIs with carriers of the same strain strengthened the case for using CPIs as a proxy for contacts leading to transmission.

Irrespective of the carried MRSA strain, CPI with a MRSA carrier was associated with increased incidence. It is known that MRSA carriage in HCWs is linked with poor adherence to infection control measures, exposure to highly prevalent patients, high work load, and other organizational factors.[21] HCWs colonized with a specific MRSA strain may be prone to be transient carriers and transmit other MRSA strains, because transient carriage of *S. aureus* is common among HCWs.[22–24] In our study, transient carriage was likely underdocumented, in part owing to the frequency of swabbing (once a week only) and also because hand carriage, for example, was not tested. Therefore, we investigated only incident episodes in patients.

The results support the role of HCWs as vectors of MRSA dissemination.[5,6,25] CPIs with HCWs were indeed associated with higher incidence than CPIs with other patients. Long contacts, common in nursing care, were the most associated with MRSA incidence, as often hypothesized.[10,26,27]

We tried to limit the effect of biases in our design and analysis. Whereas a few MRSA clones accounted for most episodes (MRSA overall prevalence was 16.6%, with >60% belonging to *spa*-types t777 or t008), MSSA carriage, although common, showed fewer identical strains carried by different individuals so that the study of transmission was less relevant (data not shown). Control periods were contemporaneous with case-defining periods to ensure equal *S. aureus* colonization pressure.[28] Classification bias (missed incident cases) may have occurred because the sensitivity of MRSA detection in swabs is not 100%. However, all results were unchanged in the analysis when limiting to the first incident episode in each case. No differential effect was expected in the CPI measurements because the carriage status of participants was not known at the date of CPI collection. An overall change in behavior, for example increased adherence to hygiene practices, may have occurred (Hawthorne effect[29,30]). Yet the protocol was little intrusive, with no external observer to remind of the ongoing study. Initial changes, if any, were likely to have waned over the 6-month-long data collection to yield CPIs illustrative of typical behaviors. Duration of hospital stay, functional status,

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and previous MRSA carriage were associated with both the number of contacts and MRSA incidence. Adjusting on these variables in the analysis did not change the results concerning association with contacts, suggesting no confusion from these. HCW compliance with hygiene measures was not considered explicitly in our study. Hygiene compliance is more common during prolonged interactions[31–34] and yet this is where we found the strongest associations. This could indicate that compliance may alter the overall prevalence rather than the nature of interactions leading to transmission.

Patients from LTCFs may frequently travel to other hospitals, acting as a reservoir for MRSA introduction in other facilities.[35] In LTCFs, social interactions between patients occur more frequently than in acute care hospitals. We nevertheless found that CPIs with HCWs were associated with MRSA incidence, a result that is relevant in other settings.

We presented evidence that CPIs measured by electronic devices are associated with an increased risk of MRSA incidence. In our study, these devices were well accepted and worn for extended periods by all participants. The results suggest that routine CPI monitoring could be used to document in-hospital contact patterns and identify situations at increased risk. It could be a useful complement to microbiologic surveillance in identifying origins and destination of transmission.

Members of the i-Bird Study Group

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SUPPLEMENTARY MATERIAL

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