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Mupirocin-Resistant Methicillin-Resistant Staphylococcus aureus (MRSA) and Vascular Surgery

P. Garvey[1,2], M. Skally[3], D. Moneley[4], K. Burns[1,3,5], K. O'Connell[3,5], F. Fitzpatrick[3,5], M. Fitzpatrick[3], S. Donlon[6], F. Duffy[6], T.P. Devassy[6], C. Finn[6], B. O'Connell[7], G.I. Brennan[7], B. Hayes[8], E. Smyth[3,5], H. Humphreys[3,5]

1. Health Service Executive (HSE) - Health Protection Surveillance Centre (HPSC), Dublin, Ireland.
2. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden.
3. Department of Microbiology, Beaumont Hospital Dublin, Ireland.
4. Department of Surgery, Beaumont Hospital, Dublin, Ireland.
5. Department of Clinical Microbiology, The Royal College of Surgeons in Ireland, Dublin, Ireland.
6. Department of Infection Prevention and Control, Beaumont Hospital, Dublin, Ireland.
7. National MRSA Reference Laboratory, St James's Hospital, Dublin, Ireland.
8. Occupational Health Department, Beaumont Hospital, Dublin, Ireland.

Abstract

Aim

An outbreak of mupirocin and methicillin resistant *Staphylococcus aureus* (MR-MRSA) occurred in a tertiary hospital, causing considerable disruption in a vascular unit. We investigated factors that might explain this large outbreak and areas for intervention to prevent a recurrence.

Methods

Cases of MRSA strain, spa type t127 or t922, were identified through databases, and healthcare records to describe affected patients in time, place and person. The adjusted matched odds ratio (amOR) for selected exposures in a matched case control study among hospital in-patients was calculated, using multivariable conditional logistic regression.

Results

Forty-one cases occurred over 18 months. Males predominated (78%), with a median age of 73 years. The specialty with the largest number of patients was vascular surgery with 18 cases (44%). Male sex (amOR=21; 95%CI 0.99-454), vascular surgery consultation (amOR=5.1; 95%CI 0.89-29), urinary catheterisation (amOR=12; 95%CI 0.98-154), occupational therapy (amOR=9.9; 95%CI 1.6-61) and length-of-stay (amOR=1.1; 95%CI 1.0-1.1 per additional overnight stay) were independently associated with an outbreak case. Control measures included; enhanced contact precautions, patient isolation/cohorting, ward closure, enhanced environmental decontamination and staff screening.

Conclusion

Vascular patients and those with underlying high dependency, i.e. urinary catheterisation and a requirement for occupational therapy had a higher risk of colonisation with MR-MRSA. Recording patient dependency prospectively, avoiding excessive bed occupancy, and a formal hospital policy on staff MRSA screening, are recommended to prevent/control future outbreaks in vascular units and elsewhere in hospitals.

Introduction

Recognised risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) include prolonged hospitalisation, long-term illness and multiple antimicrobial courses.[1] Furthermore, MRSA colonisation increases the risks for MRSA infection in patients undergoing invasive procedures.[2]

Colonisation may arise directly via the hands of staff or visitors, and indirectly through inadequately cleaned equipment and the healthcare environment.[3] Overcrowding and high antimicrobial use increase the risk of acquisition and spread.[4,5] Carriers can remain colonised with MRSA for up to four years.[6]

Infection with MRSA amongst vascular surgery patients has significant consequences. In a review of 408 patients in a Canadian vascular unit, there were 110 infections, of which MRSA accounted for 22.[7] The presence of MRSA predicted in-hospital death as well as length of stay, the need for admission to the intensive care unit and repeat surgery.[7] Plotkin and colleagues reviewed 27 mycotic aortic infections, of which 20 had bloodstream infection, with 10 of these due to MRSA, the most common pathogen.[8] Overall mortality was 59%, and 100% in those with MRSA.[8] Hence, all reasonable efforts are required to prevent vascular patients acquiring infection with MRSA.

Recognised control measures include the use of personal protective equipment (PPE), contact screening, isolation/cohorting and decolonisation using mupirocin nasal ointment (2%).[1] Nasal decolonisation can prevent colonisation progressing to infection and reduces onward transmission.[1]

Mupirocin resistant MRSA strains (MR-MRSA) have increased in Ireland, with high-level mupirocin resistance doubling between 1999-2005 and 2006-2007.[9] Earls *et al* studied 89 spa type t127 MRSA isolates, fifty of which were MR-MRSA.[10]

We describe the epidemiological characteristics of a hospital outbreak of MR-MRSA, centered on a vascular unit, identify potential factors which contributed to spread, discuss the challenges involved in outbreak management, and outline measures that could be undertaken to control further outbreaks.

Methods

The setting is an 820-bed adult tertiary referral hospital with a regional vascular surgery unit. The primary ward affected contained 35 beds, distributed among four six-bedded bays, a four-bedded bay, a two-bedded room and five single rooms. Bed occupancy levels in the hospital regularly exceeded 100% for much of the time period described. All new cases of MRSA are systematically reviewed and discussed by the infection prevention and control team (IPCT) to ensure prompt identification of cross-transmission events.

Cases associated with the outbreak were initially identified during routine testing of clinical specimens, and during the screening of in-patients with risk factors for MRSA in accordance with national guidelines.[1]

Patients were screened periodically (i.e. once weekly) during the initial two-month period of the outbreak. The identification of additional cases led to implementation of active case finding by screening patients (nose and groin) for MRSA on admission, and weekly. The National MRSA Reference Laboratory (NMRSARL) confirmed the outbreak strain by DNA microarray profiling and *spa* typing.[10] The outbreak MR-MRSA case definition is outlined below:

Case definition for a confirmed outbreak case

A confirmed case was defined as a patient or staff member with MRSA colonisation and/or infection with the specific antibiogram of tetracycline resistance (TetR); ciprofloxacin susceptibility (CipS), high-level mupirocin resistance (MupR), neomycin resistance (NeoR), urease positivity, and *spa* type t127 or t922, identified for the first time.

We reviewed the temporal distribution of outbreak cases using the date of the first specimen positive for the outbreak strain. We mapped ward transfer**s** during in-patient admissions and other hospital attendances over the course of the outbreak.

We undertook a matched case control study to investigate potential risk factors such as; exposure to selected procedures, contact with healthcare workers (HCW) and hospital locations. Exposures identified in more than 50% of cases during a hypothesis generating exercise were selected for assessment. Using https://www.openepi.com/Menu/OE_Menu.htm (accessed 9-9-2021), we calculated that with 25 cases, six controls per case would be required for the detection of an odds ratio (OR) of 5.0 at 5% alpha error, with 80% of power, and an expected prevalence for being a vascular surgery patient among controls of 15%. The analytical study was confined to outbreak cases who were hospital in-patients and who had a confirmed outbreak isolate for the first time. Controls were selected randomly from wards with outbreak cases that had screening swabs from which MRSA was not detected within 10 days of identification of their matched case, were also in-patients for at least one week before their negative screen, and had never previously been known to be MRSA positive. We used hospital databases and patient healthcare records to collect information on risk factors. We compared cases and controls using multivariable conditional logistic regression and calculated matched ORs (mOR). The model initially included all variables with a positive association with the outcome of interest and $p<0.150$ in univariate analyses. A likelihood ratio test p-value of >0.07 was used to determine whether an exposure be omitted from the multivariable model. All statistical analyses were performed using Stata version 15.1 http://www.stata.com (accessed 8-9-2021)

Results

Descriptive analyses

Forty-one cases met the outbreak case definition (Figure 1), with 39 (95%) being *spa* type t127 and two being the closely related *spa* type t922. The median age was 73 years (range 47-96); 32 (78%) were male. Patients were admitted under the following specialties: vascular surgery (n=18; 44%), general medicine (n=14; 34%) and other surgical specialties (n=8; 20%) (Figure 1).

Thirty-one cases were colonised, eight were infected and the status of two was unavailable. Seven patients died of which five were colonised and two infected with MR-MRSA.

Figure 1.

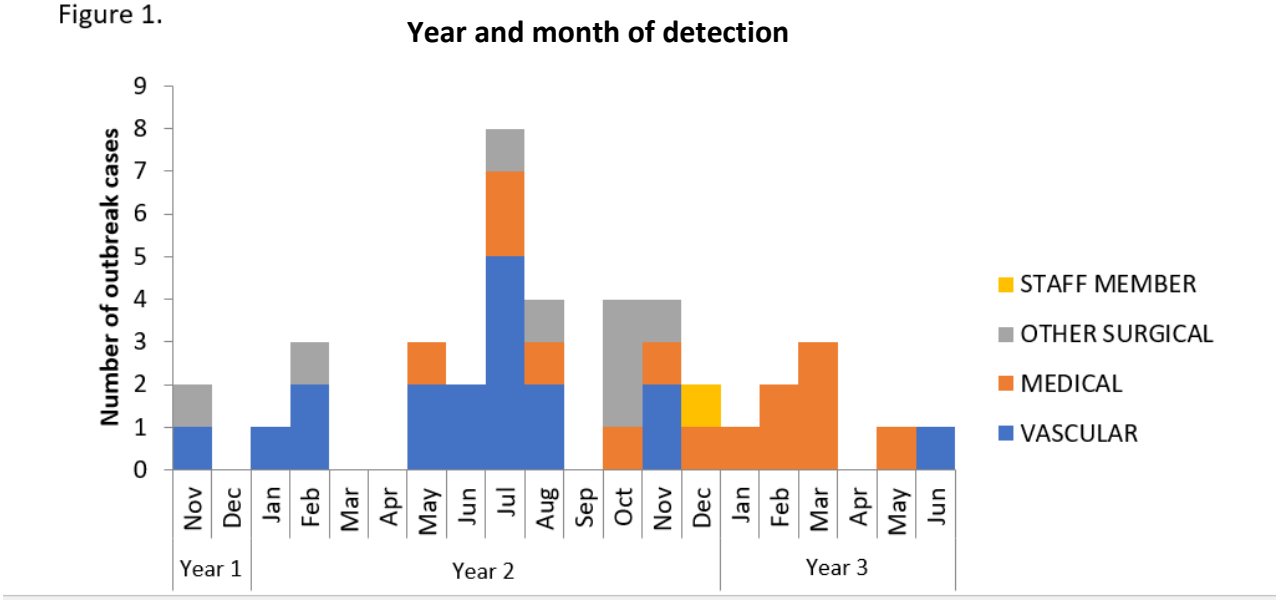

Figure 1. Distribution of outbreak cases by speciality during a MR-MRSA hospital outbreak.

Bed mapping and patient timelines

Initially there was one main cluster (18 cases) on a predominantly vascular surgery ward (designated Ward W). A second cluster on Ward W involving three cases probably arose from exposure to a case, not previously admitted to the hospital, which was positive on admission to Ward W. However, no single point source was identified.

The outbreak cohort was transferred to another ward (Ward Q) after three months to continue vascular services and for enhanced decontamination of Ward W. Three new cases were detected between January and April in year 2 indicating continuing transmission there. No obvious spatial-temporal links with existing recognised cases were identified for 11 cases.

Aspects of Ward W

The large increase in cases on Ward W was preceded by a four-week period when bed occupancy (103%) was above the normal complement of 245 weekly bed days (Figure 2). The bed occupancy dropped to 60-80% for seven consecutive weeks, in response to outbreak control measures. This temporary closure of beds and the reduction in vascular patient numbers was followed by a fall in new cases (Figure 2).

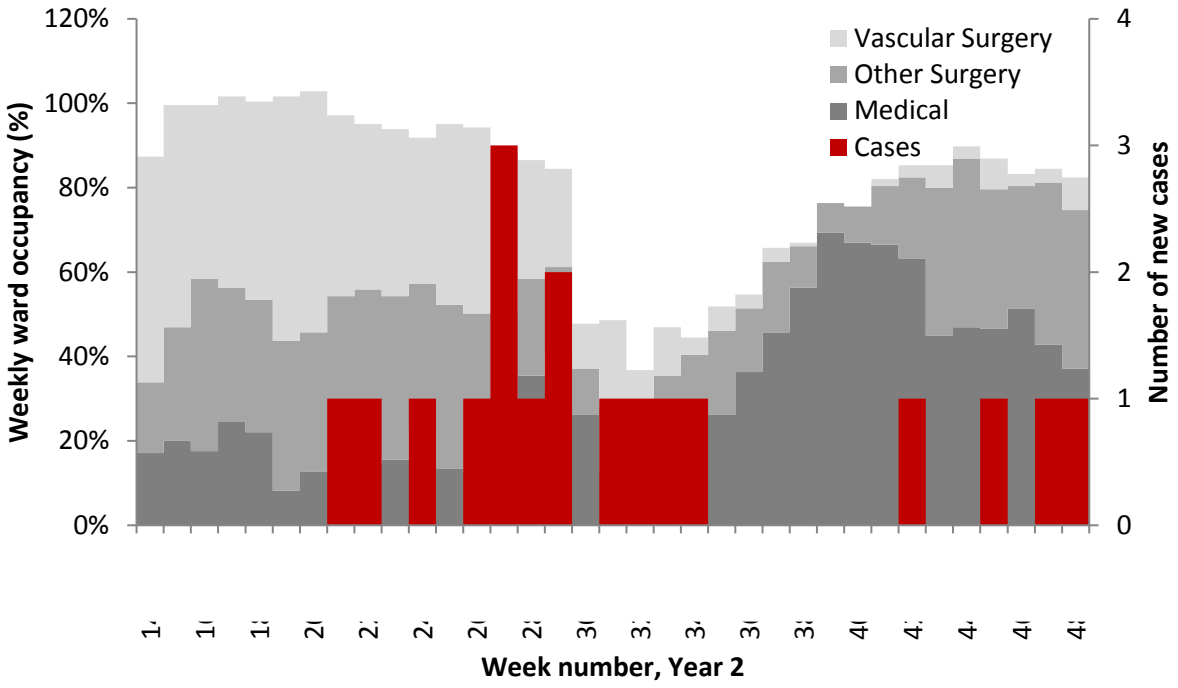

Figure 2. Distribution of patients with MR-MRSA on Ward W and weekly bed occupancy rates (%) by specialty.

Case control study

Twenty-two cases were enrolled in the case control study and on average, 5.2 controls were recruited per case. Eight variables were significantly positively associated with being a case and one was negatively associated on univariate analyses (Table 1). In the final multivariable conditional logistic regression model, being male, having a urinary catheter, having occupational therapy, and prolonged hospitalisation were significantly and independently associated with being a case. Having an in-patient vascular consultation was found to be borderline associated. None of the significant variables accounted for all cases, but male sex was the most predictive at 91%.

Table 1. Risk factors for the acquisition of mupirocin-resistant MRSA (MR-MRSA) spa type t127 or t922 colonisation/infection in a matched case control study during a MR-MRSA hospital outbreak.

Exposure	Cases			Controls			Univariate analyses			Multivariable analyses		
	Total	No.	%	Total	No.	%	Crude mOR	95% CI	P value	amOR	95% CI	P value
Male sex	22	20	91	114	71	62	**5.9**	**(1.3-27)**	**0.019**	**21**	**(0.99- 454)**	**0.050**
Ward W	22	18	82	114	51	45	**5.1**	**(1.6-16)**	**0.005**			
Emergency room consultation	21	10	48	112	78	70	**0.37**	**(0.14-0 .96)**	**0.040**	-		-
In-patient geriatric consultation	21	7	33	112	14	13	**3.3**	**(1.1-9.9)**	**0.038**			
In-patient vascular consultation	21	10	48	113	26	23	**3.2**	**(1.1-9.1)**	**0.027**	**5.2**	**(0.89-29)**	**0.066**
Peripheral vascular catheter	20	19	95	102	96	94	1.2	(0.14-10)	0.869	**-**		**-**
Urinary catheter	18	15	83	107	74	69	2.9	(0.79-11)	0.109	**12**	**(0.98-154)**	**0.051**
Wound for dressing	17	12	71	94	55	59	1.9	(0.61-6.2)	0.266	-		-
Antimicrobials	20	16	80	110	83	75	1.2	(0.38-3.9)	0.734	-		-
Surgical procedure	18	11	61	106	54	51	1.6	(0.53-5.0)	0.398	-		-
Physiotherapy	22	19	86	110	70	64	**4.0**	**(1.1-14)**	**0.037**			
Occupational therapy	22	16	73	109	30	28	**8.1**	**(2.6-25)**	**0.000**	**9.9**	**(1.6-61)**	**0.014**
Care from a social worker	22	13	59	109	32	29	**3.4**	**(1.3-9.0)**	**0.012**			
X-ray other than portable	22	21	95	114	93	82	4.3	(0.56-34)	0.159	-		-
Per in-patient day within two months of detection							**1.0**	**(1.0- 1.1)**	**0.002**	**1.1**	**(1.0-1.1)**	**0.013**

mOR=matched odds ratio; amOR =adjusted matched odds ratio; Bold indicates those factors analysed in multivariable conditional logistical regression analysis

Environmental investigations

Forty-five random samples of the environment, patient equipment and air were undertaken on and near ward W. One air sample taken in a nearby corridor/open area was positive for the outbreak strain.

Control measures

Each newly identified case was isolated or cohorted. Enhanced contact precautions, including the use of long-sleeved gowns for staff PPE, were instituted. An enhanced environmental and equipment cleaning regimen was implemented.

Ward W was closed to new admissions and enhanced decontamination efforts with hydrogen peroxide vaporisation (HPV) were undertaken.

Over a period of time to facilitate uptake, all healthcare workers (HCW) caring for Ward W patients were invited for screening for MRSA on a once-off voluntary basis. Of 55 tested, none was positive for the outbreak strain, but there was one staff member positive for the outbreak strain but this was unrelated to Ward W and occurred some time afterwards.

Nasal decolonisation using octenidine dihydrochloride (Octenisan® nasal gel) was attempted in three patients but none was successfully decolonised of MR-MRSA.

Discussion

This outbreak was the largest MRSA outbreak nationally reported in Ireland since outbreaks became notifiable in 2004.[11] Overall, 41 cases were identified over a 20-month period. It presented substantial challenges for elderly vascular surgery patients with the presence of mupirocin resistance making decolonisation difficult. For a period, all elective vascular surgery was suspended, and beds were unavailable due to ward closure.

Uptake of MRSA screening among staff was suboptimal but did not indicate any source among those who volunteered to be screened for MRSA carriage. Based on spatio-temporal analyses of cases, it seems likely that direct or indirect spread from existing known or unknown cases contributed to transmission, with overcrowding exacerbating spread. Apart from male gender, the other risk factors were indicators of underlying high dependency. Recent exposure to antimicrobials was not identified as a common feature among outbreak cases.

Male gender is a recognised risk factor for MRSA infection.[12] It has been proposed that poorer hand hygiene behaviour and/or gender differences in immune responses to infection may predispose males to higher MRSA colonisation and infection rates. The association found between cases here and occupational therapy consultation may be a proxy for dependence of patients or may reflect an increased risk associated with this professional activity, e.g. contaminated occupational therapy equipment. However, we did not target sampling of occupational therapy equipment as part of environmental screening. It is possible that MRSA-contaminated occupational therapy equipment might have played a role, and therefore consideration might be given to sampling this in the future. The association with vascular surgery, probably reflects poorer skin condition, ulcers, or co-morbidities in these patients. Studies have previously highlighted the risk of skin and soft tissue infections due to MRSA in patients with diabetes mellitus and peripheral vascular disease.[13]

A recent systematic review and meta-analysis of publications up to 2018 found that the prevalence of MR-MRSA was 13.8%, with 8.1% for high level mupirocin-resistance, and resistance was more common in Asia than Europe.[14] Widespread use of mupirocin ointment has previously been linked with the development of mupirocin resistance. [15-18] Just one patient had undergone attempted decolonisation with mupirocin within two months of subsequently being detected; thus, previous exposure to mupirocin does not appear to have been a contributory factor during our outbreak.

Older age was previously associated with MR-MRSA colonisation compared to colonisation with mupirocin susceptible MRSA.[19] Cases had a median age of 72 years, but as controls were frequency matched for age in the case control study, increasing age could not be assessed further as a risk factor.

Several studies suggest that overcrowding contributes to the transmission of healthcare associated infections. For MRSA, decreased healthcare worker hand-hygiene compliance, increased movement of staff and patients between wards, decreased opportunities for cohorting and isolation, and/or reduced efficiency of patient screening are recognised factors.[20,21] As the peak on Ward W was preceded by a period in which bed occupancy rates were above 100%, overcrowding may have played a role. As vascular surgery patients made up approximately one-third of all patients on Ward W, this may have facilitated additional spread, and the closure of Ward W to new admissions was followed by a reduction in new cases. Building guidelines for acute hospitals in Ireland published recently recommend that newly-built acute hospitals should compromise 100% single-room accommodation, multiple-bedded rooms should not contain more than four beds and that there should be a minimum floor space of 19m^2 around each bed.[22] The facilities in our hospital, albeit built well before when these were published, did not fulfil these criteria with excess bed occupancy and many beds too close together, thus likely contributing to the spread of MRSA.

Options for topical nasal decolonisation were extremely limited due to mupirocin and neomycin resistence. Octenidine is bactericidal, most isolates are susceptible[23] and the agent has potential,[24] but there is little local experience in its use. Cases probably remained colonised for longer than is typical, creating pressure for single rooms and cohort areas for longer, and serving as a potential reservoir for ongoing transmission. However, a recent mathematical model calculated the proportion of ICU patients with MRSA that are usually decolonised with mupirocin and chlorhexidine but found that there was significant room for improvement in current practice.[25]

Limitations to the epidemiological study include: (i) the date a person was first recognised as positive is more a reflection of screening activities than the actual time of acquisition, as colonisation *per se* goes undetected in the absence of screening, (ii) we chose two months as the window used for exposure assessment; a shorter or longer interval might have impacted on the findings, (iii) there were relatively large confidence intervals in the multivariable analyses (iv) heavily-dependent patients appear to have been at greatest risk, but there is no system in the hospital to prospectively capture the dependency level of patients and its variation during outbreak and non-outbreak periods, and (v) voluntary staff screening resulted in relatively few being screened.

Patients with underlying high dependency had a higher risk of colonisation with an unusual t127 strain of MR-MRSA. Spatio-temporal analyses suggested that direct or indirect spread from existing cases contributed to transmission, with overcrowding exacerbating spread. Recording the dependency of patients prospectively to inform patient needs, avoiding excessive bed occupancy levels, early closure of affected wards where possible, enhanced decontamination, the recording of individual HCW to individual patients, and a formal hospital policy on staff screening, are all recommended to prevent and support the management and investigation of any future outbreak.

Keywords:
Methicillin-Resistant *Staphylococcus aureus*; Mupirocin Resistance; Hospital Outbreak; Vascular Surgery; Prevention & Control; Bed Occupancy.

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Ethical Approval:
The data was anonymised and was collected as part of routine surveillance as mandated by national and other standards, and as part of outbreak investigations.

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Declaration of Conflicts of Interest:
H.H. has recently received research funds from Pfizer and Astellas and has in the recent past received a consultancy fee from Pfizer. All other authors report no conflicts of interest relevant to this article.

Corresponding Author:
Prof Hilary Humphreys,
Department of Clinical Microbiology,
RCSI Education and Research Centre,
Beaumont Hospital,
Dublin D09 YD60,
Ireland.
E-Mail: hhumphreys@rcsi.ie

References:

1. National Clinical Effectiveness Committee. 2013. Prevention and Control Meticillin-Resistant *Staphylococcus aureus* (MRSA). National Clinical Guideline No. 2 available at http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,14478,en.pdf (accessed 8-9-2021)
2. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; 32:470.

3. Boyce JM, Potter-Bynoe G, Chenevert C, King T. Environmental contamination due to methicillin-resistant *Staphylococcus aureus*: possible infection control implications. *Infect Control Hosp Epidemiol* 1997; 18:622-627.

4. Asensio A, Guerrero A, Quereda C, Lizán M, Martinez-Ferrer M. Colonization and infection with methicillin-resistant *Staphylococcus aureus*: associated factors and eradication. *Infect Control Hosp Epidemiol* 1996; 17:20-28.

5. Couderc C, Jolivet S, Thiébaut AC, Ligier C, Remy L, Alvarez AS, et al. Fluoroquinolone use is a risk factor for methicillin-resistant *Staphylococcus aureus* acquisition in long-term care facilities: a nested case-case-control study. *Clin Infect Dis* 2014; 59:206-215.

6. Shenoy ES, Paras ML, Noubary F, Walensky RP, Hooper DC. Natural history of colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus (VRE): a systematic review. *BMC Infect Dis* 2014; 14:177.

7. Cowie SE, Ma I, Lee SK, Smith M, Hsaing YN. Nosocomial MRSA infection in vascular surgery patients: impact on patient outcome. *Vasc Endovasc Surg* 2005; 39: 327-333.

8. Plotkin A, Magee G, Elsayed RS, Byerly S, Ham SW, Han SM., et al. Methicillin-resistant *Staphylococcus aureus* portends a poor prognosis after endovascvular repair of mycotic aortic aneurysms and aortic graft infections. *J Vasc Surg* 2020; 72: 276-85.

9. Rossney A and S. O'Connell, 2008 Emerging high-level mupirocin resistance among MRSA isolates in Ireland. *Euro Surveill.* 2008 Apr 3;13(14). pii: 8084.

10. Earls, MR, Kinnevey PM, Brennan, GI, Lazaris A, Skally M, O'Connell B et al. The recent emergence in hospitals of multidrug-resistant community-associated sequence type 1 and spa type t127 methicillin-resistant *Staphylococcus aureus* investigated by whole-genome sequencing: Implications for screening. *PLoS One*. 2017 Apr 11;12:e0175542. doi: 10.1371/journal.pone.0175542. eCollection 2017.

11. Computerised Infectious Disease Reporting database at the Health Protection Surveillance Centre as of 19th June 2015.

12. Humphreys, H, F Fitzpatrick, and BJ. Harvey. 2015. Gender differences in rates of carriage and bloodstream infection caused by methicillin-resistant *Staphylococcus aureus*: are they real, do they matter and why? *Clin Infect Dis*. 2015 61:1708-1714.

13. Dryden M, Baguneid M, Eckmann C, Corman S, Stephens J, Solem C et al. Pathophysiology and burden of infection in patients with diabetes mellitus and peripheral vascular disease: focus on skin and soft-tissue infections. *Clin Microbiol Infect. 2015* Suppl 2:S27-32.

14. Dadashi M, Hajikhani B, Darban-Sarokhalil D, van Belkum A. Mupiriocon resistance in *Staphylococcus aureus*: a systematic review and meta-analaysis. *J Global Antimicrobial Res* 2020; 20: 238-247.

15. Poovelikunnel T, Gethin G, Humphreys H. 2015 Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA*. J Antimicrob Chemother.* 2015; 70: 2681-92.

16. Chaturvedi P, Singh AK, Singh AK, Shukla S, Agarwal L. Prevalence of mupirocin resistant *Staphylococcus aureus* isolates among patients admitted to a tertiary care hospital. *North Am J Med Sci*. 2014;6:403-407.

17. Miller MA, Dascal A, Portnoy J, Mendelson J. Development of mupirocin resistance among methicillin-resistant *Staphylococcus aureus* after widespread use of nasal mupirocin ointment. *Infect Control Hosp Epidemiol.* 1996;17:811-813.

18. Deeny SR, Worby CJ, Tosas Auget O, Cooper BS, Edgeworth J, Cookson B, et al. Impact of mupirocin resistance on the transmission and control of healthcare-associated MRSA. *J Antimicrob Chemother* 2015; 70: 3366-3378.

19. Clements A, Halton K, Graves N, Pettitt A, Morton A, Looke D. Overcrowding and understaffing in modern health-care systems: key determinants in meticillin-resistant *Staphylococcus aureus* transmission. *Lancet Infect Dis.* 2008;8:427-434.

20. Waterhouse M, Morton A, Mengersen K, Cook D, Playford G . Role of overcrowding in meticillin-resistant *Staphylococcus aureus* transmission: Bayesian network analysis for a single public hospital. *J Hosp Infect*. 2011;78:92-96.

21. Jones JC, Rogers TJ, Brookmeyer P, Dunne WM Jr, Storch GA, Coopersmith CM et al. Mupirocin resistance in patients colonized with methicillin-resistant *Staphylococcus aureus* in a surgical intensive care unit. *Clin Infect Dis.* 2007;45:541-547.

22. Health Service Executive Antimicrobial Resistance Infection Control (AMRIC) Implementation Team. Infection Control Guiding Principles for Building Acute |Hospitals and Community Settings. August 2020

    www.hpsc.ie/az/respiratory/coronavirus/novelcoronavirus/guidance/infectionpreventionandcontrolguidance/residentialcarefacilities/Infection%20Control%20Guiding%20Principles%20for%20Building.pdf (access 8-9-2021).

23. Conceição T, de Lencastre H, Aires-de-Sousa M. Efficacy of octenidine against antibiotic-resistant *Staphylococcus aureus* epidemic clones. *J Antimicrob Chemother* 2016; xx; 2991-2994.

24. Chow A, Hon PY, Tin G, Zhang W, Poh BF, Ang B. Intranasal octenidine and universal antiseptic bathing reduce methicilliln-resistant *Staphylococcus aureus* (MRSA) prevalence in extended care facilities. *Epidemiol Infect* 2018; 146: 2036-2041.

25. Lofgren ET, Mietchen M, Dicks KV, Moehring R, Anderson D for the Centers for Disease Control Modeling Infectious Diseases in Healthcare Program. *JAMA Network Open.*

    2021;4(3):e210652.doi:10.1001/jamanetworkopen.2021.0652.