

# **Hospital antibiotic use in Norway**

## **Epidemiology and surveillance methodology**

PhD thesis

Jon Birger Haug

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UiO : **University of Oslo**



Institute of Clinical Medicine

Faculty of Medicine, University of Oslo, Oslo, Norway

Department of Pharmacology and Department of Infectious Diseases

Oslo University Hospital Trust, Oslo, Norway

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## INSPIRATIONS

Some experts say we are moving back to the pre-antibiotic era.

No.

This will be a post-antibiotic era. In terms of new replacement antibiotics, the pipeline is virtually dry. A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill.

*Margaret Chan, WHO Director (1947- )*

If you cannot measure it,  
you cannot improve it.

*Lord Kelvin, scientist (1824-1907)*

Progress is made by lazy men  
looking for easier ways to do things.

*Robert A. Heinlein, sci-fi author (1907-1988)*

Give me six hours to chop down a tree  
and I will spend the first four sharpening the axe.

*Abraham Lincoln, American president (1809-1865)*



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### Acknowledgements

My motivation for this PhD project has been a long-lasting interest in hospital epidemiology, initially triggered by my assignment in the early 1990's at the National Institute of Public Health. I was working with a pioneer in national infection control, professor **Arve Lystad**, who was the creator of MSIS. This simple and brilliant surveillance national notification system for infectious diseases has for decades been of great importance for Norwegian health care. For Arve's early inspiration, I am very grateful.

My most special thanks goes to my main supervisor, professor **Åsmund Reikvam**. To him I wish to express a sincere gratitude. Without his scientific experience, extensive knowledge in pharmacoepidemiology and eminent writing skills this thesis would have been very much harder to complete. He represents great working capacity with a remarkable persistence and sufficient patience blended in, and the combination has benefited me tremendously. Above all, he is a colleague I have come to respect and like a lot. Åsmund, thank you for all your help and support.

A new employment at the Aker university hospital almost 10 years ago fuelled an interest for antibiotic stewardship that had been pre-existing, but dormant. At this excellent – now unfortunately extinct – hospital **Signe Ringertz** and **Dag Berild** were important catalysts for this PhD thesis: Signe always encouraging in the initial planning phase, and Dag a perpetual source of good ideas, always blending in his sound common sense and tons of good humour. I wish to thank them both for their support, Dag especially for trying – but not succeeding – in being the “stern” co-supervisor. Nevertheless, he has been a strong motivating force for me especially in times of trouble. Moreover, he generously left me in charge of the Helse Sør-Øst Regional Competence centre for hospital antibiotic use at an early stage, thus providing some precious time for my scientific work.

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Several individuals have helped in various ways to complete this thesis, and deserve my most sincere thank you. The bulk of national data on antibiotic consumption would have been far more difficult to acquire without the relentless support from the efficient and patient **Skule Ingeberg**, chief of analytics at the Hospital Pharmacy Regional Health Enterprise. Three statisticians have been my consultants for the choices of statistical methods and have aided in the interpretation of the results. I wish to extend my gratitude to **Lien My Diep** and **Leiv Sandvik** for their contributions to Paper I, and **Tron Moger** for a critical review of the regression analyses in Paper IV.

Main companions in my investigations of antibiotic use epidemiology have been the products of **Bill Gates**, in particular Microsoft Access and Excel – especially in the process of data mining and presentation.

Although I wish to express a minor praise to Bill, I am not sure my family shares this entirely. PhD activities and an intimate relationship to the computer keyboard have often been given priority over family life. A deeply felt praise go to the love of my life, Nina, who has endured all of this with great patience. My three wonderful children Linn, Jonas and Mathias have been very supportive but have during this process become, I suspect, more certain than ever that the father's choice of profession was not theirs to follow.

## List of publications

- 1. Pharmacy sales data versus ward stock accounting for the surveillance of broad-spectrum antibiotic use in hospitals.**  
Haug JB, Myhr R, Reikvam Å.  
*BMC Medical Research Methodology* 2011; 11(1): 166.  
<http://www.biomedcentral.com/1471-2288/11/166>
- 2. Increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate.**  
Haug JB, Berild D, Walberg M, Reikvam Å.  
*Journal of Antimicrobial Chemotherapy* 2011; 66(11): 2643-6. doi:10.1093/jac/dkr361
- 3. WHO defined daily doses versus hospital adjusted daily doses: impact on surveillance results of antibiotic use.**  
Haug JB, Reikvam Å.  
*Journal of Antimicrobial Chemotherapy* 2013; 68(12): 2740-2747. doi:10.1093/jac/dkt268
- 4. Explanatory factors for differences in hospital antibiotic use: analysis of national data from 2006 to 2011.**  
Haug JB, Berild D, Walberg M, Reikvam Å.  
Submitted.



### 1. General background

#### *1.1. Antibiotics and modern medicine*

No class of drug can compete with antibiotic agents in terms of a definite cure of disease and, above all, the extent of mortality reduction these drugs have contributed over the last 70 years. Nonetheless, infectious diseases even today kill and disable on a large scale in developing countries and regions with little economic resources. A fortunate minority of the world population has almost unlimited access to diagnostic and therapeutic resources, including antibiotic supplies, which is taken for granted. The inhabitants of the industrialized societies have limited understanding of the tremendous impact that infectious diseases made on the lives of their ancestors only a few decades ago.

With the historical backdrop in mind, there is no doubt that the control of infectious diseases by use of antibiotics is one of the most important achievements in the history of medicine. To keep this precious asset intact, the prescribing of antibiotics should be an exclusive domain of physicians, which indeed is the case in many industrialized countries. Unfortunately, these basic conditions are non-existing in large parts of the world. Thus, lack of money or non-availability of drugs are the only factors that constrain an uncontrolled and potential limitless use.

#### *1.2. An antibiotic paradox*

Soon after the discovery of antibiotics, bacteria with resistance to the drugs emerged.



Alexander Fleming, the discoverer of penicillin, made a prophetic statement in 1945 when he was interviewed in the New York Times about the future of the miracle drug: “... the public will demand [penicillin] ...then will begin an era...of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can

## INTRODUCTION: GENERAL BACKGROUND

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*be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. – I hope the evil will be averted.”*<sup>1</sup>

Unfortunately, the evil has not been averted.

The increase in antibiotic resistance is proportional to the use of antibiotics.<sup>2-5</sup> Although this has long been a common knowledge, antibiotic use has increased tremendously over the last decades. This is because of the immediate benefits that emerged for a wide range of medical specialties with the use of antibiotics. Combined with the simultaneous advances in anaesthesiology and antisepsis it became possible to cure patients on a scale never before imagined. The drawback has been that modern medicine also causes an increasing number of immunocompromised patients and complications, for example in relation to advanced surgery. This, in turn, necessitates even more use of antibiotics and the demand for more sophisticated antibiotics arises. This spiral of events – which may seem as a paradox, but is in fact a consequence of evolutionary processes in nature – has led to a global epidemic of antibiotic resistance. Already for many years, this unfortunate development has been perceived as one of the most serious threats to human health.<sup>6,7</sup>

### ***1.3. The antibiotic resistance challenge***

At least three elements of antibiotic use make it difficult to reverse the global escalation of antibiotic resistance.

First, there is a contradiction between the need to treat seriously infected patients effectively and the need to restrict antibiotic use to prevent antimicrobial resistance development.<sup>8</sup> This dilemma is ubiquitous in the physician-patient setting, be it in the intensive ward of a modern hospital or in a remote village in Africa. In recent years the ethical question has been raised, at least in industrialized settings, if today's patients may be requested to refrain from special antibiotics, or even being actively withheld antibiotic treatment altogether for mild and moderate infections, in order to preserve these life-saving drugs for future generations.<sup>9</sup>

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Second, new antibiotics are urgently needed but their development is hampered by generally modest income prospects for the pharmaceutical industry.<sup>10-14</sup> Almost no new substances, only variations of the old, have been developed in recent decades. The development of new drugs is seriously restricted by a lack of investments, partly due to a concern shared by most companies that resistance will render a new antibiotic – developed at a high cost – ineffective after a relatively short time.

The final and maybe most easily accessible element of the resistance problem deals with counteracting an overuse and misuse of antibiotics, caused by physician's lack of knowledge and ignorance of the ecological side effects<sup>15-17</sup> and the influence from profit-makers.<sup>18</sup>

Norway and the other Scandinavian countries (and the Netherlands) still have a relatively low level of antibiotic resistance among pathogenic bacteria as compared with most other countries<sup>19</sup> (Figure 1.1).

There are several reasons for this; not all of them are obvious and well identified. Cultural and socio-economic factors play a role<sup>20</sup> and the extent of self-medication with antibiotics also differs widely between countries.<sup>21,22</sup>

To some degree, one is left to hypothesize about the reasons for the county differences. One very probable explanation is the fact that there are fewer antibiotic substances registered in countries with a lower level of resistance than what is the case in countries with extensive resistance. A survey in 2001 of 139 European hospitals concluded that the number of registered antibiotics had an impact on antibiotic consumption. With increasing number of available antibiotics, higher consumption figures could be observed (Spearman rank correlation 0.40,  $P < 0.01$ ).<sup>23</sup> The numbers of registered antibiotics in various countries are surprisingly difficult to obtain but in 2010 the

Figure 4.3B: *Staphylococcus aureus*: percentage (%) of invasive isolates resistant to methicillin (MRSA), by country, EU/EEA countries, 2008–2011

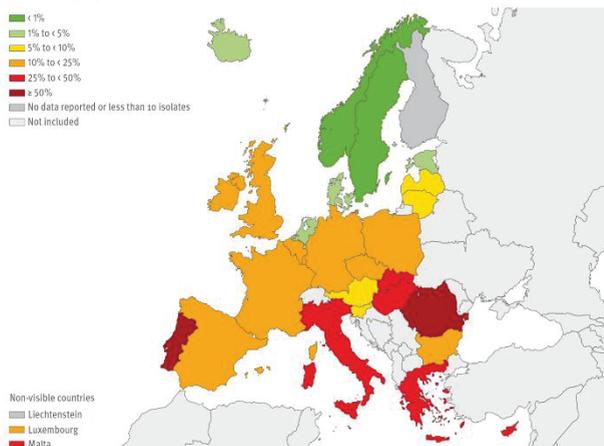


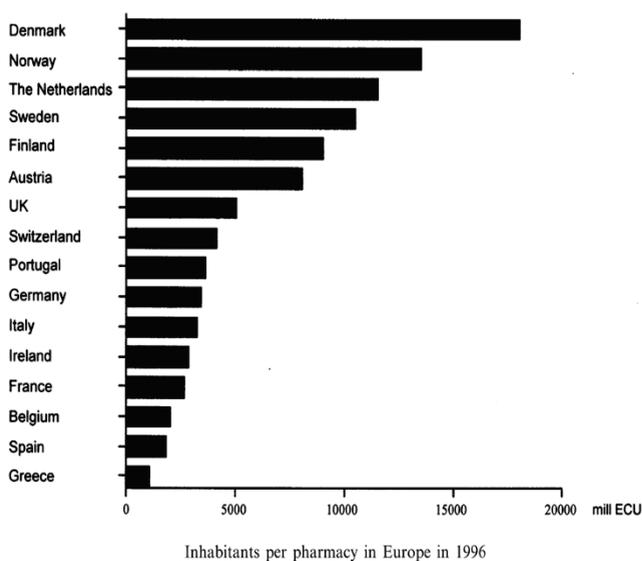
Figure 1.1 ECDC 2012: Methicillin-resistant *Staphylococcus aureus* (MRSA) in Europe, 2011. (From ECDC 2012 Resistance Report, Europe)

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international ATC J01 (Antibacterials for systemic use) registry listed 229 antibiotic substances or their combinations (e.g. J01CA04 benzylpenicillin), classified into 33 chemical groups (e.g. J01CE, penicillinase-sensitive penicillins) and furthermore into 10 pharmacological subgroups (e.g. J01C, penicillins).<sup>24</sup> The corresponding numbers for Norway were 44, 22 and 8.

**Figure 1.2** Number of inhabitants per pharmacy in Europe, 1996

T. Bergan / *International Journal of Antimicrobial Agents* 18 (2001) 279–282



Moreover, a greater availability of antibiotics may also be related to a larger density of pharmaceutical services. A review article from 2001<sup>25</sup> showed a large variation in the number of inhabitants per pharmacy between selected European countries in 1996 (Figure 1.2). The ranking order of countries by use of this measure is largely a reverse order of the antimicrobial resistance ranking in Europe today, almost 20 years later.

A favourable resistance situation – like it presently is in Scandinavia countries – should be an added incentive to monitor the situation very closely and to respond

appropriately. There is ample evidence that development of antibiotic resistance is easier to prevent or delay in a situation with low-grade resistance than it is to attack and reduce after it has reached a certain level.<sup>26</sup>

Several mechanisms and factors are contributing to the development of antimicrobial resistance. While there is no dispute concerning the relationship between antibiotic use and antibiotic resistance in microorganisms, a simple “drug-bug” connection is rarely straightforward.<sup>27</sup> For instance, it has been shown that the penicillin-resistance in pneumococci is less promoted by the use of beta-lactam antibiotics than by the use of macrolides.<sup>28</sup> The drivers for methicillin-resistance in *Staphylococcus aureus* (MRSA) are to a larger extent quinolones, glycopeptides

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and cephalosporins than are penicillins.<sup>29</sup> For emergence and persistence of vancomycin-resistant enterococci (VRE) in hospitals, extensive use of extended-spectrum cephalosporins, quinolones and antibiotics against anaerobic infections probably have a more significant impact than a high-level use of vancomycin.<sup>30</sup>

### ***1.4. Antibiotic resistance in hospitals***

Antibiotic use in hospitals account roughly for only 5-15% of total use in the community, and this proportion is more or less the same, and has been relatively stable, all over the developed world. Although accounting only for only a fraction of total antibiotic use, hospitals are beyond doubt the most important sources for antibiotic resistance development. Hospital environments are also prone to establish a high endemicity for opportunistic and resistant microorganisms.

In a joint SHEA/IDSA\* guideline for antibiotic resistance prevention, Shales *et al* referred to early insights about antibiotic resistance presented in a seminal work by McGowan<sup>31</sup> and summarized seven main mechanisms for the appearance or spread of resistance in hospital organisms:<sup>32</sup>

- Greater severity of illness of hospitalized patients.
- More severely immunocompromised patients.
- Newer devices and procedures in use.
- Increased introduction of resistant organisms from the community.
- Ineffective infection control and isolation practices and compliance.
- Increased empirical polymicrobial antimicrobial therapy.
- High antimicrobial usage for geographical area per unit time.

More risk factors are present in hospitals than in the community and the interactions between them are complex. Apart from the larger volumes of advanced antibiotics being used, the risk of resistance development is imminent because of the particular environments, with multiple sick individuals living in contained areas.

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\* SHEA: *The Society for Healthcare Epidemiology of America*, IDSA: *Infectious Diseases Society of America*

### ***1.5. Resistance surveillance***

Resistance surveillance, no matter how accurate and sophisticated, will be of little use without further analyses and interpretations based on knowledge of resistance mechanisms and the interactions between microorganisms. Monitoring of antibiotic resistance is needed to be able to reverse or at least delay the escalation of the problem. On a national scale, a routine monitoring is necessary because significant national resistance trends may have an impact on general recommendations for antibiotic use. In addition, it is important to identify hospitals with outlier resistance values e.g. in order to adjust recommendations for antibiotic therapy and to detect outbreaks. Finally, international surveillance networks have been established for which it is pivotal to contribute national data.<sup>19,33,34</sup>

Resistance monitoring on the local hospital level should be performed for several reasons:

- Deviations from national resistance rates may be observed and call for local adjustments of recommendations for antibiotic use.
- Local resistance statistics may be used for education purposes to change physician's prescription habits.
- Surveillance may facilitate the detection of outbreaks with multiresistant microorganisms.

### ***1.6. The antibiotic stewardship program***

Many determinants for the rational use of antibiotics are similar whether the antibiotics are prescribed in hospitals or in the community. Nonetheless, physicians working in hospitals encounter different, and mostly more complex, clinical scenarios than those dealt with by colleagues working in the community. In recognition of this fact, the concept of an “antibiotic stewardship program” has been specifically developed for health care institutions.

A concise definition has been proposed by Tamma and Cosgrove<sup>35</sup> who state that antimicrobial stewardship “- refers to a program or series of interventions to monitor and direct antimicrobial use at a health care institution, thus providing a standard, evidence-based approach to judicious antimicrobial use.” Extensive American guidelines for antimicrobial stewardship in hospitals

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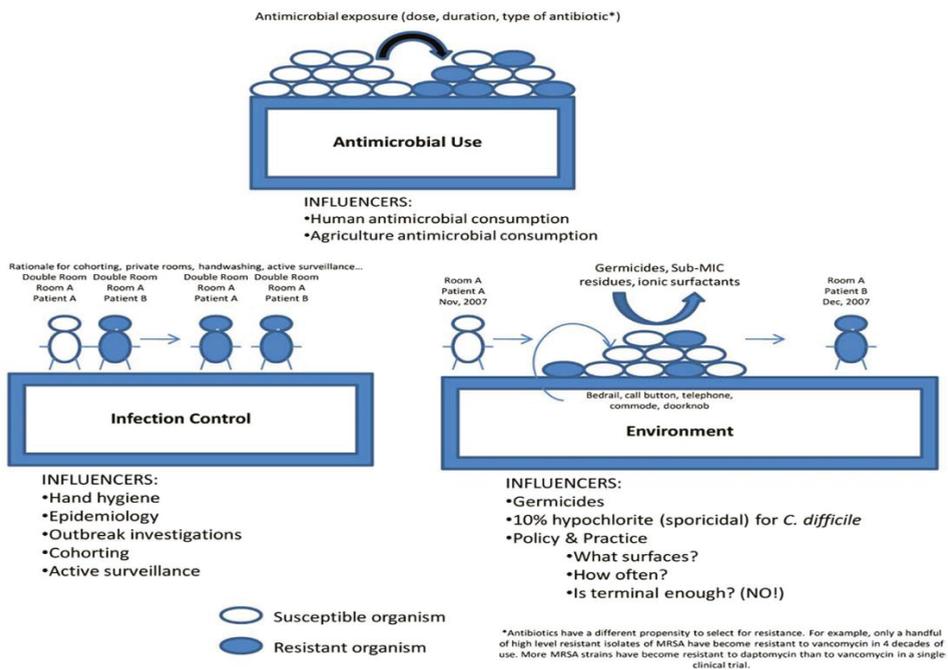
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were endorsed in 2007.<sup>36</sup>

The choice of measures should be based on the evidence of the measures' effect and the probability of success in the local hospital setting. Cost considerations are also important, in particular as an argument to allocate sufficient resources for the program.

In what was called the “holy trinity” of resistant development and dissemination ( Figure 1.3), a recent review of modern antimicrobial stewardship describes the interplay between infection control factors, environmental influencers and the exposure to antibiotics.<sup>37</sup>

**Figure 1.3.** The «holy trinity» of antibiotic resistance and spread (Owens, 2008)



In recognition of the fact that antibiotic resistance has multiple causes and no single action or measure can eliminate the problem, the concept of “intervention bundles” has been introduced. The utility of implementing a set of measures, tailored to local needs, have since been reported in several studies.<sup>38-40</sup> The bundles may be seen as sets of locally adjusted and practically designed procedures with the purpose to operationalize an antibiotic stewardship program, which is often designed and introduced at a higher administrative level.

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The implementation of evidence-based and updated antibiotic guidelines, establishing of clinical pathways and prescription audits with feedback to prescribing physicians are important and basic elements of the antibiotic stewardship program. Furthermore, in the work towards a more rational antibiotic use in hospitals, the magnitude of antibiotic utilisation must be calculated and presented on a regular basis. A proper system for surveillance of antibiotic use is therefore needed to facilitate and supplement a complete stewardship program. The ultimate purpose for collecting levels of antibiotic use on a routine basis is to expose inappropriate prescribing which may harm the patients, incur unnecessary costs for the health systems, and cause antibiotic resistance. Other reasons for surveillance are the possibility to identify factors that influence antibiotic use and to monitor the effect of implementation strategies. <sup>41</sup>

### *1.7. Legislative and strategic measures*

Norway has always had a strong legislative framework for the prevention of infectious diseases. A strong, but historically quite fragmented collection of laws on various communicable diseases was in 1994 incorporated into one single Act (“Smittevernloven”). <sup>42</sup> The § 4-7 of this Act states that measures to prevent hospital infections should be described in one central regulation. A regulation was then drafted and endorsed in 1996. As one of several impositions, this regulation lays down that every health institution shall have written guidelines for use of antibiotics i.e. updated recommendations for appropriate antibiotic use.

Two subsequent national strategic action plans since 2003 (Figure 1.4, page 9) have listed multiple measures to combat antibiotic resistance and avoid the high levels seen in most other countries. The last revision in the plan for the period 2008–2012 <sup>43</sup> determined that hospitals should have an antibiotic policy that includes reporting of the consumption of antibiotics and of antibiotic resistance.

Two initiatives evolving from these strategic plans in recent years are particularly important for the improvement of antibiotic prescribing practices in Norwegian hospitals, namely

1. the funding and establishment of a national “Competence centre for hospital antibiotic use” in 2011, and
2. publication of a revised national guideline for hospital antibiotic use in 2013.

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Unfortunately, the intentions regarding surveillance of antibiotic use and resistance at the hospital level have not been followed up. Moreover, it was decided to refrain from the publication of a new strategic plan for 2013 and beyond.

**Figure 1.4.** Norwegian national strategic plans for prevention of hospital infections and antibiotic resistance, since 2003

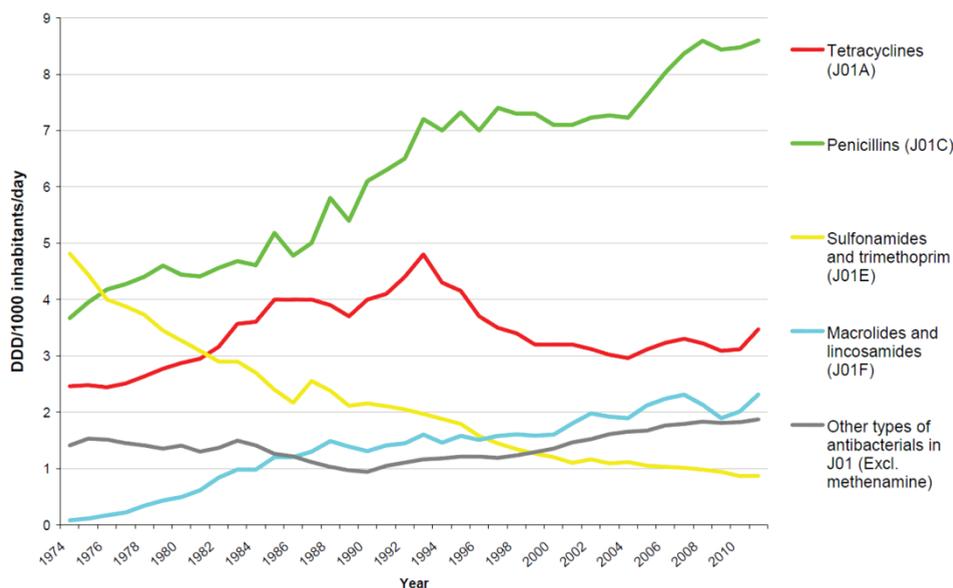


## 2. Epidemiology of antibiotic use

### 2.1. Antibiotic use in the community (outpatient use)

**Norway.** National statistics on antibiotic use have been available in Norway since 1974. The estimated figures have been based on gross annual sales of antibiotics to from wholesalers to pharmacies, and the utilization by patients in the community and patients treated in institutions have commonly been reported as one entity, at least before the year 2001 (see also “Wholesalers’ data”, page 17). However, a differentiation between ambulatory care and hospital care sales data has been made by subtracting deliverances to hospital pharmacies from the total number of doses.<sup>44</sup> The gross consumption of antibiotics in Norway has been relatively stable at least since the early 1990ies but the pattern of use has changed (Figure 2.1). In a publication reporting data from the period 1980–1992, the national use of all systemic antibiotics varied between 14 and 17 DDDs/1000 inhabitants/day.<sup>45</sup> Narrow-spectrum penicillins dominated, and the greatest concern expressed was a perceived high consumption of tetracyclines and co-trimoxazole.

**Figure 2.1.** NORM/NORM-VET 2011. Antibiotic use in Norway, 1974-2011.



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Bergan<sup>25</sup> published an overview of antibiotic use for the period 1994–1998, in which the Nordic countries were compared. He found striking differences between these neighbouring countries with the highest levels of total antibiotic use in Iceland and Finland, the double of what was measured in Sweden and Norway. The Norwegian antibacterial consumption was an estimated 14.4–15.4 DDDs/1000 inhabitants per day. The narrow-spectrum penicillins (ATC J01CE, benzylpenicillin and phenoxymethylpenicillin) accounted for ~40% of the total use. National figures from 2011 showed that the overall use – i.e. both in the communities and the hospitals – of antibacterial agents (excluding methenamine) had increased to 17.2 DDDs/1000 inhabitants/day. The narrow-spectrum penicillins' proportion of the total use has decreased significantly over the recent decades, to 26% in 2011, but altogether the penicillin group (ATC J01C) still accounts for as much as 50%. This is the result of a shift towards a relatively higher usage of penicillins with extended-spectrum and betalactamase-resistant penicillins. In the same period, the use of macrolides increased notably, which is a cause of concern.

In contrast to most other countries, no oral form of the broad-spectrum antibiotics except fluoroquinolones (almost exclusively ciprofloxacin) is registered in Norway. Oral formulations of cefuroxime and penicillins with an enzyme inhibitor, notably amoxicillin/clavulanic acid, are widely used abroad and this fact is most certainly a factor contributing to the high resistance levels observed.

Swedish national studies of antibiotic use go back as far as 1975. In an investigation mainly of the economic aspects of antibiotic use during the period 1975–1992, the conclusion was the following: *“An increase of more than 25% in Swedish consumption of antibiotics during the study period was found. There is no obvious clinical explanation; indeed, improved hospital hygiene as well as decreased frequencies of some common bacterial infections should have resulted in a decrease in total consumption”*.<sup>46</sup>

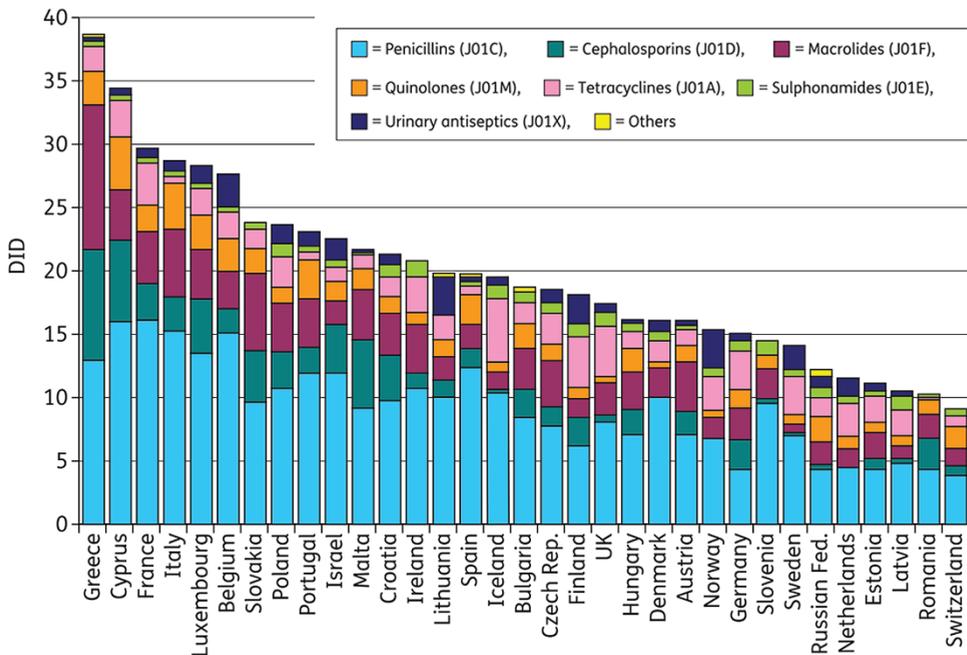
Obviously, the concern about inappropriate use of valuable antibiotics is not new.

**International data.** In a study from 1997, Cars *et al* published a review of non-hospital antibiotic sales data from 15 EU member state (i.e. not including Norway) where the large dissimilarities in consumption first was documented.<sup>47</sup> Subsequently, international comparisons were made possible through the project European Surveillance of Antibiotic Consumption (ESAC). This organisation has undertaken several studies on outpatient antibiotic use.<sup>48-59</sup> Aggregated data, initially based on wholesaler's databases but in recent years obtained from hospital pharmacies,

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has been reported from Norway to the ESAC network since 2001. In the period 2001–2009, the national outpatient use was stable at 14.8–16.8 DID (DDD/100 inhabitants/day). There might be some methodological limitations inherent in international comparisons, but the variation in pattern of utilization throughout Europe remains remarkable (Figure 2.2).

**Figure 2.2.** European outpatient antibiotic use, 2009 (from Adriaenssens *et al.*, 2011)



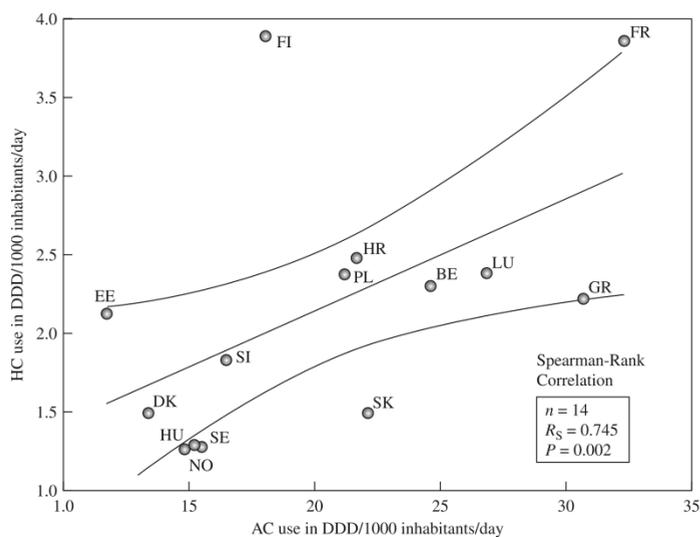
### 2.2. Antibiotic use in hospitals

In Norway, by now a continuous, standardized national surveillance of hospital antibiotic use has not been established. However, a national surveillance system on antibiotic resistance (NORM) has been established, and given rise to annual publications since 1999. These publications have given a short report on national antibiotic use, where the overall hospital use has been presented on the ATC levels 2 and 3 as DDDs/1000 inhabitants/day. <sup>60</sup>

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Few surveys from Norwegian hospitals have been conducted. In one study, large differences in patterns of antibiotic use were demonstrated between two university hospitals for the period 1993–2001.<sup>61</sup> The total use of antibiotics was similar in both institutions and varied between 47–57 and 48–60 DDDs/100 bed days (BDs) per year, respectively. For the years from 1993 to 1997, the penicillin group dominated (~70%) but extended-spectrum penicillins constituted 32% of total use in one hospital and 13% in the other.<sup>62</sup> By contrast, the latter used three times more second- and third-generation cephalosporins. This disparity was surprising since both were university hospital of comparable size. Furthermore, there were no evident differences in guidelines for antibiotic use and both hospitals had similar antibiotic resistance patterns. A possible explanatory factor, as the author duly emphasized, was that differences in the hospitals' patient populations were difficult to adjust for.

In another study, the use of antibiotics in 13 Norwegian hospitals in the period 1998–1999 was analysed. Neither hospital size or type nor geographical locations were found to be predictors for the scale of total antibiotic use.<sup>63</sup> The annual average registered was 45 DDDs/100 BDs. However, the relative use of antibiotic classes varied; smaller hospitals used less broad-spectrum agents than large hospitals and university institutions.



**Figure 2.3.** Relationship between antibiotic use in ambulatory care (AC) and hospital care (HC) in Europe, 2002.

Belgium (BE), Denmark (DK), Greece (GR), Finland (FI), France (FR), Luxembourg (LU), Sweden (SE), Estonia (EE), Hungary (HU), Malta (MT), Poland (PL), Slovakia (SK), Slovenia (SI), Croatia (HR), Norway (NO)

From Vander Stichele *et al.* (ESAC 2006)

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Through the ESAC network, accumulated national data are available for Norway, thus making comparisons with other European countries possible. However, only a few Norwegian hospital have participated in the ESAC subprojects where data from single hospitals have been analysed. ESAC presented an analysis of antibiotic consumption in hospital care for the six years 1997–2002, based on a retrospective data collection.<sup>51</sup> In this review of 15 European countries, a striking correlation (Spearman coefficient 0.745;  $P= 0.002$ ) was found when comparing antibiotic utilization in ambulatory care with hospital care antibiotic use (Figure 2.3, page 13).

Moreover, a point-prevalence survey was conducted in 2006 that included 20 European hospitals.<sup>64,65</sup> Interestingly, the protocol aimed at identifying quality indicators, and the following were identified: 1) surgical prophylaxis not continued after 24 h; 2) antibiotic prescription documented in journal, and 3) no use of quinolones or third-generation cephalosporins for community-acquired pneumonia. In total, 30.1% (range 19%–59%) of all hospitalized patients received antibacterial treatment and the respiratory tract was the most frequent infection site.

In Denmark, a nation-wide epidemiological study published in 2004 demonstrated an increase in hospital antibiotic use and changes in the patterns of use.<sup>66</sup> Total antibiotic use increased 18% from 1997 to 2001 (38.0 to 44.8 DDDs/100 BDs). Although antimicrobial resistance had not risen, there was a slightly higher proportion of broad-spectrum antibiotic use (second- and third-generation cephalosporins, quinolones and carbapenems) in 2001 (19%) than in 1997 (16%).

In a study from Sweden, Erlandsson *et al*<sup>67</sup> registered antibiotic use in 23 Swedish intensive care units during two weeks in 2000 and found that in tertiary care hospitals 84% (range 58%–87%) of patients were administered antibiotics compared to 67% of patients (range 35%–93%) in secondary hospitals and 38% in primary hospitals (range 24%–80%). In this study, a main finding was that the empiric prescribing was adequate when related to the bacteriological findings, probably because of a low prevalence of antibiotic resistance at that time.<sup>68</sup> A surveillance project of seven hospital departments in the Stockholm area used Internet for prescription aid as early as in 1999. The Internet site was also used to collect prescription data and served as a survey database. Total antibiotic use was 39–57 DDDs/100 BDs in departments of general internal medicine and 102–161 DDDs/100 BDs in infectious diseases departments.<sup>69</sup>

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In a questionnaire-based survey of 49 hospitals in southwestern France, the antibiotic use in 1999 was on average 40.2 DDDs/100 BDs (range 6 to 70.4).<sup>70</sup> Psychiatric institutions were included, which explains the low values observed. Interestingly, broad-spectrum antibiotics, mainly penicillins with enzyme inhibitor, 13.6, third-generation cephalosporins, 2.5, and fluoroquinolones, 5 DDDs/100 BDs, were the most frequently used drugs. Units of intensive care, infectious diseases and haematology exhibited the highest levels of antibiotic use.

de With *et al*<sup>71</sup> investigated antibiotic use in German university hospitals in the years 1998–2000. Overall use was on average 60.1 DDDs/100 BDs for surgical services and there was an increase in use of 16% during the study period; corresponding figures for medical services were 79.3 DDDs/100 BDs; an increase of 20%. The betalactam antibiotics, especially narrow- and intermediate-spectrum compounds, were the antibiotics most frequently used in surgical facilities (55%–73%) but lower figures were found for medical services (39%–60%). The fluoroquinolones were in second place; 9.6 DDD/100 BDs (range, 3.5–17.5) and 17.7 DDD/100 BDs (range, 8.6–30.7) in surgical and in medical services, respectively. These authors also studied two cohorts of German intensive care units<sup>72</sup> and found significant differences in antibiotic use related to hospital's affiliation and size, largely confirming the conclusions of the Swedish study cited above.<sup>67</sup>

It seems justified to state that at present (2013), no European country has established a permanent national surveillance of hospital antibiotic utilization. However, over the last decades several studies have been conducted, with use of different approaches for data collection and analysis. Accumulated sales data from reimbursement databases or pharmacy records have been the preferred sources for data acquisition. So far, electronic prescriptions databases have rarely been available. Standards for measurements of antibiotic use and reporting of results have been proposed, but an internationally accepted consensus has not been reached. However, the European surveillance network ESAC has established protocols both for longitudinal and point-prevalence studies and those have been adapted and endorsed by the European Centre for Disease Prevention and Control (ECDC).

### 3. Antibiotic surveillance methodology

Surveillance in broader sense has been described by the WHO as being “*the systematic collection and use of epidemiologic information for the planning, implementation, and assessment of disease control*”.<sup>73</sup>

In a recent Norwegian strategic plan to combat antibiotic resistance, surveillance of antibiotic use was defined as a “*...continual, systematic gathering, analysis and interpretation of data on the use of antibiotics for people and animals for use in the planning, implementation and evaluation of measures for the optimization of this use.*”<sup>74</sup>

There is a need for validated and robust surveillance methods in order to unveil areas of untoward antibiotic use in hospitals and of the methods of surveillance need adaption to the settings where they are planned to be used. The acquisition of data on hospital antibiotic utilization is often difficult because of the complexity of hospital structures and patient logistics. Moreover, when using the data for benchmarking, the surveillance results are difficult to interpret if case-mix and severity of underlying patient illnesses are not taken into account.<sup>75,76</sup>

Norwegian authorities have decided that continuous and active hospital surveillance of antibiotic use is a basic and important task that should be performed at both the level of the individual hospital and at the national level.<sup>77</sup> The main objective is to expose misuse, especially of the broad-spectrum antibiotics, which elicit resistance.

#### ***3.1. Sources for data on antibiotic use***

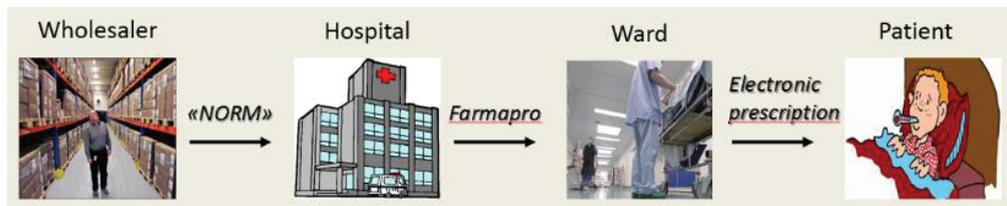
Several levels of storage and distribution are involved before an antibiotic reaches the patient in a hospital (Figure 3.1, page 17). In 2004, the ESAC network published an overview of the methods used for their outpatient and hospital care surveys in the period 1997–2001.<sup>44</sup> Of the 23 countries providing information about their sources for hospital antibiotic consumption data, 15 used pharmacy distribution data while the remaining countries obtained data from wholesalers, manufacturers or marketing research companies. Only half of the 31 participating countries could deliver valid antibiotic consumption data for hospital care and only five countries for all registration years.

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Wholesalers' data and pharmacy sales data have been used in Norway. Presently, for the routine surveillance of hospital antibiotic utilization, pharmacy sales data is still the preferred source in most European countries.<sup>78,79</sup>

Antibiotic use at the patient level, or "point of care", is in most hospitals only possible to monitor through laborious and time-consuming manual registrations (e.g., chart reviews). Data mining based on electronic drug prescriptions has the potential to provide huge opportunities for antibiotic stewardship.

**Figure 3.1** The chain of storage and distribution of antibiotics in Norway.



### 3.1.1. Wholesalers' data

Historically, in Norway gross sales data from the manufacturers have been the sources for estimations of hospitals' antibiotic consumption. A national institution, "Norsk Medicinaldepot" was established in 1953 with a monopoly with regard to wholesale and distribution of drugs. A new Pharmacy Act was passed in 2001, which privatized drug distribution. This led to the sale of the former national monopoly to one of three large pharmacy chains that are presently the main players in the Norwegian market. However, the Pharmacy Act states that a delivery of drugs is the ultimate responsibility of the chains, and that any pharmacy acquiring a license is committed to ensure a safe delivery of drugs to the end user.

With regard to hospital surveillance, the obvious shortcoming of the wholesalers' data is a lack of information about the use within hospitals. Prior to 2001, the monopoly provided some rough estimates of consumption, thus ensuring some degree of consistency in the data reported. Since then, however, a more complicated situation has arisen as the liberation of the market allows for hospitals to acquire drugs from several sources.

### **3.1.2. Pharmacy sales to hospital wards**

A measure of the consumption of antibiotics in the hospital is possible to obtain through the collection and analysis of accumulated sales data from the hospital pharmacy to each hospital unit. There are variations in the distribution of drugs in different health care systems, the two main distribution lines being:

1. Delivery in bulk to the wards or the unit stocks (“medicine rooms”), based on requisitions from the health care workers, a task usually performed by nurses.
2. Prescription orders for individual patients are sent to the pharmacy, which prepare and deliver the doses to the units and wards.

The first alternative has been the routine in most hospitals in Northern Europe, including Norway.<sup>78</sup> The drawback, both with use of wholesalers’ data and pharmacy sales data, is that information on individual patient prescriptions are not available. It is not possible to evaluate indications for antibiotic use, patient diagnoses or other information that is important for evaluation of appropriateness of prescriptions, such as drug doses and duration of therapy.

### **3.1.3. Electronic hospital charts with prescription data**

In Norway as in most other European countries, the development of analytic tools integrated in hospital computer systems has historically been driven, for a large part, by administrative and economic incentives. This applies both to large clinical systems and to specialized pharmacy-related applications. Thus, the focus has been on databases that contain little or no clinical information, or where the relevant information is difficult to access. An exception is Diagnosis Related Groups (DRGs) which relate to clinical information, but the use of this system is also financially motivated. For example, reliable dosing information regarding individual patient’s prescriptions has not been available for the purpose of pharmacoepidemiological studies and surveillance of antibiotic utilization.

In the United States, information technology in hospitals, at least in some centres, has been helpful in providing tools for a more patient-based routine surveillance of the drugs that are actually administered to the patients.<sup>80,81</sup> This is mainly because the US health care system is

based on a revenue of hospital services where all prescribed drugs are charged the insurance companies. By contrast, the European health care systems are more state-financed with a general transfer of money and resources to the hospitals.

### *3.2. Overview of measurement units and terms*

As with most measurable entities, there will be numerous ways of defining units. However, while units of daily life (like time in minutes and hours, distance in yards or meters) are clearly defined, many measures related to quality indicators in hospital care are less precisely defined, and thus opening for various interpretations. The measure of drug (antibiotic) utilization belong to these less concise figures.

#### **3.2.1. The numerators: measures of drug amounts used**

The numerators in the relevant equations are the measures of use of an active antibiotic compound or use of a group of antibiotics. Most used is the WHO-determined Defined Daily Dose (DDD). However, DDDs have been criticised for not being accurate when used for hospital patients, who are often receiving higher doses per day than those given to patients treated outside hospitals. Alternative numerator measures, both for hospitalized patients and patients in the community, are listed in Table 3.1.

**Table 3.1.** Main numerator measures (amount units) used in surveillance of antibiotic use.

Numerator	References	Used in settings
WHO DDD (Defined Daily Dose)	82-84	All, international
PDD (Prescribed Daily Dose)	85-89	Hospitals, (mainly national)
Packages (i.e. fixed units, “complete packages”)	24,52,90	Outpatients, national (international?)

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### Defined daily doses (DDD)

The DDDs as a general measurement unit for pharmaceutical compounds is, in essence, a joint Scandinavian invention that was first introduced at a WHO symposium held in Oslo, Norway, in 1969.<sup>91</sup> A need was recognised for an international unit of drug utilization, to make international comparisons meaningful and allow for pharmacoepidemiological studies across geographical borders. Even before the term “DDD” was coined, however, an “agreed defined dose” was used in an international study of antidiabetic drugs.<sup>82</sup> In 1979, Bergman *et al.* launched the term DDDs for audits of drug use in hospitals and, furthermore, suggested to relate the dose amounts to the length of hospital stay i.e. the number of patient bed days.<sup>83</sup> The first comprehensive national list of DDDs was published in Norway in 1975.<sup>92</sup> This unit of measurement has since been evaluated extensively<sup>56,57</sup> and has gradually become an international standard, although some countries have been slow to recognize and adopt this entity.

The WHO Collaborating Centre of Drug Statistics Methodology (Oslo, Norway) maintains both the Defined Daily Dose (DDD) and the Anatomical Therapeutic Chemical (ATC) classification system. The WHO publishes new DDD definitions annually. Thus, in order to arrive at valid (comparable) results when temporal trends are explored the DDDs should be updated and be in accordance with the latest WHO definitions.<sup>93,94</sup>

A DDD is a technical measurement unit, defined as “ – *the assumed average maintenance dose per day for a drug used for its main indication in adults* ”.

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DDD's have successively gained acceptance internationally as a *de facto* standard unit for drug comparison studies. The system has an obvious advantage as it is owned and managed by the WHO. The organization maintains it, thus securing robustness and trustworthiness. Moreover, the DDD has a clear, uncomplicated definition and the single purpose of being a technical measurement unit. In the ATC/DDD guidelines, it is stated that DDDs for antibacterial substances are defined with respect to their use in mild to moderately severe infections that are mostly treated outside hospitals. Accordingly, DDDs have been shown to reflect ambulatory care antibiotic dosing<sup>96</sup> and doses used in the community.

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However, the WHO DDDs also have several limitations:

- It does not always reflect the dose actually given to hospital patients; often the DDDs are set lower than the doses used in hospitals and consequently the hospital use of these antibiotics – measured in DDDs – will be too high.<sup>87</sup>
- DDDs are not useful for measuring the antibiotic use in paediatric patients.<sup>97,98</sup>
- DDD values do not take into account the frequently encountered clinical situation of dose adjustments, for example related to renal impairment<sup>99</sup> and weight differences.
- DDDs for combination products represent a challenge. Usually the DDD definition is linked to the recommendation for use of the combination rather than the DDD of each ingredient, but this practice may differ between countries.<sup>94</sup>

Alternate dose units have been proposed that seek to alleviate some of these shortcomings.

### Prescribed daily doses (PDD)

Some authors have suggested the use of “prescribed daily doses” (PDDs) as a measurement unit for hospitalised patients.<sup>85-87,100</sup> Various sources have been used to come up with reliable definitions for PDDs. Guidelines giving recommended dose regimens is one such source, another is the accumulated results of point-prevalence surveys from which may be PDDs calculated. One may encounter difficulties when trying to use point-prevalence surveys for estimation of a “correct” average daily dose in a defined patient population (e.g. hospital patients). For one, the number of antibiotic regimens examined to establish a certain dose must be high, and, secondly, it may be debated what is “the main indication” for each single antibiotic substance. This is related to the choice of the WHO definition – and if this is not chosen, what alternate criterion should be used? Lastly, to be optimal a PDD definition based on prevalence surveys must evaluate every regimen for dose adjustments related to for example organ failure, weight extremes and drug-drug interactions.

### Other numerator units

Some alternate units in addition to the WHO DDD have been discussed but they have not obtained acceptance.<sup>101</sup> One proposed measurement unit is the number of prescribed packages

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of antibiotics.<sup>24</sup> This unit is of interest in countries where pharmacies dispense whole packages containing an amount of drug that corresponds to a full treatment course. The number of packages then approximates the number of prescribed antibiotic treatments. Since the measure is only applicable for orally administered drugs, it is intended for use in surveillance of community (outpatient) antibiotic use and not for use in hospitals. As has been demonstrated in some studies,<sup>52,90</sup> the number of packages (PID) give other – and mostly lower – results as compared with measures in WHO DDDs per 1000 inhabitants per day. It has been claimed that temporal trends may be reliably followed with this method, provided the number of units per package is not altered.

Another unit is the MMD, the “*minimum marketed dose*”, i.e. the minimum daily dose that will produce a desired therapeutic effect. In practice, it is the lowest dose of an antibiotic declared by the manufacturer to give a cure for the infection at hand. Units such as “*average daily dose*” (ADD) or “*equipotential dose*” (ED) have also been suggested.<sup>101</sup> None of these units offers any advantage over DDD. They are less precisely defined and not in use.

### **3.2.2. The denominators: units against which antibiotic use is related**

#### Doses per inhabitants per day (DID)

For reporting outpatient antibiotic use, the amount in DDDs of antibiotics per day, usually related to 1000 inhabitants, has commonly been the measurement unit. The advantage is that usage is related to one day of use, that is to say the denominator relates to the numerator, which also describe the use of a daily dose of the drug. This makes DID a sensible measure to use in the community (outpatient) setting. As a measure for antibiotic use in hospitals, DIDs are less suited because the denominator does not relate to the hospital population but rather its related community population. It is often difficult to define the population that relates to a hospital (the “catchment area”), especially when several institutions operate within a large municipality or a city.

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### Patient bed days (BDs)

The patient bed days has been, by far, the most used denominator in indices of hospital antibiotic use. That length of stay relates to the exposure for antibiotics seems plausible. However, the antibiotic exposure is in no way proportional to the number of days hospitalized. For example, short average stays may imply high-density antibiotic exposure due to intensive treatment periods before discharging patients to lower levels of care, or short average stays may represent elective surgical treatments where little or no antibiotics are being prescribed. Conversely, longer stays in hospitals may be either low-risk rehabilitation (risk in terms of exposure to antibiotics) or high-risk intensive care treatments.

### Number of hospital discharges (admittances)

The number of patient admittances and patient discharges will be equal provided the in-hospital patient deaths are registered in the hospital discharge statistics. While the two terms may be used interchangeably as denominators, the norm has been to state the number of discharges. In most industrialized countries, the number of hospital discharges has increased and the average length of stay has decreased over time. This means that rates of antibiotic use are low when number of discharges is used as the denominator, while the opposite is true when patient bed days are used. Recognition of this fact is particularly important when temporal trends are evaluated.

Table 3.2, page 24 gives an overview of the main denominators use in surveillance of antibiotic use; at least those currently relevant to use in European hospitals.

### Other denominator units

Several other denominators have been suggested and some of these offer substantial advantages with regard to accuracy compared to denominators acquired from administrative databases. However, their routine use is restricted to health care systems that allow for more detailing of the antibiotic courses, for example to the level of individual prescriptions.

*Days of treatment (DOT)*. This is a measure of the duration in number of days for one antibiotic regimen, for a specific infectious condition, regardless of the number of substances used.

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*Patient-days receiving antibiotics.* This is the total number of days that a hospitalized patient receives antibiotics, irrespective of the number of substances, doses or administration. The term *therapeutic courses* is used synonymously.<sup>102</sup>

**Table 3.2.** Rates and ratios used to relate antibiotic use measurements for comparison purposes (adapted after Schechner *et al*<sup>103</sup>).

Measures	Advantage(s)	Disadvantage(s)
Proportions of doses (related e.g. to total antibiotic use)	Easy to collect, useful for clinicians	Biased estimates from a public health perspective
Doses per unit time (e.g., year)	Easy to collect and interpret	No account for difference in population size No account for occupancy or turnover
Doses per occupied bed - or hospital days - per unit time (e.g., year)	Accounts for occupancy	Often difficult to collect; no account for turnover
Doses per hospital admissions per unit time (e.g., year)	Easy to collect and interpret; accounts for turnover	Does not account for occupancy

*Days of therapy.* Bacteria exert different strategies to resist the mechanisms of action of antibiotic substances.<sup>104</sup> In antibiotic regimens where two or more substances are combined – often for a discordant number for days – these effects are not properly accounted for when the number of patient days on antibiotics is used as denominator. For this reason, the term Days of therapy (DOT)<sup>81</sup> or Antibiotic days<sup>105</sup> has been introduced. The unit represents the accumulated number of treatment days for each separate antibiotic substance in the regimen. In particular, days of therapy may be a useful measurement unit if the effects on resistance development is a main study aim.

Alternate denominators have been proposed such as the *number of physician contacts* or the *number of insured individuals* (for instances when the amounts of antibiotics are collected from reimbursement databases).<sup>24</sup> A *finished consultant episode* (FCE) is the time a patient spends in

the care of one consultant in one health-care provider. For hospital in-patients this translates to “a period of healthcare under one consultant in one provider hospital”.<sup>106</sup> One hospital stay normally consists of a series of FCEs.

**Figure 3.1.** Reporting recommendations (Kuster, 2008).

**Recommendations for reporting methodological information in publications on hospital antibiotic use.**

1. Report hospital size, composition (e.g., types of intensive care units, with/without bone marrow transplant or burn units, etc.) and affiliation
2. Report mean length of stay, total number of bed-days, numbers of patients admitted and numbers of admissions including multiple admissions of individual patients to multiple hospital sites
3. Describe in detail the hospital wards that were included in the analysis; independently summarize ‘all wards’ (including Intensive Care Units), ‘all Intensive care units’ and ‘all wards, excluding intensive care units’
4. Report DDD/100 bed-days and DDD/100 admissions
5. Provide a clear definition of the term ‘bed-day’; count admission and discharge day together as 1 bed-day if possible
6. Report the version of the ‘WHO guidelines for ATC classification and DDD assignment’ that were used; use the most recent version at time of publication
7. Select antimicrobials according to the ATC classification. Include all drugs of ATC group ‘J01’ (antibiotics) and/or ATC group ‘J’ (antimicrobials)
8. For antibiotic use data in pediatrics, use days of therapy (DOTs) instead of DDDs, if possible

Antibiotics are all substances of ATC group ‘J01’ (antibiotics for systemic use); Antimicrobials are all substances of ATC group ‘J’ (anti-infectives for systemic use, including antibiotics for systemic use, antimycotics for systemic use, antimycobacterials, antivirals for systemic use, immune sera and immunoglobulins and vaccines); DDD: defined daily dose; ATC: anatomical therapeutic chemical classification index for antibiotics

The *number of blood cultures* drawn has been hypothesised as a useful surrogate marker for infection burden<sup>107</sup> and was found, in one small study, to be of value. The argument is that use of this denominator would help overcome the inability of occupancy markers, such as bed days, with regard to adjustment for case-mix in hospitals. There has, to date, been no further publications to support this interesting proposal.

### 3.3. “Standards of reporting” of antibiotic use

There are numerous challenges and several pitfalls associated with the reporting of antibiotic use in hospitals.<sup>100</sup>

One set of standards has been proposed<sup>88</sup> ( Figure 3.1) but to date no guidelines have been published that have earned a normative status for how

antibiotic use should be measured and reported in the hospital setting.

The WHO Collaborating Centre for Drug Statistics Methodology have, since 2003, published a thorough “Introduction to drug utilization research”<sup>92</sup> which is highly relevant for antibiotic use surveillance and research. However, the focus is strongly on the DDD methodology and the Anatomic-Therapeutic Index (ATC/DDD-system) for which maintenance the centre is responsible.<sup>108</sup>

### ***3.4. Methods for surveying antibiotic use***

Pharmacoepidemiology is the study of drug use and drug effect. It is a relatively new field, combining aspects of clinical pharmacology (the study of clinical effect of drugs in humans) and epidemiology (the study of disease distribution and the factors determining diseases in the population). Antibiotic utilization in hospitals may be explored by different means, but two main epidemiological methods are commonly in use: prevalence studies and incidence studies.

#### **3.4.1. Prevalence surveys**

Prevalence is the number of cases with an active disease (or any other targeted determinant, for instance the number of therapeutic antibiotic courses) present in a defined population at a certain point in time.<sup>109</sup> The point prevalence rate is the number of these occurrences at a specific time, divided by the total number in the population under investigation – usually reported per one hundred or one thousand.

In the investigation of the prevalence rates of patients’ antibiotic use, one may obtain valuable information by linking the physician’s prescriptions with the indications, i.e. the perceived infectious condition in individual patients. This information may be used to evaluate the appropriateness of antibiotic use, based on a set of criteria or adherence to published recommendations. Importantly, the ultimate propose is to provide feedback to the prescribers.

Infection control in Norway has since 1991 focused on the prevalence of health-care acquired infections both in hospitals<sup>110,111</sup> and more recently in long-term care facilities.<sup>112,113</sup> An obvious next step is to add to such surveys the details about antibiotic use. An adequate registration of antibiotic specifics requires involvement of infectious diseases physicians or clinical

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pharmacists.<sup>114,115</sup> Several European studies of antibiotic use have been published, foremost from the ESAC (European Surveillance of Antimicrobial Consumption) project<sup>52,64,65</sup> – which has reported prevalence rates of antibiotic use in both hospital patients and outpatients across countries. Besides the mere reporting of rates to observe trends,<sup>116,117</sup> repeated prevalence surveys have been successfully used to investigate the importance of patient case-mix for inter-hospital comparisons<sup>118-120</sup> and to evaluate the appropriateness of antibiotic prescribing.<sup>121,122</sup>

Even in its simplest form with little information registered, prevalence surveys of infections – with or without antibiotic use – to be undertaken, are valuable. Nevertheless, other kinds of surveillance activities should probably be prioritised. First, a positive effect has been demonstrated on health care workers hygiene and antibiotic prescription habits through the mere act of performing surveys. This has been called the “Hawthorne effect” of being under surveillance.<sup>123,124</sup> More importantly, prevalence surveys may reveal certain high-risk areas in hospitals that should be more extensively examined.

A new method for point-prevalence surveys of hospital antibiotic use has recently been published by the ECDC in a light version, and as an extended protocol.<sup>125</sup> In this protocol, the well-proven ESAC methodology<sup>126</sup> is incorporated. In addition, the extended ECDC version include variables that should be registered for all hospitalized patients, such as demographics, a score system for underlying diseases, and the usage of urinary and vascular catheters. This allows for a far better characterisation of the complete patient population, not only for the patients infected and/or given antibiotics. As long as the methodological limitations are taken into account,<sup>116,118,127</sup> risk factors may be identified and conclusions drawn that are relevant for surveillance interpretation.<sup>119-122</sup>

### **3.4.2. Incidence surveys**

Incidence is the number of new cases occurring over a defined period in a population.<sup>109</sup> In the study of infections, the population “at risk” of contracting the infectious disease(s) is chosen. Accordingly, for the study of antibiotic use, the population is the selection of individuals that may possibly be administered antibiotics. Because of the longitudinal nature of incidence surveys, the work load involved in conducting them may be formidable. This represents a challenge – not least if a prospective study design is chosen. The “gold standard” in the surveillance of antibiotic use is a manual, time-consuming registration of every antibiotic dose

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administered to each individual within a (hospital) population, preferably together with an evaluation of the appropriateness of the antibiotic use. Whereas this has often been done in specific and limited areas, for example in the prophylaxis of surgical infections,<sup>38,128-131</sup> routine surveillance in hospitals is rarely feasible because of resource limitations. Hospital-wide incidence surveys are currently not recommended from a cost-benefit perspective but may be appropriate for limited projects, for example to evaluate prescription practices. With the advent of electronic prescription systems, incidence surveillance of hospital antibiotic use may be possible and represent a great advance.

### Analysis of accumulated consumption data

The European Surveillance of Antibiotic Consumption (ESAC) network has published an overview of the methodology used by different European countries for accumulated antibiotic use in hospitals and in ambulatory care (outpatient antibiotic use).<sup>44</sup> Large differences were observed with regard to the sources of antibiotic utilization data, including manufacturers' statistics, data from pharmaceutical companies, reimbursement data from insurance companies and social services, and sales data from pharmacies. The different data sources have inherent peculiarities that make comparisons difficult. In publications that attempt to benchmark antibiotic use between countries, these factors should be regarded. In Norway, the National institute of public health has been responsible for national statistics. The methods that have been used are described in chapter 3.1.

### Drug utilization methodology

A longitudinal study method that rests on the ranking of the amounts of drugs used, rather than rates, was first used by Bergman to report drug utilization (DU) in Sweden. Later it was used to assess the quality of drug prescribing.<sup>132,133</sup> This assessment was applied to record general practitioners' number of drugs within the 90% segment of their total lists of drug used. The quality of drug prescribing was measured by the proportion of the DU90% drugs that corresponded to substances recommended in official guidelines. In a study from 1999, Bergman *et al* investigated Stockholm hospitals' antibiotic use by this methodology (see also page 14). The number of drugs used was shown to range from 9 to 13 in orthopaedic departments and from

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16 to 23 in infectious disease departments. Except for this study, DU90% has not – to our knowledge – been applied for antibiotic use prior to 2006. The method will be further discussed in relation to our own studies in Chapter 7.3, page 46.

## **4. Aims of the thesis**

As described in the introduction, antibiotics are precious drugs that have saved lives and prevented suffering in an unprecedented scale. Their discovery have contributed immensely to the success of modern medicine. In the last decades, however, resistance has accelerated rapidly on a global basis. New antibiotics are rarely developed. One of the remaining strategies to combat resistance development is preservation of the existing drugs, in particular measures that can prevent inappropriate antibiotic use. Then it is vital to understand factors that determine inappropriate prescribing and to perform adequate surveillance of antibiotic utilization.

The main objective of this thesis was to contribute to such knowledge by investigating the methods used in hospital antibiotic surveillance and, furthermore, to follow the consumption patterns of the various antibiotics used in hospitals and to reveal temporal utilization trends. We also aimed to explore the factors that explain variations in antibiotic utilization between hospitals in order to facilitate antibiotic stewardship efforts.

The specific aims were as follows:

- To investigate the reliability of data sources that antibiotic utilization measurements are based on – pharmacy sales data versus ward stock accounting.
- To investigate how choice of dose unit (numerator) – WHO DDDs versus hospital adjusted DDDs (haDDDs) – affects hospital antibiotic surveillance results.
- To evaluate how the denominator – number of bed days and number of discharges – affects hospital’s antibiotic surveillance results.
- To investigate temporal trends in use of antibiotics in Norwegian hospitals, with special emphasis on broad-spectrum antibiotics.
- To identify modifiable and non-modifiable factors that are decisive for hospital antibiotic use.

### 5. Material and methods

The methods used to acquire data for this thesis have been chosen with the intention that they should be simple and reproducible. To be useful for a future national surveillance system, all data should be obtained from easily accessible and validated sources. We have used the methodological recommendations set by the ESAC collaboration in the surveys of antibiotic use in European countries<sup>44</sup> and have also adhered to the standards for antibiotic surveillance published by Kuster<sup>88</sup> (see “Standards of reporting” of antibiotic use” on page 25).

#### *5.1. Data on antibiotic use*

##### Selection of antibiotic agents

We used the range of antibacterial agents chosen by the “ESAC II Hospital Care Study Group” in their 2009 point-prevalence survey<sup>65</sup> and, in addition, we adhered largely to the protocol for the ESAC longitudinal hospital care survey.<sup>134</sup> Being part of the study group, our centre at the time – Aker university hospital – had access to the ESAC protocol. We adopted their selection at an early stage because it appeared sensible to implement a future European standard. Accordingly, for all papers in this thesis, the selected systemic antibacterial agents were the ATC/DDD group J01 except J01XX05 (methenamine, a urine antiseptic widely used in Norway), as well as A07AA09 oral vancomycin, J04AB02 rifampicin, and P01AB01 oral metronidazole. These were denoted “total antibiotics”. Two additional subgroups of antibiotic classes were defined as “broad-spectrum antibiotics” (second- and third-generation cephalosporins, fluoroquinolones, carbapenems, and penicillins with enzyme inhibitors) and “all penicillins” (penicillinase-sensitive, penicillinase-resistant, and extended spectrum penicillins).

##### Defined daily doses (DDDs)

Antibiotic sales data used in all the analyses that are part of this thesis originate from a standard, commercial pharmacy system (FarmaPro<sup>®</sup> version 4.1.0a, NAF-data Corp., Norway). By the use of a “statistical factor” assigned to each single drug package and taking into account the number of items sold, the number of DDDs for each transaction are automatically calculated by the pharmacy data system.

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The amounts of antibiotics were reported as DDDs according to the 2007<sup>135</sup> (paper I and II) and 2011<sup>95</sup> (paper III and IV) WHO definitions. Changes in defined daily doses (DDD) made by the WHO during the study period were adjusted for as recommended by the WHO.<sup>93</sup> For substances available both as a parenteral and oral formulation, the sum of both were reported unless stated otherwise. No hospital in Norway has yet implemented electronic data systems that monitor daily prescriptions to individual patients. Thus, neither “days-of-therapy” (DOT)<sup>81</sup> nor the actual “prescribed daily doses” (PDDs)<sup>89</sup> are obtainable on a routine basis and were not investigated in our studies.

### Hospital-acquired defined daily doses (haDDDs)

We introduced the term hospital-adjusted defined daily doses (haDDDs). Twenty-seven haDDD assignments were undertaken for 24 antibiotic substances (ATC level 5), that is to say, for the three substances cloxacillin, dicloxacillin and trimethoprim both the oral and the parenteral formulations were adjusted. Also for metronidazole, both the oral and the parenteral formulations were adjusted but these have different ATC codes. Rectal formulations of metronidazole were assigned to the oral administrated group since they accounted for only 0.6% of the total doses of antibiotics and 2.7% of non-parenteral antibiotic doses. The process of antibiotic dose adjustment is described below.

Co-amoxiclav (amoxicillin + clavulanic acid) have been considered to be too low set by the WHO in studies from Europe, where it is the most used drug in many countries. The drug is not registered in Norway, and the consumption during the six study years was very low (3 285 oral and 394 parenteral WHO DDDs, 0.024 % of the total use). Moreover, no indications for the use of the drug existed in any guideline, and we therefore chose to omit it from the list of altered WHO DDDs, together with other unregistered flucloxacillin and ampicillin/sulbactam. Because these antibiotics were rarely used, omitting them from dose alterations does not change our overall results and conclusions.

The assignment of haDDDs was done, true to the WHO definition, by estimation of the therapeutic maintenance dose of each drug in adult individuals without a renal impairment. The recommended antibiotic regimens were acquired from one national guideline (published 2001) and from four regional guidelines for hospital antibiotic use (published 2006 – 2009). In a few cases where the doses for the same conditions differed in the guidelines, an average dose was estimated. The exact haDDDs (in grams) were calculated from the average daily doses

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administered for the most common indication of the agent, evaluating one moderately severe and one severe infection separately. A specific haDDD was set as the estimated mid-value between the dose recommendation for a severe and for a moderately severe infection. To arrive at some of these mid-values, we explored an anonymised dataset from a large Health Region of South-Eastern Norway. From the main ICD-10 diagnoses, we estimate the ratio between the occurrences of several common moderately severe and severe infections, for which guidelines recommended the antibiotic substances in question (see Methods, Paper III). Infectious conditions of minor severity were disregarded because these are infrequently seen in hospitalized patients.

### Data acquisition and processing

Sales data for antibacterial agents were extracted from the data systems of single hospital pharmacies and from a central national database. All pharmacies in Norway, in and outside hospital, use the commercial system Farmapro®. Paper I analysed five high-consumption wards at Aker university hospital, Paper II eight Health Enterprises of the former Eastern Norway Regional Health Enterprise, while Papers III and IV included data from somatic departments of all 22 HEs in Norway. In all studies, we excluded specialized private institutions for elective orthopaedics, rheumatology, heart surgery and rehabilitation. Neither were psychiatric wards and institutions and substance abuse units included.

For Papers I and II, the antibiotic datasets were imported from the local hospital pharmacies' Farmapro® data systems. After receipt, the data were quality assessed by means of spot-checking against the original data sources. The first author undertook this quality check. The data files were imported into a Microsoft Access® database (Paper II) and analysed in Microsoft Excel® by means of pivot tables.

For Paper I, two data sets on broad-spectrum antibiotic use were compared for the same 26 weeks period (from Oct 2006 to Apr 2007):

1. Pharmacy sales data (from Farmapro®) at five wards at Aker university hospital.
2. A weekly ward stock accounting done at the same five wards by a clinical pharmacist.

The ward stock accounting was a manual counting of the ward stock of broad-spectrum antibiotics, undertaken at the same time every week. Parenteral and oral formulations of the study drugs (broad-spectrum antibiotics) were analysed separately.

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For Paper II, a complete antibiotic dataset was imported from each single hospital pharmacy situated at eight Health Enterprises (HEs) of the former Eastern Norway Health Region. These HEs represent a multitude of wards and units, and an objective of the study was to allocate antibiotic use to clinical specialties within the HEs. Accordingly, an extensive and manual code mapping was necessary in order to connect the antibiotic (pharmacy) data with the administrative data (bed days and number of discharges) – see “Administrative data” below.

For Papers III and IV, we obtained the dataset on antibiotic agents from a centralized database maintained by the national Hospital Pharmacy Enterprise (“Sykehusapotekene HF”). This database contains accumulated data since 2006. The data system imports in real-time sales figures from all Norwegian hospital pharmacies and contains relevant information on all drugs that are dispensed (sold) to the hospitals wards and units. The system has largely been in function since 2010.

### *5.2. Administrative data and patient-related factors*

Data on the length of hospital stay (LOS) and the number of patients treated (discharges) were derived from the official National Patient Registry, “Norsk Pasientregister” (NPR). A hospital stay lasting > 24 hours was defined as an in-patient treatment, and length of hospital stay (LOS) was calculated as the difference between date of discharge and date of admittance.

For Paper II, a link between the antibiotic pharmacy sales data and the administrative data was established through a meticulous, manual mapping of hospital units within each Health Enterprise by means of linked tables in a Microsoft Access database (see also chapter 7.1). This labour-intensive manual procedure was a consequence of a complete lack of coding standardization for the hospital wards, both within and between the Health Enterprises and the hospital pharmacies. The effort was essential, however, to allocate a correct clinical specialty category to all the wards, and to be able to distinguish hospitalized (in-patients) from ambulatory and day-care patients. The wards were then assigned their main clinical specialties, which subsequently became a main grouping variable in the study. After assembly of all variables in the Excel spreadsheets, datasets were exported to statistical software for the final analyses.

In Papers III and IV, we investigated the antibiotic use in somatic wards of the 22 Norwegian HEs. They constitute the whole Norwegian hospital population except for some small private and specialised institutions. The sources of administrative and clinical data were from the NPR,

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as in Paper II. However, we could not perform any allocation of data to the specialties/wards within the HEs as had been done in Paper II. With the routinely acquired information in these public databases such analyses were not possible to undertake. Furthermore, we were not able to distinguish the number of day-care patients from hospitalized patients in the analyses for Papers III and IV.

An additional source of information for the Paper IV was the database of Statistics Norway, the data from which we established some of the explanatory variables for the multivariate analyses, such as the individual HE's employment rates for registered nurses and physicians. The national database contained data on antibiotic use for 22 Health Enterprises over a period of six years (2006–2011). Thus, 132 data records were the basis for the analyses. Fourteen variables had been selected and were analysed in 12 multiple linear regression models with regard to their explanatory value for the variances of three dependent (outcome) variables, these being the HE's use of all antibiotics, broad-spectrum antibiotics and all penicillins. For each of these three outcome variables, four indices were used separately in the regression models: WHO DDDs per 100 bed days and per 100 discharges, and hospital-adjusted DDDs (haDDDs) per 100 bed days and per 100 discharges.

### ***5.3. Hospitals' antibiotic resistance***

Information about antibiotic resistance for common pathogens in blood cultures was obtained from the annual reports from the national microbiological surveillance system NORM/NORM-Vet.<sup>136</sup> In the NORM system, all 23 microbiological laboratories in Norway adhere to an identical sampling strategy, applying identical criteria for the inclusion of microbial strains (one isolate per patient and blood culture episode). Bacterial species are identified by standard methods and susceptibility tested by disk diffusion and E-test using breakpoints established by EUCAST (The European Committee on Antimicrobial Susceptibility Testing).

Resistance data from NORM/NORM-Vet report from 2007<sup>60</sup> was used for the study periods in paper II and the report from 2011 for the Papers III and IV.<sup>137</sup> The individual HEs maintain no local databases that enable the acquisition of detailed antibiotic resistance data. Consequently, it has not been possible to investigate any link between antibiotic consumption and antibiotic use.

**5.4. Statistical analyses**

STATA ® software version 11 and 12 was used for all statistical analyses in the thesis. Microsoft Excel ® was used for labelling and preparing of data for export to STATA ® and all ranking of variables for drug utilization (DU 90%) analyses. The Table 6.1 (page 36) gives a summary of statistical methods used in the thesis.

**Table 6.1.** Statistical analyses in the thesis, overview according to purpose and paper.

<b>Method</b>	<b>Purpose in the study</b>	<b>Paper</b>
Bland-Altman statistics	Visual (graph) and measure (limits of agreement) of the reliability of one method of measurement, compared to a perceived “gold standard”.	I
Intraclass correlation	Assesses the degree of agreement of two methods of measurement applied on the same sample.	I
Student-T test (two-sided)	Compare continuous variables between groups.	II, II, IV
Single linear regression	Determines the contribution of one (independent) factor to a single outcome (dependent) variable.	II
Pearson correlation coefficients	Investigates correlations between numerical variables.	II, III
Analysis of variance (ANOVA)	Evaluation of trends in antibiotic use.	III
Kruskal-Wallis rank-sum test	Trend analysis if group variances are large, (as determined by the Bartlett’s test for equal variances).	III
Multiple linear regression	Determines the contribution of several (independent) factors to a single outcome (dependent) variable.	IV

Paper I

The Bland Altman plot. The methodological considerations for appraising the agreement between one measurement unit and another unit, perceived as the “gold standard”, were reviewed by Bland and Altman in a seminal work (1986).<sup>138</sup> A general error in statistical analyses is to report the Pearson’s correlation coefficient as a measure of agreement between methods. A very

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poor agreement may produce very high correlations, e.g. the agreement between the series 10-20-30-40 and 100-200-300-400 is very poor, but the correlation is 1.0. The Bland Altman method is to plot, in an  $x$ - $y$  diagram, the difference in parallel values of the two measurements against their mean value. The term “limits of agreement” was introduced by the authors, defined as the  $\pm$  standard deviation (SD) of the average difference between the methods (provided these are normally distributed). It will then be a clinical decision to determine whether the values range, which represents the 95% error range by the new method, is clinically relevant or not. In a visual inspection of the plot, one may also determine if the differences are similarly distributed for various ranges of means – that is, if the limits of agreement remain constant or changes significantly for low and high mean values. In our study, the ranges were the percent DDD representing  $\pm$  one SD of the average mean DDD values.

Intraclass correlation coefficient (ICC). For determining agreement between the two methods for measurement, we also used the ICC.<sup>139</sup> Variance in ICC is relying on the pooled variability of the two matched measurements, and not the variability in each group as in Pearson’s correlation. The objective of the ICC is to determine how much of the total measurement variation that is due to difference between the methods and how much is due to difference in measurement for each method (the “within” variation). The mean square of the differences between the values (MSB) and the mean square within them (MSW) are used for calculation

$$ICC = \frac{MSB - MSW}{MSB + MSW}$$

If the “within” difference MSW is very small, ICC will be close to one. Conversely, if MSB = MSW, ICC will be zero and there is absolutely no agreement between the measures. Interpretation of ICC as for Pearson’s correlation, with an ICC value of  $> 0.7$  considered to indicate a sufficient agreement between the methods. ICC was calculated with the STATA® procedure ‘icc’.

### Paper II

Linear regression. A linear regression procedure (‘regress’ in STATA) was used to analyse the temporal trends for different groups of antibiotics (total antibiotic use, broad-spectrum antibiotics and all penicillins). The regression gave the regression coefficient with confidence intervals, i.e. the changes in DDDs per year, and the effect size (or coefficient of determination)

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which, in linear regression, is interpreted as a correlation coefficient. Lastly, an adjusted  $R^2$  gave the strength of the relationship for the equation, which is a conservative estimate of how large a part of the variation in antibiotic use could be explained by the time factor.

### Paper III

We used Pearson correlation coefficients (STATA ® procedure ‘pccorr’) for univariate analyses of correlation between numerical variables. The Chi-square test was used for categorical variables in contingency tables.<sup>140</sup> For differences between group means of normally distributed numerical data, a Student-T test (STATA procedure ‘ttest’) was used, while analysis of variance (STATA procedure ‘anova’) was used for multiple-group analysis. For all analyses, a two-tailed  $P < 0.05$  was considered statistical significant.

For the drug utilization 90% (DU90%) ranking,<sup>133</sup> antibiotic substances and groups were ranked according to their total amount of DDDs (respective haDDDs) over the study period. The list was limited to the antibiotics that, accumulated, fell within 90% of the total antibiotics used.

### Paper IV

The Pearson correlation coefficient was calculated as described for Paper III. Multiple linear regression (STATA ® procedure ‘regress’) was used for all 12 regression models with a backward stepwise approach. As a test for collinearity between independent variables, we calculated the variance inflation factor (‘vif’) at each regression step and rejected the variable with the largest vif value until no variable had a vif  $> 5$ .<sup>141</sup> The coefficient of determination  $R^2$  was calculated for all regression models.  $R^2$  may be defined as the proportion of possible perfect prediction represented by the regression model.<sup>142</sup> Because of a relatively large number of independent variables, the adjusted R square ( $aR^2$ ) was calculated for each regression model to show how well it fitted the data. For all analyses,  $aR^2 > 0.3$  was considered a strong correlation, i.e. inferring a high degree of causal influence. A two-tailed  $P$ -value  $< 0.05$  was set as a limit for statistical significance.

### 6. Synopsis of the studies

Here, we give the synopsis (abstracts) of the four publications that this thesis is based on. To aid in the interpretation of our findings, an extra Table 6.1 (page 41) for the Paper II and a Figure 6.1 (page 42) for the Paper III supplement the results given in the published articles.

#### *6.1. Paper I*

**Background:** Antibiotic consumption in hospitals is commonly measured using the accumulated amount of drugs delivered from the pharmacy to ward held stocks. The reliability of this method, particularly the impact of the length of the registration periods, has not been evaluated and such evaluation was aim of the study.

**Methods:** During 26 weeks, we performed a weekly ward stock count of use of broad-spectrum antibiotics – that is second- and third-generation cephalosporins, carbapenems, and quinolones – in five hospital wards and compared the data with corresponding pharmacy sales figures during the same period. Defined daily doses (DDDs) for antibiotics were used as measurement units (WHO ATC/DDD classification). Consumption figures obtained with the two methods for different registration intervals were compared by use of intraclass correlation analysis and Bland-Altman statistics.

**Results:** Broad-spectrum antibiotics accounted for a quarter to one-fifth of all systemic antibiotics (ATC group J01) used in the hospital and varied between wards, from 12.8 DDDs per 100 bed days in a urological ward to 24.5 DDDs in a pulmonary diseases ward. For the entire study period of 26 weeks, the pharmacy and ward defined daily doses figures for all broad-spectrum antibiotics differed only by 0.2%; however, for single wards deviations varied from -4.3% to 6.9%. The intraclass correlation coefficient, pharmacy versus ward data, increased from 0.78 to 0.94 for parenteral broad-spectrum antibiotics with increasing registration periods (1-4 weeks), whereas the corresponding figures for oral broad-spectrum antibiotics (ciprofloxacin) were from 0.46 to 0.74. For all broad-spectrum antibiotics and for parenteral antibiotics, limits of agreement between the two methods showed, according to Bland-Altman statistics, a deviation of  $\pm 5\%$  or less from average mean DDDs at 3- and 4-weeks registration intervals. Corresponding deviation for oral antibiotics was  $\pm 21\%$  at a 4-weeks interval.

## SYNOPSIS OF THE STUDIES

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**Conclusions:** There is a need for caution in interpreting pharmacy sales data aggregated over short registration intervals, especially so for oral formulations. Even a one-month registration period may be too short. Antibiotic consumption in hospitals is commonly measured using the accumulated amount of drugs delivered from the pharmacy to ward held stocks. The methodological issue addressed in this study was to assess the reliability of this method for short registration intervals periods.

### *6.2. Paper II*

**Objectives:** Although antibiotic use and resistance are low in Norway, the situation risks changing for the worse. We investigated trends in antibiotic use and assessed them in relation to antibiotic resistance in Norway.

**Methods:** We drew on hospital pharmacy sales data to record antibiotic use from 2002 to 2007 in eight hospitals serving 36% of the nation's population. Antibiotic use was measured using different indices with defined daily doses (DDDs) as the numerator (WHO ATC/DDD classification).

**Results:** Total antibiotic use increased from 1.02 to 1.30 DDDs/1000 inhabitants/day (DIDs) and from 61.7 to 72.4 DDDs/100 bed-days (BDs) (17.4%); related to the number of discharges, no significant DDD change was shown. Their use in core units (adult intensive care units, recovery/post-operative wards and departments of internal medicine and surgery with all subspecialties) increased from 64.1 to 80.8 DDDs/100 BDs (26.1%) and by 3.1% related to the number of discharges. The total use of broad-spectrum antibiotics increased by 47.9% when measured as DDDs/100 BDs, and by 19.1% based on the number of discharges; the corresponding figures for core units were 60.5% and 31.2%, respectively.

The total use of different antibiotic classes for all specialties in 2007 and the changes in use since 2002 are given in Table 6.1, page 41.

**Conclusions:** There was a substantial increase in total antibiotic use, and an even more pronounced increase in the use of broad-spectrum antibiotics, which seems unjustified considering the current low antibiotic resistance in Norway.

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**Table 6.1.** Antibiotic use in eight HEs<sup>a</sup> in Eastern Norway (all specialties) according to class or generic substance in 2007 and changes from 2002 to 2007

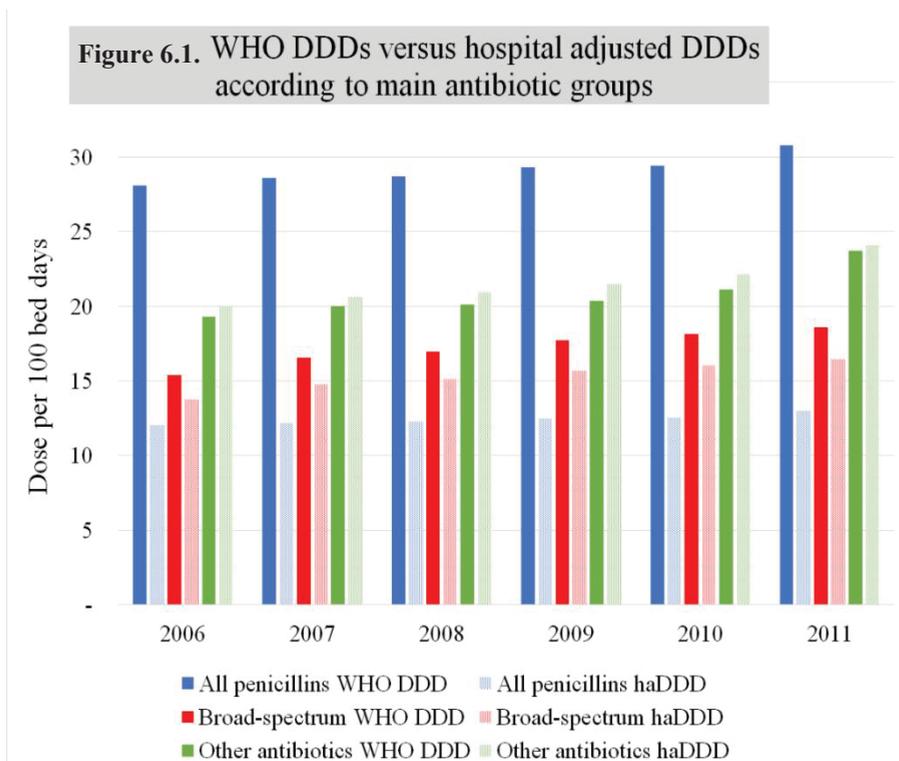
ATC	Antibiotic class or compound (registered substances)	DDD <sup>b</sup>		Per 100 bed days		Per 100 discharges	
		2007	2007	2007	2007	2007	2002-07 (%)
J01CE	Beta-lactamase-sensitive penicillins (benzyl-/phenoxymethylpenicillin)	164 074	13.21	0.72	(5.8)	61.92	-7.78 (-11.2)
J01CA	Ext. spectrum penicillins (piv-/ampicillin, piv-/mecillinam, amoxicillin)	157 661	12.69	2.71	(27.1)	59.50	3.76 (6.8)
J01CF	Beta-lactamase-resistant penicillins (cloxacillin, dicloxacillin)	82 738	6.66	0.91	(15.9)	31.22	-0.84 (-2.6)
J01DC	Second-generation cephalosporins (cefuroxime)	62 684	5.05	0.76	(17.8)	23.66	-0.26 (-1.1)
J01DD	Third-generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)	55 921	4.50	2.14	(91.1)	21.10	7.95 (60.5)
J01MA	Fluoroquinolones (ciprofloxacin, ofloxacin)	55 618	4.48	1.65	(58.6)	20.99	5.23 (33.2)
J01XD01	Metronidazole, parenteral	40 058	3.22	0.59	(22.5)	15.12	0.42 (2.9)
J01DB	First-generation cephalosporins (cephalexin, cephalotin)	34 580	2.78	0.83	(42.3)	13.05	2.13 (19.5)
J01AA	Tetracyclines	26 691	2.15	0.26	(14.0)	10.07	-0.45 (-4.3)
J01GB	Aminoglycosides (gentamicin, netilmicin, tobramycin)	24 130	1.94	-0.02	(-1.2)	9.11	-1.87 (-17.1)
J01FF01	Clindamycin	23 468	1.89	0.49	(35.4)	8.86	1.07 (13.7)
J01FA	Macrolides (erythromycin, azithromycin, clarithromycin)	20 031	1.61	0.40	(33.1)	7.56	0.80 (11.8)
J01EE01	Co-trimoxazole	13 424	1.08	-0.05	(-4.0)	5.07	-1.22 (-19.4)
J01DH	Carbapenems (meropenem, imipenem-cilastatin, ertapenem)	13 248	1.07	0.66	(159.6)	5.00	2.71 (118.0)
J01EA01	Trimethoprim	10 902	0.88	-0.36	(-29.3)	4.11	-2.81 (-40.6)
P01AB01	Metronidazole, oral	10 846	0.87	0.24	(37.4)	4.09	0.55 (15.4)
J01CR	Penicillins with beta-lactamase-inhibitors (piperacillin/tazobactam)	7 200	0.58	0.51	(746.4)	2.72	2.34 (610.9)
J01XA	Glycopeptide antibiotics (vancomycin, teicoplanin)	4 994	0.40	0.19	(90.9)	1.88	0.71 (60.3)
J04AB	Rifampicin	4 682	0.38	0.23	(158.8)	1.77	0.95 (117.3)
J01XE	Nitrofurantoin	2 406	0.19	-0.02	(-8.0)	0.91	-0.27 (-22.7)
J01XX08	Linezolid	1 425	0.11	0.09	(318.1)	0.54	0.38 (251.1)
J01BA01	Chloramphenicol	371	0.030	-0.036	(-54.4)	0.140	-0.23 (-61.7)
A07AA09	Oral vancomycin	336	0.027	0.015	(130.0)	0.127	0.06 (93.2)
J01XC01	Fusidic acid	330	0.027	0.001	(-5.3)	0.125	-0.03 (-20.5)
J01DF01	Aztreonam	314	0.025	-0.019	(-43.4)	0.118	-0.13 (-52.5)
J01GA01	Streptomycin	130	0.010	0.004	(54.9)	0.049	0.01 (30.1)
J01XB01	Colistin	117	0.009	0.006	(178.1)	0.044	0.03 (133.6)
	All antibiotics	818 379	65,9	12,9	(24,5)	308,8	13,2 (4,5)

<sup>a</sup> HEs: Health Enterprises <sup>b</sup> DDDs: defined daily doses

**6.3. Paper III**

**Objectives:** To investigate effects on surveillance results of hospital antibiotic use when WHO defined daily doses (WHO DDDs) are adjusted to doses recommended for hospitalized patients [hospital-adjusted defined daily doses (haDDDs)].

**Methods:** Data for antibiotic use in 2006–11 for all 22 Norwegian Health Enterprises were analysed with both WHO DDDs and haDDDs as numerators. The haDDDs were determined from recommendations given in regional and national guidelines on antibiotic use in hospitals. The two ways of calculating the amount of antibiotic use were compared, with either the number of bed days (BDs) or the number of discharges as the denominator. The drug utilization 90% methodology was applied for ranking the use of the various antibiotics.



**Results:** DDD adjustments altered the figures for total antibiotic use from 67.1 WHO DDDs/100 BDs to 49.3 haDDDs/100 BDs (–26.4%). The most marked difference was found for penicillins: 31.1 WHO DDDs/100 BDs versus 13.4 haDDDs/100 BDs (–56.8%) (Figure 6.1). The corresponding figures for broad-spectrum antibiotics were 17.3 and 15.5 (–10.4%), respectively;

## SYNOPSIS OF THE STUDIES

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for these antibiotics, the conversion changes varied significantly between institutions, from -16.7% to -3.3%. Ranking antibiotic use based on haDDDs resulted in higher positions for metronidazole, cefuroxime, cefotaxime and cefalotin/cefalexin compared with the WHO DDD-based ranking, where the penicillins dominated.

**Conclusions:** The low-set WHO DDDs for penicillins caused skewed surveillance results that concealed the real magnitude of broad-spectrum antibiotic use and distorted interhospital comparisons. For surveillance of antibiotic use in hospitals, WHO DDDs should be supplemented with haDDDs.

### *6.4. Paper IV*

**Objectives:** To identify factors that may contribute to differences in antibiotic use in hospitals. Based on pharmacy sales data (2006–2011), use of all antibiotics, all penicillins, and broad-spectrum antibiotics was analysed for 22 Health Enterprises (HEs).

**Methods:** Antibiotic utilization was measured in World Health Organization defined daily doses (DDDs) and hospital-adjusted (ha)DDDs, each related to the number of bed days (BDs) and the number of discharges. Fourteen potentially explanatory variables for the observed antibiotic use were examined in 12 multiple linear regression models with four different measurement units: DDD/100 BDs, DDD/100 discharges, haDDD/100 BDs and haDDD/100 discharges.

**Results:** Eight explanatory variables were independently associated with antibiotic use, but with a variable pattern depending on the regression model. High levels of nurse staffing, high proportions of short (< 2 days) and long (> 10 days) hospital stays, infectious diseases being the main ICD-10 diagnostic codes, and surgical diagnosis-related groups were correlated with a high use of all antibiotics. University HEs had a lower level of antibiotic utilization than other institutions in all 12 models, and carried a high unique explanatory strength. The use of broad-spectrum antibiotics correlated strongly with short and long hospital stays. There was a residual variance (30%–50% for all antibiotics; 60%–70% for broad-spectrum antibiotics) that our analysis did not explain.

**Conclusions:** The factors that predicted hospital antibiotic use were mostly non-modifiable. By adjusting for these factors, differences between hospitals may be more confidently acted upon. The residual variation is presumed to largely reflect prescriber-related factors.

### 7. Discussion of antibiotic surveillance methods

Paper I is a study of the reliability of pharmacy sales figures as a data source in the recording of hospitals' use of antibiotics, in particular the use of broad-spectrum antibiotics. The Papers II–IV report trends in the hospital use of antibiotics, however the main purpose of these studies was to investigate methodological aspects and to identify factors that may explain differences in antibiotic utilization patterns between institutions.

These methodological issues are discussed in the following.

#### *7.1. Reliability of pharmacy sales data*

We conclude from the results of Paper I that pharmacy sales data were reliably reflecting the number of DDDs of broad-spectrum antibiotics (BSAs), dispensed to patients in five high-consumption wards at a medium-sized university hospital and with a registration period of six measured months. For shorter registration intervals, however, measures of BSAs were less reliable for oral than for parenteral formulations. The pharmacy sales measures for parenteral BSAs, as a group, were reliable over the time intervals 1, 2, 3 and 4 weeks. For oral formulation of ciprofloxacin even the 4-week interval seemed to be too short. This is probably a consequence of oral formulations being cheaper and less voluminous than parenteral antibiotics, and thus more prone to excessive stockpiling.

The short registration intervals for antibiotic utilization investigated by us are highly relevant for antibiotic resistance studies using time-series analyses <sup>143-145</sup> and for studies of the effect of interventions to improve antibiotic use, for which the interrupted time-series methodology is also relevant. <sup>146-148</sup> One of our objectives was to use the results in a subsequent study of a possible relationship between the antibiotic use and antibiotic resistance. Unfortunately, with limited resources, we could not acquire data of sufficient quality from the laboratories of microbiology.

We think our results are of general interest, not least because some authors have recommended routine surveillance of ward-stock antibiotics with use of one-month registration intervals to detect the patterns and time trends in hospitals' antibiotic utilization. <sup>149,150</sup> Furthermore, hospital administrators are increasingly requesting results dealing with consumption of antibiotics.

## DISCUSSION OF SURVEILLANCE METHODS

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Probably, such data inquiries will be even more frequent in the future, both for hospital quality benchmarking purposes and for budgeting and economic planning.

The reliability of pharmacy sales data as a measure of patient antibiotic use in hospitals has not been thoroughly investigated before. Although the system of ward stock piling of drugs is the standard in northern Europe, it has been reported that in 39% of southeast European hospitals the pharmacies dispense the antibiotics directly to the patients.<sup>78</sup> Solano *et al*<sup>151</sup> found poor correlation between antibiotics dispensed and antibiotics administered in an Australian ICU, based on reviews of sales data and patients chart records, respectively. Interestingly, for oral ciprofloxacin they found an exceptionally high short-term deviation of 48% between the two measurements.

We conclude that short-term evaluation of broad-spectrum antibiotic use based on pharmacy sales data should not be advocated. However, the validity of our findings for other types of hospitals may be questioned, especially so when it comes to other countries. Still, for Scandinavian hospitals – given their relatively low consumption of BSAs – caution should be exercised when short-term fluctuations are recorded and interpreted.

### ***7.2. Bed days versus discharges as denominator unit***

The results of Papers II and III confirm the importance of reporting the antibiotic use with different measurement indices.

A main result is the lower increase in utilization of total antibiotics and BSAs when DDDs are related to number of discharges as compared to using hospital bed days, that is to say with different denominator units. Several authors have pointed out that the calculation and reporting of both indices are important in the interpretation of data on antibiotic use.<sup>79,86,88,89,100</sup> Largely, one may hypothesise as to the correct interpretation of these antibiotic use indices. One conceptual approach may be that the “truth” lies in the middle, between measurements related to doses per patient bed days and doses per patient discharges. For certain hospital settings, it has been proposed that an intensification of antibiotic use per patient bed day may be associated with shorter duration of antibiotic therapies, a situation that may lower the resistance pressure exerted by the antibiotics.<sup>79</sup>

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It is of particular importance to report temporal trends by use of both the number of bed days and number of discharges, since the average length of stay (LOS) has decreased considerably in most hospitals. The Hospital Trust system, introduced in Norway in 2002, has had a particular focus on costs and coding based on diagnosis-related groups (DRG). This has accelerated a tendency towards shorter LOS, thereby allowing for an increased number of hospital stays.

The substantial result differences reported in Papers II and III by use of the two different indices (denominators) strongly support the view that both measurements should be used, not only in a scientific context but also in the routine surveillance.

### ***7.3. WHO DDDs versus hospital adjusted DDDs***

In Paper III, we used a countrywide database of 22 Health Enterprises' antibiotic use to examine the effect of introducing hospital-adjusted DDDs. The results found with the use of this index was compared with those obtained based on WHO DDDs.

The high proportion of penicillins used by Norwegian hospitals and the particularly low set WHO DDDs for penicillins was the main reason why the surveillance results became significantly different with use of haDDD. The consumption of all penicillins was less than one half and that of broad-spectrum antibiotics 9/10 of the findings based on WHO DDDs.

No significant differences in temporal trends could be demonstrated for the national utilization of antibiotics, which means that the WHO DDD to haDDD conversion apparently did not influence the main conclusions regarding the development over time. However, there were inter-institutional differences, in particular for broad-spectrum antibiotics. In addition, although the increase over time for all penicillin use was similar with WHO DDDs and haDDD, there were diverging results for subclasses of penicillins.

We found that the use of haDDD had an impact on drug utilization ranking (DU90%). The DU90% methodology has been proposed by Zarb *et al*, who used it for analyses of temporal trends when comparing antibiotic use in European hospitals.<sup>152</sup> In that study, the method was deemed best suited in the evaluation of a single hospital's temporal trends and when comparisons were made between hospitals with similar characteristics and antibiotic formularies. We used the DU90% method in a novel way, namely to demonstrate the implications of hospital dose adjustments with regard to surveillance results. The method proved especially useful in this

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context, since the alterations in ranking could be visually evaluated and thus were easy to interpret.

Importantly, we demonstrated a more pronounced diversity in surveillance results with the DU90% ranking method when haDDD<sub>s</sub> were applied. Thus, the use of a more correct daily dose definition unveils more surveillance details.

A common challenge when attempting to establish alternate dose definitions is to find convincing methods to determine the “correct” dose for all antibiotics used. In countries where electronic prescription data are not available at the patient level (i.e. in most European countries) two methods have been used. One is to use doses recommended in guidelines, as we have done, the other is to apply results from repeated prevalence surveys of antibiotic use to calculate locally administered daily doses for various indications. The latter option has not been available in Norway because, up until now, only few hospitals have participated in the national point-prevalence surveys.

The WHO DDD-based method for recording antibiotic use in hospital patients has been evaluated previously. A one-year survey in 2001 from a French hospital with the number of antibiotic days of treatment (DOT) available, calculated prescribed daily doses (PDDs) by dividing WHO DDDs with DOT for various antibiotic substances.<sup>87</sup> They found a 40% overestimation of treatment days by use of WHO DDDs, mostly because the WHO DDDs for penicillins, macrolides and aminoglycosides were set to low. Using pharmacy dispensing data from 1992 to 2003, de With *et al* evaluated antibiotic use in one large German university hospital by use of WHO DDDs and an alternate dose definition based on guideline recommendations.<sup>86</sup> An overestimation of antibiotic use, as measured in WHO DDDs, was caused, for a large part, by too low set DDDs for amoxicillin-clavulanic acid. The authors also published a two-year survey of antibiotic use in 40 non-university hospitals from the same region, using both PDDs and WHO DDDs.<sup>85</sup> Finally, the same authors performed a prevalence survey at another German university hospital in 2006. They also determined PDDs from 471 antibiotic prescriptions in 971 adult patients and, in addition, calculated recommended daily doses (RDDs) from local antibiotic guidelines.<sup>86</sup> They found that WHO DDDs overestimated antibiotic use by 36% when compared with PDDs, whereas RDDs, compared with PDDs, only led to a slight underestimation. Their conclusion, in accordance with our in Paper III, was that guideline-recommended dose definitions deviate from WHO DDDs, and the former is better suited for the measurement of hospital antibiotic use.

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Few authors have focused on the WHO dose definition for antibiotic substances in the hospital environment. Previous publications have based their analyses on data from single institutions or hospitals belonging to a certain region, a fact that may question their external validity. Our study encompasses all Norwegian hospitals, which strengthens the generalizability of our findings.

### *7.4. Factors decisive for hospital antibiotic use*

In Paper IV, we aimed to identify structural, geographical and clinical variables that may explain differences in hospital antibiotic use.

A prerequisite for choosing the variables was that they should be easy to acquire and that they had been validated by official bodies (the Norwegian Patient Registry <sup>153</sup> and Statistics Norway <sup>154</sup>). Furthermore, the variables were selected with regard to both their clinical relevance and to their plausibility as explanatory factors for antibiotic use.

Largely, the same factors independently predicted use of all antibiotics, broad-spectrum antibiotics and penicillins – this was the case for all four indices used in the regression models. We conclude that the explanatory factors identified are valid regardless of which dose unit that was applied but they had different impact, depending on the denominator.

Few longitudinal studies have used aggregated antibiotic consumption data to investigate factors that determine antibiotic use in hospitals. Our study is the first to apply such analyses on a whole country. In a study of 74 southwestern French hospitals, antibiotic use and extent of antibiotic stewardship measures (ASM) were registered by use of questionnaires, and the relationship between ASM and trends for antibiotic use over five years were analysed. <sup>155</sup> A stable or decreasing use of ciprofloxacin and total antibiotics correlated with increased time used by a practice advisor and with a high frequency of antibiotic audits. The same authors published easily available adjustment criteria for 77 French hospitals' antibiotic use in 2005 based on the same retrospective methodology. <sup>156</sup> They concluded that 84% of the variability in use between public hospitals could be explained by the proportion of patient days in the intensive care, surgical and medical wards.

Prevalence surveys (see chapter 3.4.1, page 26) may be used to explore factors related to hospital antibiotic use. The advantage compared to longitudinal studies with aggregated data is that patient level information is available. Zarb and Amadeo, using ESAC point-prevalence studies

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from 2008 and 2009, <sup>157</sup> investigated antibiotic use in different age groups and found, not surprisingly, that extended use of antibiotics with a narrow therapeutic index (aminoglycosides and glycopeptides) represented a target for quality improvement in elderly patients. Two point-prevalence surveys in France with 294 participating, non-teaching hospitals explored the use of antibiotics for hospital-acquired infections. <sup>158</sup> In this large study, low-level and high-level utilization hospitals were defined by below 25 and over 75 percentiles of total antibiotic use, respectively. Linear regression analysis showed that hospital size, high proportion of patients with immunodeficiency and patients with infection characteristics explained 45% of the variance in antibiotic use between hospitals. No regional (geographical) effect could be observed after adjusting for patient characteristics.

Studies on the topic of hospital-acquired infections (HAIs) have been published in higher numbers than studies on antibiotic use. Because patients who are prescribed antibiotics usually have infections, studies of case-mix indices to adjust surveillance results for HAIs may be relevant also for antibiotic use. A Finnish nation-wide prevalence survey in 2005 aimed to establish a case-mix index to adjust inter-hospital differences in prevalence of HAIs. In a logistic regression analysis, urinary and central venous catheter use and a high McCabe and Jackson score <sup>159,160</sup> were the factors that significantly increased the odds for a presence of HAIs. The McCabe and Jackson score has been adapted for use in a recent European protocol dealing with prevalence surveys of antibiotic use in hospitals. Prevalence surveys of HAIs for case-mix adjustment has also been used to benchmark hospital's infection rates in Cyprus and Greece. <sup>118</sup>

Clearly, it is desirable to stratify antibiotic utilization to comparable specialties in order to reduce the case-mix problems that arise when different hospitals are compared. An Israeli study of 26 internal medicine departments used a multiple linear regression model to analyse factors that contributed to differences in antibiotic use. <sup>161</sup> Using a centralized hospital computer system, a series of variables were available for analysis. In addition to data on antibiotic use, variables related to hospital stay and patient-related variables were extracted. The latter included the Charlson co-morbidity index, <sup>162</sup> the rate of patients with neutropenia, pneumonia, urinary tract infections and cellulitis. They found that the rate of hospital stay lasting one day and hospital affiliation were the sole predictors of total antibiotic use, the former contributing only 7% and the latter 43% to the variance.

In our study of explanatory factors in Paper IV, we were not able to include in the regression analyses stratification to single hospital units or a grouping of specialties. However, we could

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show that a non-university affiliation correlated with a higher use of all antibiotics, while a medium HE size and HE location in certain geographical regions correlated with higher use of broad-spectrum antibiotics.

We conclude from Paper IV that after identifying explanatory factors that contributed to differences in hospitals' antibiotic use, there remained an unexplained residual variance of 60%–70% for broad-spectrum antibiotics and 30%–50% for all antibiotics. The factors we identified were mostly non-modifiable and we presume that the residual variations largely reflect prescriber-related factors. The identification of non-modifiable factors and the magnitude of their impact on variations in antibiotic use may help indicate areas where stewardship measures should be implemented.

## 8. General discussion

### *8.1. Utilization of antibiotics in hospital – temporal trends*

During six years, from 2002 to 2007, the use of all antibiotics and in particular broad-spectrum antibiotics (BSAs) increased to an extent that could not be explained from the national antibiotic resistance situation at that time. A European study of antibiotic consumption in hospitals from the period 1997–2002 demonstrated that Scandinavian countries had lower total antibiotic use than other European countries.<sup>64</sup> In particular, they used less third-generation cephalosporins and penicillins with a  $\beta$ -lactamase-inhibitor. Consumption studies from other Scandinavian countries are of interest, since the neighbouring countries presumably have similar health care systems and prescribing habits. Jensen *et al* surveyed the use of antibiotics in Danish hospitals from 2001 to 2007 and found a 43% increase in total antibiotic use (44.7 to 69.4 DDDs/100 BDs) and a 180% increase in BSA use (9.4 to 26.3 DDDs/100BDs).<sup>163</sup> The proportion of BSAs related to all antibiotic use doubled, from 19.2% to 38.2%. These changes, from 2001 up until 2007, were more pronounced than the 18% increase in use of all antibiotics found in an earlier Danish study (1997–2001), which also demonstrated an increase in the proportion the broad-spectrum antibiotics constituted of all antibiotic use – but only from 16% to 19%.

The Danish studies did not relate antibiotic use to the number of discharges. However, the authors did point out that the total number of patient bed days had successively decreased in Denmark, and that this lower number of bed days contributed by as much as 11% of the measured increase in hospital antibiotic use observed in the period 2001–2007. While the level of total antibiotic use, measured by DDDs/100 BDs, were almost identical in Denmark and Norway for the period 2001–2007, BSA use was almost twice as high in Denmark in 2007 as it was in Norway (26.3 versus 15.7 DDDs/100 BDs). The scale of the relative increase, both for all antibiotics and for BSAs, were also significantly higher in Denmark. In fact, the corresponding increases for Norway, 24.4% and 55.2% respectively, were more similar to the figures presented in the earlier Danish study (for the years 1997 to 2001).

An Italian 3-year survey of five hospitals (2002-2004)<sup>164</sup> illustrates the disparity of the antibiotic profile between southern and northern European countries. In this study, BSAs constituted two thirds of the total of 78.8 DDDs/100 BDs in 2004, the main BSA being penicillins with a

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betalactamase-inhibitor, which amounted to almost one third of the total use. By comparison, in Norway the use of agents belonging to this antibiotic class has been negligible. Moreover, the Italian hospitals' use of fluoroquinolones and third-generation cephalosporins was three to four times higher than our figures from 2004.

In a large survey of 530 hospitals from the south of France, it was found that in 2007 BSAs accounted for 25% of the total antibiotic use of 37.6 DDDs/100 patient days.<sup>165</sup> When including penicillins with enzyme-inhibitors in the BSA group, as we did in our studies, the proportion of BSAs was 59%. The French hospitals' use of betalactamase-susceptible and -resistant penicillin was 0.15 DDDs/100 BDs and 1.0 DDDs/100 BDs, respectively, i.e. narrow-spectrum penicillins constituted 3.1% of the total use.

Along the European north/south-axis, there is a striking difference in pattern of antibiotic use. The HEs from eastern Norway (Paper II, the period 2002–2007) used 19.9 DDDs/100 BDs (30.2%) of narrow-spectrum penicillins but only 16.8 DDDs/100 BDs (25.5%) of BSAs. A significant difference in total antibiotic use is also evident. The Norwegian hospitals' total use, 65.8 DDDs/100BDs, is higher than the French use by a factor of 1.75. This may in part have methodological explanations because 1) in the French study, psychiatric and rehabilitation wards with low antibiotic usage were included, and 2) the WHO DDDs for the narrow-spectrum penicillins are set lower than the doses actually used in hospital patients, a fact that inflates the number of doses registered for these substances.

Consumption data derived from the Norwegian pharmacy database, partially reported in Paper III, give interesting information on temporal trends for the period 2006–2011. For Norway, the increase in all HEs' total antibiotic use (DDDs/100 BDs) from 2006 to 2011 was almost of the same size as the one noted for the eight HEs of Health Region East from 2002 to 2007 (16.5% and 17.4%, respectively). Of note, though, is the increase in use of BSAs, which was considerably lower in the latest national figures than in the first observation period in Health Region East (21% versus 50%).

Since the two databases are different with regard to their hospital patient populations, unequivocal conclusions cannot be drawn by comparing the two periods. However, for the two years that the study databases overlap, 2006 and 2007, the total antibiotic use – measured for all HEs and including paediatric patients – was practically identical (regional data 62.7 and 65.1 versus national data 63.4 and 65.8 DDDs/100 BDs). For broad-spectrum antibiotics, the

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respective rates for 2006 and 2007 were 14.2 and 15.7 versus 15.4 and 16.5 DDDs/100 BDs. Altogether, this lends some support to the view that the use of resistance-driving antibiotics continues to increase, but at a lower grade in the recent years compared with the larger increase observed from 2002 to 2007.

Using Drug Utilization (DU) 90% ranking, we found that all 22 Norwegian HEs had narrow-spectrum penicillins as the number one used drugs when WHO DDDs were applied, whereas this was the case for only eight HEs when measured with haDDD. Metronidazole, the cephalosporins and ciprofloxacin advanced in ranks while the penicillins received lower ranking with the haDDD measurements. Since narrow-spectrum penicillins are part of the Norwegian standard antibiotic regime for empiric treatment of community-acquired sepsis and pneumonia, an overall high ranking for these drugs is to be expected. The higher ranking of metronidazole is also plausible because it is the most used antibiotic for anaerobic infections. Furthermore, metronidazole is the first choice drug in gastrointestinal surgical prophylaxis, in combination with doxycycline. The advancement in ranking for first generation cephalosporins, mainly cefalotin, is probably also because of its extensive use in infection prophylaxis as a first choice antibiotic for almost all types of surgical procedures. Because of a short half-life of cefalotin, prophylaxis doses are often repeated two or three times during lengthy operations. In view of the high number of surgical procedures being performed, cefalotin prophylaxis generates a substantial number of doses that may most correctly be measured by use of haDDD.

### ***8.2. Antibiotic use in relation to resistance***

A high utilization of broad-spectrum antibiotics is documented beyond doubt to be the main driver of antibiotic resistance. Numerous studies have proved the role of increased antibiotic use for resistance development. This evidence has been inferred after use of various analytical methods and for a variety of “drug-bug” combinations, both in the hospital setting and in the community.<sup>2,143,145,166-168</sup> However, as is evident from several of these studies, antibiotic resistance appears after a variable time lag following an increase in antibiotic use. Furthermore, the picture is often complicated by lack of a clear relationship between the usage of a specific antibiotic and resistance towards the same drug.

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We documented a doubling of BSA use measured in DDDs/100BDs, and a 20% increase when measured as DDDs/100 discharges, in eight Norwegian HEs in the period 2002–2007. However, no antibiotic resistance existed that could explain the increase in BSA use, neither were difficult-to-treat infections in hospitals observed in larger numbers – at least not at the national level. In 2007, the MRSA rate among *Staphylococcus aureus* was  $\ll$  1% of isolates (as it still is in 2013). The rates of extended-spectrum betalactamase (ESBL)-producing *Enterobacteriaceae* were still ~1% and ciprofloxacin-resistance in *Escherichia coli* was 2.2%. In general, the percentage of major pathogens that were non-susceptible to most registered BSAs was very low. For community-acquired, severe systemic infections, more than 95% were adequately treated with a regimen of benzylpenicillin plus an aminoglycoside, with the addition of metronidazole if an abdominal focus was suspected. The mismatch observed between a rise in antibiotic consumption and concomitant low resistance levels supports the notion, unfortunately, that future increases in antibiotic resistance will be partly due to a current misuse of antibiotics.

All countries in the world with the exception of Scandinavia and the Netherlands, experience an ongoing crisis of antibiotic resistance.<sup>169</sup> The presently favourable situation in the Norwegian health care system is destined to change, and most probably to the worse. There are current trends to indicate that we are now commencing a progressive upward slope of an exponential antibiotic resistance curve. At the initiation of our studies presented in the Papers III and IV, covering the period 2006–2011, there were negligible problems in Norway with regard to resistance. Since then, a rise in the prevalence of multiresistant bacteria (e.g. ESBL-producing *Enterobacteriaceae*, carbapenase-producing *Klebsiella* and vancomycin-resistant enterococci) has been reported internationally. The proportions of ESBL-producing *Escherichia coli* and *Klebsiella* in blood cultures and urine samples have also increased at an alarming pace, although the rates are still low in Norway. In this situation, it is important to prevent a misuse of carbapenems since this antibiotic class is the last resort for the treatment of infections with ESBL-producing organisms. Carbapenem use increased in Norwegian HEs from 1.4 to 1.8 DDDs/100BDs between 2006 and 2011 (34%). The increase for this antibiotic class may be even higher in intensive wards and certain medical and surgical specialties, in accordance with what we have shown for the “core units” in the previous period (2002–2007). These hospital units should be targets for further scrutiny and subjected to educational efforts and, preferably, even more active interventions.

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Of similar concern is the recent surge of gentamicin-resistance and a marked increase in ciprofloxacin-resistance in *E. coli* over the last 5–6 years. The increased resistance rates observed may not be explained by an increase in aminoglycoside use alone (from 2.1 to 2.7 DDDs/100BDs between 2006 and 2011). However, since aminoglycoside resistance is often transferred on mobile genetic elements, a co-selection of resistance may have occurred through the extended use of fluoroquinolones and third-generation cephalosporins,<sup>170</sup> increases that were documented in our studies throughout the period 2002–2011. Aminoglycosides are the backbones in many empiric combination treatments in Norway, which means that we until now have avoided the use of more resistance-driving broad-spectrum agents as a first choice.<sup>171-174</sup>

We found a significantly lower increase in the use of BSAs when analysing the national data (2006–2011) than for the Health Region East (2002–2007), which may well reflect a real difference between the national and regional utilization pattern. However, as discussed in chapter 8.1 we believe that the recent lower trend observed for the BSA increase is real. One explanation could be that the Norwegian resistance development may have alerted clinicians to reduce their BSA use. It seems to be a paradox, then, to observe a reduced use of BSAs if increased numbers of resistant microorganisms are indeed causing infections in our hospitals. However, this strengthens a belief that antibiotic prescribing is guided less by bacteriological findings than by other factors, not all of them rational, but some of them with the potential to be influenced in a positive way.<sup>175</sup>

### ***8.3. Strengths and limitations***

A common strength of our studies is the uniformity with which data on antibiotic use have been collected. We used a common source with pre-calculated DDDs and with detailed information about the hospital units that received the drugs. Because we did not rely on voluntary hospital participation by requesting them to supply study data, participation bias was not a problem. Furthermore, we used official sources for administrative data, thus providing precise counts, for example for patients' bed days. In this way, the often used but less accurate, indirect calculations of these parameters by means of occupancy rates and number of ward beds could be avoided. Above all, some shortcomings and errors that may arise based on methods where data are

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requested from hospitals, e.g. by means of questionnaires, are entirely avoided by our methodology.<sup>155</sup>

Moreover, the results reported in the Papers III and IV are arrived at after analyses of a complete, national dataset. The database includes all Norwegian HEs and represent census data, not a population sample. Thus, no selection bias exists that could distort the applicability of the study results. This obviates the need for inferential statistics and adds to the strength of our conclusions.

There are also some limitations of the studies. First, the centralization of medical services to fewer hospital units – mostly for fiscal reasons – represents a methodical challenge for hospital benchmarking of antibiotic use. Obviously, because data on antibiotic use should be evaluated locally, antibiotic surveillance results should preferably be reported for geographically separate hospitals and their specialties, rather than for whole Health Enterprises.

In Paper II, data were acquired from each hospital pharmacy and administrative unit of the eight Health Enterprises. This enabled us to calculate antibiotic use densities for single hospital units and for medical specialties. However, the nationwide data for the Papers III and IV were extracted from a national database where administrative information was restricted to whole HEs. While this limitation was not important for our adjustment of WHO DDDs to haDDDs, in our exploration of explanatory factors the lack of an independent variable for the distribution of antibiotic use in medical specialties was disadvantageous. However, this limitation was not regarded a major drawback since one explicit purpose was to evaluate the existing data sources, and with a long-term objective of a possible role in a future national surveillance system.

An inherent limitation of aggregated pharmacy sales data, used throughout this thesis, is the lack of information about the number of patients prescribed antibiotics and, furthermore, the unavailability of indications for use and duration of the antibiotic courses. Such information on the individual patient level represents is important in the evaluation of appropriate antibiotic prescribing. A most pertinent issue concerning data on antibiotic use data is feedback to local health care workers and administrators who are considered the most capable persons in the interpretation process, preferably in collaboration with the surveyors.

### 9. Conclusions

From this thesis, knowledge has been obtained about hospital antibiotic utilization in Norway. Up until now most of this information has not been present. We found a significant increase by almost 50% in the use of broad-spectrum antibiotics (BSAs) from 2002 to 2007 for all specialties and about 60% for “core units” (i.e. internal medicine, surgery and intensive care specialties). Corresponding increases related to hospital discharges were 20% and 30%. We observed that the increase in BSA use may have been abating in recent years. Still, the extent of BSA use in our hospitals is a concern because levels of antibiotic resistance in Norway are still low. Misuse will facilitate and open for a further resistance development.

Although pharmacy sales data still represent aggregated measures of antibiotic use, the figures identified in this way are closer to the point of patient care than data from wholesalers. We have shown how caution must be exercised when the surveillance of hospitals’ short-term BSA use is based on pharmacy sales data. Another aspect of this thesis is the evaluation of antibiotic dose measurements in hospitals. We addressed the discrepancy between WHO assigned defined daily doses and the daily doses actually administered to hospital patients. With regard to some antibiotics, notably penicillins, the dose discrepancies are so pronounced that the surveillance results will become skewed.

Moreover, a main conclusion is that both the number of bed days and the number of discharges should be used as denominators in antibiotic surveillance indices. This is because the length of the patients’ hospital stays has declined steadily over time. Finally, our identification of explanatory factors that determine hospital antibiotic use are important in both a national and an international context.

Today’s Norwegian health system, with large administrative units organised as Health Enterprises, implies some limitations when national surveillance data are applied on the level of single institutions. On a general national level, our findings of antibiotic dose adjustments and explanatory factors will be useful for benchmarking of antibiotic use in the Health Enterprises.

### 10. Implications and future research

This thesis was conducted with a practical purpose in mind, namely that the methods we evaluated might facilitate the introduction of a future national surveillance system of hospital antibiotic use. Consequently, we described in detail both practical approaches for collecting and presenting surveillance data and the difficulties encountered. We propose efforts for overcoming some of the identified obstacles, for example easier access to the clinical and administrative data needed for optimal benchmarking of hospitals.

The methodological issues addressed by this thesis have the following implications:

1. Understanding the limitation of pharmacy sales data for short registration intervals (Paper I) is crucial both for evaluation of short-term surveillance results and intervention studies applying interrupted time-series design. <sup>134,143,146</sup>
2. The application of hospital-adjusted defined daily doses (haDDD), described by us in Paper III, should be considered a supplement to the WHO DDDs in a future routine surveillance – possibly in combination with drug utilization (DU90%) ranking, which also has been evaluated by others. <sup>133,152</sup>
3. More resources should be allocated to the issue of adjusting antibiotic use in accordance with patient case-mix. Our study of explanatory factors for antibiotic use (Paper IV), applied on all Health Enterprises in Norway, revealed structural and geographical factors that explained antibiotic use dissimilarities, but there is a need for more research in this field.

At an international level, Norway has participated in a surveillance network for hospital antibiotic use called European Surveillance of Antibiotic Consumption (ESAC) since its start as a project in 2001. <sup>44</sup> However, too few Norwegian institutions have contributed data to these surveys to make them representative of a national sample. The ESAC project is currently incorporated as ESAC-Net in the European Centre of Diseases Control (ECDC) surveillance network for nosocomial infections and antibiotic use. ESAC's methods have largely been adopted and elaborated on, for example in a European protocol for point-prevalence surveillance of antibiotic use. <sup>125</sup>

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More interaction with the ECDC and a higher degree of participation in European surveys should be encouraged by Norwegian health authorities. Such initiatives are in particular a responsibility of the National Institute of Public Health. National scientific projects, such as the studies presented in this thesis, may also serve as a basis for further protocols, for example for projects involving other Scandinavian countries. These countries have similarly structured health care systems, a fact that makes pharmacoepidemiological studies relatively easy to perform. Moreover, the low antibiotic resistance levels in Scandinavia provide unique opportunities for investigation of preventive measures that are not possible in “high-resistance countries”.

Some future scientific questions and issues of interest:

1. To develop more sophisticated and standardized methods for surveillance.
  - i. To investigate new indices obtainable through routine surveillance that may be used to measure hospital antibiotic use.
  - ii. Further evaluations of established methods of surveillance, and new approaches for their use – e.g. repeated prevalence surveys.<sup>119,120,176-179</sup>
  - iii. Investigations of the appropriateness of individual prescribing practices, monitored by various methods.<sup>120,180-183</sup>
2. To establish and evaluate determinants for antibiotic prescriptions, important in the work to change physician’s behaviour.
  - i. Interviews and surveys of physicians’ prescription habits to investigate common behaviour determinants.<sup>175,184</sup>
  - ii. Investigate the rationale and strategies that underlie the process of writing and publishing guidelines.<sup>185</sup>
  - iii. Evaluate the following, in the search for effective stewardship measures: electronic decision aids, compulsory documentation of indications for antibiotic prescribing,<sup>186</sup> and automated stop orders for selected BSAs.<sup>187,188</sup>
3. To identify factors of importance for the development of antibiotic resistance in hospitals.

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- i. Host- and bacteria-level studies to link individual antibiotic exposure to the emergence of resistance (typing, pathogenicity, pK/pD, etc). <sup>189-193</sup>
- ii. Investigate risk factors for development of multiresistant bacterial strains <sup>104,167,193,194</sup> and factors which might reverse antibiotic resistance. <sup>26,103,195,196</sup>

This thesis has not addressed related issues, such as the optimal presentation of surveillance results at the hospital level, or the implementation of strategies to counteract antibiotic misuse. <sup>147</sup> As a vehicle for activities in these fields, a “National competence centre for hospital antibiotic use” was established in Bergen (Helse Bergen - Haukeland University Hospital) in 2011. Also, the scientific community working for a prudent antibiotic prescribing has increased its activity in recent years. New national guidelines for antibiotic use in primary care has recently been revised <sup>197</sup> and new guidelines for antibiotic prescription in hospital patients have been developed. <sup>198</sup> More relevant PhD projects than ever are underway. Hopefully, these will throw light on important issues of antibiotic prescribing and thus help combat antibiotic resistance.

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RESEARCH ARTICLE

Open Access

# Pharmacy sales data versus ward stock accounting for the surveillance of broad-spectrum antibiotic use in hospitals

Jon B Haug<sup>1\*</sup>, Randi Myhr<sup>2</sup> and Åsmund Reikvam<sup>3</sup>

## Abstract

**Background:** Antibiotic consumption in hospitals is commonly measured using the accumulated amount of drugs delivered from the pharmacy to ward held stocks. The reliability of this method, particularly the impact of the length of the registration periods, has not been evaluated and such evaluation was aim of the study.

**Methods:** During 26 weeks, we performed a weekly ward stock count of use of broad-spectrum antibiotics - that is second- and third-generation cephalosporins, carbapenems, and quinolones - in five hospital wards and compared the data with corresponding pharmacy sales figures during the same period. Defined daily doses (DDDs) for antibiotics were used as measurement units (WHO ATC/DDD classification). Consumption figures obtained with the two methods for different registration intervals were compared by use of intraclass correlation analysis and Bland-Altman statistics.

**Results:** Broad-spectrum antibiotics accounted for a quarter to one-fifth of all systemic antibiotics (ATC group J01) used in the hospital and varied between wards, from 12.8 DDDs per 100 bed days in a urological ward to 24.5 DDDs in a pulmonary diseases ward. For the entire study period of 26 weeks, the pharmacy and ward defined daily doses figures for all broad-spectrum antibiotics differed only by 0.2%; however, for single wards deviations varied from -4.3% to 6.9%. The intraclass correlation coefficient, pharmacy versus ward data, increased from 0.78 to 0.94 for parenteral broad-spectrum antibiotics with increasing registration periods (1-4 weeks), whereas the corresponding figures for oral broad-spectrum antibiotics (ciprofloxacin) were from 0.46 to 0.74. For all broad-spectrum antibiotics and for parenteral antibiotics, limits of agreement between the two methods showed, according to Bland-Altman statistics, a deviation of  $\pm 5\%$  or less from average mean DDDs at 3- and 4-weeks registration intervals. Corresponding deviation for oral antibiotics was  $\pm 21\%$  at a 4-weeks interval.

**Conclusions:** There is a need for caution in interpreting pharmacy sales data aggregated over short registration intervals, especially so for oral formulations. Even a one-month registration period may be too short.

## Background

Antibiotic use in hospitals accounts for 10% or less of total antibiotic consumption in most countries, but is characterized by the use of large quantities of broad-spectrum antibiotics (BSAs). Furthermore, hospital departments are densely populated with patients who are at particular risk of acquiring infections of resistant microorganisms [1,2]. Thus, active surveillance of in-hospital antibiotic use to prevent inappropriate

prescribing is a fundamental measure in the struggle against the development of antimicrobial resistance [3,4].

The most common way of measuring antibiotic use in hospitals is to apply sales data extracted from hospital pharmacy computer systems. However, until now in most European countries pharmacies have not dispensed antibiotics directly to the patients. A ward-held stock of antibiotics has been the routine. In a recent survey of hospital pharmacy practice in Europe it was found that 70% of hospitals hold antibiotic stocks at the wards [5]. When wards purchase drugs from the pharmacy, there will necessarily be a time lag from ordering until

\* Correspondence: jobhau57@gmail.com

<sup>1</sup>Department of Infectious Diseases, Oslo University Hospital Aker, Trondheimsveien 235, NO-0514 Oslo, Norway

Full list of author information is available at the end of the article

consumption. Differences between sales figures and actual drug use might be expected because of variation of stock size over time, discarding of expired drugs, and exchanges of drugs between wards.

Moreover, the duration of the registration intervals may affect the results. In general, short registration intervals have been advocated, especially when the purpose has been to evaluate the effects of specific drug interventions [6-8]. However, the appropriateness of using short registration intervals has not been assessed. How the duration of the registration interval impacts the recording of antibiotic use has not been scrutinized.

Aim of the study was to explore whether the number of defined daily doses (DDDs) reported from the pharmacy, that is to say the sales data to the wards, reflects actual patient consumption of BSAs. In particular, we wanted to evaluate the importance of the length of the registration intervals for the reliability of the pharmacy data.

## Methods

### Study population

Oslo University Hospital Aker is a 350-bed tertiary hospital with adult surgical and medical specialities including regional functions for urology, vascular surgery, and endocrinology. In 2007, the number of somatic hospital beds was 356 and 20 060 patients were admitted for 116 251 days of in-patient treatment. Data on occupied bed-days were obtained from the hospital administration, where days of admission and discharge were counted together as one day.

Five hospital wards were included in the study: a pulmonary diseases ward, a combined gastrointestinal and infectious diseases ward, a combined endocrinology and haematology ward, and two urological wards. These wards accounted for 28% of all patient treatment in terms of occupied bed days. The specialties were selected because of a historically relatively high per-ward total use of BSAs, which in our hospital are ciprofloxacin (parenteral and oral) and parenteral formulations of cefuroxime, cefotaxime, ceftazidime, ceftriaxone, meropenem, and imipenem/cilastatin. Ciprofloxacin is the only oral BSA registered in Norway. Piperacillin+tazobactam is the only registered penicillin with an enzyme inhibitor, but this agent was not used in our hospital during the study period.

In Norway, a full assortment of antibiotics is normally stock-piled in the wards and administered by the ward nurses. Antibiotics are not ordered from the pharmacy on a per-patient basis. The ward nurses routinely prepare parenteral antibiotics, retrieved from the ward stock, just prior to administration. On rare occasions, when a drug is out of stock, it will be available from another ward or, in the daytime, from the hospital pharmacy. An emergency pharmacy service exists for essential and rarely used drugs; however, this does not apply for antibacterial agents.

### Ward stock accounting

During 26 weeks from October 2006 to April 2007, a pharmacist performed weekly counts of BSA stock in the five wards. The number of vials, infusion bags, and tablets were registered for each ward once a week, before daily orders of antibiotics were placed to the pharmacy, but after morning doses of antibiotics were administered to the patients. The milligram amounts for each antibiotic were converted to defined daily doses units in accordance with the latest WHO ATC/DDD version [9].

The weekly amount of antibiotics consumed by patients (henceforth designated as "ward BSA") was calculated as the difference between the previous and the current week count, and also taking into account input and output to ward stock. Factors increasing the ward stock size were delivery from the pharmacy and loan from other wards. Factors reducing the ward stock size were loan to other wards, BSAs sent with patients for use after discharge, and discarding of old drugs. Discarded drugs were registered electronically in the pharmacy sales system while the other stock reducing factors were registered manually by ward nurses.

Because of the lack of a ward stock count during holidays in study weeks 10 - 12 and 25 - 26, a weekly average was used for these weeks. Also, two weeks had to be omitted from a total of 26 weeks to establish complete 3- and 4-weeks registration intervals. We chose to omit the weeks 12 and 26, weeks with incomplete data acquisition, thus probably reducing the risk of error.

### Pharmacy sales data

For each ward, weekly sales figures for BSA DDDs for the same 26-week period were extracted from the hospital's pharmacy computer system (FarmaPro version 4.1.0a, NAF-data Corp. 2007, Oslo, Norway). In addition to economic data, the system registers the number of DDDs for each antibiotic order placed by the separate wards, as well as total amounts of antibiotics returned by the same wards to the pharmacy provided that shelf-life and condition allow for further use. The resulting sales figures for different time intervals, designated as "pharmacy BSA", were compared with "ward BSA". We chose to assign a weekly average for the study weeks 10 - 12 and 25 - 26 also for the pharmacy sales data (see Discussion). The shortest registration interval was one week, and accumulated periods of two, three, and four weeks were also investigated.

### Statistical analysis

The numbers of DDDs for each BSA and for each ward obtained by the two methods were entered into a Microsoft Excel (version 2007) spreadsheet. All entries and subsequent calculations were double-checked by two of the investigators (JBH and RM).

All statistical analyses were performed using Stata software version 11 (StataCorpLP, College Station, TX USA). The reliability or overall agreement of the pharmacy BSA with ward BSA was assessed by intraclass correlation coefficients (ICC) using a mixed model ANOVA. The theoretical formula for is  $ICC = \frac{\sigma_s^2}{\sigma_s^2 + \sigma_e^2}$ , where  $\sigma_s^2$  is the between-subject variance and  $\sigma_e^2$  is the within-subject variance. The ICC will be high if the measures are in agreement (i.e., the slopes of the regression lines are near 1), and the variation between ward data is large relative to the variation between pharmacy data measurements. A calculated ICC = 1 reflects perfect reliability of the method as evaluated against the assumed "gold standard". An ICC of 0.7 is commonly used as a threshold of sufficient reliability [10].

Using the method described by Bland and Altman [11,12], the differences between pairs of DDD measurements for pharmacy BSAs and for ward BSAs were

plotted against their averages. Twelve plots (all antibiotics, parenteral antibiotics, and oral antibiotics assessed for one to four weeks registration intervals) were inspected for aberrant trends over the measurement range. Levels of agreement for different combinations were then determined and related to the average of mean DDDs for the two measurements.

## Results

### Use of broad-spectrum antimicrobial agents

BSA use during the 26 study weeks ranged from 12.8 DDDs/100 bed days in one urological ward to 24.5 DDDs/100 bed days in the pulmonary diseases ward. BSA amounts ranged from 615.3 DDDs at one urological ward to 1144.8 DDDs at the pulmonary diseases ward (Table 1), which represents 19.4% - 26.3% of the total consumption of all systemic anti-bacterial agents (ATC group J01). In

**Table 1 Use of broad-spectrum antibiotics (BSAs) <sup>1</sup> during 26 weeks, pharmacy sales data versus ward stock data.**

Wards BSAs	PharmacyBSA DDDs <sup>2</sup>	WardBSA DDDs	Diff. (%)
<b>Pulmonary diseases</b>	<b>1 144.8</b>	<b>1 194.2</b>	<b>-4.3</b>
2 <sup>nd</sup> generation cephalosporins	445.0	432.5	-2.8
3 <sup>rd</sup> generation cephalosporins	328.8	360.3	-9.6
Carbapenems	180.0	171.0	5.0
Ciprofloxacin parenteral	16.0	26.4	-65.0
Ciprofloxacin oral	175.0	204.0	-16.6
<b>Gastrointestinal/infectious diseases</b>	<b>877.3</b>	<b>898.1</b>	<b>-2.4</b>
2 <sup>nd</sup> generation cephalosporins	205.0	231.0	-12.7
3 <sup>rd</sup> generation cephalosporins	161.3	152.5	5.5
Carbapenems	103.0	96.3	6.5
Ciprofloxacin parenteral	128.0	130.0	-1.6
Ciprofloxacin oral	280.0	288.3	-3.0
<b>Endocrinology/haematology</b>	<b>668.3</b>	<b>676.1</b>	<b>-1.2</b>
2 <sup>nd</sup> generation cephalosporins	125.0	128.0	-2.4
3 <sup>rd</sup> generation cephalosporins	101.3	111.3	-9.9
Carbapenems	80.0	76.0	5.0
Ciprofloxacin parenteral	52.0	46.8	10.0
Ciprofloxacin oral	310.0	314.0	-1.3
<b>Urology 1</b>	<b>615.3</b>	<b>572.8</b>	<b>6.9</b>
2 <sup>nd</sup> generation cephalosporins	70.0	62.5	10.5
3 <sup>rd</sup> generation cephalosporins	46.3	32.8	29.2
Carbapenems	0	0	-
Ciprofloxacin parenteral	124.0	131.2	-5.8
Ciprofloxacin oral	375.0	346.3	7.7
<b>Urology 2</b>	<b>671.5</b>	<b>628.7</b>	<b>6.4</b>
2 <sup>nd</sup> generation cephalosporins	72.5	63.0	13.1
3 <sup>rd</sup> generation cephalosporins	30.0	19.0	36.7
Carbapenems	0	0	-
Ciprofloxacin parenteral	144.0	144.4	-0.3
Ciprofloxacin oral	425.0	402.3	5.3
<b>All specialties</b>	<b>3 977.2</b>	<b>3 969.7</b>	<b>0.2</b>

<sup>1</sup>BSAs: ciprofloxacin (oral and parenteral), cefuroxime, cefotaxime, ceftazidime, ceftriaxone, meropenem and imipenem/cilastatin

<sup>2</sup>DDD: defined daily doses

the urology and endocrinology/haematology wards, ciprofloxacin was the predominant BSA used. In the pulmonary diseases ward, cephalosporins accounted for two-thirds of total BSA use, whereas the use of the various antibiotics was more evenly distributed in the gastroenterology/infectious diseases ward.

#### Pharmacy versus ward DDD registrations

During the 26 study weeks there were 1040 dual registrations (pharmacy versus ward data) of the eight BSAs at the five wards. In 550 of these registrations, no use was registered by either of the two methods and this was primarily caused by a very low use of carbapenems (e.g. no use in the urological wards). The number of DDDs that were discarded (10.5), sent with patients on discharge (18.0) or loaned to other wards (14.5) represented 1.1% of the total consumption. Only nine DDDs were borrowed from other wards.

Total BSA use over 26 weeks measured as ward BSA was 3 970 DDDs with a weekly range of 104.7 - 257.2

DDD. The corresponding total number for pharmacy sales data were almost identical at 3 977 DDDs, with a weekly range of 41.5 - 324.5 DDDs (Figure 1). The largest discrepancy between total ward and pharmacy BSAs was noted in observation weeks 17 - 18 and was related to oral ciprofloxacin. Half of the total BSA use in this study was found to be ciprofloxacin and 77% of this was oral formulation. In both urological wards, the total pharmacy BSA was markedly higher than ward BSA (6.4% - 6.9%). This is in contrast to the three medical wards where the total pharmacy BSA was somewhat lower than ward BSA (1.2% - 4.3%).

The pharmacy sale to the wards per individual order of antibiotics varied little for the various parenteral formulations (median 5 - 10 DDDs) as distinct from oral formulations (ciprofloxacin tablets) for which both larger bulks and a wider range of order size (5 - 50 DDDs, median 20) were registered (Figure 2). The total number of orders varied considerably from 14 (ceftriaxone) to 110 (cefuroxime).

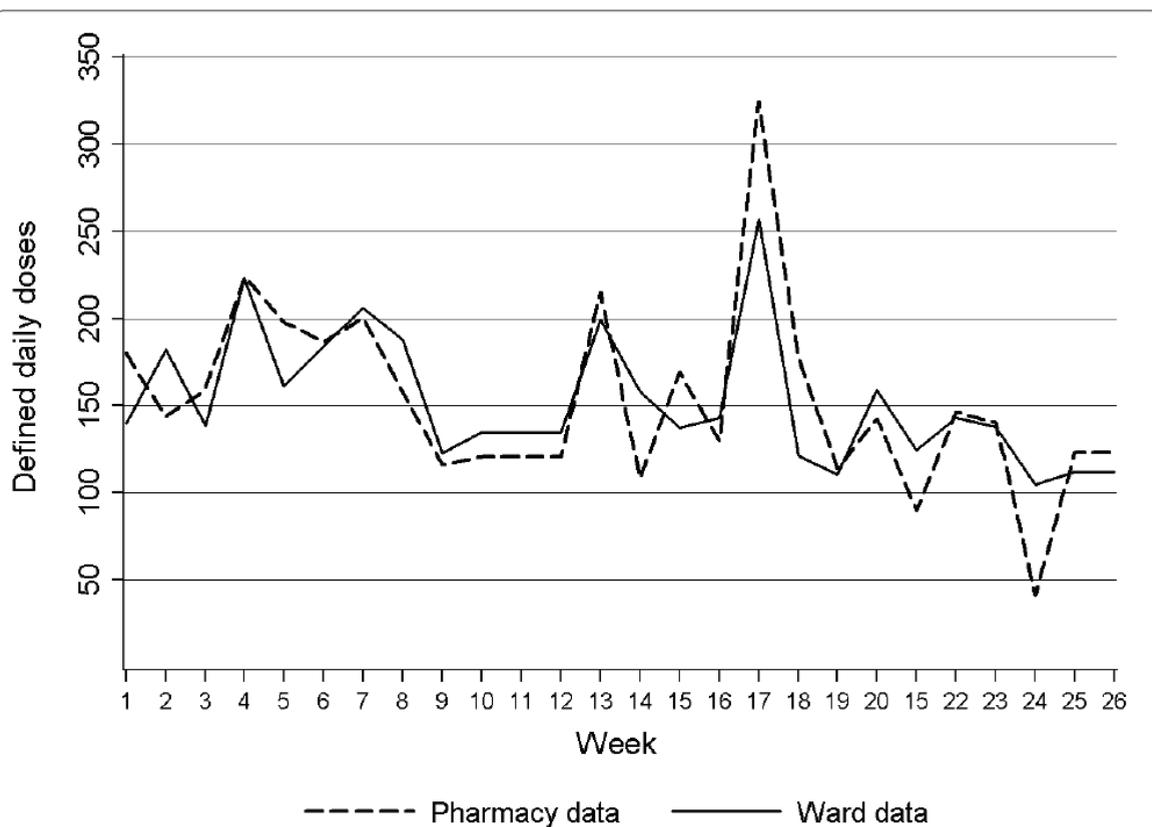
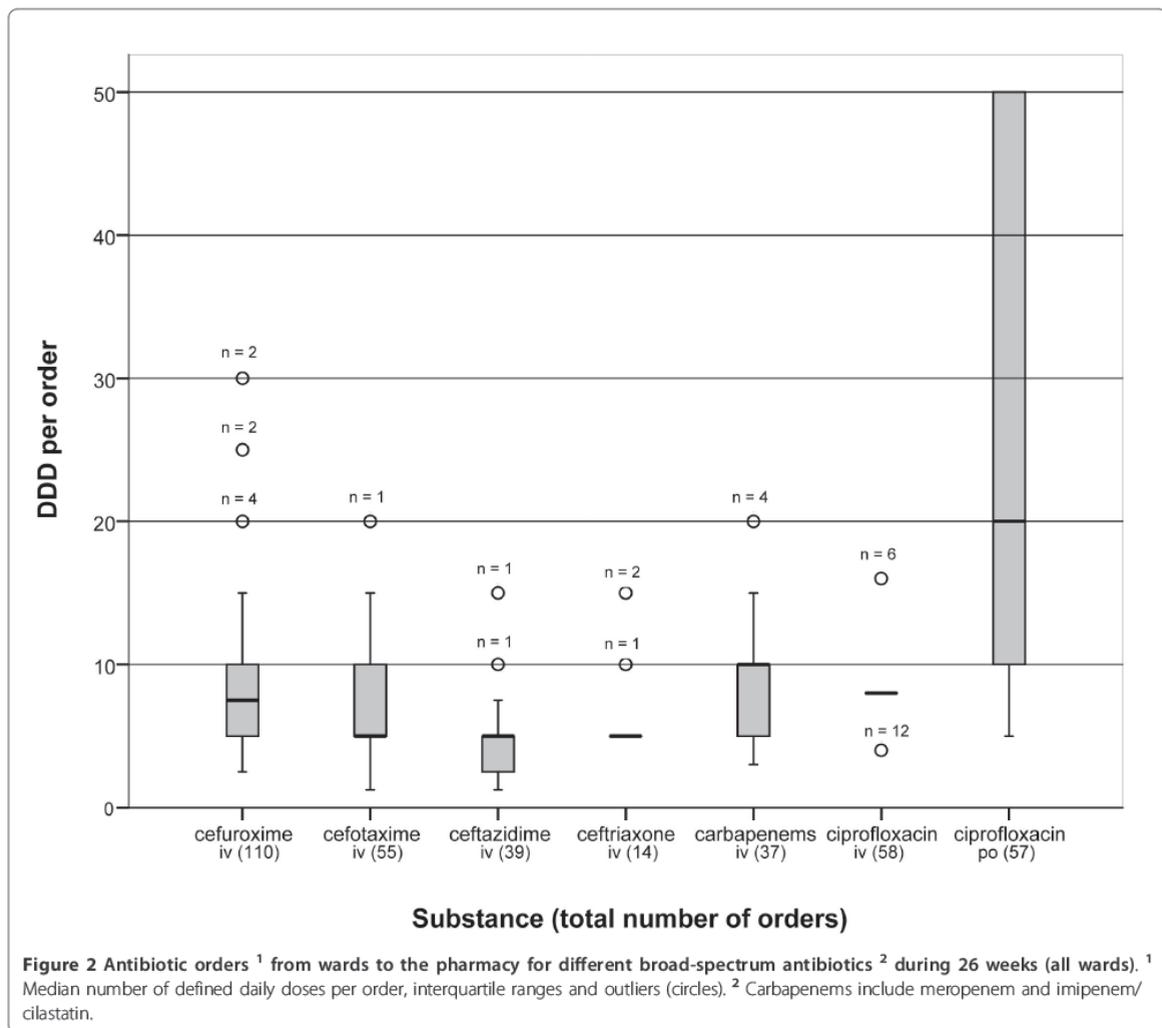


Figure 1 Consumption of broad-spectrum antibiotics in defined daily doses (DDD) during 26 weeks; pharmacy sales data versus ward stock measurements (all wards).



**Reliability analysis**

The reliability of pharmacy data as compared to ward stock accounting increased with longer surveillance intervals (Table 2). For total BSAs, all wards included, an intraclass correlation coefficient (ICC) of 0.65 (CI

0.61 - 0.69) was found for one-week intervals whereas for 4-week registration intervals the ICC was 0.90 (CI 0.88 - 0.93). The reliability of pharmacy data was markedly higher for parenteral than for oral BSAs, the latter achieving an ICC of 0.74 (CI 0.58 - 0.90) only at four-

**Table 2 Reliability of pharmacy sales compared with ward stock data of broad-spectrum antibiotics (BSAs)<sup>1</sup> for different registration intervals**

Interval	No. reg.	ICC <sup>2</sup> all BSA (CI <sup>3</sup> )	ICC parenteral BSA (CI)	ICC oral BSA (CI)
1 week	1 040	0.65 (0.61-0.69)	0.78 (0.76 - 0.81)	0.46 (0.32 - 0.59)
2 weeks	520	0.77 (0.74 - 0.81)	0.87 (0.85 - 0.89)	0.53 (0.35-0.70)
3 weeks	360	0.82 (0.79-0.86)	0.93 (0.92 - 0.95)	0.54 (0.32-0.76)
4 weeks	280	0.90 (0.88-0.93)	0.94 (0.92 - 0.95)	0.74 (0.58 - 0.90)

<sup>1</sup> Broad-spectrum antibiotics: ciprofloxacin (parenteral and oral), cefuroxime, cefotaxime, ceftazidime, ceftriaxone, meropenem, and imipenem/cilastatin

<sup>2</sup> ICC: intraclass correlation coefficient

<sup>3</sup> CI: 95% confidence interval

week registration, whereas parenteral BSAs had already reached this level at the one-week registration interval.

For all of the 12 combinations of antibiotics (all, parenteral, oral) and periods of registrations (one to four weeks), Bland-Altman statistics revealed mean differences between -0.136 to 0.158 DDDs. The limits of agreement for each of the above combinations were converted to corresponding DDD ranges (Table 3). For all BSAs and parenteral BSAs, limits of agreement of  $\pm 5\%$  were found for 3- and 4-weeks registration intervals while oral antibiotics (ciprofloxacin) deviated  $\pm 21\%$  from the average mean DDD use even at the 4-week registration interval. Bland-Altman plots (Figure 3) showed diverging differences with increasing averages of DDDs for oral BSAs and for the shorter registration intervals in general; a trend which was far less pronounced for parenteral BSAs and all BSAs at the 4-weeks intervals.

## Discussion

Accurate information regarding antibiotic consumption is a prerequisite for evaluating antibiotic use and implementing measures to avoid excessive prescribing and increased bacterial resistance. To achieve efficient monitoring, short registration periods have been advocated, preferably as short as one month [13]. In this study, we found that surveillance by use of pharmacy sales data was sufficiently reliable for the total registration period of six months. A small mean difference between

measurements for all registration intervals, as demonstrated by Bland-Altman statistics, implies that our comparison of pharmacy with ward registrations was not burdened with systematic bias. However, when data for the shorter periods, such as one to four weeks, were investigated, ICCs indicated that pharmacy sales data were not sufficiently reliable, particularly so for the one to three-week registrations. It will be a clinical decision to define acceptable limits of agreement. Nonetheless, the wide DDD range for oral BSAs ( $\pm 21\%$ ) even at a four weeks registration interval seems unacceptable by any standards.

The amount of BSAs exchanged between wards, discarded due to exceeded durability or given to patients at discharge was less than 2%, and it was the stock size fluctuations in the wards that accounted for the main discrepancy between pharmacy and ward data. The greatest variations were observed for ciprofloxacin tablets, which largely explain the less reliable pharmacy figures for oral compared to parenteral formulations. This in turn is related to the fact that tablets usually are less voluminous and also cheaper per DDD and may be stored for longer periods than injectable preparations.

Few other studies have evaluated the common method of measuring hospital use of antibiotics by recording pharmacy dispensing or sales data and, to our knowledge, none has previously evaluated the impact of the length of the registration interval. One short report found a poor correlation between a pharmacy dispensing system and

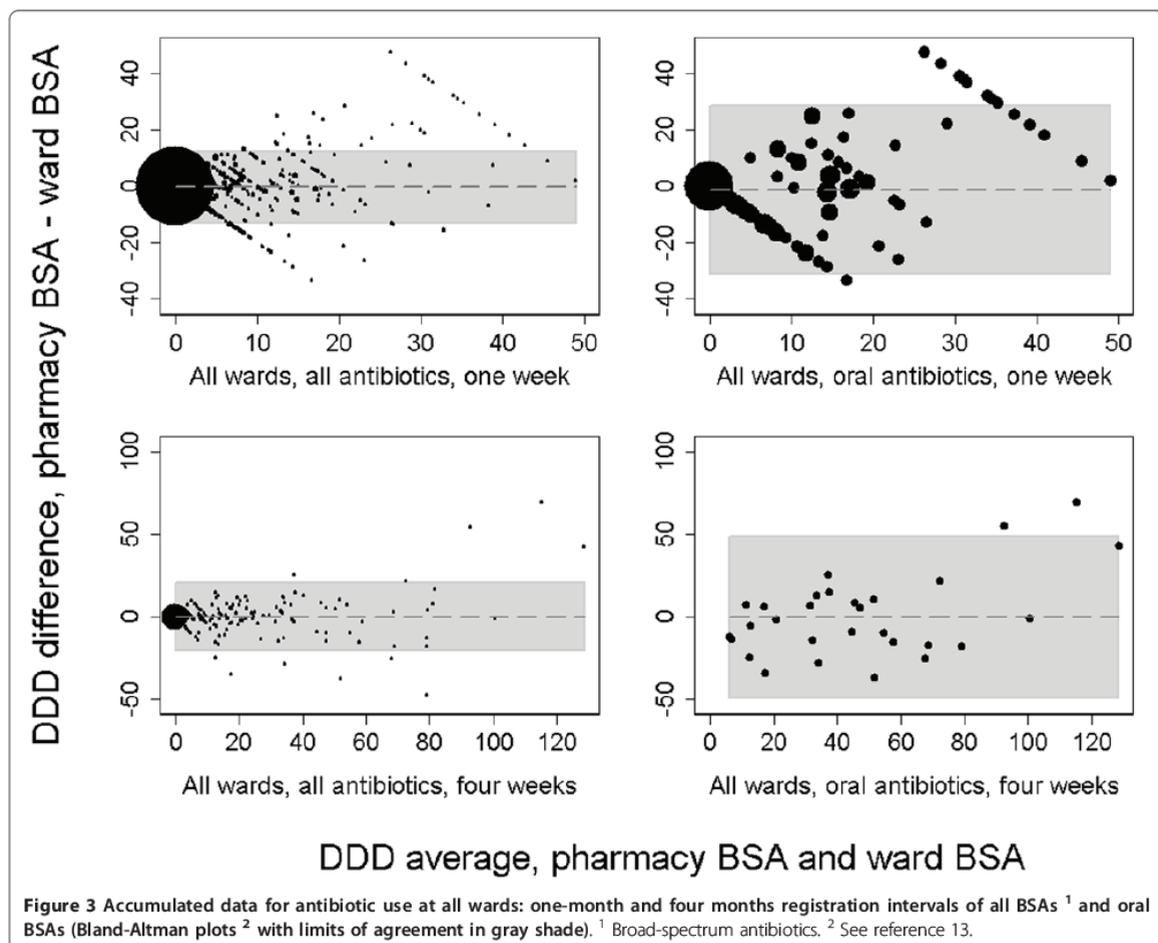
**Table 3 Mean average DDD use<sup>1</sup> of all broad-spectrum antibiotics and corresponding limits of agreement<sup>2</sup> (DDD use range) for different registration intervals (all wards combined)**

Interval Antibiotics	Defined daily doses (DDDs)		
	Mean use	Use range (- %; + %)	Mean difference
1 week			
All	152.8	144.1 - 167.5 (9.6; 9.6)	0.007
Parenteral	92.8	85.0 - 100.6 (8.4; 8.4)	-0.003
Oral	60.0	23.9 - 96.2 (60.2; 60.4)	0.079
2 weeks			
All	305.6	287.1 - 324.1 (6.1; 6.1)	0.014
Parenteral	185.6	175.5 - 195.7 (5.5; 5.4)	-0.006
Oral	120.0	74.9 - 165.4 (37.6; 37.8)	0.158
3 weeks <sup>3</sup>			
All	466.0	442.8 - 489.2 (5.0; 5.0)	0.031
Parenteral	288.7	274.5 - 294.9 (3.5; 3.6)	0.050
Oral	181.3	120.7 - 241.7 (33.4; 33.3)	-0.102
4 weeks <sup>3</sup>			
All	621.3	600.6 - 642.1 (3.3; 3.3)	0.042
Parenteral	379.6	367.6 - 391.8 (3.2; 3.2)	0.067
Oral	241.7	191.6 - 291.5 (20.7; 20.6)	-0.136

<sup>1</sup> Sum of averages of paired results (pharmacy sales DDDs and ward stock DDDs)

<sup>2</sup> Limits of agreement according to Bland-Altman statistics are expressed as the range of DDDs and percent DDD deviation below and over the mean average use

<sup>3</sup> Weeks 12 and 26 were discarded (see Methods)



an intensive care unit (ICU) based electronic chart as source of data. The investigators speculated that transfer of antibiotics between wards, wastage, and data-entry errors may have been the reasons for the discrepancy [14]. Another study compared pharmacy sales data, based on pharmacy dispensing, with data from nursing records and found that up to 20% of parenteral doses of antibiotics dispensed at the pharmacy were not administered to patients [15]. Such a marked deviation is probably due to delayed transmission of drug information between the ward and the pharmacy, a situation that arises when parenteral antibiotics are prepared at the pharmacy and not near the patient. Neither of the studies evaluated the length of the registration period.

A limitation of our study is the relatively low BSA consumption in our institution, such that the number of registered DDDs was moderate. In hospitals with more extensive BSA consumption and a larger assortment of antibiotic substances, the findings may differ. Also of

note, for two periods weekly ward data were missing because of holidays, and for the weeks in question, weekly averages were the basis for the analyses. However, since the corresponding pharmacy sales data were averaged accordingly, this deviation tend to introduce bias towards higher levels of agreement (alpha error), particularly so for the short registration intervals.

We propose that our method of weekly ward stock DDD accounting is an accurate method for indicating actual antibiotic use by patients. Only a much more labour-intensive patient chart review would be more accurate. Although also our method is demanding and therefore not practical for routine surveillance, we regard it as well suited for scientific purposes and for quality assessments of pharmacy sales figures. In some hospitals, electronic patient charts have been introduced and this allows for another method, probably with a high level of accuracy, for measuring drug consumption [16]. However, for the immediate future in most European hospitals, the

pharmacy will remain the principal data source for surveillance of use of antibiotics.

## Conclusions

Pharmacy sales data for total BSA use were representative for the actual drug consumption when longer registration periods were used. For the data to be sufficiently reliable, a four-week registration period is required for parenteral formulations, whereas for oral medications one month is not sufficient. For analyses of BSA subclasses and separate hospital units, even these intervals are probably too short, at least in hospitals with a low-to-moderate consumption profile.

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## Author details

<sup>1</sup>Department of Infectious Diseases, Oslo University Hospital Aker, Trondheimsveien 235, NO-0514 Oslo, Norway. <sup>2</sup>Regional medicines information and pharmacovigilance centre (RELIS), Oslo University Hospital Ullevål, Kirkeveien 166, NO-0407 Oslo, Norway. <sup>3</sup>Institute of Pharmacology, Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Sognsvannsveien 20, NO-0424 Oslo, Norway.

## Authors' contributions

JBH designed the study, analyzed and interpreted the data and drafted the manuscript. RM contributed to study design, acquired the ward stock data and helped in interpretation and writing of the manuscript. ÅR advised on design and interpretation of the study, and contributed significantly with critical revisions of the manuscript. All authors have read and approved of the final manuscript.

## Competing interests

The authors declare that they have no competing interests.

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## Increased antibiotic use in Norwegian hospitals despite a low antibiotic resistance rate.

Haug JB<sup>1</sup>, Berild D, Walberg M, Reikvam A.

### Author information

#### Abstract

**OBJECTIVES:** Although antibiotic use and resistance are low in Norway, the situation risks changing for the worse. We investigated trends in antibiotic use and assessed them in relation to antibiotic resistance in Norway.

**METHODS:** We drew on hospital pharmacy sales data to record antibiotic use from 2002 to 2007 in eight hospitals serving 36% of the nation's population. Antibiotic use was measured using different indices with defined daily doses (DDDs) as the numerator (WHO ATC/DDD classification).

**RESULTS:** Total antibiotic use increased from 1.02 to 1.30 DDDs/1000 inhabitants/day (DIDs) and from 61.7 to 72.4 DDDs/100 bed-days (BDs) (17.4%); related to the number of discharges, no significant DDD change was shown. Their use in core units (adult intensive care units, recovery/post-operative wards and departments of internal medicine and surgery with all subspecialties) increased from 64.1 to 80.8 DDDs/100 BDs (26.1%) and by 3.1% related to the number of discharges. The total use of broad-spectrum antibiotics increased by 47.9% when measured as DDDs/100 BDs, and by 19.1% based on the number of discharges; the corresponding figures for core units were 60.5% and 31.2%, respectively.

**CONCLUSIONS:** There was a substantial increase in total antibiotic use, and an even more pronounced increase in the use of broad-spectrum antibiotics, which seems unjustified considering the current low antibiotic resistance in Norway.







## WHO defined daily doses versus hospital-adjusted defined daily doses: impact on results of antibiotic use surveillance.

Haug JB<sup>1</sup>, Reikvam Å.

### Author information

#### Abstract

**OBJECTIVES:** To investigate effects on surveillance results of hospital antibiotic use when WHO defined daily doses (WHO DDDs) are adjusted to doses recommended for hospitalized patients [hospital-adjusted defined daily doses (haDDDs)].

**METHODS:** Data for antibiotic use in 2006-11 for all 22 Norwegian Health Enterprises were analysed with both WHO DDDs and haDDDs as numerators. The haDDDs were determined from recommendations given in regional and national guidelines on antibiotic use in hospitals. The two ways of calculating the amount of antibiotic use were compared, with either the number of bed days (BDs) or the number of discharges as the denominator. The drug utilization 90% methodology was applied for ranking the use of the various antibiotics.

**RESULTS:** DDD adjustments altered the figures for total antibiotic use from 67.1 WHO DDDs/100 BDs to 49.3 haDDDs/100 BDs (-26.4%). The most marked difference was found for penicillins: 31.1 WHO DDDs/100 BDs versus 13.4 haDDDs/100 BDs (-56.8%). The corresponding figures for broad-spectrum antibiotics were 17.3 and 15.5 (-10.4%), respectively; for these antibiotics, the conversion changes varied significantly between institutions, from -16.7% to -3.3%. Ranking antibiotic use based on haDDDs resulted in higher positions for metronidazole, cefuroxime, cefotaxime and cefalotin/cefalexin compared with the WHO DDD-based ranking, where the penicillins dominated.

**CONCLUSIONS:** The low-set WHO DDDs for penicillins caused skewed surveillance results that concealed the real magnitude of broad-spectrum antibiotic use and distorted interhospital comparisons. For surveillance of antibiotic use in hospitals, WHO DDDs should be supplemented with haDDDs.

**KEYWORDS:** DDDs; drug utilization; methodologies

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RESEARCH

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# Hospital- and patient-related factors associated with differences in hospital antibiotic use: analysis of national surveillance results

Jon Birger Haug<sup>1\*</sup>, Dag Berild<sup>1</sup>, Mette Walberg<sup>2</sup> and Åsmund Reikvam<sup>3,4</sup>

## Abstract

**Background:** Surveillance data of antibiotic use are increasingly being used for benchmarking purposes, but there is a lack of studies dealing with how hospital- and patient-related factors affect antibiotic utilization in hospitals. Our objective was to identify factors that may contribute to differences in antibiotic use.

**Methods:** Based on pharmacy sales data (2006–2011), use of all antibiotics, all penicillins, and broad-spectrum antibiotics was analysed in 22 Health Enterprises (HEs). Antibiotic utilization was measured in World Health Organisation defined daily doses (DDDs) and hospital-adjusted (ha)DDDs, each related to the number of bed days (BDs) and the number of discharges. For each HE, all clinical specialties were included and the aggregated data at the HE level constituted the basis for the analyses. Fourteen variables potentially associated with the observed antibiotic use – extracted from validated national databases – were examined in 12 multiple linear regression models, with four different measurement units: DDD/100 BDs, DDD/100 discharges, haDDD/100 BDs and haDDD/100 discharges.

**Results:** Six variables were independently associated with antibiotic use, but with a variable pattern depending on the regression model. High levels of nurse staffing, high proportions of short (<2 days) and long (>10 days) hospital stays, infectious diseases being the main ICD-10 diagnostic codes, and surgical diagnosis-related groups were correlated with a high use of all antibiotics. University affiliated HEs had a lower level of antibiotic utilization than other institutions in eight of the 12 models, and carried a high explanatory strength. The use of broad-spectrum antibiotics correlated strongly with short and long hospital stays. There was a residual variance (30%–50% for all antibiotics; 60%–70% for broad-spectrum antibiotics) that our analysis did not explain.

**Conclusions:** The factors associated with hospital antibiotic use were mostly non-modifiable. By adjusting for these factors, it will be easier to evaluate and understand observed differences in antibiotic use between hospitals. Consequently, the inter-hospital differences can be more confidently acted upon. The residual variation is presumed to largely reflect prescriber-related factors.

**Keywords:** Antibiotic use, Antibiotic surveillance, Hospitals, Risk factors

## Background

In working towards rational use of antibiotics in hospitals, one needs to establish and maintain a suitable system for surveillance of antibiotic use [1]. However, the surveillance commonly applied is hampered by methodological pitfalls that impede the interpretation of the surveillance findings [2].

First, antibiotic utilization measurement using the number of patient bed days (BDs) as denominator may give results and interpretations that differ from those obtained when the number of patient discharges is used. By applying both denominators, a better understanding of the temporal trends in antibiotic use can be gained [3–5].

Second, the World Health Organisation (WHO)-derived system of defined daily doses (DDDs), although internationally accepted as units of measurement for drug utilization, is not always suitable for showing

\* Correspondence: jobhau57@gmail.com

<sup>1</sup>Department of Infectious Diseases, Oslo University Hospital Trust, Oslo, Norway

Full list of author information is available at the end of the article

antibiotic use in hospitalized patients because the WHO doses may differ from the recommended antibiotic doses or the doses that are actually prescribed [6,7]. Alternative units have been considered [8,9]. In a recent study, we found a marked difference between WHO defined doses (WHO DDDs) and doses recommended in hospital guidelines, especially for the penicillins [10]. The discrepancy had consequences for the interpretation of the data on antibiotic use and we suggested that WHO DDDs should be supplemented with hospital-adjusted defined daily doses (haDDDs) in the surveillance of antibiotic use.

A further challenge in surveillance methodology is to identify factors that affect the use of antibiotics in hospitals. Few studies have addressed this issue. The aim of the present study was to investigate, by use of a national surveillance data set, the extent to which relevant, validated hospital- and patient-related variables can explain differences in antibiotic use.

## Methods

### Study hospitals (Health Enterprises, HEs)

We registered data on antibiotic use in the period from 2006 to 2011 (six years) for the 19 public HEs (five university-affiliated and 14 large general HEs) and three large private HEs in Norway. Each public HE consists of one to seven hospital units and covers a complete and comparable spectrum of specialties, except specialized units for transplantation, heart surgery, neurosurgery, burns and multitrauma that are established only at the university hospitals. The three private institutions include mainly general internal medicine and surgery and intensive care units. We excluded four private institutions with specialized functions for elective orthopaedics and rheumatology, cardiac surgery and rehabilitation, and all psychiatric and drug abuse institutions.

Ideally, analyses of antibiotic use should be performed at the level of hospital units, and the distribution of clinical specialties within each hospital should be known. However, at present administrative and clinical data of this kind are not routinely available from official and validated national sources. The lowest level at which this information may be acquired is the HE. Consequently, data on antibiotic use were analysed for whole HEs.

### Antibiotic use

We have previously reported the method for antibiotic data acquisition [10]. Briefly, we acquired data on hospital antibiotic use from a national pharmacy database. The data set was processed in a Microsoft Excel spreadsheet and further analysed in the statistical program Stata version 12 (StataCorp LP, College Station, TX). All systemic antibacterial agents except methenamine included in the Anatomical Therapeutic Chemical (ATC) DDD group J01 were registered. From other ATC DDD

groups, we included oral vancomycin, rifampicin and oral metronidazole.

Data on antibiotic use was expressed in DDDs using the 2011 WHO ATC/DDD classification [11]. DDDs were related to length of stay, which was measured in BDs, defined as the date of discharge minus the admission date. The number of patient discharges was used as an additional denominator for measure of antibiotic use [12].

In a previous study, we adjusted the WHO DDDs for a number of antibiotic substances [10]. These DDDs, designated haDDDs, were based on dose recommendations outlined in regional and national antibiotic guidelines [13]. The same haDDD values supplemented the WHO DDDs in the current study.

### Dependent (outcome) variables

Total antibiotic use ("all antibiotics") in the period 2006 to 2011 for the 22 HEs was the main dependent variable in the regression analyses. We also designated two subgroups as dependent variables: use of "broad-spectrum antibiotics" (second- and third-generation cephalosporins, fluoroquinolones, carbapenems, and penicillins with enzyme inhibitors) and use of "all penicillins" (penicillinase sensitive, penicillinase resistant and extended-spectrum penicillins). Each of these three antibiotic groups was analysed using the following measurement units: DDD/100 BDs, DDD/100 discharges, haDDD/100 BDs and haDDD/100 discharges.

### Independent variables

Administrative data and candidate explanatory variables for each HE were derived from publicly available on-line databases maintained by Statistics Norway [14]. For the regression analyses, we included independent variables that were considered clinically plausible and thus possibly associated with antibiotic use. Moreover, we required the variables to be clearly defined, quality assessed by a recognized national body, and easily accessible. These requirements were set to establish a reproducible, robust data set of optimal quality.

The 11 continuous variables (Table 1) were: per cent of hospital stays lasting < 2 days, per cent of hospital stays lasting > 10 days, number of physicians per 100 hospital beds, number of registered nurses per 100 hospital beds, per cent of discharges with a cancer ICD-10 main diagnosis, per cent of discharges with an infectious diseases ICD-10 main diagnosis, per cent of discharges with a surgical main diagnosis-related group (DRG), per cent of discharges with a medical main DRG, number of day care treatments, number of ambulatory consultations for all patients and number of ambulatory consultations for patients with infectious diseases (the last three variables measured per 100 hospital beds). The variables for day care and ambulatory patients were included because

**Table 1 Measurement units and value ranges for continuous variables entered into 12 linear regression models**

Continuous variables	Unit	Data point <sup>a</sup> range	Mean
Hospital stay < 2 days	% of discharges	24.5–40.5	32.4
Hospital stay > 10 days	% of discharges	5.2–17.3	9.7
Number of physicians <sup>b</sup>	per 100 hospital beds	38.8–128.3	63.9
Number of nurses	per 100 hospital beds	132.5–300.1	197.6
ID <sup>c</sup> main ICD-10 diagnosis	% of discharges	1.6–6.0	2.9
Cancer main ICD-10 diagnosis <sup>b</sup>	% of discharges	3.6–17.1	8.0
Surgical DRGs	% of discharges	18.0–39.8	27.5
Medical DRGs <sup>b</sup>	% of discharges	46.4–79.6	65.9
All ambulatory consultations <sup>b</sup>	per 100 hospital beds	89.9–543.3	327.6
ID <sup>c</sup> ambulatory consultations <sup>d</sup>	per 100 hospital beds	0.5–7.7	2.7
Day-care treatments <sup>d</sup>	per 100 hospital beds	10.1–79.5	35.9

<sup>a</sup>132 data points: six years of 22 Health Enterprise's annual data.

<sup>b</sup>Variable removed from the regression models due to collinearity.

<sup>c</sup>ID: (any) infectious diseases.

<sup>d</sup>Variable included in model, but not significantly associated with antibiotic use.

these patients were given antibiotics from the same ward stock as the in-patients.

Three categorical independent variables were also included (Table 2). These were university versus non-university affiliation, size of the HE (<300 hospital beds, 300–600 beds and > 600 beds) and geographical region (i.e. belonging to one of four Norwegian Health Regions).

All HEs used the same DRG version based on the WHO ICD-10 classification (NordDRG, version NOR PR1) during the study period. A surgical main DRG denotes a hospital stay during which a procedure was performed in an operating theatre. A medical main DRG was registered when no such procedure took place.

### Statistical analyses

Collection of the annual data on antibiotic use for 22 HEs over six years resulted in data sets containing 132

observations. Analyses were done with Stata statistical software version 12 (StataCorp LP, College Station, TX). For correlations between continuous variables, Pearson correlations (Stata procedure: 'pwcorr') was used. Since our data were normally distributed and the dependent variables continuous, we analysed 12 different multiple linear regression models (procedure: 'regress'). The same 14 independent variables were introduced in all regression models.

To account for possible dependence of observations within the individual HEs, that is to say dependence related to repeated and possibly correlated annual measures for the 22 HEs, we performed robust linear regression analyses with HEs as clusters (variance estimator option 'cluster').

In a stepwise approach, a test for collinearity of the independent variables (i.e. the extent to which the variables are related to each other) was performed to fit the final model. We used the variance inflation factor (vif) which tests for multivariate multicollinearity (procedure: 'estat vif'). In each regression step, the variable was excluded that had the highest vif, i.e. for which the least amount of its variance was associated with the outcome. This was repeated until no variable had a vif > 5 [15].

Because of a relatively large number of independent variables, the adjusted R square ( $aR^2$ ) was calculated for each regression model to show how well it fitted the data. For all analyses,  $aR^2 > 0.3$  was considered a strong correlation. A two-tailed *P*-value < 0.05 was set as a limit for statistical significance. To assess the unique contribution of each independent variable to the increment in  $aR^2$  in the final models, a conservative semi-partial  $R^2$  was calculated for each variable using Stata procedure 'pcorr' [15].

**Table 2 Description of three categorical variables<sup>a</sup> entered into 12 linear regression models**

Variables (No. of data points)	% of beds	% of bed days	% of discharges	Average HE stay (d)
University HEs <sup>b</sup> (30)	40.6	40.7	38.5	4.9
Non-university HEs (102)	59.4	59.3	61.5	4.5
Health Region 1 (60)	54.0	54.2	55.5	4.5
Health Region 2 (30)	20.3	20.8	20.5	4.7
Health Region 3 (18)	14.3	14.5	13.8	4.8
Health Region 4 (24)	11.4	10.4	10.2	4.7
HEs < 300 beds (35)	9.0	8.6	8.3	4.8
HEs 300–600 beds (50)	31.0	31.7	33.3	4.4
HEs > 600 beds (47)	60.0	59.7	58.5	4.7

132 data points (22 HEs<sup>b</sup> over 6 years) for each independent variable.

<sup>a</sup>Of the three categorical variables, only university affiliation was independently associated with antibiotic use in eight of the 12 regression models.

<sup>b</sup>HE = Health Enterprise.

## Results

### All antibiotic and broad-spectrum antibiotic use

From 2006 to 2011, the mean annual use, measured by WHO DDDs per 100 bed days, increased for “all antibiotics” from 62.7 to 73.0 and for “broad-spectrum antibiotics” (BSAs) from 15.4 to 18.7 (Figure 1). For each year a lower level was registered for university HEs than for non-university HEs, all specialties combined, with regard to both all antibiotic use and BSA use. However, for BSA use this difference diminished during the study period. For all antibiotic use and BSA use related to number of discharges no significant increases were found during the period (data not shown).

### Multivariate regression analyses

Fourteen independent variables were entered into the multiple linear regression models, of which four were removed from the analyses because of collinearity: medical DRGs, infectious diseases ambulatory consultations, cancer main ICD-10 diagnosis, and number of physicians. Of the remaining ten variables that were included in the models, six were found to be independently and significantly correlated with antibiotic use. A correlation was found for between two and five of these six variables depending on the outcome measure, i.e. one of the 12 combinations of antibiotic group and units of measurement (Tables 3 and 4).

We found that for all regression models, except for BSA use measured in WHO DDDs and haDDD per 100 discharges, the  $ar^2$  equalled or significantly exceeded 0.3, which indicates that the overall models fitted the data well [15].

### Hospital characteristics and geographical area

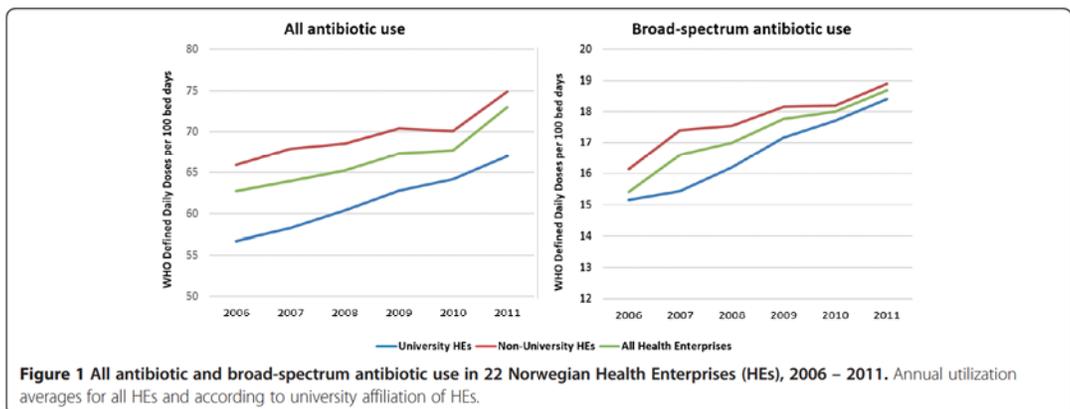
Of the three categorical variables (Table 2), only a university affiliation of the HE was independently associated with antibiotic use (Tables 3 and 4). A university affiliation

of the HE was strongly and negatively correlated with the use of all antibiotics and use of BSAs, both when BDs and discharges were used as denominator. No significant difference was found between university and non-university HEs with regard to penicillin use. The lower level of utilization in university HEs, measured in WHO DDDs/100 BDs, amounted to  $-11.8$  for all antibiotics and  $-2.7$  for BSAs (Table 3). University HE status strongly affected the results by exhibiting a high unique explanatory strength (4%–13%), particularly with the use of BDs as denominator.

### Physician and nurse staffing and the length of hospital stay

The variable describing the rate of physicians per hospital bed was found redundant in the regression analyses because of collinearity. By contrast, a change in the number of nurses per hospital bed correlated positively and strongly with all antibiotic use and all penicillin use, demonstrated by all four measurement units, but only marginally with BSA use measured with haDDD. One unit change between HEs of nurse staffing rate (inter-HE range, 167.6 nurses/100 hospital beds, Table 2) was independently associated with a difference of 0.17 DDDs/100 BDs for all antibiotics and of 0.1 DDDs/100 BDs for all penicillins (Table 3).

A positive and moderate to strong correlation with antibiotic use was found for the two variables characterizing the length of hospital stay. The proportion of hospital stays of  $<2$  days was significantly correlated with increased antibiotic use in relation to 100 BDs (Table 3). In particular, the percentage of short hospital stays correlated strongly with high BSA use both for DDDs and for haDDD, and the variable contributed 7% and 8% to the observed variances in the two models, respectively. A change of 1% in the proportion of short hospital stays resulted in a dose change of 0.3 for both indices. A high proportion of hospital stays  $>10$  days correlated



**Table 3** Explanatory factors significantly related to antibiotic use (number of bed days as denominator) in Norwegian Health Enterprises, 2006–2011, derived from six multiple linear regression models

Independent variables	WHO DDDs/100 bed days			Hospital-adjusted DDDs/100 bed days		
	All antibiotics	Broad-spectrum <sup>a</sup>	All penicillins <sup>b</sup>	All antibiotics	Broad-spectrum <sup>a</sup>	All penicillins <sup>b</sup>
<b>Overall model, R<sup>2</sup> (adjusted R<sup>2</sup>)</b>	<b>0.49 (0.43)</b>	<b>0.40 (0.33)</b>	<b>0.55 (0.50)</b>	<b>0.43 (0.37)</b>	<b>0.36 (0.30)</b>	<b>0.59 (0.54)</b>
<b>Infect. disease ICD-10 main diag. (%)</b>						
Regression coeff. (95% C.I.)	5.35 <sup>***</sup> (2.33; 8.38)		3.83 <sup>***</sup> (1.34; 6.33)	2.86 <sup>**</sup> (1.00; 4.71)		1.56 <sup>**</sup> (0.59; 2.54)
Beta weight	0.47		0.45	0.41		0.44
Increment in R <sup>2</sup>	0.0690		0.0633	0.0509		0.0606
<b>Registered nurses per 100 beds</b>						
Regression coeff. (95% C.I.)	0.17 <sup>***</sup> (0.08; 0.26)		0.10 <sup>***</sup> (0.04; 0.15)	0.10 <sup>**</sup> (0.04; 0.17)	0.02 <sup>†</sup> (0.001; 0.04)	0.04 <sup>**</sup> (0.02; 0.06)
Beta weight	0.56		0.44	0.57	0.28	0.39
Increment in R <sup>2</sup>	0.1141		0.0706	0.1163	0.0293	0.0548
<b>Hospital stay &lt; 2 days (%)</b>						
Regression coeff. (95% confidence interval (C.I.))	0.81 <sup>†</sup> (0.04; 1.57)	0.31 <sup>†</sup> (0.05; 0.58)			0.29 <sup>†</sup> (0.04; 0.53)	
Beta weight	0.29	0.38			0.40	
Increment in R <sup>2</sup>	0.0422	0.0718			0.0829	
<b>University hospital (binary)</b>						
Regression coeff. (95% C.I.)	-11.82 <sup>**</sup> (-20.5; -3.2)	-2.65 <sup>***</sup> (-4.01; -1.29)		-8.22 <sup>***</sup> (-12.3; -4.1)	-2.72 <sup>***</sup> (-3.53; -1.91)	
Beta weight	-0.55	-0.41		-0.62	-0.49	
Increment in R <sup>2</sup>	0.1078	0.0607		0.1354	0.0868	
<b>Surgical DRG<sup>c</sup> per 100 beds</b>						
Regression coeff. (95% C.I.)		0.15 <sup>*</sup> (0.01; 0.30)		0.52 <sup>*</sup> (0.06; 0.97)		
Beta weight		0.29		0.48		
Increment in R <sup>2</sup>		0.0222		0.0589		

Significance levels: \*P &lt; 0.05, \*\*P &lt; 0.01, \*\*\*P &lt; 0.001.

<sup>a</sup>Broad-spectrum antibiotics: second- and third-generation cephalosporins, fluoroquinolones, carbapenems, and penicillins with enzyme inhibitors.<sup>b</sup>All penicillins: penicillinase sensitive, penicillinase resistant and extended-spectrum penicillins.<sup>c</sup>DRG: Diagnosis-related groups.

**Table 4 Explanatory factors related to antibiotic use (number of discharges as denominator) in 22 Norwegian Health Enterprises, 2006–2011, derived from six multiple linear regression models**

Independent variables	WHO DDDs/100 discharges			Hospital-adjusted DDDs/100 discharges		
	All antibiotics	Broad-spectrum <sup>a</sup>	All penicillins <sup>b</sup>	All antibiotics	Broad-spectrum <sup>a</sup>	All penicillins <sup>b</sup>
<b>Overall model, R<sup>2</sup> (adjusted R<sup>2</sup>)</b>	<b>0.71 (0.67)</b>	<b>0.30 (0.22)</b>	<b>0.68 (0.65)</b>	<b>0.71 (0.68)</b>	<b>0.34 (0.26)</b>	<b>0.72 (0.69)</b>
<b>Infect. disease ICD-10 main diag. (%)</b>						
Regression coeff. (95% confidence interval (C.I.))	30.6 <sup>***</sup> (15.9; 45.2)		21.9 <sup>***</sup> (10.0; 33.8)	16.4 <sup>***</sup> (7.5; 25.4)		8.95 <sup>***</sup> (4.3; 13.6)
Beta weight	0.44		0.45	0.36		0.44
Increment in R <sup>2</sup>	0.0588		0.0614	0.0406		0.0591
<b>Registered nurses per 100 beds</b>						
Regression coeff. (95% C.I.)	0.78 <sup>***</sup> (0.37; 1.20)		0.46 <sup>***</sup> (0.21; 0.72)	0.49 <sup>***</sup> (0.21; 0.77)		0.17 <sup>**</sup> (0.07; 0.27)
Beta weight	0.43		0.36	0.42		0.43
Increment in R <sup>2</sup>	0.0657		0.0463	0.0625		0.0357
<b>Hospital stay &gt; 10 days (%)</b>						
Regression coeff. (95% C.I.)	12.1 <sup>**</sup> (5.1; 19.2)	2.38 <sup>**</sup> (0.9; 3.86)	7.46 <sup>*</sup> (1.2; 13.7)	8.27 <sup>***</sup> (4.4; 12.2)	2.75 <sup>**</sup> (1.2; 4.3)	2.99 <sup>***</sup> (0.4; 5.6)
Beta weight	0.48	0.45	0.42	0.51	0.56	0.41
Increment in R <sup>2</sup>	0.0861	0.0753	0.0663	0.0956	0.1157	0.0616
<b>University hospital (binary)</b>						
Regression coeff. (95% C.I.)	-47.6 <sup>***</sup> (-84.6; -10.7)	-9.8 <sup>**</sup> (-15.5; -4.1)		-33.6 <sup>***</sup> (-51.1; -16.2)	-10.9 <sup>***</sup> (-14.5; -7.2)	
Beta weight	-0.36	-0.35		-0.39	-0.42	
Increment in R <sup>2</sup>	0.0458	0.0441		0.0545	0.0626	
<b>Surgical DRGs<sup>c</sup> per 100 beds</b>						
Regression coeff. (95% C.I.)				2.43 <sup>*</sup> (0.2; 4.6)		
Beta weight				0.35		
Increment in R <sup>2</sup>				0.0316		

Significance levels: \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001.<sup>a</sup>Broad-spectrum antibiotics: second- and third-generation cephalosporins, fluoroquinolones, carbapenems, and penicillins with enzyme inhibitors.<sup>b</sup>All penicillins: penicillinase sensitive, penicillinase resistant and extended-spectrum penicillins.<sup>c</sup>DRG: Diagnosis-related groups.

positively and strongly with antibiotic use in all six models using number of discharges as the denominator (Table 4). This variable contributed significantly to the observed variances in these models, particularly for BSA use where the explanatory strength was as high as 8% and 12% for WHO DDDs and haDDD, respectively.

#### Diagnosis-related variables

Two variables related to the medical condition of the patients were correlated with antibiotic use. The proportion of patient hospital stays with an infectious disease main ICD-10 diagnosis was highly significant ( $P < 0.01$ ) and strongly correlated (beta weights of 0.36 to 0.47) with all antibiotic use and with the use of penicillins, but not with BSA use. One percent change in the proportion of ICD-10 infectious diseases main diagnosis was associated with a difference between two HEs in all antibiotic use of 5.35 DDDs/100 BDs and in penicillin use of 3.83 DDDs/100 BDs (see regression coefficients, Table 3). However, the interpretation of this finding should take into consideration that the interval of the observed data range was only 4.4% (Table 1), i.e. the range of unit differences between HEs for this explanatory variable was narrow. Also of note, ICD-10 infectious diseases main diagnosis contributed uniquely to 4%–7% of the observed variances in the eight models (increments in  $R^2$ ).

The proportion of hospital stays with surgical DRGs contributed 6% and 3% to the overall variances in the models for all antibiotics use, measured with haDDD per 100 BDs and per 100 discharges, respectively. The proportion of surgical DRGs varied between HEs with an interval of 21.8% (Table 2) and each percentage difference between two HEs was associated with a change in all antibiotic use of 0.15 haDDD/100 BDs and 0.51 haDDD/100 discharges.

#### Discussion

An increase in all antibiotic use and BSA use observed during the six-year study period has been reported in more detail [10]. We have also previously, by use of another data set, reported sizeable differences in antibiotic use between various Norwegian HEs [16].

In the present study, we identified several factors that were associated with dissimilarities in antibiotic use between HEs in Norway. High levels of nurse staffing, a high proportion of hospital stays with an infectious disease main ICD-10 diagnosis or a principal surgical DRG, and high proportions of short or long hospital stays were associated with increased antibiotic use. On the contrary, university affiliation was strongly associated with lower antibiotic use. The other hospital-associated variables—hospital size and geographical location—were not correlated with the levels of antibiotic use.

A main finding was the robustness that these variables exhibited across all models. Regardless of the measurement unit, with few exceptions the same explanatory variables were significantly related to antibiotic use within each of the three outcome (antibiotic) groups. Thus, in our opinion, the variables are valid for the evaluation of antibiotic surveillance results when different units of measurements are applied [9,11].

Our finding that the university HEs had significantly lower consumption of antibiotics than non-university hospitals in all models may seem surprising. For example, it contrasts the result of a German study of 145 acute care hospitals where regional variances in all antibiotic use were investigated [17]. Regional variances were not identified, but higher levels of use correlated significantly with hospital university affiliation. However, the German study did not include all specialties of the university hospitals but targeted only high-consumption units (surgical and internal medical wards, intensive care and haematology/oncology units). Contrary to this, our analyses were done on whole HEs because administrative data on the level of medical specialties were not available for the period in question.

The most probable explanation for the discrepancy is the relatively large subset in our university hospitals of units with a low usage of antibiotics, such as maternity/obstetric units, rehabilitation wards and paediatric specialties.

In support of this view is an additional analysis, which we undertook of a published data set for the period 2002–2007 [16]; this data set contained information about the various specialties. We found that the proportion of bed days in core units, out of all HE bed days, were significantly lower in university hospitals than in non-university hospitals (64% versus 79%; other data of the analysis not shown here). Furthermore, the use of antibiotics in core units was similar in university and non-university hospitals. Also, the antibiotic utilization level was almost four-fold higher in core units than in other units.

A French study also lends support to the explanation above [18]. In a study of 77 public hospitals, it was found that the relative number of patient days spent in internal medicine, surgical and intensive care units could explain most of the variability in antibiotic utilization. The authors concluded that there is a need to establish country-specific factors to aid interpretation of surveillance results. This is in accordance with our view that separate analyses should be carried out for university and non-university institutions.

Our finding of a strong positive correlation between high levels of nurse staffing and antibiotic use does not imply a causal relationship, but rather that high nurse ratios may be a surrogate marker for high proportions of

severely ill patients [19]. In general, higher nurse staffing is related to higher levels of intensive care and more patients with complicated medical conditions.

Both shorter stays (<2 days) and longer stays (>10 days) were strongly associated with increased BSA use. It appears that the proportion of short hospital stays should be used as an adjustment factor when interpreting surveillance results using number of BDs as the denominator. By contrast, longer stays have an impact on the results when the number of discharges is the denominator. A possible explanation for the positive correlation between short stays and BSA use may be more extensive empiric antibiotic treatment on hospital admission, before culture results and other diagnostic results are available. The correlation to prolonged hospital stays may be explained by more frequent BSA use in patients treated for complicated conditions. That short hospital stays are linked to extensive utilization of antibiotics is consistent with the finding in an Israeli study where one-day hospitalizations were associated with high consumption of antibiotics [20].

The strong relationship between an infectious disease main ICD-10 diagnosis and all antibiotic and all penicillin use is plausible. The reason why this variable showed no independent association with BSA use may be related to a sparse data set, as use of BSAs in Norwegian hospitals, although exhibiting an alarming increase, is still limited [16]. In addition, in severely ill patients for whom BSAs are extensively used, a serious underlying condition rather than the superimposed infections tends to be registered as the main diagnosis.

A positive correlation between all antibiotic use and surgical DRGs may reflect a high consumption of antibiotics for preoperative prophylaxis and for treatment of postoperative infections. The finding that surgical services were associated with higher antibiotic use than medical services may seem unexpected since the latter are often considered more antibiotic-intensive units. However, this opinion could be challenged. Of note, a strong association was only found when haDDD was applied, not with the use of WHO DDDs. In a previous study, we have shown that the use of haDDD reflects hospital prescription recommendations better than WHO DDDs. Among other things, an underestimation of the proportion of metronidazole, cefalotin and doxycycline use, which appears when WHO DDDs are applied, is abrogated with use of haDDD. These drugs are used extensively – and cefalotin almost exclusively – for surgical prophylaxis in Norwegian hospitals [10,13]. Accordingly, more nuances are needed when comparing medical and surgical departments.

The lack of data on the distribution of medical specialties within the various HEs may be considered a limitation of our study. To request these administrative data

from each HE would be a task not compatible with a routine national surveillance and, moreover, doubts might be raised with regard to the quality of locally obtained data. In addition, a correct allocation of patients to their specialties merely based on the wards designation is made difficult because of increasingly complex internal logistics in hospitals, mainly resulting from space limitations and task sharing between departments. However, in the future antibiotic data may be more reliably linked to specialties through electronic prescribing modules integrated in patient-administrative systems.

Another potential limitation is the fact that we were not in possession of any specific parameter defining the severity of illness. A main challenge in the benchmarking of hospital performance, including the use of antibiotics, is to adjust for patient case-mix [21]. However, to date no case-mix model has been generally and unambiguously endorsed. Moreover, certain limitations are present in studies investigating case-mix for limited time periods [22] or case-mix based on repeated prevalence surveys [23]. It should also be noted that the longitudinal studies discussed above [18,20] examined specific clinical variables and morbidity indices, such as the Charlson score [24], but none were found to be independently correlated with antibiotic use.

Finally, we have not considered any hospital data on antibiotic resistance. On a national scale, antibiotic resistance in hospital- or community-acquired pathogens is unlikely to be a major determinant for differences in antibiotic use. The reason for this is that the prevalence of resistance in Norwegian hospitals remains low [16,25].

A particular strength of our study is the inclusion of all Norwegian hospitals and the long observation period of six years. In addition, the independent variables investigated were based on official information from validated and easily available national sources, which makes them applicable for a routine surveillance system. To our knowledge, this is the first study to apply this kind of data set.

Furthermore, with regard to the statistical analyses we assessed the possible non-independence of repeated measures within HEs. The possibility of such non-independence made us introduce HEs as clusters in the regression models. However, the results obtained by use of this robust model were largely the same as those found with a standard multiple regression technique (data not shown).

Other outcome variables related to antibiotic utilization, for example health-care associated infections [26-28] and antibiotic-resistant infections [29], have been investigated for the purpose of adjusting for inter-hospital differences. Probably, these methods may be applicable also for benchmarking of hospital antibiotic use.

Although the factors identified in our study contributed substantially to differences in utilization of antibiotics in

hospitals, there is still a sizable residual variance (30%–50% for all antibiotic use and 60%–70% for BSA use) that cannot be explained by these factors. Of these non-identified factors, attitudes and personal preferences of leading prescribing physicians are probably of special relevance [30]. Medical culture in general, levels of education, whether or not guidelines exist, and where they do, their content and quality, are elements that should be considered. Particular attention should be given to the use of BSAs because their use may lead to the development of resistant microbes. There is a need for heightened awareness with regard to the consequences of untoward use of these antibiotics.

Almost none of the explanatory factors demonstrated in this study are modifiable through interventions by health care workers or hospital administrators. However, it is crucial to reveal inappropriate antibiotic use and to establish prudent prescription behaviour [31,32]. Knowledge about existing non-modifiable conditions provides a much-needed in-depth understanding of antibiotic surveillance results. With this background knowledge, it becomes easier to identify which findings are related to inappropriate prescribing practices.

## Conclusions

While several strategies may be used to achieve a prudent use of antibiotics in hospitals [33], one initial step should be to identify the factors that are not prescriber related. Adjustments for non-modifiable factors, such as the ones we have established, may increase the confidence in observed surveillance results. This method thus enables us to better identify and target explicit areas for intervention measures.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

JBH conceptualized the project, performed literature search, collected and analysed data, responded to reviewers and wrote the first and revised drafts of the manuscript; DB and MW contributed to literature search, interpretation of data analyses and revision of drafts; ÅR contributed to analysis and interpretation of data, response to reviewers and revision of the drafts. All authors read and approved the final manuscript.

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## Author details

<sup>1</sup>Department of Infectious Diseases, Oslo University Hospital Trust, Oslo, Norway. <sup>2</sup>Microbiology Section, Laboratory Centre, Vestre Viken Hospital Trust, Drammen, Norway. <sup>3</sup>Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. <sup>4</sup>Department of Pharmacology, Oslo University Hospital Trust, Oslo, Norway.

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