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Rapid communications

Case of Legionnaires' disease in a neonate following a home birth in a heated birthing pool, England, June 2014 2
by N Phin, T Cresswell, F Parry-Ford, on behalf of the Incident Control Team

Research articles

Characterisation of a new group of Francisella tularensis subsp. holarctica in Switzerland with altered antimicrobial susceptibilities, 1996 to 2013 5
by FC Origgi, J Frey, P Pilo

Surveillance and outbreak reports

Surveillance for outbreaks of gastroenteritis in elderly long-term care facilities in France, November 2010 to May 2012 15
by AS Barret, N Jourdan-da Silva, K Ambert-Balay, G Delmas, A Bone, JM Thiolet, V Vaillant

Review articles

Systematic literature analysis and review of targeted preventive measures to limit healthcare-associated infections by meticillin-resistant Staphylococcus aureus 23
by R Köck, K Becker, B Cookson, JE van Gemert-Pijnen, S Harbarth, J Kluytmans, M Mielke, G Peters, RL Skov, MJ Struelens, E Tacconelli, W Witte, AW Friedrich

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Case of Legionnaires' disease in a neonate following a home birth in a heated birthing pool, England, June 2014

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Public Health England was notified of Legionnaires' disease in a neonate following a home birth in a heated birthing pool filled from the domestic hot water supply two weeks earlier. We describe the incident, sampling results, and public health actions. It is recommended that heated birthing pools should not be used for home births. Neonates developing pneumonia within 14 days of labour or birth in any birthing pool should be tested for Legionnaires' disease.

In early June 2014, Public Health England (PHE) were notified that *Legionella pneumophila* was identified in bronchoalveolar lavage specimens from a neonate requiring extracorporeal membrane oxygenation (ECMO). The neonate was born at home in a heated birthing pool which had been filled approximately two weeks before birth. The baby became unwell on Day 3 and was admitted to hospital on Day 5, requiring immediate respiratory support followed by ECMO on Day 6, at which time the bronchoalveolar lavage sample was taken. The result was later confirmed as *L. pneumophila* serogroup1 ST 48.

Background

Legionnaires' disease is a severe pneumonia usually caused by inhaling water droplets containing *Legionella* bacteria. It is very rare in children. During 2012, only 0.5% of all reported European cases of Legionnaires' disease were in persons under the age 19 years [1]. However, several instances of infection among neonates are documented, usually in association with hospital water systems or respiratory equipment [2-4]. We are aware of three published instances of neonatal Legionnaires' disease associated with birthing pools [5-7]. Two cases were related to birthing pools in hospitals in 1999 and 2002 [5,6]. The third case occurred following a home birth in a domestic spa pool in 1999, and was fatal [7].

In the United Kingdom (UK), there are companies who hire birthing pools for domestic use. The majority of these are filled at the time of onset of labour and then emptied. However, some products incorporate a heating and recirculation system, and may be filled and operated for up to two weeks before to birth.

Public health actions

Initial public health response

A multi-agency incident control team was convened to investigate the incident and institute control measures. The supplier who had hired out the pool was contacted and voluntarily recalled all heated pools that were currently out for hire. A national alert was sent out to National Health Service (NHS) staff by NHS England, advising that this type of pool should not be used in the home setting and raising awareness with neonatologists and microbiologists. PHE issued an internal briefing and initially identified 10 other suppliers in England. The local regulating authorities in which these suppliers were based were contacted and advised that local suppliers should recall heated pools that were in use.

Environmental investigations

The birthing pool used by the case had been drained but not returned to the supplier and so it was possible to obtain swabs and some water samples. Samples were also taken from the domestic water system in the house where the neonate was born and from other birthing pools which had been returned to the supplier and cleaned ready for hiring out.

Using polymerase chain reaction (PCR), three swabs from the birthing pool used by the case were found to be positive for *Legionella* spp and *L. pneumophila*. Further analysis was undertaken at the Respiratory and Vaccine Preventable Bacteria Reference Unit at PHE Colindale, and *L. pneumophila* serogroup 1 ST48 was confirmed.

Samples from the domestic hot water system and from other birthing pools held by the supplier were negative for *L. pneumophila* in both PCR and culture. The results

of the environmental and clinical samples support the hypothesis that the baby acquired the infection from the water in the heated birthing pool.

Further public health response

Six companies were finally identified in England that together hired out around 60 birthing pools incorporating a heater and recirculation pump. Three other companies acted as agents or intermediaries, and two had ceased trading. The heated birthing pools were either adapted spa pools or custom-made from spa pool components. The recommended disinfection and maintenance routines differed between the suppliers and there was no specific advice in relation to *Legionella* control provided to customers by suppliers.

A risk assessment was undertaken by national experts in Legionnaires' disease and the control of *Legionella* in water systems as follows:

- Neonates can be at particular risk of very severe illness if they develop lung infections.
- Due to the potential for microbial growth it is not considered good practice to recirculate heated water for prolonged periods of time, i.e. more than a week [8], even with filtration and chemical disinfection.
- The temperature at which the water in the birthing pool is maintained is within the optimal range for the growth of *Legionella* and other pathogenic organisms.
- Chemical regimes to disinfect water that require manual biocide dosing are dependent on good user compliance, making this approach at risk control unsuitable for use in the domestic setting.
- The skin and mucous membranes of neonates can be particularly sensitive to chemical exposure. It is not clear whether the recommended dosing levels would achieve effective control of *Legionella* while at the same time avoiding exposure risks to the neonate.
- The information available to those hiring the pools recommends use of the filled pools by family members before use at the time of labour. This will increase the overall organic and bacterial load and reduce effectiveness of the chemical regime.
- The birthing pools from the suppliers which have been reviewed to date contain pipework and consequently may harbour biofilm. This could be difficult to remove during cleaning and could be the source of *Legionella* during any subsequent use.
- *Legionella* may be present in up to 10–20% of household water supplies, which constitutes a potential contamination source when the birthing pools are filled from a domestic source.
- Although aspiration of fluid by babies at birth is an uncommon event, the likelihood of acquiring Legionnaires' disease, should this happen, is increased.

Discussion and conclusions

It is likely that a combination of recirculation of heated water and a disinfection regime that was inadequate resulted in growth of *Legionella* in the birthing pool over the two week period. During birth, the baby was probably exposed to *Legionella*, possibly via aspiration of water. Although there is previous evidence of transmission of *Legionella* to neonates via birthing pools at home [7], this is the first reported case within Europe and the first for 10 years. No national or international standard or guidance for the safe use of heated birthing pools in the home appears to have been developed, and birthing pools are not specifically covered in wider guidance on the safe operation of spa pools [8].

Until the manufacturers and suppliers are able to provide evidence of a system that is safe to use, PHE recommends that heated birthing pools (incorporating a recirculation pump and heater), filled in advance of labour, should not be used for labour or birth in the home setting. This recommendation does not apply to hospital birthing pools or to pools in the home that are filled immediately prior to birth.

As with adults, prompt identification and treatment with antibiotics effective against *Legionella* reduces morbidity and mortality [9]. However, the relative rarity of Legionnaires' disease among children and neonates may result in reduced suspicion amongst clinicians, and a delay in recognition and treatment. We recommend that all neonates who develop a severe respiratory infection in the 14 days following labour or birth in any birthing pool are screened for *Legionella*.

Note added in proof:

On 17 July 2014, results were obtained from samples from another five heated birthing pools, taken by local authorities following the PHE advice. Three pools tested positive by PCR for *Legionella* species. In two of them (and in the index pool), other organisms including *Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Elizabethkingia meningoseptica, Enterobacter* sp. and *Cupriavidus* sp. were cultured and identified by MALDI-TOF mass spectrometry.

This reinforces serious concerns about the safety of heated birthing pools (incorporating a recirculation pump and heater), filled in advance of labour and used in the home setting.

Members of the incident management team

PHE - Tricia Cresswell (Chair), Nick Phin, Jimmy Walker, Heather Aird, Karen Lloyd, Georgina Fletcher, Anne Halewood, Kelly Stoker, Alison Mason, Lisa Harvey-Vince, Tim Harrison, Vicki Chalker, Baharak Afshar, Samuel Collins. Local Authority (a)– Carol Wood, Stewart Sorrell, Lorna Elliott; Local Authority (b) – Colin Giddings, Laura Annetts; NHS England- Michele Upton, Kate Morrow; Hospital (c) NHS FT –Julie Samuel; Hospital (d) NHS FT- Joanne Crawford; Health and Safety Executive – Paul McDermott; Royal College of Midwives – Louise Silverton. Acknowledgements

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Conflict of interest

None declared.

Authors' contributions

N Phin, T Cresswell and F Parry-Ford drafted and revised the manuscript. All members of the incident control team contributed to the gathering of information and analysis.

References

1. European Centre for Disease Prevention and Control (ECDC). Legionnaires' disease in Europe, 2012. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/legionnaires-disease-surveillance-2012.pdf
2. Yiallouros PK, Papadouri T, Karaoli C, Papamichael E, Zeniou M, Pieridou-Bagatzouni D, et al. First outbreak of nosocomial Legionella infection in term neonates caused by a cold mist ultrasonic humidifier. Clin Infect Dis. 2013;57(1):48-56. http://dx.doi.org/10.1093/cid/cit176
3. Shachor-Meyouhas Y, Kassis I, Bamberger E, Nativ T, Sprecher H, Levy I, et al. Fatal hospital-acquired Legionella pneumonia in a neonate. Pediatr Infect Dis J. 2010;29(3):280-1. http://dx.doi.org/10.1097/INF.0b013e3181c176c9
4. Aubert G, Bornstein N, Rayet I, Pozzetto B, Lenormand PH. Nosocomial infection with Legionella pneumophila serogroup 1 and 8 in a neonate. Scand J Infect Dis. 1990;22(3):367-70. http://dx.doi.org/10.3109/00365549009027062
5. Franzin L, Scolfaro C, Cabodi D, Valera M, Tovo PA. Legionella pneumophila pneumonia in a newborn after water birth: a new mode of transmission. Clin Infect Dis. 2001;33(9):e103-4. http://dx.doi.org/10.1086/323023
6. Schrijver DK. Legionairsziekte bij een pasgeborene na een onderwaterbevalling [Legionnaires' disease in a newborn after an underwater birth]. Vlaams infectieziektebulletin. 2002(1):p8-9. Dutch. Available from: http://www.infectieziektebulletin.be/defaultSubsite.aspx?id=10078#.U8PoN7EghnU
7. Nagai T, Sobajima H, Iwasa M, Tsuzuki T, Kura F, Amemura-Maekawa J, et al. Neonatal sudden death due to Legionella pneumonia associated with water birth in a domestic spa bath. J Clin Microbiol. 2003;41(5):2227-9. http://dx.doi.org/10.1128/JCM.41.5.2227-2229.2003
8. Health Protection Agency (HPA). HSE document. Management of spa pools. Controlling the risks of infection. London: HPA; 2006. ISBN: 0 901144 80 0. Available from: http://www.hpa.org.uk/webc/hpawebfile/hpaweb_c/1200471667418
9. Greenberg D, Chiou CC, Famigilleti R, Lee TC, Yu VL. Problem pathogens: paediatric legionellosis--implications for improved diagnosis. Lancet Infect Dis. 2006;6(8):529-35. http://dx.doi.org/10.1016/S1473-3099(06)70553-9

Characterisation of a new group of *Francisella tularensis* subsp. *holarctica* in Switzerland with altered antimicrobial susceptibilities, 1996 to 2013

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Molecular analysis of *Francisella tularensis* subsp. *holarctica* isolates from humans and animals revealed the presence of two subgroups belonging to the phylogenetic groups B.FTNF002-00 and B.13 in Switzerland. This finding suggests a broader spread of this group in Europe than previously reported. Until recently, only strains belonging to the Western European cluster (group B.FTNF002-00) had been isolated from tularaemia cases in Switzerland. The endemic strains belonging to group B.FTNF002-00 are sensitive to erythromycin, in contrast to the strains of the newly detected group B.13 that are resistant to this antibiotic. All the strains tested were susceptible to ciprofloxacin, streptomycin, gentamicin, nalidixic acid and chloramphenicol but showed reduced susceptibility to tetracycline when tested in a growth medium supplemented with divalent cations. The data show a previously undetected spread of group B.13 westwards in Europe, associated with changes in the antibiotic resistance profile relevant to treatment of tularaemia.

Introduction

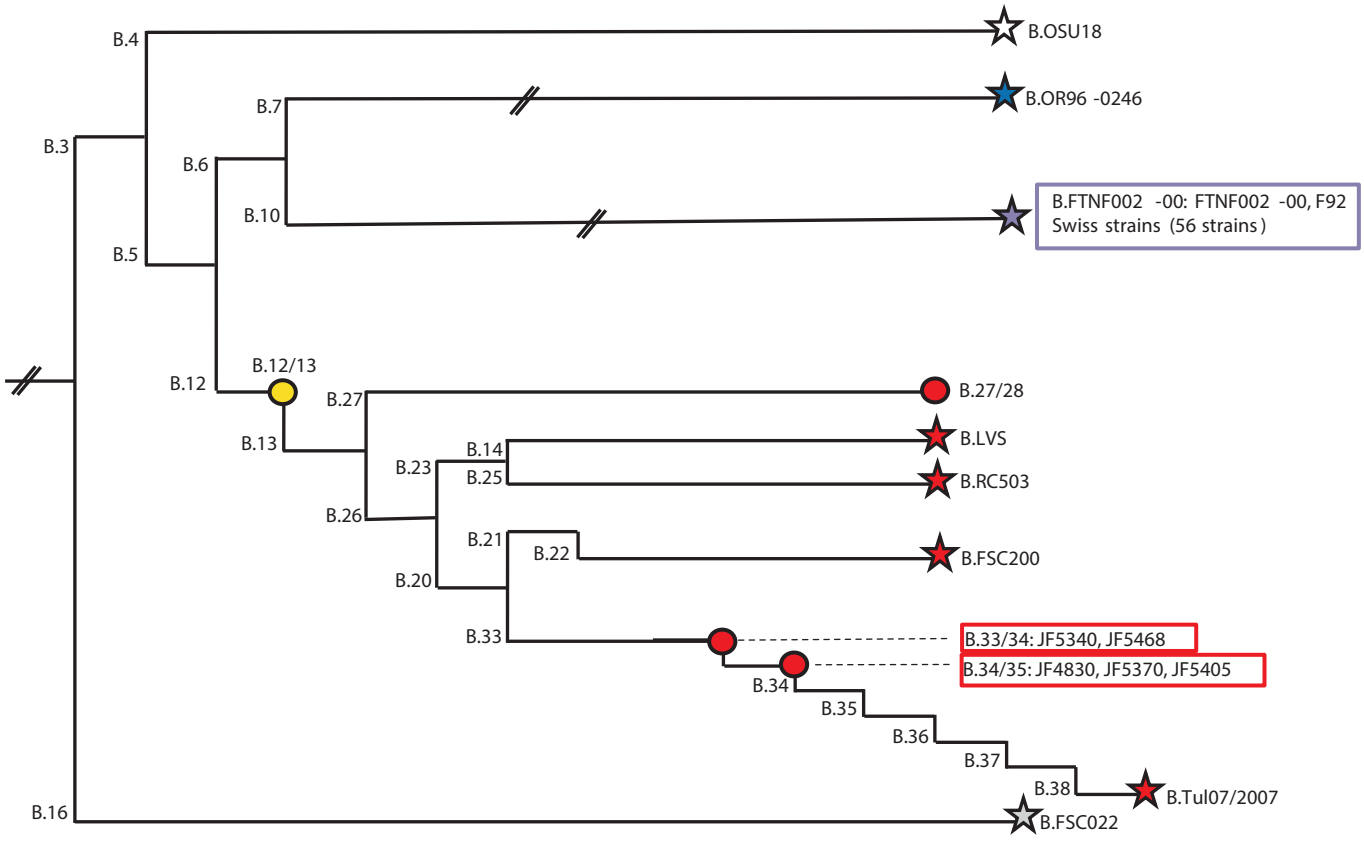
Francisella tularensis is a Gram-negative bacterium causing the zoonotic disease tularaemia. The two clinically relevant subspecies are *F. tularensis* subsp. tularensis and *F. tularensis* subsp. *holarctica*. Of the two, only the latter subspecies is present in Europe. Human infections mainly occur through inhalation, ingestion, or by direct contact with infected animal species and contaminated animal tissues, water and aerosols [1]. In general, it is difficult to trace the source of infection [2]. Analyses of molecular genetic markers of the strains circulating in the environment provide valuable information on the dynamics of infection in people and in animals, and improve the knowledge of the biology of this bacterium. Genetic and phenotypic data are also necessary to determine the most suitable antimicrobial substances to use to treat humans and animals [3-8].

With the recent growing interest in *F. tularensis* biology, several tools have been developed to investigate the molecular epidemiology of this genetically monomorphic bacterium following a hierarchical scheme [9-13]. Genomes of different strains are screened for canonical single nucleotide polymorphism (canSNP) signatures. With the advent of novel technologies, an increasing number of strains are sequenced, leading to the discovery of new canSNP markers and signatures specific to new subgroups. The growing information involves adjustments in the phylogenetic nomenclature of *F. tularensis* and allows better resolution within the subgroups [11,12,14]. Throughout this manuscript, we will follow the nomenclature based on the canSNPs (for nomenclature clarity, refer to schema in Figure 1). In Europe, strains belonging to groups B.13 and B.FTNF002-00 are those predominantly isolated [12]. The group B.13 extends geographically from Scandinavia to the eastern European rim, with co-circulation of several of its subgroups in some countries. In Western Europe, a specific group, B.FTNF002-00, is circulating in France, Germany, Italy, Spain and Switzerland [11-19]. Recently, it was observed that Germany represents a geographical diaphragm virtually separating group B.13 from group B.FTNF002-00 [18].

Interestingly, strains belonging to group B.FTNF002-00 are described as sensitive to erythromycin, whereas strains belonging to other groups show variability in this marker [3-5,7,18]. Historically, strains of *F. tularensis* subsp. *holarctica* have been separated in two biovars: biovar I, strains sensitive to erythromycin, and biovar II, strains resistant to erythromycin [20]. Although this marker is principally used for epidemiological purposes, there may be significant clinical implications in areas with co-circulation of different groups. A paradigmatic example of this is the recent recommendation of treating pregnant women infected with *F. tularensis* with azithromycin in geographical

Figure 1

Schematic of *Francisella tularensis* subsp. *holarctica* nomenclature based on canonical single nucleotide polymorphisms



Canonical single nucleotide polymorphisms (canSNP), adapted from and according to the colours and symbols previously described [11-13], showing the position of Swiss strains within the subspecies. Stars represent terminal subgroups (sequenced strains), while circles indicate collapsed branches. The length of branches is not scaled. Only canSNP relevant to this study are presented to clarify the phylogenetic position of groups and subgroups discussed. Parallel bars indicate missing intermediate canSNPs and corresponding nodes and branches. CanSNPs are indicated to the left of the nodes. Strains for which whole-genome sequencing information is available and which were used for comparisons, are highlighted in bold at the end of the branches. Groups and subgroups identified in this study are boxed. Dashed lines do not represent branches.

areas where strains sensitive to erythromycin are circulating [21].

This study describes the first isolation of erythromycin-resistant strains of *F. tularensis* subsp. *holarctica* belonging to group B.13 in Switzerland. We discuss how these findings impact on the phylogeography of *F. tularensis* subsp. *holarctica* in Europe and on antibiotic treatment of affected individuals living in areas with co-circulating groups [12].

Methods

Bacterial strains, DNA templates, identification and typing

All manipulations with live cultures were performed in a BSL3 containment laboratory. *F. tularensis* strains were cultivated on chocolate agars with IsoVitaleX (Becton Dickinson, Allschwil, Switzerland) for three days at 37 °C with 5% CO_2. Lysates from cultures were prepared, filter-sterilised [22] and tested by real-time PCR for the presence of the fopA gene to confirm the species *F. tularensis* [22,23]. The subspecies was subsequently determined by amplification of the region of difference (RD)1 [24]. Strains were further characterised by PCR for the presence of deletions in two different markers, RD23 and Ft-M24, specific to the group B.FTNF002-00 [16,17,24] and by multilocus variable-number tandem repeat (VNTR) analysis (MLVA) with six VNTRs markers (Ft-M3, Ft-M6, Ft-M20, Ft-M21, Ft-M22 and Ft-M24) [17,25]. The MLVA results were further confirmed by analysis of the following canSNP markers B.11, B.12 B.20, B.21, B.22, B.23 and B.33 to B.38 [11,12].

Minimal inhibitory concentrations of antimicrobial agents

The minimal inhibitory concentration (MIC) values of antibiotic drugs relevant to clinical use such as gentamicin (0.12–16 mg/L), streptomycin (1–16 mg/L), ciprofloxacin (0.06–4 mg/L), tetracycline (0.25–16 mg/L), nalidixic acid (2–64 mg/L), chloramphenicol (2–32 mg/L) and erythromycin (0.5–32 mg/L), were determined in two different broth media: (i) modified Cation-Adjusted Mueller Hinton Broth (mCAMHB):

Cation-Adjusted Mueller Hinton Broth (Becton Dickinson, Heidelberg, Germany) supplemented with 2% PolyViteX Enrichment (BioMérieux, Marcy l'Etoile, France), and (ii) modified Mueller Hinton II (mMHII) broth: mCAMHB with 0.1% glucose, 63 mM $CaCl_2$, 53 mM $MgCl_2$ and 34 mM ferric pyrophosphate using custom 96-well Sensititre susceptibility plates (Trek Diagnostics Systems, East-Grinstead, England and MCS Diagnostics BV, JL Swalmen, the Netherlands), according to the Clinical and Laboratory Standards Institute (CLSI) guidelines [26] and the informational supplement [27]. Antibiotics of the class of the beta-lactams were not tested because of the known natural resistance of *F. tularensis* strains to these antimicrobial substances [6,28]. The 96-well plates were incubated at 37 °C in 5% CO_2 atmosphere for 48 hours. The MIC values were defined as the lowest concentration exhibiting no visible growth. MICs were read after 24 and 48 hours incubation. For quality assurance, the reference strains of *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 were also tested by broth microdilution in mMHII broth and in mCAMHB.

Genetic characterisation of erythromycin resistance

The genetic characterisation of erythromycin resistance was carried out by PCR amplification and further sequencing of the genes encoding for the 23S rRNA (*rrl*), the L4 (*rplD*) and L22 (*rplV*) ribosomal proteins as previously described by Gestin and colleagues [29]. The sequences obtained were edited, aligned and compared in Sequencher (GeneCodes, Ann Arbor, United States) with the corresponding genes of the completely sequenced strains FTNF002-00 (group B.FTNF002-00, isolated in France [16]), F92 (group B.FTNF002-00, isolated in Germany [30]), FSC200 (group B.13, isolated in Sweden [31]) and LVS (group B.13, isolated in Russia) (NCBI/GenBank accession numbers: CP000803, CP003932, CP003862 and AM233362, respectively).

Results

Sixty-one strains were isolated between 1996 and 2013 from human and animal cases of tularaemia from a representative area of the Swiss territory (Table 1, Figure 2). Thirteen strains isolated before 2009 (JF3820, JF3821, JF3822, JF3824, JF3825, JF3826, JF3828, JF3829, JF3859, JF4092, JF4128, JF4212 and JF4242) had previously been characterised as *F. tularensis* subsp. *holarctica* belonging to group B.FTNF002-00 [17]. All other strains (n=48) were identified here as *F. tularensis* subsp. *holarctica*, and 43 of them were determined as group B.FTNF002-00 (Table 1) [17], while five strains JF4830, JF5340, JF5370, JF5405 and JF5468 did not harbour the deletions specific to the group B.FTNF002-00 in the RD23 and Ft-M24 markers. MLVA confirmed the clustering of the 56 strains (isolated between 1996 and 2013) belonging to group B.FTNF002-00 (data not shown). The highest variability among the markers used for MLVA was observed within markers Ft-M3 and Ft-M6 as previously reported for the group B.FTNF002-00 (Table 1) [15,17,18]. Concerning the strains not belonging to group B.FTNF002-00, the three strains, JF5340, JF5370 and JF5405 isolated from two human patients and one hare between 2012 and 2013, shared the same VNTR profile, while strains JF4830, isolated in 2010 from a patient returning from a vacation in eastern Europe (possibly corresponding to an imported case), and JF5468, isolated from a hare in 2013, revealed a distinct VNTR profile, with one variation in the Ft-M3 marker (Table 1). The four strains, JF5340, JF5370, JF5405 and JF5468 were isolated from a large geographical area of Switzerland extending from the central west to the east sides of the country (Figure 2).

CanSNP analyses were performed on a panel of 24 representative strains (shaded in grey in Table 1). All strains belonging to group B.FTNF002-00 and harbouring the specific deletions within markers RD23 and Ft-M24 showed the canSNP profile characteristic of the group B.FTNF002-00 (Table 1) [11,32]. All other strains (JF4830, JF5340, JF5370, JF5405 and JF5468) had a canSNP profile not corresponding to group B.FTNF002-00 (Table 1) [11]. In order to further characterise the strains not belonging to group B.FTNF002-00, the canSNP markers B.21, B.22 and B.23 were sequenced. They showed the SNP profile corresponding to group B.13 according to the genotypes described by Svensson et al. (Table 1) [11,32]. Moreover, a higher resolution of the genetic characterisation of the strains in group B.13 was obtained through analysis of the canSNP markers B.33 to B.38 [12]. Two subgroups were observed: the B.33/34 (JF5468 and JF5340) and the B.34/35 (JF4830, JF5370 and JF5405) according to the nomenclature described by Gyuranecz et al. [12] (Table 1 and Figure 1).

Antibiotic susceptibility profiles were determined for the panel of 24 representative strains (Table 2) by broth microdilution method using two broth media, mCAMHB and mMHII, for seven antibiotic drugs and read after 48 hours. The *F. tularensis* strains did not show any visible growth at the concentrations tested for nalidixic acid, chloramphenicol and ciprofloxacin in either broth medium, tested (Table 2). The MIC values for chloramphenicol and ciprofloxacin were below the breakpoint values provided in the CLSI guidelines, ≤8 µg/mL for chloramphenicol and ≤0.5 µg/mL for ciprofloxacin, while no breakpoint value is available for nalidixic acid [27]. MIC values for gentamicin ranged between 1 and 4 µg/mL in mMHII, but between ≤0.12 and 0.25 µg/mL in mCAMHB. The breakpoint value for gentamicin given in the CLSI guidelines for *F. tularensis* is ≤4 µg/mL [27]. The discrepancy in the MIC values observed for gentamicin between cultures of *F. tularensis* in mMHII and mCAMHB was confirmed for reference strains *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 (Table 2). MIC values for streptomycin ranged between 2 and 4 µg/mL in mMHII and were all at 4 µg/mL in mCAMHB (Table 2). The breakpoint value provided for streptomycin in the CLSI guidelines is ≤16 µg/mL when testing is performed in a CO_2 atmosphere [27]. MIC values for

Table 1a

Genetic characterisation of Swiss strains of *Francisella tularensis* subsp. *holarctica* by MLVA and SNPs, Switzerland, 1996–2013 (n=61)

Strain	Host, geographic origin, year of isolation	Subgroup according to [12] and [13]	MLVA						SNPs											
			Ft-M3	Ft-M6	Ft-M20	Ft-M21	Ft-M22	Ft-M24	B.11	B.12	B.20	B.21	B.22	B.23	B.33	B.34	B.35	B.36	B.37	B.38
JF3826	Monkey, Jura, 1996	B.FTNF002-00	342	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3821	Hare, Jura, 1997	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3820	Hare, Jura, 1998	B.FTNF002-00	333	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3822	Hare, Jura, 1998	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3859	Hare, eastern Switzerland, 1998	B.FTNF002-00	333	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3829	Monkey, Zurich, 2002	B.FTNF002-00	288	332	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3828	Human, Aargau, 2004	B.FTNF002-00	342	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3824	Human, Bern, 2005	B.FTNF002-00	333	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF3825	Monkey, St. Gallen, 2006	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF4092	Hare, Bern, 2007	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF4128	Human, Lucerne, 2008	B.FTNF002-00	297	332	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF4212	Human, Nidwald, 2008	B.FTNF002-00	297	353	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF4242	Hare, Bern, 2008	B.FTNF002-00	306	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF4429	Human, Jura, 2008	B.FTNF002-00	351	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4455	Hare, Bern, 2008	B.FTNF002-00	333	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4456	Human, Lucerne, 2008	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4458	Hare, Bern, 2008	B.FTNF002-00	297	353	255	403	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4496	Human, Basel, 2009	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4515	Human, Aargau, 2008	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4516	Human, Aargau, 2009	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4517	Human, Aargau, 2009	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4565	Hare, Bern, 2009	B.FTNF002-00	333	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4628	Human, Zurich, 2009	B.FTNF002-00	297	353	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4829	Human, Zurich, 2010	B.FTNF002-00	333	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF4830	**Human, Zurich, 2010**	**B.13**	**315**	**332**	**255**	**396**	**254**	**480**	**C[a]**	**A[d]**	**G[d]**	**G[a]**	**G[a]**	**G[a]**	**T[d]**	**A[d]**	**C[a]**	**C[a]**	**C[a]**	**T[a]**
JF4997	Hare, Graubünden, 2011	B.FTNF002-00	297	332	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5142	Human, Vaud, 2011	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5341	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5342	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5343	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5344	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5345	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-

–: not available; MLVA: multilocus variable-number tandem repeat analysis; SNPs: single nucleotide polymorphisms.

Strains selected for further analysis (canSNPs and antimicrobial agent susceptibilities, n=24) are shaded in grey. Strains belonging to the clade B.13 are highlighted in bold.

[a] Ancestral state.

[d] Derived state.

Table 1B

Genetic characterisation of Swiss strains of *Francisella tularensis* subsp. *holarctica* by MLVA and SNPs, Switzerland, 1996–2013 (n=61)

Strain	Host, geographic origin, year of isolation	Subgroup according to [12] and [13]	MLVA						SNPs											
			Ft-M3	Ft-M6	Ft-M20	Ft-M21	Ft-M22	Ft-M24	B.11	B.12	B.20	B.21	B.22	B.23	B.33	B.34	B.35	B.36	B.37	B.38
JF5346	Human, St. Gallen, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5349	Hare, Solothurn, 2012	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5350	Monkey, Bern, 2012	B.FTNF002-00	288	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5351	Hare, Solothurn, 2012	B.FTNF002-00	288	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5353	Marten, Aargau, 2012	B.FTNF002-00	306	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5355	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5356	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5357	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5368	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5369	Hare, Bern, 2012	B.FTNF002-00	297	353	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5372	Hare, Solothurn, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5373	Hare, Bern, 2012	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5374	Hare, Solothurn, 2012	B.FTNF002-00	288	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5375	Hare, Fribourg, 2012	B.FTNF002-00	324	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5379	Hare, Aargau, 2012	B.FTNF002-00	306	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5380	Hare, Jura, 2012	B.FTNF002-00	351	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5386	Hare, Bern, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5387	Hare, Jura, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5388	Hare, Jura, 2012	B.FTNF002-00	288	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5389	Hare, Bern, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5390	Human, Lucerne, 2012	B.FTNF002-00	306	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5393	Hare, Basel, 2012	B.FTNF002-00	306	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5394	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5409	Mouse, Zurich. 2012	B.FTNF002-00	297	311	255	396	254	464	T[d]	C[a]	A[a]	-	-	-	-	-	-	-	-	-
JF5410	Mouse, Zurich, 2012	B.FTNF002-00	297	311	255	396	254	464	-	-	-	-	-	-	-	-	-	-	-	-
JF5370	**Human, Bern, 2012**	**B.13**	**306**	**332**	**255**	**396**	**254**	**480**	**C[a]**	**A[d]**	**G[d]**	**G[a]**	**G[a]**	**G[a]**	**T[d]**	**A[d]**	**C[a]**	**C[a]**	**C[a]**	**T[a]**
JF5340	**Human, Lucerne, 2012**	**B.13**	**306**	**332**	**255**	**396**	**254**	**480**	**C[a]**	**A[d]**	**G[d]**	**G[a]**	**G[a]**	**G[a]**	**T[d]**	**G[a]**	**C[a]**	**C[a]**	**C[a]**	**T[a]**
JF5405	**Hare, Solothurn, 2012**	**B.13**	**306**	**332**	**255**	**396**	**254**	**480**	**C[a]**	**A[d]**	**G[d]**	**G[a]**	**G[a]**	**G[a]**	**T[d]**	**A[d]**	**C[a]**	**C[a]**	**C[a]**	**T[a]**
JF5468	**Hare, St. Gallen, 2013**	**B.13**	**315**	**332**	**255**	**396**	**254**	**480**	**C[a]**	**A[d]**	**G[d]**	**G[a]**	**G[a]**	**G[a]**	**T[d]**	**G[a]**	**C[a]**	**C[a]**	**C[a]**	**T[a]**

–: not available; MLVA: multilocus variable-number tandem repeat analysis; SNPs: single nucleotide polymorphisms.

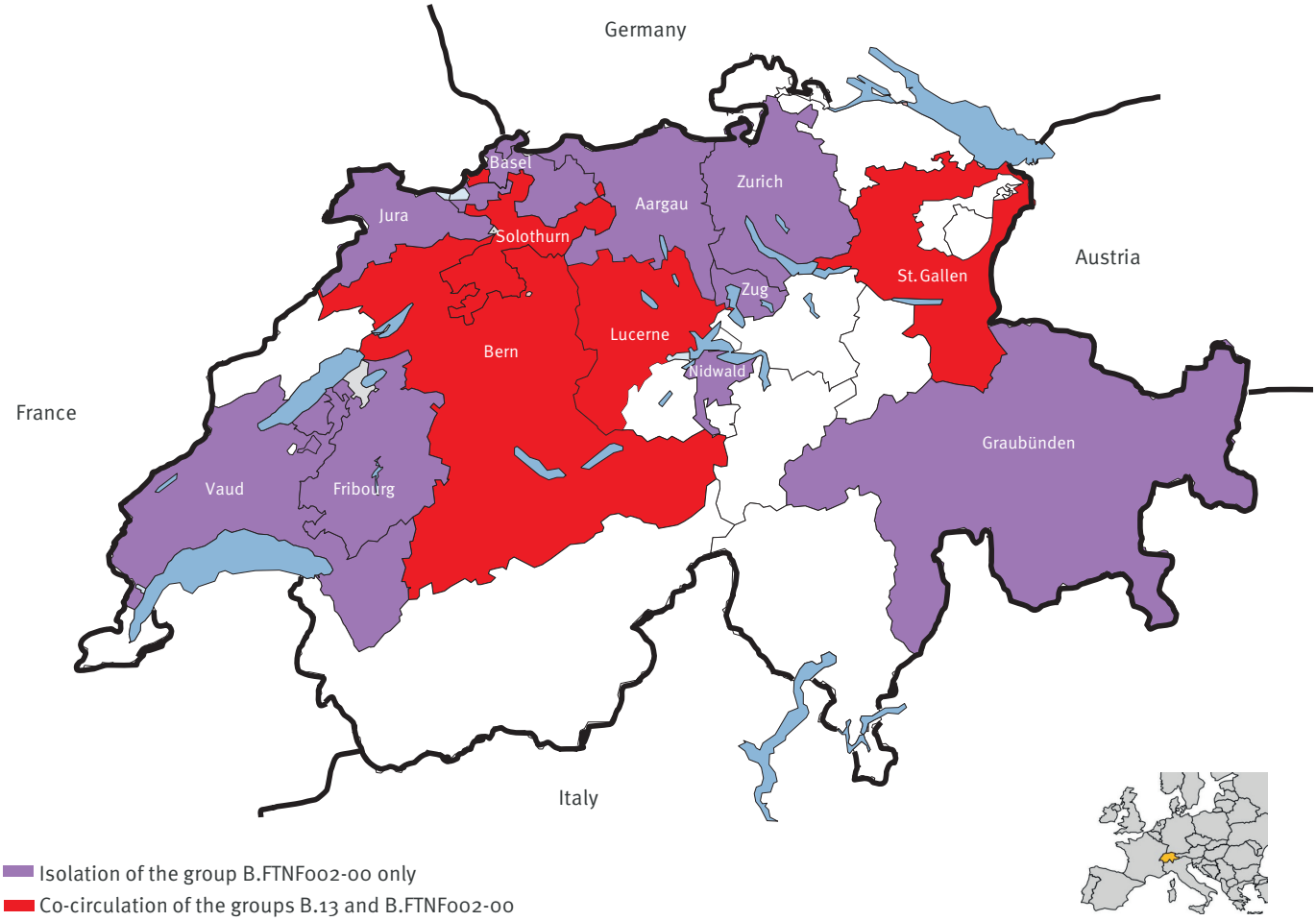
Strains selected for further analysis (canSNPs and antimicrobial agent susceptibilities, n=24) are shaded in grey. Strains belonging to the clade B.13 are highlighted in bold.

[a] Ancestral state.

[d] Derived state.

Figure 2

Francisella tularensis subsp. *holarctica* isolated in Switzerland, 1996–2013 (n=61)



Cantons where both groups B.FTNF002-00 and B.13 were circulating are coloured in red, while cantons where only the group B.FTNF002-00 was isolated are coloured in purple.

Map background downloaded from http://www.presentationmagazine.com/

tetracycline ranged between 2 and 8 µg/mL in mMHII, but were all ≤0.25 µg/mL in mCAMHB (Table 2). For this reason, MIC values for tetracycline were also tested by Etest in order to confirm the results obtained with mCAMHB. With this method, MIC values for tetracycline ranged between 0.19 and 0.38 µg/mL, which was similar to the ones measured by broth microdilution method with mCAMHB (Table 2). The breakpoint value given in the CLSI guidelines for tetracycline is ≤4 µg/mL [27]. Moreover, a difference in MIC values for tetracycline in mMHII and mCAMHB was also observed for reference strains *E. coli* ATCC 25922 and *S. aureus* ATCC 29213 (Table 2). MIC values for erythromycin exhibited a bimodal distribution: Strains belonging to group B.13 exhibited erythromycin resistance with MIC values higher than 32 µg/mL, while all the strains belonging to group B.FTNF002-00 were sensitive to erythromycin, showing MIC values ranging from 1 to 8 µg/mL (Table 2). However, no breakpoint value for *F. tularensis* is provided for any macrolides in the CLSI guidelines [27].

Genetic characterisation of erythromycin resistance was performed by PCR amplification and sequencing of the three copies of the *rrl* gene and of the *rplD* and the *rplV* genes of the five strains showing phenotypic resistance to erythromycin and belonging to group B.13 (JF4830, JF5340, JF5370, JF5405 and JF5468). The sequences were compared to the corresponding genes of strains FTNF002-00 (group B.FTNF002-00), F92 (group B.FTNF002-00), FSC200 (group B.13) and LVS (group B.13). All five strains isolated in Switzerland, belonging to group B.13 and showing phenotypic resistance to erythromycin, had two mutations in all three copies of the *rrl* gene when compared to the available sequences of the strains FTNF002-00 and F92 of the group B.FTNF002-00. The first mutation was detected in domain I of the *rrl* gene, A453G (*E. coli* numbering), while the second mutation was observed in domain V of the *rrl* gene, A2059C (*E. coli* numbering). A silent mutation G to A at the third position of codon 181 (*E. coli* numbering) was found in the *rplD* gene encoding

Table 2

Antibiotic susceptibilities of *Francisella tularensis* subsp. *holarctica* strains after 48 hours in mMHII broth and mCAMH, Switzerland, 1996–2013 (n=24)

Strain	Subgroup according to [12] and [13]	mMHII broth MIC (µg/mL)							mCAMH broth MIC (µg/mL)						
		GEN	STR	CIP	TET	ERY	NAL	CHL	GEN	STR	CIP	TET	ERY	NAL	CHL
Escherichia coli ATCC 25922		8	16	≤0.06	>16	>32	≤2	4	0.5	>16	≤0.06	2	>32	≤2	4
Staphylococus aureus ATCC 29213		8	16	0.5	16	2	32	16	1	>16	0.5	1	2	32	16
JF3820	B.FTNF002-00	4	4	≤0.06	4	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3821	B.FTNF002-00	2	4	≤0.06	2	1	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3822	B.FTNF002-00	4	4	≤0.06	4	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3824	B.FTNF002-00	4	4	≤0.06	8	4	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3825	B.FTNF002-00	4	4	≤0.06	8	4	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3826	B.FTNF002-00	2	4	≤0.06	4	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3828	B.FTNF002-00	2	4	≤0.06	8	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3829	B.FTNF002-00	2	4	≤0.06	4	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF3859	B.FTNF002-00	2	4	≤0.06	8	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF4092	B.FTNF002-00	2	2	≤0.06	4	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF4128	B.FTNF002-00	2	2	≤0.06	8	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF4212	B.FTNF002-00	1	2	≤0.06	4	1	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF4242	B.FTNF002-00	2	4	≤0.06	8	2	≤2	≤2	≤0.12	4	≤0.06	≤0.25	4	≤2	≤2
JF4830	B.13	2	2	≤0.06	4	>32	≤2	≤2	0.25	4	≤0.06	≤0.25	>32	≤2	≤2
JF5340	B.13	2	4	≤0.06	4	>32	≤2	≤2	≤0.12	4	≤0.06	≤0.25	>32	≤2	≤2
JF5349	B.FTNF002-00	2	4	≤0.06	4	8	≤2	≤2	0.25	4	≤0.06	≤0.25	4	≤2	≤2
JF5350	B.FTNF002-00	2	4	≤0.06	4	2	≤2	≤2	0.25	4	≤0.06	≤0.25	2	≤2	≤2
JF5353	B.FTNF002-00	2	4	≤0.06	4	1	≤2	≤2	0.25	4	≤0.06	≤0.25	2	≤2	≤2
JF5370	B.13	2	2	≤0.06	4	>32	≤2	≤2	≤0.12	4	≤0.06	≤0.25	>32	≤2	≤2
JF5373	B.FTNF002-00	2	2	≤0.06	4	2	≤2	≤2	0.25	4	≤0.06	≤0.25	2	≤2	≤2
JF5380	B.FTNF002-00	2	4	≤0.06	4	2	≤2	≤2	0.25	4	≤0.06	≤0.25	2	≤2	≤2
JF5405	B.13	2	4	≤0.06	4	>32	≤2	≤2	≤0.12	4	≤0.06	≤0.25	>32	≤2	≤2
JF5409	B.FTNF002-00	2	4	≤0.06	4	4	≤2	≤2	0.25	4	≤0.06	≤0.25	8	≤2	≤2
JF5468	B.13	2	4	≤0.06	4	>32	≤2	≤2	≤0.12	4	≤0.06	≤0.25	>32	≤2	≤2

CHL: chloramphenicol; CIP: ciprofloxacin; ERY: erythromycin; GEN: gentamicin; mCAMH: modified cation-adjusted Mueller Hinton broth; MIC: minimum inhibitory concentration; mMHII: modified Mueller Hinton II broth; NAL: nalidixic acid; STR: streptomycin; TET: tetracycline.

for the ribosomal protein L4, while no mutation was detected in the *rplV* gene encoding for the ribosomal protein L22. These mutations observed in Swiss strains belonging to group B.13 were exactly the same as those of the strain LVS and FSC200 belonging to group B.13.

The EMBL/GenBank accession numbers for the nucleotide sequences of the *rrl*, the *rplD* and the *rplV* genes are: KF712467, KF712466 and KF712465, respectively.

Discussion

This study describes the characterisation of *F. tularensis* strains isolated in Switzerland during the last 17 years. Until 2012, only strains belonging to group B.FTNF002-00 have been isolated in Switzerland from humans and animals. A single exception is strain JF4830 that was isolated from a human patient in 2010, who most probably acquired the infection travelling in eastern Europe. The new strains JF5340 and JF5370 were isolated from human patients with no history of travelling abroad for several months before the appearance of the first tularaemia-associated symptoms. The only exception is a stay at Lago Maggiore in Italy, at the border to Switzerland, a month before the initial symptoms, for the patient infected with strain JF5340. Strains JF5405 and JF5468 were isolated from the carcass of two wild hares in 2013. All four strains (JF5340, JF5370, JF5405 and JF5468) belonged to group B.13 and resolved with distinct MLVA profiles (Table 1). Moreover, the analysis of canSNP B.33 to B.38 led to identification of the subgroups B.33/34 and B. 34/35 previously described by Gyuranecz et al. [12]. Both subgroups were isolated in central and eastern Europe and from countries bordering Switzerland, such as Austria and Germany, but not from countries east of Romania [12]. Moreover, the subgroup B.33/34 is also known to be circulating in Sweden [12].

These findings reveal that group B.13 is currently circulating in Switzerland in the same areas as strains of group B.FTNF002-00 (Figure 2) and are affecting both human patients and free-ranging animals. This is in contrast to neighbouring Germany, where a strict separation between groups was described [18]. Strains isolated between 1996 and 2011 from humans, hares and captive non-human primates all belonged to group B.FTNF002-00. Because of the small number of strains isolated between 1996 and 2008, it is difficult to draw conclusions about a recent introduction of strains belonging to group B.13 or a long-lasting co-circulation of both groups following the expansion of group B.FTNF002-00 of *F. tularensis* subsp. holarctica.

Strains belonging to group B.FTNF002-00 are known to be sensitive to erythromycin [7,29,33]. Also the Swiss *F. tularensis* subsp. *holarctica* strains belonging to group B.FTNF002-00 are sensitive to erythromycin, while the new strains belonging to group B.13 are resistant (Table 2). Since strains resistant to erythromycin are actually circulating in Switzerland, macrolides are not recommended for the treatment of cases of tularaemia acquired in Switzerland and possibly also in neighbouring areas unless analysis of the infecting strains reveals sensitivity to this antibiotic. Because of the toxicity of recommended antibiotics against tularaemia for pregnant women and foetuses, Dentan et al. [21] proposed to treat it, in areas where the group B.FTNF002-00 is endemic, with a macrolide, more specifically with azithromycin. However, the spread to western Europe of strains resistant to macrolides poses serious concerns and needs to be carefully considered by the clinicians when facing a therapeutic choice in this context. Several studies suggest that strains of *F. tularensis* from western Europe are sensitive to macrolides [4,7,18,29,33,34].

Genetic analysis of the strains resistant to erythromycin revealed two mutations in the three copies of the *rrl* gene and a silent mutation in the *rlpD* gene encoding the ribosomal protein L4, compared with the strains belonging to group B.FTNF002-00: FTNF002-00 and F92. Interestingly, the same mutations are present in the strains LVS and FSC200, both belonging to group B.13. This finding may suggest that these mutations are shared among subgroups belonging to B.13 and may have appeared in a common ancestor. However, this hypothesis should be validated by testing a larger panel of strains.

Broth microdilution testing was performed in mMHII broth and in mCAMHB [4,7]. Results were compatible for all antibiotics tested in both media except for the MIC values recorded for gentamicin and tetracycline that showed higher values in mMHII broth than in mCAMHB (Table 2). This discrepancy was confirmed by testing the reference strains, *E. coli* ATCC 25922 and *S. aureus* ATCC 29213, which also showed higher MIC values for gentamicin and tetracycline in mMHII broth than the quality control ranges for broth microdilution method in mCAMHB reported in the CSLI guidelines [27], confirming that MIC values for these two antibiotics are higher using mMHII broth than mCAMHB (Table 2). High MIC values of reference strains for gentamicin and to a lesser extent for tetracycline tested in mMHII broth were previously described by Baker et al. [35]. They explained these results to be due to the addition of the bivalent cations Ca^{2+} and Mg^{2+} in the medium. MIC values for tetracycline were within the range considered clinically effective when tested with mCAMHB and by Etest. Nevertheless, given the high number of tularaemia cases for whom tetracycline-associated treatment failure has been described, including doxycycline [36-39], these antibiotics are not recommended in case of infection with *F. tularensis*.

MIC values for gentamicin, chloramphenicol, streptomycin and ciprofloxacin were within the range indicative of clinical efficacy in both media, although MIC values of four strains for gentamicin in mMHII were very close to the breakpoint value given in the CLSI guidelines [27]. Ciprofloxacin showed the lowest MIC values and prevented growth of all strains at 0.06 µg/

mL. The finding is consistent with previous reports on type A and type B tularaemia [5, 40-44] and supports the experience that ciprofloxacin may be an attractive treatment option for tularaemia [37].

Conclusion

In conclusion, at least two groups of *F. tularensis* subsp. *holarctica* are currently co-circulating in Switzerland. Of these, the group B.FTNF002-00 seems to be more prevalent and has been identified in tularaemia cases since 1996, while B.13 was less commonly isolated in Switzerland and not before 2012. Since strains belonging to the subgroups B.33/34 and B.34/35 are erythromycin-resistant, this antibiotic is not recommended to treat cases of tularaemia acquired in Switzerland without prior typing of the strains. These concerns should also apply in countries where the group B.FTNF002-00 seems to be prevalent given that the exact limits of the co-circulation areas are not known. The mutations resulting in erythromycin resistance in group B.13 strains are exactly the same as those present in the strain LVS belonging to the same group. Further investigations are warranted in order to understand if they are shared by all strains of the group B.13. In view of the in vitro results and of previous clinical observations, tetracyclines should not be a first choice of treatment for tularaemia, while ciprofloxacin appears suitable for tularaemia treatment. Moreover, because of the fastidious growth requirements of F. tularensis, supplements always need to be added to growth media to test antibiotic susceptibility [7,35]. Recently, Georgi et al. published the validation of a protocol for a broth microdilution method (medium not supplemented with divalent cations) for *F. tularensis* [4]. The use of a medium without supplemented divalent cations, mCAMH, has been compared with the previously described methods using mMHII broth (medium supplemented with divalent cations). Considering the discrepancy in the MIC values measured for gentamicin and tetracycline depending on the broth used, it is considered more appropriate the use of mCAMHB for antimicrobial testing of *F. tularensis* strains because it achieves results, at least relatively to some antimicrobial substances, that are less ambiguous than those achieved with the mMHII broth.

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Conflict of interest

None declared.

Authors' contributions

FCO: performed the experiments, analysed the data, drafted and revised the manuscript. JF: analysed the data and critically revised the manuscript. PP: designed the study, performed the experiments, analysed the data, drafted and revised the manuscript.

References

1. Johansson A, Tomaso H, Padeshki P, Sjöstedt A, Silman N, Pilo P. Francisella tularensis: Tularemia. In: Elschner M, Cutler SJ, Weidmann M, Butaye P, editors. BSL3 and BSL4 Agents: Epidemiology, Microbiology, and Practical Guidelines. Weinheim: Wiley-Blackwell; 2012. http://dx.doi.org/10.1002/9783527645114.ch6 http://dx.doi.org/10.1002/9783527645114.ch20
2. Martin C, Gallardo MT, Mateos L, Vián E, García MJ, Ramos J, et al. Outbreak of tularaemia in Castilla y León, Spain. Euro Surveill. 2007;12(45): pii=3302.
3. Kreizinger Z, Makrai L, Helyes G, Magyar T, Erdelyi K, Gyuranecz M. Antimicrobial susceptibility of Francisella tularensis subsp. *holarctica* strains from Hungary, Central Europe. J Antimicrob Chemother. 2013;68(2):370-3. http://dx.doi.org/10.1093/jac/dks399
4. Georgi E, Schacht E, Scholz HC, Splettstoesser WD. Standardized broth microdilution antimicrobial susceptibility testing of Francisella tularensis subsp. holarctica strains from Europe and rare Francisella species. J Antimicrob Chemother. 2012;67(10):2429-33. http://dx.doi.org/10.1093/jac/dks238
5. Tomaso H, Al Dahouk S, Hofer E, Splettstoesser WD, Treu TM, Dierich MP, et al. Antimicrobial susceptibilities of Austrian Francisella tularensis holarctica biovar II strains. Int J Antimicrob Agents. 2005;26(4):279-84. http://dx.doi.org/10.1016/j.ijantimicag.2005.07.003
6. Antunes NT, Frase H, Toth M, Vakulenko SB. The Class A -Lactamase FTU-1 is Native to Francisella tularensis. Antimicrob Agents Chemother. 2012;56(2):666-71. http://dx.doi.org/10.1128/AAC.05305-11
7. García del Blanco N, Gutíerrez Martín CB, de la Puente Redondo VA, Rodríguez Ferri EF. In vitro susceptibility of field isolates of Francisella tularensis subsp. holarctica recovered in Spain to several antimicrobial agents. Res Vet Sci. 2004;76(3):195-8. http://dx.doi.org/10.1016/j.rvsc.2003.12.002
8. Sutera V, Levert M, Burmeister WP, Schneider D, Maurin M. Evolution toward high-level fluoroquinolone resistance in Francisella species. J Antimicrob Chemother. 2014;69(1):101-10. http://dx.doi.org/10.1093/jac/dkt321
9. Johansson A, Farlow J, Larsson P, Dukerich M, Chambers E, Byström M, et al. Worldwide genetic relationships among Francisella tularensis isolates determined by multiple-locus variable-number tandem repeat analysis. J Bacteriol. 2004;186(17):5808-18. http://dx.doi.org/10.1128/JB.186.17.5808-5818.2004
10. Larsson P, Svensson K, Karlsson L, Guala D, Granberg M, Forsman M, et al. Canonical insertion-deletion markers for rapid DNA typing of Francisella tularensis. Emerg Infect Dis. 2007;13(11):1725-32. http://dx.doi.org/10.3201/eid1311.070603
11. Svensson K, Granberg M, Karlsson L, Neubauerova V, Forsman M, Johansson A. A real-time PCR array for hierarchical identification of Francisella isolates. PLoS One. 2009;4(12):e8360. http://dx.doi.org/10.1371/journal.pone.0008360
12. Gyuranecz M, Birdsell DN, Splettstoesser W, Seibold E, Beckstrom-Sternberg SM, Makrai L, et al. Phylogeography of Francisella tularensis subsp. holarctica, Europe. Emerg Infect Dis. 2012;18(2):290-3. http://dx.doi.org/10.3201/eid1802.111305
13. Vogler AJ, Birdsell D, Price LB, Bowers JR, Beckstrom-Sternberg SM, Auerbach RK, et al. Phylogeography of Francisella tularensis: global expansion of a highly fit clone. J Bacteriol. 2009;191(8):2474-84. http://dx.doi.org/10.1128/JB.01786-08
14. Chanturia G, Birdsell DN, Kekelidze M, Zhgenti E, Babuadze G, Tsertsvadze N, et al. Phylogeography of Francisella tularensis subspecies holarctica from the country of Georgia. BMC

Microbiol. 2011;11:139.
http://dx.doi.org/10.1186/1471-2180-11-139

15. Vogler AJ, Birdsell DN, Lee J, Vaissaire J, Doujet CL, Lapalus M, et al. Phylogeography of Francisella tularensis ssp. holarctica in France. Lett Appl Microbiol. 2011;52(2):177-80. http://dx.doi.org/10.1111/j.1472-765X.2010.02977.x
16. Dempsey MP, Dobson M, Zhang C, Zhang M, Lion C, Gutiérrez-Martín CB, et al. Genomic deletion marking an emerging subclone of Francisella tularensis subsp. holarctica in France and the Iberian Peninsula. Appl Environ Microbiol. 2007;73(22):7465-70. http://dx.doi.org/10.1128/AEM.00646-07
17. Pilo P, Johansson A, Frey J. Identification of Francisella tularensis cluster in central and western Europe. Emerg Infect Dis. 2009;15(12):2049-51. http://dx.doi.org/10.3201/eid1512.080805
18. Müller W, Hotzel H, Otto P, Karger A, Bettin B, Bocklisch H, et al. German Francisella tularensis isolates from European brown hares (Lepus europaeus) reveal genetic and phenotypic diversity. BMC Microbiol. 2013;13:61. http://dx.doi.org/10.1186/1471-2180-13-61
19. Gehringer H, Schacht E, Maylaender N, Zeman E, Kaysser P, Oehme R, et al. Presence of an emerging subclone of Francisella tularensis holarctica in Ixodes ricinus ticks from south-western Germany. Ticks Tick Borne Dis. 2013;4(1-2):93-100. http://dx.doi.org/10.1016/j.ttbdis.2012.09.001
20. Kudelina RI, Olsufiev NG. Sensitivity to macrolide antibiotics and lincomycin in Francisella tularensis holarctica. J Hyg Epidemiol Microbiol Immunol. 1980;24(1):84-91.
21. Dentan C, Pavese P, Pelloux I, Boisset S, Brion JP, Stahl JP, et al. Treatment of tularemia in pregnant woman, France. Emerg Infect Dis. 2013;19(6):996-8. http://dx.doi.org/10.3201/eid1906.130138
22. Maho A, Rossano A, Hächler H, Holzer A, Schelling E, Zinsstag J, et al. Antibiotic susceptibility and molecular diversity of Bacillus anthracis strains in Chad: detection of a new phylogenetic subgroup. J Clin Microbiol. 2006;44(9):3422-5. http://dx.doi.org/10.1128/JCM.01269-06
23. Wicki R, Sauter P, Mettler C, Natsch A, Enzler T, Pusterla N, et al. Swiss Army Survey in Switzerland to determine the prevalence of Francisella tularensis, members of the Ehrlichia phagocytophila genogroup, Borrelia burgdorferi sensu lato, and tick-borne encephalitis virus in ticks. Eur J Clin Microbiol Infect Dis. 2000;19(6):427-32. http://dx.doi.org/10.1007/s100960000283
24. Broekhuijsen M, Larsson P, Johansson A, Bystrom M, Eriksson U, Larsson E, et al. Genome-wide DNA microarray analysis of Francisella tularensis strains demonstrates extensive genetic conservation within the species but identifies regions that are unique to the highly virulent F. tularensis subsp. tularensis. J Clin Microbiol. 2003;41(7):2924-31. http://dx.doi.org/10.1128/JCM.41.7.2924-2931.2003
25. Byström M, Böcher S, Magnusson A, Prag J, Johansson A. Tularemia in Denmark: identification of a Francisella tularensis subsp. holarctica strain by real-time PCR and high-resolution typing by multiple-locus variable-number tandem repeat analysis. J Clin Microbiol. 2005;43(10):5355-8. http://dx.doi.org/10.1128/JCM.43.10.5355-5358.2005
26. Clinical and Laboratory Standards Institute (CLSI). Approved standard M07-A8. In: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. 8th ed. Wayne: CLSI; 2009;29(2).
27. Clinical and Laboratory Standards Institute (CLSI). Approved guideline M45-A2. In: Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria. 2nd ed. Wayne: Clinical and Laboratory Standards Institute; 2010;30(18).
28. Bina XR, Wang C, Miller MA, Bina JE. The Bla2 beta-lactamase from the live-vaccine strain of Francisella tularensis encodes a functional protein that is only active against penicillin-class beta-lactam antibiotics. Arch Microbiol. 2006;186(3):219-28. http://dx.doi.org/10.1007/s00203-006-0140-6
29. Gestin B, Valade E, Thibault F, Schneider D, Maurin M. Phenotypic and genetic characterization of macrolide resistance in Francisella tularensis subsp. holarctica biovar I. J Antimicrob Chemother. 2010;65(11):2359-67. http://dx.doi.org/10.1093/jac/dkq315
30. Splettstoesser WD, Mätz-Rensing K, Seibold E, Tomaso H, Al Dahouk S, Grunow R, et al. Re-emergence of Francisella tularensis in Germany: fatal tularaemia in a colony of semi-free-living marmosets (Callithrix jacchus). Epidemiol Infect 2007; 135(8):1256-65. http://dx.doi.org/10.1017/S0950268807008035
31. Svensson K, Back E, Eliasson H, Berglund L, Granberg M, Karlsson L, et al. Landscape epidemiology of tularemia outbreaks in Sweden. Emerg Infect Dis. 2009;15(12):1937-47. http://dx.doi.org/10.3201/eid1512.090487
32. Karlsson E, Svensson K, Lindgren P, Byström M, Sjodin A, Forsman M, et al. The phylogeographic pattern of Francisella tularensis in Sweden indicates a Scandinavian origin of Eurosiberian tularaemia. Environ Microbiol. 2013;15(2):634-45. http://dx.doi.org/10.1111/1462-2920.12052
33. Abril C, Nimmervoll H, Pilo P, Brodard I, Korczak B, Seiler M, et al. Rapid diagnosis and quantification of Francisella tularensis in organs of naturally infected common squirrel monkeys (Saimiri sciureus). Vet Microbiol. 2007;127(1-2):203-8. http://dx.doi.org/10.1016/j.vetmic.2007.08.006
34. Valade E, Vaissaire J, Mérens A, Hernandez E, Gros C, Le Doujet C, et al. Susceptibility of 71 French isolates of Francisella tularensis subsp. holarctica to eight antibiotics and accuracy of the Etest method. J Antimicrob Chemother. 2008;62(1):208-10. http://dx.doi.org/10.1093/jac/dkn146
35. Baker CN, Hollis DG, Thornsberry C. Antimicrobial susceptibility testing of Francisella tularensis with a modified Mueller-Hinton broth. J Clin Microbiol. 1985;22(2):212-5.
36. Enderlin G, Morales L, Jacobs RF, Cross JT. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. Clin Infect Dis. 1994;19(1):42-7. http://dx.doi.org/10.1093/clinids/19.1.42
37. Tärnvik A, Chu MC. New approaches to diagnosis and therapy of tularemia. Ann N Y Acad Sci. 2007;1105:378-404. http://dx.doi.org/10.1196/annals.1409.017
38. Penn RL, Kinasewitz GT. Factors associated with a poor outcome in tularemia. Arch Intern Med. 1987;147(2):265-8. http://dx.doi.org/10.1001/archinte.1987.00370020083041 http://dx.doi.org/10.1001/archinte.147.2.265
39. Pérez-Castrillón JL, Bachiller-Luque P, Martín-Luquero M, Mena-Martín FJ, Herreros V. Tularemia epidemic in northwestern Spain: clinical description and therapeutic response. Clin Infect Dis. 2001;33(4):573-6. http://dx.doi.org/10.1086/322601
40. Johansson A, Berglund L, Gothefors L, Sjöstedt A, Tärnvik A. Ciprofloxacin for treatment of tularemia in children. Pediatr Infect Dis J. 2000;19(5):449-53. http://dx.doi.org/10.1097/00006454-200005000-00011
41. Scheel O, Hoel T, Sandvik T, Berdal BP. Susceptibility pattern of Scandinavian Francisella tularensis isolates with regard to oral and parenteral antimicrobial agents. APMIS. 1993;101(1):33-6. http://dx.doi.org/10.1111/j.1699-0463.1993.tb00077.x
42. Ikäheimo I, Syrjälä H, Karhukorpi J, Schildt R, Koskela M. In vitro antibiotic susceptibility of Francisella tularensis isolated from humans and animals. J Antimicrob Chemother. 2000;46(2):287-90. http://dx.doi.org/10.1093/jac/46.2.287
43. García Del Blanco N, Gutiérrez CB, De La Puente V, Rodríguez Ferri EF. Biochemical characterisation of Francisella tularensis strains isolated in Spain. Vet Rec. 2004;154(2):55-6. http://dx.doi.org/10.1136/vr.154.2.55
44. Johansson A, Urich SK, Chu MC, Sjöstedt A, Tärnvik A. In vitro susceptibility to quinolones of Francisella tularensis subspecies tularensis. Scand J Infect Dis. 2002;34(5):327-30. http://dx.doi.org/10.1080/00365540110080773

Surveillance for outbreaks of gastroenteritis in elderly long-term care facilities in France, November 2010 to May 2012

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This article describes outbreaks of gastroenteritis in elderly long-term care facilities (LTCF) in France from November 2010 to May 2012 reported through the surveillance system for gastroenteritis outbreaks in LTCF. A total of 1,072 outbreaks were reported, causing 26,551 episodes of illness and 60 deaths. The median attack rate (AR) among residents was 32%. Norovirus and person-to-person transmission were the most frequently reported aetiology and mode of transmission. Control measures were implemented in 1,054 (98%) outbreaks and for 928 outbreaks, the timing of such measures could be inferred. Of these, 799 (86%) had put control measures into effect within three days of the occurrence of the first case. Outbreaks of gastroenteritis in LTCF cause substantial morbidity and mortality among elderly people in France. LTCF are encouraged to develop infection prevention and control plans and to notify any gastroenteritis outbreak to health authorities to ensure rapid control.

Introduction

Outbreaks of gastroenteritis are frequent in elderly long-term care facilities (LTCF). Because of the increased susceptibility and vulnerability of the residents, they can be associated with significant morbidity and mortality [1–3]. Their detection and control can be challenging. Prompt identification, thorough epidemiological and microbiological investigations, and rapid implementation of control measures are key elements to control outbreaks and limit the impact on the residents and the healthcare service.

In France, elderly LTCF were identified as the most frequent setting for gastroenteritis outbreaks between 2006 and 2009 [4]. In 2010, a specific surveillance system for gastrointestinal outbreaks in elderly LTCF was implemented in mainland France as part of a national plan to reduce the risk of infection in healthcare settings [5]. The objectives of the surveillance system were to promote the early notification of outbreaks, to facilitate the implementation of control measures and to describe the epidemiology of outbreaks in elderly LTCF. This system was implemented in addition to the surveillance systems already in operation for the surveillance of acute gastroenteritis in France [6], which include: (i) the surveillance of acute diarrhoeal disease in the general population by the sentinel network of general practitioners since 1990 [7]; (ii) the syndromic surveillance system based on emergency departments morbidity data (OSCOUR) since 2004 [8]; (iii) the notification of gastroenteritis outbreaks in healthcare settings since 2001; (iv) the mandatory notification of foodborne gastroenteritis outbreaks since 1987; and (v) the confirmation and characterisation of enteric viruses at the National Reference Centre (NRC) of enteric viruses.

The surveillance system for gastrointestinal outbreaks in elderly LTCF was deployed by the regional health agencies in coordination with their partners in the prevention of healthcare-associated infections. In some regions (North, East), a pilot study or a pre-existing enhanced surveillance system had already been implemented prior to 2010.

This article describes the gastroenteritis outbreaks that occurred in elderly LTCF in France between November 2010 and May 2012.

Methods

Surveillance system for gastroenteritis outbreaks in elderly long-term care facilities

The surveillance system for gastroenteritis outbreaks in elderly LTCF has been operating since November 2010. It is based on voluntary notification of any gastroenteritis outbreak occurring in LTCF. Acute gastroenteritis is defined as the sudden onset of diarrhoea (i.e. at least two stools more than usual, soft or watery) within 24 hours or the sudden onset of at least two

episodes of vomiting within 24 hours, in the absence of a non-infectious aetiology (e.g. use of laxatives or chronic conditions). An outbreak is defined as at least five cases of gastroenteritis within four days among elderly LTCF residents or staff. The coordinator of elderly LTCF informs the health authorities and transmits a standardised notification form by email or fax. Health authorities can advise on the outbreak management, assist in further microbiological and epidemiological investigations and check that appropriate control measures have been implemented. Stool samples are sent to local or hospital laboratories and/or directly to the NRC for enteric viruses. Noroviruses are detected by real-time reverse transcription-polymerase chain reaction (RT-PCR), as previously described [9,10]. Rotaviruses, astroviruses, adenoviruses and sapoviruses are detected by RT-PCR as previously described [11].

Surveillance data are then entered by the health authorities in a web-based entry application hosted at the French Institute for Public Health Surveillance. This system enables real-time surveillance and exchange of information.

Data collection and study period

According to the national recommendations, a notification form should be sent to the health authorities as soon as an outbreak of gastroenteritis is recognised in a facility. The notification form collects the following information:

- Characteristics of the facility: address, type of facility, number of residents, number of staff members, number of units, mean level of dependence in the facility assessed by the French 'autonomie, gérontologie, groupe isoressources' (AGGIR) grid. This grid is used to classify each resident in six levels of dependence, which are then weighted and scored to calculate the mean level of dependence in the facility (for example, the mean level of dependence would be 1,000 if all residents had completely lost their autonomy and needed a continuous support in all their activities); the mean level of dependence in elderly LTCF in France was 575 in 2007 [12,13];
- Aggregated data on outbreaks: date of notification, number of cases among residents, number of cases among staff members, number of deaths and transfers to acute care facilities among residents, date of symptom onset in first and last case, number of affected units, whether the majority of cases (≥50% cases) present with diarrhoea, whether the majority of cases (≥50% cases) present with vomiting, presence of at least one case with fever ≥38.5°C, presence of at least one case with bloody diarrhoea, estimated mean duration of symptoms (in days or hours), laboratory testing performed, suspected or confirmed aetiological agent;
- Outbreak management and control measures: help needed for the implementation of control measures, implementation of an epidemiological investigation (agency in charge of the investigation, type of investigation: descriptive study, review of cases' food consumption, analytical study), suspected mode of transmission, implemented control measures (predefined list: reinforcement of hand hygiene, contact precautions, cleaning or disinfection, etc.), problems in the management of the outbreak (predefined list: understaffing, organisational problems, financial problems, shortage of materials, other),

Gastroenteritis outbreaks that were notified between 01 November 2010 and 31 May 2012 were included in the study. Winter season was defined as the period from 1 November to 31 May.

Descriptive analysis

Data analysis was conducted using Microsoft Excel 2003 and Stata Version 11. The outbreak notification rate was calculated overall and by region (number of outbreaks reported in the study period divided by the number of elderly LTCF registered in the national administration files [12]). Characteristics of outbreaks and facilities were described as well as investigation and management of outbreaks.

The proportion of affected units was calculated in facilities with at least two units, as the number of affected units divided by the total number of units in the facility reported on the notification form.

The duration of the outbreak was calculated by the difference between the date of symptom onset of the first and last cases. The notification delay was calculated by the difference between the date of symptom onset of the first case and the date of notification to health authorities. The delay in the implementation of control measures was calculated by the difference between the date of symptom onset of the first case and the date of implementation of control measures.

We compared the attack rate (AR) and duration of outbreaks by different characteristics. For categorical variables, rates were compared using Kruskall–Wallis test. For quantitative variables, we computed the Spearman correlation coefficient r. For trend analysis, we used the chi-squared test for trend and the nonparametric Cuzick's test for trend.

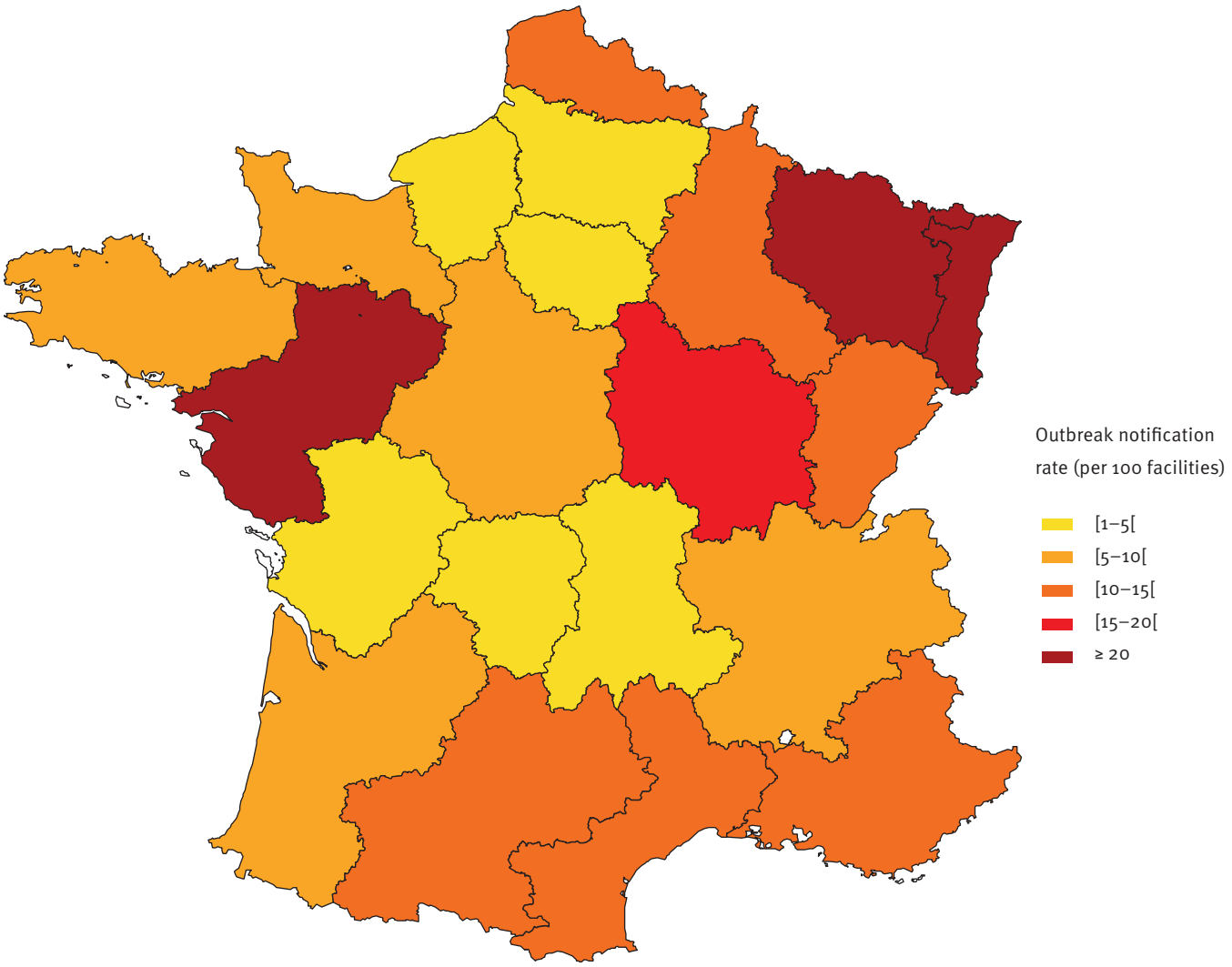
Results

Number of outbreaks and characteristics of the reporting facilities

Of 10,205 elderly LTCF recorded in mainland France in 2007, 1,040 (10%) facilities reported at least one gastroenteritis outbreak between 1 November 2010 and 31 May 2012, yielding a total of 1,072 gastroenteritis outbreaks in these facilities. Over the study period, 1,013 facilities reported one outbreak, 22 facilities reported two outbreaks and five facilities reported three outbreaks.

Figure 1

Outbreak notification rate from elderly long-term care facilities, by region, France, November 2010–May 2012 (n=1,072 outbreaks)



The outbreak notification rates were calculated over the 19 month study period so as to include two winter seasons.

The median number of residents in the facilities was 78 (N=999 outbreaks; range: 12–545). The median number of staff members was 45 (N=794 outbreaks; range: 6–434). The median number of staff member per resident was 0.62 (N=793 outbreaks; range: 0.08–2.5). The median level of dependence among residents was 700 (N=219 outbreaks; range: 3–937). The median number of units in facilities was three (N=715 outbreaks; range: 1–12).

Outbreak reporting by place and time

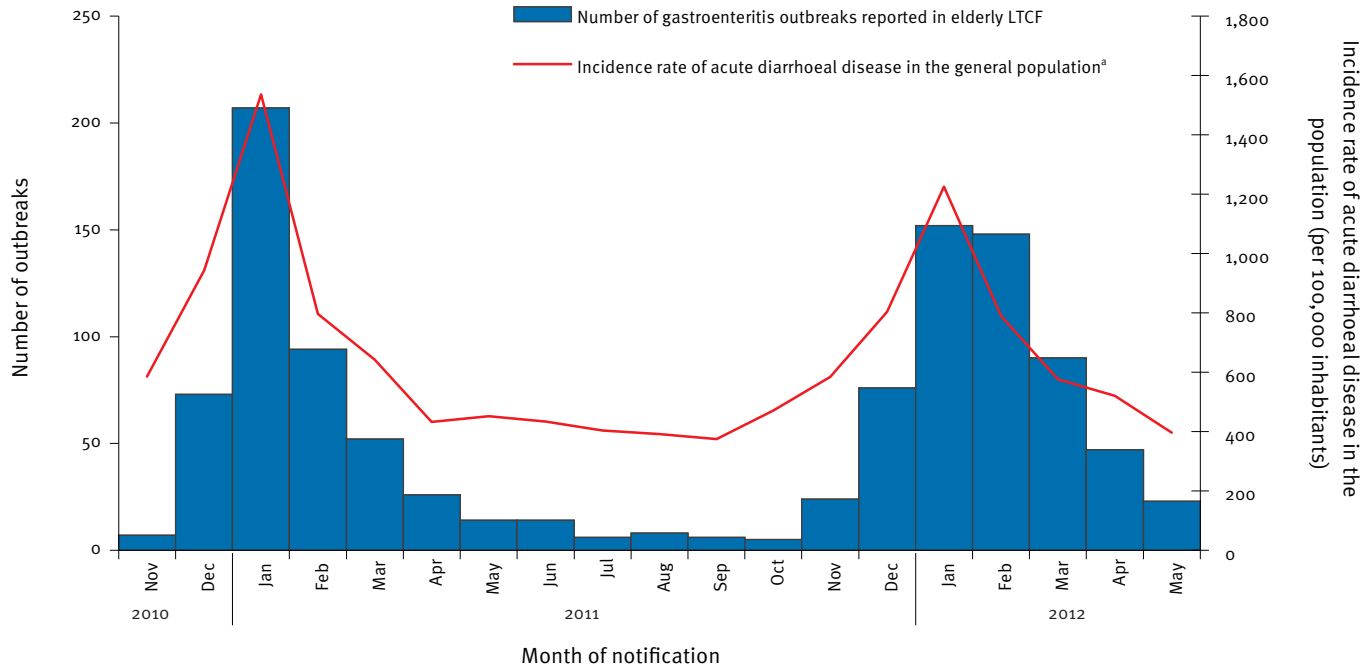
During the 2010/11 winter season, 442 facilities reported 473 outbreaks, giving an outbreak notification rate of 4.6 outbreaks per 100 facilities. During the 2011/12 winter season, 544 facilities reported 560 outbreaks, giving an outbreak notification rate of 5.5 outbreaks per 100 facilities. Over the 19 months study period, there was a great variation in the outbreak notification rate between regions, ranging from 2.7 outbreaks per 100 facilities in Picardie (in the Northern region) to 30.1 outbreaks per 100 facilities in Alsace (in the Eastern region) (Figure 1). As observed by the sentinel network for acute diarrhoeal disease in the general population, the distribution of gastroenteritis outbreaks in elderly LTCF by month followed a seasonal pattern with a peak during winter months (Figure 2).
by month, France, November 2010–May 2012 (n=1,072 outbreaks)

Characteristics of outbreaks

The 1,072 outbreaks caused a total of 26,551 episodes of illness among residents, 5,548 episodes of illness among staff members, 227 transfers to acute care facilities and 60 deaths. Table 1 shows the characteristics of outbreaks. Of 1,025 outbreaks with available information, there were 899 outbreaks (88%) with at least one staff member ill.

Figure 2

Number of gastroenteritis outbreaks reported in elderly long-term care facilities and incidence rate of acute diarrhoeal disease in the general population[a] by month, France, November 2010–May 2012 (n=1,072 outbreaks)



LTCF: long-term care facilities.

[a] Source of data on incidence of acute diarrhoeal disease: Réseau sentinelles, Institut national de la santé et de la recherche médicale (INSERM), Université Pierre et Marie Curie (UPMC) (http://www.sentiweb.fr).

Mode of transmission

Of 429 outbreaks (40%) for which a suspected mode of transmission was specified, person-to-person accounted for 408 (95%) outbreaks, foodborne for 10 (2%) outbreaks, foodborne and person-to-person for six (1%) outbreaks and waterborne for one (<1%) outbreak.

Causative organisms

Laboratory testing was performed in 603 (56%) outbreaks and of these outbreaks, a pathogen was identified in 298 (49%). Norovirus and rotavirus were the most frequent organisms (Table 2). Norovirus and/or rotavirus were identified in 287 (96%) outbreaks. Mixed pathogens were reported in 16 (5%) outbreaks. Of 774 outbreaks without confirmed aetiology (either no laboratory testing or negative laboratory test results), a hypothesis on the causative organism based on clinical or epidemiological information was reported in 182 (24%) outbreaks. Of the latter 182, a viral aetiology was suspected in 179 outbreaks (98%).

Investigation and management of the outbreak

The median delay in notifying the outbreak to health authorities was five days (N=1,062 outbreaks; range: 0–94 days). An epidemiological investigation was conducted in 169 (15.8%) of the total 1,072 outbreaks. It was a descriptive study in 126 outbreaks, a descriptive analysis of cases' food consumption in 22 outbreaks and an analytical study in 12 outbreaks.

Control measures were implemented in 1,054 (98%) outbreaks. Of 928 outbreaks with available information, the median delay between the first case and implementation of control measures was one day (minimum: 0; maximum: 34). In 799 (86%) outbreaks, control measures were implemented within three days after the first case occurred. Considering the total 1,072 outbreaks, control measures put into effect included reinforcement of hand hygiene in 1,015 (95%) outbreaks, contact precautions in 934 (87%), cleaning or disinfection of the environment in 927 (86%), restriction of patient movements in 904 (84%), stopping or limitation of group activities in 617 (58%) outbreaks, measures on food preparation/preservation/distribution in 468 (44%) outbreaks. For the 899 outbreaks comprising at least one ill member of staff, exclusion of symptomatic staff was implemented in 578 (64%).

For 197 (18%) outbreaks, problems in the management of the outbreak were reported: understaffing in 107 (54%) outbreaks, organisational problems in 88 (45%) outbreaks, shortage of materials (e.g. gloves, single-use clothing, etc.) in 23 (12%) outbreaks, financial problems in 11 (6%) outbreaks.

Table 1

Characteristics of gastroenteritis outbreaks reported in elderly long-term care facilities, France, November 2010–May 2012

Characteristics (N=number of outbreaks with available information)	n (%)	Mean	Median	Range
Majority of cases (≥50%) presenting with diarrhoea (N=981)	934 (95)	NA	NA	NA
Majority of cases (≥50%) presenting with vomiting (N=953)	635 (67)	NA	NA	NA
Majority of cases (≥50%) presenting with diarrhoea and vomiting (N=946)	588 (62)	NA	NA	NA
Fever ≥38.5°C (N=882)	205 (23)	NA	NA	NA
Bloody diarrhoea (N=876)	17 (2)	NA	NA	NA
Number of illnesses (residents and staff) (N=1,025)	NA	30.1	26	5–140
Attack rate among residents (%) (N=998)	NA	32.5	30.6	1.3–100
Attack rate among staff members (%) (N=786)	NA	12.4	9.0	0–100
Case fatality rate (%) (N=965)	NA	0.3	0	0–17[a]
Mean duration of symptoms (N=800)	NA	2.2 days	2 days	3 hours–9 days
Duration of outbreak (days) (N=980)	NA	10.1	9	0[b]–57
Proportion of affected units in facilities with at least 2 units (%) (N=526)	NA	82.2	100	1–100

NA: not applicable

[a] For three outbreaks the case fatality rate was 17%. In these outbreaks six cases of illness including one death were reported among residents.

[b] Duration of outbreak: 0 day if the last case occurred the same day than the first case.

In 143 outbreaks (16% of 886 outbreaks with available information), facilities requested some advice from health authorities for the outbreak management and control.

Factors associated with outbreaks characteristics

Laboratory testing was significantly associated with the size of the facility and with the AR among residents. The proportion of outbreaks with laboratory testing increased together with the size of the facility (Table 3, chi-squared test for trend p-value=0.01). The AR among residents was greater in outbreaks with laboratory testing than without laboratory testing (AR=35% vs. 29%, p=0.0001). On the other hand, the AR among residents decreased as the size of the facility (characterised by the number of residents) increased (nonparametric test for trend p-value<0.001).

The AR among residents and staff members were significantly different according to the aetiological agents identified in outbreaks, with highest AR observed in outbreaks due to norovirus or mixed pathogens (including norovirus). Longer duration of outbreaks was observed in outbreaks due to rotavirus or to mixed pathogens (including norovirus). The AR among residents and staff was lower and the duration of outbreaks was shorter when control measures were implemented within three days of date of symptom onset of the first case (Table 4). The case fatality rate (CFR) did not vary significantly according to these parameters.

There was no significant difference in the AR among residents according to the suspected mode of transmission (p=0.61), type of setting (p=0.35), mean level of dependence in the facility (r=-0.01; p=0.79) or number of staff per residents (r=0.04; p=0.16). The CFR did not vary significantly according to these parameters.

Discussion

This study shows that outbreaks of gastroenteritis in elderly LTCF cause substantial morbidity and mortality in France. The most frequent cause of gastroenteritis outbreaks in elderly LTCF is enteric viruses (and particularly norovirus) with spread from person to person, resulting in high AR among residents and staff members. These findings have been described in other countries [3,14–19].

Table 2

List of confirmed aetiological agents in outbreaks reported in elderly long-term care facilities, France, November 2010–May 2012 (n=298 outbreaks)

Aetiological agents	Number of outbreaks with confirmed aetiology (%)
Norovirus	218 (73)
Rotavirus	58 (19)
Norovirus and rotavirus	11 (4)
Clostridium difficile	4 (1)
Salmonella	2 (<1)
Norovirus and *C. difficile*	2 (<1)
Norovirus and *Salmonella*	1 (<1)
C. difficile and *Campylobacter* species	1 (<1)
Norovirus and rotavirus and *C. difficile*	1 (<1)

Table 3

Characteristics of outbreaks in relation with the size of the elderly long-term care facility, France, November 2010–May 2012

Size of the facility (number of residents)	Number of outbreaks with laboratory testing (%)	Mean AR among residents (%) (p25–p75)
0–49	66 (54)	40.1 (25.5–55.5)
50–74	175 (58)	33.6 (18.5–46.5)
75–100	194 (59)	32.5 (19.1–44.9)
100–149	82 (63)	27.8 (14.5–37.3)
≥150	46 (74)	19.1 (7.9–24.8)

AR: attack rate; p25–p75: 25th–75th percentile.

Some of the results are subject to bias inherent to the voluntary and passive nature of the surveillance system. We observed a great variation in the outbreak notification rate between regions. Since the outbreak notification rate is not influenced by the disparity in the number of facilities in different regions, this variation probably reflects differences in investigation policies and reporting to health authorities. Indeed higher rates were observed in regions, which implemented specific studies or enhanced surveillance systems for outbreaks in elderly LTCF [20,21]. The true burden of outbreaks in elderly LTCF is probably greatly underestimated, especially in regions, which had a low outbreak notification rate. It is also possible that large or more severe outbreaks were more frequently reported than others. However, if under-reporting is constant over time, trends can be monitored. In our study, the impact of the under-reporting bias seems to be stable over the entire study period since we observed the same seasonal pattern in the surveillance system for gastroenteritis outbreaks in elderly LTCF and in the surveillance of the incidence rate of acute diarrhoeal disease in the general population from the sentinel network from November 2010 to April 2012. The surveillance system for outbreaks in elderly LTCF could be an additional system (complementary to the existing one) to detect the beginning of seasonal gastroenteritis every year.

In France, outbreaks suspected to be linked to food (in any setting) are mandatory notifiable through a specific surveillance system for point source foodborne outbreaks. Data collected on foodborne outbreaks in LTCF through the mandatory system were not included in this study. Since outbreaks are not necessarily notified in both systems, we may have underestimated the frequency of foodborne outbreaks in elderly LTCF.

In approximately half of the outbreaks, laboratory testing had been performed to confirm the aetiological agent. The frequency of laboratory testing was associated with the size of the LTCF and with the AR among residents, with a greater proportion of laboratory testing in larger facilities and in outbreaks with a greater AR. It is important to continue to perform microbiological testing using standardised reference techniques on a substantial proportion of outbreaks in order to document the circulating strains/viruses and characterise them. However the microbiological investigation should not influence the outbreak management since the delay in getting the results can be long (and these sometimes become available when the outbreak is over). The outbreak control measures should be implemented as soon as possible based on the first clinical information and the suspected aetiological agent.

In half of outbreaks with laboratory testing, the aetiological agent was not reported, possibly because laboratory results were negative or because results were not updated in the database following reception of laboratory results.

Norovirus outbreaks in LTCF can be challenging to control because of the infectivity of the virus, the

Table 4

Comparison of attack rate and duration of outbreaks in elderly long-term care facilities according to aetiological agent and delay in implementing control measures, France, November 2010–May 2012

Characteristics	Median AR among residents (%) (p25–p75)	P-value (Kruskal–Wallis)	Median AR among staff (%) (p25–p75)	P-value (Kruskal–Wallis)	Median duration of outbreaks in days (p25–p75)	P-value (Kruskal–Wallis)
Pathogens						
Norovirus	38.2 (24.1–50.0)	0.004	11.6 (5.9–24.1)	0.0001	10 (6–13)	0.006
Rotavirus	28.2 (16.4–37.9)		3.8 (2.1–9.8)		13 (8–17)	
Clostridium difficile	32.5 (18.8–44.2)		6.7 (2.7–7.5)		10 (8.5–15.5)	
Salmonella	18.6 (5.7–31.5)		12.2 (0–24.1)		4.5 (3–6)	
Mixed pathogens	34.3 (23.5–51.7)		18.1 (1.4–26.0)		13 (9.5–18.5)	
Delay in implementing control measures after first case						
Within 3 days	30.3 (17.0–45.3)	0.002	8.6 (3.6–16.7)	0.002	8 (5–12)	0.0001
After 3 days	35.0 (24.4–46.3)?		13.3 (5.9–20.6)		12 (8–17)	

AR: attack rate; p25-p75: 25th–75th percentile.

environmental persistence and the possible long-term shedding by cases [22,23]. In our analysis, control measures had been implemented in a large proportion of outbreaks (98%), suggesting that recommendations on managing gastrointestinal outbreaks in LTCF are well known and applied. However reported outbreaks are probably better managed and this proportion may not reflect the true knowledge and practices of LTCF when an outbreak occurs.

The efficacy of each specific control measure was not specifically studied but implementation of control measures tends to be associated with a lower AR and shorter duration of the outbreak when implemented within three days after the first case occurred This was also observed in a study of norovirus outbreaks in the Netherlands [24]. Of note, in our study, some control measures were less frequently implemented than others (e.g. exclusion of symptomatic staff members, limitation of group activities) although they can contribute to prevent transmission in outbreaks with person-to-person transmission [14]. Given the high proportion of outbreaks with at least one staff member ill (88%) and their possible role in the transmission of infection to the residents, requiring that ,staff members temporarily stop from working while symptomatic is a relevant measure in outbreak management. The observation that this measure was implemented in only 64% of the outbreaks with at least one ill staff member raises concern. This may be due to difficulties encountered because of the resulting disorganisation of staff and services. It shows the need for contingency plans addressing these problems and identifying solutions for staff replacement.

The surveillance system for outbreaks of gastroenteritis in elderly LTCF provides valuable information to document the epidemiology of these outbreaks, to follow the evolution of associated morbidity and mortality and to assess the impact of national policies in order to guide public health actions. Data can also be used to estimate the implementation and effectiveness of recommended infection control measures.

Elderly LTCF are encouraged to continue to develop infection prevention and control plans and to notify any gastroenteritis outbreak to health authorities to ensure that they are rapidly controlled. Information on surveillance and notification should be largely distributed in order to increase participation in the system and improve the geographical representativeness of the surveillance data.

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Conflict of interest

None declared.

Authors' contributions

All authors contributed to the interpretation of the results, the revision of the draft manuscript and approved the final version. Anne-Sophie Barret conducted the data analysis and wrote the manuscript; Nathalie Jourdan-Da Silva was involved in the design of the surveillance system for gastroenteritis outbreaks in elderly LTCF and in the data collection, study methods, data analysis; Katia Ambert-Balay was responsible for the viral laboratory analyses; Gilles Delmas was involved in the design of the surveillance system for gastroenteritis outbreaks in elderly LTCF and in defining the study methods; Angie Bone was involved in the data analysis; Jean-Michel Thiolet was involved in the design of the surveillance system for gastroenteritis outbreaks in elderly LTCF and in the data collection; Véronique Vaillant was involved in the design of the surveillance system for gastroenteritis outbreaks in elderly LTCF and in the data collection, study methods, and data analysis.

References

1. Garibaldi RA. Residential care and the elderly: the burden of infection. J Hosp Infect. 1999;43 Suppl:S9–18. http://dx.doi.org/10.1016/S0195-6701(99)90061-0
2. Strausbaugh LJ, Sukumar SR, Joseph CL. Infectious disease outbreaks in nursing homes: an unappreciated hazard for frail elderly persons. Clin Infect Dis. 2003;36(7):870–6. http://dx.doi.org/10.1086/368197
3. Kirk MD, Veitch MG, Hall GV. Gastroenteritis and food-borne disease in elderly people living in long-term care. Clin Infect Dis. 2010;50(3):397–404. http://dx.doi.org/10.1086/649878
4. Carillo-Santisteve P, Ambert-Balay K, Arena C, Poujol I, Caillère N, Delmas G, et al. Epidémies hivernales de gastro-entérites aiguës en France, bilan de trois saisons (2006/2007, 2007/2008 et 2008/2009). Bull Epidemiol Hebd. 2010;31:349–51. French.
5. Ministère du travail, de l'emploi et de la santé, Direction Générale de la Santé. Ministères des solidarités et de la cohésion sociale. Circulaire interministérielle N°DGCS/DGS/2012/118 du 15 mars 2012 relative à la mise en oeuvre du programme national de prévention des infections dans le secteur médico-social 2011/2013; 11 Apr 2012.French.
6. Institut de veille sanitaire (InVs). Gastro-entérites aiguës virales. [Surveillance of acute gastroenteritis in France]. InVs; 2013. French. [Accessed 10 Jul 2014]. Available from: http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Risques-infectieux-d-origine-alimentaire/Gastro-enterites-aigues-virales/Contexte-et-dispositif-de-surveillance
7. Flahault A, Blanchon T, Dorléans Y, Toubiana L, Vibert JF, Valleron AJ. Virtual surveillance of communicable diseases: a 20-year experience in France. Stat Methods Med Res. 2006;15(5):413–21.
8. Caillère N, Caserio-Schönemann C, Fournet N, Fouillet A, Pateron D, Leroy C, et al. Surveillance des urgences - Réseau OSCOUR® (Organisation de la surveillance coordonnée des urgences) - Résultats nationaux 2004/2011. 12 p. Saint-Maurice: Institut de veille sanitaire; 2011. French.
9. Lyman WH, Walsh JF, Kotch JB, Weber DJ, Gunn E, Vinjé J. Prospective study of etiologic agents of acute gastroenteritis outbreaks in child care centers. J Pediatr. 2009;154(2):253–7. http://dx.doi.org/10.1016/j.jpeds.2008.07.057
10. Da Silva AK, Le Saux JC, Parnaudeau S, Pommepuy M, Elimelech M, Le Guyader FS. Evaluation of Removal of Noroviruses during Wastewater Treatment, Using Real-Time Reverse Transcription-PCR: Different Behaviors of Genogroups I and II. Appl Environ Microbiol. 2007;73(24):7891–7. http://dx.doi.org/10.1128/AEM.01428-07

11. Sdiri-Loulizi K, Gharbi-Khélifi H, de Rougemont A, Chouchane S, Sakly N, Ambert-Balay K, et al. Acute infantile gastroenteritis associated with human enteric viruses in Tunisia. J Clin Microbiol. 2008;46(4):1349–55. http://dx.doi.org/10.1128/JCM.02438-07
12. Direction de la recherche,des études,de l'évaluation et des statistiques (DREES). Les établissements d'hébergement pour personnes âgées. Activité, personnel et clientèle au 31 décembre 2007. Document de Travail.Paris: Ministère des Affaires sociales et de la Santé DREES; Feb 2010. French.
13. Benaim C, Froger J, Compan B, Pélissier J. [The assessment of autonomy in elderly people]. Ann Readapt Med Phys. 2005;48(6):336–40. French. http://dx.doi.org/10.1016/j.annrmp.2005.04.005
14. Greig JD, Lee MB. Enteric outbreaks in long-term care facilities and recommendations for prevention: a review. Epidemiol Infect. 2009;137(2):145–55. http://dx.doi.org/10.1017/S0950268808000757
15. Kirk MD, Fullerton KE, Hall GV, Gregory J, Stafford R, Veitch MG, et al. Surveillance for outbreaks of gastroenteritis in long-term care facilities, Australia, 2002-2008. Clin Infect Dis. 2010;51(8):907–14. http://dx.doi.org/10.1086/656406
16. Ryan MJ, Wall PG, Adak GK, Evans HS, Cowden JM. Outbreaks of infectious intestinal disease in residential institutions in England and Wales 1992-1994. J Infect. 1997;34(1):49–54. http://dx.doi.org/10.1016/S0163-4453(97)80009-6
17. Green KY, Belliot G, Taylor JL, Valdesuso J, Lew JF, Kapikian AZ, et al. A predominant role for Norwalk-like viruses as agents of epidemic gastroenteritis in Maryland nursing homes for the elderly. J Infect Dis. 2002;185(2):133–46. http://dx.doi.org/10.1086/338365
18. Van Duynhoven YT, de Jager CM, Kortbeek LM, Vennema H, Koopmans MP, van Leusden F, et al. A one-year intensified study of outbreaks of gastroenteritis in The Netherlands. Epidemiol Infect. 2005;133(1):9–21. http://dx.doi.org/10.1017/S0950268804002936
19. Rosenthal NA, Lee LE, Vermeulen BA, Hedberg K, Keene WE, Widdowson MA, et al. Epidemiological and genetic characteristics of norovirus outbreaks in long-term care facilities, 2003-2006. Epidemiol Infect. 2011;139(2):286–94. http://dx.doi.org/10.1017/S095026881000083X
20. Barataud D'Aury K, Leclère B, Hubert B. Surveillance des épidémies d'infections respiratoires aiguës et de gastro-entérites aiguës dans les établissements d'hébergement pour personnes âgées dépendantes de la région des Pays de la Loire. Résultats de la surveillance au cours de l'hiver 2010-2011. Evaluation du dispositif de surveillance. Saint-Maurice: Institut de veille sanitaire; 2011. French.
21. Thouillot F, Delhostal C, Edel C, Bettinger A, Pothier P, Ambert-Balay K, et al. Gastroenteritis outbreaks in elderly homes in the east of France during winter 2009/10: aetiology research for a series of 37 outbreaks. Euro Surveill. 2012;17(9):pii=20103.
22. Said MA, Perl TM, Sears CL. Healthcare epidemiology: gastrointestinal flu: norovirus in health care and long-term care facilities. Clin Infect Dis. 2008;47(9):1202–8. http://dx.doi.org/10.1086/592299
23. Koopmans M. Noroviruses in healthcare settings: a challenging problem. J Hosp Infect. 2009;73(4):331–7. http://dx.doi.org/10.1016/j.jhin.2009.06.028
24. Friesema IH, Vennema H, Heijne JC, de Jager CM, Morroy G, van den Kerkhof JH, et al. Norovirus outbreaks in nursing homes: the evaluation of infection control measures. Epidemiol Infect. 2009;137(12):1722–33. http://dx.doi.org/10.1017/S095026880900274X

Systematic literature analysis and review of targeted preventive measures to limit healthcare-associated infections by meticillin-resistant *Staphylococcus aureus*

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Meticillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare-associated infections in Europe. Many examples have demonstrated that the spread of MRSA within healthcare settings can be reduced by targeted infection control measures. The aim of this systematic literature analysis and review was to summarise the evidence for the use of bacterial cultures for active surveillance the benefit of rapid screening tests, as well as the use of decolonisation therapies and different types of isolation measures. We included 83 studies published between 2000 and 2012. Although the studies reported good evidence supporting the role of active surveillance followed by decolonisation therapy, the effectiveness of single-room isolation was mostly shown in non-controlled studies, which should inspire further research regarding this issue. Overall, this review highlighted that when planning the implementation of preventive interventions, there is a need to consider the prevalence of MRSA, the incidence of infections, the competing effect of standard control measures (e.g. hand hygiene) and the likelihood of transmission in the respective settings of implementation.

Background

Meticillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of healthcare-associated infections in Europe. In 2008, the European Centre for Disease Prevention and Control (ECDC) estimated that a total number of 171,200 nosocomial MRSA infections are acquired annually in the Member States of the European Union (EU), and in Iceland and Norway, resulting in 5,400 attributable excess deaths, more than 1 million excess days of hospitalisation and EUR 380 million excess in-hospital costs [1]. The burden of MRSA infections was also shown in an analysis of data on healthcare-associated infections collected prospectively from European intensive care units (ICU) between 2005 and 2008, where 1.7% of all patients developed *S. aureus* pneumonia or bloodstream infections. A mean of 35% of these infections were caused by MRSA. Moreover, the hazard ratio for mortality was 5.6-times higher (95% confidence interval (CI): 3.4–9.4) for patients with MRSA bloodstream infection than for patients without *S. aureus* bacteraemia [2].

Among the proposed methods to prevent MRSA, many (e.g. hand hygiene and transmission-based precautions) have been used for general infection control, and their effectiveness has been reviewed extensively [3,4]. However, there is an ongoing discussion about the evidence for the effectiveness of several more specific prevention methods which, nevertheless, have been included in standards for the prevention and control of MRSA in a majority of European countries [5]. Therefore, the scope of this review was to analyse systematically recent literature (published after 2000) with respect to the following questions related to MRSA prevention and control:

1. Does screening of patients before or on admission reduce the incidence of MRSA infection or transmission? How do PCR-based rapid tests for the direct detection of MRSA from screening specimens influence the incidence of MRSA colonisation or infection compared with culture-based methods?
2. Does the decolonisation of nasal MRSA or *S. aureus* carriage using mupirocin nasal ointment, alone or in combination with other agents, reduce colonisation or the development of infections?
3. Does isolation in single rooms of patients colonised or infected with MRSA prevent the spread of MRSA better than the use of transmission-based precautions (hand hygiene, gloves, aprons) alone? What is the effect of pre-emptive isolation of risk patients for MRSA carriage (until screening results are available)?

Methods

A systematic literature analysis and review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. To identify relevant publications, PubMed, EMBASE and Scopus were searched for articles published between 1 January 2000 and 31 October 2012 in English language. The search terms were: MRSA AND (prevention OR control OR prophylaxis OR preventive measures OR preventive therapy OR preventive treatment OR precaution OR screening OR active surveillance OR decolonization OR mupirocin OR surveillance culture* OR chromogenic OR PCR OR polymerase chain reaction OR rapid test OR isolation OR hygiene OR efficien* OR effective*) AND (healthcare OR hospital OR nursing home OR long-term care facilit*); the search terms were adapted for search in EMBASE: "MRSA AND decolonization", "MRSA AND isolation", "MRSA AND screening".

Titles and abstracts were screened independently by two reviewers (RK and AWF). Studies with outcomes measuring the incidence of MRSA colonisation or infection were included. Exclusion criteria were: Studies that did not report on the effects of the preventive measures on infection or transmission; studies performed in settings other than hospitals, long-term care facilities and nursing homes; case series, outbreak reports and

Figure

Flow diagram for the selection of studies on preventive measures against to limit healthcare-associated infections by meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=9,340)

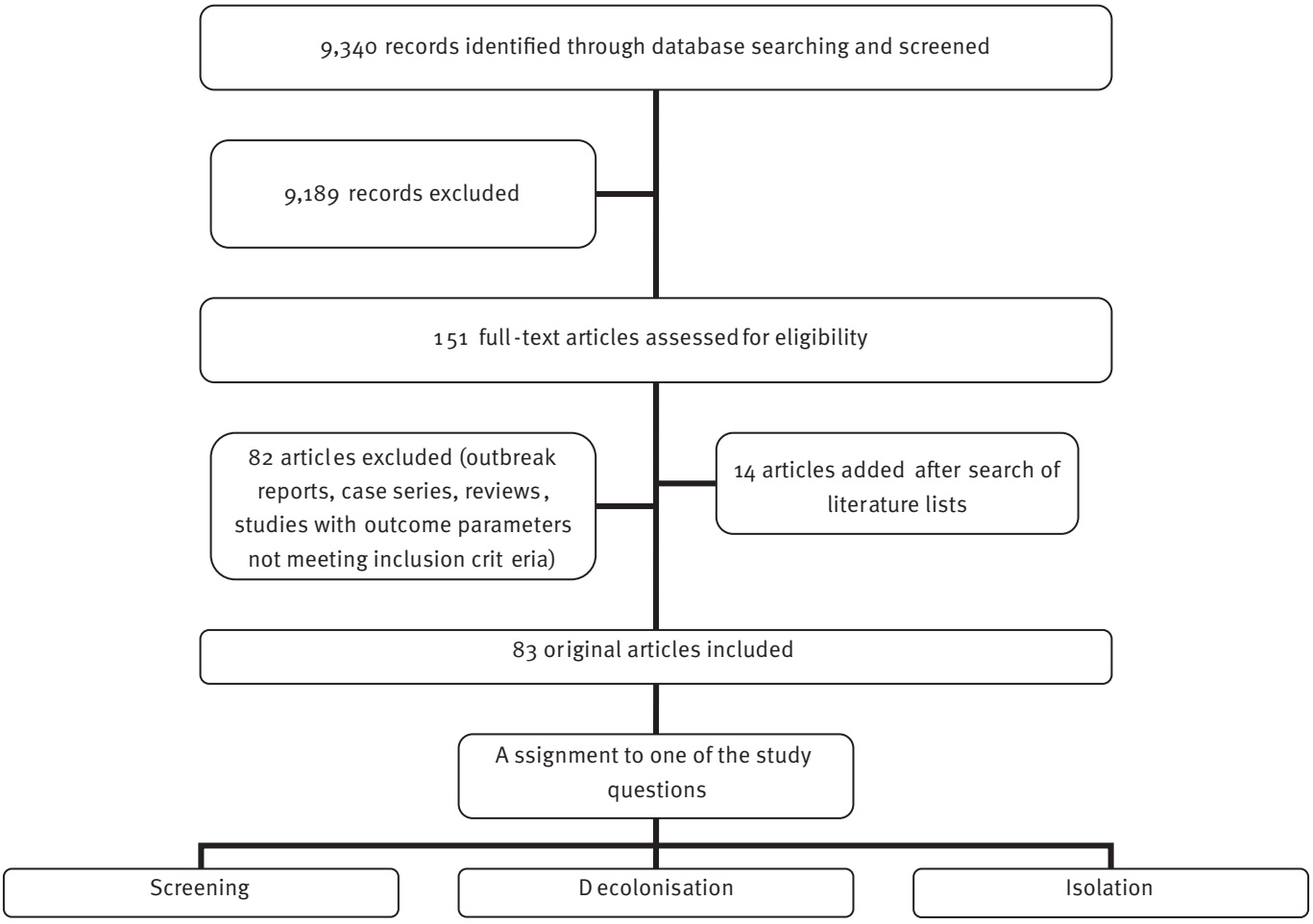

Table 1a

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
Culture-based tests					
Camus [9]; 4.8–9%; 2002–03; France; MICU; RCT.	NA	Intervention: screening of high-risk patients (nose, perineum, wounds, aspirates) at admission, weekly thereafter and at discharge; Control: same methods as in the intervention group, but the screening results were not reported.	Gloves, gowns, mask (also pre-emptively), decolonisation	A, I	MRSA acquisition in the intervention group vs the control group: 6.5% vs 5.3%; p=0.58; Proportion of patients who acquired MRSA infection was identical: 1.6% (n=4) vs 1.6% (n=4); p>0.99; Rate of ICU-acquired infection was identical: 16.5% vs 16.5%, p=0.98.
Chaberny [10]; NA; 2002–06; Germany; ICU and surgery; CS (interrupted time series).	48 h	Intervention: screening (nose, throat, wounds) of all patients; Control: selective screening of contact patients or patients with a history of MRSA carriage.	Private rooms, gowns, gloves, decolonisation	I	Change in the level of infections: -0.163 MRSA infected patients/1,000 pd (95% CI: -0.276 to -0.05); Slope: -0.01 MRSA-infected patients/1,000 pd (95% CI: 0.018–0.003).
Clancy [12]; 3.7%; 2003–04; United States; MSICU; CS (before-and-after).	48 h	Intervention: nasal screening of all patients at admission and weekly thereafter; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves	I	Decrease of MRSA infections (6.1 vs 4.1 infections/1,000 census-days; p=0.01) and of nosocomial (>72 h after admission) MRSA infections (4.5 vs 2.8 infections/1,000 census-days; p=0.01).
Ellingson [15]; NA; 1999–2008; United States; Hospital-wide; CS (interrupted time series).	NA	Intervention: screening (nose, wounds) of all patients at admission and at discharge + behavioural change strategies, hand hygiene, environmental disinfection; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves	C/I	Incidence of MRSA colonisation or infection decreased by 21.8% (95% CI: 8.8–33.7) from 2.40 cases/1,000 pd to 1.88/1,000 pd at risk.
Eveillard [42]; 4.7–12.1%; 2003; France; Hospital-wide; CS.	NA	Intervention: screening of all patients admitted to ICUs (nose, axilla, rectal) and of high-risk patients admitted to other wards; prospective data acquisition without historical or prospective control group.	Contact precautions similar to guidelines from the United States Centers for Disease Control and Prevention	I	Incidence of MRSA from clinical specimens/100 days of hospitalisation for MRSA carriers identified at admission of was 3.1% when the programme was completely implemented, compared with 10.4% when no screening was performed (p<0.001).
Gould [47]; 6–16%; 1999–2003; United Kingdom; MSICU; CS (interrupted time series).	NA	Intervention: screening (nose, throat, groin, axilla) of all patients at admission; Control: phase without any or non-compulsory screening.	Private rooms, barrier-nursing (unspecified), decolonisation	C/I, B	By time series regression analysis, the proportion of patients with MRSA (infection and colonisation) decreased from 15% to 5% (95% CI: 3.5–19.3; p=0.005); no significant effect on MRSA bacteraemia rates.

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1B

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
Culture-based tests					
Holzmann-Pazgal [19]; 2.7–8.3%; 2007–09; United States; PICU; CS (before-and-after).	48 h	Intervention: nasal screening of all patients at admission and weekly thereafter; Control: phase without any or with non-compulsory screening.	Gloves, gowns	C/I	Yearly MRSA incidence density decreased from 2006 to 2009 (6.88 vs 1.45/1,000 pd; p<0.01); and from 2007 to 2009 (7.32 vs 1.45/1,000 pd; p<0.01).
Lawes [38]; 3.1%; 2006–10; United Kingdom; Hospital-wide; CS without control (times series analysis).	mostly <24 h	Intervention: nasal screening of all patients at admission; isolation facilities and decolonisation; hand-hygiene campaign; Compared to: no control group; observation over time.	Private rooms, decolonisation	B	Reduction of MRSA bacteraemia (0.26/1,000 acute occupied bed days (AOBD) vs 0.07/1,000 AOBD; p<0.001). In a multivariate time-series analysis, introduction of screening resulted in reduction of MRSA bacteraemia, hospital-associated incidence density and 30-day mortality after MRSA bacteraemia (p<0.001).
Huang [21]; 12%; 1996–2004; United States; MSICU; CS (interrupted time series).	48 h	Intervention: campaigns for catheter placement, hand hygiene, nasal screening of all patients at admission and weekly thereafter introduced step by step; Control: phase without any or with non-compulsory screening.	Contact isolation precautions (unspecified)	B	MRSA screening was associated with a 67% decrease in the incidence density of MRSA bacteraemia in ICUs (p<0.002), a 39% decrease in non-ICUs, and a 53% decrease hospital-wide.
Huskins [20]; 9.5–12.6%; 2005–06; United States; MSICU; RCT.	5.2 ± 1.4 d	Intervention: nasal screening of all patients at admission, weekly thereafter; Control: control ICUs where screening was performed as in intervention ICUs but without reporting of the results.	Gloves, gowns	C/I	Incidence of events of colonisation or infection with MRSA/1,000 pd did not differ significantly between intervention and control ICUs after adjustment for the baseline incidence (40.4 vs 35.6; p=0.35).
Kelly [40]; 1.13–1.63%; 2005–07; Ireland; Orthopaedic surgery; CS (before-and-after).	NA	Intervention: period 1: pre-admission screening (nose, axillae, groin) of all elective orthopaedic patients; period 2: separation (admission to another hospital) of trauma patients from elective patients; Control: phase without any or with non-compulsory screening.	Decolonisation prior to admission	C/I	Incidence of MRSA infections declined from 0.49% in the control phase to 0.35% (p=0.108) in period 1, and to 0.23% (p=0.05) in period 2. MRSA colonisation detected rose from 1.13% (control phase) to 1.63% (period 1) and 1.59% (period 2) (p=0.002).

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1c

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
Culture-based tests					
Lucet [43]; 6.5%; 1995–2001; France; MSICU; CS.	NA	Intervention: in period 1 and 2, nasal screening of all patients at admission and weekly thereafter; Control: prospective data acquisition without control group, in period 2 promotion of hand hygiene.	Private rooms, gloves, gowns	A	Incidence of MRSA acquisition/100 exposed patients (per 1,000 pd) decreased from 7% (5.43) in period 1 to 2.8% (2.39) in period 2. Period 2 was an independent protective factor influencing the incidence of MRSA acquisition (OR vs period 1: 0.49; p<0.0001).
Malde [37]; 3.2–6.7%; 1996–2004; United Kingdom; Vascular surgery; CS (before-and-after).	NA	Intervention: nasal screening of all patients at admission or for elective admissions 1– 3 weeks prior to admission; Control: phase without any or with non-compulsory screening.	Decolonisation	W/SSI	MRSA wound infections among MRSA-positive elective admissions reduced from 20/36 (56%) to 15/67 (22%) (p=0.002); among MRSA-positive emergency admissions from 35/56 (63%) to 53/121 (44%) (p=0.042). Major limb amputation rates among MRSA-positive admissions reduced from 10/36 (18%) to 6/67 (9%) (p=0.026).
Pan [28]; NA; 1996–2001; Italy; Hospital-wide; CS (before-and-after).	NA	Intervention: nasal screening of high-risk patients on high-risk wards at admission and in different intervals thereafter. Control: phase without any or with non-compulsory screening.	Gloves, decolonisation, gowns (only for infected patients)	B	Incidence rate of MRSA bacteraemia decreased by 42% from 0.64 to 0.37/1,000 admissions (RR 0.57; 95% CI: 0.35–0.92; p=0.03). This effect was mostly due to reduction of bacteraemia cases related to central venous catheters.
Reilly [27]; 3.9%; 2008–09; United Kingdom; Hospital-wide; CS (before-and after).	NA	Intervention: nasal screening of all patients at admission; Control: phase without any or with non-compulsory screening.	Private rooms, other precautions unspecified, decolonisation	C/I	MRSA infections (7.5/1,000 pd) reduced significantly over the study period (p=0.0209); admission prevalence decreased from 5.5% to 3.5% (p< 0.0001).
Rodriguez-Bano [30]; ca 9%; 1995–2008; Spain; Hospital-wide; CS (interrupted time series).	NA	Intervention: phase 2 screening of all patients (nose and various specimens) at admission and weekly thereafter and healthcare workers; phase 3 screening of patients admitted from other facilities; Control: phase without any or with non-compulsory screening.	Private rooms, contact precautions, decolonisation	C/I	MRSA colonisation and infection rates (0.56 cases/1,000 pd; 95% CI: 0.49–0.62) decreased significantly to 0.28 cases/1,000 pd (95% CI: 0.17–0.40) in phase 2 and to 0.07/1,000 pd (95% CI 0.06–0.08) in phase 3.

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1d

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
Culture-based tests					
Shitrit [31]; 1.6–5.6%; 2002–04; Israel; MSICU; Geriatric ward; CS (before-and-after).	NA	Intervention: screening (nose, sputum for intubated, perineum, wounds) of high-risk patients at admission and in different intervals thereafter; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves, decolonisation	B	Mean number of MRSA bacteraemia cases per month decreased from 3.6 cases to 1.8 cases after the intervention (p<0.001).
Souweine [46]; NA; 1994–06; France; MSICU; CS (before-and-after).	NA	Intervention: screening (nose, rectum) of all patients at admission, weekly thereafter and at discharge; Control: phase without any or with non-compulsory screening.	Gloves, gowns, decolonisation	I	Number of patients infected by MRSA (including cases of bacteraemia, pneumonia, urinary tract infection, catheter infection, wound infection) decreased from 5.2% to 1.7% (p=0.018).
Thompson [32]; 8.1%; 1996–2008; United Kingdom; MSICU; CS (before-and-after).	NA	Intervention: screening (nose, throat) of all patients at admission and weekly thereafter; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves, decolonisation	A, B	MRSA acquisition/1,000 bed-days decreased from 49.0 (95% CI: 34.4–63.6) to 28.3 (95% CI: 21.7– 34.9), 19.3 (95% CI: 16.3–22.3) and 11.8 (95% CI: 7.3–16.3), respectively; MRSA bacteraemia cases/1,000 bed-days decreased from 7.6 (95% CI: 4.7–10.5) to 3.7 (95% CI: 2.6–4.8) and 0.4 (95% CI: 0–2.9).
Tomic [45]; NA; 1998–2002; Slovenia; MSICU; CS (before-and-after).	NA	Intervention: screening (nose, throat, wounds and devices) of high-risk patients at admission; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves, decolonisation	C/I	MRSA cases increased from 4.5 to 8.0/1,000 admissions after implementation of screening (p=0.02); the proportion of acquired MRSA cases decreased from 50% in 1999 to 6% in 2002 (p=0.001).
Troché [44]; 4.2%; 1995–2000; France; ICU; CS.	NA	Intervention: nasal screening of all patients at admission, weekly thereafter and at discharge; prospective data acquisition without historical or prospective control group.	(All patients in private rooms), gloves, gowns, decolonisation	A	The overall MRSA acquisition rate was 7.9 cases/1,000 pd (p=NA); it declined in the first three years after the implementation of screening but increased again, when the admission prevalence increased.
Wang [33]; 17.6–26.5%; 2005–06; Taiwan; MSICU; CS (before-and-after).	3d	Intervention: screening (nares, throat/sputum, axillae, inguinal area, wounds) of all patients at admission, every 3 days thereafter and at discharge; Control: as in intervention phase but results were not reported.	Private rooms, gloves, gowns	A, I	The incidence of acquiring MRSA during ICU stay did not differ significantly during intervention and control phases in two participating hospitals (9.6% vs 9.98%; p=0.94; 13.92% vs 13.52%; p=0.81). The incidence of MRSA infection did not differ either (p=0.719; p=0.932).

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1e

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
Culture-based tests					
Warren [34]; 7.2–11.4%; 2002–04; United States; SICU; CS (before-and-after).	72 h	Intervention: nasal screening of all patients at admission, weekly thereafter and at discharge; Control: phase without any or with non-compulsory screening.	Private rooms, gloves, gowns	A	MRSA admission prevalence increased (7.2% vs 11.4%; p=0.001); MRSA acquisition rate constant (7.0 vs 5.5 MRSA cases/1,000 pd; p=0.29).
Wernitz [36]; 20.6%; 1999–2002; Germany; Hospital-wide; CS (before-and-after).	NA	Intervention: screening (nose, throat, skin, devices, wounds) of high-risk groups at admission; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves, decolonisation	I	The standardised infection ratio was 0.52 (95% CI: 0.37–0.71), indicating that 48% of the expected hospital-acquired MRSA infections were prevented.
West [35]; 5.3–9.7%; 2001–03; United States; Hospital-wide; CS (before-and-after).	NA	Intervention: nasal MRSA screening of risk patients at admission and weekly thereafter; Control: phase without any or with non-compulsory screening.	Contact isolation, gowns, gloves	I	Mean number of nosocomial MRSA infections decreased by 39% from 0.76 to 0.45/1,000 pd (p=0.05) in one, and by 21% from 0.72 to 0.57 /1,000 pd (p=0.35) in another hospital.
PCR-based tests					
Aldeyab [7]; 6.8–7.3%; 2006–07; United Kingdom; Medical/surgical ward; CS (before-and-after).	19.3–22.7 h / 42.2–51.8 h	Intervention: phase 1: rapid test on surgical ward (nares, axillae, groin) for all patients at admission and discharge; culture-based screening (nares, axillae, groin, throat) on medical ward (4 months) for all patients at admission and discharge; Control: phase 2: switch of wards and tests.	Private rooms (not for all); contact precautions (unspecified)	C/I	Hospital-acquired MRSA incidence (cases of colonisation and infection) on surgical ward not reduced: 20 (phase 1) vs 22.1/1,000 bed-days (phase 2) (p=0.69); hospital-acquired MRSA incidence rate in medical ward increased in rapid test phase: 11.8 (phase 1) vs 20.3/1,000 bed-days (phase 2) (p=0.03).
Awad [8]; 18%; 2005–08; United States; Hospital-wide; CS (before-and-after).	NA	Intervention: multiple measures (nasal screening of all patients at admission/transfer and discharge; contact isolation of MRSA infected or colonised patients, hand hygiene campaign, cultural transformation campaign; Control: phase without any or with non-compulsory screening.	Contact isolation (unspecified)	A, B, I, W/SSI	MRSA transmission decreased from 5.8 to 3.0/1,000 bed-days (p=0.05); overall MRSA nosocomial infections decreased from 2.0 to 1.0/1,000 bed days (p=0.016); overall SSI decreased (p<0.05); nosocomial MRSA bloodstream infections decreased from 2.9 to 2.5/1,000 bed-days (p> 0.05).

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1f

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
PCR-based tests					
Chowers [11]; 2.7–3.7%; 2003–08; Israel; Hospital-wide; CS (interrupted time series).	24 h / 2–4 d	Intervention: period 1: high-risk patients screened at admission (sample unspecified) + compliance monitoring; period 2: compliance monitoring with screening/ contact isolation discontinued; period 3: PCR-based screening of high-risk patients introduced (sample unspecified); period 4: monitoring re-introduced and decolonisation discontinued; Control: period 0 without any or with non-compulsory screening (screening of contact patients only).	Contact isolation (unspecified), decolonisation	B	Period 0 vs period 1: average number of bacteraemia cases per 1,000 pd was reduced by factor 0.55 (95% CI: 0.36–0.83); period 0 vs period 4: average number of bacteraemia cases per 1,000 pd decreased by a factor of 0.27 (95% CI: 0.14–0.58); period 1 vs period 4: average number of bacteraemia cases per 1,000 pd reduced by factor 0.51 (95% CI: 0.27–0.88) (p=0.02).
Conterno [13]; ca 2%; 2000–5; Canada; ICU; Medical/surgical ward; CS (interrupted time series).	1.6 d / 3.8 d	Intervention: admission screening of high-risk patients (nose, rectum, skin lesions, catheter exit sites) using PCR-based test; Control: admission screening of high-risk patients using culture-based test.	Private rooms, gloves, gowns; discontinued if PCR not confirmed by culture	C/I	Insignificant decrease of 0.14 nosocomial (detected >48 h after admission) MRSA cases/1,000 pd per month (95% CI: 0.18–0.46) after the introduction of PCR detection (p=0.39).
Cunningham [14]; 7.0%; 2005–06; Unired Kingdom; MSICU; CS (before-and-after).	<1 d / 3 d	Intervention: PCR-based nasal screening of all patients at admission and discharge; Control: screening with conventional cultures of all patients at admission.	Private room (if available), standard infection control precautions, decolonisation	A	Incidence of MRSA transmission 13.89 vs 4.9/1,000 pd during culture and PCR-phase (RR reduction: 0.65; 95% CI: 0.28– 1.07).
Harbarth [16]; 6.7%; 2003–05; Switzerland; MSICU; CS (before-and-after).	22 h / 93 h	Phase 1: screening (nose, perineum) of high-risk patients (culture-based); phase 2: universal screening (PCR-based) of all patients; phase 3: same as phase 2 but general pre-emptive isolation.	Gowns, gloves, masks, decolonisation	I	Reduction in medical ICU-acquired MRSA infections (RR: 0.3; 95% CI: 0.1–0.7); no effect in surgical ICU (RR: 1.0; 95% CI: 0.6–1.7).

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/ SSI=wound infections/surgical-site infections.

Table 1G

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
PCR-based tests					
Harbarth [17]; 5.1%; 2004–06; Switzerland; Surgical wards; Prospective cohort study.	22.5 h	Intervention: nasal PCR-based screening of all patients admitted to intervention wards; Control: phase without any or with non-compulsory screening (switch of intervention and control wards after 9 months).	Private rooms (if available), gowns, gloves, masks, decolonisation	A, I, W/SSI	Intervention vs control phase: nosocomial (>48 h after admission) MRSA infection rate 1.11 vs 0.91/1,000 pd (adjusted incidence rate ratio: 1.20; 95% CI: 0.85–1.69); acquisition rate 1.69 vs 1.59/1,000 pd (incidence rate ratio: 1.1; 95% CI: 0.8–1.4); MRSA SSI rate 1.14 vs 0.99/100 surgical interventions (incidence rate ratio: 1.2; 95% CI: 0.8–1.7).
Hardy [18]; 3.6%; 2005–07; United Kingdom; Surgical wards; Prospective cohort study.	0.9 d / 3.3 d	Intervention: Nasal PCR-based screening of all patients admitted to wards assigned to intervention group; Control: control wards with culture-based screening; switch of wards in intervention and control groups after 8-month period.	Private rooms, gowns, gloves, decolonisation	A	Rapid screening reduced MRSA acquisition by 1.49 times (95% CI: 1.115–2.003; p=0.007).
Jeyarathnam [23]; 6.7%; 2006–07; United Kingdom; Medical/surgical ward; RCT.	22 h / 46 h	Intervention: all patients at 10 wards randomised to perform rapid or conventional screening (nose, axilla, groin, skin breaks) at admission and discharge; after a 'washout' period the wards swabbed the screening methods; Control: patients screened using conventional cultures.	Private rooms, gowns, gloves, decolonisation	A	No change in adjusted acquisition rate (adjusted OR: 0.91, 95% CI: 0.61–1.34; p=0.63); MRSA wound infections in the control arm vs the rapid-test arm (OR: 0.91; 95% CI: 0.48–1.7; p=0.77).
Jog [24]; 2.5%; 2004–06; United Kingdom; Cardiac surgery; CS (before-and-after).	NA	Intervention: nasal screening of patients admitted for cardiac surgery; Control: phase without any or with non-compulsory screening.	Private rooms, standard precautions, decolonisation	W/SSI	Overall SSI rate (all organisms) 3.3% in control vs 2.2% in intervention phase; significant reduction of MRSA SSIs (1.15% vs 0.26%; p<0.05; RR: 0.77; 95% CI: 0.056–0.95).
Kjoonegaard [41]; 11.6%; 2009–10; United States; MICU/SICU; CS (before-and-after).	NA	Intervention: nasal (and initially perineal) screening of all ICU patients at admission; Control: phase without any or with non-compulsory screening.	Contact precautions	I	Increase of healthcare-associated MRSA infections after introduction of screening (0.8/1,000 admissions vs 1.6/1,000 admissions; p=0.037).

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

Table 1h

Studies on the effectiveness of the use of active surveillance (screening) for meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=41)

Study; MRSA[a]; Time; Country; Setting; Study type.	Turnaround time (PCR/ culture)[b]	Design	Screening followed by	Outcome[c]	Result
PCR-based tests					
Kurup [22]; 13%; 2007–08; Singapore; MSICU; CS (before-and-after).	NA	Intervention: nasal screening of all patients at admission to the ICU, weekly thereafter and at discharge; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves, decolonisation	I	No statistically significant difference in MRSA infection rate in both ICUs combined (2.7 to 2.4/1,000 pd; p=0.48).
Leonhardt [25]; 1.8–4%; 2009–10; United States; Hospital-wide; CS (before-and-after).	24 h in 90% of all cases	Intervention: nasal screening of all adult patients at admission or before in one intervention hospital; Control: phase with targeted screening of high-risk patients.	Private rooms, gowns, gloves, mask, decolonisation	I	Non-significant decline in hospital-acquired MRSA infections of 0.12 percentage points (p=0.34) during the intervention period.
Martinez-Capolino [26]; 13–23%; 2007–8; United States; MSICU; CS (before-and-after).	<24 h / ca 18–28 h	Intervention: nasal screening of all patients at admission and weekly thereafter; Control: phase without any or with non-compulsory screening.	Private rooms, gowns, gloves	I, B	Decrease in MRSA ventilator-associated pneumonia from 0.95 to 0.17/1,000 pd and 0.47 to 0.0/1,000 pd in Hospital 1 and 2, respectively; decrease of MRSA bloodstream infections from 0.22 to 0.13/1,00 pd and 0.93 to 0.31/1,000 pd in Hospital 1 and 2, respectively; decrease of overall hospital-wide MRSA infections only in Hospital 2 (0.63 vs 0.31/1,000 pd); statistical analysis NA.
Parvez [39]; 10.8%; 2008; United States; Hospital-wide; CS (before-and-after).	NA	Intervention: nasal screening of all patients at admission; Control: phase without any or with non-compulsory screening.	Contact isolation	W/SSI	No change in the MRSA SSI rate (22/3,862 (0.56%) vs 30/4,076 (0.73%); p=0.362).
Robicsek [29]; 6.3–8.3%; 2003–07; United States; MSICU; CS (before-and-after).	Phase 2: ca 2.5 d (in-house PCR); phase 3: 0.67 d (commercial PCR)	Intervention: nasal screening of all patients in the ICU (phase 2) and general hospital-wide screening and retesting upon ICU admission (phase 3); Control: patients without screening in phase 1.	Private rooms, gowns, gloves, decolonisation	I	Aggregate hospital-associated MRSA disease prevalence density changed by -36.2% (95% CI: -65.4% to 9.8%; p=0.17) from baseline to phase 2, and by -69.6% (95% CI: -89.2% to -19.6%; p=0.03) from baseline to phase 3.

CI: confidence interval; CS: comparative study; ICU: intensive care unit; MICU: medical ICU; MRSA: meticillin-resistant *Staphylococcus aureus*; MSICU: medical/surgical ICU; NA: not available; OR: odds ratio; PICU: paediatric ICU; pd: patient-days; RCT: randomised controlled trial; RR: relative risk; SICU: surgical ICU; SSI: surgical-site infections;

[a] MRSA prevalence in the study setting per 100 patients admitted (except stated differently).

[b] Turnaround time of the screening test result (stratified by PCR-based test vs culture-based test, if both were compared in the respective study).

[c] Outome measures: A=MRSA acquisition/transmission; B=MRSA bacteraemia; C/I=cases of colonisation or (all/unspecified types of) infection; I=cases of several or unspecified types of infection; W/SSI=wound infections/surgical-site infections.

reviews (the literature lists of the reviews were manually screened for additional relevant publications).

Data were extracted by AWF and RK independently using a standardised form. The study designs were assigned according to a modified study design scheme published by the Centre for Reviews and Dissemination at the University of York, United Kingdom, in the NHS economic evaluation database handbook from 2007. Formal assessment of the quality of studies was not performed. Due to the different study outcomes included, formal meta-analysis was considered inappropriate. Heterogeneity in methodology and outcome measures also prevented quantitative assessment of publication bias.

Results

The literature search identified 9,340 articles, 151 of which were retrieved as full texts after review of titles and abstracts. Of these, 69 articles fulfilled the criteria for inclusion and a further 14 articles were added after search through the literature lists of excluded review articles (Figure). Overall, 83 articles were included in the review [7-89].

Screening

We identified 41 studies that investigated the question whether screening for MRSA carriers before or on admission had an impact on MRSA acquisition or infection rates (Table 1) [7-47].

Culture-based screening

Twenty-five studies used culture-based screening approaches, including two randomised controlled trials (RCTs) and 23 comparative studies mostly using a before-and-after design [9,10,12,15,19-21,27,28,30-38,40,42-47]. Of these 25 studies, seven used unspecified culture-based techniques [12,21,27,28,37,40,46], eight used MRSA chromogenic media (at least partially) [19,31-34,38,45,47] and the others used mannitol salt, oxacillin salt or blood agars. An estimate for the turnaround times (TAT) of screening results was only reported in eight of the 25 studies (1 d–5.2 d) [10,12,19-21,33,34,38]. Overall, 19 of the 23 comparative studies included reported trends of decreasing rates of MRSA infection or colonisation [10,12,15,19,21,27,28,30-32,35-38,40,42,43,45,46], two reported ambiguous results [44,47], and two reported no reduction of MRSA infections or transmission [33,34]. The two RCTs found no reduction of MRSA infections or transmission [9,20].

PCR-based screening

Sixteen studies used PCR-based screening techniques in their intervention phases, including one RCT, two prospective cohort studies and 13 comparative studies [7,8,11,13,14,16-18,22-26,29,39,41]. The TAT of the PCR screening result was reported in 11 of 16 studies (0.67 d–1.5 d) [7,11,13,14,16-18,23,25,26,29]. Overall, seven of 16 studies documented positive effects on the occurrence of MRSA infections or transmissions after implementation of screening [8,11,14,18,24,26,29]. One study reported ambiguous results [16]. Among the studies reporting a decrease of infection or transmission, five compared the intervention group (PCR-based screening) to a control group without active surveillance, with non-compulsory active surveillance or with screening of limited risk groups [8,11,24,26,29], and two compared with a control group where routine culture-based screening was performed [14,18]. Among the eight studies which could not document decreasing trends in MRSA infections or transmission following the implementation of screening, three compared PCR-based screening with culture-based screening [7,13,23], four compared the intervention to control periods without any active surveillance of MRSA [17,22,39,41], and one compared the intervention with a baseline period where PCR-based screening of selected risk patients was performed [25].

Screening (PCR-based and culture-based) vs no screening stratified by outcome measure

In eight of nine studies (89%) using this outcome parameter, MRSA bacteraemia rates decreased after implementation of screening [8,11,21,26,28,31,32,38,47]. Incidence of MRSA acquisition or transmission decreased in three of eight studies (38%) assessing this outcome parameter [8,9,17,32-34,43,44]. Three of five studies (60%) using wound infection and surgical-site infections (SSI) as an outcome parameter showed decreasing SSI rates after implementation of screening [8,17,24,37,39]. A decrease of MRSA was observed in 20 of 23 studies (87%) using all or unspecified MRSA infections or cases of colonisation/infection as their outcome parameters [8-10,12,15-17,19,20,22,25-27,29,30,35,36,40-42,45-47]; among these studies, one found a decrease only in medical ICUs [16].

PCR-based vs culture-based screening

Five investigations compared PCR-based to culture-based screening [7,13,14,18,23]. All five documented that the TAT was reduced when compared to culture-based approaches (Table 1). However, three studies found no difference in MRSA acquisition or infection rates [7,13,23]. In contrast, one before-and-after study found a reduction in the incidence of MRSA transmission after introduction of the PCR-based test which almost reached statistical significance, and one cohort study reported a reduction in MRSA acquisition rates [14,18].

Decolonisation

A total of 11 RCTs, 23 comparative studies and one prospective cohort study evaluated the effectiveness of mupirocin-based nasal decontamination regimens for the prevention of *S. aureus* infections (Table 2) [48-82]. Of all 11 RCTs, six demonstrated significantly decreasing infection trends after implementation of decolonisation [48,51,52,72,73,75]; for one of these, this was only observed when selective digestive decontamination was added to nasal decolonisation [52], and for one RCT, the effect was only analysed for Gram-positive infections (which were mostly MRSA) [75]. Stratified by

types on infections prevented, the RCTs showed that decolonisation decreased deep *S. aureus* SSI [48], overall *S. aureus* infections [48,51,73], overall infection rates [52], Gram-positive pneumonia [75] and *S. aureus* exit-site infections [72].

Among the 24 non-randomised studies identified, 19 reported evidence that the use of mupirocin was effective in reducing infection. Of the seven studies performed in ICUs, six (86%) demonstrated an effect; specifically, a decrease in pneumonia and hospital-acquired *S. aureus* infection [59], in the overall infection rates in ICUs [50,70], in MRSA SSI and bloodstream infections (BSI) in ICUs [55], and in the overall number of MRSA infections in ICUs [80,81]. Non-controlled studies implementing decolonisation in non-ICU settings led to a decrease in overall and peristomal MRSA infections [57,76], in the incidence of S.aureus/MRSA SSI in surgical units [55,58,64,65,71,77,79], in overall *S. aureus*/MRSA infections in gastrointestinal surgery and orthopaedics [49,82], and in the total rate of SSI or wound infections [53,60,67].

Stratified by different implementation settings, four of five studies documented success among patients undergoing cardiothoracic surgery [53,65,66,71,77], four of six in orthopaedic departments [49,60,61,63,64,79], and six of seven in other or mixed surgical departments [54,55,58,67,73,75,82]. Moreover, seven of eight studies performed in ICU settings [50,52,55,59,68,70,80,81], two of two performed in haemodialysis units [51,72], two of five performed in different non-surgical departments [56,57,69,76,78], and one of three studies performed hospital-wide or in both medical and surgical departments [48,62,74], demonstrated successful effects of mupirocin-treatment.

Stratified by different causative organisms, eight studies showed that mupirocin-treatment led to a decrease in the overall incidence of infections due to all organisms [49,53,60,64,65,67,70,77]. In the same studies, this effect was partially non-significant for *S. aureus*/MRSA infections in particular [53,60,67,70]. Four studies reported a decrease in infections caused by methicillin-sensitive *S. aureus* (MSSA) [48,51,55,65]. Twelve investigations revealed a reduction in MRSA infections [49,50,55,57,58,64,76,77,79-82], six showed decreasing trends for *S. aureus* (MRSA and/or MSSA) infections [50,59,71-73,82] and one reported reduction of pneumonia caused by Gram-positive bacteria (mostly MRSA) [75].

Many of the studies identified in this review used mupirocin-only regimens [51,55,59,60,63,67,70-73,75,78,82]. Others combined nasal mupirocin with other topical agents to support decolonisation, including chlorhexidine [48,50,53,56-58,61,62,64-68,74,81], triclosan [49,76,79], extra-nasal use of mupirocin [69,77,80], selective digestive decontamination [52], povidone-iodine [49], and systemic antibiotics [54].

Isolation

Focusing on the physical isolation of patients in separate single or cohort rooms, we identified one cohort study and seven comparative studies reporting on the effectiveness of this measure (Table 3) [16,83-89]. Five studies were performed in ICU settings [16,83-85,88], one in a vascular surgery ward, one in a diabetic food unit, and one hospital-wide [86,87,89]. In two of these studies, nurse cohorting was performed in addition to single-room isolation [83,86]. Overall, one cohort and three comparative studies reported on beneficial effects of single-room isolation (not performed pre-emptively) on MRSA colonisation or infection [85,86,88] and on acquisition rates [84]. Two comparative studies did not find a reduction of transmission [83] or MRSA prevalence [87].

Three studies assessed the role of pre-emptive isolation measures pending the results of screening [16,86,89]. In one before-and-after study, pre-emptive isolation precautions led to a reduction of the MRSA acquisition rate (0.21% vs 0.07%; p=0.04) [89]. In a retrospective comparative study placing all admitted patients in pre-emptive isolation, the number of nosocomial MRSA isolates was reduced (p=0.005). However, simultaneous introduction of a cohort isolation facility with dedicated staff makes the effects of this measure indistinguishable from the effects of pre-emptive isolation [86]. The third was a study that evaluated the effects of simultaneous implementation of pre-emptive isolation and a rapid screening test on the incidence of MRSA infections in two ICUs [16] resulting in a significant reduction of ICU-acquired infections in a medical but not in a surgical ICU.

Discussion

Improving the rational use of antibiotics and the implementation of hand hygiene are clearly cornerstones of MRSA prevention and control [90-92]. Moreover, benchmarking and public reporting systems have recently been demonstrated to successfully support infection control measures [93]. However, the effectiveness of screening, decolonisation and isolation for MRSA prevention when implemented routinely in settings with endemic MRSA, remains controversial. For example, it is debated to what extent microbiological, strain-specific factors have contributed to the decreasing MRSA trends [94,95]. Therefore, the present review aimed to focus on three important measures and to summarise the current evidence for their impact on MRSA prevention.

Screening

The strategy of screening is based on the finding that microbiological cultures performed for clinical reasons fail to detect previously unknown MRSA carriers at admission in 69 to 85% of patients [96,97]. Technically, screening can be performed by culture-based methods (screening swab streaked onto non-selective or chromogenic media) or PCR-based tests.

TABLE 2A

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Bode [48]; 2005–07; Netherlands; Surgery and internal medicine; Randomised placebo-controlled trial.	Mupirocin 2xd and chlorhexidine gluconate (40 mg/mL) soap for 5 days; further courses of same treatment for patients staying >3 weeks.	*S. aureus* carriers only	NA	NA	NA	↓	Reduction of hospital-acquired MSSA infection (3.4% vs 7.7%; RR: 0.42; 95% CI: 0.23–0.75), deep MSSA SSI (RR: 0.21; 95% CI: 0.07–0.62) but not of superficial MSSA SSI 0.45 (0.18–1.11) and MSSA lower respiratory infections 0.82 (RR: 0.82; 95% CI: 0.12–5.78).	Diverse, SSI, VAP/LRTI, (BSI, UTI assessed, but small numbers)
Boelaert [51]; NA; Belgium; Haemodialysis; Randomised placebo-controlled trial.	Mupirocin 3xd for 2 weeks; subsequently 3x per week for 9 months.	*S. aureus* carriers only	NA	NA	NA	↓	Reduction of MSSA infections (1/104 patient-months vs 6/147 patient-months; p<0.05).	Diverse
Camus [52]; 1996–08; France; MICU; Randomised placebo-controlled trial.	Group 1: mupirocin 3xd for 5 days; again 5 days if nasal *S. aureus*; chlorhexidine gluconate (4%) total-body washing 2xd (until 24 h after extubation; max 90 days); Group 2: same as group 1 plus selective digestive decontamination	All patients irrespective of carriage	↓[b]	NA	NA	NA	Group 1: number of acquired infections did not differ (OR: 0.98; 95% CI: 0.6– 1.58; p=0.92). Group 2: number of acquired infections incl. VAP, UTI, catheter-related infections differed (OR: 0.42; 95% CI: 0.25–0.73; p=0.002).	Diverse, VAP, UTI, BSI
Cimochowski [53]; 1995–99; United States; Cardiothoracic surgery; Prospective comparative study with control (before-and-after).	Mupirocin the night and morning before surgery, before surgery, then 2xd for 5 days; chlorhexidine shower before surgery.	All patients irrespective of carriage	↓	n.s	NA	NA	Reduction of overall SSI (0.9 vs 2.7%; p=0.005), but not *S. aureus* SSI (4/854 vs 11/992; p>0.05).	Sternal SSI
Cordova [54]; NA; United States; Dermatology (Mohs surgery); Retrospective comparative study with control (before-and-after).	Mupirocin 2xd for 5–7 days and oral trimethoprim-sulfamethoxazole for 5–7 days	Only MRSA carriers	NA	NA	NS	NA	MRSA SSI: 0.3% in historical cohort (12/3,633) vs 0% in treatment group (0/962); statistical analysis NA; Fisher's exact test performed by the authors of this review: p=0.08).	SSI

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

TABLE 2B

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Dupeyron [56]; 1999–2001; France; Digestive disease unit; Prospective comparative study with control (before-and-after).	Mupirocin 3xd for 5 days; chlorhexidine (4%) every second day during mupirocin treatment; further treatment courses in case of failure.	Only MRSA carriers	NA	NA	NS	NA	Overall MRSA infections: 1.41/1,000 pd in control period and 1.46/1,000 pd in intervention period (statistical analysis NA).	Diverse
Dupeyron [57]; 2000–04; France; Gastroenterology; Prospective comparative study with control (interrupted-time-series).	Mupirocin 3xd for 5 days; chlorhexidine (4%) every second day during mupirocin treatment; further courses in case of failure.	Only MRSA carriers	NA	NA	↓	NA	Reduction of overall MRSA infections (1.41/1,000 pd in the year before intervention to 1.40, 0.74, 0.59/1,000 pd in different periods thereafter, p=0.002).	Diverse
Fraser [59]; 2006–07; United States; MICU; Retrospective comparative study with control (before-and-after).	Mupirocin (5 doses)	*S. aureus* carriers only	NA	↓	NA	NA	Reduction of *S. aureus* VAP (p=0.03; RR 0.12; 95% CI: 0.01–0.83), overall *S. aureus* infections (p=0.03; RR 0.37; 95% CI: 0.14–0.90), but NS effect on *S. aureus* BSI (p=0.28).	Diverse, BSI, VAP/LRTI
Gernaat-van der Sluis [60]; 1992–06; The Netherlands; Orthopaedic wards; Prospective comparative study with control (before-and-after).	Mupirocin thrice before surgery	All patients irrespective of carriage	↓	NS	NA	NA	Reduction of overall SSI (p=0.02), but NS reduction of *S. aureus* SSI (p=0.3).	SSI
Hadley [61]; 2007–09; United States; Orthopaedic wards; Retrospective comparative study with control (before-and-after).	Mupirocin (2%) for 5 days (dose unspecified); chlorhexidine once preoperatively.	All patients irrespective of carriage	NS	NA	NS	NA	No reduction of SSI rate (1.28% in the treatment vs 1.45% in the control group; p=0.809) and no reduction of MRSA SSI (0.24% vs 0.30%; NS).	SSI

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

Table 2c

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Harbarth [62]; 1995–07; Switzerland; Hospital-wide; Randomised placebo-controlled trial.	Mupirocin 2xd for 5 days; chlorhexidine for 5 days.	Only MRSA carriers	NA	NA	NS	NA	No reduction of overall MRSA infections (3/48 vs 7/50; p=0.32).	Diverse
Huang [80]; 2003–06; Taiwan; Neonatal ICU; Prospective comparative study (before-and after).	Mupirocin 2xd for 5 days	Only MRSA carriers	NA	NA	↓	NA	Reduction of overall MRSA infections in the group of neonates treated (92/783 vs 5/450; OR: 11.85; 95% CI: 4.6-33.3).	Diverse
Kalmeijer [63]; 1997–09; The Netherlands; Orthopaedic wards; Randomised placebo-controlled trial.	Mupirocin 2xd until day of surgery (at least 2 doses before surgery).	All patients irrespective of carriage	NA	NS	NA	NA	No significant reduction of endogenous *S. aureus* SSI (0.3% in treatment vs 1.7% control group; RR: 0.19; 95% CI: 0.02-1.62).	SSI
Keshtgar [55]; 2000–06; United Kingdom; ICU and surgery; Prospective comparative study (before-and after).	Mupirocin 3xd for 5 days; chlorhexidine (use unspecified except for hairwash on days 1, 3, 5).	Only MRSA carriers	NA	NA	↓	↓↑	Reduction of MRSA BSI by 38.5% (p<0.001), MSSA BSI by 30.4% (p<0.001), MRSA SSI by 12.7% (p=0.021); but increase of MSSA SSI by 12.7% (p=0.006).	BSI, SSI
Kim [64]; 2005–07; United States; Orthopaedic wards; Prospective comparative study with control (before-and-after).	Mupirocin 2xd for 5 days; chlorhexidine 1xd for 5 days (3 days for MSSA).	*S. aureus* carriers only	↓	NA	↓	NS	Reduction of overall SSI (p=0.0093), MRSA SSI (0.19% vs 0.06%, p=0.0315), MSSA SSI (0.26% vs 0.13%, p=0.0937).	SSI
Kluytmans [65]; 1989–92; The Netherlands; Cardiothoracic surgery; Retrospective comparative study with control (before-and-after).	Mupirocin 2xd for 5 days; chlorhexidine before surgery.	All patients irrespective of carriage	↓	NA	NA	↓[c]	Reduction of the overall rate of SSI (7.3% vs 2.8%; p<0.001) and of *S. aureus*/coagulase-negative staphylococcal SSI (p=0.0032).	SSI

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

TABLE 2D

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Konvalinka [66]; 1997–2003; Canada; Cardiothoracic surgery; Randomised placebo-controlled trial.	Mupirocin 2xd for 7 days before surgery for *S. aureus* carriers only; standard pre-operative clinical practice for all patients included chlorhexidine 12 h before surgery.	*S. aureus* carriers only	NS	NS	NA	NA	No reduction of overall SSI (1.6% vs 2.4%; p=0.672) and *S. aureus* SSI (0% vs 1.6%; p=0.243).	SSI
Lipke [67]; 2005–07; United States; Surgery; Retrospective comparative study with control (before-and-after).	Mupirocin 2xd for 5 days; all patients: chlorhexidine morning before surgery.	Only MRSA carriers	↓	NA	NS	NA	Reduction of overall SSI (7/1,094 to 7/1,225; p=0.0196), but NS for MRSA SSI (8/1,094 vs 2/1,225; p=0.0538).	SSI
Milstone [68]; 2002–09; United States; Neonatal ICU; Retrospective comparative study with control (before-and-after).	Mupirocin for infants >36 weeks of gestational age or >4 weeks of chronological age with MRSA carriage; chlorhexidine; duration of therapy: unspecified.	Only MRSA carriers	NA	NA	NS	NA	No reduction of overall MRSA infections (95% CI: 0.002–1.03).	Diverse
Mody [69]; NA; United States; Long-term care facility; Randomised placebo-controlled trial.	Mupirocin 2xd for 14 days; mupirocin treatment of wounds.	*S. aureus* carriers only	NA	NS	NA	NA	No significant reduction of overall *S. aureus* infections (3/55 vs 7/47; p=0.1).	Diverse
Muller [70]; 1999–2003; France; MICU; Retrospective comparative study with control (before-and-after).	Mupirocin for 5 days (dose unspecified)	Only MRSA carriers	↓	NA	NS	NA	Reduction of overall infections (1/9 infections vs. 11/17; p=0.006), but NS for overall MRSA infections (p=0.24).	Diverse
Nicholson [71]; 2002–04; United States; Cardiothoracic surgery; Prospective comparative study with control (before-and-after).	Mupirocin 2xd for 7 days (if *S. aureus* carriage was confirmed) or less than 7 days (if screening was negative).	All patients irrespective of carriage	NA	↓	NA	NA	Reduction of *S. aureus* SSI rate (1.68% to 0.37%; p=0.006) and reduction of deep sternal *S. aureus* infections (p=0.0087).	SSI

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

Table 2e

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Perl [73]; 1995–08; United States; Surgery; Randomised placebo-controlled trial.	Mupirocin 2xd for 5 days before surgery	All patients irrespective of carriage	NS	↓	NA	NA	Reduction of nosocomial *S. aureus* infection among *S. aureus* carriers (4% vs 7.7%; p=0.02); no reduction of *S. aureus* SSIs.	Diverse, SSI
Pofahl [58]; 2004–07; Unites States; Surgery; Retrospective comparative study (before-and after).	Mupirocin 2xd for 5 days; chlorhexidine (4%) days 1, 3, 5.	Only MRSA carriers	NA	NA	↓	NA	Reduction of MRSA SSI (0.23% vs 0.09%); pronounced in joint-replacement surgery (0.30– 0%; p=0.04).	SSI
Ridenour [81]; 2003–04; United States; MICU; Retrospective comparative study (before-and after).	Mupirocin 2xd for 5 days; chlorhexidine 1xd for 7 days.	Only MRSA carriers	NA	NA	↓	NA	Reduction of MRSA incidence density of colonisation or infection (8.45 vs 4.05/1,000 pd; p=0.048).	Diverse
Robicsek [74]; 2006–07; United States; Hospital-wide; Prospective cohort study.	Mupirocin 2xd for 5 days and chlorhexidine (4%) days 1, 3, 5	Only MRSA carriers	NA	NA	NS	NA	No reduction of overall MRSA infections (NS); trend towards delayed infections in treatment group (15.5 days vs 50 days until infection; p=0.06).	Diverse
Sandri [50]; 1999–2003; Brazil; General ICU; Prospective comparative study without control group.	Mupirocin 3xd for 5 days and chlorhexidine 1xd for 3 days	Only MRSA carriers	NA	↓	↓	NA	Reduction of nosocomial *S. aureus* infections (9.9% vs 3.3%; p=0.001) and MRSA infections (8.2% vs 2.8%; p=0.001).	Diverse
Sankar [49]; 2000–01; United Kingdom; Orthopaedic wards; Prospective comparative study (before-and after).	Mupirocin or povidone iodine or triclosan (unspecified treatment)	Only MRSA carriers	↓	NA	↓	NA	Reduction of overall hospital-acquired infections (8.5% vs 3.5%; p<0.05) and overall MRSA infections (p<0.05).	Diverse

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

TABLE 2F

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Suzuki [75]; 1998–2000; Japan; Abdominal digestive surgery; Randomised controlled trial.	Mupirocin 3xd for 3 days before the operation	All patients irrespective of carriage	NS	NA	↓[d]	NA	No reduction of overall infections (mostly caused by Gram-negative bacteria); reduction of VAP due to Gram-positive bacteria (mostly MRSA) (p=0.028).	Diverse, VAP/ LRTI, SSI
The Mupirocin Study Group [72]; NA; Europe; Haemodialysis; Randomised placebo-controlled trial.	Mupirocin 2xd for 5 consecutive days every 4 weeks	*S. aureus* carriers only	NS	↓	NA	NA	Reduction of *S. aureus* exit-site infections (p=0.006); no reduction of overall exit-site infections (p=0.17), tunnel infections and peritonitis (NS).	Exit-site infections
Thomas [76]; 2002–06; United Kingdom; Gastroenterology; Prospective comparative study with control (before-and-after).	Mupirocin 3xd and daily 2% triclosan for 5 days	Only MRSA carriers	NA	NA	↓	NA	Reduction of peristomal MRSA infections (5/42–7/24 vs 1/47, p<0.01).	Peristomal infections
Walsh [77]; 2004-10; United States; Cardiothoracic surgery; Prospective comparative study with control (before-and-after).	Mupirocin (dose unspecified) for 5 days; sterile gauze coated with mupirocin on exit site.	All patients irrespective of carriage	↓	NA	↓	NS	Reduction of overall wound infections (p<0.01); 93% reduction of MRSA SSIs (32/2,766 vs 2/2,496; p<0.001); MSSA SSI rate NS (5/2,766 vs 2/2,496; p=0.27).	SSI
Wertheim [78]; 1999–2001; The Netherlands; Non-surgical departments; Randomised placebo-controlled trial.	Mupirocin 2xd for 5 days	*S. aureus* carriers only	NS	NA	NA	NS	No reduction of overall nosocomial *S. aureus* infections (2.6% vs. 2.8%, risk difference 0.2 percentage points; 95%CI: -1.5-1.9). Trend towards delayed time of infection onset (12 days vs 25 days; p=0.28).	Diverse
Wilcox [79]; 1999–2000; United Kingdom; Orthopaedic wards; Prospective comparative study with control (before-and-after).	Mupirocin for 5 days (dose unspecified), starting one day before surgery and ending 4 days after surgery; triclosan 2% on the day before surgery.	All patients irrespective of carriage	NS	NA	↓	NS	Reduction of MRSA SSI (23/1,000 operations vs 3.3/1,000 operations; p<0.001); no reduction of overall SSI rate and MSSA SSI rate (NS).	SSI

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

Table 2G

Studies on the effectiveness of *Staphylococcus aureus* decolonisation using mupirocin-based regimens, published 2000–2012 (n=35)

Study; Time; Country; Setting; Study type.	Treatment regimen[a]	Treatment of	Effects of treatment stratified by pathogen				Effect of treatment	Types of infections analysed separately
			All organisms	MRSA+ MSSA	MRSA	MSSA		
Yano [82]; 1996–08; Japan; Gastrointestinal surgery; Prospective comparative study with control (before-and-after).	Mupirocin 3xd for 3 days preoperatively	All patients irrespective of carriage	NS	↓	↓	NS	Reduction of MRSA infections after upper gastrointestinal surgery (9/128 vs 0%; p=0.001); NS for MSSA infections (p=0.056).	Diverse

BSI: bloodstream infections; CI: confidence interval; diverse: diverse or all types of infections ICU: intensive care unit; LRTI: lower respiratory tract infections; MICU: medical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; MSSA: meticillin-sensitive *Staphylococcus aureus*; NA: no data available; NS: not significant; ↓ reduction; ↑ increase; OR: odds ratio; pd: patient-days; RR: relative risk; SSI: wound infections or surgical-site infection, VAP: ventilator-associated pneumonia; UTI: urinary tract infections;

[a] Mupirocin refers to mupirocin nasal ointment unless specified otherwise. Chlorhexidine and triclocan body washes, 1xd or 2xd or 3xd refers to application 1x, 2x or 3x per day.

[b] Only when selective digestive decontamination was added to mupirocin-treatment.

[c] MSSA and coagulase-negative staphylococci.

[d] Gram-positive infections (mostly MRSA).

Screening vs no screening

Of 36 cohort and comparative studies investigating the effectiveness of compulsory screening compared with no or non-compulsory screening, 27 reported decreasing trends in the rates of MRSA infection or acquisition; this is in accordance with a meta-analysis describing a decrease in MRSA bloodstream infections (relative risk (RR): 0.54; 95% CI: 0.41–0.71) and surgical site infections (RR: 0.69; 95% CI: 0.46–1.01) [98]. On the other hand, two RCTs found that MRSA acquisition or infection in the intervention groups did not differ significantly from the control groups [9,20]. However, in both studies, the median time for reporting a positive screening result was very long (3 days and 5.2±1.4 days), which led to delayed implementation of contact precautions. In addition, compliance with transmission-based precautions was not as required [20] and the prevalence of MRSA infection was low in one of the studies [9]. Comparing successful and unsuccessful interventions, we did not find clear differences between the studies regarding the specimens used for screening (nasal swab only vs other swabs in addition) or the patient population included (all patients admitted vs high-risk patients only).

There was a tendency that studies including 'incidence of MRSA acquisition' as an outcome parameter, reported a success less frequently (three of eight studies) compared with studies focusing on MRSA infection rates using the outcome parameters 'occurrence of bacteraemia' (eight of nine studies) or 'SSI' (three of five studies). The reason for this effect is not known, but it could highlight that screening does not necessarily affect the rate of cross-transmission on the ward, unless it is linked to additional preventive measures; decolonisation, for instance, was not performed in two of the the studies measuring incidence of acquisition [33,34], while in two others, single-room isolation was omitted or only performed if available [9,17].

In conclusion, we found evidence that screening can help decrease MRSA infection rates in hospitals. This is also supported by macro-epidemiological data and mathematical models showing that without screening, other infection control measures might fail to effectively reduce MRSA spread [99-102]. However, the included RCTs did not confirm the findings of non-controlled studies. This makes it impossible to firmly recommend the implementation of screening in all settings. However, the evidence provided can support the introduction of a programme for active surveillance of MRSA in settings that have hyperendemic MRSA cross-infections in spite of a high level of compliance with standard precautions. Clearly, the implementation of screening needs to be linked to other targeted infection control measures (e.g. hand hygiene) to achieve optimal impact.

Culture-based screening vs PCR-based screening

Screening for MRSA colonisation of patients at admission using culture-based approaches requires 24 to

Table 3a

Studies on the effectiveness of isolation measures against meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=8)

Study	MRSA	Time	Country	Specialty	Study type	Design	Outcome [a]	Result
Bracco [84]	1.1%	2002– 04	Canada	MSICU	Prospective cohort study	Intervention: patients hosted in single rooms and bay rooms; allocation was not randomized; rates of nosocomial cross-contamination among patients hosted in single-rooms were assessed; Compared to: rates of nosocomial cross-contamination among patients hosted in bay rooms with 2–6 beds.	A	Incidence density of MRSA acquisition was 4.1/1,000 pd in bay rooms compared with 1.3/1,000 pd in single rooms (p<0.001); the RR of acquiring MRSA was 0.65 in single vs bay rooms; rates of BSI and positive catheter tips were also significantly reduced in single rooms compared to bay rooms.
Cepeda [83]	NA	2000– 01	United Kingdom	MSICU	Prospective comparative study with control (interrupted) time-series	Intervention: phase 1 and 3: MRSA patients moved to single rooms or bays; Compared to: phase 2: no move to single rooms or bays.	A	No difference regarding transmission between the move and non-move phase; 0.73 (95% CI: 0.49–1.10; p=0.94)
Cheng [85]	NA	2002– 09	China	MSICU	Retrospective comparative study with control (interrupted-time-series)	Intervention: phase 2 (2004–06): patients with MRSA detected in clinical specimens were placed in single rooms; phase 3 (2006–09) MRSA patients were cared for in single rooms and a hand hygiene campaign was introduced; Compared to: phase 1 (2002–04): patients with MRSA detected from clinical specimens were not moved to single rooms.	B, I	ICU-onset non-bacteraemic MRSA infections decreased from 3.54/1,000 pd in phase 1 to 2.26 in phase 2 (p=0.042) and 1.02 (p=0.006) in phase 3; bacteraemic MRSA infection decreased from 1.94/1,000 pd (phase 1) to 0.9 (phase 2, p=0.005) and 0.28 (phase 3, p =0.021).
Curran [86]	NA	2002– 04	United Kingdom	Vascular surgery ward	Retrospective comparative study with control (interrupted-time-series)	Intervention: opening of a cohort area for MRSA colonised or infected patients; all admissions were placed in an isolation facility and then transferred to the cohort or the non-cohort area dependent on the results of screening; Compared to: time before the cohort area was opened.	C/I	Reduction of the number of nosocomial MRSA isolates (p=0.005) after opening of the cohort area; reduction was sustained after cohort area was discontinued.
Fazal [87]	NA	1991– 94	Unites States	Hospital-wide	Retrospective comparative study with control (before-and-after)	Intervention: patients with MRSA no longer placed in private rooms plus transmission-based precautions (gloves, gowns, masks); the latter (without single room) were continued only on the ICU; Compared to: all patients with MRSA were placed in single rooms with transmission-based precautions.	C/I	Decrease of the percentage of MRSA among all *S. aureus* isolates (from 34% to 20%; p=0.001); discontinuing single room isolation did not result in an increase in the prevalence of MRSA.
Gregory [88]	1.3%	2000– 07	United States	Neonatal ICU	Retrospective comparative study without control	Intervention: screening of all patients; in case of MRSA: isolation in a cohort plus contact precautions (gloves and gowns); Compared to: no control group; observation over time.	C/I	Incidence of MRSA decreased from 1.79/1,000 pd in 2000 to 0.15 in 2005 (yearly 31% decrease; p=0.001). However, incidence increased to 1.26/1,000 pd in 2007, accompanied by the occurrence of CA-MRSA types.
Harbarth [16]	6.7%	2003– 05	Switzerland	MSICU	Prospective comparative study with control (before-and-after)	Phase 1: screening of high-risk patients (culture-based); phase 2: universal screening (PCR-based); phase 3: same as phase 2 but general pre-emptive isolation.	I	On-admission screening and pre-emptive isolation reduced medical ICU-acquired MRSA infections (RR: 0.3; 95% CI: 0.1–0.7), but had no effect in the surgical ICU (RR: 1.0; 95% CI: 0.6–1.7).

BSI: bloodstream infection; CA: community-acquired; ICU: intensive care unit; MSICU medical-surgical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; pd: patient-days; RR: relative risk.

[a] Outcome measures: A=MRSA acquisition/transmission, B=MRSA bacteraemia, C/I=cases of colonisation or infection, I=cases of several or unspecified types of infection.

Table 3B

Studies on the effectiveness of isolation measures against meticillin-resistant *Staphylococcus aureus*, published 2000–2012 (n=8)

Study	MRSA	Time	Country	Specialty	Study type	Design	Outcome [a]	Result
Lecornet [89]	31%	1997– 2003	France	Diabetic foot unit	Prospective comparative study with control (before-and-after)	Intervention: pre-emptive contact isolation of all patients until the screening results were negative; Compared to: isolation precautions performed after MRSA was isolated from the screening sample.	A	The acquisition rate was 7/10,154 MRSA-free pd (0.07%) in the intervention phase vs 6/2,854 MRSA-free pd (0.21%) in the phase without pre-emptive isolation (p=0.04). The relative risk of acquiring MRSA was 0.33 (95% CI: 0.11–0.98) in the intervention vs the control phase.

BSI: bloodstream infection; CA: community-acquired; ICU: intensive care unit; MSICU medical-surgical intensive care unit; MRSA: meticillin-resistant *Staphylococcus aureus*; pd: patient-days; RR: relative risk.

[a] Outcome measures: A=MRSA acquisition/transmission, B=MRSA bacteraemia, C/I=cases of colonisation or infection, I=cases of several or unspecified types of infection.

72 hours until the results are available on the wards [103,104]. During this time MRSA can spread among inpatients. Therefore, various PCR-based methods have been developed to reduce the TAT [105,106]. Reduction of TAT was indeed confirmed by all studies on PCR-based tests identified in this review. But these studies mostly did not find a significant reduction of MRSA infection or acquisition rates. These results are in accordance with data from a meta-analysis showing that, compared with cultures, the use of rapid tests was not associated with a significant decrease in MRSA acquisition rates (risk ratio 0.87; 95% CI: 0.61–1.24) [98]. On the other hand, we found two studies reporting on a significant reduction of MRSA acquisition and a trend towards declining transmission [14,18]. They demonstrate that implementation of PCR-based surveillance can be beneficial at least in facilities where culture results have a very long TAT (>3 days) [14,18].

We conclude that in settings where MRSA screening based on cultures, followed by the implementation of additional precautions, is already implemented, the current evidence does not suggest replacing or supplementing culture-based surveillance with rapid tests. However, besides accelerating the implementation of additional precautions, the high negative predictive value of MRSA rapid tests may also be useful when discontinuing contact precautions (including single-room isolation) in settings where they are implemented pre-emptively for suspected MRSA carriers [103]. However, the reliability of a negative nasal rapid test has not been evaluated in situations where pre-emptive isolation is performed for high-risk patients, who are often carrying MRSA at extranasal sites (e.g. wounds). Furthermore, using rapid tests in low prevalence settings may increase the number of false-positive tests (positive predictive values: 31–78%) [103,107-110].

Decolonisation

The effectiveness of mupirocin nasal ointment to eradicate MRSA has been estimated to be 94% one week after treatment and 65% after a 14-day follow-up period [111,112]. Effectiveness of MRSA decolonisation therapy is obviously limited when extranasal sites are colonised [113]. Since nasal carriage of *S. aureus* is a major risk factor for subsequent nosocomial infection, there is a theoretical rationale that eradicating *S. aureus* from the nares can reduce the development of infection. It is, however, controversial to what extent studies assessing the effectiveness of decolonisation among patients carrying MSSA also hold lessons for MRSA [114]. In this review, we have identified only four studies in which mupirocin-treatment was not restricted to MRSA carriers and where effects on MRSA and MSSA infections were reported separately. All four documented a decrease in MRSA, but found insignificant results for MSSA [64,77,79,82]. However, this does not mean that mupirocin-based decolonisation is ineffective against MSSA in general, since two randomised trials have reported a reduction of MSSA infections [48,51]. The reasons for this discrepancy are

unknown, and the question whether results obtained for MSSA can be transferred to MRSA is unresolved. Despite potential local differences in mupirocin susceptibility and the occurrence of clonal lineages [114], a plausible biological explanation why results on MSSA decolonisation treatment should not be applied for MRSA, is currently lacking. Therefore, we have explicitly included studies dealing with *S. aureus* decolonisation. However, future studies will have to assess in detail the differences between the preventive effectiveness of MSSA and MRSA decolonisation.

Regarding the setting of implementation, we found that 14 of 18 studies carried out mostly in surgical settings have found a reduction in infection rates, whereas six of 10 studies which did not report effectiveness, were performed mostly in non-surgical settings [56,62,68,69,74,78]. However, preventive effects have been documented for non-surgical patients, e.g. in haemodialysis units, ICUs or in gastroenterology [50 ,51,55,57,59,68,70,72,76,81].

Overall, we conclude that, taking into account local rates of healthcare-associated infections and infection control conditions, mupirocin-based decolonisation therapy should be considered for selected *S. aureus* carriers who are at high risk of developing nosocomial *S. aureus* infections. The best evidence is available for patients undergoing cardiothoracic or orthopaedic surgery. Of note, the preventive use of mupirocin for decolonisation is constrained by the development of resistance, found in 1% of all subjects when mupirocin was used for short-term prophylaxis. Increasing low-level mupirocin resistance (8–256 µg/mL) has recently been reported in parallel to increased mupirocin consumption [112,115,116].

Isolation

There are multiple approaches to organise isolation measures: Patients can be transferred to special isolation wards, housed in nursing cohorts with designated staff, isolated in single or cohort rooms on general wards without designated personnel, or housed in the same room as patients not affected by MRSA while applying barrier precautions (e.g. gloves and gowns) when caring for the MRSA patient. In this review, we focussed on single room or cohort room isolation because this measure is sometimes debated as it can be associated with disadvantages for the isolated patient [117]. Moreover, in settings with a high prevalence of MRSA, isolation of patients may be hindered due to insufficient side room capacity and financial constraints, if isolation results in bed-blocking.

Overall, we found four studies showing that single room isolation led to a reduction in nosocomial MRSA acquisition and in the incidence of MRSA infection [84-86,88]. In contrast, in a prospective interrupted-time-series study it was found that, MRSA acquisition was not different in phases during which MRSA-colonised or infected patients were moved to single or cohort isolation, compared with phases during which they were not moved [83]. However, limitations of this study are delayed notification of screening results, a high number of missed screenings (80–87% of patients at admission and 71–75% at discharge) and low compliance with hand hygiene (21% compliance) [83]. Moreover, a retrospective comparative study showed that discontinuing single-room isolation and applying transmission-based precautions (e.g. masks, gowns, gloves) for MRSA patients did not lead to an increase in the prevalence of MRSA. However, that study did not measure the occurrence of transmission on the wards and the incidence of MRSA infections [87].

We conclude that the limited evidence from non-controlled studies which is available to support the use of single-room isolation for MRSA (outside of outbreaks) should inspire further research in this field to facilitate the development of evidence-based guidance in future, also for the prevention and control of other multidrug-resistant organisms. However, the majority of studies identified and observations made during outbreaks support the use of single-rooms [3]. Therefore, where facilities (isolation wards, single rooms, cohort rooms) for the isolation of MRSA patients are available, their use should be recommended.

In all investigations identified, it is difficult to estimate to what extent the observed preventive effects were attributable to pre-emptive isolation or to other measures implemented in parallel [16,86,89]. Consequently, there is a need to assess the evidence for the use of pre-emptive isolation measures in hospitals. This is of major importance, because authors evaluating PCR-based screening tests often suggested that rapid tests could accelerate the start of isolation precautions [16,103,118]. However, these advantages cannot be assessed adequately as long as the additional value of pre-emptive isolation is unclear.

Conclusion

We have documented that the evidence for the effectiveness of three major MRSA prevention and control measures does not allow for clear guidance offering 'one-size-fits-all' solutions, because the effectiveness of these interventions seems highly depending on the prevalence of MRSA, compliance with general infection control measures (e.g. hand hygiene), the incidence and type of infections and the transmission rates within the respective setting of implementation. This is documented by the ambiguous study results presented here. In addition, models on the effectiveness of MRSA prevention strategies in different settings have shown that even measures which are performed highly effectively in outbreaks or low-prevalence areas, failed to control MRSA when applied for long-term control or in high-prevalence settings [119]. These difficulties have led to the development of models describing the effects and costs associated with universal vs selective MRSA screening in different settings, which may facilitate the implementation of local

standards [104,120]. Moreover, some authors have recently described the effectiveness of several preventive bundles comprising the measures reviewed here in combination with other interventions. For example, it was shown that universal nasal screening, contact precautions for patients colonised or infected with MRSA, hand hygiene, and changes in the institutional culture of responsibility reduced MRSA infections by 62% [99]. Others have identified that structural factors such as engaging front-line staff, building multidisciplinary teams, providing monitoring and feedback, and acquiring management support were key measures for the success of MRSA prevention [121]. The evaluation of such bundles with respect to their effects, feasibility and applicability in different healthcare systems (e.g. different countries), clinical departments and patient collectives could in the future guide preventive efforts. Compared to assessing the effects of single preventive measures separately (as done in this review), the main advantage of assessing the effects of bundles is that they are planned specifically for targeted healthcare sectors, and the assessment can take into account the financial and other structural conditions in the respective settings.

In this review, we did not restrict the eligibility criteria to controlled studies such as RCTs, although quasi-experimental study designs are prone to be associated with various biases (e.g. selection bias or size of study population). This was done because only very few controlled investigations have been published. In addition, among the 14 RCTs included, most of which were performed for assessing the effectiveness of decolonisation therapy, a majority did either include patients affected by MSSA or did not stratify their outcomes for MSSA and MRSA infections. This makes the results, even of these formally 'high-quality' studies, disputable. Against this background, we decided not to perform a formal grading of the quality of the included studies, but rather to present the study results holistically and leave their use in various settings and countries open for interpretation.

The controversy about different implementation pathways for screening, isolation and decolonisation should not obscure the fact that the beneficial effects of MRSA control measures in general [120] support the recommendations made in many European national MRSA policies from low prevalence countries (e.g. the Nordic countries and the Netherlands) and high prevalence countries (e.g. France, Germany, and the United Kingdom), where a combination of these measures are the standard of care and a reduction in MRSA infections has recently been achieved by coordinated efforts even in high prevalence settings [5,122].

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Conflict of interest

SH is member of the speakers' bureau for bioMérieux and Pfizer, the scientific advisory board of Destiny Pharma, DaVolterra and bioMérieux. RLS is member of the Novartis advisory board. AWF has received fees from Siemens, Boehringer Ingelheim and Bayer; RLS from Pfizer, Leo Pharma, RibXrom and The Medicines Company; BDC from Sanofi Pasteur, Pfizer, Esoform/Ecolab and Vemacare.
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Authors' contributions

RK and AWF did the literature search and screened titles and abstracts for relevant articles. RK and AWF extracted data from the full-texts. RK, AWF, KB, BC, JEvGP, SH, JK, MM, GP, RLS, MJS, ET and WW contributed to data collection, formulating the conclusions and writing of the manuscript.

References

1. European Centre for Disease Prevention and Control (ECDC)/ European Medicines Agency (EMEA) joint technical report: The bacterial challenge: time to react. Stockholm: ECDC; 2009. Available from: http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf
2. Wolkewitz M, Frank U, Philips G, Schumacher M, Davey P. Mortality associated with in-hospital bacteraemia caused by Staphylococcus aureus: a multistate analysis with follow-up beyond hospital discharge. J Antimicrob Chemother. 2011;66(2):381-6. http://dx.doi.org/10.1093/jac/dkq424
3. Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol. 2003;24(5):362-86. http://dx.doi.org/10.1086/502213
4. Loveday HP, Pellowe CM, Jones SR, Pratt RJ. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant Staphylococcus aureus (1996-2004): report to the Joint MRSA Working Party (Subgroup A). J Hosp Infect. 2006;63 Suppl 1:S45-70. http://dx.doi.org/10.1016/j.jhin.2006.01.002
5. Kalenic S, Cookson BD, Gallagher R, Popp W, Asensio-Vegas A, Assadian O, et al. Comparison of recommendations in national/regional Guidelines for prevention and control of MRSA. Int J Infect Control. 2010;6(2). doi: 10.3396/ijic.V6i2.016.10. http://dx.doi.org/10.3396/ijic.V6i2.016.10
6. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62(10):1006-12. http://dx.doi.org/10.1016/j.jclinepi.2009.06.005
7. Aldeyab MA, Kearney MP, Hughes CM, Scott MG, Tunney MM, Gilpin DF, et al. Can the use of a rapid polymerase chain screening method decrease the incidence of nosocomial meticillin-resistant Staphylococcus aureus? J Hosp Infect.

2009;71(1):22-8.
http://dx.doi.org/10.1016/j.jhin.2008.10.011

8. Awad SS, Palacio CH, Subramanian A, Byers PA, Abraham P, Lewis DA, et al. Implementation of a methicillin-resistant Staphylococcus aureus (MRSA) prevention bundle results in decreased MRSA surgical site infections. Am J Surg. 2009;198(5):607-10.
http://dx.doi.org/10.1016/j.amjsurg.2009.07.010

9. Camus C, Bellissant E, Legras A, Renault A, Gacouin A, Lavoue S, et al. Randomized comparison of 2 protocols to prevent acquisition of methicillin-resistant Staphylococcus aureus: results of a 2-center study involving 500 patients. Infect Control Hosp Epidemiol. 2011;32(11):1064-72.
http://dx.doi.org/10.1086/662180

10. Chaberny IF, Schwab F, Ziesing S, Suerbaum S, Gastmeier P. Impact of routine surgical ward and intensive care unit admission surveillance cultures on hospital-wide nosocomial methicillin-resistant Staphylococcus aureus infections in a university hospital: an interrupted time-series analysis. J Antimicrob Chemother. 2008;62(6):1422-9.
http://dx.doi.org/10.1093/jac/dkn373

11. Chowers MY, Paitan Y, Gottesman BS, Gerber B, Ben-Nissan Y, Shitrit P. Hospital-wide methicillin-resistant Staphylococcus aureus control program: A 5-year follow-up. Infect Control Hosp Epidemiol. 2009;30(8):778-81.
http://dx.doi.org/10.1086/599019

12. Clancy M, Graepler A, Wilson M, Douglas I, Johnson J, Price CS. Active screening in high-risk units is an effective and cost-avoidant method to reduce the rate of methicillin-resistant Staphylococcus aureus infection in the hospital. Infect Control Hosp Epidemiol. 2006;27(10):1009-17.
http://dx.doi.org/10.1086/507915

13. Conterno LO, Shymanski J, Ramotar K, Toye B, van Walraven C, Coyle D, et al. Real-time polymerase chain reaction detection of methicillin-resistant Staphylococcus aureus: impact on nosocomial transmission and costs. Infect Control Hosp Epidemiol. 2007;28(10):1134-41.
http://dx.doi.org/10.1086/520099

14. Cunningham R, Jenks P, Northwood J, Wallis M, Ferguson S, Hunt S. Effect on MRSA transmission of rapid PCR testing of patients admitted to critical care. J Hosp Infect. 2007;65(1):24-8.
http://dx.doi.org/10.1016/j.jhin.2006.09.019

15. Ellingson K, Muder RR, Jain R, Kleinbaum D, Feng PJ, Cunningham C, et al. Sustained reduction in the clinical incidence of methicillin-resistant Staphylococcus aureus colonization or infection associated with a multifaceted infection control intervention. Infect Control Hosp Epidemiol. 2011;32(1):1-8.
http://dx.doi.org/10.1086/657665

16. Harbarth S, Masuet-Aumatell C, Schrenzel J, Francois P, Akakpo C, Renzi G, et al. Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant Staphylococcus aureus in critical care: an interventional cohort study. Crit Care. 2006;10(1):R25.
http://dx.doi.org/10.1186/cc3982

17. Harbarth S, Fankhauser C, Schrenzel J, Christenson J, Gervaz P, Bandiera-Clerc C, et al. Universal screening for methicillin-resistant Staphylococcus aureus at hospital admission and nosocomial infection in surgical patients. JAMA. 2008;299(10):1149-57.
http://dx.doi.org/10.1001/jama.299.10.1149

18. Hardy K, Price C, Szczepura A, Gossain S, Davies R, Stallard N, et al. Reduction in the rate of methicillin-resistant Staphylococcus aureus acquisition in surgical wards by rapid screening for colonization: a prospective, cross-over study. Clin Microbiol Infect. 2010;16(4):333-9.
http://dx.doi.org/10.1111/j.1469-0691.2009.02899.x

19. Holzmann-Pazgal G, Monney C, Davis K, Wanger A, Strobel N, Zhong F. Active surveillance culturing impacts methicillin-resistant Staphylococcus aureus acquisition in a pediatric intensive care unit. Pediatr Crit Care Med. 2011;12(4):e171-5.
http://dx.doi.org/10.1097/PCC.0b013e3181f39222

20. Huskins WC, Huckabee CM, O'Grady NP, Murray P, Kopetskie H, Zimmer L, et al. Intervention to reduce transmission of resistant bacteria in intensive care. N Engl J Med. 2011;364(15):1407-18.
http://dx.doi.org/10.1056/NEJMoa1000373

21. Huang SS, Yokoe DS, Hinrichsen VL, Spurchise LS, Datta R, Miroshnik I, et al. Impact of routine intensive care unit surveillance cultures and resultant barrier precautions on hospital-wide methicillin-resistant Staphylococcus aureus bacteremia. Clin Infect Dis. 2006;43(8):971-8.
http://dx.doi.org/10.1086/507636

22. Kurup A, Chlebicka N, Tan KY, Chen EX, Oon L, Ling TA, et al. Active surveillance testing and decontamination strategies in intensive care units to reduce methicillin-resistant Staphylococcus aureus infections. Am J Infect Control. 2010;38(5):361-7.
http://dx.doi.org/10.1016/j.ajic.2009.09.018

23. Jeyaratnam D, Whitty CJ, Phillips K, Liu D, Orezzi C, Ajoku U, et al. Impact of rapid screening tests on acquisition of meticillin resistant Staphylococcus aureus: cluster randomised crossover trial. BMJ. 2008;336(7650):927-30.
http://dx.doi.org/10.1136/bmj.39525.579063.BE

24. Jog S, Cunningham R, Cooper S, Wallis M, Marchbank A, Vasco-Knight P, et al. Impact of preoperative screening for meticillin-resistant Staphylococcus aureus by real-time polymerase chain reaction in patients undergoing cardiac surgery. J Hosp Infect. 2008;69(2):124-30.
http://dx.doi.org/10.1016/j.jhin.2008.02.008

25. Leonhardt KK, Yakusheva O, Phelan D, Reeths A, Hosterman T, Bonin D, et al. Clinical effectiveness and cost benefit of universal versus targeted methicillin-resistant Staphylococcus aureus screening upon admission in hospitals. Infect Control Hosp Epidemiol. 2011;32(8):797-803.
http://dx.doi.org/10.1086/660875

26. Martinez-Capolino C, Reyes K, Johnson L, Sullivan J, Samuel L, Digiovine B, et al. Impact of active surveillance on meticillin-resistant Staphylococcus aureus transmission and hospital resource utilisation. J Hosp Infect. 2010;74(3):232-7.
http://dx.doi.org/10.1016/j.jhin.2009.10.018

27. Reilly JS, Stewart S, Christie P, Allardice GM, Stari T, Matheson A, et al. Universal screening for meticillin-resistant Staphylococcus aureus in acute care: risk factors and outcome from a multicentre study. J Hosp Infect. 2012;80(1):31-5.
http://dx.doi.org/10.1016/j.jhin.2011.09.008

28. Pan A, Carnevale G, Catenazzi P, Colombini P, Crema L, Dolcetti L, et al. Trends in methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections: effect of the MRSA "search and isolate" strategy in a hospital in Italy with hyperendemic MRSA. Infect Control Hosp Epidemiol. 2005;26(2):127-33.
http://dx.doi.org/10.1086/502515

29. Robicsek A, Beaumont JL, Paule SM, Hacek DM, Thomson RB, Jr., Kaul KL, et al. Universal surveillance for methicillin-resistant Staphylococcus aureus in 3 affiliated hospitals. Ann Intern Med. 2008;148(6):409-18.
http://dx.doi.org/10.7326/0003-4819-148-6-200803180-00003

30. Rodriguez-Bano J, Garcia L, Ramirez E, Lupion C, Muniain MA, Velasco C, et al. Long-term control of endemic hospital-wide methicillin-resistant Staphylococcus aureus (MRSA): the impact of targeted active surveillance for MRSA in patients and healthcare workers. Infect Control Hosp Epidemiol. 2010;31(8):786-95.
http://dx.doi.org/10.1086/654003

31. Shitrit P, Gottesman BS, Katzir M, Kilman A, Ben-Nissan Y, Chowers M. Active surveillance for methicillin-resistant Staphylococcus aureus (MRSA) decreases the incidence of MRSA bacteremia. Infect Control Hosp Epidemiol. 2006;27(10):1004-8.
http://dx.doi.org/10.1086/507914

32. Thompson DS, Workman R, Strutt M. Decline in the rates of meticillin-resistant Staphylococcus aureus acquisition and bacteraemia in a general intensive care unit between 1996 and 2008. J Hosp Infect. 2009;71(4):314-9.
http://dx.doi.org/10.1016/j.jhin.2008.12.010

33. Wang JT, Lauderdale TL, Lee WS, Huang JH, Wang TH, Chang SC. Impact of active surveillance and contact isolation on transmission of methicillin-resistant Staphylococcus aureus in intensive care units in an area with high prevalence. J Formos Med Assoc. 2010;109(4):258-68.
http://dx.doi.org/10.1016/S0929-6646(10)60051-4

34. Warren DK, Guth RM, Coopersmith CM, Merz LR, Zack JE, Fraser VJ. Impact of a methicillin-resistant Staphylococcus aureus active surveillance program on contact precaution utilization in a surgical intensive care unit. Crit Care Med. 2007;35(2):430-4.
http://dx.doi.org/10.1097/01.CCM.0000253813.98431.28

35. West TE, Guerry C, Hiott M, Morrow N, Ward K, Salgado CD. Effect of targeted surveillance for control of methicillin-resistant Staphylococcus aureus in a community hospital system. Infect Control Hosp Epidemiol. 2006;27(3):233-8.
http://dx.doi.org/10.1086/500372

36. Wernitz MH, Swidsinski S, Weist K, Sohr D, Witte W, Franke KP, et al. Effectiveness of a hospital-wide selective screening programme for methicillin-resistant Staphylococcus aureus (MRSA) carriers at hospital admission to prevent hospital-acquired MRSA infections. Clin Microbiol Infect. 2005;11(6):457-65.
http://dx.doi.org/10.1111/j.1469-0691.2005.01152.x

37. Malde DJ, Abidia A, McCollum C, Welch M. The success of routine MRSA screening in vascular surgery: A nine year review. Int Angiol. 2006;25(2):204-8.

38. Lawes T, Edwards B, Lopez-Lozano JM, Gould I. Trends in Staphylococcus aureus bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis. BMJ Open. 2012;2(3):pii: e000797.

39. Parvez N, Jinadatha C, Fader R, Huber TW, Robertson A, Kjar D, et al. Universal MRSA nasal surveillance: Characterization of outcomes at a tertiary care center and implications for infection control. South Med J. 2010;103(11):1084-91. http://dx.doi.org/10.1097/SMJ.0b013e3181f69235

40. Kelly JC, O'Briain DE, Walls R, Lee SI, O'Rourke A, Mc Cabe JP. The role of pre-operative assessment and ringfencing of services in the control of methicillin resistant Staphylococcus aureus infection in orthopaedic patients. Surgeon. 2012;10(2):75-9. http://dx.doi.org/10.1016/j.surge.2011.01.008

41. Kjonegaard R, Fields W, Peddecord KM. Universal rapid screening for methicillin-resistant Staphylococcus aureus in the intensive care units in a large community hospital. Am J Infect Control. 2013;41(1):45-50. http://dx.doi.org/10.1016/j.ajic.2012.01.038

42. Eveillard M, Lancien E, Barnaud G, Hidri N, Gaba S, Benlolo JA, et al. Impact of screening for MRSA carriers at hospital admission on risk-adjusted indicators according to the imported MRSA colonization pressure. J Hosp Infect. 2005;59(3):254-8. http://dx.doi.org/10.1016/j.jhin.2004.09.028

43. Lucet JC, Paoletti X, Lolom I, Paugam-Burtz C, Trouillet JL, Timsit JF, et al. Successful long-term program for controlling methicillin-resistant Staphylococcus aureus in intensive care units. Intensive Care Med. 2005;31(8):1051-7. http://dx.doi.org/10.1007/s00134-005-2679-0

44. Troche G, Joly LM, Guibert M, Zazzo JF. Detection and treatment of antibiotic-resistant bacterial carriage in a surgical intensive care unit: a 6-year prospective survey. Infect Control Hosp Epidemiol. 2005;26(2):161-5. http://dx.doi.org/10.1086/502521

45. Tomic V, Svetina Sorli P, Trinkaus D, Sorli J, Widmer AF, Trampuz A. Comprehensive strategy to prevent nosocomial spread of methicillin-resistant Staphylococcus aureus in a highly endemic setting. Arch Intern Med. 2004;164(18):2038-43. http://dx.doi.org/10.1001/archinte.164.18.2038

46. Souweine B, Traore O, Aublet-Cuvelier B, Bret L, Sirot J, Laveran H, et al. Role of infection control measures in limiting morbidity associated with multi-resistant organisms in critically ill patients. J Hosp Infect. 2000;45(2):107-16. http://dx.doi.org/10.1053/jhin.2000.0734

47. Gould IM, MacKenzie FM, MacLennan G, Pacitti D, Watson EJ, Noble DW. Topical antimicrobials in combination with admission screening and barrier precautions to control endemic methicillin-resistant Staphylococcus aureus in an Intensive Care Unit. Int J Antimicrob Agents. 2007;29(5):536-43. http://dx.doi.org/10.1016/j.ijantimicag.2006.12.019

48. Bode LG, Kluytmans JA, Wertheim HF, Bogaers D, Vandenbroucke-Grauls CM, Roosendaal R, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med. 2010;362(1):9-17. http://dx.doi.org/10.1056/NEJMoa0808939

49. Sankar B, Hopgood P, Bell KM. The role of MRSA screening in joint-replacement surgery. Int Orthop. 2005;29(3):160-3. http://dx.doi.org/10.1007/s00264-005-0649-3

50. Sandri AM, Dalarosa MG, Ruschel de Alcantara L, da Silva Elias L, Zavascki AP. Reduction in incidence of nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection in an intensive care unit: role of treatment with mupirocin ointment and chlorhexidine baths for nasal carriers of MRSA. Infect Control Hosp Epidemiol. 2006;27(2):185-7. http://dx.doi.org/10.1086/500625

51. Boelaert JR, De Smedt RA, De Baere YA, Godard CA, Matthys EG, Schurgers ML, et al. The influence of calcium mupirocin nasal ointment on the incidence of Staphylococcus aureus infections in haemodialysis patients. Nephrol Dial Transplant. 1989;4(4):278-81.

52. Camus C, Bellissant E, Sebille V, Perrotin D, Garo B, Legras A, et al. Prevention of acquired infections in intubated patients with the combination of two decontamination regimens. Crit Care Med. 2005;33(2):307-14. http://dx.doi.org/10.1097/01.CCM.0000152224.01949.01

53. Cimochowski GE, Harostock MD, Brown R, Bernardi M, Alonzo N, Coyle K. Intranasal mupirocin reduces sternal wound infection after open heart surgery in diabetics and nondiabetics. Ann Thorac Surg. 2001;71(5):1572-8; discussion 8-9. http://dx.doi.org/10.1016/S0003-4975(01)02519-X

54. Cordova KB, Grenier N, Chang KH, Dufresne R, Jr. Preoperative methicillin-resistant Staphylococcus aureus screening in Mohs surgery appears to decrease postoperative infections. Dermatol Surg. 2010;36(10):1537-40. http://dx.doi.org/10.1111/j.1524-4725.2010.01678.x

55. Keshtgar MR, Khalili A, Coen PG, Carder C, Macrae B, Jeanes A, et al. Impact of rapid molecular screening for meticillin-resistant Staphylococcus aureus in surgical wards. Br J Surg. 2008;95(3):381-6. http://dx.doi.org/10.1002/bjs.6013

56. Dupeyron C, Campillo B, Bordes M, Faubert E, Richardet JP, Mangeney N. A clinical trial of mupirocin in the eradication of methicillin-resistant Staphylococcus aureus nasal carriage in a digestive disease unit. J Hosp Infect. 2002;52(4):281-7. http://dx.doi.org/10.1053/jhin.2002.1287

57. Dupeyron C, Campillo B, Richardet JP, Soussy CJ. Long-term efficacy of mupirocin in the prevention of infections with meticillin-resistant Staphylococcus aureus in a gastroenterology unit. J Hosp Infect. 2006;63(4):385-92. http://dx.doi.org/10.1016/j.jhin.2006.03.019

58. Pofahl WE, Goettler CE, Ramsey KM, Cochran MK, Nobles DL, Rotondo MF. Active surveillance screening of MRSA and eradication of the carrier state decreases surgical-site infections caused by MRSA. J Am Coll Surg. 2009;208(5):981-8. http://dx.doi.org/10.1016/j.jamcollsurg.2008.12.025

59. Fraser S, Brady RR, Graham C, Paterson-Brown S, Gibb AP. Methicillin-resistant Staphylococcus aureus in surgical patients: identification of high-risk populations for the development of targeted screening programmes. Ann R Coll Surg Engl. 2010;92(4):311-5. http://dx.doi.org/10.1308/003588410X12628812459698

60. Gernaat-van der Sluis AJ, Hoogenboom-Verdegaal AM, Edixhoven PJ, Spies-van Rooijen NH. Prophylactic mupirocin could reduce orthopedic wound infections. 1,044 patients treated with mupirocin compared with 1,260 historical controls. Acta Orthop Scand. 1998;69(4):412-4. http://dx.doi.org/10.3109/17453679808999058

61. Hadley S, Immerman I, Hutzler L, Slover J, Bosco J. Staphylococcus aureus Decolonization Protocol Decreases Surgical Site Infections for Total Joint Replacement. Arthritis. 2010;2010:924518. doi: 10.1155/2010/924518. http://dx.doi.org/10.1155/2010/924518

62. Harbarth S, Dharan S, Liassine N, Herrault P, Auckenthaler R, Pittet D. Randomized, placebo-controlled, double-blind trial to evaluate the efficacy of mupirocin for eradicating carriage of methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 1999;43(6):1412-6.

63. Kalmeijer MD, Coertjens H, van Nieuwland-Bollen PM, Bogaers-Hofman D, de Baere GA, Stuurman A, et al. Surgical site infections in orthopedic surgery: the effect of mupirocin nasal ointment in a double-blind, randomized, placebo-controlled study. Clin Infect Dis. 2002;35(4):353-8. http://dx.doi.org/10.1086/341025

64. Kim DH, Spencer M, Davidson SM, Li L, Shaw JD, Gulczynski D, et al. Institutional prescreening for detection and eradication of methicillin-resistant Staphylococcus aureus in patients undergoing elective orthopaedic surgery. J Bone Joint Surg Am. 2010;92(9):1820-6. http://dx.doi.org/10.2106/JBJS.I.01050

65. Kluytmans JA, Mouton JW, VandenBergh MF, Manders MJ, Maat AP, Wagenvoort JH, et al. Reduction of surgical-site infections in cardiothoracic surgery by elimination of nasal carriage of Staphylococcus aureus. Infect Control Hosp Epidemiol. 1996;17(12):780-5. http://dx.doi.org/10.1086/647236 http://dx.doi.org/10.2307/30141170

66. Konvalinka A, Errett L, Fong IW. Impact of treating Staphylococcus aureus nasal carriers on wound infections in cardiac surgery. J Hosp Infect. 2006;64(2):162-8. http://dx.doi.org/10.1016/j.jhin.2006.06.010

67. Lipke VL, Hyott AS. Reducing surgical site infections by bundling multiple risk reduction strategies and active surveillance. Aorn J. 2010;92(3):288-96. http://dx.doi.org/10.1016/j.aorn.2010.01.016

68. Milstone AM, Budd A, Shepard JW, Ross T, Aucott S, Carroll KC, et al. Role of decolonization in a comprehensive strategy to reduce methicillin-resistant Staphylococcus aureus infections in the neonatal intensive care unit: an observational cohort study. Infect Control Hosp Epidemiol. 2010;31(5):558-60. http://dx.doi.org/10.1086/652449

69. Mody L, Kauffman CA, McNeil SA, Galecki AT, Bradley SF. Mupirocin-based decolonization of Staphylococcus

aureus carriers in residents of 2 long-term care facilities: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis. 2003;37(11):1467-74. http://dx.doi.org/10.1086/379325

70. Muller A, Talon D, Potier A, Belle E, Cappelier G, Bertrand X. Use of intranasal mupirocin to prevent methicillin-resistant Staphylococcus aureus infection in intensive care units. Crit Care. 2005;9(3):R246-50. http://dx.doi.org/10.1186/cc3512
71. Nicholson MR, Huesman LA. Controlling the usage of intranasal mupirocin does impact the rate of Staphylococcus aureus deep sternal wound infections in cardiac surgery patients. Am J Infect Control. 2006;34(1):44-8. http://dx.doi.org/10.1016/j.ajic.2005.07.004
72. The Mupirocin Study Group. Nasal mupirocin prevents Staphylococcus aureus exit-site infection during peritoneal dialysis. Mupirocin Study Group. J Am Soc Nephrol. 1996;7(11):2403-8.
73. Perl TM, Cullen JJ, Wenzel RP, Zimmerman MB, Pfaller MA, Sheppard D, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med. 2002;346(24):1871-7. http://dx.doi.org/10.1056/NEJMoa003069
74. Robicsek A, Beaumont JL, Thomson RB, Jr., Govindarajan G, Peterson LR. Topical therapy for methicillin-resistant Staphylococcus aureus colonization: impact on infection risk. Infect Control Hosp Epidemiol. 2009;30(7):623-32. http://dx.doi.org/10.1086/597550
75. Suzuki Y, Kamigaki T, Fujino Y, Tominaga M, Ku Y, Kuroda Y. Randomized clinical trial of preoperative intranasal mupirocin to reduce surgical-site infection after digestive surgery. Br J Surg. 2003;90(9):1072-5. http://dx.doi.org/10.1002/bjs.4269
76. Thomas S, Cantrill S, Waghorn DJ, McIntyre A. The role of screening and antibiotic prophylaxis in the prevention of percutaneous gastrostomy site infection caused by methicillin-resistant Staphylococcus aureus. Aliment Pharmacol Ther. 2007;25(5):593-7. http://dx.doi.org/10.1111/j.1365-2036.2006.03242.x
77. Walsh EE, Greene L, Kirshner R. Sustained reduction in methicillin-resistant Staphylococcus aureus wound infections after cardiothoracic surgery. Arch Intern Med. 2011;171(1):68-73.
78. Wertheim HF, Vos MC, Ott A, van Belkum A, Voss A, Kluytmans JA, et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. Lancet. 2004;364(9435):703-5. http://dx.doi.org/10.1016/S0140-6736(04)16897-9
79. Wilcox MH, Hall J, Pike H, Templeton PA, Fawley WN, Parnell P, et al. Use of perioperative mupirocin to prevent methicillin-resistant Staphylococcus aureus (MRSA) orthopaedic surgical site infections. J Hosp Infect. 2003;54(3):196-201. http://dx.doi.org/10.1016/S0195-6701(03)00147-6
80. Huang YC, Lien RI, Su LH, Chou YH, Lin TY. Successful control of methicillin-resistant Staphylococcus aureus in endemic neonatal intensive care units--a 7-year campaign. PLoS One. 2011;6(8):e23001. http://dx.doi.org/10.1371/journal.pone.0023001
81. Ridenour G, Lampen R, Federspiel J, Kritchevsky S, Wong E, Climo M. Selective use of intranasal mupirocin and chlorhexidine bathing and the incidence of methicillin-resistant Staphylococcus aureus colonization and infection among intensive care unit patients. Infect Control Hosp Epidemiol. 2007;28(10):1155-61. http://dx.doi.org/10.1086/520102
82. Yano M, Doki Y, Inoue M, Tsujinaka T, Shiozaki H, Monden M. Preoperative intranasal mupirocin ointment significantly reduces postoperative infection with Staphylococcus aureus in patients undergoing upper gastrointestinal surgery. Surg Today. 2000;30(1):16-21. http://dx.doi.org/10.1007/PL00010040
83. Cepeda JA, Whitehouse T, Cooper B, Hails J, Jones K, Kwaku F, et al. Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study. Lancet. 2005;365(9456):295-304. http://dx.doi.org/10.1016/S0140-6736(05)70193-8 http://dx.doi.org/10.1016/S0140-6736(05)17783-6
84. Bracco D, Dubois MJ, Bouali R, Eggimann P. Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant Staphylococcus aureus in intensive care units. Intensive Care Med. 2007;33(5):836-40. http://dx.doi.org/10.1007/s00134-007-0559-5
85. Cheng VC, Tai JW, Chan WM, Lau EH, Chan JF, To KK, et al. Sequential introduction of single room isolation and hand hygiene campaign in the control of methicillin-resistant Staphylococcus aureus in intensive care unit. BMC Infect Dis. 2010;10:263. http://dx.doi.org/10.1186/1471-2334-10-263
86. Curran ET, Hamilton K, Monaghan A, McGinlay M, Thakker B. Use of a temporary cohort ward as part of an intervention to reduce the incidence of meticillin-resistant Staphylococcus aureus in a vascular surgery ward. J Hosp Infect. 2006;63(4):374-9. http://dx.doi.org/10.1016/j.jhin.2006.02.017
87. Fazal BA, Telzak EE, Blum S, Turett GS, Petersen-Fitzpatrick FE, Lorian V. Trends in the prevalence of methicillin-resistant Staphylococcus aureus associated with discontinuation of an isolation policy. Infect Control Hosp Epidemiol. 1996;17(6):372-4. http://dx.doi.org/10.2307/30141139 http://dx.doi.org/10.1086/647322
88. Gregory ML, Eichenwald EC, Puopolo KM. Seven-year experience with a surveillance program to reduce methicillin-resistant Staphylococcus aureus colonization in a neonatal intensive care unit. Pediatrics. 2009;123(5):e790-6. http://dx.doi.org/10.1542/peds.2008-1526
89. Lecornet E, Robert J, Jacqueminet S, Van Georges H, Jeanne S, Bouilloud F, et al. Preemptive isolation to prevent methicillin-resistant Staphylococcus aureus cross-transmission in diabetic foot. Diabetes Care. 2007;30(9):2341-2. http://dx.doi.org/10.2337/dc07-0743
90. Grayson ML, Russo PL, Cruickshank M, Bear JL, Gee CA, Hughes CF, et al. Outcomes from the first 2 years of the Australian National Hand Hygiene Initiative. Med J Aust. 2011;195(10):615-9. http://dx.doi.org/10.5694/mja11.10747
91. Stone SP, Fuller C, Savage J, Cookson B, Hayward A, Cooper B, et al. Evaluation of the national Cleanyourhands campaign to reduce Staphylococcus aureus bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. BMJ. 2012;344:e3005. http://dx.doi.org/10.1136/bmj.e3005
92. Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant Staphylococcus aureus. Infect Dis Clin North Am. 2011;25(1):155-79. http://dx.doi.org/10.1016/j.idc.2010.11.002
93. Haustein T, Gastmeier P, Holmes A, Lucet JC, Shannon RP, Pittet D, et al. Use of benchmarking and public reporting for infection control in four high-income countries. Lancet Infect Dis. 2011;11(6):471-81. http://dx.doi.org/10.1016/S1473-3099(10)70315-7
94. Wyllie DH, Walker AS, Miller R, Moore C, Williamson SR, Schlackow I, et al. Decline of meticillin-resistant Staphylococcus aureus in Oxfordshire hospitals is strain-specific and preceded infection-control intensification. BMJ Open. 2011;1(1):e000160. http://dx.doi.org/10.1136/bmjopen-2011-000160
95. Gurieva T, Bootsma MC, Bonten MJ. Successful Veterans Affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections revisited. Clin Infect Dis. 2012;54(11):1618-20. http://dx.doi.org/10.1093/cid/cis272
96. Vos MC, Behrendt MD, Melles DC, Mollema FP, de Groot W, Parlevliet G, et al. 5 years of experience implementing a methicillin-resistant Staphylococcus aureus search and destroy policy at the largest university medical center in the Netherlands. Infect Control Hosp Epidemiol. 2009;30(10):977-84. http://dx.doi.org/10.1086/605921
97. Salgado CD, Farr BM. What proportion of hospital patients colonized with methicillin-resistant Staphylococcus aureus are identified by clinical microbiological cultures? Infect Control Hosp Epidemiol. 2006;27(2):116-21. http://dx.doi.org/10.1086/500624
98. Tacconelli E, De Angelis G, de Waure C, Cataldo MA, La Torre G, Cauda R. Rapid screening tests for meticillin-resistant Staphylococcus aureus at hospital admission: systematic review and meta-analysis. Lancet Infect Dis. 2009;9(9):546-54. http://dx.doi.org/10.1016/S1473-3099(09)70150-1
99. Jain R, Kralovic SM, Evans ME, Ambrose M, Simbartl LA, Obrosky DS, et al. Veterans Affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections. N Engl J Med. 2011;364(15):1419-30. http://dx.doi.org/10.1056/NEJMoa1007474
100. Jarlier V, Trystram D, Brun-Buisson C, Fournier S, Carbonne A, Marty L, et al. Curbing methicillin-resistant Staphylococcus aureus in 38 French hospitals through a 15-year institutional control program. Arch Intern Med. 2010;170(6):552-9. http://dx.doi.org/10.1001/archinternmed.2010.32

101. Bootsma MC, Diekmann O, Bonten MJ. Controlling methicillin-resistant Staphylococcus aureus: quantifying the effects of interventions and rapid diagnostic testing. Proc Natl Acad Sci U S A. 2006;103(14):5620-5. http://dx.doi.org/10.1073/pnas.0510077103

102. Raboud J, Saskin R, Simor A, Loeb M, Green K, Low DE, et al. Modeling transmission of methicillin-resistant Staphylococcus aureus among patients admitted to a hospital. Infect Control Hosp Epidemiol. 2005;26(7):607-15. http://dx.doi.org/10.1086/502589

103. Wassenberg MW, Kluytmans JA, Box AT, Bosboom RW, Buiting AG, van Elzakker EP, et al. Rapid screening of methicillin-resistant Staphylococcus aureus using PCR and chromogenic agar: a prospective study to evaluate costs and effects. Clin Microbiol Infect. 2010;16(12):1754-61. http://dx.doi.org/10.1111/j.1469-0691.2010.03210.x

104. Murthy A, De Angelis G, Pittet D, Schrenzel J, Uckay I, Harbarth S. Cost-effectiveness of universal MRSA screening on admission to surgery. Clin Microbiol Infect. 2010;16(12):1747-53. http://dx.doi.org/10.1111/j.1469-0691.2010.03220.x

105. Carroll KC. Rapid diagnostics for methicillin-resistant Staphylococcus aureus: current status. Mol Diagn Ther. 2008;12(1):15-24. http://dx.doi.org/10.1007/BF03256265

106. Malhotra-Kumar S, Haccuria K, Michiels M, Ieven M, Poyart C, Hryniewicz W, et al. Current trends in rapid diagnostics for methicillin-resistant Staphylococcus aureus and glycopeptide-resistant enterococcus species. J Clin Microbiol. 2008;46(5):1577-87. http://dx.doi.org/10.1128/JCM.00326-08

107. Nulens E, Descheemaeker P, Deurenberg RH, Stobberingh EE, Gordts B. Contribution of two molecular assays as compared to selective culture for MRSA screening in a low MRSA prevalence population. Infection. 2010;38(2):98-101. http://dx.doi.org/10.1007/s15010-009-9117-0

108. Laurent C, Bogaerts P, Schoevaerdts D, Denis O, Deplano A, Swine C, et al. Evaluation of the Xpert MRSA assay for rapid detection of methicillin-resistant Staphylococcus aureus from nares swabs of geriatric hospitalized patients and failure to detect a specific SCCmec type IV variant. Eur J Clin Microbiol Infect Dis. 2010;29(8):995-1002. http://dx.doi.org/10.1007/s10096-010-0958-3

109. Wong H, Louie L, Lo RY, Simor AE. Characterization of Staphylococcus aureus isolates with a partial or complete absence of staphylococcal cassette chromosome elements. J Clin Microbiol. 2010;48(10):3525-31. http://dx.doi.org/10.1128/JCM.00775-10

110. Blanc DS, Basset P, Nahimana-Tessemo I, Jaton K, Greub G, Zanetti G. High proportion of wrongly identified methicillin-resistant Staphylococcus aureus carriers by use of a rapid commercial PCR assay due to presence of staphylococcal cassette chromosome element lacking the mecA gene. J Clin Microbiol. 2011;49(2):722-4. http://dx.doi.org/10.1128/JCM.01988-10

111. McConeghy KW, Mikolich DJ, LaPlante KL. Agents for the decolonization of methicillin-resistant Staphylococcus aureus. Pharmacotherapy. 2009;29(3):263-80. http://dx.doi.org/10.1592/phco.29.3.263

112. Ammerlaan HS, Kluytmans JA, Wertheim HF, Nouwen JL, Bonten MJ. Eradication of methicillin-resistant Staphylococcus aureus carriage: a systematic review. Clin Infect Dis. 2009;48(7):922-30. http://dx.doi.org/10.1086/597291

113. Buehlmann M, Frei R, Fenner L, Dangel M, Fluckiger U, Widmer AF. Highly effective regimen for decolonization of methicillin-resistant Staphylococcus aureus carriers. Infect Control Hosp Epidemiol. 2008;29(6):510-6. http://dx.doi.org/10.1086/588201

114. Lucet JC, Regnier B. Screening and decolonization: does methicillin-susceptible Staphylococcus aureus hold lessons for methicillin-resistant S. aureus? Clin Infect Dis. 2010;51(5):585-90. http://dx.doi.org/10.1086/655695

115. Lee AS, Macedo-Vinas M, Francois P, Renzi G, Vernaz N, Schrenzel J, et al. Trends in mupirocin resistance in meticillin-resistant Staphylococcus aureus and mupirocin consumption at a tertiary care hospital. J Hosp Infect. 2011;77(4):360-2. http://dx.doi.org/10.1016/j.jhin.2010.11.002

116. Lee AS, Macedo-Vinas M, Francois P, Renzi G, Schrenzel J, Vernaz N, et al. Impact of combined low-level mupirocin and genotypic chlorhexidine resistance on persistent methicillin-resistant Staphylococcus aureus carriage after decolonization therapy: a case-control study. Clin Infect Dis. 2011;52(12):1422-30. http://dx.doi.org/10.1093/cid/cir233

117. Morgan DJ, Diekema DJ, Sepkowitz K, Perencevich EN. Adverse outcomes associated with Contact Precautions: a review of the literature. Am J Infect Control. 2009;37(2):85-93. http://dx.doi.org/10.1016/j.ajic.2008.04.257

118. Buhlmann M, Bogli-Stuber K, Droz S, Muhlemann K. Rapid screening for carriage of methicillin-resistant Staphylococcus aureus by PCR and associated costs. J Clin Microbiol. 2008;46(7):2151-4. http://dx.doi.org/10.1128/JCM.01957-07

119. Cooper BS, Medley GF, Stone SP, Kibbler CC, Cookson BD, Roberts JA, et al. Methicillin-resistant Staphylococcus aureus in hospitals and the community: stealth dynamics and control catastrophes. Proc Natl Acad Sci U S A. 2004;101(27):10223-8. http://dx.doi.org/10.1073/pnas.0401324101

120. Harbarth S, Hawkey PM, Tenover F, Stefani S, Pantosti A, Struelens MJ. Update on screening and clinical diagnosis of meticillin-resistant Staphylococcus aureus (MRSA). Int J Antimicrob Agents. 2011;37(2):110-7. http://dx.doi.org/10.1016/j.ijantimicag.2010.10.022

121. Welsh CA, Flanagan ME, Kiess C, Doebbeling BN. Implementing the MRSA bundle in ICUs: one citywide collaborative's key lessons learned. Infect Control Hosp Epidemiol. 2011;32(9):918-21. http://dx.doi.org/10.1086/661101

122. Köck R, Becker K, Cookson B, van Gemert-Pijnen J, Harbarth S, Kluytmans J, et al. Methicillin-resistant Staphylococcus aureus (MRSA): burden of disease and control challenges in Europe. Euro Surveill. 2010;15(41):19688.