

General introduction, aim and outline of this thesis

This thesis is on MRSA of Unknown Origin (MUO). MUO carriers are lacking risk factors as described in the national MRSA guideline. Without risk factors, MRSA carriers are not screened at hospital admission and go undetected. In general, MUO are detected by accident in a clinical culture or in a screening culture searching for a particular outbreak strain. Instead a genetically different strain is found. MUO will undermine our Search & Destroy (S&D) if left unattended. Important questions such as 'Which new risk factors describe MUO?', 'What is the genetic background of MUO?' and 'Is MUO a result of new transmission routes?' need answers. In this thesis we try to find these answers.

CHANGING EPIDEMIOLOGY OF MRSA

During the last decade, the total number of MRSA reported to the Dutch MRSA surveillance has increased. (Figure 1) As has the number of MUO. (Figure 1) Furthermore, Dutch MRSA prevalence was 0.03% at hospital admission in 2000¹ and 0.11% in 2007². Nethmap data from 2016 reported an 1.7% MRSA prevalence among reported clinical *S. aureus* isolates (including blood samples) collected by the Infectious Disease Surveillance and Information System for Antibiotic Resistance (ISIS-AR).³ The low Dutch prevalence is – together with the Scandinavian countries - the exception to the European rule (Table 1). Currently, the number of reported MRSA is about 3000 MRSA isolates per year⁴. This is a low number, but has increased compared to the past, as this number was under 500 MRSA isolates per year before 2001.⁵ (Figure 1) The current low MRSA numbers in The Netherlands and Scandinavia are most likely due to a combination of MRSA control measures and a prudent use of antibiotics.⁶ In this regard, Scandinavia and The Netherlands are similar. For example, in their use of MRSA risk groups for MRSA screening. Although differences exist (Table 3).

Globally, the epidemiology of MRSA has changed as well. Due to or as a consequence of this, is that the classical division between hospital-acquired (HA-) and community-acquired (CA-) MRSA has gradually faded. The result was a surge of epidemiological terms in an attempt to describe the new MRSA situation: CA-MRSA (community-acquired, community-associated), HA-MRSA (first meaning hospital-acquired, and then hospital-associated or healthcare-associated), HCA-MRSA (healthcare-associated), HCA-CO-MRSA (healthcare-associated community onset), CO-MRSA (community-onset), HCA-HACO MRSA (healthcare-associated hospital-onset), HACO-MRSA (healthcare-associated hospital-onset).⁷⁻⁹ The global change in epidemiology may be a driving factor for Dutch MUO. However, it is important to realize that MUO is not by default community MRSA (whether labelled as CA-MRSA, CO-MRSA or any of its many variants). The MUO label does not seek to impose a spatial division such as is the case with aforementioned terminology (CA-, CO-, HA-MRSA, etc.). MUO is simply the absence of known (Dutch) risk factors.

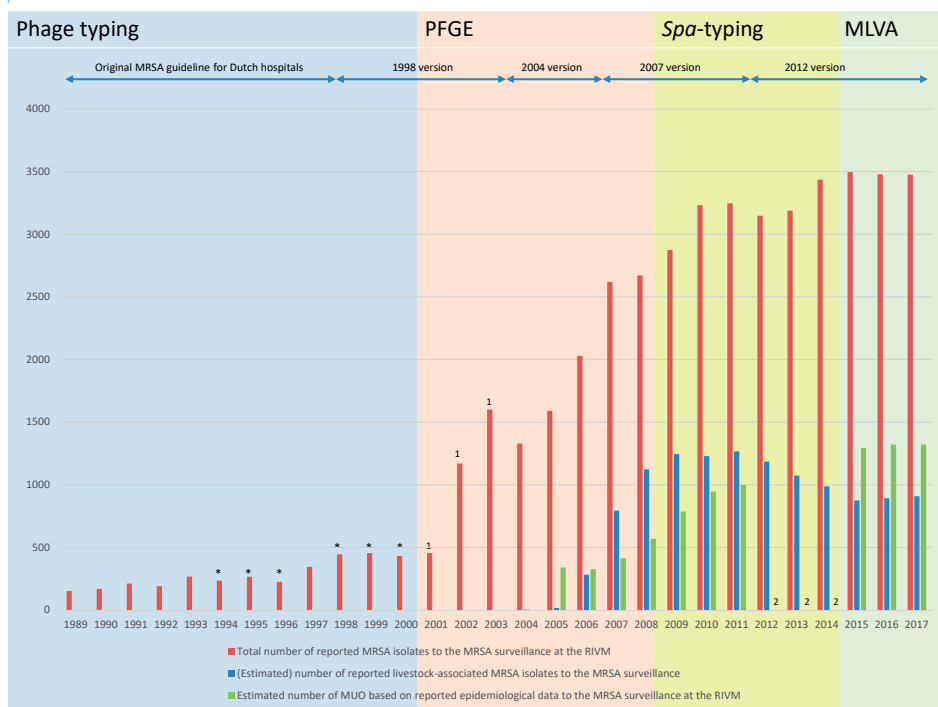


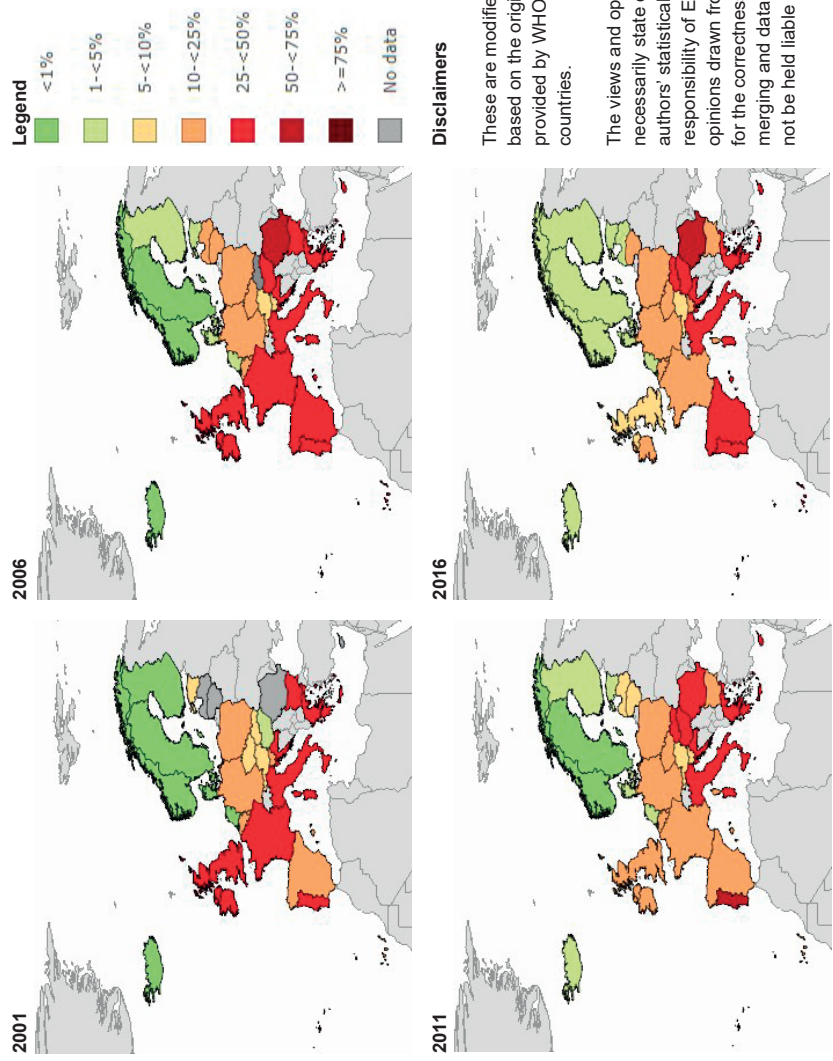
Figure 1 – Reported total, MUO and live-stock associated MRSA isolates to the Dutch MRSA surveillance between 1989 and 2017

* estimated number of MRSA isolates based on published figures (graphs ²³⁻²⁷); ¹ Only the number of MRSA isolates from patients were given, no health care workers. ² No or minimal MRSA surveillance reports these years, thus no public data to show the number of MUO. This figure was based on the following public sources: ²⁰⁻⁴⁴

CHANGING DUTCH MRSA CONTROL

As epidemiology changes, so must MRSA control. Over the years the number of risk factors described in the Dutch MRSA guideline made by the former Dutch Working Party for Infection Prevention (WIP; 1981-2017) ¹⁰ has gradually increased. (Table 2) The original guideline at the start of the 1990's, listed three risk groups: MRSA positive patient, exposure through unprotected contact with a MRSA carrier, and a stay in a healthcare centre abroad. The last, from 2012 with a 2016 Rijksinstituut voor Volksgezondheid en Milieu (RIVM) addendum, lists ten major risk factors (MRSA positive patient, exposure through unprotected contact with a MRSA carrier [now including MRSA patients under follow-up after eradication therapy and household members of MRSA carriers], and a stay in a healthcare centre abroad, being a dialysis patient, contact with pigs¹¹, contact with veal calves, contact with broiler chickens, adoption and being an asylum seeker).^{12, 13} If the targeted population described in the risk groups is sufficiently distinct of the overall population, then MRSA carriers can be successfully discerned.

Table 1 – MRSA prevalence in Europe, 2001-2016



Disclaimers

These are modified screen captures from the ECDC-website, based on the original dataset provided by ECDC based on data provided by WHO and Ministries of Health from the affected countries.

The views and opinions of the authors expressed herein do not necessarily state or reflect those of the ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.⁴⁶

Methicillin Resistant *Staphylococcus aureus* (MRSA) isolates as proportion of total *Staphylococcus aureus* isolates (%), EARSS data 2001-2016, retrieved from <https://ecdc.europa.eu/en/antimicrobial-resistance/surveillance-and-disease-data/data-ecdc>

Table 2 – Dutch MRSA risk factors in Dutch MRSA guideline by WIP working group for infection prevention (1989-2018)

Original		• MRSA positive patient • Exposure through unprotected contact with a MRSA carrier • A stay in a hospital abroad
1998	Guideline now applies for patients AND healthcare workers	
2004	<i>Added</i>	• Being a dialysis patient • Contact with pigs • Contact with veal calves • Family members of those who have contact with pigs/veal calves • Adopted children with regular hospital contact • Other
2007	<i>Removed</i>	• Family members of those who have contact with pigs/veal calves
2012	<i>Expanded</i>	• Exposure through unprotected contact with a MRSA carrier ◦ MRSA patients under follow-up eradication therapy ◦ Household members
	<i>Changed</i>	• A stay in a healthcare center abroad
	<i>Added</i>	Contact with broiler chickens
2015	<i>Added</i>	Being a refugee ¹

Major changes to the Dutch MRSA guideline by the Working group for Infection prevention (WIP).¹ Risk factor added in the post-WIP era.

In S&D, risk adjustment aims to identify every potential MRSA carrier at hospital (and nursing home) admission by screening persons at risk for MRSA carriage (search). Patients screened positive for risk on MRSA are put into isolation and these contact precautions continue awaiting the results of the medical microbiological laboratory (preemptive isolation). MRSA carriers are kept in isolation and eventually treated to eradicate the MRSA (destroy) and their environment will be disinfected (destroy).¹⁴

To continue control of MRSA despite changing epidemiology, MRSA must be surveilled. Therefore, the MRSA surveillance at the RIVM⁴, was started in 1989 at the request of the Geneeskundig hoofdinspectie (GHI; now known as Inspectie Gezondheidszorg en Jeugd / IGJ, and formerly known as the Inspectie voor de Gezondheidszorg / IGZ)¹⁵. The MRSA surveillance officially exists to gain insight as to why certain people are infected or colonized by MRSA, and to support the (then) independent Dutch WIP foundation in updating the Dutch national MRSA guideline by supplying it data.¹⁶ The surveillance keeps track of total MRSA numbers, the genetic background (before: phage-type, PFGE-type, *spa*-type; now: MLVA complex; but also the presence of Panton-Valentine Leucocidin virulence factor [PVL]) and announces any epidemiological changes to MRSA in The Netherlands.¹⁷

To surveil MRSA, the RIVM maintains a database of MRSA isolates, with one isolate per unique person per year.¹⁷ The first MRSA positive isolate of each detected MRSA carrier is sent to the RIVM along with some epidemiological information (including the risk group the carrier belonged to). Unless there is an isolate from a clinical sample (e.g. from a wound) in the same period as carriage is identified, the RIVM prefers this isolate over

Table 3 – MRSA Risk factors in national guidelines of low MRSA prevalence countries

	Denmark	Finland	Iceland	Netherlands	Norway	Sweden
Proven carrier of MRSA	X	X	X	X	X	X
Unprotected contact with MRSA carrier	X	X	X	X ^T	X	X
Inside the hospital (as part of contact tracing)	X	X	X	X	X	X
Outside the hospital (household members, partners, caretakers)	X	X	X	X	X	X
Stayed in a local care facility (unspecified) with an ongoing MRSA outbreak on the department	X	X	X	X ^T	X	X
Stayed in orphanage	.	X	X	.	.	X
Related to higher MRSA prevalence among animals						
Contact with industrial live pigs, veal calves or broiler chickens	X ^b	X ^b	.	X	X ^b	X ^b
Regardless if professional contact or not	X ^b	X ^b	.	X	X ^b	X ^b
And/or lives on such a farm	X ^b	X ^b	.	X	X ^b	X ^b
Related to higher MRSA prevalence abroad						
Adopted children from abroad living in this country	.	X	.	X	.	X
Foreign dialysis patients	.	.	X	X	X	X ^S
Local dialysis patients dialyzed abroad	.	.	X	X ^T	X	X ^S
HCW involved with patient-related activities in a foreign care facility	X	.	X	X ^{TT}	X	X ^S
HCW guided patients from a foreign to a local care facility without isolation precautions	.	.	.	X ^T	.	X ^S
Nursed in a foreign care facility	.	.	X	X ^{TT}	X	.
With risk factors (operation abroad, chronic infection or persistent skin lesions, presence of abscesses or furuncles at hospitalization in home country)	.	.	.	X ^P	.	.
Refugee Camp	X	.	X	X	X	.
Staying abroad	.	.	.	.	.	.
With risk factors (operation abroad, chronic infection or persistent skin lesions, presence of abscesses or furuncles at hospitalization in home country)	.	.	.	.	X	.
Related to MRSA eradication therapy						
During MRSA eradication treatment	.	.	.	X	.	.
During follow-up after MRSA eradication therapy	.	.	.	X	.	.

Table based on google translated online data from Scandinavia (Denmark^{46, 47}, Finland⁴⁷, Iceland⁴⁸, Norway^{47, 49} and Sweden^{47, 50-52}). Table data should be used with care as mistranslation or missing data in offline documents cannot be excluded.

^b No broilers included; ^PPatients only; ^Sin the last six months; ^Tless than two months ago; ^{TT}more than twenty-four hours and less than two months ago

the one from a screenings sample.^{4, 17} In 2004, a new category, “unknown”, was added to the request for epidemiological information, to get an idea of the number of MUO in The Netherlands. This addition has made it possible to measure the size of the MUO problem, and to study the MUO carriers for their underlying risk factors.

THE SEARCH FOR MRSA OF UNKNOWN ORIGIN

The Dutch MRSA surveillance database at the RIVM was used to estimate the potential size of the MUO problem. A raw estimation was based on data from 2005, 2006 and 2007. The potential number of yearly reported MUO was estimated to be 23-27% of MRSA patient cases reported to the RIVM.¹⁸ In the report form, accompanying the isolate, clinical microbiologists and infection prevention practitioners can do suggestions in an open text field on the possible source of the MUO carriage. Some suggestions were immigration, adoption and nursing homes. However, the reliability of the suggestions was questionable. Furthermore, the reliability of the questionnaires sent to the RIVM was unknown and not sufficient to come to an unequivocal classification and reliable count of the numbers of MRSA as MUO.¹⁹ A thorough study of MRSA surveillance data on MUO was deemed necessary, leading to the national MRSA surveillance database at the RIVM becoming the primary source for the research described in this thesis.

THESIS AIMS

The primary aim of this thesis is to map the magnitude of the presence of MUO, elucidate MUO's risk factors and/or transmission routes. While the secondary aim is to find out whether MUO carriers carried different MRSA strains compared to MRSA strains of MRSA carriers with known risk factors (MKO).

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