# *Antimicrobial drug use in hospitalized children*

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# *Antimicrobial drug use in hospitalized children*

***Antibioticagebruik bij kinderen opgenomen in het ziekenhuis***
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op donderdag 14 april 2011 des middags te 12.45 uur

door

***Tik Bing Yves Liem***

geboren op 31 juli 1976 te St. Gallen, Zwitserland

| | |
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| Promotoren: | Prof.dr. A.C.G. Egberts |
| | Prof.dr. F. van Bel |
| Co-promotoren: | Dr. C.M.A. Rademaker |
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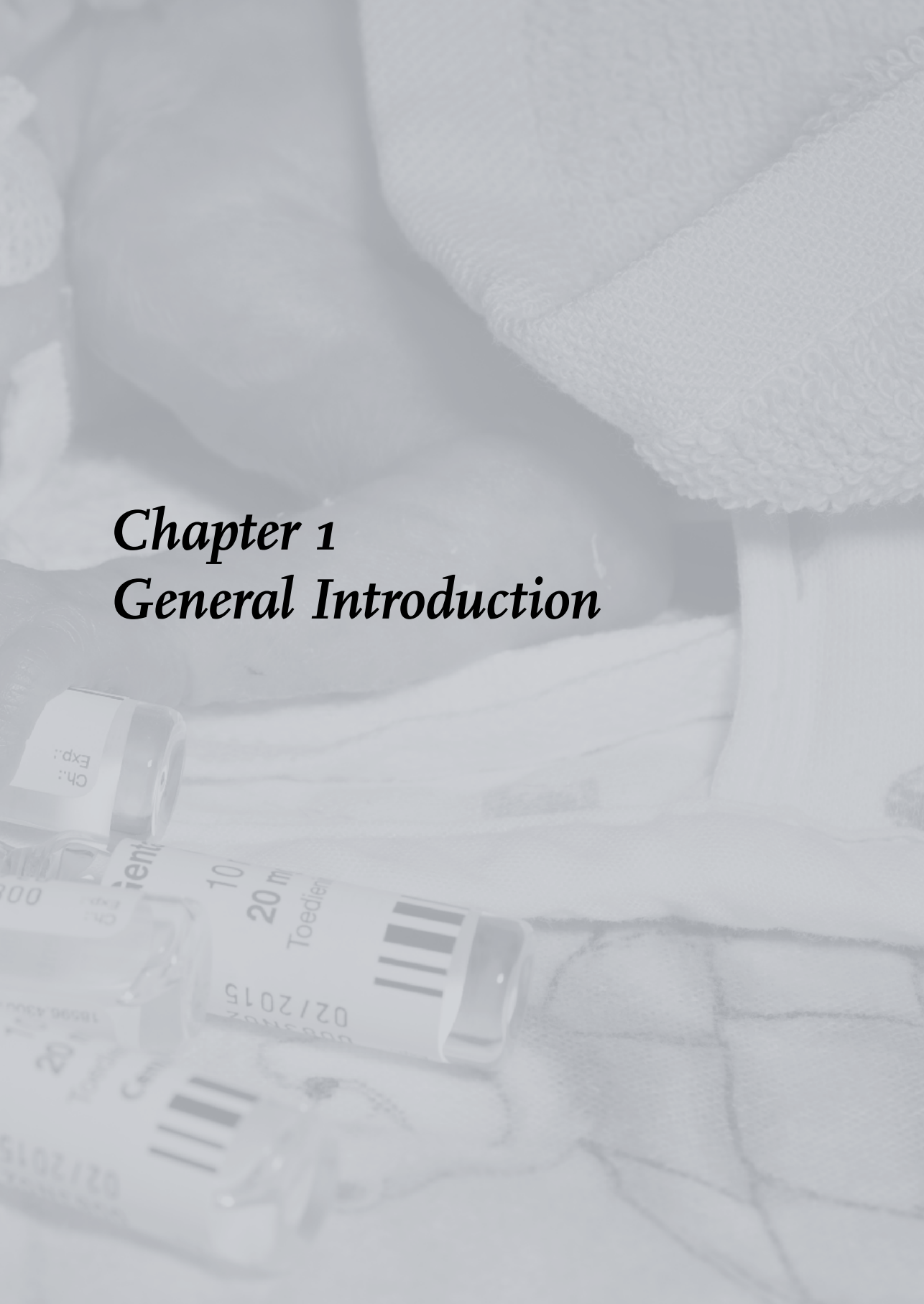

# *Chapter 1*
# *General Introduction*

The discovery of antibiotics represents one of the milestones in modern medicine and has contributed enormously to the reduced mortality and morbidity from infectious diseases. Likewise the resistance to antimicrobial drugs is a great threat to public health. The reasons for the rise in antimicrobial resistance are manifold and complex, but it has become clear that excessive and indiscriminate use of antibiotics increases the risk of the emergence and selection of antimicrobial resistant organisms. (1-5) Resistant pathogens cause infections associated with greater mortality and morbidity. (6) Hence, the development of antimicrobial resistance can often be considered as a societal adverse drug effect. (7) Moreover, antimicrobial resistance has a significant economic impact as therapy failure leads to the use of more expensive second-line therapy and longer hospital stays. (8) The threat of antimicrobial resistance has increased since it is paralleled with a nearly empty pipeline of new antibiotics since the late 1990s (9-11) which clearly hampers the management of infections caused by emerging multidrug resistant bacteria (cholera, tuberculosis etc.). Finally, it remains fascinating how microorganisms keep developing ingenious mechanisms to inactivate antibiotics (e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum beta-lactamases (ESBL)).

From this perspective, appropriate antibiotic use is essential to prevent the emergence of multidrug resistant microorganisms. (12) Several recommendations to avoid antimicrobial resistance have for this purpose recently been suggested. (7) In 1999 the EU Health Council adopted a resolution regarding future EU actions in terms of public and antimicrobial resistance. (13) In addition, in 2001 the World Health Organization (WHO) presented the Global Strategy for Containment of Antimicrobial Resistance, which recognized the worldwide implications of antimicrobial resistance (14) and in 2000, the Centres for Disease Control and Prevention launched the 12-Step Program to prevent antimicrobial resistance, which provides educational tools for clinicians as well as evidence-based interventions to decrease inappropriate antibiotic use and antimicrobial resistance among specific patient groups, including paediatrics. (15) Furthermore, in 2006, the Infectious Diseases Society of America (IDSA) published *Principles and Strategies to Limit the Spread of Antimicrobial Resistance*, which emphasized appropriate antibiotic use and infection control. (16) More recently, the European Centre for Disease Prevention and Control (ECDC) organized a European Antibiotic Awareness Day in 2010 in order to establish a wider awareness of appropriate antibiotic use across Europe. (17)

Fortunately, in the Netherlands the problem of antimicrobial resistance is smaller than in many other countries, but there are signs that resistance is increasing. (18) During the past decades several important theses from the Netherlands have addressed the issue of antibiotic use and resistance and have subsequently led to more interesting research in this field. (19-23) In 1996 the Dutch Working Party on Antibiotic Policy was founded (acronym: SWAB), which is an initiative of the Dutch societies of Medical Microbiology, Infectious Diseases and of Hospital Pharmacists. The SWAB has been assigned to coordinate the surveillance of antibiotic use and resistance in the Netherlands and to develop national guidelines for the use of antibiotics. (18)

All the above mentioned national and international initiatives aim at the same aspects, which are the development and implementation of systems for monitoring antibiotic use and resistance (and the relation between use and resistance), stimulating optimal and appropriate antibiotic practice and a successful infection control program to minimize the spread of antibiotic resistance. Although there are numerous methods for promoting good antibiotic practice focusing on prescribers, the community or both, the most successful approach is unknown. (24;25)

Overall the volume of use of antibiotics is highest in the community, but the density of the use of antibiotics is much higher within the hospitalized population, which increases the potential threat of antibiotic resistance in hospitals. Obviously, improving appropriate antibiotic use in hospitals is even more important for the control of resistance than in the community. Appropriate antibiotic use in hospitals aims at finding the right balance between their strong ability to diminish the mortality and morbidity of patients with infectious diseases and their potentially harmful consequences (such as resistance, serious adverse reactions, and drug interactions).

## Measuring antibiotic use in hospitals

Quantitative and qualitative data on the use of antibiotics in hospitals are useful to evaluate strategies that are implemented to contain antimicrobial resistance. Ideally, resistance rates also need to be measured. Measuring and comparing quantitative data on antibiotic use between hospitals, regions and countries is increasingly performed. (18;26-32) It is therefore essential to collect, analyse and present antibiotic use data in a standardized way and clearly define certain factors regarding antibiotic use in hospitals, e.g. make a selection of antibiotics to be studied, classify sources of data, decide the most appropriate unit of measurement and the required aggregation level. (33;34)

There are several sources of data on antibiotic use in hospitals. In general, antibiotic use is estimated by using pharmacy purchase records, obtained from invoices and delivery documents. These administrative data, presented for example in terms of costs or number of packages purchased, capture the total amount of antibiotic use in a specific institution. A major disadvantage of this method is overestimation of total antibiotic use, since these records may contain antibiotics not being dispensed or administered to the patient. Another data source of antibiotic use, which is used in hospitals and allow for more detailed presentation of the data, are dispensing data, which also overestimates total use as antibiotics being dispensed to the patient may not be administered. (34)

A next important key factor of measuring antibiotic use in hospitals, which needs to be clearly defined, is the best unit of measurement. Although the WHO recommends to use the Defined Daily Dose (DDD) to quantify in various settings and to compare drug use between (international) settings (35;36), there is an active debate on whether this is really the best unit of measurement of antibiotic use in hospitals. The DDD is the assumed average maintenance dose per day for a drug in its main indication for adults and is commonly expressed with a certain population size denominator such as patient days, bed days, admission days, inhabitant days. The DDD is overall well-accepted since it is generally applicable and comparison of the amount of drug use between different (international) settings and between different drugs based on grouped dispensing data is feasible without requiring utilization data on the individual patient level. The DDD methodology, however, has also some limitations, e.g. the DDD may change over time and above all, the DDD neither reflects the recommended, nor the actual prescribed daily dosage (PDD) for individual patients or specific patient populations (children).

## Antibiotic use in specific risk population: neonates

Valid data on the use of antibiotics at the hospital level are crucial for the interpretation of prescribing habits, the evaluation of compliance with clinical guidelines and the relation with resistance, but these data might be too crude for identifying subtle trends in antibiotic use of specific patient populations. Therefore, monitoring antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients; surgical and nonsurgical patients) is warranted. In this way relevant changes can be demonstrated that would be overlooked if hospital-wide data are aggregated into national trends.

Among the drugs most frequently used in neonatal intensive care units (NICU's) antimicrobial agents rank highest (37), since the multiple risk factors for infection in preterm immunocompromised infants result in a low threshold for the initiation of antimicrobial therapy. Neonatal infections, predominantly sepsis, are a significant cause of morbidity and mortality in the newborn, particularly in preterm, low birth weight infants. (38;39) Neonatal sepsis is a clinical syndrome characterized by systemic signs of infection and accompanied by bacteremia in the first month of life. (40) It is classified into two patterns of disease, early-onset and late-onset. Early-onset sepsis classically presents as a fulminant, systemic illness mostly during the first 24 hours of life with remaining cases presenting on the second day of life. The most important causative microorganisms in early-onset sepsis, i.e. group B streptococci and *Escherichia coli* (*E.coli*), are acquired hours before delivery from overt or occult rupture of membranes or from the birth canal during delivery. Mortality rates vary from 3% to as high as 50% in some series, particularly with Gram-negative microorganisms. Late-onset sepsis is variably defined as presenting after 72 hours to 6 days of life. The most predominant microorganisms responsible for late-onset sepsis, i.e. coagulase-negative staphylococci (CONS) and *Staphylococcus aureus* (*S.aureus*), comprise those acquired from the maternal genital tract and organisms acquired after birth. Mortality rates are in general lower than those for early-onset sepsis, but vary between 2-40%. The diagnosis of sepsis is confirmed when clinical signs of infection are present and the blood culture or culture of cerebrospinal fluid is positive. A blood culture positive for CONS is considered relevant when clinical signs of infection are accompanied by increased values of C-reactive protein (CRP), changed haematological parameters, and the time-to-positivity of the blood culture is within 24-48 hours. (41;42)

Although advances in neonatal intensive care have led to improved survival of premature infants, overall case-fatality rates from sepsis range from 2% to as high as 50%. (40) Numerous studies analyzed longitudinal trends in sepsis, which support the formulation of strategies to treat and prevent neonatal sepsis (43-47), ultimately leading to a decrease in morbidity and mortality. As infants with neonatal sepsis deteriorate quickly, punctual and effective treatment of neonatal sepsis with intravenous antibiotics is essential. In general, a penicillin-derivative combined with an aminoglycoside is recommended for suspected early-onset sepsis. For suspected late-onset sepsis it is usually recommended to prescribe vancomycin to cover CONS, although a recent Cochrane review revealed that there is inadequate evidence

from randomised trials in favour of any particular antibiotic regimen for the treatment of suspected late-onset sepsis. (48) For instance, in our NICU we use a first generation cephalosporin (cefazolin) based on susceptibility data (95% of all CONS isolates are susceptible to cefazolin (47)), which is combined with an aminoglycoside (gentamicin).

As mentioned earlier on, NICU's are an environment with high antibiotic pressure and consequently bear the risk of microorganisms that are colonizing infants of becoming resistant to various antibiotics. (49) Selection of multiresistant microorganisms colonizing the infants is potentially threatening, as it limits antibiotic treatment options, ultimately leading to a worst-case scenario in which infections can not be treated adequately. Antibiotic resistance among Gram-negative microorganisms that colonize neonates during hospitalization spectrum is an emerging problem in NICU's. (50;51) Moreover, a recent study has shown that repeated and/or prolonged antibiotic use in neonates resulted in an increase of hospital-acquired, antibiotic-resistant organisms such as MRSA, VRE, and multidrug-resistant Gram-negative rods. (52) Especially, the world-wide increasing incidence of ESBL-producing bacterial pathogens is a rising topic of interest. (53-56)

## Objective and outline of the thesis

The general aim of this thesis is to describe patterns of antibiotic use in hospitals, mainly but not exclusively in neonates, and its clinical consequences. This thesis consists of two parts. Firstly (*chapter 2*), studies describe the methodological aspects of measuring antibiotic use in hospitals.

- *Chapter 2.1* describes the implication of units of measurement for a significant understanding of trends in antibiotic use data with regard to antibiotic resistance risks.
- *Chapter 2.2* focuses on the variation in dosage recommendations for antibiotics in neonates provided by seven commonly used and well-established international textbooks.
- *Chapter 2.3* describes the problem of the defined daily dose (DDD) methodology for quantifying antibiotic use in the paediatric population.

*Chapter 3* of this thesis is devoted to studies describing the patterns and consequences of antibiotic use in hospitalized patients.

- *Chapter 3.1* describes trends in antibiotic use in hospitals in the Netherlands in the period 1997-2002. Data on antibiotic use are both expressed in DDD per 100 bed days and in DDD per 100 admissions.
- *Chapter 3.2* contains a national multicentre study in all ten tertiary care NICU's in the Netherlands focusing on the variation in antibiotic use.
- *Chapter 3.3* presents the findings of a study on trends in antibiotic use in our NICU over a period of 19 years.
- *Chapter 3.4* describes a study, which identified risk factors for ESBL-colonization in neonates.

In the last *chapter 4*, the key findings of the studies in this thesis are discussed in a broader perspective including some recommendations for future research.

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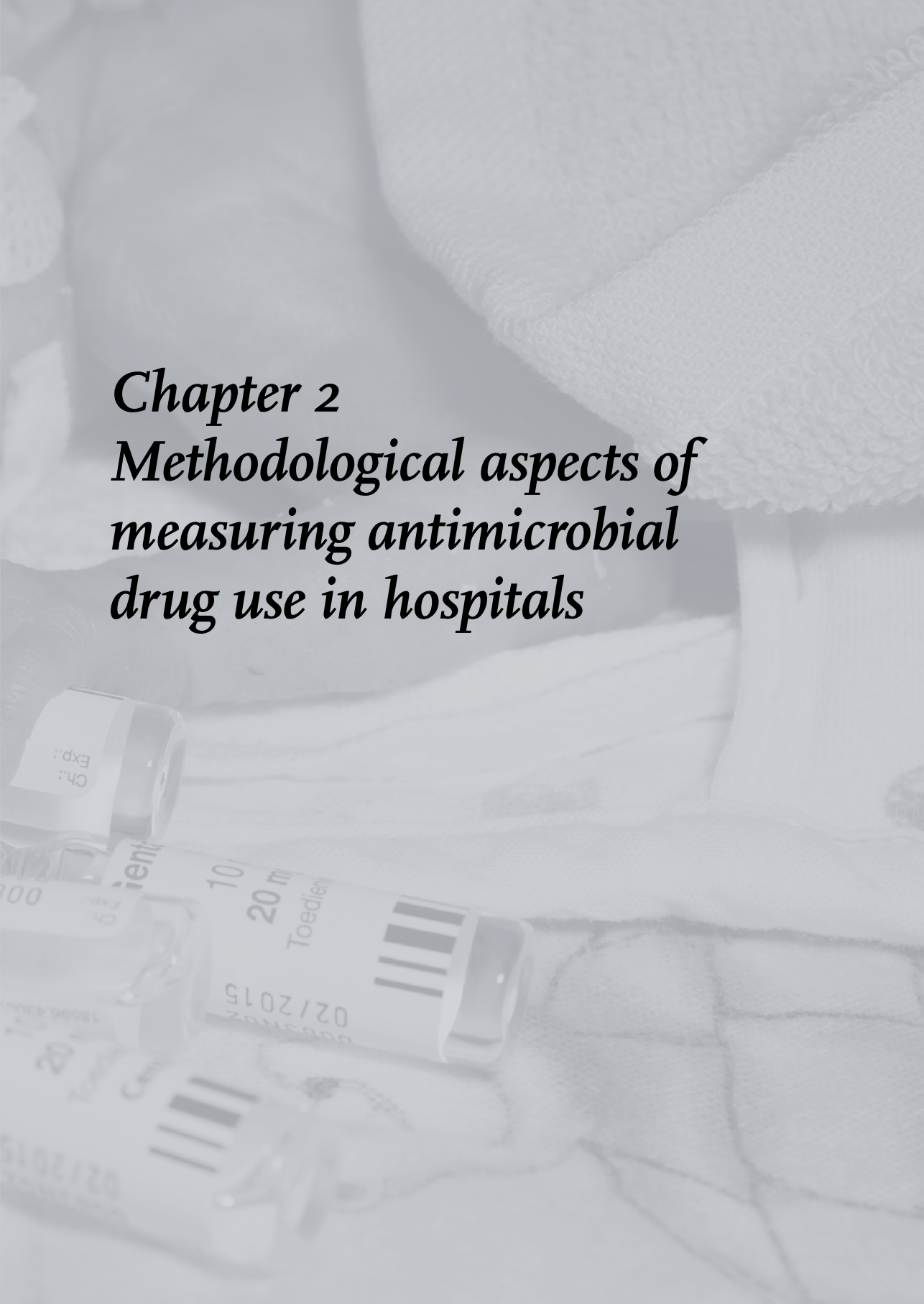
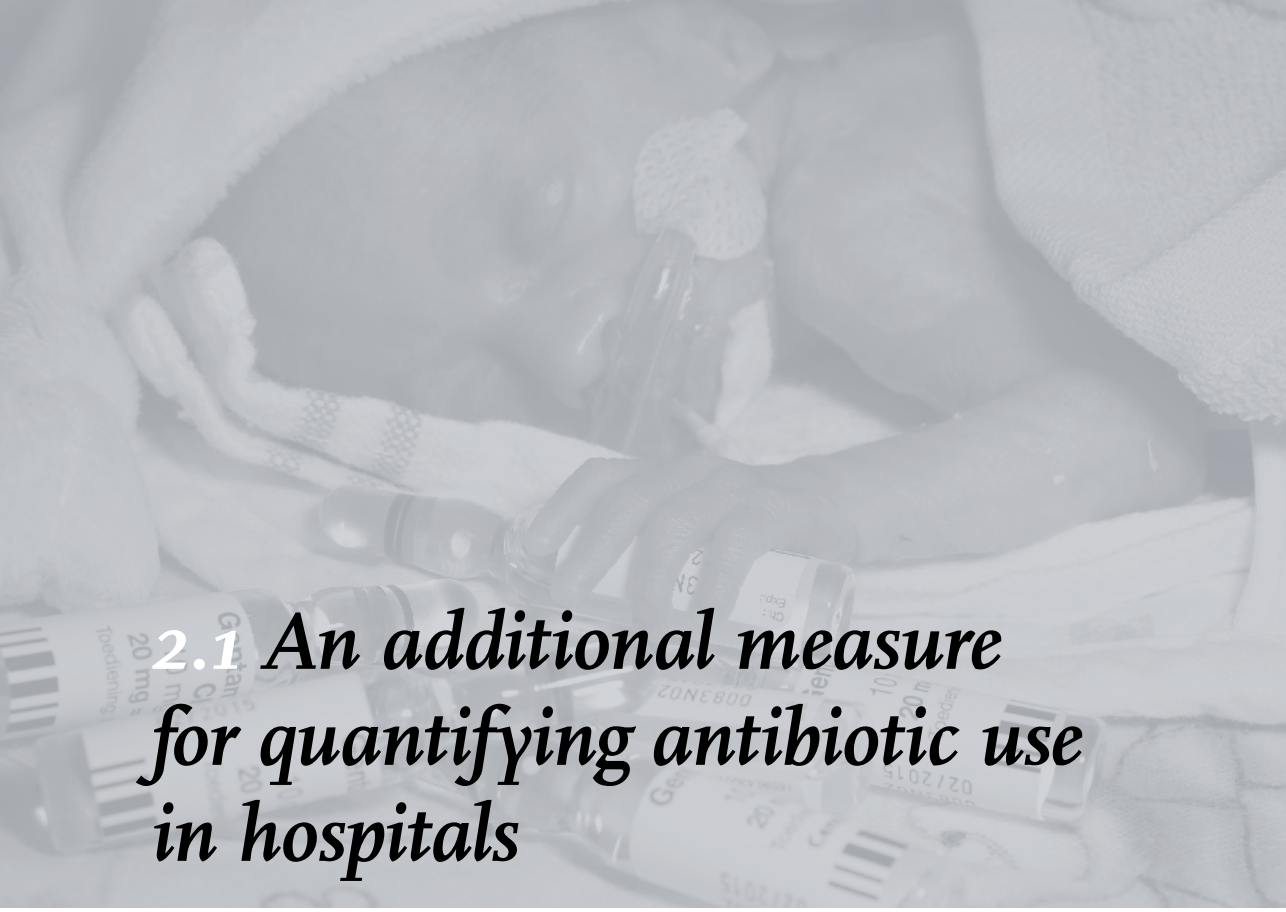


# *Chapter 2 Methodological aspects of measuring antimicrobial drug use in hospitals*



# 2.1 An additional measure for quantifying antibiotic use in hospitals

*Margreet Filius**
*T.B. Yves Liem**
*Paul D. van der Linden*
*Rob Janknegt*
*Stephanie Natsch*
*Arnold G. Vulto*
*Henri A. Verbrugh*

** The first two authors contributed equally to this study and share first authorship.*

*J Antimicrob Chemother 2005;55:805-8*

# Abstract

## Objective

The number of defined daily doses (DDD) per 100 patient days is often used as an indicator for the selection pressure exerted by antibiotics in the hospital setting. However, this unit of measurement does not fully describe the selection pressure and is sensitive to changes in hospital resource indicators. Additional information is required to facilitate interpretation of this indicator. The number of DDD per 100 admissions could be a valuable additional tool. The aim of this study is to investigate the importance of units of measurement in quantifying antibiotic use data with regards to antibiotic resistance risks.

## Methods

Trends in antibiotic use in acute care Dutch hospitals between 1997–2001 were studied. Antibiotic use was expressed in DDD per 100 patient days and in DDD per 100 admissions.

## Results

From 1997 to 2001, total systemic antibiotic use significantly increased from 47.2 to 54.7 DDD per 100 patient days, whereas expressed in DDD per 100 admissions it remained constant. Some individual antibiotics increases in DDD per 100 patient days were not accompanied by increases in DDD per 100 admissions and vice versa. The mean number of total DDD per hospital decreased (not significantly) between 1997 and 2001. The mean number of patient days, admissions and length of stay decreased significantly.

## Conclusion

Knowledge of variation in resource indicators and additional expression of the data in DDD per 100 admissions is imperative for a meaningful understanding of observed trends in antibiotic use expressed in DDD per 100 patient days. Further research is needed to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

# Introduction

The increasing prevalence of antibiotic-resistant bacteria poses a major threat to the health of hospitalized patients. (1) The relationship between emergence of resistance and antibiotic use and misuse is well recognized. It is evident that antibiotics affect not only the microorganism and the individual patient, but also the population as a whole. (2) At the hospital population level, three factors are important with respect to the selection pressure exerted by antibiotics. (3) First, the total amount of an antibiotic used in a particular geographical area (i.e. the entire hospital or a ward or unit) over a certain period of time. Secondly, the number of patients treated with the antibiotic (because they serve as the major 'sources' of resistant bacteria). Thirdly, the density of these patients, i.e. the proportion of patients on antibiotics in the hospital. Together these factors represent the selection density in the hospital environment. (3) As the selection density increases, the number of resistant strains in the hospital environment increases and the number of susceptible strains able to survive in this environment decreases. (3) This may facilitate the spread of resistant bacteria and resistance genes. Antibiotics may also exert their selective pressure after treatment, as antibiotics may affect the microbial community as long as they remain intact and at growth inhibitory levels. (3)

The World Health Organization (WHO) Collaborating Centre for Drug Statistics and Methodology recommends using the number of defined daily doses (DDD) per 100 patient days to quantify antibiotic use. (4) The DDD is a technical unit of measurement and corresponds to the assumed average maintenance dose per day, for the main indication of the drug, in adults. The number of DDD per 100 patient days has been used as a proxy for the selection density and is an indicator for the selection pressure exerted by antibiotic use in the hospital setting. However, this measure does not fully describe the actual selection density, since it does not provide information on the number and proportion of patients actually exposed to antibiotics.

Over the last decade several national surveillance systems on antibiotic use and/or resistance have been set up. (5-8) Critical assessment of the units of measurement used to quantify antibiotic use and discussions about the interpretation of these units are, however, rarely presented in the scientific literature. (9-11) Most of the surveillance systems use the number of DDD per 100 patient days to compare consumption rates over time and between hospitals, geographical regions and countries. In our view, conclusions drawn from these surveillance systems should be interpreted with care.

The number of DDD per 100 patient days does not fully address the selection density and is sensitive to changes in hospital resource indicators over time. Additional information is required to facilitate interpretation. The number of DDD per 100 admissions could be a valuable additional unit of measurement. The aim of this study is to investigate the importance of units of measurement in presenting antibiotic use data with regards to antibiotic resistance risks. We therefore compared and analysed trends in the use of antibiotics in Dutch hospitals between 1997 and 2001 expressed in both DDD per 100 patient days and in DDD per 100 admissions.

# Patients and methods

## Population

Data on the use of antibiotics in acute care Dutch hospitals between 1997–2001 were collected by means of a questionnaire distributed to Dutch hospital pharmacies by the Working Party on Antibiotic Policy (SWAB) (for source data see NethMap 2003 on-line at www.swab.nl). Pharmacies were requested to report on the annual consumption of antibiotics for systemic use, as defined by group J01 of the Anatomical Therapeutic Chemical (ATC) Classification system for the classification of drugs. Outpatient use and dispensing of antibiotics to nursing homes were excluded. For each hospital the annual number of admissions and days spent in the hospital (bed days) were recorded. The number of bed days was calculated by multiplying the number of admissions with the average length of stay or the number of beds multiplied by the average occupancy rate; the choice between these methods was dependent on the preference of the individual hospital administrations.

## Analysis

The ATC/DDD classification from the WHO, version 2002, was used to calculate the number of DDD of the various antibiotics. (4) The number of patient days was obtained by subtracting the number of admissions from the number of bed days, as the number of bed days overestimates actual treatment days by including both the day of admission and the day of discharge. For the period 1997–2001 an overall pooled mean (i.e. weighted mean) was calculated for each year by aggregating data on antibiotic use, patient days and admissions from all hospitals. The use of antibiotics was expressed in DDD per 100 patient days and in DDD per 100 admissions. Trends in antibiotic use and hospital resource indicators were studied by a mixed model for repeated measurements with the hospitals as cofactor. P values < 5% were considered statistically significant. All statistical analyses were performed using SAS 8.2 (SAS Institute, Cary, NC, USA).

# Results

In 1997 the total systemic use of antibiotics in Dutch hospitals was 47.2 DDD per 100 patient days, and use significantly increased to 54.7 DDD per 100 patient days in 2001 ($P < 0.001$) (*Table 1*). However, total systemic use expressed as DDD per 100 admissions remained constant (*Table 1*). The mean number of total DDD per hospital decreased (not significantly) from 67 176 to 59 129 (-12%).

Table 1. Use of antibiotics for systemic use (J01) in Dutch hospitals between 1997 and 2001 expressed in DDD per 100 patient days (DAY) and in DDD per 100 admissions (ADM)

| | Year | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1997 | | 1998 | | 1999 | | 2000 | | 2001 | | Trend 1997-2001 | |
| Class of antibiotic (ATC group) | DAY | ADM | DAY | ADM | DAY | ADM | DAY | ADM | DAY | ADM | P value DAY | P value ADM |
| Tetracyclines (J01A) | 1.6 | 13.4 | 1.6 | 13.2 | 1.7 | 12.8 | 1.6 | 12.2 | 1.6 | 11.2 | 0.996 | 0.514 |
| Penicillins with extended spectrum (J01CA) | 6.5 | 53.1 | 6.5 | 52.1 | 6.4 | 49.5 | 6.0 | 45.8 | 6.1 | 41.8 | 0.229 | <0.001 |
| Beta-lactamase-sensitive penicillins (J01CE) | 1.2 | 9.4 | 1.0 | 8.4 | 1.1 | 8.2 | 1.1 | 8.5 | 1.4 | 9.4 | 0.003 | 0.0885 |
| Beta-lactamase-resistant penicillins (J01CF) | 4.1 | 33.6 | 3.8 | 30.4 | 3.9 | 30.0 | 4.4 | 33.8 | 4.3 | 30.0 | 0.110 | 0.241 |
| Combinations of penicillins, including beta-lactamase inhibitors (J01CR) | 14.4 | 117.6 | 14.3 | 115.3 | 15.6 | 121.5 | 16.9 | 128.7 | 18.0 | 124.5 | <0.001 | 0.290 |
| Cephalosporins and related substances (J01DA) | 5.1 | 41.9 | 5.5 | 44.4 | 5.6 | 43.3 | 5.9 | 44.6 | 6.1 | 42.3 | <0.001 | 0.436 |
| Carbapenems (J01DH) | 0.43 | 3.5 | 0.38 | 3.0 | 0.33 | 2.5 | 0.44 | 3.3 | 0.35 | 2.4 | 0.398 | 0.722 |
| Trimethoprim and derivatives (J01EA) | 0.46 | 3.7 | 0.51 | 4.1 | 0.50 | 3.9 | 0.35 | 2.7 | 0.51 | 3.5 | 0.294 | 0.749 |
| Combinations of sulphonamides and trimethoprim (J01EE) | 2.6 | 21.1 | 2.6 | 20.6 | 2.5 | 19.1 | 2.4 | 17.9 | 2.3 | 15.6 | 0.062 | <0.001 |
| Macrolides (J01FA) | 1.9 | 15.4 | 1.9 | 15.5 | 2.2 | 17.2 | 2.1 | 16.2 | 2.3 | 15.6 | <0.001 | 0.265 |
| Lincosamides (J01FF) | 0.80 | 6.6 | 0.88 | 7.1 | 1.1 | 8.3 | 1.2 | 9.2 | 1.3 | 9.1 | <0.001 | <0.001 |
| Aminoglycosides (J01GB) | 2.0 | 16.0 | 2.1 | 16.9 | 2.0 | 15.8 | 2.2 | 16.6 | 2.0 | 14.0 | 0.214 | 0.766 |
| Fluoroquinolones (J01MA) | 4.0 | 32.7 | 4.4 | 35.3 | 5.0 | 38.9 | 4.9 | 37.2 | 5.5 | 38.0 | <0.001 | <0.001 |
| Glycopeptides (J01XA) | 0.42 | 3.4 | 0.42 | 3.4 | 0.44 | 3.4 | 0.51 | 3.9 | 0.46 | 3.2 | <0.001 | <0.001 |
| Total antibiotics for systemic use (J01) | 47.2 | 385.9 | 47.7 | 384.6 | 50.0 | 389.0 | 52.1 | 396.1 | 54.7 | 377.2 | <0.001 | 0.838 |

In addition, varying trends in antibiotic use were revealed by the two units of measurement for some subgroups of antibiotics and also for individual agents. For example, the use of beta-lactamase-sensitive penicillins, cephalosporins and macrolides increased significantly when expressed in DDD per 100 patient days, but not when expressed in DDD per 100 admissions; for penicillins with an extended spectrum and trimethoprim–sulfamethoxazole, a decrease was found when expressed in DDD per 100 admissions, but not per 100 patient days.

The use of penicillins in combination with beta-lactamase inhibitors, co-amoxiclav and piperacillin–tazobactam, increased significantly when expressed in DDD per 100 patient days. However, this increase was observed for piperacillin–tazobactam ($P = 0.003$) when only admissions were used as the criterion (data not shown).

The use of lincosamides and fluoroquinolones expressed in both DDD per 100 patient days and DDD per 100 admissions increased significantly. This increased use was due to significant increases in the use of clindamycin ($P < 0.001$) and ciprofloxacin ($P < 0.001$), respectively (data not shown).

Between 1997 and 2001 changes in hospital resource indicators were observed. The mean number of patient days per hospital decreased significantly from 142 339 to 108 128 (-24%; $P < 0.001$) and the mean number of admissions significantly decreased from 17 405 to 15 677 (-10%; $P = 0.02$). The mean length of stay decreased significantly from 8.0 to 6.9 days (-14%; $P < 0.001$).

## Discussion

The manner in which antibiotic usage is expressed does matter. Proper expression of antibiotic use is needed for the interpretation of prescribing habits, the evaluation of compliance with clinical guidelines and the linkage with antibiotic resistance data. The DDD system provides a convenient tool for the quantification of antibiotic use and allows comparisons between different settings, regions, or even countries. Different units of measurement can be used as denominator, depending on the questions posed. If antibiotic resistance development is the issue then the measure of antibiotic should be a reflection of the antibiotic selection pressure exerted. At the population level the selection pressure is thought to depend on the volume of antibiotics used in a particular geographical area, the number of patients exposed and the proportion of patients treated with antibiotics. (3) The denominator should thus preferably include information on all these factors.

In the present study, data on antibiotic use in Dutch hospitals between 1997 and 2001 were expressed using two different units of measurement, DDD per 100 patient days and DDD per 100 admissions. From our data it is evident that trends over time in DDD per 100 patient days did not always correlate with trends in DDD per 100 admissions. Differences in trends between the two units of measurement seem to be the result of changes in resource indicators over time. We measured a 24% decrease in the mean number of patient days per hospital. The mean number of admissions also decreased, but to a lesser extent (-10%). The mean length of stay decreased by 14%. The mean number of total DDD of antibiotics used also decreased (-12%). Taking these findings together we can easily understand the differences found when total use was expressed in DDD per 100 patient days (+16%) and in DDD per 100 admissions (-2%). Small discrepancies seem to be the result of the use of pooled and geometric means.

Without further information, an increase in DDD per 100 patient days might be interpreted as an actual increased use per patient. However, the number of DDD per 100 admissions remained constant. From our data we can only conclude that on average patients used the same number of DDD and were admitted to the hospital for a shorter period of time. This resulted in an intensification of antibiotic therapy per patient day.

An increase in the number of DDD per 100 patient days is often interpreted as worrisome with regards to the potential for antibiotic resistance development. However, in the Dutch situation, a constant use per patient combined with a significant decrease in the number of admissions are indicative for a

lowering of the selection pressure exerted by antibiotic use over the years. Moreover, an intensification of antibiotic therapy per patient day suggests a shortening of duration of antibiotic treatment. Short duration of therapy may lead to less selection of resistant microorganisms. (12)

It appears that the number of DDD per 100 patient days can only be used as a reliable and robust monitor of the selection density over time or between geographical areas when relevant hospital resource indicators remain constant. Furthermore, neither unit of measurement fully represents the selection density.

Neither DDD per 100 patient days nor DDD per 100 admissions indicates the number of patients exposed or the proportion of patients on antibiotics. It is arguable that the selection density does not best represent selection pressure or predict resistance development in a given geographical setting. For example, the number of exposed individual commensal microflora might best express selection pressure. However, there is a lack of studies to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

In conclusion, the data presented in this article showed that to understand trends in antibiotic use over time or between hospitals or countries, data should not only be presented in DDD per 100 patient days. Knowledge of variation in resource indicators and additional expression of the data in DDD per 100 admissions are imperative for a meaningful understanding of observed trends in antibiotic use expressed in DDD per 100 patient days. Further research is needed to determine the correlation between different measures of antibiotic use and the level of antibiotic resistance.

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# 2.2 Comparison of antibiotic dosing recommendations for neonates from established textbooks: paving the way for e-prescribing standards

*T.B. Yves Liem*
*Tannette G. Krediet*
*André Fleer*
*Toine C.G. Egberts*
*Carin M.A. Rademaker*

*Submitted*

# Abstract

## Objective

Incorrect dosing is the most frequent occurring prescribing error in paediatrics and antibiotics are the most frequently prescribed medicines. Computer physician order entry (CPOE) and clinical decision support systems can contribute to the reduction of medication errors. Although evidence-based dosing recommendations should be included in such systems, the necessary evidence is not always available and subsequently dosing recommendations mentioned in guidelines and textbooks are often based on expert opinion. The aim of this study is to compare dosage recommendations for antibiotics in neonates provided by seven commonly used and well-established international textbooks.

## Methods

Neonatal daily doses for the ten most frequently used antibiotics, classified by categories for birth weight and gestational age, were identified from seven well-respected textbooks in paediatrics/paediatric infectious diseases, and expressed as standardized average daily dosage.

## Results

Antibiotics with a wide therapeutic window (e.g. ampicillin, benzylpenicillin, ceftazidime and cefotaxime) showed greater variation in dosage recommendations compared to those with a small therapeutic window (e.g. meropenem, gentamicin, and vancomycin). The BNF showed larger variation in dosage recommendations compared to the other textbooks.

## Conclusion

Gold standard, expert opinion antibiotic dosage recommendations for neonates can be derived from important textbooks and guidelines for most, but not all antibiotics. Further exploration to overcome variation in dosage recommendations is necessary to obtain standardized dosage regimens and thus full benefit of CPOE and clinical decision support systems in neonatology.

# Introduction

The most common medication error in neonates is incorrect dosing. (1;2) Computer physician order entry (CPOE) and clinical decision support systems can contribute to the reduction of such medication errors and thereby increase patient safety. (3) To obtain full benefit of these systems, evidence-based dosing recommendations should be included, which unfortunately are not always available for neonates because of the lack of pharmacokinetic data and clinical trial evidence in this patient group. As a consequence, dosing in neonates is often based on clinical experience and expert-opinion.

Moreover, a multicentre study on paediatric antimicrobial prescribing in European hospitals demonstrated that the prescribed daily dose (PDD) in children increased with age and weight. Hence, standardization of paediatric daily doses for different paediatric age groups and neonates separately is necessary. (4) In this perspective, a first step in uniformity in neonatal antibiotic dosage recommendations was recently taken by us by means of developing a set of neonatal defined daily doses (NDDD's). (5)

The aim of this study is to compare the dosage recommendations for commonly used antibiotics in neonates from seven commonly used and well-established international paediatric textbooks.

# Methods

## Comparison of dosage recommendations for antibiotics

Based on a recent survey on antibiotic use in all ten Dutch tertiary care neonatal intensive care units (NICU's) (6), the ten most frequently used antibiotics in neonates in the Netherlands were selected: ampicillin, amoxicillin, amoxicillin-clavulanic acid, benzylpenicillin, flucloxacillin, ceftazidime, cefotaxime, meropenem, gentamicin and vancomycin.

A team of experts from our children's hospital, including a paediatrician-infectious disease specialist, medical microbiologist, neonatologist and hospital pharmacist, selected seven commonly used and well-established international textbooks in paediatrics and paediatric infectious diseases to be evaluated for dosage recommendations (5), namely: two general paediatric dosage handbooks and five paediatric infectious diseases handbooks:

- The British National Formulary for children, 2009 (BNF) (7)
- Pediatric Dosage Handbook (PDH), 2008 (8)
- Red Book, 2006 (9)
- Infectious Diseases of the Fetus and the Newborn Infant (Remington & Klein), 2006 (10)
- Principles and Practices of Pediatric Infectious Diseases (Long & Pickering), 2003 (11)
- Textbook of Pediatric Infectious Diseases (Feigin & Cherry), 2004 (12)
- Nelson's Pocket Book of Pediatric Antimicrobial Therapy (Nelson's), 2009 (13)

All intravenous dosage recommendations (recommended daily dosage, RDD) for neonates for the selected antibiotics mentioned in the included textbooks were collected, as well as any referenced evidence referring to original clinical studies in neonates.

In addition, to create uniformity among the dosage recommendations, these were (if possible) converted to the format 'mg/kg/day in x divided doses'. To avoid interpretation errors, age categories were unambiguously compared (i.e. dosage recommendations for different age-categories were excluded). Subsequently, to evaluate similarities and differences between the dosage recommendations, the average recommended daily dosage (ARDD) and standardized dosage recommendations to the ARDD was determined by the formula (RDD / ARDD *100%). To properly apply this formula, dosage recommendations with a range had to be mediated. In case of a dosage recommendation with a dosage range as well as an interval range

(e.g. 10 – 20 mg/kg/day every 6 to 8 hours) the limits were mediated as an ARDD. In the aforementioned example, the daily dose limits would be 30 - 80 mg/kg/day and the ARDD would be 55 mg/kg/day. Whenever a dosage recommendation was expressed in mg/day (and therefore was not directly comparable to the other recommendations), it was converted by the use of the nomogram for calculating body surface area in children. (8) Consequently, the dosage recommendation was adjusted to an average body weight for the child's specific age period. With this average body weight, the dosage recommendation was converted to an applicable format for the comparison.

As a primary condition for comparing dosage recommendations, at least four textbooks had to provide dosage recommendations for the specific antibiotic agent.

# Results

## Characteristics of textbooks

The BNF was the only textbook that included dosage recommendations for almost all ten selected antimicrobial agents (nine out of ten). Considering the included dosage recommendations, the BNF showed similarities to PDH. The BNF and PDH had more age-dependent categories for dosage recommendations (*Table 1*). In comparison to the other textbooks the Nelson's had a different format. This textbook approached dosing from indications rather than from drug substance.

Table 1. Characteristics of seven established textbooks in paediatrics and paediatric infectious diseases

| Characteristics | BNF (7) | PDH (8) | Red Book (9) | Remington&Klein (10) | Long&Pickering (11) | Feigin&Cherry (12) | Nelson's (13) |
|---|---|---|---|---|---|---|---|
| **Recommendations for neonates available** | yes | yes | yes | yes | yes | yes | yes |
| **Recommendations for preterms available** | yes | no | no | no | no | yes | yes |
| **Approach based on indication** | no | no | no | no | no | no | yes |
| **Approach based on antibiotic** | yes | yes | yes | yes | yes | yes | no |
| **Detailed age categorisation available** | yes | yes | no | no | no | no | no |
| **Literature references available** | no | yes | no | yes | yes | yes | no |

All textbooks included *neonatal* dosage recommendations. Only the BNF, Nelson's and Feigin & Cherry also had dosage recommendations for *preterm infants*. However, all textbooks used different age categories for both populations based on birth or current weight, gestational age (GA) or postmenstrual age (PMA).

Four textbooks used literature references regarding their dosage recommendations, i.e. PDH, Remington & Klein, Long & Pickering and Feigin & Cherry. The dosage recommendations in the latter textbook, however, were mainly based on those in Remington & Klein. The highest total number of references for each antibiotic agent in the textbooks was in Remington &

Klein, of which gentamicin had more than forty references. In each textbook with references, benzylpenicillin had the lowest number of references. Comparison of all available references illustrated that only a few were cited in common. Moreover, these common references were published before 2000.

## Dosage recommendations

In total 311 dosage recommendations were included for systematic comparison. Flucloxacillin, amoxicillin and amoxicillin-clavulanic acid were excluded because less than four textbooks included dosage recommendations for these agents. Therefore, seven of the initial ten selected antibiotics were evaluated (*Table 2*).

In this study the focus was on the variation in dosage recommendations of antibiotics for neonatal sepsis (*Table 2*). This table illustrated a substantial variation in dosage recommendations between the textbooks for ampicillin, benzylpenicillin, cefotaxime and ceftazidime. Concerning the dosing recommendations of the other antibiotics, i.e. gentamicin, meropenem and vancomycin, hardly any variation was shown between the textbooks.

*Figure 1* shows the variation in standardized dosage recommendations for each evaluated textbook. The BNF showed larger variation in dosage recommendations compared to the other textbooks. On the other hand, the Red Book demonstrated the least variation in dosage recommendations of all evaluated textbooks.

Table 2. Comparison of dosage recommendations of seven most commonly used antibiotics for sepsis in neonates from seven textbooks.

| | | Dose (mg/kg/day) | | | |
|---|---|---|---|---|---|
| **Name of antibiotic** | **Age group** | **BNF (7)** | **PDH (8)** | **Red Book (9)** | **Remington & Klein (10)** |
| **Ampicillin** | <7 days, ≤ 2000 g | 100* | 50* | 50-100* | 50* |
| | <7 days, > 2000g | 100* | 75* | 75-150* | 75* |
| | ≥ 1 week, ≤ 1200 g | 150-200* | 50* | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 150-200* | 75* | 75-150* | 75* |
| | ≥ 1 week, ≥ 2000 g | 150-200* | 100* | 100-200* | 100* |
| **Benzylpenicillin#** | <7 days, ≤ 2000 g | 83332 | 50000* | 50000-100000* | 50000* |
| | <7 days, > 2000g | 83332 | 75000* | 75000-150000* | 75000* |
| | ≥ 1 week, ≤ 1200 g | 125000 | 50000* | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 125000 | 75000* | 75000-150000* | 75000-150000* |
| | ≥ 1 week, ≥ 2000 g | 125000 | 100000* | 100000-200000* | 100000* |
| **Cefotaxime** | <7 days, ≤ 2000 g | 50* | 100* | 100* | 100* |
| | <7 days, > 2000g | 50* | 100-150* | 100-150* | 100* |
| | ≥ 1 week, ≤ 1200 g | 75-100* | n.a. | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 75-100* | 150* | 150* | 150* |
| | ≥ 1 week, ≥ 2000 g | 75-100* | 150-200* | 150-200* | 150* |
| **Ceftazidime** | <7 days, ≤ 2000 g | 25* | 100* | 100* | 100* |
| | <7 days, > 2000g | 25* | 150* | 100-150* | 150* |
| | ≥ 1 week, ≤ 1200 g | 50-75* | n.a. | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 50-75* | 150* | 150* | 150* |
| | ≥ 1 week, ≥ 2000 g | 50-75* | 150* | 150* | 150* |
| **Gentamicin** | <7 days, ≤ 2000 g | 5* | 5* | 5* | 5* |
| | <7 days, > 2000g | 5* | 5* | 5* | 5* |
| | ≥ 1 week, ≤ 1200 g | 5* | n.a. | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 5* | 5-7.5* | 5-7.5* | 7.5* |
| | ≥ 1 week, ≥ 2000 g | 5* | 7.5* | 7.5* | 7.5* |
| **Meropenem** | <7 days, ≤ 2000 g | 40* | 40* | n.a. | 40* |
| | <7 days, > 2000g | 40* | 40* | n.a. | 40* |
| | ≥ 1 week, ≤ 1200 g | 60* | 40* | n.a. | n.a.* |
| | ≥ 1 week, 1200-2000 g | 60* | 40* | n.a. | 40* |
| | ≥ 1 week, ≥ 2000 g | 60* | 60* | n.a. | 60* |
| **Vancomycin** | <7 days, ≤ 2000 g | 15-30* | 20-30* | 20-30* | 20* |
| | <7 days, > 2000g | 15-30* | 20-45* | 20-45* | 30* |
| | ≥ 1 week, ≤ 1200 g | n.a. | 15* | n.a. | n.a. |
| | ≥ 1 week, 1200-2000 g | 30-45* | 20-45* | 20-45* | 20* |
| | ≥ 1 week, ≥ 2000 g | 30-45* | 45-60* | 30-60* | 30* |

n.a. not available

* based on indication usual dosage guideline

# dose in IE/kg/day

Table 2. (continued)

| | Dose (mg/kg/day) | | | | |
|---|---|---|---|---|---|
| **Name of antibiotic** | **Long & Pickering (11)** | **Feigin & Cherry (12)** | **Nelson's (13)** | **aRDD** | **Range** |
| **Ampicillin** | 50* | 50* | 100* | 68 | 50-100 |
| | 75* | 75* | 150* | 95 | 75-150 |
| | 75* | n.a. | 150* | 113 | 50-175 |
| | 75* | 75* | 150* | 175 | 75-175 |
| | 100* | 100* | 200* | 200 | 100-200 |
| **Benzylpenicillin#** | 50000* | 50000-100000* | 100000* | 69047 | 50000-100000 |
| | 75000* | 75000-150000* | 150000* | 97619 | 75000-150000 |
| | n.a. | n.a. | n.a. | - | - |
| | 75000* | 75000-150000* | 225000* | 119643 | 75000-225000 |
| | 100000* | 100000-200000* | 200000* | 132143 | 100000-200000 |
| **Cefotaxime** | 100* | 100* | 100* | 93 | 50-100 |
| | 100-150* | 100* | 100* | 104 | 50-125 |
| | n.a. | n.a. | n.a. | - | - |
| | 150* | 150* | 150* | 141 | 87.5-150 |
| | 150-200* | 150-200* | 150* | 155 | 87.5-175 |
| **Ceftazidime** | 100* | 100* | 100* | 89 | 25-100 |
| | 100-150* | 150* | 100* | 118 | 25-150 |
| | n.a. | n.a. | n.a. | - | - |
| | 90* | 150* | 150* | 129 | 62.5-150 |
| | 90* | 150* | 150* | 129 | 62.5-150 |
| **Gentamicin** | 5* | 5* | 5* | 5 | - |
| | 5* | 5* | 5* | 5 | - |
| | n.a. | n.a. | n.a. | - | - |
| | 7.5* | 7.5* | 7.5* | 7 | 5-7.5 |
| | 7.5* | 7.5* | 7.5* | 7 | 5-7.5 |
| **Meropenem** | n.a. | n.a. | 40* | 40 | - |
| | n.a. | n.a. | 40* | 40 | - |
| | n.a. | n.a. | n.a. | - | - |
| | n.a. | n.a. | 60* | 50 | 40-60 |
| | n.a. | n.a. | 60* | 60 | - |
| **Vancomycin** | 20* | 10-30* | 15-30* | 22 | 20-25 |
| | 20-30* | 10-30* | 15-30* | 26 | 20-32.5 |
| | n.a. | n.a. | n.a. | - | - |
| | 30* | 20-45* | 30-45* | 32 | 20-37.5 |
| | 30* | 30-45* | 30-45* | 39 | 30-52.5 |

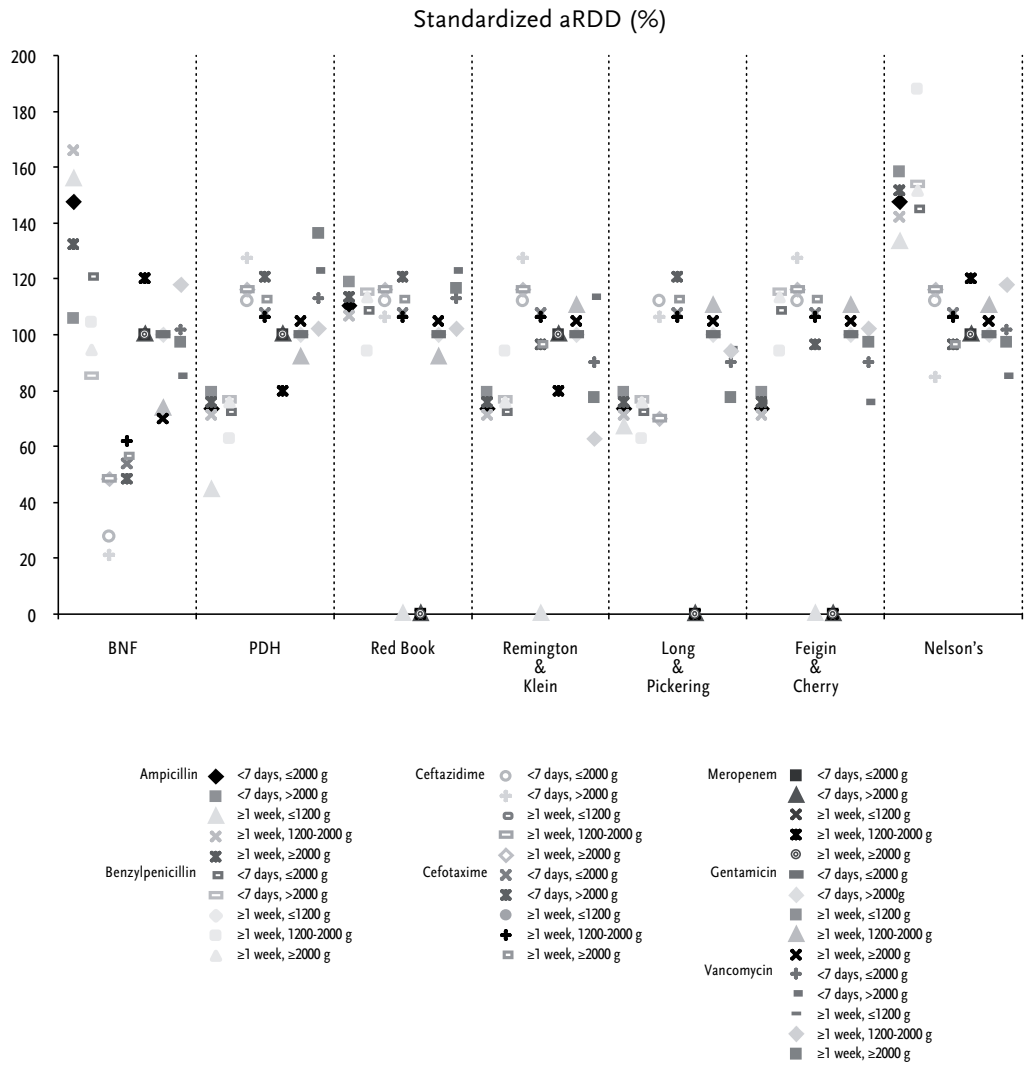


Figure 1. Standardized average dosage recommendations for antibiotics from seven commonly used and well-established textbooks.

## Discussion

To our knowledge, this is the first study that systematically reviewed seven internationally well-respected textbooks for neonatal dosage recommendations of antibiotics and showed a substantial variation between textbooks therein. The dosing recommendations of ampicillin, benzylpenicillin, ceftazidime and cefotaxime (i.e. antibiotics with a wide therapeutic window) showed a larger variation compared to those of meropenem, gentamicin and vancomycin (small therapeutic window). In addition, in comparison with the other six evaluated textbooks the BNF demonstrated a larger variation in its dosage recommendations. It is, however, difficult to explain why this textbook stands out at the comparison of dosage recommendations. For example, the more specified age categorisation and corresponding dosing recommendations in this textbook might contribute to its larger variation compared with the other textbooks.

There may be several reasons for the considerable variation between some antibiotic dosage recommendations. Firstly, the lack of pharmacokinetic data and clinical trial evidence in the neonatal population. Furthermore, large trials are required to show any differences in clinical efficacy between dosage recommendations, which are in this population in practical and ethical perspective hard to set up, let alone excellent pharmacokinetic (PK)-pharmacodynamic (PD) studies including appropriate biomarkers as endpoint. (14) Secondly, due to geographical regional variation in antimicrobial susceptibility patterns, empirical therapy should be guided by local susceptibility patterns resulting in variation in dosage recommendations. (15) Finally, one could hypothesize that the variation might be explained by the differences in the procedure of establishing the dosing recommendations between the textbooks, e.g. frequency of updating, composition of editorial board or availability of references. We illustrated that only four of the seven textbooks used references regarding their dosage recommendations and of these references only a few were in common. Moreover, one textbook (Feigin & Cherry) mentioned explicitly that their recommendations were based on and modified from those in another evaluated textbook (Remington & Klein). Strikingly, the available references were all somewhat outdated (i.e. published before 2000). Both the variation between recommendations from different sources and the use of outdated references were also seen recently by systematically comparing different sources of drug information regarding dose adjustment for renal function (16) and those on safety in lactation (17). It is obviously worrisome that these inconsistencies in textbooks, guidelines,

drug management programmes etc. might not encourage adherence to the recommendations from these sources and subsequently might lead to more *experience*-based instead of *evidence*-based medicine. (18;19)

An additional remarkable finding when comparing the seven textbooks was that in many cases the same editors and authors contributed to the majority of the *American* textbooks. Finally, each textbook evaluated in our study was a paper one. In our opinion, the era of using textbooks in book form has come to an end. One should henceforth give higher preference to available *online* (electronic) information of antibiotic dosage recommendations as these can be updated regularly.

Our systematic comparison of dosage recommendations in seven internationally well-respected textbooks led to the conclusion that the dosage recommendations for ampicillin, benzylpenicillin, ceftazidime and cefotaxime for neonatal sepsis varied considerably. It, however, remains questionable whether these differences are of clinical relevance. Ideally, further research into these individual antibiotics could answer this question, but it is not realistic that this will be performed for the already approved antibiotics. On the other hand, this might be attractive for new antibiotics.

Even if not directly clinically relevant, inconsistencies in neonatal dosage recommendations for antibiotics from these common reference sources might indirectly contribute to the difficulty in clinical practice in determining an appropriate neonatal dosage. (20) Hence, standardization of many, but not all, neonatal antibiotic dosing schemes is desirable. Further exploration to overcome variation in dosage recommendations is necessary to obtain established dosage regimens and thus full benefit of CPOE and clinical decision support systems in neonatology.

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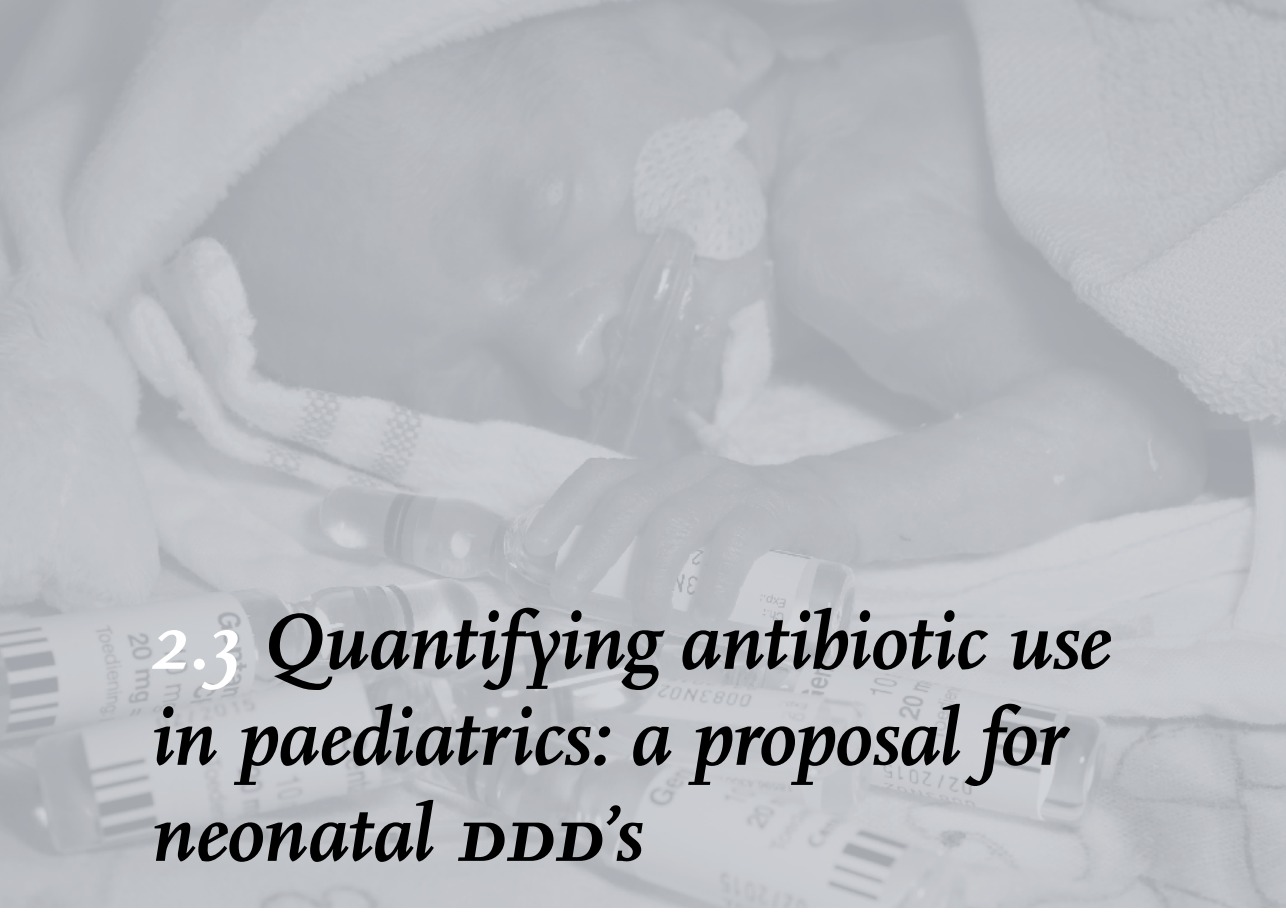

# 2.3 Quantifying antibiotic use in paediatrics: a proposal for neonatal DDD's

*T.B. Yves Liem*
*Eibert R. Heerdink*
*Toine C.G. Egberts*
*Carin M.A. Rademaker*

*Eur J Clin Microbiol Infect Dis 2010;29:1301-03*

# Abstract

## Objective

The Defined Daily Dose (DDD) as defined by the World Health Organization (WHO) has been the most frequently used unit of measurement to measure antibiotic use. However, measuring antibiotic use in paediatrics is a problem as the WHO DDD methodology is not applicable in children (aged > 1 month), because the large variation in body weight within this population. Based on the narrow range of body weights in the neonatal population, we therefore aimed to develop a set of neonatal DDD's for antibiotics.

## Methods

Eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates were consulted for the assumed maintenance dose of the 10 most frequently used antibiotics in neonatal intensive care units in its main indication for neonates.

## Results

A set of neonatal DDD's for ten commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg was proposed.

## Conclusion

Primarily in children DDD's are not applicable to quantify antibiotic use since there is large variation in body weight. In the neonatal population, however, based on its narrow range of body weights and when access to patient level data is not available, neonatal DDD's can be used as unit of measurement.

Detailed quantitative and qualitative knowledge of antibiotic use is essential to implement strategies for reducing overuse, underuse and misuse of antibiotics in order to address the threat posed by resistant microorganisms. Antibiotic use in hospitals can be quantified using several methods. The Defined Daily Dose (DDD) as assigned by the World Health Organization (WHO) has been the most commonly used unit of measurement to quantify (e.g. as the number of DDD's used per 100 hospital days) in various settings and is particularly recommended to compare drug use between (international) settings and has shown its value for this purpose. (1;2) The DDD is the assumed average maintenance dose per day for a drug in its main indication for adults and is commonly expressed with a certain population size denominator such as patient days, bed days, admission days, inhabitant days. The popularity of the DDD mainly originates from its general applicability and its advantage that comparison of the amount of drug use between different (international) settings and between different drugs based on grouped dispensing data is possible without requiring utilization data on the individual patient level. The main disadvantage is that the DDD neither reflects the recommended, nor the actual prescribed daily dosage (PDD) for individual patients or specific patient populations. (3-7) Hence, in an ideal situation, the actual consumption of antibiotics should be measured at the level of the individual patient and subsequently aggregated over patient groups and settings. This gives more precise estimates but more importantly also allows to study associations on an individual patient level between patient characteristics, setting characteristics (e.g. antibiotic policy), antibiotic use and clinically relevant outcomes, including antibiotic resistance. (4)

One of the other main shortcomings of the DDD methodology is its applicability in paediatrics. In an editorial commentary, Monnet concluded that in addition to the revision of WHO DDD, more research is needed to address other problems, such as the difficulty in measuring antibiotic use in children in those hospitals where data at patient level are not available. (5) Problems arise because dosing of antibiotics in children is based on body weight. Therefore, in order to calculate a paediatric DDD, an average body weight for the paediatric population needs to be assumed. However, in our opinion, this methodology is questionable as there is a large variation in body weight within the paediatric population. This view is supported by the WHO International Working Group for Drug Statistics Methodology's publication 'Guidelines for ATC classification and DDD assignment'. (8) In this, the WHO states that it is impossible to define paediatric DDD's because dose recommendations for use in children vary according to age and body weight (and setting).

Furthermore, many drugs used in paediatrics are not even approved for such use and dosing information is not available. In response to the WHO's negative comments about paediatric DDD's, several alternative measurement systems for antibiotic use in children have been proposed, e.g. an estimation of antibiotic exposure by controlling for patient weight and amount of wasted drug. (9;10)

Nevertheless, regarding the issue on variation in body weight, one should distinguish children (>1 month of age) from neonates (<1 month of age) as the variation in body weight in children (mean body weight at age 1 month: 4.2 kg (11); mean body weight at age of 17 years: 60 kg (12)) is larger compared to the neonatal population (mean body weight: 2.1 kg ± 1.0, based on own data). Consequently, in our view the disadvantage of the DDD methodology in paediatrics is more relevant for children than for neonates. Therefore, we aimed to devise a set of neonatal DDD's for antibiotics. We consulted eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates for the assumed maintenance dose of the 10 most frequently used antibiotics in NICU's in its main indication for neonates (i.e. neonatal sepsis) (*Table 1*). (13) Considering these antibiotics we did not find discrepancies in the dosage recommendations between the various evaluated sources. In addition, this overview of assumed maintenance dosages was evaluated and approved by two external experts: a hospital pharmacist and a paediatrician-infectious disease specialist. As a result, we propose a set of neonatal DDD's for commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg. (*Table 1*) Regarding these proposed neonatal DDD's, one should, however, take into account the general limitations of the DDD but also limitations specific to this patient group such as the policy on handling of waste of unused antibiotics in a NICU setting. After all, waste of unused antibiotics would not reflect a real estimate of neonatal DDD's.

Obviously, our proposed neonatal DDD's do not alter the fact that there is a lack of data on antibiotic use on the individual patient level. Yet, with the increasing use of computerised medical information systems it will be considerably easier to get access to data on the level of the individual patient, such as days of therapy (DOT). DOT is not influenced by discrepancies between the DDD and the PDD, by changes in the WHO assigned DDD and is independent of age- and weight-related differences in dosage. (7;14) A major disadvantage of this parameter is, however, that currently such detailed data on the individual patient level are not readily available. Moreover, if one would like to link data on antibiotic use to resistance, preferably both units of measurement, DOT (*in*dependent of dosage) and DDD (dependent of dosage),

Table 1. Overview neonatal DDD's top 10 antibiotics NICU's

| | Maintenance dose in mg/kg/day in its main indication for neonates | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Name of antibiotic | (16) | (17) | (18) | (12) | (11) | (19) | (20) | (21) | Assumed maintenance dose in mg/kg/day in its main indication for neonates | Neonatal DDD (g) (assumed average body weight of 2 kg) | Adult DDD (WHO 2005) (g) (assumed body weight of 70 kg) | Factor (adult vs neonatal DDD) |
| **Ampicillin** | n.a. | 100 | 100 | 100 | 100-200 | 100-200 | 100 | 200 | 100 | 0.2 | 2 | 10 |
| **Amoxicillin** | 75-100 | n.a. | n.a. | n.a. | 100-150 | n.a. | n.a. | n.a. | 100 | 0.2 | 1 | 5 |
| **Amoxicillin and enzyme inhibitor** | 100 | n.a. | n.a. | n.a. | 90 | n.a. | n.a. | n.a. | 100 | 0.2 | 3 | 15 |
| **Flucloxacillin** | 100 | n.a. | n.a. | n.a. | 100 | n.a. | n.a. | n.a. | 100 | 0.2 | 2 | 10 |
| **Ceftazidime** | 150 | 150 | 150 | 150 | 75 | 150 | 150 | 150 | 150 | 0.3 | 4 | 13 |
| **Cefotaxime** | 150 | 150 | 150-200 | 150-200 | 75-100 | 150-200 | 150-200 | 150 | 150 | 0.3 | 4 | 13 |
| **Meropenem** | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 0.12 | 2 | 17 |
| **Erythromycin** | 30 | n.a. | n.a. | 30 | 50 | n.a. | n.a. | n.a. | 30 | 0.06 | 1 | 17 |
| **Gentamicin** | 4 | 5 | 5 | 5 | 4 | 5 | 5 | 5 | 4 | 0.008 | 0.24 | 30 |
| **Vancomycin** | 30 | 30 | 30 | 30-60 | 45 | 30-60 | 30 | 30 | 30 | 0.06 | 2 | 33 |

n.a. not available

should be used, since it is unidentified which of these measurement methods is most predictive of resistance. (7) A recent study has shown that repeated and/or prolonged antibiotic use in neonates resulted in an increase of hospital-acquired, antibiotic-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and multidrug-resistant Gram-negative rods. (15)

In conclusion, in order to quantify antibiotic use the DDD methodology is not applicable in the paediatric population, mainly in children aged between 1 month-18 years, because of the large variation in body weight within this population. Although in the neonatal population, until patient level data are widely available and based on its narrow range of body weights, we suggest, illustrated by the example of antibiotics, that the neonatal DDD (NDDD) is a good alternative unit of measurement, both in research and for benchmarking purposes.

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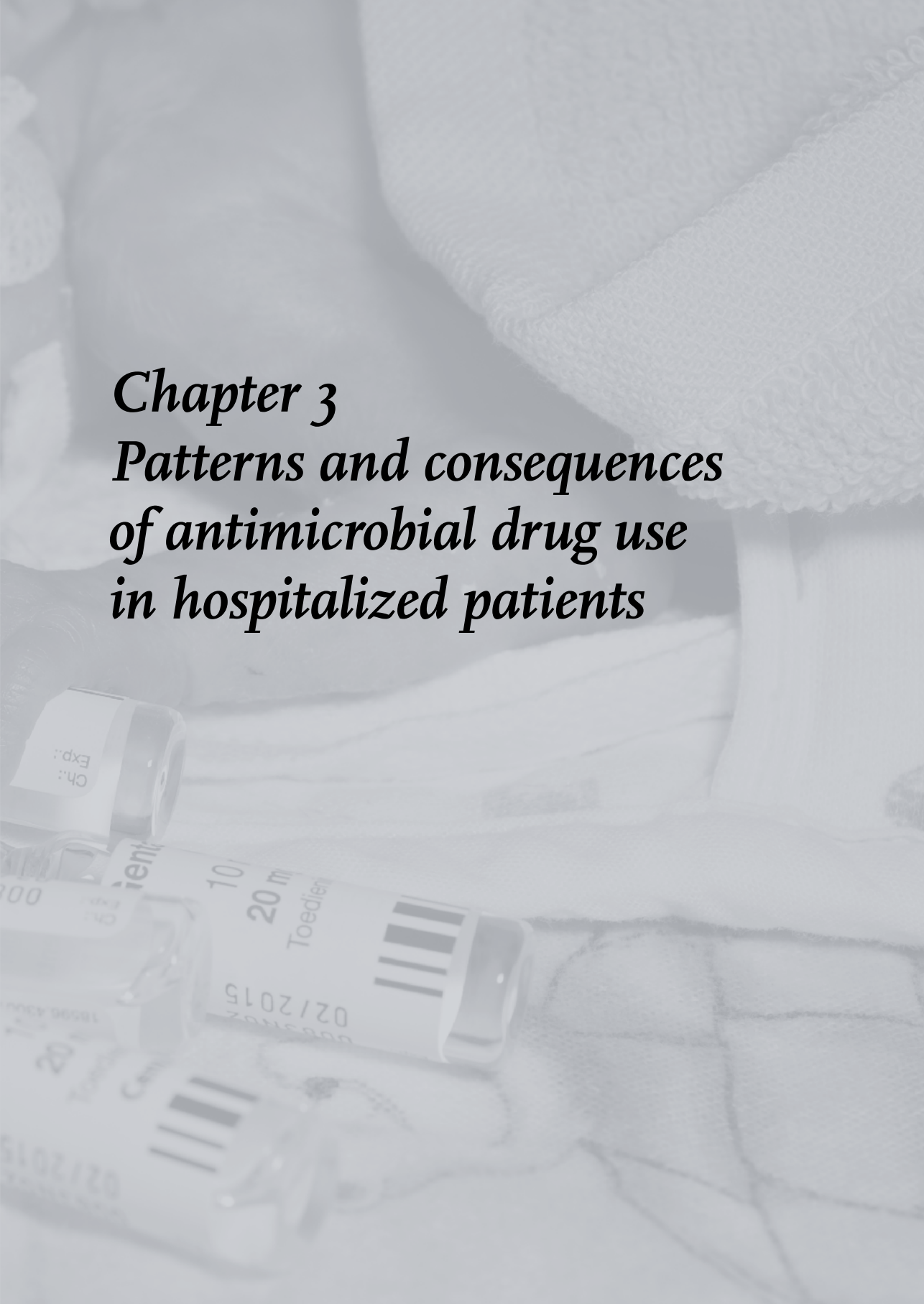

# *Chapter 3*
# *Patterns and consequences of antimicrobial drug use in hospitalized patients*

# 3.1 Changes in antibiotic use in Dutch hospitals over a 6-year period: 1997-2002

*T.B. Yves Liem*
*Margreet Filius*
*Paul D. van der Linden*
*Rob Janknegt*
*Stephanie Natsch*
*Arnold G. Vulto*
*on behalf of SWAB's working group on the use of antimicrobial agents*

**The first two authors contributed equally to this study and share first authorship*

*Neth J Med 2005;63(9):354-60*

# Abstract

## Objective

To analyse trends in antibiotic use in Dutch hospitals over the period 1997-2002.

## Methods

Data on the use of antibiotics and hospital resource indicators were obtained by distributing a questionnaire to all Dutch hospital pharmacies. Antibiotic use was expressed as the number of defined daily doses (DDD) per 100 patient days and as DDD per 100 admissions.

## Results

Between 1997 and 2002, mean length of stay decreased by 18%. The mean number of admissions remained almost constant. Total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient days in 2002 ($p<0.001$), whereas expressed as DDD per 100 admissions it remained constant. Antibiotic use varied largely between the hospitals. Moreover, the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16%, 38%, 39%, 50% and 52%, respectively. Total antibiotic use was higher in university hospitals than in general hospitals.

## Conclusion

Between 1997 and 2002 patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient days increased. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient days and in DDD per 100 admissions were observed. It is arguable whether these trends result in an increase in selection pressure towards resistance in the hospitals. Continuous surveillance of antibiotic use and resistance is warranted to maintain efficacy and safety of antibiotic treatment.

# Introduction

The increasing prevalence of antibiotic resistant micro-organisms poses a major threat to the health of hospitalised patients. (1;2) Its relationship with antibiotic use and misuse is well recognised. Specific criteria for appropriate use of antibiotics in order to avoid resistance should therefore be developed. (3) Quantitative and qualitative data on the use of antibiotics in hospitals are needed to evaluate strategies that are implemented to contain antimicrobial resistance. Obviously, resistance rates also need to be measured.

In Sweden, Denmark and the Netherlands yearly reports are issued in which resistance rates and antibiotic use data are reported. (4-6) In the Netherlands, Janknegt et al. collected data on the use of antibiotics in Dutch hospitals during the period 1991-1996. (7) In 1996 the Working Party on Antibiotic Policy (acronym is SWAB; www.swab.nl) was founded by the Dutch Society for Medical Microbiology (N.V.M.M.), the Society for Infectious Diseases (V.I.Z.) and the Dutch Association of Hospital Pharmacists (N.V.Z.A.). Main activities of the SWAB are development of guidelines and educational programs to promote appropriate use of antibiotics and the surveillance of antibiotic use and resistance. These activities are supported with a structural grant by the Ministry of Health, Welfare and Sport of the Netherlands. In 2000 SWAB's working group on the use of antimicrobial agents started with the collection of national data on antibiotic use in hospitals. These data are presented in NethMap, the annual report of the SWAB. (6)

In a recent editorial of this journal it was stated that physicians would not directly benefit from these national reports in their daily practice, but that these reports may help to increase their general awareness of the problem of antibiotic resistance. (8) Furthermore these reports may provide a knowledge base for policy decisions, guidelines and research strategies.

The aim of this study was therefore to analyse and report on antibiotic use in Dutch hospitals between 1997 and 2002.

# Materials and methods

## Population

All Dutch hospitals, 94 general hospitals and 8 university hospitals, were approached to participate in the national surveillance system of the SWAB. Specialised hospitals, such as psychiatric and orthopaedic hospitals as well as rehabilitation centres were excluded. Data on the use of antibiotics in acute care Dutch hospitals between 1997 and 2002 were collected by means of a questionnaire distributed to all Dutch hospital pharmacies by the SWAB. Data from inpatient wards as well as day care wards had to be included, whereas outpatient use and dispensing to nursing homes had to be excluded from the data report.

## Antibiotic use

Pharmacies were requested to report on the annual consumption of antibiotics for systemic use, group J01 of the Anatomical Chemical Classification (ATC) system. The use of different (sub) classes of antibiotics was expressed as defined daily doses (DDD) per one hundred patient days and per one hundred admissions. (9)

The ATC/DDD classification from the World Health Organization (WHO), version 2002, was used to calculate the number of DDD of the various antibiotics. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in an adult. (10)

## Hospital resource data

For each hospital the annual number of admissions and days spent in the hospital (bed days) were recorded. The number of patient days was obtained by subtracting the number of admissions from the number of bed days as the number of bed days over estimates actual treatment-days by including both the day of admission and the day of discharge. The mean length of stay was calculated by dividing the mean number of patient days by the mean number of admissions.

## Statistical analysis

Regarding the period 1997-2002 an overall pooled mean (i.e. weighted mean) was calculated for each year by aggregating data on antibiotic use and patient days of all hospitals. Drug utilisation was compared between hospitals and over time by a mixed model for repeated measurements. The response variables applied were the number of DDD per 100 patient days and

the number of DDD per 100 admissions. P values less than 5% were considered statistically significant. All statistical analyses were performed by SAS 8.2 (SAS Institute, N.C., USA).

# Results

## Hospital resource indicators

Between 1997 and 2002 a decrease in the mean length of stay was found in both the total cohort of hospitals and the subgroups of university and general hospitals (*Table 1*). The mean number of admissions remained almost constant. As the mean number of patient days is calculated by multiplying the mean number of admissions with the mean length of stay, a decrease was also found in the mean number of patient days.

Table 1. Resource indicators of Dutch hospitals, 1997-2002

| | Hospitals | | Admissions | | | Patient days | | | Length of stay | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1997 (n) | 2002 (n) | 1997 (mean) | 2002 (mean) | % change 1997-2002 | 1997 (mean) | 2002 (mean) | % change 1997-2002 | 1997 (mean) | 2002 (mean) | % change 1997-2002 |
| **All hospitals** | 49 | 59 | 17405 | 17038 | -2.1 | 142339 | 114038 | -19.9 | 8.2 | 6.7 | -18.3 |
| **University hospitals** | 8 | 7 | 25670 | 24441 | -4.8 | 226264 | 191374 | -15.4 | 8.8 | 7.8 | -11.4 |
| **General hospitals** | 41 | 52 | 15793 | 16041 | +1.6 | 125963 | 103628 | -17.7 | 8.0 | 6.5 | -18.9 |

## Hospital use

The number of hospitals that issued data on antibiotic use varied from 49 (48%) in 1997 to 59 (58%) in 2002. The reasons given for not participating were other priorities (56%), not able to generate data on antibiotic use (25%) or no interest (19%).

In 1997 total systemic use in hospitals was 47.2 DDD per 100 patient days and significantly increased by 24% to 58.5 DDD per 100 patient days in 2002 ($p<0.001$) (*Table 2*). However, total systemic use expressed as DDD per 100 admissions remained almost constant at 385.9 in 1997 and 391.6 in 2002 ($p=0.866$) (*Table 3*).

The mean number of total DDD per hospital did not change between 1997 and 2002 (67176 and 66714 DDD in 1997 and 2002 respectively).

Regarding trends in antibiotic use over the years five main categories can be distinguished:

1. For macrolides, lincosamides and fluoroquinolones we found a significant increase over the years for both units of measurement;

Table 2. Antibiotic use in Dutch hospitals (DDD per 100 patient days), 1997-2002

| ATC code | Antimicrobial group | Relevant example antibiotic(s) | DDD per 100 patient days 1997 | 2002 | Absolute change 1997-2002 | Average change per year (%) | Trend 1997-2002 (P value) |
|---|---|---|---|---|---|---|---|
| **J01AA** | Tetracyclines | Doyxcycline | 1.6 | 1.6 | 0.00 | 0.071 | 0.933 |
| **J01BA** | Amphenicols | Chloramphenicol | 0.017 | 0.0039 | 0.00 | -62.1* | 0.007 |
| **J01CA** | Penicillins with extended spectrum | Amoxicillin | 6.5 | 6.2 | -0.34 | -1.1 | 0.212 |
| **J01CE** | Beta-lactamase-sensitive penicillins | Benzylpenicillin | 1.2 | 1.2 | 0.082 | 1.4 | 0.004 |
| **J01CF** | Beta-lactamase-resistant penicillins | Flucloxacillin | 4.1 | 4.5 | 0.36 | 1.7 | 0.116 |
| **J01CR** | Combinations of penicillins, incl. beta-lactamase-inhibitors | Amoxicillin with clavulanic acid, piperacillin with tazobactam | 14.4 | 20.6 | 6.2 | 7.4 | <0.001 |
| **J01DA** | Cephalosporins and related substances | Cefazolin, cefuroxim, ceftazidim | 5.1 | 6.3 | 1.1 | 4.0 | <0.001 |
| **J01DF** | Monobactams | Aztreonam | 0.011 | 0.0021 | -0.009 | -27.7* | 0.018 |
| **J01DH** | Carbapenems | Imipenem, meropenem | 0.43 | 0.46 | 0.034 | 1.6 | 0.246 |
| **J01EA** | Trimethoprim and derivatives | Trimethoprim | 0.46 | 0.48 | 0.021 | 0.90 | 0.353 |
| **J01EC** | Intermediate-acting sulfonamides | Sulfadiazine | 0.061 | 0.00013 | -0.061 | -70.8* | 0.229 |
| **J01EE** | Combinations of sulfonamides and trimethoprim | Sulfamethoxazole with trimethoprim | 2.6 | 2.4 | -0.22 | -1.7 | 0.0715 |
| **J01FA** | Macrolides | Clarithromycin | 1.9 | 2.7 | 0.77 | 7.1 | <0.001 |
| **J01FF** | Lincosamides | Clindamycin | 0.80 | 1.5 | 0.67 | 12.9 | <0.001 |
| **J01GB** | Aminoglycosides | Gentamycin, tobramycin | 2.0 | 2.1 | 0.13 | 1.3 | 0.334 |
| **J01MA** | Fluoroquinolones | Ciprofloxacin | 4.0 | 5.7 | 1.7 | 7.3 | <0.001 |
| **J01MB** | Other quinolones | Pipemidic acid | 0.030 | 0.077 | 0.046 | 20.4* | # |
| **J01XA** | Glycopeptides | Vancomycin | 0.42 | 0.51 | 0.092 | 4.1 | <0.001 |
| **J01XD** | Imidazole derivatives | Metronidazole | 1.2 | 1.4 | 0.26 | 4.1 | 0.622 |
| **J01XE** | Nitrofuran derivatives | Nitrofurantoin | 0.21 | 0.52 | 0.31 | 20.4* | # |
| **J01** | Antibiotics for systemic use (total) | | 47.2 | 58.5 | 11.3 | 4.4 | <0.001 |

P value < 0.05 = statistically significant

# not able to calculate P value due to too small number of observations

* due to the low absolute use of these compounds the average change per year bears little practical importance

2. for amphenicols and monobactams a significant decrease in both units of measurement was found;
3. for tetracyclines, beta-lactamase resistant penicillins, carbapenems, trimethoprim and derivatives, intermediate-acting sulfonamides,

aminoglycosides and imidazole derivatives a constant use in both units of measurement was found;

4. for total systemic use, combinations of penicillins including betalactamase inhibitors, betalactamase sensitive penicillins, cephalosporins and glycopeptides a significant increase in DDD per 100

Table 3. Antibiotic use in Dutch hospitals (DDD per 100 admissions), 1997-2002

| | | | DDD per 100 admissions | | | | |
|---|---|---|---|---|---|---|---|
| ATC code | Antimicrobial group | Relevant example antibiotic(s) | 1997 | 2002 | Absolute change 1997-2002 | Average change per year (%) | Trend 1997-2002 (P value) |
| **J01AA** | Tetracyclines | Doyxcycline | 13.4 | 11.0 | -2.4 | -3.9 | 0.482 |
| **J01BA** | Amphenicols | Chloramphenicol | 0.14 | 0.03 | -0.1 | -28.1* | 0.001 |
| **J01CA** | Penicillins with extended spectrum | Amoxicillin | 53.1 | 40.1 | -13.0 | -5.4 | <0.001 |
| **J01CE** | Beta-lactamase-sensitive penicillins | Benzylpenicillin | 9.4 | 8.0 | -1.4 | -3.2 | 0.080 |
| **J01CF** | Beta-lactamase-resistant penicillins | Flucloxacillin | 33.6 | 28.9 | -4.7 | -2.9 | 0.265 |
| **J01CR** | Combinations of penicillins, incl. beta-lactamase-inhibitors | Amoxicillin with clavulanic acid, piperacillin with tazobactam | 117.6 | 135.5 | 17.9 | 2.9 | 0.159 |
| **J01DA** | Cephalosporins and related substances | Cefazolin, cefuroxim, ceftazidim | 41.9 | 41.8 | -0.1 | -0.05 | 0.415 |
| **J01DF** | Monobactams | Aztreonam | 0.09 | 0.01 | -0.07 | -30.5* | 0.007 |
| **J01DH** | Carbapenems | Imipenem, meropenem | 3.5 | 3.1 | -0.4 | -2.4 | 0.754 |
| **J01EA** | Trimethoprim and derivatives | Trimethoprim | 3.7 | 3.2 | -0.5 | -3.1 | 0.902 |
| **J01EC** | Intermediate-acting sulfonamides | Sulfadiazine | 0.5 | 0.00087 | -0.5 | -71.9* | 0.268 |
| **J01EE** | Combinations of sulfonamides and trimethoprim | Sulfamethoxazole with trimethoprim | 21.1 | 15.9 | -5.3 | -5.6 | <0.001 |
| **J01FA** | Macrolides | Clarithromycin | 15.4 | 17.8 | 2.4 | 2.9 | 0.012 |
| **J01FF** | Lincosamides | Clindamycin | 6.6 | 9.8 | 3.3 | 8.5 | <0.001 |
| **J01GB** | Aminoglycosides | Tobramycin | 16.0 | 13.9 | -2.0 | -2.7 | 0.458 |
| **J01MA** | Fluoroquinolones | Ciprofloxacin | 32.7 | 38.0 | 5.3 | 3.1 | <0.001 |
| **J01MB** | Other quinolones | Pipemidic acid | 0.25 | 0.51 | 0.3 | 15.7* | # |
| **J01XA** | Glycopeptides | Vancomycin | 3.4 | 3.4 | 0.0 | -0.01 | 0.026 |
| **J01XD** | Imidazole derivatives | Metronidazole | 9.6 | 9.5 | -0.01 | -0.01 | 0.458 |
| **J01XE** | Nitrofuran derivatives | Nitrofurantoin | 1.7 | 3.5 | 1.8 | 15.7* | # |
| **J01** | Antibiotics for systemic use (total) | | 385.9 | 391.6 | 5.6 | 0.3 | 0.866 |

P value < 0.05 = statistically significant

# not able to calculate P value due to too small number of observations

* due to the low absolute use of these compounds the average change per year bears little practical importance

patient days and a constant use in DDD per 100 admissions has been observed;

5. for penicillins with extended spectrum and combinations of sulfonamides and trimethoprim we found a constant use when expressed in DDD per 100 patient days and a significant decrease in the number of DDD per 100 admissions.

The proportion of all penicillins combined represented 55% of total systemic use in both 1997 and 2002. In an in-depth study of the individual antibiotics we found that the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16%, 38%, 39%, 50% and 52%, respectively.

In university hospitals, total systemic antibiotic use increased significantly by 16.5% (from 57.6 in 1997 to 67.1 DDD per 100 patient days in 2002 ($p=0.002$)), whereas in general hospitals total use increased significantly by 29.4% (from 43.6 in 1997 to 56.4 DDD per 100 patient days in 2002 ($p<0.001$)). However, total systemic antibiotic use expressed as DDD per 100 admissions in university hospitals remained almost constant at 507.4 in 1997 and 525.2 in 2002. In general hospitals no increase was found when use was expressed as DDD per 100 admissions as well: 347.4 in 1997 and 364.2 in 2002. In university hospitals the mean number of DDD per hospital decreased by 1.5%, whereas in general hospitals an increase of 6.5% has been observed.

Moreover, a large variation in quantitative antibiotic use was found between the participating hospitals, in particular in general hospitals (*Figure 1*).

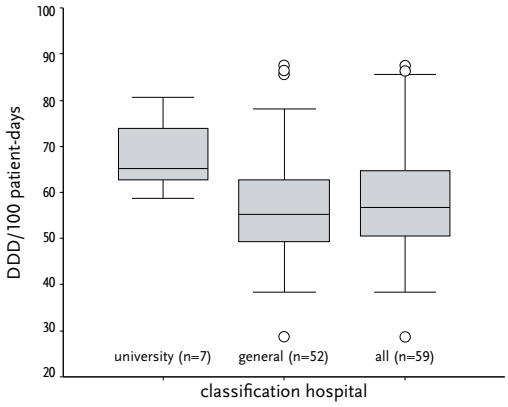


Figure 1. Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2002: university versus general hospitals.

## Discussion

Our data showed a decrease in the mean length of stay during the study period and a more or less constant mean number of admissions. These trends in hospital resource indicators are consistent with the demographics of all hospitals as registered by Statistics Netherlands (*http://www.cbs.nl*). In addition, we found that trends over time in DDD per 100 patient days did not consistently correlate with trends in DDD per 100 admissions.

In the present study total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient days in 2002. The total number of DDD and admissions remained almost constant between 1997 and 2002. However, length of stay decreased significantly during this period. This means that on average patients used the same number of DDD in a shorter period of time, which might be interpreted in different ways. Firstly, no changes in treatment policies occurred since most patients were already treated with antibiotics during the first days of hospitalisation. Due to intensification of general care length of stay decreased. Another explanation might be that antibiotic courses are completed at home with antibiotics supplied by the hospital.

Between 1991 and 1996 total antibiotic use in Dutch hospitals increased by 14% from 37.2 to 42.5 DDD per 100 patient days in 1996. (7) This might also be the result of a decreasing length of stay over the years (12%) rather than an increase in DDD per admission. The first results of a European surveillance program demonstrated that the Nordic countries and the Netherlands all show a low total antibiotic use compared with other European countries. (11)

In both university and general hospitals we found a constant use in DDD per 100 admissions and an increase in DDD per 100 patient days as well. Total systemic antibiotic use was notably higher in university hospitals than in general hospitals. This might be explained by the admission of patients with more complex infections or undergoing complex surgery and transplantations requiring prophylaxis.

In the total cohort of hospitals the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16%, 38%, 39%, 50% and 52%, respectively. As the number of admissions remained almost constant over the years this means an increase in the consumption of these antibiotics per admission. The increase in the use of cefazolin, an agent that is merely used for perioperative prophylaxis may be explained by the publication of a national guide-

line on perioperative antibiotic prophylaxis in 2000. This guideline strongly recommends the use of cefazolin for surgical prophylaxis. (12) In our cohort of hospitals the percentage of hospitals using cefazolin increased from 37% in 1997 to 69% in 2002 ($p = 0.001$). It is not clear why the use of the other antibiotics is increasing. Audits on antibiotic prescribing practices at the individual patient level are needed to clarify the increasing use of these antibiotics.

We distinguished five categories concerning trends in antibiotic use over the years. With regard to resistance development it appears that an increase in both the number of DDD per 100 patient days and the number of DDD per 100 admissions (category 1) is worrisome and that no significant change or a significant decrease in both units of measurement (category 2, 3 and 5) are not worrisome. The trend in category 4 is less easy to interpret. An increase in the number of DDD per 100 patient days may be interpreted as an increase in the selection pressure towards resistance. However, this is arguable since the number of admissions and the total number of DDD remained almost constant over the years. Moreover, an intensification of antibiotic therapy suggests a shortening of duration of antibiotic treatment. Short duration of therapy may lead to less selection of resistant microorganisms. (13;14)

In the present study some methodological problems were encountered. Firstly, one possible source of bias was the variety of methods used by the different Dutch hospital pharmacies to quantify their antibiotic use. The majority of hospitals delivered data based on hospital purchases, only a few hospitals provided actual dispensing data. Ideally, one would prefer actual administration data as a source to measure antibiotic use in hospitals, with every dose actually administered to a patient electronically.

Secondly, we aimed to provide census data, covering at least 90% of the acute care hospital population in the Netherlands. The overall response to the enquiry was however 58%. In contrast with for example Denmark, the Dutch government does not make it compulsory for hospitals to deliver their data on the use of antibiotics. (15) Consequently aiming at 90% coverage will be unrealistic. Since the variance in antibiotic use is very large between the hospitals, a representative selection of hospitals is only possible when insight is obtained in the determinants of hospital antibiotic use.

Another possible source of bias may be that as a result of earlier discharge of the less sick patients, patient days may increasingly originate from sicker patients who more often require antibiotic treatment. However, this is not likely, as the total number of DDD remained constant.

In this survey, data was collected by a questionnaire and processed manually, which is a relatively slow process. In the near future the SWAB wishes to start a national project in order to collect data on hospital drug use in a central data warehouse. This will facilitate the collection of data and the conversion to DDD per 100 patient days.

Data on the use of antibiotics at hospital level might be too crude for identifying subtle trends in antibiotic use of specific patient populations. Therefore, monitoring antibiotic use patterns by specific populations within the hospital (e.g. intensive care and general ward patients; surgical and non-surgical patients) is warranted. In this way substantial changes can be demonstrated that would be overlooked if hospital-wide data is aggregated into national trends.

In conclusion, patients hospitalized in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient days increased. It is arguable whether this results in an increase in selection pressure towards resistance in the hospitals, since the total number of DDD remained almost constant over the years. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient days and DDD per 100 admissions were observed between 1997 and 2002. This might be worrisome since this trend is more likely to be associated with an increase in the selection pressure. Further research is needed to determine the relationship between antibiotic use, selection pressure and the emergence of resistance. To maintain efficacy and safety of antibiotic treatment, continuous surveillance of antibiotic use and resistance is necessary.

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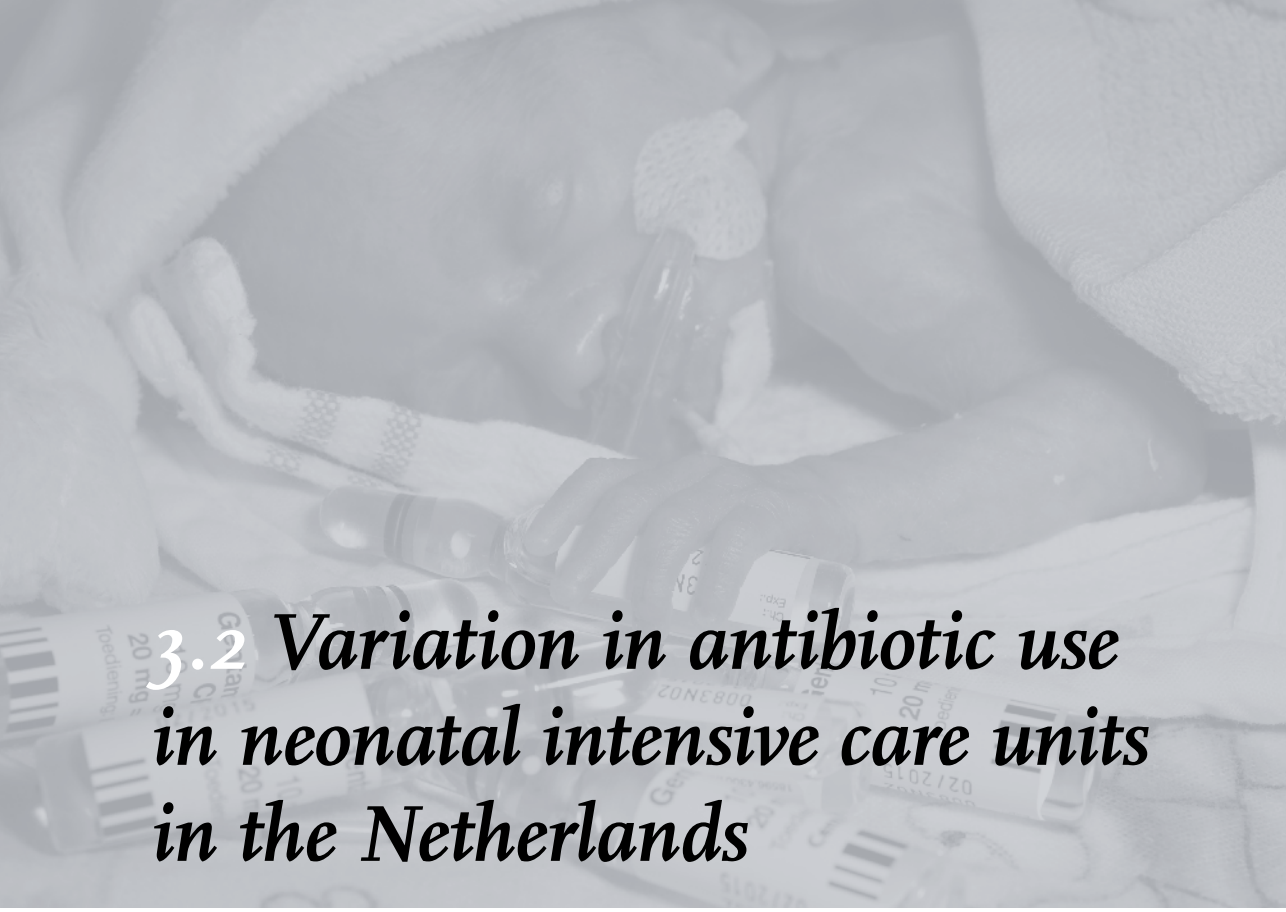

# 3.2 Variation in antibiotic use in neonatal intensive care units in the Netherlands

*T.B. Yves Liem*
*Tannette G. Krediet*
*André Fleer*
*Toine C.G. Egberts*
*Carin M.A. Rademaker*

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# Abstract

## Objectives

To examine the variation in quantity and classes of antibiotics used in all 10 tertiary care neonatal intensive care units (NICU's) in the Netherlands during 2005.

## Methods

We collected data from all tertiary care NICU's in the Netherlands on clinical and demographic characteristics and the type and quantity of systemic antibiotic use (expressed as Defined Daily Doses (DDD)/100 admissions) in 2005. Antibiotics were ranked by volume of DDD's, and those antibiotics which accounted for 90% of the total volume of use (Drug Utilization (DU) 90%) were noted.

## Results

Antibiotic consumption ranged from 130-360 DDD/100 admissions. In total, 9-24 different antibiotics were used, of which 3-10 were in the DU90%-segment.

## Conclusions

By comparing antibiotic use in Dutch NICU's we found a considerable variation in the number of different antibiotics used and in the total amount of antibiotic use. Further exploration of the opportunities to reach consensus in antibiotic policy, and to increase attention to antibiotic stewardship, is recommended.

# Introduction

Antibiotics are the most frequently used medicines in neonatal intensive care units (NICU's). (1-6) High antibiotic exposure rates (75-94%) have been reported; they are most likely based on the common practice of administering antibiotics pending bacterial culture results, to sick neonates and to neonates with risk factors for developing infectious diseases. (6)

By now it is well-recognized that the total amount of antibiotic use as well as the number of patients treated with antibiotics, is a risk factor for the selection of resistant bacteria. Detailed quantitative and qualitative knowledge of antibiotic use is essential in order to implement strategies for reducing the overuse and misuse of antibiotics and thereby address the threat posed by resistant microorganisms. (7;8) Evaluation of antibiotic use is therefore important, since the prevalence of hospital-acquired antibiotic-resistant microorganisms is increasing in hospitalized infants. (9)

Previous studies have demonstrated a large variation in out- and inpatient antibiotic use among European countries. (7;10) This variation is caused not only by differences in patient mix but also by differences in patterns in prescribing based on differences in physicians' and patients' attitudes to antibiotics, as well as cultural and social factors, and health-care systems. This supports the belief that antibiotics could be used more effectively in many countries. (7)

In this national multicentre study, the aim was to examine the variation in quantity and classes of antibiotics used in all 10 tertiary care NICU's in the Netherlands during 2005.

# Materials and Methods

## Setting

This study included all ten tertiary care NICU's in the Netherlands. These NICU's are distributed geographically all over the Netherlands and are responsible for the treatment of the entire Dutch target population. The corresponding hospitals of the NICU's involved in this study, therefore, were: Academic Medical Centre (AMC), Amsterdam; Free University Medical Centre (VUmc), Amsterdam; University Medical Centre Groningen (UMCG), Groningen; University Hospital Maastricht, Maastricht (azM); Leiden University Medical Centre (LUMC), Leiden; Erasmus University Medical Centre (Erasmus MC), Rotterdam; Máxima Medical Centre (MMC), Veldhoven; Isala Clinics, Zwolle; University Medical Centre St. Radboud (UMCN), Nijmegen; University Medical Center Utrecht, Wilhelmina Children's Hospital (UMC Utrecht, WKZ), Utrecht. For the purposes of this study we labelled the NICU's at random with the characters A-J.

## Data collection

*Collection of clinical and demographic characteristics of NICU's*

All data on the various clinical and demographic characteristics of NICU's were collected from the national neonatology registry. This registry belongs to the professional organisation of paediatricians/neonatologists and is part of a larger network of medical registries owned by The Netherlands Perinatal Registry (PRN-foundation). The PRN-foundation is a joint effort of the four professional organisations that provide perinatal care in the Netherlands.

The number of admissions per NICU in 2005 was collected. Each NICU has its own patient mix which was characterised by the following patient characteristics: birth weight, length of stay and neonatal sepsis. (I) The criteria for neonatal sepsis are identical for all NICU's in the Netherlands. Neonatal sepsis is defined by the occurrence of clinical signs of infection and a positive blood culture. Infants with clinical signs of sepsis including suggestive laboratory parameters, but without a positive blood culture, are not considered as proven sepsis.

## Collection of data on antibiotic use

Data on the quantitative and qualitative use of antibiotics in 2005, in all ten tertiary care NICU's, were collected by means of a survey distributed to the corresponding hospital pharmacies by the investigator. Data represented the dispensing of antibiotics from the hospital pharmacies to the NICU's.

The hospital pharmacies were requested to report on the annual total volume of prescription of antibiotics for systemic use in 2005 group J01 of the Anatomical Therapeutic Chemical Classification (ATC) system.

Total antibiotic use was expressed in defined daily doses (DDD) per one hundred admissions. The ATC/DDD classification from the World Health Organization (WHO), version 2009, was used to calculate the number of DDD's of the various antibiotics. (11) Neonatologists of all NICU's were asked for their local treatment guidelines on neonatal sepsis, meningitis and necrotizing enterocolitis (NEC).

## Data analysis

We analysed the quantity of total antibiotic use for each NICU expressed in DDD per one hundred admissions. Furthermore, for each NICU, antibiotics were ranked by volume of DDD's and the number of antibiotics that accounted for 90% and 100% of the total volume; i.e. the DU90% and DU100% respectively (where DU stands for drug utilization). (12)

Finally, for each NICU we measured which part of the number and volume of antibiotic use included those antibiotics mentioned in the treatment guidelines in place at that specific NICU.

# Results

*Table 1* shows the clinical and demographic characteristics of each NICU in 2005. The number of admissions per NICU in 2005 ranged from 278 to 585. The proportion of infants with extremely low birth weight (ELBW) <1000 g varied between 6 and 15%. In all NICU's the highest proportion of infants

Table 1. Clinical and demographic characteristics and empirical treatment guidelines in all NICU's in the Netherlands, 2005

| | | | | | |
|---|---|---|---|---|---|
| **Total number of admitted patients (n)** | A (506) | B (293) | C (539) | D* (278) | E (585) |
| **Birth weight (g), n (%)** | | | | | |
| **< 1000** | 46 (9) | 25 (9) | 68 (13) | 38 (14) | 38 (6) |
| **1000-1499** | 111 (22) | 59 (20) | 147 (27) | 68 (24) | 120 (21) |
| **>1500** | 349 (69) | 209 (71) | 324 (60) | 172 (62) | 419 (72) |
| **Unknown** | | | | | 8 (1) |
| **Length of stay (days), median (IQR)** | 4 (1-13) | 8 (3-15) | 4 (2-11) | 9 (4-18) | 5 (2-10) |
| **Neonatal sepsis, n (%)** | 57 (11) | 28 (10) | 88 (16) | 32 (12) | 102 (18) |
| **Empirical treatment guidelines** | | | | | |
| **Early-onset sepsis** | benzylpenicillin, gentamicin | amoxicillin, gentamicin | benzylpenicillin, gentamicin | amoxicillin, ceftazidime | amoxicillin, gentamicin |
| **Late-onset sepsis** | benzylpenicillin, flucloxacillin, gentamicin | flucloxacillin, gentamicin | flucloxacillin, gentamicin | ceftazidime, vancomycin | ceftazidime, vancomycin |
| **Meningitis** | penicillin-derivative, cefotaxime | n.a. | cefotaxime, amoxicillin | amoxicillin, meropenem | <72h after birth: amoxicillin, ceftazidime; >72h after birth: vancomycin, ceftazidime |
| **NEC** | amoxicillin-clavulanic acid, gentamicin | n.a. | amoxicillin-clavulanic acid, gentamicin | ceftazidime, vancomycin, metronidazole | <72h after birth: amoxicillin, gentamicin, metronidazole; >72h after birth: vancomycin, ceftazidime, metronidazole |

n.a. not available
IQR interquartile range
* Two NICU's were part of a general hospital; eight NICU's were part of a university medical centre

was in the category of birth weight >1500 g (range of 56-72%). Furthermore, there was a substantial variation in the proportion of infants with sepsis (range of 10-24%).

Table 1. (continued)

| | | | | | |
|---|---|---|---|---|---|
| **Total number of admitted patients (n)** | F* (286) | G (508) | H (374) | I (550) | J (407) |
| **Birth weight (g), n (%)** | | | | | |
| **< 1000** | 44 (15) | 56 (11) | 45 (12) | 50 (9) | 46 (11) |
| **1000-1499** | 80 (28) | 97 (19) | 68 (18) | 125 (23) | 71 (17) |
| **>1500** | 161 (56) | 355 (70) | 261 (70) | 375 (68) | 290 (71) |
| **Unknown** | 1 (0) | | | | |
| **Length of stay (days), median (IQR)** | 9 (4-16) | 4 (2-9) | 4 (2-12) | 5 (2-8.25) | 6 (2-13) |
| **Neonatal sepsis, n (%)** | 49 (17) | 63 (12) | n.a. | 84 (15) | 97 (24) |
| **Empirical treatment guidelines** | | | | | |
| **Early-onset sepsis** | amoxicillin-clavulanic acid, gentamicin | amoxicillin, gentamicin | benzylpenicillin, amikacin | amoxicillin-clavulanic acid, gentamicin | amoxicillin, gentamicin |
| **Late-onset sepsis** | teicoplanin | amoxicillin-clavulanic acid, gentamicin | vancomycin or flucloxacillin | cefazolin, gentamicin | ceftazidime, vancomycin |
| **Meningitis** | n.a. | amoxicillin, cefotaxime | meropenem | <48 h after birth: amoxicillin, cefotaxime; >48h after birth: vancomycin, ceftazidime | n.a. |
| **NEC** | n.a. | n.a. | n.a. | amoxicillin-clavulanic acid, gentamicin | amoxicillin-clavulanic acid, gentamicin |

Treatment guidelines for neonatal sepsis were in place at all NICU's (*Table 1*). Treatment guidelines for meningitis and NEC were in place at seven NICU's. All NICU's, except one, used amoxicillin, amoxicillin-clavulanic acid or benzylpenicillin in combination with gentamicin or amikacin for treatment of early-onset sepsis. For the treatment of late-onset sepsis, the NICU's used the following antibiotics: a penicillin-derivative (benzylpenicillin, flucloxacillin, amoxicillin-clavulanic acid) in combination with gentamicin or ceftazidime, ceftazidime in combination with vancomycin, cefazolin in combination with gentamicin, or monotherapy with teicoplanin, vancomycin, cefazolin or flucloxacillin.

*Table 2* shows the overall consumption of antibiotics, NICU G had the highest total antibiotic use (360.2 DDD/100 admissions), whereas NICU *E* had the lowest (129.9 DDD/100 admissions) (mean 222.1 DDD/100 admissions).

Table 2. Antibiotic use in all NICU's in the Netherlands during 2005, based on hospital pharmacy dispensing data

| NICU | Quantity of antibiotic use (DDD/100 admissions) | DU90% | DU100% | Number of used antibiotics as mentioned in protocols (%) | Quantity of antibiotic use mentioned in protocols (DDD/100 admissions) (%) |
|---|---|---|---|---|---|
| **A** | 201.5 | 8 | 16 | 6 (38) | 151.1 (75) |
| **B** | 345.9 | 5 | 17 | 5 (29) | 263.9 (76) |
| **C** | 228.5 | 10 | 24 | 7 (29) | 161.3 (71) |
| **D** | 239.4 | 4 | 9 | 4 (44) | 63.0 (26) |
| **E** | 129.9 | 3 | 12 | 5 (42) | 127.3 (98) |
| **F** | 158.3 | 6 | 14 | 4 (29) | 127.7 (81) |
| **G** | 360.2 | 5 | 17 | 7 (41) | 330.7 (92) |
| **H** | 134.2 | 7 | 18 | 5 (28) | 69.2 (52) |
| **I** | 183.2 | 6 | 13 | 10 (77) | 161.2 (88) |
| **J** | 239.5 | 7 | 16 | 4 (25) | 128.6 (54) |

In total, 9-24 different antibiotics were used in the participating NICU's. In the DU90% segment a mean of 6.1 different antibiotics were found (range of 3-10). *Figure 1* shows the overall patterns of antibiotic use in the participating NICU's in 2005. All NICU's used penicillins (amoxicillin, amoxicillin-clavulanic acid, benzylpenicillin, ampicillin) in the DU90% segment. Additionally, the DU90% segment in 8 of 10 NICU's included aminoglycosides (mostly gentamicin). NICU *1* is the only NICU using a first-generation cephalosporin (cefazolin) in the DU90% segment, whereas 4 out of 10 NICU's used a third-generation cephalosporin (cefotaxime, ceftazidime) in their

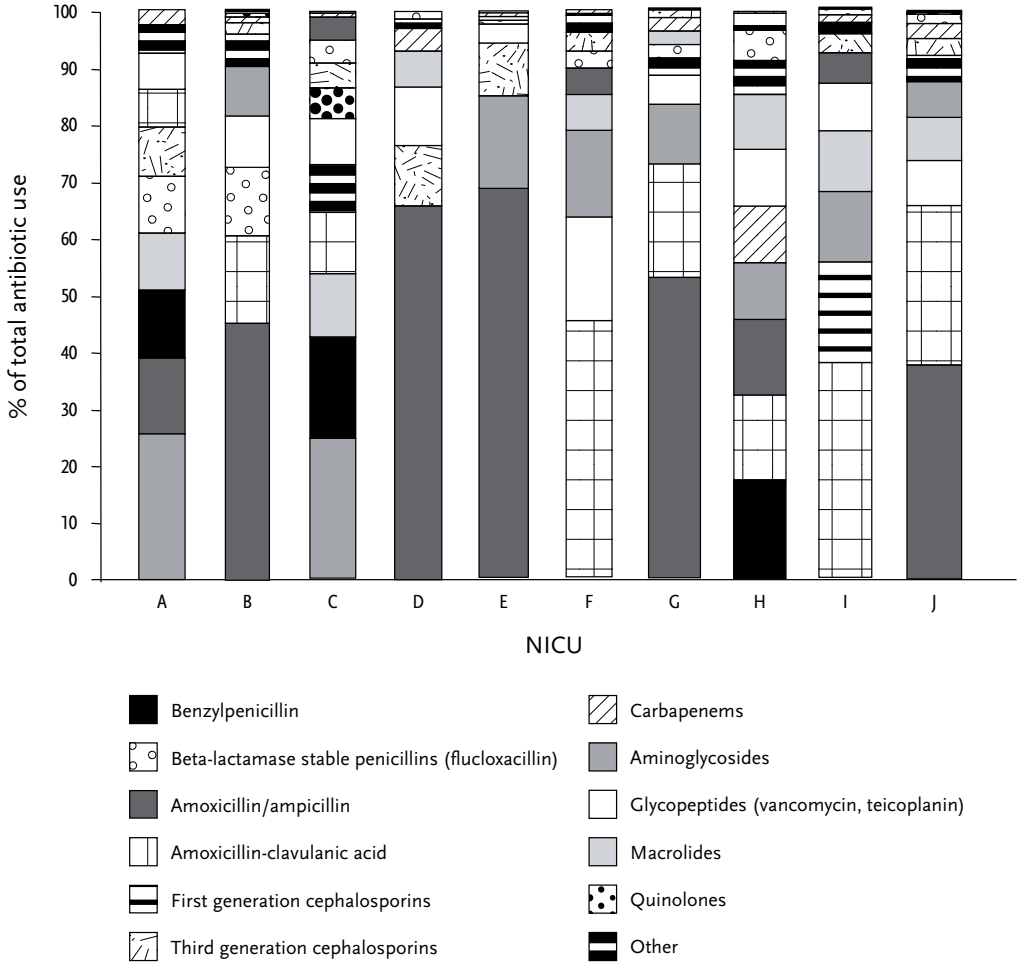


Figure 1. Overall patterns of antibiotic use of all NICU's in the Netherlands in 2005, based on hospital pharmacy dispensing data

*data of NICU E were based on patient-level data instead of hospital pharmacy dispensing data

DU90% segment. Apart from one NICU, all other NICU's used a glycopeptide in their DU90% segment (seven NICU's used vancomycin, whereas two NICU's used vancomycin and teicoplanin). Finally, only three NICU's (*B*, *C* and *J*) used quinolones (ciprofloxacin).

*Table 2* also shows the number of used antibiotics that were mentioned in the treatment guidelines on neonatal sepsis, meningitis and NEC. In NICU *J* 4 antibiotics (25%) were both used and mentioned in the treatment guidelines, whereas this number was 10 (77%) in NICU *I*. In the majority of the NICU's (6 out of 10), penicillins with extended spectrum (amoxicillin, amoxicillin-clavulanic acid), beta-lactamase resistant and sensitive penicillins (flucloxacillin, benzylpenicillin respectively), aminoglycosides (gentamicin, amikacin), cephalosporins (first and third generation) and glycopeptides (vancomycin, teicoplanin) were both used and mentioned in the relevant treatment guidelines.

In addition, the quantity of antibiotic use mentioned in the treatment guidelines in NICU *D* was 63.0 DDD/100 admissions (26% of total antibiotic use), whereas this was 127.3 DDD/100 admissions (98% of total antibiotic use) in NICU *E*.

## Discussion

This study is the first one to analyse and compare quantitative and qualitative antibiotic use in all NICU's in one single country, in this case, the Netherlands. We have demonstrated a considerable variation in the number of different antibiotics used in NICU's, as well as in the total amount of antibiotic use expressed in DDD/100 admissions. In our study the number of antibiotics in the DU90% segment ranged from 3 to 10. It is remarkable that in a relatively small country such as the Netherlands, one NICU used only 3 antibiotics in the DU90% segment, whereas another NICU used more than twice as many antibiotics in this segment.

The DU90% has been proven to be an important tool to assess the quality of drug prescription. In addition to the number of drugs in the DU90% segment, the presence of, and adherence to, treatment guidelines may serve as general quality indicators. (12) In our study we have demonstrated that each NICU had treatment guidelines on neonatal sepsis at least, and the majority had treatment guidelines on meningitis and NEC as well. Overall, the treatment guidelines on early-onset sepsis, meningitis and NEC were fairly similar, whereas those on late-onset sepsis varied widely. Although vancomycin is generally recommended, several NICU's used penicillin-derivatives or first-generation cephalosporins. Fernando et al. found a rather comparable pattern by comparing antimicrobial policies in more than 200 British and Irish neonatal units. (13)

In comparison with other countries (e.g. United States of America and United Kingdom), the recommended treatment guidelines for neonatal sepsis, meningitis and NEC in the participating NICU's in the Netherlands were more or less similar. (14;15)

It is difficult to explain why there is such a large variation between the number of different antibiotics used in each NICU as shown in *Figure 1*. One could hypothesize that this might be explained by the emergence of resistance of specific microorganisms in a particular NICU, resulting in usage of a broad range of different antibiotics. Although antibiotic resistance data for each individual NICU were not available at the time of our study, adjusting the treatment guidelines was not necessary according to antimicrobial resistance data from the Netherlands, as published in the annual report 'Nethmap' by the National Institute of Health (RIVM) and the Dutch Working Party on Antibiotic Policy (SWAB). (16) Another reason could be the presence and influence of antibiotic stewardship on the prescription of antibiotics in a NICU. Antibiotic stewardship has been shown to contribute positively to the

accuracy of antibiotic therapy. (17-21) In addition, stewardship of the empiric use of antibiotic regimens does matter in the control of antimicrobial resistance in a NICU. (22)

As far as we know there have been very few studies comparing the differences in antibiotic use among NICU's. (4) Nevertheless, several studies have recently compared and reported on antibiotic use in different pediatric intensive care units (PICU's), (23-25) in specific types of pediatric wards, (26;27) in hospitalized pediatric inpatients (28) and in numerous children's hospitals in one country. (29-33) In comparison with a few of these previous studies, the mean number of antibiotics in the DU90% segment in NICU's in the Netherlands was relatively low, i.e. 6. For example, in China this number varied between 16 and 20, (30) in Russia it was 8 (out of a total of 22 antibiotics used) and in Croatia 11 (out of a total of 35). (29)

Our study had some limitations. Firstly, we measured antibiotic use in the NICU's in adult DDD's. The recently proposed way to measure antibiotic use in children in 'days of therapy' (34) was not possible since data on antibiotic use of the participating NICU's on the patient level were not available. Since the range of body weight of the neonatal population did not vary that much, antibiotic dosages did not fluctuate. Moreover, we compared the differences in antibiotic use between different NICU's. Therefore, measuring antibiotic use in NICU's in DDD/100 admissions was legitimate. Secondly, data on antibiotic use were based on the purchase data of the hospital pharmacy. It only gives a rough estimate of antibiotic use, as it is not unusual in a neonatal population to use one vial of antibiotic for more than one infant. However, there is waste of unused antibiotics, which could be measured by collecting all discarded vials and aspirating the contents into syringes, (35) a method not applied in the present study. Thirdly, our study period was just one year (i.e. 2005). Nevertheless, the antibiotic policies in the NICU's have not changed from 2005 to the present day. Therefore, data on antibiotic use investigating total antibiotic use in different NICU's over a period of one year was considered sufficiently reliable to make comparisons. It is very important to implement antibiotic stewardship across all NICU's in the Netherlands and to make an effort to harmonise antibiotic prescribing.

In conclusion, we found a considerable variation in the total amount of antibiotic use as well as in the number of antibiotics used in all NICU's in the Netherlands. We recommend further exploration of the opportunities to accomplish uniformity in antibiotic policy on the treatment of infections in NICU's in the Netherlands. Moreover, antibiotic stewardship is recommended

to improve the accuracy of antibiotic treatment and to limit the use of antibiotics beyond the protocol.

## Acknowledgements

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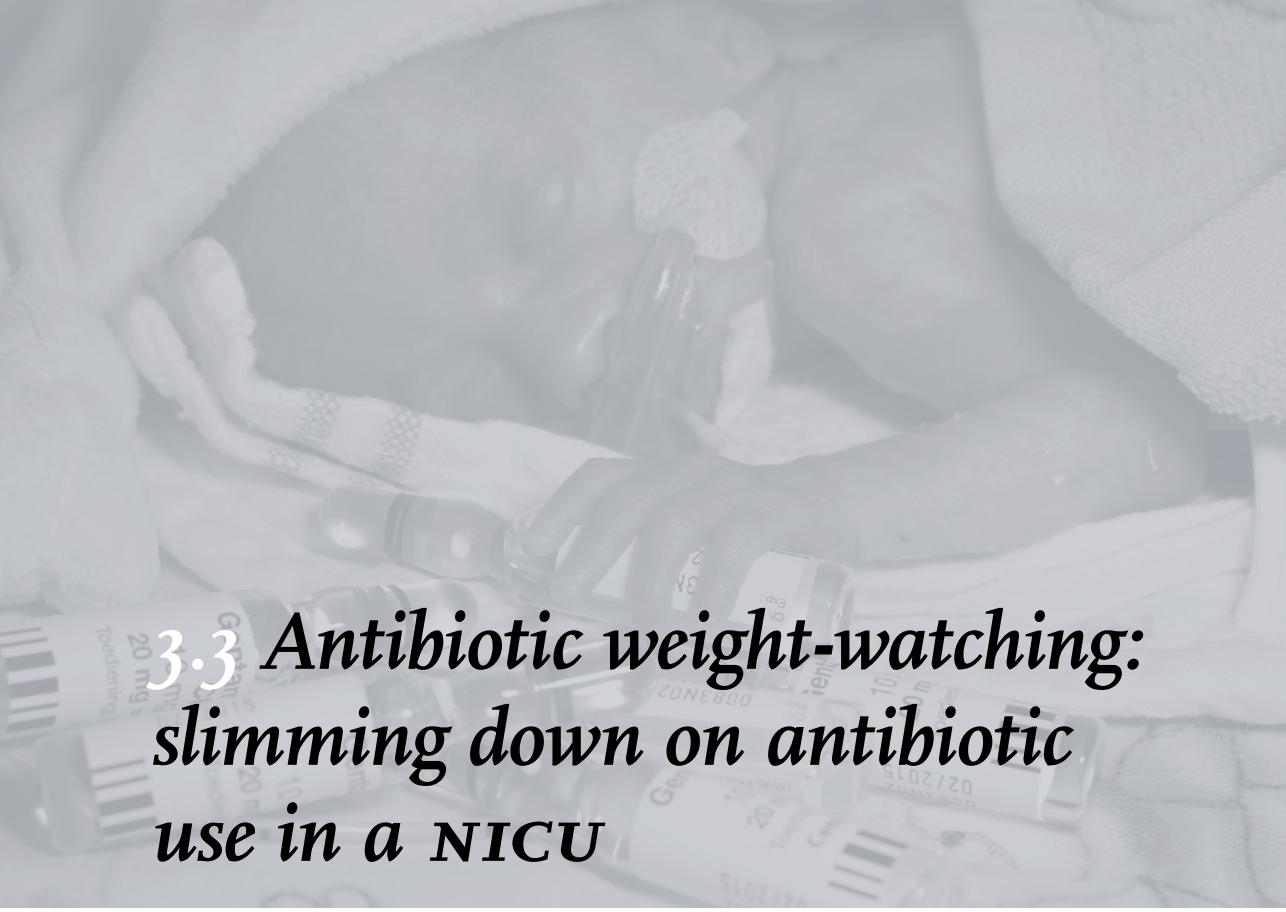

# 3.3 Antibiotic weight-watching: slimming down on antibiotic use in a NICU

*T.B. Yves Liem*
*Agnes van den Hoogen*
*Carin M.A. Rademaker*
*Toine C.G. Egberts*
*André Fleer*
*Tannette G. Krediet*

*Acta Paediatrica 2010;99:1900-02*

# Abstract

## Objective

To study antibiotic use in the NICU over a period of 19 years (1990-2008).

## Methods

Antibiotic use and clinical characteristics of all infants admitted to the NICU during each second year since 1990 were studied retrospectively. Antibiotic use was compared over time by linear regression analysis.

## Results

Clinical characteristics, length of stay and incidence of proven sepsis did not change significantly over 19 years. A constant and high proportion (85-90%) of admitted infants received antimicrobial therapy during any time of their stay, which was in contrast to the much lower incidence of proven sepsis (14.1-16.6%). Total antimicrobial use expressed as days of therapy (DOT) decreased significantly over time (from 9.0 to 5.8, p=0.007), for amoxicillin-clavulanic acid (p=0.007), gentamicin (p=0.002) and cefazolin (p=0.001).

## Conclusion

Over a period of 19 years no change was noted in the high percentage of infants treated with antibiotics in the NICU. However, a significant decrease was noted in the length of therapy for amoxicillin-clavulanic acid, gentamicin and cefazolin, without an increase in incidence of sepsis and mortality. The correct identification of infants with sepsis remains a major challenge in attempts to further reduce antibiotic use and postpone the emergence of antibiotic resistant microorganisms.

In hospital units with high use of antibiotics such as neonatal intensive care units (NICU's) preventing resistance is a major challenge. (1) Infections are increasingly caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and extended-spectrum ß-lactamase (ESBL)-producing pathogens. (2) Antibiotic therapy is applied in almost all patients on NICU's, since symptoms of infection are aspecific, immune defences immature, and risk factors for infection are abundantly present among preterm infants due to invasive treatment procedures. Ruling out infection is difficult in these infants, resulting in extensive use of antimicrobial agents, which carries a high risk of the emergence and spread of antimicrobial resistance, with a major impact on morbidity, mortality and healthcare costs. (3-5) A policy of restricted and appropriate antibiotic use is therefore essential to prevent the emergence of multidrug resistant microorganisms in NICU's. (6) To cope with the problem of over-treatment, multidisciplinary infectious disease teams (IDT's) contribute positively to the accuracy of antimicrobial therapy. (7-9) Identified trends in antibiotic use are crucial information for IDT's for their task in antibiotic stewardship. Therefore, monitoring antimicrobial use is highly recommended to enable antibiotic stewardship. (10;11) In our NICU, during daily routine care, all cases of infection and policies for antibiotic treatment are discussed with the IDT, which includes a pediatric infectious disease specialist, a medical microbiologist and neonatologists interested in neonatal infectious diseases. In addition, during weekly meetings attended by all members of the IDT, neonatologists, fellows and registrars, cases of all patients with suspected or proven infection are discussed systematically to monitor the accuracy of antimicrobial therapy and determine the duration of treatment.

Evaluation of antibiotic use in our NICU since 1990 revealed that 85-90% of all admitted infants received antibiotic treatment for reasons of suspected infection or risk factors, which was in sharp contrast to the proportion of infants with proven sepsis (*Figure 1*).

Total antimicrobial use, expressed as mean days of therapy (DOT), decreased significantly, from 9.0 to 5.8 (B = -0.226; 95% CI -0.369; -0.082; p=0.007), despite the high proportion of infants that received antimicrobial agents. Importantly, the clinical and demographic characteristics of all admitted infants to our NICU, such as birth weight, gestational age and length of stay, did not change significantly during the study period. A most prominent decrease was noted in mean DOT of antimicrobials indicated for suspected early-onset sepsis and risk for infection after birth (amoxicillin-clavulanic acid and gentamicin), but also for the first generation cephalosporins (cefazolin), as shown in *Figure 2*. The decrease in length of therapy was

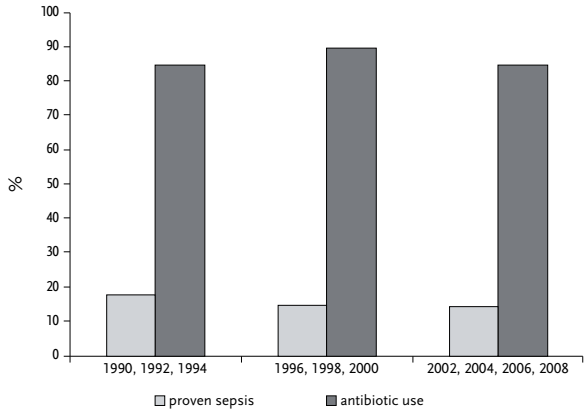


Figure 1. Percentage of infants treated with any antimicrobial agent versus incidence of proven sepsis (1990–2008)

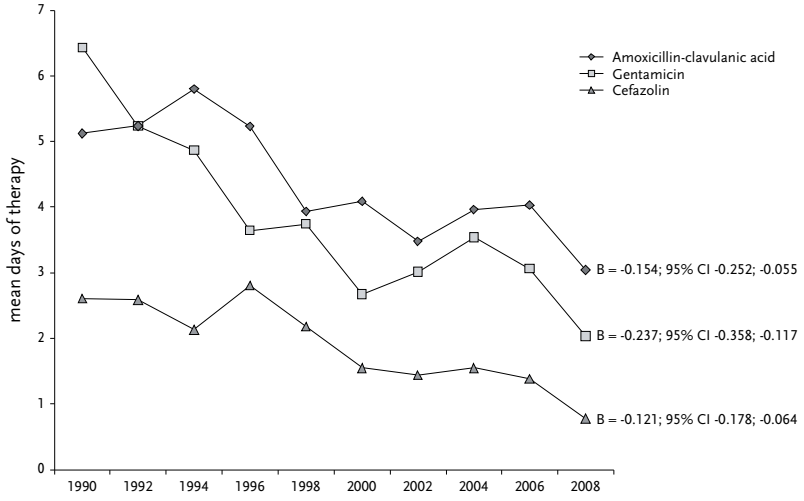


Figure 2. Duration of treatment with the most frequently used antimicrobial agents in the NICU, expressed as mean number of days of treatment for each admitted infant (1990-2008)

significant for all three antimicrobial agent groups and most strongly both for amoxicillin-clavulanic acid (B = -0.154; 95% CI -0.252; -0.055; p=0.007) and gentamicin (B = -0.237; 95% CI -0.358; -0.117; p=0.002) and to a lesser extent for cefazolin (B = -0.121; 95% CI -0.178; -0.064; p=0.001). The use of

vancomycin was limited (mean number of DOT was between 0.1 and 1) and did not show a specific trend.

The decrease in antimicrobial use was not attributable to changes in incidence of early-onset sepsis, or number of infants at risk for infection, neither to important changes in incidence of late-onset sepsis, or causative microorganisms, as was shown in a previous study. (12) On the other hand, the decrease in antimicrobial use did neither result in an increased incidence of infection, which was 15-18% during 1990-2008, nor in a higher mortality, which decreased from 17 to 9%. Since the duration of treatment for sepsis is contained in a protocol (7-14 days), the decrease in duration of treatment can be attributed to a shorter treatment for cases of suspected but unproven infection and for cases treated because of risk factors. The protocol for the choice of antimicrobial agents to treat neonatal sepsis was not changed during the entire period of 19 years. In this way, antimicrobial agents such as third generation cephalosporins and carbapenems, in addition to vancomycin, were used infrequently and did not substantially contribute to the antibiotic pressure in the NICU. Moreover, our previous study did not reveal increasing antibiotic resistance among the four most frequently isolated causative microorganisms. (12) Although increasing antibiotic resistance is observed among Gram-negative microorganisms that colonize the infants during hospitalisation, sepsis due to these microorganisms did not occur during the study period.

The results of our study suggest that in the struggle to reduce antimicrobial consumption in NICU's, antimicrobial stewardship is valuable. However, since no reduction was found in the total percentage of infants treated with antibiotics, the correct identification of infants with infections remains a major challenge in the attempts to further reduce antibiotic use and postpone the emergence of antibiotic resistant microorganisms. Until better diagnostic tools are available to identify truly infected infants, the most important decision clinicians can make is to stop antibiotics in those in whom infection can be ruled out. Use of guidelines and a multidisciplinary IDT can facilitate antimicrobial decision-making.

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# 3.4 Risk factors and early-warning markers for colonization with Extended-Spectrum Beta-Lactamase (ESBL)-producing Escherichia coli and Klebsiella species in neonatal intensive care unit patients

*T.B. Yves Liem*
*Tannette G. Krediet*
*André Fleer*
*Hanneke den Breeijen*
*Wouter W. van Solinge*
*Toine C.G. Egberts*
*Carin M.A. Rademaker*

# Abstract

## Objective

To identify clinical risk factors and leukocyte hematocytometry parameters as early-warning markers for colonization by extended-spectrum beta-lactamase–producing *E. coli* or *Klebsiella* species in NICU patients.

## Methods

A nested case-control study in our NICU was performed using data between 2007 and 2009, assembled retrospectively through records of the Eijkman-Winkler Centre of Microbiology, Infectious Diseases and Inflammation, UMC Utrecht. The infants were classified as case patients if any of their *E. coli* or *Klebsiella* species isolates produced ESBL. Potential controls were all hospitalized neonates in the same time period without ESBL-colonization. Potential risk factors and early-warning markers (i.e. total number of leukocytes, neutrophilic granulocytes, lymphocytes, monocytes, basophilic granulocytes and eosinophilic granulocytes) for the isolates demonstrating ESBL-mediated resistance in infants were ascertained by means of a review of medical records and Utrecht Patient Oriented Database (UPOD).

## Results

Among 1833 infants admitted to the NICU during the study period, a total of 26 infants were found to be colonized with ESBL-producing *Enterobacteriaceae*. Univariate analysis showed that the cases had significantly more frequently a mother who had used antibiotics prior to birth (OR: 4.9; 95% CI: 1.98-12.1) compared to the controls. In addition, the cases had significantly more often used cefazolin (OR: 2.8; 95% CI: 1.18-6.52) compared to the controls. There were, however, no significant differences in leukocyte hematocytometry parameters between cases and controls. Multivariable regression analysis revealed that only antibiotic use prior to birth by the mother (OR: 4.0; 95% CI: 1.45-11.0) was an independent risk factor for ESBL-colonization.

## Conclusion

We concluded that maternal antibiotic use prior to birth is an independent risk factor for neonatal ESBL-colonization, suggesting a so called 'vertical' transmission of ESBL-positive strains. We were not able to identify early-warning markers. Further prospective studies are needed to confirm the risk factors and to identify early-warning markers for ESBL-colonization among infants admitted at NICU's.

# Introduction

Multidrug resistance in clinical practice (e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium*, third-generation cephalosporin-resistant *Escherichia coli* (*E. coli*), and *Klebsiella pneumoniae* (*K. pneumoniae*), and carbapenem-resistant *Pseudomonas aeruginosa*) is a global rising problem and presents a major threat to successful treatment in almost all branches of medical practice. (1)

Also in neonatal intensive care units (NICU's) antibiotic resistant Gram-negative microorganisms that colonize infants during hospitalization are an emerging problem. (2) Especially, the world-wide increasing incidence of Extended-Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae* is of interest in this patient group. (3-6) ESBL-producing organisms were first detected in Western Europe in the mid 1980s (7) and subsequently in the United States in 1989. (8-10) ESBL's are plasmid-mediated enzymes that confer resistance to all penicillins and cephalosporins, including clavulanic acid and sulbactam containing combinations and monobactams (e.g. aztreonam). ESBL production can be detected in many species of *Enterobacteriaceae*, but is mainly found in *E. coli* and *Klebsiella species*. (11)

There are several reasons which make infections caused by ESBL-species alarming. The multidrug resistance and underestimation of the incidence of ESBL's, the latter as a result of the limitations of the existing methods of identification (12), leads to an increased risk for clinical failure and death, a significantly longer length of stay and higher costs in comparison to patients without ESBL-infections. (11;13-16) Interestingly, in our NICU we recently found during routine surveillance an elevation in the number of infants with ESBL-colonization. It is important that risk factors for ESBL-infections are identified in order to develop and implement effective strategies to limit outbreaks of these infections. (14) In addition, biomarkers for ESBL-infection are useful to timely detect those infants who have an ESBL-infection, which may help to take timely measures for these patients. It could be hypothesized that leukocyte differential parameters and absolute leukocyte counts show changes in the period prior to the ESBL-infection, since it has been demonstrated that leukocyte hematocytometry parameters can be used as biomarkers for discriminating between different phenotypes of an inflammatory disease, i.e. asthma. (17)

The aim of the present study is to identify clinical risk factors and leukocyte hematocytometry parameters as early-warning markers for colonization by ESBL-producing *E. coli* or *Klebsiella* species in NICU patients.

# Methods

## Setting

The Wilhelmina Children's Hospital is a 200 bed referral centre for a population of approximately 2 million inhabitants (12% of the Dutch population) and part of the UMC Utrecht, located in the central part of the Netherlands. The NICU is a 28-bed unit with over 600 annual admissions, from an area with 30,000 annual live births (15% of the total annual birth rate in the Netherlands). The NICU is one of eight university and one of a total of ten neonatal referral centres. The indications for admission at the NICU are in agreement with guidelines implemented by the Dutch Society of Neonatology.

## Study population

A nested case-control study was performed. A cohort consisting of all infants admitted to our NICU between January 1, 2007 to December 31, 2009, was assembled retrospectively through records of the Eijkman-Winkler Centre of Microbiology, Infectious Diseases and Inflammation, UMC Utrecht. Within this department, screening for ESBL-mediated resistance in surveillance cultures (skin, nose, throat, umbilicus, endotracheal tube and rectal swab or faeces) of *E. coli* and *Klebsiella* species is performed on a weekly basis. The infants were classified as case patients if any of their *E. coli* or *Klebsiella* species isolates produced ESBL. The infants were colonized, there were no cases of infection due to ESBL-producing microorganisms. Each patient was included as a case patient only once. If ESBL-producing *E. coli* or *Klebsiella* species was isolated on multiple occasions, only the first episode was reviewed. ESBL production was screened by the Phoenix automated system (Becton Dickinson Biosciences, Sparks, MD, USA) and confirmed by the ESBL E-test (AB Biodisk, Solna, Sweden). Susceptibilities of the infecting organism to all antimicrobial agents were determined according to criteria of the Clinical and Laboratory Standards Institute (CLSI). (18)

Potential controls were all hospitalized neonates in the same time period without ESBL-colonization. Controls were randomly sampled in a 4:1 ratio to case patients matched on date of admission.

## Risk factors for colonization with ESBL–producing *E. coli* of *Klebsiella* species

Potential risk factors for the isolates demonstrating ESBL-mediated resistance in infants were ascertained by means of a review of medical records and

Utrecht Patient Oriented Database (UPOD). UPOD is an infrastructure of relational databases, comprising administrative data since January 2004 on patient characteristics, laboratory test results, medication orders, discharge diagnoses and medical procedures for all patients treated at the UMC Utrecht, a 1042-bed tertiary teaching hospital in the Netherlands. All UPOD research is in accordance with current Dutch privacy and ethical regulation. A more complete description of UPOD has been published elsewhere. (19)

Data obtained included sex, birth weight (BW), birth date, gestational age (GA), length of stay until date of positive culture, indication of admission (ICD-9). The presence of a central venous catheter (CVC), urinary catheter, mechanical ventilation, total parenteral nutrition (TPN), and proven neonatal sepsis was also assessed. All antimicrobial therapy (both for neonate and mother) that was administered during admission was documented.

## Early-warning markers for colonization with ESBL–producing *E. coli* or *Klebsiella* species

Data were obtained from UPOD. Cell-Dyn Sapphire automated hematocytometers (Abbott Diagnostics, St. Clara, CA, USA) were used as the routine haematology analyzers at the UMC Utrecht. Five morphological differential parameters provided information about the size, complexity, lobularity, depolarization, and cell damage of leukocytes. These morphological differential parameters were used as input for the default Cell-Dyn algorithm to classify leukocytes. Since routine hematocytometry analyzers generate vast amounts of data on circulating blood cells that may be valuable biomarkers, the raw data from these analyzers were incorporated in UPOD. Data mining techniques can be useful for identifying important markers in the management of certain patient groups and to facilitate better discriminative power for clinicians. (17)

From UPOD several leukocyte hematocytometry parameters were documented as potential early-warning markers for ESBL-colonization: total number of leukocytes, neutrophilic granulocytes, lymphocytes, monocytes, basophilic granulocytes and eosinophilic granulocytes. At five different time-points prior to the date of first positive or negative culture with ESBL (i.e. index date), the highest value of these hematocytometry parameters were collected, namely:

- on the day of birth
- on the day before the index date
- time window 2-3 days prior to the index date
- time window 4-7 days prior to the index date
- time window 1-7 days prior to the index date

## Data analysis

Demographic and clinical variables between cases and controls were compared. Descriptive analyses were performed to assess the distribution and frequency of the dependent and independent variables. Univariate analysis on potential risk factors for ESBL-colonization was performed. Continuous variables were compared using Wilcoxon rank sum test. Multivariable analysis was performed using conditional logistic regression to adjust for the presence of confounding. All variables with a P-value < 0.20 on univariate analysis were considered for inclusion in the multivariable model. A two-tailed P-value < 0.05 on multivariable analysis was considered statistically significant. Statistical analyses were performed by SPSS for Windows, version 15.0 (SPSS Inc., Chicago, Il, USA).

# Results

Among 1833 infants admitted to the NICU during the study period, a total of 26 infants were found to be colonized with ESBL-producing *Enterobacteriaceae*. There was no significant difference in the frequency distribution of the investigated risk factors: sex, birth weight, gestational age, length of stay until first date of positive or negative culture, presence of mechanical ventilation, a central venous catheter, total parenteral nutrition, proven sepsis, antibiotic use by infant, number of days of any antibiotic use by infant, and presence of an urinary catheter between cases and controls (*Table 1*). However, the cases had significantly more frequently a mother who had used antibiotics prior to birth (OR: 4.9; 95% CI: 1.98-12.1) compared to the controls. In addition, the cases had significantly more often used cefazolin (OR: 2.8; 95% CI: 1.18-6.52) compared to the controls. There were no significant differences in leukocyte hematocytometry parameters between

Table 1. Demographic and clinical characteristics of hospitalized infants colonized with ESBL-producing *E. coli* and *Klebsiella* sp.

| Variable | | Cases (n=26) | Controls (n= 153) | OR (95% CI) | P-value |
|---|---|---|---|---|---|
| **Gender** | Male, n (%) | 17 (65.4) | 87 (56.9) | 0.70 (0.29-1.66) | 0.43 |
| **Birth weight (grams)** | ≥ 1500, n (%) | 11 (42.3) | 61 (39.9) | 1.11 (0.48-2.57) | 0.82 |
| **Gestational age (weeks, mean)** | ≥ 32, n (%) | 8 (30.8) | 49 (32.0) | 0.94 (0.38-2.32) | 0.90 |
| **Length of stay until first date of ESBL-colonization, median days (IQR )** | | 17 (13-26) | 13 (8.25-22) | 1.02 (1.00-1.05) | 0.09 |
| **Mechanical ventilation, n (%)** | | 25 (96.1) | 122 (79.7) | 6.35 (0.83-48.72) | 0.08 |
| **Central venous catheter, n (%)** | | 26 (100) | 125 (81.7) | - | - |
| **Total Parenteral Nutrition, n (%)** | | 24 (92.3) | 122 (79.7) | 3.09 (0.68-13.60) | 0.14 |
| **Proven neonatal sepsis, n (%)** | | 10 (38.5) | 44 (28.8) | 1.55 (0.65-3.67) | 0.32 |
| **Antibiotic use by infant, n (%)** | | 26 (100) | 136 (88.9) | - | - |
| **Length of any antibiotic use by infant, median number of days (IQR)** | | 7 (4-11.25) | 6 (3-10) | 1.04 (0.99-1.10) | 0.12 |
| **Use of amoxicillin-clavulanic acid by infant, n (%)** | | 18 (69.2) | 115 (75.2) | 0.74 (0.30-1.85) | 0.52 |
| **Use of gentamicin by infant, n (%)** | | 21 (80.8) | 115 (75.2) | 1.39 (0.49-3.93) | 0.54 |
| **Use of cefazolin by infant, n (%)** | | 16 (61.5) | 56 (36.6) | 2.77 (1.18-6.52) | 0.02 |
| **Antibiotic use prior to birth by mother, n (%)** | | 12 (50) | 26 (17) | 4.89 (1.98-12.07) | 0.001 |
| **Urinary catheter, n (%)** | | 2 (8.0) | 3 (2.0) | 4.35 (0.69-27.44) | 0.12 |

cases and controls (*Table 2*). Multivariable regression analysis revealed that only antibiotic use prior to birth by the mother (OR: 4.0; 95% CI: 1.45-11.0) was an independent risk factor for ESBL-colonization.

Table 2. Potential early-warning markers of hospitalized infants colonized with ESBL-producing *E. coli* and *Klebsiella* sp.

| Variable | Cases | Controls | OR (95% CI) | P-value |
|---|---|---|---|---|
| **Total number of leucocytes within period of 4-7 days prior to index date > 21.0 * $10^9$/L, n (%)*** | 7 (33.3) | 22 (18.6) | 2.18 (0.79-6.04) | 0.13 |
| **Total number of leucocytes on one day before index date > 21.0 * $10^9$/L, n (%)*** | 4 (20) | 7 (15.5) | 1.37 (0.41-4.59) | 0.61 |
| **Total number of neutrophilic granulocytes within period of 4-7 days prior to index date < 1.0 * $10^9$/L, n (%)*** | 0 | 1 (0.8) | - | - |
| **Total number of neutrophilic granulocytes on one day before index date < 1.0 * $10^9$/L, n (%)*** | 0 | 0 | - | - |
| **Total number of neutrophilic granulocytes within period of 4-7 days prior to index date > 10.0 * $10^9$/L, n (%)*** | 10 (47.6) | 37 (31.4) | 1.99 (0.78-5.10) | 0.15 |
| **Total number of neutrophilic granulocytes on one day before index date > 10.0 * $10^9$/L, n (%)*** | 3 (14.3) | 25 (22.9) | 0.56 (0.15-2.06) | 0.38 |
| **Total number of lymphocytes within period of 4-7 days prior to index date > 17.0 * $10^9$/L, n (%)*** | 0 | 0 | - | - |
| **Total number of lymphocytes on one day before index date > 17.0 * $10^9$/L, n (%)*** | 0 | 0 | - | - |
| **Total number of monocytes within period of 4-7 days prior to index date > 0.8 * $10^9$/L, n (%)*** | 21 (100) | 110 (94.0) | - | - |
| **Total number of monocytes on one day before index date > 0.8 * $10^9$/L, n (%)*** | 20 (95.2) | 102 (94.4) | 1.18 (0.13-10.31) | 0.88 |
| **Total number of basophilic granulocytes within period of 4-7 days prior to index date > 0.2 * $10^9$/L, n (%)*** | 0 | 1 (0.8) | - | - |
| **Total number of basophilic granulocytes on one day before index date > 0.2 * $10^9$/L, n (%)*** | 0 | 2 (1.8) | - | - |
| **Total number of eosinophilic granulocytes within period of 4-7 days prior to index date > 0.4 * $10^9$/L, n (%)*** | 10 (52.6) | 57 (51.4) | 1.05 (0.40-2.79) | 0.92 |
| **Total number of eosinophilic granulocytes on one day before index date > 0.4 * $10^9$/L, n (%)*** | 10 (47.6) | 55 (54.5) | 0.76 (0.30-1.95) | 0.57 |

* ranges of values derived from (32)

## Discussion

This is, to our knowledge, the first study that demonstrates that use of antibiotics by the mother prior to birth is a statistically significant risk factor for ESBL-colonization of infants hospitalized in the NICU. Our finding suggests a so called 'vertical' transmission of ESBL-positive strains.

Compared to other studies (4-6;13;20-24), our study did not find any significant association between the use of third-generation cephalosporins by infants and ESBL-colonization or infection. This can be explained by the fact that third-generation cephalosporins are hardly prescribed in our NICU. In addition, compared to other studies, we did not find that length of stay (23;25;26), use of ampicillin and gentamicin (5;25;27), low birth weight (20;23), lower gestational age (6) or mechanical ventilation and TPN (23) were independent risk factors of ESBL-colonization or infection.

Regarding our primary finding that maternal antibiotic use prior to birth is a significant risk factor for neonatal ESBL-colonization, it would be interesting to identify in what way mothers, who used antibiotics prior to birth, have been colonized by ESBL. Unfortunately, we did not find a potential early-warning marker for ESBL-colonization, but by further analysis, one can, for instance, additionally measure morphological differential parameters of leukocytes, neutrophilic, basophilic and eosinophilic granulocytes, lymphocytes, monocytes and thrombocytes, in order to evaluate the potential added value of these morphological differential parameters to our already existing infrastructure of databases, i.e. UPOD.

In our study and until now we fortunately have identified no cases of ESBL-infection, but only ESBL-colonization, which was in contrast to reports from other countries (5;13;20;23;24;27-30), where drastic interventions, such as restriction of cephalosporins (30) or oral administration of colistin as prophylaxis, were needed. (31) Nevertheless, information on both maternal antibiotic use and microbial colonization is important to identify infants at risk for ESBL-colonization or infection.

There were several potential limitations to our study. Firstly, the relatively small sample size, consequently leading to wide confidence interval estimates. A second limitation was the absence of molecular epidemiological analysis for ESBL-positive strains. It would be interesting to identify whether the ESBL isolates are closely related. One might hypothesize that there is not only 'vertical' but also 'horizontal' transmission (e.g. import from the NICU through healthcare workers) of ESBL in our NICU. Thirdly, it would have been interesting to include other potential risk factors which were not included in

our present study, such as occurrence of Caesarean section, medical microbiological information from the mother (e.g. ESBL-colonization), and additional clinical data of the infant, such as previous use of corticosteroids, or surgical procedures, since the latter factors affect leukocyte counts.

In conclusion, our study demonstrates that maternal antibiotic use prior to birth is an independent risk factor for neonatal ESBL-colonization. We were not able to identify early-warning markers. Further prospective studies are needed to confirm the risk factors and to identify early-warning markers for ESBL-colonization among infants admitted at NICU's.

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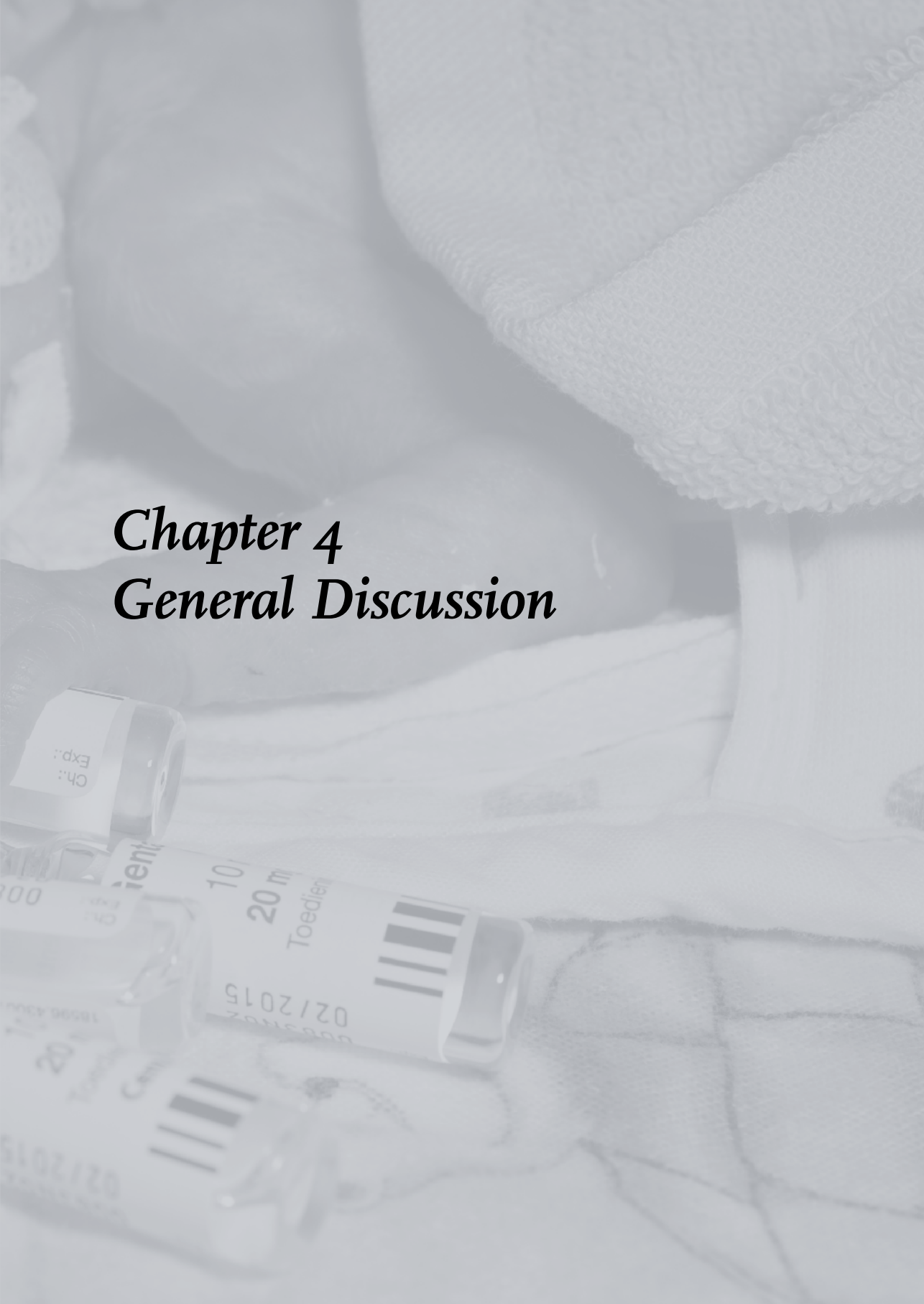
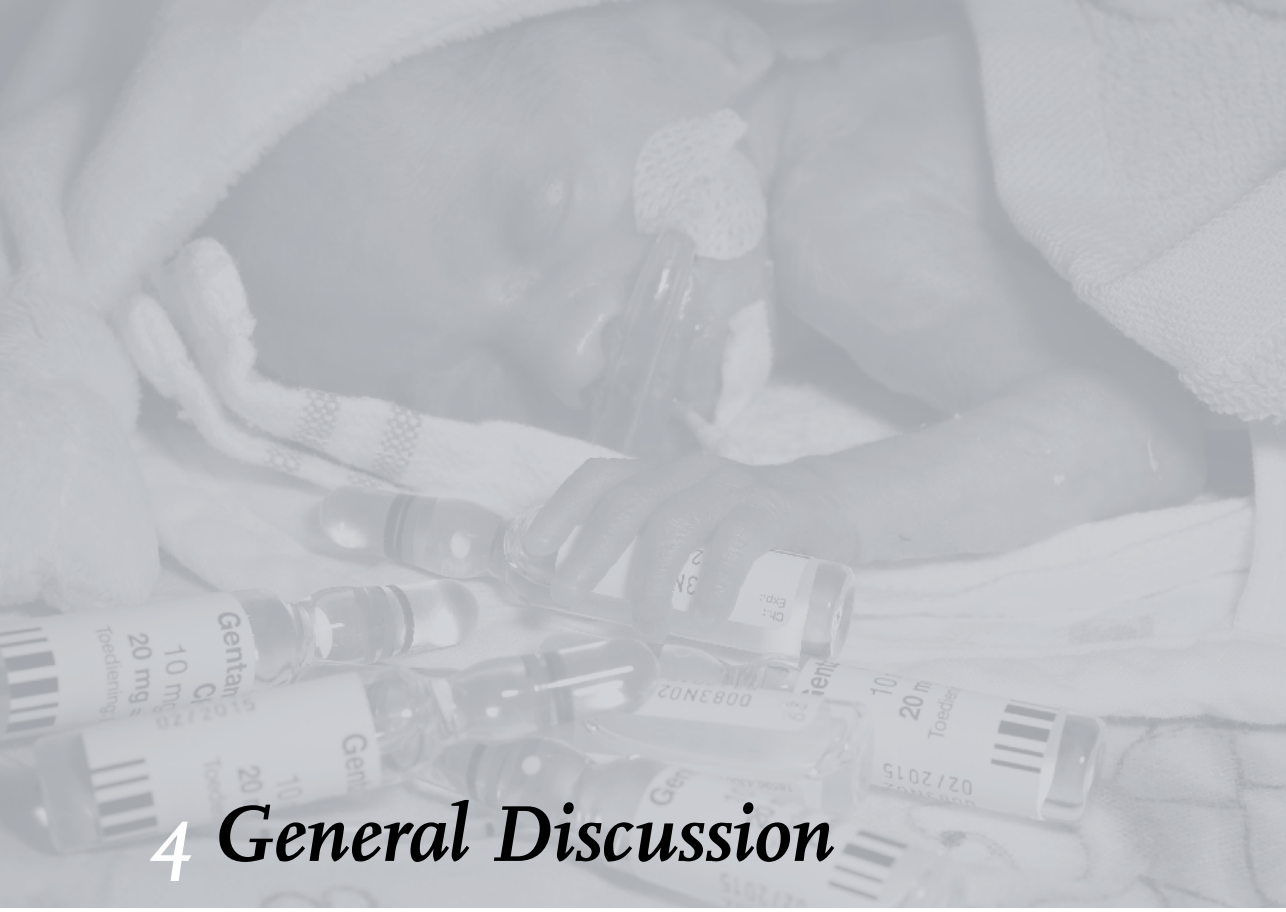


# *Chapter 4*
# *General Discussion*



# 4 General Discussion

The general aim of this thesis was to describe patterns of antibiotic use in hospitals, primarily in children, and its clinical consequences. This thesis consisted of two parts. In *chapter 2* the main theme of the studies was the methodological aspects of measuring antibiotic use in hospitals. *Chapter 3* addressed the patterns of antibiotic use in hospitalized patients and the consequences of antibiotic use in a NICU.

In the present chapter the main findings of the thesis are discussed, focussing on two main topics namely 'measuring antibiotic use in hospitals' and 'variability in antibiotic use'. Finally, implications for clinical practice and perspectives for future research are presented.

## Measuring antibiotic use in hospitals

Most European countries currently collect data to monitor drug consumption by measuring volume as well as expenditures on a nationwide level. In order to compare drug consumption on an international scale, a drug classification system was developed by the WHO, i.e. the Anatomical Therapeutic and Chemical Classification including a standardised expression of drug use in Defined Daily Doses (ATC/DDD system). (1;2) Subsequently, in numerous studies the extent of drug consumption of different therapeutic classes, expressed in volume and/or costs, has been compared between several European countries. (3-11) More recently these national surveillance systems on drug consumption have been increasingly used for another goal, namely to measure the quality of prescribing (e.g. regarding antibiotics (12)). In this perspective, however, one has to recognize (both the opportunities and) the pitfalls of measuring prescribing quality using indicators derived from drug consumption databases, such as the taxonomy, the nature of the available data sources and especially the validity of these indicators for prescribing quality. (13;14)

It is generally accepted that measuring antibiotic use is essential for the successful implementation of strategies to contain antimicrobial resistance. Data from so called epidemiological surveillance systems on antibiotic use give insight how to plan, implement and evaluate interventions in order to optimize antibiotic use in a particular setting. In the past two decades several international and national surveillance systems on antibiotic use have been set up and presented their data. (4;15-35)

Numerous methods exist to measure antibiotic use, but before collecting and analyzing data on antibiotic use, it is essential to clearly define different key factors for a surveillance system for antibiotic use in hospitals, such as selection of antibiotics, identification of sources of valid and available data,

assessment of appropriate units of measurement, assessment of the frequency of data collection and reporting and assessment of the detail and level of aggregation (*Table 1*). (36;37)

Table 1. Crucial issues in measuring antibiotic use in hospitals

| Issue | Options |
|---|---|
| **Determination of the goal** | ○ Measure the volume and expenditures of prescribing<br>○ Measure the quality of prescribing |
| **Identification of sources of valid and available data** | ○ Administrative data (invoices, costs)<br>○ Pharmacy delivery data<br>○ Prescription data<br>○ Patient administration data |
| **Assessment of the (detail and) level of aggregation** | ○ Specific patient group level<br>○ Hospital level<br>○ National level<br>○ International level |
| **Assessment of the appropriate units of measurement** | ○ Numerator: number of grams, DDDs, number of packages, prescriptions, days of therapy (DOT). In paediatrics: no DDDs, but preferably DOT or for neonates: neonatal DDDs<br>○ Denominator: patient days, admissions, (occupied) bed days |

Several units of measurement have been used to express the quantity of antibiotic use. In general, these units of measurement consist of a numerator and a denominator. The number of grams, defined daily doses (DDD), number of packages, prescriptions, days of therapy or number of exposed patients have all been used as numerator. Regarding the first three examples, one has to recognize the potential difference between the delivered or prescribed quantity of antibiotics and the administered quantity. As mentioned earlier on, the WHO recommends the DDD for drug utilization studies. The most frequently used unit of measurement to compare antibiotic use over time, in and between hospitals, various geographical regions and countries in these studies/reports, as recommended by the WHO, is the number of DDD's per 100 patient days. As denominator, the number of patient days may be calculated by subtracting the number of admissions from the number of bed days as the number of bed days overestimates actual treatment days by including both the day of admission and the day of discharge. (37) The number of bed days may be obtained by multiplying the number of admissions with the average length of stay or the number of beds multiplied by the average occupancy rate. Other denominators can be the number of admissions or discharges and the number of (occupied) beds

(number of patients). In the meantime, however, several critics debated on the issue which unit of measurement for antibiotic use is the best. (21;38-42) Apart from this discussion, the question which of the numerous methods to estimate prevalence of drug use in general is recommended, was already raised earlier on. (43)

In one of our studies we illustrated that it is important which unit of measurement is used for the interpretation of trends in antibiotic use in relation with resistance. (44) Total antibiotic use between 1997-2001 in nearly 60 hospitals in the Netherlands was analyzed, which significantly increased over time when antibiotic use was expressed in DDD per 100 patient days while expressed in DDD per 100 admissions it was stable over time. In addition, several individual antibiotics showed increases over time when expressed in DDD per 100 patient days without the same trend when expressed in DDD per 100 admissions. Moreover, one has to realize that in the period 1997-2001 the mean number of admissions, bed days and length of stay decreased substantially, but total antibiotic use expressed in DDD's slightly decreased. Hence, in this study period patients in hospitals did not receive *more* antibiotics, but as the length of stay of these patients decreased, the number of DDD per 100 patient days increased. This at itself is frequently interpreted as alarming considering the emergence of antibiotic resistance. Nevertheless, our study showed a stable antibiotic use per patient and a reduction in the number of admissions, representing a lower selection pressure. Additionally, shorter length of antibiotic therapy may result in not as much selection of resistant micro-organisms as with longer length of therapy. (45-50) In conclusion, the unit of measurement for antibiotic use, DDD per 100 admissions, is preferred in studies comparing antibiotic use over time or between different settings, such as hospitals, geographical regions or countries, since it is not as susceptible to changes in hospital resource indicators over time as DDD per 100 patient days. Therefore in our view, in order to interpret trends in antibiotic use with regard to antibiotic resistance risks, one should present data on antibiotic use both in DDD per 100 patient days and DDD per 100 admissions, including presentation of potential trends in hospital resource indicators.

Yet, regarding measuring antibiotic use in children it is known that the WHO DDD methodology is unfortunately not applicable in paediatrics, mainly in children aged between 1 month-18 years, because the large variation in body weight within this population. But in the neonatal population, until patient level data are widely available and based on its narrow range of body weights, we suggested in one of our studies, that the neonatal DDD (NDDD) is

a good alternative unit of measurement, both in research and for benchmarking purposes. (51) Hence, standardization of neonatal antibiotic dosing schemes is desirable, since this can serve as a basis for developing a set of NDDD's. On the other hand, one of our studies illustrated variation in neonatal dosage recommendations of several antibiotics from different international textbooks on paediatrics and paediatric infectious diseases, which should be preferably eliminated to obtain established dosage regimens and thus full benefit of computerized physician order entry (CPOE) and clinical decision support systems in neonatology.

Concerning another key factor of a surveillance system on antibiotic use in hospitals, i.e. the level of aggregation of data, it is crucial to define the aim of collecting data on antibiotic use. When the aim is to analyze antibiotic use in an individual hospital including linkage with local resistance data, one should analyze antibiotic use by unit or discipline. In the case of monitoring antibiotic use aiming at comparison or benchmark of antibiotic use with other hospitals at regional or national level, antibiotic use data collection at hospital level or distinction between different wards will suffice. As discussed in one of our studies in which trends in antibiotic use in Dutch hospitals between 1997 and 2002 were analyzed and interpreted, however, data on the use of antibiotics at hospital level might be too crude for identifying subtle trends in antibiotic use of specific patient populations. (52) Hence, monitoring antibiotic use trends by specific populations within the hospital is necessary, as this allows us to detect substantial changes that would be overlooked if hospital-wide data are aggregated into national trends. Moreover, since the DDD neither reflects the recommended, nor the actually prescribed daily dosage (PDD) for individual patients or specific patient populations (38;40;41;53;54), ideally, the actual consumption of antibiotics should be measured at the level of the individual patient and subsequently aggregated over patient groups and settings. This leads to more precise estimates but more importantly also allows to study associations on an individual patient level between patient characteristics, setting characteristics (e.g. antibiotic policy), antibiotic use and clinically relevant outcomes, including antibiotic resistance.

Therefore and based on the facts that antibiotics are the most frequently prescribed medicines in neonatology (55-61), all other studies in this thesis focussed on patterns of antibiotic use in the neonatal population. These studies monitored antibiotic use on two different aggregation levels, i.e. on national level (between all tertiary care NICU's in the Netherlands) and on local hospital level (NICU of the Wilhelmina Children's Hospital, University

Medical Center Utrecht); in the latter case antibiotic use was even based on patient data.

## Variability in antibiotic use

Most strikingly, it seems that there is some kind of 'paradox' in this thesis, since both studies on trends in antibiotic use between different Dutch hospitals and between all Dutch tertiary care NICU's demonstrated a considerable variability in total amount of antibiotic use and number of different antibiotics used, which was in large contrast to the more or less stable pattern (over 19 years) shown in the NICU of our hospital. The 'sixty-four thousand dollar question' is obviously what the explanation for this contrast could be. Several factors might explain the variability in antibiotic use between different hospitals and NICU's, such as the differences in (hospital's) case mix of patients and in local resistance levels, or those factors related to local antibiotic policies including presence of guidelines and restricted lists of antibiotics, and last but not least, the presence of an antimicrobial stewardship programme (ASP). Such variability in antibiotic use between hospitals and NICU's cries for explanation. Apart from that, variability in antibiotic use is not an isolated phenomenon, since it recently also has been demonstrated in other classes of drugs, such as thiazolidinediones (rosiglitazone) (62) or blood products (allogeneic red blood cell, fresh-frozen plasma, and platelet transfusions). (63)

Moreover, in a recent study on the variability in antibiotic use between US children's hospitals, the variability even remained after normalizing for differences in patients' case mix, meaning that either children at some hospitals were undertreated with antibiotics and consequently were at risk of treatment failure or that some hospitalized children were overtreated with antibiotics and therefore were prone to developing antibiotic resistant infections and antibiotic-related adverse effects. (64)

Although it has not been investigated by ourselves as primary objective of one of our studies (65), one might carefully conclude that the ASP in our NICU positively contributed to the accuracy of antimicrobial therapy (in other words: a significantly decreased total antibiotic use, despite the high proportion of infants that received antibiotics, and moreover a rather unchanged protocol for the choice of antibiotics to treat neonatal sepsis during the entire period of 19 years).

ASP's, or antimicrobial management programmes, support the appropriate use of antimicrobial agents; it should include optimization of the agent selected, the dose, route, and duration of therapy aiming at improvement of

patient care and outcomes. Previous evaluations have confirmed that ASP's improve patient care. (66-75) Despite the success stories of ASP's, Charani et al recently raised the discussion on what is missing in these programmes. (76) They stated that not only rules and guidelines aimed at prescribers, as main principle of ASP's, are sufficient to encourage prudent antibiotic use, but also an environment that facilitates and supports optimal prescribing choices. Therefore they suggested implementing a whole-system approach in order to make prudent antibiotic management a fundamental part of the behaviour of all healthcare professionals.

To put the abovementioned in the perspective of the NICU's in the Netherlands, it is remarkable that until now there is no national treatment guideline for the most important infectious diseases in neonates (i.e. neonatal sepsis, meningitis or necrotizing enterocolitis). In one of our studies, the available treatment protocols for neonatal sepsis for all NICU's showed variation. Furthermore, although it was unfortunately not investigated in this study, it is informally known that a large minority of the NICU's in the Netherlands have an implemented ASP. In order to overcome the variability in antibiotic use in NICU's (and hospitals and other settings/wards/units) in the Netherlands and to limit the use of antibiotics beyond that determined by the protocol, it is essential to implement antimicrobial stewardship across all NICU's and to make an effort to achieve uniformity in antibiotic policy for the treatment of infections in NICU's in the Netherlands, especially supported by the Dutch Working Party on Antibiotic Policy (acronym: SWAB).

Nevertheless, in our view and as also suggested by Charani et al, antibiotic management programmes focussing on evidence-based guidelines and policy should also consider effective systems that force prescribers (e.g. neonatologists) to prescribe in such a way that is helpful both to the patient and to broader public health. (12;76) These systems need to raise and maintain an awareness of the basic principles of appropriate antibiotic use among healthcare professionals, supported by education on key issues of microbiology and infectious diseases and rational pharmacotherapy. It has been demonstrated that bad-designed decision systems, e.g. poorly designed drug charts and outdated guidelines, lead to inappropriate antibiotic prescribing (77;78) and therefore suboptimal decisions, e.g. a longer than necessary duration of therapy and use of broad-spectrum antibiotics where narrow-spectrum antibiotics would suffice. Hence, in order to optimize current antibiotic prescribing practice not only 'the whole environment' but also clinical decision support systems for antibiotic prescribing should be addressed. (76) Developing and implementing such well-designed clinical

decision support systems for antibiotic prescribing, which already demonstrated to improve the percentage of appropriate antibiotic treatment and patients' outcome, while reducing the use of broad-spectrum antibiotics (79;80), should play a key role in antimicrobial stewardship in neonatology. Eventually, this multifaceted approach might help to overcome the evident variability in antibiotic use in paediatrics and therefore in neonatology.

# Conclusion

Based on the results of the studies in this thesis, we provide some recommendations for clinical practice and future studies in order to encourage appropriate antibiotic use in hospitals in general and specifically hospitalized children and therefore to conquer the emerging problem of antimicrobial resistance.

## Implications for clinical practice

- Implement an antibiotic stewardship programme or team in NICU's and other hospital departments
- Achieve uniformity in antibiotic policy for the treatment of infections in NICU's in the Netherlands
- Implement education programmes on paediatric infectious diseases and treatment thereof for medical and pharmacy students and paediatricians
- Set up a surveillance system on antibiotic use linked to antimicrobial resistance (e.g. ESBL), analogous to Nethmap, in all NICU's in the Netherlands
- Collect information on both maternal antibiotic use and microbial colonization in order to identify infants at risk for ESBL-colonization or infection.
- Report antibiotic use in hospitals in both DDD/100 patient days and DDD/100 admission and always report hospital resource indicators (e.g. length of stay, total number of admissions and number of bed days). Additionally, link these antibiotic use data to resistance data
- Achieve uniformity in neonatal dosage recommendations of antibiotics, based on information from established international textbooks and corresponding 'Summaries of Product Characteristics (SmPCs)'. Additionally, include these dosage recommendations in the SmPCs, in case these are not mentioned herein.
- Implement a clinical decision support system for antibiotic prescribing in neonatology, including standardized neonatal antibiotic dosing recommendations for CPOE

## Implications for research

- Studies to validate the optimal unit of measurement of antibiotic use in children for the various purposes
- More specifically, studies to validate the optimal numerator of the unit of measurement of antibiotic use in children, i.e. neonatal DDD (NDDD) and pediatric DDD (PDDD)
- Qualitative studies to unravel reasons for variability in antibiotic use between settings and quantitative studies to evaluate the clinical consequences (including resistance) of variability
- Prospective studies on the efficacy of an antibiotic stewardship programme or team in a NICU (and other hospital departments) on optimal use of antibiotics
- Prospective studies to determine risk factors and early-warning biomarkers for ESBL-colonization among neonates and to evaluate the impact on antibiotic use and hospital hygiene.
- Further analysis in our NICU in close collaboration with the departments of clinical pharmacy, clinical chemistry and medical microbiology to identify how morphological differential parameters of leukocytes, neutrophilic granulocytes, lymphocytes, thrombocytes etc. differ between neonates with ESBL-colonization/infection and those without, in order to better understand these potential early-warning markers and to evaluate the potential added value of these morphological differential parameters to UPOD.

In conclusion, in this thesis we faced several methodological challenges in measuring antibiotic use in hospitals and hospitalized children (e.g. appropriate unit of measurement for antibiotic use and variability in neonatal dosage recommendations). Moreover, our results of monitoring antibiotic use in hospitals and hospitalized children showed clear variability in total antibiotic use, which is potentially worrisome. Antibiotics are true medical treasures. Nevertheless, they are the only class of drugs whose efficacy reduces when approved for extensive use. Emerging problems, such as multidrug resistance and hardly any development of new antibiotics emphasizes the importance of appropriate antibiotic use. Therefore, we should recognize the intangible costs and collateral damage associated with inappropriate antibiotic use and take all measures to tackle this global rising problem.

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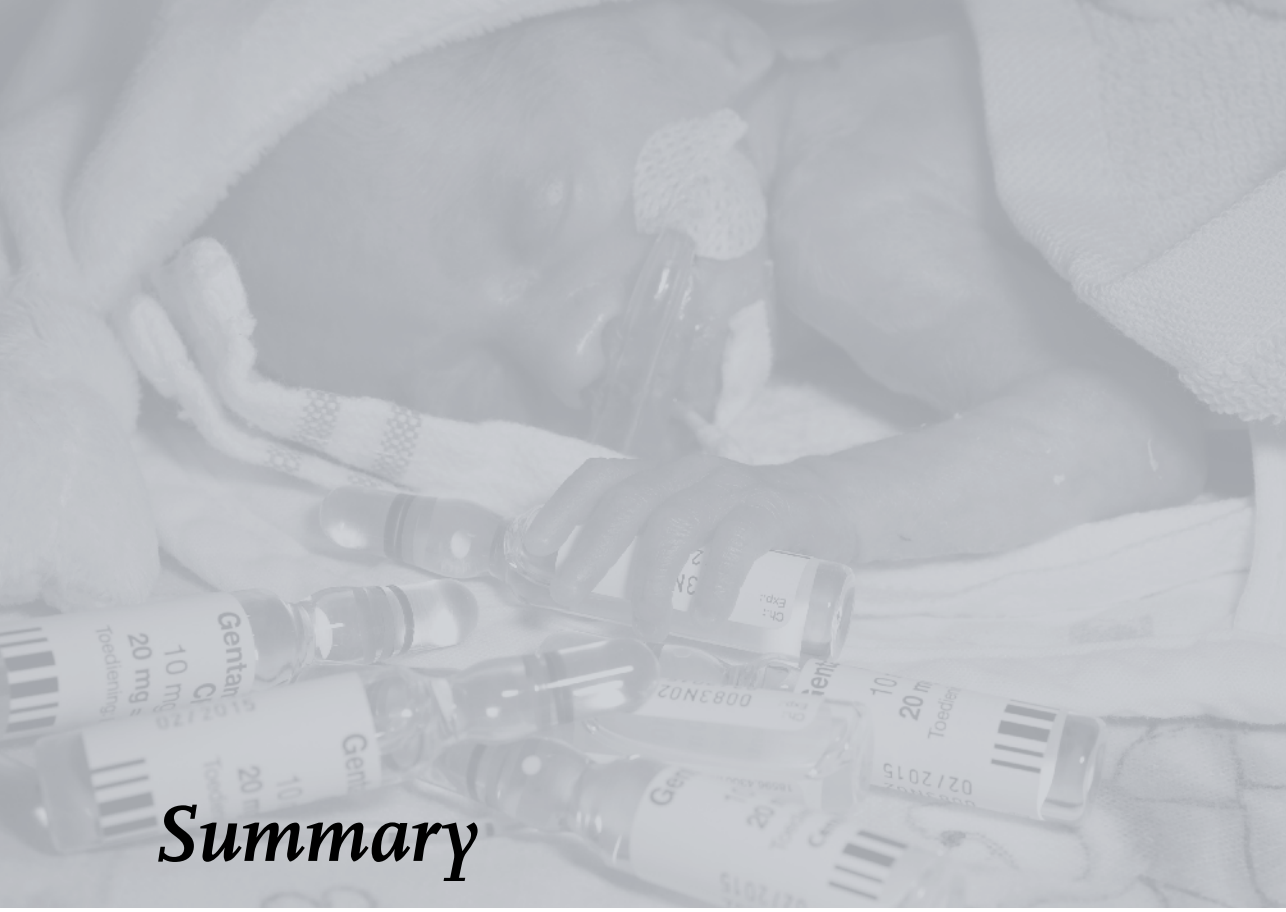


# *Summary*

The discovery of antibiotics represents one of the milestones in modern medicine, saving countless lives over the last 60 years. Likewise the resistance to antimicrobial drugs is a great threat to public health. The reasons for the rise in antimicrobial resistance are manifold and complex, but it has become clear that excessive use of antibiotics increases the risk of the emergence and selection of antimicrobial resistant organisms. From this perspective, appropriate antibiotic use is crucial to prevent the emergence of multidrug resistant microorganisms.

Quantitative and qualitative data on the use of antibiotics in hospitals are useful to evaluate strategies that are implemented to contain antimicrobial resistance. Ideally, resistance rates also need to be measured. It is important to collect, analyse and present antibiotic use data in a standardized way and clearly define certain key factors regarding antibiotic use in hospitals, e.g. determination of the goal, identification of sources of valid and available data, assessment of the (detail and) level of aggregation, and assessment of the appropriate units of measurement.

Valid data on the use of antibiotics at the hospital level are crucial for the interpretation of prescribing habits, the evaluation of compliance with clinical guidelines and the relation with resistance, but these data might be too crude for identifying subtle trends in antibiotic use of specific patient populations. Therefore, monitoring antibiotic use patterns by specific populations within the hospital is warranted. In this way relevant changes can be demonstrated that would be overlooked if hospital-wide data are aggregated into national trends.

Among the drugs most frequently used in neonatal intensive care units (NICU's) antimicrobial agents rank highest, since the multiple risk factors for infection in preterm immunocompromised infants result in a low threshold for the initiation of antimicrobial therapy. Consequently, NICU's bear the risk of microorganisms that are colonizing infants of becoming resistant to various antibiotics.

The general aim of this thesis is to describe patterns of antibiotic use in hospitals, predominantly in neonates, and its clinical consequences. This thesis consists of two parts. In the first part, studies describe the methodological aspects of measuring antibiotic use in hospitals, whereas in the second part, studies describe the patterns and consequences of antibiotic use in hospitalized patients.

*Chapter 2* is entitled '*Methodological aspects of measuring antimicrobial drug use in hospitals*'. Although, it sounds rather simple to measure antibiotic use,

one has to recognize several methodological issues, which will be described in this chapter.

In *Chapter 2.1* we focused on the implication of units of measurement for a significant understanding of trends in antibiotic use data with regard to antibiotic resistance risks. Trends in antibiotic use in acute care Dutch hospitals between 1997 and 2001 were studied. Antibiotic use was expressed in Defined Daily Dose (DDD) per 100 patient days and in DDD per 100 admissions.

From 1997 to 2001, total systemic antibiotic use significantly increased from 47.2 to 54.7 DDD per 100 patient days, whereas expressed in DDD per 100 admissions it remained constant. Some individual antibiotics increases in DDD per 100 patient days were not accompanied by increases in DDD per 100 admissions and vice versa. The mean number of total DDD per hospital decreased (not significantly) between 1997 and 2001. The mean number of patient days, admissions and length of stay decreased significantly. In conclusion, this study showed that knowledge of variation in resource indicators and additional expression of the data in DDD per 100 admissions is imperative for a meaningful understanding of observed trends in antibiotic use expressed in DDD per 100 patient days.

In *Chapter 2.2* we compared dosage recommendations for antibiotics in neonates provided by commonly used and well-established international textbooks. Therefore, neonatal daily doses for the ten most frequently used antibiotics, classified by categories for birth weight and gestational age, were identified from seven well-respected textbooks in paediatrics/paediatric infectious diseases, and expressed as standardized average daily dosage (standardized ARDD). We found that antibiotics with a wide therapeutic window (e.g. ampicillin, benzylpenicillin, ceftazidime and cefotaxime) showed greater variation in dosage recommendations compared to those with a small therapeutic window (e.g. meropenem, gentamicin, and vancomycin). One textbook, namely 'BNF for children', showed larger variation in dosage recommendations compared to the other textbooks. In conclusion, gold standard, expert opinion antibiotic dosage recommendations for neonates can be derived from important textbooks and guidelines for most, but not all antibiotics. Further exploration to overcome variation in dosage recommendations is necessary to obtain standardized dosage regimens, which can be implemented in CPOE and clinical decision support systems in neonatology in order to reduce medication errors. Finally, the variation in

dosage recommendations, illustrated in this chapter, might explain the variability in total antibiotic use in NICU's as demonstrated in *Chapter 3.2*.

The DDD as defined by the World Health Organization (WHO) has been the most frequently used unit of measurement to measure antibiotic use. However, measuring antibiotic use in paediatrics is a problem as the WHO DDD methodology is not applicable in children (aged > 1 month), because the large variation in body weight within this population. In *Chapter 2.3*, we aimed to develop a set of neonatal DDD's for antibiotics, based on the narrow range of body weights in the neonatal population. Therefore, eight well-respected (inter)national sources for dosage recommendations of antibiotics in children and neonates were consulted for the assumed maintenance dose of the ten most frequently used antibiotics in NICU's in its main indication for neonates. As a result a set of neonatal DDD's for ten commonly used antibiotics in neonates based on an assumed neonatal weight of 2 kg was proposed. Thus, although primarily in children DDD's are not applicable to quantify antibiotic use since there is large variation in body weight, we conclude that in the neonatal population, based on its narrow range of body weights and when access to patient level data is not available, neonatal DDD's can be used as unit of measurement.

In *Chapter 3* we focused on patterns and consequences of antimicrobial drug use in hospitalized patients. Trends in antibiotic use were analyzed at different levels: at national, hospital and specific patient group (i.e. neonates) level.

*Chapter 3.1* described trends in antibiotic use in Dutch hospitals over the period 1997-2002. Data on antibiotic use and hospital resource indicators were obtained by distributing a questionnaire to all Dutch hospital pharmacies. Antibiotic use was expressed as the number of DDD per 100 patient days and as DDD per 100 admissions. We illustrated that between 1997 and 2002, the mean length of stay decreased by 18%. The mean number of admissions, however, remained almost constant. Total antibiotic use significantly increased by 24%, from 47.2 in 1997 to 58.5 DDD per 100 patient days in 2002 ($p<0.001$), whereas expressed as DDD per 100 admissions it remained constant. Antibiotic use varied largely between the hospitals. Moreover, the mean number of DDD per hospital of amoxicillin with clavulanic acid, clarithromycin, cefazolin, clindamycin and ciprofloxacin increased with 16%, 38%, 39%, 50% and 52%, respectively. Total antibiotic use was higher in university hospitals than in general hospitals. In conclusion, between 1997

and 2002 patients hospitalised in the Netherlands did not receive more antibiotics but, since they remained in the hospital for fewer days, the number of DDD per 100 patient days increased. For macrolides, lincosamides and fluoroquinolones increases in both DDD per 100 patient days and in DDD per 100 admissions were shown. It is arguable whether these trends result in an increase in selection pressure towards resistance in the hospitals. Continuous surveillance of antibiotic use and resistance is warranted to maintain efficacy and safety of antibiotic treatment.

In *Chapter 3.2* we examined the variation in quantity and classes of antibiotics used in all ten tertiary care NICU's in the Netherlands during 2005 in a national multicentre study. Data from all tertiary care NICU's in the Netherlands on clinical and demographic characteristics and the type and quantity of systemic antibiotic use (expressed as DDD/100 admissions) in 2005 were collected. Antibiotics were ranked by volume of DDD's, and those antibiotics which accounted for 90% of the total volume of use (Drug Utilization (DU) 90%) were noted. We demonstrated that antibiotic use ranged from 130-360 DDD/100 admissions. In total, 9-24 different antibiotics were used, of which 3-10 were in the DU90%-segment. In conclusion, by comparing antibiotic use in Dutch NICU's we found a substantial variation in the number of different antibiotics used and in the total amount of antibiotic use. Further exploration of the opportunities to reach consensus in antibiotic policy, and to increase attention to antibiotic stewardship, is recommended.

*Chapter 3.3* analyzed trends in antibiotic use in our NICU over a period of 19 years (1990-2008). Antibiotic use and clinical characteristics of all infants admitted to the NICU during each second year since 1990 were studied retrospectively. A constant and high proportion (85-90%) of admitted infants received antimicrobial therapy during any time of their stay, which was in sharp contrast to the much lower incidence of proven sepsis (14.1-16.6%). Total antimicrobial use expressed as days of therapy (DOT) decreased significantly over time from 9.0 to 5.8 (B = -0.226; 95% CI -0.369; -0.082; $p$=0.007), despite the high proportion of infants that received antimicrobial agents. Importantly, the clinical and demographic characteristics of all admitted infants to our NICU, such as birth weight, gestational age and length of stay, did not change significantly during the study period. The decrease in length of therapy was also significant for amoxicillin-clavulanic acid (B = -0.154; 95% CI -0.252; -0.055; $p$=0.007) and gentamicin (B = -0.237; 95% CI -0.358; -0.117; $p$=0.002) and to a lesser extent for cefazolin (B = -0.121; 95% CI -0.178; -0.064; $p$=0.001). Thus, over a period of 19 years no change was noted in the high percentage of infants treated with antibiotics in the

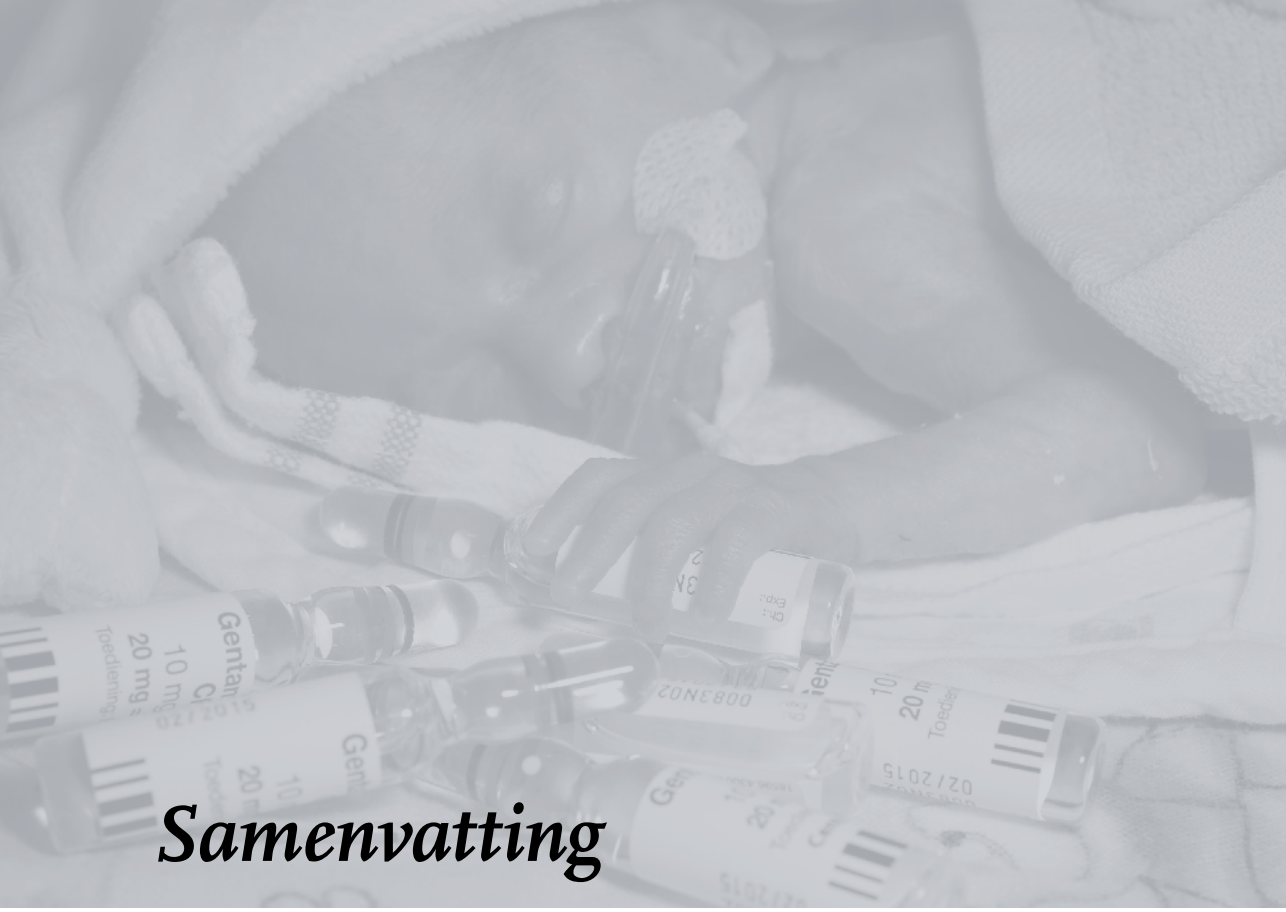
NICU. However, a significant decrease was noted in the length of therapy for amoxicillin-clavulanic acid, gentamicin and cefazolin, without an increase in incidence of sepsis and mortality. The correct identification of infants with sepsis remains a major challenge in attempts to further reduce antibiotic use and postpone the emergence of antibiotic resistant microorganisms.

In *Chapter 3.4* a nested case-control study in our NICU was performed to identify clinical risk factors and leukocyte hematocytometry parameters as early-warning markers for colonization by ESBL–producing *E. coli* or *Klebsiella* species in infants. A cohort consisting of all infants admitted to our NICU between 2007 and 2009 was assembled retrospectively through records of the Eijkman-Winkler Centre of Microbiology, Infectious Diseases and Inflammation, UMC Utrecht. The infants were classified as case patients if any of their *E. coli* or *Klebsiella* species isolates produced ESBL. Potential controls were all hospitalized neonates in the same time period without ESBL-colonization. Controls were randomly sampled in a 4:1 ratio to case patients matched on date of admission.

Potential risk factors and early-warning markers (i.e. total number of leukocytes, neutrophilic granulocytes, lymphocytes, monocytes, basophilic granulocytes and eosinophilic granulocytes) for the isolates demonstrating ESBL-mediated resistance in infants were ascertained by means of a review of medical records and Utrecht Patient Oriented Database (UPOD). As a result, among 1833 infants admitted to the NICU during the study period, a total of 26 infants were found to be colonized with ESBL-producing *Enterobacteriaceae*. Univariate analysis showed that the cases had significantly more frequently a mother who had used antibiotics prior to birth (OR: 4.9; 95% CI: 1.98-12.1) compared to the controls. In addition, the cases had significantly more often used cefazolin (OR: 2.8; 95% CI: 1.18-6.52) compared to the controls. There were, however, no significant differences in leukocyte hematocytometry parameters between cases and controls. Multivariable regression analysis revealed that only antibiotic use prior to birth by the mother (OR: 4.0; 95% CI: 1.45-11.0) was an independent risk factor for ESBL-colonization. We concluded that maternal antibiotic use prior to birth is an independent risk factor for neonatal ESBL-colonization, suggesting a so called 'vertical' transmission of ESBL-positive strains. We were not able to identify early-warning markers. Further prospective studies are needed to confirm the risk factors and to identify early-warning markers for ESBL-colonization among infants admitted at NICU's.

In *Chapter 4* the key findings of the studies in this thesis are discussed in a broader perspective, focusing on two main topics namely 'measuring antibiotic use in hospitals' and 'variability in antibiotic use'. We conclude with implications for clinical practice and perspectives for future research.

In conclusion, in this thesis we presented several methodological challenges in measuring antibiotic use in hospitals and hospitalized children. Moreover, our results of monitoring antibiotic use in hospitals and hospitalized children showed clear variability in total antibiotic use, which is potentially worrisome. Global threats, such as multidrug resistance and a nearly empty pipeline of new antibiotics, emphasizes the importance of appropriate antibiotic use. Therefore, we should recognize the enormous impact of inappropriate antibiotic use and tackle this global rising problem.



# *Samenvatting*

De ontdekking van antibiotica kan worden beschouwd als één van de mijlpalen binnen de moderne geneeskunde en heeft de afgelopen 60 jaren bijgedragen aan een substantiële afname van het aantal sterftegevallen als gevolg van infectieziekten. Helaas is de resistentie tegen antibiotica een steeds groter wordende bedreiging voor de gezondheidszorg. De redenen voor de toenemende antimicrobiële resistentie zijn complex, maar het is inmiddels wel duidelijk dat overmatig antibioticagebruik het risico van verspreiding en selectie van resistente micro-organismen verhoogt. Daarom is het zorgvuldig toepassen van antibiotica ('goed antibioticagebruik') van groot belang om het ontstaan en de verspreiding van multiresistente micro-organismen te voorkomen.

Kwantitatieve en kwalitatieve gegevens over antibioticagebruik in de diverse settings van gezondheidszorg zijn nodig om geïmplementeerde richtlijnen en resistentiebeperkende maatregelen te evalueren. Vanzelfsprekend dienen tevens resistentiegegevens te worden verzameld. Het is van belang om antibioticagebruiksgegevens op een gestandaardiseerde wijze te verzamelen, te analyseren en te presenteren. Hierbij moet tevens met een aantal belangrijke aspecten rekening worden gehouden, zoals het doel van het verzamelen van antibioticagebruik, de bronnen voor valide en beschikbare antibioticagebruiksgegevens, het detailniveau van de antibioticagebruiksgegevens en een goede meeteenheid voor antibioticagebruik.

Valide antibioticagebruiksgegevens van ziekenhuizen zijn essentieel voor het interpreteren van voorschrijfgedrag van artsen, maar deze gegevens kunnen soms te grof zijn om bepaalde subtiele trends in antibioticagebruik bij specifieke patiëntenpopulaties te herkennen. In die gevallen is het monitoren van antibioticagebruik binnen specifieke patiëntenpopulaties in een ziekenhuis noodzakelijk. Op deze manier kunnen relevante trends worden opgemerkt, die niet zouden zijn opgevallen bij het verzamelen van de gegevens op ziekenhuisniveau (binnen één ziekenhuis of meerdere ziekenhuizen).

Een voorbeeld van zo'n specifieke patiëntenpopulatie is neonaten. Antibiotica zijn de meest voorgeschreven geneesmiddelen in neonatale intensive care units (NICU's). Dit is te verklaren door het feit dat diverse risicofactoren voor infectie bij premature immuungecompromiteerde kinderen leiden tot een lage drempel om antibiotica te starten, met als gevolg een verhoogd risico van multiresistente micro-organismen in NICU's.

Het doel van dit proefschrift is het beschrijven van de gebruikspatronen (o.a. behandelingsduur, antibioticumkeuze en totale hoeveelheid) van

antibiotica in ziekenhuizen, in het bijzonder in neonaten, en de klinische gevolgen daarvan. Dit proefschrift bestaat uit twee delen. In het eerste deel worden onderzoeken beschreven die de methodologische aspecten van het meten van antibioticagebruik in ziekenhuizen aan de orde stellen. Het tweede deel bevat onderzoeken die de gebruikspatronen van antibiotica en gevolgen daarvan in opgenomen patiënten beschrijven.

*Hoofdstuk 2* van dit proefschrift is getiteld '*Methodologische aspecten van het meten van antibioticagebruik in ziekenhuizen*'. Hoewel het eenvoudig klinkt om antibioticagebruik te meten, is het toch van groot belang om rekening te houden met verschillende methodologische aspecten, die in dit deel van het proefschrift worden besproken.

In het onderzoek in *Hoofdstuk 2.1* wordt het belang van gebruikte meeteenheden om antibioticagebruik uit te drukken benadrukt. Hiertoe zijn de trends in antibioticagebruik in Nederlandse ziekenhuizen in de periode 1997-2001 geanalyseerd. Het antibioticagebruik wordt uitgedrukt in het aantal 'defined daily doses (DDD) per 100 patiëntdagen', zoals ook door de World Health Organization (WHO) wordt aanbevolen. In dit onderzoek wordt daarnaast een nieuwe meeteenheid voor antibioticagebruik geïntroduceerd, te weten het aantal DDD per 100 opnamen. Uit dit onderzoek blijkt dat gedurende de periode 1997-2001 het totale antibioticagebruik is gestegen van 47,2 naar 54,7 DDD per 100 patiëntdagen, terwijl het aantal DDD per 100 opnamen in dezelfde periode niet is gestegen. De discrepantie tussen deze twee trends in antibioticagebruik is te verklaren door een afname in de gemiddelde ligduur per opname (in 1997: 8,2 dagen; in 2001: 6,9 dagen) en een 10% afname in het aantal opnamen gedurende de onderzoeksperiode. Geconcludeerd kan worden dat het uitsluitend presenteren van antibioticagebruik in het aantal DDD per 100 patiëntdagen niet voldoende is voor een zinvolle interpretatie van de trends over een bepaalde periode, aangezien deze meeteenheid gevoelig is voor wijzigingen in de kengetallen van een ziekenhuis, voornamelijk voor die in de gemiddelde ligduur en het aantal opnamen. Deze kengetallen zijn immers van grote invloed op de noemer (namelijk het aantal patiëntdagen). Daarom dient men het antibioticagebruik zowel in DDD per 100 patiëntdagen als in DDD per 100 opnamen uit te drukken, evenals het expliciet weergeven van de kengetallen van de ziekenhuiszorg.

In *Hoofdstuk 2.2* zijn bestaande dosisadviezen voor antibiotica bij neonaten, afkomstig uit een selectie van gerenommeerde internationale handboeken

op het gebied van de kindergeneeskunde/neonatologie en kinderinfectieziekten, onderling vergeleken. Hiertoe zijn de dosisadviezen van de tien meest toegepaste antibiotica bij neonaten, gecategoriseerd voor geboortegewicht en zwangerschapsduur, uit zeven internationale handboeken vergeleken en uitgedrukt als gestandaardiseerde gemiddelde dagdosering. Op basis van deze vergelijking is geconstateerd dat de dosisadviezen van antibiotica met een grote therapeutische breedte, zoals ampicilline, benzylpenicilline, ceftazidim en cefotaxim, meer variatie vertonen dan die van antibiotica met een smalle therapeutische breedte, zoals meropenem, gentamicine en vancomycine. Eén handboek, namelijk de 'BNF for children', valt op en laat überhaupt een grotere variatie zien in dosisadviezen ten opzichte van de andere zes geselecteerde handboeken. Aangezien het voor de reductie van medicatiefouten zeer wenselijk is om standaarddosisadviezen van antibiotica bij neonaten te incorporeren in elektronische voorschrijfsystemen, is het noodzakelijk om de geconstateerde variatie in dosisadviezen nader te onderzoeken en uiteindelijk om te zetten naar standaarddosisadviezen. Een eerste poging hiertoe is door ons ondernomen in het onderzoek beschreven in *Hoofdstuk 2.3*. Tot slot: de gevonden variatie in dosisadviezen zou mogelijk de variatie in het totale antibioticagebruik tussen NICU's kunnen verklaren, zoals beschreven in *Hoofdstuk 3.2*.

De DDD, zoals gedefinieerd door de WHO, is de meest toegepaste meeteenheid voor antibioticagebruik. Deze geeft de aangenomen gemiddelde onderhoudsdosering per dag van een antibioticum bij de primaire indicatie bij volwassenen weer. Er is echter een probleem bij het uitdrukken van antibioticagebruik bij kinderen (ouder dan 1 maand) in de door de WHO gedefinieerde DDD's, gezien de grote variatie in lichaamsgewicht in deze populatie. Aangezien er bij neonaten (kinderen jonger dan 1 maand) een minder grote range aan lichaamsgewicht is dan bij oudere kinderen, is er in *Hoofdstuk 2.3* een voorstel gedaan voor een set van zogenaamde neonatale DDD's voor antibiotica. Daarvoor zijn zeven gerenommeerde internationale handboeken en één nationaal handboek voor dosisadviezen van antibiotica bij kinderen en neonaten geraadpleegd voor de onderhoudsdosering van de tien meest toegepaste antibiotica bij neonaten bij de primaire indicatie. Uitgaande van een gemiddeld lichaamsgewicht van een neonaat van 2 kg zijn er vervolgens voor deze tien antibiotica bijbehorende neonatale DDD's opgesteld. Deze voorgestelde DDD's kunnen een goed alternatief bieden als meeteenheid voor antibioticagebruik bij de neonatale populatie.

In *Hoofdstuk 3* van het proefschrift ligt de focus op de gebruikspatronen van antibiotica en de consequenties daarvan in opgenomen patiënten. In de hoofdstukken in dit deel van het proefschrift worden trends in antibioticagebruik geanalyseerd op verschillende detailniveaus: landelijk, ziekenhuis en specifieke patiëntengroep (namelijk neonaten).

In *Hoofdstuk 3.1* is de nadruk gelegd op de interpretatie van de geanalyseerde trends in antibioticagebruik in Nederlandse ziekenhuizen over de periode 1997-2002, uitgedrukt in zowel aantal DDD per 100 patiëntdagen als in aantal DDD per 100 opnamen. Het totale antibioticagebruik varieert aanzienlijk tussen de Nederlandse ziekenhuizen, waarbij de universitair medische centra een hoger antibioticagebruik hebben dan de algemene ziekenhuizen. Evenals in *Hoofdstuk 2.1* wordt een toename in het totale antibioticagebruik gezien wanneer het wordt uitgedrukt in aantal DDD per 100 patiëntdagen in tegenstelling tot een stabiel gebruik wanneer het wordt uitgedrukt in aantal DDD per 100 opnamen. Hetzelfde is geconstateerd bij het gebruik van amoxicilline-clavulaanzuur, betalactamase gevoelige penicillines, cefalosporines en glycopeptiden. Deze waargenomen trend suggereert dat er per opname, m.a.w. per patiënt, niet meer antibiotica worden voorgeschreven, maar aangezien de patiënt gemiddeld steeds korter in het ziekenhuis is (18% afname in gemiddelde ligduur over de onderzoeksperiode), het totale aantal DDD per 100 patiëntdagen wel toeneemt. De noemer wordt immers kleiner en dus de resterende uitkomst van de breuk groter. Voor de macroliden, lincosamiden en fluorchinolonen is echter zowel een toename in het totale aantal DDD per 100 patiëntdagen als in DDD per 100 opnamen waargenomen. Een discussiepunt is wat beide verschillende trends zeggen over de selectiedruk. De omvang van antimicrobiële resistentie wordt namelijk beïnvloed door de mate van antibioticagebruik (selectiedruk) en de mate waarin verspreiding mogelijk is. Zo zou men kunnen stellen dat in geval van de eerstgenoemde trend (d.w.z. stijging in aantal DDD per 100 patiëntdagen en een constant aantal DDD per 100 opnamen) er wel een toegenomen selectiedruk is, aangezien er meer antibiotica per ligdag worden gebruikt. Echter, de selectiedruk op ziekenhuisniveau neemt daarmee uitsluitend toe indien het aantal bedden en de bedbezetting stabiel is, wat niet het geval is in ons onderzoek. Bij de laatstgenoemde trend (d.w.z. stijging in aantal DDD per 100 patiëntdagen en aantal DDD per 100 opnamen) is een toegenomen selectiedruk aannemelijker.

In *Hoofdstuk 3.2* is middels een landelijk multicenter onderzoek de variatie in kwantitatief en kwalitatief antibioticagebruik op alle tien NICU's in Nederland in 2005 in kaart gebracht. Het totale antibioticagebruik per NICU

is uitgedrukt in DDD per 100 opnamen. Verder is per NICU een Drug Utilization (DU) 90% gemeten, een internationaal geaccepteerde maat voor de kwaliteit van voorschrijven van geneesmiddelen. De DU90% geeft de hoeveelheid geneesmiddelen weer, in ons geval antibiotica, die 90% van het totale geneesmiddelengebruik representeert. Het onderzoek laat zien dat ook hier het totale antibioticagebruik tussen NICU's aanzienlijk varieert (130-360 DDD per 100 opnamen). Verder verschilt het arsenaal aan totaal aantal verschillende gebruikte antibiotica per NICU (9-24), waarvan bij de ene NICU de DU90% drie is en bij de andere NICU tien. M.a.w. de ene NICU heeft in totaal slechts drie antibiotica nodig om 90% van het totale antibioticagebruik te vertegenwoordigen, terwijl dit in een andere NICU meer dan drie keer zoveel is. Concluderend kan worden gesteld dat er tussen de Nederlandse NICU's een grote variatie is in het aantal verschillende toegepaste antibiotica en het totale antibioticagebruik.

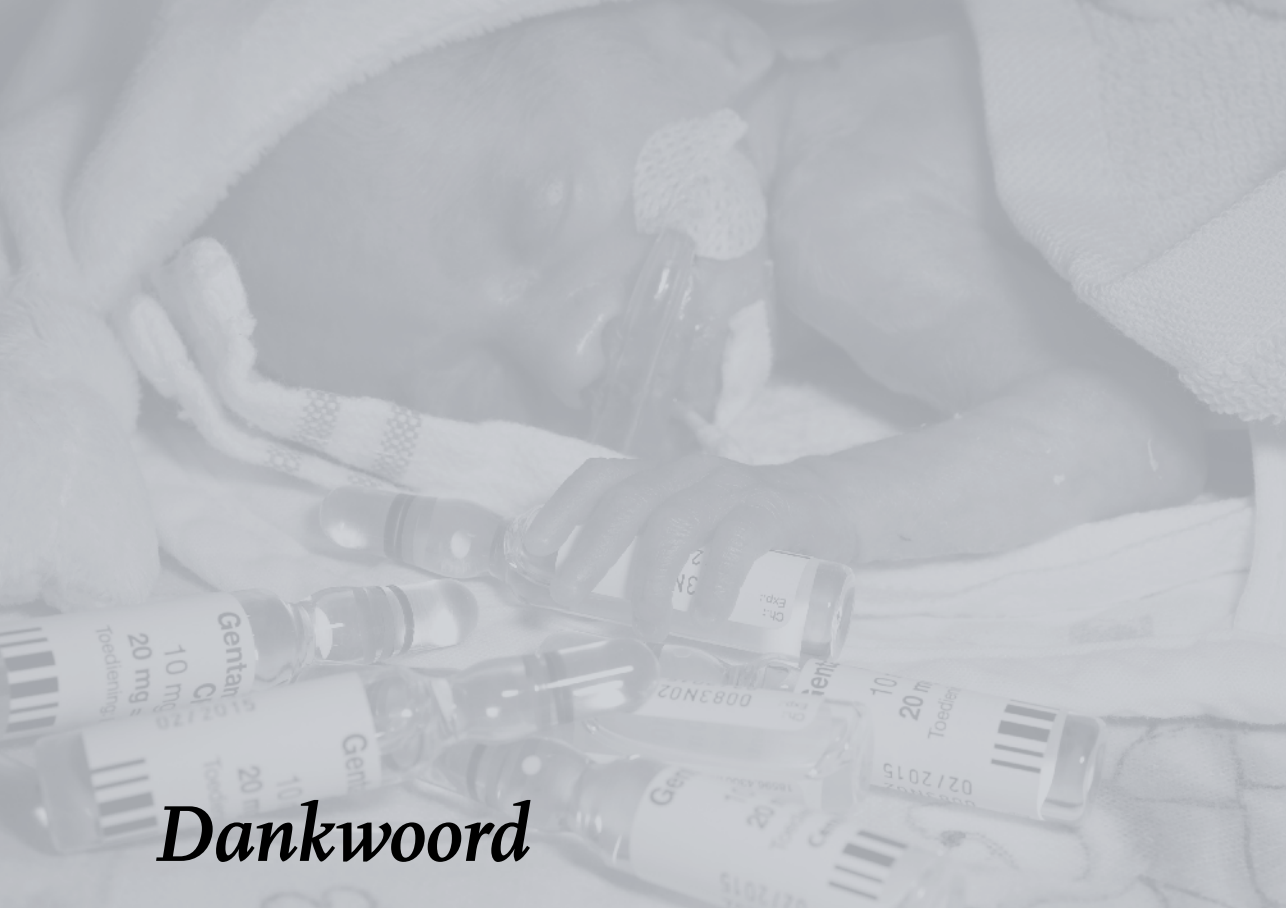
In *Hoofdstuk 3.3* zijn de trends in antibioticagebruik in de NICU in het Wilhelmina Kinderziekenhuis (WKZ) over een periode van 19 jaren (1990-2008) geanalyseerd. Het percentage opgenomen neonaten, dat gedurende de opname antibiotica krijgt, is tijdens de gehele onderzoeksperiode stabiel en hoog (85-90%). Desalniettemin blijft de incidentie van een bewezen sepsis, de meest voorkomende infectieziekte bij neonaten, waarvoor antibiotica worden voorgeschreven, laag. Het totale antibioticagebruik, uitgedrukt in aantal behandelingsdagen per patient, daalt gedurende de onderzoeksperiode van 9 naar 5.8 dagen (B = -0.226; 95% CI -0.369; -0.082; $p$=0.007), ondanks het hoge percentage neonaten dat antibiotica krijgt voorgeschreven. Dezelfde dalende trend is gezien bij amoxicilline-clavulaanzuur (B = -0.154; 95% CI -0.252; -0.055; $p$=0.007) en gentamicine (B = -0.237; 95% CI -0.358; -0.117; $p$=0.002) en in mindere mate bij cefazoline (B = -0.121; 95% CI -0.178; -0.064; $p$=0.001). Hoewel het niet is onderzocht in dit onderzoek, lijkt het erop dat de aanwezigheid van een multidisciplinair infectieziektenteam in de NICU van het WKZ, mede heeft bijgedragen aan de afname in het antibioticagebruik. Echter, aangezien er gedurende de onderzoeksperiode geen afname is in het percentage neonaten, dat met antibiotica wordt behandeld, is de juiste identificatie van neonaten met sepsis, als voornaamste infectieziekte bij neonaten, een belangrijke uitdaging om het antibioticagebruik nog verder te laten afnemen en hiermee de resistentie tegen te gaan.

In *Hoofdstuk 3.4* beschrijven wij de resultaten van een nested case-control onderzoek, uitgevoerd in de NICU van het WKZ. Het doel van het onderzoek was om risicofactoren en 'early-warning markers' voor kolonisatie door

extended-spectrum beta-lactamase (ESBL)-producerende *E. coli* of *Klebsiella*-micro-organismen in neonaten vast te stellen. ESBL is een verzamelnaam voor een groep door bacteriën gemaakte enzymen die in staat zijn cefalosporinen en penicillinen te hydrolyseren, waardoor deze antibiotica onwerkzaam worden. In ons onderzoek zijn uit een cohort van alle opgenomen neonaten in de NICU gedurende 2007 t/m 2009 cases en controles geïncludeerd. Cases waren neonaten met ESBL-kolonisatie en controles degene zonder ESBL-kolonisatie. Mogelijke risicofactoren (o.a. geboortegewicht, zwangerschapsduur, antibioticagebruik) en 'early-warning markers' (o.a. totaal aantal leukocyten, neutrofiele granulocyten, lymfocyten) zijn uit medische statussen en uit Utrecht Patient Oriented Database (UPOD) verzameld. In totaal zijn uit een cohort van 1833 neonaten, 26 cases en 153 controles geïncludeerd. Er is aangetoond dat neonaten met een moeder die antibiotica voorafgaande aan de geboorte gebruikten een bijna vijf keer zo hoge kans hebben op ESBL-kolonisatie (OR: 4.9; 95% CI: 1.98-12.1) ten opzichte van de controles. We vinden echter geen verschillen in leukocyten gerelateerde parameters tussen cases en controles. Concluderend kan worden gesteld dat uitsluitend maternaal antibioticagebruik een onafhankelijke risicofactor is voor ESBL-kolonisatie bij neonaten, wat suggereert dat er een zogenaamde verticale transmissie is van ESBL-positieve stammen. We konden geen 'early-warning markers' voor ESBL-kolonisatie bij neonaten identificeren.

In het laatste *Hoofdstuk 4* worden de onderzoeken en daarbij behorende belangrijkste resultaten in dit proefschrift, in een bredere context geplaatst, waarbij de focus ligt op twee hoofdthema's, namelijk 'het meten van antibioticagebruik' en 'de variabiliteit in antibioticagebruik'. Wij eindigen met diverse aanbevelingen voor de klinische praktijk en toekomstig onderzoek.

Concluderend kan worden gesteld dat wij in dit proefschrift zijn geconfronteerd met verschillende methodologische uitdagingen van het meten van antibioticagebruik in ziekenhuizen en opgenomen kinderen. Bovendien tonen de resultaten van onze onderzoeken naar het antibioticagebruik in deze ziekenhuizen en opgenomen kinderen een uitgesproken variabiliteit in antibioticagebruik aan, wat mogelijk als zorgwekkend kan worden opgevat. Wereldwijde bedreigingen, zoals toename van multiresistente micro-organismen en een nagenoeg stilstaande ontwikkeling van nieuwe antibiotica, onderstrepen het belang van goed antibioticagebruik.



# *Dankwoord*

Op zich vreemd om te bedenken dat blijkbaar het meeste en eerste gelezen hoofdstuk van een proefschrift het 'dankwoord' is, terwijl volgens mij het meeste werk en energie in de andere hoofdstukken heeft gezeten. Wat zou het 'dankwoord' dan toch tot zo'n voor de lezer populair onderdeel van een proefschrift maken? Ben je ook meteen bij het openen van de envelop met mijn proefschrift naar dit onderdeel gebladerd, dan is de grote vraag: waarom? Voor mij in elk geval de schone taak om dit dankwoord enigszins lezenswaardig te maken:

Het is en blijft een cliché, maar dit proefschrift was absoluut niet tot stand gekomen zonder hulp van anderen. Natuurlijk ben ik best trots op mijzelf dat ik het 'zover' heb geschopt, maar ik moet daarbij zeker verschillende mensen bedanken. Mocht je jezelf echter niet terugvinden bij het lezen van dit dankwoord, dan hierbij excuses … ik ben je niet bewust vergeten.

Allereerst mijn promotor, Toine Egberts, beste Toine, het staat mij nog goed bij dat ik voor het eerst via Marieke jouw naam in de hoedanigheid van haar opleider en directe collega hoorde. Vervolgens was je bij ons thuis met enige regelmaat onderwerp van gesprek, waarbij onder andere jouw ongelofelijke gedrevenheid en jouw buitengewone wijze van motivatie van anderen aan de orde kwamen. Dit zijn slechts een paar kenmerkende eigenschappen die ik, sinds ik jou als directe collega en als promotor ken, van dichtbij heb mogen ervaren en heb kunnen bevestigen bij Marieke. Verder is mij sindsdien jouw passie voor de ziekenhuisfarmacie en het wetenschappelijke onderzoek opgevallen. Jouw nauwe betrokkenheid bij mijn promotie en het altijd goed op de hoogte zijn van de stand van zaken hiervan is in zoverre bijzonder te noemen, aangezien je naast mij nog veel meer promovendi begeleid. De afgelopen jaren heb je mij veel geleerd over de fijne kneepjes van het onderzoek en het schrijven van wetenschappelijke artikels. Ik vind het een grote eer dat je mijn eerste promotor bent.

Mijn andere promotor, Frank van Bel, beste Frank, ik ken je eigenlijk nog niet zo heel lang, maar ik heb je in de afgelopen jaren, sinds ik met het onderzoek ben begonnen, leren kennen als een zeer sympathieke, humoristische en bescheiden persoon. Ondanks dat je mij herhaaldelijk hebt aangegeven dat je je meer passant dan promotor voelde, heb ik dat zeker niet als zodanig ervaren en daarom ook telkens tegengesproken. Ik vind het geweldig dat ik mijn onderzoek in samenwerking met jouw afdeling heb mogen doen en kijk nog altijd met heel veel plezier terug op de SPR in Baltimore in 2009, waar ik een aantal van jouw collega's EN ook jou iets beter heb leren kennen.

Mijn co-promotor, Karin Rademaker, beste Karin, als de dag van gisteren zie ik mij nog voor het eerst in 1999 als farmaciestudent vakantiewerk doen bij jou in de nieuwe apotheek in het WKZ. Het was mijn allereerste kennismaking met de ziekenhuisapotheek en in die tijd, toen ik net terug kwam van mijn onderzoeksproject in San Diego en echt niet wist wat ik na mijn studie wilde doen, heb je mij enthousiast gemaakt voor de ziekenhuisfarmacie. Je nam mij toen al mee naar de afdeling als er een interessante patiënt was te zien, en stimuleerde mij om 's ochtends bij de overdracht in het WKZ te gaan zitten (ik had toen serieus geen flauw idee waar men het daar over had). En nu ruim 12 jaar verder ben je een van mijn co-promotores. Je was de eerste die mij na mijn start in de ziekenhuisapotheek van het UMC Utrecht aansprak of ik nog iets wilde gaan doen in het onderzoek. Niet lang daarna heb je het eerste contact tussen de collega's van de NICU en mij gelegd, wat min of meer aan de basis van dit proefschrift heeft gestaan. Jouw enorme betrokkenheid bij en kritische blik op het onderzoek heb ik als zeer waardevol ervaren. En dan niet te vergeten de zeer prettige samenwerking met jou als directe collega in het WKZ.

Mijn andere co-promotor, Tannette Krediet, beste Tannette, ook jou ken ik eigenlijk pas kort, maar eerlijk gezegd lijkt het alsof het helemaal niet zo kort is. Ik heb jou de afgelopen jaren tijdens het onderzoek leren kennen als een zeer bescheiden, plezierige en pragmatische persoon. Je bent altijd kritisch geweest op wat het doel van de verschillende onderzoekenwas en wat we in de praktijk met de resultaten konden doen. Daarnaast heb ik je ervaren als een collega, die alles direct tegen je zei en er geen doekjes om wond. De samenwerking tussen de NICU en de apotheek vond ik tijdens mijn onderzoek erg plezierig en vruchtbaar en is volgens mij echt nog lang niet ten einde.

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Margreet Filius, beste Margreet, in de periode dat ik ben begonnen in het toenmalige Academisch Ziekenhuis Rotterdam (het huidige Erasmus MC) als projectapotheker, ben ik vrijwel direct in contact gebracht met jou, jouw promotie en daarmee ook de SWAB. Ik heb het als heel leerzaam ervaren om met jou een aantal onderzoeken voor jouw proefschrift, en inmiddels ook die van mij, te doen. Hetgeen ik destijds samen met jou op onderzoeksgebied heb gedaan, vormt een significant onderdeel van dit proefschrift. De samenwerking binnen de SWAB werkgroep surveillance antibioticagebruik was altijd plezierig, mede dankzij jou, en het was dan ook een domper dat je een tijdje geleden als zeer actieve coördinator van deze werkgroep je taak neerlegde. Verder heb ik het nog steeds een eer gevonden dat ik in 2005 één van jouw paranimfen was.

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van dit proefschrift (waaronder dit deel). Of het daadwerkelijk tot inspiratie heeft geleid, weet ik niet en maakt ook niet uit, want *Flamenco Sketches*, *Blue in Green* of *All Blues* op de achtergrond, is op zich al een puur genot om naar te luisteren. Dank voor al die prachtige nummers.

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Lieve Marieke, Ward en Krijn:

*You are the sunshine of my life*
*That's why I'll always be around*
*You are the apple of my eye*
*Forever you'll stay in my heart*

*('You are the sunshine of my life', Stevie Wonder)*

*Yves Liem*
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# *List of co-authors presented in this thesis*

*Affiliations at the time which the research was conducted*

**Hanneke den Breeijen**
Department of Clinical Pharmacy, University Medical Center Utrecht, The Netherlands

**Toine C.G. Egberts**
Department of Clinical Pharmacy, University Medical Center Utrecht, The Netherlands
&
Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands

**Margreet Filius**
Department of Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

**André Fleer**
Eijkman-Winkler Centre of Microbiology, Infectious Diseases and Inflammation, University Medical Center Utrecht, The Netherlands

**Eibert R. Heerdink**
Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, The Netherlands
&
Department of Clinical Pharmacy, University Medical Center Utrecht, The Netherlands

**Agnes van den Hoogen**
Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

**Rob Janknegt**
Department of Clinical Pharmacy and Toxicology, Maasland Ziekenhuis, Sittard, The Netherlands

**Tannette G. Krediet**
Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

**Paul D. van der Linden**
Department of Pharmacy, Apotheek Haagse Ziekenhuizen, The Hague, The Netherlands

**Stephanie Natsch**
Department of Clinical Pharmacy, University Medical Centre Nijmegen and Nijmegen University Centre for Infectious Diseases, The Netherlands

**Carin M.A. Rademaker**
Department of Clinical Pharmacy, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands

**Wouter W. van Solinge**
Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, The Netherlands

**Henri A. Verbrugh**
Department of Medical Microbiology and Infectious Diseases, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

**Arnold G. Vulto**
Department of Hospital Pharmacy, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, The Netherlands

# *List of publications related to this thesis*

Liem TBY, Filius PMG, van der Linden PD, Janknegt R, Natsch S, Vulto AG.
Changes in antibiotic use in Dutch hospitals over a six-year period: 1997 to 2002.
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# *Curriculum Vitae*

Yves Liem was born on July 31st 1976 in St. Gallen, Switzerland. When he was almost four years old he moved with his parents and younger brother to the Netherlands. He grew up in Emmeloord and completed high school at the 'Zuyderzee College' in Emmeloord in 1994. Subsequently, he started his studies Pharmacy at Utrecht University and received his pharmacist degree in 2001. During his studies he completed a research project at 'The Scripps Research Institute' in the Department of Neuropharmacology in San Diego, United States of America (supervisors: prof.dr. B. Olivier and prof.dr. A. Markou).

In 2001 he started working as a pharmacist at the St. Anna hospital, Geldrop. After almost a year he went to the Erasmus MC, University Medical Center Rotterdam, to work as a pharmacist, and shortly thereafter he started his training to become a hospital pharmacist in 2002 (supervisor: prof.dr. A.G. Vulto). During this training he was involved in the PhD research project of Margreet Filius entitled 'Antimicrobial use and resistance in hospitalized patients'. As a result he became member of the 'SWAB (Stichting Werkgroep AntibioticaBeleid) working group on surveillance of antimicrobial use'. In his last year of his training of hospital pharmacist, he specialized in 'paediatric clinical pharmacy' in the Erasmus MC-Sophia (supervisor: dr. L.M. Hanff). He received his degree as hospital pharmacist in 2006.

From mid-2006 he holds a position as a registered hospital pharmacist at the Department of Clinical Pharmacy (locations Wilhelmina Children's Hospital and AZU) at the University Medical Center Utrecht. Since 2008 he combines this position with a PhD research project, performed in close collaboration with the Department of Neonatology, of which the results are presented in this thesis. Since 2007 he is also chairman of the Special Interest Group (SIG) 'Paediatrics' of the Dutch Association of Hospital Pharmacists (NVZA). In 2009 he became one of the supervisors of the education programme on pharmacology and pharmacotherapy within the medical school of the Utrecht University (CRU'06).

Yves is married to Marieke. They are proud parents of two sons, Ward (2007) and Krijn (2009).

The discovery of antibiotics represents one of the milestones in modern medicine and has since the beginning of the 20th century made a major contribution to the reduction in mortality and morbidity from infectious diseases. The shadow side of their success is antimicrobial drug resistance which is a great threat to public health. The reasons for the rise in antimicrobial resistance are manifold and complex, but it has become clear that excessive and indiscriminate use of antibiotics increase the risk of selection of and emergence of antimicrobial resistant organisms. The resistance problem along with a nearly empty pipeline of innovative antimicrobial agents emphasizes the importance of appropriate use of the available antibiotics. Valid quantitative and qualitative data on the use of antibiotics in hospitals are necessary to detect patterns of potentially inappropriate use and to evaluate strategies to contain antimicrobial resistance. Antimicrobial agents are among the most frequently used drugs in neonatal intensive care units (NICU's), since the multiple risk factors for infection and the severe consequences thereof in preterm immunocompromised infants result in a low threshold for the initiation of antimicrobial therapy. The general aim of this thesis is to describe patterns of antibiotic use in hospitals, predominantly in neonates, to establish valid measures thereof and describe its clinical consequences.


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