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Sachgebiet Arbeits- und Umweltmedizin/Epidemiologie
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# Besiedlung von gesunden Schwangeren und Neugeborenen mit multiresistenten Erregern (MRE) und *Staphylococcus aureus* (SA): Prävalenz und Klinische Relevanz

Dissertation
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aus
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## 1. Eidesstattliche Versicherung


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Brandenburg an der Havel, 04.01.2020 Antchen Dammeyer

Ort, Datum Unterschrift Doktorandin

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## 2. Abkürzungsverzeichnis

| | |
|---|---|
| AMRB | Antimicrobial-resistant Bacteria |
| ARS | Antibiotic Resistance Surveillance for Germany |
| CATI | Computer Assisted Telephone Interview |
| CA-MRSA | Community-acquired MRSA |
| *E. coli* | *Escherichia coli* |
| ESBL | Extended-spectrum Beta-lactamase |
| KRINKO | Commission for Hospital Hygiene and Infection Prevention |
| LA-MRSA | Livestock-associated MRSA |
| LGL | Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit |
| MRE | Multiresistente Erreger |
| MRGN | Multiresistente gramnegative Stäbchen |
| MRSA | Methicillin-resistant *Staphylococcus Aureus* |
| MSSA | Methicillin-sensitive *Staphylococcus Aureus* |
| NICU | Neonatal Intensive Care Unit |
| PFGE | Pulsed-field Gel Electrophoresis |
| PICU | Postnatal Intensive Care Unit |
| QARKS | Qualitätssicherung von Antibiotikaresistenzen bei Kindern und Schwangeren |
| SA | *Staphylococcus Aureus* |
| SSPS | Statistik- und Analysesoftware von IBM |
| SSTI | Skin and Soft Tissue Infection |
| StMGP | Bayerisches Staatsministerium für Gesundheit und Pflege |
| u. a. | unter anderem |

| | |
|---|---|
| UTI | Urinary Tract Infections |
| USA | Vereinigte Staaten von Amerika |
| U1 | Untersuchung 1 – Kindervorsorgeuntersuchung (1. bis 3. Lebenstag) |
| U2 | Untersuchung 2 – Kindervorsorgeuntersuchung (3. bis 10. Lebenstag) |
| z. B. | zum Beispiel |

## 3. Publikationsliste

Veröffentlichung I

**A. H. Dammeyer**, S. Heinze, A. C. Adler, L. Nasri, L. Schomacher, M. Zamfir, K. Heigl, B. Karlin, M. Franitza, S. Hörmansdorfer, C. Tuschak, G. Valenza, U. Ochmann, C. Herr.

“Clinical relevance of colonization with antimicrobial-resistant bacteria (AMRB) and methicillin susceptible Staphylococcus aureus (MSSA) for mothers during pregnancy”

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Veröffentlichung II

K. Heigl, M. Zamfir, A. C. Adler, **A. H. Dammeyer**, L. Schomacher, B. Karlin, M. Franitza, S. Hörmansdorfer, C. Tuschak, G. Valenza, U. Ochmann, C. Herr, S. Heinze.

“Prevalence of methicillin-sensitive (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase *Escherichia coli* (ESBL-producing *E. coli*) in newborns – a cross-sectional study”

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# 4. Einleitung

Die Prävalenz der Besiedelung mit multiresistenten Keimen gewinnt zunehmend an Bedeutung. Die hieraus resultierende Resistenzsituation kann zur Beschränkung therapeutischer Möglichkeiten führen (1). Die wichtigsten Erreger sind dabei die multiresistenten Erreger (MRE), wie etwa dem Methicillin-resistenten *Staphylococcus aureus* (MRSA) und den multiresistenten gramnegativen Stäbchen (MRGN) sowie dem *Staphylococcus aureus* (SA) als Surrogatparameter im Hinblick auf Übertragungswege und Infektionsgeschehen (2),(3). Aus der Besiedlung mit multiresistenten Erregern (MRE) und dem Methicillin-sensiblem *Staphylococcus aureus* (MSSA) können verschiedene Infektionen resultieren, die einen längeren Krankenhausaufenthalt sowie zusätzliche Kosten und erschwerte Therapiemöglichkeiten bedingen können (1). Häufig auftretende Infektionen aufgrund einer Besiedelung mit multiresistenten Keimen können u.a. Haut- und postoperative Wundinfektionen, postpartale Mastitis und Harnwegsinfektionen sein (1), (3). Gerade die Suche nach potentiellen Risikofaktoren könnte beim Screening eine bedeutende Rolle spielen.

Bisher liegen nur Forschungsergebnisse zur allgemeinen Krankenhauspopulation bzw. zu Hochrisikopatienten in ausreichendem Maße vor, Daten zur Prävalenz der Besiedelungen mit multiresistenten Erregern und den Risikofaktoren bei Schwangeren und Neugeborenen sind bisher jedoch noch sehr limitiert. Schwangere sind eine besonders sensible Population, da die Behandlungsmöglichkeiten bei Infektionen während der Schwangerschaft sehr eingeschränkt sind. Ungeklärt ist auch weiterhin, ob eine Besiedlung mit multiresistenten Erregern Auswirkungen auf die Schwangerschaft und die Geburt hat und, ob es eine Übertragung der Besiedlung von der Mutter auf das Kind gibt (4).

## 4.1. Zur Studie QARKS

Die Studie „Qualitätssicherung von Antibiotikaresistenzen bei Kindern und Schwangeren“ (im Folgenden: QARKS) wurde vom Bayerischen Staatsministerium für Gesundheit und Pflege (StMGP) gefördert und vom Bayerischen Landesamt für Gesundheit und Lebensmittelsicherheit (LGL) durchgeführt. Ziel der Studie war die Prävalenz und die klinische Relevanz der Besiedelung mit MRE bei gesunden Schwangeren und Neugeborenen zu untersuchen.

Die Studie wurde im Zeitraum von Oktober 2013 bis Dezember 2015 mit den nachstehenden Kooperationspartnern durchgeführt:

- Bayerisches Landesamt für Gesundheit und Lebensmittelsicherheit;
- Institut für Arbeits-, Sozial- und Umweltmedizin, Klinikum der Universität München;
- Rotkreuzklinikum München, Frauenklinik, Taxisstraße 3, 80637 München;
- Universitätsklinikum Augsburg, Frauenklinik, Stenglinstraße 2, 86156 Augsburg.

Eine unabhängige Ethikkommission der Ludwig-Maximilians-Universität München hat die Studie im Vorfeld begutachtet und genehmigt.

Die gesunden Schwangeren aus dem Rotkreuzklinikum München und dem Klinikum Augsburg, die zum Zeitpunkt der stationären Aufnahme vor der Geburt rekrutiert wurden, wurden nur unter schriftlicher Einwilligung in die Studie aufgenommen. Eine Aufklärung der Patientinnen erfolgte durch ein ausführliches persönliches Aufklärungsgespräch und anhand der Patienteninformationen zur Studie. Es wurden nur gesunde Schwangere in die Studie aufgenommen, welche die schriftliche Einwilligung sowohl zur Studie als auch zu den Abstrichen bei den Neugeborenen abgegeben und mindestens das 18 Lebensjahr vollendet hatten. Hierbei wurden im Vorfeld Risikoschwangerschaften, vorzeitige Blasensprünge, geplante Sectiones sowie ambulante Geburten von der Studie ausgeschlossen. Darüber hinaus wurden nur vaginalentbundene Neugeborene in die Studie aufgenommen, die nicht im Rahmen einer Notfall-Sectio entbunden wurden oder intensivpflichtig waren. Auch wurden auf speziellen Wunsch oder bei Verlegung in eine andere Klinik die gesunden Schwangeren / Mütter einschließlich der Neugeborenen in der Studie nicht berücksichtigt.

Nach entsprechender Aufklärung und schriftlicher Einwilligung der schwangeren Frauen wurden im Kreissaal kurz vor der Geburt Abstriche im Mamillen-, Nasen-, Perianal- und Vaginalbereich entnommen und anschließend im Labor auf MRE (MSSA, MRSA und ESBL) mit Hilfe von Kultur- und Molekularmethoden untersucht. Für die Datenerhebung über den Zeitraum der Schwangerschaft wurden ferner die schwangeren Frauen anhand von standardisierten Interview-Fragebogen befragt und darüber hinaus ergänzende Daten aus den Mutterpässen und den Krankenakten im

Rahmen des Krankenhausaufnahmeverfahrens extrahiert. Den Neugeborenen wurden unmittelbar nach der Geburt Abstriche im Nasen- und Nabelbereich, sowie nach weiteren drei Tagen im Rahmen der „U2“ Abstriche im Nasen-, Nabel- und Perianalbereich entnommen.

Sämtliche Teilnehmerinnen konnten im Vorfeld entscheiden, ob sie bei positiver Befundung über das Ergebnis Ihrer Abstriche informiert werden möchten.

Im Nachgang der labortechnischen Untersuchungen wurden die Mütter, sofern die Einwilligung vorlag, telefonisch nachbefragt, um weitere Daten und Informationen zum Gesundheitszustand der Mütter und deren Neugeborenen für den Zeitraum von bis zu sechs Wochen nach der Entbindung zu erlangen.

Die Studie „QARKS“ soll primär zur Beantwortung nachstehender Fragestellungen dienen:

- Welche Prävalenzen von Besiedlungen mit *Staphylococcus aureus*, MRSA und ESBL finden sich bei Schwangeren und ihren Neugeborenen?
- Können Übertragungen von Mutter auf Kind gezeigt werden (identischer Klon)?
- Gibt es eine klinische Relevanz der Kolonisierung für die Mutter während und nach der Schwangerschaft sowie für das Neugeborene?
- Geben die Daten Hinweise auf notwendige Screening-Untersuchungen oder prophylaktische Sanierungen bei gesunden Schwangeren?

Das Forschungsvorhaben „QARKS“ wurde primär eigenfinanziert und die Laboruntersuchungen vom Bayerischen Staatsministerium für Gesundheit und Pflege (früher Bayerisches Staatsministerium für Umwelt und Gesundheit) gefördert.

### 4.2. Veröffentlichung I

Wie vorangegangene Studien bereits gezeigt haben, können nosokomiale Infektionen zu einem Anstieg der Morbidität und Mortalität führen (5). Vor diesem Hintergrund gewinnt die Prävention sowie der Nachweis nosokomialer Infektionen aber auch die Intervention zur Kontrolle und zur Bekämpfung von Antibiotikaresistenzen immens an Bedeutung. Die meisten Studien in diesem Zusammenhang stützen sich auf die Prävalenzen von MSSA, MRSA und ESBL bei Hochrisikopopulationen, Studien zu den Prävalenzen dieser MRE bei Schwangeren sind jedoch noch sehr begrenzt. Daher

beschreiben die meisten der verfügbaren Studien die Prävalenz von MSSA oder MRSA auf Intensivstationen (5). Darüber hinaus gibt es nur Studien, die die Besiedlung mit MRE bei Schwangeren in den USA betrachten, wo die Prävalenzraten im geburtshilflichen Umfeld viel höher sind als in der westeuropäischen Region (6).

Daher liegt der Fokus der ersten Veröffentlichung „Clinical relevance of colonization with antimicrobial-resistant bacteria (AMRB) and methicillin susceptible *Staphylococcus aureus* (MSSA) for mothers during pregnancy“ auf der Besiedlung mit MRE/MSSA der geburtshilflichen Bevölkerung innerhalb Deutschlands. Das Ziel der Studie war sowohl die Prävalenz der Besiedlung gesunder schwangerer Frauen mit MRE/MSSA, als auch die klinische Relevanz und die Identifizierung möglicher Risikofaktoren auf die geburtshilfliche Bevölkerung zu untersuchen.

Zu diesem Zwecke wurden im Zeitraum von Oktober 2013 bis Dezember 2015 schwangere Frauen kurz vor der Geburt nach entsprechender schriftlicher Einwilligung auf eine etwaige Besiedlung mit MRE/MSSA aus dem Mamillen-, Nasen-, Perianal- und Vaginalbereich abgestrichen und anschließend im Labor auf die zuvor genannten Erreger getestet. Im Vorfeld wurden ebendiese schwangeren Frauen anhand eines standardisierten Interview-Fragebogen befragt und bei gegebener Unvollständigkeit die Daten aus den Krankenakten im Rahmen des Krankenhausaufnahmeverfahrens miteinbezogen.

Die Ergebnisse der Studie zeigten im Vergleich zu anderen Studien eine niedrige Gesamtbesiedlungsrate mit MRE/MSSA sowie einen niedrigen Prozentsatz kolonisationsbedingter Infektionen. Weiterhin zeigte sich, dass mehrfach gebärende Frauen ein wesentlich höheres Risiko für eine Besiedlung mit MRE/MSSA haben als jene Frauen, die ihr erstes Kind gebaren. Die Studie zeigt, aufgrund der geringen Prävalenz von MRE/MSSA, dass ein grundsätzliches allgemeines Screening von nicht risikobehafteten schwangeren Frauen nicht zu empfehlen ist.

### 4.3. Veröffentlichung II

Sowohl Lungenentzündungen, als auch Haut- und Weichteilinfektionen und weitere schwere systemische Infektionen können aus einer Besiedlung mit MSSA resultieren. Eine entsprechende Besiedlung mit MRSA erschwert die Behandlungsmöglichkeiten, da diese gegen eine Vielzahl von Antibiotika resistent sind (7). Eine besondere

Risikogruppe stellen in diesem Zusammenhang Neugeborene mit niedrigem Geburtsgewicht (8), Frühgeborene (9) und Neugeborene mit längeren Krankenhaus-aufenthalten (10) dar. Auch die Besiedlung mit *Escherichia coli* (ESBL-produzierende *E. coli*) bei Neugeborenen erhöht das Risiko einer gramnegativen Sepsis (11).

Andere Studien zeigten, dass bei Neugeborenen eine Prävalenz von MSSA in Höhe von 5% (12) sowie eine MRSA-Prävalenz bei der Aufnahme auf eine NICU oder PICU eine Prävalenz in Höhe von 1,9% (13) vorliegt. Jedoch gibt es nur wenige Studien zu den Prävalenzen von MSSA, MRSA oder ESBL-produzierenden *E. coli* bei Neugeborenen innerhalb Deutschlands.

Die zweite Veröffentlichung „Prevalence of methicillin-sensitive (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum beta-lactamase *Escherichia coli* (ESBL-producing *E. coli*) in newborns – a cross-sectional study“ untersucht daher die Prävalenz von MSSA, MRSA und ESBL-produzierenden *E. coli* bei Neugeborenen. Darüber hinaus wurden Antibiotikaresistenzen und *spa*-Typen sowie die Übertragung von MSSA/MRSA und ESBL-produzierenden *E. coli* von den Müttern auf ihre Neugeborenen eingehend untersucht.

Im Rahmen der Studie wurden bei den schwangeren Frauen unmittelbar vor der Geburt und bei den Neugeborenen unmittelbar nach der Geburt Abstriche entnommen und nach schriftlicher Einwilligung auf eine etwaige Besiedlung mit MSSA, MRSA und ESBL-produzierenden *E. coli* im Labor mit Hilfe von Kultur- und Molekularmethoden untersucht. Die Abstriche wurden bei den schwangeren Frauen aus dem Mamillen-, Nasen-, Perianal- und Vaginalbereich und bei den Neugeborenen im Nasen- und Nabelbereich, sowie nach drei weiteren Tagen ergänzend im Perianalbereich entnommen.

Die Studie kam zu dem Ergebnis, dass die Besiedlung der Mutter mit MSSA, MRSA und ESBL-produzierenden *E. coli* in den meisten Fällen auch auf das Neugeborene übertragen wird, jedoch konnte nicht jede Besiedlung durch eine Mutter-Kind-Übertragung erklärt werden. Weiterhin besteht kein Zusammenhang zwischen einer Besiedlung mit MSSA, MRSA und ESBL-produzierenden *E. coli* des Neugeborenen und einer anschließenden Infektion.

### 4.4. Eigenanteil der Autorin

Die Autorin war mit der Planung und Durchführung, insbesondere der Datenerhebung am Standort München, welche u.a. neben der Aufnahme und Aufklärung der Patientinnen, deren ausführliche Befragung, die Durchführung der Screening-Abstriche bei Mutter und Kind auch aus der telefonischen Nachbefragung bestand, sowie der Auswertung der Studie betraut.

Die Aufnahme und Aufklärung der gesunden Schwangeren umfasste in diesem Zusammenhang die vorausgehende Bewertung der Geeignetheit anhand der Ausschlusskriterien zur Teilnahme an der Studie, sowie die ausführliche Befragung der gesunden Schwangeren im Kreissaal anhand des eigens hierfür entworfenen Fragebogens. Hierbei wurden neben den allgemeinen Angaben, wie z.B. Größe, Alter, Gewicht, Herkunft und beruflicher Tätigkeit, auch Aussagen zu etwaigen Kontaktpersonen und Kontaktorten mit erhöhtem Vorkommen von MSSA, MRSA und MRGN aufgenommen sowie zu etwaigen Infektionen in der Schwangerschaft.

Weiterhin wurde zu diesem Zeitpunkt auch die schriftliche Einwilligung der Patientin zur Aufnahme in die Studie, zur mikro- und molekularbiologischen Untersuchung der Abstriche der Patientin und ihres Neugeborenen eingeholt.

Darüber hinaus wurden seitens der Autorin im Kreissaal des Rotkreuzklinikums München 406 Screening-Abstriche auf MSSA, MRSA und MGRN durchgeführt. Die Abstriche wurden bei der Patientin sowohl nasal, vaginal, perianal als auch mamillär abgenommen. Die Abstriche bei den Neugeborenen wurden im Rahmen der U1 und U2 vom Klinikpersonal durchgeführt. Hierfür wurden bei der U1 Abstriche nasal und umbilikal und im Rahmen der U2 sowohl nasal, umbilikal als auch perianal durchgeführt.

Seitens der Autorin erfolgte weiterhin die Datenextraktion relevanter Daten aus dem Mutterpass und der Krankenakte zu etwaigen Vorerkrankungen, zur Medikation sowie zur Geburt des Kindes, Daten zu U2 und zu etwaigen Geburtskomplikationen.

Sofern es zu einem positiven Befund der Abstriche kam, wurden die Patientinnen umgehend von der Autorin benachrichtigt, sofern dies im Vorfeld erwünscht wurde.

Darüber hinaus übernahm die Autorin die statistische Auswertung der Studienergebnisse mit Hilfe der Statistik- und Analysesoftware SPSS 23.0 (IBM). In diesem Zusammenhang wurden kategorische Variablen mit Hilfe des Chi-Quadrat-testes und dem exakten Test nach Fisher bestimmt.

Im Speziellen erstreckt sich der Eigenanteil der Autorin an den beiden Veröffent-lichungen wie folgt:

Bei der ersten Veröffentlichung ist die Verfasserin Erstautorin. Der zuvor beschriebene Eigenanteil wurde im Zuge der ersten Veröffentlichung eigenverantwortlich und vollumfänglich von der Autorin erbracht. Darüber hinaus verfasste die Autorin das Manuskript, wertete anhand geeigneter Methoden die erhobenen Daten aus und war darüber hinaus für den kompletten Veröffentlichungsprozess verantwortlich.

Im Zuge der zweiten Veröffentlichung unterstützte die Autorin die Erstautorin sowohl bei der Durchführung der Datenerhebung als auch bei der Auswahl und Spezifizierung der geeigneten Methoden sowie der folgenden Analyse der gewonnen Daten. Darüber hinaus arbeitete die Autorin maßgeblich an der Erstellung des Manuskriptes mit und unterstützte beim Veröffentlichungsprozess.

# 5. Zusammenfassung

## 5.1. Hintergrund

Es gibt bisher keine Daten zur Prävalenz und die klinische Relevanz der Besiedlung asymptomatischer Schwangerer mit Methicillin-senstitiven *Staphylococcus aureus* (MSSA), Methicillin-resistenten *S. aureus* (MRSA) oder mit *Escherichia coli* produzierenden *Escherichia coli* mit erweitertem Spektrum β-Laktamase (ESBL) innerhalb Deutschlands. Weiterhin gibt es bisher auch keine Daten zur Prävalenz der Besieldung bei gesunden Neugeborenen mit den zuvor genannten Bakterien sowie zur Prävalenz der mütterlichen Übertragung auf das Neugeborene.

Im Zuge der Studie „QARKS“ wurde sowohl ebendiese Prävalenz der Besiedlung mit MRE/MSSA im erweiterten Spektrum bei gesunden Schwangeren und ihren Neugeborenen, als auch die klinische Relevanz und die Identifizierung möglicher Risikofaktoren auf die geburtshilfliche Bevölkerung untersucht. Darüber hinaus wurde im Rahmen der Studie eine mögliche Übertragung der MRE/MSSA auf das gesunde

Neugeborene sowie eine Antibiotika-Empfindlichkeit von MSSA-, MRSA- und ESBL-produzierenden *E. coli*-Isolaten untersucht.

## 5.2. Methodik

Im Untersuchungszeitraum, von Oktober 2013 bis Dezember 2015, wurden schwangere Frauen und ihre Neugeborenen nach schriftlicher Einwilligung aus dem Rotkreuzklinikum München und dem Klinikum Augsburg auf eine mögliche Besiedlung mit MRE/MSSA untersucht.

Für eine fundierte Datenerhebung wurden sowohl die Teilnehmerinnen im Vorfeld durch einen geschulten Interviewer anhand eines standardisierten Interview-Fragebogen befragt als auch ergänzende Daten aus dem Mutterpass und der Krankenakte im Rahmen des Krankenhausaufnahmeverfahrens extrahiert. Daraufhin wurden den Teilnehmerinnen im Kreissaal kurz vor der Geburt Abstriche im Mamillen-, Nasen-, Perianal- und Vaginalbereich entnommen. Den Neugeborenen wurden unmittelbar nach der Geburt Abstriche im Nasen- und Nabelbereich sowie nach weiteren drei Tagen im Rahmen der „U2“ Abstriche im Nasen-, Nabel- und Perianalbereich entnommen.

Die Proben wurden anschließend im Labor auf MRE (MSSA, MRSA und ESBL) mit Hilfe von Kultur- und Molekularmethoden untersucht. Die statistischen Analysen wurden im Nachgang mit SPSS 23.0 (IBM) durchgeführt.

## 5.3. Ergebnisse

Im Rahmen der Studie wurden Proben von 651 schwangeren Frauen und 658 Neugeborenen gesammelt und auf MRE/MSSA untersucht. Nach der labortechnischen Untersuchung zeigte sich, dass bei 651 schwangeren Frauen eine Besiedlung mit MSSA in Höhe von 14,3% (n = 93) und mit MRE in Höhe von 3,5% [(n= 23); MRSA: n = 3; ESBL: n = 20] festgestellt wurde.

Die Prävalenz entsprach derer im Zuge vorangegangener Studien gefundener Prävalenz in der Allgemeinbevölkerung oder war etwas niedriger. Bei mehrfach gebärdenden Frauen konnte eine signifikant höhere Besiedlung mit MRE/MSSA festgestellt werden als bei Frauen, die nulliparös waren ($p < 0,05$). Es zeigte sich, dass eine MSSA-Besiedlung signifikant mit selbstberichteten Atemwegserkrankungen während der Schwangerschaft assoziiert war ($p < 0,05$), hingegen aber eine MRE/MSSA-Besiedlung statistisch nicht mit anderen Infektionstypen assoziiert war.

Die Prävalenz bei den Neugeborenen für MSSA lag bei 10,9% (n = 71) und für MRSA bei 0,5% (n = 3) bzw. für ESBL -produzierende *E. coli* bei 2,5% (n = 16). Es zeigte sich, dass die Übertragung von MSSA, MRSA oder ESBL-produzierenden *E. coli* von der Mutter auf das Neugeborene ein Risikofaktor für die Besiedlung des Neugeborenen ist, jedoch zeigte sich keine Assoziation zwischen der Besiedlung des Neugeborenen und einer späteren Infektion.

### 5.4. Schlussfolgerung

Unsere Ergebnisse zeigen eine niedrige Gesamtbesiedlungsrate mit MRE/MSSA sowie einen niedrigen Prozentsatz besiedelter gesunder Schwangerer, die assoziierte Infektionen entwickelten. Darüber hinaus konnte keine Assoziierung zwischen auftretenden Infektionen und dem Kolonisierungsstatus der Neugeborenen festgestellt werden. Nicht jeder Fall einer Neugeborenen-Besiedlung konnte durch eine Mutter-Kind-Übertragung erklärt werden, jedoch spielt die mütterliche Besiedlung eine entscheidende Rolle bei der Besiedlung der Neugeborenen.

Ein generelles Screening schwangerer Frauen ohne Risikofaktoren wird nicht empfohlen, da die Prävalenz von MRE/MSSA grundsätzlich gering ist. Weiterhin wird aufgrund der Studienergebnisse im Zusammenhang mit etwaiger Antibiotika-resistenzen im Vorfeld einer Behandlung von MRE/MSSA assoziierter Infektionen ein Antibiogram empfohlen, um die Wirksamkeit der Antibiotika sicherzustellen.

## 5. Summary

### 5.1. Background

There are no data on the prevalence and clinical relevance of colonization of asymptomatic pregnant women with methicillin-susceptible Staphylococcus aureus (MSSA), methicillin-resistant S. aureus (MRSA) or with *Escherichia coli* producing *Escherichia coli* with extended spectrum β lactamase (ESBL) within Germany. Furthermore, there are no data on the prevalence of colonisation in healthy newborns with the above-mentioned bacteria and the prevalence of maternal transmission to the newborn.

In the "QARKS" study, the prevalence of colonisation with AMRB/MSSA in the extended spectrum in healthy pregnant women and their newborns was investigated, as well as the clinical relevance and identification of possible risk factors for the

obstetric population. In addition, the study investigated a possible transmission of AMRB/MSSA to the healthy newborn as well as antibiotic susceptibility of MSSA-, MRSA- and ESBL-producing *E. coli* isolates.

## 5.2. Methods

During the study period, from October 2013 to December 2015, pregnant women and their newborns were examined for possible colonization with AMRB/MSSA following written consent from the Red Cross Hospital Munich and the Augsburg Hospital.

For a profound data collection, the participants were interviewed beforehand by a trained interviewer using a standardized interview questionnaire, and additional data were extracted from the maternity record and the medical file as part of the hospital admission procedure. Thereupon, in the delivery room shortly before the birth, the participants were given smear tests in the nipple, nose, perianal and vaginal areas. Smears were taken from the newborns immediately after birth in the nasal and umbilical region and after a further three days in the "U2" in the nasal, umbilical and perianal region.

The samples were then analyzed in the laboratory for AMRB (MSSA, MRSA and ESBL) using culture and molecular methods. The statistical analyses were subsequently performed using SPSS 23.0 (IBM).

## 5.3. Results

Samples from 651 pregnant women and 658 newborns were collected and analyzed for AMRB/MSSA. After the laboratory examination, it was found that 651 pregnant women were colonized with MSSA in 14.3% (n = 93) and with AMRB in 3.5% [(n = 23); MRSA: n = 3; ESBL: n = 20].

The prevalence was similar or slightly lower than the prevalence found in previous studies in the general population. Multiparous women were found to have significantly higher colonisation with AMRB/MSSA than women who were nulliparous ($p < 0.05$). MSSA colonisation was found to be significantly associated with self-reported respiratory disease during pregnancy ($p < 0.05$), but AMRB/MSSA colonisation was not statistically associated with other types of infection.

The prevalence in newborns was 10.9% (n = 71) for MSSA and 0.5% (n = 3) for MRSA and 2.5% (n = 16) for ESBL-producing *E. coli*. It was shown that transmission of MSSA, MRSA or ESBL-producing *E. coli* from mother to newborn is a risk factor for

colonisation of the newborn, but no association was found between colonisation of the newborn and later infections.

## 5.4. Conclusion

Our results show a low total colonization rate with AMRB/MSSA and a low percentage of colonized healthy pregnant women who developed associated infections. In addition, no association between emerging infections and the colonization status of newborns was found. Not every case of newborn colonization could be explained by mother-to-child transmission, but maternal colonization plays a crucial role in the colonization of newborns.

A general screening of pregnant women without risk factors is not recommended because the prevalence of AMRB/MSSA is generally low. Furthermore, based on the results of studies on possible antibiotic resistance, an antibiogram is recommended prior to treatment of AMRB/MSSA-associated infections to ensure the efficacy of antibiotics.

## 6. Veröffentlichung I

Titel:

Clinical relevance of colonization with antimicrobial-resistant bacteria (AMRB) and methicillin susceptible *Staphylococcus aureus* (MSSA) for mothers during pregnancy

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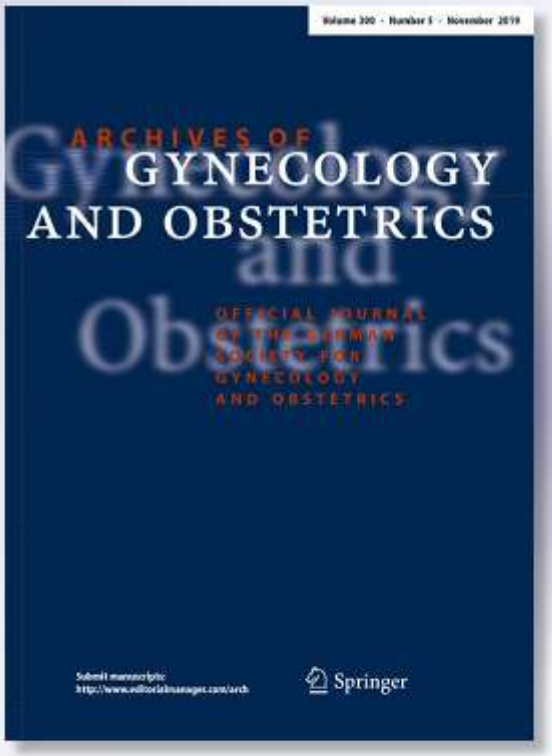


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GENERAL GYNECOLOGY

# Clinical relevance of colonization with antimicrobial-resistant bacteria (AMRB) and methicillin susceptible *Staphylococcus aureus* (MSSA) for mothers during pregnancy

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## Abstract

**Purpose** The impact of colonization with antimicrobial-resistant bacteria (AMRB) and methicillin-sensitive *Staphylococcus aureus* (MSSA) of healthy pregnant women is not described in detail in Germany. In this study, we screened for MSSA and AMRB, especially for methicillin-resistant *S. aureus* (MRSA) as well as extended-spectrum beta-lactamase (ESBL)-producing *E. coli*. Potential risk factors for colonization with AMRB/MSSA and the potential effects of colonization with these on the obstetric population were investigated.

**Methods** From October 2013 until December 2015 pregnant women were screened before birth for colonization with AMRB/MSSA from the mammillae, nose, perianal and vaginal area. Before birth, the expectant mother was administered a standardized interview questionnaire by a trained interviewer. Data from the hospital admission records were also included.

**Results** Samples from 651 pregnant women were analyzed. Colonization with MSSA was detected in 14.3% ($n = 93$), AMRB in 3.5% [($n = 23$); MRSA: $n = 3$/ESBL: $n = 20$]. Significantly more colonization of AMRB/MSSA could be detected in women who had previously given birth compared to women who were nulliparous ($p < 0.05$). MSSA colonization was significantly associated with self-reported respiratory diseases during pregnancy ($p < 0.05$), but AMRB/MSSA colonization was not statistically associated with other types of infection.

**Conclusion** Our results demonstrate a low overall rate of colonization with AMRB/MSSA, as well as a low percentage of colonized pregnant women who developed infections. Multiparous women are at higher risk for colonization with MSSA/MRSA or ESBL. Because the prevalence of AMRB/MSSA is low, this study suggests that general screening of pregnant women without risk factors is not recommended.

**Keywords** MRSA · MSSA · ESBL · AMR · AMRB · Pregnancy · Prevalence · Risk factors

## Introduction

The colonization with microorganisms such as antimicrobial-resistant bacteria (AMRB) and methicillin-sensitive *Staphylococcus aureus* (MSSA) can lead to infections [1]. The consequences of AMRB and MSSA-related infections in healthy pregnant women may be prolonged hospital stays, additional hospital costs and more difficult treatment conditions [2]. Therefore, it is important to know the prevalence and clinical impact of colonization with antibiotic-resistant bacteria. The impact of colonization with AMRB and MSSA of healthy pregnant women is not described in detail in Germany. The increasing prevalence of infections as well as the reduced discovery of new drugs makes treatment more challenging [3]. It is questionable whether colonization with

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AMRB and MSSA is relevant for pregnancy and childbirth and whether there is transmission from mother to child.

## Prevalence of colonization

Methicillin-resistant *Staphylococcus aureus* (MRSA) as well as extended-spectrum beta-lactamase (ESBL)-producing microorganisms are some of the most common multiresistant bacteria [4, 5]. MSSA is often used as surrogate parameter for MRSA due to similar characteristics (e.g. in terms of PVL production), transmission pathways and caused infections. Similarly to MRSA, carriage of MSSA does not necessarily lead to infection; it is a facultative pathogen [6].

A study on the prevalence of ESBL-producing *E. coli* among infection control personal revealed a colonization rate of 3.5% [7] which continues to increase [1]. Furthermore, the number of ESBL-producing *E. coli* in German outpatient care increased from 2.7% in 2008 to 5.6% in 2012 [8]. Increases in ESBL-*E. coli* colonization in both hospital and community setting are an emerging threat [9].

In the German general population, MSSA was carried at least once in 40.9% [10] and in German hospitals MRSA prevalence decreased from 14.0% in 2010 to 9.0% in 2015 taken from swabs [11].

However, studies with the prevalence of AMRB in pregnant women are limited. It is difficult to find sources stating coherent prevalence of MSSA, MRSA and ESBL in Germany in the healthy, pregnant women population as most studies focus on high-risk populations. Therefore, most of the data available describe the prevalence of MSSA or MRSA in intensive care units [2], and colonization in the USA where prevalence rates in the obstetric setting are much higher than in the Western European region [12]. Various studies report MSSA colonization with 17–24.3% and MRSA colonization with 0.5–3.5% [12–14] in the USA in pregnant women. A literature review from 2010, which included the data of Medline, EMBASE and the Cochrane database, showed that the prevalence of MRSA in the obstetric population is generally low [15]. Exact numbers about the total incidence of MRSA and ESBL colonization in the obstetric population in Germany are not available. Given the limited availability of use of antibiotics, it is vital that research is focused on this particular risk group.

## Infections

Evidence has been provided that shows an association between colonization with AMRB/MSSA and higher probability of infection [16]. MRSA or MSSA caused infections are not clinically distinguishable [5], but MRSA infection is associated with a higher mortality rate (36.4% with MRSA and 27% with MSSA in intensive care patients). The reason for that is not adequately clarified, but a possible explanation could be the delayed effect of antibiotics therapy or different pharmacokinetic properties of the antibiotic [5].

MRSA infections in the general population are often locally limited skin and soft tissue infection or recurrent abscess [17].

The prevalence of MRSA colonization in the obstetric population is comparable with the prevalence in the general population [18]. Most commonly it presents as skin and soft tissue infection (SSTI) with multiple sites and recurrences [18, 19].

Serious infectious syndromes have been reported [18] and can affect the obstetric population. Urinary tract infections (UTI) caused by ESBL colonization are one of the most frequent infections appearing during pregnancy [20]. The colonization with antibiotic-resistant bacteria complicates the treatment of these infections. Some epidemiologic reviews state, that the presence of an ESBL colonization is associated with a threefold increase in the risk to develop an urinary tract infection [21].

## Risk factors

Various sources show different potential risk factors for colonization with AMRB or MSSA. Among the generally known and well described risk factors are hospitalization [22–25] contact with the health care setting [26, 27] chronic diseases or comorbidities [3, 27, 28] and previous antibiotic use [3, 23, 24].

There is no immediate risk of infection after colonization for healthy people. At risk for infection after AMRB colonization are people with chronic wounds, skin lesions, chronic diseases like diabetes or undergoing immunosuppressive therapy [3, 5, 29].

Another potential risk factor for AMRB colonization and spread could be travelling or time spent abroad [30, 31]. Studies determined that a colonized family member is also a high-risk factor for colonization with AMRB/MSSA (intra-familial transmission) [32, 33]. In this context, Kellie shows that contact with children in day-care could be a further cause of MRSA acquisition [18]. Further risk groups for a MRSA colonization are pregnant women who had a cesarean section or who are multiparous [19].

A potentially higher risk for colonization with livestock-associated MRSA (LA-MRSA), are also persons either coming in direct contact with industrial livestock or via inhalation of contaminated barn dust [34]. The actual number of ambulant LA-MRSA infections in Germany is unknown [35]. LA-MRSA is not less virulent than other MRSA but can be differentiated in its epidemics in health care institutions [36].

### Objective

Thus, it is particularly relevant to find how colonization with AMRB affects the obstetric population. So far there are scarcely any research results on the clinical relevance and risk factors for the colonization with MSSA, MRSA or ESBL in the obstetric population.

The aim of this study was to detect the prevalence of colonization of healthy pregnant women with AMRB/MSSA as well as its clinical relevance and corresponding risk factors.

## Methods

### Population

Participants from two large Bavarian clinics were recruited from October 2013 until December 2015 to participate in this (cross-sectional) study. Therefore, they had to sign an informed consent form, be at least 18 years of age and have a planned vaginal delivery. Primary, selected or emergency caesarean section, outpatient birth, multiple pregnancies or cervical incompetence (pessary, cerclage) were excluded from the study. Data from participants who withdrew their consent or moved to another health care facility were removed from the study. All the collected data and the microbiological samples were pseudo-anonymized via an internal encryption code which did not contain the name, initials or date of birth. The methodology has already been described in detail in the work of Adler et al. and Zamfir et al. [37, 38].

The study was developed by the Bavarian Health and Food Safety Authority, Munich and was funded by the Bavarian State Ministry for Public Health and Care Services. The Institutional review board of Ludwig-Maximillians-University Munich approved the study.

### Data collection

Before birth, the expectant mother was administered a standardized in-person interview questionnaire by a trained interviewer. The expectant mother answered questions regarding potential contact with fomites, exposure to known risk factors or persons belonging to a group with higher prevalence of AMRB. The questions in the questionnaire were designed to assess prospectively designated selected risk factors for AMRB/MSSA-colonization. Of particular importance were the issues of occupational activity, infections and hospital stays during pregnancy. The mother's medical history and medication intake were self-reported during this interview (Fig. 1). Data from the hospital admission records such as delivery date, weight and size of the mother were also included. The child's birth data, possible complications and the discharge from the hospital were collected from medical records. After about six weeks, a follow-up Computer Assisted Telephone Interview (CATI) was conducted concerning any infection the child or the mother developed after hospital leave.

### Screening

Before birth, four samples were taken from the woman. In prevention service U1 and prevention service U2 a total of 5 samples were taken from the newborn. In total, samples were taken from the following sites: Mother: mammillae, nose, vaginal, perianal; infant (U1): nose, perianal; infant (U2): nose, perianal, umbilical. All samples were screened for MSSA, MRSA and ESBL-*E. coli*. Antibiotic resistance screening for MRSA and ESBL was performed. The isolates were tested for antibiotic susceptibility, for detailed description see the article by Zamfir et al. [37].

### Statistical methods

To compare categorical variables, the $\chi^2$-test and Fisher's exact test were used. A logistic regression model building was done with the potential factors with influence on colonization status selected a priori. A $p$ value $< 0.05$ was considered as statistically significant. All statistical analyses were performed using SPSS 23.0 (IBM).

## Results

### Descriptive statistics and prevalence

This study analyzed data from 651 pregnant women. Out of initially 763 participating pregnant women, 112 were excluded due to missing questionnaires. 62.5% ($n = 406$) of data were collected in clinic 1 as well as 37.6% ($n = 245$) in clinic 2. Post-delivery 420 women were interviewed per follow-up CATI.

The average age of pregnant women at hospital admission was 32 years (SD = 4.8). The underlying average BMI before pregnancy was 23.7 (SD = 6.0) with a minimum of 12.9 and a maximum of 51.3. A summary of the socio-demographic data is given in Table 1. AMRB/MSSA colonization was detected in 17.4% ($n = 113$), whereof MSSA was found in 14.3% (n = 93) and AMRB in 3.5% ($n = 23$) (MRSA: $n = 3$; ESBL $n = 20$) of the pregnant women.

### Analysis of risk factors and clinical relevance

Different potential risk factors for infections were analyzed to examine an association between the colonization with AMRB/MSSA and clinical relevance.

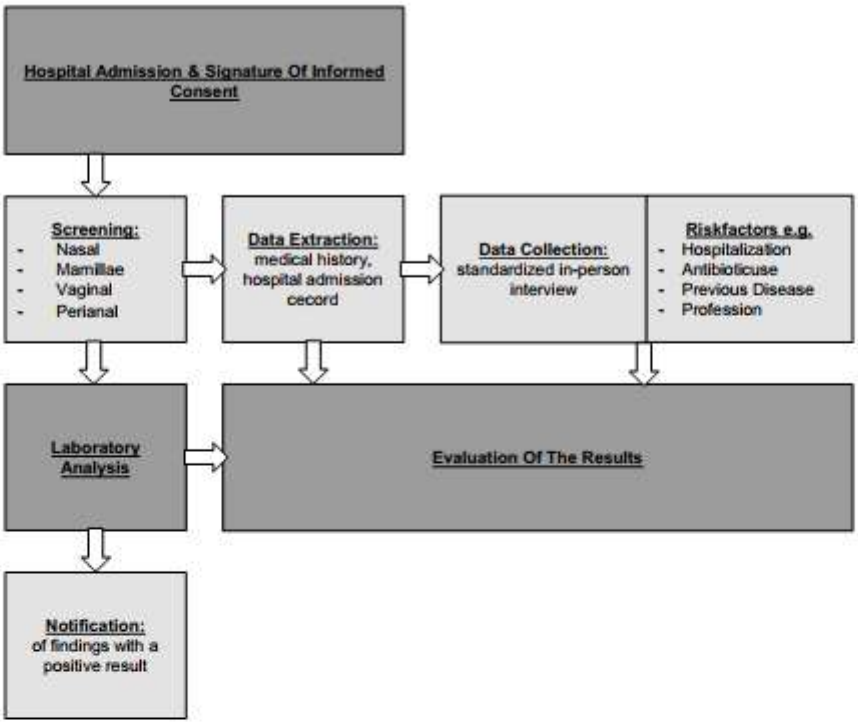


**Fig. 1** Data collection

**Table 1** Sociodemographic characteristics of pregnant women

| | Total ($N=651$) | | Clinic 1 ($N=406$) | | Clinic 2 ($N=245$) | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| Age in years | | | | | | |
| 18–29 | 197 | 30.6 | 114 | 28.5 | 83 | 34.2 |
| 30–34 | 253 | 39.3 | 156 | 39.9 | 97 | 39.9 |
| > 34 | 193 | 30.0 | 130 | 32.5 | 63 | 25.9 |
| BMI | | | | | | |
| Underweight (< 19) | 47 | 7.2 | 29 | 7.1 | 18 | 7.4 |
| Normalweight (19–25) | 400 | 61.4 | 246 | 60.6 | 154 | 62.9 |
| Overweight/Adipositas (≥ 25) | 186 | 28.6 | 119 | 29.3 | 67 | 27.4 |
| Previous birth | | | | | | |
| Nulliparous | 433 | 66.5 | 290 | 71.4 | 143 | 58.4 |
| Multiparous (1) | 165 | 25.4 | 82 | 20.2 | 83 | 33.9 |
| Multiparous (2) | 40 | 6.1 | 25 | 6.2 | 15 | 6.1 |
| Multiparous (3 or more) | 13 | 2.0 | 9 | 2.2 | 4 | 1.6 |

Regarding the delivery mode, 79% ($n=514$) of the pregnant woman had a vaginal delivery. The remaining 21% ($n=137$) delivered with a secondary Cesarean Section due to different unpredictable reasons. The mode of delivery did not predict colonization with AMRB/MSSA.

Another factor considered was previous pregnancies. About one third (33.5%; $n=218$) of the women were multiparous. From them, 16.9% ($n=37$) were colonized with MSSA, 0.9% ($n=2$) with MRSA and 4.1% ($n=9$) with ESBL-*E. coli*. From the woman who were nulliparous (66.5%; $n=433$), MSSA colonization could be detected in 12.9% ($n=56$), MRSA colonization in 0.2% ($n=1$) and 2.5% ($n=11$) colonization was detected with ESBL-*E. coli*. Consequently, significantly more colonization of MRSA/MSSA and ESBL-*E. coli* could be detected in women who had previous birth compared to women who were nulliparous ($p<0.05$).

Differences due to hospital location were not significant (Clinic 1: $n=12$; 2.4% ESBL-*E. coli*/Clinic 2: $n=8$; 3.2% ESBL-*E. coli*). 258 (40%) women reported travelling abroad during their pregnancy. Overall, no significant increase was detected in the colonization with MRSA ($n=0$; 0%), MSSA ($n=38$; 15%) or ESBL-*E. coli* ($n=5$; 2%) (Table 2). Of the women who traveled abroad, 5% ($n=12$) reported having had contact with health care facilities (2 as guests and 10 as patients). From the 651 mothers included in the study, 10 mothers reported having had contact with the medical services outside the country as patients (3 stationary) and 2 were visitors. The factors "professional activity in the healthcare sector" and "leisure/professional activity within agriculture or with animals" showed no statistically significant differences with regard to AMRB/MSSA colonization.

Furthermore, pregnant women self-reported preexisting diseases (long-term medication, cardiovascular diseases, kidney or thyroid diseases, hypertension and diabetes) in 16.9% of the cases and medical conditions during pregnancy (gestational hypertension, gestational diabetes) in 8.9%. Both factors did not predict AMRB/MSSA colonization. Likewise, antibiotic use did not predict AMRB/MSSA colonization during pregnancy. When looking at hospitalization, it was found that the median hospital stay was four days. The days were not significantly different when the mother was colonized with MSSA, MRSA or ESBL-*E. coli*. The odds ratio of colonization with AMRB for pregnant woman who were hospitalized was 0.87 (CI 0.11–6.96) and 0.42 (CI 0.16–1.17) for pregnant woman who travelled abroad after adjusting for clinic and antibiotic use in the logistic model. The odds ratio without adjusting were 0.70 (CI 0.09–5.33) and 0.55 (CI 0.20–1.51), respectively.

From the 113 (17.4%) women positive for MRSA/MSSA or ESBL colonization during pregnancy, 8.8% had a vaginal infection, 5.3% had a urinary tract infection (UTI), 0.9% a soft tissue infection and 11.5% a respiratory disease such as bronchitis, sinusitis or otitis, as indicated in Table 3.

Figure 2 compares the infections of patients with AMRB/MSSA colonization and without. Patients suffering from a self-reported respiratory disease had a higher percentage of AMRB/MSSA colonization. Thus, MSSA colonization was significantly associated with respiratory diseases ($p<0.05$), but MRSA, MSSA or ESBL colonization were not statistically associated with other types of infections.

The data from the post-survey were evaluated and can be found in Table 4. There is no significant evidence that AMRB/MSSA induced infections after delivery are higher than infections that are not due to colonization, based on data of colonization before birth.

With regards to the antibiotic resistance of the bacterial isolates, 100% of MSSA isolates were resistant to penicillin. MRSA isolates were 100% resistant to cefoxitin, imipinem, oxacillin and penicillin. In ESBL isolates, amoxicillin, ampicillin, cefotaxime, cefuroxim, piperacilin and tazobactam resistance was found in all isolates (Fig. 3).

## Discussion

Our results demonstrate a low overall rate of colonization with MSSA (14.3%), MRSA (0.5%) and ESBL-*E. coli* (3.1%). Other sources reported comparable results with a MSSA prevalence of 17–24.3% [13], MRSA prevalence of 0.5–3.5% [12–14] and ESBL-*E. coli* prevalence of 6.3–8.6% [26, 39]. The colonization with AMRB/MSSA was not significantly associated with any demographic or obstetrical

**Table 2** Travelling

| | Total ($N=258$) | | MSSA ($N=38$) | | MRSA ($N=0$) | | ESBL ($N=5$) | |
|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % |
| North-/West Europe | 59 | 22.9 | 9 | 23.7 | 0 | 0.0 | 0 | 0.0 |
| East-/South Europe | 166 | 64.3 | 22 | 57.9 | 0 | 0.0 | 4 | 80.0 |
| North America | 10 | 3.9 | 1 | 2.6 | 63 | 0.0 | 0 | 0.0 |
| Central-/South America | 10 | 3.9 | 1 | 2.6 | 0 | 0.0 | 0 | 0.0 |
| Asia | 15 | 5.8 | 4 | 10.5 | 0 | 0.0 | 1 | 20.0 |
| Africa | 3 | 1.2 | 1 | 2.6 | 0 | 0.0 | 0 | 0.0 |

**Table 3** Analysis of risk factors and clinical relevance

| | Total ($N=651$) | | AMRB + SA pos ($N=113$) | | AMRB + SA neg ($N=23$) | | MRSA ($N=3$) | | SA ($N=93$) | | ESBL ($N=20$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Mode of delivery | | | | | | | | | | | | |
| Vaginal | 514 | 79.0 | 89 | 78.8 | 20 | 87.0 | 3 | 100.0 | 71 | 77.2 | 17 | 85.0 |
| Cesarean[c] | 137 | 21.0 | 24 | 21.2 | 3 | 13.0 | 0 | 0.0 | 21 | 22.9 | 3 | 15.0 |
| Previous pregnancy | | | | | | | | | | | | |
| Nulliparous | 433 | 66.5 | 65* | 57.5 | 12 | 55.2 | 1 | 33.3 | 55 | 60.0 | 11 | 55.0 |
| Multiparous | 218 | 33.5 | 48 | 42.5 | 11 | 47.9 | 2 | 66.6 | 37 | 40.0 | 9 | 45.0 |
| Risk factors | | | | | | | | | | | | |
| Stay Abroad | 252 | 38.7 | 43 | 38.1 | 5 | 21.7 | 0 | 0.0 | 38 | 41.0 | 5 | 25.0 |
| Profession Healthcare | 28 | 4.3 | 5 | 4.4 | 0 | 0.0 | 0 | 0.0 | 5 | 5.4 | 0 | 0.0 |
| Profession Agriculture | 173 | 26.6 | 31 | 27.4 | 4 | 17.4 | 1 | 33.3 | 27 | 29.4 | 3 | 15.0 |
| Previous disease[a] | 110 | 16.9 | 19 | 16.8 | 2 | 8.7 | 0 | 0.0 | 17 | 17.9 | 2 | 10.0 |
| Disease during pregnancy[b] | 58 | 8.9 | 10 | 8.8 | 1 | 4.3 | 0 | 0.0 | 9 | 9.5 | 1 | 5.0 |
| Antibiotic use | 80 | 12.3 | 15 | 13.3 | 1 | 0.2 | 0 | 0.0 | 14 | 14.7 | 1 | 0.2 |
| Hospitalzation | 46 | 7.1 | 10 | 1.5 | 1 | 0.2 | 0 | 0.0 | 9 | 1.4 | 1 | 0.2 |
| Infections in pregnacy | | | | | | | | | | | | |
| Vaginal | 57 | 8.8 | 10 | 8.8 | 4 | 17.4 | 0 | 0.0 | 6 | 6.3 | 4 | 20.0 |
| Urinary tract | 43 | 6.6 | 6 | 5.3 | 0 | 0.0 | 0 | 0.0 | 6 | 6.5 | 0 | 0.0 |
| Purupent Skin | 1 | 0.2 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| Soft tissue | 14 | 2.2 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 |
| Otitis | 6 | 0.9 | 1 | 0.9 | 0 | 0.0 | 0 | 0.0 | 1 | 1.1 | 0 | 0.0 |
| Respiratory[d] | 41 | 6.3 | 12** | 10.6 | 1 | 4.4 | 0 | 0.0 | 11*** | 12.0 | 1 | 5.0 |
| Operation | 5 | 0.8 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

*$p$ 0.026

**$p$ 0.038

***$p$ 0.016

[a]Long-term medication/cardio vascular/kidney, thyroid/hypertension/diabetes I, II

[b]Gestational hypertension/diabetes

[c]Only secondary C-section (not emergency or primary)

[d]Respiratory = sinusitis, bronchitis

variable except increased parity and self- reported respiratory infections during pregnancy.

Comparing our results with the available data is opaque due to methodological differences, as well as sampling from different skin regions and at different time points.

## Infections and diseases

Different determinants like the ability to spread, as well as virulence factors (e.g. pathogenity, resistance and factors from the environment like hygiene) influence whether colonization leads to infection or not [40]. Our study showed, that only a small percentage of colonized pregnant women also have infections. It can also be mentioned that colonized women are more susceptible to later reinfections [41]. Huang et al. [41] found that about 29% of patients developed MRSA reinfections.

A previously reported association between chronic disease or comorbidities and higher incidence of AMRB/MSSA colonization [3, 42] could not be detected in our study. Self-reported preexisting or chronic medical conditions were not significantly associated with colonization (Table 3).

With respect to acute infections, AMRB/MSSA colonization resulted in more respiratory infections in pregnant women. MSSA colonization in particular, which is used as a surrogate parameter for MRSA due to similar characteristics, was associated with respiratory diseases, as confirmed by Lowy [3]. A point prevalence survey reported lower respiratory tract infections as the most frequent documented nosocomial infection [43]. Respiratory infection is one of the major consequence of MRSA colonization, with the more serious results of MRSA induced pneumonia [35].

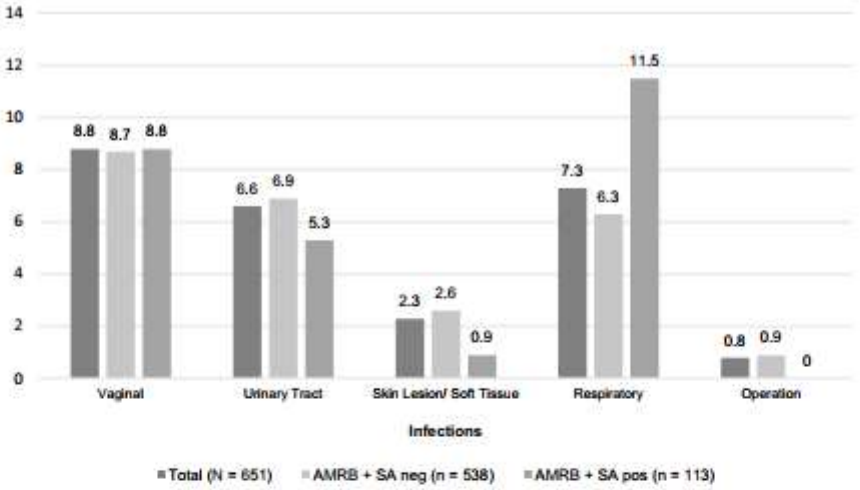


**Fig. 2** Infections of pregnant women with/without colonization

Clinically, the most common result of MSSA/MRSA colonization is skin and soft tissue infection [17, 28, 44]. Numerous studies suggested that colonization with AMRB/MSSA correlates with a higher risk of postpartum infections like increased risk for postoperative or post-cesarean wound infections as well as postpartum mastitis [45]. Other studies stated that there is no higher risk of infection through MRSA colonization [13], which was coherent with our results. In our study population only 15 cases of SSTI (2.4%) were found, from them only 1 case (6.7%) was colonized with MSSA and none with MRSA. Similar results were found for postoperative condition—in our study sample, only 5 women had surgical intervention during pregnancy. A larger study population would have been needed to reliably detect comparable results.

UTI is one of the most common nosocomial infections [43] and presents a particular problem for pregnant women and their children since they are the most frequent infections appearing during pregnancy [20]. Most frequently they are due to colonization with gram-negative pathogens [27]. Studies show that the numbers of community-acquired UTI with ESBL-*E. coli* keep increasing [4, 46, 47]. Ascending microorganisms in the vaginal tract can lead to possible problems during pregnancy, for example ascending ESBL-*E. coli* in the urinary tract. In our sample 6.6% ($n=43$) self-reported having had an UTI, 5.3% ($n=6$) of them also having colonization with ESBL-*E. coli* or MSSA (none with MRSA). This is comparable to the incidence of bacteriuria in pregnancy as reported by the German Society of Urology [48].

Pregnant women are more inclined to develop a vaginal or urinary tract infection due to hormonal and physiologic changes [20]. Vaginal infection was the most self-reported infection in our sample during pregnancy. 8.8% ($n=57$) of women, from them 17.5% ($n=10$) being colonized with ESBL-*E. coli* or MSSA. In the literature, incidence bacterial vaginosis (bacterial disturbance of the vaginal flora) is reported to be 5 to 20% in pregnancy [49, 50].

## Risk factors

Risk factors for infections have been analyzed in studies before, but scarcely in the combination of MSSA/MRSA and ESBL-*E. coli*. Well known risk factors like hospitalization, antibiotic use, chronic disease and contact with health care have been associated with AMRB infection [3, 22–24, 24, 26, 27]. However, other studies found that traditional risk factors do not predict MRSA carriage in pregnant women [45]. Reusch [14] investigated risk factors (prior abscess, afterschool/daycare program, antibiotic use, hospitalization) for colonization with MRSA in pregnancy and could not identify statistically significant risk factors [12].

In our study, there are several possible explanations for the weak associations between traditional risk factors and colonization with AMRB/MSSA. Particularly the low prevalence of colonization with AMRB/MSSA restricted our statistical power. On the other hand, the low prevalence was expected, as the majority of pregnant women without additional risk factors are healthy individuals who rarely

**Table 4** Questionnaire follow up

| Infections before delivery | Present (see Table 3) | | | | | Non-existent (see Table 3) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Infections after delivery | Uncolonized | | Colonized | | *p* | Uncolonized | | Colonized | | *p* |
| | *n* | % | *n* | % | | *n* | % | *n* | % | |
| Vaginal infections | *N* = 320 | | *N* = 61 | | 0.52 | *N* = 34 | | *N* = 5 | | 0.58 |
| Negative | 310 | 96.9 | 60 | 98.4 | | 32 | 94.1 | 5 | 100.0 | |
| Positive | 10 | 3.1 | 1 | 1.6 | | 2 | 5.9 | 0 | 0.0 | |
| Skin infections | *N* = 354 | | *N* = 66 | | 0.82 | *N* = 0 | | *N* = 0 | | - |
| Negative | 345 | 97.5 | 64 | 96.9 | | 0 | 0.0 | 0 | 0.0 | |
| Positive | 9 | 2.5 | 2 | 3.1 | | 0 | 0.0 | 0 | 0.0 | |
| Urinary tract infections | *N* = 326 | | *N* = 61 | | 0.29 | *N* = 28 | | *N* = 5 | | 0.67 |
| Negative | 318 | 97.5 | 58 | 95.1 | | 27 | 96.4 | 5 | 100.0 | |
| Positive | 8 | 2.5 | 3 | 4.9 | | 1 | 3.6 | 0 | 0.0 | |
| Respiratory infections | *N* = 326 | | *N* = 57 | | 0.05* | *N* = 28 | | *N* = 9 | | 0.57 |
| Negative | 324 | 99.4 | 55 | 96.5 | | 27 | 96.4 | 9 | 100.0 | |
| Positive | 2 | 0.6 | 2 | 3.5 | | 1 | 3.6 | 0 | 0.0 | |
| Overall infections | *N* = 270 | | *N* = 51 | | 0.40 | *N* = 84 | | *N* = 17 | | 0.54 |
| Negative | 247 | 91.5 | 43 | 87.8 | | 75 | 89.3 | 16 | 94.1 | |
| Positive | 23 | 8.5 | 6 | 12.2 | | 9 | 10.7 | 1 | 5.9 | |


Fig. 3 Antibiotic resistance

need inpatient treatment. Other investigations have shown similar results [12].

These amongst others are reasons why the risk of MRSA acquisition and thus infection for healthy pregnant is not increased compared to the general population [5]. There are studies stating antibiotic use as a risk factor for colonization with MSSA or MRSA [51]; but there are also studies stating the contrary [29, 32].

Hospitalization is regarded as a strong risk factor for AMRB acquisition, but our results do not confirm this statement. Woman, who were hospitalized during pregnancy did not show a higher incidence of AMRB acquisition. In addition, the hospital stay for the delivery has been looked at and like Saiman et al. [22], we conclude that the days were not significantly different when the mother was colonized with MSSA, MRSA or ESBL-*E. coli*.

In this context, we noted that women who are multiparous show statistically significantly higher prevalence of AMRB/MSSA colonization ($p < 0.05$) compared to woman without previous deliveries. This variable is significant but a weak risk factor. Other studies point out that a risk of colonization is increased with multiparity [19, 52, 53]. Prior studies showed that multiparous women and women who have had a cesarean delivery were more likely to have CA-MRSA (community-acquired MRSA) infections [19].

A possible explanation could be recent visits to outpatient medical facility like visits at the gynecologist, prenatal care and visits at the emergency department. There the risk is higher for AMRB/MSSA colonization [45, 54]. Another reason could be more exposure with AMRB/MSSA for multiparous women who were previously hospitalized for the births of the first children.

Another variable considered was travelling or rather time spent abroad. From the 258 women (40%) travelling during pregnancy, no significant increase was detected in the colonization with MRSA.

Trips to areas with high AMRB prevalence or increased contact with potentially contaminated surfaces (e.g. airports) [30] could be risk factors [35]. Further studies showed that rectal colonization with ESBL-producing Enterobacteriaceae was associated with travelling [26]. Maier et. al. [31] showed that an increased number of MRSA cases were associated with travelling or contact with persons originating from countries with high MRSA prevalence. Similar results were found in the Netherlands or Sweden, where after return from Asia approximately 30% of individuals were colonized with ESBL [30, 55]. These findings are similar to our data where 33% ($n = 5$) of the women travelling to Asia ($n = 15$) were colonized (7% with ESBL-*E. coli* and 27% with MSSA).

Based on our study, local differences in prevalence can be traced between the two participating clinics. The difference between the two clinics in the prevalence of MSSA and ESBL-*E. coli* illustrates that prevalence is dependent on regional and local conditions and the way institution-specific factors are influencing the spread of bacteria.

Professional activity in health care was also considered as a risk factor influencing AMRB acquisition. Studies show that with 1–5% MRSA colonization, health care employees have considerably higher prevalence [43]. Contact with the health care setting is particularly also a known risk factor for ESBL infection [27]. We cannot confirm these results, but our dataset is too small to make an accurate statement. Therefore, additional special protection measures in the context of maternity protection seem to be unnecessary.

In some studies, the contact with agriculture is handled as another risk factor [35]. Köck et. al. [26] demonstrated, that people with agricultural livestock were 31 times more likely to acquire MRSA. Although frequently acquired, colonization was tested negative within 24 h [56]. The main reservoir of LA-MRSA is agricultural livestock which can be transmitted from animals to humans. A possible threat would be the introduction from the colonized human to the hospital setting [35]. Because we had so few mothers colonized with AMRB in our study population, the variable "contact with agriculture" could not clearly highlight a risk factor. The value of MRSA outside the hospital gains in importance and becomes a new challenge.

## Antibiotic resistance

The therapy for MSSA and MRSA has to be differentiated. Up to 80% of MSSA strains are resistant to all penicillins. This is also reflected in our data. The therapy has to be adapted to the antibiogram and to the clinical picture [57]. According to recommendations of the Robert Koch Institute, infections with MSSA are treated with „penicillinase-resistant penicillin (e.g. flucloxacillin) as well as 1st generation cephalosporins and inhibitor-protected penicillin. Alternatives are combinations with rifampicin [40]. For skin and soft tissue infections as well as penicillin allergy a therapy with clindamycin is recommended. The total duration of treatment depends on the clinical course, but it should at least be 7–10 days [57].

In the case of an MRSA infection, the treatment will be more selective because MRSA is a variant of Staphylococcus aureus with the formation of an additional penicillin-binding protein PBP2a which has a low affinity for beta-lactam antibiotics and that results in resistances to almost all antibiotics in the beta-lactam group [40]. Vancomycin from the glycopeptide group was long time first-line therapy, but the resistances in hospitals are increasing and alternative antibiotics have to be used. This was not reflected in our data, we found 100% susceptibility for vancomycin (Fig. 3). In case of uncomplicated bacteraemia, it is still used as a standard. A series of antibiotics are available as alternative

therapy. Clindamycin, for example, is rarely effective in nosocomial MRSA infections. It is often effective in community acquired MRSA, but our data showed 33% resistance for clindamycin. Further alternatives to vancomycin are available; Teicoplanin is another representative of glycopeptides or linezolid as well as daptomycin or tigecycline can also be used [58]. Our data do also reflect 100% susceptibility in these alternative antibiotics.

In the event of a gram-negative infection, ESBL formers are considered. Extended-spectrum β-Lactamase is a beta-Lactamase with an extended-spectrum, which inactivates penicillin and cephalosporins, which are highly resistant to many antibiotics. Data from a study in France found an increasing resistance from 2001 to 2016 in the third generation of cephalosporin group for invasive *E. coli* strains [59]. Our data also showed resistance to this group, ESBL-*E. coli* was susceptible with only 19% to ceftazidim. Further resistances exist for amoxicillin, ampicillin, piperacillin and tazobactam, cefepim, ceftazidim, cefotaxim and cefuroxim. Equally, substances from the group of flouroquinolones (ciprofloxacin and levofloxacin each up to 35%) as well as substances from the groups of glycosides (azithromycin 73%) and aminoglycosides (gentamicin 42%) show resistances. Today, this might constitutes a greater therapeutic problem in Europe than MRSA [60]. Currently, available therapy options are beta-Lactamase inhibitors in combination with a penicillin or cephalosporin as well as temocillin, carbapenems, colistin, fosfomycin and tigecycline [60]. Resistance to fosfomycin and tigecycline are very rare until now.

## Prevention and screening

The Hospital-Infections-Surveillance-System (KISS), a German surveillance system for nosocomial infections, proposes a focus on the improvement of prevention instead of treatment [2].

Basic hand hygiene represents a very important factor. In most cases the bacteria are transferred through the hands of medical staff (nurses and physicians). In the case of nasopharyngeal colonization, the transmission occurs via skin and can then spread further [40]. In medical institutions, the hands of employees are the most important transmission way for infections [5], a good established and consequent basic hygiene is, therefore, the basis to prevent infections and spread of bacteria [61].

Another aspect to be considered is the careful handling of antibiotics. Kallen et al. [62] showed that a uniform and transparent approach to the use of antibiotics is essential to measure the qualitative and quantitative use of antibiotics and to ensure reliable use [62]. Any use of antibiotics should be subject to a strict indication to prevent the rise of new antibiotic resistance [63].

Commission for Hospital Hygiene and Infection Prevention (KRINKO) recommends that universal screening in pregnant is ineffective [64], the prevalence is low, resulting in massive costs without additional benefits [12, 18, 65]. Our results support this approach, that there is no dependence between AMRB/MSSA colonization and associated infections.

In the case of MRSA colonization, a local eradication/decolonization is a useful prevention strategy to prevent colonization [15, 66–68].

Further, we have to mention that there is no danger for the pregnant and their unborn because Staphylococcus does not pass the placental barrier. In the situation of MRSA carriage, it is recommended to take swabs and to apply a local eradication/decolonization to prevent wound infections of the newborn [40]. Standard procedure for the eradication on skin is body washings of intact skin with antiseptic solutions, nasal eradication therapy is mupirocin treatment [40].

However, we also have to say that MRSA is rare and the burden is modest but decolonization is still recommend when the risk for infections needs to be minimized [12].

For patients colonized with ESBL-*E. coli*, it was found that ESBL will stay for some month and will then disappear in the majority of cases [63]. There are only weak data for eradication therapy, which did not give satisfying results. The appropriateness of eradication has not yet been conclusively clarified and it is not advisable so far [63].

## Limitations and future studies

As previously noted, we could not demonstrate strong risk factors predicting AMRB/MSSA colonization and consequent infections. The low prevalence of colonization provided limited statistical power to determine a large number of risk factors. We recognize that there may have been many potential risk factors that could have been evaluated given a larger sample size. The analysis of risk factors reveals the multitude/variety of conflicting results. In relation to the study population, geographical location and the different strains, a variety of different aspects were considered. Samples were collected in two hospitals from two different cities from the same federal state; therefore, we can assume that the population is not fully representative for the whole German obstetric population. However, a comparison of two hospital populations is possible, with one of them in a more rural area and one with urban population.

## Conclusion

Summarizing, AMRB/MSSA colonization rates in expectant mothers were low and concordant with the general population. Increased parity can be a risk factor for colonization with MSSA/MRSA or ESBL.

The colonization with MSSA/MRSA or ESBL of healthy pregnant woman did not seem relevant for infections during pregnancy. As the percentage of infections is similar in colonized and uncolonized healthy pregnant women, this study suggests that routine screening is not necessary in a population with low prevalence, when no complicated pregnancy conditions are given. Prophylactic screening or further investigations should be considered individually for every case. Awareness should be raised on problems surrounding AMRB spread, colonization and infection. Information and medical consultation of the patient are of special interest. Early detection of resistant isolates is getting more and more important because that is the only way to prevent spreading in hospitals and the community.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Research involving human participants** Ethical approval was provided by the Ludwig-Maximilians-University, Munich, Germany. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent: Informed consent was obtained from all individual participants included in the study.

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## 7. Veröffentlichung II

Titel:

Prevalence of methicillin-sensitive (MSSA), methicillin-resistant Staphylococcus aureus (MRSA) and extended-spectrum beta-lactamase *Escherichia coli* (ESBL-producing *E. coli*) in newborns – a cross-sectional study

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ORIGINAL ARTICLE

# Prevalence of methicillin-sensitive, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum beta-lactamase-producing *Escherichia coli* in newborns: a cross-sectional study

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ABSTRACT

**Background:** The prevalence of antimicrobial-resistant bacteria and methicillin-sensitive *Staphylococcus aureus* (MSSA) in healthy newborns and the role of maternal transmission are scarcely discussed.

**Objectives:** The objective of this study was to evaluate the prevalence of MSSA, MRSA, and ESBL among healthy newborns. Additionally, mother-to-newborn transmission rates were investigated as well as antibiotic susceptibility of MSSA, MRSA, and ESBL isolates.

**Methods:** Swabs of 658 newborns and their mothers were collected to investigate the presence of MSSA, MRSA, and ESBL. Swabs were taken from the nose and umbilicus immediately after birth. Additional swabs were taken from the nose, perianal area, and umbilicus 3 days after birth. Samples were screened and further characterized using culture and molecular methods.

**Results:** Prevalence of MSSA, MRSA, and ESBL colonization was 10.9, 0.5, and 2.6%, respectively. There was no association between the colonization status of the newborn and infections at any time point. Mother-to-newborn transmission rates (confirmed by PFGE) were 53.6% for MSSA/MRSA and 100% for ESBL. Maternal carriage of MSSA, MRSA, or ESBL was a risk factor for colonization of the newborn. Some isolates were resistant to the antibiotics recommended for therapy, including clindamycin and daptomycin for MSSA/MRSA isolates and ertapenem, fosfomycin, and tigecyclin for ESBL isolates.

**Conclusion:** No association between infections and the newborns' colonization status could be detected. Maternal colonization played an important role in newborn colonization, but not every case of colonization could be explained by mother-to-newborn transmission. General screening of pregnant women and healthy newborns in the absence of other risk factors is not necessary. To prevent the possibility of transmission in the healthcare setting, professionals, pregnant women, parents, hospital visitors, and obstetricians should receive regular training on appropriate hygiene measures. With regard to the emergence of resistance to recommended antibiotics, an antibiogram should be conducted before treating MSSA/MRSA/ESBL infections to ensure the efficacy of the antibiotics.

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## Introduction

*Staphylococcus aureus* (*S. aureus*) can cause pneumonia, skin, and soft tissue infections, as well as severe systemic infections, among other diseases. Treatment is becoming an increasingly difficult task due to the presence of methicillin-resistant *S. aureus* (MRSA) strains resistant to a variety of antibiotics [1]. Especially newborns with low birthweight [2], preterm birth [3], and prolonged hospital stay [4] are at higher risk to develop severe infections caused by MSSA and MRSA. Another issue is presented by extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL) because newborns colonized with ESBL have an increased risk of being diagnosed with Gram-negative sepsis [5].

Studies reporting *S. aureus* colonization in the German population found rates between 21.9% and 40.9% [6–8], whereas MRSA colonization rates were between 0.7% and 1.29% [6–8]. Colonization with

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Supplemental data for this article can be accessed here.

ESBL in the German community was reported to be 6.3% [9]. In newborns, colonization with *S. aureus* was found to be 5% [10]. A meta-analysis on the prevalence of MRSA colonization on admission to a NICU or PICU showed an overall prevalence of 1.9% [11]. Prevalence rates of MSSA, MRSA, or ESBL in newborns were difficult to determine, as there is not much literature on this topic in Germany.

Therefore, this study investigates the prevalence of MSSA, MRSA, and ESBL colonization among newborns in two Bavarian hospitals. Additionally, antibiotic resistance and *spa* types were examined. Furthermore, transmission rates of MSSA/MRSA and ESBL from mothers to their newborns were determined.

## Materials and methods

Materials and methods for this study have previously been described [12]. The following briefly outlines the procedures applied.

### Study design and population

This cross-sectional study took place in two Bavarian hospitals from April 2013 to December 2015. Pregnant women over 18 years of age with a planned vaginal delivery were included in the study. During hospitalization, data were collected by a trained interviewer using a standardized questionnaire and by extraction from medical records. All women who participated gave their written informed consent and had the choice to be notified if they or their children were colonized with MRSA or ESBL. Overall, 763 pregnant women participated in the study (clinic1 $n = 511$, clinic2 $n = 252$). Women with a planned vaginal delivery, but who ultimately had a C-section were still included. In the analysis, 658 newborns with at least one swab at any time point were included (clinic1 $n = 421$, clinic2 $n = 237$).

The ethics committee of Ludwig-Maximilians-University Munich approved the study.

### Sample collection

Dry smears (eSwabs™, Copan, Italy) were used for sample collection. Samples from five different locations at two different time points were collected; (1) from the nose and umbilicus shortly after birth; and (2) 3 days after birth from the nose, the umbilicus, and the perianal area.

### Culture media and identification of MRSA/MSSA and ESBL

All collected samples were cultured on Columbia agar with sheep blood (Oxoid, Germany), CHROMagar™ ESBL (Mast, Germany) and chromID® MRSA (bioMérieux, France). Sensitivity of MRSA testing was increased by inoculating Contrast™ MRSA Broth (Oxoid, Germany) with a 30 µl sample aliquot. Growth was interpreted after incubation at 36 ± 2 °C for approximately 24 h. In the event of a positive result for MSSA, MRSA, or ESBL, pure colonies were plated again on the corresponding culture medium and incubated under the same conditions as previously stated. Potential positive colonies of *S. aureus* were verified with an agglutination test.

### Antibiotic susceptibility and identification of isolates

The pure isolates of MSSA, MRSA, and ESBL were tested for antibiotic susceptibility using the BD Phoenix™ system (BectonDickinson, Heidelberg). The isolates were tested against different antibiotics (see Figure 1). Interpretation of the results followed the EUCAST guidelines [13]. To determine the genetic relationships of *S. aureus* isolates, *spa*-typing of strains was done by amplifying and sequencing the polymorphic x region of the *S. aureus* protein A (*spa* gene) [14]. *Spa*-types were deduced from the Ridom SpaServer [15]. Relationships of strains and mother-to-child transmission were confirmed by pulsed-field gel electrophoresis (PFGE) using the CHEF Bacterial Genomic DNA Plug Kit and a CHEF-DR III PFGE-system (Bio-Rad, Hercules, CA).

### Data analysis

Chi-square test and Fisher's exact test were used to compare categorical variables between colonized and non-colonized newborns. Wilcoxon–Mann–Whitney test was used for continuous variables. A *p*-value less than .05 was considered to be significant. All data analysis was done using SAS 9.4 (SAS Institute, NC).

## Results

### Study population

Overall, 658 newborns were included with at least one swab at any time point for analysis (clinic1 $n = 421$, clinic2 $n = 237$). Of these, 454 newborns had swab data for both time points (clinic1 $n = 274$, clinic2 $n = 180$), 127 newborns had swab data only for the first time point (clinic1 $n = 92$, clinic2 $n = 35$), and 77

newborns had swab data only for the second time point (clinic1 $n = 55$, clinic2 $n = 22$). Six out of the 658 included newborns could not be linked to a mother. Of those six, four were not colonized at all, one carried MSSA only, and one carried ESBL only.

Supplementary Table S1 characterizes the study population in detail. There was no association between infections at any point in time and newborns' colonization status. No association between colonization status and the number of siblings of the newborns or trips taken abroad by the mother during pregnancy could be detected (not shown in Supplementary Table S1).

### Prevalence of MSSA, MRSA, and ESBL colonization

Out of 658 newborns, 87 (13.2%) were colonized with MSSA, MRSA, and/or ESBL. Sixty-eight newborns (10.3%, clinic1 $n = 40$, clinic2 $n = 28$) were colonized with MSSA only and two newborns (0.3%, one in each clinic) with MRSA only. ESBL only was detected in 12 newborns (1.8%, clinic1 $n = 4$, clinic2 $n = 8$). Four newborns (0.6%, two in each clinic) were colonized with both MSSA and ESBL and one (0.2%, clinic1) with both MRSA and ESBL.

Overall prevalence of colonization, including cases with multiple colonization, was found to be 10.9, 0.5, and 2.6%, respectively, for MSSA, MRSA, and ESBL.

### Mother–newborn pairs and transmission rates

Table 1 shows the colonization status of the 652 mother–newborn pairs. Supplementary Figure S1 details the transmission from a mother to her newborn. Twenty-eight of the mother–newborn pairs were colonized with MSSA/MRSA; two of which were detected with MRSA. In 18 out of these 28 pairs (64.3%, one of which with MRSA), the mother and her newborn exhibited corresponding *spa* types. According to PFGE analyses, clonal identity was confirmed for 15 (83.3%) out of these 18 pairs. For one mother–newborn pair PFGE did not confirm the relationship between the mother-newborn isolates. In a second case, the relationship could not be confirmed with certainty; in a third case PFGE could not be performed. Overall, 53.6% of the mother–newborn pairs colonized with MSSA/MRSA were due to transmission from the mother to her newborn. The remaining newborns of the colonized pairs became colonized during their hospital stay. Of the 15 newborns with the confirmed transmission, two were born by emergency C-section and four were delivered with an episiotomy. ESBL was detected in eight mother–newborn pairs with a 100% transmission rate verified by PFGE.

Table 1. Colonization status of mother–newborn pairs.

| 652 mother–newborn pairs | Newborn colonized | Newborn noncolonized |
|---|---|---|
| MSSA | | |
| Mother colonized | 26 (4.0%) | 69 (10.6%) |
| Mother noncolonized | 45 (6.9%) | 512 (78.5%) |
| MRSA | | |
| Mother colonized | 2 (0.3%) | 1 (0.2%) |
| Mother noncolonized | 1 (0.2%) | 648 (99.4%) |
| ESBL | | |
| Mother colonized | 8 (1.2%) | 11 (1.7%) |
| Mother noncolonized | 8 (1.2%) | 625 (95.5%) |

To find out whether a colonized mother was a risk factor for the colonization of her newborn, relative risks were calculated. For MSSA, there were 14 (2.1%) newborns with confirmed transmission, 95 (14.6%) newborns (colonized and noncolonized) with a colonized mother, 45 (6.9%) colonized newborns from noncolonized mothers, and 557 (85.4%) newborns (colonized and noncolonized) from noncolonized mothers. A relative risk of 1.8 (95% confidence interval (CI) 1.05, 3.16) could be calculated. For MRSA, there was one newborn (0.2%) with confirmed transmission, three newborns (0.5%) (colonized and noncolonized) with colonized mothers, one colonized newborn (0.2%) from a noncolonized mother, and 649 newborns (99.5%) (colonized and non-colonized) from noncolonized mothers. These results in a relative risk of 216.3 (95% CI 69.59, 672.53). For ESBL, there were eight newborns (1.2%) with the confirmed transmission, 19 newborns (2.9%) (colonized and noncolonized) from colonized mothers, eight (1.2%) colonized newborns from noncolonized mothers and 633 newborns (97.1%) (colonized and noncolonized) from noncolonized mothers. This results in a relative risk of 33.3 (95% CI 15.38, 72.19).

### Spa types and antibiotic susceptibility

In total, 104 isolates were collected from 75 newborns carrying MSSA or MRSA; 39 isolates from 16 newborns carrying ESBL were collected. For MSSA/MRSA, 47 different *spa* types were detected, including one nontypeable strain. There was one newborn with two different *spa* types in one location (t230 and t358), and one newborn with two different *spa* types in two different locations (t091, t359).

The most frequent *spa* types found in MSSA positive newborns were t091 (16.7%), t084 (8.3%), t005 (5.6%), t012, and t021 (both 4.2%). MRSA positive

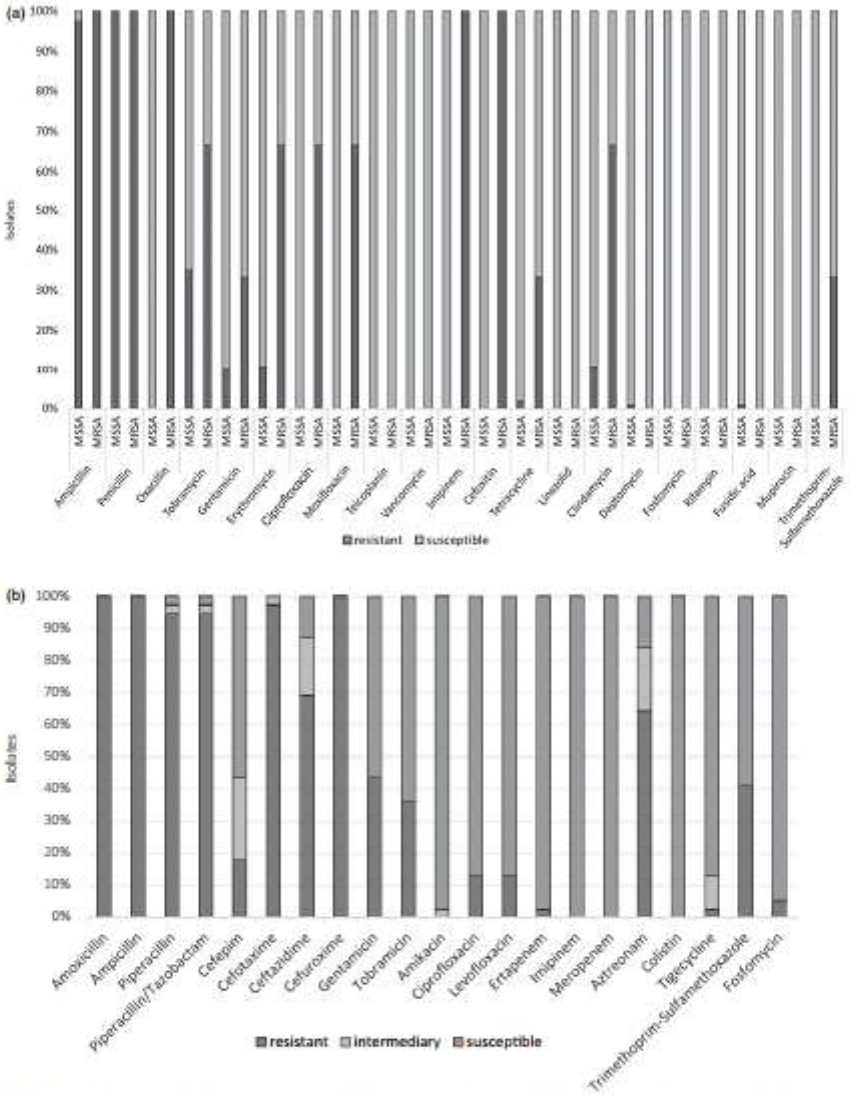


Figure 1. (a) Antibiotic resistance profile for methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) isolates. (b) Antibiotic resistance profile for extended-spectrum beta-lactamase-producing *Escherichia coli* (ESBL) isolates.

cases carried *spa* types t003, t011, and t685. Figure 1(a) shows the resistance profile of MSSA/MRSA isolates to the tested antibiotics.

With regard to the *spa* types transferred from mother to newborn, it could be detected that in three of the 14 MSSA cases t005 was transferred. The same applies to *spa* type t091. The remaining transferred *spa* types were t021, t050, t084, t148, t159, t179, t2614, and t11956. In the case of MRSA transmission, *spa* type t011 was transferred.

Figure 1(b) details the antibiotic resistance profile of ESBL isolates.

## Discussion

### Prevalence rates of MSSA, MRSA, and ESBL

The overall prevalence of MSSA colonization in this study was higher and the prevalence of MRSA colonization was lower compared to the literature. For MRSA, the literature refers to newborns admitted to a NICU or PICU and not to healthy newborns. The prevalence of ESBL colonization was found to be lower in the study population than in the German population. Unfortunately, there are no data regarding ESBL colonization in healthy newborns in Germany.

### Transmission rates

The transmission of MSSA/MRSA was found in 53.6% of mother-newborn pairs and lies in between the findings of other studies. Lesham et al. as well as Andrews et al. found genetically identical strains for *S. aureus* in 80% of mother–newborn pairs [10,16]; another study reported a transmission rate of 68% [17]. A transmission rate of 100% was detected for ESBL, which is considerably higher compared to other findings with transmission rates of ESBL-producing *Enterobacteriaceae* of 35.7% [18] and 34.3% [19]. The high transmission rate in our study could be due to the low number of events we found.

It has been shown that a newborn from a MSSA-, MRSA-, or ESBL-colonized mother has a significantly higher risk of being colonized than a newborn from a noncolonized mother. This was also suggested by other studies [16,20]. Nevertheless, not every case of colonization with MSSA/MRSA could be explained by mother-to-newborn transmission. Hospital staff, contact with colonized surfaces, and visitors are further possible sources of colonization.

However, the results must be viewed critically, as there were only 14 cases of transmission regarding MSSA, one case regarding MRSA, and eight cases regarding ESBL. Studies with larger sample sizes need to be conducted in order to confirm these findings.

### Spa types and antibiotic resistance

Depending on the type of infection with MSSA, treatment with different antibiotics is recommended: among others, clindamycin and daptomycin [21]. However, some of the MSSA isolates tested showed a beginning resistance to recommended antibiotics (clindamycin: 10.9%, daptomycin: 1.0%). For MRSA infection, therapy with glycopeptides is recommended as well as linezolid, daptomycin, tigecyclin, and ceftobiprole medocaril or ceftaroline fosamil. Depending on susceptibility, other antibiotics are also used, e.g. clindamycin. Nevertheless, the isolates tested have already shown resistance to clindamycin (66.7%). Resistance of *S. aureus* to clindamycin is known to exist, such as the Antibiotic Resistance Surveillance for Germany (ARS) of the Robert Koch Institute (RKI) [22] shows. It reports 15.8% resistance and 1.0% intermediary susceptibility of *S. aureus* isolates against clindamycin for outpatients, as well as 18.2% resistance and 0.4% intermediary susceptibility for inpatients. A decreasing development of resistance against clindamycin could be detected from 2009 to 2017. MRSA resistance to clindamycin in this study is rather high compared to the numbers reported by the ARS. In the ARS database, there are no data for specifically MRSA nor for daptomycin.

Depending on the type of infection with ESBL-producing *Enterobacteriaceae*, therapy with the following antibiotics is recommended: beta-lactamase inhibitors such as avibactam, clavulanic acid, and tazobactam in fixed combination with a penicillin or a cephalosporin with temocillin, a carbapenem, colistin, fosfomycin, and tigecyclin [21]. ESBL isolates showed a beginning resistance to the recommended antibiotics ertapenem (2.6%), fosfomycin (5.1%), and tigecyclin (2.6% resistant, 10.3% intermediary). On the ARS database, there are only data available for *E. coli* in general but no data specifically for ESBL-*E. coli*. The ARS reports 0.1% resistance to ertapenem for both outpatients and inpatients. In the case of fosfomycin, 0.9% resistance for outpatients and 1.2% for inpatients are reported. For tigecyclin, 0.1% resistance, and 0.2% intermediary susceptibility in outpatients are listed, as well as 0.2% resistance and 0.4% intermediary susceptibility in inpatients. This study examined higher numbers of resistance to ertapenem, fosfomycin, and tigecyclin than the ARS database. One reason could be that ARS only reports the values for *E. coli* and not specifically for ESBL-*E. coli*. In Germany, *E. coli* resistance to ertapenem in outpatients was first reported in 2015. Since then, the numbers are stable; for inpatients, the numbers remain constant since 2008. The numbers for fosfomycin resistance for outpatients and inpatients initially decreased and then stabilized. For tigecyclin, numbers remained constant for out- and inpatients.

The most common *spa* types for MSSA in the general German population in 2011/2012 were t084 (7.7%), t091 (6.1%), t012 (5.2%), and t015 (4.1%) [8]. This is similar to the results of our study: t091 (16.0%)

and t084 (8.0%) were found to be the most common *spa* types for MSSA in the study population. Relative global frequencies for these *spa* types are 1.7% for t084 and 0.9% for t091 [15]. Regarding MRSA, we found *spa* types t003, t011, and t685. Relative global frequencies were observed to be 8.8% for t003, 3.2% for t011, and 0.04% for t685 [15]. One of the studies investigating MRSA isolates in Germany found t003 and t011 to be some of the most frequent *spa* types [23]. *Spa* type t011 is indicative of the LA-MRSA clonal lineage ST398 [23] and was the only MRSA *spa* type suspected of being transferred from a MRSA-positive mother to her newborn. Indeed, the mother reported regular contacts with the farming community, livestock breeding/slaughterhouses, and animals during her pregnancy.

### *Limitations of the study*

The study was performed in two different clinics, which could lead to discrepancies in the methodology across the study centers. This is reflected by the significantly higher prevalence of ESBL in clinic2 compared to clinic1. It is assumed that the swabs taken in clinic2 were conducted in deeper perianal areas than in clinic1, leading to a higher number of positive results for ESBL colonization. Additionally, the prevalence of MSSA, MRSA, and ESBL colonization was quite low which can lead to an inaccurate evaluation of prevalence and transmission rates.

## Conclusion

A significant link between newborns' colonization status and the development of infections could not be established. Although it could be confirmed that a mother colonized with MSSA/MRSA/ESBL presents a risk for her newborn to be colonized as well, not every case of newborn colonization could be attributed to the mother. General screening of pregnant women or healthy newborns for the investigated bacteria in the absence of other risk factors does not seem to be necessary. To reduce the possibility of transmission in the healthcare setting and to prevent infections, pregnant women, parents, hospital visitors, and obstetricians should be regularly informed about appropriate hygiene measures. However, screening for these bacteria in population groups at higher risk of developing an infection, should be considered. This includes groups such as premature and critically ill newborns, whose immature immune system, length of hospital stay, and need for invasive devices increase the risk associated with MSSA/MRSA/ESBL colonization.

With regard to the onset of resistance to recommended antibiotics, an antibiogram should be conducted before treating MSSA/MRSA/ESBL infections to ensure the efficacy of the antibiotics.

The results of this study might be useful for antimicrobial stewardship activities (AMS).

## Disclosure statement

No potential conflict of interest was reported by the author(s).

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