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Viridans group streptococci (VGS) – antimicrobial resistance in children with sepsis. A scoping review.

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Summary/abstract

Background: The Viridans group streptococci (VGS) is a common commensal bacterium and is historically counted as a contaminant when cultured in blood. Over the past years there seem to be an increase in the incidence of invasive VGS infections, especially in children and neutropenic patients. The knowledge about VGS as source of severe infections in children is limited. The purpose of this scoping review is to summarize data from current available literature on the antimicrobial resistance (AMR) profiles of VGS as cause of sepsis in neonates and children after the neonatal period.

Method: A systematic literature search was performed in MEDLINE and Embase, and matching studies published between 1st of January 2015 – 31st of December 2023 were considered. We aimed to identify articles reporting VGS as cause of sepsis in children and neonates. After full text-screening all included studies also reporting AMR patterns for VGS were included in this sub-study. Two reviewers independently screened abstracts and full text articles. The study is registered in an international prospective register for systematic reviews (PROSPERO ID: CRD42022282804) but was later changed to a scoping review.

Results: In total, 18 articles were included after screening 9219 abstracts and 1287 potentially relevant full text articles. In total, 194/776 (25%) isolates were resistant to penicillin, 92/276 (33.3%) isolates were resistant to ampicillin/amoxicillin, 14/29 (48.3%) isolates were resistant to gentamicin, 164/748 (21.9%) isolates were resistant to 3rd generation cephalosporines, 275/393 (70.0%) to erythromycin, 10/442 (2.3%) isolates were resistant to vancomycin and 57/565 (10.1%) were resistant to fluoroquinolones.

Conclusion: In conclusion, the data showing antibiotic susceptibility patterns for VGS-bacteremia in children are still limited, and findings from existing literature are diverse. To examine this matter closer, we suggest more research on AMR in VGS.

Abbreviations

VGS	Viridans Group Streptococci
BSI	Blood stream infection
S.	Streptococcus
AMR	Antimicrobial resistance
MALDI-TOF MS	Matrix-assisted laser desorption–ionization time of flight mass spectrometry
mef	macrolide efflux
PBP	penicillin-binding protein
SCCM	Society of Critical Care Medicine
EOS	Early-onset sepsis
LOS	Late-onset sepsis
GBS	Group B streptococcus
JBI	Joanna Briggs Institute
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRIMSA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
MeSH	Medical Subject Headings
IC	Immunocompromised
TMS	trimethoprim-sulfamethoxazole
NORM	Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway

1. Background

1.1 Viridans group streptococci

Viridans Group Streptococci (VGS) is a heterogenous group of Gram-positive catalase-negative streptococci. The group is alfa hemolytic, producing a green discoloration on blood agar. Hence, the bacteria group is also known as green streptococci; “viridans” means green in latin. Note that some of the species, i.e. *Streptococcus anginosus*, are beta-hemolytic and leave a clear zone around the bacterial growth on blood agar, not a green color. VGS comprises 26 different species, arranged in five phenotypic groups: *S. mutans*, *S. salivarius*, *S. anginosus*, *S. sanguinus* and *S. mitis* (1) (table 1).

VGS are a large component in oral flora (2) and a common commensal bacterium of the upper respiratory tract and the gastrointestinal tract. They are also commonly found in the female genital tract and as part of the skin flora (3-5). VGS are often counted as contaminants in blood culture (6-8). In an immunocompetent adult host VGS are usually not considered pathogenic, except for being able to cause infectious endocarditis (4). Under immunocompromised conditions on the other hand, they can cause severe infections by invading sterile body sites. Including infections such as blood stream infection (BSI) and sepsis. It is mainly in newborns and immunocompromised patients these bacteria cause disease (9-12). According to a study from 2019 there has been an increase in the incidence of VGS infections, particularly among neutropenic patients (9).

1.1.1 Species identification

Throughout history, clinicians and microbiologists have used various methods to distinguish clinically isolated bacteria from each other. These methods have evolved over time, each contributing to our understanding of microbial diversity and aiding in diagnosis and treatment. One of the earliest methods involved observing bacteria under a microscope, differentiating bacteria by size, shape and staining characteristics (13). Later, the development and introduction of methods like culturing medias, biochemical tests such as catalase test and serological techniques to detect antigens and antibodies associated with certain bacterial species, as well as antimicrobial susceptibility testing, has been applied.

As stated by Facklam, VGS display positive leucine aminopeptidase activity, are pyrrolidonyl-aryl-amidase negative and do not grow in 6.5% NaCl. Additionally, nearly all

species demonstrate a negative growth response on bile esculin agar. They are similar to pneumococci in many ways and distinction between them can be difficult (1). In fact, *Streptococcus mitis* and *Streptococcus oralis* share more than 99% sequence homology in the 16S rRNA gene with *Streptococcus pneumoniae* (14, 15). However, in contrast to pneumococci the VGS are optochin resistant and not bile soluble (1).

Over the past years matrix-assisted laser desorption–ionization time of flight mass spectrometry (MALDI-TOF MS) has emerged as an alternative for clinical microbiology laboratories to identify various bacteria, mycobacteria and fungi (16). MALDI-TOF MS has been shown to be accurate and rapid, which is both clinically and financially beneficial (16-18).

MALDI-TOF MS works by analyzing the mass-to-charge ratio (m/z) of ions produced from molecules of a microbial sample and compare it to the mass spectra of known microorganisms stored in a database. This requires a microbial sample, typically obtained by growing a microorganism, in our case a bacterial isolate, on a preferred medium and then isolating a small portion of the grown colony for analysis. After adding a matrix with energy-absorbent properties, the sample is irradiated with a laser beam. This causes molecules from the sample to desorb from the surface and get ionized with av positive charge. The ions are then accelerated by an electric field into what is called a flight tube. When reaching the detector at the end of the flight tube, the arrival time is recorded. The time it takes for each ion to travel through the flight tube is directly proportional to its m/z-ratio; lower m/z-ratios take longer to reach the detector. This data is used to construct a mass spectrum which shows the distribution of ion masses in the sample. The mass spectrum is then compared to information stored in a database, containing the mass spectra of known microorganisms. The software then matches the observed spectrum with those in the database to determine the identity of the microorganism (19).

Even though the MALDI-TOF MS technology is one of the most efficient methods used to identify bacteria in clinical practice today, there are still reports of difficulties distinguishing VGS from *S. pneumoniae* (18, 20).

1.1.2 Virulence factors

Virulence factors are essential for a bacterium to survive and cause disease in its host. VGS have several common virulence factors. Adhesins are prerequisite in bacterial attachment to host tissues. It enables adherence and colonization of the host and is therefore an important initial step of infection. VGS expresses adhesin molecules to a great extent and can adhere to human tissue as well as catheters (21, 22). Through the mechanism of adhesion some VGS subspecies, such as *S. mutans*, are capable of forming bacterial biofilm. This property gives them the ability to alter environmental conditions and make them more resistant to antibiotics (23).

S. mitis can produce IgA1 protease, proteolytic enzymes that cleaves peptide bonds in human IgA antibodies, and in that way avoid the immune system (22). Additionally, studies show that some VGS can avoid the host immune system, especially the complement system (24, 25). For example, gluncan binding protein B found in *S. mitis*, is shown to increase complement evasion by facilitating bacterial adherence to sucrose-derived glucan which contributes to biofilm formation (26). Another example is endopeptidase O and C3-degrading protease inhabited by *S. sanguinus.* These proteins compromises C3b deposition and contribute to recruitment of down-regulators of C4b-binding protein and factor H, impairing bacterial recognition (27). The presence of certain kinds of capsules in *S. mitis* have shown increased bacterial survival in human blood models (28).

1.2 Antimicrobial resistance (AMR)

Antimicrobial resistance is considered one of the most important global health threats causing 1,27 million deaths globally in 2019 (29).

1.2.1 AMR mechanisms

Bacteria exhibit three primary mechanisms for antimicrobial resistance: alteration of bacterial drug target site, inhibition or reduction of drug uptake and enzymatic inactivation of the drug (30). Alterations in drug target sites prevent the drugs from effectively entering the bacterial cytoplasm, as observed in methicillin-resistant *Staphylococcus aureus* (31). Inhibition of drug uptake is often due to modifications in porins, which are proteins located in the bacterial cell wall. Mutations in the *ompF* gene for instance, lead to the loss of porins in *Escherichia coli,*

making the bacteria resistant to beta-lactam antibiotics (32, 33). Drug uptake can also be inhibited by activation of drug efflux pumps. Once the drug has entered the bacterial cytoplasm, efflux pumps eject antimicrobial agents out of the bacterial cell, exemplified by *Mycobacterium tuberculosis*, a bacteria exhibiting resistance to multiple drugs (34). These mechanisms lead to lower drug concentration inside the bacterial cytoplasm. Beta-lactamases, enzymes produced by resistant *E. coli*, hydrolyze beta-lactam antibiotics and thereby inactivates beta-lactam antimicrobial drugs (35).

1.2.2 AMR mechanisms in VGS

Antibacterial prophylaxis is a crucial part of reducing the risk of BSI in high-risk patients. There are concerns regarding increased rates of VGS BSI despite prophylactic measures, as well as VGS isolates exhibiting diminished susceptibility to antibiotics (36). VGS exhibit various resistance mechanisms, with macrolide resistance being predominantly attributed to three major mechanisms.

First, the majority (~80%) of macrolide-resistant isolates from elderly patients were due to membrane-bound efflux proteins (37). This mechanism, known as the M-phenotype, is encoded by macrolide efflux (mef) genes (36). These efflux proteins actively transport the antibiotic out of the bacterial cytoplasm, resulting in low intracellular antibiotic concentrations. Iannidou et al. suggest that this is the predominant resistance mechanism in many streptococcal species (38). However, another study reported that the M-phenotype was found exclusively in *S. sanguinis* (36). Second, a smaller proportion (~20%) of erythromycin-resistant isolates exhibited the macrolide-lincosamide-streptogramin B phenotype (37, 39). This phenotype is encoded by the erythromycin ribosome methylation gene (39), which modifies the drug target site for erythromycin, conferring resistance not only to macrolides, but also to lincosamides and streptogramin b antibiotics. Lastly, ribosomal mutations in key antibiotic binding sites have been proposed as another AMR mechanism against macrolides in VGS (40).

Penicillin resistance in *S. mitis* has been attributed to mutations in penicillin-binding protein (PBP) genes, as well as the formation of mosaic PBPs (40). These altered PBPs exhibit reduced affinity for beta-lactam antibiotics (41), thereby diminishing the efficacy of penicillin

in treatment. Whether this mutation causes as much resistance to other beta-lactams as to penicillin, is divided in the literature (42).

Tetracycline resistance is predominantly mediated by *tet* genes (43). Studies indicates a higher prevalence of tetracycline resistance in VGS-isolates that also harbor macrolide resistant genes (41, 44). The *tet*(M) gene commonly found in tetracycline-resistant isolates, is frequently associated with the *mef*(E) gene, which confer resistance to erythromycin (45).

Some studies in adults suggest that VGS exhibit low pathogenicity in healthy individuals. However, as VGS are part of the oral (2) and gastrointestinal flora (3, 4), they are exposed to antibiotics during infection treatment, facilitating the development of resistance. Thus, VGS becomes reservoir of AMR genes. Some studies propose VGS as a pool of resistance mechanisms, because VGS can transfer AMR genes to cohabitating bacteria (39). As previously mentioned, *S. oralis* shares 99% of its genome with *S. pneumoniae* (14, 15). Therefore, transfer of resistance determinants from VGS to pathogenic streptococci, such as *S. pneumoniae*, is plausible (38, 41).

1.3 Sepsis in children

According to the World Health Organization, neonatal sepsis accounts for 15% of neonatal annual deaths globally, and in high-income countries preterm infants are particularly at risk. The burden of neonatal sepsis is highest in South-Asia and Sub-Saharan Africa, but data is sparse from low- and middle-income countries (46). In adults, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine defined sepsis in 2016 as life-threatening organ dysfunction caused by a dysregulated host response to infection (47). For children, SCCM published the Phoenix sepsis criteria for sepsis and septic shock in children in 2024. It relies on organ dysfunction of respiratory, cardiovascular, coagulation and/or the neurological system and is intended to be globally applicable. With a score of 2 or more a child with suspected infection fills the sepsis criteria. If it is sepsis with one or more cardiovascular point, meaning that the patient is in need of vasoactive medication, has lactate over 5 mmol/L or low mean arterial pressure (indexed by age), it is categorized as septic shock (48). These criteria do not apply to preterm neonates and

newborns who are hospitalized directly after birth, and unfortunately there is still no consensus definition of preterm neonatal sepsis, which take organ failure into account.

1.3.1 Neonatal sepsis and VGS as causative pathogen

Neonatal sepsis is commonly divided into two groups: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS is defined as sepsis occurring the first 72 hours of life. LOS occurs after 72 hours of life but within 28 days of life. LOS is mostly seen among preterm neonates (49). According to Norwegian guidelines, diagnostic criteria for neonatal sepsis is growth of pathogens in blood culture, or blood and cerebrospinal fluid culture, together with clinical signs of systemic infection. Without growth of pathogen in blood culture, four criteria must be fulfilled: clinical signs of infection, C-reactive protein (CRP) > 30 mg/L, antibiotic treatment for at least 5 days or death from clinical sepsis within 5 days since onset of symptoms and elimination of other possible conditions (49).

The immune system of the infant is poorly developed compared to adults and infants are therefore more susceptible to infections. However, administering antibiotics too liberal to newborns may also have downside effects. Studies suggest that antibiotic treatment disturbs the normal gut microbiota development and may lead to loss of “colonization resistance”, which in turn can give bloom of opportunistic pathogens in the infant's gut (50, 51). Infants treated with antibiotics are also at risk of being colonized with AMR-organisms (52). At the same time, antibiotic treatment is crucial in treatment of severe infectious conditions, such as neonatal sepsis.

Most studies on neonatal sepsis report group B streptococci (GBS), *E. coli* (53-55) and *S. aureus* (53) as the most common causative pathogens. While these studies do not report any cases of VGS, other studies report VGS as a frequent cause for neonatal sepsis (56, 57). One study found that three of five cases of culture positive sepsis were caused by VGS (58). Another study showed that VGS was the second most common pathogen after GBS, causing 24% of 99 cases of sepsis (57).

Early antibacterial treatment is crucial for survival of sepsis. Conflicting results regarding VGS prevalence raise concerns about whether our empiric antibiotic treatment is targeting the appropriate pathogens.

1.3.2 Sepsis after the neonatal period and VGS as causative pathogen

In 2017, there were approximately 20.3 million sepsis cases in children under 5 years of age, 4.9 million in the age group 5-19, and 23.7 million in adults 20 years and older, leading to more than 11 million deaths that year. 2,9 million of these deaths were in children younger than 5 years and 454 000 were in those between 5-19 years, reflecting that the risk and mortality of sepsis is higher in the earliest years of life (59). The Phoenix sepsis criteria for sepsis and septic shock applies to children younger than 18 years (48). Former definitions of sepsis, such as the International Pediatric Sepsis Consensus Conference (IPSCC) criteria based on systemic inflammatory response syndrome (SIRS), should not be used in children due to its low specificity and sensitivity in diagnosing critical illness in this patient group (60, 61).

In children with cancer and children receiving stem cell transplantation, VGS seem to be an increasingly frequent cause of sepsis (62). In a study from 2018 VGS is reported as the most common cause of sepsis in children undergoing hematopoietic stem cell transplantation and in children with acute leukemia, followed by *E. coli* and coagulase negative staphylococci (CoNS) (63). In a study from 2020 VGS is reported as the most common cause of sepsis in children with febrile neutropenia (64), and are in several studies described as the main cause of sepsis and pneumonia in neutropenic patients (12).

Known predisposing factors for developing VGS sepsis in children includes severe neutropenia, oral mucositis, treatment with high dose cytarabine (a part of chemotherapy treatment in acute leukemias) and acute myeloid leukemia (AML) (10). In children with febrile neutropenia VGS-sepsis is associated with high-dose cytarabine and pneumonia (65). Presentation of symptoms in VGS-infection vary. Some patients present with modest symptoms such as fever or cough, while others present with what is called a VGS-shock syndrome (VSSS) (10, 11). VSSS is characterized as a toxic shock resembling syndrome with hypotension and acute respiratory distress syndrome. It is associated with admission at intensive care units and has high mortality, varying from 0-23% (11).

1.4 Systematic evidence synthesis

The field of evidence-based healthcare is continually growing. Together with the continual increase in the availability of primary research, the conduct of reviews has also increased and evolved (66). Early instances of knowledge synthesis in philosophy date back to the 12th century, while statistical methods for synthesizing literature were prevalent in astronomy during the 17th century. One of the first papers published with a meta-analytical method in health care literature was published in 1904 (67, 68). Since then, different forms of evidence, alongside various review objectives and questions, have spurred the development of novel approaches aimed at synthesizing evidence more effectively (66). By the 1970's, publications of systematic reviews began to appear more regularly in healthcare publications (69). In 2009, Grant and Booth outlined 14 types of reviews (70). By 2016, Tricco and her team had identified 25 different methods for synthesizing knowledge (66, 71), reflecting a significant expansion of approaches in the field of evidence synthesis.

1.4.1 Systematic review

A systematic review is a summary of evidence from all available publications that evaluate the research question posed. Publications must meet certain inclusion criteria, the quality of the study is evaluated and key findings presented (72). According to the Cochrane handbook, a systematic review "seek to collate evidence that fits pre-specified eligibility criteria in order to answer a specific research question. They aim to minimize bias by using explicit, systematic methods documented in advance with a protocol." (73).

The base of evidence in systematic reviews is withdrawn from a wide range of study populations. The total study population increases in size, and findings are therefore more generalizable than conclusions from single studies. The study form allows a systematic evaluation of study quality and a presentation of weaknesses and strengths. It responds to a narrow research question based on results from all relevant publications. Systematic reviews present a summary of evidence and is therefore a credible source of information for clinicians and guidelines and can be seen as a pillar in evidence-based healthcare (72, 74).

As in any research, the quality of systematic reviews varies. The value and utility of a systematic review depends on numerous factors. It should be possible to assess strengths and weaknesses of a review, and to do so one should be able to follow the researchers' steps. It is

also important that it is possible to tell what populations, interventions and outcomes were assessed, so the reader of the review can evaluate the relevance to their own practice (72).

To ensure transparency and avoid duplication of efforts, all systematic review protocols should be registered in PROSPERO; an international database for systematic review protocols in health care (75).

Munn et. al presents five broad indications for conducting a systematic review (69):

1. Uncover the international evidence.
2. Confirm current practice/address any variation/identify new practices.
3. Identify and inform areas for future research.
4. Identify and investigate conflicting results.
5. Produce statements to guide decision-making.

Even though the list above covers a broad range of applications for a systematic review, there are cases where they fall short of meeting the specific objectives or criteria. In such cases "structured and preliminary searching and scoping activity", as stated by Munn et al. (69), can be more fitting. There are several types of evidence synthesis methods available, such as scoping reviews, integrative reviews, mixed study reviews, realist reviews and others (69). In our master thesis we ended up doing a scoping review.

1.4.2 Scoping review

According to the Oxford English Dictionary "scoping" means "to invest or assess" or "to examine" (76). As the name suggests, scoping reviews are intended to provide an overview of the available literature and the volume of it, as well as where the focus within a field is placed.

Scoping reviews are similar to systematic reviews in their structured approach but serve different purposes and exhibit some important methodological differences. For example, both methods require a priori review protocol, but when conducting a systematic review this protocol, as previously mentioned, has to be registered in PROSPERO prior to the search and screening-process, whereas this is not compulsory for scoping reviews as per now. Additionally, all included articles in a systematic review must undergo risk of bias assessment, the findings from each study must undergo synthesis and a generation of

summary findings must be presented, which also is not required in a scoping review. Even though a risk of bias assessment isn't mandatory in a scoping review, it can in some cases be necessary, depending on the research question (69).

One significant difference between the two methods lies in the review question; scoping reviews typically have a broader aim compared to traditional systematic reviews, resulting in more expansive inclusion criteria. Munn et al. suggest the following bullet points as purposes for conducting a scoping review (69).

- To identify the types of available evidence in a given field.
- To clarify key concepts/definitions in the literature.
- To examine how research is conducted on a certain topic or field.
- To identify key characteristics or factors related to a concept.
- As a precursor to a systematic review.
- To identify and analyze knowledge gaps.

Where a systematic review is intended to investigate research clearly defined questions with harder end point such as the efficacy of a medication, a scoping review is better for investigating different characteristics and concepts presented in the literature (69, 77).

These purposes have also been cited by the Joanna Briggs institute (JBI) Manual for Evidence Synthesis. JBI is an international organization dedicated to evidence-based healthcare, working with various entities worldwide, collectively known as the JBI Collaboration. Their work is focused on improving global health outcomes through generation and dissemination of evidence-based knowledge. Their Manual of Evidence Synthesis is a manual guide meant to support authors in the process of conducting systematic and scoping reviews (66).

Even though they have distinctions from systematic reviews, scoping reviews should not be confused with “traditional literature reviews”. The quality of traditional literature/narrative reviews is more reliant on the experience and knowledge held by the authors. This reliance can introduce bias and reduce objectiveness, as narrative reviews may not provide an impartial or comprehensive summary of the available literature (69).

1.4.3 PRISMA

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 is an evidence-based selection of items made to increase transparency and reproducibility of systematic reviews and meta-analyses. The guideline was first formulated in 2009 and is later updated several times, last in 2021. The PRISMA statement includes a checklist with key steps that the researcher should follow during the process of conducting a systematic review (78, 79). It is also completed by several PRISMA extensions, who each offer direction on how to report different types of evidence synthesis, including a checklist for scoping reviews, called "PRISMA Analyses extension for Scoping Reviews" (PRISMA-ScR) (80).

The checklist for systematic reviews includes seven sections with 27 different items, some which have sub-items, making a total of 42 checklist items. The seven sections address the title, abstract, introduction, methods, results and discussion of a systematic report. As a prospective view of the checklist increases the chance of including all items in the process, it is recommended to introduce PRISMA early in the process of conducting a systematic review (79). The checklist for scoping reviews should likewise be used from the beginning, but includes fewer items; in total 22, where 20 of them are essential, and two are optional. The items left out of the PRISMA-ScR are summary measures, risk of bias across studies, risk of bias across study results, additional analyses and additional analyses results. Because scoping reviews include studies with different study designs and don't implement risk of bias assessment in included studies, the item regarding risk of bias in individual studies is optional (77).

The PRISMA statement also includes a flow diagram documenting the flow of studies through the systematic review process. The diagram should present the number of studies identified, included and excluded, and reason for and where in the process it was excluded (after screening in abstract and titles, or after full text screening). It should also identify records excluded before screening, typically due to duplicates. The flow chart gives the reader a better insight into the selection process (78).

2. Aim

The knowledge about VGS as a source of severe infections in children is still limited. Moreover, if VGS is an emerging pathogen in sepsis in children, it is important to know the antibiotic susceptibility pattern of these bacteria.

This scoping review aims to collate and summarize data from current scientific literature on the AMR profiles of VGS that cause sepsis or other severe infections in neonates and children after the neonatal period.

3. Material and methods

Our master thesis is part of a more extensive scoping review where we also aim to investigate the prevalence of VGS as source of sepsis in neonates and children after the neonatal period.

We acknowledge occasional use of ChatGPT (81) for help in finding synonyms and formulation of sentences. E.g. under the headings *1.2 Antimicrobial resistance* and *1.4 Systematic evidence synthesis.* We would like to emphasize that sentences have been used as inspiration, not complete "copy-paste". We have also used it to find reference number (33) and during the drafting stage for our background information. All suggestions presented by ChatGPT have been double checked and compared to other sources, so no incorrect information should be presented.

In our master thesis we carried out a scoping review following the PRISMA and the JBI Review guideline with the following specific review questions, also registered in our PROSPERO-protocol:

What is the AMR profile of VGS from blood culture obtained 1) in the neonatal population and 2) in children after the neonatal period?

The question format in a systematic or scoping review that aims to determine the prevalence and/or incidence of a certain conditions are sometimes referred to as: Condition, Context and Population.

- **Condition:** We will be assessing studies that investigate and/or report prevalence of VGS and AMR profiles of VGS in children with severe VGS infections where blood culturing is part of the diagnostic work-up.
- **Context**: We will include all studies from 01.01.2015 to 01.01.2024, conducted in single hospitals, or as part of national or international multicenter studies. All studies must be peer-reviewed.
- **Population:** We will include studies focusing on children with sepsis, including neonates and children up to 18 years of age, both sexes, and any underlying condition. For studies with a mixed population (i.e., adults and children), inclusion will be based on whether the results for the mixed population are reported separately.

3.1 Inclusion criteria

- Children (neonates and/or children up to 18 years of age) must be part of the study population.
- Studies must report results where it is possible to estimate the prevalence of VGS as causative sepsis pathogens.
- Blood culture must be part of the diagnostic work-up and results must be presented.
- AMR profile must be reported.

3.2 Exclusion criteria

- Animal studies.
- Studies not including the complete etiological results of blood cultures.
- Studies including less than 10 positive blood cultures.
- Studies not including any prevalence/incidence data on VGS.
- Studies not including AMR profiles for VGS.
- Publication older than 2015.
- Descriptive, narrative, or systematic reviews.

3.3 Main outcome

AMR profile of VGS found in blood cultures of children with sepsis.

3.4 Search strategy

Together with a librarian with expertise in systematic reviews, we developed a search strategy and performed a literature search for studies in Embase and Medline.

The search conducted in Embase and Medline is developed to answer the research question raised by the previously mentioned scoping review regarding the prevalence of VGS in septic children. All full-text articles yielded in this study that also reported AMR patterns in VGS were included in our master's thesis.

Literature search results were cumulated in EndNote and uploaded to Covidence software, an internet-based software program that facilitates collaboration among reviewers. Citation abstracts and full-text articles were uploaded to Covidence, as well as the study eligibility criteria list. Based on the exclusion criteria, a list of reasons for exclusion was made. Each excluded abstract was tagged with a reason for exclusion. Throughout the beginning of the screening process, reasons for exclusions were added to the list to adapt to the study material.

Data was screened by two reviewers (Synnøve Holmebukt (S.H) and Oda Gundersen (O.G)). Potential eligible full-text articles were independently selected by S.H. and O.G. according to predetermined inclusion and exclusion criteria. Exclusion of articles would only occur if reviewers (S.H and O.G.) mutually agreed. Hildegunn Norbakken Granslo and Claus Klingenberg would have the decisive vote in case of disagreement.

Publications between 01.01.2015-01.01.2024 matching the Medline or Embase search were accumulated for screening.

3.5 The search and search words

The search words were chosen in several steps. First, we read through ten key articles studying sepsis in children or antibiotic resistance patterns. These were publications from 2003-2021. We searched the articles for keywords to see if we could find words appropriate for the search. Some of these keywords were included in our first search. Some of them were later removed and other words considered more important were added. We modified the search several times for it to include most of our key articles. For each word in the search, we

chose whether we wanted the word to appear exclusively in abstract, title or keywords (ab,ti,kw.), or in full text. We also used the term "multi-purpose" (.mp), searching several fields at once; title, original title, abstract, subject headings etc. Other words were terms from the Medical Subject Headings (MeSH), a vocabulary produced and controlled by the National Library of Medicine in America. Terms are organized hierarchically (82). These terms are used for indexing and cataloging and can be used to search for biomedical or health-related information in databases like Medline (82). We limited the search to include only studies on humans, English language, and publications from 2015 to present. The final search in Embase and Medline is presented in figure 1 and figure 2.

3.6 Study design

We originally planned this project as a systematic review, but after reconsidering the topic and the huge challenges of creating a specific search without obtaining too much "noise" of irrelevant literature, we decided that a scoping review was better suited to answer our research questions. We also felt that at least two of the six criteria suggested by Munn et al. as purposes for conducting a scoping review were appropriate for our study (69).

- To identify the types of available evidence in a given field.
- To identify and analyze knowledge gaps.

3.7 Data collection

We created a standardized form that we used to extract data from the included studies. All randomized control trials, clinical control trials, other randomized studies, and observational studies (case-control studies, retrospective cohort studies, prospective cohort studies, cross-sectional studies, before-after studies, case-series) meeting the inclusion criteria were considered. Systematic reviews and meta-analysis were excluded, but studied articles were considered for inclusion if they responded to our research questions. Descriptive or narrative reviews and case studies were excluded.

3.8 Data extraction

The extracted variables were:

- Title, first author, year of publication, country, journal and full reference details
- Study design
- Study population (age, sex, total number, number of participants within age groups)
- Number of newborns with EOS and EOS with VGS, and LOS and LOS with VGS.
- Selected population of newborns (mother with chorioamnionitis, necrotizing enterocolitis, EOS, LOS, no specified group)
- Selected population after newborn period (cancer/chemotherapy, endocarditis, transplantation patients, burn injuries, respiratory tract infections, osteoarticular infections, post-operative complications, sickle cell disease)
- Setting (single center, multicenter national or multicenter international)
- Number of total positive blood culture in the population
- Prevalence of different subspecies of VGS
- AMR profile (resistant or not) of the VGS to penicillin, ampicillin, gentamicin and cephalosporins, clindamycin, trimethoprim-sulfa, linezolid, vancomycin/teicoplanin, cefoxitin, amikacin, carbapenem, ciprofloxacin, levofloxacin, erythromycin.

3.9 Formal applications

The original review-protocol was registered in PROSPERO. Approval from the regional ethical committee was not required as no personal data was collected for this study.

4. Results

4.1 Study selection and description

Our search identified 11469 articles which were imported to Covidence software. The Prisma Flow figure depicts the selection process (figure 3). A total of 18 studies reported AMR profiles. One study was later excluded because VGS AMR profiles could not be quantified (83). Another study on VGS, which was excluded because it did not yield VGS prevalence, was brought back because it presented AMR profiles, leaving us with a total of 18 included studies.

4.2 Demographics

Study demographics is presented in table 2.

4.3 AMR Patterns

4.3.1 Newborn period

Adnan et al. (84) studied 84 newborns at Ayub Teaching Hospital in Pakistan from June to December in 2019. 42 neonates had EOS, and 42 had LOS. Only one VGS-isolate was found in blood culture among 84 positive cultures. VGS subspecies were not specified. The isolate was resistant to ampicillin/amoxicillin. It was also tested for antimicrobial resistance to clindamycin, vancomycin and ciprofloxacin, and found to be sensitive to these antibiotics.

Topcuoglu et al. (85) studied suspected EOS in 8229 patients admitted to the neonatal intensive care unit at the University of Health Sciences and the Children's Training and Research Hospital in Turkey from August 2013 to August 2020. A total of 101 blood cultures were positive, and 11 VGS isolates were identified. One isolate was resistant to combination therapy with ampicillin and gentamicin.

Zamarano et al. (86) included 122 neonates with suspected sepsis attending the Kilembe Mines Hospital in Uganda during a four-month period. 72 blood cultures were positive, of which 61 were EOS and 53 were LOS. One of the EOS cases was caused by VGS. This isolate was resistant to ampicillin, gentamicin, amoxicillin-clavulanic acid, ceftriaxone,

cefoxitin, and cotrimoxazole. It was sensitive to amikacin, linezolid, vancomycin, netilmicin, and cefotaxime.

Tetteh et al. (87) recruited 471 neonates with clinically suspected sepsis from a tertiary-level military hospital in Ghana during a four-year period, of which 139 neonates were culture-positive. 85 of these were LOS. One isolate showed growth of a multi-drug resistant *S. mitis*. This isolate was resistant to ampicillin, chloramphenicol, cotrimoxazole, gentamicin, oxacillin, penicillin, tetracycline, and vancomycin. It was susceptible to amoxicillin clavulanic acid, cefotaxime, ciprofloxacin, erythromycin and levofloxacin.

Worku et al. (88) conducted a study at a University Specialized hospital in Ethiopia during a two-year period. They included 250 neonates, of which 125 were culture-positive and 125 were culture-negative controls. Among the cases, 37 were LOS and 88 EOS. Eight isolates showed growth of VGS, making it the fourth most isolated bacteria. Three of the isolates were resistant to penicillin, two to amoxicillin, two to ceftriaxone, two to cefoxitin and one to vancomycin. Four of the VGS isolates were susceptible to penicillin, four to ceftriaxone and one to chloramphenicol. The authors do not specify how many isolates they tested per antibiotic.

Mangeni et al. (89) included 1025 neonates with “physician-diagnosed sepsis” from the general pediatric ward at a hospital in South Africa. Of these 166 had culture-confirmed sepsis. In total 200 “putative pathogens” were isolated. VGS were the most common pathogens with 46 positive isolates in blood culture. In addition, VGS showed growth in 7 CSF-cultures. Of the 53 VGS-isolates only 3 were susceptibility-tested, all of which were sensitive to penicillin. No other antimicrobial sensitivity-patterns were reported.

Abro et al. (90) included 332 neonates with clinical symptoms or “certain high risk” of sepsis from a neonatal unit in Pakistan during a six-month period. 200 were EOS and 132 were LOS. In total 93 were blood culture positive, with four of them being VGS. All VGS isolates showed resistance to gentamicin, amikacin and cefotaxime, while all were susceptible to ampicillin, vancomycin, meropenem, ceftriaxon and cefuroxim.

4.3.2 After newborn period

Banawas et al. (91) included both adults and children in their study, but VGS prevalence was reported separately. Samples were collected at the Department of Microbiology at King Fahd Medical City in Saudi Arabia from January to December 2020. Out of 282 positive blood cultures from children, 15 were positive for VGS. Two were *S. sanguinus*, one *S. anginosus* and one *S. mitis*. The rest were not specified VGS subspecies. Not specified VGS species was the only subgroup of VGS that was tested for AMR. A resistance profile was presented for adults and children together. In total, there were 30 non-specified VGS isolates from the whole study population. 11 isolates came from children (0-12 years old), 16 from adults (13-64 years old), and three from elderly patients (over 65 years old). Among VGS isolates, 16.66% (N=5) were resistant to cefotaxime, 16.66% (N=5) were resistant to cephalothin, 13.33% (N=4) were resistant to ceftolozane-tazobactam, 20% (N=6) were resistant to ampicillin, 16.66% (N=5) were resistant to penicillin and 3.3% (N=1) were resistant to vancomycin.

Abebe et al. (92) studied infants, children, and adults at the University of Gondar Comprehensive Specialized Hospital. There were 498 positive blood cultures collected between January 2012 and January 2018 among infants and children, and 22 isolates were VGS. In the age group 21->41 years there were 3 VGS isolates. VGS resistance against antimicrobial agents was presented for both children and adults together. 3 of 6 tested isolates were resistant to gentamicin, 3/9 were ceftriaxone resistant, 1/1 was trimethoprim-sulphamethoxazole (TMS) resistant, 2/18 were resistant to vancomycin, 5/8 were resistant to cefoxitin, 1/7 was resistant to ciprofloxacin, 8/11 was resistant to tetracycline, 1/2 was resistant to oxacillin and 6/14 was resistant to erythromycin.

Al-Samkari et al. (93) studied 44 children aged 0-20 years old with a congenital coagulation factor deficiency (hemophilia) diagnosis. The study was conducted between October 1995 and December 2017 at the Boston Children's Hospital in USA. Included patients needed to have a permanent central venous access. There were 56 positive blood cultures, one was positive for VGS. The isolate was tested for resistance to ceftriaxone, to which it was sensitive.

Alali et al. (64) studied 268 children with cancer and/or stem cell transplant. The study was conducted between March 2009 to December 2016, at the University of Chicago Medicine Comer Children's Hospitals. In total, 143 had positive blood culture, 34 of them were VGS. Out of 27 isolates, three were resistant to penicillin, two of 27 were resistant to ceftriaxone and three of three tested isolates were vancomycin resistant.

Haeusler et al. (94) studied 462 cancer patients under 18 years of age from eight tertiary pediatric cancer centers in Australia. In total, 149 blood cultures were positive, and 34 were VGS. No subgroup was specified. Two of 34 VGS isolates were resistant to penicillin.

Nielsen et al. (95) studied VGS sepsis in 70 children between 2003 and 2013 Samples were collected from a pediatric oncology/hematology unit at a pediatric hospital in the United Kingdom. The study does not report prevalence of VGS and was therefore excluded from the main study. However, it was brought back for the AMR sub study because it reports VGS antimicrobial resistance pattern. They initially identified 86 episodes of VGS BSI. Of these, 46 patients were included in the study, yielding 54 positive blood cultures. During the study period, four patients died. Among the 54 included VGS cases, three had *S. salvarius*, one had *S. sanguinus*, 35 grew *S. mitis*, 10 grew *S. oralis* and three plates grew both *S. oralis* and *S. mitis*. There were two non-speciated isolates. Seven patients with *S. mitis* and one patient with *S. oralis* isolated in blood culture developed VGS shock syndrome. Resistance to penicillin was tested in these isolates. Three *S. mitis* isolates were resistant to penicillin. One *S. mitis* had intermediate sensitivity, and three were sensitive to penicillin. The one *S. oralis* isolate was sensitive to penicillin.

Quintero et al. (96) studied 223 patients from 0-21 years of age with VGS bloodstream infection between January 2010 to December 2021. Participants were treated at the Nationwide Children's Hospital in USA and were candidates for receiving levofloxacin prophylaxis. 125 VGS isolates and 121 clinical sepsis episodes were identified in immunocompromised (IC) patients. They would have underlying malignancy and receive chemotherapy, severe aplastic anemia, severe congenital neutropenia or receive a hematopoietic cell transplant within two years post-transplant. Non-IC patients had 139 VGS isolates identified in 127 clinical sepsis episodes. 26 of the non-IC patients were neonates. In total, there were 264 positive VGS blood cultures, and 248 episodes of bloodstream infection.

41 isolates were resistant to penicillin (25/125 episodes in IC and 16/138 in non-IC), 30 to ampicillin (18/74 IC and 12/90 non-IC), 16 to clindamycin (8/116 IC, and 8/124 non-IC), 21 to ceftriaxone (12/123 IC, 9/133 non-IC), 18 to levofloxacin (16/96 IC, 2/102 non-IC) and 28 were resistant to cefepime (19/96 IC, 12/102 non-IC). Five participants died during the study period.

Sharma et al. (97) studied 845 patients from 0-23 years old with underlying malignancy at St. Jude, a pediatric hematology-oncology center from January 2012 to December 2016. The median age was 3.7. Among the patients, 43 had possible bloodstream infection, 52 blood cultures were positive, and three were positive for VGS. Isolates were tested only for ceftriaxone, and all isolates were resistant.

Wang et al. (98) had 14 107 patients between the age of 0-14 years old in their study on BSI in hospitalized children. Samples were collected from 162 hospitals in the Shandong province in China from 2015 to 2018. 4362 patients were neonates, and 5538 participants were between 29 days and one year old. 1561 patients were between three and five years old, and 4207 patients were more than one year old. 81189 isolates were identified from blood culture, and 352 of the isolates were VGS. VGS bloodstream infection was most frequently seen between the age of three and five years. 25.2% of VGS isolates were resistant to penicillin, 60.4% to clindamycin, 29.6% to ceftriaxone, 19.1% to cefepime, 10.1% to levofloxacin, 0 % to linezolid and vancomycin, and 71.0% to erythromycin. The resistance rate for VGS increased during the period 2015-2016 to 2017-2018 for clindamycin and erythromycin ($p<0.05$).

Obeng-Nkrumah et al. (99) present a four-year retrospective analysis of blood cultures from all patients excluding neonates, form a teaching hospital in Ghana. In total 1451 of the 15683 blood cultures were positive for pathogens among all ages. 1083 of the analyzed blood cultures belonged to infants (29 days – one year), of which 226 grew pathogens. There were 8000 isolates in children (1-15 years) and 708 were positive. Among infants, 10 cultures (4.4%) grew VGS, and in children, 23 (3.2%) blood cultures yielded VGS. Susceptibility patterns were presented for adults and children together. It showed that 41/45 VGS-isolates were non-susceptible to penicillin, 35/42 to ampicillin, 8/13 to amoxicillin-clavulanic acid,

24/40 to cefuroxime, 1/20 were non-susceptible to vancomycin, 15/20 to erythromycin, 12/40 to cefotaxime and 21/25 to chloramphenicol.

Rezaee et al. (100) analyzed medical records of 96 children hospitalized for malignancy with febrile neutropenia and positive blood culture in a children's hospital in Iran during a seven-year period. Six of the children had VGS isolated in their blood culture. Of the tested isolates (absolute numbers are not specified) 20% were resistant to vancomycin, 50% to cephalexin, 20% to ceftriaxone, 33.3% to cefotaxime, 66.7% to ceftizoxime, 60% to oxacillin, 100% were resistant to penicillin, 50% to rifampin, 66.7% to erythromycin, none to clindamycin, 16.7% to chloramphenicol, 66.7% to TMS, 25% to ciprofloxacin, 100% to ampicillin, 83.3% to amikacin and 33.3% were resistant to gentamicin.

5. Discussion

The NORM (Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway) surveillance program publishes an annual report on the use of and resistance to antimicrobial agents in Norway. The report shows an increase in VGS occurring in blood cultures over the past years. The proportion of VGS isolates in blood cultures was 6.8% and 7.7 % of all isolates, in 2013 and 2022, respectively. This is an increase from 2009, when VGS accounted for 4.7% of positive blood cultures. The NORM reports do not report the prevalence of resistance, antimicrobials used against VGS or what age groups or type of patients VGS-bacteremia occurs in (101, 102).

5.1 Antibiotics

5.1.1 Penicillin

In the past VGS was generally considered to be penicillin sensitive, with some strains known to be resistant (103, 104). Now, there is more consensus around resistance-abundance among VGS (105), and mechanisms such as mutations in PBP-genes as mentioned earlier are well known. Some report up to 50% AMR against penicillin among *S. mitis,* although this data is not from children and not all isolates were from blood (106).

In our included studies we found that a total of 194/776 (25.0%) tested isolates showed resistance to penicillin (11, 64, 87-89, 91, 94, 96, 98, 100), but the numbers vary from 0-100%. Among studies in children with malignancy our included studies report AMR against penicillin in 39/200 (19.5%) isolates (11, 64, 94, 96, 100). This number is lower than many other reports. In a study from 2013 conducted in Korea by Han et al. they found that 39/61 (63.9%) VGS isolates from blood cultures were not susceptible to penicillin (107). In a Canadian study conducted from 1996-2001, Husain et al. found non-susceptibility in 17/33 (51.5%) of tested VGS isolates in blood cultures (108), both studies were in children with underlying malignancy. Husain et al. found that penicillin-resistant VGS-infections are linked to more severe outcomes in children, but this was not observed in the study from Korea. A surveillance study from Canada reports that 37% of VGS isolates in the year 2000 had reduced penicillin-susceptibility, which is an increase from similar studies in 1995-1997 which showed reduced susceptibility in 28% (109).

Resistance to penicillin in VGS is also linked to resistance or reduced susceptibility to other beta-lactams (108, 110). The occurrence of AMR against penicillin in VGS is high in countries that also have high rates of AMR in *S. pneumoniae* (105). This is consistent with what is known about the mechanism for transferring resistance genes between the two bacteria groups and may play an important role in the spread of penicillin resistance in VGS (103, 105).

5.1.2 Ampicillin/Amoxicillin

In our included studies we found that a total of 92 of 276 (33.3%) tested isolates showed resistance against ampicillin and/or amoxicillin. In one study, six out of six isolates were resistant to ampicillin (100), while another study found no resistance in four isolates (90). While nine studies tested VGS AMR against ampicillin (84-87, 90, 91, 96, 99, 100), only four studies reported resistance patterns to amoxicillin (84, 87, 88, 99) one study had one of one resistant isolate (84), one had zero of one resistant isolate (87) and the last had two of two resistant isolates (88). All three studies were conducted on neonates.

In a study on adults at risk of endocarditis who tested antimicrobial susceptibility pattern in oral samples, 27 of 49 VGS isolates were non susceptible to ampicillin (111). They found that *S. salivarius* was most resistant, with three of three non-susceptible isolates to ampicillin. Five of our included studies also yielded 100% resistance to ampicillin in tested isolates (84, 86-88, 100). Another study found 190 ampicillin resistant isolates of 869 VGS isolates (112). They also reported that, *S. mitis* was the most resistant species. Out of 589 *S. mitis* isolates, 134 were resistant (22.7%). A third study on BSI in adults in Korea, reported 24 resistant VGS isolates of 54 tested (113). AMR to ampicillin and amoxicillin varies both in included studies and others. We did not have sufficient data to report differences in AMR rates between VGS-species.

5.1.3 Gentamicin

In total 14 of 29 (48.3%) VGS isolates were resistant to gentamicin, among our included studies. Six studies examined gentamicin resistance (85-87, 90, 92, 100). AMR-rates varied from 50-100%, except from one study where gentamicin was tested in combination with ampicillin. Only 9% were resistant to ampicillin and gentamicin in combination therapy. The studies with resistance rates from 50-100% tested from one to 11 isolates. Other recent studies

show lower rates of resistance. A study from the Unites States reported antimicrobial susceptibility pattern for VGS isolates tested with gentamicin from 2010 to 2020 (114). Susceptibility varied from 50-100% for VGS isolates. Another study isolating VGS species from dental plaque, showed that all isolates were 90-100% susceptible to gentamicin, and among 635 tested VGS isolates, only 0.6% were gentamicin resistant (115).

5.1.4 3rd generation cephalosporins

Among the included studies, 13 studies reported AMR or non-susceptibility pattern for 3rd generation cephalosporin resistance (64, 86-88, 90-93, 96-100), making this group the most studied antibiotics. Nearly 20% (N=748 isolates) of VGS isolates were resistant to 3rd generation cephalosporines, with resistant isolates ranging from 0% to 100%. Other studies investigating AMR in VGS to cephalosporines found low AMR-rates. Isolates collected from sterile body sites in Korean adults found that approximately 11% of VGS strains were resistant to cefotaxime and ceftriaxone, with *S. mutans* being the most resistant isolate (112). A total of 43% of *S. mutans* isolates were resistant to 3rd generation cephalosporins. In the period 1998-2002 to 2011-2013 AMR to cefotaxime increased by 4%. The increase in resistance was not significant (p=0.074). Among our included studies with larger study populations, resistance among VGS isolates to 3rd generation cephalosporins was higher. One study examined ceftriaxone-resistance in 352 isolates and found that nearly 30% of isolates were resistant (98). Cefepim, a 4th generation cephalosporin, was AMR tested in two studies (N=192 isolates), and 43% of isolates were resistant. Among isolates AMR tested for 1st and 2nd generation cephalosporines, 30% were resistant (N=53 isolates).

A study from Spain conducted as early as 2001, revealed high resistance rates among VGS isolates collected from neutropenic patients (116). In the *S. mitis* group, 20% of isolates were resistant to cephalosporins. Ceftazidime was the least active agent of the tested cephalosporins, in fact, four cases developed breakthrough bacteremia whilst treated with ceftazidime because of resistant strains. In Norway, cephalosporins are alternative sepsis treatment in children under certain circumstances, after empiric combination treatment with a beta-lactam and gentamicin (117). Together with the findings from our work, this makes 3rd generation cephalosporins an important group to keep studying the AMR specter.

5.1.5 Erythromycin

A total of 275/393 (70.0%) (87, 92, 98-100). VGS isolates showed reduced susceptibility to erythromycin, and 260/373 (69.7%) were resistant. This is the highest proportion of AMR to an antibiotic group among the included studies. Lower rates, but the same trend, was found in a study from 2004, where erythromycin showed the poorest activity against VGS in 155 febrile patients with infections, with 43% of isolates having "high levels of resistance" (118). The proportion of AMR was highest in *S. salivarius* (60%), *S. oralis* (51%), and *S. mitis* (40%). A surveillance study from 2000 found AMR to macrolides in 81/191 (42.4%) of tested isolates among clinical isolates in Canada (109), an increase compared to what they found between 1995 and 1997 which showed 29% AMR. On the contrary, lower rates were found in a study from Sweden published in 2006 where 19% of VGS isolates showed reduced susceptibility to erythromycin and 17% showed resistance. Overall, 24/25 of these patients had underlying hematological disease. In *S. mitis* the rate of non-susceptibility was 11/34 (32.4%) and only 1/27 (3.7%) in *S. oralis* (119).

Another study, this one conducted in Finland in 1998-2001 found higher rates of non-susceptibility to erythromycin among 49/108 (45.4%) of VGS isolates, 29 (26.8%) were resistant. A total of 32 of the patients had hematological malignancy and 17 did not. They also note that among patients with penicillin-resistant-VGS, resistance to other antimicrobials, especially erythromycin, was common (120).

In addition to penicillin resistance, it has been shown that VGS can exchange erythromycin resistance genes with *S. pneumoniae* (121) and *streptococcus pyogenes* (122). This raise concerns that commensal VGS inhabiting erythromycin-resistance can transfer resistance to the more virulent *S. pneumoniae* and *S. pyogenes* and by that indirectly lead to infections potentially resistant to treatment.

In summary, the data we present here indicates that there is a relatively high abundance of erythromycin AMR among VGS-species. Even though the occurrence varies between studies, all of which we have looked at present substantial numbers.

5.1.6 Clindamycin

Among included studies, a total of 229/600 (38.2%) VGS-isolates showed resistance to clindamycin (84, 86, 96, 98, 100). Wang et al. found higher resistance (60.5%) than the other included studies, which varied between 0-6.9% (84, 86, 96, 98). A study from the United States conducted between 2010-2020 found reduced susceptibility in 18.7% among 6752 isolates from "all cultures" in adult patients. They report that the proportion of VGS isolates susceptible to clindamycin significantly decreased with 11.9% (p=0.0033) over the ten-year period, this was also significant for isolates from blood (114). Similar numbers are also reported in children; in the previously mentioned study by Han et al. conducted in children with VGS bacteremia, they found reduced susceptibility to clindamycin in 19.3% of cases (107). On the contrary a recent study conducted in South India including 219 VGS blood-isolates from adults and children (12.8%) found non-susceptibility in 34% (123), which is more comparable to the numbers presented by Wang et al.

In summary, based on the data we present, there seem to be relatively big variations in abundance of AMR against clindamycin among VGS. Local variations might be an important role in this matter.

5.1.7 Vancomycin

In total, 442 isolates were tested for vancomycin, and only 2.3% were resistant (64, 87, 88, 90-92, 96, 98-100). Two of the included studies with few VGS isolates reported no cases of resistance. Similar results were found in studies conducted in adults in Turkey and Korea (111, 112). Oral VGS isolates from patients at risk of endocarditis showed that 100% of isolates (N=49) were susceptible to vancomycin (111), and likewise in 1448 isolates from blood and other sterile body sites (112). Vancomycin was the only drug in the two studies that yielded 100% susceptibility. This is also supported by a study from the United Kingdom from 2001 who found 100% susceptibility among 67 VGS isolates from children with malignancy (110), and a study conducted in 2001 on both adults with and without cancer from USA, Canada and Latin America with 438 clinical VGS bloodstream isolates (124). Finally, a study from Sweeden from 2001 also found 100% susceptibility in VGS isolates where 24/25 had underlying malignancy (124). Among included studies, two studies report 100% vancomycin resistance, but only four isolates were tested. Another study reports 20% resistance among six tested isolates.

Even though VGS are highly sensitive to vancomycin, there are concerns to consider before treatment. One study from Germany published in 2020 reported failure of the hearing screening test in infants treated with vancomycin, aminoglycosides and furosemide in combination, but also independently when infants were small for gestational age and had bronchopulmonary dysplasia (125). In the vancomycin treated cohort, mainly consisting of infants with clinical sepsis (45%), 18% failed the hearing screening test. However, those who failed the test were treated with higher concentrations of vancomycin. Infants were followed up until five years of age, and those who were exposed to vancomycin had a higher risk of hearing deficit compared to non-exposed infants. Another study found that acute kidney injury induced by vancomycin in neonates was significant if postmenstrual age was less than 29 weeks, vancomycin trough levels over 20 mg/L, the patient had hypotension or they were treated with furosemide(126).

5.1.8 Fluoroquinolones

In total 57/565(10.1%) of the strains from our included studies found AMR against fluoroquinolones (92, 96, 98, 100), which is the lowest rates of AMR after vancomycin (2.3%). Resistance against levofloxacin was most often reported, with an AMR share of 54/550 (9.81%) (96, 98). Two studies found no resistance, but they only tested one isolate each (84, 87).

Patients at high risk of developing sepsis often receive prophylactic antimicrobial treatment. American guidelines for antimicrobial use in neutropenic patients from 2010 recommend treatment with fluoroquinolones in high-risk patients with prolonged neutropenia, especially in cases with simultaneous oral mucositis due to an increased risk of invasive VGS-infections. They also state that this should apply to “very high-risk situations” in children, even though some clinicians are hesitant due to side effects (127). This is supported by international guidelines for antibacterial prophylaxis administration in pediatric cancer published in 2020 who states that “Levofloxacin is the preferred agent if antibacterial prophylaxis is planned” (128).

On the other hand, prophylaxis with levofloxacin seem to be a driver for resistance against fluoroquinolones in VGS and are in some studies reported as a risk factor for developing VGS BSI in both children and adults (129, 130). Quintero et al. found an increase in non-

susceptible levofloxacin VGS in IC-patients receiving levofloxacin-prophylaxis over a 12-year period; increasing from none to 19% after implementation of prophylaxis. Although they report lower susceptibility-rates, this trend is supported by a study from 2014 in USA where VGS-bacteremia patients receiving fluoroquinolone prophylaxis were non-susceptible in 74/79 (94%) of isolates, versus 16/36 (44%) in those who did not receive prophylaxis (131).

5.2 Strengths and limitations

5.2.1 Change of study design

As previously mentioned, we changed the study design from a systematic review to a scoping review during full-text screening. This had no effect on our research question, inclusion -, or exclusion criteria, nor did it affect our data extraction. The change mainly affected us methodologically by leaving out “risk of bias” assessment of the included studies.

Changing the methodology of a study midway can lead to several weaknesses and limitations. It introduces potential inconsistency in the approach, which could affect the reliability and validity of our findings. In our case, we found it reasonable to change the study design because we did not intend to find results that were meant to be directly applicable to decision-makers or clinicians but rather aimed to identify what is reported in the literature of AMR patterns in VGS in neonates and children and map this evidence. The risk of bias assessment is therefore not as critical.

A shift in methodology will often have an impact on the interpretation and generalizability of the findings. The results obtained through a scoping review may not be directly comparable to those obtained through a systematic review due to their differences in methodology and objectives. Systematic reviews aim to answer specific research questions while scoping reviews focus on mapping the breadth of literature on a topic without necessarily assessing the quality or conducting meta-analysis (69).

Changing the methodology mid-study also raises questions about transparency and reporting. It is generally essential to clearly document the reason for the change, the criteria used to make the decision, and any implications for the interpretation of the results. This is crucial for maintaining the integrity and credibility of the research. Munn et al. mention possible abuses

of scoping reviews and state reasons not to choose a scoping over a systematic review. Some reviewers may choose to conduct a scoping review instead of a systematic review to avoid the critical appraisal stage of the review process. This may be driven by a desire to quicken the review process or perceived difficulty in conducting critical appraisal. However, by omitting critical appraisal, reviewers risk including low-quality or biased studies in their synthesis, which can compromise the validity and reliability of the findings (69).

In conclusion, a change in study design raises many possible weaknesses and limitations. Despite the weaknesses associated with changing the methodology, we concluded that we had valid reasons for switching from a systematic to a scoping review because we considered the potential strength of an improved fit of study design to our research objectives as most important. We believe that this change did not make our findings less trustworthy.

5.2.2 Changes in inclusion and exclusion criteria

Before the change of study design, we submitted our systematic review protocol to PROSPERO. After launching the search in Medline and Embase, a great number of articles were included for title and abstract screening. To narrow down the number of publications and to better answer our research questions, we made minor changes to our inclusion and exclusion criteria.

Our submitted inclusion criteria were as follows:

- Children (both neonates and children up to 18 years of age) must be part of the study population.
- Studies must report results possible to estimate the prevalence of VGS and other bacteria as causative sepsis pathogens.
- Blood culture must be part of the diagnostic work-up and results presented.

Point one was modified to “children (both neonates **and/or** children up to 18 years of age) must be part of the study population”. Point two was changed to “Studies must report results where it is possible to estimate the prevalence of VGS as causative sepsis pathogens”. This was changed because several studies reported pathogen prevalence, but not VGS prevalence. These studies gave us no information about VGS in the population since we did not know if VGS was not reported because it was not present, considered a contaminant or not identified by laboratory procedures, and were therefore excluded. Point three was kept without

modification. For this sub study, we added one inclusion criterion regarding the AMR profile: "Antibiotic resistance profile must be available.".

As this scoping review is carried out with the same search strategy as the scoping review studying the prevalence of VGS, the AMR criterion was added during full-text screening. If this criterion had been added earlier, we assume that we would have included the same studies, as it is rarely possible to know if a study reports AMR patterns based on the abstract.

Our submitted exclusion criteria were as follows:

- Animal studies.
- Studies not including the results of blood cultures.
- Publications older than 2015.
- Descriptive or narrative reviews.

The modifications in exclusion criteria took place after screening of the titles and abstracts. Since many studies did not report full etiology of blood cultures, we did not know if VGS was among the findings that were not reported. Point two was therefore changed to "studies not including **the complete etiological** results of blood cultures". In point four we added systematic reviews, because they too did not present VGS prevalence.

We also added three exclusion criteria. The first one "Studies including less than 10 positive blood cultures" was added to ensure epidemiological value and avoid case-like reporting in included studies. Secondly, we added "Studies not including prevalence/incidence data on VGS" to decrease the number of eligible studies for data extraction, to better answer our research question and to make it possible to present our findings more organized. To quantify the number of studies we lost by adding this exclusion criterion, we created one reason for exclusion tag called "No data on VGS, pathogen distribution reported". Thirdly, for this sub study only, we excluded studies not including antibiotic resistance patterns for VGS.

5.2.3 Calculations of absolute numbers

Some of the included studies reported VGS AMR in percentage and not absolute numbers. We therefore had to calculate number of resistant isolates based on the reported percentage and total number of examined isolates. This is accounted for and set as annotation in table 3.

5.2.4 Data on susceptibility testing

We did not collect data regarding the AMR testing process. The studies might have used different methods and different cut of values for resistance which can affect AMR-pattern reporting.

5.2.5 Missing full text

A considerable number of articles (1605 of 2892) could not be retrieved in full text by the EndNote reference software despite guidance from librarians with expertise in EndNote. We do not know why these were not found. This could potentially result in less complete mapping of the evidence and reduced detail in reporting. However, based on those we did identify, only a small proportion of studies reported AMR, indicating that the actual number of lost studies for this thesis is substantially lower than 1605 articles. We also did random sampling among the unretrieved studies and discovered that many of them were conference abstracts and was therefore not possible to find in full text. Additionally, during comparison with other studies in the discussion-section, we came across only a few studies published after 2015 that would have fitted our search-criteria. Although this is not systematic searching, it gives us an indication that most relevant studies are already included.

5.2.6 Broad search-criteria

Because this was part of a bigger study, the search, as well as the inclusion and exclusion criteria were constructed based on broader research questions. A narrower search including an AMR-box could have resulted in fewer and potentially more relevant publications. We ended up with 18 relevant studies, some of which reported AMR for only one single isolate. Nevertheless, as mentioned in the above paragraph, we did not find significant studies matching our study criteria during the discussion.

5.3 Species identification and categorization

5.3.1 Species identification

Al Majid et al. suggest that “Failure to properly identify the species in streptococcal isolates in routine diagnosis is a probable explanation for why the pathogenicity of these species may have previously been overlooked.” (132). This could be a plausible explanation for why few studies report VGS causing BSI in children. In many excluded studies, the differentiation of streptococci on species level is limited. Sometimes all streptococci are grouped together and

identified as “streptococci” or “streptococci spp” (133, 134). A study testing the accuracy of bacterial identification panels in blood cultures from immunosuppressed children showed that several identification systems had difficulties with species-level identification of streptococcus species (135).

Another reason is the earlier explained similarity between VGS species and traditionally pathogenic species like *S. pneumoniae* (14, 15), causing difficulties in correct reporting of pathogens. In three of three cases, the ePlex blood culture identification panel for gram-positives identified VGS as *S. pneumonia*, while standard of care-testing and whole-genome sequencing identified the isolates as VGS (135).

A third reason could be that VGS traditionally has been categorized as a contaminant, not a pathogen.

5.3.2 Categorization and global variation

Through the screening process, we observed that there were several reasons for researchers to categorize a positive blood culture as contaminant; positive blood culture without clinical sepsis symptoms (136, 137); growth of known commensals from the normal flora (138); a patient with only one positive blood culture yielding a bacteria (138, 139); bacteria considered being a contaminant by local laboratory standards (140); bacteria commonly considered to be contaminants (141); studies referring to Centers for disease control and prevention national healthcare safety network common commensal list (140, 142); no description of contaminant definition (143). One scoping review found that 53.6% of included studies described how contaminants were defined (8). In the review, 59.5% defined an isolate as contaminant or pathogen based only on the organism’s identity, 29.7% used a multifactorial approach, including both the organism’s identity and supplementary clinical information about the patient, and 10.8% based the definition solely on the interpretation of the clinical situation.

They also showed that VGS classification varies. Of 16 studies reporting VGS isolated from blood culture, three studies considered VGS as pathogen, 12 studies considered VGS a contaminant, and one study categorized VGS based on the context (8). In one study, VGS was considered a contaminant, but was reclassified as pathogen when a 16-year-old hypotensive patient was admitted requiring fluid resuscitation (144). When studies consider VGS as contaminants, the reporting of VGS induced bacteremia decreases and prevalence becomes

more difficult to interpret. This also affect the AMR-pattern reported. For our thesis, this means lower volume and less reliable data.

In total we included three studies from USA, six studies from Asia, six studies from Africa, one from Australia and one from Europe. The numbers of isolates susceptibility-tested in each study vary from one to 352. We also have a relatively low number of included studies, and many of the studies in our search were not found in full text. Therefore, we cannot conclude or say anything certain about variations of AMR abundance in different parts of the world.

6. Conclusion

In our findings the highest abundance of AMR among VGS in children was to erythromycin with a rate of 70%. There was also AMR to gentamicin in about half of isolates and 40% to clindamycin, but with a spread from 7% to 60% in the two biggest studies. The lowest proportion of AMR was found in vancomycin, an antibiotic used as "reserve" due to its potentially severe side effects. It is rarely used empirically for children in Norway. The second lowest rate of AMR was found in fluoroquinolones. However, there are data indicating that resistance to this antimicrobial group is emerging, which is concerning since it up until now is used as prophylaxis in vulnerable groups in certain parts of the world. In penicillin and 3rd generation cephalosporins we found that susceptibility was reduced in approximately one in five isolates. Low AMR against these antibiotics is critical regarding their importance as first and second choice in treating infections with gram positive bacteria in children.

In sepsis in newborns ampicillin and gentamicin is frequently used. According to the data we have collected, who displays AMR to gentamicin in nearly half of isolates and in 1/3 to ampicillin, there are reasons to be worried regarding empirical coverage of invasive VGS-infections. It is important to note that we do not have data applicable to a global population due to the limited numbers of countries in our included studies.

In conclusion, the data showing antibiotic susceptibility patterns for VGS-bacteremia in children are still limited, and findings from existing literature are diverse. To examine this matter closer, we suggest more research on AMR in VGS.

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Tables

Table 1: The five major groups of viridans group streptococci and its species, as presented by Facklam (2).

Mutans group	***Salivarius group***	***Anginosus group***	***Sanguinus group***	***Mitis group***
S. mutans[1]	*S. salivarius*[1]	*S. anginosus*[1]	*S. sanguinus*[1]	*S. mitis*[1]
S. sorbinus[1,3]	*S. vestibularius*[1]	*S. constellatus*[1]	*S. parasangunis*[1]	*S. oralis*[1]
S. cricetus[1,3]	*S. intantarius*[1]	*S. intermedius* [1]	*S. gordonii*[1]	*S. cristatus*[1]
S. ratti[1,3]	*S. thermophilus*[2]			*S. infantis*[1]
S. downei[5]	*S. alactolyticus*[4]			*S. perois*[1]
S. ferus[3]	*S. hyointestinalis*[4]			*S. orisratti*[3]
S. macaccae[5]				
S. hyovaginalis[4]				

1: Origin from humans, 2: origin from dairy producuct , 3: origin from rat, 4: origin from swine 5: origion from monkey

***Table 2*:** Study demographics

First author, year, country, journal	Population	N	Positive blood cultures (n)	Study design	Setting	Sex (% female)
Adnan, 2020, Pakistan, Rawal Medical Journal	Newborn	84	84	Cross-sectional	Single center	35.7
Topcuoglu, 2022, Turkey, Children	Newborn, only EOS patients	8229	101	Retrospective cohort	Single center	-
Zamarano, 2021, Uganda, BMC Mircobiol	Newborn	122	72	Cross-sectional	Single center	43.0
Tetteh, 2022, Ghana, Intr J Environ Res Public Health	Newborn	417	139	Cross-sectional	Single center	44.0
Worku, 2022, Ethiopia, BMC Pediatr	Newborn	250	125	Cross-sectional	Single center	42.0
Mangeni, 2021, South Africa, S Afr Med J	Newborn	1025	166	Retrospective cohort	Single center	45.0
Abro, 2019, Pakistan, Journal Of Liaquat University Of Medical & Health Sciences	Newborn	332	93	Retrospective cohort	Single center	46.0
Al-Samkari, 2021, USA, Pediatr Emerg Care	After newborn period, patients with congenital coagulation factor deficiency	44	56	Cross-sectional	Single center	4.5
Alali, 2020, USA, J Pediatr Hematol Oncol	After newborn period, cancer patients	268	143	Retrospective cohort	Single center	45.,0
Haeusler, 2021, Australia, J Pediatric Infect Dis Soc	After newborn period, cancer patients	462	149	Prospective cohort	Multicenter national	48.,0
Nielsen, 2016, United Kingdom, Medicine	After newborn period, cancer patients	70	86	Retrospective cohort	Single center	-

Sharma, 2021, USA, J Pediatr Hematol Oncol	After newborn period, cancer patients	48	52	Retrospective cohort	Single center	37.5
Abebe, 2021, Ethiopia, Clin Lab	Newborn and after newborn period	1820	498	Retrospective cohort	Single center	46.8
Banawas, 2023, Saudi Arabia, Pathogens	Newborn and after newborn period	282	282	Retrospective cohort	Single center	-
Quintero, 2023, USA, J Pediatric Infect Dis Soc	Newborn and after newborn period	223	223	Prospective cohort	Single center	56.,0
Wang, 2021, China, J Trop Pediatr	Newborn and after newborn period	14107	14107	Retrospective cohort	Multicenter national	40.7
Obeng-Nkrumah, 2016, Ghana, Ann Clin Microbiol Antimicrob	After newborn period	9083	934	Retrospective cohort	Single center	47.0
Rezaee, 2017, Iran, Iran J Pediatr	After newborn period. Cancer patients with febrile neutropenia.	96	96	Retrospective cohort	Single center	52.0

Table 3: Antimicrobial susceptibility patterns for VGS-isolates in the included studies

			Number of resistant isolates (%)							
First author	**N positive BC**	**N isolated VGS**	**PEN**	**AMP/AMO**	**GENTA**	**3rd gen CEPH**	**ERY**	**CLIN**	**VAN**	**FQ**
Adnan	84	1	-	2/2 (100)	-	-	-	0/1	-	0/1
Topcuoglu	101	11	-	1*/11 (9)	1*/11 (9)	-	-	-	-	-
Zamarano	72	1	-	1/1 (100)	1/1 (100)	1/1 (100)	-	0/1	-	-
Tetteh	139	1	1/1 (100)	1/1 (100)	1/1 (100)	0/1	0/1	-	1/1 (100)	0/1
Worku	125	8	3/7 (42.9)	2/2 (100)	-	2/6 (33.3)	-	-	1/8 (12.5)	-
Mangeni	166	46	0/3	-	-	-	-	-		-
Abro	93	4	-	0/4	4/4 (100)	4/4 (100) (CFM)	-	-	0/4	-
Al-Samkari	56	1	-	-	-	0/1	-	-	-	-
Alali	143	34	3/27 (11.1)	-	-	2/27 (7.4) (CFN)	-	-	3/3 (100)	-
Haeusler	149	34	2/34 (5.9)	-	-	-	-	-	-	-
Nielsen	86	86	3/8 (37.5)	-	-	-	-	-	-	-
Sharma	52	3	-	-	-	3/3 (100)	-	-	-	-
Abebe**	498	22	-	-	3/6 (50)	3/9 (33,3) (CFN)	6/14 (42.9)	-	2/18 (11.1)	1/7 (14.3)
Banawas**	282	15***	5/30 (16.7)	6/30 (20)	-	5/30 (16.7)	-	-	1/30 (3.3)	-
Quintero	223	IC: 125	25/125 (20.0)	18/74 (24.3)	-	12/123 (9.8)	-	8/116 (6.9)	-	16/96 (16.7)

		Non-IC: 139	16/138 (11.6)	12/90 (13.3)	-	9/133 (6.8)	-	8/124 (6.5)	-	2/102 (2.0)
Wang****	14 107	352	89/352 (25.2)	-	-	104/352 (29,6) (CFN)	250/352 (71.0)	213/352 (60.4)	0/352	36/352 (10.1)
Obeng-Nkrumah**[1]	934	45	41/45 (91.1)	35/42 (83.3) (AMP) 8/13 (61.5) (AMO)	-	12/40 (30) (CFM)	15/20 (75)	-	1/20 (5)	-
Rezaee****	96	6	6/6 (100)	6/6 (100)	4/6 (66.7)	1/6 (20.0) (CFN) 2/6 (33.3) (CFM) 4/6 (66.7) (CTZ)	4/6 (66.7)	0/6	1/6 (20.0)	2/6 (25.0)
Total:	**17 406**	**934**	**194/776 (25%)**	**92/276 (33.3%)**	**14/29 (48.3%)**	**164/748 (21.9%)**	**275/393 (70.0%)**	**229/600 (38.2%)**	**10/442 (2.3%)**	**57/565 (10.1%)**

BC; blood culture PEN; penicillin, AMP; ampicillin, AMO; amoxicillin, GENTA; gentamicin, CEPH; cephalosporins, ERY; erythromycin, CLIN; clindamycin, VAN; vancomycin, FQ; fluoroquinolones, CIP; ciprofloxacin, LEV; levofloxacin, TETRA; tetracykline, CFN; ceftriaxone, CFM; cefotaxime, CTZ; ceftizoxime, IC; immunocompromised, non-IC; non immunocompromised

- not tested/reported

** combination therapy with ampicillin and gentamicin*

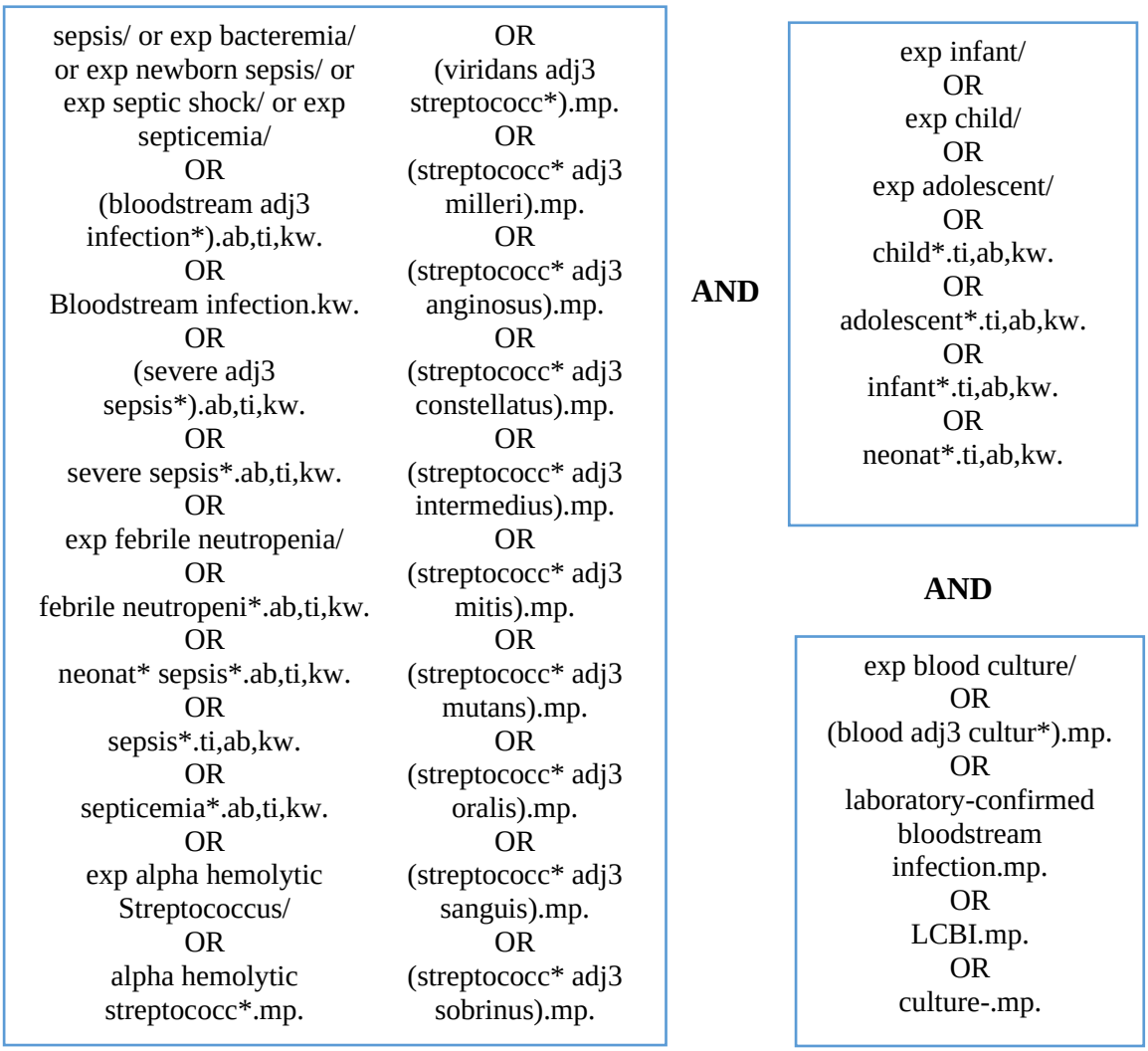
*** AMR patterns are presented for children and adults together*

**** 15 VGS-positive blood cultures for children, but the study reports children and adults together, in total 30 VGS isolates were susceptibility tested.*

***** Resistance pattern was only presented in percent; we estimated the numbers not susceptible given that all isolates (6 for Rezaee and 352 for Wang) were tested. Percentages listed here are the same as presented in the respective studies.*

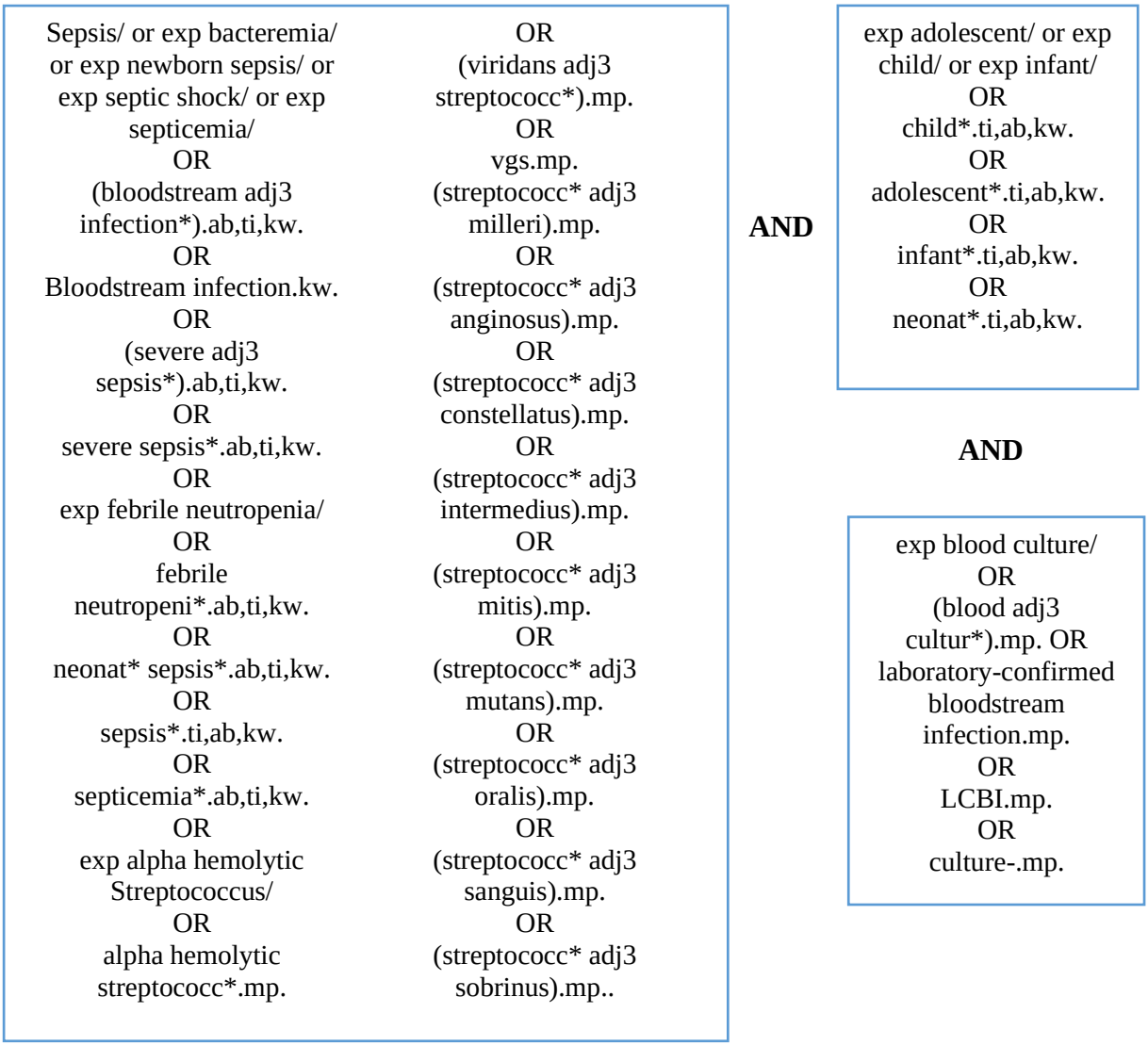
[1] Only reported non-susceptibility, not resistance

Figures



Limits: human, English language and year 2015-current

Figure 1: Final search words in Embase.



Limits: human, English language and year 2015-current

Figure 2: Final search words in MEDLINE

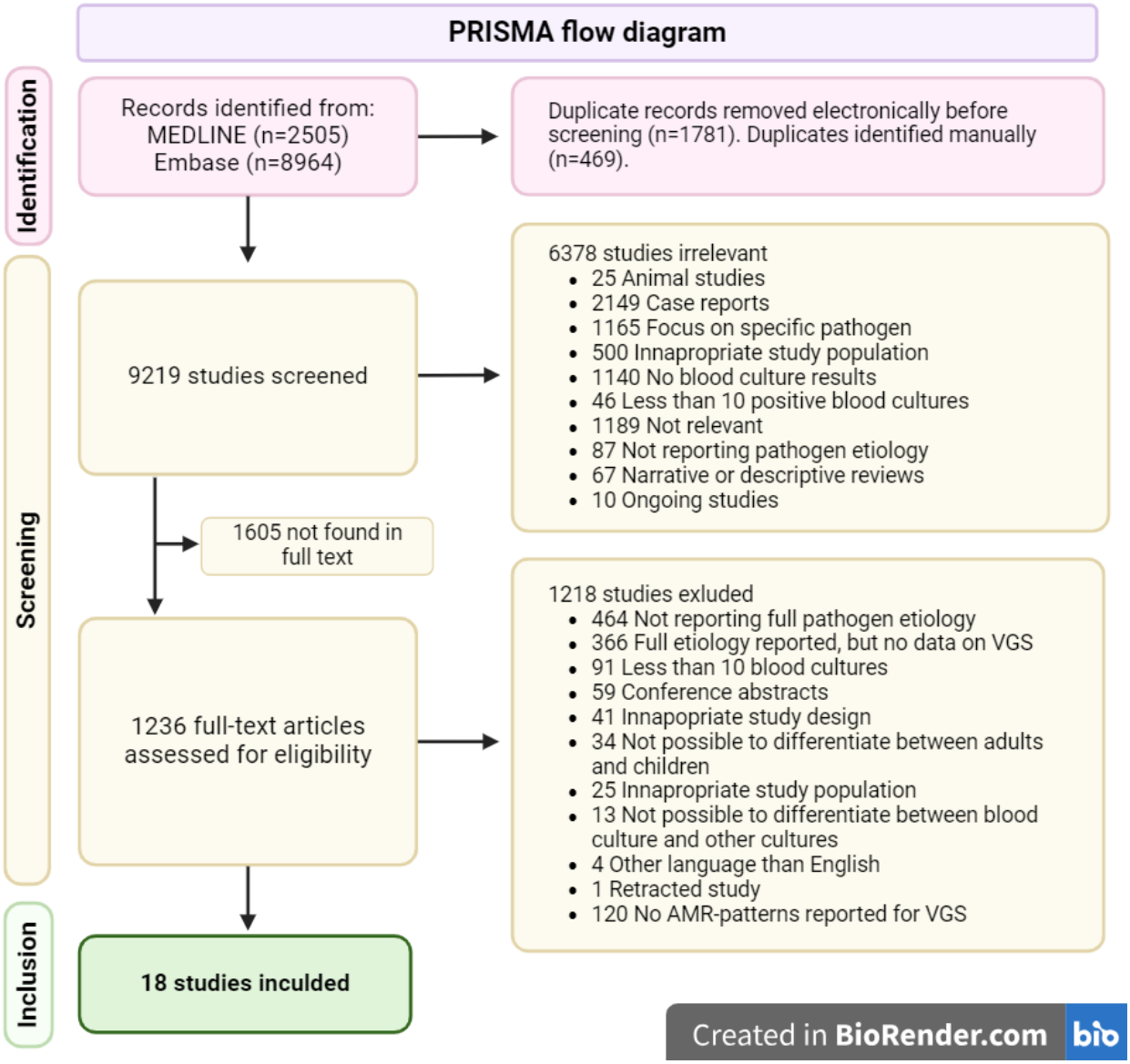


***Figure 3**:* PRISMA flow diagram
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