Influence of prescription patterns in general practice on anti-microbial resistance in Norway

MORTEN LINDBÆK

DAG BERILD

JØRUND STRAAND

PER HJORTDAHL

SUMMARY

Background. *The global pandemic of antibiotic resistance is causing considerable concern, and a major reason for the growing world-wide resistance problem is the overuse of anti-infective drugs, especially the use of broad spectrum antibiotics. This is still a relatively minor problem in most of the Nordic countries where the consumption of antibiotics is less than half of that reported from southern Europe and the United States of America (USA).*

Aim. *To describe the resistance pattern among common respiratory tract pathogens in Norwegian general practice, the national consumption of antibiotics, and GPs' prescription patterns for respiratory tract infections. To offer some suggestions as to why Norway has maintained a favourable situation regarding resistant microbes during the past 10 years.*

Method. *An analysis of the prescription patterns in Norwegian general practice.*

Results. *There is a low total prescription volume of antibiotics compared with other countries. Penicillin V is the most commonly used antibiotic for the most common airway diseases in general practice in Norway.*

Conclusion. *Although there is a low prevalence of antibiotic resistance in Norway, there is still a great potential for reducing the unnecessary antibiotic prescribing for the most common respiratory illnesses.*

Keywords: prescribing patterns; antibiotics; antibiotic resistance; Norway.

Introduction

THE global pandemic of antibiotic resistance is causing considerable concern among doctors, lay people, and political authorities.[1,2] A major reason for the growing worldwide resistance problem is the overuse of anti-infective drugs,[3-5] especially the use of broad spectrum antibiotics. This problem is considerable in southern and central Europe, although it is still a relatively minor problem in most of the Nordic countries where the antibiotic consumption is less than half of that reported from southern Europe and the United States of America (USA).[3] About 85% of all antibiotic prescriptions are issued by general practitioners (GPs).[6] Three-quarters of these are prescribed as a result of common respiratory tract infections, for which the Norwegian national guidelines recommend penicillin V (PCV) as the drug of choice.[7]

This article describes the resistance pattern among common respiratory tract pathogens in Norwegian general practice, Norway's national consumption of antibiotics, and GPs' prescription patterns for respiratory tract infections. Furthermore, it offers some suggestions as to why Norway has maintained a favourable situation regarding resistant microbes during the past 10 years.

Method

Data concerning the resistance patterns for the most common respiratory pathogens, the consumption of antibiotics between 1981 and 1997, and antibiotic prescription patterns in Norway were obtained and studied.

Resistance patterns for the most common respiratory pathogens.

The antibiotic susceptibility for the most common respiratory pathogens found in Norwegian general practice in 1995 are given in Table 1.[8] All Group A β-haemolytic streptococci and more than 98% of all pneumococci were susceptible to PCV, erythromycin, and clindamycin, and only 6% of the pneumococci were found to be resistant to doxycycline. Betalactamase-producing *Haemophilus influenzae* constituted between 7% (summer) and 10% (winter) of this strain. Fifty-seven per cent of the *Haemophilus influenzae* bacteria were, however, intermediately susceptible to PCV and more than 90% were susceptible to ampicillin. Two-thirds of the *Moraxella catarrhalis* and *Staphylococcus aureus* specimens were betalactamase-producing strains, but almost 100% of them were susceptible to erythromycin and to doxycycline. Except for sporadic cases, mostly imported from southern Europe, we, as yet, do not have problems with methicillin resistant staphylococci (MRSA) in Norway. The susceptibility testing was performed according to national guidelines.[9] Pneumococci were considered as sensitive to benzylpenicillin with a minimal inhibitory concentration (MIC) <0.06 mg/l, as having intermediate sensitivity with MIC between 0.06 mg/l and 2 mg/l, and as resistant with MIC >2 mg/l. The corresponding phenoxymethylpenicillin breakpoints for *Haemophilus influenzae* were 1 mg/l and 4 mg/l.

Antibiotic consumption 1981–97

The volume of the national human antibiotic consumption (in terms of average numbers of defined daily doses [DDDs] per 1000 inhabitants per day) for 1981, 1987, 1993, and 1997 are given in Figure 1 — data extracted from the national drug statistics.[10,11] Penicillins, tetracyclines, macrolides, and co-trimoxazole constituted more than 95% of the antibiotics consumed during this period. Between 1970 and 1980, the antibiotic consumption remained relatively stable. From 1981 to 1993 the total antimicrobal consumption increased by about 30%; however, it decreased by 9% from 1993 to 1997. PCV was the most used antibiotic during the whole period, and its proportion of the total volume increased from 27% (1981) to 34% (1997). The consumption of amoxicillin has tripled during the past 10 years: it constitutes the main part of 'other penicillins'. The use of co-

M Lindbæk, MD, PhD, senior lecturer; and P Hjortdahl, MD, PhD, professor, Division of General Practice, University of Oslo, Norway. D Berild, MD, consultant in infectious diseases, Aker University Hospital, Oslo, Norway. J Straand, MD, senior lecturer, Division for General Practice, University of Bergen, Norway.

Submitted: 12 October 1998; final acceptance: 16 February 1999.

Table 1. The antibiotic susceptibility for the most common respiratory pathogens in Norwegian general practice, numbers are percentages.

Antibiotic	Streptococcus pneumoniae (n = 100)			Haemophilus influenzae (n = 102)			Streptococcus pyogenes (n = 101)			Moraxella catarrhalis (n = 53)			Staphylococcus aureus (n = 1353)		
	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Penicillin V	98	2	0	36	57	7	100	0	0	32	0	68	24	0	76
Ampicillin	–	–	–	93	0	7	–	–	–	32	0	68	–	–	–
Erythromycin	98	0	2	27	70	3	98	0	2	100	0	0	97	<1	2
Doxycycline	100	0	0	72	26	2	93	1	6	100	0	0	–	–	–
Clindamycin	98	0	2	–	–	–	100	0	0	–	–	–	99	<1	<1

Division of sensitivity: S = sensitive, I = intermediate sensitive, R = resistant. Data from a survey of bacteriological samples in general practice from the western part of Norway in 1995.[8]

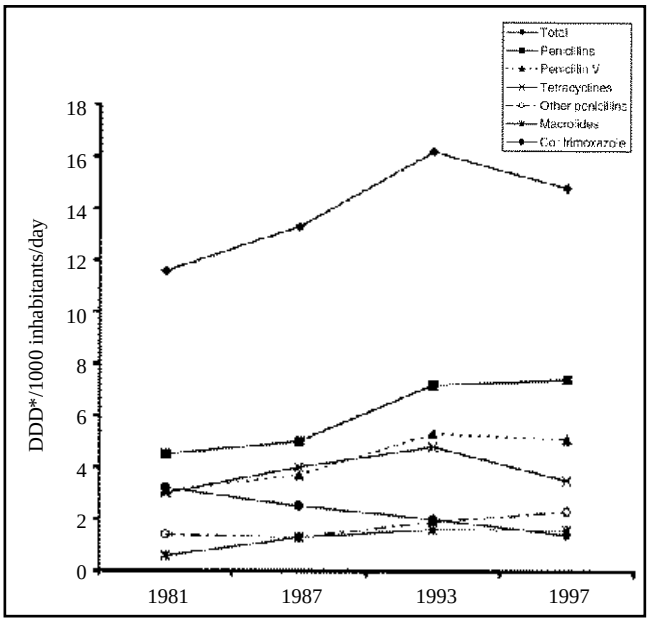

Figure 1. The total amount of antibiotics sold for human use in Norway 1981–1997 by average DDD*/1000 inhabitants/day. (Data are total amounts of antibiotics sold for human use gathered from national statistics 1981–1997.10,11Antimycotics and antiviral agents are not included. *DDD = defined daily dose.)

trimoxazole has been halved during the 17-year period. The consumption of tetracyclines increased significantly until 1993, after which their use has declined. The macrolide consumption has shown a modest increase during this 17-year period but their use did not escalate after the introduction of the newer macrolides, such as clarithromycin and azithromycin. The use of cephalosporins has always remained low in Norway.

Antibiotic prescription patterns

General practitioners' prescription patterns for antibiotics were extensively studied (1988–89) in the Norwegian county of Møre and Romsdal (Tables 2 and 3).[12,13] More than 95% of the GPs in the county participated in the survey. Table 2 lists the most frequently recorded diagnoses for prescribing the various antibiotics.[12] Of all the respiratory tract infections, acute bronchitis, otitis, and upper respiratory tract infection (URTI) were the most frequently recorded diagnoses that prompted an antibiotic prescription. PCV was the most commonly prescribed antibiotic for patients suffering otitis, URTI, tonsillitis, and sinusitis, whereas erythromycin and tetracyclines were most frequently prescribed for lower respiratory tract infections.[12]

Seven out of 10 children (aged 0–12 years) who were prescribed an antibiotic, received it as a result of respiratory tract infections (Table 3).[13] More than eight out of 10 children who consulted a GP for sinusitis, tonsillitis, acute bronchitis, or pneumonia were prescribed an antibiotic.[13] For ear infections, an antibiotic prescription was given during 44% of all consultations, but this proportion increased to 64% when follow-up contacts for this diagnosis were excluded (Table 4).[13]

Penicillin V was the most frequently prescribed antibiotic for children with ear infection, URTI, tonsillitis, sinusitis, and skin infections, whereas erythromycin was given to a considerable proportion of those with bronchitis or pneumonia (Table 3).[13]

Discussion

Resistance patterns

The resistance patterns reported from specimens collected by a representative sample of GPs (Table 1)[8] suggest that antibiotic resistance is still a limited problem in Norway. There are no indications that these patterns have changed to show an increased usage of antibiotics between 1981 and 1993. Furthermore, this finding is consistent with other Norwegian surveys from the last decade,[14] indicating that the extent of antimicrobial resistance has remained stable for some time.

In general, pneumococci have been sensitive to PCV. *Haemophilus* has intermediary sensitivity to penicillin V but there is some variation in the findings. In a study from Oslo University Hospital from 1993,[14] a higher proportion of *Haemophilus* is sensitive to penicillin V. The proportion of resistant strains has been constant during the past 10 years and varies between 7% and 10%, with a seasonal variation giving a higher proportion in the winter.[14] Most of the *Haemophilus* strains have only intermediary sensitivity to PCV but are sensitive to amoxicillin. Nevertheless, according to Norwegian guidelines, penicillin V is recommended as the antibiotic of choice for infections such as otitis media and sinusitis, where *Haemophilus* is one of the major pathogens.[7] This recommendation may be controversial as amoxicillin is the drug of choice for these infections in countries outside Scandinavia. However, a study of antibiotic treatment for acute sinusitis found no significant difference in clinical recovery depending on whether the patients received amoxicillin or high dosages of PCV.[15] *Moraxella* has developed a considerable resistance to antibiotics, but the clinical importance of this microbe still remains obscure.[14]

In the USA and in southern Europe, the situation regarding antibiotic resistance is more dramatic.[3,4,16] Here, the proportions of multi-resistant pneumococci and resistant *Haemophilus* are

Table 2. Antibiotic prescriptions (n = 7905) in Norwegian general practice by the antibiotic prescribing profile for each diagnosis.

Diagnoses	Antibiotic prescriptions (%)							
	PCV	Extended spectrum penicillins	Erythromycin	Tetracyclines	Co-trimoxazole	Others	Sum (%)	n (%)
Respiratory tract infections (RTI)								
Acute bronchitis	24	2	31	34	9	–	100	1035 (13)
Ear infections	58	1	26	3	12	–	100	717 (9)
Upper RTI	51	2	23	17	7	–	100	663 (8)
Tonsillitis	76	1	14	3	6	–	100	651 (8)
Sinusitis	55	1	13	25	5	1	100	570 (7)
Pneumonia	29	4	30	30	5	1	100	360 950
Chronic bronchitis	14	3	30	43	10	0	100	63 (1)
Other infections								
Urinary tract infections	–	18	–	2	45	34	100	1871 (24)
Skin infections	34	2	12	34	16	2	100	564 (7)
Genital infections	3	6	1	42	40	8	100	139 (2)
Other diagnoses	31	6	15	26	17	5	100	1272 (16)
Total (%)	2516 (32)	506 (6)	1232 (16)	1396 (18)	1517 (19)	815 (10)	100	7905 (100)

Data are from the Møre & Romsdal Prescription Study.[12]

Table 3. GP–patient contacts (n = 2810) and antibiotic prescriptions (n = 1265) for respiratory tract infections in children (0–12 years), and the antibiotic prescribing profile for each diagnosis.

Diagnoses	Doctor–patient contacts				Antibiotic prescriptions (%)				
	Total number of patient contacts	Patients getting prescriptions			PCV	Erythromycin	Co-trimoxazole	Others	Sum (%)
		n	%	95% CI					
Ear infections	819	359	43.8	40.4–47.2	54	30	15	1	100
Acute bronch(iol)itis	386	310	80.3	76.3–84.3	23	57	17	3	100
Tonsillitis	301	280	93.0	89.5–95.6	65	24	10	1	100
Upper RTI	1106	161	14.6	12.5–16.6	45	42	11	2	100
Pneumonia	126	102	81.0	74.1–87.8	27	52	4	17	100
Sinusitis	47	39	83.0	69.2–92.4	51	28	13	8	100
Chronic bronchitis	25	14	56.0	34.9–75.6	21	71	–	8	100
Total	2810	1265	45.0	43.2–46.9	40	35	18	7	100

Data are from the Møre & Romsdal Prescription Study.[13]

steadily increasing, now comprising about 20% of the strains.[3] This has most probably turned into a vicious circle: more use of the broad spectrum antibiotics contributing to even more resistant microbes. In a study from USA, Kunin *et al* demonstrated that half of the antibiotics contributing to this unfortunate development were actually prescribed unnecessarily.[17]

Antibiotic use

A strength of the Norwegian health care system is the high quality of the national drug use statistics, being official and non-commercial at a national level.[11] No known changes in general disease patterns during 1981 to 1993 can explain the more than 30% increase in the antimicrobal consumption in Norway during this period (Figure 1). In spite of this, the Norwegian antibiotic consumption per 1000 inhabitants per day has remained only about half of that reported from countries in southern Europe and the USA.[3]

The proportion of PCV of the total antibiotic use during the period has risen from 27% to 34%, and PCV is by far the most commonly prescribed antibiotic in Norway. There has been a relatively low proportion of macrolides and tetracyclines used. The rise in tetracyclines, which took place from 1987 to 1993, has been reversed during the past years; partly because of an active campaign against the extended use of tetracyclines.[14]

There may be several explanations as to why PCV, contrary to what is taking place in other countries, is still the most commonly prescribed antibiotic for respiratory tract infections in Norway. One reason may be that most Norwegian GPs are loyal to the national recommendations naming PCV as the antibiotic of choice for most of the respiratory tract infections.[7] Another factor may be that Norwegian patients suffering from acute infections must pay all drug costs themselves; therefore they often ask for the cheapest effective treatment.

Antibiotic resistance is closely linked to the antimicrobial spectrum of the drugs used.[3-5] Broad-spectrum agents have a considerable impact on the normal bacterial flora in (and on) the human body, and their action favours the survival of resistant bacteria. The preference of the narrow spectrum PCV by the GPs is probably one of the most important explanatory factors as to why Norway has had only minor problems with antibiotic resistance so far.[14] Another important factor is that the total consumption of antibiotics per capita is relatively low compared with that of most other countries.[3]

A major increase in antimicrobial resistance has occurred in other Nordic countries. In Finland, a high frequency of erythromycin resistant streptococci was reported in 1990,[18] possibly owing to the over-liberal use of erythromycin in the 1980s. A significant reduction of resistant strains could be demonstrated after an extensive campaign promoting new guidelines for more restricted prescribing of erythromycin.[19] This Finnish experience is a good example of how interventions aimed at general practice can, in fact, reduce the antimicrobial resistance in a population. Similar experiences have been made in Iceland where penicillin resistant pneumococci were a considerable problem during the early 1990s.[5]

Diagnosis in primary care related to antibiotic prescription

Respiratory tract infections constitute more than 60% of the diagnoses leading to antibiotic prescriptions in Norwegian general practice. The basis for these diagnoses is symptoms and signs, often with a low predictive value, rather than microbiologically confirmed diagnoses. The uncertainty of the diagnoses is considerable for sinusitis,[20] for pneumonia,[21] and for sore throat.[22] In some cases it may be tempting for the clinician to record a diagnosis that justifies antibiotic treatment instead of vice versa (e.g. tonsillitis instead of sore throat).[23]

During the past years, semi-quantitative, immunological diagnostic rapid tests for C-reactive protein (CRP) and group A streptococci have increasingly been used in Norwegian general practice. As these tests can be performed in the GP's surgery, giving results within minutes, they have a direct impact both on diagnoses and treatment. In a recent study, a potential reduction of antibiotic prescriptions by 25% by the use of CRP tests was demonstrated for patients with respiratory tract infections.[24] The introduction of these tests may therefore be one possible explanation for the decreased use of antibiotics in Norway during the past five years.

A number of comparative studies focusing on diagnosis and treatment of common respiratory infections have been carried out. Antibiotics have shown to be of little or no value in the treatment of acute otitis media,[25] and acute bronchitis.[26] The use of antimicrobials are even more controversial in the treatment of the sore throat[22] and in acute sinusitis.[15,27] Patients with acute bronchitis and ear infections should only be given antibiotic treatment in special cases. These are the two most common airway diagnoses that lead to antibiotic prescription in both children and adults. Taking these findings into consideration, it can be seen from Table 2 and 3 that there is a considerable potential for reducing antibiotic usage also in Norwegian general practice.

Attitudes to antibiotic prescription in the population

Howie has previously shown that paramedical reasons such as examinations and holidays can influence the extent of antibiotic usage.[28] Commercial (e.g. promotional activities by the pharmaceutical companies), geographical, cultural, and other social factors can also influence the doctors' prescribing practices.[28,29] Unnecessary antibiotic prescriptions create patient expectations and demands for antibiotics during later illnesses.[22,28] It has not been demonstrated that patient satisfaction depends on antibiotic prescription for respiratory tract infections. Hamm *et al* looked for, but did not find, such an association; patient satisfaction was, however, well correlated with the patients' understanding of their illness and the time the doctor spent with them.[30] Among Norwegian GPs, there now appears to be a growing awareness of patient expectations and the ecological problems related to unnecessary use of antibiotics.

Conclusions

Norway currently has a limited problem with antibiotic resistance and this situation has been stable for some years. The most likely reason for this favourable situation is the use of PCV for most of the common airway diseases in general practice and a low total prescription volume of antibiotics compared with other countries. There is, however, still a great potential for reducing the unnecessary antibiotic prescribing for the most common respiratory illnesses.

References

1. Hart CA. Antibiotic resistance: an increasing problem? *BMJ* 1998; **316:** 1255-1256.
2. Abbasi K. Report calls for action on antibiotic resistance. *BMJ* 1998; **316:** 1261.
3. Espersen F, Frimodt-Møller N. Kampen mod mikroberne – et internationalt anliggende (The fight against microbes – an international challenge). *Ugeskr Læger* 1996: **158:** 251-252.
4. Tenover FC, Hughes JM. The challenges of emerging infectious diseases. Development and spread of multiple-resistant bacterial pathogens. *JAMA* 1996; **275:** 300-304.
5. Arason VA, Kristinsson KG, Sigurdsson JA, *et al*. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? [Cross sectional prevalence study.] *BMJ* 1996; **313:** 387-391.
6. Mølstad S, Ekedahl A, Hovelius B, Thomansson H. Antibiotics prescription in primary care: a 5-year follow-up of an educational program. *Fam Pract* 1994; **11:** 282-286.
7. Vennerød AM (ed). *Norsk Legemiddelhåndbok 1998-1999 for helsepersonell* (Norwegian drug and therapeutic formulary for health personnel 1998-1999). Oslo: Norsk Legemiddelhåndbok I/S, 1998.
8. Digranes A. Antibiotikafølsomhet for de vanligste luftveispatogene bakteriene (Antibiotic sensivitity for the most common airway pathogen bacteriae). *Astra: Therapia Medica* 1997; **4:** 17-21.
9. Bergan T, Bruun JN, Digranes A, *et al*. Susceptibility testing of bacteria and fungi. Report from 'the Norwegian working group on antibiotics'. *Scand J Infect Dis Suppl* 1997; **107:** 19-21.
10. Andrew M, Solberg CO. Forbruket av antimikrobielle midler i Norge 1980-92 (Consumption of antimicrobial agents in Norway 1980-92). *Tidsskr Nor Lægeforen* 1994; **114:** 169-173.
11. Øydvin K (ed). *Legemiddelforbruket i Norge 1993-97* (Drug consumption in Norway 1993-97). Oslo: Norsk Medisinaldepot, 1997.
12. Straand J, Rokstad KS, Sandvik H. Prescribing systematic antibiotics in general practice. A report from the Møre & Romsdal prescription study. *Scand J Prim Health Care* 1998; **16:** 121-127.
13. Straand J, Rokstad KS, Heggedal U. Drug prescribing for children in general practice. A report from the Møre & Romsdal prescription study. *Acta Pædiatr* 1998; **87:** 218-224.
14. Melby K. Microbiology in acute upper respiratory tract infections. In: Madsen S, Warsted A, Westbye O, *et al. Treatment of acute infections of the respiratory tract in primary health service*. Oslo: Statens legemiddelkontroll and Läkemedelsverket, 1995.
15. Lindbæk M, Hjortdahl P, Johnsen UL-H. Randomised, double blind, placebo controlled trial of penicillin V and amoxicillin in treatment of acute sinus infections in adults. *BMJ* 1996; **313:** 325-329.
16. Venkatesan P, Innes JA. Antibiotic resistance in common acute respiratory pathogens. *Thorax* 1995; **50:** 481-483.
17. Kunin CM, Tupasi T, Craig WA. Use of antibiotics. A brief exposition of the problem and some tentative solutions. *Ann Intern Med* 1973; **79:** 555-560.
18. Seppälä H, Nissinen A, Järvinen H. Resistance to erythromycin in group A streptococci. *N Engl J Med* 1992; **326:** 292-297.
19. Seppälä H, Klaukka T, Vuopio-Varkila J, *et al*. The effects of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med* 1997; **337:** 441-446.
20. Lindbæk M, Hjortdahl P, Johnsen UL-H. Use of symptoms, signs and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med* 1996; **28:** 183-188.
21. Melbye H, Straume B, Aasebø U. Diagnosis of pneumonia in adults in general practice. The relative importance of typical symptoms and abnormal chest signs, evaluated against a radiographic reference standard. *Scand J Prim Health Care* 1992; **10:** 226-233.
22. Little P, Williamson I, Warner G, *et al*. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997; **314:** 722-727.
23. Pitts J, Vincent J. What influences doctors' prescribing? Sore throats revisited. *J R Coll Gen Pract* 1989; **39:** 65-66.

24. Lindbæk M, Hjortdahl P. C-reactivt protein i allmennpraksis – et viktig diagnostisk hjelpemiddel ved infeksjoner (C-reactive protein in primary care – a useful diagnostic tool in infections). *Tidsskr Nor Lægeforen* 1998; **118:** 1176-1179.
25. Browning G. Childhood otalgia: acute otitis media. Antibiotics not necessary in most cases. *BMJ* 1990; **300:** 1005-1006.
26. Fahey T, Nigel Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotics with placebo for acute cough in adults. *BMJ* 1998; **316:** 906-910.
27. van Buchem FL, Knottnerus JA, Shcrijnemaekers VJJ, Peeters MF. Primary-care-based randomised placebo-controlled antibiotic treatment in acute maxillary sinusitis. *Lancet* 1997: **349:** 683-687.
28. Howie JGR. Clinical judgement and antibiotic use in general practice. *BMJ* 1976; **2:** 1061-1064.
29. Stephenson MJ Henry N, Norman GR. Factors influencing antibiotic use in acute respiratory tract infections in family practice. *Can Med Physician* 1988; **34:** 2149-2153.
30. Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: are patients more satisfied when expectations are met? *J Fam Pract* 1996; **43:** 56-62.

Address for correspondence

Morten Lindbæk/Per Hjortdahl, Division of General Practice, University of Oslo, Box 1130 Blindern, 0317 Oslo, Norway.