Follow-up cultures for MRSA after eradication therapy: Are three culture-sets enough?

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SUMMARY

Objectives: We compared the standard procedure of three MRSA follow-up culture-sets to six to determine the number of recurrences detected between the third and sixth follow-up culture-set, and studied possible risk factors for MRSA recurrence.

Methods: A retrospective carrier cohort (2005-2010) was studied. Data was collected on MRSA culture-sets, follow-up, risk factors and outcome (recurrences during follow-up). We compared outcome between three and six follow-up MRSA culture-sets, between HCWs and patients groups for complicated or uncomplicated carriers, and between nose-throat carriers and other carriers.

Results: Of 406 MRSA carriers, 179 had received eradication therapy and had a negative first follow-up MRSA culture-set. Between the third and sixth follow-up culture-set 54% (35/65) of total recurrences occurred. Over 88% of all recurrences were detected within two months. Combined nose and throat carriage (OR 25.5 (1.6-419.1)) and intravascular lines (OR 13.6 (1.2-156.2)) were risk factors for early recurrence.

Conclusions: We recommend five culture-sets till one year after successful eradication therapy with a distinction between those at risk for early recurrence and HCWs who require frequent culturing in the beginning and those not at risk for early recurrence. This recommendation is a balance between the need for swift detection of MRSA recurrence and the patients' burden.

INTRODUCTION

The Netherlands is one of the few countries in the world with a low meticillin-resistant Staphylococcus aureus (MRSA) prevalence. This is most likely due to a rigourous control strategy, which includes decolonization treatment of MRSA carriers and their household members.[1] Decolonization treatment of MRSA carriers (MRSA eradication therapy) is a worldwide used strategy, but consensus and/or documentation on follow-up to determine MRSA clearance (successful MRSA decolonization after MRSA eradication therapy) varies per region or nation, or is even absent.[2] In The Netherlands, the current national guideline to prevent MRSA in healthcare centres (Working Party on Infection Prevention (WIP) guideline on MRSA[3]), recommends the use of three follow-up culture-sets to prove successful decolonization after eradication therapy. To the best of our knowledge, the only data reported on this issue, is a study from our research group in 2010 by Mollema et al., who studied 165 MRSA-positive individuals in a prospective observational follow-up study. This study concluded for a reliable assessment of successful MRSA eradication (>90%) at least five negative culture-sets would be required.[4] However the study did not address when the follow-up culture-sets should be collected after eradication therapy; nor the number of recurrences that would have been missed between the third and the sixth follow-up culture set; nor any risk factors for early or late recurrence. Although the Dutch national MRSA guideline suggests a minimum of three sets after eradication therapy is considered sufficient (with at least seven days between each set) at the Erasmus Medical Centre six culture-sets are routinely collected post MRSA eradication therapy. Therefore, we have data to compare the two approaches of three and six follow-up culture-sets.

In this study we determined the number of recurrences of MRSA detected between the third and sixth follow-up culture-sets after eradication therapy, and identified any risk factors associated with MRSA recurrence, and whether the risk factors were associated with early (first three follow-up culture-sets) or late (follow-up culture-sets four, five and six) MRSA recurrence.

PATIENTS AND METHODS

I - carriers and follow up

A retrospective cohort (2005-2010) of carriers (patients and healthcare workers (HCWs)) was studied. Carriers were retrospectively selected from reports on the MRSA carrier population that visited or worked at the Erasmus Medical Center, Rotterdam (Erasmus MC). All carriers, who had received MRSA eradication therapy and whose first culture-set after treatment was negative, were included in our routine follow-up procedure. Eradication therapy was described by Mollema et al. and derived from the Dutch guideline on the

treatment of MRSA carriage.[1,4] A follow-up culture-set comprised a culture of the nose, throat, perineum and, if present, wounds. Specimen collection was performed by self-collection by the carriers after receiving written instructions, by their general practitioner or in the hospital. Exclusion criteria were loss to follow-up, or incomplete data or reports. (Figure 1) A complete follow-up period was defined as the time period between the negative results of the first follow-up culture-set after eradication therapy and the sixth follow-up culture-set, or earlier in case of MRSA recurrence. The major outcome of this study was either recurrence, defined as growth of MRSA with the same *spa*-type as before eradication therapy, at any screened site or successful eradication defined as no growth of MRSA at all screened sites at the end of a complete follow-up period. For each patient, data were collected on recurrence or successful eradication, number of culture-sets taken, follow-up period and data to analyse whether carriers were complicated or uncomplicated carriers, as defined by the guideline of the Dutch Working Party on Antibiotic Policy.[1] Furthermore, we analysed the outcome in defined subgroups, such as patients, health care workers, complicated or uncomplicated carriers and for combined nose throat carriers versus other

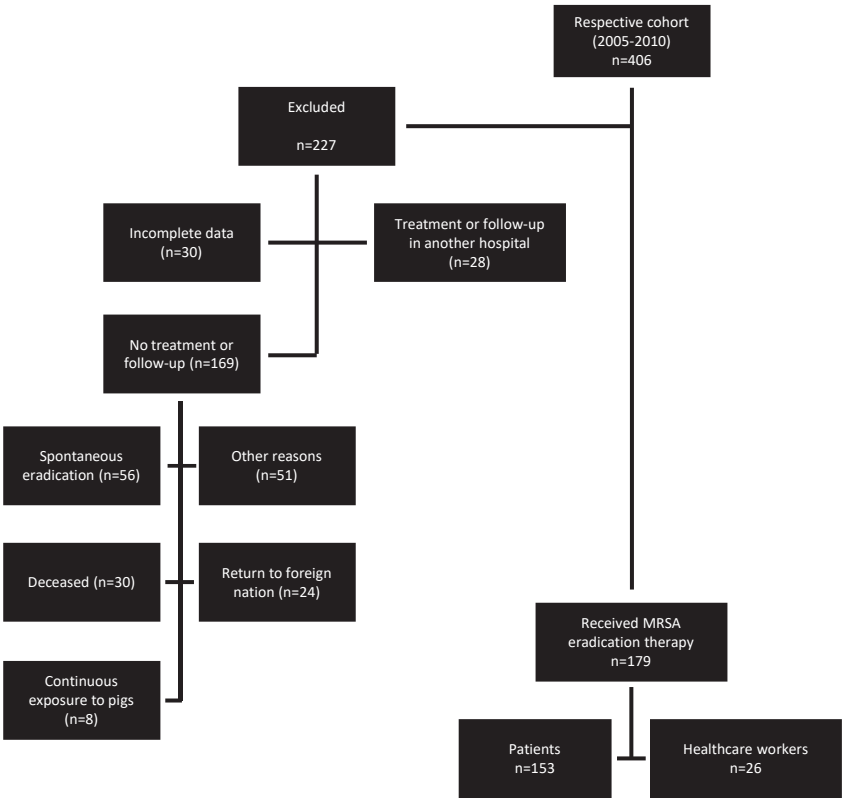

Figure 1 – Flowchart

carriers. Between 2005 and 2007 the microbiological method to detect MRSA was similar as described previously by Vos et al.[5] After 2007, an additional step was included. Swabs of newly suspected MRSA carriers that had been inoculated on phenol red mannitol enrichment broth were incubated for 24 h at 35°C, after which they were put in a PCR pool. If the PCR pool result was negative, this information was passed on to infection prevention team and the broth incubated for another 24 h, followed by subculture on a blood agar plate as usual. With a positive PCR pool result, PCR was redone for each individual isolate, followed by a subculture on blood agar plate for the positive isolate, as opposed to waiting another 24 h. Sampling was deemed improper if the number of colony forming units on the initial blood agar plate, incubated at the same time as the phenol enrichment broth, was under fifteen. Statistical analyses were performed with SAS Enterprise Guide 4.2 and included descriptive analyses, multiple regression and Kaplan Meier survival curves with Mantel-Cox test.

II - risk factors for outcome

By using search terms in Pubmed (MRSA combined with one or more of the following search terms: drug effects, treatment failure, treatment outcome, anti-bacterial agents, therapeutic use, recurrence, risk factors, factors, determinants), risk factors for MRSA recurrence were extracted from the literature and selected for our analysis. Out of 56 original abstracts, ten remained based on relevance. One study was excluded because it described a risk factor (household infection) not obtainable from our hospital's electronic medical record system. Risk factors for recurrence were defined at start of eradication therapy and included sex, age,[6] complicated MRSA carriage,[6-8] presence of artificial devices,[8,9] presence of drains,[8] artificial ventilation,[10] presence of intravascular lines,[8] use of immunosuppressives[11] and presence of an underlying disease (presence of anatomical abnormality, auto-immune disease, cardiovascular disease, cerebrovascular disease, congenital disease, gastro-enteric disease, iatrogenic, infectious disease, neoplasm, psychiatric disease or traumatic events).[7-10,12-14] Furthermore, we added risk factors for acquisition of MRSA based on the Dutch (WIP) guideline on MRSA (MRSA of Known Origin/MRSA of Unknown Origin)[15] and risk factors described in literature: total duration of hospitalization,[10] Barthel index (Activities of Daily Living scale),[7] use of antibiotics (12 months prior to start eradication therapy),[10] drug abuse and the presence of Panton-Valentine leukocidin (PVL) in the carriage strain. Data on these risk factors were collected from the electronic medical record system. Risk factors with 50% or more missing values were omitted from statistical analysis. Statistical analysis was performed with SAS Enterprise Guide 4.2 using c2 and Fisher exact test. A p-value of <0.05 was considered significant. A multiple regression model was made, using all risk factors with p-values of <0.20.

RESULTS

I - carriers and follow up

Four hundred and six MRSA carriers were detected during the inclusion period of which 179 received eradication therapy and had a negative first follow-up culture-set (Figure 1), and were therefore included in the study (HCWs: n= 26, patients: n=153). The mean age of the study population was 32 years and 94 were male (52.5%; 94/179). Between the second and sixth set 36% (65/179) of participants showed a recurrence of MRSA carriage. Median period between the first negative culture-set (considered initially successful eradication therapy) and the occurrence of recurrence for the second, third, fourth, fifth or sixth culture-set, was 7, 14, 24, 38 and 49 days respectively (Table 1). Cumulative non MRSA recurrence at three sets was 0.88, and at six sets 0.71 (Figure 2). The difference (0.88-0.71) equalled 35 recurrences, which is 54% (35/65) of total recurrences during follow-up (Table 1, Figure 2). The median number of days to detect a recurrence was 24 (range 4-185 days; IQR 14-42). The first 2 months (61 days) of follow-up, 88% (57/65) of recurrences were detected. The remaining 12% was detected between 62 and 200 days (one at the second culture set, one at the third culture set, two at the fourth, three at the fifth culture set and one at the sixth culture set). All recurrences in HCWs were detected within 61 days. For all 153 patients, 55 showed recurrences with eight occurring after two months (15%; 8/55). Complicated carriers were 50% (13/26) of all HCWs and 83% (127/153) of all patients. There was insufficient data for 17 patients (two with recurrence) to conclude whether they were complicated or uncomplicated carriers (Figure 3). Recurrence in the subgroups was 1/9 (11%) for uncomplicated patient carriers, 52/127 (41%) for complicated patient carriers, 4/13 (31%) for uncomplicated HCWs and 6/13 (46%) for complicated HCWs. There were no significant differences for the patient, HCW and complicated carrier subgroups (log-rank, p = 0.3371, Wilcoxon p = 0.3343). The recur-

Table 1 – Follow-up culture-sets after MRSA eradication therapy

Culture set #	Days from the end of eradication therapy until the culture set was taken			Number of recurrences [a]	MRSA negative persons left
	Range	Median	Mean		
1[b]	-	-	-	-	179
2	(4-128)	7	22	11	168
3	(8-77)	14	21	19	149
4	(16-200)	24	40	16	133
5	(27-185)	38	70	8	125
6	(36-117)	49	60	11	114

[a] The number of MRSA recurrences during follow-up after MRSA eradication therapy.
[b] If positive at culture set #1, there has not been a successful eradication therapy in the first place. Therefore, all persons in this study were negative in the first culture set.

rence in the uncomplicated patient carrier subgroup was at 24 days. For combined nose throat carriers, recurrence was 17/31 (55%), in all other carriers recurrence was 38/116 (33%) (log-rank, p = 0.01. Wilcoxon p = 0.009). There was missing data for 27 carriers (26 HCWs and 1 patient for a total of 11 recurrences) on sites of carriage.

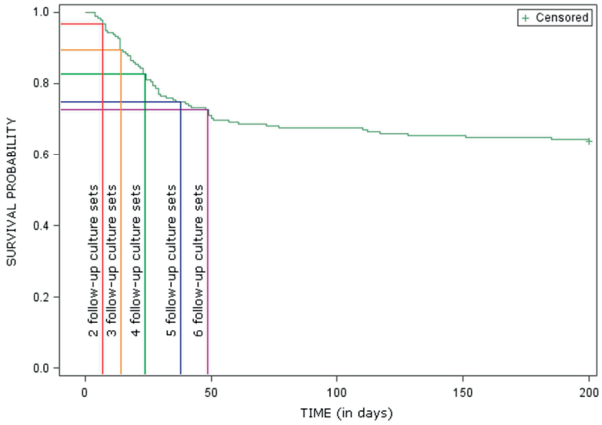

Figure 2 – Follow-up culture-sets after MRSA eradication therapy and detection of MRSA recurrence.

At day 0, all cases had completed their MRSA eradication therapy and had once tested negative for MRSA (first follow-up culture-set). The data was censored at 200 days, leaving a cumulative non MRSA recurrence of 0.64 for the remaining 114 cases (successfully decolonized as determined with six culture-sets). The median number of days at which the second, third, fourth, fifth or sixth culture-sets was taken, intersects with the non MRSA recurrence curve.

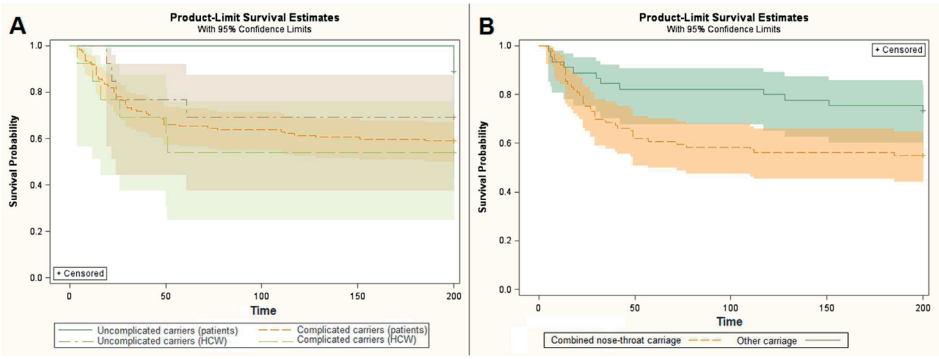

Figure 3 – Subgroup analysis of HCWs, patients, complicated carriers and combined nose throat carriers.

A: There was insufficient data for 17 patients to conclude whether they were complicated or uncomplicated carriers. Complicated/uncomplicated MRSA carriage definitions were according to the guideline of the Dutch Working Party on Antibiotic Policy.[1] There were no significant differences between the subgroups (log-rank, p = 0.3015, Wilcoxon p = 0.2543). B: There was a significant difference between combined nose throat carriers and other carriers (log-rank, p = 0.01, Wilcoxon p = 0.008).

II - risk factors for outcome

For the 150 patients the average age was 31 years, 85 were male (56.7%; 86/150), and 31.3% were MUO (MRSA of Unknown Origin; no presence of described risk factors from the Dutch national guideline)[15] and 86% (129/150) were complicated MRSA carriers. Combined nose and throat carriage was a risk factor for early recurrence in multiple regression analysis (p = 0.02, OR 25.5 (1.6-419.1)), as was the presence of intravascular lines (p = 0.04, OR 13.6 (1.2-156.2)). Interestingly, ventilation at detection was a protective factor for recurrence itself in univariate and multiple regression (p = 0.02, OR 0.016 (0.03-0.75)), while age under 30 was a protective factor for early recurrence in multiple regression analysis (p = 0.04, OR 0.07 (0.01-0.85)). The backward elimination models for recurrence had a R2 of 0.11, with an area under the ROC curve (AUC) of 0.6170, and for early recurrence the R2 was 0.42, with an AUC of 0.8210. The univariate and multiple regression results for the analysis of risk factors are given in Table 2.

DISCUSSION

Using six follow-up culture-sets, 88% of MRSA recurrences were identified within two months of follow up (after eradication therapy and one negative culture set). In contrast, using three culture-sets only 46% (30/65) of MRSA recurrences were identified. These results question the current recommendation by the Dutch national guideline, as pre-emptive declaration of successful decolonization may result in transmission within healthcare centres or in the community. To detect a recurrence, a test with a high negative predictive value (NPV) is required. Current PCR MRSA assays and chromogenic agars have very high NPV (between 99.1 and 99.5),[16] so the chance for a false negative outcome when screening for MRSA recurrence is small. A single swab at two months could detect the majority of the recurrences with a sufficient NPV. However, quick detection of a recurrence is desirable as it allows the carrier to readily receive repeat eradication therapy and prevents MRSA transmission. Especially in the household of the recurrent carrier, the chance of (re-)transmission of the strain to household members will be reduced. Also, in the healthcare setting, isolation measures would be continued thereby preventing transmission. The right balance between the number of culture-sets taken and the patient's burden needs to be found. We therefore recommend that carriers with risk factors for early recurrence are more frequently cultured at the start of follow-up, and we advise the same for HCWs because the duration of the follow-up has a strong impact on when they can start working again. In line with Mollema et al.[4] we recommend five culture-sets after the initial culture-set taken to confirm success of eradication therapy. Treated carriers at risk for early recurrence and HCWs should be cultured three times during the first month, then once more at two and six months after completion of MRSA

Table 2 – Risk factors for recurrence after MRSA eradication therapy

	No recurrence (n=94)	Recurrence (n=56)	Univariate p-value [a]	OR (95%CI)	Early recurrence (n=29)	Late recurrence (n=27)	Univariate p-value [a]	OR (95%CI)
Risk factors	**n (%)**	**n (%)**			**n (%)**	**n (%)**		
Sex								
Male	56 (60)	29 (52)	0.40	-	18 (61)	11 (41)	0.18[f]	-
Female	38 (40)	27 (48)	-	-	11 (39)	16 (59)	-	-
Age								
≤ 30 years	48 (51)	25 (45)	0.50	-	10 (36)	15 (56)	0.18 [f]	0.07 (0.01-0.85)
> 30 years	46 (49)	31 (55)	-	-	19 (64)	12 (44)	-	-
Complicated MRSA [e]	76 (90)	53 (98)	0.09	-	29 (100)	24 (96)	0.46	-
MRSA Carriage								
N (Nose)	11 (12)	1 (2)	0.03	-	0 (0)	1 (4)	0.48	-
T (Throat)	11 (12)	7 (13)	1.00	-	3 (10)	4 (15)	0.70	-
P (Perineum)	7 (7)	2 (4)	0.48	-	0 (0)	2 (7)	0.23	-
W (Wound)	6 (6)	4 (7)	1.00	-	3 (10)	1 (4)	0.61	-
N, T	14 (15)	17 (30)	0.04	-	12 (41)	5 (19)	0.08 [f]	25.5 (1.6-419.1)
T, P	0 (0)	1 (2)	0.37	-	1 (3)	0 (0)	1.00	-
T, W	0 (0)	0 (0)	-	-	0 (0)	0 (0)	-	-
N, P	2 (2)	3 (5)	0.36	-	2 (7)	1 (4)	1.00	-
P, W	0 (0)	1 (2)	0.37	-	0 (0)	0 (0)	-	-
N, W	2 (2)	2 (4)	0.63	-	2 (7)	0 (0)	0.49	-
N, T, P	14 (15)	10 (18)	0.65	-	3 (10)	7 (26)	0.17	-
N, T, P, W	4 (4)	3 (5)	1.00	-	2 (7)	1 (4)	1.00	-
N, T, W	6 (6)	2 (4)	0.71	-	1 (3)	1 (4)	1.00	-
N, P, W	3 (3)	0 (0)	0.29	-	0 (0)	0 (0)	-	-
T, P, W	1 (1)	0 (0)	1.00	-	0 (0)	0 (0)	-	-

Table 2 – Risk factors for recurrence after MRSA eradication therapy (continued)

	No recurrence (n=94)	Recurrence (n=56)	Univariate p-value [a]	OR (95%CI)	Early recurrence (n=29)	Late recurrence (n=27)	Univariate p-value [a]	OR (95%CI)
Risk factors	n (%)	n (%)			n (%)	n (%)		
Presence of wounds	36 (42)	14 (25)	0.05	-	10 (34)	4 (15)	0.13	-
Artificial devices	38 (40)	10 (18)	<0.01	-	7 (24)	3 (11)	0.30	-
Drains	27 (33)	7 (16)	0.06	-	5 (26)	2 (8)	0.21	-
Intravascular lines	28 (34)	8 (20)	0.14	-	6 (35)	2 (9)	0.05 [f]	13.6 (1.2-156.2)
Ventilation	25 (29)	3 (7)	< 0.01 [f]	0.16 (0.03-0.75)	2 (11)	1 (4)	0.56	-
Other	14 (17)	2 (6)	0.15	-	2 (12)	0 (0)	0.48	-
Hospitalization before therapy	33 (35)	15 (27)	0.37	-	10 (34)	5 (19)	0.23	-
Hosp. Duration								
≤ 1 week	10 (30)	4 (27)	1.00	-	3 (30)	1 (20)	1.00	-
>1 week	-	-	-	-	7 (70)	4 (80)	-	-
Underlying disease[c]	66 (84)	36 (84)	1.00	-	20 (91)	16 (76)	0.24	-
Antibiotic use [b]	20 (29)	10 (27)	1.00	-	5 (33)	5 (23)	0.71	-
Imm.supp. use	13 (16)	6 (15)	1.00	-	2 (12)	4 (18)	0.68	-
MUO [d]	32 (34)	15 (27)	0.37	-	8 (28)	7 (26)	1.00	-
PVL-positive	18 (23)	9 (18)	0.66	-	3 (13)	6 (23)	0.47	-

[a] 2x2 tables with Fisher Exact test.

[b] In the 12 months prior to MRSA eradication therapy

[c] Presence of anatomical abnormality, auto-immune disease, cardiovascular disease, cerebrovascular disease, congenital disease, gastroenterestic disease, iatrogenic, infectious disease, neoplasm, psychiatric disease or traumatic events.

[d] MRSA without described risk factors in the Dutch WIP guideline. (MRSA of Unknown Origin)

[e] Complicated MRSA defined according to Dutch SWAB guideline.

[f] The backward elimination model for early recurrence with the following risk factors: male sex, age under 30, combined nose and throat carriage, presence of intravascular lines. AUC: 0.8210, R^2max 0.42. Risk and protective factors remaining significant: age under 30 years p=0.04, OR 0.07 (0.01-0.85), presence of intravascular lines p=0.04, OR 13.6 (1.2-156.2) and combined nose and throat carriage p=0.02, OR 25.5 (1.6-419.1).
The backward elimination model for recurrence had the following risk factors: complicated MRSA, combined nose and throat carriage, the presence of any wounds, the presence of drains, the presence of intravascular lines, having been ventilated, other applied artificial devices. AUC 0.6170, R^2max 0.11. Protective factor remaining significant: having been ventilated p=0.02, OR 0.16 (0.03-0.75)

eradication therapy. For all others we recommend two culture-sets during the first month, followed by a culture-sets at 2 and 6 months, and finally the last culture-set at 1 year after eradication therapy ended (Figure 4).

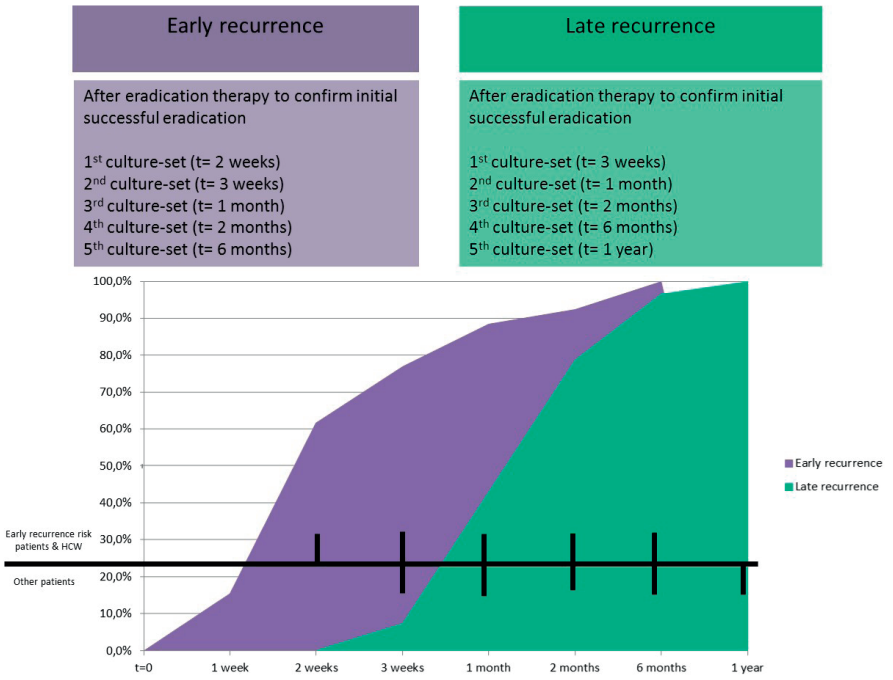

Figure 4 – Recommendations for follow-up culture-sets.
HCWs: Healthcare workers. HCWs follow-up is similar to early recurrence risk patients for fast recovery of personnel.

As risk factors for recurrence, we found colonization of the nose in combination with the throat, as well as presence of intravascular lines. The high risk on recurrence in nose-throat carriers cannot be explained by treatment failure due to the sole use of topical antibiotics, since MRSA eradication therapy for complicated carriers consisted of two oral antibiotics in addition to nasal ointment of mupirocin and chlorhexidin wash for skin and hair. Ventilation was protective for recurrence, however, we did not understand this finding. Possibly this is a confounder for other, unknown determinants, or it is related to the amount of antibiotics ventilated patients receive. We found that ventilated patient carriers received more antibiotics ($p < 0.01$), had more drains ($p < 0.01$) and artificial devices ($p < 0.01$), but both ventilated as non-ventilated carriers were similar in age, combined nose throat carriage or complicated carriage composition. Limitations of this study were its retrospective design, the use of data from a single hospital, and the omission of risk factors due to missing data. Furthermore, in our patient population 86% were complicated

carriers, due to colonization on other sites than the nose only and/or the presence of active skin lesions or medical artificial devices. This is higher than the 54% reported before in a national study.[7] Our data showed that a regime of three follow-up cultures was not sufficient, and would have missed 54% (35/65) of total recurrences, which is in line with the previously recommended minimum of five culture-sets by Mollema et al.[4] Since culture-sets were not always taken with equal time intervals, we calculated the median number of days that each culture-set was collected from start of follow up, using the median number of days to determine the number of recurrences for each culture-set.

Although small group sizes were inevitable due to the low prevalence in The Netherlands (0.11% at hospital admission[17]), current group sizes are the result of six years of patient data (2005-2010). To our knowledge, these data are the only available data worldwide specifically addressing the question on the required number of culture-sets during follow-up after eradication therapy to establish success of eradication. Our recommendation is a five culture-set scheme up till one year after successful eradication therapy with a distinction between those at risk for early recurrence and HCWs who require more frequent culturing in the beginning and those not at risk for early recurrence. The reason to still culture at half or one year is to catch the last remnants of recurring MRSA after two months as cost-effective as possible. This recommendation is a balance between the need for swift detection of recurrence and the patients' burden. Nevertheless, it remains most important that household members of the carrier are also screened and if necessary treated to prevent recurrence due to household transmission.[18]

REFERENCES

1. SWAB (Dutch Working Party on Antibiotic Policy). Optimaliseren van het antibioticabeleid in Nederland XII: Herziening SWAB richtlijn Behandeling MRSA dragers [Optimalisation of the antibiotic policy in The Netherlands XII: Revision of the SWAB guideline 'Treatment of MRSA carriers']. 2012. Available at: http://www.swab.nl/swab/cms3.nsf/uploads/51DB72E670CAC33BC12579BF00342A95/$FILE/SwabrichtlijnMRSAherziening%2015022012_EN.pdf [Last accessed June 2014].
2. Shenoy ES, Kim J, Rosenberg ES, Cotter JA, Lee H, Walensky RP, et al. Discontinuation of contact precautions for methicillin-resistant staphylococcus aureus: a randomized controlled trial comparing passive and active screening with culture and polymerase chain reaction. Clin Infect Dis 2013 Jul;57(2):176e84 [PubMed PMID: 23572482. Pubmed Central PMCID: 3689342. Epub 2013/04/11. eng].
3. Working Party of Infection Prevention (WIP). WIP guideline MRSA. 2012. Available at: http://www.wip.nl/UK/disclaim.asp?urlZhttp://www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf [Last accessed June 2014].
4. Mollema FP, Severin JA, Nouwen JL, Ott A, Verbrugh HA, Vos MC. Successful treatment for carriage of methicillinresistant Staphylococcus aureus and importance of follow-up. Antimicrob Agents Chemother 2010 Sep;54(9):4020e5 [PubMed PMID: 20547792. Pubmed Central PMCID: 2934988. Epub 2010/06/16. eng].
5. 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 Oct;30(10): 977e84 [PubMed PMID: 19712031. Epub 2009/08/29. eng].
6. Gilpin DF, Small S, Bakkshi S, Kearney MP, Cardwell C, Tunney MM. Efficacy of a standard methicillin-resistant Staphylococcus aureus decolonisation protocol in routine clinical practice. J Hosp Infect 2010 Jun;75(2):93e8 [PubMed PMID: 20299134. Epub 2010/03/20. eng].
7. Ammerlaan HS, Kluytmans JA, Berkhout H, Buiting A, de Brauwer EI, van den Broek PJ, et al. Eradication of carriage with methicillin-resistant Staphylococcus aureus: determinants of treatment failure. J Antimicrob Chemother 2011 Oct; 66(10):2418e24 [PubMed PMID: 21719471. Epub 2011/07/02.eng].
8. Yoon YK, Kim JY, Park DW, Sohn JW, Kim MJ. Predictors of persistent methicillin-resistant Staphylococcus aureus bacteraemia in patients treated with vancomycin. J Antimicrob Chemother 2010 May;65(5):1015e8 [PubMed PMID: 20200036. Epub 2010/03/05. eng].
9. Saginur R, Suh KN. Staphylococcus aureus bacteraemia of unknown primary source: where do we stand? Int J Antimicrob Agents 2008 Nov;32(Suppl. 1):S21e5 [PubMed PMID: 18757183. Epub 2008/09/02. eng].
10. Aston JL, Dortch MJ, Dossett LA, Creech CB, May AK. Risk factors for treatment failure in patients receiving vancomycin for hospital-acquired methicillin-resistant Staphylococcus aureus pneumonia. Surg Infect (Larchmt) 2010 Feb;11(1):21e8 [PubMed PMID: 19689198. Epub 2009/08/20. eng].
11. Moore CL, Lu M, Cheema F, Osaki-Kiyan P, Perri MB, Donabedian S, et al. Prediction of failure in vancomycin treated methicillin-resistant Staphylococcus aureus bloodstream infection: a clinically useful risk stratification tool. Antimicrob Agents Chemother 2011 Oct;55(10): 4581e8 [PubMed PMID: 21825294. Pubmed Central PMCID: 3186992. Epub 2011/08/10. eng].

12. Kollef MH, Rello J, Cammarata SK, Croos-Dabrera RV, Wunderink RG. Clinical cure and survival in Gram-positive ventilator-associated pneumonia: retrospective analysis of two double-blind studies comparing linezolid with vancomycin. Intensive Care Med 2004 Mar; 30(3):388e94 [PubMed PMID: 14714107. Epub 2004/01/10. eng].
13. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two doubleblind studies of patients with methicillin-resistant Staphylococcus aureus nosocomial pneumonia. Chest 2003 Nov; 124(5):1789e97 [PubMed PMID: 14605050. Epub 2003/11/08.eng].
14. Uhlemann AC, Knox J, Miller M, Hafer C, Vasquez G, Ryan M, et al. The environment as an unrecognized reservoir for community-associated methicillin resistant Staphylococcus aureus USA300: a case-control study. PLoS One 2011;6(7): e22407 [PubMed PMID: 21818321. Pubmed Central PMCID: 3144231. Epub 2011/08/06. eng].
15. Lekkerkerk WS, van de Sande-Bruinsma N, van der Sande MA, Tjon ATA, Groenheide A, Haenen A, et al. Emergence of MRSA of unknown origin in the Netherlands. Clin Microbiol Infect 2011 Aug 30 [PubMed PMID: 21967090. Epub 2011/10/05. Eng].
16. Wassenberg MW, Kluytmans JA, Bosboom RW, Buiting AG, van Elzakker EP, Melchers WJ, et al. Rapid diagnostic testing of methicillin-resistant Staphylococcus aureus carriage at different anatomical sites: costs and benefits of less extensive screening regimens. Clin Microbiol Infect 2011 Nov;17(11): 1704e10 [PubMed PMID: 21595786. Epub 2011/05/21. eng].
17. Bode LG, Wertheim HF, Kluytmans JA, Bogaers-Hofman D, Vandenbroucke-Grauls CM, Roosendaal R, et al. Sustained low prevalence of meticillin-resistant Staphylococcus aureus upon admission to hospital in The Netherlands. J Hosp Infect 2011 Nov;79(3):198e201 [PubMed PMID: 21763031. Epub 2011/07/19. eng].
18. Mollema FP, Richardus JH, Behrendt M, Vaessen N, Lodder W, Hendriks W, et al. Transmission of methicillin-resistant Staphylococcus aureus to household contacts. J Clin Microbiol 2010 Jan;48(1):202e7 [PubMed PMID: 19923490. Pubmed Central PMCID: 2812253. Epub 2009/11/20. eng].