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Potential for More Rational Use of Antibiotics in Hospitalized Children in a Country with Low Resistance - Data From Eight Point Prevalence Surveys

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Abstract

Background: Antimicrobial resistance (AMR) is low in Norway, but to prevent an increase the Norwegian Government has launched a National Strategy including a 30% reduction of broad-spectrum antibiotics (BSA) in hospitals within 2020. BSA are defined as second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and quinolones. There are no recent studies of antibiotic use in Norwegian hospitalized children.

Aim of the study: To describe the use of antibiotics with emphasis on BSA in Norwegian hospitalized children and neonates in order to detect possibilities for optimization.

Methods: Data were extracted from eight national point prevalence surveys of systemic antibiotic prescriptions in Norwegian hospitals between 2015 and 2017. The choices of antibiotics were compared with the empirical recommendations given in available Norwegian guidelines. In total, 1323 prescriptions were issued for 937 patients.

Results: Twenty-four percent of pediatric inpatients were given antibiotics. Adherence to guidelines was 48%, and 30% (95% CI 27%-33%) of all patients on antibiotics received BSA. We identified only small variations in use of BSA between hospitals. One third of the patients on antibiotic therapy received prophylaxis whereof 13% where given BSA. In 30% of prescriptions with BSA, no microbiological sample was obtained prior to treatment.

Conclusion: This study reveals an excess of prescriptions with BSA in relation to the low resistance rate in Norway. Our findings reveal areas for improvement that can be useful in the forthcoming antibiotic stewardship programs in Norwegian pediatric departments.

Key words: broad-spectrum antibiotics; antimicrobial resistance; guidelines; pediatric antibiotic stewardship

Introduction

Increasing antimicrobial resistance (AMR) is partly caused by inappropriate use of antibiotics [1, 2]. Compared with other countries the prevalence of AMR in Norway is low and narrow-spectrum antibiotics like beta-lactamase sensitive penicillins, aminopenicillins and aminoglycosides can still be used for most indications [3, 4] (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D185 which shows selected resistance rates).

Despite low resistance rates, use of broad-spectrum antibiotics (BSA) has increased in Norwegian hospitals during the last 10 years [3]. BSA are defined as second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and quinolones according to the Norwegian National Strategy against antibiotic resistance, where the aim is a 30% reduction in BSA from 2012 to 2020 [5].

Outpatient antibiotic use in Norwegian children has decreased significantly during the recent years [6]. Studies in Scandinavian inpatient term born infants indicate that antibiotic use can be reduced and that empirical treatment for sepsis varies [7, 8]. Furthermore, Raastad et al revealed a significantly increased consumption of BSA in a highly specialized Norwegian pediatric department [9]. Except from this, there is a lack of studies exploring antibiotic use in hospitalized Norwegian children and neonates. Rational use of antibiotics in children and neonates is especially important since exposures to antibiotics (especially BSA) in childhood also may increase the risk of metabolic and immunologic diseases [10, 11].

The aim of this study was to describe the use of antibiotics with emphasis on BSA in Norwegian hospitalized children and neonates. Furthermore, we wanted to compare antibiotic prescriptions to available Norwegian guidelines to define areas of improvement.

Materials and Methods

Data collection

We collected data from eight nationwide point prevalence surveys organized by the Norwegian Institute of Public Health (NIPH). All surveys were conducted by the same method [12], that is very similar to the ones used by European Centre of Disease Prevention and Control (ECDC) [13]. The surveys were conducted in May, August, and November in 2015, February, May, August and October in 2016, and February in 2017. Four of the surveys were mandatory for all hospitals in Norway, while four were voluntary.

Infections and antibiotic use in all inpatients were anonymously registered by applying a registration form developed by the NIPH [12]. Antibiotics were here defined as antibacterials for systemic use (J01), oral vancomycin (A07AA09) and oral metronidazole (P01AB01). Tuberculostatics were not included. The registrations were performed at 08.00 AM on the day of registration.

In each department the total number of hospitalized patients and the number of patients receiving antibiotics were noted. Information about the patient's gender, age, name of antibiotic, dosage, route of administration, indication, prescriber's medical specialty (including junior doctors) and whether a microbiologic sample was obtained prior to the prescription were recorded. Antibiotics were registered either as treatment or as prophylaxis (medical or surgical). Surgical prophylaxis was defined as use of antibiotics immediately before, during and shortly after an operative procedure to prevent infection by reducing the bacterial load in the operating range and prevent spreading to blood and tissue. Prophylaxis that patients had received during the 24 hours prior to the point prevalence survey were registered. Medical prophylaxis was defined as use of

antibiotics to prevent infection in patents at risk, e.g. urinary tract infections in patients with vesicoureteral reflux.

Furthermore, it was noted whether an infection was healthcare-associated or community-acquired. Healthcare associated infections were defined as infections that occurred two days or later after admission to hospital or infections arising after discharge leading to readmission or post-operative infections [13]. All other infections were classified as community-acquired. Indications and classifications were based on the medical records and/or statements from the doctor in charge of the patient, and should be classified in accordance with definitions/indication lists of the point prevalence survey manual [12].

In each department the registration forms were completed by a doctor or pharmacist who had received detailed information about registration criteria by the NIPH. Quality control was performed by an infection-control doctor or nurse in each hospital before electronical submission to the NIPH.

Population and hospitals

The study population consisted of all hospitalized children (0-19 years) and neonates on the dates of the surveys. Neonates are defined as patients admitted in a neonatal unit and mainly consist of admissions from the maternity ward, but in some unites they also treat critically ill infants < 3 months admitted from primary care. The data do not give us access to the total number of admitted children in wards mixed with adults, so for this group we could only identify those receiving systemic antibiotics.

There are 68 hospitals in Norway registered in the database of the NIPH and for the mandatory surveys the number of participating hospitals were 51 (75%), 60 (88%), 61 (90%) and 62 (91%). For the voluntary survey the numbers were 21 (31%), 30 (44%), 24 (35%) and 31 (46%). The

hospitals missing from the mandatory surveys were mainly small private institutions. For our analyses the hospitals were anonymous.

Antibiotic guidelines

To evaluate adherence to guidelines we used three national guidelines, and deviation was defined as treatment different from the empirical recommendations with respect to the diagnosis made by the clinician. Data on allergies, prior treatment failure history and treatment based on sensitivities from microbiologic samples were not available.

For most indications we compared prescriptions with recommendations in the Norwegian Supervisor of Acute Pediatrics, version 2013 [14]. For treatment of neonatal sepsis we compared prescriptions with the recommendations in the Norwegian Neonatal Supervisor [15], and for treatment of intraabdominal infections we used The National Guidelines of Antibiotic use in Hospitals (for adults) [16]. A summary of the recommendations is shown in Table 1. Only the treatment options in Table 1 were assessed and included in the adherence analyses.

Analyses

Data were extracted from the database of the NIPH and all eight prevalence registrations were analyzed together. During the study period, no new guidelines or recommendations were issued. The use of BSA is presented as proportion of all prescriptions and as proportion of all patients. The data are categorical and presented as numbers and percentages. Confidence intervals (CI) for proportions was calculated using binomial distribution. Statistical comparisons were performed using a chi-square test with p-value <0.05 for significance. For analyses we used Microsoft Excel 2016 and Stata version 15.1.

Ethics

The data were collected according to the Regulations for the Norwegian surveillance system for antibiotic use and healthcare-associated infections [17]. No further approvals were required.

Results

Total antibiotic use

Antibiotics for children were prescribed in 43 different hospitals, 23 had a pediatric department and of these, 15 also had a neonatal department.

In pediatric wards, 672 (24%) out of 2827 children and neonates were given systemic antibiotics (Table 2). When including children in wards mixed with adults, 937 patients were given 1323 antibiotics (in average 1.4), and 30% (95% CI 27%-33%) of the patients received BSA. Figure 1 shows only small variations in the rate of BSA prescriptions for the hospitals accounting for most of the prescriptions. There were no significant differences in the proportions of inpatients on antibiotics or the proportions of treated patients on BSA when comparing the voluntary with the mandatory surveys.

More than half of the prescriptions were for neonates and children less than 5 years, but the proportion of patients on BSA were higher for children between 5 and 19 years (22% versus 38%) ($p < 0.01$). Parenteral route for administrating antibiotics was used in 73% of prescriptions in children and 95% of neonatal prescriptions. Eighty percent of the children received one type of antibiotics and 69 % of neonates received two. Of 285 prescriptions with BSA (children and neonates), 62% were prescribed as monotherapy while 38% was combined with at least one other antibiotic.

Lower respiratory tract infection was the most frequent indication for antibiotic use in children (11%), while neonatal sepsis accounted for most of the neonatal prescriptions (43%). Lower

respiratory tract infections and intraabdominal infections accounted for 19 % of all BSA prescriptions.

Treatment

Sixty percent of all patients on antibiotics where treated for an infection, whereof 34% were treated with BSA. Community acquired infections accounted for 69% of the BSA prescriptions while hospital acquired infections accounted for 31%. Intraabdominal and central nervous system (CNS) infections accounted for the highest proportion of BSA prescriptions (Table 3). Adherence to guidelines was 48%, varying from 19% to 82% depending on the indication (Table 3).

Phenoxymethyl- and benzylpenicillin were the most commonly used antibiotics in children and aminoglycosides in neonates (combined with ampicillin in 64% of the cases and benzylpenicillin in 36% of the cases). Third-generation cephalosporins were the most commonly used BSA in both groups (Figure 2).

Prophylaxis

Of all children on antibiotics, 17% received surgical prophylaxis and 15% received medical prophylaxis (Table 2). The proportion of patients treated with BSA was 14% whereof piperacillin/tazobactam and third-generation cephalosporins accounted for 68% (Figure 2). Of all neonates on antibiotics, 10% received surgical prophylaxis and 17% medical prophylaxis, only two patients received BSA.

Microbiologic testing

Microbiologic sampling was obtained prior to treatment in 135 (70%) of 192 prescriptions with BSA, and prior to 433 (75%) of 581 prescriptions with other antibiotics. The rate was lowest for

patients treated for intraabdominal infection, namely 60% for BSA and 58% for other antibiotics. For more results, Table, Supplemental Digital Content 2, http://links.lww.com/INF/D186.

For sepsis and/or neutropenic fever, 6 (12%) of 50 patients had a positive blood culture, whereof two patients were given BSA. For neonatal sepsis 16 (28%) of 58 patients had a positive blood culture, whereof one patient was given BSA.

Discussion

The main finding in this study was that nearly one third of the patients treated with antibiotics received BSA, and that adherence to guidelines was less than 50%.

Compared with the entire Norwegian hospitalized population, the pediatric inpatients in our study were prescribed less BSA and more aminoglycosides [18]. However, for children between 5 and 19 years, the proportion of BSA was close to the average of the entire population [18].

The proportion of children and neonates receiving antibiotics were comparable with the results from eight earlier point prevalence surveys conducted in a Norwegian pediatric department between 1996-1998 [19]. However, we found that the use of BSA was doubled despite a persistent low resistance rate [3]. There is no good explanation for this observation, although resistance rates have increased slightly also in Norway [3]. International treatment trends could possibly have had an impact on prescribing habits and may explain part of the increase in the BSA use. It should be noted that the prescription rate of carbapenems and third generation cephalosporins was considerably lower in our study than in a study conducted in a single Norwegian hospital treating a large number of immunodeficient children [9].

Both children and neonates in our study were given less antibiotics compared with international pediatric point prevalence studies [20-23], and less BSA and more aminoglycosides compared with most other parts of the world [22]. Furthermore, the proportion of prescriptions for lower

respiratory tract infections was lower compared with international surveys [21, 22]. This may be because vaccines for Streptococcus pneumococci and Haemophilus influenza are offered to all Norwegian children, and that a larger number of pneumonias in our study probably were regarded as viral [24].

Adherence to guidelines was much lower than in an older study from Norway [19]. Penicillin allergy could be a reason for choosing BSA instead of penicillin, but the prevalence of true penicillin allergy is estimated to be very low, only 0.01 – 0.05% [25], and recently it was found that among children reported to have allergy to penicillin, only around 20% had true allergy [26]. For community acquired lower respiratory tract infections, there is a potential for increased use of narrow-spectrum antibiotics because of the favorable resistance rates in Norway [3]. For health care associated pneumonia we question the necessity of BSA as first line therapy for all cases of infections. Furthermore, the use of BSA can be reduced by good hygiene routines [27].

In Norway, resistance to aminoglycosides is low [3]. Hence, for most cases of urinary tract infections, septicemia, and neutropenic fever, aminoglycosides can safely be used if combined with benzylpenicillin or ampicillin. Chronic renal failure is a contraindication to aminoglycosides, but this is uncommon in children [28]. The high rate of BSA use in intensive wards could partly be explained by fear of acute kidney failure due to aminoglycosides. Regarding neonates with sepsis, the high use of ampicillin on behalf of benzylpenicillin may increase selection of gram-negative bacteria in neonatal units [29]. Ampicillin for this indication is not consistent with the guidelines [15] and is in contrasts to results from point prevalence surveys from other countries in northern Europe and Africa [22]. For intraabdominal infections our results may indicate that BSA are preferred over narrow spectrum alternatives when ranked equally in the guideline.

Mistrust to guidelines could be a reason for low adherence to guidelines in clinical practice. Mistrust could be the result of biased information. For example, a randomized controlled trial on adult patients with febrile neutropenia performed in Norway demonstrated significantly higher failure rates and mortality in patients empirically treated with benzylpenicillin and an aminoglycoside relative to carbapenems [30]. On the other hand, a retrospective study from Norway comparing children with febrile neutropenia receiving either benzylpenicillin or ampicillin and an aminoglycoside or a regimen based on third-generation cephalosporins revealed no significant difference in clinical outcome [31]. Furthermore, as resistance to gentamycin has increased slightly in Norway (from 4% to 6% from 2007-2016 in Escherichia coli blood culture isolates) [3], this might have decreased the threshold for choosing BSA empirically when sepsis is suspected. In the future it will be important to agree on the balance between acceptable resistance rates, empirically treatment and the ecologic advantages of choosing narrow-spectrum antibiotics.

The high use of other narrow-spectrum antibiotics than those suggested in the guidelines may also indicate a degree of mistrust and that time is ripe for a revision of pediatric antibiotic guidelines in Norway. Moreover, there is a need for resistance data exclusively for Norwegian children to tailor pediatric antibiotic guidelines better. A study from Canada revealed that AMR in general was lower in children compared with adults, whereas a multinational study found higher resistance rates in children for some selected bacteria-antibiotic combinations [32, 33]. Other pediatric studies have highlighted the high proportion of antibiotics used for medical prophylaxis [20, 22, 23], and we found a similar proportion in our study. Thus, there is a need for further clarification regarding the prescription of antibiotics for medical prophylaxis in both children and neonates. Furthermore, none of the guidelines recommends the use of BSA for

prophylaxis. Different antibiotics than those used for treatment should be used to minimize the risk of increasing resistance [16]. Thus, the high use of BSA for prophylactic purposes may be an area for improvement.

The rate of microbiologic sampling before the initiation of antimicrobial therapy with BSA was disappointingly low in our study. A higher rate of sampling may reduce the use of BSA as susceptibility patterns could help adjust antimicrobial treatment according to the infectious agent at hand. The low proportion of neonates on BSA out of those with culture positive sepsis (1/16), indicate that most bacteria are susceptible to narrow-spectrum antibiotics.

Limitations and strengths of the study

A disadvantage of point prevalence surveys is that casualties on the prevalence day, like an ongoing epidemic, may influence the results. We reduced this problem by using data from eight different surveys conducted in different seasons with a high number of participants. The small variations in BSA prescription rate between the hospitals also increase the credibility of our findings.

The high proportion of prescriptions with an unknown classification and indication for treatment may have impacted our results, but we could not find any differences in age, prescriber's specialty, gender or institutions, that deviated from the group of children with a known classification or indication.

For the calculation of adherence to guidelines, one should optimally include targeted treatment based on microbiologic samples. Worldwide, approximately 20% of prescriptions are targeted, thus our adherence rate would most likely increase if targeted treatment was included [22].

Conclusion

This study serves as a valuable baseline for antibiotic surveillance in Norwegian hospitalized children and highlights the need for improved antibiotic stewardship in a country with low resistance rates. It reveals an overuse of BSA, low compliance with guidelines for antimicrobial therapy, and failure of obtaining bacteriologic samples before starting treatment with BSA. These areas should be targeted in the Norwegian antibiotic stewardship program for children and neonates.

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Figure legends

Figure 1) Funnel plot comparing prescriptions with broad-spectrum antibiotics (second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam, quinolones) for children and neonates in 43 Norwegian hospitals based on point prevalence surveys between 2015-2017.

Figure 2) Proportion of prescribed antibiotics for children and neonates in Norwegian hospitalized children (2015-2017) differentiating between treatment and prophylaxis. Broad-spectrum antibiotics are shown at the bottom of the bars.

List of Supplemental Digital Content

Supplemental Digital Content 1. Table showing resistance rates in Norwegian blood cultures

Supplemental Digital Content 2. Table showing obtaining rate of microbiologic samples

Table 1) Empirical recommendation for treatment of infections in Norwegian children and neonates

Indication	**First line empirical recommendation in guidelines**[1]
Community acquired pneumoniae	- Phenoxymethyl- or benzylpenicillin
Hospital acquired pneumoniae	- Cefotaxime - Cefotaxime plus clindamycin
Urinary tract infection	- Aminoglycoside plus ampicillin - Pivmecillinam or amoxicillin/clavulanic acid
Neonatal sepsis	- Aminoglycoside plus benzylpenicillin (early onset sepsis) - Aminoglycoside plus cefalotin (late onset sepsis)
Sepsis and neutropenia	- Aminoglycoside plus ampicillin
Intraabdominal infection	- Aminoglycoside, ampicillin, metronidazole, trimethoprim/sulfamethoxazole (two or more of these in combination) - Piperacillin/tazobactam
Infections in skin, soft tissue, bone and joint	- Cloxacillin, dicloxacillin, clindamycin, phenoxymethyl- or benzylpenicillin (alone or in combination)
Infection in ear, eye, nose and throat	- Phenoxymetyl- or benzylpenicillin (throat and ear) - Cefotaxime or clindamycin (severe infections)
CNS infections	- Cefotaxime or ceftriaxone

1 First line treatment options in the Norwegian guidelines for neonatal septicaemia [15], intraabdominal infections [16] and all other infections [14]

Table 2) Overview of paediatric patients (0-19 years) on systemic antibiotics/broad-spectrum antibiotics (BSA) for different patient groups in Norwegian hospitals (eight point prevalence surveys between 2015-2017)

Patient groups	Patients on antibiotics, N	Proportion of treated patients on BSA[1], % (95% CI)	Prescriptions with antibiotics, N	Proportion of antibiotics being BSA[1], % (95% CI)
Age groups				
Neonates	126	16 (10-23)	231	9 (5-13)
0 to 4 (except neonates)	362	24 (20-29)	502	18 (15-21)
5 to 9	133	44 (35-53)	179	32 (26-40)
10 to 19	316	36 (31-42)	411	29 (24-33)
Gender				
Female	410	29 (24-33)	572	21 (18-25)
Male	527	31 (27-35)	751	22 (19-25)
Classification neonates				
Community aquired infection	28	4 (0-18)	52	2 (0-10)
Hospital aquired infections	44	34 (21-50)	78	19 (11-30)
Surgical phrophylaxis	13	0 (0-25)	22	0 (0-15)
Medical phrophylaxis	21	10 (1-30)	39	5 (1-17)
Unknown	21	10 (1-30)	40	5 (1-17)
Classification children				
Community aquired infection	393	33 (28-38)	533	25 (21-29)
Hospital aquired infections	97	44 (34-55)	136	34 (26-42)
Surgical phrophylaxis	146	19 (13-27)	166	17 (12-23)
Medical phrophylaxis	126	9 (4-15)	128	9 (4-15)
Unknown	90	54 (44-65)	129	38 (30-47)

	Admitted patients, N	Patients on antibiotics, N (%)	Proportion of treated patients on BSA[1], % (95% CI)	Prescriptions with antibiotics, N	Proportion of antibiotics being BSA[1], % (95% CI)
Prescriber`s specialty					
Pediatrician[2]	1786	444 (25)	32 (28-37)	634	23 (20-26)
Neonatologist	657	126 (19)	16 (10-23)	231	9 (5-13)
Pediatric surgeon	384	102 (27)	21 (13-30)	122	17 (11-25)
Intensivist	n/a	52 (n/a)	44 (31-59)	75	32 (22-44)

Other specialities[3]	n/a	213 (n/a)	35 (28-42)	261	29 (23-35)
Total					
Pediatric specialities	2827	672 (24)	27 (24-31)	987	19 (17-21)
All children and neonates	n/a	937 (n/a)	30 (27-33)	1323	22 (19-24)

1 Second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and quinolones

2 Pediatric intensivists included

3 Surgical specialities (134), medical specialities (79)

Table 3) Use of broad-spectrum antibiotics and adherence to guidelines for various indications in Norwegian hospitalized children and neonates treated for infections (2015-2017). Neonates are only included when specified.

Indication	Number of treatments (number of prescriptions)	Broad-spectrum antibiotics[1], number of treatments (%)	Narrow-spectrum antibiotics[2], number of treatments (%)	Adherence to the guideline[3], number of treatments (%)
Community acquired pneumonia	87 (106)	22 (25)	65 (75)	34 (39)
Hospital acquired pneumonia	12 (15)	8 (67)	4 (33)	4 (33)
Urinary tract infections	78 (108)	18 (23)	60 (77)	37 (47)
Neonatal sepsis	59 (100)	11 (19)	48 (81)	11 (19)
Sepsis and neutropenia	52 (85)	14 (27)	38 (73)	17 (33)
Intraabdominal infections	32 (43)	23 (72)	9 (28)	26 (81)
Infections in skin, soft tissue, bone and joint	67 (86)	21 (31)	46 (69)	38 (57)
Infections in ear, eye, nose and throat	51 (60)	10 (20)	41 (81)	42 (82)
CNS infections	23 (28)	17 (74)	6 (26)	13 (57)
Other infections[4]	93 (138)	40 (43)	53 (57)	n/a
Other neonatal infections[5]	17 (30)	4 (24)	13 (76)	n/a
All infections	571 (799)	188 (33)	383 (66)	222 (48)[6]

1 Second- and third-generation cephalosporins, carbapenems, piperacillin/tazobactam and quinolones. Monotherapy or in combination with any other antibiotic

2 Alone or in combination

3 Recommendation for first line empirical treatment in Norwegian guidelines for neonatal sepsis [15], intraabdominal infections [16] and all other infections [14]

4 Surgical site infections (21), gastroenteritis (12) infection with unknown origin (10), infection in heart and blood vessels (5), gynaecological infection (1), prostatitis/epidymiditis (1), unknown (43)

5 Pneumonia (3), infection with unknown origin (2), surgical site infection (1), unknown (11)

6 Treatments for "Other infections" and "other neonatal infections" were not included when calculating total adherence with guideline

Figure 1

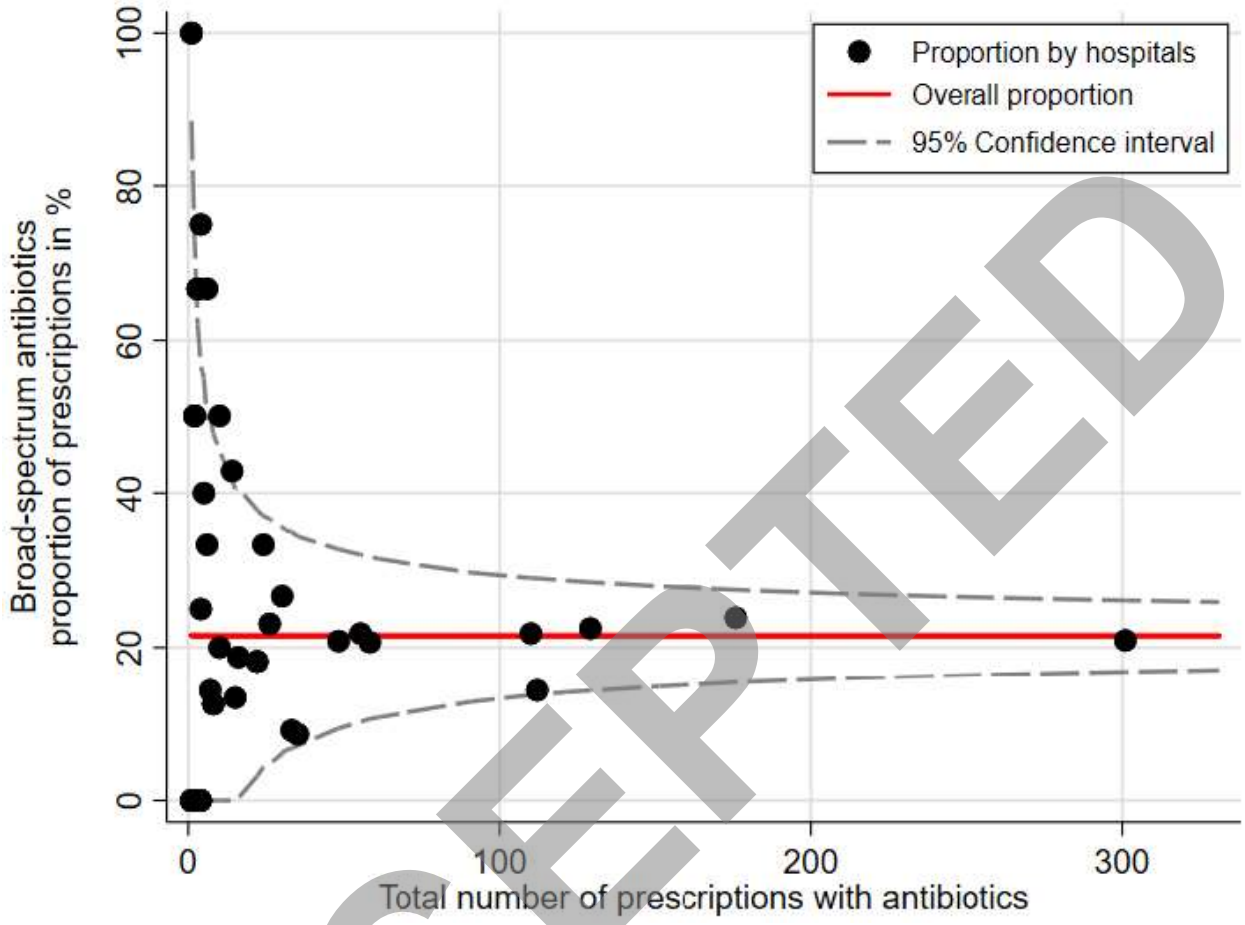

Figure 2