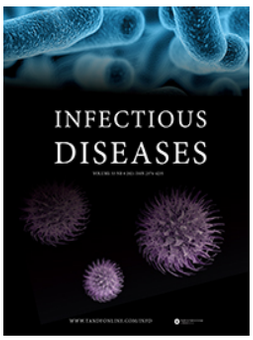

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ORIGINAL ARTICLE

Antibiotic resistance among major pathogens compared to hospital treatment guidelines and antibiotic use in Nordic hospitals 2010–2018

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ABSTRACT

Background: The Nordic countries have comparable nationwide antibiotic resistance surveillance systems and individual antibiotic stewardship programmes. The aim of this study was to assess antibiotic resistance among major pathogens in relation to practice guidelines for hospital antibiotic treatment and antibiotic use in Nordic countries 2010–2018.

Methods: Antibiotic resistance among invasive isolates from 2010–2018 and aggregated antibiotic use were obtained from the European Centre for Disease Prevention and Control. Hospital practice guidelines were obtained from national or regional guidelines.

Results: Antibiotic resistance levels among *Escherichia coli* and *Klebsiella pneumoniae* were similar in all Nordic countries in 2018 and low compared to the European mean. Guidelines for acute pyelonephritis varied; 2nd generation cephalosporin (Finland), 3rd generation cephalosporins (Sweden, Norway), ampicillin with an aminoglycoside or aminoglycoside monotherapy (Denmark, Iceland and Norway). Corresponding guidelines for sepsis of unknown origin were 2nd (Finland) or 3rd (Sweden, Norway, Iceland) generation cephalosporins, carbapenems, (Sweden) combinations of penicillin with an aminoglycoside (Norway, Denmark), or piperacillin-tazobactam (all Nordic countries). Methicillin-resistant *Staphylococcus aureus* rates were 0–2% and empirical treatment with anti-MRSA antibiotics was not recommended in any country. Rates of penicillin non-susceptibility among *Streptococcus pneumoniae* were low (<10%) except in Finland and Iceland (<15%), but benzylpenicillin was recommended for community-acquired pneumonia in all countries.

Conclusion: Despite similar resistance rates among Enterobacteriaceae there were differences in practice guidelines for pyelonephritis and sepsis. National surveillance of antibiotic resistance can be used for comparison and optimization of guidelines and stewardship interventions to preserve the low levels of antibiotic resistance in Nordic countries.

KEYWORDS
Antibiotic resistance
practice guidelines as topic
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Supplemental data for this article can be accessed here.

Introduction

Antibiotic resistance (ABR) is a global health problem, and the World Health Organisation (WHO) has developed a global action plan to tackle ABR. The action plan aims to improve awareness and understanding of antibiotic resistance, to strengthen knowledge through surveillance and research, to reduce the incidence of infection, to optimize the use of antibiotic agents, and to support sustainable investment in new medicines, diagnostic tools, vaccines and other interventions [1].

The Nordic countries have a long history of nationwide antibiotic resistance surveillance programmes, and collaboration with the European Centre for Disease Prevention and Control (ECDC) [2–5]. ECDC compiles data on ABR and antibiotic consumption submitted by the European countries. Thus data from the Nordic countries can be compared with other European countries except Switzerland, on the ECDC website [6].

Antibiotic stewardship first started in Iceland in the field of veterinary medicine, leading to a ban on the use of antibiotics as livestock growth promoters in 1978. This was followed by Sweden in the 80s and Norway in the 90s [7], while the Danish and Finnish livestock industry voluntarily stopped the use of growth promoters during the 90s [8]. Antibiotic stewardship in human medicine was introduced in 1995 in Sweden in the form of STRAMA (Strategy Group for the Rational Use of Antibiotics and Reduction of Antibiotic Resistance). This was a reaction to clonal outbreaks of antibiotic resistance among *Streptococcus pneumoniae* and the increasing use of antibiotics in community care [9]. At the same time, an outbreak of macrolide resistance among *Streptococcus pyogenes* led to a nationwide campaign to reduce macrolide use in Finland [10].

It is well established that antibiotic use is an important driver of antibiotic resistance [11]. To optimise the use of antibiotics, treatment guidelines must be adapted to resistance levels [12]. However, comparison of ABR with practice guidelines (PG) for antibiotic treatment in Nordic hospitals has, to our knowledge, never been evaluated.

The aim of this study was to assess ABR among major pathogens in relation to hospital PGs and antibiotic use in Nordic hospitals 2010–2018.

Material and methods

This study covered all Nordic countries, that is, Denmark, Finland, Iceland, Norway and Sweden.

Antibiotic susceptibility

Susceptibility patterns for *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pneumoniae* (*S. pneumoniae*) in blood and spinal fluid were acquired from the ECDC Surveillance Atlas of Infectious Diseases, as well as national reports for the years 2010–2018 [2–6].

For *E. coli* and *K. pneumoniae*, data were obtained for resistance to 3rd generation cephalosporins, fluoroquinolones, aminoglycosides and carbapenems. For *S. aureus*, data were obtained for methicillin-resistant *S. aureus* (MRSA), and for *S. pneumoniae*, resistance to macrolides and penicillin non-susceptibility (PNSP).

Additionally, resistance rates among *E. coli* and *K. pneumoniae* to piperacillin-tazobactam and 2nd generation cephalosporins were obtained from national reports when available. This information provided percentages not actual numbers of resistant isolates, and statistical analyses could not be performed.

Definitions of susceptibility and resistance were according to EUCAST [13], and only data on resistance are shown, apart from PNSP which includes both resistant isolates and isolates with decreased susceptibility.

Due to the lack of a universal standard for antibiotic susceptibility testing on any specific bacterial species, sample sizes may differ between antibiotic classes from year to year as local microbiology labs in collaboration with clinicians decide which antibiotics to test.

Antibiotic consumption

Data on antibiotic consumption based on sales statistics were obtained from the European Surveillance System (TESSy) [14]. Antibiotic consumption was divided into community care and hospital care. Community consumption refers to all antibiotics prescribed in general practice. Icelandic data were provided as total consumption 2010–2013 and community consumption for 2014–2018. Hospital consumption constituted 10–11% of the total consumption according to the Icelandic Medicines Agency [15].

Antibiotic consumption was measured as a defined daily dose (DDD) per 1000 inhabitants per day (DID) as described by WHO [16].

The broad-spectrum antibiotic was defined as a cephalosporin, carbapenem, combinations of penicillin and beta-lactamase inhibitor, and fluoroquinolone.

Practice guidelines (PG) for antibiotic treatment in hospitals

Hospital care in Denmark is organized into five regions, each having guidelines for the empirical use of antibiotics. In this survey, national sepsis guidelines from 2017 were accessed from the Danish Society of Infectious Diseases [17] while regional (Hovedstaden, Midtjylland, Nord, Sjaelland, and Syddanmark) PGs in hospitals were accessed from the Danish Society of Clinical Microbiology [18] and merged: treatment recommendations occurring in at least two regional guidelines were included. For individual Danish regional guidelines, see Supplement 1. Regional Danish PGs were updated as follows: Hovedstaden 2018, Midtjylland 2019, Nord 2019, Sjaelland 2018 and Syddanmark 2019. Finland has regional PGs, but only those from the Hospital District of Helsinki and Uusimaa (HUS) [19], updated 2017, were used. The Norwegian government agency's (Helsedirektoratet) national hospital guidelines from 2018 were used [20]. Sweden has a national PG issued by the Swedish Society of Medicine, Section for Infectious Diseases [21] and STRAMA [22] and these, updated as of 2019, were included. PGs for hospital use of antibiotics in Iceland were provided and updated in 2019 by the Director of Infectious Diseases at Landspitali University Hospital, Reykjavik (Personal communication from Kristjánsson M).

The most recently available PGs were grouped according to indications.

Pneumonia was divided into two subcategories: community-acquired pneumonia with high and low mortality risk using the scoring system CRB-65 (or CURB 65 in Denmark and Iceland) where 0–2 (0–2) points is defined as low mortality risk and 3–4 (3–5) defined as high risk for mortality requiring intensive care.

Guidelines for sepsis of unknown origin have been issued by all countries. Norway and Finland use systemic inflammatory response syndrome (SIRS) criteria [23] or modified SIRS criteria to define sepsis and septic shock. Denmark, Sweden, and Iceland use Sepsis 3 criteria on the sequential organ failure assessment score (SOFA) [24].

Pyelonephritis was divided into two subcategories: pyelonephritis without complications or with complications/urosepsis.

Statistical analysis

Antibiotic resistance over time and DID over time were analyzed using linear regression. Analyses were carried out with Stata/MP 14.1, StataCorp LLC, College Station, TX, USA. A p-value $<.05$ was considered statistically significant. All significant changes described in the results relate to significant trends over the study period.

Results

Antibotic resistance: trends and levels in 2018

Resistance rates for each pathogen and the respective antibiotics are presented country-wise in Tables 1–4.

In 2010, Denmark had the highest 3rd generation cephalosporin, fluoroquinolone and aminoglycoside resistance among *E. coli,* but these levels did not change significantly during the study period. In contrast, 3rd generation cephalosporin, fluoroquinolone and aminoglycoside resistance among *E. coli* increased significantly in Sweden, Norway, and Finland. Sample sizes in Iceland were small and no changes in resistance rates among the species examined reached statistical significance.

In 2018, resistance to 3rd generation cephalosporin in invasive isolates of *E. coli* was highest in Sweden (8.3%) and lowest in Norway (6.8%).

Denmark likewise had the highest 3rd generation cephalosporin, fluoroquinolone, and aminoglycoside resistance levels among *K. pneumoniae*, but over the study period aminoglycoside and 3rd generation cephalosporin resistance decreased significantly. Apart from Denmark, no decrease in antibiotic resistance among *K. pneumoniae* was seen, whereas resistance to fluoroquinolones increased in Finland, resistance to 3rd generation cephalosporins and aminoglycosides increased in Norway, and resistance to 3rd generation cephalosporins, fluoroquinolones and aminoglycosides increased in Sweden.

In 2018, resistance to 3rd generation cephalosporins among *K. pneumoniae* was highest in Norway (7.5%) and lowest in Finland (4.5%) There were too few isolates in Iceland to be valid in any comparison.

MRSA rates were 0–2.0%, the highest (2.0%) being in Finland and lowest (0.9%) in Norway. The rates of PNSP were highest in Finland (11.5%) followed by Iceland (9.7%), Denmark (5.5%), Sweden (5.2%), and Norway (5.0%).

Practice guidelines for antibiotic treatment in hospitals

Practice guidelines country-wise for selected indications are shown in Table 5.

Table 1. *Escherichia coli* in blood and spinal fluid samples, 2010–2018.

Resistance among *E. coli* in blood and spinal fluid samples (%)	2010	2011	2012	2013	2014	2015	2016	2017	2018	*p*-Value	Sample sizes (*n*)
Denmark											
Fluoroquinolones	13.7	14.1	14.1	12.4	12.3	11.9	11.0	12.8	13.3	.245	3166–5386
3rd generation Cephalosporins	7.6	8.5	7.9	8.1	7	7.5	6.6	6.9	7.7	.294	2408–4883
Aminoglycosides	5.8	6.4	7.3	6.5	7.3	6.8	6.1	6.0	5.8	.764	3412–5393
Carbapenems	0	0	0	0	0	0	0.0	0.0	0	N/A	2011–5117
Piperacillin and inhibitor*	N/A	N/A	N/A	N/A	N/A	N/A	4.0	4.5	3.8	N/A	4838–5113
Finland											
Fluoroquinolones	9.2	11	11.7	13.2	11	11.2	11.5	12.0	11.4	.001	2550–5305
2nd generation Cephalosporins*	4.6	7.2	8.6	10	8.1	8.2	9.0	9.8	10.7	N/A	3019–5286
3rd gen Cephalosporins	3.7	5	6.2	7.1	5.4	6.1	6.9	6.9	7.6	<.001	2509–5223
Aminoglycosides	3.8	5.2	6.1	6.5	4.6	5.4	4.9	5.0	4.3	.028	2356–4982
Carbapenems	0	0	0	0	0	0	0.0	0	0	N/A	2471–5315
Piperacillin and inhibitor*	2.3	2.7	2.3	2.6	2.1	2.2	1.5	1.6	1.5	N/A	2332–5397
Iceland											
Fluoroquinolones	10.5	14	9.7	14.7	7.8	6.8	9.6	11.6	17.2	.805	95–199
3rd generation Cephalosporins	3.8	6.2	5.1	5	3.3	1.7	4.2	6.1	8.1	.419	104–213
Aminoglycosides	2.9	6.2	3.6	4.1	5.3	2.9	3.6	5.6	6.1	.3	104–213
Carbapenems	0	0	0	0	0	0	0	0	0	N/A	0–52
Norway											
Fluoroquinolones	8.7	9	11.3	10.9	11	10.2	10.9	13.6	12.9	<.001	2267–3877
3rd generation Cephalosporins	3.7	3.6	4.9	5.5	5.8	6	5.6	5.9	6.8	<.001	2275–3879
Aminoglycosides	4.3	4.1	5.8	6.4	5.9	6	5.5	7.2	5.8	<.001	2246–3880
Carbapenems	0	0	0	0.1	0	0	0.1	0.1	0	N/A	2089–3879
Piperacillin and inhibitor*	N/A	N/A	N/A	N/A	N/A	N/A	1.9	1.5	2	N/A	1940–2136
Sweden											
Fluoroquinolones	10.5	10.1	11.1	11.6	11.3	12.6	13.7	15.8	18.1	<.001	3998–7356
3rd generation Cephalosporins	2.9	3.6	4.5	5.2	5.6	6.2	8.3	7.4	8.3	<.001	4470–7532
Aminoglycosides	3.4	4.8	5.8	6	6.1	6.4	7.2	6.5	7.7	<.001	4239–7100
Carbapenems	0	0	0	0	0	0.1	0.1	0.0	0	N/A	3866–7347
Piperacillin and inhibitor*	N/A	N/A	N/A	N/A	2.3	2.7	3.3	3.0	2.7	N/A	5149–6285

Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Iceland, Norway, and Sweden, and released by ECDC. *p*-Value <.05 indicates significant change compared to 2010 levels.
*Antibiotics not monitored by ECDC, and reported as presented by national reports. Piperacillin and inhibitor refer to a combination of piperacillin and a beta-lactamase inhibitor.

Table 2. *Klebsiella pneumoniae* in blood and spinal fluid samples, 2010–2018.

Resistance rates among *K. pneumoniae* in blood and spinal fluid samples (%)	2010	2011	2012	2013	2014	2015	2016	2017	2018	*p*-Value	Sample sizes
Denmark											
Fluoroquinolone	11.3	11.6	8.8	8.9	6.9	5.3	5.3	9.1	8.5	.155	673–1279
3rd generation cephalosporins	10.6	11.1	10.5	11.5	7.6	7.8	7.5	7.3	6.5	.03	529–1159
Aminoglycosides	6.1	5.8	6.0	4.4	4.9	2.6	3.2	3.2	3.3	.003	799–1278
Carbapenems	0	0	0.3	0.2	0.2	0	0.3	0.3	0.5	N/A	491–1185
Piperacillin and inhibitor*	N/A	N/A	N/A	6	8	6	6	7.4	6.1	N/A	879–1280
Finland											
Fluoroquinolone	2.5	2.7	2.1	2.6	4.6	3.3	2.7	7.9	6.3	.001	401–808
3rd generation cephalosporins	4	2.5	1.7	2.2	2.4	3	4.1	4.6	4.5	.679	397–805
Aminoglycosides	3.8	1.2	0.4	1.7	2.3	1.9	2.3	2.9	2.6	.458	372–774
Carbapenems	0	0	0	0	0	0	0.3	0.3	0.6	N/A	391–810
Piperacillin and inhibitor*	2.1	3.2	2.8	1.8	2.6	2	2.2	2.4	2.5	N/A	317–758
Iceland											
Fluoroquinolone	0	4.2	7.1	0	3.6	2.9	0	6.3	0	N/A	14–35
3rd generation cephalosporins	3.7	7.7	21.4	0	0	0	0	5.9	0	N/A	14–36
Aminoglycosides	0	0	0	0	3.6	0	0	11.8	0	N/A	16–36
Carbapenems	0	0	0	0	0	0	0	0	0	N/A	0–13
Norway											
Fluoroquinolone	7.4	3.5	4	4.9	6.2	5	4.3	10.2	13.1	.102	427–808
3rd generation cephalosporins	2.1	2.9	3.2	4	5.9	5	5.8	5.8	7.5	.004	421–811
Aminoglycosides	1.7	2.8	2.4	2.3	4.8	3.6	3.3	4.2	5.3	.021	426–809
Carbapenems	0	0	0.5	0.2	0	0.1	0	0	0.1	N/A	443–810
Piperacillin and inhibitor*	1.1	2.6	0.7	2.6	2.9	2.3	3.7	2.9	3.5	N/A	454–685
Sweden											
Fluoroquinolone	5.8	3.8	3.7	3.9	4.1	4.5	5.4	9.8	10.1	.004	742–1533
3rd generation cephalosporins	2.4	2.3	2.9	3.6	4.5	3.3	4.9	5.6	5.5	.001	842–1537
Aminoglycosides	1.6	2.0	2.5	2.9	3.3	3.2	3.4	4.7	3	.001	795–1235
Carbapenems	0.3	0	0.1	0	0	0	0.1	0.1	0.2	N/A	708–1531
Piperacillin and inhibitor*	N/A	N/A	N/A	N/A	4	3.8	4.1	4.1	6.9	N/A	958–1035

Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Iceland, Norway, and Sweden, and released by ECDC. *p*-Value <.05 indicates significant trend during the study period.
*Antibiotics not monitored by ECDC and reported as presented by national reports.

Table 3. *Streptococcus pneumoniae* in blood and spinal fluid samples, 2010–2018.

Resistance among *S. pneumoniae* in blood and spinal fluid samples (%)											
	2010	2011	2012	2013	2014	2015	2016	2017	2018	*p*-Value	Sample sizes
Denmark											
PNSP	3.6	4.8	5.1	6.6	5.6	4.7	6.1	3.9	5.5	.057	707–954
Macrolides	4.1	5.0	5.8	4.8	6.6	5.2	4.8	3.6	2.5	.597	707–954
Finland											
PNSP	14.2	12.9	17.0	13.9	12.5	12.7	10.3	10.5	11.5	.185	553–706
Macrolides	27.0	24.5	21.8	18.3	14.2	14.0	11.4	15.0	12.1	<.001	607–808
Iceland											
PNSP	5.4	9.4	3.7	16.7	8.0	24.0	10.5	18.5	9.7	.523	18–37
Macrolides	10.8	21.9	7.4	16.7	12.5	12.0	0.0	18.5	12.9	.422	18–37
Norway											
PNSP	3.7	3.4	5.9	3.3	5.1	5.4	4.4	4.8	5.0	.289	429–619
Macrolides	3.7	4.0	5.3	3.8	4.3	4.0	5.3	5.5	7.6	.184	403–570
Sweden											
PNSP	3.7	3.3	5.1	6.8	7.9	9.8	7.1	6.1	5.2	.157	420–1016
Macrolides	3.9	4.5	4.7	6.2	6.2	6.6	5.3	4.7	4.5	.420	750–1030

Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Iceland, Norway and Sweden, and released by ECDC. *Streptococcus pneumoniae* with resistance to macrolides and/or decreased susceptibility to penicillin. *p*-Value <.05 indicates significant trend during the study period.

Table 4. Methicillin-resistant *Staphylococcus aureus* (MRSA) in blood and spinal fluid samples 2010–2018.

Methicillin-resistant *Staphylococcus aureus* (MRSA) in blood and spinal fluid samples (%)											
	2010	2011	2012	2013	2014	2015	2016	2017	2018	*p*-Value	Sample sizes
Denmark											
MRSA	1.3	1.2	1.3	1.7	2.5	1.6	2.0	2.5	1.7	.441	1362–2181
Finland											
MRSA	2.3	3.2	2.1	1.8	2.6	1.9	2.2	2.0	2.0	.591	1094–2439
Iceland											
MRSA	1.5	2.8	1.7	0.0	3.3	0.0	1.3	1.4	0	.999	58–88
Norway											
MRSA	0.6	0.3	1.3	0.7	1.0	1.2	1.2	1.0	0.9	.349	1047–1547
Sweden											
MRSA	0.5	0.8	0.7	1.0	1.0	0.8	2.3	1.2	1.9	<.001	2662–4099

Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Iceland, Norway and Sweden, and released by ECDC. *p*-Value <.05 indicates significant trend during the study period.

Sepsis of unknown origin

Norway and Denmark recommended a combination of benzylpenicillin or ampicillin and an aminoglycoside, while Sweden recommended cefotaxime or piperacillin-tazobactam ± an aminoglycoside. Finnish guidelines did not include an aminoglycoside. All countries considered piperacillin-tazobactam a treatment option, and all except Denmark recommended cephalosporins, either 2nd (Finland) or 3rd generation (Iceland, Norway, and Sweden). Empirical treatment with anti-MRSA drugs was not included in any of the guidelines.

Pyelonephritis

Sweden recommended monotherapy with ceftibuten, trimethoprim-sulfamethoxazole or ciprofloxacin, or as intravenous alternatives cefotaxime, piperacillin-tazobactam, or an aminoglycoside. Finland recommended monotherapy with cefuroxime, oral ciprofloxacin or piperacillin-tazobactam for complicated cases. Denmark, Norway and Iceland recommended an aminoglycoside combined with ampicillin. Danish guidelines also included a combination of mecillinam and an aminoglycoside. Norwegian guidelines had trimethoprim/sulfamethoxazole as an option.

Norwegian guidelines define pyelonephritis with complications as febrile infection of the upper urinary tract combined with septic symptoms, functional or anatomical abnormalities in the urinary tract, diabetes mellitus, immune deficiency/cytostatics, or pregnancy. Icelandic guidelines did not specify complications.

Swedish and Danish PGs did not have the concept of pyelonephritis with complications but offered recommendations for urosepsis, that is, comparable to 'septic symptoms' in the Norwegian definition. For pyelonephritis with complications or urosepsis, recommendations were as follows: Danish guidelines included piperacillin-tazobactam; Norwegian guidelines included ampicillin together with gentamicin or cefuroxime as an alternative; while Swedish and Icelandic guidelines included carbapenems.

Community-acquired pneumonia CRB-65/CURB-65 0–2

All guidelines recommended benzylpenicillin. When atypical pneumonia is suspected, a fluoroquinolone or macrolide was advised.

Table 5. Empirical practice guidelines for hospital use.

Antibiotic	Sweden	Norway	Denmark**	Finland	Iceland
Sepsis of unknown origin					
Ampicillin + gentamicin ± metronidazole			x		
Penicillin + gentamicin		x			
Cefuroxime				x	
Cefotaxime	x*	x			
Ceftriaxone ± metronidazole					x
Piperacillin-tazobactam	x*	x*	x*	x	x
Imipenem/meropenem	x*				
Pyelonephritis/urosepsis					
Aminoglycoside	x				
Ampicillin + gentamicin		x	x		x
Mecillinam + gentamicin			x		
Cefuroxime		c		x	
3rd generation cephalosporin	x	c			x
Ceftibuten	x				
Ciprofloxacin	x			x	
Trimethoprim-sulfamethoxazole	x	x			
Piperacillin-tazobactam	x		c	x	
Carbapenem	c				c
Pneumonia community-acquired CRB 65 0-2, CURB 65 0-2					
Benzylpenicillin	x	x	x	x	x
Amoxicillin ± clavulanic acid					x
Cefuroxime				x	
Pneumonia community-acquired CRB 65 3-4, CURB-65 3-5					
Penicillin + fluoroquinolone	x				
Penicillin + aminoglycoside ± macrolide		x			
Penicillin + macrolide			x		
3rd generation cephalosporine ± macrolide	x	x			x
Ceftriaxone + fluoroquionolone				x	
Cefuroxime + fluoroquinolone				x	
Piperacillin-tazobactam + macrolide			x		

Treatment recommended by country marked by an 'X'. *Sweden/Norway/Denmark: add aminoglycoside in septic shock or when at risk for developing septic shock. **In sepsis with unknown focus, four out of 5 danish regions recommended ampicillin and gentamicin and two regions additionally recommended considering combination with metronidazole, and all regions recommended piperacillin-tazobactam. For pyelonephritis, one Danish region recommended monotherapy only with mecillinam, three of 5 mecillinam and gentamicin, two of 5 ampicillin and gentamicin, and one recommended monotherapy with piperacillin-tazobactam as an alternative. In addition, for urosepsis, four of 5 regions advised ampicillin and gentamicin, and four of 5 monotherapy with piperacillin-tazobactam (two regions recommended only one of these two options). c: pyelonephritis with complications/urosepsis.

Community-acquired pneumonia CRB-65/CURB-65 3–4/3–5

Norway recommended a combination of benzylpenicillin and an aminoglycoside, with the addition of a macrolide when suspecting Mycoplasma or Legionella. Iceland, Finland, and Sweden recommended a cephalosporin combined with either a fluoroquinolone or a macrolide. Denmark recommended either benzylpenicillin or piperacillin-tazobactam combined with a macrolide.

Recommendations on when to cover ESBL-producing bacteria were as follows

Swedish (STRAMA) PG state conditions when ESBL-producing pathogens should be covered: previous infection or colonization caused by ESBL-forming bacteria in the last 6 months; stay in countries with a high prevalence of ESBL-producing bacteria in the last 6 months; or inpatient care in hospitals outside the Nordic region in the last 6 months.

Norwegian PG recommended carbapenem treatment when there is a high prevalence of ESBL-producing Enterobacteriaceae locally.

Danish National sepsis PG: when the patient has been abroad within the last three months, contact the infectious disease department regarding possible resistance. No regional PGs gave advice regarding ESBL.

Icelandic PG: contact infectious disease department when suspecting resistant pathogen based on patient history, such as previous colonization with ESBL-producing bacteria.

Finnish PG: Prior hospitalization; broad-spectrum antibiotic therapy in the previous 3 months; known carrier or family member of the known carrier of a multi-resistant bacteria; or previous hospitalization outside the country.

Antibiotic consumption

Overview of total and community antibiotic consumption

Overall, 88% of all antibiotics consumed in the Nordic countries 2018 were prescribed within community care, and 12% in-hospital care.

Community- and hospital-prescribed antibiotic consumption figures over the study period for each country

Table 6. Antibiotic consumption measured as defined daily dose per 1000 inhabitants per day, aggregated data from all antibiotic classes.

Antibiotic consumption	2010	2011	2012	2013	2014	2015	2016	2017	2018	*p*-Value
Denmark	**17.509**	**18.305**	**17.305**	**17.539**	**17.150**	**17.501**	**17.007**	**16.240**	**15.551**	
Community	15.876	16.692	15.705	16.660	15.176	15.310	15.166	14.334	13.611	.001*
Hospital sector	1.633	1.614	1.653	1.880	1.974	2.191	1.841	1.906	1.939	.047**
Finland	**19.726**	**21.513**	**20.638**	**19.554**	**19.103**	**18.118**	**17.412**	**15.701**	**15.444**	
Community	17.014	18.555	17.983	16.927	16.594	15.763	15.034	13.592	13.166	<.001*
Hospital sector	2.711	2.958	2.655	2.626	2.509	2.356	2.378	2.109	2.278	.001*
Iceland	**19.818**	**19.812**	**19.667**	**19.438**	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	
Community	N/A	N/A	N/A	N/A	**17.112**	**17.588**	**18.167**	**18.845**	**20.450**	N/A
Hospital sector	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Norway	**16.803**	**17.531**	**17.928**	**17.184**	**16.906**	**16.790**	**16.232**	**15.742**	**15.279**	
Community	15.406	16.106	16.533	15.831	15.544	15.432	14.893	14.366	13.982	.007*
Hospital sector	1.396	1.425	1.395	1.352	1.362	1.357	1.339	1.376	1.297	.010*
Sweden	**15.203**	**15.413**	**15.279**	**14.245**	**13.972**	**13.514**	**13.231**	**12.772**	**12.435**	
Community	13.756	13.886	13.709	12.650	12.481	11.924	11.673	11.258	10.783	<.001*
Hospital sector	1.447	1.527	1.571	1.595	1.491	1.590	1.558	1.514	1.652	.120

Total consumption in bold. Iceland reported only total consumption 2010–2013, and thereafter only community consumption. Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Iceland, Norway and Sweden, and released by ECDC. *p*-Value <.05 indicates significant trend during the study period.
N/A: not available.
Broad-spectrum antibiotics defined as carbapenems, cephalosporins, combinations of a penicillin and beta-lactam inhibitor, and fluoroquinolones.
*Significant decrease; **Significant increase.

are shown in Table 6. There was a significant decrease in community consumption in Denmark, Finland, Norway and Sweden over the study period. Iceland submitted total consumption data for 2010–2013 and community consumption from 2014 and onwards, so no trend could be calculated. In 2018, Iceland had the highest community-prescribed antibiotic consumption (20.45 DID) and Sweden the lowest (10.78 DID). Community consumption figures in Norway, Denmark and Finland were similar (13.98, 13.61 and 13.17 DID respectively). Community consumption of fluoroquinolones was highest in Iceland (0.82 DID) followed by Finland (0.62 DID), Sweden (0.61 DID), Denmark (0.41 DID), and lowest in Norway (0.32 DID). Fluoroquinolone consumption decreased in all five Nordic countries.

Hospital antibiotic consumption

The most common antibiotic classes used in the Nordic hospitals in 2018 are shown in Figure 1. There was a slight but significant decrease in hospital antibiotic consumption in Finland over the study period, but the consumption (2.28 DID) remained the highest in 2018, followed by Denmark (1.94 DID), Sweden (1.65 DID), and Norway (1.30 DID).

Beta-lactamase-sensitive penicillin (benzylpenicillin) and beta lactamase-resistant penicillin (isoxazolylpenicillins) as well as penicillins with extended-spectrum (ampicillin and amoxicillin), were commonly used in all Nordic hospitals. In 2018, penicillins constituted 53% of the total hospital antibiotic consumption in Sweden, while the corresponding figure for Norway was 44%, for Denmark 39%, and Finland 18%.

The use of first-generation cephalosporins (i.e. cefalexin and cefalotin) was highest in Finland (0.12 DID), followed by Norway (0.09 DID), while use in Denmark and Sweden was close to zero. Finland was the highest consumer of 2nd generation cephalosporins, mainly cefuroxime, at 0.74 DID. This was also the most commonly used antibiotic in-hospital care in Finland. The use of 2nd generation cephalosporins in Sweden and Norway was very low (0.01 and 0.02 DID respectively), whereas consumption in Denmark was 10–20 times higher (0.17 DID) but still less than half of that in Finland. The use of 3rd generation cephalosporins was highest in Norway (0.13 DID) followed by Sweden (0.11 DID) and Finland (0.09 DID), while use in Denmark (0.03 DID) was less than 25% of Norwegian consumption.

Combinations of penicillin and a beta-lactamase inhibitor (amoxicillin with clavulanic acid and piperacillin with tazobactam) increased in all countries between 2010 and 2018, with the largest increase being in Denmark from 0.12 to 0.32 DID. The lowest use, and increase, was in Norway from 0.02 in 2010 to 0.06 DID in 2018.

The use of fluoroquinolones in hospitals was highest in Finland (0.20 DID), followed by Sweden (0.14 DID), Denmark (0.13 DID), and lastly Norway (0.04 DID).

Among antibiotics not shown in Figure 1, the consumption of aminoglycosides was highest in Norway (0.08 DID) followed by Denmark (0.04 DID) and Sweden (0.02 DID), and lowest in Finland (0.01 DID).

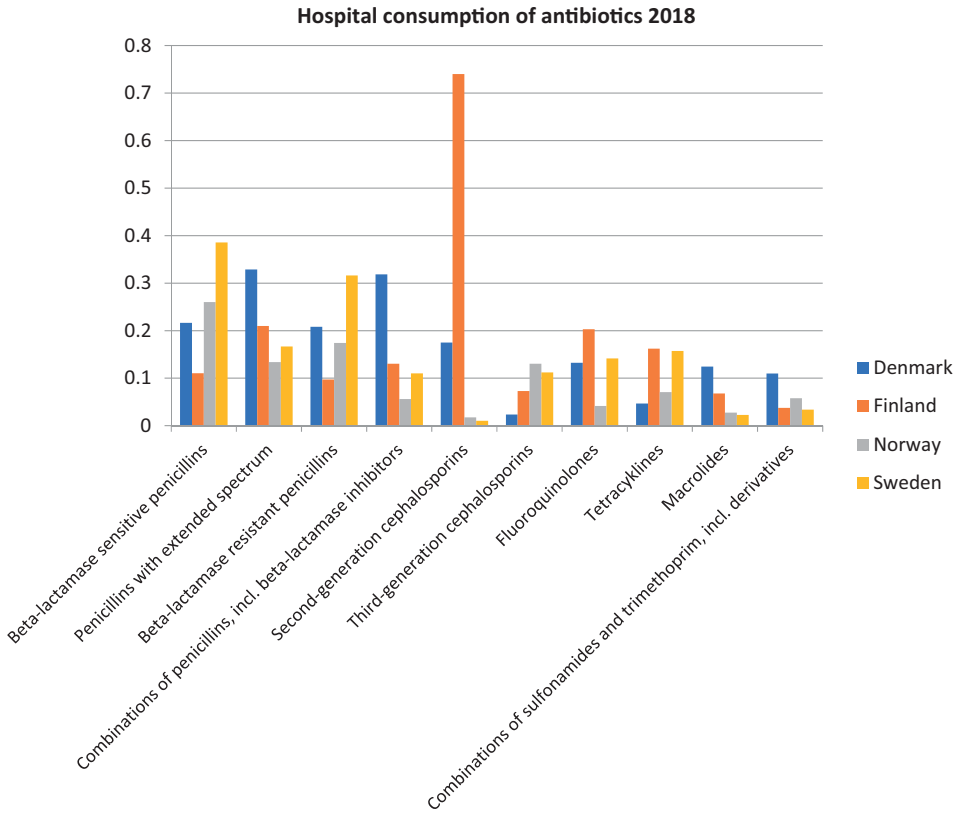

Figure 1 Defined daily dose per 1000 inhabitants per day of the 10 most commonly used antibiotic groups of the 5th ATC level in the Hospital sector 2018. Data from the European Surveillance System – TESSy, provided by Denmark, Finland, Norway and Sweden, and released by ECDC. No data available from Iceland on hospital consumption of antibiotics.

Corresponding figures for macrolides were in Denmark 0.12 DID, Finland 0.07 DID, Norway 0.03 DID, and Sweden 0.02 DID.

Broad-spectrum antibiotic consumption as a proportion of total hospital consumption was 58% in Finland, followed by 36% in Denmark, 28% in Norway, and 25% in Sweden.

Discussion

Antibiotic resistance levels among major pathogens causing bacteraemia were similar in all Nordic countries in 2018, and low compared to other European countries, whereas antibiotic consumption and PGs differed widely (except community-acquired pneumonia). In 2018, the European population-weighted mean of 3rd generation resistant *E. coli* (ESBL phenotype) was 15%, but only 7–8% in the Nordic countries. Likewise, 31% of *K. pneumoniae* strains were ESBL phenotype in Europe, but only 5–8% in the Nordic countries. The mean European MRSA rate was 17%, but only 0–2% in the Nordic countries [25]. While ESBL-producing *E. coli* is mainly associated with travel and migration followed by a spread in the community, *K. pneumoniae* is more often a nosocomial pathogen. Thus, the link between aggregated antibiotic use in hospitals and antibiotic resistance among *E. coli* and *K. pneumoniae* must be assessed separately. Furthermore, antibiotic consumption in outpatient care constitutes 90% of total consumption and thus likely to have a greater impact on resistance among *E. coli* than hospital consumption. Even though both hospital and community fluoroquinolone consumption decreased in all countries during the study period, fluoroquinolone resistance in *E. coli* continued to increase and was above 10% in 2018. This makes fluoroquinolones no longer a first-line choice for empirical monotherapy in pyelonephritis or urosepsis.

All Nordic countries except Denmark recommended a 2nd or 3rd generation cephalosporin for pyelonephritis or sepsis, where *E. coli* and *K. pneumoniae* are the two major pathogens. If the rates of cephalosporin-resistant (ESBL-producing) Enterobacteriaceae continue to rise, treatment strategies will have to shift. The inclusion of piperacillin-tazobactam for pyelonephritis in PG in Sweden, Denmark, and Finland bears witness to this. Although Nordic countries have low antibiotic resistance rates among *E. coli* and *K. pneumoniae* they are not exempted from the global ESBL pandemic and should

therefore comply with multitarget actions proposed by WHO in the future [1,26].

The consumption of combinations of penicillin and a beta-lactamase inhibitor (amoxicillin with clavulanic acid and piperacillin-tazobactam) increased in all countries between 2010 and 2018, the largest increase being in Denmark. This may be the result of measures taken to reduce the selective pressure of cephalosporins and quinolones on ESBL-producing and quinolone-resistant Enterobacteriaceae. Carbapenem consumption increased in Denmark in 2012–2013 and has remained high ever since. Since carbapenems are the most reliable treatment option for ESBL-producing *E. coli* and *K. pneumoniae*, an increase in use will probably be seen in all Nordic countries following the global increase in ESBL-producing Enterobacteriaceae. However, it is important to consider and find carbapenem-saving alternatives such as temocillin and new beta-lactam inhibitor combinations [27,28].

Finland, in contrast to all other Nordic countries, did not recommend adding an aminoglycoside to beta-lactam antibiotics in empirical therapy for sepsis with or without septic shock. A Cochrane meta-analysis and recent mainly observational studies have shown that a combination of a beta-lactam antibiotic with an aminoglycoside does not provide any survival benefit for patients with sepsis compared to beta-lactam monotherapy, but does increase the risk for nephrotoxicity [29–31]. A large study using propensity scoring showed that adding an aminoglycoside to a beta-lactam (excluding broad-spectrum beta-lactams with effect on *Pseudomonas aeruginosa* such as carbapenems), increased survival in septic shock [32]. Combination therapy is still recommended in surviving sepsis guidelines and several national guidelines [33–35], and there is still debate on whether to add an aminoglycoside [36]. A recently published Swedish retrospective single-centre study showed lower mortality in sepsis with or without septic shock when using combinations of various beta-lactam antibiotics and an aminoglycoside, compared to monotherapy [37]. Thus, there is still a knowledge gap if, when, and for which beta-lactam antibiotics to add an aminoglycoside in sepsis, which explains the variations in PG's. Pyelonephritis PG's in Denmark, Norway and Iceland recommended a combination of aminoglycoside and beta-lactam antibiotics as an alternative to broad-spectrum beta-lactam monotherapy.

Antibiotic stewardships have several goals, including optimization of clinical outcomes; lowered costs; and minimizing unintended consequences of antibiotic therapy such as toxicity, *Clostridium difficile* diarrhoea, and the emergence of antibiotic-resistant bacteria [38]. This may be implemented, for example, by promoting compliance to PG including use of narrow-spectrum antibiotics while still effective, and surveillance of antibiotic use and resistance. Data on antibiotic exposure of the individual patient are needed to evaluate appropriate use but were not available in this study. This made it difficult to determine any causal relationship between, for example, consumption of 3rd generation cephalosporins and risk for emergence of ESBL-producing *E. coli* and *K. pneumoniae*. Even so, it is important to monitor antibiotic use and promote the use of narrow-spectrum antibiotics, since it is well known that broad-spectrum antibiotics have a negative effect on the microbiome and are a risk factor for the emergence of antibiotic resistance [39]. National antibiotic resistance data are also crucial when revising national antibiotic treatment guidelines. Furthermore, aggregated antibiotic consumption may also be used as one parameter when evaluating stewardship interventions, or to identify the need for such interventions.

The rates of PNSP in Finland were more than three times higher than in Sweden, Norway and Denmark in 2010 and twice as high at the end of the study. The Icelandic PNSP rates varied greatly over the study period but were similar to Finnish levels in 2018. Increases in PNSP and macrolide-resistant *S. pneumoniae* in Finland are considered to be mainly due to the expansion of several clones [40–42]. However, studies have also shown a correlation between antibiotic use and PNSP [43,44]. Finland had a significant reduction in community consumption of antibiotics and slightly decreased PNSP rates during the study period. That may have been caused by several factors beyond the reduced consumption such as the Finnish pneumococcal vaccination program [45]. A similar decrease in resistant strains of *S. pneumoniae* has been observed in Iceland after the introduction of pneumococcal vaccine [46]. Despite the successful reduction in community and total antibiotic consumption in Sweden, invasive PNSP increased from 4% in 2008 to 10% in 2015, but then decreased to 5% during 2018. The fall in rate between 2015 and 2018 may also have been the effect of pneumococcal vaccination, since the fall in invasive PNSP rate was not seen in nasopharynx samples which remained at 10% [5]. Hospital consumption probably had only a minor or no effect on the PNSP rate since this is a community-acquired infection, and it is outside the hospital that antibiotic use has the greatest impact on PNSP. All

countries recommended narrow-spectrum benzylpenicillin for community-acquired pneumonia with no suspicion of atypical pneumonia. This results in less concomitant disruption of the bowel flora compared to broad-spectrum antibiotics [47].

The rate of MRSA was very low (0–2%) compared to the population-weighted European mean of 17% [25], and consequently, no Nordic country included MRSA treatment in their guidelines for sepsis of unknown origin.

The strengths of this study are the completeness of consumption data, large sample sizes because of the high frequencies of the pathogens chosen, and the long observation time.

Comparisons of total antibiotic use and antibiotic treatment guidelines in this survey were limited by the fact that total aggregated consumption was compared to empirical treatment guidelines for only three major indications. Another limitation regarding sepsis guidelines is that Norwegian and Finnish guidelines use SIRS-criteria [23] or modified SIRS-criteria for sepsis, severe sepsis, and septic shock while Danish, Icelandic and Swedish use the SOFA score [24], thus limiting the comparison of treatment guidelines for sepsis. Furthermore, PGs in this study was structured in several different ways and varied greatly in comprehensiveness such as recommendations for ESBL-coverage and frequency of updates.

A Dutch study on adaptation of national to local guidelines showed that implementing national PGs at the local level by providing an online infrastructure increased compliance and comprehensiveness, as well as the frequency of updates [48]. Our data show similarly low levels of antibiotic resistance throughout the Nordic countries, supporting the use of Nordic guidelines. Practice guidelines for pneumonia not requiring intensive care are already similar in the Nordic countries and could be extended to include other indications such as pyelonephritis and sepsis. However, before implementation, guidelines should be adapted to those at regional and local levels. Nordic guidelines could regularly be updated based on changes in levels of resistance, new breakpoints, new evidence of the most optimal dosing strategy, length of treatment, new drugs, etc. In addition, Nordic guidelines could include practice guidelines for special patient groups with identified risk factors or resistance problems needing broader empirical treatment, but also de-escalation policy and recommendations for directed treatment based on aetiology and resistance patterns. Common Nordic guidelines might also outweigh the international guidelines that are usually based on other settings with higher rates of antibiotic resistance.

This is the first Nordic study comparing ABR, antibiotic use, and practice guidelines in Nordic countries. It shows that guidelines differ widely in Nordic countries even though levels of ABR among *E. coli* and *K. pneumoniae* were similar. Future collaboration and research should be directed at determining which treatments of pyelonephritis and gram-negative sepsis provide the best clinical outcomes with the least unintended consequences including the emergence of ABR.

We believe that the data provided by this study will be helpful in designing antibiotic stewardship interventions aiming to preserve the low level of antibiotic resistance in hospitals in Nordic countries.

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