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Chapter 3.6

Community-associated meticillin-resistant *Staphylococcus aureus* transmission in households of infected cases: a pooled analysis of primary data from three studies across international settings

Justin Knox, MPH[1*], Miranda van Rijen, MSc[2], Anne-Catrin Uhlemann, MD[1], Maureen Miller, PhD[3], Cory Hafer, MEd[1], Peter Vavagiakis, MS[4], Qiuhu Shi, PhD[5], Paul D. R. Johnson, PhD[6], Geoffrey Coombs, PhD[7], Marjolein Kluytmans - van den Bergh, MD[2,8], Jan Kluytmans, MD[2,9], Catherine M. Bennett, PhD[10], Franklin D. Lowy, MD[1,11]

1. Division of Infectious Diseases, Department of Medicine, Columbia University, College of Physicians & Surgeons, New York, United States;

2. Laboratory for Microbiology and Infection Control, Amphia Hospital, Breda, Netherlands;

3. Department of Epidemiology, Mailman School of Public Health, Columbia University; New York, United States;

4. Panna Technologies, New York, United States;

5. Department of Epidemiology and Community Health, School of Health Sciences and Practice, New York Medical College, Valhalla, United States;

6. Austin Health, Melbourne, Victoria, Australia;

7. Australian Collaborating Centre for Enterococcus and Staphylococcus Species (ACCESS) Typing and Research, School of Biomedical Sciences, Curtin University, Perth, Western Australia, Australia;

8. Julius Centre for Health Sciences & Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands;

9. Department of Medical Microbiology and Infection Control VU University Medical Centre, Amsterdam, Netherlands;

10. Deakin University, Melbourne, Victoria, Australia;

11. Department of Pathology, Columbia University, College of Physicians & Surgeons, New York, United States.

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Abstract

Diverse strain types of meticillin resistant *Staphylococcus aureus* (MRSA) cause infections in community settings worldwide. To examine heterogeneity of spread within households and to identify common risk factors for household transmission across settings, primary data from studies conducted in New York, US, Breda, NL, and Melbourne, AU were pooled. Following MRSA infection of the index patient, household members completed questionnaires and provided nasal swabs. Swabs positive for *S. aureus* were genotyped by *spa*-sequencing. Poisson regression with robust error variance was used to estimate prevalence odds ratios for transmission of the clinical isolate to non-index household members. Great diversity of strain types existed across studies. Despite differences in strains and colonisation patterns, the index patient being colonised with the clinical isolate at the home visit ($p<.01$) and the percent of household members <18 years ($p<.01$) were independently associated with transmission. Targeted decolonisation strategies could be used across geographic settings to limit household transmission of MRSA.

Introduction

Since the mid-1990's, meticillin-resistant *Staphylococcus aureus* (MRSA) infections have been increasingly encountered in community settings worldwide.[1-3] Multiple dominant clonal lineages have driven this pandemic.[4] Despite such rapid dissemination, it remains unclear how community-associated (CA)-MRSA clones spread and become established within communities. Multiple studies conducted across different settings have identified the household as an important reservoir for *S. aureus*.[5-10] After a household member becomes infected, high levels of *S. aureus* colonisation and infection often occur among other household members.[11-15] Reports have observed that epidemic clones tend to "ping pong" between family members, resulting in a high rate of recurrent infections.[16-18] Eradicating *S. aureus* from the household and reducing the frequency of these infections has proven difficult.[19,20] A greater understanding of how *S. aureus* spreads among household members is essential for the design of evidence-based prevention and treatment strategies.

Various studies have examined the spread of *S. aureus* among households in discrete geographical locations.[9,21-24] These studies have identified various risk factors associated with household transmission in these distinct settings. However, these studies have been limited to analyses of the *S. aureus* strains that were predominant in those discrete locations. To date, no study has pooled primary data across multiple countries in order to assess the spread of *S. aureus* in the household setting. Such an analysis would allow for an examination of heterogeneity in the spread of *S. aureus* among households and identify common risk factors for household transmission across settings and diverse strain types.

In order to assess these issues, we pooled primary data from 3 studies conducted in New York, United States (US), Breda, the Netherlands (NL), and Melbourne, Australia (AU).[9,10,25] These studies utilised similar procedures to assess risk factors for household transmission of CA-MRSA among the households of infected cases.

Methods

Populations

The current study is a retrospective, observational study that pooled primary data from three cross-sectional studies assessing household transmission of *S. aureus*.[9,10,25] These studies used similar methods but were conducted across diverse geographic regions, demographically different populations, and featured unique clinical *S. aureus* strains. The study locations had similar levels of economic development and population access to healthcare. Table 1 provides a comparison of the characteristics of the three

Table 1: Characteristics of included studies in pooled analysis.

Study Location	United States (US)	Netherlands (NL)	Australia (AU)
Study Design	Cross-sectional	Cross-sectional	Cross-sectional
Study Setting	Major metropolitan area	Throughout the country	Major metropolitan area and surrounding suburbs
Case identification	Inpatient and outpatient screening at a hospital	Inpatient and outpatient screening at 16 hospitals located across the country	Community-based private pathology service
Exclusion criteria	- Inpatients ≥72 hours after hospital admission - Living outside the hospital catchment area - Resident in a long-term care facility - Hospitalized within the past 6 months - Homeless or living in a shelter - Having a chronic illness (e.g. on dialysis) - Younger than 2 years	- Previous history of MRSA colonization or infection - Resident in a long-term care facility - Living abroad - Admitted to a foreign hospital in past year - Underwent dialysis in a foreign hospital - Direct contact with living pigs and/or veal calves - Adopted child - Re-admission to hospital between infection and home visit - Younger than 1 year	- Inpatients >48 hours after hospital admission - Infection reported ≤2 weeks after hospital discharge
Number of cases	N=139	N=61	N=96
Control selection (not included in pooled analyses)	Uninfected community-based controls	Hospitalized non-MRSA cases	MSSA infected cases
Study procedures	Home visit after infection	Home visit after infection	Home visit after infection
Average interval between infection and home visit	33 days	43 days	114 days
Interview	Interviewer-administered questionnaire	Interviewer-administered questionnaire	Self-completed questionnaire
Risk factor recall period	6 months prior to infection	1 year prior to infection	1 year prior to infection
Body sites sampled	- Anterior nares	- Anterior nares - Oropharyngeal	- Anterior nares - Axilla crease
Strain characterization	*Spa*-typing	*Spa*-typing	*Spa*-typing

studies. One of the studies (US) sampled exclusively from a major metropolitan area, another (AU) sampled from a major metropolitan area and the surrounding suburbs, and the third (NL) sampled from 16 hospitals located throughout the country. In all three studies, a patient with CA-MRSA infection was identified through inpatient and outpatient screening at a hospital (US & NL), or through a community-based private pathology service (AU). In all studies, relevant exclusion criteria were applied to isolate community-associated infections from healthcare-associated infections. Once potential

index cases were identified, they were contacted and home visits were scheduled with those who were willing to participate. At the time of the home visit, all household members were asked to participate and provided informed consent. On average, home visits were conducted 61 days (SD = 59) after the infection was cultured.

Procedures

The 3 studies followed similar procedures. At the time of the home visit, all household members who were willing to participate provided swabs from the anterior nares and answered a questionnaire. Anterior nares cultures were collected with sterile swabs from all consenting household members, excluding children <1 year old. Culture swabs were incubated overnight in high-salt 6.5% broth and plated onto selective media agar for 18-48 hours at 35–37°C. *S. aureus* was confirmed by coagulase, Protein A detection kit or both. Meticillin resistance was determined by selective media agar, disc diffusion antibiotic sensitivity testing, or PCR was used to test for the presence of Staphylococcal Chromosomal Cassette (SCC)*mec*. *S. aureus* positive isolates were genotyped by *spa*-sequencing.[9,10,25-27] The clinical infection isolates were also retrieved for all index cases. These isolates were obtained from identified sites of infection and underwent the same analyses as all other isolates.

The questionnaires administered in the 3 studies captured information on a number of risk factors for CA-MRSA acquisition and household transmission. These variables included sociodemographic information (e.g. age, gender, education, income), index community exposures (e.g. work, school, daycare, sports participation, travel), health information (recent skin infection, hospital admission, antibiotic use, insulin use), and household characteristics (presence of pets, presence of children < 18 years old, towel sharing, razor sharing). Variables shared across all three studies were included in statistical analyses.

Ethics statement

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All studies were approved by their respective ethical review boards (US: the Institutional Review Board of Columbia University Medical Center; NL: the medical ethics committee of the St Elisabeth Hospital in Tilburg; AU: the University of Melbourne Human Research Ethics Committee).

Measures

Only risk factors assessed in all studies were included in these analyses. Risk factors were categorised as index sociodemographic characteristics (e.g. gender, age, born in

country, education), index acquisition risk factors (e.g. day care attendance, school attendance, sports participation, international travel), index transmission factors (recent skin condition, recent abscess, being colonised with the clinical isolate at the time of the home visit), other household member acquisition risk factors (recent surgery), household transmission risk factors (e.g. presence of a pet, sharing towels, sharing razors), and household sociodemographic characteristics (e.g. household size, percent of children in the household). Acquisition risk factors were considered potential factors that could lead to *S. aureus* acquisition in the community while transmission risk factors were considered potential factors that could lead to the spread of *S. aureus* in members of a shared household. In the US study, risk factors were assessed over the previous 6 months. In the NL and AU study, risk factors were assessed over the previous year. Household transmission was defined as colonisation of a non-index household member with the same strain type as the index patient's clinical isolate.[28]

Statistical analyses

For comparisons of frequencies of index case and household descriptive data by study, chi-square tests and t-tests were used. In analyses comparing households with evidence of transmission to those without on sociodemographic and risk factor data, Poisson regression models with robust error variance were used to estimate prevalence odds ratios. Prevalence odds ratios (PORs) are reported instead of traditional odds ratios because of the high prevalence of the outcome in our sample (23% (n = 67)).[29-31] Initially bivariate analyses were run and all variables associated with intra-household *S. aureus* transmission at $p<0.20$ were considered for inclusion in multivariate analyses.[9,32-34] Once these variables were identified, multivariate analyses were run among each individual study and effect estimates were compared to look for heterogeneity of effects across studies. Effect estimates were similar across studies. Heterogeneity of effects across studies was also assessed by running meta-analyses using the effect estimates and 95% confidence intervals to generate a Q-statistic for each risk factor. No heterogeneity was observed (p-values ranged from 0.51 to 0.87) and so the primary data from the 3 studies were pooled and analysed using a fixed effects model. Any residual effect of combining data across study sites was controlled for in all models using pooled data through inclusion of study site as a covariate in multivariate analyses. We subsequently repeated these analyses using generalized estimating equations (GEE) analysis in order to account for potential clustering within study site, assuming an independent covariance structure, and observed similar effects to the previous analyses; thus the results of the initial analyses are reported. Additionally, all analyses controlled for household size as a potential covariate. Heterogeneity of effects was assessed in the pooled data analyses by entering interaction terms for each risk factor by study site in the multivariate model. Again, no heterogeneity of effects

was observed and the analyses were run with only main effects. To limit the impact of collinearity, correlations between covariates were examined. It was determined that no variables were correlated enough to affect our models. Prevalence odds ratios and 95% confidence intervals are presented. All statistical tests were 2-sided and $p<0.05$ was considered statistically significant. Data were analyzed using SAS version 9.2 software (SAS Institute Inc., USA).

Results

Study population characteristics

The total study sample consisted of 296 index cases and 798 household members. The US study included 139 index cases and 467 household members, the NL study included 61 index cases and 114 household members, and the AU study included 96 index cases and 217 household members. Of the 296 index cases, 44% (n = 131) were male and 24% (n = 70) were under 18 years of age. Among those over 18 years of age (n = 226), 74% (n = 167) had completed high school. The average household size was 3.7 people (SD = 1.7).

Table 2 presents the distribution of index- and household-level sociodemographic characteristics, acquisition and transmission risk factors by study. Studies differed on multiple variables. For example, a relatively low proportion of index participants in the US study were born in the US. Also, a relatively low proportion of indexes had recent

Table 2: Distribution of index and household sociodemographic characteristics and risk factors by study

	US N= 139		NL N= 61		AU N= 96			Pooled N= 296	
	N	**%**	**N**	**%**	**N**	**%**	***P***	**N**	**%**
Index sociodemographic characteristics									
Male	51	37%	29	48%	51	53%	0.04	131	44%
≤18 years	41	29%	9	15%	20	21%	0.06	70	24%
Born in country	19*	14%	55*	90%	70*	73%	<.001	144	49%
Graduated high school	63	45%	40	66%	64	67%	0.00	167	56%
Index acquisition risk factors									
In day care	9	6%	3	5%	2	2%	0.30	14	5%
In school	42*	30%	6	10%	9*	9%	<.001	57	19%
Working	53	38%	28	46%	35	36%	0.47	116	39%
Plays sports	36*	26%	28	46%	52*	54%	<.001	116	39%
Recent international travel	29*	21%	32*	52%	48*	50%	<.001	109	37%
Recent surgery	16*	12%	33*	54%	17	18%	<.001	66	22%
Recent hospital admission	31*	22%	34*	56%	37	39%	<.001	102	34%

Table 2 (continued)

Index transmission risk factors									
Recent skin condition	32	23%	15	25%	33	34%	0.14	80	27%
Recent abscess	129*	93%	32	52%	34*	36%	<.001	195	66%
Index colonised with the clinical isolate	21*	15%	37*	61%	23	24%	<.001	81	27%
Other HH member acquisition risk factors									
Recent surgery	11	8%	16*	26%	10	10%	0.00	37	13%
HH transmission risk factors									
Pet	43	31%	24	39%	45	47%	0.05	112	38%
Towel sharing	37*	27%	20	33%	83*	86%	<.001	140	47%
Razor sharing	19	14%	8	13%	9	9%	0.57	36	12%
Recent skin condition	53	38%	27	44%	48	50%	0.19	128	43%
Recent abscess	130*	94%	34	58%	55*	57%	<.001	219	74%
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P***	**Mean**	**SD**
HH sociodemographic characteristics									
Size	4.4	1.8	2.9	1.1	3.3	1.5	<.001	3.7	1.7
Percent of males	44.5	22.3	46.1	17.0	50.1	16.7	0.03	46.6	19.7
Percent of children <18 years	30.8	23.4	18.0	23.7	21.1	24.7	<.001	25.0	24.5
Time to Interview									
Days from clinical culture to interview	33	20	43	25	114	76	<.001	61	59

Notes: * indicates standardised residuals are>1.96 or <−1.96

exposure to healthcare settings. In the NL study, a relatively large proportion of index participants and non-index household members had recent exposure to healthcare settings. In the AU study, a relatively large proportion of index participants played sports and had recently traveled internationally. Towel sharing was more common among household members in the AU study and less common in the US study. Index colonisation with the clinical isolate was more common in the NL study and less common in the US study. In summary, the three studies included very different sample populations with regards to index- and household-level sociodemographic characteristics, acquisition and transmission risk factors.

Molecular characterisation of *S. aureus* isolates

Overall, there was diversity of index infection clinical strain types between each study. Figure 1 presents the distribution of index infection clinical *spa* types by study. In the US study, MRSA t008 (USA300) was the predominant strain type, accounting for 73% (n=101) of index infections. In the NL study, there was a much wider assortment of strain types causing index infection, with 29 different strain types accounting for 61 infections and USA300 only accounting for 7% (n=4) of index infections. The most commonly identified strain was MRSA t011, which accounted for 18% (N=11) of infections. In the AU study, there was not a single predominant epidemic strain. The most common strain types were MRSA t019 (13%, n = 13), MRSA t037 (11%, n = 11), and MRSA

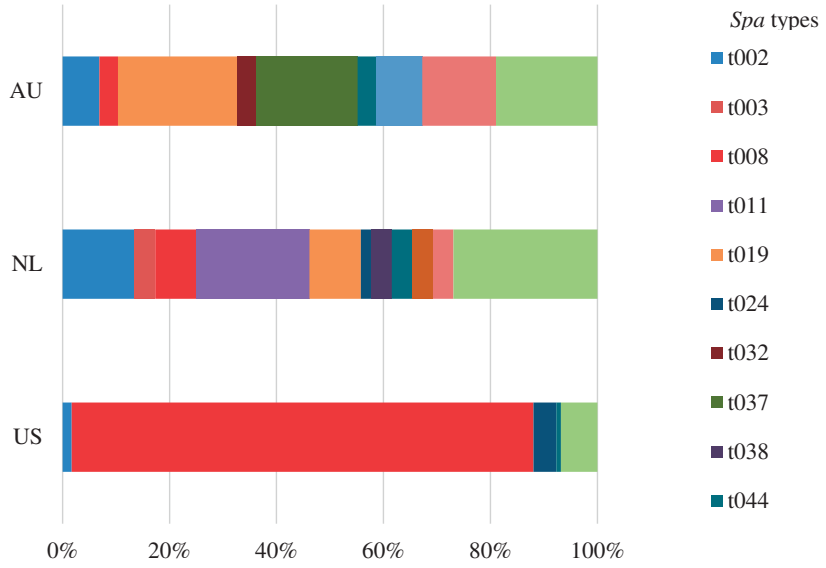

Figure 1. Distribution of clinical isolate *Spa* types by study.

t202 (10%, n = 10). USA300 only accounted for 3% (n=2) of index infections. A few strain types were identified across multiple studies, notably MRSA t002 (US: 1%, n=2; NL: 11%, n=7; AU: 5%, n=5), and MRSA t008 (US: 73%, n=101; NL: 7%, n=4; AU: 2%, n=2). MRSA t019 was relatively common in the NL (13%, n = 13) and AU (17%, n = 13) studies.

One fifth (20%, n=18) of the 97 index patient clinical isolates in the AU study could not be *spa*-typed because the specimens retrieved from the private pathology service was no longer viable. In these cases, antibiograms run by the private pathology service were used to confirm that the clinical isolates were MRSA. In one of these 18 households, a non-index household member was colonised with MRSA; however, it had a different resistance pattern than the clinical isolate and was therefore excluded as a transmission event. No other possible transmission episodes occurred in the households where the index patient isolate was not available for typing.

S. aureus colonisation and transmission

Colonisation patterns were different among the studies. Table 3 presents the distribution of *S. aureus* colonisation among indexes, *S. aureus* colonisation among non-index household members, and *S. aureus* transmission by study. In the NL study, the index case had a high level of colonisation with MRSA (62%) compared with the other studies. Among non-index household members, the NL study had a low level (20%) of colonisation with meticillin susceptible *S. aureus* (MSSA) compared with the other studies. Sixty-seven households (23%) had evidence of transmission of the clinical isolate.

Table 3: Colonisation and transmission of *S. aureus* by study

	US N= 139		NL N= 61		AU N= 96		*P*	Pooled N= 296	
	N	**%**	**N**	**%**	**N**	**%**		**N**	**%**
***S. aureus* colonisation among indexes**									
Colonised with *S. aureus*	37*	27%	41*	67%	44	46%	<.001	122	41%
Colonised with MRSA	22*	16%	38*	62%	25	26%	<.001	85	29%
Colonised with MSSA	15	11%	3	5%	19	20%	0.06	37	13%
***S. aureus* colonisation among non-index HHMs**									
Colonised with *S. aureus*	89	64%	23	38%	52	54%	<.01	164	55%
Colonised with MRSA	39	28%	13	21%	24	25%	0.59	76	26%
Colonised with MSSA	63	45%	12*	20%	39	41%	<.01	114	39%
***S. aureus* transmission of the clinical isolate**									
≥1 non-index HHM colonised with the clinical strain	37	27%	13	21%	17	18%	0.27	67	23%

* indicates standardised residuals are >1.96 or <−1.96;
HHM = household member

Despite the different levels of colonisation among the studies, levels of transmission of the clinical isolate were not different across the studies (US: 27%, n=37; NL: 21%, n=13; AU: 18%, n=17; p=0.27).

Risk factors for household transmission

Bivariate analyses assessing risk factors for household transmission of the clinical isolate were conducted among each study. In the US study, the index being colonised with the clinical isolate at the time of the home visit was positively associated with household transmission of the clinical isolate (p=0.02). In the AU study, household size was positively associated with household transmission of the clinical isolate (p=0.04).

The data were pooled to assess risk factors for household transmission of *S. aureus* across studies and strain types. Table 4 presents the results of these analyses. In bivariate models, being born in country, the index being colonised with the clinical isolate at the time of the home visit, household size, and percent of children in the household were positively associated with transmission at p<0.20. An increased time interval between the sampling of the clinical isolate and colonisation among the household was negatively associated with transmission at p<0.20. These variables were selected for multivariate analyses.

In multivariate analyses using pooled data, the index being colonised with the clinical isolate at the time of the home visit (POR 2.18, 95% CI 1.37-3.48, p=0.001) and the percent of household members that were children <18 years (POR=1.13, 95% CI 1.03-1.24, p=0.008, for a 10% increase) were both independently associated with household transmission of the clinical isolate (see table 5).

Table 4: Bivariate analyses of index and HH characteristics by HH transmission of the infectious isolate among pooled data

	HH transmission N = 67		No HH transmission N = 229		POR	(95% CI)	*P*
	N	**%**	**N**	**%**			
Index sociodemographic characteristics							
Male	27	40%	104	45%	0.9	0.6 - 1.4	0.65
≤18 years	20	30%	50	22%	1.2	0.8 - 1.9	0.46
Born in country	32	48%	112	49%	1.5	0.9 - 2.5	0.15
Graduated high school	38	57%	129	56%	1.2	0.8 - 1.8	0.44
Index acquisition risk factors							
In day care	5	7%	9	4%	1.4	0.7 - 2.8	0.28
In school	12	18%	45	20%	0.8	0.4 - 1.3	0.33
Working	23	34%	93	41%	0.8	0.5 - 1.2	0.30
Plays sports	27	40%	89	39%	1.2	0.7 - 1.8	0.50
Recent international travel	19	28%	90	39%	0.7	0.5 - 1.2	0.24
Recent surgery	13	19%	53	23%	0.9	0.5 - 1.6	0.75
Recent hospital admission	18	27%	84	37%	0.8	0.5 - 1.3	0.28
Index transmission risk factors							
Recent skin condition	14	21%	66	29%	0.7	0.4 - 1.3	0.28
Recent abscess	47	70%	148	65%	0.9	0.5 - 1.7	0.84
Index colonised with the clinical isolate	26	39%	55	24%	2.2	1.4 - 3.5	<.001
Other HH member acquisition risk factors							
Recent surgery	9	13%	28	12%	1.1	0.6 - 2.0	0.82
HH transmission risk factors							
Pet	27	40%	85	37%	1.1	0.7 - 1.7	0.63
Towel sharing	32	48%	108	47%	1.2	0.8 - 1.9	0.34
Razor sharing	9	13%	27	12%	1.0	0.5 - 1.9	0.98
Recent skin condition	26	39%	102	45%	0.8	0.5 - 1.3	0.43
Recent abscess	54	82%	165	72%	1.2	0.7 - 2.3	0.51
	Mean	**SD**	**Mean**	**SD**	**POR**	**(95% CI)**	***P***
HH sociodemographic characteristics							
Size	4.1	1.9	3.6	1.6	1.1	1.0 - 1.3	0.05
Percent of males (x 10)	0.5	0.2	0.5	0.2	1.0	0.9 - 1.1	0.98
Percent of children <18 years (x10)	33.5	24.0	22.5	24.1	1.1	1.0 - 1.2	0.01
Time to Interview							
Days from clinical culture to interview (x10)	49	42	65	63	1.0	0.9 - 1.0	0.07

HH = household

Table 5: Multivariate analyses of index and HH characteristics by HH transmission of the infectious isolate among each study and pooled data

	US N= 139			NL N= 61			AU N= 96			POOLED N= 296		
	POR	**(95% CI)**	***P***	**POR**	**(95% CI)**	***P***	**POR**	**(95% CI)**	***P***	**POR**	**(95% CI)**	***P***
Index sociodemographic characteristics												
Born in country	1.0	0.4 - 2.3	1.00	0.7	0.1 - 5.0	0.71	3.6	0.7 - 17.1	0.11	1.4	0.8 - 2.5	0.23
Index transmission risk factors												
Index colonised with the clinical isolate	1.9	1.0 - 3.6	0.04	3.7	1.0 - 14.4	0.06	2.1	0.8 - 5.5	0.14	2.2	1.4 - 3.5	<.01
HH sociodemographic characteristics												
Size	1.1	0.9 - 1.2	0.40	1.0	0.7 - 1.6	0.88	1.2	0.9 - 1.6	0.33	1.1	1.0 - 1.2	0.19
Percent of children <18 years (x10)	1.1	1.0 - 1.2	0.12	1.2	0.9 - 1.4	0.20	1.2	0.9 - 1.4	0.15	1.1	1.0 - 1.2	<.01
Time to Interview												
Days from clinical culture to interview (x10)	0.9	0.7 - 1.0	0.12	1.0	0.8 - 1.2	0.99	1.0	0.9 - 1.0	0.10	0.9	0.9 - 1.0	0.05

HH = household

Discussion

We examined heterogeneity of spread of CA-MRSA within households of infected cases across multiple geographic regions and attempted to identify common risk factors for household transmission. A diverse set of household characteristics, colonisation patterns, and clonal lineages accounting for the burden of *S. aureus* infections in each study were observed. Despite this variability, levels of household CA-MRSA transmission were similar across studies and we identified several common risk factors for transmission within the household. Nasal colonisation of the index subject with the clinical isolate and the percent of children in the household were risk factors for CA-MRSA household transmission.

There was great diversity in clinical strain types across studies. The US study was dominated by the epidemic strain USA300, which has emerged as the most common cause of CA-MRSA infections in North America.[4] While USA300 was present in the NL and AU studies, most infections were caused by a diverse set of non-USA300 clonal lineages. It has been speculated that, without adequate control to halt its spread, USA300 will continue to gain ground around the world as the predominant epidemic clone.[35] Our findings suggest, however, that household transmission of the clinical isolate is equally likely to occur across strain types, regardless of the presence of an epidemic clone, which argues against using strain targeted intervention strategies.[9]

Household colonisation patterns also differed between studies, particularly among the NL study. Despite these differences in the epidemiology of *S. aureus* across studies, and the aforementioned differences in biology, overall levels of CA-MRSA household transmission did not differ between studies, and were similar to other reports in the community setting.[5-8]

Our analyses indicate that certain risk factors are stronger correlates of transmission than clonal background. Colonisation of the index subject with the clinical isolate was a risk factor for the colonisation of other household members with the identical clone. Failure to eliminate colonisation in a household member could serve as a potential reservoir for ongoing household transmission, increasing the risk of recurrent colonisation and infection even after antibiotic treatment.[16-18] These findings suggest that strategies to limit *S. aureus* transmission in the community setting should consider decontamination of infected individuals and their household contacts.[36]

Alternatively, given that multiple strain types can often be found colonising index patients and their household contacts after an initial infection, which has been observed in this study and others, another potential solution for interrupting *S. aureus* transmission and subsequent infection could be re-colonisation strategies focused on not inadvertently eliminating less pathogenic *S. aureus* strains and thus disrupting commensal flora.[28,37] Further research into this area is needed.

Our analyses also identified the presence of children in the household as a risk factor for *S. aureus* transmission. A higher proportion of children may represent an elevated level of physical contact among household members. In a previous study conducted among a sample of households with children who had a CA-MRSA infection, bathing the child was identified as a risk factor for the spread of the infectious isolate to the other household members.[24] The presence of young children was also identified as a risk factor for transmission of all *S. aureus* by the US research group in a case-control study of households with and without *S. aureus* infection.[9] However, neither children (5–18 years) nor young children (<5 years) with CA-MRSA infections were more likely to transmit the clinical strain to other household members compared with infected adults (19-65 years) in another multi-site study.[28] While our findings suggest that efforts to limit the spread of CA-MRSA should take into consideration host factors and the composition of infected cases' households, particularly with regard to the presence of children, however further research is still needed.

The time from culture to interview was not found to be an independent predictor of household transmission, although we did observe a trend (P=.054) that transmission was less likely to be identified when more time passed between the initial infection and the home visit. This near-finding is in accordance with the results of a previous study that showed that colonisation of non-index household members decreased over time, and that colonisation was more likely to persist when multiple members of a household

were colonised.[13] This is further supported by another study that showed that MRSA carriage can often be fleeting and that minimizing the time between infection and sampling can increase the odds of identifying a positive isolate.[38] Because of the far longer and more variable time from clinical culture to interview among the AU study versus the two other studies in our analyses (US and NL), we also ran the same staged analyses excluding the AU cases and achieved notably similar results, with only the index patient being colonised with the clinical isolate at the time of the home visit and the percent of children in the household being independent predictors of household transmission of the clinical isolate in multivariate analyses.

The results from the individual studies when compared to the findings from the pooled analyses were, overall, very similar. Effect estimates from the individual studies are almost all in the same direction and only vary by orders of magnitude and the pooled results resemble a summary of the individual results. Of note, the pooled results are able to achieve statistical significance in many instances where the results from the individual studies do not, thus highlighting the increased statistical power achieved by pooling data from multiple studies. This may be of particular use as CA-MRSA infections remain relatively rare in non-epidemic settings, and thus studies often struggle to identify enough participating cases to adequately explore relevant research questions.[4]

There are certain limitations to the current study. First, this is a retrospective, observational study that uses a proxy variable as evidence of probable household transmission. Therefore, neither the directionality nor the source of transmission may be ascertained and the shared strains among household members potentially indicate a shared exposure. Second, our analyses were limited to variables shared across all studies. There were other potential risk factors that were not assessed because they were not included in all three studies or were not measured uniformly. These include environmental contamination and poultry consumption, which were associated with *S. aureus* carriage in previous analyses using data from these studies.[9,10,25] Additionally, these three studies did not use uniform time periods for assessing previous risk factors (US: 6 months; NL and AU: 1 year) and these data were unable to be harmonised. Third, different culture techniques were used across studies. Ideally, uniform methods would be used across geographic locations to maximize comparability. Last, this study did not assess the impact of colonisation of other body sites as the anterior nares was the only body site sampled in all three studies, even though this has emerged as a common feature of CA-MRSA carriage.[28,32,39] Underestimation of *S. aureus* colonisation may, in turn, underestimate household transmission. Despite these limitations, our pooled analysis benefits from a large, diverse sample size resulting in strong analytic power and increased generalisability.

Our study identifies shared features of CA-MRSA household transmission despite geographic difference in strain profiles. The spread of CA-MRSA among households

increases the likelihood of re-infection among its members.[10,16-18] Furthermore, the ability of infectious *S. aureus* strains to persist in households increases the likelihood that they will spread through the community.[11-14] Our findings suggest that decontamination strategies targeting the household unit may be effective in reducing the transmission of *S. aureus* colonisation and infection in the community setting. Such interventions may be applicable across diverse, international patient populations. Prospective, multicentre studies are needed to further define the transmission patterns of this prevalent and highly pathogenic organism.

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