



Westfälische
Wilhelms-Universität
Münster

Universitätsklinikum Münster • Institut für Hygiene • 48129 Münster

European Commission
Health and Consumer Protection Directorate-
General
Health services consultation
B232 8/102
B-1049 Brussels
Belgium

health-services-consultation@ec.europa.eu



Universitätsklinikum
Münster

Institut für Hygiene

Direktor: Univ.-Prof. Dr. rer. nat. H. Karch

Robert-Koch-Straße 41
48149 Münster

Krankenhaushygiene
PD Dr. med. Alexander W. Friedrich

Durchwahl: +49-(0)2 51 83 – 52317
Fax: +49-(0)2 51 83 – 55344
E-Mail: alexf@uni-muenster.de
www.klinikum.uni-muenster.de

Vermittlung: (02 51) 83 – 0

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Dear Sirs,

with the attached description we would like to comment on question 3 of the **Consultation regarding Community action on health services**.

As a Dutch-German cross border health care network, we would like to communicate to you the problems we face with cross border health care from the point of quality of care, especially regarding nosocomial infections with MRSA, but of course also regarding cross border infectious disease management in general.

If any further question rises, please do not hesitate to contact us at any time.

With kind regards for the network coordinators,

PD Dr. Alex W. Friedrich
Project leader Germany



Het project wordt gesubsidieerd door de Europese Unie in het kader van het Communautaire Initiatief INTERREG-IIIa met middelen van het Europees Structuurfonds voor Regionale Ontwikkeling alsmede het Ministerie van Economische Zaken van de Duitse deelstaat Nordrhein-Westfalen



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EUREGIO

EUREGIO MRSA-net Twente/ Münsterland

<http://www.mrsa-net.eu>

Project leader (Germany): PD Dr. med. A. W. Friedrich	Address: Institut für Hygiene, Universitätsklinikum Münster Robert Koch Str. 41 48149 Münster Germany	
Phone: +49-251-83 55366	Fax +49-251-83 55688	E-Mail: alex@uni-muenster.de
Project leader (The Netherlands): M.G.R. Hendrix MD PhD	Address: Laboratorium Microbiologie Twente-Achterhoek "Streeklab" Burg. E. Bergsmalaan 1 NL-7500 AJ Enschede	
Phone: +31-53-43 13263	Fax +31-53-4 341 631	E-Mail: rhendrix@labmicta.nl
Coordinator of the Public Health Authority (Germany): Dr. med. Daniels-Haardt	Address: Landesinstitut für den Öffentlichen Gesundheitsdienst (LÖGD) v. Stauffenbergstr 11 48151 Münster Germany	
Phone: +49-251 7793-124	Fax: +49-251 7793-250	E-Mail: inka.daniels-haardt@loegd.nrw.de
Coordinator UniTwente (The Netherlands): Dr. J.E.W.C. van Gemert-Pijnen	Address: University of Twente (Universiteit Twente) Universiteit Twente- Cubicus C-205 Postbus 217 NL - 7500 AE Enschede The Netherlands	
Phone: +31 (53) 48 94 795	Fax: +31 (53) 48 94 259	E-Mail: j.vangemert-pijnen@utwente.nl

Summary

Nosocomial infections and antimicrobial resistance is a major topic in health care and infectious disease medicine europe-wide. As *pars pro toto* stands one biological marker for both problems, Methicillin resistant Staphylococcus aureus (MRSA). S. aureus is the cause of most hospital-acquired infections worldwide. Thereby the proportion of Methicillin-resistant Staphylococcus aureus (MRSA) is varying strongly throughout Europe and causing invasive infections, for which there are only few, if any, possibilities of antibiotic therapy. It has been clearly demonstrated by various authors that Methicillin resistance is directly associated with increased mortality and morbidity with S. aureus infections. In the last 10 years an increase in the MRSA rate from 2% to approx. 25% was observed in Germany. In the Netherlands and Scandinavia a stable rate under 3% has been recorded for years. Particularly, for the Netherlands, adhering to a consequent "search and destroy" policy, MRSA fell off to very low rates and is now under control. Often national guidelines (Robert Koch and WIP) are focussed on a national strategy and do not specify the handling of MRSA in cross-border situations. In the Netherlands the main focus will be on control of antibiotic prescription, isolating and controlling CA-MRSA, which is a possible danger for the public health outside hospitals. This difference in MRSA rate makes a difference in quality of health care for patients seeking cross border health care, both, Germans coming transferred from a German hospital to a Dutch hospital, because they are classified as risk category 1 and kept in strict isolation for prevention and Dutch patients seeking health care in a German hospital and running a higher risk of being infected with MRSA. The goal of a cross-border network, such as EUREGIO MRSA-net is the connection of the major health care providers in the region and the achievement of a lower MRSA rate, a reduction of the number of MRSA infections and thus a shorter stay in hospital as a result. Consequently, it is meant to harmonise quality of health care on both sides of the border. Furthermore, due to MRSA, problems arise for German staff working in Dutch hospitals. Often they live across the border and are married with somebody working in a German hospital. As MRSA is much higher endemic in German hospitals, import of MRSA into the Dutch hospital and transmission to Dutch patients become a daily danger. In these cases detailed information and continuous medical advice is needed. As an example for such a cross-border strategy stands the EUREGIO MRSA-net Twente/Münsterland. It is a cross-border quality group of hospitals, public health authorities and laboratories that has been created since

summer 2005. A cross-border helpdesk (<http://www.mrsa-net.eu>) assists the cross border management of the MRSA problems in two neighbouring countries with different MRSA-rates. At the end, MRSA is a biological surrogate marker for prevention, antibiotic policy and intra-mural healthcare in general. It stands for any kind of infectious disease and structures built for the battle against MRSA can be used for any other infectious disease threat to the public health (e.g. influenza, SARS, imported disease)

1.1. The MRSA problem

Staphylococcus aureus (*S. aureus*) is the most causative agent for hospital-acquired infections world-wide. Thereby infections are particularly critical by Methicillin resistant *Staphylococcus aureus* (MRSA), for which there are only few, if any, possibilities of the antibiotic therapy. Moreover there is a strong statistical trend towards death due to nosocomial MRSA infection and bacteremia as compared with susceptible *S.aureus*. Apart from more serious, and often lethal, courses of disease the occurrence of MRSA is associated with labor-intensive and very expensive consequences for the hospitals because of extended infection control measures. Extreme example is the closure of whole wards. Nosocomial infections with MRSA lead to a greater duration of hospitalization of the patient as well as to additional costs due to increased nursing care and costs for infection management (e.g. isolation in the single room) and limited antibiotic therapy only with expensive (e.g. Linezolid) antibiotics and substances with known adverse reactions (e.g. Vancomycin). Engemann et al., 2003, found additional average costs caused by patients with MRSA surgical site infections (SSI) of 92363 \$. Actually, the increasing amount of attending seriously ill patients and the rising number of complex medical measures aggravate this situation in hospitals additionally. With increasingly empty cashes in our health system this could lead to hardly more solvable conflicts. In the last 10 years a rise of the MRSA rate was observed from 2% to approx. 25% in Germany. In the Netherlands and Scandinavia the portion holds itself on firm rates for years under 3%. Besides, the occurrence of MRSA is not fateful. Particularly for the Netherlands adhering to a consequent "search and destroy" policy MRSA is felt off to very low rates and under control. In many other countries no efforts are made to control the nosocomial spread of MRSA resulting in MRSA rates exceeding 80%. Within these settings MRSA become resistant to all available antibiotics as is the case in Japan where up to 30% of all MRSA infections are untreatable. Also in the USA MRSA isolates resistant to all antibiotics are

reported at the moment. In this view the fact that no effective new antibiotics will be available within the next 20 years is quite disturbing. Based on valid evidence the major concern now is that many bacteria, other than MRSA, will follow this pattern (Vancomycin resistant Enterococci, Extended Spectrum Beta-Laktamase resistant bacteria). The structures of an network to combat MRSA can be easily used also to reduce the incidence of other multiresistant micro-organisms. MRSA do not develop from susceptible *S.aureus* under antibiotic pressure but represent a discrete number of clones which spread throughout the world. MRSA should therefore be regarded as a classical epidemic where spread is from patient to patient due to insufficient hygienic measures. The only ways to combat this organism is by strict search and destroy procedures adding to strict standard hygienic protocols, a rationale antibiotic policy and continuing education to people in the health service as well as to a broad public.

Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, Briggs JP, Sexton DJ, Kaye KS. 2003. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin. Infect. Dis. 36:592-598.

1.2. New threat

Until now the MRSA problem was considered to be a strictly nosocomial problem. The emergence of MRSA in patients without established risk factors outside hospitals signifies a new threat. These so called "community acquired"- (CA-) MRSA represent a new stage of danger for the population worldwide and also in Germany and in the Netherlands. Additionally it becomes apparent by newer studies that the portion of MRSA rises also outside of hospitals and therefore leads to large problems in out-patient departments, ambulatory dialysis mechanisms as well as nursing homes. Since the past efforts towards the fight against MRSA in both countries were concentrated on the hospitals these efforts must expand to outpatient sectors. Sooner or later most of these CA-MRSA colonized patients will enter the hospitals adding to the already existing nosocomial problem. Up to now the non-existence of awareness, training, insufficient co-ordination of the main participants in the health service, the missing alignment of the proceedings, the lack of consistent follow-up assistance after dismissal from the hospital through organizational or financial reasons and the absence of sufficient infectious supply of MRSA patients form largest obstacles.

1.3. Strategy

Basis of all efforts for the fight against MRSA is the

1. Prevention:

- conversion of the hygiene measures in accordance with guidelines
- isolation of potential MRSA carriers

2. Surveillance:

- early laboratory-diagnostic identification of carriers, in order to avoid a nosocomial transmission as soon as possible,
- molecular classification of the MRSA isolates in order to recognize transmission chains and to win an overview of the dynamics of the spreading and persistence by the patient,

3. Therapy:

- therapy and decontamination of the infected and/or colonized persons during and also after being hospitalized as well as the

4. Education:

- education of the population as well as further training of personnel in the health care service.

5. Regional Networking:

- creating regional networks of the main actors of the health care system
- synchronisation of national guidelines and adaptation to cross-border problems

Surveillance cultures on hospital admission and bacteriological routine cultures to detect MRSA are accomplished in many hospitals. But the bare proof of MRSA does not give any information about the epidemiological connection or hints over possible transmission ways. From literature it becomes clear that some MRSA clones behave completely different than other clones. Some clones transmit hardly from one patient to another while other clones can spread within two weeks to 20% or more of the patients in a ward or

even a hospital. Also a marked variation exists in the potential to cause disease between the various clones. Basically epidemiological studies rely on defined incubation period or elimination duration of the causative agent which does not exist at a clonal level for MRSA infections and which frequently appears to be endemic in hospitals. Therefore, an effective and rational evaluation of the hygiene measures for the prevalent clones in our region is not possible. In hospital, frequently several MRSA are found in several patients at the same time. Nevertheless no transmission has occurred because of the diversity of the MRSA isolates. Surveillance cultures on hospital admission can prevent nosocomial transmission of MRSA but neither risk assessment can be performed nor can a complete epidemiological profit (early warning system) be achieved. Besides, the prevalence of MRSA will not be lowered.

2.1. Target

The long-term target must be to lower the MRSA-rates on both sides of the border to acceptable levels in both the hospitals and the community leading to a liberal flow of both patients and health-care personnel across this border, and substantially lowering the MRSA associated costs. The lowering of these MRSA rates should be based on the development of an adequate set of protocols for the prevention of MRSA spread, detection and treatment of colonised patients which eventually can be used in the complete Dutch-German border region.

The first goal is the creation of transborder networks, in our case in the region Münsterland/Twente. First the MRSA and hygienic protocols of the hospitals in this region are to be synchronised according to national, both German and Dutch standards. Much attention should be given to the accessibility, comprehensibility, applicability and acceptability of these protocols to ensure compliance in the participants of the health care service. Quite some experience in this field is already established in Enschede in collaboration with the University of Twente. Furthermore, active education of the public will open greater awareness to preventable problems in the health care sector. With this to lower the colonisation and infection rate with MRSA on the German side towards Dutch level could be a possible destination. Decreasing the infection rate in the region Münsterland the Dutch partner will benefit likewise, since the danger of transmitting MRSA from Germany to the Netherlands is lowered. Additionally this will provide an advantage of location for the hospitals of the region. Apart from a decontamination therapy, which can

decrease the prevalence of MRSA, a matter of special importance is an arrangement /coordination between the hospitals. This arrangement/ coordination has to take place via classification of all MRSA isolates. Only by this classification the complete epidemiological distribution can be observed real time in the EUREGIO and an outbreak can be differed from coincidental coexistence of MRSA on one ward. In addition it gives evidence if a decontamination therapy was successful.

In the Netherlands the main focus will be on seizing and controlling CA-MRSA. Basic requirement for this is the active education of the region's population by the EUREGIO network. A transborder quality group from hospitals, public health authorities and laboratories is therefore to created. The network is to consolidate more subsidiary those already locally established resources (e.g. laboratories, hygiene specialists etc.). An early warning system which is already established in Muenster is in process for all participating members with the help of this modern classification network. If there is for example an occurrence of unusually high rates of a special MRSA clone (e.g. CA-MRSA) identification and coordination can be afforded in real time through network focused measures.

In addition, extended hygiene measures (isolation in the single room, subsequent investigations) can be abandoned. Besides higher therapy costs are avoidable. Calculations for Germany by Geldner et al., 1999, and Herr et al., 2003, amount to extra costs per MRSA patient by hygiene measures and the MRSA specific patient need on 371 € for normal wards and approx. 1600 € for intensive care units. Extra therapy costs and consequential charges were not considered. Cost minimization through this leads to a clear improvement of the medical supply of the region's population and medium-term an advantage of location for the region also beyond the region`s borders.

Geldner, G. M. Ruoff, H.-J. Hoffmann, P. Kiefer, M. Georgieff, H. Wiedeck. 1999. eine Kostenanalyse von MRSA Infektionen auf einer operativen Intensivstation. *Anästhesiol. Intensivmed. Notfallmed. Schmerzther.* 34; 409-413

Herr, C.E., T.H. Heckrodt, F.A. Hofmann, R. Schnettler, T.F. Eikmann. 2003. Additional costs for preventing the spread of Methicillin resistant *S. aureus* and a strategy for reducing these costs on a surgical ward. *Infect. Control Hosp. Epidemiol.* 24: 673-678.

2. 2. Approach

2.2.1. Co-ordination and partner

For the co-ordination, two headquarters are needed on both side of the border. In the EUREGIOs case it is the Institute for Hygiene in Muenster, co-ordinator: PD Dr. med. A. W. Friedrich and the laboratory Microbiologie Twente Achterhoek, co-ordinator Dr. M.G.R. Hendrix, Netherlands. The scientific co-ordination of public health authorities is carried out by the Landesinstitut für den öffentlichen Gesundheitsdienst Nordrhein-Westfalen (LOEGD), Standort Münster, co-ordinator Mrs. Dr. Daniels-Haardt, and directly through the Laboratorium Microbiologie TA in cooperation with the Dutch health authorities (GGD, RIVM) in the Netherlands.

2.2.2. “Round tables”

The co-ordinators need establish cross-border “round tables”. These round tables bring together the respective players of the health systems in the region which are facing the MRSA-problem. Representatives, each from the Dutch and German public health authorities, chief executive officers and clinical directors of hospitals, infection control personnel, representatives of the health insurances, medical doctor’s associations, consumer protection agencies, patient’s organisations and the press will meet their counterparts at the round table to exchange their experiences regarding the MRSA-problem under the mederation of the co-ordinators. At an early stage, there must be built an advisory board consisting of responsible doctors for hygiene of the major euregional hospitals, experts in the field of hygiene from local laboratories and other experts. The main aim of the round tables will be to analyse the different MRSA-situation in the neighbouring regions and to find consensus for a common approach in the region. The results must be written down in a common position paper and serve as future regional (possibly interregional or European) guidelines.

2.2.3. Surveillance und reference laboratories

Secondly, as many hospitals of the region as possible are encouraged to participate in this project, e.g. join the education programmes. It is a precondition for participation to conform to the recommendations compiled in the position paper. Active surveillance (screening for MRSA) on hospital admission on the basis of the current valid national guidelines to exclude early the transmission of MRSA is the basic principle, as far as it is not yet established. Genotyping is the implementation of modern laboratory methods (sequencing) in combination with new bioinformation application. For the first time world-

wide it is possible to provide a real time evidence of a pathogen which enables for an area-wide, network-adaptable and affordable surveillance. This so-called *spa*-typing can be interlaced with the help of an integrated cross-border data base containing all necessary epidemiological information. Within the scope of a binational network it is to come to a mutual transfer of know-how, technology, and classification data into the EUREGIO Twente/ Münsterland. All MRSA-related data (type-frequency, regional *spa*-frequency) is made available to all partners on-line through an Internet-based geographical information system. Note, that no person related information is exchanged within the database. Additionally, the data can be used for an automatic early warning system [Friedrich et al., 2006. Eurosurveillance] (see also <http://www.seqnet.eu>). This draws the attention of the participants to unusual accumulation of MRSA on the level of genotyping and/or let exclude coincidental accumulation of MRSA which are without epidemiological connection. Time-based management of active surveillance enables the real time elimination of any MRSA with the advantages mentioned above. This early warning/typing system also provides the opportunity to evaluate the effectiveness of the hygiene measures taken for the prevalent clones in our region and makes it possible to tune these measures in accordance with the suspected epidemiology of the MRSA detected. In some cases we should sound a great alarm since some MRSA types easily spread throughout the population while other types hardly spread at all.

Friedrich, A.W., Rosenkötter N., Harmsen D., Mellmann A., Karch H., Reintjes R. 2004. An Automated Early Warning System for MRSA in a Hospital Setting Based on Molecular Typing Data. American Society for Microbiology, 104th General meeting, New Orleans, USA (May 25-29).

Friedrich A.W., Witte W., Harmsen D., de Lencastre H., Hryniewicz W., Scheres J., Westh H.: On behalf of the SeqNet.org participants, 2006: SeqNet.org: A European laboratory network for sequence-based typing of microbial pathogens. Euro. Surveill. we 11:1

2.2.4 Information and education

The hospital staff must be trained by their infection control personnel (infection control nurse, hygienist, infectious disease specialist, and microbiologist) in collaboration with the local public health office and the MRSA-net coordination institutes. Especially, through the border-crossing perspective and the motivation to reduce the MRSA prevalence in the whole EUREGIO by participating in the project, a high rate of participation and compliance

with infection control and hygienic measures is expected. On the other side, the project partners will have the possibility to communicate to the public their participation in the project and the quality assurance concomitant to this. Sensitization of the public opinion through broad range information of the population within the region (e.g. MRSA-Mobil) about the reasons and the chances of the project will offer all participating hospitals an advantage of location throughout the region. The participation in the project could be supported by a uniform quality seal on the homepages of the hospitals. All education about community acquired CA-MRSA will lead into a prompt identification and eradication of these dangerous strains and lower directly morbidity and mortality in the region.

2.3. Added value

2.3.1. Benefit through cooperation

The establishment of MRSA cross-border networks for the EUREGIOs is the urgently needed answer to the situation that each hospital tries for itself to get the MRSA problem under control. Because of the emergence of CA-MRSA out-patient departments, nursing homes and general practitioners should be included into the MRSA-control program. By using a modern typing-technology regional and cross-border early-warning systems can be established in order to detect special dangers as local or regional outbreaks or the identification of special clones as the community-acquired CA-MRSA.

An advantage of this network is the transparency outside the borders of the EUREGIO, as 20 other countries are able to view this information. Experiences and awareness with leading experts and expert organizations in and outside the EUREGIO on an ongoing basis is nowadays already in place. Herewith again the ideology within this project is underlined that the quality of MRSA protocols depends on the cross border MRSA typing. The constant gained scientific outcome is a condition for optimizing the MRSA protocols and adjust them to a workable and for each group tailor made (for instance for employees and patients) cross border manual.

2.3.2. Benefit through focussing and standardisation

The infection control measures can be established at an early stage and focused on the hot-spots. The standardisation of the infection control- and eradication- program together with the focused infectious disease competence of the whole region, the MRSA

prevalence can be brought to the Dutch level on both sides of the border.

In the current situation each country and therefore institute uses its own terminology for MRSA types. The Institute for Hygiene already started an initiative (SeqNet.org) that connects more than 20 European countries in order to use a standardisation of terminology for MRSA type and therefore speak the same laboratory language throughout Europe. This is only possible because of the research work done before and was not possible on such a broad scale with the up to date used technologies (e.g. PFGE, MLST). The whole EUREGIO will establish an early-warning system to detect outbreaks and the introduction of community-acquired CA-MRSA in the EUREGIO at an early stage. The whole EUREGIO also profits from a centralised knowledge centre from where up to data protocols of high comprehensibility, applicability and acceptability for the treatment and eradication of MRSA can be easily obtained. This knowledge centre also provides the opportunity for direct consultations for difficult problems.

2.3.3. Benefit through better quality in health care services

The reduction of the MRSA prevalence within the population will decrease the infection rate with multiresistant micro-organisms that are associated with morbidity and mortality rates. Cost of therapy will be lower and especially time of stay in hospital will be reduced. In addition, the quality of health care will be improved, if through a low prevalence of MRSA all obligatory infection control and hygienic measure will not be necessary (e.g. unused bed in isolation room). The EUREGIO would come into a clear advantage of location for health and socio-economic reasons. The EUREGIO Twente/Münsterland suites especially for such a network. As the EUREGIO stands relatively isolated with clear health care structures concentration around two major tertiary medical centers in Münster and Enschede, the MRSA-net project offers the possibility for a border-crossing transfer of know-how and technology. The Dutch partner will benefit from the reduction of the MRSA-rate at the German side so that the continuous import of MRSA could be decreased. The lessons learned in the EUREGIO can be used for the establishment of cross-border networks focussing on infectious disease in other border regions in Europe.

2.3.4 Cross border benefits

The successful policy for keeping the MRSA rates in the Netherlands so extremely low will be implemented as far as possible in Germany, so that the whole EUREGIO will benefit from this directly. The danger of MRSA-influx into the Netherlands which consist because

of the considerable difference in MRSA rates on each side of the EUREGIO border constitutes a possible barrier for the free movement of persons in form of patients, medical employees and medical students. By lowering the high MRSA-rate in Germany by means of cooperation and exchange of all information between the two leading hygiene institutes in the EUREGIO, this project can help to decline the barrier for the free movement of persons and help to realize a goal of the EU. This goal is particularly interesting for the EUREGIO Twente/Münsterland because of the estimated shortages of 20% of health care employees already in 2005 in the Region Twente on the one hand and on the other hand a growing unemployment rate in Münsterland in the health care sector. This benefit is most obvious in case of a nosocomial MRSA-influx but is also indirectly applicable in case of the CA-MRSA-influx, taking into account that approximately 50% of the MRSA in the Netherlands are CA-MRSA and spread by all kinds of cross border traffic.

2.3.5. Results

The running results and activities of the cross-border network EUREGIO MRSA-net are published on the homepage <http://www.mrsa-net.eu>

2.4. Conclusion (MRSA: *pars pro toto*)

MRSA is health care problem for its own. Differences in MRSA rates are differences in quality of health care for the patient crossing the border and facing nosocomial infection which in most cases is not preventable. Failure of antibiotic treatment due to multiresistance, such as it is the case for MRSA, is though preventable by keeping the level of multiresistant microorganisms low. Patients seeking health care across the border need to be aware of this problem. Moreover, MRSA stands *pars pro toto* as a biological surrogate marker for prevention, antibiotic policy and intra-mural healthcare in general. It stands for any kind of infectious disease. Health care structures and regional networks built for the battle against MRSA can be used for any other infectious disease threat to the public health (e.g. influenza, SARS, imported disease).

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