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List of abbreviations

- AMR Antimicrobial resistance
- AMS Antimicrobial stewardship
- ARS Antibiotic resistance surveillance
- ASP Antibiotic stewardship programmes
- AWaRe WHO Access, Watch and Reserve categories
- CDC Centers for Disease Control and Prevention
- (cg)MLST (Core genome) Multilocus sequence typing
- CT Complex type
- ED Emergency Department
- MDR Multidrug-resistant
- MRSA Methicillin-resistant *Staphylococcus aureus*
- NICU Neonatal intensive care units
- PDR Pandrug-resistant
- PERFORM Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management
- PICU Paediatric intensive care units
- RKI Robert Koch Institute
- ST Sequence type
- vanA VanA genotype (resistant against vancomycin and teicoplanin)
- vanB VanB genotype (only resistant against vancomycin, not teicoplanin)
- VREfm Vancomycin-resistant *Enterococcus faecium*
- WHO World Health Organization
- XDR Extensively drug-resistant

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- Kolberg L, Forster F, Gerlich J, Weinmayr G, Genuneit J, Windstetter D et al. Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study. ERJ Open Res 2020; 6(1).

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  Laura Kolberg presented the data as a poster presentation at the “ESPID annual meeting 2023” in Lisbon (#597) (awarded with best poster award) and as an oral presentation at the “KIT 2023” in Leipzig (#A-135).

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This cumulative doctoral thesis consists of the following three publications:

1. **Kolberg, Laura***; Khanijau, Aakash*; van der Velden, Fabian J. S.; Herberg, Jethro; De, Tisham; Galassini, Rachel et al. (2024): Raising AWaRe-ness of antimicrobial stewardship challenges in pediatric emergency care: results from the PERFORM study assessing consistency and appropriateness of antibiotic prescribing across Europe. In: Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 78 (3). DOI: 10.1093/cid/ciad615. (1)
   *These authors contributed equally to this work

2. Trautmannsberger, Ilona; **Kolberg, Laura**; Meyer-Buehn, Melanie; Huebner, Johannes; Werner, Guido; Weber, Robert et al. (2022): Epidemiological and genetic characteristics of vancomycin-resistant *Enterococcus faecium* isolates in a University Children's Hospital in Germany: 2019 to 2020. In: Antimicrobial resistance and infection control 11 (1). DOI: 10.1186/s13756-022-01081-3. (2)

3. **Kolberg, Laura**; Buschbeck, Judith; Wagner, Annabelle; Jonat, Susanne; Wolf, Gerhard; Peters, Jochen et al. (2022): Evaluating current practice and knowledge about antibiotic stewardship principles in paediatric tertiary hospitals to identify target areas for future teaching activities. In: Infection 50 (5). DOI: 10.1007/s15010-022-01807-w. (3)

1. Contribution to the publications

1.1 Contribution to paper I

Raising AWaRe-ness of antimicrobial stewardship challenges in pediatric emergency care: results from the PERFORM study assessing consistency and appropriateness of antibiotic prescribing across Europe (1)

Kolberg, Laura*; Khanijau, Aakash*; van der Velden, Fabian J. S.; Herberg, Jethro; De, Tisham; Galassini, Rachel et al. (2024)

*L. K. and A. K. contributed equally to this work

Three institutions (all part of the PERFORM (Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management) consortium) in the UK (University of Liverpool and Newcastle University) and Germany (University Hospital LMU Munich) collaborated closely in analysing the data and writing the manuscript. Laura Kolberg shared the position of first author with A. Khanijau (Liverpool). Both were responsible for data quality control, analysis and interpretation of the data and drafting and writing the manuscript. They were supervised and supported by the three joint last authors, Enitan Carrol (Liverpool), Marieke Emonts (Newcastle) and Ulrich von Both (Munich).

Laura Kolberg contributed to the following (with support of A. Khanijau):

- Data collection at the local study site and data entry
- Global data review and data quality check
- Performing analysis
- Interpretation of the results
- Creation, design and editing of tables, figures and supplementary material
- Drafting and revising the manuscript
- Revision of the manuscript based on co-authors' comments
- Preparation and submission of the manuscript to the Journal: Clinical Infectious Diseases
- Revisions of the manuscript based on peer-reviewer comments and answering peer-reviewer comments
- Editing revised manuscript based on journal Copy Editor feedback

Laura Kolberg presented the preliminary data as a poster at the "Kongress für Kinder- und Jugendmedizin 2021" in Berlin (Poster #43899). The final data were presented as an oral presentation at the "ESPID annual meeting 2023" in Lisbon (#599) and at the "KIT 2023" in Leipzig (#135) (awarded with a presentation award).

1.2 Contribution to paper II

Epidemiological and genetic characteristics of vancomycin-resistant *Enterococcus faecium* isolates in a University Children's Hospital in Germany: 2019 to 2020 (2)

Trautmannsberger, Ilona; **Kolberg, Laura**; Meyer-Buehn, Melanie; Huebner, Johannes; Werner, Guido; Weber, Robert et al. (2022)

Laura Kolberg is not the first author of this paper. The paper is the result of the master's thesis of Ilona Trautmannsberger, the first author of this paper. Laura Kolberg was the first author's supervisor during the master's thesis and provided repeated help and feedback. Laura Kolberg and the first author were supported by the last author, the master thesis advisor.

Laura Kolberg contributed to the following:

- Preparation of the study protocol
- Application to the local ethics committee
- Conception and design of the study (study objective, analysis plan)
- Supervision of data collection
- Interpretation of the results
- Input into descriptive data presentation
- Supporting creation, design and editing of figures and tables and supplementary material
- Revision of the manuscript (drafting the manuscript was mainly done by the first author as part of the master thesis)
- Revision of the manuscript based on co-authors' comments
- Preparation and submission of the manuscript to the Journal: Antimicrobial Resistance & Infection Control
- Revisions of the manuscript based on peer-reviewer comments and answering peer-reviewer comments
- Editing revised manuscript based on journal Copy Editor feedback

Laura Kolberg presented the data as a poster presentation at the "ESPID annual meeting 2022" in Athens (Poster #884) and the "DZIF and DGI joint annual meeting 2022" in Stuttgart (Poster #213).

1.3 Contribution to paper III

Evaluating current practice and knowledge about antibiotic stewardship principles in paediatric tertiary hospitals to identify target areas for future teaching activities (3)

Kolberg, Laura; Buschbeck, Judith; Wagner, Annabelle; Jonat, Susanne; Wolf, Gerhard; Peters, Jochen et al. (2022)

Laura Kolberg was the first author of this paper. She was not involved in the study's conceptualisation, design or data acquisition. She was responsible for data quality control and performed most of the final analysis (J. Buschbeck performed preliminary analyses). During interpretation of the results and drafting of the manuscript, she was supported by the last author.

Laura Kolberg contributed to the following:

- Performing final analysis
- Interpretation of the results
- Input into data presentation
- Creation, design and editing of tables and supplementary material
- Drafting and revising the manuscript
- Revision of the manuscript based on co-authors' comments
- Preparation and submission of the manuscript to the Journal: Infection
- Serving as corresponding author and answering reviewer comments
- Revisions of the manuscript based on peer-reviewer comments
- Editing revised manuscript based on journal Copy Editor feedback

2. Introduction

2.1 Antibiotic misuse

2.1.1 Antibiotic use in paediatrics

Whether to prescribe antibiotics is the question paediatricians face whenever there is an ill child with a fever or other symptoms of a possible bacterial infection. It is also one of the most important questions healthcare professionals must answer. Antibiotics are used to treat or prevent bacterial infections. Nowadays, a variety of antibiotics with different types of mechanisms exist and are used in daily medical practice. Choosing the correct antibiotic for treatment is essential and depends on various factors, including the site where the antibiotic needs to act, whether it should be bactericidal (kill bacteria) or bacteriostatic (inhibit bacterial growth), the method of administration (intravenous, oral or inhalation), whether it is empirical or targeted treatment, the potential side effects of antibiotic use, and whether any antimicrobial resistance (AMR) needs to be considered.

As part of the 2017 Model List of Essential Medicines, the World Health Organization (WHO) developed the AWaRe classification to evaluate and monitor the appropriateness of antibiotic use to optimise antibiotic prescribing worldwide. (4, 5) The AWaRe classification divides antibiotics into three antibiotic stewardship categories: Access, Watch and Reserve. Access antibiotics are narrow-spectrum first- or second-line antibiotics with low resistance potential used for common infections. When these Access antibiotics are no longer effective, broader-spectrum Watch antibiotics are prescribed as first-choice antibiotics. Reserve antibiotics are used as last-choice antibiotics for the treatment of multidrug-resistant infections. The WHO's target is a global Access antibiotic use of at least 60% to contain the worldwide increase of (multi-)resistances. (5)

Due to the high incidence of infections in children, especially in younger children, antibiotics are currently used excessively in paediatric hospitals around the world. Depending on the availability, up to 33% of children receive antibiotics in the emergency department (ED) (6, 7), and 60% get at least one antibiotic prescribed per stay. (8) Considering that many children with fever have self-limiting or viral infections, this high use of antibiotics is alarming. Additionally, medication errors (wrong dose, route or duration of antibiotics) happen regularly in paediatrics. (9, 10) Due to the ever-increasing threat of AMR, it is of utmost importance to use the currently available antibiotics in a rational and sustainable way and, if possible, to find new antibiotics, preferably with novel mechanisms of action. Unfortunately, the discovery of antibiotics with entirely new mechanisms has decreased in recent years. This makes antimicrobial stewardship programmes (ASPs) promoting the rational use of antibiotics even more crucial in limiting the threat of AMR to public health.

Therefore, this doctoral thesis aimed to analyse antibiotic use and misuse, its consequences, and strategies for improvement, focusing on paediatric hospitals. First, appropriateness and consistency of antibiotic prescription in nine European paediatric hospitals were investigated. Second, a local outbreak of a resistant bacterial pathogen was

analysed to assess consequences of antibiotic misuse. Finally, as one of the most important measures to address antimicrobial resistance, the effect of antibiotic stewardship programmes on paediatricians' knowledge was evaluated, and future target areas for teaching activities were identified.

2.1.2 Antibiotic misuse in paediatric hospitals: the PERFORM study

In paper one, appropriateness and consistency of antibiotic use in European paediatric hospitals were evaluated. Data from participants in the Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management (PERFORM) study were analysed. PERFORM is a multicentre, prospective cohort study conducted between August 2016 and December 2019. Children and adolescents (< 18 years of age) attending European EDs with fever or suspected infection and requiring blood tests were recruited. They were phenotyped using the PERFORM phenotyping algorithm based on clinical and laboratory data. (11) Clinical diagnoses, syndrome classifications, and presumed aetiology were recorded. For our analysis, 2130 febrile episodes were categorised into bacterial and viral groups based on the assigned phenotype. The bacterial group accounted for 72.7% of cases and included the phenotypes "definite bacterial", "probable bacterial", and "bacterial syndrome", where bacteria were detected accounting for all features or a clear bacterial diagnosis was made. The viral group, which accounted for 27.3% of the cases, included "definite viral" and "viral syndrome" phenotypes, with a detected virus accounting for all features. Prescribed antibiotics were categorised into antibiotic classes and WHO AWaRe categories. (1)

A total of 1587 of 2130 patients (74.5%) with febrile episodes received empiric antibiotics within two days after hospital admission. Most of them, almost 90%, were administered parenteral (intravenous or intramuscular). Patients with febrile episodes in the viral group who do not require antibiotics often received antibiotics (46.3%), with 80.3% classified as WHO Watch antibiotics. Among patients with presumed viral or non-infectious aetiology, 37.8% (95/251 episodes) were prescribed antibiotics. Conversely, 11.0% (98/887 episodes) with presumed bacterial aetiology did not receive antibiotics. Of the 992 episodes from patients with an inconclusive aetiology, unspecified infection, or undifferentiated fever, antibiotics were prescribed in 71.3% (707 episodes). Resulting in half of those categorised into the viral group receiving antibiotics. (1)

The results show an overuse of antibiotics in European paediatric EDs. Access and Watch antibiotics were frequently prescribed in both groups (bacterial and viral). Astonishingly, Watch antibiotics were administered more often in the viral group (80.3%) than in the bacterial group (61.0%), highlighting the inappropriate use of antibiotics in paediatric EDs. Only 49.1% of the antibiotics prescribed were Access antibiotics; thus failing to meet the WHO target of 60% Access antibiotic use. It is difficult for paediatricians to withhold antibiotics in ill children on first presentation to the ED, especially if no causative pathogen or only a viral pathogen is detected. (1) Since bacterial and viral pathogens are often jointly detected, it can be difficult to differentiate between bacterial and viral infections. (12) Clinical uncertainty, suspicion of infection, and the fear of missing a

bacterial cause may lead paediatricians to prescribe antibiotics more often. Considering that in most cases (87.2%), paediatricians caring for the child and responsible for prescribing the antibiotics were correct in their initial diagnosis (viral or bacterial syndrome classification), it is worrying that antibiotics are used so inconsistently and excessively. In 37.8% of febrile episodes from patients with viral or non-infectious aetiology, antibiotics were prescribed. Age also seems to play an important role in the prescription of antibiotics, as antibiotic use was higher in younger children. In patients under five years of age with febrile episodes and viral or non-infectious aetiology, 45.5% were prescribed antibiotics. Overprescription was also found in those with an inconclusive presumed aetiology (bacterial and viral, unspecified or undifferentiated fever). Antibiotics were prescribed in half of the episodes from patients with a viral phenotype. (1) Due to this misuse of antibiotics in paediatric hospitals, AMR rates will continue to increase. Without easier-to-use, faster and more accurate point-of-care tests to help clinicians make the right decisions, this inappropriate and inconsistent antibiotic use in paediatric hospitals is likely to continue, further exacerbating the global problem AMR pose for children and adolescents worldwide.

2.2 Consequences of antibiotic misuse

2.2.1 Antimicrobial resistant pathogens

Antimicrobial resistance is not a new development and has existed since the beginning of antibiotic treatment, dating back to the discovery of penicillin by Alexander Flemming in 1929. (13) Shortly after its discovery, the first warning was issued. In his Nobel Prize acceptance speech in 1945, Flemming predicted: "The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." (14) AMR occurs when bacteria adapt to antibiotic use by developing resistance mechanisms. These resistance mechanisms are embedded in the bacteria's DNA, giving them an advantage over other bacteria and enabling them to spread more effectively. As a result, antibiotics become ineffective in treating infections caused by these bacteria. This makes infections more challenging or, in the worst case, impossible to treat. Ultimately, the risk of severe illness, spreading of diseases and mortality increases. (15, 16) Together with HIV, Dengue, Ebola and non-communicable diseases, antimicrobial (antibiotic) resistance was among the top 10 global health threats in 2019 (17), and it was listed again in 2021. (18) In September 2024, a high-level meeting discussing AMR will take place at the United Nations General Assembly. (19) According to the first global burden of AMR analysis in 2019, 1.27 million deaths were directly attributable to AMR. For most of these deaths (>900,000 deaths), six pathogens could be identified: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Especially in high-income regions, *Staphylococcus aureus* and *Escherichia coli* were attributable to most deaths. (20) AMR not only contributes substantially to global mortality rates but also increases healthcare costs. The World Bank estimates AMR could cost an additional 1 trillion US$ in health care

costs by 2050. (21) As we now have a large number of different antibiotics at our disposal and use them more frequently, AMR has also become more common.

In most cases, it is not a problem if a pathogen is resistant to one antibiotic because there are enough alternatives from different antibiotic classes and with different working mechanisms that can be used instead. However, multidrug-resistant (MDR) bacteria with limited treatment options have long since developed. MDR bacteria are resistant (non-susceptible) to at least one antibiotic in three or more antibiotic categories. Even more difficult to treat than MDR are extensively drug-resistant (XDR) bacteria, which are non-susceptible to at least one antibiotic in all but two or fewer antibiotic categories. They can often only be treated with WHO Reserve antibiotics, which might cause severe side effects. In the case of pandrug-resistant (PDR) bacteria, which are non-susceptible to all antibiotics in all antibiotic categories, no effective treatment options are available. (22) Unfortunately, there is now a large number of AMR and MDR bacteria that complicate the treatment of infected patients. The WHO pathogen prioritization list from 2017 (23) and the Centers for Disease Control and Prevention (CDC) antibiotic resistance threats report from 2019 (24) named the most dangerous resistant pathogens, including among others carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacteriaceae (including *Klebsiella pneumonia*, *Escherichia coli* and *Enterobacter spp.*), *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant Salmonellae and *Streptococcus pneumoniae* as well as vancomycin-resistant *Enterococcus faecium* (VREfm). An outbreak of these drug-resistant bacteria poses difficulties for inpatient and outpatient settings and is particularly dangerous for the most vulnerable, such as hospitalised children.

In order to prevent spreading or to at least respond faster and more effectively in the event of an outbreak, it is essential to understand spread dynamics and transmission routes of antibiotic resistant and clinically relevant bacteria in hospitals and to identify the population at highest risk. For this reason, a recent VREfm outbreak at the Dr. von Hauner Children's Hospital was analysed in more detail, resulting in the second publication as part of this doctoral thesis. (2)

2.2.2 VREfm outbreak at the Dr. von Hauner Children's Hospital

Enterococcus faecium belongs to the microflora and is one of the most common commensal pathogens in humans, which can persist for a long time in hospitals. (25) Normally, they do not play a major role in paediatric hospitals (26, 27), but according to the antibiotic resistance surveillance (ARS) of the Robert Koch Institute (RKI), the proportion of VREfm increased in recent years in Germany (11.2% in 2014 to 26.1% in 2017). (28) April 2019 was the beginning of an unusual accumulation of VREfm at the Dr. von Hauner Children's Hospital in Germany. The descriptive retrospective analyses focused on identifying and describing the colonised and infected population (including risk factors) and evaluating possible transmission routes. As part of the LMU clinic, the Dr. von Hauner Children's Hospital and the neonatal ward of the Polyclinic for Gynaecology and Obstetrics were investigated. Children who tested positive for VREfm in microbiological

testing of rectal swabs were included in the analysis. Clinical and epidemiological data were collected from medical records and compared with genome analysis carried out at the German National Reference Centre for Staphylococci and Enterococci at the RKI. Species and genotypes (vanA and vanB) were identified, and (core genome) multilocus sequence typing ((cg)MLST) was performed to determine clonal relatedness. Isolates with less than 15 varying alleles and the same van type were considered closely related. A minimum spanning tree was constructed based on these data. (2, 29–31)

Of 693 children screened for VREfm between April 2019 and August 2020, 4.8% (33 children) tested positive. Most of them were premature infants from neonatal/paediatric intensive care units (NICU/PICU), and the median age was six months. Of the 33 VREfm-positive children, seven were infected, while 26 children were only colonised with VREfm. Of note, all seven infected children were treated with WHO Reserve antibiotics (linezolid and daptomycin) and were significantly more likely to have an underlying haemato-oncological disease (p=0.011) compared to VREfm-colonised children. In accordance with current literature, neonates and immunocompromised children with chemotherapy or an underlying haemato-oncological disease were identified as high-risk populations. (26) The cgMLST identified seven distinct clusters consisting of two to nine isolates with less than 15 varying alleles and eight singletons (isolates with no relatedness). A mother of two preterm neonates (twins) also tested positive and was included in the genome analysis. (2)

The results of the genome analysis together with the demographic data collected, showed that children from five of the seven clusters were admitted to the same wards at the same time or within seven weeks of each other. Cluster 1 was detected at the Polyclinic for Gynaecology and Obstetrics and consisted of five neonates, including twins and the twins' mother, who was the first to test positive for VREfm. Cluster 3 and Cluster 5 both occurred in PICU. The two patients in Cluster 6 were both NICU patients, and the patients in Cluster 7 were previously admitted to another site of the LMU hospital. (2) Children from the same ward and testing positive one after another may indicate nosocomial transmission, which is often seen with VREfm. (32) For a patient staying in a room previously occupied by a VRE colonised patient (up to two weeks prior), the risk of contracting VRE is significantly higher than staying in a room of a non-VRE colonised patient. (33) Therefore, decontamination measures must be carried out correctly. During this VREfm outbreak, for example, a neonatal ward at the Polyclinic for Gynaecology and Obstetrics had to be temporarily closed for decontamination. One cluster (Cluster 4) consisted of patients with an underlying haemato-oncological disease suspecting VREfm transmission via hospital staff. The biggest cluster (Cluster 2), composed of isolates of nine children, did not show convincing clinical-epidemiologic similarities. (2) However, since most of the isolates from this cluster belong to the ST80 (sequence type)/CT1065 (complex type) vanB genotype, predominantly found in Bavaria, an inter-hospital spread and cross-contamination with other external hospitals can be assumed. (34) These results indicate a VREfm transmission within and between hospitals. Considering that the most effective prevention methods against VREfm transmission are simple and hopefully well-known hygiene measures like basic hand hygiene in combination with regular screening of patients, these findings are worrying. (2)

Protecting the vulnerable population of children, especially those admitted to intensive care units, against antibiotic resistant pathogens should be one of our future top priorities. Strategies to improve outbreak management or, even better, to prevent outbreaks and transmission events not only of VREfm but any resistant pathogen are critically needed. Effective preventive strategies include hygiene measures, infection control programmes, and regular educational activities. Strategies are required in order to reduce antibiotic misuse and to stop the increase of AMR and the associated threat not only in paediatrics but globally.

2.3 Strategies for improvement of antibiotic use

2.3.1 Antibiotic Stewardship Programmes

Antibiotic stewardship programmes are implemented to optimise antimicrobial use, reduce AMR rates, and improve patient health. They are one of the most cost-effective interventions available today. (15) It is of utmost importance to implement new ASPs and to improve already existing ones. A lot of different ASPs with various combinations of antimicrobial stewardship (AMS) interventions exist. The WHO Antimicrobial Stewardship Guide (35) lists the most common AMS strategies, which can be divided into interventions prior to or during antibiotic prescription (initial evaluation) and interventions after antimicrobial prescription (retrospective evaluation). Interventions prior to or during prescribing include educational measures for clinicians, patients and the public. Ongoing education (individual and global) is essential for raising awareness of AMR and its consequences. Clinicians need to maintain their knowledge of correct antimicrobial use. Based on this knowledge, healthcare institutions can develop specific guidelines and recommendations. Additionally, AMS teams can help to advise colleagues. Targeted education and audits adapted to local hospital conditions can facilitate infection management. Local antibiograms and statistical data on resistances can provide information on the best-suited antibiotics for clinical use. They can also give an overview of antibiotic resistance development. To further optimise antimicrobial use and benefit prescribing clinicians, AMS teams can establish a restrictive antimicrobial prescribing system to ensure targeted antimicrobial prescribing and more frequent use of first-line antibiotics. With that, patient health will improve, and healthcare costs will decrease. Prospective audit and feedback are two important interventions carried out after antimicrobial prescribing. Reassessment of prescribed antibiotics provides an opportunity for AMS teams to personalise the education of attending clinicians. One way clinicians can optimise patient care whilst not restricting the prescribing clinicians' autonomy is to adjust prescriptions by establishing antibiotic timeouts (e.g., for WHO Watch and Reserve antibiotics) or by optimising antibiotic dose and duration. Discontinuing unnecessary and incorrectly administered antibiotics can reduce adverse effects and improve patient outcomes. (35) Different interventions are required depending on the specific circumstances and the setting in which the ASP should be executed. Furthermore, it is advisable to use a combination of different approaches (bundle approaches) to increase the success rates of the implemented ASP. The extent to which an ASP at the Dr. von

Hauner Children's Hospital impacted paediatricians' current practice and knowledge of antibiotic stewardship principles was investigated in the third paper. At the same time, target areas for further teaching activities were identified. (3)

2.3.2 Evaluation of ASPs in paediatric hospitals in and around Munich

In general, the concept of antibiotic stewardship is promising. Since ASPs are easier to establish in inpatient rather than outpatient settings, most stewardship programmes are designed for hospitals and adult medicine. Implementing them in paediatric settings is more challenging, but if done correctly, they positively impact antibiotic use, healthcare costs and AMR rates. While bundle approaches show promising outcomes, measuring the exact impact of ASPs is difficult due to the heterogeneity of interventions, measurements and outcomes. (36) There is no one-fits-all approach in terms of AMS interventions, and the various programmes do not always have the desired effect. It is unknown which and how long ASPs need to be done to change and optimise antimicrobial prescribing, and it is unclear how often educational ASPs, audits and feedback for healthcare professionals are required. Even though these programmes exist, clinicians need to participate and act accordingly.

At the Dr. von Hauner Children's Hospital, an ASP was initiated in 2015, mainly focusing on de-escalating broad-spectrum antibiotics. An AMS team carried out infectious disease ward rounds, established a consultation service for paediatric colleagues and developed internal guidelines for antibiotic prescription. (37) Evaluating the impact of this ASP on paediatricians' knowledge about antibiotic stewardship and infection control principles was evaluated as part of this doctoral thesis. The understanding of antibiotic stewardship principles among paediatricians of different training grades working at the Dr. von Hauner Children's Hospital was compared to that of paediatricians from other hospitals in the greater Munich area without ASPs. Additionally, areas for future educational activities were identified. (3)

In 2016, an anonymised questionnaire-based cross-sectional survey was conducted in five paediatric hospitals in and near Munich. Paediatricians had two months to answer a modified version of a questionnaire previously published by Bowes et al. (38) either online or on paper. The survey covered six sections, the first and the last of which focused on assessing participant characteristics and their work environment. The four remaining sections concentrated on 1. antibiotic handling and bacterial resistance, 2. microbial aspects of infectious disease, 3. hospital hygiene/infection control, and 4. antibiotic stewardship and therapy standards. Data from 111 participating paediatricians, including 47 junior doctors, 34 middle-grade doctors, and 30 consultants were analysed. Almost 60% of these paediatricians worked at the Dr. von Hauner Children's Hospital. Results revealed a relatively low level of understanding of antibiotic stewardship principles in general. Further, no difference in knowledge of antibiotic stewardship measures was found between different training grades of paediatricians or between the Dr. von Hauner Children's Hospital and other participating hospitals. Overall, the knowledge about antibiotic handling and bacterial resistance was 54.1%. The proportion of correct answers

in the microbial aspects of the infectious disease section was 56.8%. The knowledge about hospital hygiene/infection control was relatively high. Nevertheless, only 72.9% of the participants answered the questions from this section correctly. Lastly, the proportion of correct answers in the section of antibiotic stewardship and therapy standards was 55.9%. The results of the questionnaire study indicate that there are a lot of deficits for junior doctors, middle-grade doctors, and consultants regarding the understanding of antibiotic stewardship and infection control principles. (3) A recent review discovered similar results of insufficient AMS knowledge, although educational programmes were in place. Clinicians' and consumers' (children and parents) knowledge and adherence to infection prevention and control were analysed, highlighting a gap in current AMS practice. (39) Considering that an ASP existed at the Dr. von Hauner Children's Hospital for one year prior to conducting this survey study, our findings are disappointing. The ASP did not significantly impact paediatricians' knowledge regarding antibiotic stewardship and infection control when comparing the results of participants from the Dr. von Hauner Children's Hospital with those from other participating hospitals. The section regarding hospital hygiene/infection control achieved the highest proportion of correct answers, probably because almost every paediatrician could identify hand hygiene as the most important infection control measure. Future teaching activities should focus on all four investigated sections, predominantly on antibiotic handling and bacterial resistance, microbial aspects of infectious disease and antibiotic stewardship and therapy standards. (3)

2.4 The future of antibiotic prescribing

The results presented in this doctoral thesis refer to data from Europe, Germany and a local hospital in Munich and, therefore, may not be generalisable on a global scale. Nevertheless, the data highlight the current misuse and overuse of antibiotics and the associated impact on AMR, which can be observed all over the world and poses similar challenges everywhere. Optimising antibiotic prescribing should be one of the main goals worldwide to stop the increase of AMR. In 2022, the One Health Quadripartite (WHO, the Food and Agriculture Organization of the United Nations, the United Nations Environment Programme and the World Organisation for Animal Health) developed the One Health Joint Plan of Action to better prevent, predict, detect and respond to global health threats, including AMR. (40) Humans, animals and the environment are closely linked and cannot be considered independently of one another. With the One Health approach, these sectors work together to improve public health. It is crucial to apply the One Health approach to combat the threat of emerging AMR rates. Reducing the transmission of antibiotic-resistant pathogens between humans, animals, plants, and the environment is essential. ASPs and, with them, awareness and education about AMR, as well as the appropriate antibiotic use, must be increased. (40, 41)

3. Summary

This thesis consists of three original publications and analyses antibiotic use, its consequences and strategies for improvement in paediatric hospitals.

First, data from participants in the PERFORM (Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management) study were analysed. Antibiotic prescribing in European febrile children and adolescents with bacterial and viral infections was investigated, revealing inappropriate and inconsistent antibiotic use. More than 80% of children with febrile episodes received parenteral antibiotics, even though many had a viral infection. Additionally, most antibiotics belonged to the WHO Watch category. Clinical uncertainty or fear of missing bacterial coinfection leads clinicians to prescribe antibiotics more often. Patients with viral or non-infectious aetiology were inconsistently prescribed antibiotics (37.8% of febrile episodes). Therefore, improvements in point-of-care tests to help differentiate between bacterial and viral infections are needed in future medical care to optimise antibiotic prescribing and prevent further increase of antimicrobial resistance.

Second, the increased detection of vancomycin-resistant *Enterococcus faecium* (VREfm) at the Dr. von Hauner Children's Hospital from April 2019 to August 2020 was analysed as an example of consequences of antibiotic misuse. Epidemiological and clinical data from 33 VREfm-positive children were collected retrospectively, and core genome multilocus sequence typing (cgMLST) was performed on the isolates. The genomic analyses detected related isolates and identified seven distinct clusters. Combining these findings with demographic data showed that the unusual accumulation of VREfm-positive children was partly due to nosocomial transmission between wards, hospitals and healthcare workers, as most patients in each cluster were admitted to the same ward at some point during their hospital stay, or were treated by the same clinicians for the same underlying diseases. Antibiotic-resistant bacteria can spread quickly in hospitals, highlighting the importance of protecting those most at risk, such as children in intensive care and neonates. Highlighting the need of prevention measures to combat the spread of antimicrobial-resistant pathogens.

Despite all the antibiotic stewardship programmes (ASPs) and infection control measures currently available and in place, much remains to be improved, as shown in the third publication. Knowledge gaps regarding antibiotic stewardship principles were identified among hospital based paediatricians in Munich, Germany, indicating important areas for future educational activities. A total of 111 paediatric junior doctors, middle grade doctors and consultants from five paediatric hospitals in Munich participated in a questionnaire-based study in 2016. The questionnaire focused on four sections related to antibiotic stewardship and infection control (antibiotic handling and bacterial resistance, microbial aspects of infectious disease, hospital hygiene/infection control, and antibiotic stewardship and therapy standards). The analysis showed that paediatricians' understanding of the four areas was relatively low. It ranged from 54.1% to 72.9% correct answers, identifying areas on which future ASPs should focus to further improve paediatricians' knowledge of antibiotic stewardship.

4. Zusammenfassung

Diese Doktorarbeit besteht aus drei Publikationen, die den Antibiotikaeinsatz, seine Folgen und Verbesserungsstrategien in pädiatrischen Krankenhäusern analysieren.

In der ersten Publikation wurden Daten der PERFORM-Studie (Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management) analysiert. Untersucht wurde der Antibiotikaverbrauch bei fiebernden Kindern in europäischen Kinderkliniken. Sowohl bei Kindern mit bakteriellen als auch mit viralen Infektionen wurden Antibiotika häufig und teilweise inkonsistent verordnet. Mehr als 80% der Kinder mit Fieberepisoden erhielten parenterale Antibiotika, obwohl viele von ihnen an einer Virusinfektion litten. Hinzu kommt, dass die meisten der verordneten Antibiotika der WHO-Watch-Kategorie zuzuordnen sind. Klinische Unsicherheit und die Angst, eine bakterielle Co-Infektion zu übersehen, führen insbesondere bei kleinen Kindern mit viraler oder nicht-infektiöser Ätiologie häufig dazu, dass Ärzte Antibiotika verschreiben (37,8% der Fieberepisoden). Daher sind künftig bessere und schnellere Point-of-Care-Tests in der Pädiatrie erforderlich, um den Antibiotikaverbrauch zu optimieren und die Zunahme von Antibiotikaresistenzen einzudämmen.

Die zweite Publikation analysierte einen Ausbruch von Vancomycin-resistentem *Enterococcus faecium* (VREfm) im Dr. von Haunerschen Kinderspital zwischen April 2019 und August 2020 und identifizierte mögliche Übertragungswege. Daten von 33 VREfm-positiven Kindern wurden retrospektiv analysiert und die Isolate einer Genomsequenzierung unterzogen. Insgesamt konnten sieben verschiedene Cluster und acht einzelne (nicht verwandte) Isolate identifiziert werden. Zusammenfassend wurde festgestellt, dass die VREfm-Akkumulation wahrscheinlich auf eine nosokomiale Übertragung zwischen Stationen, medizinischem Personal und Krankenhäusern zurückzuführen ist. Die meisten Patienten, die einem Cluster zugeordnet werden konnten, waren zu einem Zeitpunkt ihres Krankenhausaufenthaltes auf der gleichen Station oder wurden von denselben Ärzten behandelt. Neugeborene und Kinder auf Intensivstationen waren am stärksten von dem Ausbruch betroffen, was verdeutlicht, wie wichtig es ist, diese besonders vulnerablen Patienten besser zu schützen.

In der dritten Publikation wurde abschließend das Wissen von Kinderärzten aus Münchner Kinderkliniken über Antibiotic Stewardship untersucht und Bereiche identifiziert, auf die sich zukünftige Fort- und Weiterbildungen konzentrieren sollten. Im Jahr 2016 nahmen insgesamt 111 Pädiater aus fünf Kinderkliniken an einer Fragebogenstudie teil. Der Fragebogen konzentrierte sich auf vier Abschnitte zum Thema Antibiotic Stewardship: Umgang mit Antibiotika und Antibiotikaresistenzen, mikrobielle Aspekte von Infektionskrankheiten, Krankenhaushygiene sowie Antibiotic Stewardship und Therapiestandards. Die Analyse ergab, dass das Wissen der Ärzte in allen vier Bereichen relativ gering war. Der Anteil der richtig beantworteten Fragen lag zwischen 54,1% und 72,9% und ist somit deutlich verbesserungswürdig. Zukünftige Fort- und Weiterbildungen zum Thema Antibiotic Stewardship sollten sich auf alle vier untersuchten Bereiche konzentrieren und zum Ziel haben, das Wissen und Verständnis von Pädiatern weiter zu verbessern.

5. Paper I

Title of article: Raising AWaRe-ness of antimicrobial stewardship challenges in pediatric emergency care: results from the PERFORM study assessing consistency and appropriateness of antibiotic prescribing across Europe

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Clinical Infectious Diseases

MAJOR ARTICLE

Raising AWaRe-ness of Antimicrobial Stewardship Challenges in Pediatric Emergency Care: Results from the PERFORM Study Assessing Consistency and Appropriateness of Antibiotic Prescribing Across Europe

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Background. Optimization of antimicrobial stewardship is key to tackling antimicrobial resistance, which is exacerbated by overprescription of antibiotics in pediatric emergency departments (EDs). We described patterns of empiric antibiotic use in European EDs and characterized appropriateness and consistency of prescribing.

Methods. Between August 2016 and December 2019, febrile children attending EDs in 9 European countries with suspected infection were recruited into the PERFORM (Personalised Risk Assessment in Febrile Illness to Optimise Real-Life Management) study. Empiric systemic antibiotic use was determined in view of assigned final "bacterial" or "viral" phenotype. Antibiotics were classified according to the World Health Organization (WHO) AWaRe classification.

Results. Of 2130 febrile episodes (excluding children with nonbacterial/nonviral phenotypes), 1549 (72.7%) were assigned a bacterial and 581 (27.3%) a viral phenotype. A total of 1318 of 1549 episodes (85.1%) with a bacterial and 269 of 581 (46.3%) with a viral phenotype received empiric systemic antibiotics (in the first 2 days of admission). Of those, the majority (87.8% in the bacterial and 87.0% in the viral group) received parenteral antibiotics. The top 3 antibiotics prescribed were third-generation cephalosporins, penicillins, and penicillin/β-lactamase inhibitor combinations. Of those treated with empiric systemic antibiotics in the viral group, 216 of 269 (80.3%) received ≥1 antibiotic in the "Watch" category.

Conclusions. Differentiating bacterial from viral etiology in febrile illness on initial ED presentation remains challenging, resulting in a substantial overprescription of antibiotics. A significant proportion of patients with a viral phenotype received

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systemic antibiotics, predominantly classified as WHO Watch. Rapid and accurate point-of-care tests in the ED differentiating between bacterial and viral etiology could significantly improve antimicrobial stewardship.

Keywords. antimicrobial stewardship; pediatric emergency care; antibiotic prescription; AWaRe; infectious diseases.

Febrile illness is among the most common pediatric presentations at the emergency department (ED), contributing to 14% of attendances [1]. Most febrile children attending EDs likely have a self-limiting or viral infection, with the incidence of serious bacterial infection ranging from 5%–15% [2, 3], but approximately 33% receive antibiotics, and frequently broad-spectrum antibiotics [3, 4]. Discrepancy between confirmed bacterial infection and antibiotic prescription is partly explained by diagnostic uncertainty; in up to a fifth of presentations, no obvious cause of fever is found on clinical examination [5, 6]. This uncertainty gives rise to antimicrobial use for nonbacterial infections and drives antimicrobial resistance (AMR).

Given the ever-increasing threat to public health posed by AMR [7], judicious use of antimicrobials in the pediatric emergency setting is vital. The World Health Organization (WHO) global action plan encourages identifying patterns of antimicrobial use to optimize antimicrobial stewardship (AMS) programs in pediatric settings [8].

Work in recent years has shown that AMS programs need to be improved in pediatric primary, secondary, and tertiary care [3, 9, 10]. While there are significant data on prescribing patterns in primary care and the inpatient setting, there are fewer data on antimicrobial use in EDs [11–13].

The WHO AWaRe classification, developed as a tool to optimize antimicrobial use [14] classifies antibiotics into 3 AMS categories: Access, narrow-spectrum antibiotics considered as first- or second-line options for common infections; Watch, key targets for AMS initiatives, with higher potential for inducing resistance, and Reserve, "last-resort" options against multidrug-resistant or extensively drug-resistant bacteria [15].

We aimed to describe patterns of empiric systemic antibiotic use in the context of the WHO AWaRe classification to assess how the use of Access, Watch, and Reserve antibiotics varies across European pediatric EDs, microbiological etiology and clinical syndromes. We evaluated the appropriateness and consistency of antibiotic prescribing.

METHODS

Study Population and Study Design

The study population consisted of children (aged 0–18 years) enrolled in the Personalised Risk Assessment in Febrile Illness to Optimise Real-Life Management (PERFORM) study between August 2016 and December 2019. PERFORM is a multicenter, prospective, observational cohort study seeking to improve the diagnosis of febrile illness in children across Europe (https://www.perform2020.org/). Children who attended EDs with suspicion of infection and were considered to require blood tests were recruited, independent of the decision for inpatient or outpatient care [16]. Clinical data were prospectively collected by local study teams. Each patient was assigned final syndrome classification(s) and a phenotype by local study teams, including local principal investigators, based on collected clinical and laboratory data, following clear guidance of the PERFORM phenotyping algorithm (Supplementary Figure 1) [17]. To ensure accuracy and consistency of data entry and phenotyping, regular cross-site checks of randomly selected patients were performed. This was complemented by electronic quality control for all patients in the database.

Written informed consent was obtained from legal guardians of participants or participants themselves, per national guidance. The study was approved by the ethics committees of local recruitment sites and the coordinating site (Imperial College London; 16/LO/1684) (Supplementary Table 1).

Recording of Diagnoses and Clinical Syndrome Classifications

Initial and final diagnoses were recorded from prespecified lists of clinical syndrome classifications within the case record form (CRF), by the patients' clinicians (Supplementary Table 2). Presumed etiology was recorded with initial diagnosis and was categorized as "presumed bacterial," "presumed viral," "presumed noninfectious" (eg, for inflammatory syndromes), or unspecified.

Phenotyping of Participants

Febrile episodes were phenotyped using the PERFORM phenotyping algorithm (Supplementary Figure 1) and then analyzed in 1 of 2 groups defined as "bacterial" or "viral" [17]. For the bacterial group, we included patients with a "definite bacterial" phenotype (509 episodes), and those with a "probable bacterial" (599 episodes) or "bacterial syndrome" (441 episodes) phenotype (with bacteria detected accounting for all features or clear bacterial diagnosis). Patients who were assigned a final "definite viral" (487 episodes) or "viral syndrome" (with virus detected accounting for all features) (94 episodes) phenotype were included in the viral group. Patients categorized as "probable viral" were not included, because no definitive causative viral pathogen had been identified. Participants with hospital-acquired infections (symptom/fever onset >2 days after presentation to hospital) were excluded from the analysis, as well as participants with unknown symptom and fever onset and those for whom research blood samples could not be obtained within 2 days after admission (Figure 1).

Antibiotic Classes and AWaRe Classification

Empiric systemic antibiotics were defined as those prescribed within 2 days after presentation to hospital. These were categorized by antibiotic classes following the 3 WHO AWaRe categories (Access, Watch, and Reserve) (Supplementary Table 3).

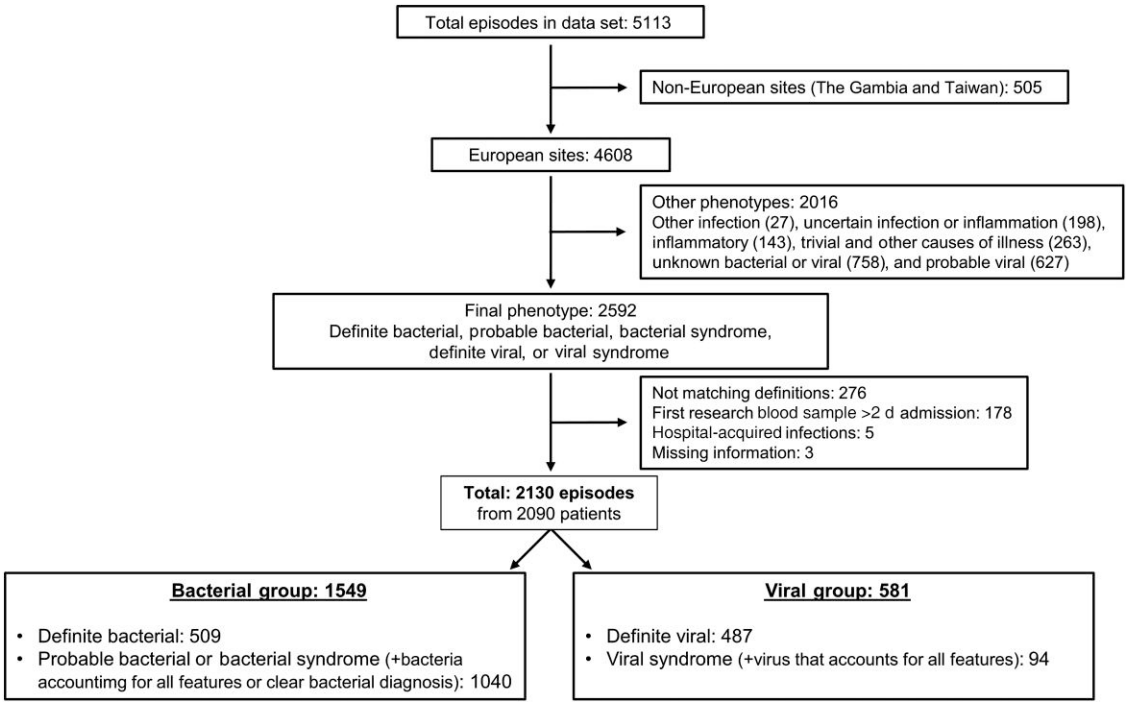

Figure 1. Febrile episodes selected for analysis.

Outcomes

Primary outcomes were appropriateness and consistency of empiric antibiotic use, considering the final phenotype and syndrome classification (Supplementary Table 4). For the bacterial group, withholding antibiotics was defined as inappropriate, unless in certain diagnoses (Supplementary Table 5). This judgment was made by review of final syndrome classification by study clinicians. For the viral group, any antibiotic use was defined as inappropriate (Supplementary Table 4). In addition, for the bacterial group, we described antibiotic use, stratified by both initial and final syndrome classification. Only patients with a single main syndrome classification (Supplementary Table 2) were included in the latter analysis, to remove conflicting indications for antibiotic use. We evaluated consistency considering the recorded presumed etiology (bacterial vs viral or noninfectious), where consistency was defined as using antibiotics only when the presumed etiology was bacterial. A secondary outcome was describing empiric antibiotic use for the 3 most common bacterial and viral pathogens.

Statistical Analysis

Distribution of variables was described in absolute numbers and percentages. We used χ^2 tests to determine whether the variables explored were independent of each other, using R software, version 4.0.2 (R Foundation for Statistical Computing) [18].

RESULTS

We included 2130 febrile episodes (from 2090 patients) from 9 European countries in this study. Of these episodes, 1549 (72.7%) were classified as bacterial, and 581 (27.3%) as viral. Of the 2130 episodes, 1156 (54.3%) were in male participants. Their median age was 5 years (bacterial) and 3 years (viral). Most patients (714 episodes, 33.5%) were from UK sites (Table 1). The most common main initial and final syndrome classifications were lower respiratory tract infection (initial, 421 [19.8%]; final, 501 [23.5%]) and upper respiratory tract infection (URTI) (initial. 399 [18.7%]; final, 435 [20.0%]) (Supplementary Table 6).

Overall, in 1587 episodes (74.5%) patients received empiric systemic antibiotics, with significant variation between countries. The 3 most frequently prescribed antibiotics in both groups (bactrial and viral) were third-generation cephalosporins (prescribed in 34.6% vs 60.6%, respectively, of those who received antibiotics), penicillin/β-lactamase inhibitor combinations (31.1% and 24.5%) and penicillins (26.9% and 23.4%) (Supplementary Tables 7 and 8).

Appropriateness of Antibiotic Use

Of 1549 patients presenting with a febrile episode in the bacterial group, 1318 (85.1%) received empiric systemic antibiotics administered parenterally (intravenously or intramuscularly) in 1157 of 1318 (87.8%). In the bacterial group, 231 patients presenting with a febrile episode (14.9%) did not receive

Table 1. Patient Characteristics for Febrile Episodes Included in Analysis (n = 2130)

Characteristic	Episodes, No. (%)			*P* Value[a]
	Bacterial (n = 1549)	Viral (n = 581)	Total (n = 2130)	
Sex				.57
Male	847 (54.7)	309 (53.2)	1156 (54.3)	
Female	702 (45.3)	272 (46.8)	974 (45.7)	
Age, y				<.001
<1	220 (14.2)	160 (27.5)	380 (17.8)	
1–5	640 (41.3)	240 (41.3)	880 (41.3)	
6–14	553 (35.7)	150 (25.8)	703 (33.0)	
15–17	136 (8.8)	31 (5.3)	167 (7.8)	
Country				<.001
Austria	148 (9.6)	46 (7.9)	194 (9.1)	
Germany	21 (1.4)	10 (1.7)	31 (1.5)	
Greece	149 (9.6)	107 (18.4)	256 (12.0)	
Latvia	194 (12.5)	46 (7.9)	240 (11.3)	
Netherlands	186 (12.0)	55 (9.5)	241 (11.3)	
Slovenia	127 (8.2)	24 (4.1)	151 (7.1)	
Spain	152 (9.8)	64 (11.0)	216 (10.1)	
Switzerland	79 (5.1)	8 (1.4)	87 (4.1)	
United Kingdom	493 (31.8)	221 (38.0)	714 (33.5)	
Regional Ancestry [b]				<.001
European	1316 (85.0)	447 (77.0	1763 (82.8)	
(North) African	35 (2.3)	22 (3.8)	57 (2.7)	
Asian	58 (3.7)	49 (8.4)	107 (5.0)	
Middle Eastern	36 (2.3)	26 (4.5)	62 (2.9)	
South American	3 (0.2)	0 (0.0)	3 (0.1)	
Other	10 (0.6)	7 (1.2)	17 (0.4)	
Mixed	26 (1.7)	14 (2.4)	40 (1.9)	
Antibiotic use within 7 d before presentation				.13
Yes	370 (23.9)	120 (20.7)	490 (23.0)	
No	1179 (76.1)	461 (79.3)	1640 (77.0)	
Patient status after presentation to ED				.36
Admitted	1305 (84.2)	477 (82.1)	1782 (83.7)	
Discharged	210 (13.6)	86 (14.8)	296 (13.9)	
Transferred	30 (1.9)	14 (2.4)	44 (2.1)	
Unknown	4 (0.3)	4 (0.7)	8 (0.4)	

Abbreviation: ED, emergency department.

[a] *P* values calculated using χ^2 test.

[b] Regional Ancestry was missing or unknown in 81 episodes (3.8%).

empiric antibiotics; in 120 (7.7%), withholding antibiotics was considered inappropriate (Supplementary Table 5). Of 581 (46.3%) patients presenting with a febrile episode in the viral group, 269 (46.3%) received inappropriate empiric antibiotics (87.0% intravenous or intramuscular).

Of patients receiving antibiotics for a febrile episode in the bacterial group, 70.0% received ≥1 Access antibiotic and 61.0% ≥ 1 Watch antibiotic. Of patients receiving antibioticsfor a febrile episode in the viral group, 50.2% received ≥1 Access antibiotic and 80.3% ≥1 Watch antibiotic (Figure 2*A* and 2*B* and Supplementary Tables 7 and 8). There was significant variation in the proportions of AWaRe antibiotics used in different countries, with Slovenia having the highest (89.2%) and Germany the lowest (39.3%) proportion of Access antibiotic use. We identified 49.1% Access use across all countries. (Figure 2*C*).

Most patients with a single initial main syndrome classification—1326 of 1520 febrile episodes (87.2%)—were attributed the same main final syndrome classification (Supplementary Figure 2). Among patients in the bacterial group with a single initial syndrome classification, the most common antibiotic classes prescribed varied by syndrome—however, penicillins, penicillin/β-lactamase inhibitor combinations, and second- and third-generation cephalosporins accounted for the majority of antibiotics (Figure 3*A* and 3*C*). The central nervous system showed the highest proportion of Watch antibiotic use. In patients with a single final syndrome classification, antibiotic choice and the use of Watch antibiotics followed a similar pattern (Figure 3*B* and 3*D*).

Consistency of Antibiotic Use

Of 251 episodes with a presumed viral or noninfectious etiology, 41 (16.3%) were subsequently phenotyped as bacterial, of which 30 (73.2%) received antibiotics; the remaining 210 episodes (83.7%) were assigned a viral phenotype, of which 65 (31.0%) received antibiotics (Figure 4*A*). Of the 251 episodes in this group, 95 (37.8%) received antibiotics inconsistent with the presumed etiology. An age-stratified overview of antibiotic prescribing patterns for patients with an initial viral or noninfectious initial syndrome classification is shown in Supplementary Table 9.

Of 887 episodes with a presumed bacterial etiology, 825 (93.0%) were assigned a final bacterial phenotype, of which 741 (89.8%) received antibiotics. Of 62 episodes (7.0%) assigned a final viral phenotype, 48 (77.4%) received antibiotics (Figure 4*B*). Of the 887 episodes in this group, 98 (11.0%) did not receive antibiotics, which is inconsistent with the presumed etiology.

For episodes in which the initial syndrome classification included both presumed bacterial and viral etiologies, unspecified infection, or undifferentiated fever (n = 992), 683 (68.9%) were attributed a final bacterial phenotype of which 550 (80.5%) received antibiotics. Of 992 episodes, 309 (31.1%) were attributed a final viral phenotype, of which 157 (50.8%) received antibiotics (Figure 4*C*).

The most common pathogens in the bacterial group were *Escherichia coli, Streptococcus pyogenes* (group A *Streptococcus*), and *Staphylococcus aureus* (Supplementary Table 10). Many patients with infections caused by these 3 pathogens received systemic Watch antibiotics (63.3%, 47.8%, and 49.0% respectively) (Supplementary Table 11). The most common viral pathogens in the viral group were influenza A/B, rhino/enterovirus, and respiratory syncytial virus (RSV) (Supplementary Table 10). Among patients with these pathogens, many received antibiotics (35.3%, 64.0%, and 66.7%. respectively). Of all the patients who received systemic antibiotics, 79.7% received ≥1 Watch antibiotic (73.8% with influenza A and B, 84.2% with rhino/enterovirus, and 81.0% with RSV) (Supplementary Table 12).

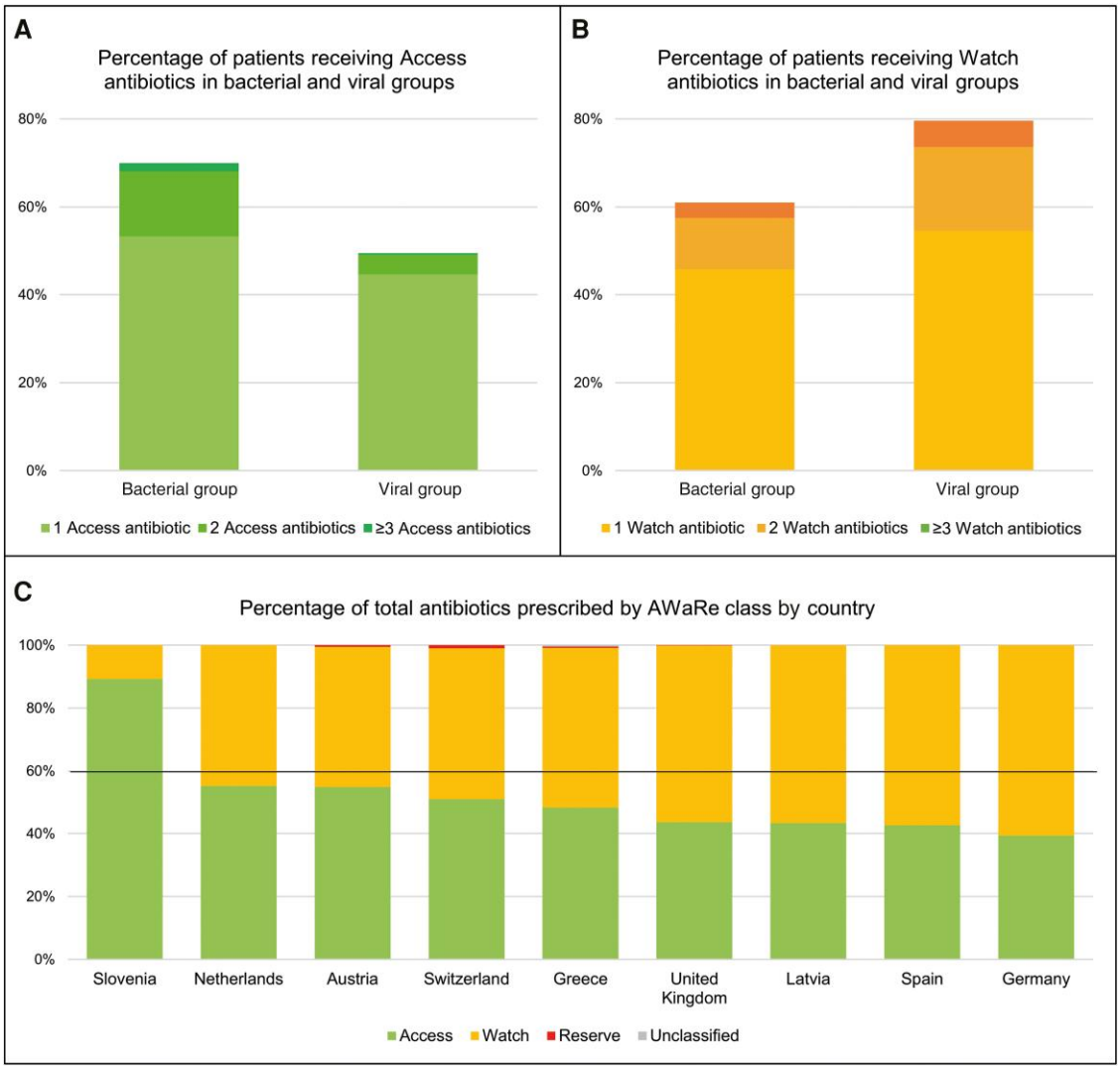

Figure 2. Proportions of Access, Watch, and Reserve antibiotics, in the World Health Organization (WHO) AWaRe classification, prescribed in the "bacterial" and "viral" groups. Line in (*C*) indicates the WHO target for 60% Access use.

DISCUSSION

We assessed the appropriateness and consistency of empiric antibiotic use in European EDs using data from the PERFORM study, for children attending EDs with suspected infection and considered to require blood tests, and we describe antibiotic use per the AWaRe classifications.

We demonstrated that a significant proportion of children within this cohort receive systemic antibiotics, including substantial use of Watch antibiotics, with some variation between European countries. Across the cohort, the proportion of empiric antibiotics prescribed from the Access category (49.1%) fell below the WHO target of 60%, illustrating an excessive use of Watch antibiotics [14]. A national AWaRe-based analysis of prescription data from pediatric outpatient and EDs in 16 secondary and tertiary care hospitals in China reported similar results. Watch antibiotics were most frequently prescribed (82.2%), third-generation cephalosporins (43.3%) in particular [19]. Variation in antibiotic use is not limited to EDs, and continuous monitoring of Watch antibiotic use in pediatric hospitals will be important for AMS interventions.

We show that many patients with viral illness receive empiric antibiotics at presentation to the ED. Of particular note, the proportion of patients receiving Watch antibiotics was higher in the viral than in the bacterial group (Figure 2).

In a small proportion (7.7%) of febrile episodes from patients with a bacterial phenotype, empiric antibiotics were withheld, for conditions where this would be considered inappropriate. However, a small proportion (32%) of those received antibiotics in the last 7 days before attending the ED. In general, this

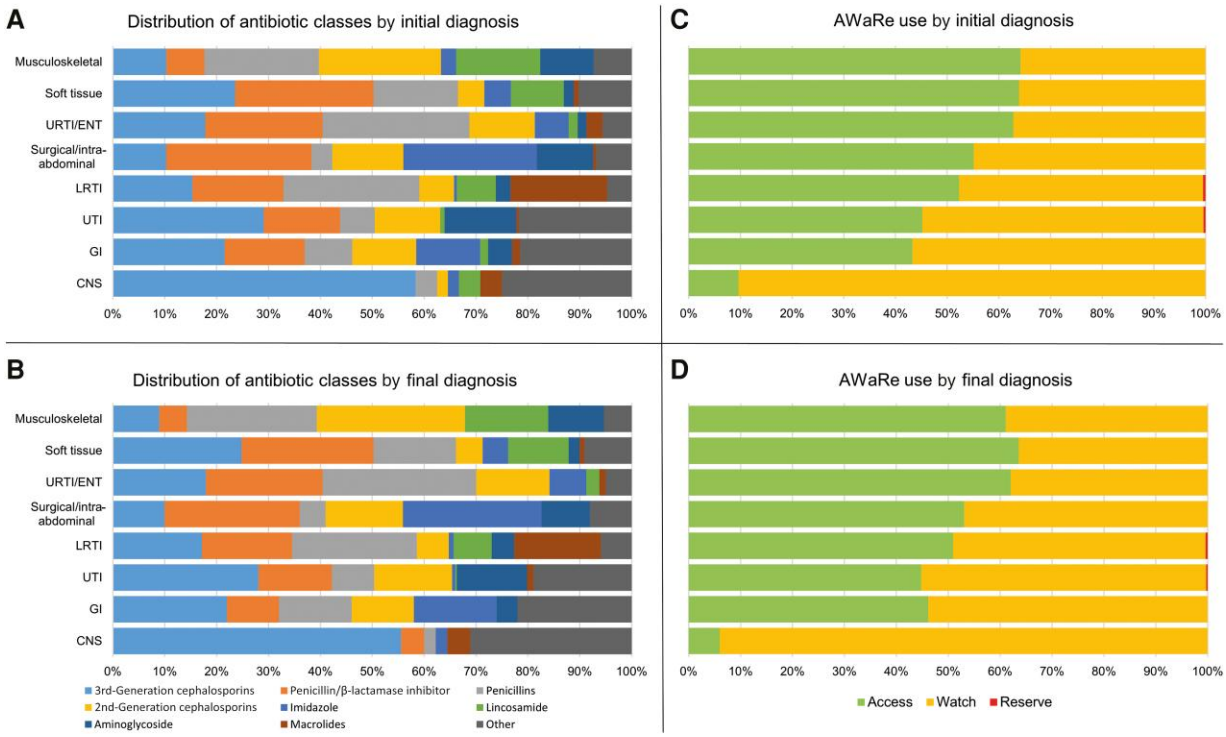

Figure 3. Distribution of antibiotics (classes and World Health Organization AWaRe classification) by single main initial and final syndrome classification in the "bacterial" group. The "other" category includes first-generation cephalosporins, glycopeptide, fluoroquinolones, carbapenems, dihydrofolate reductase inhibitors, fourth-generation cephalosporins, nitrofurantoin, oxazolidinones, rifamycins, tetracyclines, amphenicols and unknown antibiotics. Abbreviations: CNS, central nervous system; GI, gastrointestinal; LRTI, lower respiratory tract infection; URTI/ENT, upper respiratory tract infection or ear, nose, and throat; UTI, urinary tract infection.

lack of consistency in antibiotic prescribing highlights the critical need for improved diagnostics and AMS.

Our data suggest that diagnostic uncertainty contributes to inappropriate antibiotic use in viral diseases. While most often the presumed etiology was correct and treated appropriately (Figure 4*A* and 4*B*) when bacterial or viral etiologies were not clearly identified (Figure 4*C*), >50% of cases in the viral group received empiric antibiotics. Since molecular testing often detects both bacterial and viral pathogens in febrile children, it seems difficult for clinicians to withhold antibiotics when a viral cause is identified with the remaining possibility of an additional bacterial infection, while slow diagnostic tools such as cultures are still pending [20]. More than a third of children for whom only viral or noninfectious etiology was recorded as the initial syndrome classification received antibiotics, suggesting that diagnostic uncertainty is not the only driver of inappropriate antibiotic initiation. This effect was particularly seen in the very young: clinicians were more likely to start empiric antibiotics in patients <5 years of age ($P = .01$) (Supplementary Table 9), suggesting that clinicians may be less confident withholding antibiotics in very young febrile children. It was not possible to retrospectively determine whether other factors influenced the decision, such as time of day, social circumstances, parental concerns, or overcrowding.

The Watch antibiotic use for patients within each given final syndrome classification was similar to those with that same initial syndrome classification (Figures 3*A* and 3*C* vs Figure 3*B* and 3*D*), suggesting that in these groups it is not only uncertainty but perhaps other factors such as age and severity of disease that influence clinicians to act cautiously, thus driving excess Watch use. The role of sepsis mandates [21, 22] or fear of missing sepsis and potential litigation may also contribute, at the expense of optimal AMS. The high proportion of Watch antibiotics appears appropriate in some groups, such as central nervous system infections, where third-generation cephalosporins are recommended as first line, or urinary tract infections and intra-abdominal infections caused by gram-negative bacteria with varying resistance profiles.

The most common causative bacteria were *E. coli, S. pyogenes* (group A *Streptococcus*), and *Staphylococcus aureus* and were all associated with considerable empiric Watch antibiotics use. While the resistance pattern of *E. coli* is variable, warranting broader-spectrum antibiotics, this finding is particularly striking for *S. pyogenes,* where often penicillin is a suitable choice [23]. This may reflect the wide variety of syndromes and severity of syndrome associated with this pathogen, ranging from URTIs or soft-tissue infections to severe pneumonia or (toxin-mediated) septic shock.

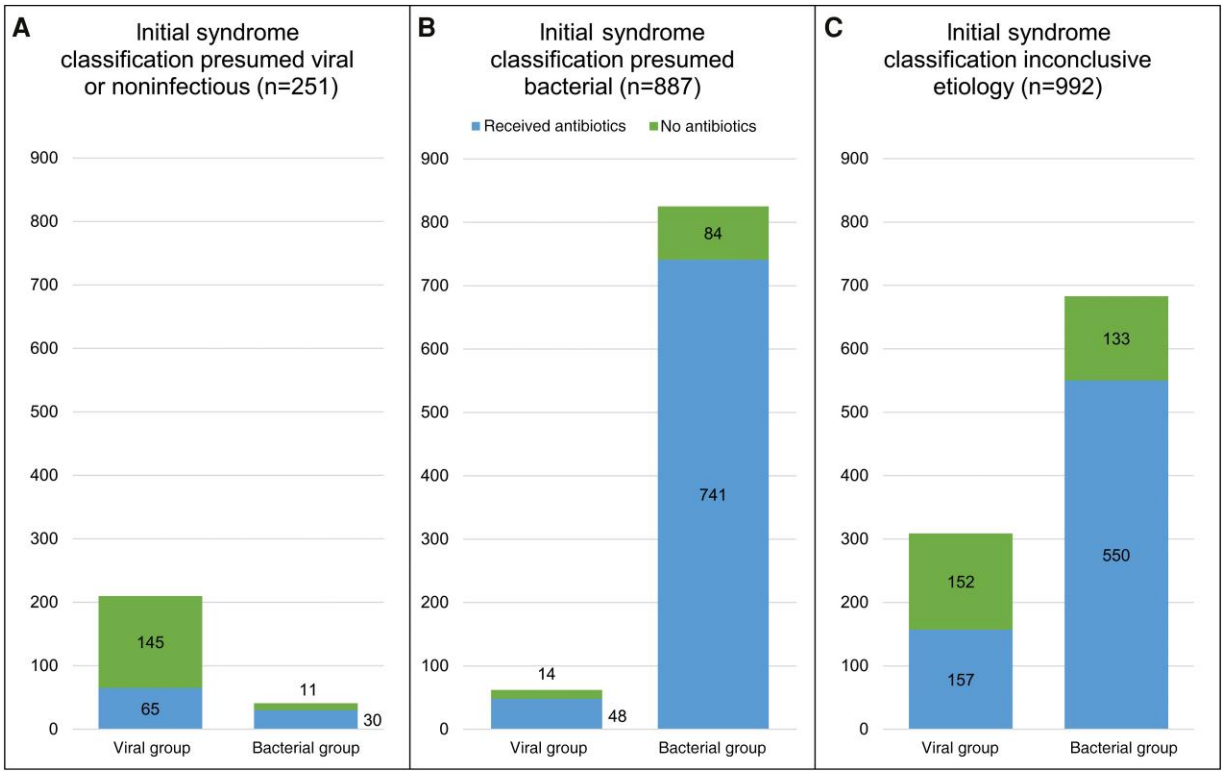

Figure 4. Number of febrile episodes with "bacterial" or "viral" phenotype receiving antibiotics in relation to the presumed etiology of the initial syndrome classification.

The most common causative viruses were influenza A/B, rhino/enterovirus, and RSV. More than 60% of patients with RSV and rhino/enterovirus received antibiotics, and overall, 79.7% received Watch antibiotics. Because most of these common viruses can cause sepsislike systemic disease, this may trigger sepsis screening and empiric use of Watch antibiotics [24]. The coronavirus disease 2019 (COVID-19) pandemic has highlighted how sepsislike presentations of viral illness in adult patients can lead to increased use of inappropriate antibiotics [25, 26], showing the pertinence of this phenomenon in the adult setting too.

The strengths of our study are a large prospectively collected multicenter, international cohort over 4 years, stratified by AWaRe classification to characterize antibiotic use. Data from 9 European countries were included, although the largest proportion was recruited from UK centers.

Among the limitations of the study, children recruited in PERFORM are not representative of all febrile children, as only those needing blood tests were recruited; however, diagnostic uncertainty and antibiotic prescribing are likely more relevant in these more severe presentations of illness. In addition, we only used a clearly defined subset of the PERFORM cohort. We did not include patients with a final phenotype of "other infection" (27 episodes), "uncertain infection or inflammation" (198 episodes), "inflammatory" (143 episodes) or "trivial" and "other causes of illness" (263 episodes), nor did we include patients categorized as "unknown bacterial or viral" (758 episodes), probable viral (627 episodes), or viral syndrome where there was no viral pathogen identified (193 episodes) [17] (Figure 1), as it would not be possible to consider the appropriateness of antibiotic use in these phenotypes. This skewed our population toward those with a bacterial phenotype, but on the other hand it made the analysis and respective results much clearer.

This data set includes patients with a range of comorbid conditions, some of whom were deemed high risk for infection, and our analysis did not stratify by comorbid condition or by severity of disease. Data on bacterial antibiotic resistance profiles were unavailable, so retrospectively commenting on the appropriateness of using AWaRe antibiotics in view of the actual resistance profile of the detected pathogens was not possible. Data were not available on penicillin allergy status, so antibiotic choices could therefore not be corrected for that.

In conclusion, the differentiation of bacterial or viral etiology of febrile illness on presentation to the ED is challenging. A significant proportion of patients with a final viral phenotype received antibiotics during admission, predominantly classified as Watch. Even when the clinician's judgment suggests a syndrome not requiring antibiotics, clinical uncertainty or concern about a bacterial coinfection or superinfection can result in

high Watch antibiotic use until a bacterial cause can be excluded, or a specific pathogen is identified. A recent report from the PERFORM study concluded that it is not always possible to distinguish between bacterial and viral infections, as both pathogens are often jointly detected, leading to broad-spectrum antibiotic use [20]. The tension between AMS and urgent treatment for presumed sepsis is well recognized. However, current guidelines suggest that unless there is septic shock, there is time to wait up to 3 hours for further assessment to decide on the appropriateness of antibiotics [24]. It is here where novel rapid diagnostics could improve AMS, while ensuring that those who need urgent antibiotics receive them.

Future research into improved diagnostic tools is critical for AMS, such as the development of rapid discriminatory point-of-care tests (POCTs). Current POCTs that aid clinicians in differentiating between bacterial and viral infection have limited clinical utility and are not ubiquitously available or favored by clinicians [27]. In some instances, such rapid tools could be useful for improving Access antibiotic use, such as the correct use of rapid antigen testing for *S. pyogenes*, strictly following recommended McIsaac Score assessment [28]. A positive rapid antigen test result may give clinicians confidence to use phenoxymethylpenicillin rather than broader-spectrum alternatives for children presenting with URTIs but would not be as useful for other syndromes caused by this pathogen. Future studies are needed to understand current variability in use and integration of these tests into ED workflow.

Host response–based blood biomarkers can provide reliable prediction of etiology [29]. Clinical trials evaluating the impact of implementing novel host response POCTs on antibiotic prescribing decisions for febrile children in the ED will be crucial. Clinicians worldwide should develop AMS programs that incorporate the AWaRe classification into their strategies, using WHO-defined targets for Access use as a pragmatic framework for monitoring and optimizing antibiotic use. Ultimately, this will enable clinicians worldwide to be more "AWaRe" of the importance of shifting from Watch to Access antibiotic use.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. H., A. J. C., R. G., V. J. W., M. K., T. K., F. M-T., H. M., M. P., A. J. P., P. K. A. A., L. J. S., M. N. T., S. Y., D. Z., W. Z., M. v. d. F., R. d. G., E. U., F. M., K. F., M. L., E. D. C., M. E., and U. v. B. contributed to the design of the study and funding acquisition. All authors contributed to sample and data collection. T. D. set up, maintained and was primarily responsible for technical aspects of the clinical database, including quality control. P. S. and C. W. were responsible for the database implementation and quality control. L. K. and A. K. were responsible for research-related and clinical quality control of data, performed the statistical analysis and wrote the first draft of the manuscript. L. K., A. K., E. D. C., M. E., and U. v. B. interpreted the data and wrote the final manuscript. All authors have contributed significantly to the drafting and revising of the manuscript and approved the final manuscript. All authors confirm that they had full access to the data and hold responsibility for its content.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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6. Paper II

Title of article: Epidemiological and genetic characteristics of vancomycin-resistant *Enterococcus faecium* isolates in a University Children's Hospital in Germany: 2019 to 2020

Authors: Ilona Trautmannsberger, **Laura Kolberg**, Melanie Meyer-Buehn, Johannes Huebner, Guido Werner, Robert Weber, Valerie Heselich, Sebastian Schroepf, Hans-Georg Muench and Ulrich von Both

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Antimicrobial Resistance and Infection Control

RESEARCH

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Epidemiological and genetic characteristics of vancomycin-resistant *Enterococcus faecium* isolates in a University Children's Hospital in Germany: 2019 to 2020

Ilona Trautmannsberger[1,2,3], Laura Kolberg[1], Melanie Meyer-Buehn[1], Johannes Huebner[1,4], Guido Werner[5], Robert Weber[5,6], Valerie Heselich[7], Sebastian Schroepf[7], Hans-Georg Muench[7] and Ulrich von Both[1,4*]

Abstract

Background: Vancomycin-resistant *Enterococcus faecium* (VREfm) strains are one of the most important pathogens causing nosocomial infections in Germany. Due to limited treatment options and an increased risk for acquisition in immunocompromised children, surveillance to monitor occurrence of VREfm in paediatric clinical facilities is of critical importance. Following an unusual accumulation of VREfm positive patients between April 2019 and August 2020 at Dr. von Hauner Children's Hospital in Munich, Germany, our study aimed to identify dynamics and routes of transmission, and analyse the affected population in view of previously described host risk factors for VREfm colonisation or infection.

Methods: The hospital database was used to collect epidemiological and clinical data of VREfm cases. Descriptive statistical analyses were conducted to outline patient characteristics and depict possible differences between VREfm-colonised and -infected children. An outbreak investigation determining genetic relatedness among VREfm isolates was performed by core genome multilocus sequence typing (cgMLST). To examine potential transmission pathways, results of genome analysis were compared with epidemiological and clinical data of VREfm positive patients.

Results: VREfm acquisition was documented in a total of 33 children (< 18 years). Seven VREfm-colonised patients (21.2%), especially those with a haemato-oncological disease (4/7; $p = 0.011$), showed signs of clinical infection. cgMLST analysis revealed seven distinct clusters, demonstrating a possible connection within each clonal lineage. Additional eight singletons were identified. Comparison with epidemiological and clinical data provided strong evidence for a link between several VREfm positive patients within the hospital.

Conclusions: A nosocomial spread—at least in part—was the most likely reason for the unusual accumulation of VREfm cases. The study highlights that there is a constant need to increase efforts in hygiene measures, infection control and antibiotic stewardship to combat VREfm transmission events within German paediatric hospitals. Continuous monitoring of adherence to respective policies might reduce the occurrence of clustered cases and prevent future outbreaks.

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Keywords: Vancomycin-resistant *Enterococcus faecium*, Paediatrics, Epidemiology, Outbreak investigation, Nosocomial cluster, Germany

Background

Enterococci are Gram-positive, catalase-negative, facultative anaerobic bacteria that commonly inhabit the gastrointestinal tract of humans and animals. Of all *Enterococcus* species known to date, *Enterococcus faecalis* and *E. faecium* are the most common commensal organisms in humans [1]. Both are characterised by great tenacity to hostile environmental conditions, including high NaCl concentration, bile salts, pH (4.5–10.0) and extreme temperature (5–65 °C), enabling them to persist, grow and spread under a range of stresses [1, 2]. In addition to their role as an essential part of the microflora, *E. faecium* and *E. faecalis* are of great medical significance. They are important nosocomial pathogens causing a variety of infections, such as urinary tract and surgical site infections, peritonitis, bacteraemia and in severe cases bloodstream infections and endocarditis [3–6]. A major challenge is the occurrence of intrinsic and acquired antibiotic resistance, which significantly reduces possibilities for therapy. In particular, the glycopeptide resistance genotypes *vanA* and *vanB* in vancomycin-resistant *E. faecium* (VREfm) isolates cause fundamental therapeutic problems [4, 6–8].

Considering the increased risk for persistence and transmission in hospitals, VREfm infections and their treatment play an important role in clinical practice [1, 2, 9–11]. Since the beginning of the twenty-first century, an increased spread of *vanA*- and *vanB*-positive *E. faecium* strains has been detected in German hospitals [5, 12, 13]. This resulted in major outbreaks of VREfm infections and colonisations, which led to a continuous expansion of resistance rates in subsequent years [5, 12–14]. According to a recent analysis of data on *E. faecium* isolates from the Antibiotic Resistance Surveillance (ARS) of the Robert Koch Institute (RKI), the proportion of existing vancomycin resistance in German hospitals increased significantly from 11.2% in 2014 to 26.1% in 2017 [15]. Due to proven evidence on prolonged hospital stay, higher costs and excess mortality amongst VREfm-colonised and -infected patients, the World Health Organization (WHO) assigned VREfm as a high priority pathogen on its global priority list of antibiotic-resistant bacteria [16–18].

Despite the fact that paediatric facilities are currently not considered classic risk areas for VREfm occurrence, hospitalised children and neonates especially those with severe comorbidities are highly susceptible for VREfm acquisition, colonisation and subsequent infection after contact with these bacteria [19–25]. Possessing immunological naivety and requiring intensive care, they present a fundamentally vulnerable patient group, for whom infections remain an important cause of death [22, 23, 26]. Therefore, it is of great interest to investigate frequent occurrence of VREfm in neonatal, interdisciplinary paediatric and paediatric surgical facilities, examine the affected population and identify spread dynamics. Potential VREfm clusters can thus be detected and current measures for prevention and control of healthcare-associated infections can be reviewed, adapted and improved.

Between April 2019 and August 2020, an unusual accumulation of VREfm cases was observed at Dr. von Hauner Children's Hospital in Munich, Germany. The aim of the study was to identify or exclude a clonal spread, determine possible nosocomial transmission routes, analyse the affected population in view of previously described host risk factors for VREfm colonisation or infection, give suggestions to improve prevention measures and thereby reduce the rate of future VREfm-colonised and -infected patients at Dr. von Hauner Children's Hospital.

Methods

Study design and study population

This study was designed as a monocentric, descriptive retrospective analysis investigating data of children aged < 18 years with acquired VREfm isolates between April 2019 and August 2020. The analysis focused on both colonised and infected patients at Dr. von Hauner Children's Hospital, a 180-bed paediatric tertiary teaching hospital in Munich, Germany. As a part of the Ludwig-Maximilians-University (LMU) Klinikum, it combines general paediatrics and paediatric surgery, provides outpatient care and treats about 7500 inpatient cases every year [27]. Following local proximity and a high number of patient referrals, affected newborns on the neonatal intensive care unit (NICU) in the Polyclinic for Gynecology and Obstetrics (LMU Klinikum Campus Inner City) were included as well. During the study period, the bacteriological laboratory of Dr. von Hauner Children's Hospital isolated VREfm from 33 patients in total. Cases of VREfm (colonisation or infection) were identified either by a microbiological analysis of rectal swabs examined due to screening for multidrug-resistant pathogens or any other clinical specimen tested for presumed bacterial infection. Routine screening using rectal swabs was performed on NICU and PICU (paediatric intensive care unit) on a weekly basis and on any patient

newly admitted to these wards (starting August 2020). Rectal swabs were directly applied to VRE selection agar plates (VRE Select, reference number 63751, Bio-Rad, 85622 Feldkirchen, Germany).

VREfm isolates and cgMLST

VREfm isolates detected at the Dr. von Hauner Children's Hospital were sent to the German National Reference Centre for Staphylococci and Enterococci at the Robert Koch Institute for further analysis. Antibiotic susceptibility testing was performed by broth microdilution and subsequent determination of the minimum inhibitory concentrations according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines and breakpoints (v10) [28]. Species identification and detection of resistance genes (*vanA, vanB*) were conducted using standard polymerase chain reaction (PCR) assays. An outbreak investigation determining possible clonal relatedness among the isolates was initiated by whole-genome sequencing (WGS) and typing. For this purpose, DNA derived from pure bacterial culture was isolated using the DNeasy Blood & Tissue Kit (Qiagen, Hilden, Germany). Sequencing libraries were generated with the Nextera XT DNA Library Preparation Kit (Illumina, San Diego, CA, United States) and paired-end sequencing was performed using a NextSeq instrument with a read length of 150 bp (Illumina, San Diego, CA, United States). The quality of the raw sequence data was checked using FastQC v0.11.5 [29]. Additionally, Kraken v0.10.6 was used to verify taxonomic read classification [30]. Subsequently, SPAdes v3.12.0 was used in the assembly mode 'careful' with default parameters for de novo assembly of high-quality sequencing reads [31]. Multilocus sequence typing (MLST) and core genome MLST (cgMLST) were performed using contigs and Ridom SeqSphere + v6.0.0 (Ridom; Münster, Germany) and established typing schemes [32, 33]. Sequence types (ST) and complex types (CT) were derived from MLST and cgMLST, respectively. Based on cgMLST (including 1423 core genes), a Minimum Spanning Tree (MST) was inferred by ignoring pairwise missing values. VREfm isolates, assigned to the same *van*-genotype and differing in less than 15 core genes were considered as (closely) related [34].

Data collection and variables

Epidemiological and clinical data of the study population were extracted from electronic and paper-based medical records provided by the hospital database. Variables collected were age at initial detection of VREfm, sex, hospital wards patients were present during the study period and information about whether the patient had a presumed clinical infection or was colonised. Predisposition to known risk factors was identified by literature search and included in the analysis. In addition to multiple patient-related factors such as preterm birth (including young gestational age and low gestational weight), underlying immunosuppressive comorbidity (e.g. malignancy), performed surgical procedures, use of invasive devices (e.g. catheters and feeding or breathing tubes) and invasive treatments (ventilation, chemotherapy), the exposition to antibiotics was recorded [19, 20, 23, 24, 35–38]. Antibiotics prescribed within six months before initial VREfm detection were analysed and categorised into antibiotic classes and *Access*, *Watch*, or *Reserve* groups according to the WHO AWaRe classification of antibiotics [39]. In case of a suspected infection, the respective antibiotic used for treatment was included in the analysis.

Statistical analysis

Statistical analysis was performed using R version 4.0.5 [40]. Distribution of categorical variables in the study population was described in absolute numbers and percentages, continuous variables were illustrated with measures (median, range). Patient characteristics were further analysed regarding suspected VREfm infection (VREfm-I) and VREfm colonisation (VREfm-C). Parameters were compared with Fisher's exact test for categorical variables and Mann–Whitney U test for continuous variables, as all quantitative data were not normally distributed. The significance level was set at 5%. Missing values were excluded for analysis. A timeline was generated to combine results from cgMLST with epidemiological and clinical data of the study population and thereby investigate potential transmission pathways within the hospital.

Results

Between April 2019 and August 2020, a total of 693 children were screened for VREfm (154 (22.2%) children in non-ICU settings and 539 (77.8%) while being treated on intensive care units (NICU, PICU)). 33/693 patients were found to be colonised, accounting for a prevalence of 4.8%. Compared to previous years, the number of detected VREfm isolates showed a notable increase during the study period (see Fig. 1). Detailed baseline characteristics of children found to be VREfm positive are outlined in Table 1. Cases predominantly originated from infants with a median age of 6 months (range 0–16 years) and a male/female ratio of 1.54. At the time of VREfm detection, 26 children were treated on neonatal/paediatric intensive care units, four were identified on surgical wards, one on the bone marrow transplantation unit and two were patients cared for on general wards. Antibiotics prescribed within six months prior to detection of VREfm are shown in Table 2.

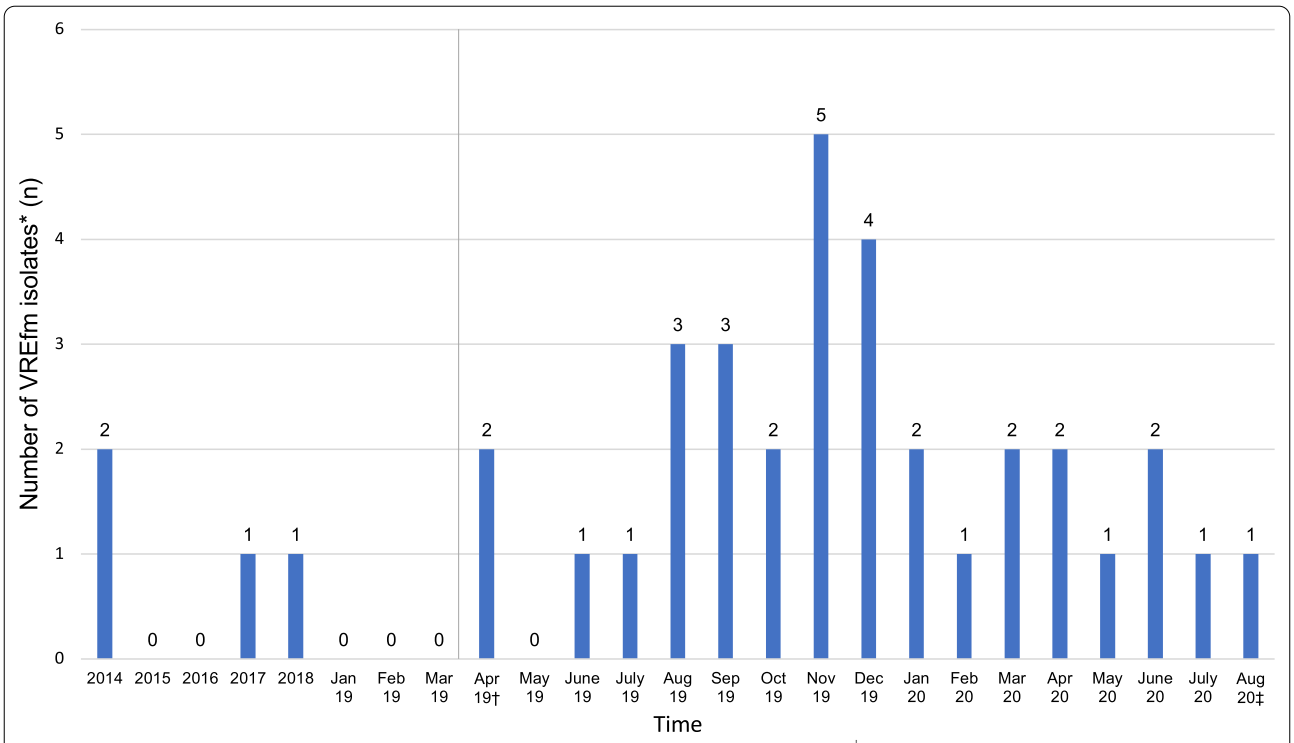

Fig. 1 Time trend of detected vancomycin-resistant *E. faecium* isolates from 2014 to August 2020. †beginning of the study period at Dr. von Hauner Children's Hospital, ‡end of the study period at Dr. von Hauner Children's Hospital

A clinical VREfm infection was presumed in seven patients (21.2%), all of whom were previously colonised with the respective VREfm strain. Central-line associated infection was detected in three patients. Two patients suffered a surgical wound infection, one patient was diagnosed with a urinary tract infection and another one showed positive blood cultures, suggesting an invasive systemic infection. Demographic and clinical findings from patients with suspected VREfm-I and VREfm-C are presented in Table 1. Our data demonstrate that children who developed signs of a bacterial infection were significantly more likely to have had a temporary artificial stoma ($p=0.006$), to have undergone a recent surgical procedure ($p=0.009$) or to have received carbapenems ($p=0.039$) or chemotherapy ($p=0.023$) before initial VREfm detection. Similarly, the presence of an underlying haemato-oncological diagnosis ($p=0.011$) was significantly more likely in VREfm-infected compared to VREfm-colonised children. An underlying respiratory disease ($p=0.027$) was significantly less likely in patients with a presumed VREfm-I than in those without clinical symptoms.

All suspected VREfm infections were treated with *Reserve* antibiotics. Six patients received linezolid, one patient received daptomycin and another child was treated with a linezolid/daptomycin combination.

Genome analysis (MLST) showed that VREfm isolates belonged to seven different STs. The most commonly detected STs were ST80 (n=18), ST721 (n=4), ST117 (n=3), ST424 (n=3) and ST1299 (n=3). Regarding detection of resistance genes, PCR analysis identified *vanB* cluster in 54.5% (n=18) and *vanA* cluster in 45.5% of isolates (n=15). More detailed cgMLST analysis revealed genetic links, divided into seven distinct clusters (allele difference ≤15, Fig. 2). The clonal lineage ST80/CT1065 *vanB* represented the largest group, containing almost one third (n=10) of all VREfm isolates. The combination of cgMLST with epidemiological and clinical data of the study population is shown in Fig. 3.

Cluster 1 was found at the Polyclinic for Gynecology and Obstetrics. It contained five premature babies and a mother, who had been hospitalised due to complications with twin pregnancy. The mother (corresponding VREfm isolate ID UW20653, see Fig. 2 and 3), screened positive for VREfm on 24 October 2019, representing the initial case of this cluster. The first newborn (UW20642) was found to be colonised on 19 November, followed by both twins of the initial case (UW20651, UW20644) on 28 November. Subsequently, two additional patients (UW20649, UW20640) were screened positive beginning of December. All newborns were inpatients during the same time.

Table 1 Demographic and clinical data of the study population (patients < 18 years)

	Missing n (%)	All patients (n = 33)	VREfm-colonised patients (n = 26)	VREfm-colonised patients with suspected infection (n = 7)	*p* value*
Sex, n (%)	0 (0.0)				
Male		20 (60.6)	17 (65.4)	3 (42.9)	0.393
Female		13 (39.4)	9 (34.6)	4 (57.1)	
Age (in months)	0 (0.0)				
Median (range)		6 (0–198)	5.5 (0–198)	13 (1–184)	0.143
Prematurity, n (%)	4 (12.1)				
Preterm born		16 (48.5)	14 (53.8)	2 (28.6)	0.632
Mature born		13 (39.4)	10 (38.5)	3 (42.9)	
Gestational age (in completed weeks of gestation)	4 (12.1)				
Median (range)		34 (23–41)	33.5 (23–41)	34 (24–40)	0.885
Gestational weight (in grams)	8 (24.2)				
Median (range)		2150 (465–4430)	2150 (465–4430)	1665 (730–2600)	0.96
Twin, n (%)	0 (0.0)				
Yes		4 (12.1)	4 (15.4)	0 (0.0)	0.555
Invasive devices†, n (%)	0 (0.0)				
NG/NJ tube		16 (48.5)	13 (50.0)	3 (42.9)	1.000
PEG/PEJ tube		7 (21.2)	6 (23.1)	1 (14.3)	1.000
Peripheral venous catheter		21 (63.6)	15 (57.7)	6 (85.7)	0.223
Central venous catheter		17 (51.5)	13 (50.0)	4 (57.1)	1.000
Arterial line		9 (27.3)	6 (23.1)	3 (42.9)	0.358
Port		1 (3.0)	1 (3.8)	0 (0.0)	1.000
Hickman catheter		5 (15.2)	2 (7.7)	3 (42.9)	0.052
Urinary catheter		10 (30.3)	6 (23.1)	4 (57.1)	0.161
Ventricular drain		3 (9.1)	3 (11.5)	0 (0.0)	1.000
Tracheostomy tube		2 (6.1)	2 (7.7)	0 (0.0)	1.000
Chest drain		2 (6.1)	2 (7.7)	0 (0.0)	1.000
Artificial stoma		3 (9.1)	0 (0.0)	3 (42.9)	**0.006**
Surgical procedures†, n (%)	0 (0.0)	18 (54.5)	11 (42.3)	7 (100.0)	**0.009**
Endoscopic procedure		8 (24.2)	7 (26.9)	1 (14.3)	0.652
Cardiothoracic surgery		4 (12.1)	3 (11.5)	1 (14.3)	1.000
Intrabdominal surgery		5 (15.2)	0 (0.0)	5 (71.4)	**< 0.0001**
Brain surgery		2 (6.1)	2 (7.7)	0 (0.0)	1.000
Biopsy		2 (6.1)	1 (3.8)	1 (14.3)	0.385
Bone marrow aspiration		1 (3.0)	0 (0.0)	1 (14.3)	0.212
Tumour resection		3 (9.1)	0 (0.0)	3 (42.9)	**0.006**
Other surgical procedures‡		2 (6.1)	1 (3.8)	1 (14.3)	0.385
Underlying diseases, n (%)	0 (0.0)				
Haemato-oncological diseases		6 (18.2)	2 (7.7)	4 (57.1)	**0.011**
Cardiovascular diseases		8 (24.2)	6 (23.1)	2 (28.6)	1.000
Diseases of the respiratory system		13 (39.4)	13 (50.0)	0 (0.0)	**0.027**
Endocrine diseases		3 (9.1)	3 (11.5)	0 (0.0)	1.000
Gastrointestinal diseases		15 (45.5)	11 (42.3)	4 (57.1)	0.674
Genitourinary diseases		3 (9.1)	1 (3.8)	2 (28.6)	0.107
Neurological diseases		9 (27.3)	8 (30.8)	1 (14.3)	0.642
Malformation syndromes affecting multiple systems		3 (9.1)	2 (7.7)	1 (14.3)	0.524
Chromosomal abnormalities		3 (9.1)	3 (11.5)	0 (0.0)	1.000

Table 1 (continued)

	Missing n (%)	All patients (n = 33)	VREfm-colonised patients (n = 26)	VREfm-colonised patients with suspected infection (n = 7)	*p* value*
Ventilation†, n (%)	0 (0.0)				
Invasive ventilation		14 (42.4)	10 (38.5)	4 (57.1)	0.422
Non-invasive ventilation		17 (51.5)	13 (50.0)	4 (57.1)	1.000
Chemotherapy~, n (%)	0 (0.0)				
Yes		4 (12.1)	1 (3.8)	3 (42.9)	**0.023**
Reanimation~, n (%)	0 (0.0)				
Yes		5 (15.2)	3 (11.5)	2 (28.6)	0.282
Overall hospitalisation before initial detection of VREfm°	0 (0.0)				
Length of stay (in days), median (range)		38 (0–276)	38 (0–276)	28 (0–106)	0.659
Number of hospital admissions, median (range)		1 (1–34)	1 (1–34)	1 (1–15)	0.484
Glycopeptide resistance genotype, n (%)	0 (0.0)				
vanA		15 (45.5)	14 (53.8)	1 (14.3)	0.095
vanB		18 (54.5)	12 (46.2)	6 (85.7)	

Signficant values (marked in bold) were defined as $p < 0.05$

VREfm, Vancomycin-resistant *Enterococcus faecium*; NG/NJ tube, nasogastric/nasojejunal tube; PEG/PEJ tube, percutaneous endoscopic gastrostomy/jejunostomy tube

* Fisher's exact test or Mann–Whitney U test ($p \leq 0.05$ was considered significant)

† Within four weeks prior to detection of VREfm

‡ Including one surgery of the anus, rectum and colon and one ovarian surgery for fertility preservation

~ Within six months prior to detection of VREfm

°Including hospitalisation at Dr. von Hauner Children's Hospital, NICU Clinic and Polyclinic for Gynecology and Obstetrics and LMU Klinikum Großhadern

Cluster 2 contained nine different isolates, detected within a period of ten months. Regarding the clinical history of affected patients, four children (patients 1, 4, 5, 8; UW20643, UW20645, UW20650, UW21368) had already been tested positive for VREfm during a previous external hospitalisation. After admission to Dr. von Hauner Children's Hospital, patient 1 was an inpatient on NICU during the same time (June 2019) as patient 3 (UW20646), patient 2 (UW20389) was an inpatient on the general infant ward during the same time (August/September 2019) as patient 4 and patients 2 and 3 both had a gastroscopy on the same day (29 July 2019) performed by the same surgical team. Apart from two negative test results from patients 1 and 4, no screening tests were performed before initial VREfm detection.

Cluster 3 occurred on PICU. The first colonised patient (UW20352) was a child with a malignant solid tumour, who was transferred to Munich for elective surgical treatment in June 2019. Seventy-four days after the primal case a second patient (UW20648) was screened positive for VREfm. In both cases, no screening tests were performed before initial detection of the respective bacterial strain.

Another three isolates, identified in 2019 within a period of nine months, built **Cluster 4**. All three affected children had an underlying oncological disease but were present on different wards when they were first screened VREfm positive. Except for one negative test result (patient 3; UW20641), no screening tests were performed before initial detection. Patients 1 (UW20355) and 3 were hospitalised at the same surgical ward end of March/beginning of April and patient 2 (UW20353) was admitted several times to the oncology ward for chemotherapy during the same period as patient 3. In addition, patients 1 and 2 had a surgical procedure one day apart (01 April and 31 March) performed by the same surgeon.

Cluster 5 was detected on PICU in January/February 2020. Two patients (UW20842, UW20844) were screened positive for VREfm within 40 days. Before initial detection the patients were screened negative several times, however, patient 2 was temporarily hospitalised at another site of the LMU Klinikum, where no data for potential screening tests were available.

Further two isolates formed **Cluster 6**. The initial case (UW21370) in this cluster was an infant screened positive for VREfm on first day of admission (27 May 2020) to the NICU of Dr. von Hauner Children's Hospital. A second patient (UW21371) was found to be colonised on 08 June, located at the same hospital ward during the same time as the initial case. Before detection of VREfm, patient 2 was screened negative several times.

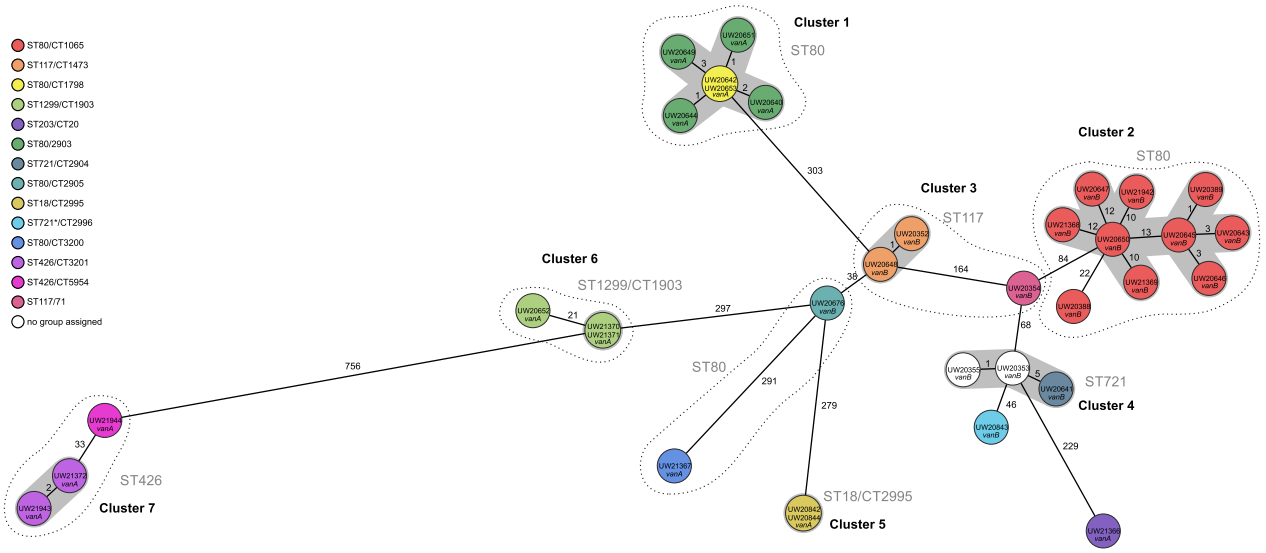

Fig. 2 Minimum spanning tree of 34 vancomycin-resistant *E. faecium* isolates from 33 children and one mother. The number of varying alleles is shown next to the black lines. Colouring was based on cgMLST (analysis of 1423 genes of the nuclear genome). Grey areas connect isolates that belong to a cluster based on the definitions of SeqSphere + (maximum allele difference = 15 alleles). Dashed lines include isolates that belong to one sequence type (ST). ST = sequence type (multilocus sequence typing (MLST), analysis of 7 housekeeping genes), CT = complex type (core genome MLST (cgMLST)). SeqSphere option: pairwise ignoring missing values. Task templates: *E. faecium* cgMLST v1.1; *E. faecium* MLST v1.0. *adk: Novel allele, ST may indicate nearest ST. MLST-Finder: http://www.genomicepidemiolog

Table 2 Antibiotic use within six months prior to detection of VREfm in the study population

	All patients (n = 33)	VREfm-colonised patients (n = 26)	VREfm-colonised patients with suspected infection (n = 7)	*p* value*
Antibiotics total, median (range)	5 (0–14)	5 (0–14)	7 (3–14)	0.150
Antibiotic classes, n (%)				
Aminoglycosides	5 (15.2)	5 (19.2)	0 (0.0)	0.559
Beta-lactam/beta-lactamase inhibitor	22 (66.7)	16 (61.5)	6 (85.7)	0.378
Carbapenems	16 (48.5)	10 (38.5)	6 (85.7)	**0.039**
First-generation cephalosporins	3 (9.1)	3 (11.5)	0 (0.0)	1.000
Fluoroquinolones	1 (3.0)	0 (0.0)	1 (14.3)	0.212
Glycopeptides	11 (33.3)	9 (34.6)	2 (28.6)	1.000
Imidazoles	4 (12.1)	3 (11.5)	1 (14.3)	1.000
Macrolides	6 (18.2)	6 (23.1)	0 (0.0)	0.301
Penicillins	12 (36.4)	11 (42.3)	1 (14.3)	0.223
Phosphonics	1 (3.0)	0 (0.0)	1 (14.3)	0.212
Second-generation cephalosporins	8 (24.2)	7 (26.9)	1 (14.3)	0.652
Third-generation cephalosporins	14 (42.4)	13 (50.0)	1 (14.3)	0.195
Trimethoprim/sulfonamide combinations	9 (27.3)	5 (19.2)	4 (57.1)	0.068
Unknown antibiotic class	2 (6.1)	2 (7.7)	0 (0.0)	1.000
Antibiotic groups AWaRe classification†				
Access Antibiotics, median (range)	1 (0–6)	1 (0–6)	1 (0–3)	0.629
Watch Antibiotics, median (range)	4 (0–13)	3 (0–13)	4 (2–12)	0.120

Signficant values (marked in bold) were defined as $p < 0.05$

VREfm, Vancomycin-resistant *Enterococcus faecium*

* Fisher's exact test or Mann–Whitney U test ($p < 0.05$ was considered significant)

† excluding two unknown antibiotics

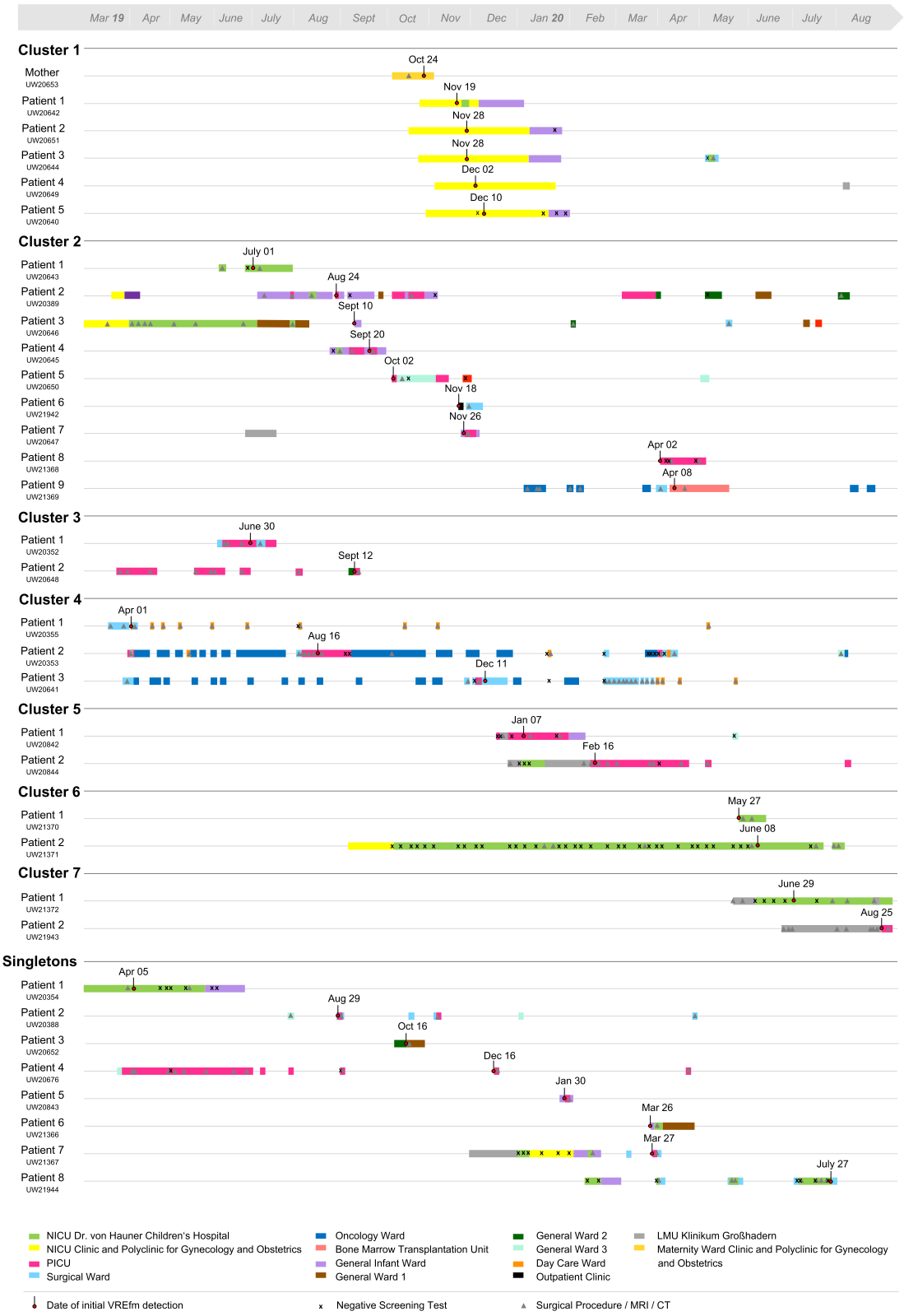

Fig. 3 Timeline for each patient combining results from cgMLST with epidemiological and clinical data

Cluster 7 included two isolates. The first patient (UW21372) with detected VREfm on 29 June 2020, was a child suffering from cardiac defect and severe postischemic brain injury who was transferred from another site of the LMU Klinikum to the NICU of Dr. von Hauner Children's Hospital for further treatment. Before initial detection, the patient was tested negative several times. Patient 2 (UW21943) was screened positive on first day of admission to PICU on 25 August 2020. Regarding clinical history, patient 2 had evidence for VREfm colonisation during a previous hospital stay (10 August 2020) at another site of the LMU Klinikum, where patient 1 had been present two months before. In addition, patient 1 had a temporal overlap regarding hospital ward with both patients from **Cluster 6**.

Eight remaining isolates were considered **singletons** (a single clone that has no close relatives in the cgMLST). However, clinical-epidemiological data revealed evidence for a possible link between several cases (Fig. 2). The hospitalisation of patient 1 (UW20354) was congruent with the hospitalisation of patient 3 (UW20646) from **Cluster 2**. Patient 4 (UW20676) was present on PICU during the same time as both patients (UW20352, UW20648) from **Cluster 3** and patients 7 (UW21367) and 8 (UW21944) showed an epidemiological connection in terms of hospital wards with children (UW20844, UW21370, UW21371, UW21372) from **Cluster 5–7**. A temporal and personnel concordance in several performed surgical procedures presented another potential connection for some patients with no cluster assignment.

Discussion

In this retrospective study, we aimed to investigate the accumulation of VREfm isolates during April 2019 and August 2020 at Dr. von Hauner Children's Hospital. The main objective was to investigate a clonal spread, determine possible nosocomial transmission routes and analyse the affected population while in parallel evaluating previously described host risk factors for VREfm carriage or infection. In total, we found 33 children to be VREfm positive during the study period. CgMLST of all isolates revealed a polyclonal structure with a suspected spread demonstrated within seven distinct clusters and eight singletons. In combination with epidemiological and clinical data, our observations provided compelling evidence for transmission of VREfm between patients within the hospital.

Cluster 1, 3, 5, **6** and **7** consisted of isolates from children, who were present on identical hospital wards either during the same time or during a period following shortly thereafter (maximum seven weeks). These findings suggest a likely nosocomial transmission—a frequent and relevant issue that has been described in particular for VREfm compared to other multidrug-resistant microorganisms [41]. This fits well with the current state of research, where direct transmission between colonised or infected patients as well as indirect transmission via the patient's surroundings are discussed as the most probable routes of spread [2, 10, 11, 42, 43]. Regarding the duration of VREfm-C in paediatric patients, periods ranging from several weeks to over six months are described [44–47]. Due to their extensive resilience, enterococci are known to survive even longer (up to several years) in hospital environments [1, 2]. Drees et al. found that patients admitted to rooms previously occupied by VRE carriers had a significantly higher risk of VRE acquisition [48]. Contaminated drip stands, ventilation tubes, incubators, thermometers, and other VRE positive surfaces were confirmed to play an important role in transmission pathways and multiple cleaning practices were shown to be inefficient for their decontamination [49–53]. In addition to transmission dynamics via the environment, these findings could be the result of close and constant interaction between patients and healthcare staff. Especially hands or gloves have been shown to act as a potential reservoir and transmission vehicle for nosocomial bacteria [9, 54, 55]. Moreover, we have shown that **Cluster 4** included VREfm positive patients, detected at different hospital wards. However, all three children had an underlying haemato-oncological disease and two patients had undergone a surgical procedure with the same surgical team one day apart from each other. These results indicate potential transmission via nursing staff or attending physicians in oncology or contamination of the hospital environment in general. **Cluster 2**, containing isolates from nine patients, showed a poor clinical-epidemiological linkage. Multiple children had been tested positive for VREfm during a previous external hospitalisation or had a positive test result on their first day of admission, assuming that they had already been colonised before initial detection at Dr. von Hauner Children's Hospital. Nevertheless, we found some temporal overlap in terms of hospital wards or performed surgical procedures, again suggesting nosocomial transmission of VREfm.

Overall, our findings are in line with other reports, confirming VREfm transmission within and between wards by WGS/cgMLST and epidemiological data [10, 33, 56–58]. An inter-hospital spread can be assumed since the predominant clonal lineage in Bavaria ST80/CT1065 *vanB* represented the most commonly detected group (n = 10) at Dr. von Hauner Children's Hospital [59]. Especially isolates of **Cluster 2** harboured the ST80/CT1065 *vanB* group, which may explain the poor clinical-epidemiological linkage and thus indicate a cross-contamination event with external hospitals. Frequent patient referrals between hospitals and specialities, in particular

within different sites of the LMU Klinikum, may demonstrate a reason for the dissemination.

Interestingly, some of the genetically unrelated VREfm isolates showed a relevant connection in terms of epidemiological and clinical data of affected patients (patients of **Cluster 6** and **Cluster 7**; patients of the **singleton** group and **Cluster 2, 3, 5, 6** or **7**). In each case, VREfm isolates harboured *van*-genotypes, which were identical with genotypes of possible connected clusters (Fig. 2). This could refer to genetic mobility of *vanA* and *vanB* variants, allowing resistance to spread among different clonal lineages by horizontal gene transfer (HGT) [8, 60, 61]. Arredondo-Alonso et al. as well as Pinholt et al. previously identified high frequencies in HGT, especially of the *vanA* transposon Tn*1546* and corresponding *vanA* plasmids among unrelated *E. faecium* isolates as an alternative route of vancomycin resistance transmission in hospitals [62, 63].

To improve prevailing measures for the prevention of nosocomial VREfm spread at Dr. von Hauner Children's Hospital, we evaluated affected patients, especially those with a presumed clinical infection requiring antibiotic therapy. Thereby, we have shown that more than half of all VREfm positive children were premature babies with young gestational age and low gestational weight. Regarding possible differences between VREfm-colonised and VREfm-infected patients, the presence of a temporary artificial stoma, a recent surgical procedure, previous treatment with carbapenems, preceding chemotherapy and underlying haemato-oncological disease were significantly associated with the development of clinical symptoms. These findings are in line with current studies, identifying preterm babies as well as immunosuppressed paediatric intensive care patients—in particular children with a haematological/oncological diagnosis—as a high-risk population for VREfm-C and VREfm-I [19, 20, 35, 64–67]. High exposure to antibiotics, especially third-generation cephalosporins, seems to further increase the risk [19, 35, 68].

Some important limitations need to be taken into account when interpreting our results. First, our study lacked negative test results in some patients prior to initial VREfm detection making it difficult to determine the exact time point of VREfm acquisition. This temporal imprecision may have influenced the accuracy of epidemiological data. Furthermore, we neither had information on patients' room numbers or bays on NICU/PICU (to identify direct roommates) nor were samples of the patients' environment available. Therefore, we were only able to make statements on ward level. Transmission via environmental contamination or healthcare staff (hands/gloves) could only be assumed, not confirmed. Second, it must be noted that clonal lineages such as ST80/CT1065 seem to have a very stable core genome (low allele differences), which often leads to the formation of clusters in cgMLST with no epidemiological link (neither temporally nor spatially) [59]. Third, focusing on cgMLST may have led to miss the confirmation of potential epidemiological links as a result of an overestimation of non-related isolates by excluding the analysis of possible HGT [62]. A polyclonal VREfm colonisation (also as a result of HGT) is conceivable, as usually only one colony (1 clone) per patient and time point is microbiologically processed, which does not necessarily reflect the totality of possible colonisation.

However, our findings regarding VREfm spread are still relevant and valuable. Future efforts should and will aim on exploring new and better ways to reduce nosocomial transmission events at Dr. von Hauner Children's Hospital. In essence, the majority of existing international recommendations on the prevention of VREfm-C and VREfm-I in hospital call for improved hygiene measures, educational activities and screening as key interventions in suspected outbreak scenarios in clinical settings [69–74]. Following this study's outbreak investigation it is essential to continuously review adherence to basic (hand) hygiene measures, in particular to the implementation of the "Five Moments for Hand Hygiene" [69–73]. Furthermore, we will aim to establish a new action plan consisting of a prevention bundle tailored to our affected population. Considering our findings we conclude that the bundle should include an active screening of rectal swabs for high-risk patients namely children and infants on intensive care units, surgical wards, the oncology ward and the bone marrow transplantation unit as well as a passive screening of every specimen taken for clinical indication [69–72, 74]. Routine surveillance of women with a high-risk pregnancy and high prenatal antibiotic use hospitalised at the Clinic and Polyclinic for Gynecology and Obstetrics should be considered. To achieve a reduction in clonal spread and horizontal transmission events, screening should be performed at regular intervals beginning on the first day of hospital admission [74, 75]. A subsequent isolation strategy for every VRE carrier including individual sanitary facilities for older children and mothers as well as enhanced barrier measures (gowns/gloves) for all contact persons constitute meaningful measures to reduce nosocomial VREfm dissemination [69–72, 75–77]. Improved cleaning and disinfection methods during and after hospitalisation of VREfm carriers and the involvement of affected patients and accompanying persons in hygiene measures can magnify the effect [50, 70–72, 74, 78]. Complementary to our current standard hygiene measures (disinfectant: Kohrsolin FF 0.5% or Terralin protect 0.5%) we consider to use ultraviolet-C (UV-C) light as an additional method

to enhance terminal disinfection of patient rooms [79]. UV-C radiation has been used after detection of Cluster 1 at the Clinic and Polyclinic for Gynecology and Obstetrics. In general, it has been shown that efforts to reduce the use of unnecessary antibiotics are key to avoid selection of multidrug-resistant pathogens [80]. Despite no consistent scientific consensus about the impact of antibiotic stewardship programs (ASP) on VRE acquisition in general, an implementation in paediatric patients seems to be promising [69, 81, 82]. Further studies should regularly monitor the effectiveness of infection control measures and adherence to respective policies using defined suitable target variables. Finally, refinements to the examination of genomic data by a new approach that also includes the analyses of HGT mobilisation and polyclonal colonisation to effectively confirm potential epidemiological links may provide more accurate results for surveillance [62, 83].

Conclusions

In conclusion, the Dr. von Hauner Children's Hospital witnessed a substantial increase in the detection of VREfm isolates between April 2019 and August 2020, a dynamic that can be—at least in part—attributed to suggested nosocomial transmission events. Our study highlights the importance of protecting intensive care patients, who were mainly affected by the outbreak. In view of the monocentric character of this study, results may not entirely be generalisable to other clinical settings. However, findings and conclusions can serve as an example for comparable paediatric tertiary teaching hospitals. To achieve a reduction of transmission it is critical to further investigate VREfm genetic profiles and epidemiological links between colonised/infected patients, hospital environment and healthcare staff. Additional prospective studies are needed to continuously improve preventive efforts in hygiene measures, infection control and ASP to combat the spread of VREfm between hospitalised children and infants in Germany.

Abbreviations

ASP: Antibiotic stewardship program; AWaRe: Access Watch Reserve; cgMLST: Core genome multilocus sequence typing; CT: Complex type; *E. faecalis*: *Enterococcus faecalis*; *E. faecium*: *Enterococcus faecium*; EUCAST: European Committee on Antimicrobial Susceptibility Testing; HGT: Horizontal gene transfer; LMU: Ludwig-Maximilians-University; MLST: Multilocus sequence typing; MST: Minimum Spanning Tree; NICU: Neonatal intensive care unit; PCR: Polymerase chain reaction; PICU: Paediatric intensive care unit; RKI: Robert Koch Institute; ST: Sequence type; UV-C: Ultraviolet-C; VRE: Vancomycin-resistant enterococci; VREfm: Vancomycin-resistant *Enterococcus faecium*; VREfm-C: VREfm colonisation; VREfm-I: VREfm infection; WGS: Whole-genome sequencing; WHO: World Health Organization.

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Authors' contributions

IT, LK, MM, JH and UvB contributed to the conception and design of the study. GW and RW performed the genome analysis of VREfm isolates. IT and MM were responsible for data acquisition. IT, LK and UvB analysed and interpreted the results. IT, LK and UvB drafted and/or revised the manuscript. VH and SS were involved in clinical care of patients and provided additional clinical input. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ludwig-Maximilians-University ethics committee under project number 21–0334. Due to the retrospective character of the study, no informed consent was required. The processing of personal data was anonymised and in full accordance with local data protection laws.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

7. Paper III

Title of article: Evaluating current practice and knowledge about antibiotic stewardship principles in paediatric tertiary hospitals to identify target areas for future teaching activities

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ORIGINAL PAPER

Evaluating current practice and knowledge about antibiotic stewardship principles in paediatric tertiary hospitals to identify target areas for future teaching activities

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Abstract

Purpose Antibiotic exposure among hospitalized children is very high. With inappropriate antimicrobial use resulting in increased rates of antimicrobial resistance, the implementation of antibiotic stewardship programs is critically needed. This survey study aimed to identify current practice and knowledge about antibiotic stewardship and infection control among paediatricians in tertiary care paediatric hospitals in and around Munich, Germany.

Methods A prospective cross-sectional study based on an anonymous questionnaire, structured into different sub-sections regarding antibiotic use, antimicrobial resistance, antibiotic stewardship and infection control, was conducted between 1st of May and 30th of June 2016 in five paediatric hospitals.

Results In total, 111 paediatricians across all grades were eligible for participation. The overall proportion of correct answers for all sub-sections of the survey ranged from 54.1% correct answers in the antibiotic handling and bacterial resistance section to 72.9% correct answers in the hospital hygiene/infection control section. In general, knowledge across all categories was similar for junior doctors, middle-grade doctors or consultants. Advocating empiric use of narrow-spectrum instead of broad-spectrum antibiotics was considered to be the most difficult measure to implement in daily practice (36.9%). De-escalation from broad-spectrum empirical therapy to targeted treatment was considered the easiest measure to achieve (43.2%).

Conclusion Our results demonstrate that principles of antimicrobial stewardship and aspects of hospital hygiene/infection control are not satisfactorily known among hospital-based paediatricians in and around Munich. We identified four important target areas for future educational interventions that should play a more prominent role in both pre- and postgraduate medical training.

Keywords Antibiotic stewardship · ASP · Paediatrics · Germany · Training · Education

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Purpose

Organisms resistant to antibiotics are increasing rapidly resulting in a global public health threat. Increasing rates of antimicrobial resistance (AMR) are a direct consequence of inappropriate antimicrobial use. [1] Hospitalized children and adolescents have a very high antibiotic exposure, with 60% of them receiving at least one antibiotic per stay. [2] Furthermore, a great amount of administered antibiotics is unnecessary or inadequately prescribed. [1, 3]

Therefore, optimization of antimicrobial use and improvement towards rational prescribing of these valuable drugs is critically needed. This will result in a decrease of antibiotic resistance rates, improvement of patient care and reduced hospital stay for inpatients as well as a reduction in costs attributable to the inappropriate use of antibiotics. [4, 5] To achieve these goals antibiotic stewardship programs (ASP) with different strategies and bundle approaches for rational use of antibiotics are implemented in hospital and ambulatory care. [1, 6]

The aim of this survey study was to identify current practice and knowledge related to antibiotic stewardship aspects in paediatric junior doctors, middle-grade doctors and consultants in tertiary care paediatric hospitals in a south-eastern region in Germany using a questionnaire. The results of the survey should subsequently help to identify areas for future educational activities.

Methods

Setting and survey design

A prospective cross-sectional study was conducted in five German paediatric teaching hospitals in and around Munich (south-eastern region of Germany). The study was based on an anonymous questionnaire distributed among 278 active hospital-based paediatricians at the Dr. von Hauner Children's Hospital, the children's hospital Dritter Orden and the Children's Hospital Schwabing as well as in two regional district general hospitals (Klinikum Traunstein and Starnberg).

Questionnaire structure and implementation

The design of the survey was adjusted based on the work published by Bowes et al., with specific adaptations to better assess relevant areas of knowledge. [7] It was distributed between 1st of May and 30th of June 2016. Participants were able to fill in the survey via an online platform or complete a paper questionnaire that was subsequently entered into the online database—survey monkey (www.surveymonkey.de). If not stated otherwise only one answer was allowed for each question. For some questions 'I don't know' was given as a possible answer option (which was considered 'incorrect' for the analysis). (see supplementary file 1).

The questionnaire was structured into six different subsections: questions regarding participants' characteristics and education (5 questions), the handling of antibiotics and bacterial resistance (5 questions), the understanding of microbial aspects of infectious disease (4 questions), the knowledge about hospital hygiene (3 questions), antibiotic stewardship and treatment standards (7 questions) as well as questions assessing the individual respondent's work environment (4 questions).

Statistical analysis

Distribution of variables in the survey population was described in absolute numbers (n) and percentages (%) for junior doctors (doctors in paediatric training), middle-grade doctors (board certification, clinical registrar level) and consultants (board certification, clinical consultant level) separately. Knowledge for different sections was computed as the proportion of questions correctly answered to the total number of questions in the regarding section. The data were checked for independency using Fischer's exact tests. The statistical software R (version 3.6.0) was used to perform the statistical analysis. [8]

Results

Demographics

A total of 118 participants returned the survey. Two questionnaires were answered by medical students and were therefore excluded from the analysis. Of the remaining 116 questionnaires returned by paediatricians (response rate 42%) five additional participants were excluded (one who did not state his/her position and four due to insufficient data, leaving 111 questionnaires for analysis. Of these, 47 were junior doctors, 34 were middle-grade doctors and 30 were consultants. Overall, 66/111 (59.5%) physicians were working at the Dr. von Hauner Children's Hospital with the remaining respondents (45/111; 40.5%) distributed among other paediatric hospitals. More consultants (4; 13.3%) reported having advanced training in infectious disease, microbiology or hospital hygiene in comparison to junior doctors ($n=1$) and middle-grade doctors ($n=0$; p-value = 0.02). Two among them were working at the Dr. von Hauner Children's Hospital and the remaining three were from other paediatric hospitals.

Overview of all questions and answers of the 111 participating paediatricians can be found in supplementary file 2.

Antibiotic handling and bacterial resistance

The following proportion of respondents correctly answered questions regarding antibiotic prescribing and drivers of AMR: lower versus higher dosing of antibiotics, 101 (91.0%); longer versus shorter duration of therapy 77 (69.4%); use of piperacillin versus ampicillin 62 (55.9%); use of azithromycin versus clarithromycin 63 (56.8%). With regards to aspects of local data on AMR, knowledge on macrolide-resistant group A *Streptococcus* (GAS) and penicillin-resistant *Streptococcus pneumoniae* isolates yielded an astonishingly low number of correct answers (Table 1). In both cases, consultants demonstrated better knowledge (36.7 and 20.0% correct answers) compared to junior doctors (23.4 and 4.3%) and middle-grade doctors (20.6 and 2.9%). In addition, many physicians were unsure (answering "I don't know") about the correct answers regarding macrolide-resistant group A *Streptococcus* isolates (23/111) and penicillin-resistant *Streptococcus pneumoniae* isolates (3/111). Community carrier rate of ESBL was correctly estimated by 58 (52.3%) physicians and 57 (51.4%) identified cefotaxime as a risk factor for the selection of Clostridium difficile. In summary, the proportion of correct answers in the section of antibiotic handling and bacterial resistance was 46.5% for junior doctors, 50.7% for middle-grade doctors and 57.5%

Table 1 Knowledge of antimicrobial stewardship principles and individual opinions on implementing respective measures amongst 111 hospital-based paediatricians—selected questions and answers

	Missing (*n*)	%	*n*	%	*p*-value*
What is the current prevalence of macrolide resistance in the group A *Streptococcus* (GAS) population according to national/regional data?	1	0.9			0.36
Correct (>10%)			29	26.1	
Incorrect			81	73.0	
What is the prevalence of penicillin resistance in the *Streptococcus pneumoniae* population according to national/regional data?	0	0			**0.03**
Correct (<1%)			9	8.1	
Incorrect			102	91.9	
An inpatient with evidence of MRSA in a nasopharyngeal swab should be isolated according to which isolation scheme?	2	1.8			**0.04**
Correct (basic measures + droplet isolation)			43	38.7	
Incorrect			66	59.5	
An inpatient with pulmonary tuberculosis should be isolated according to which isolation scheme?	3	2.7			0.85
Correct (basic measures + aerogenic isolation)			82	72.9	
Incorrect			26	23.4	
Which antibiotics require therapeutic drug monitoring (TDM)?	4	3.6			0.30
Correct (vancomycin and amikacin)			37	33.3	
Incorrect			70	63.1	
Which of the following do you consider the most difficult measure to implement to improve antibiotic therapy *in your work environment*?	17	15.3			0.90
De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram			8	7.2	
Rapid conversion from IV to oral antibiotic therapy			7	6.3	
Reduction of therapy duration			15	13.5	
Stop antibiotic therapy in the absence of documented infection			23	20.7	
Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics			41	36.9	
Which of the following do you consider the easiest measure to implement to improve antibiotic therapy *in your work environment*?	15	13.5			0.75
De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram			48	43.2	
Rapid conversion from IV to oral antibiotic therapy			21	18.9	
Reduction of therapy duration			8	7.2	
Stop antibiotic therapy in the absence of documented infection			18	16.2	
Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics			1	0.9	

*Fisher's exact test

Bold values: significant difference (p-value < 0.05)

for consultants resulting in an overall mean of 54.1% (SD 25.2%) (Table 2).

Microbial aspects of infectious disease

For the section regarding the microbial aspects of infectious diseases, the overall proportion of respondents identifying the correct answers was 58.1%. Answer patterns were similar for junior doctors, middle-grade doctors and consultants. The overall mean was 56.75% (SD 14.2%) (Table 2).

Hospital hygiene/infection control

Hand hygiene was identified as the most important infection control measure by almost all 104/111 (93.7%) paediatric physicians. The appropriate isolation scheme for a patient with nasal MRSA colonization (basic measures + droplet isolation) was only reported in 43/111 (38.7%). The majority of paediatricians considered basic measures + contact isolation sufficient measures in this situation (40.5%; 45/111). Of note, consultant-level doctors showed a significantly higher rate of false answers (24/30, 80.0%) compared to middle-grade (18/34, 52.9%) or junior doctors (24/47, 51.1%; p value = 0.04). On the other hand, an inpatient with pulmonary tuberculosis was correctly identified as requiring aerogenic isolation measures by 82/111 (72.9%) respondents, showing no significant difference between training grades of physicians (Table 1). In summary, the proportion of correctly answered questions in the section of hospital hygiene was 70.2% for junior doctors, 72.5% for middle-grade doctors and 62.2% for consultants resulting in an overall mean of 72.9% (SD 27.8%) (Table 2).

Antibiotic stewardship and treatment standards

Overall, the knowledge of antibiotic stewardship and treatment standards was 51.7% for junior doctors, 48.7% for middle-grade doctors and 54.8% for consultants resulting in an overall mean of 55.9% (SD 24.4%) (Table 2). Only one third of the physicians correctly identified vancomycin and amikacin as antibiotics requiring therapeutic drug monitoring (TDM) (Table 1). When sub analysing the knowledge on TDM, a significantly greater proportion of physicians was aware that vancomycin requires TDM compared to aminoglycosides (86.6 vs. 34.2%; p-value < 0.001). When evaluating correct empiric antibiotic choice for common clinical scenarios correct answers were provided by 16.2% (preferred antibiotic therapy for a patient with appendicitis) and 82.0% (preferred antibiotic therapy for a patient with pneumonia), respectively.

Structure of the work environment

While consultants predominantly rely on guidelines when choosing the best antibiotic (24/30, 80.5%) only 48.9% of junior doctors and 67.6% of middle-grade doctors consult these sources. Both middle and junior grade doctors are more likely to ask for advice from their superiors or colleagues than to consult guidelines (p value < 0.01). Overall, 74 (66.7%) physicians were aware of and considered local resistance data and 19 (17.1%) mentioned national resistance data as most relevant for prescribing antibiotics. Of note, the most difficult measure to implement to improve antibiotic therapy was the use of narrow-spectrum antibiotics versus broad-spectrum antibiotics (36.9%), whereas the majority (43.2%) considered de-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram as the easiest measure to achieve (Table 1).

Discussion

This survey study aimed to identify current practice and knowledge on aspects of antibiotic use, ASP and infection control in tertiary care paediatric hospitals in and around Munich, Germany. Our analysis demonstrates an overall proportion of correct answers for all sub-sections of the survey of only just above 50%, thus elucidating the critical importance of continuing and improving educational activities covering all areas of antibiotic stewardship. In general, practice and knowledge across all categories did not differ significantly between junior doctors, middle-grade doctors or consultants. This is in line with similar studies, such as the survey of Bowes et al. assessing comparable sections in a survey published in 2014. [7] Alshengeti et al. developed and analysed the effectiveness of an online virtual patient learning module for paediatric residents about antimicrobial stewardship in 2016. A modified version of Bowes et al. survey [7] was used to measure the residents' knowledge. The overall knowledge score before the implementation of the ASP module was 58.2%, which is quite similar to the

Table 2 Overall percentage of correct answers per sub-section (mean and standard deviation, SD)

Antibiotic handling and bacterial resistance	Mean: 54.1%; SD = 25.2%
Microbial aspects of infectious disease	Mean: 56.75%; SD = 14.2%
Hospital hygiene/infection control	Mean: 72.9%, SD = 27.8%
Antibiotic stewardship and treatment standards	Mean: 55.9%; SD = 24.4%

55.0% we saw in our survey study. [9]The biggest lack of knowledge was observed regarding the local antibiotic resistance pattern. Knowledge on macrolide-resistant group A *Streptococcus* (GAS) and penicillin-resistant *Streptococcus pneumoni*ae isolates yielded an astonishingly low number of correct answers (26.1 and 8.1%, respectively). Of note, the pneumococcal local resistance rate was primarily correctly estimated by consultants (6/9; 66.7%). The vast majority (74.1%) of participating paediatricians did not know that more than 10% of group A *Streptococcus* (GAS) are resistant to macrolides and thus underestimated the issue. Only a very small minority (8.1%) was aware of the local penicillin-resistance rate (prevalence of <1%) in *Streptococcus pneumoniae*. Therefore, penicillin resistance in pneumococcus is likely to be overestimated leading to less frequent use of penicillins in common conditions such as community-acquired pneumonia (CAP). Bowes et al. found similar results in their study and pointed out, that this overestimation of antibiotic resistance levels can be an important reason for inappropriate prescribing and de-escalation strategies, resulting in increased use of broad-spectrum antibiotics. [7]

Regarding hospital hygiene and infection control, basic hygiene measures such as hand hygiene appeared to be well known and common practice across all participating hospitals. But only less than half of the participants were aware of the correct isolation scheme for a patient with MRSA colonization of the upper respiratory tract and pointed out that droplet rather than contact precautions are required in this scenario. [10] Of note, consultants did significantly worse when answering this question compared to middle-grade and junior doctors (p value = 0.04). Though consultant-grade doctors should certainly be aware of the correct precautions to be implemented on the ward, the middle-grade and junior doctors are practically dealing with this every day. On the other hand, for the scenario of pulmonary tuberculosis the majority of respondents provided the correct answer for the precautions required (72.9%) with no significant difference between grades of paediatricians. [11]

Two clinical scenarios were assessed in terms of empiric antibiotic choice. It is noteworthy to emphasize that while the choice of antibiotics for appendicitis was very variable, participants were rather uniformly suggesting ampicillin or amoxicillin for CAP. This reflects a direct effect of establishing and communicating internal guidelines because such a document had only recently been established for CAP at the Dr. von Hauner Children's Hospital in early 2015, whereas no such document was available for a case of appendicitis at that time. Nevertheless, there is a national reference for appendicitis and pneumonia available in all hospitals (DGPI Handbuch [12]) Hence, this is additional practical proof of how implementing local guidelines is a very effective measure to improve rational antibiotic use. [13]

Therapeutic drug monitoring is an essential requirement when administering the glycopeptide vancomycin or aminoglycosides such as amikacin [13] and is a standard laboratory service available for all participating hospitals. Overall, only 37/111 (33.3%) paediatricians correctly identified both antibiotics as requiring TDM. Thus, our results clearly demonstrate that these drugs, though frequently used in paediatric and, in particular, in neonatal care [14], are most likely inappropriately applied and monitored putting the respective patients at risk for both an ineffective and potentially toxic therapy. Junior, middle-grade and consultant-level doctors were equally uninformed about the critical need for TDM. Still, when a paediatrician thinks about TDM, he/she is more likely to be aware of measuring serum levels when prescribing vancomycin than amikacin. There is a clear need to address TDM in targeted educational activities in the future.

When assessing the practical use of local, national or international guidance, consultants appeared to be the group most frequently turning to advice published in guidelines while junior and middle-grade doctors were more likely to directly consult their superiors when choosing an empiric or targeted antibiotic therapy. To a certain extent, this finding reflects an interesting difference between the Anglo-Saxon and the German medical system. While frequent rotation between workplaces (i.e. tertiary-care centres, district general hospitals) is an established standard in UK paediatric training, the majority of German junior and middle-grade doctors are spending their entire training period in the same hospital. Hence, inter-collegial bonds and influences of superiors, as well as an "in-house common practice" mode of action, is more common in Germany than in the UK system where NHS hospitals follow a more national guidelines-oriented and evidence-based-medicine approach (https://www.nice.org.uk/guidance; https://www.rcpch.ac.uk/resources/clinical-guidelines-evidence-reviews). However, only recently and after this survey study was conducted, a first national paediatric antibiotic stewardship guideline has been published. [13] In addition, recent years have seen more national guidelines being developed on topics such as paediatric community-acquired pneumonia. [15] A national paediatric guideline on appendicitis is currently under development (https://www.awmf.org/leitlinien/detail/anmeldung/1/ll/006-003.html). These activities clearly reflect that the importance and need for coherent and evidence-based guidance for paediatric ASP have been recognised by the responsible scientific bodies and societies.

The easiest and most difficult ASP measures to be implemented in one's own clinical working environment were identified. While using less broad-spectrum antibiotics as part of empirical antibiotic therapy was considered the most difficult measure, de-escalating a broad empirical therapy after receiving the pathogen differentiation and antibiogram was considered the easiest measure to

achieve. Of note, switching from IV to oral therapy was regarded as the second easiest measure to implement, while reducing the duration of therapy or stopping an antimicrobial in the context of missing signs for infection were identified as rather difficult. These results might be mirroring the activities of the ASP at the Dr. von Hauner Children's Hospital since 2015 where an initial focus was laid on de-escalation of broad-spectrum antibiotic therapies in the light of microbiological results. [16] Similarly, participants in Bowes et al. survey considered discontinuation of antimicrobials in cases with no documented infection as most difficult. However, half of the trainees were in accordance with our findings and considered the empiric use of narrow-spectrum antibiotics versus broad-spectrum antibiotics as most difficult to achieve. [7] Various studies, such as Levy et al. [3], concluded that the failure of discontinuation and de-escalation of therapy was the most common reason for inappropriate antibiotic use. This is consistent across many publications and reflects the dilemma any clinician is facing when having to decide on continuation or discontinuation of antibiotics. There is an obvious need for better diagnostics and biomarkers to help in the decision making process towards de-escalation or discontinuation of antibiotic therapies. [13] Unfortunately, the highest number of missing entries was observed in this section of the questionnaire, again reflecting the dilemma illustrated above. Nevertheless, these discontinuation and de-escalation aspects need to be a clear focus of future educational activities of local ASPs.

Given that at the Dr. von Hauner Children's Hospital an ASP was initiated in 2015, the results of this survey were rather sobering. [16] There was no significant difference in the knowledge of ASP measures between the Dr. von Hauner Children's Hospital and other participating institutions.

This may be due to the rather short period of time that the ASP at the Dr. von Hauner Children's Hospital had been in place. Furthermore, the ASP was not focused on teaching individual doctors but rather consisted of infectious diseases consultation service, development and provision of internal guidelines on empiric antibiotic therapy and clinical ward rounds of an antibiotic stewardship team formulating recommendations to assist paediatric colleagues on ward. [16] While this approach improves the quality of patient care, it may not have the same effect on the knowledge of antimicrobial stewardship principles amongst paediatricians. Thus, the implementation of a structured teaching program would be a key measure to address this aspect of improving knowledge on the individual doctor's level.

Our results indicate that the knowledge of hospital-based paediatricians of the south-eastern region of Germany regarding the different areas of ASP is only moderate and clearly needs further improvement to optimise the clinical care in paediatric hospitals.

In contrast to the Anglo-Saxon medical system where infectious diseases training and ASP aspects have long been integrated into the medical training curricula, starting at the medical student's level only a very small minority (5/111, 5.6%) of all clinicians participating in our study had previous training in the respective areas. Specialist training in this area is an established component of medical postgraduate training in other European countries, such as the UK, or in the USA. Unfortunately, Germany does not yet have an equivalent focus on training in infectious disease, antibiotic stewardship and hospital hygiene. Thus, the results of this study strongly suggest this area as a critical focus for university and post graduate training in paediatrics. Only sustainable educational efforts in ASP and infectious diseases will be able to tackle this evident lack of knowledge in almost all areas covered by our survey and to help us improve patient care in the years and decades to come. That ASP training improves the knowledge was shown in a recent publication analysing knowledge scores of Canadian residents. A significantly higher knowledge score (71.6%) was found four months after implementation of an ASP module compared to before the pre-implementation period (58.2%). [9]

Our study has several obvious limitations, some of which are due to the simple fact that this was only a survey study. Since we analysed data of German paediatric physicians in and around Munich (south-eastern region of Germany) and the response rate was quite low (42%) our results are not fully generalizable and may not be representative for other paediatric hospitals. We could not perform a non-responder analysis and therefore we do not know to what extent the non-responders differ from the participating clinicians.

Conclusion

Assessment of current practice and knowledge about antimicrobial stewardship principles and aspects of hospital hygiene/infection control amongst 111 hospital-based paediatricians in and around Munich (south-eastern region of Germany) has yielded a rather unsatisfactory result. None of the areas assessed scored above 75% when evaluating the accuracy of answers to topic-related questions; three areas rather revealed an overall score of <60%. Thus, we have identified four important target areas for future educational interventions that should be given a more prominent role to play in both pre- as well as postgraduate medical training.

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Author contributions UvB and JH were responsible for the conception of the study and writing of the study protocol. AW was responsible for data collection and both LK and JB were responsible for data analysis. LK and UvB wrote the first draft of the manuscript and were responsible for overseeing data quality control and data analysis. All authors have contributed significantly to the drafting and revising of the manuscript. All authors have approved the manuscript as submitted, and they are willing to take responsibility for its content.

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Declarations

Conflict of interests On behalf of all authors, the corresponding author states that there is no conflict of interest. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no relevant financial or non-financial interests to disclose.

Ethics approval This survey sought responses from healthcare professionals and did not contain any patient identifiable data; ethics approval was therefore not required, as confirmed by the Health Regulation, Authority research decision tool. [17]

Consent to participate Not applicable.

Consent to publish Not applicable.

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Appendix 1: Supplement paper I

Supplementary Table 1: Ethic committees of the participating sites		
Country	**Partner**	**Ethics**
United Kingdom	Imperial College of Science, Technology and Medicine, Section of Paediatrics, Wright-Fleming Institute Chief investigator/PERFORM coordinator: Michael Levin Principal Investigators: Jethro Herberg Clinical recruitment at Brighton and Sussex University Hospitals Principal Investigator: Katy Fidler The University of Liverpool Institute of Infection and Global Health, Department of Clinical Infection, Microbiology and Immunology Principal Investigator: Enitan D Carrol London School of Hygiene and Tropical Medicine, Department of Clinical Research Faculty of Tropical and Infectious Disease Principal Investigator: Shunmay Yeung John Radcliffe Hospital Oxford Principal Investigators: Andrew J. Pollard, Rama Kandasamy, Stéphane Paulus University of Newcastle Upon Tyne: Newcastle upon Tyne Hospitals NHS Foundation Trust, Great North Children's Hospital Paediatric Immunology, Infectious Diseases & Allergy Principal Investigator: Marieke Emonts	United Kingdom (Ethics Committee, ID: 16/LO/1684, IRAS application no. 209035, Confidentiality advisory group reference: 16/CAG/0136).
Spain	Servizo Galego de Saude SERGAS Hospital Clínico Universitario de Santiago de Compostela (CHUS)- Spain Genetics, Vaccines, Infections and Pediatrics Research group (GENVIP) Principal Investigator: Federico Martinón-Torres	Spain (Comité Autonómico de Ética de la Investigación de Galicia, ID: 2016/331)
Latvia	Rīgas Stradiņa universitāte (RSU), Department of Pediatrics Children clinical university hospital Principal Investigator: Dace Zavadska	Latvia (Centrala medicinas etikas komiteja, ID: 14.07.201 6. No. Il 16-07 - 14)
The Netherlands	ERASMUS universitair medisch centrum Rotterdam, Sophia's Childrens Hospital Principal Investigators: Henriëtte A. Moll, Clementien L Vermont Academic Medical Hospital & Sanquin Research Institute, Amsterdam Principal Investigator: Taco Kuijpers Radboud University Medical Center (RUMC) Stichting Katholieke Universiteit Principal Investigators: Ronald de Groot, Michiel van der Flier, Marien I. de Jonge	The Netherlands (Commissie Mensgebonden onderzoek, ID: NL58103.091.16)
Switzerland	University Bern, Children Hospital Department of Pediatrics Principal Investigators: Philipp Agyeman, Luregn J Schlapbach	Kantonale Ethikkommission Bern, KEK-Gesuchs-Nr.: 029/11
Greece	National and Kapodistrian University of Athens (NKUA), Second Department of Paediatrics, Principal investigator: Professor Maria Tsolia	Greece (Ethics committee, ID: 9683/18.07.2016)
Austria	Medical University of Graz, (MUG), Department of General Paediatrics Principal Investigator: Werner Zenz	Austria (Ethikkommission Medizinische Universitat Graz, ID: 28-518 ex 15/16)
Germany	Ludwig-Maximilian-University Munich (LMU), Division of Paediatric Infectious Diseases Principal Investigator: Ulrich von Both	Germany (Ethikkommission der LMU München, ID: 699-16)
Slovenia	University Medical Centre Ljubljana, Department of Infectious Diseases Principal Investigator: Marko Pokorn	Slovenia (Republic of Slovenia National Medical Ethics Committee, ID: 0120-483/2016- 3)

Supplementary Table 2: List of the syndrome classification on the PERFORM CRF

Syndrome classification	
LOWER RESPIRATORY TRACT INFECTION (LRTI)	Main syndromes
UPPER RESPIRATORY TRACT INFECTION / EAR, NOSE, THROAT (URTI/ENT)	
MUSKULOSKELETAL	
CENTRAL NERVOUS SYSTEM INFECTION	
GASTROINTESTINAL INFECTION / SURGICAL OR INTRA-ABDOMINAL INFECTION	
SOFT TISSUE INFECTION	
URINARY TRACT INFECTION	
PATHOGEN SYNDROME	
SEPSIS SYNDROME	
UNDIFFERENTIATED FEVER	
FEBRILE NEUTROPENIA	
OTHER INFECTIONS	

For the purposes of analysis a number of changes were made:
- GASTROINTESTINAL INFECTION / SURGICAL OR INTRA-ABDOMINAL INFECTION was split into GastrointestinaI (GI) and surgical/intra-abdominal infection (SURG/INTRA-ABDO)
- PATHOGEN SYNDROME was split into (Bacterial pathogen syndrome, Viral pathogen syndrome and Other pathogen syndrome)
- SEPSIS SYNDROME was re-named Sepsis syndrome/Endovascular infection (SEPSIS/ENDO) to avoid confusion with separate analysis of patients meeting 'Goldstein criteria'
- Febrile neutropenia and Neutropenic sepsis were separated into their own category: neutropenia
- Inflammatory syndrome was created

Supplementary Table 3: Empiric antibiotic classes and AWaRe classes prescribed in our dataset

Access	Cefadroxil, Cefalexin, Cefazolin, Amikacin, Gentamicin, Chloramphenicol, Trimethoprim, Trimethoprim Sulfamethoxazole (co-trimoxazole), Metronidazole, Clindamycin, Nitrofurantoin, Ampicillin/sulbactam, Co-amoxiclav (Augmentin, amoxicillin-clavulanate), Amoxicillin, Ampicillin, Benzlypenicillin (Pencillin G), Cloxacillin, Flucloxacillin, Phenoxymethylpenicillin (Penicillin V), Doxycycline
Watch	Cefaclor, Cefuroxime, Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone, Cefepime, Meropenem, Ciprofloxacin, Teicoplanin, Vancomycin, Azithromycin, Clarithromycin, Erythromycin, Piperacillin/tazobactam, Rifampicin, Tobramycin, Ofloxacin
Reserve	Linezolid

3 antibiotics were unclassified (Ethambutol, Isoniazid and Pyrazinamide)

Supplementary Table 4 Definition of antibiotic use

CONSISTENT antibiotic use	presumed viral/ non-infectious etiology + NO antibiotics presumed bacterial etiology + antibiotics
INCONSISTENT antibiotic use	presumed viral/ non-infectious + antibiotics presumed bacterial etiology + NO antibiotics
APPROPRIATE antibiotic use	final viral phenotype + NO antibiotics final bacterial phenotype + antibiotics *
INAPPROPRIATE antibiotic use	final viral phenotype + antibiotics final bacterial phenotype + NO antibiotics *

*unless certain diagnoses, defined in Supplementary Table 5

Supplementary Table 5: 231 patients with final bacterial phenotype in whom no empiric antibiotics are initiated in the first 48 hours (n)

Final syndrome classification	**Diagnoses within syndrome classification that were considered appropriate to withhold antibiotics for:**	**Total number (231)**	**Appro-priate (81)**	**Inappro-priate (120)**	**Unable to judge (29)**	**Condition warranting antibiotics, that had antibiotics in last 7 days (39)**
LRTI	Undefined LRTI, Bronchitis, Bronchiolitis, Pulmonary TB	37	3	34	0	6
URTI	Otitis Media, Tonsillitis/Pharyngitis, URTI non specific, Stomatitis	31	25	0	6*	
MSK	-	4	0	4	0	2
CNS	-	3	0	3	0	0
GI	Gastroenteritis with any bacterial pathogen other than *C·difficile*	46	46	0	0	
SURG/INTRA-ABDO	Mesenteric adenitis	19	0	1	19**	0
SOFT TISSUE	Soft tissue abscess	18	2	15	1***	12
UTI	-	31	0	31	0	13
VPS	Any	0				
BPS	-	1	0	1	0	0
SEPSIS/ENDO	-	6	0	6	0	0
UNDIFF FEVER	Febrile convulsion, Fever without source	0				
OTHER	Conjunctivitis	0	0	0	0	
LRTI + URTI	Included the above diagnoses for individual syndrome classifications	2	1	1	0	0
LRTI + SEPSIS/ENDO		2	0	2	0	0
LRTI + OTHER		2	1	1	0	0
LRTI + VPS		1	0	1	0	0
URTI + GI		4	4	0	0	0
URTI + SURG/INTRA-ABDO		1	0	0	1**	
URTI + CNS + OTHER		1	0	1	0	0
URTI+SOFT TISSUE		1	0	1	0	1
URTI+VPS		1	1	0	0	
URTI+BPS		1	0	1	0	0
URTI+SOFT TISSUE + UNDIFF FEVER		1	0	1	0	0
MSK+GI		1	0	1	0	0
MSK+SEPSIS/ENDO		4	0	4	0	1
CNS+BPS		1	0	1	0	0
CNS+SEPSIS/ENDO		3	0	3	0	0
GI + SEPSIS/ENDO		1	0	1	0	0
SURG/INTRA-ABDO+VPS		1	0	0	1**	
SOFT TISSUE + SEPSIS/ENDO		1	0	1	0	1
SOFT TISSUE+VPS		2	0	1	1***	1
UTI+SEPSIS/ENDO		2	0	2	0	0
SEPSIS/ENDO+UNDIFF FEVER+OTHER		1	0	1	0	1
LRTI+URTI+SEPSIS/ENDO		1	0	1	0	1

*Timing of onset of bacterial infection unclear in relation to presentation to hospital
**Varying policy by country re: antibiotic use in children with appendicitis
***Received topical antibiotics
LRTI: lower respiratory tract infection
URTI: upper respiratory tract infection, ear nose throat
CNS: central nervous system infection
MSK: musculoskeletal infection
GI: gastrointestinal infection
BPS: bacterial pathogen syndrome
VPS: viral pathogen syndrome
SEPSIS/ENDO: sepsis syndrome/endovascular infection
SURG/INTRA-ABDO: surgical/intra-abdominal infection
UTI: urinary tract infection
SOFT TISSUE: soft tissue infection
UNDIFF FEVER: undifferentiated Fever

Supplementary Table 6: Spectrum of initial and final diagnoses in ‘bacterial’ and ‘viral’ group (n; %)

	initial diagnosis						final diagnosis					
	‘bacterial’ group		‘viral’ group		total		‘bacterial’ group		‘viral’ group		total	
LRTI	289	18·7	132	22·7	421	19·8	357	23·0	144	24·8	501	23·5
URTI/EAR NOSE THROAT	283	18·3	116	20·0	399	18·7	292	18·9	130	22·4	425	20·0
SOFT TISSUE INFECTION	298	19·2	16	2·8	314	14·7	321	20·7	9	1·5	330	15·5
UNDIFFERENTIATED FEVER	180	11·6	72	12·4	252	11·8	25	1·6	28	4·8	53	2·5
URINARY TRACT INFECTION	202	13·0	4	0·7	206	9·7	272	17·6	1	0·2	274	12·9
VIRAL PATHOGEN SYNDROME	59	3·8	146	25·1	205	9·6	44	2·8	224	38·6	268	12·6
GASTROINTESTINAL INFECTION	121	7·8	57	9·8	178	8·4	95	6·1	58	10·0	153	7·2
SEPSIS/ENDO	116	7·5	42	7·2	158	7·4	189	12·2	2	0·3	191	9·0
SURG/INTRA-ABDO	119	7·7	6	1·0	125	5·9	116	7·5	1	0·2	117	5·5
CNS INFECTION	38	2·5	44	7·6	82	3·8	44	2·8	57	9·8	101	4·7
MUSCULOSKELETAL INFECTION	60	3·9	13	2·2	73	3·4	53	3·4	15	2·6	68	3·2
OTHER	37	2·4	18	3·1	55	2·6	25	1·6	14	2·4	39	1·8
BACTERIAL PATHOGEN SYNDROME	35	2·3	2	0·3	37	1·7	47	3·0	0	0	47	2·2
FEBRILE NEUTROPENIA	14	0·9	10	1·7	24	1·1	6	0·4	2	0·3	8	0·4
INFLAMMATORY SYNDROME	9	0·6	7	1·2	16	0·8	0	0	0	0	0	0
OTHER PATHOGEN SYNDROME	4	0·3	4	0·7	8	0·4	3	0·2	0	0	3	0·1
UNKNOWN	5	0·3	1	0·2	6	0·3	0	0	0	0	0	0

LRTI: lower respiratory tract infection

URTI: upper respiratory tract infection

CNS: central nervous system

SURG/INTRA-ABDO: surgical/intra-abdominal infection

SEPSIS/ENDO: sepsis syndrome/endovascular infection

Supplementary Table 7: Total antibiotic use by country in 'bacterial' group (n; %)

Country (n)	Austria 148		Germany 21		Greece 149		Latvia 194		Slovenia 127		Spain 152		Switzerland 79		Netherlands 186		United Kingdom 493		Total 1549	
Received systemic antibiotics	121	81·8	15	71·4	140	94·0	178	91·8	112	88·2	54	35·5	67	84·8	169	90·9	462	93.7	1318	85.1
ALL % BELOW IS OUT OF THOSE WHO RECEIVED SYSTEMIC ANTIBIOTICS																				
IV/IM* antibiotics	103	85.1	10	66.7	127	90.7	153	86	104	92.9	39	72.2	56	83.6	137	81.1	428	92.6	1157	87.8
First Generation Cephalosporins	4	3.3	0	0	0	0	3	1.7	3	2.7	0	0	0	0	2	1.2	40	8.7	52	3.9
Second Generation Cephalosporins	32	26.4	6	40	23	16.4	67	37.6	4	3.6	4	7.4	26	38.8	22	13	24	5.2	208	15.8
Third Generation Cephalosporins	11	9.1	3	20	53	37.9	39	21.9	8	7.1	25	46.3	8	11.9	58	34.3	251	54.3	456	34.6
Fourth Generation Cephalosporins	3	2.5	0	0	5	3.6	0	0	0	0	0	0	3	4.5	0	0	0	0	11	0.8
Aminoglycoside	0	0	0	0	22	15.7	8	4.5	16	14.3	2	3.7	3	4.5	25	14.8	57	12.3	133	10.1
Carbapenems	4	3.3	3	20	4	2.9	0	0	1	0.9	4	7.4	0	0	2	1.2	16	3.5	34	2.6
DHFR inhibitors	2	1.7	0	0	0	0	2	1.1	9	8	0	0	1	1.5	6	3.6	3	0.6	23	1.7
Fluoroquinolones	1	0.8	0	0	1	0.7	3	1.7	0	0	0	0	2	3	8	4.7	18	3.9	33	2.5
Glycopeptides	5	4.1	0	0	9	6.4	5	2.8	1	0.9	3	5.6	1	1.5	13	7.7	37	8	74	5.6
Imidazoles	1	0.8	1	6.7	2	1.4	20	11.2	0	0	0	0	14	20.9	12	7.1	57	12.3	107	8.1
Lincosamides	10	8.3	0	0	23	16.4	17	9.6	3	2.7	4	7.4	6	9	10	5.9	46	10	119	9
Macrolides	7	5.8	0	0	6	4.3	26	14.6	2	1.8	5	9.3	2	3	6	3.6	52	11.3	106	8
Nitrofurantoin	0	0	1	6.7	0	0	0	0	0	0	0	0	0	0	1	0.6	1	0.2	3	0.2
Oxazolidinones	1	0.8	0	0	1	0.7	0	0	0	0	0	0	1	1.5	0	0	2	0.4	5	0.4
Penicillin/Beta-lactamase Inhibitor Combinations	67	55.4	5	33.3	9	6.4	5	2.8	38	33.9	10	18.5	19	28.4	63	37.3	194	42	410	31.1
Penicillins	12	9.9	2	13.3	46	32.9	51	28.7	52	46.4	16	29.6	7	10.4	47	27.8	121	26.2	354	26.9
Rifamycins	1	0.8	0	0	1	0.7	0	0	0	0	0	0	0	0	0	0	1	0.2	3	0.2
Tetracyclines	0	0	0	0	0	0	1	0.6	0	0	0	0	1	1.5	0	0	0	0	2	0.2
Other**	1	0.8	0	0	0	0	10	5.6	1	0.9	0	0	1	1.5	2	1.2	2	0.4	17	1.3
Unknown	0	0	0	0	0	0	0	0	1	0.9	0	0	0	0	0	0	0	0	1	0.1
1 Access	77	63.6	7	46.7	70	50	79	44.4	64	57.1	30	55.6	42	62.7	78	46.2	255	55.2	702	53.3
2 Access	9	7.4	0	0	14	10	14	7.9	38	33.9	1	1.9	4	6	30	17.8	85	18.4	195	14.8
3 Access	0	0	0	0	1	0.7	0	0	0	0	0	0	0	0	8	4.7	13	2.8	22	1.7
4 Access	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0.6	3	0.2
At least one Access	86	71.1	7	46.7	85	60.7	93	52.2	102	91.1	31	57.4	46	68.7	116	68.6	356	77.1	922	70
1 Watch	43	35.5	8	53.3	66	47.1	101	56.7	11	9.8	24	44.4	38	56.7	86	50.9	227	49.1	604	45.8
2 Watch	10	8.3	2	13.3	16	11.4	20	11.2	3	2.7	7	13	3	4.5	11	6.5	82	17.7	154	11.7
3 Watch	3	2.5	1	6.7	3	2.1	1	0.6	0	0	0	0	0	0	3	1.8	24	5.2	35	2.7
4 Watch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8	1.7	8	0.6
5 Watch	0	0	0	0	0	0	0	0	0	0	1	1.9	0	0	0	0	2	0.4	3	0.2
At least one Watch	56	46.3	11	73.3	85	60.7	122	68.5	14	12.5	32	59.3	41	61.2	100	59.2	343	74.2	804	61
1 Reserve	1	0.8	0	0	1	0.7	0	0	0	0	0	0	1	1.5	0	0	2	0.4	3	0.2
1 Unclassified**	0	0	0	0	1	0.7	0	0	0	0	0	0	0	0	0	0	0	0	1	0.1

*IV/IM: intravenous/intramuscular

**Ethambutol, Isoniazid and Pyrazinamide

Supplementary Table 8: Total antibiotic use by country in 'viral' group (n; %)

Country (n)	Austria 46		Germany 10		Greece 107		Latvia 46		Slovenia 24		Spain 64		Switzerland 8		Netherlands 55		United Kingdom 221		Total 581	
Received systemic antibiotics	12	26.1	5	50	23	21.5	16	34.9	1	4.2	4	6.3	3	37.5	36	65.5	169	76.5	269	46.3
ALL % BELOW IS OUT OF THOSE WHO RECEIVED SYSTEMIC ANTIBIOTICS																				
IV/IM* antibiotics	10	83.3	3	60	20	87	9	56.3	1	100	2	50	3	100	31	86.1	155	91.7	234	87
First Generation Cephalosporins	1	8.3	0	0	0	0	0	0	0	0	1	25	0	0	0	0	2	1.2	4	1.5
Second Generation Cephalosporins	3	25	1	20	3	13	1	6.3	0	0	0	0	2	66.7	5	13.9	2	1.2	17	6.3
Third Generation Cephalosporins	3	25	0	0	9	39.1	6	37.5	0	0	2	50	1	33.3	21	58.3	121	71.6	163	60.6
Fourth Generation Cephalosporins	3	25	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1.1
Aminoglycoside	0	0	0	0	2	8.7	1	6.3	0	0	0	0	0	0	5	13.9	13	7.7	21	7.8
Carbapenems	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.8	3	1.8	4	1.5
DHFR inhibitors	0	0	1	20	0	0	1	6.3	0	0	0	0	0	0	1	2.8	3	1.8	6	2.2
Fluoroquinolones	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.8	4	2.4	5	1.9
Glycopeptides	0	0	0	0	0	0	0	0	0	0	1	25	0	0	2	5.6	7	4.1	10	3.7
Imidazoles	1	8.3	0	0	0	0	0	0	0	0	0	0	0	0	1	2.8	2	1.2	4	1.5
Lincosamides	1	8.3	0	0	1	4.3	0	0	0	0	0	0	0	0	1	2.8	2	1.2	5	1.9
Macrolides	0	0	1	20	1	4.3	2	12.5	0	0	0	0	0	0	2	5.6	43	25.4	49	18.2
Nitrofurantoin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oxazolidinones	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Penicillin/Beta-lactamase Inhibitor Combinations	2	16.7	1	20	1	4.3	1	6.3	1	100	0	0	0	0	7	19.4	53	31.4	66	24.5
Penicillins	0	0	2	40	9	39.1	7	43.8	0	0	2	50	0	0	10	27.8	33	19.5	63	23.4
Rifamycins	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Tetracyclines	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Other**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.8	1	0.6	2	0.7
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1 Access	5	41.7	4	80	11	47.8	10	62.5	1	100	1	25	0	0	18	50	71	42	120	44.6
2 Access	0	0	0	0	1	4.3	0	0	0	0	1	25	0	0	3	8.3	7	4.1	12	4.5
6 Access	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.6	1	0.4
At least one Access	5	41.7	4	80	12	52.2	10	62.5	1	100	2	50	0	0	21	58.3	80	47.3	135	50.2
1 Watch	9	75	2	40	13	56.5	9	56.3	0	0	0	0	3	100	18	50	93	55	147	54.6
2 Watch	0	0	0	0	0	0	0	0	0	0	2	50	0	0	6	16.7	43	25.4	51	19
3 Watch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	8.3	14	5.2
4 Watch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.8	0	0	1	0.4
5 Watch	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0.6	1	0.4
At least one Watch	9	75	2	40	13	56.5	9	56.3	0	0	2	50	3	100	25	69.4	153	90.5	216	80.3
1 Reserve	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*IV/IM: intravenous/intramuscular

**Ethambutol, Isoniazid and Pyrazinamide

Supplementary Table 9: Age-based comparison of patients with an initial viral or non-infectious working diagnosis (n=251) receiving / not receiving empiric antibiotics

	< 5 years	≥5 years	p-value*
initial presumed viral/ non-infectious etiology receiving antibiotics (96/252; 38.0%)	71 (45.5%)	24 (25.3%)	<0.01
initial presumed viral/ non-infectious etiology not receiving antibiotics (156/252; 62.0%)	85 (54.5%)	71 (74.7%)	

*chi-square

Supplementary Table 10: The most common bacterial pathogens in the 'bacterial' group and the most common viral pathogens in the 'viral' group

Bacterial pathogens	number of patients	% of bacterial patients	**Viral pathogens**	number of patients	% of viral patients
Escherichia coli (E. Coli)	213	23.5	Influenza A/B	135	20.5
Streptococcus Group A (*Strep. pyogenes*)	125	13.8	Rhinovirus/Enterovirus	127	19.3
Staphylococcus aureus	121	13.3	Respiratory syncytial virus (RSV)	85	12.9
Streptococcus pneumoniae (pneumococcus)	55	6.1	Adenovirus	76	11.6
Pseudomonas aeruginosa	33	3.6	Epstein-Barr Virus (EBV)	45	6.8
Neisseria meningitidis (meningococcus)	30	3.3	Measles	30	4.6
Mycoplasma pneumoniae	29	3.2	Rotavirus	27	4.1
Campylobacter spp.	28	3.1	Metapneumovirus	16	2.4
Salmonella spp.	26	2.9	Herpes simplex type 1	14	2.1
Staphylococcus - coagulase negative (includes *capitis*, *epidermidis*, *haemolyticus*, *hominis*)	22	2.4	Varicella zoster virus (VZV)	14	2.1
Enterobacter cloacae	14	1.5	Coronavirus	12	1.8
*Haemophilus influenzae**	14	1.5	Norovirus	12	1.8
Enterococcus faecalis	13	1.4	Parainfluenza type 3	10	1.5
Borrelia burdorferi	11	1.2	Parvovirus	8	1.2
Klebsiella pneumoniae	11	1.2	Tick borne encephalitis virus	7	1.1
Streptococcus viridans group (includes *mitis*, *mutans*, *salivarius*, *sanguinis*)	11	1.2	Hepatitis A virus	6	0.9
Bacteroides fragilis	8	0.9	Bocavirus	5	0.8
Kingella kingae	7	0.8	Cytomegalovirus (CMV)	5	0.8
Mycobacterium tuberculosis	7	0.8	Human herpesvirus 6 (HHV6)	4	0.6
Streptococcus - alpha haemolytic, no further information	7	0.8	Herpes simplex*	3	0.5
Bordetella pertussis	6	0.7	Parainfluenza type 4	3	0.5
Streptococcus Group F (includes *anginosus*, *milleri*)	6	0.7	Dengue virus	2	0.3
Clostridium difficile	5	0.6	human herpes type 7	2	0.3
Klebsiella oxytoca	5	0.6	Parainfluenza type 2	2	0.3
Proteus spp.	5	0.6	Picornavirus	2	0.3
Streptococcus Group B (includes *Strep. agalactae*)	5	0.6	Parechovirus	2	0.3
Citrobacter freudii	4	0.4	HIV 1	1	0.2
Enterococcus spp.	4	0.4	Parainfluenza type 1	1	0.2
Fusobacterium spp.	4	0.4	Parainfluenza type 5	1	0.2
Anaerobes*	4	0.4			
Mycoplasma spp.	4	0.4			
Shigella spp.	4	0.4			
Yersinia enterocolitica	4	0.4			
Acinetobacter spp.	3	0.3			
Clostridium perfringens	3	0.3			
Enterococcus faecium	3	0.3			
Coliforms	3	0.3			
Streptococcus Group C	3	0.3			

Unidentified bacteria	3	0.3			
Aerococcus urinae	2	0.2			
Citrobacter spp.	2	0.2			
Corynebacteria spp.	2	0.2			
Klebsiella spp.	2	0.2			
Moraxella catarrhalis	2	0.2			
Neisseria spp.	2	0.2			
Prevotella spp.	2	0.2			
Serratia marcescens	2	0.2			
Stenotrophomonas maltophilia	2	0.2			
Streptococcus anginosus	2	0.2			
Acinetobacter calcoaceticus-baumannii complex	1	0.1			
Actinobaculum spp.	1	0.1			
Actinomyces odontolyticus	1	0.1			
Bacteroides thetaiotaomicron	1	0.1			
bartonella henselae	1	0.1			
Borellia spp.	1	0.1			
Chlamydia pneumoniae	1	0.1			
Chlamydia spp.	1	0.1			
Eikenella corrodens	1	0.1			
Erlichia spp.	1	0.1			
Francisella tularensis	1	0.1			
Gordonia spp.	1	0.1			
Granulicatella elegans	1	0.1			
Haemophilus parainfluenzae	1	0.1			
Hafnia alvei	1	0.1			
Lactobacillus rhamnosus	1	0.1			
Micrococcus spp.	1	0.1			
Morganella morganii	1	0.1			
Mycobacterium spp.	1	0.1			
Pseudomonas spp.	1	0.1			
Roseomonas mucosa	1	0.1			
Staphylococcus warneri	1	0.1			
streptococcus constellatus	1	0.1			
Streptococcus Group G (includes *Strep.dysgalactiae*)	1	0.1			

* unspecified

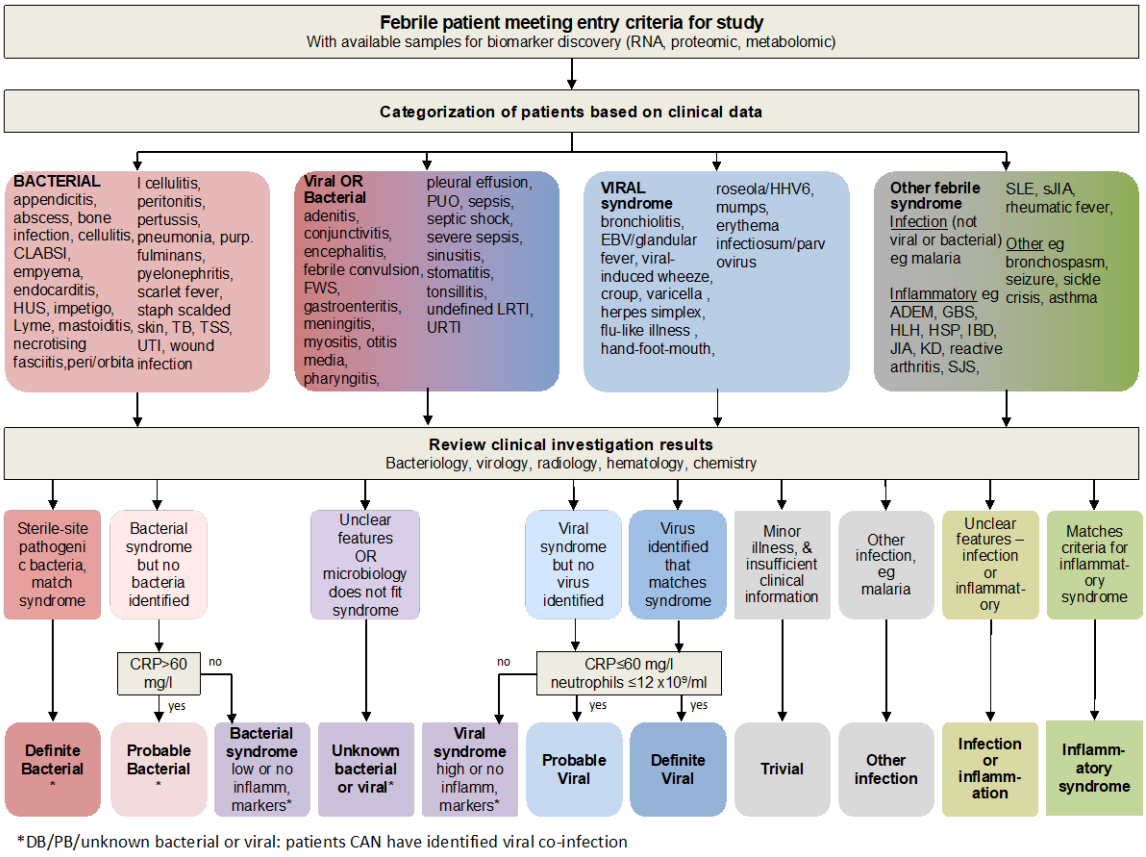
Supplementary Table 11: systemic antibiotic use in three most common bacterial pathogens (Escherichia coli, Streptococcus pyogenes (GAS) and Staphylococcus aureus in the 'bacterial' group– where single pathogen isolated (n; %)

	patients with only *Escherichia coli* (n=188)		patients with only GAS (n=115)		patients with only *Staphylococcus aureus* (n=104)	
First Generation Cephalosporins	14	7.4	4	3.5	4	3.8
Second Generation Cephalosporins	36	19.1	21	18.3	9	8.7
Third Generation Cephalosporins	64	34.0	35	30.4	35	33.7
Fourth Generation Cephalosporins	2	1.1	0	0.0	1	1.0
Aminoglycoside	44	23.4	6	5.2	9	8.7
Carbapenems	10	5.3	3	2.6	1	1.0
DHFR inhibitors	11	5.9	0	0.0	1	1.0
Fluoroquinolones	8	4.3	2	1.7	3	2.9
Glycopeptides	3	1.6	4	3.5	11	10.6
Imidazoles	7	3.7	3	2.6	7	6.7
Lincosamides	1	0.5	20	17.4	31	29.8
Macrolides	5	2.7	8	7.0	3	2.9
Nitrofurantoin	0	0.0	0	0.0	0	0.0
Oxazolidinones	0	0.0	1	0.9	1	1.0
Penicillin/Beta-lactamase Inhibitor Combinations	42	22.3	24	20.9	27	26.0
Penicillins	20	10.6	44	38.3	41	39.4
Rifamycins	0	0.0	0	0.0	0	0.0
Tetracyclines	0	0.0	0	0.0	0	0.0
Other	1	0.5	0	0.0	6	5.8
Unknown	0	0.0	0	0.0	1	1.0
At least one Access	97	51.6	83	72.2	86	82.7
At least one Watch	120	63.3	55	47.8	51	49.0

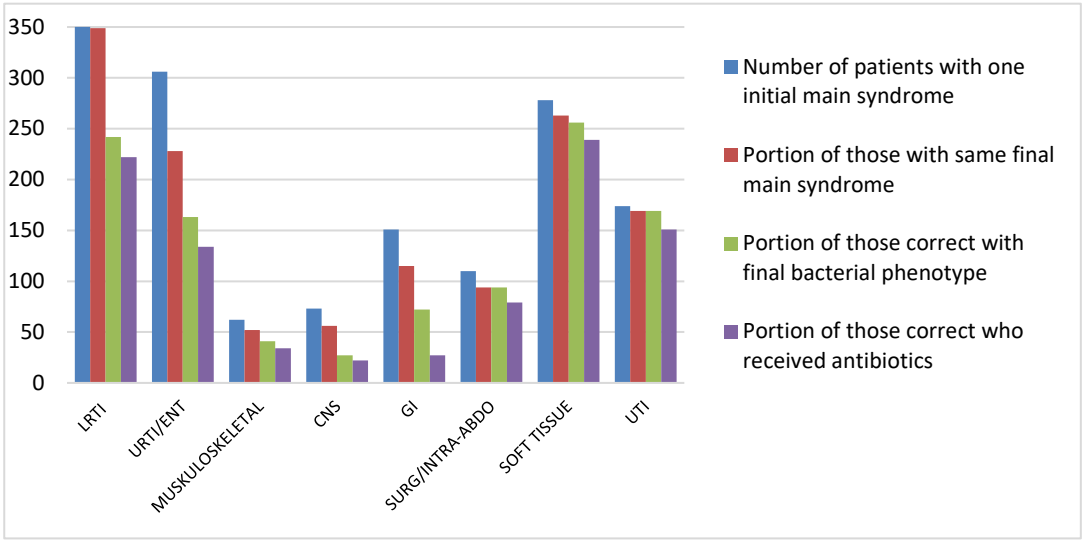
Supplementary Table 12: antibiotic use in three most common viral pathogens (Influenza A and B, Rhino-/Enterovirus and respiratory syncytial virus (RSV)) (n; %)

	patients with only Influenza A and B (n=119)		patients with only Rhino-/Enterovirus (n=89)		patients with only RSV (n=66)	
Received systemic antibiotics	42	35.3	57	64.0	44	66.7
ALL % BELOW IS OUT OF THOSE WHO RECEIVED SYSTEMIC ANTIBIOTICS						
IV/IM antibiotics*	38	90.5	52	91.2	35	83.3
First Generation Cephalosporins	0	0.0	0	0.0	0	0.0
Second Generation Cephalosporins	3	7.1	1	1.8	1	2.4
Third Generation Cephalosporins	24	57.1	42	73.7	24	57.1
Fourth Generation Cephalosporins	0	0.0	1	1.8	0	0.0
Aminoglycoside	3	7.1	6	10.5	4	9.5
Carbapenems	1	2.4	0	0.0	1	2.4
DHFR inhibitors	2	4.8	0	0.0	1	2.4
Fluoroquinolones	3	7.1	1	1.8	0	0.0
Glycopeptides	1	2.4	3	5.3	2	4.8
Imidazoles	2	4.8	1	1.8	0	0.0
Lincosamides	1	2.4	0	0.0	0	0.0
Macrolides	8	19.0	5	8.8	15	35.7
Nitrofurantoin	0	0.0	0	0.0	0	0.0
Oxazolidinones	0	0.0	0	0.0	0	0.0
Penicillin/Beta-lactamase Inhibitor Combinations	17	40.5	7	12.3	12	28.6
Penicillins	4	9.5	20	35.1	11	26.2
Rifamycins	0	0.0	0	0.0	0	0.0
Tetracyclines	0	0.0	0	0.0	0	0.0
Other	0	0.0	0	0.0	1	2.4
Unknown	0	0.0	0	0.0	0	0.0
At least one Access	25	59.5	28	49.1	21	50.0
At least one Watch	31	73.8	48	84.2	34	81.0

*IV/IM: intravenous/intramuscular



Supplementary Figure 1: PERFORM phenotyping algorithm



Supplementary Figure 2: Consistency of initial diagnosis with final diagnosis and antibiotic prescription
LRTI: lower respiratory tract infection
URTI/ENT: upper respiratory tract infection, ear nose throat
MUSCULOSKELETAL: musculoskeletal infection
CNS: central nervous system infection
GI: gastrointestinal infection
SURG/INTRA-ABDO: surgical /intra-abdominal infection
SOFT TISSUE: soft tissue infection
UTI: urinary tract infection

Appendix 2: Supplement paper III

Supplementary Information 1

Questionnaire „Antibiotic Stewardship“

Bold print indicates correct answers

Basic aspects and education of participant

1 Where do you work as a paediatrician?
a Dr. von Hauner Children’s Hospital
b children hospital Dritter Orden
c Children’s Hospital Schwabing
d Hospital Starnberg
e Hospital Traunstein

2 What is your professional role?
a consultant
b middle grade doctor
c junior doctor
d medical student

3 How often do you prescribe antibiotics per day?
a 0-1 x/day
b 2-4 x/ day
c >4 x/ day

4 Have you treated patients with infection caused by antibiotic-resistant pathogens (e.g. ESBL, MRSA, VRE, 3MRGN or 4 MRGN) within the last year?
a Yes
b No
c I don’t know

5 Did you ever participate in any advanced training course in infectious diseases, microbiology or infection control / hospital epidemiology?
a Yes
b No

Handling of antibiotics and bacterial resistance

6 What of the following options, do you think, contributes most to antimicrobial resistance?
6.1a **low dosing**
b high dosing

6.2a **long duration of therapy**
b short duration of therapy (< 7 days)

6.3a prescription of ampicillin
b **prescription of piperacillin**

6.4a **prescription of azithromycin**

b prescription of clarithromycin

7 What is the current prevalence of macrolide resistance in the group A streptococcus (GAS) population according to national / regional data?

a < 1 %
b 1 - 5 %
c 5 - 10 %
d **> 10 %**
e I don't know

8 What is the prevalence of penicillin resistance in the *Streptococcus pneumoniae* population according to national / regional data?

a **< 1 %**
b 1 - 5 %
c 5 - 10 %
d > 10 %
e I don't know

9 What, do you think, is the community carrier rate of ESBL?

a 0 %
b 0-5%
c **5-10%**
d 10-20%
e >20%

10 Which of the following antibiotics, do you think, contributes most to an increased risk for *Clostridium difficile* infection?

a **Cefotaxime**
b Penicillin G
c Azithromycin
d Vancomycin
e I don't know

Microbial aspects of infectious disease

11 Smaller minimal inhibition concentration (MIC) values are…

a **better**
b worse
c I don't know

12 *Haemophilus influenzae* is…

a gram-positive
b **gram-negative**
c I don't know

13 After what incubation time can a result be considered "negative" in the vast majority of cases (>90%) if there is no growth in the blood culture?

a After 1 day
b **2-3 days**
c 4-5 days
d After 1 week
e After 10 days

14 You get a call from the bacteriology lab informing you that *P. aeruginosa* **3MRGN** has grown in your patient's blood culture. Which of the following antibiotic classes does not play a role in this resistance assessment and nomenclature?

a 3rd and 4th Generation Cephalosporine
b Carbapeneme
c **Aminoglykoside**
d Fluorchinolone
e Penicillins with extended activity spectrum e.g. piperacillin

Hospital hygiene

15 What is the most important infection control measure?

a consequent screening of all patients for colonization
b consequent Isolation measures
c **strict adherence to hand hygiene**
d consequent disinfection of patient surroundings
e I don't know

16 An inpatient with evidence of MRSA in a nasopharyngeal swab should be isolated according to which isolation scheme?

a No isolation, basic hospital hygiene measures
b Basic measures + contact isolation
c **Basic measures + droplet isolation**
d Basic measures + aerogenic isolation

17 An inpatient with pulmonary tuberculosis should be isolated according to which isolation scheme?

a No isolation, basic hospital hygiene measures
b Basic measures + contact isolation
c Basic measures + droplet isolation
d **Basic measures + aerogenic isolation**

Antibiotic stewardship and treatment standards

18 Which antibiotics require therapeutic drug monitoring (TDM)?
(More than 1 answer is possible)

a Meropenem
b **Vancomycin**
c **Amikacin**
d Linezolid
e I don't know

19 You are asked to prescribe perioperative antibiotic prophylaxis for a healthy teenager who is going to have an elective neurosurgical procedure on the spine and spinal cord. Which antibiotic would you prescribe in this case?

a Carbapenem (e.g. Meropenem) IV
b **1st or 2nd generation Cephalosporine (e.g. Cefazolin or Cefuroxime) IV**
c Piperacillin/tazobactam IV
d Vancomycin IV
e No prophylaxis

20 If you recommend perioperative prophylaxis, for how long?

a **Preoperative single dose**

b max. continuation of antibiotic administration until 24 h post-op

c Continuation of antibiotic administration > 24 h post-op

d I don't know

21 A 3-year-old child with all STIKO-recommended vaccinations gets admitted. The child presents with cough, fever and chest pain for about 4 days. The temperature is 38.5 °C, respiratory rate 30/min, heart rate 90/min and oxygen saturation in air is 98%. The chest X-ray shows an infiltrate of moderate size in the right middle lobe. Which antibiotic with the lowest possible activity spectrum would be indicated in this case?

a A makrolid (e.g. clarithromycin) PO

b 2nd generation Cephalosporin (e.g. cefuroxime) IV

c **Ampicillin or penicillin IV**

d Cefuroxime and clindamycin IV

e I don't know

22 The child mentioned above shows clinical improvement (fever resolution after 48 hours and good appetite) and blood cultures are negative. What would you prescribe to continue oral therapy on an outpatient basis?

a Cefuroxime PO

b **Amoxicillin PO**

c Amoxicillin and clavulanic acid PO

d Clarithromycin PO

e I don't know

23 What is the recommended therapy duration in this case of above mentioned uncomplicated bacterial pneumonia in childhood?

a 5 days

b **7 days**

c 10 days

d 14 days

e I don't know

24 You are asked to prescribe antibiotic therapy for a previously healthy 11-year-old girl who is now on her way to surgery with signs of clinical appendicitis. Which of the following antibiotics would be your first choice?

a Cefotaxime und metronidazol IV

b Cefotaxime monotherapy IV

c Gentamicin and clindamycin IV

d Gentamicin and metronidazol IV

e **Amoxicillin and clavulanic acid IV**

f I don't know

Structure of work environment

25 When deciding on antibiotic therapy for a patient, who or what do you turn to first if you have questions?

a junior doctor colleagues on ward

b Consultant

c Pharmacists/hospital pharmacists

d Guidelines (e.g. Hauner AntibiotiCard, Sanford Guide, Red Book, Blue Book, DGPI manual)

e Other source, please specify:_____

26 When prescribing antibiotics, which type of bacterial resistance data do you consider most relevant?

a local resistance data
b national resistance data
c global resistance reports
d Other, please specify:_____
e None

27 Which of the following do you consider the **most difficult** measure to implement to improve antibiotic therapy *in your work environment*?

a Stop antibiotic therapy in absence of documented infection
b Reduction of therapy duration
c Rapid conversion from IV to PO antibiotic therapy
d De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram
e Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics

28 Which of the following do you consider the **easiest** measure to implement to improve antibiotic therapy *in your work environment*?

a Stop antibiotic therapy in absence of documented infection
b Reduction of therapy duration
c Rapid conversion from IV to PO antibiotic therapy
d De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram
e Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics

Supplementary Information 2

Bold print indicates correct answers

Overview of all questions and answers of the 111 participating paediatricians				
	Missing			
	n	%	n	%
Basic aspects and education of participant				
1. Where do you work as a paediatrician?	0	0		
Dr. von Hauner Children's Hospital			66	59.5
Other			45	40.5
2. What is your professional role?	0	0		
junior doctor			47	
middle grade doctor			34	
consultant			30	
3. How often do you prescribe antibiotics per day?	0	0		
0-1 x/day			65	58.6
2-4 x/ day			39	35.1
>4 x/ day			7	6.3
4. Have you treated patients with infection caused by antibiotic-resistant pathogens (e.g. ESBL, MRSA, VRE, 3MRGN or 4 MRGN) within the last year?	0	0		
Yes			96	86.5
No			12	10.8
I don't know			3	2.7
5. Did you ever participate in any advanced training course in infectious diseases, microbiology or infection control / hospital epidemiology?	0	0		
Yes			5	4.5
No			106	95.5
Handling of antibiotics and bacterial resistance				
6. What of the following options, do you think, contributes most to antimicrobial resistance?				
6.1	4	3.6		
low dosing (correct)			101	91.0
high dosing			6	5.4
6.2	4	3.6		
long duration of therapy (correct)			77	69.4
short duration of therapy (< 7 days)			30	27.0
6.3	7	6.3		
prescription of piperacillin (correct)			62	55.9
prescription of ampicillin			42	37.8
6.4	7	6.3		
prescription of azithromycin (correct)			63	56.8
prescription of clarithromycin			41	36.9

7. What is the current prevalence of macrolide resistance in the group A streptococcus (GAS) population according to national / regional data?	1	0.9		
correct **(> 10 %)**			29	26.1
incorrect			81	73.0
8. What is the prevalence of penicillin resistance in the *Streptococcus pneumoniae* population according to national / regional data?	0	0		
correct (**< 1 %**)			9	8.1
incorrect			102	91.9
9. What, do you think, is the community carrier rate of ESBL?	0	0		
correct (**5-10%)**			58	52.3
incorrect			53	47.7
10. Which of the following antibiotics, do you think, contributes most to an increased risk for *Clostridium difficile* infection?	0	0		
correct **(Cefotaxime)**			57	51.4
incorrect			54	48.6
Microbial aspects of infectious disease				
11. Smaller minimal inhibition concentration (MIC) values are…	0	0		
correct **(better)**			92	82.9
incorrect			19	17.1
12. *Haemophilus influenzae* is…	0	0		
correct **(gram-negative)**			83	74.8
incorrect			28	25.2
13. After what incubation time can a result be considered "negative" in the vast majority of cases (>90%) if there is no growth in the blood culture?	1	0.9		
correct **(2-3 days)**			43	38.7
incorrect			67	60.4
14. You get a call from the bacteriology lab informing you that *P. aeruginosa* **3MRGN** has grown in your patient's blood culture. Which of the following antibiotic classes does not play a role in this resistance assessment and nomenclature?	2	1.8		
correct **(Aminoglykoside)**			40	36.0
Incorrect			69	62.2
Hospital hygiene				
15. What is the most important infection control measure?	3	2.7		
correct (**strict adherence to hand hygiene**)			104	93.7
incorrect			4	3.6
16. An inpatient with evidence of MRSA in a nasopharyngeal swab should be isolated according to which isolation scheme?	2	1.8		
correct (**Basic measures + droplet isolation**)			43	38.7
incorrect			66	59.5
17. An inpatient with pulmonary tuberculosis should be isolated according to which isolation scheme?	3	2.7		
correct **(Basic measures + aerogenic isolation)**			82	72.9
incorrect			26	23.4

Antibiotic stewardship and treatment standards				
18. Which antibiotics require therapeutic drug monitoring (TDM)? *(More than 1 answer is possible)*	4	3.6		
correct (**Vancomycin and amikacin**)			37	33.3
incorrect			70	63.1
19. You are asked to prescribe perioperative antibiotic prophylaxis for a healthy teenager who is going to have an elective neurosurgical procedure on the spine and spinal cord. Which antibiotic would you prescribe in this case?	4	3.6		
correct **(1st or 2nd generation Cephalosporine (e.g. Cefazolin or Cefuroxime) IV)**			62	55.9
incorrect			45	40.5
20. If you recommend perioperative prophylaxis (n=106), for how long?	5	4.5		
correct **(Preoperative single dose)**			36	38.2
incorrect			64	61.8
21. A 3-year-old child with all STIKO-recommended vaccinations gets admitted. The child presents with cough, fever and chest pain for about 4 days. The temperature is 38.5 °C, respiratory rate 30/min, heart rate 90/min and oxygen saturation in air is 98%. The chest X-ray shows an infiltrate of moderate size in the right middle lobe. Which antibiotic with the lowest possible activity spectrum would be indicated in this case?	7	6.3		
correct **(Ampicillin or penicillin IV)**			91	82.0
incorrect			13	11.7
22. The child mentioned above shows clinical improvement (fever resolution after 48 hours and good appetite) and blood cultures are negative. What would you prescribe to continue oral therapy on an outpatient basis?	6	5.4		
correct **(Amoxicillin PO)**			80	72.1
incorrect			5	22.5
23. What is the recommended therapy duration in this case of above mentioned uncomplicated bacterial pneumonia in childhood?	7	6.3		
correct **(7 days)**			77	69.4
incorrect			27	24.3
24. You are asked to prescribe antibiotic therapy for a previously healthy 11-year-old girl who is now on her way to surgery with signs of clinical appendicitis. Which of the following antibiotics would be your first choice?	10	9		
correct (**Amoxicillin and clavulanic acid IV**)			18	16.2
incorrect			83	74.8
Structure of work environment				
25. When deciding on antibiotic therapy for a patient, who or what do you turn to first if you have questions?	16	14.4		
junior doctor colleagues on ward or Consultant			23	20.7
Guidelines (e.g. Hauner AntibiotiKarte, Sanford Guide, Red Book, Blue Book, DGPI manual)			70	63.1
other source			2	1.8

26. When prescribing antibiotics, which type of bacterial resistance data do you consider most relevant?	11	9.9		
none			2	1.8
local resistance data			74	66.7
national resistance data			19	17.1
global resistance reports			4	3.6
other			1	0.9
27. Which of the following do you consider the **most difficult** measure to implement to improve antibiotic therapy *in your work environment*?	17	15.3		
De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram			8	7.2
Rapid conversion from IV to PO antibiotic therapy			7	6.3
Reduction of therapy duration			15	13.5
Stop antibiotic therapy in absence of documented infection			23	20.7
Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics			41	36.9
28. Which of the following do you consider the **easiest** measure to implement to improve antibiotic therapy *in your work environment*?	15	13.5		
De-escalation from broad-spectrum empirical therapy to targeted treatment following receipt of pathogen differentiation and antibiogram			48	43.2
Rapid conversion from IV to P antibiotic therapy			21	18.9
Reduction of therapy duration			8	7.2
Stop antibiotic therapy in absence of documented infection			18	16.2
Increased use of narrow-spectrum antibiotics instead of broad-spectrum antibiotics			1	0.9

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