Epidemiology and antimicrobial susceptibility of invasive bacterial infections in children – a population-based study from Norway

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Contributorship

CMT, DB and HSB were involved in the development of the protocol. CMT and DB was responsible for the data collection. CMT, TÅM, SH and PCL quality assured the data and did the analyses. CMT and CK wrote the first drafts. All the authors contributed to the interpretation of the data and revisions of the manuscript and approved the final version of the manuscript.

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Abbreviations used in the paper: Antimicrobial susceptibility testing (AST), Cerebrospinal fluid (CSF), Minimum inhibitory concentration (MIC), Coagualse-negative staphylococci (CoNS), Norwegian Surveillance System of Antimicrobial Resistance (NORM), Susceptible (S), Intermediate restistant (I), Resistant (R), *Streptococcus agalactiae* (GBS), confidence interval (CI), interquartile range (IQR), Systemic Inflamatory Response Syndrome (SIRS).

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Abstract

Objective: To describe epidemiology and antimicrobial susceptibility testing (AST) data of bacteria causing invasive infections in Norwegian children (0-18 years).

Methods: Population-based observational study using prospectively collected AST data from the Norwegian Surveillance System of Antimicrobial Resistance from 2013 to 2017. We included all clinically relevant bacterial isolates (blood and cerebrospinal fluid), and compared incidence of invasive infections and AST data in isolates from children and adults.

Results: We included 1173 isolates from children and 44 561 isolates from adults. *Staphylococcus aureus* accounted for 220/477 (46.2%, 95% CI 41.6-50.7) of all isolates in schoolchildren (6-18 years). Compared to *Streptococcus pneumonia* isolates from adults (N=2674), we observed higher non-susceptibility rates to penicillin in isolates from children (N=151), 11.9% versus 5.8%, p <0.01; and also higher resistance rates to erythromycin (11.3% versus 4.9%, p<0.01), clindamycin (9.3% versus 3.6%, p<0.001) and trimethoprim/sulfamethoxazole (17.9% versus 6.4%, p<0.001). Compared to *Escherichia coli* isolates in adults (N=9073), we found lower rates of ESBL in isolates from children (N=212), 2.4% versus 6.4%, p<0.05.

Conclusion: The study indicates the importance of microbiological surveillance strategies in children and highlights the need for pediatric AST data. The high rates of non-susceptibility to commonly used antibiotics among *S. pneumoniae* in children and the high burden of invasive *S. aureus* infections in schoolchildren calls for modifications of Norwegian guidelines.

Introduction

Bacterial infections are one of the most frequently causes of death in children,[1, 2] and increasing antimicrobial resistance is a major health concern worldwide.[3] Surveillance of epidemiology and antimicrobial susceptibility testing (AST) data for bacteria causing serious infections is of high importance,[4] but data specific for children are often lacking, also in Norway.[5] Specific antibiograms for children improve treatment quality,[6] and pediatric surveillance programs are recommended.[7, 8]

The distribution of the most frequent bacteria recovered in pediatric bloodstream infections varies in different countries and settings [8-11] and with age.[1, 9] Studies comparing AST data in bacterial isolates from children versus adults are limited.[8, 12, 13] A Canadian study reported lower rates of resistance to commonly used antibiotics in *Escherichia coli* and *Staphylococcus aureus* isolates from children than adults.[12] A European study reported higher resistance rates to macrolides in pediatric *Streptococcus pneumonia* blood isolates than in adult isolates.[8]

Norway is a high-income country with low rates of antimicrobial resistance.[5, 14] Empirical recommendations for antibiotic regimen in children emphasize penicillin for pneumonia and gentamicin combined with penicillin or ampicillin for sepsis.[15] However, adherence rate to the guideline varies.[16, 17]

The aims of this study were to report the incidence of invasive bacterial infections, the distribution of causative pathogens and AST-data, in Norwegian children compared to adults.

Materials and Methods

Data collection and bacterial isolates

This is an observational population-based study using prospectively collected data from the Norwegian Surveillance System for Antimicrobial Resistance (NORM) between 2013 and 2017. NORM was established in 2003 and collects clinically relevant AST-data from different sites within defined time ranges for each bacterium. All 22 primary diagnostic laboratories and 11 reference laboratories in Norway participate in the collection. A specially designed web-based computer program (eNORM) is used for registration. The reporting of AST-data is mandatory and is regulated by the National Regulation of Resistance Registry.[18] All samples from both primary care and hospitals (including 22 pediatric centers) in entire Norway are covered by these laboratories. Thus, the expected national coverage is close to 100% within the defined time ranges of collection for each bacterium. Patients with more than one phenotypically identical isolate of the same species from the same site within one month are registered with only one isolate, but if the same isolate is observed in both blood and spinal fluid, they are registered as two isolates. Results from AST are interpreted in accordance with clinical breakpoints from EUCAST.[19] Further details on testing are described in the NORM reports.[5]

We included all relevant systemic isolates from blood and cerebrospinal fluid (CSF), Table 1. NORM also collects isolates from urine, wounds and the respiratory tract, but these are not registered in relation to systemic infections and were therefor not included in our study. Data on Coagulase-negative staphylococci (CoNS) and Viridans group streptococci were not reported to NORM in the collection period and could not be included in our analyses, but these are also

often defined as contaminants in pediatric blood culture studies.[20] We excluded anaerobic isolates, as there were not a single isolate obtained in children, during a 12 months collection period. This can be explained by less frequently use of anaerobic blood culture bottles among children, but also by less observations of anaerobe bacteria in children.[21]

Data on children (0-18 years), extracted from NORM, included birth month and year, county of residence, laboratory name, date of culture, name of antibiotic and the minimum inhibitory concentration (MIC) value. We divided the children in three different age categories; infants (0-1 years of age, up to the month of turning one year); preschool children (1-6 years of age, from the first month after turning one year to the month of turning six years); schoolchildren (6-18 years of age, from the first month after turning six years to the month of turning 18 years). Additionally, we also report selected data separately for infants 0-3 months of age (up to the month of turning three months). The isolates from adults were separated from the year-specific NORM reports by subtracting the pediatric isolates from the total number of isolates presented in the reports.[5] This was done separately for each bacteria-antibiotic combination so that all pediatric results were eliminated. In 41 pediatric *Streptococcus agalactiae* (GBS) isolates and in one *S. aureus* isolate, susceptibility data were missing. These isolates were included in the demographic overview for children, but for comparison of resistance rates, they remained in the adult group because it was not possible to extract them.

Definitions, analyses and statistics

All data and specifically the translation into susceptibility pattern were quality assured. We used the EUCAST clinical breakpoints corresponding to the year after data collection to define susceptibility into three categories: susceptible (S), intermediate resistant (I) or resistant (R). We

used the old SIR definition since we used historical data and breakpoints. Non-susceptibility (NS) rate was defined as isolates being I or R, and was only used in relation to *S. pneumoniae*/penicillin, as this is a well-established method of describing susceptibility pattern for this combination.[22] We used the non-meningitis breakpoints for penicillin.[19]

Demographic data were described in numbers; age groups were described with corresponding percentages and the different bacteria in children were described with corresponding risk ratio (RR) and 95% confidence intervals (CI) compared to adults. As an example, RR for *E. coli* was calculated as the rate of all *E. coli* isolates deriving from children divided by the rate of all isolates deriving from adults. The 95% CI were calculated by generating the natural log (Ln) of the RR and then the antilog of the upper and lower limits of the CI for Ln (RR).

As some bacteria were not sampled for five fully years, we estimated the total number by multiplying the number of isolates obtained for each bacterium with the factor needed to hypothetically get five complete years of registration data. These were used to describe distribution of bacteria and crude incidence of culture-confirmed bacterial infections based on census data from Statistics Norway.[23] We also estimated the age-standardized incidence, using the European standard population as reference.[24] We excluded *Proteus spp.*, *Enterobacter spp*., and *Pseudomonas aeruginosa* from the incidence calculation because we regarded the collection period too short for these more rarely detected species. Both the distribution of isolates and the incidence rates were presented as figures and reported as percentages with corresponding 95% CI (distribution) and as number per 100 000 inhabitants in Norway (incidence).

All pediatric isolates were analyzed according to susceptibility for relevant antibiotics. For comparisons with adults, we included bacteria with more than 50 isolates, and we compared the proportion of isolates being R. The exception was *S. pneumoniae* where we compared the NS rate to penicillin. Resistance pattern were described in number and percentages with corresponding 95% CI. We also performed year-by-year sensitivity analyses comparing resistance rates in all bacteria-antibiotic combinations with at least five R isolates in total. For *E. coli*, *S. aureus* and *S. pneumoniae*, we also compared resistance rates within our three defined pediatric age categories and for *S. pneumoniae* also the median MIC values for penicillin with corresponding interquartile range (IQR) between infants and older children.

For comparison of proportions, we based the statistical tests on two-way frequency tables including the observed frequencies and the expected frequencies. The expected frequency in a two-way frequency table is: (row total x column total) / total number of observations. If any expected frequencies were < 5 we used Fisher`s exact test and in all other cases we used a chi-square test. Comparison of MIC values were performed using a Mann-Whitney U test. We used Stata SE version 16.1 for analyses. A p-value <0.05 was considered significant.

Ethics

The data were collected according to the National Regulation of Resistance Registry,[18] and was approved by the data protection official at Haukeland University Hospital (ID 1075).

Results

Epidemiology

In total 1173 isolates (1144 from blood, 29 from CSF) were included from children, compared to 27 735 isolates (27 621 from blood, 114 from CSF) from adults. Four percent of all blood culture isolates and 20.3% of all CSF isolates came from children (Table 2). Infants (0-12 months) accounted for 566 (48.2%) of the pediatric isolates, whereof 449 (79.3%) came from the age group 0-3 months. Of 181 GBS isolates, 175 (96.7%) came from infants 0-3 months of age. Estimated annual crude national incidence rate of invasive bacterial infections in children (excluding *Proteus spp*, *Enterobacter spp.* and *Pseudomonas Aeruginosa*) was 26.4 per 100 000 (95% CI 23.6-29.5), corresponding to an age-standardized incidence rate of 26.2 per 100 000 (95% CI 23.4-29.4). Incidence was strongly related to age, infants presenting with the highest rate, 274.4 per 100 000 (95% CI 234.2-320.2) (Figure 1). Age-standardized incidence for *S. aureus* was 7.0 per 100 000 (95% CI 5.6-8.7). Figure 2 show that *E. coli* and GBS dominated among infants (58.1%, 95% CI 54.7-61.5), *S. aureus* and *S. pneumoniae* dominated among preschool children (40.7%, 95% CI 35.3-46.2), and *S. aureus* dominated among schoolchildren (46.2%, 95% CI 41.6-50.7). The *Enterococcus faecalis/faecium* ratio was 64/9 (7.1) in children and 2013/865 (2.3) in adults.

Resistance rates

Figure 3 highlights differences between children and adults. For a detailed description of resistance pattern in children compared to adults, see Supplementary Digital Content 1. For year-by-year resistance rates and susceptibility pattern in pediatric isolates not included for comparison, see Supplementary Digital Content 2.

Compared to *S. pneumoniae* isolates from adults (N=2674), we observed higher NS rates in isolates from children (N=151) to penicillin, 11.9% versus 5.8%, p<0.01. Two of the *S. pneumoniae* isolates from children were R, and 16 were I. All *S. pneumoniae* isolates from children that were collected from the CSF were S (MIC ≤ 0.06) to penicillin. Compared to *S. pneumoniae* isolates from adults, we also revealed higher resistance rates in isolates from children to erythromycin (11.3% versus 4.9%, p<0.01), clindamycin (9.3% versus 3.6%, p <0.001) and trimethoprim/sulfamethoxazole (17.9% versus 6.4%, p<0.001). Out of the 18 isolates expressing NS to penicillin, six were resistant to all the antibiotics mentioned above, five were resistant to only erythromycin and clindamycin and three isolates were resistant to only trimethoprim/sulfamethoxazole. None of the pediatric *S. pneumoniae* isolates were R to cefotaxime, but four (2.6%) were I.

Compared to GBS isolates from adults (N=895), we observed higher resistance rates in isolates from children (N=143) to erythromycin (29.4% versus 17.1%, p<0.001) and clindamycin (25.2% versus 11.6%, p<0.001). In *S. aureus* isolates from children, we observed only one MRSA positive case (0.3%) out of 330 isolates. Compared to *E. coli* isolates from adults (N=9073), we observed lower rates of ESBL production in isolates from children (N=212), 2.4% versus 6.1%, p<0.05. All five ESBL isolates in children were S to piperacillin-tazobactam and meropenem. Compared to *E. coli* isolates from adults, we also observed lower resistance rates to ciprofloxacin in isolates from children, 7.5% versus 13.0%, p<0.05).

Resistance rates within the children group are shown in Supplemental Digital Content 3. For *S. pneumoniae*, NS rate to penicillin was 5.0% (95% CI 0.6-16.9) in isolates from infants, 13.7%

(95% CI 6.8-23.8) from preschool children and 15.8% (95% CI 6.0-31.3) from schoolchildren. The median penicillin MIC value for *S. pneumoniae* were lower in infants (0.016, IQR 0.016) than in older children (0.032, IQR 0.016), $p < 0.01$. For *E. coli*, resistance rate to gentamicin was 11.3% (95% CI 4.3-23.0) in schoolchildren.

Discussion

To our knowledge, this is the first study from the Nordic countries describing national epidemiology and susceptibility pattern in pediatric invasive bacterial isolates.

The estimated annual incidence of invasive bacterial infections in Norway (age 0-18, 26.2/100 000) was very similar to data on blood culture proven sepsis in Switzerland (age 0-16, 25.1/100 000).[1] However, the annual incidence for infants was somewhat higher in our study (274.4/100 000) compared to the Swiss study (231.3/100 000). This could mirror that the latter only included isolates associated with clinical proven sepsis (by SIRS criteria). On the other hand, a substantial proportion of isolates (such as CoNS) were not included in our estimation. CoNS are often regarded as contamination, but may cause infections in immunosuppressed children.[25]

Age stratified distribution of pathogens from children were in the same range as in a large Swiss study.[1] The *E. faecalis/faecium* ratio was high (7.1) in our study compared to a European point-prevalence survey (1.9).[8] Given that *E. faecium* mostly causes nosocomial infections,[26] this finding is supported by the soemwhat lower rate of nosocomial infections among children in

Norwegian hospitals (19.8%) compared to the average rates reported in a selection of European countries (27.6%).[16 27]

In our study, the incidence of invasive bacterial infections was lower in children (except infants) than in adults. Antibiotic administration prior to first blood culture could stop bacteria from growing. A study in Norwegian children revealed that any microbiological testing was missing in 23% of children before start of antibiotic treatment for any indications.[16] In children, blood culture procedures are more challenging than in most adults, which may lead to antibiotic administration without a corresponding blood culture. Especially during transport to hospital (when circumstances is challenging), this is relevant. A recently published study reported that multiple blood cultures with age adjusted volume prior to antibiotics increased the chance of pathogen isolation in children.[28] Regarding pattern of antibiotic use, reports from Norwegian hospitals show that children use less broad-spectrum antibiotics compared to the entire population.[5, 16]. This is relevant since detection of pathogen is more difficult if broad-spectrum antibiotics are administrated before blood culture is obtained.

Empirical antibiotic guidelines for pediatric sepsis in Norway (gentamicin plus penicillin/ampicillin) are based on low resistance rates, a long treatment tradition favoring this regime and by a limited number of studies.[25, 29, 30] In neonates, this regime is applied world-wide, but for older children most guidelines emphasizes broad-spectrum antibiotics such as third-generation cephalosporins or piperazillin-tacobactam[31, 32]. Based on the results in our study and as part of this discussion, we have compared four different empirical antibiotic regimens for pediatric sepsis in our population (Figure 4). On one side, one should aim for antibiotics

categorized as *access* in the acknowledged WHO AWaRe classification system to slow down resistance,[3] but one should neither underestimate the morbidity and mortality rate of sepsis for the individual patient.[2] Clinical studies in children comparing the established antibiotic regime with a third-generation cephalosporin or piperacillin-tazobactam are warranted.

The high burden of *S. aureus* bacteremia among schoolchildren in our study is in line with observations from otherwise healthy Swiss children (10-16 years).[1] In comparison to the annual incidence of *S. aureus* bacteremia reported in our study (7.0/100 000), other high-income countries have reported incidences from 3.7 to 14.4/100 000.[1, 33] Fatality of invasive *S. aureus* infections in children is considerable, 4.7% in Australia/New Zealand.[33] Thus, adequately covering of *S. aureus* should be high priority in empirical guidelines. Many invasive *S. aureus* infections present with typical infection-sites such as bone and soft-tissue, but a notable proportion (36%[33]) presents with no or less typical organ specific symptoms. Gentamicin resistance was low in S. aureus isolates in our population, but there is a lack of evidence using this drug as monotherapy for other than Enterobacterales.[34] Thus, the empirical sepsis regime in Norway could be problematic. To continue using antibiotics listed as *access* in the WHO AWaRe classification system,[35] we speculate whether gentamicin combined with a narrow-spectrum beta-lactamase stable penicillin (such as cloxacillin) could be suitable for initial treatment of suspected sepsis in schoolchildren. Another option is to use a first-generation cephalosporin.

We could not find other studies reporting higher NS rate to penicillin in invasive *S. pneumoniae* isolates from children than adults, but a Canadian study from 2012 (including both blood and

respiratory tract isolates) observed that a higher proportion of isolates from children than adults had MIC values > 1.0 mg/L.[12] Opposite to our results, one study observed higher NS rates in infants (20.6%) compared to older children (10.6%).[8] Our observation of more resistance in isolates from children to both erythromycin, clindamycin and trimethoprim/sulfamethoxazole is not mirrored in other comparative studies.[8, 12] Particularly striking was the high resistance rate (17.9%) to trimethoprim/sulfamethoxazole, reflected by high use of this agent in Norwegian children.[36] The 13 valent pneumococcal conjugate vaccine was introduced in the Norwegian children vaccine program in 2011. A population-based study reported an increase in non-susceptible clones in invasive pneumococcal disease that was mainly non-vaccine serotypes imported to Norway from 2011-2016.[22] Susceptibility pattern in these serotypes corresponded to our observation.

Despite the high NS rate in *S. pneumoniae* isolates, we argue that penicillin should continue as first-line empirical drug in severe pneumonia because most isolates were intermediate resistant, and relevant alternatives have even higher odds of treatment failure or an unfavorable ecological profile. However, one should aim for high dose exposure (up to 50 mg/kg every four hours).[37] For the future, serotype independent vaccines may help combat invasive pneumococcal infections.[38]

Our observation of lower ESBL rates in *E. coli* isolates from children than from adults is comparable with studies from North America,[12, 39] and the lower resistance rate to ciprofloxacin is even more dominant in other reports.[8, 12] In Canada, gentamicin resistance in isolates from children was reported lower than in adults,[12] while a European study reported the opposite.[8] The

high resistance rates in *E. coli* isolates from schoolchildren to multiple antibiotic classes observed in our study is of concern, but it corresponds to other observations of increasing *E. coli* resistance during childhood.[8, 40] Despite the latter, our study supports that gentamicin continues as an appropriate drug for Enterobacterales for most children in our population.

In this large study, we used national prospectively collected data from a high-quality register using identical methods in all data collection. In contrast to another study that used the entire population as reference group,[8] we have compared resistance rates in two homogenous groups of children and adults. The lack of clinical data is a limitation when interpreting the results of the study. We acknowledge that studies with focus on the connection between microbiological findings and clinical parameters are needed. Unfortunately, we could not include all microbes with fully registration periods. We compensated by calculating an estimated number of total isolates, but we excluded bacteria that were not collected ≥ 50% of the entire period (2013-2017) from the incidence calculation. The 41 GBS isolates from children that had to remain in the adult group has to be considered when interpreting the resistance rates. Finally, we had to use breakpoints corresponding to the year of the different NORM reports because we did not have MIC values available for the adult population. However, we also analyzed all isolates from children in accordance with the 2020 breakpoints from EUCAST and we revealed different resistance rate in only four bacteria/antibiotic combinations and in total only eight single isolates was added or subtracted in the R category, see Supplemental Digital Content 4.

Conclusion

This study gives valuable microbiological data in characteristics of pediatric invasive bacterial isolates in a high-income country, emphasizing the need for separate surveillance strategies in children, and should motivate for more publications of pediatric AST data. We observed important aspects to be considered when revising pediatric antibiotic guidelines in Norway; the high burden of invasive *S. aureus* isolates in schoolchildren and the higher degree of NS (penicillin) and resistance (erythromycin, clindamycin and trimethoprim/sulfamethoxazole) in invasive *S. pneumoniae* isolates from children than from adults.

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Figure legends

Figure 1) Estimated incidence rate for different age groups of invasive bacterial infections confirmed by isolates from blood/CSF in Norway. Vertical line represents the 95% CI around the point estimate for each category. The number of isolates is estimated based on sampling from the Norwegian Surveillance System for Antimicrobial resistance (NORM) 2013-2017.

[#] Bacteria included: *S. aureus, S. pneumoniae, S. pyogenes, S. agalactiae, Enterococcus spp., E. coli, Klebsiella spp., H. influenza, N. meningitidis*

Figure 2) Distribution of (a) bacterial species and (b) Gram-negative/Gram-positive bacteria in blood/CSF isolates in Norway for different age groups; adults (n=44 000), 0-1 years (n=834), 1-5 years (n=327), 6-18 years (n=477). The number of isolates is estimated based on sampling from the Norwegian Surveillance System for Antimicrobial resistance (NORM) 2013-2017.

Figure 3) Comparison of susceptibility pattern between invasive (blood/CSF) isolates from Norwegian children (0-18 years) and adults, (a) Gram-positive bacteria and (b) Gram-negative bacteria. 95% CI are shown as the vertical line on the column. Penicillin NS (Pencillin non-susceptible), SXT (Trimethoprim-sulfamethoxazol), Gentamicin Hi (High level gentamicin resistance), TZP (Piperacillin-tazobactam). Data are based on sampling from the Norwegian Surveillance System for Antimicrobial Resistance (NORM), 2013-2017.

Figure 4) Alternative antibiotic empirical regimes for pediatric/neonatal sepsis in Norway and their expected effect on the most common bacteria. Resistance rates are based on national collected data on children (0-18 years) from blood/CSF 2013-2017. CSF; Cerebrospinal fluid

[¤] Access and Watch antibiotics are defined by the WHO

[#] If resistance rate for a certain bacteria/antibiotic combination was not available, the most appropriate category was evaluated based on resistance rates for similar antibiotics and/or available literature

[§] Breakpoints for this figure are based on the 2020 version of EUCAST cut-off limits. EUCAST; European Committee on Antimicrobial Susceptibility Testing.

List of Supplemental Digital Content

Supplemental Digital Content 1: Table showing comparison of susceptibility patterns between children and adults

Supplemental Digital Content 2: Tables showing year-by-year resistance rates in children and adults, and susceptibility pattern in pediatric isolates not included for comparison

Supplemental Digital Content 3: Table showing comparison of resistance rates within the children group

Supplemental Digital Content 4: Comparison of resistance rates in blood culture isolates from Norwegian children using breakpoint from different years.

	2013 Months	**2014** Months	**2015** Months	**2016** Months	**2017** Months
Bacteria					
S. aureus	9	9	9	9	9
S. pneumoniae	12	12	12	12	12
S. pyogenes	12	12	12	12	12
S. agalactiae	-	12	12	12	12
Enterococcus spp.	9	9	9	9	9
E. coli	6	6	6	6	6
Klebsiella spp.	9	9	9	9	9
H. influenzae	12	12	12	12	12
N. meningitidis	12	12	12	12	12
P. aeruginosa	-	-	9	-	-
Enterobacter spp.	-	-	-	9	
Proteus spp.	-	-	-	-	9

Table 1: Collection periods for blood and cerebrospinal fluid (CSF) isolates in the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) 2013-2017

* CSF isolates were only obtained from *S. pneumonia, S. pyogenes, S. agalactiae, H. influenzae and N. meningitidis*

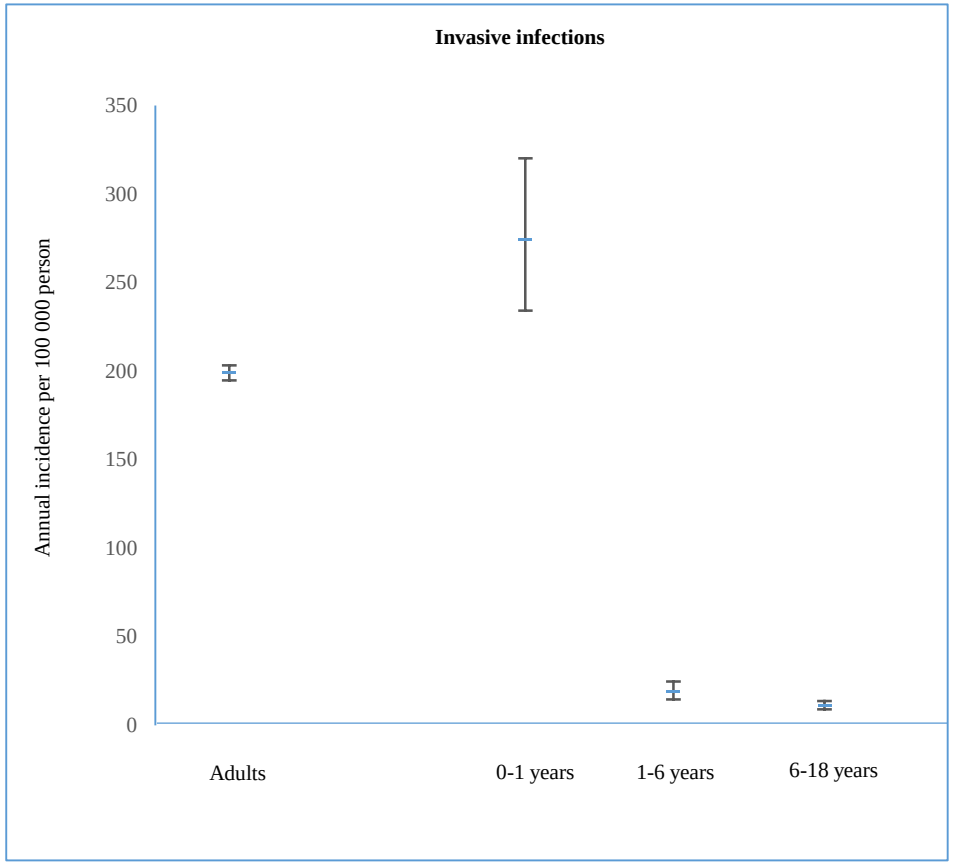
	Blood	CSF
All, n	28 403	143
Children n (% of all)	1144 (4.0)	29 (20.3)
Age groups (n, % of paediatric isolates)		
< 1	566 (49.5)	9 (31.0)
1-5	233 (20.4)	12 (41.4)
6-18	342 (29.9)	8 (27.6)
Unknown	3 (0.3)	
Microbes, n (RR to adults, 95% CI)		
0-1 years		
All gram positive bacteria	382 (1.38, 1.31-1.47)	-
S. aureus	119 (0.98, 0.84-1.15)	-
S. agalactiae	175 (9.93, 8.63-11.42)	3 (5.43, 1.68-17.5)
S. pneumoniae	35 (0.65, 0.47-0.90)	5 (0.75, 0.42-1.37)
Enterococcus spp.[*]	42 (0.70, 0.52-0.94)	-
S. pyogenes	11 (0.60, 0.33-1.08)	0 (n/a)
All gram negative bacteria	184 (0.63 0.56-0.71)	-
E. coli	131 (0.70, 0.60-0.81)	-
Klebsiella spp.[*]	38 (0.47, 0.35-0.64)	-
H. influenzae	9 (1.08, 0.56-2.08)	0 (n/a)
N. meningitidis	3 (2.49, 0.78-7.93)	1 (0.84, 0.13-5.69)
Others [#]	3 (0.16, 0.04-0.62)	-
1-6 years		
All gram positive bacteria	171 (1.50, 1.39-1.62)	-
S. aureus	45 (0.90, 0.69-1.17)	-
S. pneumoniae	65 (2.93, 2.38-3.62)	8 (0.90, 0.60-1.37)
S. pyogenes	46 (6.01, 4.65-7.93)	0 (n/a)
S. agalactiae	0 (0.07, 0.00-1.09)	0 (n/a)
Enterococcus spp.[*]	15 (0.56, 0.34-0.91)	-
All gram negative bacteria	63 (0.53, 0.43-0.65)	-
E.coli	28 (0.36, 0.25-0.51)	-

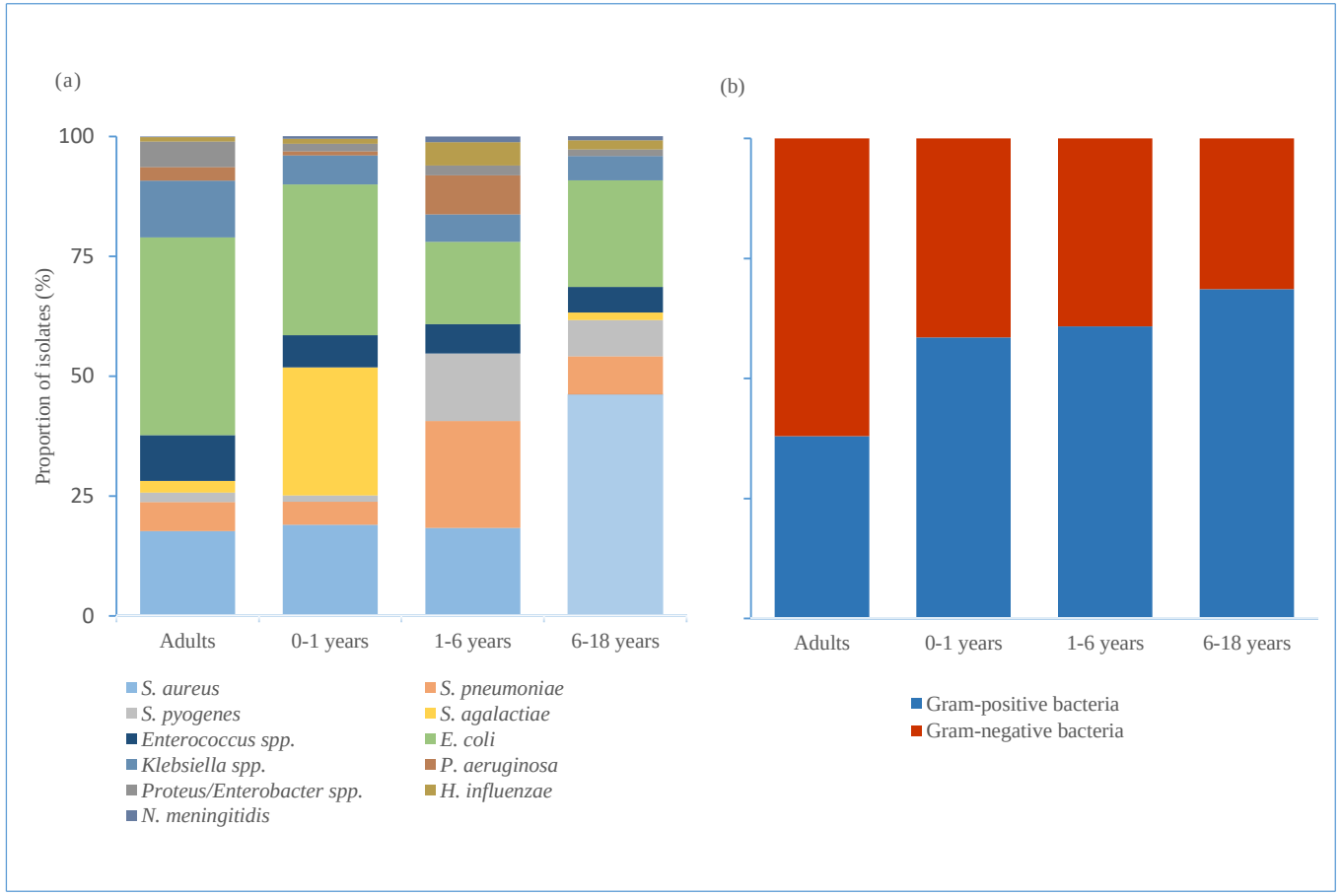
Klebsiella spp.[*]	14 (0.42, 0.25-0.70)	-
H. influenzae	12 (3.49, 1.99-6.10)	4 (4.75, 1.67-13.47)
N. meningitidis	4 (8.03, 2.94-21.95)	1 (0.84, 0.13-5.69)
Others[#]	5 (1.08, 0.45-2.59)	-
6-18 years		
All gram positive bacteria	261 (1.57, 1.48-1.67)	-
S. aureus	165 (2.26, 2.02-2.53)	-
S. pneumoniae	36 (1.11, 0.82-1.52)	2 (0.34, 0.10-1.13)
S. pyogenes	35 (3.17, 2.30-4.37)	1 (38.33, 1.68-875.03)
S. agalactiae	6 (0.56, 0.25-1.25)	0 (n/a)
Enterococcus spp.[*]	19 (0.48, 0.31-0.75)	-
All gram negative bacteria	85 (0.46, 0.38-0.55)	-
E. coli	53 (0.47, 0.36-0.60)	-
Klebsiella spp.[*]	18 (0.37, 0.24-0.58)	-
H. influenzae	7 (1.40, 0.67-2.92)	2 (3.56, 0.90-14.07)
N. meningitidis	1 (1.38, 0.19-9.92)	3 (2.85, 1.04-7.84)
Others	1 (0.15, 0.02-1.05)	-

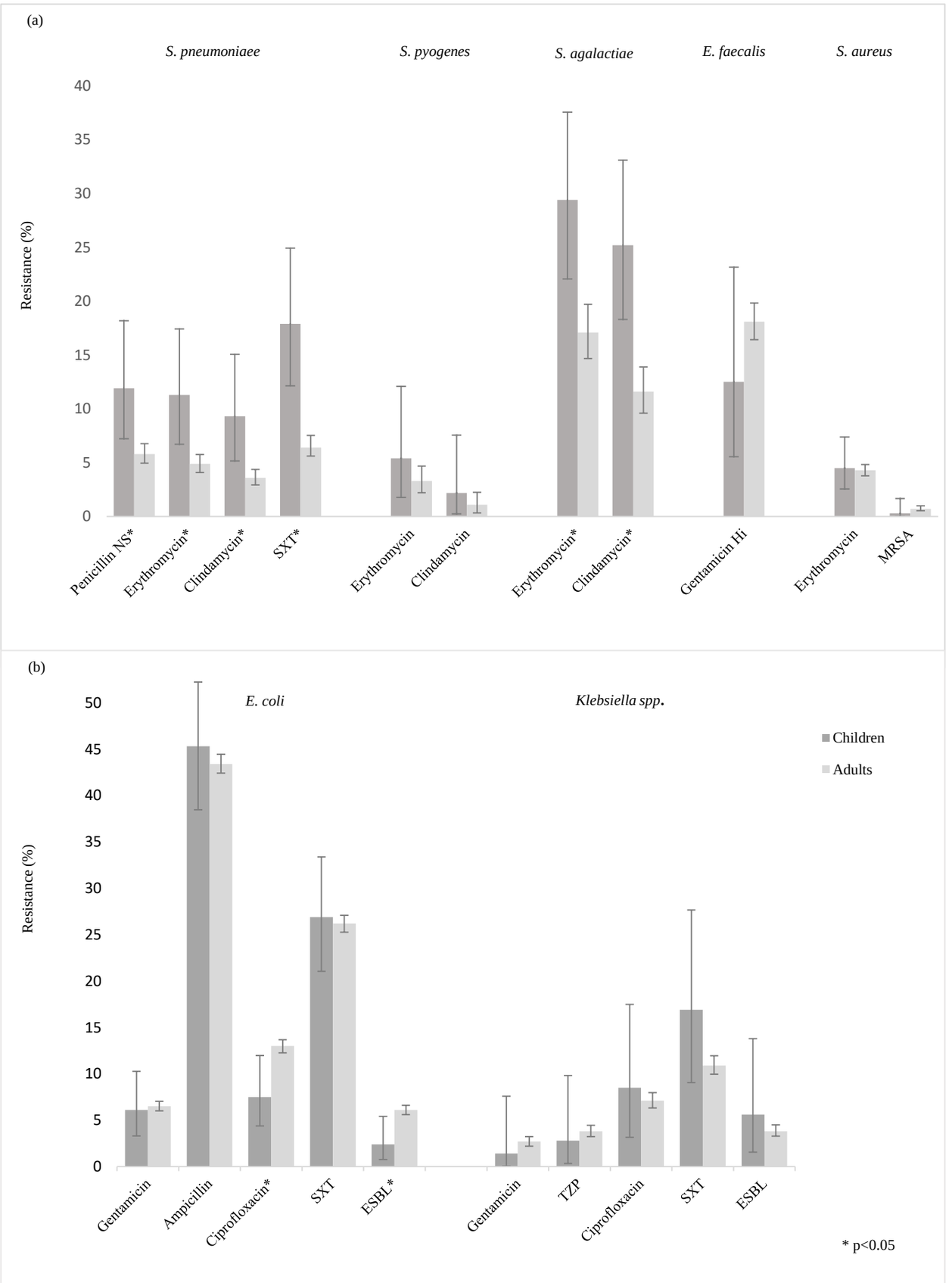
Table 2) Bacterial isolates from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) 2013-2017 - total number, main bacterial pathogens in children (0-18 years) and relative risk ratio (RR) in children to adults.

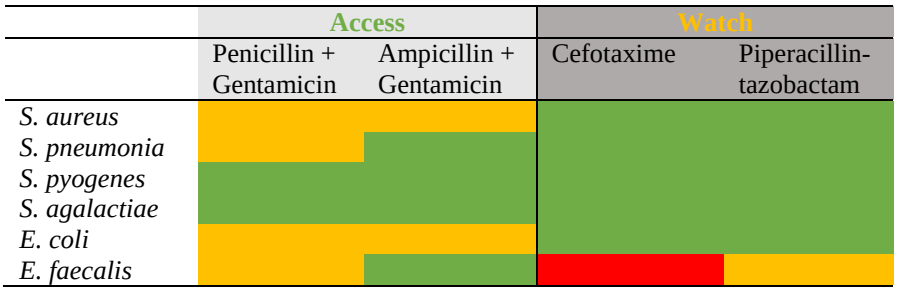
* All age gropus: *E. faecalis* (64)), *E. faecium* (9), *Enterococcus spp.* (3), *K. pneumoniae* (54), *K. oxytoca* (13), *Klebsiella spp*. (3).

All age groups: *Proteus spp*. (2), *Enterobacter spp*. (2), *P. aeruginosa* (5).


Invasive infections
Annual incidence per 100 000 person
350
300
250
200
150
100
50
0
Adults
0-1 years
1-6 years
6-18 years


(a)
(b)
100
75
50
25
0
Proportion of isolates (%)
Adults
0-1 years
1-6 years
6-18 years
S. aureus
S. pneumoniae
S. pyogenes
S. agalactiae
Enterococcus spp.
E. coli
Klebsiella spp.
P. aeruginosa
Proteus/Enterobacter spp.
H. influenzae
N. meningitidis
Gram-positive bacteria
Gram-negative bacteria


(a)
S. pneumoniaee
S. pyogenes
S. agalactiae
E. faecalis
S. aureus
Resistance (%)
0
5
10
15
20
25
30
35
40
Penicillin NS*
Erythromycin*
Clindamycin*
SXT*
Erythromycin
Clindamycin
Erythromycin*
Clindamycin*
Gentamicin Hi
Erythromycin
MRSA
(b)
E. coli
Klebsiella spp.
Children
Adults
Resistance (%)
0
5
10
15
20
25
30
35
40
45
50
Gentamicin
Ampicillin
Ciprofloxacin*
SXT
ESBL*
Gentamicin
TZP
Ciprofloxacin
SXT
ESBL
* p<0.05



Go!	Resistance < 5 %
Be aware	*Resistance 5-10 % * Resistance < 5%, but limited clinical evidence, or increased exposure needed for > 10%
No!	Resistance > 10 %

Access: antibiotics with less resistance potential Watch: antibiotics with more resistance potential

	Children			Adults			
	S*, n (%)	**I, n (%)**	**R, n (%)**	**S, n (%)**	**I, n (%)**	**R, n (%)**	**P#**
***S. pneumoniae* (n=151/2674)**							
Penicillin	133 (88.1)	16 (10.6)	2 (1.3)	2512 (94.2)	148 (5.5)	7 (0.3)	***0.002***
Erythromycin	134 (88.7)	0 (0.0)	17 (11.3)	2537 (95.1)	0 (0.0)	130 (4.9)	***0.001***
Clindamycin	137 (90.7)	-	14 (9.3)	2571 (96.4)	-	96 (3.6)	***<0.001***
SXT	120 (79.5)	4 (2.6)	27 (17.9)	2421 (90.8)	75 (2.8)	174 (6.4)	***<0.001***
Cefotaxime	147 (97.4)	4 (2.6)	0 (0.0)	2656 (99.3)	16 (0.6)	2 (0.1)	1.000
***S.pyogenes* (n=93/883)**							
Penicillin	93 (100)	-	0 (0)	883 (100)	0 (0)	0 (0)	n/a
Erythromycin	88 (94.6)	0 (0.0)	5 (5.4)	854 (96.7)	0 (0)	29 (3.3)	0.364
Clindamycin	91 (97.8)	-	2 (2.2)	866 (98.1)	-	17 (1.9)	0.701
SXT	90 (96.8)	0 (0)	3 (3.2)	863 (97.7)	3 (0.3)	17 (1.9)	0.428
***S. agalactiae* (n=143/895)**							
Penicillin	143 (100)	-	0 (0)	895 (100)	-	0 (0)	n/a
Erythromycin	96 (67.1)	5 (3.5)	42 (29.4)	702 (78.4)	40 (4.5)	153 (17.1)	***<0.001***
Clindamycin	107 (74.8)	-	36 (25.2)	791 (88.4)	-	104 (11.6)	***<0.001***
Vancomycin	143 (100)	-	0 (0)	895 (100)	-	0 (0)	n/a
***E. faecalis* (n=64/2013)**							
High level gentamicin	-	56 (87.5)	8 (12.5)	-	1649 (81.9)	364 (18.1)	0.252
Ampicillin	64 (100)	0 (0.0)	0 (0.0)	2011 (99.9)	1 (0.0)	1 (0.0)	1.000
Imipenem	63 (98.4)	1 (1.6)	0 (0.0)	1990 (98.9)	19 (0.9)	4 (0.2)	1.000
Vancomycin	64 (100)	-	0 (0.0)	2011 (99.9)	-	2 (0.1)	1.000
***S. aureus* (n=330 / 5832)**							
Beta-lactamase	89 (27.0)	-	241 (73.0)	1626 (27.9)	-	4206 (72.1)	0.719
MRSA	329 (99.7)	-	1 (0.3)	5789 (99.3)	-	43 (0.7)	0.730
Gentamicin	327 (99.1)	-	3 (0.9)	5809 (99.6)	-	23 (0.4)	0.160
Erythromycin	315 (95.5)	-	15 (4.5)	5571 (95.6)	7 (0.1)	250 (4.3)	0.824
Clindamycin	324 (98.2)	4 (1.2)	2 (0.6)	5738 (98.4)	24 (0.4)	70 (1.2)	0.592
SXT	329 (99.7)	1 (0.3)	0 (0.0)	5808 (99.6)	8 (0.1)	16 (0.3)	1.000
Ciprofloxacin	324 (98.2)	-	6 (1.8)	5609 (96.2)	-	223 (3.8)	0.061
***E. coli* (n=212 / 9073)**							
Gentamicin	198 (93.4)	1 (0.5)	13 (6.1)	8445 (93.1)	37 (0.4)	591 (6.5)	0.824
Ampicillin	116 (54.7)	-	96 (45.3)	5133 (56.6)	-	3940 (43.4)	0.590
Cefotaxime	207 (97.6)	0 (0.0)	5 (2.4)	8484 (93.5)	21 (0.2)	568 (6.3)	***0.020***
Piperacillin/tazobactam	209 (98.6)	2 (0.9)	1 (0.5)	8548 (94.2)	346 (3.8)	179 (2.0)	0.197
Meropenem	212 (100.0)	0 (0.0)	0 (0.0)	9071 (100.0)	2 (0.0)	0 (0.0)	n/a
Ciprofloxacin	191 (90.1)	5 (2.4)	16 (7.5)	7723 (85.1)	175 (1.9)	1175 (13.0)	***0.020***
SXT	154 (72.6)	1 (0.5)	57 (26.9)	6626 (73.0)	72 (0.8)	2375 (26.2)	0.816
ESBL	207 (97.6)	-	5 (2.4)	8521 (93.9)	-	552 (6.1)	***0.018***
***Klebsiella spp*. (n=71 / 3897)&**							
Gentamicin	70 (98.6)	0 (0.0)	1 (1.4)	3774 (96.8)	19 (0.5)	104 (2.7)	1.000
Cefotaxime	67 (94.4)	1 (1.4)	3 (4.2)	3726(95.6)	19 (0.5)	152 (3.9)	0.756
Piperacillin/tazobactam	66 (93.0)	3 (4.2)	2 (2.8)	3461 (88.8)	288 (7.4)	148 (3.8)	1.000
SXT	58 (81.7)	1 (1.4)	12 (16.9)	3428 (88.0)	43 (1.1)	426 (10.9)	0.112
Ciprofloxacin	64 (90.1)	1 (1.4)	6 (8.5)	3503 (89.9)	117 (3.0)	277 (7.1)	0.663
ESBL	67 (94.4)	-	4 (5.6)	3747 (96.2)	-	150 (3.8)	0.355

SDC 1) Susceptibility pattern in Norwegian invasive (blood/CSF) isolates in children (0-18 years) and adults based on sampling from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) 2013-2017. SXT; trimethoprim/sulfamethoxazole

* S=susceptible, I=intermediate resistant, R=resistant

Chi squared test comparing R with SI, except for S. pneumoniae/Penicillin G were we compared S with RI. Fisher`s exact test was used if any expected frequency <5

& Children: Klebsiella pneumonia (55, 77.5%), Klebsiella oxytoca (13, 18.3%), not identified species (3, 4.2%), Adults: Klebsiella pneumonia (3071, 77.4%), Klebsiella oxytoca (746, 18.8%), not identified species (151, 3.8%)

	2013		2014		2015		2016		2017		P*
	Total n	Resistant n(%)	Total n	Resistant n(%)	Total, n	Resistant n(%)	Total n	Resistant n(%)	Total n	Resistant n(%)	
Children											
S. pneumoniae											
Penicillin NS	33	2 (6.1)	28	5 (17.9)	27	3 (11.1)	39	1 (2.6)	24	7 (29.2)	***0.017***
Erythromycin	33	0 (0.0)	28	5 (17.9)	27	1 (3.7)	39	3 (7.7)	24	8 (33.3)	***0.001***
Clindamycin	33	0 (0.0)	28	4 (14.3)	27	1 (3.7)	39	1 (2.6)	24	8 (33.3)	***0.000***
SXT	33	3 (9.1)	28	5 (17.9)	27	8 (29.6)	39	5 (12.8)	24	6 (25.0)	0.215
S. pyogenes											
Erythromycin	13	0 (0.0)	20	0 (0.0)	18	2 (11.1)	16	1 (6.3)	26	2 (7.7)	0.572
S. agalactiae											
Erythromycin	n/a	n/a	47	10 (21.3)	50	12 (24.0)	14	6 (42.9)	32	14 (43.8)	0.079
Clindamycin	n/a	n/a	47	9 (19.2)	50	9 (18.0)	14	7 (50.0)	32	11 (34.4)	***0.040***
E. faecalis											
High level gentamicin	12	3 (25.0)	12	0 (0.0)	15	1 (6.7)	12	2 (16.7)	13	2 (15.4)	0.396
S. aureus											
Beta-lactamase	81	61 (75.3)	62	43 (69.4)	70	51 /72.9)	45	33 (73.3)	72	53 (73.6)	0.957
Erythromycin	81	4 (4.9)	62	0 (0.0)	70	3 (4.3)	45	5 (11.1)	72	3 (4.2)	0.099
Ciprofloxacin	81	0 (0.0)	62	1 (1.6)	70	1 (1.4)	45	1 (2.2)	72	3 (4.2)	0.376
E.coli											
Gentamicin	33	3 (9.1)	35	2(5.7)	46	2(4.3)	47	2(4.3)	51	4(7.8)	0.870
Ampicillin	33	18(54.6)	35	16(45.7)	46	22(47.8)	47	13(27.7)	51	27 (52.9)	0.079
Cefotaxime	33	1(3.0)	35	0(0.0)	46	0(0.0)	47	1(2.1)	51	3 (5.9)	0.368
Ciprofloxacin	33	3(9.1)	35	1(2.9)	46	2(4.4)	47	2(4.3)	51	8(15.7)	0.160
SXT	33	13(39.4)	35	10(28.6)	46	16(34.8)	47	5(10.6)	51	13(25.5)	***0.033***
ESBL	33	1(3.0)	35	0(0.0)	46	0(0.0)	47	1(2.1)	51	3(5.9)	0.368
Klebsiella spp.											
SXT	10	5 (50.0)	9	1 (11.1)	12	0 (0.0)	25	2 (8.0)	15	4 (26.7)	***0.012***
ESBL	10	1 (10.0)	9	0 (0.0)	12	0 (0.0)	25	1 (4.0)	15	2 (13.3)	0.479
Ciprofloxacin	10	0 (0.0)	9	0 (0.0)	12	0 (0.0)	25	3 (12.0)	15	3 (20.0)	0.286
Adults											
S. pneumoniae											
Penicillin NS	575	17 (3.0)	533	26 (4.9)	492	36 (7.3)	555	31 (5.6)	512	45 (8.8)	***0.001***
Erythromycin	575	22 (3.8)	533	20 (3.8)	492	24 (4.9)	555	30 (5.4)	512	34 (6.6)	0.159
Clindamycin	575	15 (2.6)	533	14 (2.6)	492	18 (3.7)	555	24 (4.3)	512	25 (4.9)	0.174
SXT	575	20 (3.5)	533	30 (5.6)	492	41 (8.3)	555	42 (7.6)	512	38 (7.4)	***0.008***
S. pyogenes											
Erythromycin	149	3 (2.0)	168	7 (4.2)	182	5 (2.8)	171	6 (3.5)	213	8 (3.8)	0.829
Clindamycin	149	1 (0.7)	168	4 (2.4)	182	3 (1.7)	171	3 (1.8)	213	6 (2.8)	0.690
SXT	149	5 (3.4)	168	5 (3.0)	182	2 (1.1)	171	3 (1.8)	213	2 (0.9)	0.356
S. agalactiae											
Erythromycin	n/a	n/a	196	34 (17.4)	229	38 (16.6)	267	42 (15.7)	203	39 (19.2)	0.791
Clindamycin	n/a	n/a	196	22 (11.2)	229	30 (13.1)	267	28 (10.5)	203	24 (11.8)	0.835
E. faecalis											
High level gentamicin	401	94 (23.4)	395	76 (19.2)	368	49 (13.3)	409	77 (18.8)	440	68 (15.5)	***0.003***
S. aureus											
Beta-lactamase	1074	772 (71.9)	1101	805 (73.1)	1207	881 (73.0)	1210	879 (72.6)	1240	869 (70.1)	
MRSA	1074	3 (0.3)	1101	9 (0.8)	1207	8 (0.7)	1210	13 (1.1)	1240	10 (0.8)	0.265
Erythromycin	1070	41 (3.8)	1101	47 (4.3)	1207	66 (5.5)	1210	59 (4.9)	1240	37 (3.0)	***0.029***
Clindamycin	1074	17 (1.6)	1101	9 (0.8)	1207	20 (1.7)	1210	16 (1.3)	1240	8 (0.7)	0.085
SXT	1074	6 (0.6)	1101	0 (0.0)	1207	4 (0.3)	1210	3 (0.3)	1240	3 (0.2)	0.132
Ciprofloxacin	1074	33 (3.1)	1101	32 (2.9)	1207	28 (2.3)	1210	86 (7.1)	1240	44 (3.6)	***0.000***
Gentamicin	1074	3 (0.3)	1101	5 (0.5)	1207	2 (0.2)	1210	5 (0.4)	1240	8 (0.7)	0.404
E. coli											
Gentamicin	1579	87(5.6)	1610	125(7.8)	1906	113(5.9)	1893	120(6.3)	2085	146(7.0)	0.068
Ampicillin	1579	670(42.4)	1610	685(42.6)	1906	839(44.0)	1893	831(43.9)	2085	915(43.9)	0.779
Cefotaxime	1579	86(5.5)	1610	100(6.2)	1906	127(6.7)	1893	115(6.1)	2085	140(6.7)	0.531
Piperacillin/tazobactam	1579	34(2.2)	1610	47(2.9)	1906	29(1.5)	1893	37(2.0)	2085	32(1.5)	***0.019***
Ciprofloxacin	1579	187(11.8)	1610	206(12.8)	1906	222(11.7)	1893	243(12.8)	2085	317(15.2)	***0.007***
SXT	1579	397(25.1)	1610	447(27.8)	1906	509(26.7)	1893	495(26.2)	2085	527(25.3)	0.389
ESBL	1579	80(5.1)	1610	95(5.9)	1906	127(6.7)	1893	112(5.9)	2085	138(6.6)	0.266
Klebsiella spp.											
Gentamicin	642	7 (1.1)	745	19 (2.6)	811	22 (2.7)	830	29 (3.5)	869	27 (3.1)	0.061
Cefotaxime	642	15 (2.3)	745	27 (3.6)	811	24 (3.0)	830	40 (4.8)	869	46 (5.3)	***0.013***

ESBL	642	17 (2.7)	745	26 (3.5)	811	24 (3.0)	830	38 (4.6)	869	45 (5.2)	***0.043***
Piperacillin/tazobactam	642	23 (3.6)	745	29 (3.9)	811	27 (3.3)	830	34 (4.1)	869	35 (4.0)	0.922
SXT	64	64 (10.0)	745	71 (9.5)	811	80 (9.9)	830	91 (11.0)	869	120 (13.8)	***0.033***
Ciprofloxacin	642	19 (3.0)	745	30 (4.0)	811	29 (3.6)	830	93 (11.2)	869	106 (12.2)	***0.000***

SDC 2a) Year-by-year resistance rates in invasive (blood/CSF) bacterial isolates for children (0-18 years) and adults from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM). SXT; trimethoprim/sulfamethoxazole; Penicillin NS; penicillin non-susceptibility

* Chi squared test comparing proportion of resistance. Fisher`s exact test was used if any expected frequency <5.

	S*, n (%)	**I, n (%)**	**R, n (%)**
E. faecium **(n=9)**			
Ampicillin	2 (22.2)	0 (0.0)	7 (77.8)
Gentamicin	9 (100.0)	-	0 (0.0)
Imipenem	1 (11.1)	1 (11.1)	7 (88.8)
Vancomycin	9 (100.0)	-	0 (0.0)
H. influenzae **(n=34)**			
Beta-lactamase	32 (94.1)	-	2 (5.9)
Ampicillin	31 (91.2)	-	3 (8.8)
Cefotaxime	34 (100.0)	-	0 (0.0)
Ciprofloxacin	34 (100.0)	-	0 (0.0)
Trimethoprim/sulfamethoxazole	30 (88.2)	-	4 (11.8)
N. meningitidis **(n=12)**			
Penicillin G	6 (50.0)	5 (41.7)	1 (8.3)
Ceftriaxone	12(100.0)	-	0 (0.0)
Azithromycin	12 (100.0)	-	0 (0.0)
P. aeruginosa **(n=5)**			
Gentamicin	5 (100.0)	-	0 (0.0)
Tobramycin	5 (100.0)	-	0 (0.0)
Ceftazidime	4 (80.0)	-	1 (20.0)

SDC 2b) Susceptibility pattern for selected bacteria in invasive (blood/CSF) isolates in children (0-18 years) from the Norwegian Surveillance System for Antimicrobial Drug Resistance (NORM) 2013-2017

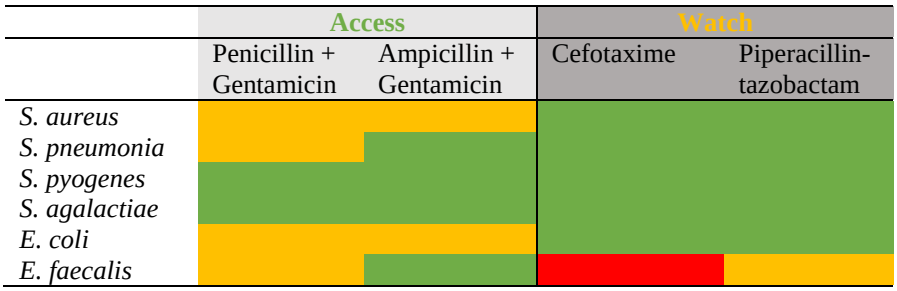
* S (sensitive), I (intermediate resistant), R (resistant)

	0-1 years % (95% CI)	1-6 years % (95% CI)	6-18 years % (95% CI)	P-value*
S. pneumonia				
All isolates, n	40	73	38	
Resistance rates, % (95% CI)				
Penicillin NS	5.0 (0.6-16.9)	13.7 (6.8-23.8)	15.8 (6.0-31.3)	0.252
Erythromycin	7.5 (1.6-20.4)	11.0 (4.9-20.5)	15.8 (6.0-31.3)	0.530
Clindamycin	7.5 (1.6-20.4)	8.2 (3.1-17.0)	13.2 (4.4-28.1)	0.670
SXT	7.5 (1.6-20.4)	24.7 (15.3-36.1)	15.8 (6.0-31.3)	0.070
Multi-resistance#	2.5 (0.06-13.2)	9.6 (3.9-18.8)	7.9 (1.7-21.4)	0.685
S. aureus				
All isolates, n	119	45	165	
Resistance rates, % (95% CI)				
Beta-lactamase	79.0 (70.1-85.9)	73.3 (58.1-85.4)	68.3 (60.6-75.3)	0.135
Erythromycin	7.6 (3.5-13.9)	2.2 (0.06-11.8)	3.1 (1.0-7.0)	0.167
Ciprofloxacin	0.8 (0.2-4.6)	4.4 (0.5-15.1)	1.8 (0.4-5.3)	0.237
E. coli				
All isolates, n	131	28	53	
Resistance rates, % (95% CI)				
Gentamicin	3.8 (1.3-8.7)	7.1 (0.9-23.5)	11.3 (4.3-23.0)	0.121
Ampicillin	42.0 (33.4-50.9)	39.3 (21.5-59.4)	56.6 (42.3-70.2)	0.155
Ciprofloxacin	6.1 (2.7-11.7)	7.1 (0.9-23.5)	11.3 (4.3-23.0)	0.442
SXT	19.6 (13.4-27.8)	28.6 (13.2-48.7)	43.4 (29.8-57.7)	***0.005***
ESBL	2.3 (0.5-6.5)	7.1 (0.9-23.5)	0.0 (0.0-6.7)	0.120

SDC 3) Comparison of resistance rates for selected bacteria between different age-groups in Norwegian children, 2013-2017. Penicillin NS; penicillin nonsusceptibility; SXT; trimethoprim/sulfamethoxazole

* Chi squared test comparing the proportion of resistant isolates. Fisher`s exact test was used if any expected frequency <5.

Resistant (or non-susceptible to penicillin) to three or more of the antibiotics above



Go!	Resistance < 5 %
Be aware	*Resistance 5-10 % * Resistance < 5%, but limited clinical evidence, or increased exposure needed for > 10%
No!	Resistance > 10 %

Access: antibiotics with less resistance potential Watch: antibiotics with more resistance potential