An additional measure for quantifying antibiotic use in hospitals

P. M. G. Filius¹*,† T. B. Y. Liem²†, P. D. van der Linden³, R. Janknegt⁴, S. Natsch⁵, A. G. Vulto² and H. A. Verbrugh¹

Departments of ¹Medical Microbiology and Infectious Diseases and ²Hospital Pharmacy, Erasmus MC, University Medical Center Rotterdam, Dr Molewaterplein 40, 3015 GD Rotterdam; ³Department of Pharmacy, Apotheek Haagse Ziekenhuizen, The Hague; ⁴Department of Clinical Pharmacy and Toxicology, Maasland Ziekenhuis, Sittard; ⁵Department of Clinical Pharmacy, University Medical Center Nijmegen and Nijmegen University Center for Infectious Diseases, The Netherlands

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Objectives: 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.

Patients and 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.

Conclusions: 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.

Keywords: antibiotic usage, defined daily doses, selection density, selection pressure

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.

*Corresponding author. Tel: +31-10-4633511; Fax: +31-10-4633875; E-mail: p.filius@erasmusmc.nl
†P. M. G. Filius and T. B. Y. Liem contributed equally to this work and share first authorship.
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 (\(-12\%)\).

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...
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)

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

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.

Acknowledgements

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References