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### Antibiotic stewardship

*Studies on measuring guideline adherence and expediting the IV-oral switch*

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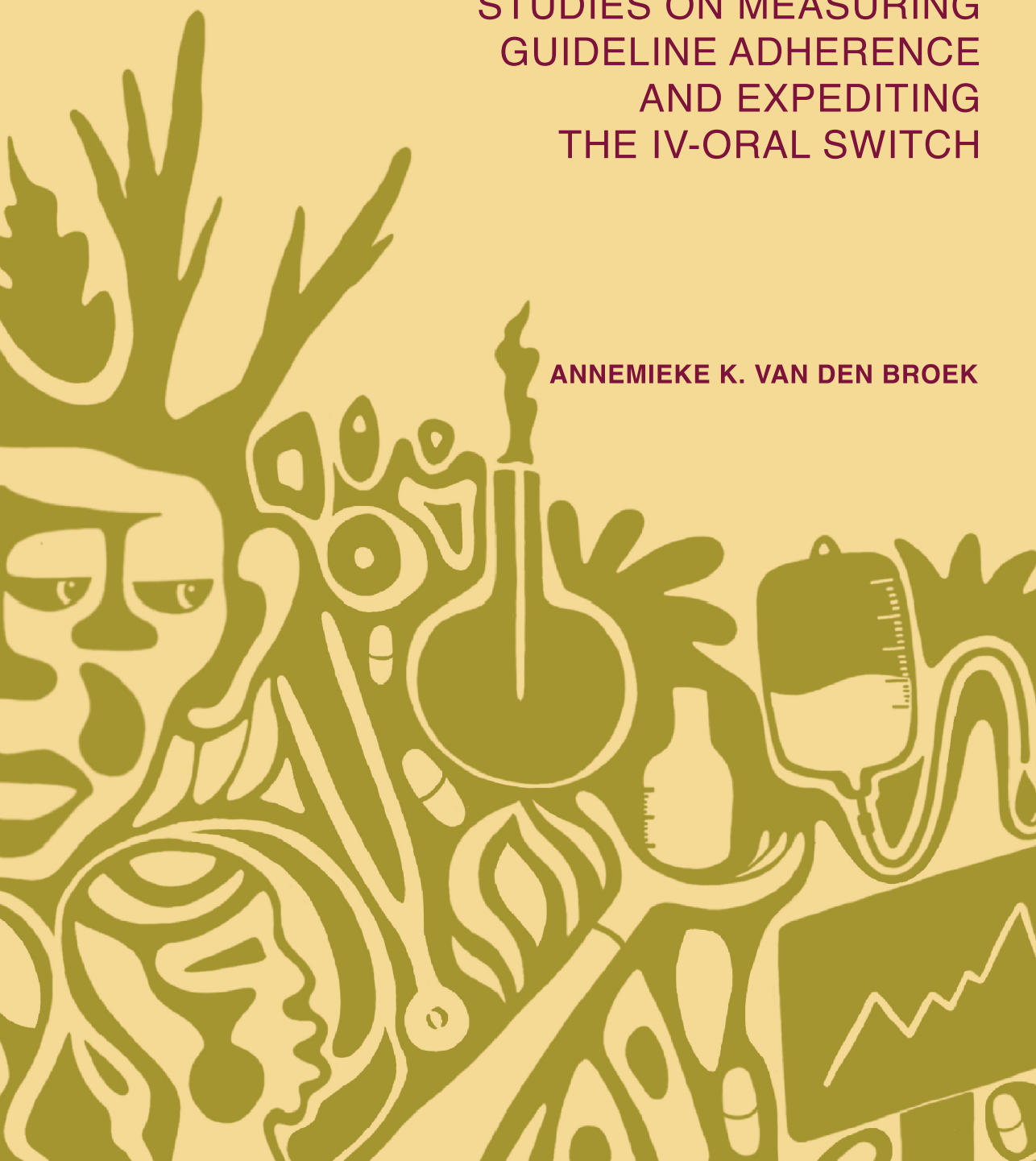
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# ANTIBIOTIC STEWARDSHIP

STUDIES ON MEASURING  
GUIDELINE ADHERENCE  
AND EXPEDITING  
THE IV-ORAL SWITCH

ANNEMIEKE K. VAN DEN BROEK





# **Antibiotic stewardship**

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**Antibiotic stewardship:** studies on measuring guideline adherence and expediting the iv-oral switch

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# ANTIBIOTIC STEWARDSHIP

## STUDIES ON MEASURING GUIDELINE ADHERENCE AND EXPEDITING THE IV-ORAL SWITCH

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### ACADEMISCH PROEFSCHRIFT

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aan de Universiteit van Amsterdam  
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prof. dr. ir. P.P.C.C. Verbeek

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*Aan mijn familie*  
*Aan lensie*

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## CHAPTER 1:

# General introduction and outline of the thesis

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## General introduction

### Antimicrobial resistance

*“But I would like to sound one note of warning. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”* **Alexander Fleming, Nobel Prize speech in 1945<sup>1</sup>**

This passage is part of the speech that Sir Fleming gave when he received the Nobel Prize for his work in developing one of the first antibiotics accessible for the general public: penicillin. Since then, infection-related mortality has declined rapidly.<sup>2</sup> As Sir Fleming said, microbes that are exposed to non-lethal quantities of antibiotics can become resistant, as every living organism will always look for ways to survive and resist threats. However, due to the widespread use of antimicrobials since 1950 the resistance rate has accelerated, leading to: 1) decreased possibilities to treat common infectious diseases and thereby increasing infection-related mortality once again, 2) an increase of societal healthcare costs, 3) a threat to the safety of interventions such as surgery, organ and bone marrow transplantation and chemotherapy.<sup>3</sup> Antimicrobial resistance (AMR) has therefore become a growing public health threat, for which global action needs to be taken.

In order to treat multi-resistant pathogens it is urgently needed that new antimicrobial agents are being developed, which has unfortunately stagnated throughout the years.<sup>4</sup> However, development of new antibiotics would only be a short term solution. Currently, it is estimated that up to 50% of antimicrobial use is inappropriate.<sup>5</sup> As long as we do not change our behaviour, pathogens will become resistant to new agents as well. In order to contain antimicrobial resistance and make it more attractive to develop new antimicrobial agents, we need to optimise our current antimicrobial use.

### Antimicrobial Stewardship Programmes

Antimicrobial Stewardship Programmes (ASPs) have been globally developed to measure and subsequently improve the appropriateness of antimicrobial use while minimizing unintended consequences of antimicrobial use.<sup>6</sup> The importance of ASPs in the Netherlands was acknowledged in 2012, when the Dutch Working Party on Antibiotic Policy (SWAB) drafted their vision document regarding this matter at the request of the Dutch Healthcare Inspectorate (IGZ). As a result, local Antimicrobial Stewardship teams (A-teams) have become mandatory in every

Dutch hospital since 2014. The prerequisites of these A-teams are described in the “Praktijkgids Antimicrobial Stewardship in Nederland”.<sup>7</sup> In summary, A-teams should include at least one infectious diseases specialist, hospital pharmacist and clinical microbiologist; the A-team should be supported by an infrastructure to track local antibiotic use and resistance rates; and local diagnostic and therapeutic antibiotic guidelines, including a list of restricted antibiotics, should be available.<sup>6</sup>

In order to develop and implement a successful ASP, international guidelines and policy statements have been developed<sup>6, 8</sup>, describing the **structural or system prerequisites for an ASP**, as mentioned above. Furthermore, these guidelines encompass recommendations to guide the activities of Antimicrobial Stewardship teams on two different aspects of stewardship:

1. Guidance on the **ASP objectives** to focus on. These describe appropriate antibiotic use at the patient level, based on quality indicators (QIs) (table 1).<sup>9</sup>
2. Guidance on **ASP improvement strategies**. These describe how to change the behaviour of individual prescribers. For example by performing audits with feedback.

ASP objectives are the subject of this thesis, with particular focus on the following QIs:

1. Empirical systemic antibiotic therapy should be prescribed according to the local guideline. If local guidelines are missing, prescribe according to national guideline. If national guidelines are also missing, prescribe according to international guideline.
2. Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate. Adequate is defined as: (1) when the antibiotic is available orally, (2) when oral intake and gastrointestinal absorption are adequate, (3) adequate in terms of diagnosis (exceptions are, e.g., endocarditis, meningitis, empyema).

**Table 1: Quality indicators for hospitalised antimicrobial use<sup>9</sup>**

Empirical systemic antibiotic therapy should be prescribed according to the local guideline (If local guidelines are missing, prescribe according to national guideline. If national guidelines are also missing, prescribe according to international guideline.)

Before starting systemic antibiotic therapy, at least 2 sets of blood cultures should be taken

When starting systemic antibiotic therapy, specimens for culture from suspected sites of infection should be taken as soon as possible, preferably before antibiotics are started.

Empirical antibiotics should be changed to pathogen-directed therapy if culture results become available

Dose and dosing interval of systemic antibiotics should be adapted to renal function.

Systemic antibiotic therapy should be switched from intravenous to oral antibiotic therapy within 48–72 h on the basis of the clinical condition and when oral treatment is adequate. Adequate: (1) when antibiotic is available orally, (2) when oral intake and gastrointestinal absorption are adequate, (3) adequate in terms of diagnosis (exceptions, eg, endocarditis, meningitis, empyema).

An antibiotic plan should be documented in the case notes at the start of systemic antibiotic treatment.

Therapeutic drug monitoring should be performed when the treatment duration is >3 d for aminoglycosides and >5 d for vancomycin.

Empirical antibiotic therapy for presumed bacterial infection should be discontinued based on the lack of clinical and/or microbiological evidence of infection. The maximum duration of empirical systemic antibiotic treatment should be 7 d.

A current local antibiotic guideline should be present in the hospital and an evaluation whether an update should be considered should be done every 3 y.

Local antibiotic guidelines should correspond to the national antibiotic guidelines, but should deviate based on local resistance patterns.

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### **Q1: Guideline-adherence empirical therapy**

Antimicrobial guidelines reflect the current state of knowledge and therefore define appropriate antibiotic use.<sup>6</sup> Guideline-adherent empirical therapy is associated with a lower rate of development of antibiotic resistance, lower costs and a relative risk reduction for mortality of 35%. Optimizing guideline adherence is therefore one of the core activities elements of A-teams. To do so, insight in the local guideline-adherence rate is pivotal, for which structurally performed audits are needed.<sup>10</sup>

Unfortunately, the ability to perform audits regarding guideline-adherence and actually improve antimicrobial use is hampered by lack of stewardship personnel

and funding.<sup>11</sup> A frequently used method to perform an audit is the point prevalence survey (PPS), in which all antimicrobial prescriptions and their indications are retrieved during a certain time period.<sup>12, 13</sup> This requires manual review of the (electronic) medical record (EMR) in combination with contacting the attending physician in case of incomplete records. Evaluation of appropriateness can therefore be very time-consuming, resulting in the evaluation of a relatively small number of patients and a low frequency of analysis.<sup>14</sup> A more efficient method to evaluate the appropriateness of antimicrobial use is therefore urgently needed, so that the time that is available for ASPs is not mainly spend on measuring the quality of antimicrobial use, but on improving the quality of antimicrobial use.

## **Q2: IV-to-oral switch therapy**

In order to improve patient outcome, it is of paramount importance that antibiotic treatment is timely initiated and that sufficient antibiotic exposure is reached as soon as possible.<sup>15</sup> Seriously ill patients hospitalized with systemic infectious diseases are initially treated with intravenous (IV) antibiotic therapy, because of the short time of achieving maximum plasma concentrations and 100% bioavailability,<sup>16</sup> in other words: to be sure to achieve the highest systemic exposure possible given the prescribed dose. Guidelines recommend to switch to oral therapy when the patient has been treated intravenously for at least 48-72 hours, provided that the clinical condition has improved.<sup>17</sup> Switching to oral therapy has been shown to lower the length of hospital stay, the risk of new infections and healthcare costs, without compromising clinical outcome.<sup>10</sup>

In the Netherlands, measurement of the appropriateness of antimicrobial use regarding the IV-to-oral switch is already efficient, as the identification of potential IV-to-oral switch candidates is supported by many EMRs.<sup>18</sup> This greatly facilitates the A-teams' work. However, it is not only necessary to improve antimicrobial use, but the IV-oral switch criteria might also be optimized.

The main reason why oral therapy is not administered during the first 48-72 hours of infection is because of clinicians' belief that the systemic response to an infection may alter the pharmacokinetics of antibiotics, as has been postulated in critically ill patients.<sup>19</sup> This may end up in a systemic exposure that is considerably lower than the highest exposure possible given the prescribed dose. The question is whether this is also the case in non-critically ill patients. Further, an IV-oral switch is usually discouraged for infections of which the site of infection is difficult to access, such as empyema, in which case a prolonged IV treatment duration of at least 2 weeks is recommended.<sup>17, 20</sup> Both assumptions are not evidence-based,

which raises the question whether the benefits of oral therapy could be achieved earlier.

## **Outline of this thesis**

This thesis contributes to answering the following questions:

- 1) What are the possibilities to use the Electronic Patient Record for more efficiently measuring guideline-adherence of antimicrobial therapy for treatment of an infection? This will be covered in part 1: Optimizing the measurement of the QI 'Guideline-adherent therapy'.
- 2) Is it possible to shorten the currently recommended duration of IV therapy in non-critically ill patients admitted to general wards without negatively affecting effectivity? This will be covered in part 2: Optimizing IV-to-oral switch therapy.

### **Part I: Optimizing the measurement of the QI 'Guideline-adherent therapy'**

In **Chapter 2** we measured guideline-adherence of antimicrobial therapy in the outpatient clinic. ASPs commonly have an in-hospital focus. Little is known about antimicrobial guideline-adherence in hospital outpatient clinics. We used the EMR to identify patients receiving antimicrobial therapy, resulting in a more efficient way to screen eligible patients. However, in order to obtain the remaining relevant data needed to perform the PPS, manual data collection and contacting the treating physician was still required. We therefore implemented a tool in the EMR that obliged physicians to document the indication for all antibiotic prescriptions, using predefined order sets. In **Chapter 3** we investigated the real-life feasibility of using this tool for automated evaluation of guideline-adherence of empirical therapy in hospitalized non-critically ill patients. We only focused on whether the antibiotic prescribed was according to the guideline. In **Chapter 4** we evaluated whether it is also possible to evaluate guideline-adherence with regard to duration of antimicrobial therapy.

### **Part II: Optimizing the QI IV to oral switch**

The main reason why therapy is administered intravenously during the first 48-72 hours of infection is because of clinicians' belief that in critically ill patients the

systemic response to an infection may alter the pharmacokinetics and the bioavailability of orally administered antibiotics, which would end up in a systemic exposure after oral administration that is too low. In **Chapter 5** we systematically reviewed the literature on the effect of the acute phase of infection on bioavailability of oral antibiotics in non-critically ill patients. Following this systemic review, in **Chapter 6** we investigated whether the acute phase of infection influenced the exposure to orally administered amoxicillin and ciprofloxacin in febrile patients admitted to a general ward (the EXPO-AB study). Furthermore, to date it is not known whether ceftriaxone – globally one of the most empirically used IV antibiotics in hospitalized patients - achieves adequate antibiotic exposure during the acute phase of infection in non-critically ill patients. Consequently, we do not know whether febrile patients are initially adequately treated. In **Chapter 7** we therefore investigated whether the currently recommended dosing regimen of 2 gram every 24h is sufficient for pharmacokinetic/pharmacodynamic (PK/PD) target attainment in non-critically ill, hospitalized patients.

Finally, in the last part of this thesis we present a general discussion, final conclusions and implications for further research, and a summary of the main findings in English and in Dutch.

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## **PART I:**

# **Optimizing the measurement of the QI 'Guideline-adherent therapy'**

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## CHAPTER 2:

# The appropriateness of antimicrobial use in the outpatient clinics of three hospitals in the Netherlands

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*Antimicrob Resist Infect Control.* 2020 Feb 22;9(1):40.

## Abstract

**Objectives:** Antimicrobial Stewardship Programs commonly have an in-hospital focus. Little is known about the quality of antimicrobial use in hospital outpatient clinics. We investigated the extent and appropriateness of antimicrobial prescriptions in the outpatient clinics of three hospitals.

**Methods:** From June 2018 to January 2019, we performed ten point prevalence surveys in outpatient clinics of one university hospital and two large teaching hospitals. All prophylactic and therapeutic prescriptions were retrieved from the electronic medical records. Appropriateness was defined as being in accordance with guidelines. Furthermore, we investigated the extent to which the dose was adjusted to renal function and documentation of an antibiotic plan in the case notes.

**Results:** We retrieved 720 prescriptions for antimicrobial drugs, of which 173 prescriptions (24%) were prophylactic. A guideline was present for 95% of prescriptions, of which the guideline non-adherence rate was 25.6% ( $n=42/164$ ) for prophylaxis and 43.1% ( $n=224/520$ ) for therapy. Of all inappropriate prescriptions ( $n=266$ ), inappropriate prescriptions for skin and soft tissue infections ( $n=60/226$ ) and amoxicillin-clavulanic acid ( $n=67/266$ ) made up the largest proportion. In only 13 of 138 patients with impaired or unknown renal function the dosage regimen was adjusted. Amoxicillin-clavulanic acid was the drug for which most often renal function was not taken into account. In 94.6% of prescriptions the antibiotic plan was documented.

**Conclusions:** In hospital outpatient clinics, a substantial part of therapeutics were inappropriately prescribed. Amoxicillin-clavulanic acid was the most inappropriately prescribed drug, due to non-adherence to the guidelines and because dose adjustment to renal function was often not considered.

## Background

Antimicrobial resistance leads to increased morbidity, mortality and healthcare costs worldwide.<sup>1</sup> In order to contain antimicrobial resistance, Antibiotic Stewardship Programs (ASP) have been developed to measure and improve the appropriateness of antimicrobial use.<sup>2</sup> A common way to measure the appropriateness of antimicrobial use is by evaluating whether antimicrobials are prescribed according to local guidelines and if not available, to national or international guidelines.<sup>3</sup>

ASPs are commonly focused on in-hospital therapeutic and perioperative prophylactic antimicrobial use.<sup>4</sup> However, up to 90% of antimicrobial use occurs in the outpatient setting, of which, next to family practice, internal medicine and paediatrics are the largest contributors.<sup>5, 6</sup> Available studies evaluating outpatient antibiotic use addressed therapeutic antimicrobial use in the ambulatory setting in general, of which 30-50% was inappropriately prescribed.<sup>7-9</sup> However, due to the variety of clinical practice locations that are considered ambulatory care settings, there is little in-depth information on these settings individually, and in particular the appropriateness of antimicrobial prescribing practices in hospital-based outpatient clinics has received little attention.<sup>4</sup> Analysis of antibiotic utilization across the spectrum of inpatient and ambulatory care would be useful to direct antibiotic stewardship efforts.<sup>10</sup> Also, mainly antibiotics have been investigated. Antifungal and antiviral drug resistance is emerging and should therefore not be overlooked when measuring the appropriateness of antimicrobial use.<sup>11-14</sup>

The aim of this study was to quantify the extent and appropriateness of therapeutic and prophylactic antimicrobial prescribing at the outpatient departments of a tertiary and two secondary hospitals, during ten point prevalence surveys (PPS)<sup>15</sup> in each hospital. Appropriateness was measured using established and validated quality indicators, of which the prescription being in accordance with the guideline was our main parameter.<sup>3</sup>

## Materials and methods

### Study design and setting

The study was performed in the outpatient departments of three hospitals in The Netherlands, covering the period June 2018 to January 2019. The participating hospitals were Amsterdam UMC, location Academic Medical Center (AMC), a

1000-bed university-affiliated tertiary care hospital with >300,000 outpatient clinic visits per year, the Onze Lieve Vrouwe Gasthuis Hospital, location West (OLVG W), a 225-bed secondary care hospital, treating 200,000 outpatients a year; and the MC Slotervaart (SLZ) a 150-bed secondary care hospital with 90,000 outpatient clinic visits per year. An ASP was present in all hospitals, including an Antibiotic stewardship team (AST) consisting of an infectious diseases specialist, hospital pharmacist and medical microbiologist. Approval from the Ethics committee was not required for this study because we used data for quality optimization purposes. The procedures were in accordance with the General Data Protection Regulation.<sup>16</sup>

### **Data collection and procedures**

We performed in each hospital ten point-prevalence surveys (PPS)(15) on consecutive workdays to generate a representative sample size. Prior to the PPS, we developed an algorithm for the electronic medical records (EMR) of the hospitals that generated all prescriptions of the Anatomical Therapeutic Chemical (ATC) groups A02B, A07A, J01, J02, J04, J05, P01 and P02, per day and per outpatient clinic. The AMC and OLVG W utilize EPIC as EMR and SLZ utilizes Chipsoft. The EMR reports were verified on completeness by comparing the electronically generated data with data retrieved by manually checking all patient files of the outpatient departments, during three days for AMC and SLZ, and during one day for the OLVG W, because the EMR report of that hospital had already been used and validated for other purposes. If the reports showed to be incomplete, the algorithms were adjusted, after which a re-run followed until the manually collected results and the electronically collected results corresponded for at least 90%.

During the PPS, we collected the antimicrobial prescriptions of all outpatients aged 16 year or above. We excluded the outpatient clinics of paediatrics and neonatology and prescriptions of peri-operative prophylaxis, antiretroviral therapy and hydrochloroquine, since the latter is only used in the Netherlands as an anti-rheumatic drug. The data collected were the number of antimicrobial prescriptions per outpatient department, the type of antimicrobial agent (ATC), dosage and duration of therapy and the route of administration. For each prescription we collected data from the patients' EMR about the diagnosis and indication for prescribing, which we categorized into therapeutic indications and prophylactic indications (medical prophylaxis versus post-surgical/intervention prophylaxis, i.e. prophylaxis lasting >24hours after the intervention). If the indication of the prescription was not clearly documented in the patient files, we contacted the treating physician. Next, we checked the presence of local guidelines (antimicrobial

guidelines derived from national guidelines, with adjustments made according to resistance patterns in the hospital) and if not available, national (by the Dutch Working Party on Antibiotic Policy, [www.swab.nl](http://www.swab.nl), or by professional societies) or international guidelines. If the prescription differed from the recommended first choice therapy in the guideline, we contacted the treating physician for a clarification. In case the clarification made clear that the deviation from the first choice therapy was justified, the prescription was labelled as appropriate. An example is a deviation from the first choice therapy because of intolerance for the first choice agent which was not documented in the EMR. We checked whether the antibiotic plan was documented in the case notes. Finally, we retrieved the renal function of each subject so that it could be checked whether dose adjustment because of impaired renal function was indicated.

### **Study endpoints**

The primary endpoints were the amount of antimicrobial prescriptions in hospital outpatient clinics, both therapeutic and prophylactic, and the appropriateness of these prescriptions, expressed as the percentage of antimicrobial prescriptions that were prescribed according to the available guidelines. The secondary endpoint was the percentage of antimicrobial prescriptions with documentation of the antibiotic plan in the case notes and the percentage of antimicrobial prescriptions with correct adjustment of the dosage regimen to renal function.

### **Data analysis**

The proportion of prophylactic prescriptions was expressed as percentage of the total number of antimicrobial prescriptions. The proportion of guideline (non)-adherent prescriptions was expressed as percentage of the total number of antimicrobial prescriptions for which a guideline was present. We evaluated whether antimicrobial therapy or prophylaxis was indicated according to the guideline, whether the right antimicrobial agent was chosen and whether the right dose and duration of therapy was prescribed. Prescriptions that differed from the recommended first choice agent in the guideline because of former culture results or known intolerances/allergies were considered appropriate. The reason of non-adherence (treatment/prophylaxis not indicated, inappropriate agent, inappropriate dose/duration) was presented as percentage of the total number of antimicrobial prescriptions that did not adhere to the guideline. Prescriptions were reviewed by one investigator, and in case of uncertainties discussed with the other investigators (antimicrobial stewardship team members of the three hospitals).

The proportion of prescriptions with a documented antimicrobial plan was expressed as percentage of the total number of prescriptions. The proportion of prescriptions with an appropriately adjusted dosage regimen in case of renal impairment was presented as percentage of the total number of prescriptions for which dose adjustment was recommended in case of renal impairment, according to the national SWAB guidelines (Dutch Working Party on Antibiotic Policy).<sup>17</sup> The renal function had to be obtained within 6 months prior to the PPS and was otherwise reported as renal impairment unknown. These latter prescriptions were added to the denominator. Because the prevalence of patients with an eGFR<10 is expected to be low, we excluded from this analysis antimicrobial drugs that are only recommended to be adjusted in patients with an eGFR<10, to avoid overestimation of the non-adherence rate for dose adjustment in renal impairment.

Since this was an exploratory study, only descriptive statistics were presented, for which IBM SPSS statistics version 25 was used.

## Results

### Characteristics of antimicrobial prescriptions

The total number of outpatient antimicrobial prescriptions retrieved during the ten point prevalence surveys of the three hospitals combined was 720, all prescribed by medical specialist and medical specialists in training. Antibiotics (ATC-code J01) were the most commonly prescribed drugs and accounted for 569 (79%) prescriptions. Table 1 presents the characteristics of the antimicrobial prescriptions per hospital. The proportion of prophylaxis versus therapy was similar for the three hospitals. Therapeutic prescriptions accounted for 547 antimicrobial prescriptions (76%) and prophylaxis for 173 (24%). The main indication for antimicrobial therapy was skin and soft tissue infections (n=144, 26.3%). The main indication for prophylaxis was medical prophylaxis (n=134, 77.5%). Limited variation was seen between the hospitals in this respect (table 1).

Figure 1 and figure 2 show the distribution of the prescribed antimicrobial agents per indication (therapy and prophylaxis) and per hospital. For therapeutics, the distribution of prescribed agents was comparable for the three hospitals. For prophylaxis, cotrimoxazole and nucleosides and nucleotides (excluding HIV reverse transcriptase inhibitors) were the most commonly prescribed (both n=32, 18.5%). However, the distribution of prescribed prophylactic antimicrobials varied between the hospitals. Cotrimoxazole represented the largest group of prophylactic antibiotics in the AMC (tertiary care university hospital). AMC has a large HIV,

haematology and nephrology department, where patients receive kidney- and stem cell transplantations and other extensive haematology immunosuppressive treatment. In these patients cotrimoxazole is often used. Of the 27 cotrimoxazole prescriptions, 26 were for such patients. Macrolides were the most used prophylactic antibiotics in the OLVG W. A possible explanation could be that, unlike the other hospitals, the PPS in this hospital were performed during the winter, when macrolides are used as prophylaxis for COPD patients.<sup>18, 19</sup> Broad spectrum penicillins represented the largest group of prophylactic antibiotics in the SLZ, which corresponds with the extent of post-surgical intervention prescriptions (table 1).

### **Appropriateness of antimicrobial prescriptions - Guideline adherence**

Table 2 shows an overview of the guideline adherence, separated for therapy and prophylaxis. A guideline was present for most prescriptions (n=684(95%), of which n=488 local guidelines), and this did not differ between prophylaxis and therapy. Altogether, 266 (38.9%) prescriptions did not adhere to the guideline. Of the prescribed therapeutics, 224 (43.1%) were inappropriate, mainly because the choice of agent or dose/duration were not in compliance with the guideline. Of the prescribed prophylaxis, 42 (25.6%) were inappropriate, mainly because there was no indication for prophylaxis. Guideline adherence varied between the hospitals. The presence or absence of local guidelines, with national/international guidelines coming in place when local guidelines are absent, was not statistically significant associated with the adherence rate ( $\chi^2$ -test, p-value: 0.21).

Guideline adherence per indication and per antimicrobial agent are presented in table 3 and 4 respectively. Overall, prescriptions for skin and soft tissue infections (n=60, 22.6%) and amoxicillin-clavulanic acid (n=67, 25.2%) made up the largest proportion of guideline non-compliant prescriptions. For skin and soft tissue infections, this was most often because of an inappropriate dose or duration of therapy (n=43, 71.7%) and for amoxicillin-clavulanic acid because the choice of the agent was not recommended by the guideline (n=38, 56.7%). Variation was seen between the hospitals. For instance, in the SLZ prescriptions for post-surgical prophylaxis were more often inappropriate (n=18, 28.1%) and in the OLVG W, macrolides were more often inappropriately prescribed (n=21, 23.1%).

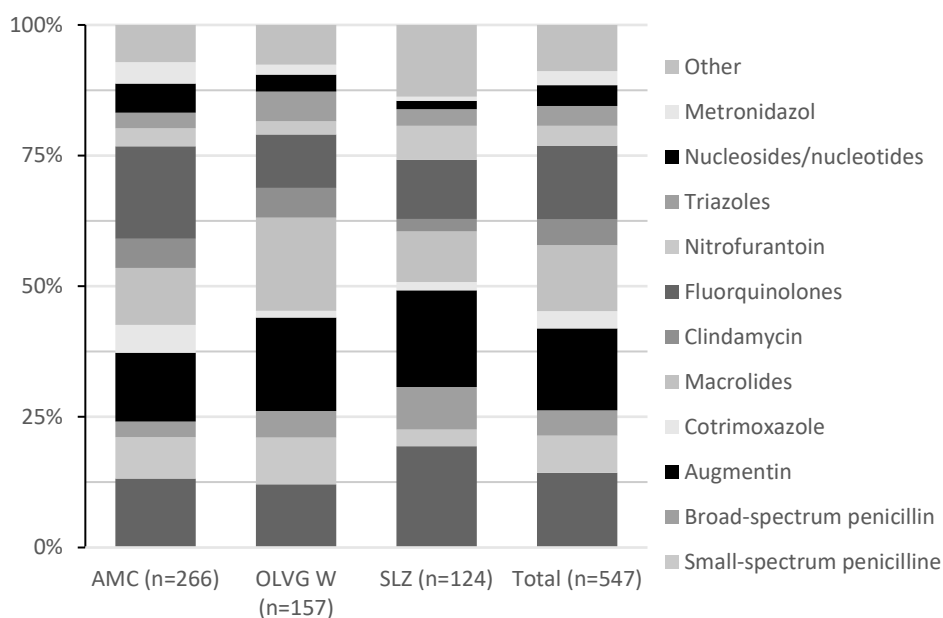
**Table 1. Characteristics of antimicrobial prescriptions**

	Hospital			
	AMC	OLVG W	SLZ	Total
<b>Number of prescriptions</b>	364	199	157	720
Antibiotics (%)	276 (75.8)	159 (79.9)	134 (85.4)	569 (79)
Antimycotics (%)	15 (4.1)	12 (6.0)	7 (4.5)	34 (4.7)
Antimycobacterials (%)	9 (2.5)	3 (1.5)	3 (1.9)	15 (2.1)
Antivirals (%)	38 (10.4)	12 (6)	4 (2.5)	54 (7.5)
Antiprotozoals (%)	20 (5.5)	5 (2.5)	2 (1.3)	27 (3.8)
Anthelmintics (%)	5 (1.4)	2 (1)	0	7 (1)
Other <sup>a</sup> (%)	1 (0.3)	6 (3)	7 (4.5)	14 (1.9)
<b>Indications for therapy (% of total prescriptions)</b>	266 (73.1)	157 (78.9)	124 (79)	547 (76)
Skin and soft tissue (%)	65 (24.4)	50 (31.8)	29 (23.4)	144 (26.3)
Urogenital tract (%)	41 (15.4)	29 (18.5)	38 (30.6)	108 (19.7)
Respiratory tract (%)	41 (15.4)	38 (24.2)	19 (15.3)	98 (17.9)
Gastro-intestinal tract (%)	37 (13.9)	10 (6.4)	13 (10.5)	60 (11)
Ear-nose-throat (%)	26 (9.8)	9 (5.7)	10 (8.1)	45 (8.2)
Oral-maxillofacial (%)	7 (2.6)	10 (6.4)	15 (12.1)	32 (5.9)
Ophthalmology (%)	16 (6)	6 (3.8)	-	22 (4)
Other <sup>b</sup> (%)	33 (12.4)	5 (3.2)	-	38 (6.9)
<b>Indication for prophylaxis (% of total prescriptions)</b>	98 (26.9)	42 (21.1)	33 (21)	173 (24)
Medical prophylaxis (%)	85 (86.7)	34 (81)	15 (45.5)	134 (77.5)
Surgical/intervention prophylaxis (%)	13 (13.3)	8 (19)	18 (54.5)	39 (22.5)

Abbreviations: AMC = Amsterdam UMC, location Academic Medical Center; OLVG W = Onze Lieve Vrouwe Gasthuis Hospital, location West; SLZ = MC Slotervaart

<sup>a</sup>Other: *H. pylori* eradication, <sup>b</sup>Other: <10 prescriptions.

**Figure 1: Antimicrobial prescriptions - Therapy**



**Figure 2: Antimicrobial prescriptions - Prophylaxis**

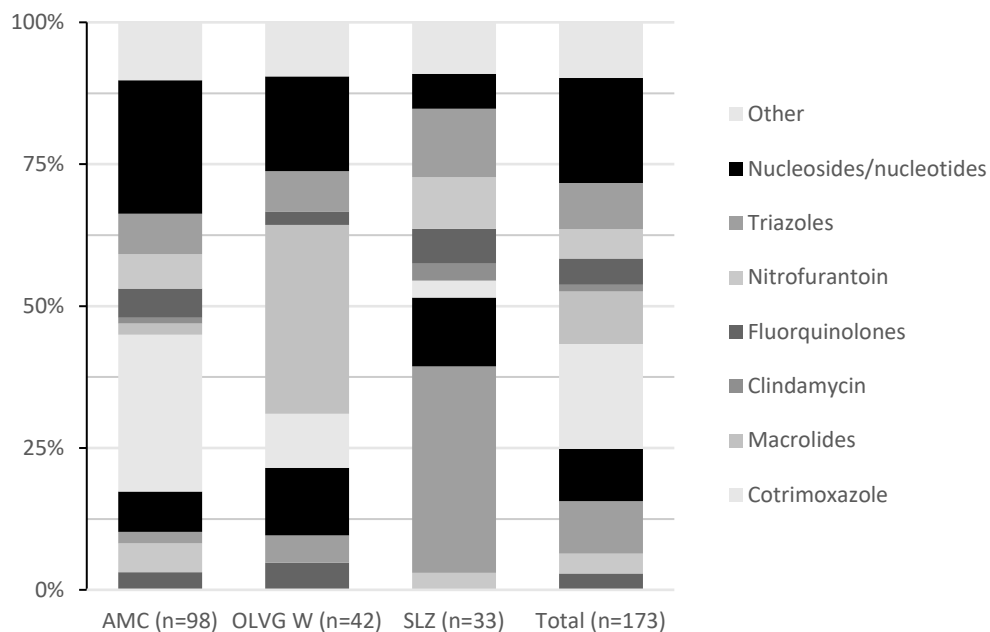


Table 2. Guideline adherence

	Therapy			Prophylaxis				Total	
	AMC	OLVG W	SLZ	Total	AMC	OLVG W	SLZ		
Number of prescriptions	266	157	124	547	98	42	33	173	720
Guideline available (%)	249 (93.6)	149 (94.9)	122 (98.4)	520 (95.1)	96 (98)	36 (85.5)	32 (97)	164 (94.8)	684 (95)
Guideline non-adherence (%)	95 (38.2)	84 (56.4)	45 (36.9)	224 (43.1)	16 (16.7)	7 (19.4)	19 (59.4)	42 (25.6)	266 (38.9)
No indication (%)	17 (17.9)	13 (15.5)	10 (22.2)	40 (17.9)	15 (93.8)	6 (85.7)	18 (94.7)	39 (92.9)	79 (29.7)
Inappropriate agent (%)	31 (32.6)	37 (44)	24 (53.3)	92 (41.1)	-	-	-	-	92 (34.5)
Inappropriate dose/duration (%)	47 (49.5)	34 (40.5)	11 (24.4)	92 (41.1)	1 (6.3)	1 (14.3)	1 (5.3)	3 (7.1)	95 (35.7)

Table 3. Guideline non-adherence per indication

	Hospital			Total
	AMC	OLVG W	SLZ	
Respiratory tract (%)	15 (13.5)	27 (29.7)	6 (9.4)	48 (18)
Gastro-intestinal tract (%)	10 (9)	2 (2.2)	3 (4.7)	15 (5.6)
Urogenital tract (%)	8 (7.2)	14 (15.4)	14 (21.9)	36 (13.5)
Skin and soft tissue (%)	26 (23.4)	28 (30.8)	6 (9.4)	60 (22.6)
Ear-nose-throat (%)	25 (22.5)	7 (7.7)	7 (10.9)	39 (14.7)
Oral-maxillofacial (%)	2 (1.8)	3 (3.3)	9 (14.1)	14 (5.3)
Ophthalmology (%)	5 (4.5)	2 (2.2)	0	7 (2.6)
Other (%)	4 (3.6)	1 (1.1)	0	5 (1.9)
Medical prophylaxis (%)	5 (4.5)	2 (2.2)	1 (1.6)	8 (3)
Surgical/intervention prophylaxis (%)	11 (9.9)	5 (5.5)	18 (28.1)	34 (12.8)
Total	111	91	64	266

Table 4. Guideline non-adherence per antimicrobial agent

	Hospital			Total
	AMC	OLVG W	SLZ	
Tetracycline (%)	6 (5.4)	7 (7.7)	2 (3.1)	15 (5.6)
Small-spectrum penicillin (%)	18 (16.2)	11 (12.1)	3 (4.7)	32 (12)
Broad-spectrum penicillin (%)	4 (3.6)	6 (6.6)	16 (25)	26 (9.8)
Amoxicillin-clavulanic acid (%)	24 (21.6)	19 (20.9)	24 (37.7)	67 (25.2)
Cotrimoxazole (%)	5 (4.5)	2 (2.2)	1 (1.6)	8 (3)
Macrolides (%)	11 (9.9)	21 (23.1)	6 (9.4)	38 (14.3)
Clindamycin (%)	7 (6.3)	7 (7.7)	1 (1.6)	15 (5.6)
Fluoroquinolones (%)	18 (16.2)	10 (11)	4 (6.3)	32 (12)
Nitrofurantoin (%)	3 (2.7)	1 (1.1)	2 (3.1)	6 (2.3)
Triazoles (%)	4 (3.6)	4 (4.4)	1 (1.6)	9 (3.4)
Nucleosides/nucleotides (%)	8 (7.2)	2 (2.2)	1 (1.6)	11 (4.1)
Metronidazole (%)	1 (0.9)	0	0	1 (0.4)
Other (%)	2 (1.8)	1 (1.1)	3 (4.7)	6 (2.3)
Total (%)	111	91	64	266

### Appropriateness of antimicrobial prescriptions – documented plan and dosage adjustment

A documented plan was available in 94.6% (range between hospitals: 89.8%-97.5%) of the prescriptions.

There were 138 antimicrobial prescriptions for which dosage adjustment was recommended because of renal impairment (table 5). Of these, only 13 (9.6%) were adjusted. The antimicrobial agent in which most frequently renal function was not taken into account was amoxicillin-clavulanic acid: of all amoxicillin-clavulanic acid prescriptions (n=102), 62.7% was incorrectly not adjusted, which accounted for 50% of the not-adjusted prescriptions in patients with impaired or unknown renal function.

**Table 5. Prescriptions adapted to renal function**

	Hospital			
	AMC	OLVG W	SLZ	Total
<b>Nr. of prescriptions to be adjusted to renal function</b>	63	41	34	138
<b>Nr. adjusted</b>	12	1	0	13
<b>Nr. not adjusted</b>	51	40	34	125
<b>Antimicrobial agents not adjusted (% of total<sup>a</sup>)</b>				
Amoxicillin-clavulanic acid (n=102)	22	22	20	64 (62.7)
Cotrimoxazole (n=50)	4	1	0	5 (10)
Macrolides (n=85)	3	4	1	8 (9.4)
Fluoroquinolones (n=85)	12	9	5	26 (30.6)
Nitrofurantoin (n=30)	4	2	4	10 (33.3)
Triazoles (n=85)	1	1	1	3 (8.6)
Nucleosides/nucleotides (n=54)	5	1	2	8 (9.3)
Other (n=65)	-	-	1	1 (1.5)

<sup>a</sup>n=total number of prescriptions for that agent, regardless of renal function

## Discussion

We investigated the prescription rate and appropriateness of prophylactic and therapeutic antimicrobials in the outpatient clinics of one tertiary care university hospital and two secondary care hospitals. In the outpatient clinics a quarter of the antimicrobials were prescribed for prophylaxis. We identified several targets for

quality improvement projects. Although guidelines were present for most prescriptions (95%), these were not followed in a substantial proportion of cases (38.9%). Of these, mainly therapeutic antibiotics were inappropriately prescribed, which contributed for 84.2% to the total inappropriate prescriptions. Amoxicillin-clavulanic acid was the most frequent inappropriately prescribed antimicrobial agent, due to non-adherence to the guideline and also because dosage adjustment in case of renal impairment was often not applied. An antimicrobial plan was present in the case notes of most prescriptions.

The overall proportion of prophylaxis prescribed in hospital outpatient clinics was similar to what is reported in the hospital wards in the recent global PPS (25.2%).<sup>20</sup> To the best of our knowledge, the average proportion of prophylaxis in the ambulatory setting is unknown. Inappropriately prescribed prophylaxis made up only 15.8% of the inappropriate prescriptions. Although in the outpatient clinics the majority of the prophylaxis was indicated for medical prophylaxis, still almost a quarter of prophylaxis were prescribed for post-surgical/intervention prophylaxis. In general, prolonged use of surgical prophylaxis has not been associated with better clinical outcome, but rather with emerging antimicrobial resistance and *Clostridium difficile* infections.<sup>21, 22</sup> Therefore, prophylaxis that is continued after 24 hours is in general considered inappropriate. This explains our findings: prophylaxis that was not in compliance to the available guidelines was primarily due to unnecessarily prescribed post-surgical/intervention prophylaxis.

Of all therapeutic prescriptions 43.1% did not adhere to the guideline, mainly due to an inappropriate choice of antimicrobial agent or dose/duration of therapy, which is almost twice as much as was reported for hospital wards (22.6%).<sup>20</sup> Previous studies addressing the appropriateness of antibiotic prescriptions in the ambulatory care setting described a non-adherence rate similar to ours. However, in these studies it was unclear whether it also included prophylaxis.<sup>7,9</sup> Our results showed that prescriptions for skin and soft tissue infections (SSTI) were the most frequently inappropriate, while previous studies in the ambulatory care setting mainly showed inappropriate prescriptions for respiratory tract infections.<sup>7, 8, 23, 24</sup> Antibiotic use for respiratory tract infections is seasonal driven.<sup>25</sup> In two of the three hospitals the PPS were performed during the summer.<sup>25</sup> Also, it is conceivable that consultations for respiratory tract infections are more common in general practice than in hospital outpatient clinics. Finally, antibiotic use for respiratory tract infections has received extensive attention from ASPs, which might have led to less inappropriate prescriptions.<sup>7, 8, 23, 24</sup> In previous studies it was already shown that antimicrobial treatment of uncomplicated SSTI had a low guideline adherence rate, 11-20.2%, due to an inappropriate length of treatment and due to an inappropriate choice of broad spectrum antibiotic agents.<sup>9, 26, 27</sup> Altogether, these

findings suggest that there is considerable room for quality improvement for SSTI prescriptions and emphasize the need of information on antibiotic use per clinical care setting to direct ASP efforts.<sup>10, 24</sup>

The main focus of ASP should be the use of amoxicillin-clavulanic acid. Amoxicillin-clavulanic acid (ACA) has become the most frequently used antimicrobial agent globally.<sup>12, 28-30</sup> The high use of ACA has been directly linked to an increased antimicrobial resistance, of which the resistance of *Klebsiella pneumoniae* and *Escherichia coli* to ACA has become a significant and clinically relevant problem.<sup>12, 31</sup> Our findings showed that ACA not only was the most frequently prescribed antimicrobial agent in hospital outpatient clinics, but also the most often inappropriately prescribed, which was also reported in previously performed PPS on hospital wards.<sup>32, 33</sup> In addition, we showed that when ACA was prescribed, dosage in case of renal impairment was often not adjusted, while the dosage should be adjusted in case of an estimated glomerular filtration rate below 30 ml/min. Previous reports have shown that restricting ACA use effectively reduces ACA resistance.<sup>31, 34</sup> In Croatia, this restriction has led to a decrease of *E.coli* resistance from 37% to 11%.<sup>34</sup> Altogether, we found opportunities for ASP to enhance the quality of ACA use, for patients' safety and ACA resistance.

There are several possibilities that could explain the prescribing behaviour of antimicrobials in hospital outpatient clinics and why the non-adherence rate in the outpatient clinics was twice as high as what was observed in the hospital wards.<sup>23</sup> First, in hospital outpatient clinics patients have to be seen, diagnosed and treated within a short time frame and because of the time constraints clinicians might not be able to search for the guideline. Second, due to the inability of daily observing the clinical outcome of the patient, it is possible that clinicians are more cautious and prone to prescribe broad spectrum antimicrobials such as ACA, or prolonged surgical prophylaxis. Third, it is possible that clinicians are habituated to certain treatment practices which have proven to be effective, regardless of whether they are in accordance with current guidelines, and are therefore less motivated to change this habit. Further qualitative studies should be performed to elucidate the reasons of this high non-compliance rate.

### **Strengths and limitations**

This study has several strengths and limitations. The PPS were performed on ten different time points, in all adult hospital outpatient clinics of three different hospitals. Therefore, we were able to detect a certain pattern, rather than a local observation. However, the three hospitals were localized in the same geographic area and therefore we do not know to which extent our data is nationally or internationally representative. A strength is that we used the EMR to generate the

data regarding antimicrobial use, which we validated manually in all three hospitals. Hereby, we reduced the risk of missing prescriptions. Although some pharmacies still accept handwritten prescriptions, which would be missed in our study, this is the exception rather than the rule. Additionally, we evaluated therapy and prophylaxis using several quality indicators, which enabled us to find several targets for quality improvement for ASPs. When we evaluated the prescriptions with regard to dosage adjustment to renal function, the prescriptions for patients of whom the renal function was unknown were labelled as inappropriate. By doing this, we may have overestimated the number of prescriptions in which the dose was incorrectly not adjusted according to renal function. However, the result that in 118 of 138 prescriptions the renal function was unknown shows that testing for renal function is often not considered, even though these agents require dosage adjustment when the renal function is impaired. We think it is important to raise awareness on this matter.

## Conclusion

In the hospital outpatient clinics, prophylaxis accounted for a quarter of the antimicrobial prescriptions and had in general a good guideline-adherence rate, with the exception of unnecessarily prescribed post-surgical/intervention prophylaxis, whereas a substantial part of the therapeutic prescriptions were inappropriate. Amoxicillin-clavulanic acid was the most inappropriately prescribed antimicrobial agent, regarding non-adherence to the guideline and also regarding the lack of considering renal function for dosage adjustment. Altogether, we believe that antimicrobials prescribed at the hospital outpatient clinics warrant ASP attention. The variation of the guideline adherence rate between the investigated hospitals, as well as the differences with prior studies addressing antibiotic use in ambulatory settings in general, emphasize that (hospital) outpatient antimicrobial use should be audited locally.

## List of abbreviations

ACA:	Amoxicillin-clavulanic acid
AMC:	Amsterdam UMC, location Academic Medical Center
ASP:	Antibiotic stewardship programs
ATC:	Anatomical Therapeutic Chemical
EMR:	Electronic medical records
OLVG W:	Onze Lieve Vrouwe Gasthuis Hospital, location West
PPS:	Point-prevalence surveys
SLZ:	MC Slotervaart
SSTI:	Skin- and soft tissue infections

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## CHAPTER 3:

# **A mandatory indication-registration tool in hospital electronic medical records enabling systematic evaluation and benchmarking of the quality of antimicrobial use: a feasibility study**

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## Abstract

**Objectives:** Evaluation of the extent and appropriateness of antimicrobial use is a cornerstone of antibiotic stewardship programs, but it is time-consuming. Documentation of the indication at the moment of prescription might be more time-efficient. We investigated the real-life feasibility of mandatory documentation of the indication for all hospital antibiotic prescriptions for quality evaluation purposes.

**Methods:** A mandatory prescription-indication format was implemented in the Electronic Medical Record (EMR) of three hospitals using EPIC or ChipSoft software. We evaluated the retrieved data of all antibiotics (J01) prescribed as empiric therapy in adult patients with respiratory tract infections (RTI) or urinary tract infections (UTI), from January through December 2017 in Hospital A, June through October 2019 in Hospital B and May 2019 through June 2020 in Hospital C. Endpoints were the accuracy of the data, defined as agreement between selected indication for the prescription and the documented indication in the EMR, as assessed by manually screening a representative sample of eligible patient records in the EMR of the three hospitals, and appropriateness of the prescriptions, defined as the prescriptions being in accordance with the national guidelines.

**Results:** The datasets of hospitals A, B and C contained 9588, 338 and 5816 empiric antibiotic prescriptions indicated for RTI or UTI, respectively. The selected indication was in accordance with the documented indication in 96.7% (error rate: 10/300), 78.2% (error rate: 53/243), and 86.9% (error rate: 39/298), respectively. A considerable variation in guideline adherence was seen between the hospitals for severe community acquired pneumonia (adherence rate ranged from 35.4% to 53.0%), complicated UTI (40.0%-67.1%) and cystitis (5.6%-45.3%).

**Conclusions:** After local validation of the datasets to verify and optimize accuracy of the data, mandatory documentation of the indication for antibiotics enables a reliable and time-efficient method for systematic registration of the extent and appropriateness of empiric antimicrobial use, which might enable benchmarking both in-hospital and between hospitals.

## Background

Antibiotic Stewardship Programmes (ASPs) have been developed to measure and improve the appropriateness of antibiotic use while minimizing unintended consequences of antibiotic use.<sup>1-3</sup> To measure appropriateness, quality indicators (QIs) have been established and validated.<sup>4</sup> One of the QIs is prescribing antimicrobials in accordance with the local guideline, or, if not available, national or international guidelines. Guideline-adherent empiric therapy has shown to be associated with improved clinical outcome.<sup>1, 5</sup>

A frequently used method to evaluate the appropriateness of antimicrobial use in a hospital is the point prevalence survey (PPS), in which all antimicrobial prescriptions and their indications are retrieved during a certain time period.<sup>6, 7</sup> This is done by manually reviewing the (electronic) medical record (EMR). In many cases contact with the attending physician is necessary because of incomplete records, and therefore the evaluation of appropriateness can be very time-consuming. This often results in the evaluation of a relatively small number of patients and a low frequency of analysis, limited to hospitals with available personnel and resources.<sup>8</sup> This calls for a more efficient method to evaluate the appropriateness of antimicrobial use, in order to perform measurements more often or on a larger scale.

EMR tools have already been shown to facilitate ASPs, by computerised decision support, and surveillance of the use of restricted antimicrobials and potential IV-to-oral switch candidates.<sup>9-12</sup> In previous studies it was also shown that in a study setting EMR tools are able to link antibiotic orders to indications, which could facilitate standardized data collection and an automated assessment of antibiotic appropriateness as well.<sup>12-18</sup>

The aim of this study was to investigate the real-life feasibility of mandatory documentation of the indication for all antibiotic prescriptions, for the purpose of systematic evaluation of not only the extent, but also the appropriateness of antimicrobial use. This might also facilitate national antimicrobial use surveillance and benchmarking on the hospital level. We implemented a standardized prescription-format in the EMR of three hospitals, two hospitals using EPIC and the other using ChipSoft EMR software, and subsequently extracted the data. This is a feasibility study, as we describe the technical aspects of incorporating these order menus into the EMR and validated the extracted data against the source data in the EMR.<sup>19, 20</sup> In addition, we assessed whether the extracted data can be used to evaluate the compliance rate to national guidelines. For the purpose of this study, we focused on antibiotics prescribed as empiric therapy for patients with

respiratory tract infections (RTI) or urinary tract infections (UTI), since these are the most common infections in hospitals.

## Methods

### Study design and setting

The study was performed in three hospitals in the Netherlands. The participating hospitals were the OLVG Hospital (Hospital A), Amsterdam, a 663-bed non-academic teaching hospital, treating more than 500,000 patients annually; the Antonius Hospital (Hospital B), Sneek, a 300-bed non-academic hospital, treating 200,000 patients annually; and the Radboud University Medical Center (Hospital C), Nijmegen, a 593-bed academic teaching hospital, treating over 300,000 patients annually. At all hospitals an ASP is present, including an Antibiotic stewardship team (AST), consisting of an infectious diseases specialist, hospital pharmacist and medical microbiologist. The study consisted of two phases: 1) assessment of feasibility in hospitals using different EMR and prescribing software: Hospital A using EPIC software, and Hospital B using Chipsoft HIX software (August 2018 – January 2020); 2) confirmation of feasibility in another hospital using the same EMR and prescribing software: Hospital C using EPIC software (May 2020 – September 2020).

Approval from the Institutional review boards was not required for this study because we used retrospective, pseudonymized data for quality optimization purposes. Procedures were in accordance with the General Data Protection Regulation.<sup>21</sup>

### Data collection and procedures

A standardized prescription-format was implemented in the EMR and prescribing software of the participating hospitals by software-specific IT specialists. The format obliges physicians to select the indication for the prescription from a predefined list whenever they prescribe an antimicrobial agent to be administered systemically. The possible indications are empiric therapy, targeted therapy or prophylaxis. Subsequently they have to select the main focus of infection, first on tract level, followed by a further specification (*Supplemental figure 1 - 3*).

Hospital A already implemented the mandatory indication registration in 2015. This prescription format was used as the basis for our feasibility study. Hospital A retrieved data covering the period January 1, 2017, until December 31, 2017. After visual inspection of the data, amendments were made for a more detailed

indication registration, which was implemented in the prescription-format of Hospital B in 2018 and Hospital C in 2019. Hospital B provided data covering the period June 1, 2019 until October 31, 2019 and Hospital C covering the period May 14, 2019 until June 9, 2020.

The hospitals extracted datasets from the EMR containing the following parameters:

Coded patient identifier and admission identifier

- All antibiotic prescriptions for systemic use belonging to Anatomical Therapeutic Chemical (ATC) class J01
- The duration of therapy (start and stop date), dose regimen and route of administration
- The specialty/department of the authorizing and ordering prescriber, and ward of admission of the patient
- Time and date of admission and discharge, i.e. duration of admission
- The chosen focus of infection on tract level, specified in case of RTI or UTI

Further procedures were performed by the authors of the study. For the purpose of this study, we selected the antibiotic prescriptions of all hospitalized patients aged 18 years and older, admitted to any general ward, and receiving empiric antibiotic treatment for an RTI or UTI. Hospitalized clinical patients were defined as patients admitted to the ward for at least 12 hours. Empiric therapy was defined as the prescribed antibiotic (combination) therapy at time point 24 hours of hospitalization, or the last prescribed antibiotic therapy at the time of discharge in patients who were hospitalized for 12-24 hours. This definition of empiric therapy was chosen because febrile patients often receive empiric antibiotic treatment as soon as possible after presentation. During the first hours of admission incoming diagnostic results may lead to adjustment of the initial indication and therapy. Therefore, we reasoned that the prescriptions that were prescribed at time point 24 hours of hospitalization would most accurately reflect the empiric therapy for the indications of interest. After 24 hours, empiric therapy is usually adjusted to targeted therapy. We considered antibiotics that were prescribed simultaneously for the same specified indication as antibiotic combination therapy. We excluded ICU patients, because the ICU of Hospital A and B use another EMR; readmissions (defined as an admission within 30 days after the initial hospital discharge), because guideline-recommended empiric treatment is usually not applicable; prescriptions of patients

with both RTI and UTI; and erroneous prescriptions, these were prescriptions of which the start date of the antibiotic fell before the date of admission. Furthermore, we excluded the prescriptions for RTI in hospital C that were prescribed after March 2020, because initially no guideline was available for COVID-19 RTI. Exclusion criteria were applied electronically.

The primary endpoint of the study was the accuracy of the dataset, defined as percentage agreement between the selected indication for the prescription and the documented indication in the EMR. The secondary endpoint was the percentage of antibiotic prescriptions in each hospital that was prescribed according to the national guidelines.

### **Validation of the dataset**

We determined what data had to be extracted from the EMR to be able to select the prescriptions that met the inclusion criteria, and we evaluated the correctness of the datasets. This was first done through general inspection and if deemed necessary through manual chart review of records. Counterintuitive results were resolved. Next, we verified the accuracy of the datasets by manually screening a representative sample of eligible patient records in the EMR of the three hospitals on:

1. whether the indications RTI or UTI and their subsequent specifications selected as indication for the antibiotic prescription were in accordance with the documented diagnosis in the patient record. For this, we screened 200 electronically, randomly selected patient records in Hospital A and C and the 143 patient records with these indications in Hospital B.
2. whether selected indications other than RTI/UTI were in accordance with the documented diagnosis and RTI/UTI infections were thus not accidentally excluded. For this we screened 100 electronically, randomly selected records in all hospitals.

### **Appropriateness of prescriptions**

After validating the dataset, we measured the appropriateness of the prescriptions. This was done by evaluating whether the prescribed antibiotics for the selected indications were in accordance with the national guidelines of the Dutch Working party on Antibiotic Policy ([www.swabid.nl](http://www.swabid.nl)), which contain treatment recommendations for all common infections. In the Netherlands, the national guidelines often provide several possible empiric treatment recommendations,

from which the local hospital guidelines can select a number of options.<sup>22</sup> By using the national guidelines as a reference, it is possible to benchmark inpatient antibiotic use between hospitals. The prescribed antibiotics were categorised as A) in accordance with the guideline-recommended first choice agents; B) in accordance with the guideline-recommended second choice agents; C) discordant with the guideline. The appropriateness of the prescriptions linked to the RTI/UTI sub-indication “other” was not measured.

### **Data analysis**

Descriptive data are presented in numbers with or without percentages, for which SAS version 9.4 (SAS Institute Inc., USA) was used. We did not aim to statistically compare the appropriateness of prescriptions between the three hospitals, as the purpose of the study was to show the feasibility of quality measurements with the use of the mandatory prescription-indication tool with subsequent data extraction from the EMR.

## **Results**

### **Dataset characteristics and validation**

The datasets of the three hospitals contained 31769 (Hospital A), 2841 (Hospital B) and 25058 (Hospital C) systemic antibiotic (J01) prescriptions, respectively (*figure 1*). Of these, 9588 (30%), 338 (12%) and 5816 (23%), respectively, had the indication RTI or UTI or both. The datasets were first checked on correctness by general inspection. Counterintuitive results were further investigated and resolved. For example, the number of antibiotic prescriptions in Hospital B was initially very low, which turned out to be caused by the setting of the EMR tool that enabled optional indication registration instead of mandatory registration. For the final dataset we therefore used the data that was extracted after this problem was solved (from June 2019 onwards).

Next, for the data elements provided in addition to the antibiotic prescriptions and indications, we investigated what data needed to be extracted to get the most accurate presentation of our predefined selections. For example, to get the most accurate presentation of the patient's department of admission, for Hospital A the variable “specialty of authorizing prescriber” had to be extracted, and “specialty of admission” for Hospital B.

Furthermore, we evaluated 87 (n=30+27+30 for Hospital A, B and C, respectively) patients in whom hospital-acquired pneumonia (HAP) or prophylaxis was selected. HAP was evaluated to determine what definition for HAP was used by the prescribers in the three hospitals. In all hospitals HAP was (correctly) defined as pneumonia acquired after recent hospital or healthcare centre admission, for instance nursing homes. Prophylaxis was evaluated because the EMR tool in Hospital A required registering the focus of infection when selecting the indication prophylaxis, indicating that the antibiotic might be prescribed as therapy instead of prophylaxis. Evaluation of a sample of the prophylactic prescriptions confirmed that 48 out of 53 (n=15+23+15 for Hospital A, B and C, respectively) prescriptions were truly prescribed as prophylaxis and not as therapy, and these prescriptions were therefore justly excluded.

To verify the accuracy of the data, we compared the selected indication with the diagnosis as recorded in the EMR for 300 patients (Hospital A and C) and 243 patients (Hospital B) (table 1). Overall, the selected indication did not match with the documented diagnosis in 3.3% of the 300 cases in Hospital A, 21.8% of 243 cases in Hospital B and 13.1% of 298 cases in Hospital C. Indication selection errors were mostly due to inaccurate sub-indications. The error rate of Hospital B and C was explained mainly by incorrect selection of cystitis when a complicated UTI (urosepsis or pyelonephritis) was documented in the case notes (n=37 for Hospital B, and n=20 for Hospital C). In Hospital C the option “other” was missing as possible RTI-specification, resulting in 7 incorrect selections, as prescribers seemed to select the second best option. Of the randomly selected records with indications other than RTI/UTI, 7 prescriptions indicated for RTI/UTI were missed in Hospital B, only 2 in Hospital C and none in Hospital A. This shows that, depending on the hospital, we have missed a number of prescriptions for RTI/UTI.

### **Appropriateness of antibiotic prescriptions**

After selecting the empirically prescribed antibiotics and excluding the records that fulfilled exclusion criteria (*figure 1*), 5% of the total amount of prescribed antibiotics remained: 2071 prescriptions for RTI (n=1492, n=74 and n=505, respectively) and 1296 prescriptions for UTI (n=684, n=68 and n=544, respectively).

Prescriptions that were simultaneously prescribed for the same indication were considered combination therapy and were therefore merged for the final analysis of empirically prescribed antibiotic therapy per patient, after which 1775 antibiotic therapies remained for RTI (n=1248, n=66 and n=461) and 1246 for UTI (n=662, n=64 and n=520). The antibiotics prescribed for all RTI and UTI subindications in the three hospitals are presented in supplemental tables 1-6.

The appropriateness of antibiotic therapy for RTI and UTI are presented in figure 2 and figure 3, respectively. The adherence rate to the national guidelines differed considerably between the hospitals, which gives a clear illustration of the opportunities for benchmarking on hospital level.

**Figure 1. Antibiotic prescriptions in Hospital A, B and C**

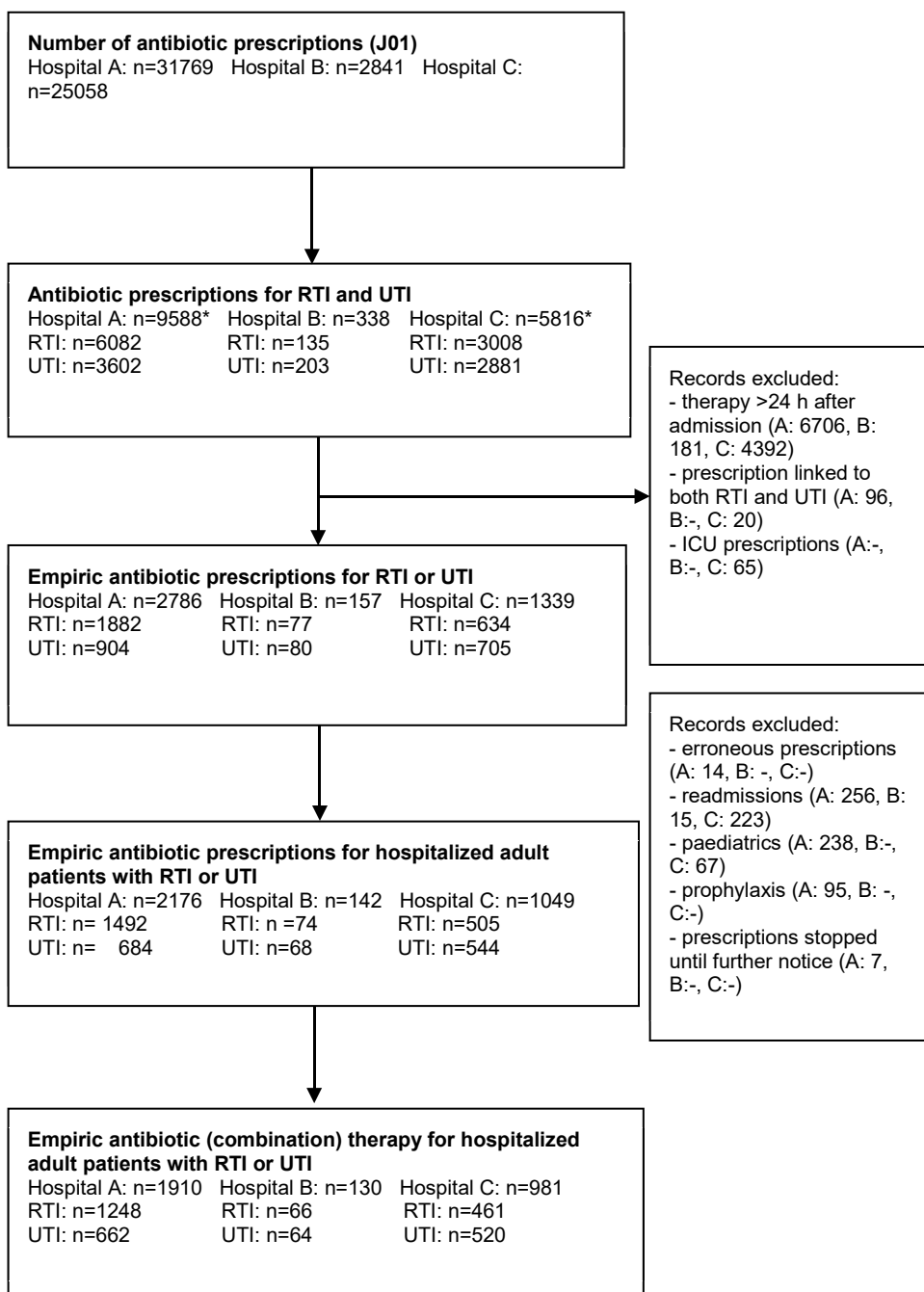
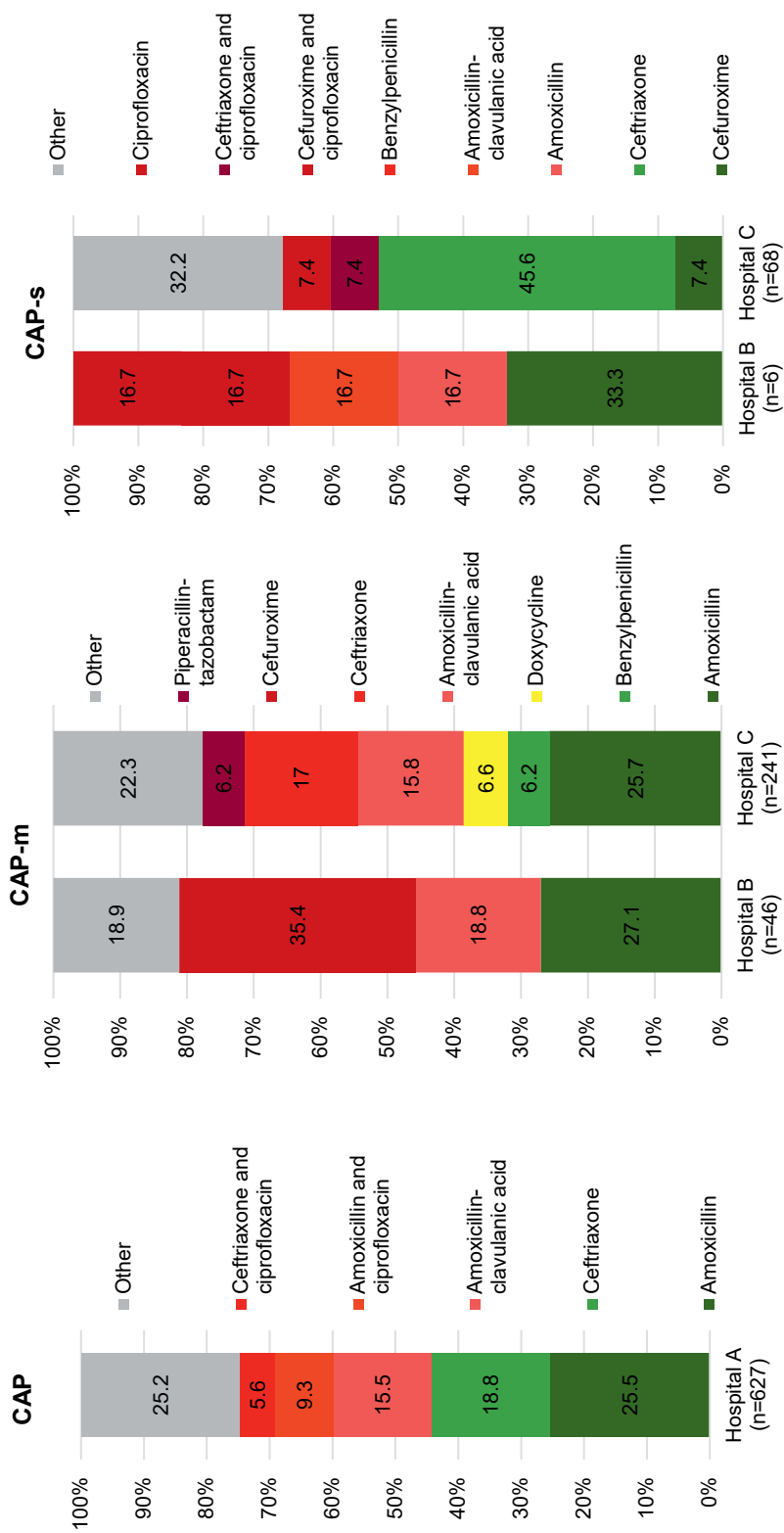


Table 1: Verification of selected indications

Samples	Hospital A (inaccurate selections/number of screened records)	Hospital B (inaccurate selections/number of screened records)	Hospital C (inaccurate selections/number of screened records)
<b>RTI – error rate (%)</b>	4/100 (4%)	7/70 (10%)	17/99* (17%)
<b>selected indication versus documented diagnosis</b>	1 prophylaxis ↔ HAP 1 CAP ↔ COPD 1 CAP ↔ bronchitis 1 other ↔ skin and soft tissue infections	3 CAP-m ↔ COPD 1 CAP-s ↔ CAP-m 2 COPD ↔ CAP-m 1 aspiration pneumonia ↔ CAP-s	4 CAP ↔ other 1 CAP-m ↔ COPD 1 Bronchitis ↔ COPD 1 Bronchitis ↔ CAP 3 CAP ↔ aspiration pneumonia 3 HAP ↔ other 1 CAP-s ↔ CAP-m 2 CAP-m ↔ HAP 1 CAP-m ↔ prophylaxis
<b>UTI – error rate (%)</b>	6/100 (6%)	39/73 (53%)	20/99* (20%)
<b>selected indication versus documented diagnosis</b>	5 cystitis ↔ complicated UTI 1 prophylaxis ↔ cystitis	37 cystitis ↔ complicated UTI 1 chronic prostatitis ↔ urosepsis 1 other ↔ urosepsis	20 cystitis ↔ complicated UTI
<b>Random – error rate (%)</b>	0/100 (0%)	7/100 (7%)	2/100 (2%)
		4 missed UTI 3 missed RTI	1 missed UTI 1 missed RTI
<b>Total error rate (%)</b>	3.3%	21.8%	13.1%

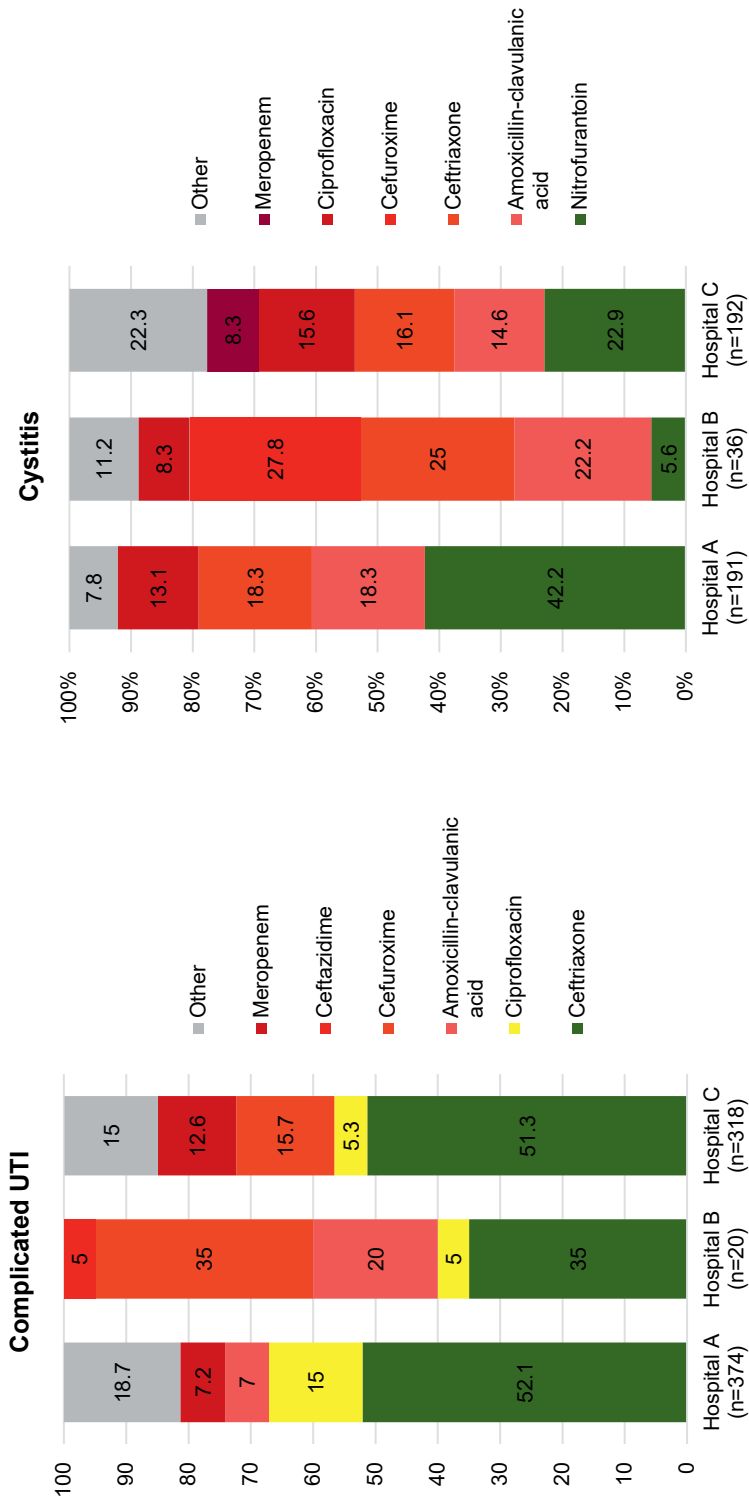
\*1 record could not be validated, because documentation regarding the indication of antibiotic treatment was missing/not accessible. <sup>a</sup>random samples, other than RTI/UTI. <sup>b</sup>CAP-m=community-acquired pneumonia – mild to moderate severe. <sup>c</sup>CAP-s=community-acquired pneumonia - severe.

Figure 2: appropriateness of antibiotics for RTI - CAP



Category A) in accordance with the guideline-recommended first choice agents, marked in green; B) in accordance with the guideline-recommended second choice agents, marked in yellow; C) discordant with the guideline, marked in red; and other: antibiotics prescribed in less than 5% of cases, marked in grey.

Figure 3: appropriateness of antibiotics for UTI



Category A) in accordance with the guideline-recommended first choice agents, marked in green; B) in accordance with the guideline-recommended second choice agents, marked in yellow; C) discordant with the guideline, marked in red; and other: antibiotics prescribed in less than 5% of cases, marked in grey.

### *Respiratory tract infections*

For Hospital A, mild to moderate-severe and severe CAP were not distinguished in the EMR. For CAP, overall guideline adherence rate was 49.5%, mainly due to the frequent appropriate use of amoxicillin (25.5%) and ceftriaxone (18.8%). Hospital B and Hospital C did distinguish between mild to moderate-severe versus severe CAP, using the CURB-65 score. The adherence rate for mild to moderate-severe CAP was similar for Hospital B and Hospital C (33.4% and 38.5% respectively). The low guideline adherence rate was mainly due to the frequent inappropriate use of cefuroxime in Hospital B (35.4%) and ceftriaxone in Hospital C (17%). In all three hospitals, amoxicillin-clavulanic acid (ACA) was inappropriately prescribed in 15.5-18.8% of cases. The adherence rate for severe CAP was 35.4% for Hospital B and 53% for Hospital C. For severe CAP a wide variation of inappropriate therapy combinations was seen.

The guideline adherence rate for COPD exacerbations and HAP (in this study: pneumonia acquired in other health care institutions, for instance nursing homes) are shown in supplemental figure 4. The guideline adherence rates ranged from 40.0% to 52.5% for COPD and 51.0%-73.2% for HAP.

### *Urinary tract infections*

The guideline adherence rate for complicated UTI was 67.1% in Hospital A, 40.0% in Hospital B and 56.6% in Hospital C. In Hospital A and C, complicated UTI was mainly treated with ceftriaxone (51.1% and 51.3% respectively). In Hospital B, complicated UTI was either treated with ceftriaxone, cefuroxime or ACA, of which the last two agents are considered inappropriate. Cefuroxime was the second most prescribed agent in Hospital C as well.

The antibiotic use for cystitis was appropriate in 45.3% in Hospital A, 5.6% in Hospital B and 28.1% in Hospital C. In all hospitals ACA, ceftriaxone or cefuroxime were commonly prescribed, which are all considered inappropriate.

## **Discussion**

With this study we demonstrated that it is feasible to introduce mandatory documentation of the indication at the moment of antibiotic prescribing, using a prescription format implemented in the EMR. In order to use the data extracted from the EMR for quality measurements, an initial local validation and if indicated optimization of the datasets is necessary, which was shown in our results. The error rate of the prescription-indication tool ranged from 3.3% (Hospital A) to 21.8%

(Hospital B) – the latter because cystitis was often not correctly used as indication for the prescription. We also demonstrated that the retrieved data enable the evaluation of the appropriateness of the prescriptions for empiric therapy. For RTI and UTI a considerable variation in guideline adherence was seen between the hospitals, giving an example of the opportunities of benchmarking on hospital level.

In previous studies, the prescription-indication tools were either implemented in hospital-specific software, or the indications were determined by and specific for the institution.<sup>16-18, 23, 24</sup> Therefore, the generalizability of these tools has been subject of debate and quality measurements were restricted to single hospitals.<sup>16-18, 23, 24</sup> In this feasibility study, we implemented the prescription-indication tool in two nationally and internationally widely used EMR software packages (ChipSoft and EPIC). Also, we standardized the indications that the prescribers could choose from, which enabled benchmarking of the results on the national level. More variables can be extracted and data can be further stratified for a more detailed examination of antibiotic use, for example when evaluation of antibiotic use on department/local level is desired. Nevertheless, the output of the extracted data of the EMR may vary between hospitals. For example, we noticed a difference in how the prescriber's department was displayed and therefore what data had to be extracted to get the most accurate presentation of the prescriber's department. Little variation in data output is expected for hospitals using ChipSoft software, since ChipSoft has an uniform EMR content. Hospitals using EPIC software, however, are able to personalize the EMR content to the needs of their facility. Thus, before the datasets of other hospitals can be used for comparison, specification of extracted data is necessary.

The feasibility study identified other points of consideration as well. A large number of antibiotic prescriptions were not evaluated for appropriateness. These were mainly the prescriptions that were excluded because they had other indications than RTI/ UTI or because they were not considered as empiric therapy. To enable electronic evaluation of the quality of antibiotic use, we focused on empiric therapy because that is prescribed according to general guidelines. The data output did not include patient characteristics or diagnostic results, which precludes electronic evaluation of targeted therapy. In addition, depending on the hospital, a number of prescriptions for RTI and UTI can be missed due to incorrectly selected indications by prescribers. Thus, one should keep in mind that this method enables to measure the appropriateness of a relatively large sample of antibiotic prescription for RTI/UTI and not the appropriateness of all antibiotic prescriptions for that indication.

The rate of discrepancy between selected indication and documented indication in the EMR was comparable to the 74% to 90% accuracy rates reported by previous studies investigating the validity of automated indication registration.<sup>16-18, 23</sup> In Hospital B and C, mismatches were mainly caused by incorrectly selected cystitis where this should have been complicated UTI (n=37 and n=20 respectively). This also explains why cefuroxime and ceftriaxone were the most frequently prescribed agents for cystitis. This underscores that the accuracy rate needs to be considered when using the data for quality measurements and benchmarking. The difference between the accuracy rates of the hospitals might be partially explained by the timing of data extraction: Hospital A implemented the automated tool in 2015, meaning the prescribers had three years to familiarize with the system, while the data from Hospital B and C was extracted only a few months after implementation. Education and feedback to prescribers by local AST may be necessary to increase the accuracy of the data.

Mandatory prescription-indication documentation and the standardized data collection may considerably reduce the workload for local AST.<sup>12, 14, 25</sup> It makes manual data collection for a PPS probably superfluous, as it presents a framework for a more comprehensive approach. The mandatory selection of an indication might be seen as burdensome for prescribers. However, during the evaluation of our feasibility study prescribers informed us that they did not consider the intervention as such. They considered it not labour-intensive or considered it standard patient care. These responses are comparable with what was previously reported by Beardsley and colleagues. In that study prescribers were surveyed on the burden of an automated prescription-indication tool. They judged it to be minor or occasionally burdensome.<sup>23</sup> In the study of ten Oever and colleagues it was shown that the time needed to perform a PPS and report the measurements was 150 and 30 hours, respectively.<sup>26</sup> As a result, quality measurements and improvement activities are either performed on smaller scale, or not performed at all. Introducing mandatory indication registration also requires time and expertise. However, as opposed to PPS, the majority of time needs to be invested once, at the start of the project. Thereafter, time is needed to repeat the analysis (semi)annually or quarterly, which is less time consuming than performing a PPS and potentially generates much more data. In our study we already saw that with increasing experience the time needed for the implementation of the mandatory prescription format, data validation and analysis was significantly shorter in Hospital C. This leaves more time for the AST to focus on quality improvement activities. Analysis and benchmarking of the data can be performed by a regional or national party, which also assures independent quality control. Ongoing surveillance of antibiotic use based on yearly results also enables evaluation of the antibiotic use for indications that occur less often, for instance HAP. These are

often missed in a PPS or the results are not interpretable because of the small numbers. Finally, benchmarking on the national level facilitates comparison of the appropriateness of antimicrobial use between hospitals, providing additional targets for improvement.<sup>14, 27</sup> This was also demonstrated in our study. We also found that ACA was frequently inappropriately prescribed for both CAP as cystitis in all three hospitals. Also, in Hospital B and C, amoxicillin was prescribed in 33.3% of exacerbations COPD. These findings suggest targets not only for local action, but also for national action.

### **Limitations**

This study is subject to several limitations. First, the accuracy of the datasets relies on accurate indication selection by the prescribers. Human errors are inevitable, and the error rate might fluctuate over time. The accuracy of a random sample of the dataset should therefore be checked regularly, for example yearly. Second, some antibiotics might be prescribed based on pre-admission used antibiotics, previously cultured pathogens, or because of patient allergies. These prescriptions are currently unjustly labelled as being inappropriate. However, in previous studies it was shown that this does not influence the overall guideline adherence rate notable and therefore can be ignored.<sup>28</sup> Another limitation is that the appropriateness of antimicrobial use was defined as being in accordance with the national guidelines, and not the local guidelines. Local guidelines are derived from the national guidelines and may contain adjustments according to local resistance patterns.<sup>4</sup> However, this would mainly pose a difficulty for countries where a wide range of local resistance is observed, which can be solved by benchmarking per region instead of on the national level. Also, we did not evaluate the appropriateness of treatment duration, which is also an important target to reduce antibiotic consumption.<sup>29</sup> However, this would require post-discharge antibiotic prescription data, which we could not retrieve from the datasets. Also, we did not evaluate the accuracy of provider's diagnosis, which is another important intervention for Antimicrobial Stewardship Teams. The evaluation tool in its current form focuses on whether the prescribed antibiotic is in accordance with the guideline for the presumed diagnosis. Finally, we compared three hospitals without considering comparability between these hospitals in terms of type, size and case-mix, which would be preferable for benchmarking on the national level.

## Conclusion

We have demonstrated the real-life feasibility of mandatory documenting the indication of all antibiotics prescribed in EMR using ChipSoft or EPIC software for quality evaluation purposes. It enables a reliable and time-efficient method for systematic registration of the extent and appropriateness of empiric antimicrobial use. Initial local validation and, if necessary, optimization of the datasets, however, is required to assure accuracy of the extracted data. The next step is now to implement this prescription-format in more hospitals in the Netherlands and internationally, for the purpose of national and international benchmarking of the quality of in-hospital antibiotic use. To further improve the quality of prescribing it would also be useful to embed local or national guidelines in the EMR, enabling direct feedback whenever an antibiotic is prescribed.

## List of abbreviations

ACA	Amoxicillin-clavulanic acid
ASPs	Antibiotic Stewardship Programmes
AST	Antibiotic Stewardship Team
ATC	Anatomical Therapeutic Chemical
CAP-m	Community-acquired pneumonia – mild to moderate severe
CAP-s	Community-acquired pneumonia – severe
EMR	Electronic Medical Record
HAP	Hospital acquired or healthcare centre associated pneumonia
PPS	Point prevalence survey
QIs	Quality indicators
RTI	Respiratory tract infections
UTI	Urinary tract infections

## Supplementary data

Figure 1. EMR prescription format EPIC - Hospital A

<b>1. Select antimicrobial agent</b>	
<b>2. Select indication</b>	<input type="checkbox"/> Prophylaxis <input type="checkbox"/> Empirical therapy <input type="checkbox"/> Targeted therapy <input type="checkbox"/> Other
<i>In case of prophylaxis: select indication prophylaxis</i>	<input type="checkbox"/> Perioperative <input type="checkbox"/> SDD <input type="checkbox"/> Other
<b>3. Select focus of infection</b>	<input type="checkbox"/> <b>Respiratory tract</b> <input type="checkbox"/> <b>Kidneys and urinary tract</b> <input type="checkbox"/> Gastrointestinal <input type="checkbox"/> Gynaecology/obstetrics <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Skin <input type="checkbox"/> Tropical diseases <input type="checkbox"/> Sepsis of unknown cause <input type="checkbox"/> Prophylaxis <input type="checkbox"/> CNS <input type="checkbox"/> Intra-abdominal <input type="checkbox"/> Joints and bones <input type="checkbox"/> Other
<b>4. Select specified indication</b>	
<i>In case of Respiratory tract</i>	<input type="checkbox"/> CAP <input type="checkbox"/> HAP <input type="checkbox"/> COPD <input type="checkbox"/> Empyema <input type="checkbox"/> Other
<i>In case of Kidneys and urinary tract</i>	<input type="checkbox"/> Cystitis <input type="checkbox"/> Complicated urinary tract infection/prostatitis <input type="checkbox"/> CAD infection <input type="checkbox"/> Other
<i>In case of CNS</i>	<input type="checkbox"/> Meningitis/encephalitis <input type="checkbox"/> Brain abscess <input type="checkbox"/> Post-surgery infection <input type="checkbox"/> Other
<i>In case of Gastrointestinal</i>	<input type="checkbox"/> Enteritis/colitis <input type="checkbox"/> Clostridium <input type="checkbox"/> Other
<i>In case of Joints and bones</i>	<input type="checkbox"/> Prosthesis infection <input type="checkbox"/> Non-prosthesis infection
<i>In case of Gynecology/obstetrics</i>	<input type="checkbox"/> PID/TOA <input type="checkbox"/> STI <input type="checkbox"/> Obstetric infection <input type="checkbox"/> Other
<i>In case of Cardiovascular tract</i>	<input type="checkbox"/> Endocarditis native valve <input type="checkbox"/> Endocarditis prosthetic valve <input type="checkbox"/> PM/ICD
<i>In case of Skin</i>	<input type="checkbox"/> Cellulitis (incl wound infections) <input type="checkbox"/> Erysipelas <input type="checkbox"/> Necrotizing fasciitis <input type="checkbox"/> Other
<i>In case of Intra- abdominal</i>	<input type="checkbox"/> SBP/CAPD peritonitis <input type="checkbox"/> Biliary tract <input type="checkbox"/> Post-surgery/complication <input type="checkbox"/> Perforation <input type="checkbox"/> Appendicitis <input type="checkbox"/> Other
<i>In case of Tropical diseases</i>	<input type="checkbox"/> Malaria <input type="checkbox"/> Other

Abbreviations: SDD= selective digestive tract decontamination; CNS= central nervous system; PID/TOA= pelvic inflammatory disease/tuba-ovarian abscess; PM/ICD= pacemaker/implantable cardioverter-defibrillator; CAP= community-acquired pneumonia; COPD= chronic obstructive pulmonary disease; HAP= hospital acquired or healthcare associated pneumonia; SBP/CAPD= spontaneous bacterial peritonitis/continuous ambulatory peritoneal dialysis

Figure 2. EMR prescription format Chipsoft – Hospital B

<b>1. Select antimicrobial agent</b>	
<b>2. Select focus of infection</b>	<input type="checkbox"/> <b>Respiratory tract</b> <input type="checkbox"/> <b>Kidneys and urinary tract</b> <input type="checkbox"/> Prophylaxis <input type="checkbox"/> Intra-abdominal <input type="checkbox"/> Joints and bones <input type="checkbox"/> Erysipelas/cellulitis <input type="checkbox"/> Switch <input type="checkbox"/> Prostheses infection <input type="checkbox"/> Meningitis/encephalitis <input type="checkbox"/> Spondylodiscitis <input type="checkbox"/> Neutropenic fever <input type="checkbox"/> Genitals <input type="checkbox"/> Endocarditis <input type="checkbox"/> Gastrointestinal <input type="checkbox"/> Sepsis of unknown cause <input type="checkbox"/> Other
<b>3. Select specified indication</b>	
<i><b>In case of Respiratory tract</b></i>	<input type="checkbox"/> <b>CAP-m</b> <input type="checkbox"/> <b>CAP- s</b> <input type="checkbox"/> <b>HAP</b> <input type="checkbox"/> <b>Bronchitis-exacerbation</b> <input type="checkbox"/> <b>COPD</b> <input type="checkbox"/> <b>Lung abscess/pleural empyema</b> <input type="checkbox"/> <b>Aspiration</b> <input type="checkbox"/> <b>Other</b>
<i><b>In case of Kidneys and urinary tract</b></i>	<input type="checkbox"/> <b>Cystitis</b> <input type="checkbox"/> <b>Pyelonephritis</b> <input type="checkbox"/> <b>Urosepsis</b> <input type="checkbox"/> <b>CAUTI</b> <input type="checkbox"/> <b>KCUTI</b> <input type="checkbox"/> <b>Chronic prostatitis</b> <input type="checkbox"/> <b>UTI KTx</b> <input type="checkbox"/> <b>Other</b>
<b>4. Select indication</b>	<input type="checkbox"/> Empirical therapy <input type="checkbox"/> Targeted therapy <input type="checkbox"/> Consulted with microbiologist

Abbreviations: CAP-m= community-acquired pneumonia – mild to moderate; CAP-s= community-acquired pneumonia severe; HAP= hospital acquired or healthcare associated pneumonia; COPD= chronic obstructive pulmonary disease; CAUTI= catheter-associated urinary tract infection; KCUTI= polycystic kidney urinary tract infection; UTI KTx= urinary tract infection in renal transplant.

Figure 3. EMR prescription format EPIC - Hospital C

<b>1. Select antimicrobial agent</b>	
<b>2. Select indication</b>	<input type="checkbox"/> Prophylaxis <input type="checkbox"/> Empirical therapy <input type="checkbox"/> Targeted therapy
<b>3. Select focus of infection</b>	<input type="checkbox"/> <b>Respiratory tract</b> <input type="checkbox"/> <b>Kidneys and urinary tract</b> <input type="checkbox"/> Gastrointestinal <input type="checkbox"/> Gynaecology/obstetrics <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Skin and soft tissue <input type="checkbox"/> Eye <input type="checkbox"/> <input type="checkbox"/> Intra-abdominal <input type="checkbox"/> Sepsis of unknown cause <input type="checkbox"/> Ear-nose-throat <input type="checkbox"/> Neutropenic fever <input type="checkbox"/> CNS <input type="checkbox"/> Confirmed bacteraemia/fungaemia <input type="checkbox"/> Joints and bones <input type="checkbox"/> <input type="checkbox"/> Other
<b>4. Select specified indication</b>	
<i><b>In case of Respiratory tract</b></i>	<input type="checkbox"/> <b>CAP: CURB 0-1</b> <input type="checkbox"/> <b>CAP: CURB 2</b> <input type="checkbox"/> <b>CAP: CURB 3-5</b> <input type="checkbox"/> <b>Lung abscess</b> <input type="checkbox"/> <input type="checkbox"/> <b>HAP</b> <input type="checkbox"/> <b>Bronchitis</b> <input type="checkbox"/> <b>Exacerbation COPD</b> <input type="checkbox"/> <b>Fungal pneumonia</b> <input type="checkbox"/> <b>Pleural empyema</b> <input type="checkbox"/> <b>Aspiration pneumonia</b>
<i><b>In case of Kidneys and urinary tract</b></i>	<input type="checkbox"/> <b>Cystitis</b> <input type="checkbox"/> <b>Urosepsis</b> <input type="checkbox"/> <b>Pyelonephritis</b> <input type="checkbox"/> <b>Chronic prostatitis</b>
<i><b>In case of CNS</b></i>	<input type="checkbox"/> Meningitis <input type="checkbox"/> Encephalitis <input type="checkbox"/> Myelitis <input type="checkbox"/> Brain abscess <input type="checkbox"/> Intracranial subdural empyema <input type="checkbox"/> Intraspinal epidural abscess <input type="checkbox"/> Intracranial epidural abscess <input type="checkbox"/> <input type="checkbox"/> Intraspinal subdural empyema
<i><b>In case of Gastrointestinal</b></i>	<input type="checkbox"/> Gastritis/enteritis <input type="checkbox"/> Clostridium difficile enterocolitis
<i><b>In case of Joints and bones</b></i>	<input type="checkbox"/> Prosthesis infection <input type="checkbox"/> Bacterial arthritis <input type="checkbox"/> Osteomyelitis
<i><b>In case of Gynecology/obstetrics</b></i>	<input type="checkbox"/> PID <input type="checkbox"/> STI <input type="checkbox"/> Vaginitis <input type="checkbox"/> Cervicitis <input type="checkbox"/> Endometritis
<i><b>In case of Cardiovascular tract</b></i>	<input type="checkbox"/> Endocarditis <input type="checkbox"/> Vascular prosthesis infection <input type="checkbox"/> PM/ICD <input type="checkbox"/> Mediastinitis <input type="checkbox"/> <input type="checkbox"/> Mycotic aneurysm <input type="checkbox"/> Pericarditis <input type="checkbox"/> Thrombophlebitis
<i><b>In case of Skin and Soft tissue</b></i>	<input type="checkbox"/> Cellulitis <input type="checkbox"/> Erysipelas <input type="checkbox"/> Necrotizing fasciitis <input type="checkbox"/> Phlebitis <input type="checkbox"/> Wound infection <input type="checkbox"/> <input type="checkbox"/> Postoperative wound infection
<i><b>In case of Ear-nose-throat</b></i>	<input type="checkbox"/> Acute tonsillitis <input type="checkbox"/> Pharyngitis <input type="checkbox"/> Otitis externa <input type="checkbox"/> Otitis media <input type="checkbox"/> Sinusitis <input type="checkbox"/> <input type="checkbox"/> Stomatitis <input type="checkbox"/> Peritonsillar abscess
<i><b>In case of Eye</b></i>	<input type="checkbox"/> Blepharitis <input type="checkbox"/> Orbital cellulitis <input type="checkbox"/> Conjunctivitis <input type="checkbox"/> Endophthalmitis <input type="checkbox"/> Keratitis <input type="checkbox"/> <input type="checkbox"/> Uveitis
<i><b>In case of Intra-abdominal</b></i>	<input type="checkbox"/> Peritonitis <input type="checkbox"/> Liver abscess <input type="checkbox"/> Intra-abdominal abscess <input type="checkbox"/> Cholecystitis <input type="checkbox"/> <input type="checkbox"/> Infected necrotizing pancreatitis <input type="checkbox"/> Cholangitis

Abbreviations: CNS= central nervous system; PID= pelvic inflammatory diseases; PM/ICD= pacemaker/implantable cardioverter-defibrillator; CAP= community-acquired pneumonia; COPD= chronic obstructive pulmonary disease; HAP= hospital acquired or healthcare associated pneumonia

Table 1. Antibiotic prescriptions for RTI in Hospital A

Antibiotic treatment	CAP	COPD	HAP	Empyema	Other	Total
<b>Amoxicillin</b>	160 (25.4)	17 (9.5)	5 (4.6)	1 (5.6)	52 (16.5)	235 (18.8)
<b>Amoxicillin and ciprofloxacin</b>	58 (9.2)	2 (1.1)	-	-	-	60 (4.8)
<b>Amoxicillin-clavulanic acid</b>	97 (15.4)	73 (40.8)	8 (7.4)	9 (5.0)	107 (33.9)	294 (23.6)
<b>Amoxicillin-clavulanic acid and ciprofloxacin</b>	16 (2.5)	7 (3.9)	-	3 (16.7)	-	26 (2.1)
<b>Azithromycin</b>	-	2 (1.1)	-	-	11 (3.5)	13 (1)
<b>Benzympenicillin</b>	7 (1.1)	-	-	1 (5.6)	-	8 (0.6)
<b>Benzympenicillin and ciprofloxacin</b>	24 (3.8)	-	-	-	-	24 (1.9)
<b>Benzympenicillin and metronidazole</b>	-	-	-	1 (5.6)	-	1 (0.1)
<b>Ceftazidime</b>	7 (1.1)	4 (2.2)	4 (3.7)	-	8 (2.5)	23 (1.8)
<b>Ceftriaxone</b>	118 (18.8)	33 (18.4)	53 (49.1)	-	42 (13.3)	246 (19.7)
<b>Ceftriaxone and ciprofloxacin</b>	35 (5.6)	6 (3.4)	10 (9.3)	-	7 (2.2)	58 (4.6)
<b>Ceftriaxone and metronidazole</b>	-	-	2 (1.9)	1 (5.6)	-	3 (0.2)
<b>Cefuroxime</b>	9 (1.4)	-	-	1 (5.6)	7 (2.2)	17 (1.4)
<b>Cefuroxime and ciprofloxacin</b>	8 (1.3)	-	-	-	-	8 (0.6)
<b>Ciprofloxacin</b>	26 (4.1)	7 (3.9)	6 (5.6)	-	8 (2.5)	47 (3.8)
<b>Clarithromycin</b>	-	-	-	-	7 (2.2)	7 (0.6)
<b>Clindamycin</b>	-	-	-	1 (5.6)	-	1 (0.1)
<b>Cotrimoxazole</b>	-	3 (1.7)	-	-	-	3 (0.2)
<b>Doxycycline</b>	17 (2.7)	19 (10.6)	-	-	30 (9.5)	66 (5.3)
<b>Meropenem</b>	9 (1.4)	-	3 (2.8)	-	7 (2.2)	19 (1.5)
<b>Other<sup>a</sup></b>	36 (5.7)	6 (3.4)	17 (15.7)	-	30 (9.5)	89 (7.1)
<b>Total</b>	627	179	108	18	316	1248

Numbers are n(%); <sup>a</sup>Other= antibiotic agents prescribed <1% per indication.

Table 2. Antibiotic prescriptions for RTI in Hospital B

Antibiotic treatment	CAP-m <sup>a</sup>	CAP-s <sup>b</sup>	COPD	HAP	Aspirati on pneumo nia	Other	Total
Amoxicillin	13 (27.1)	1 (16.7)	2 (33.3)				16 (24.2)
Amoxicillin and ciprofloxacin	1 (2.1)						1 (1.5)
Amoxicillin- clavulanic acid	9 (18.8)	1 (16.7)	2 (33.3)	1 (50)	1 (33.3)	1 (100)	15 (22.7)
Azithromycin	2 (4.2)		1 (16.7)				3 (4.5)
Azithromycin and ceftazidime			1 (16.7)				1 (1.5)
Ceftriaxone	1 (2.1)						1 (1.5)
Cefuroxime	17 (35.4)	2 (33.3)		1 (50)	2 (66.77)		22 (33.3)
Cefuroxime and ciprofloxacin	2 (4.2)	1 (16.7)					3 (4.5)
Ciprofloxacin	1 (2.1)	1 (16.7)					2 (3)
Doxycycline	1 (2.1)						1 (1.5)
Piperacillin- tazobactam	1 (2.1)						1 (1.5)
<b>Total</b>	<b>48</b>	<b>6</b>	<b>6</b>	<b>2</b>	<b>3</b>	<b>1</b>	<b>66</b>

Numbers are n(%); <sup>a</sup>CAP-m= CAP mild to moderate severe; <sup>b</sup>CAP-s= CAP severe

Table 3. Antibiotic prescriptions for RTI in Hospital C

Antibiotic treatment	CAP-m <sup>b</sup>	CAP-s <sup>c</sup>	COPD	HAP	Aspiration pneumonia	Empyema Lung abscesses	Other	Total
Amoxicillin	62 (25.7)	2 (2.9)	5 (33.3)			1 (6.7)	5 (12.8)	75 (16.3)
Amoxicillin-clavulanic acid	38 (15.8)	2 (2.9)	4 (26.7)	4 (7.1)	16 (59.3)	2 (13.3)	6 (15.4)	72 (15.6)
Azithromycin	2 (0.8)					4 (26.7)	4 (10.3)	10 (2.2)
Benzyloxylin	15 (6.2)	1 (1.5)						16 (3.5)
Ceftazidime	8 (3.3)		1 (6.7)	2 (3.6)	1 (3.7)	1 (6.7)	7 (17.9)	20 (4.3)
Ceftriaxone	41 (17)	31 (45.6)	1 (6.7)		1 (3.7)	3 (20)	3 (7.7)	80 (17.4)
Ceftriaxone and ciprofloxacin	3 (1.2)	5 (7.4)	1 (6.7)		1 (3.7)			10 (2.2)
Cefuroxime	8 (3.3)	5 (7.4)		1 (1.8)				14 (3)
Ciprofloxacin	2 (0.8)	5 (7.4)		1 (1.8)				8 (1.7)
Cotrimoxazole	4 (1.7)	2 (2.9)		1 (1.8)				7 (1.5)
Doxycycline	16 (6.6)	1 (1.5)	2 (13.3)				2 (5.1)	21 (4.6)
Levofloxacin	6 (2.5)	1 (1.5)					1 (2.6)	8 (1.7)
Piperacillin-tazobactam	15 (6.2)	3 (4.4)		40 (71.4)	6 (22.2)	1 (6.7)	5 (12.8)	70 (15.2)
Other <sup>a</sup>	21 (8.7)	10 (14.7)	1 (6.7)	7 (12.5)	2 (7.4)	3 (20)	6 (15.4)	50 (10.8)
<b>Total</b>	<b>241</b>	<b>68</b>	<b>15</b>	<b>56</b>	<b>27</b>	<b>15</b>	<b>39</b>	<b>461</b>

Numbers are n(%) <sup>a</sup>Other= antibiotic agents prescribed <1% per indication; <sup>b</sup>CAP-m= CAP mild to moderate severe; <sup>c</sup>CAP-s= CAP severe

Table 4. Antibiotic prescriptions for UTI in Hospital A

Antibiotic treatment	Complicated UTI	Cystitis	CAUTI <sup>b</sup>	Other	Total
Amoxicillin	11 (2.9)	4 (2.1)		4 (5.6)	19 (2.9)
Amoxicillin and ciprofloxacin			1 (4)		1 (0.2)
Amoxicillin-clavulanic acid	26 (7)	35 (18.3)	2 (8)	3 (4.2)	66 (10)
Amoxicillin-clavulanic acid and gentamicin			1 (4)		1 (0.2)
Ceftazidime				1 (1.4)	1 (0.22)
Ceftriaxone	195 (52.1)	35 (18.3)	11 (44)	25 (34.7)	266 (40.2)
Ceftriaxone and doxycycline				1 (1.4)	1 (0.2)
Ceftriaxone and gentamicin			1 (4)		1 (0.2)
Cefuroxime	18 (4.8)	2 (1)	1 (4)	8 (11.1)	29 (4.4)
Ciprofloxacin	56 (15)	25 (13.1)	4 (16)	10 (13.9)	95 (14.4)
Clindamycin				1 (1.4)	1 (0.2)
Cotrimoxazole	15 (4)		1 (4)	4 (5.6)	20 (3)
Doxycycline				2 (2.8)	2 (0.3)
Fosfomycin		4 (2.1)			4 (0.6)
Gentamicin	4 (1.1)		1 (4)	2 (2.8)	7 (1.1)
Meropenem	27 (7.2)	3 (1.6)	1 (4)	3 (4.2)	34 (5.1)
Metronidazole				2 (2.8)	2 (0.3)
Nitrofurantoin		81 (42.2)	1 (4)	4 (5.6)	86 (13)
Trimethoprim		2 (1)		1 (1.4)	22 (3.3)
Vancomycin				1 (1.4)	3 (0.5)
Other <sup>a</sup>	22 (5.9)	1 (0.5)			1 (0.2)
<b>Total</b>	<b>374</b>	<b>191</b>	<b>25</b>	<b>72</b>	<b>662</b>

Numbers are n(%); <sup>a</sup>Other= antibiotic agents prescribed <1% per indication; <sup>b</sup>CAUTI= catheter-associated urinary tract infection

Table 5: Antibiotic prescriptions for UTI in Hospital B

Antibiotic treatment	Complicated UTI	Cystitis	CAUTI <sup>a</sup>	Other	Total
Amoxicillin		1 (2.8)			1 (1.6)
Amoxicillin-clavulanic acid	4 (20)	8 (22.2)		1 (33.3)	13 (20.3)
Amoxicillin-clavulanic acid and nitrofurantoin		1 (2.8)			1 (1.6)
Ceftazidime	1 (5)				1 (1.6)
Ceftriaxone	7 (35)	9 (25)	1 (20)		17 (26.6)
Cefuroxime	7 (35)	10 (27.8)	1 (20)	1 (33.3)	19 (29.7)
Cefuroxime and ciprofloxacin		1 (2.8)			1 (1.6)
Cefuroxime and metronidazole		1 (2.8)			1 (1.6)
Ciprofloxacin	1 (5)	3 (8.3)	1 (20)	1 (33.3)	6 (9.4)
Flucloxacillin			1 (20)		1 (1.6)
Meropenem			1 (20)		1 (1.6)
Nitrofurantoin		2 (5.6)			2 (3.1)
<b>Total</b>	<b>20</b>	<b>36</b>	<b>5</b>	<b>3</b>	<b>64</b>

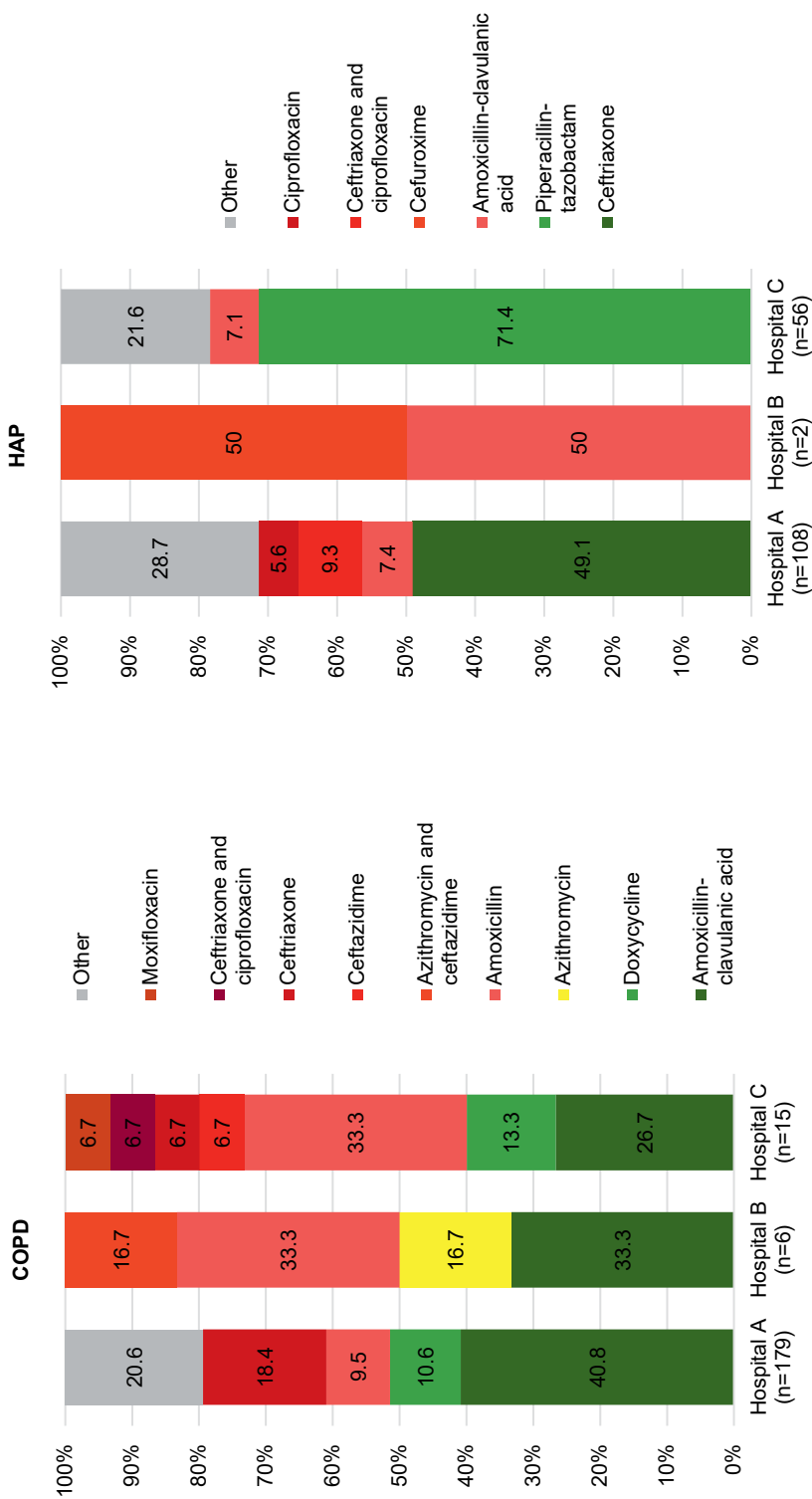
Numbers are n(%); <sup>a</sup>CAUTI= catheter-associated urinary tract infection

Table 6: Antibiotic prescriptions for UTI in Hospital C

Antibiotic treatment	Complicated UTI	Cystitis	Other	Total
Amoxicillin	1 (0.3)	8 (4.2)		9 (1.7)
Amoxicillin-clavulanic acid	8 (2.5)	28 (14.6)	2 (20)	38 (7.3)
Ceftazidime	13 (4.1)	4 (2.1)		17 (3.3)
Ceftriaxone	163 (51.3)	31 (16.1)		194 (37.3)
Cefuroxime	50 (15.7)	7 (3.6)	1 (10)	58 (11.2)
Ciprofloxacin	17 (5.3)	30 (15.6)	2 (20)	49 (9.4)
Cotrimoxazole	3 (0.9)	7 (3.6)	1 (10)	11 (2.1)
Meropenem	40 (12.6)	16 (8.3)		56 (10.8)
Nitrofurantoin	1 (0.3)	44 (22.9)	3 (30)	48 (9.2)
Piperacillin-tazobactam	10 (3.1)	2 (1)	1 (10)	13 (2.5)
Trimethoprim		7 (3.6)		7 (1.3)
Other <sup>a</sup>	12 (3.8)	8 (4.2)		20 (2.8)
<b>Total</b>	<b>318</b>	<b>192</b>	<b>10</b>	<b>520</b>

Numbers are n(%); <sup>a</sup>Other= antibiotic agents prescribed <1% per indication

24 Figure 4: appropriateness of antibiotics for RTI – COPD and HAP



Category A) in accordance with the guideline-recommended first choice agents, marked in green; B) in accordance with the guideline-recommended second choice agents, marked in yellow; C) discordant with the guideline, marked in red; and other: antibiotics prescribed in less than 5% of cases, marked in grey.

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## CHAPTER 4:

# Detecting inappropriate total duration of antimicrobial therapy using semi-automated surveillance

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## Abstract

**Objectives:** Evaluation of the appropriateness of the duration of antimicrobial treatment is a cornerstone of antibiotic stewardship programs, but it is time-consuming. Furthermore, it is often restricted to antibiotics prescribed during hospital admission. This study aimed to determine whether mandatory prescription-indication registration at the moment of prescribing antibiotics enables reliable automated assessment of the duration of antibiotic therapy, including post-discharge duration, limiting the need for manual chart review to data validation.

**Methods:** Antibiotic prescription and admission data, from 1-6-2020 to 31-12-2021, were electronically extracted from the Electronic Medical Record of two hospitals using mandatory indication registration. All consecutively prescribed antibiotics of adult patients who received empiric therapy in the first 24 hours of admission were merged to calculate the total length of therapy (LOT) per patient, broken down per registered indication. Endpoints were the accuracy of the data, evaluated by comparing the extracted LOT and registered indication with the clinical notes in 400 randomly selected records, and guideline adherence of treatment duration. Data were analysed using a reproducible syntax, allowing semi-automated surveillance.

**Results:** A total of 3,466 antibiotic courses were analysed. LOT was accurately retrieved in 96% of the 400 evaluated antibiotic courses. The registered indication did not match chart review in 17% of antibiotic courses, of which only half affected the assessment of guideline adherence. On average, in 44% of patients treatment was continued post-discharge, accounting for 60% ( $\pm 19\%$ ) of their total LOT. Guideline adherence ranged from 26 to 75% across indications.

**Conclusions:** Mandatory prescription-indication registration data can be used to reliably assess total treatment course duration, including post-discharge antibiotic duration, allowing semi-automated surveillance.

## Background

Antimicrobial Stewardship Programs (ASP) aim to reduce antimicrobial resistance and its associated morbidity, mortality and healthcare costs<sup>1</sup>. One of the elements of ASPs is to promote prescription of the shortest effective duration of antibiotic therapy<sup>2</sup>. Antibiotic courses that are longer than necessary increase the selective pressure on bacterial flora<sup>3</sup>, and each additional day of antibiotic use may increase the risk of patient harm<sup>4</sup>. It is therefore important to monitor the appropriateness of antibiotic course durations, in order to identify target-areas for improvement. The few studies evaluating treatment duration (including post-discharge antibiotic use) in general described the average quantity of antibiotic use or length of therapy, irrespective of indication and without evaluating guideline adherence<sup>5, 6</sup>.

An in-depth audit assessing the appropriateness of choice and duration of antibiotic therapy for each individual antibiotic course until recently required manual data collection from the (electronic) medical record (EMR), which is time-consuming<sup>7, 8</sup>. As a result, the number of antibiotic prescriptions that could be evaluated was limited by available personnel and resources<sup>7, 8</sup>. Recently, the use of EMR to facilitate automated ASP audits has grown in relevance, as it was demonstrated that this can provide data that enable efficient measurement of the appropriateness of antibiotic use<sup>9, 10</sup>. As a result, a considerable amount of manual chart review can be disregarded, reducing labour intensity. Utilizing indication selected at time of order entry also enable stewardship programs perform targeted real-time interventions, as many other methods (like using ICD-10s) can only occur post-discharge. Dyer and colleagues showed that it is feasible to extract from the EMR the total duration of antibiotic use prescribed to inpatients per registered ICD-10 diagnosis, including post-discharge prescriptions<sup>6</sup>. It is important to consider these post-discharge prescriptions, as they may take up to 40% of the total antibiotic course<sup>5</sup>. Unfortunately, they did not evaluate the appropriateness of treatment duration.

In a previous study we showed that it is feasible to link antibiotic indications to antibiotic prescriptions by mandatory indication registration, which enables systematic evaluation and benchmarking of the appropriateness of the empiric antimicrobial choice for respiratory tract infections (RTI) and urinary tract infections (UTI)<sup>10, 11</sup>. The aim of the present study was to demonstrate that it is also possible to reliably determine the total duration of antibiotic treatment prescribed to hospital inpatients, including post-discharge duration, broken down per indication, using data extracted from the EMR. The secondary aim was to determine whether the extracted data can be used to evaluate guideline adherence of treatment duration.

## Methods

### Study design and setting

A retrospective observational study was performed on data obtained from the Amsterdam University Medical Centres (Amsterdam UMC), a university-affiliated tertiary care hospital with two locations: AMC and VUmc. Both locations use EPIC software as their electronic medical record and prescribing software. In 2019, a standardized prescription-format (supplemental table 1), was implemented in the EMR, as described in our previous study<sup>10</sup>. This prescription-format requires physicians to select the indication for the prescription from a predefined list whenever they prescribe an antimicrobial agent for hospital inpatients. Approval from the Institutional review boards was not required for this study because we used retrospective, pseudonymised data for quality optimization purposes. Procedures were in accordance with the General Data Protection Regulation<sup>12</sup>.

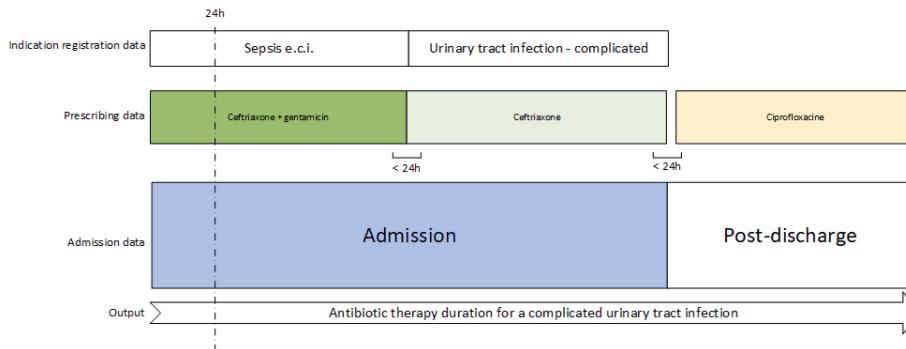
### Data collection and definitions

Data covering the period from 1-6-2020 to 31-12-2021 was extracted from the EMR. The extracted data contained all antibiotic prescription orders for systemic use belonging to Anatomical Therapeutic Chemical (ATC) class J01, the prescription-linked registered indication on tract level (anatomical location of the disease) and a further specification in case of respiratory tract infections (RTI) and urinary tract infections (UTI), the duration of hospital admission (time and date of admission and discharge), the duration of therapy (start and stop date, including the post-discharge period), and the specialty of the prescribing physician.

For the purpose of this study, we identified all antibiotic prescription in patients admitted to any general ward who were prescribed empirical antibiotic treatment. Hospitalized patients were defined as patients that were admitted for at least 12 hours. Empirical antibiotic treatment was defined as the prescription of systemic antibiotics at time point 24 hours of hospitalization, or at the time of discharge in patients who were hospitalized for 12-24 hours. These empirical inpatient prescription orders with a registered indication were merged with consecutively prescribed antibiotics during hospital admission and post-discharge, to define the total antibiotic treatment course per patient. The last registered indication during the admission was considered as the definitive indication for the full treatment course (**figure 1**), because the treatment indication can initially change as new results become available. Antibiotics that were prescribed simultaneously for the same specified indication were considered as antibiotic combination therapy. We regarded outpatient antibiotic prescriptions that were initiated within a maximum

interval of 24 hours after the final dosage of the last inpatient antibiotic prescription as part of the antibiotic course for the definitive indication.

**Figure 1. Defining the total antibiotic therapy duration for the definitive registered indication**



In case patients received non-consecutively antibiotic treatment during admission or within 30 days of readmission, only the antibiotic course for the initial episode was included. Prescriptions that were prescribed for longer than 21 days or for indications that in general require a treatment duration longer than 21 days were excluded, as the optimal treatment duration in these cases is usually guided by the characteristics of that particular patient. In addition, during initial validation of the extracted datasets, we observed that a prolonged duration was often caused by prescribed prophylaxis after discharge. Antibiotics that were linked to the indication prophylaxis were excluded. We also excluded paediatric patients (age <18 years) and patients admitted to the Intensive Care Unit, because guideline-recommended treatment is usually not applicable in this setting, as well as patients who received antibiotics for two different indications that were registered simultaneously.

### Validation of the dataset

We first extracted all aforementioned antibiotic prescribing and hospital admission data from the EMR and selected the records meeting our inclusion criteria (**Figure 2**). We inspected the correctness of all extracted data first by looking at the extracted data to investigate what data was actually extracted from the EMR and whether the extracted data provided the information that we were looking for. And if necessary, manual chart review of a number of records, to adjust the data selection until the output met all inclusion criteria. Thereafter, accuracy of the dataset was verified by manually screening a sample of 400 (200 per location) randomly selected records of patients who fulfilled the inclusion criteria. We checked whether the extracted indication and total duration of antibiotic therapy

were in accordance with the indication and duration of therapy as documented in the EMR. We hereby distinguished between: inaccurately selected indications in general and inaccurately selected indications that would affect the assessment of total treatment duration, which was the case when the recommended treatment duration differed between the inaccurately selected indication and the actual indication as documented in the clinical notes.

### **Study endpoints**

The primary endpoint was the accuracy of the electronically obtained length of therapy (LOT). LOT was defined as the number of calendar days during which antimicrobials were consecutively prescribed for the definitive indication, including post-discharge duration, irrespective of the number of agents or doses on each calendar day. Accuracy was defined as percentage agreement between 1) the electronically obtained LOT and the manually retrieved LOT from the EMR; 2) the registered indication and the manually retrieved indication from the EMR, as for determination of guideline adherence the registered indication has to be correct. Secondary endpoint was the percentage of antibiotic treatment courses of which the LOT was according to local guidelines. The local guidelines are based on the national guidelines of the Dutch Working party on Antibiotic Policy ([www.amsterdamumc.swab-id.nl](http://www.amsterdamumc.swab-id.nl)). When the LOT fell within the guideline-recommended treatment duration range we considered it guideline-adherent. We added a margin of one day, as days of therapy are registered irrespective of the number of doses (e.g., administration of a single dosage in the evening adds a full day to the LOT).

### **Data analysis**

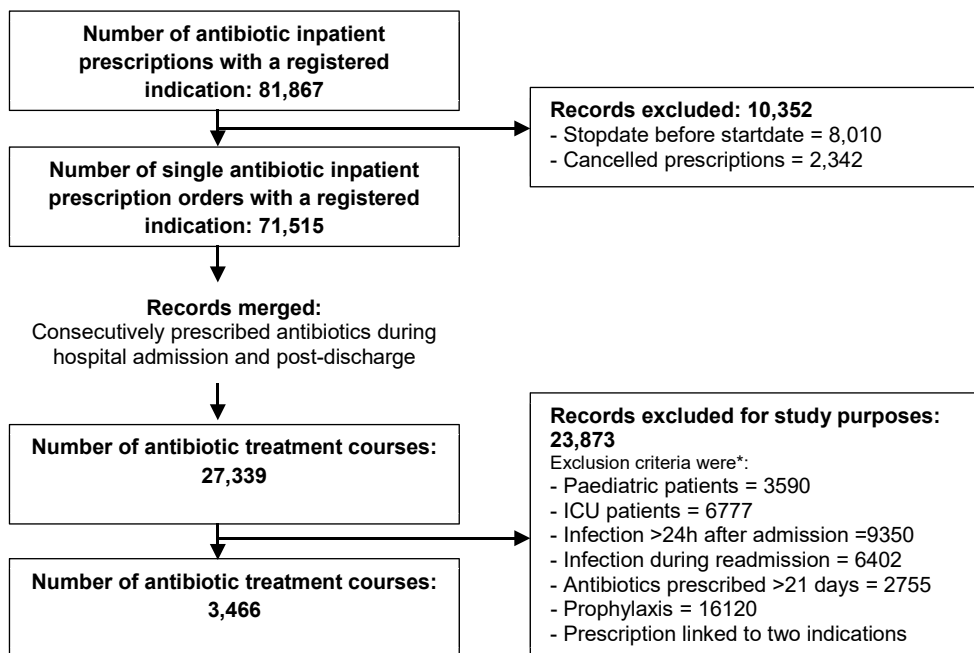
The median LOT and interquartile range (IQR) are presented for each registered indication. We provide total LOT. We calculated per indication the percentage of treatment courses in which part of the treatment was given post-discharge. For these courses we provided the proportion ( $\pm$  SD) of the total treatment duration that was given post-discharge. The proportion of guideline (non)-adherent prescriptions is expressed as percentage of the total number of antimicrobial prescriptions for that indication. All data handling and visualisation was performed using TIBCO® Spotfire®.

## Results

### Dataset characteristics and validation

The extracted data from the EMR yielded a total of 142,470 systemic antibiotic prescriptions (J01) (including post-discharge and outpatient clinic prescriptions that were not linked to an indication). Of these, 81,867 systemic antibiotic prescriptions (J01) were prescribed during hospital admission and were therefore linked to a registered indication. After general inspection of the data, including manual chart review, we excluded erroneous prescriptions, defined as prescriptions of which the start date of the antibiotic fell before the date of admission. Also, prescriptions that were labelled as cancelled were excluded, as these were not administered to patients. The remaining 71,515 prescribed systemic antibiotics (J01) represented 27,399 antibiotic courses. Applying our pre-defined in- and exclusion criteria resulted in 3,466 antibiotic courses for further analysis. A schematic overview of the selection steps and yield is presented in **figure 2**. The used syntax (pseudo-code) is available on request.

**Figure 2. Overview of the data selection steps resulting in the final dataset**



\*Exclusion criteria may overlap

**Data validation**

Of the final dataset, a random sample of 400 records was evaluated on accuracy (**table 1**). Overall, in only 4.5% of patients the electronically extracted LOT - including the post-discharge treatment duration - did not match the total treatment duration as documented in the EMR. Most of these patients were discharged with outpatient antimicrobial IV treatment (OPAT). OPAT is not yet captured in the electronic prescribing system and therefore requires written prescriptions. 32/400 patients were transferred to another centre. Their total duration of antibiotic therapy was therefore unknown.

We also compared the selected indication with the diagnosis that was recorded in the patient record and found an error-rate of 17.3% (68/400). Although the tract of infection was mostly accurate, its specification was not always. Gastro-intestinal and intra-abdominal infections were commonly selected interchangeably. Furthermore, sometimes cystitis was selected instead of complicated UTI; severe community-acquired pneumonia (CAP) instead of mild-to-moderate CAP; fever of unknown cause instead of febrile neutropenia, or therapy instead of prophylaxis. Of these incorrectly registered indications, 51.5% affected the assessment of guideline-adherent LOT. This was mainly the case for the inaccurate selection of cystitis instead of complicated UTI or therapy when it actually concerned prophylaxis.

**Total duration of antibiotic therapy**

The median LOT per indication is presented in table 2. Note that the LOT is underestimated for infections that sometimes require prolonged antibiotic treatment for >21 days, e.g., *S. aureus* bacteremia, as these patients were excluded from data analysis. Most antibiotic courses were prescribed for UTI and RTI. A large proportion of the treatment courses for ENT infections, complicated UTI and skin and soft tissue infections (SSTI) were continued post-discharge (i.e. 83%, 68% and 64% respectively), of which the post-discharge duration accounted for 62-63% of the total LOT.

**Guideline adherence of total duration of antibiotic therapy**

The guideline recommended total duration of therapy per indication and the adherence rate per indication are also presented in **table 2**. Records were excluded from adherence evaluation in case accepted guideline recommendations were not available or in case the indication “other” was selected. Guideline adherence regarding duration of therapy ranged from 26% to 75%. The proportion

of non-compliance because of excessive treatment duration varied from 10%-50%. Prescriptions for RTI were most often considered to be too long, in particular aspiration pneumonia and mild-to-moderate severe CAP.

**Table 1. Accuracy of extracted duration and selected indications**

	<b>Duration of therapy (inaccurate duration/number of screened records)</b>	<b>Indication of therapy (inaccurate selections/number of screened records)</b>
<b>Error rate location AMC (%)</b>	10/200 = 5.0%  6 prescriptions not electronically prescribed (all were OPAT prescriptions) 1 prescription of which start fell before inclusion period and therefore not included in the dataset 1 missing non-J01 antibiotic (oral metronidazole) 2 prescriptions were not terminated after discharge or death  <i>18 transfers to other hospital leading to missing data</i>	31/200 = 15.5%  Incorrectly registered indications affecting duration of therapy: 12/31 = 38.7% <sup>a</sup>
<b>Error rate location VUMC (%)</b>	8/200 = 4.0%  8 prescriptions not electronically prescribed (of which 5 were OPAT prescriptions)  <i>14 transfers to other hospital leading to missing data</i>	37/200 = 18.5%  Incorrectly registered indications affecting duration of therapy: 23/37 = 62.0% <sup>c</sup>
<b>Total</b>	18/400 = 4.5%	68/400 = 17.0%  Incorrectly registered indications affecting duration of therapy: 35/400 = 8.8%

OPAT=Outpatient Parenteral Antimicrobial Therapy

Table 2: Length of treatment (LOT) per indication

Definitive diagnosis	Total (n)	Treatment courses with post-discharge treatment (n,%)	Percentage of total treatment duration given post-discharge (%;SD)*	LOT in days, (median; IQR)	Recommended course duration**	Guideline adherence*** (%)	Treatment courses too long (%)
UTI - Cystitis	420	231 (55)	63 (21)	6.5 (4.0-10.0)	3-7 days	53	31
UTI – Complicated UTI	241	164 (68)	63 (18)	12.0 (7.0-15.0)	7-14 days	60	15
UTI - CAD	28	15 (54)	65 (18)	11.0 (4.8-14.0)	7-14 days	57	14
UTI – Kidney transplant	47	28 (60)	59 (17)	11.0 (5.5-15.0)			
UTI – Other (not specified)	89	60 (67)	68 (18)	13.0 (7.0-15.0)			
RTI – CAP-m	328	142 (43)	54 (20)	6.0 (5.0-8.0)	5 days	35	40
RTI – CAP-s	90	17 (19)	46 (24)	5.0 (3.0-7.0)	5 days	29	31
RTI - HAP	41	6 (15)	37 (24)	6.0 (4.0-8.0)	5-7 days	46	24
RTI - Aspiration	82	23 (28)	51 (20)	6.5 (5.0-9.0)	5 days	26	50
RTI - COPD	73	32 (44)	58 (18)	6.0 (3.0-8.0)	7 days	38	14
RTI - Abscess/empyema	23	9 (39)	55 (19)	8.0 (5.5-15.0)			
RTI – Other (not specified)	154	51 (33)	56 (17)	6.0 (3.0-8.8)			

<b>CNS infection</b>	51	7 (14)	70 (21)	8.0 (3.0-11.5)	
<b>CVL infection</b>	29	11 (38)	59 (17)	7.0 (4.0-13.0)	
<b>ENT infection</b>	106	88 (83)	63 (14)	10.0 (9.0-13.0)	75 10
<b>Gastro-enteritis</b>	40	14 (35)	60 (21)	5.0 (3.0-8.0)	
<b>Gynaecological infection</b>	165	91 (55)	68 (16)	7.0 (2.0-11.0)	
<b>Intra-abdominal infection</b>	464	145 (31)	52 (19)	6.0 (4.0-8.0)	
<b>Sepsis e.c.i./unkown</b>	270	53 (20)	56 (20)	4.0 (3.0-7.0)	
<b>Skin or soft tissue infection</b>	336	214 (64)	62 (19)	11.0 (7.0-15.0)	44 16
<b>Other (not specified)</b>	157	49 (31)	63 (19)	6.0 (3.0-10.0)	
<b>Total</b>	3390	1502 (44)	60 (19)	7.0 (4.0-11.0)	
<b>Excluded****</b>	232				

\*Proportions are only given for treatment courses with post-discharge treatment

\*\*Recommended by Dutch guidelines ([www.swabid.nl](http://www.swabid.nl))

\*\*\* One additional day was allowed as each calendar day on which a dose was given was counted as a full day of treatment. \*\*\*\* indications that were rarely selected, i.e. in less than 20 treatment courses, or that would require > 21 days of treatment according to our national guidelines were excluded. These included the following indications: Bone and Joint infection, S. aureus bacteraemia, Endovascular infection, Eye infection, Febrile neutropenia, Fungal infection, Mediastinitis, UTI – cyst infection and chronic prostatitis.

Abbreviations: SD = standard deviation, UTI = Urinary Tract Infection, UTI-CAD = Catheter-associated Urinary Tract Infection, RTI = Respiratory Tract Infection, CAP-m = Community-acquired Pneumonia mild-to-moderate severe, CAP-s = Community-acquired Pneumonia severe, HAP = Hospital-acquired pneumonia, COPD = Chronic Obstructive Pulmonary Disease, CNS = Central nervous system, CVL = Central Venous Lin

## Discussion

This study shows that it is feasible to reliably extract from the EMR the total duration of antibiotic therapy, broken down per indication and including post-discharge treatment, enabling an automated assessment of the appropriateness of antibiotic treatment duration. General inspection, and if indicated, optimization of the dataset (e.g., excluding erroneous prescriptions) is necessary to enable the use of data for further analysis. The total duration of therapy was accurately extracted from the EMR in 96% of infections, but the registered indication did not match the indication documented in the patient records in 17% of cases, which was mainly due to inaccurate selection of the mandatory indication in the EMR. Only 50% of these indication errors affected the evaluation of appropriateness of LOT, but local validation of the datasets is therefore necessary and the error-rate should be considered when data is used for quality measurement purposes. With regard to our secondary study aim, guideline non-adherence due to excessive treatment duration varied from 10% to 50% per indication, showing possibilities for quality optimization.

Including therapy after hospital discharge in the treatment duration is necessary, as a considerable amount of excess antibiotic use occurs after discharge, which was previously shown for CAP<sup>2</sup>. In our study, especially in ENT infection, complicated UTI and SSTI a high proportion (64%-83%) of antibiotic treatment courses was continued post-discharge, which made out 62-63% of total treatment duration. This emphasizes the need to include post-discharge prescriptions in the assessment of total treatment duration.

In previous studies the total duration of therapy linked to indication was either assessed by manual chart review<sup>7, 8, 13</sup> or by linking the antibiotic therapy to the ICD code<sup>5, 6</sup>. We used an electronic data extraction method, that can be used by all hospitals using EPIC software and that enables to assess a large amount of data more efficiently and more specifically. Determining the inclusion criteria and definitions, for example considering the last registered indication as the definitive treatment indication, and validation of the extracted data require time. However, as opposed to manual data assessment, the majority of time and expertise needs to be invested once, at the start of the project. Thereafter, surveillance can be performed automated as the syntax can be reused. A prerequisite is that the hospital EMR requires indication registration for each prescribed antibiotic. Although we did not show this in our study, the guideline-adherence of treatment duration and further specifications can be presented per hospital department, enabling the fine tuning of the targets for improvement.

Our inclusion criteria ensured a reliable dataset for the most common infections. We were able to confirm that by applying our inclusion criteria, the total duration of therapy was accurately extracted for almost all indications, with prescriptions in the OPAT setting being the most important exception. The error-rate of 4.5% of the electronically extracted LOT was far lower than the 11.5% discrepancy Dyer et al found<sup>6</sup>. As electronic prescriptions are becoming the norm, we expect error-rates due to written prescriptions to drop further in the future. Unfortunately, 17% of prescriptions were linked to an inaccurately selected indication, of which half affected the assessment of guideline-adherent LOT. In our previous study we found similar proportions of inaccurately selected indications in the hospitals where the mandatory indication registration was recently introduced<sup>10</sup>. Saini et al, recently showed that the most common barriers for accurate documentation of the prescribing indication are uncertainty in diagnosis, time, logistical challenges and alert fatigue<sup>14</sup>.

Based on the Capability-Opportunity-Motivation Behaviour model, designed by Michie and colleagues, behaviour can only occur when an individual has the capability, opportunity and motivation (including habitual process) to perform the behaviour<sup>15</sup>. The physicians of the participating centres did not receive any information yet about why the mandatory indication registration was implemented in the prescribing software and did not receive any feedback of their prescribing results, which may have caused lack of motivation. Furthermore, data was extracted one year after implementation of the mandatory indication registration. In our previous study we already saw that habituation decreases the error rate<sup>10</sup>. We therefore believe that the error rate can be decreased when information, education and feedback are given. Feedback can be given for example by providing benchmark results with other departments (locally) or other hospitals.

Finally, we showed the opportunities of using mandatory indication registration and assessment of the appropriateness of treatment duration to identify clear targets for ASP. The treatment duration for mild-to-moderate severe CAP, for example, was shown to be too long in 40% of patients, considering the guideline recommendation of five days. Each day of antibiotic therapy is associated with 4% increased odds of experiencing an adverse event<sup>4</sup>. For example, three days of  $\beta$ -lactam therapy for CAP patients was shown to be non-inferior to eight days of therapy<sup>16</sup>, while seven days of therapy instead of three is associated with a 1.19-fold increase in experiencing an adverse drug event<sup>4</sup>. This emphasizes the necessity for ASP to monitor treatment duration.

## Limitations

Due to our inclusion criteria we did not evaluate all antibiotic courses prescribed during hospital admission. We focused on patients that were initially empirically treated to enable reliable data extraction, as this method was already used and validated in our previous study<sup>10</sup>. In addition, we disregarded difficult-to-treat infections and nosocomial infections, as the local guidelines usually do not apply to these infections. Nevertheless, univocal local guideline recommendations were available for 51% (1745/3390) of the included treatment courses, in which guideline compliance could be assessed. We do believe that the records that were included gave a good representation of antibiotic use for the most common infections. Furthermore, we only evaluated antibiotic courses that were electronically prescribed. Written prescriptions, pre-admission prescriptions or antibiotics that were prescribed after transfer to other hospitals were therefore missed. When assessing the guideline adherence, this should be taken into account. The final point of consideration is the accuracy of the indication selection by prescribers. As human errors are inevitable and the error rate may fluctuate over time, the accuracy of the dataset should be checked regularly. This requires manual chart review, but that can be limited to a relatively small sample of patients, for example 10% of the extracted data.

## Conclusion

With this study we demonstrated that implementing mandatory indication registration in the EMR enables a reliable and efficient method for systemic registration of two core-elements of ASP: the guideline adherence of the total duration of antibiotic therapy and the guideline adherence of empiric antibiotic choice, the latter we showed in our previous study<sup>10</sup>. It has the potential to become a valuable aid for ASP, as it reduces the amount of manual data collection and has the ability to provide clear targets for local ASP. Datasets can be updated in a semi-automated fashion as the syntax can be reused whenever needed, enabling the regular surveillance of the extent and appropriateness of antibiotic use and the effect of ASP interventions. Regularly data validation, however, is necessary to assure accuracy of the extracted data. Furthermore, additional efforts (e.g. information, education and feedback) are important to increase the accuracy of the indication selection. The next steps are to implement mandatory indication registration in the outpatient setting, add microbiological results to the prescribing software for quality assessment of targeted therapy, and to utilize indication selected at time of order entry for targeted real-time interventions, for instance using pre-defined order sets for specific indications in which the indication and duration are recommended.

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## **PART II:**

### **Optimizing the QI “IV to oral switch”**

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## CHAPTER 5:

# **Systematic Review: The bioavailability of orally administered antibiotics during the initial phase of a systemic infection in non-ICU patients**

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## Abstract

**Background:** The systemic response to an infection might influence the pharmacokinetics of antibiotics. To evaluate the desired possibility of an earlier (<24hours) IV-to-oral switch therapy in febrile non-ICU, hospitalized patients, a systematic review was performed to assess the effect of the initial phase of a systemic infection on the bioavailability of orally administered antibiotics in such patients.

**Methods:** An electronic search was conducted in MEDLINE and Embase up to July 2020. Studies were selected when outcome data were collected during the initial stage of a febrile disease. Outcome data were (maximum) serum concentrations, time of achieving maximum serum concentration, and the area-under-the-plasma-concentration-time curve or bioavailability of orally administered antibiotics. Risk of bias was assessed.

**Results:** We identified 9 studies on 6 antibiotics. Ciprofloxacin was the most frequently studied drug. Outcomes of the studies were heterogeneous and generally had a high risk of bias. Three small studies, two on ciprofloxacin and one on clarithromycin, compared the pharmacokinetics of febrile patients with those of clinically recovered patients and suggested that bioavailability was not altered in these patients. Other studies either compared the pharmacokinetics in febrile patients with reported pharmacokinetic values from earlier studies in healthy volunteers (n=2), or provided no comparison at all and were non-conclusive (n=4).

**Conclusion:** There is a clear knowledge gap regarding the bioavailability of orally administered antibiotics in non-ICU patients during the initial phase of a systemic infection. Well-designed studies on this topic are necessary to elucidate whether patients can benefit from the advantages of an earlier IV-to-oral switch.

## Background

Patients hospitalized with serious infectious diseases are in general initially treated with parenteral antimicrobial therapy. Guidelines recommend to switch to oral therapy only when the patient has been treated intravenously (IV) for at least 48-72 hours and in case the clinical condition has improved and the fever has abated.<sup>1</sup> The question is whether or not patients can be switched to oral antibiotics earlier than 48 hours, which recently has become subject of debate.<sup>2, 3</sup> Switching to oral therapy has been shown to lower the length of hospital stay, the risk of new infections and healthcare costs, without compromising clinical outcome.<sup>4</sup> If there is a possibility to shorten the current recommended duration of IV therapy, these benefits are likely to be achieved earlier.

The main reasons why IV therapy is favoured in the beginning of the treatment of seriously ill infectious patients are the short time of achieving maximum serum concentrations (Tmax) and the 100% bioavailability.<sup>5, 6</sup> Orally administered antibiotics must undergo absorption from the gut and first pass metabolism before entering the systemic circulation, often causing a bioavailability of less than 100%, resulting in delayed and lower maximum concentrations in blood and at the site of infection compared to IV administration. From a theoretical point of view, in case the gastrointestinal tract of the patient is intact and the bioavailability of an oral antibiotic agent is adequate, it should be possible to reach sufficient antibiotic exposure with orally administered antibiotics. However, the systemic response to an infection may alter the pharmacokinetics of antibiotics<sup>7-10</sup> and thus the bioavailability of oral antibiotics.

Acute infection-induced pathophysiological changes such as organ dysfunction and increased capillary permeability are known to lead to alterations in antibiotic volume of distribution and clearance.<sup>7-10</sup> In critically ill infectious patients, both toxic antibiotic serum concentrations due to renal hypoperfusion and acute kidney injury, and subtherapeutic antibiotic serum concentrations due to increased volumes of distribution and renal hyperperfusion, i.e. Augmented Renal Clearance (ARC), have been described.<sup>7-10</sup> Although data is limited, an effect on absorption and first pass effect cannot be ruled out in advance, as possible perfusion or other yet unknown alterations to the gastrointestinal tract may be present during the acute phase of infection.<sup>11</sup> The latter two pharmacokinetic parameters are particularly of relevance, since these determine the bioavailability of oral agents. The effect of infection on bioavailability may not necessarily be negative. Infection is associated with downregulation of the cytochrome P450 (CYP) enzymes, expressed by the liver and intestines, and responsible for drug metabolism and the first pass effect.

This could lead to higher maximum concentrations in blood and the site of infection of CYP-dependent antimicrobials.<sup>12</sup>

To date, the pharmacokinetics of antibiotics have mainly been tested in healthy volunteers or critically ill patients. Reports on the pharmacokinetics in the early infectious phase of non-ICU hospitalized patients are limited. In particular, data on oral bioavailability of antibiotics in this phase of disease are scarce and contradictory.<sup>11, 13, 14</sup> Consequently, we do not know whether adequate antibiotic levels can be reached in the systemic circulation when antibiotics are administered orally during the initial stage of an infectious illness. Hence, the recommended 48 hour IV antibiotic treatment.

The aim of this study was to conduct a systematic review to assess the bioavailability of orally administered antibiotics during the initial phase of a systemic infection in non-ICU patients. The results may provide information whether starting with oral therapy or an earlier (<24 hours) IV-to-Oral switch might be possible and may guide future treatment policy and clinical research.

## **Methods**

### **Protocol**

This study was performed and reported according to the PRISMA (Preferred Reporting items for Systematic reviews and Meta-analysis) statement (Supplemental table 1).<sup>15</sup>

### **Eligibility criteria**

Studies reporting data on the pharmacokinetics of oral antibiotics in the early phase of infection were searched, preferably, but not necessarily, in comparison with the convalescence phase of infection. Studies were eligible if they included patients aged 16 years or above and febrile or acutely ill due to an infectious disease, which had to be clearly documented or illustrated with elevated infectious laboratory parameters, i.e. CRP, leucocytosis, SIRS or qSOFA criteria.<sup>16</sup> We chose a subset of antibiotics which are widely used and known to have a moderate to good bioavailability, namely amoxicillin, flucloxacillin, ampicillin, clindamycin, macrolides, fluoroquinolones, metronidazole and trimethoprim-sulfamethoxazole. The pharmacokinetic outcome parameters of interest were those related to oral bioavailability: the (maximum) serum concentrations (C<sub>max</sub>), time of achieving maximum serum concentrations (T<sub>max</sub>), the area-under-the-plasma-concentration-time curve (AUC) or bioavailability itself (F). Blood samples for these outcome

parameters had to be taken at the first day of antibiotic therapy, when patients were in the initial phase of their infectious disease. Intravenously pre-treated patients were excluded. Studies had to be reported in English or Dutch. We allowed all clinical study types, as long as they presented sufficient information to retrieve the patient inclusion criteria and the predefined outcome parameters. We excluded studies investigating healthy volunteers; patients admitted to the Intensive Care Unit; patients with impaired renal or hepatic function, because the impairment itself can already influence the predefined outcome parameters; and febrile neutropenic patients, because mucosal injury might make its findings not be generalizable to the general population.

### **Search strategy**

Together with an experienced clinical librarian, we conducted a systematic literature search in OVID MEDLINE and EMBASE for all relevant studies up to July 2020, based on the predefined objectives and eligibility criteria. In addition, we searched the reference lists of retrieved reviews. The primary records obtained were imported and de-duplicated in EndNote (complete search strategies can be found in supplemental table 2 and 3). One reviewer (A.v.d.B.) screened all the titles and abstracts, to identify studies that potentially met the eligibility criteria. 10% was randomly assigned to and independently screened by the other reviewers (R.M.v.H., C.E.V., J.M.P.) to ensure reliability and completeness. Differences in decision were resolved by consensus. We allowed a 2.5% margin of difference between the reviewers. If after discussion the difference remained more than 2.5%, all articles had to be screened by the other reviewers. Next, the full text articles of the potentially relevant studies were retrieved and assessed for eligibility by all reviewers. Any disagreement on inclusion of studies was discussed by all reviewers and resolved by consensus. Finally, the reference lists of the eligible articles were screened by A.v.d.B for additional suitable studies.

### **Data Extraction and Quality Assessment**

A standard form was used to extract and summarize the predefined outcome data and data necessary for the quality/risk of bias assessment of the included studies. Study design, patient characteristics, predefined pharmacokinetic outcome parameters and conclusions were extracted by one reviewer (A.v.d.B.) and fully checked for accuracy by another reviewer (R.M.v.H.). Discrepancies were resolved by discussion, together with the other reviewers if necessary. Next, the risk of bias of the included studies was assessed independently by three reviewers (A.v.d.B., R.M.v.H., J.M.P.), using an adjusted form of the Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized studies, and the Cochrane risk of bias tool for Randomized Controlled Trials.<sup>17, 18</sup> Studies could score points (or

stars) on three dimensions: Selection (max. 5 stars), Comparability (max. 2 stars) and Outcome (max. 3 stars). The more stars, the lower the risk of bias. We adapted sub questions of these domains to enable more appropriate quality evaluation for descriptive studies reporting pharmacokinetic parameters. The maximum NOS score was 10 and we considered the risk of bias high when the score was 5 or lower and low when above the median score of 5.

## Results

### Search results

Our literature search yielded 6011 potentially relevant studies. After removing the duplicates 4989 papers remained. Based on the eligibility criteria, 4879 studies were excluded in the initial screening phase based on title and abstract, leaving 110 records for full text screening, including two records which were added after reference screening of two reviews addressing the pharmacokinetics of ciprofloxacin and intracellular pharmacokinetics of antibiotics.<sup>19, 20</sup> Of these, 103 were excluded, and 7 included after full-text screening. In addition, we identified 2 papers by reviewing the reference lists of the included studies, resulting in 9 papers for qualitative analysis.<sup>21-29</sup> (*figure 1*)

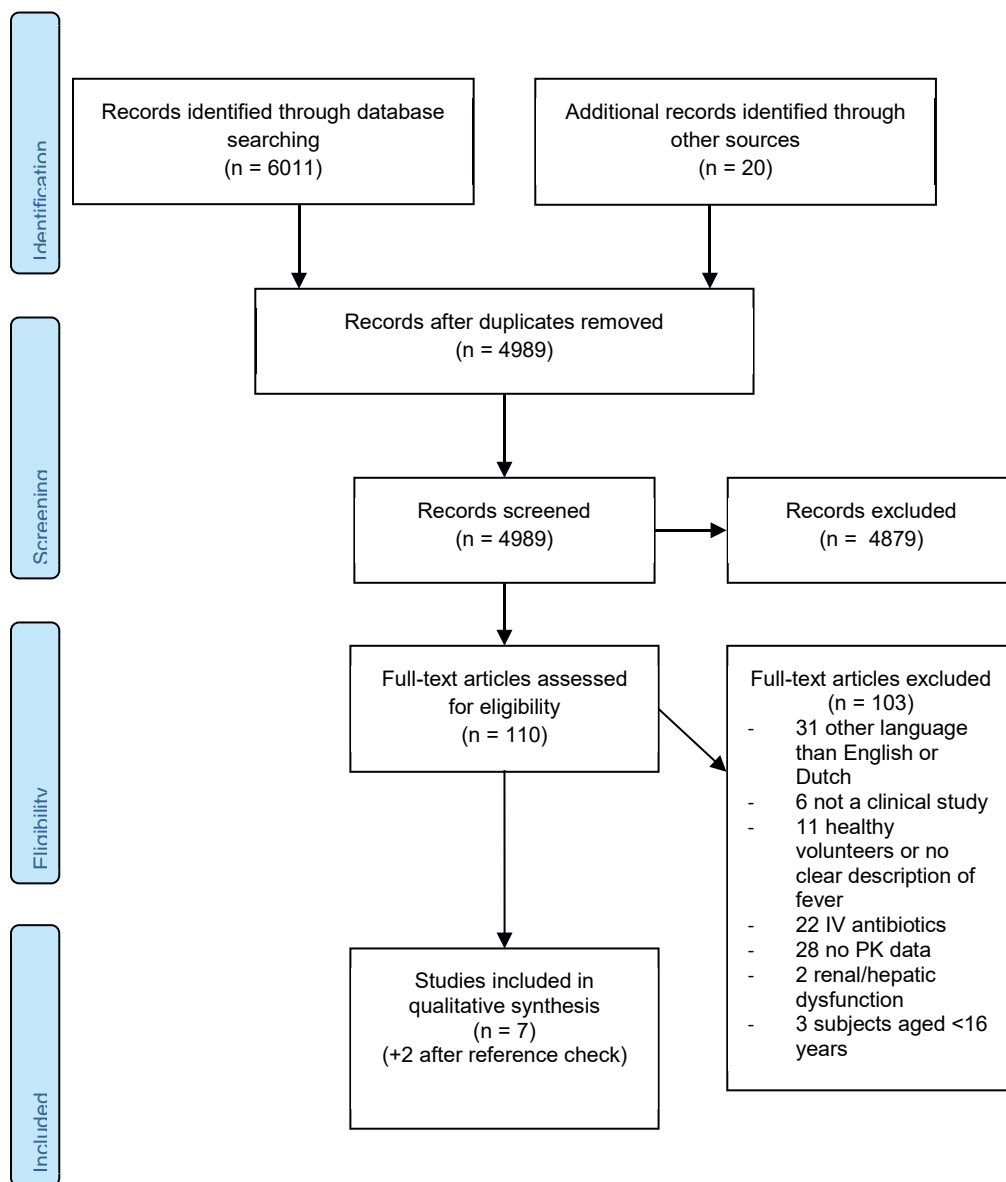
### Study characteristics

The study characteristics of the 9 included studies are presented in table 1. The studies were non-randomized, observational studies<sup>21-29</sup> All studies were performed in hospitalized patients. 6/9 studies reported fever or other signs of acute phase of febrile illness.<sup>21, 25-29</sup> In 3/9 studies, which were the studies that were added after reference screening of the retrieved reviews and the reference lists of the included studies, the febrile state of patients was unclear, which may explain why these records were not captured in our initial search. However, the patients were hospitalized for acute purulent respiratory exacerbations and were in their initial phase of illness, making it highly likely that these patients were febrile or acutely ill as well. Therefore, we chose to include these studies.<sup>22-24</sup> Four studies originated from The Netherlands<sup>21-24</sup>, two from the USA<sup>27, 29</sup>, one from Canada<sup>26</sup>, one from Egypt<sup>25</sup> and one from Guatemala<sup>28</sup>. The pharmacokinetics (PK) of amoxicillin was investigated by two studies,<sup>22, 25</sup> the PK of azithromycin<sup>21</sup>, ampicillin<sup>22</sup>, clarithromycin<sup>26</sup> and enoxacin<sup>24</sup> by one study each and the PK of ciprofloxacin by four studies<sup>23, 27-29</sup>.

Figure 2: PRISMA 2009 flow diagram



PRISMA 2009 Flow Diagram



**Quality assessment**

The risk of bias results are listed in table 2. Six out of nine studies had a low score and therefore a high risk of bias, mainly due to the sample selection, in which a sample size calculation was missing, and the outcome measurement, in which a clear description of the laboratory procedures for the measurement of drug concentrations was missing.<sup>21-25, 28</sup>

**Pharmacokinetic parameters in infectious patients during their initial state of disease***Amoxicillin and ampicillin*

Two studies reported the PK of oral amoxicillin,<sup>22, 25</sup> of which one study reported the PK of oral ampicillin as well.<sup>22</sup> The first study reported the mean C<sub>max</sub>, T<sub>max</sub> and AUC of amoxicillin (n=23) and ampicillin (n=17) measured in serum and sputum on the first day of therapy in patients diagnosed with acute respiratory exacerbations. The serum concentrations were plotted in a figure, from which we estimated the range of the C<sub>max</sub> through visual inspection.<sup>22</sup> The other study concerned patients with *Salmonella typhi* or paratyphi A bacteriuria and recurrent bacteraemia associated with schistosomiasis. All patients had acute enteric fever or were febrile. Only 5/12 patients were aged > 16 years, but since amoxicillin concentrations were reported individually, these five patients could be included. The authors reported the measured serum concentrations during the first four hours after dose administration on day 1 and day 2.<sup>25</sup> Both reports conclude that the measured serum and sputum concentrations of amoxicillin should be generally satisfactory for treatment, based on the minimum inhibitory concentration (MIC) values of the isolated pathogens, whereas ampicillin did not yield satisfactory concentrations in serum and sputum. However, none of the studies drew a clear conclusion on the bioavailability of oral amoxicillin or ampicillin during the febrile period of illness compared to the convalescence phase.

*Azithromycin*

One study reported the PK of azithromycin.<sup>21</sup> Although the report does not present the study population characteristics, the patients were derived from another trial, in which the state of disease was clearly described.<sup>30</sup> The total serum concentrations were measured at two time points within the first dosing interval in eight subjects. In five of them, one concentration was also measured after the second dose. The wide range of observed concentrations measured 3 hours after the first dose (0.06-0.25 mg/l) indicate high inter-patient variability. The authors' conclusion, that the initial phase of infection resulted in low serum levels during the first 12 hours of illness, was based on a comparison with previously reported C<sub>max</sub> levels in

healthy volunteers, ranging from 0.4-0.45 mg/l.<sup>21</sup> However, this conclusion is based on only two PK measurements per dosing interval, which increases the risk that the true C<sub>max</sub> and T<sub>max</sub> could not be accurately estimated. Also, the number of subjects (n=8) seems not sufficient to draw a sound conclusion on the bioavailability of azithromycin during the initial stage of an infectious disease.

#### *Clarithromycin*

One study reported the PK of a single dose of clarithromycin in 12 patients diagnosed with community- acquired pneumonia, when they were acutely ill and after convalescence.<sup>26</sup> The AUC of clarithromycin was higher during the febrile phase compared to the afebrile phase, 47.37 µg/h/ml vs 36.22 µg/h/ml respectively (p=0.075), which the authors considered significant based on a significance level set at 10%. No significant differences were found in C<sub>max</sub> and T<sub>max</sub> between the two phases. Therefore, the febrile phase of illness did not seem to impair the extent of oral absorption of clarithromycin. The concentrations of its metabolite were significantly decreased during this phase. An explanation may be that the infection altered the hepatic blood flow, impairing the first pass effect, which is reported to be strong for clarithromycin.<sup>31</sup> It would be interesting to know whether the patients were hypotensive or had a significantly different blood pressure between the two measurement days to strengthen this hypothesis.

#### *Ciprofloxacin and enoxacin*

Four studies investigated the PK of ciprofloxacin.<sup>23, 27-29</sup> One study reported the PK of enoxacin.<sup>24</sup> Patel and colleagues measured the C<sub>max</sub>, T<sub>max</sub> and AUC of a single oral dose of ciprofloxacin in patients diagnosed with acute infectious illnesses of any kind when they were acutely ill, compared to when they were afebrile. In this study, with a low risk of bias, no significant PK differences were seen between the two phases.<sup>27</sup> The study of Guay and colleagues also analysed the C<sub>max</sub>, T<sub>max</sub> and AUC of ciprofloxacin in the febrile phase compared with the afebrile phase, but mainly in patients diagnosed with lower respiratory tract infections. Again, no significant PK differences were seen between the two phases and also this study had a low risk of bias. However, 6/13 patients had impaired renal/hepatic function (i.e. cirrhosis and chronic liver disease). Because this study presented individual data of the subjects, patients with impaired renal/hepatic function were excluded and the remaining data of the eligible patients were summarized as described in the methods section of that study (table 1). This left only 7 patients in the febrile phase, of which 4 patients were also studied in the afebrile phase, strongly limiting the power of the study.<sup>29</sup> The ciprofloxacin study by Ramirez measured the peak and trough serum concentrations during the initial disease phase (day 1), the fourth and last day of therapy.<sup>28</sup> On all three measurements days, the drug levels in these patients were lower than previously

reported, yet there was resolution of the infectious process in 88 of 100 patients.<sup>32</sup> In addition, the mean serum levels did not differ between measurement days, so the infectious state of the patient did not seem to have an effect on the measured ciprofloxacin concentrations.

The ciprofloxacin and enoxacin studies by Davies reported the C<sub>max</sub>, T<sub>max</sub> and AUC measured in serum and sputum concentration on the first day of therapy in patients diagnosed with acute respiratory exacerbations.<sup>23, 24</sup> In the ciprofloxacin study, the PK of different doses were studied (n=20 per dosing group). In the enoxacin study (n=15), the serum concentrations were plotted in a figure, from which we estimated the range of the C<sub>max</sub> through visual inspection. The authors concluded that the gastro-intestinal absorption of enoxacin was good, with little interpatient variability. However, no formal quantitative assessment was given, which makes it unclear on what parameters this conclusion was based. Also, no comparison was made between the extent of absorption in the febrile and non-febrile phase. The study concluded these quinolones to be an effective treatment for the investigated populations, mainly based on the sufficiently high measured serum concentrations relative to the measured MIC values of the isolated pathogens.

Table 1 Characteristics of included studies

Study	Setting	Disease Phase of infection	Study design	Study drug Dosage regimen	Sample size Age (y)	Predefined outcomes										Conclusion	Risk of bias score				
						Serum Concentrations or Cmax (mg/l)															
						Tmax (h) AUC (mg/l*h) Bioavailability (F in %)															
Farid et al, 1975 [25]	Hospitalized patients (Egypt)	Salmonella bacteraemia associated with Schistosomiasis Acute enteric fever/febrile	Cross-sectional PK after first dose on the first and second day of therapy	amoxicillin PO: 250mg qd	N=5 Age: 20-29 (N total:12, 7 with age<18 y)	Day 1					Day 2					Cserum day 2 adequate for the treatment of the Salmonellae isolated from the urine and blood.	4/10				
						2h		3h		4h		2h		3h				4h			
						Cserum	0.12	4.1	3.1	3.5	-	2.4	Pat 7	2.0	1.1			-	3.3	-	0.7
						Pat 8	7.1	-	2.1	8.5	-	1.15	Pat 9	3.1	3.25			1.0	0.63	-	2.0
						Pat 10	3.5	3.95	3.65	1.57	-	3.9	Pat 11								
Davies et al, 1979 [22]	Hospitalized patients (The Netherlands)	Acute exacerbations of chronic bronchitis Initial phase	Cross-sectional PK after first dose of different antibiotics	1. amoxicillin PO: 750mg 2. ampicillin PO: 1000mg	1. N=23 2. N=17 Age: -	Amoxicillin					Ampicillin					Amoxicillin measured serum concentrations generally satisfactory to treat H. influenza and S. pneumoniae  Ampicillin does not yield satisfactory concentrations in serum and sputum	1/10				
						Cmax		11 (6-15 visual inspection)		8.3 (4-13 visual inspection)		Tmax		1.5				26.34			

Study	Setting	Disease Phase of infection	Study design	Study drug Dosage regimen	Sample size Age (y)	Predefined outcomes Serum Concentrations or Cmax T <sub>max</sub> (h) AUC (mg/l <sup>h</sup> ) Bioavailability (F in %)	Conclusion	Risk of bias score
Bohte et al, 1995 [21]	Hospitalized patients (The Netherlands)	CAP Initial phase	Cross-sectional PK around first and second dose	azithromycin PO: 500 mg bd on day 1, thereafter od during 4 days	N=8 Age: 32-75	C <sub>serum</sub>	Low C <sub>serum</sub> during the first 12h of treatment as compared to healthy volunteers.	3/10
						3h	0.06-0.25	
Offman et al, 2000 [26]	Hospitalized patients (Canada)	CAP Acutely ill	Longitudinal cohort PK after first dose acutely ill vs. convalescent phase	clarithromycin PO: 500mg single dose	N= 12 Age: 77±2	C <sub>max</sub>	No impaired oral absorption in acutely ill patients with CAP.	9/10
						T <sub>max</sub>		
						AUC	2.83 ± 0.59	
						47.37 ± 8.51	36.22 ± 6.09*	
Patel et al, 1995 [27]	Hospitalized patients (USA)	Acute infectious illnesses Acute febrile phase (oral T>38.9;rectal T>38.3)	Longitudinal cohort PK after first dose acutely ill vs. convalescent phase	ciprofloxacin PO: 500mg single dose	N=12 Age: 36 (20-62)	C <sub>max</sub>	During acute phase of significantly decreased C <sub>max</sub> and AUC of 14-hydroxy clarithromycin.	8/10
						T <sub>max</sub>		
						AUC	4.83 ± 1.29	3.08 ± 0.51
							5.84 ± 1.08	8.84 ± 1.92*
								No significant PK differences between acutely ill and convalescent phase.

Study	Setting	Disease Phase of infection	Study design	Study drug Dosage regimen	Sample size Age (y)	Predefined outcomes Serum Concentrations or Cmax ( mg/l) Tmax (h) AUC (mg/l* <sup>h</sup> ) Bioavailability (F in %)	Conclusion	Risk of bias score
<b>Ramirez et al, 1985 [28]</b>	Hospitalized patients (Guatemala)	Selected susceptible gram-negative or positive infections Initial febrile phase, or febrile phase after inadequate treatment	Cross-sectional PK at first, fourth and last day of therapy	ciprofloxacin PO: 500mg bd	N= 71 (N total = 100) Age: 38.1 (18-84)	Cpeak Cthrough Day 1: 0.77 ± 0.43 Day 4: 0.79 ± 0.49 Last day: 0.80 ± 0.41 0.29 ± 0.34 ± 0.29 ± 0.24	Drug levels in blood lower than previously reported	4/10
<b>Guay et al, 1987 [29]</b>	Hospitalized patients (USA)	Lower respiratory tract infections Acutely ill	Longitudinal cohort PK after first dose acutely ill vs. convalescent phase	ciprofloxacin PO: 750mg bd	Febrile N= 7 Afebrile N=4 Age: 77.7 (71-89) (N total = 13, but 6 with renal/hepatic impairment)	Acutely ill PK n= 4: <sup>c</sup> 6.11 ± 2.67 1.6 ± 0.45 Convalescent 9.9 ± 3.65 1.3 ± 0.6 h PK n=7: 6.83 ± 3.39 1.8 ± 0.7	No significant PK differences between acute illness and convalescent phase.	6/10

Study	Setting	Disease Phase of infection	Study design	Study drug Dosage regimen	Sample size Age (y)	Predefined outcomes Serum Concentrations or Cmax ( mg/l) Tmax (h) AUC (mg/l*h) Bioavailability (F in %)	Conclusion	Risk of bias score
<b>Davies et al, 1986 [23]</b>	Hospitalized patients (The Netherlands)	Acute exacerbations of chronic bronchitis Initial phase	Cross-sectional PK after first dose of 3 different doses	<b>ciprofloxacin</b> PO: Group 1: 500mg bd Group 2A: 750mg bd (badge 1) Group 2B: 750mg bd (badge 2) Group 3: 1000mg bd	N=80 (8)  Group 1: 20 Age: 66.2  Group 2A: 20 Age: 66.8  Group 2B: 20 Age: 60.3  Group 3: 20 Age: 65.9	Cmax  Tmax AUC  Group 1 3.36 (range 1-6) 2.4 12.9 (range 6-20.7)  Group 2A 2.3 (range 1.4-3.4) 1.68 11.1 (range 7-15.6)  Group 2B 3.13 (range 1.3-5) 2.25 14.7 (range 6.8-25.6)  Group 3 3.76 (range 2.5-6) 1.95 17.9 (range 9.9-25.8)	Measured serum concentrations were generally satisfactory to treat H. influenza or B. catarrhalis.	3/10
<b>Davies et al, 1984 [24]</b>	Hospitalized patients (The Netherlands)	Acute exacerbations of chronic bronchitis Initial phase	Cross-sectional PK after first dose	<b>enoxacin</b> PO: 600mg bd	N= 15 Age: 66.4 (50-81)	Cmax Tmax AUC <sub>0-7</sub> AUC <sub>0-12</sub>  3.7 (± 1.2 visual inspection) 2.3 17.03 25.02	Good GI- absorption. However, unclear comparator. The interpatient serum concentrations did not differ widely.	1/10

Table 2: Quality and Risk of Bias Assessment

OBSERVATIONAL STUDIES							Summary score/10
Study	Sample selection criteria			Comparability	Outcome & evaluation		
	Representativeness sample: 2 points if the sample is a truly representative of the average in the target population; 1 point if the sample is somewhat representative of target population; no points if unclear or no description	Sample size: 1 point is sample size is justified by using power analysis; no points if not justified.	Ascertainment of disease state or diagnosis: 2 points if validated or accepted tool was used; 1 point if non-validated or non-accepted, but well described; no points if unclear or no description	Comparability: 1 point if group design and groups are comparable; no points when groups are not comparable; 1 point when no comparative design was used; 1 point if the study controls for possible confounders	Assessment outcomes: 1 point if appropriate blood collection/drug concentration measurement and laboratory procedures used; No points if unclear or no description of procedure.	Statistical test (analysis of outcomes): 2 points if population pharmacokinetic modelling with co-variate analysis or conventional 2-stage method with co-variate analysis or non-compartmental analysis with rich sampling (≥3/dosing interval); 1 point if outcome variables summarized while expressing variability; no points if the statistical test is unclear, incomplete or not described.	
Bohte, 1995	★	-	-	★	-	★	3/10: low
Davies, 1986	-	-	-	★	-	★★	3/10: low
Davies, 1984	-	-	-	★	-	-	1/10: low
Davies, 1979	-	-	-	★	-	-	1/10: low
Farid, 1975	★	-	★	★	-	★	4/10: low
Guay, 1987	★	-	-	★★	★	★★	6/10: high
Offman, 2000	★	★	★★	★★	★	★★	9/10: high
Patel, 1995	★	★	★	★★	★	★★	8/10: high
Ramirez, 1985	★	-	★★	★	-	-	4/10: low

## Discussion

We systematically reviewed the literature on the oral bioavailability of antibiotics during the initial phase of infection in non-ICU patients to assess the possibility of an earlier IV-to-oral switch in these patients. Our review identified 9 studies on 6 antibiotics, which had in general a high risk of bias and did not provide sufficient information to compare bioavailability in febrile versus afebrile patients.<sup>21-29</sup> Consequently, assessments for the majority of antibiotics included in the review were uninformative. Studies on clarithromycin (n=1) and ciprofloxacin (n=2), where the same patients in the febrile and afebrile phase could be compared, were the only ones that provided an indication for the absence of an effect of acute illness on antibiotic bioavailability.<sup>26, 27, 29</sup> Although these studies had a low risk of bias, they included a very limited number of patients (n≤12). Our review therefore indicates that insufficient evidence exists to draw a sound conclusion on whether or not the bioavailability is altered in the febrile phase relative to the afebrile phase in non-ICU patients, and as such identified a clear knowledge gap.

The six studies that compared the PK of the initial phase of infection to previous reported PK values in healthy volunteers, or that had no comparison at all, should be interpreted with caution, not only because they all had a high risk of bias, but also for the following reasons.<sup>21-25, 28</sup>

First, when comparing PK values with previously reported PK values, as was the case for the studies on ciprofloxacin and azithromycin<sup>21, 28</sup>, it is unclear to which extent the study population and setting are comparable. Both studies observed lower serum levels than previously reported. Bohte presented only 2 PK measurements per dosing interval, which increases the risk that the true C<sub>max</sub> and T<sub>max</sub> could not be accurately estimated.<sup>21</sup> This is likely to contribute to an unreliable comparison with observed values of C<sub>max</sub> and T<sub>max</sub> in healthy volunteers. In addition, the number of subjects (n=8) seems not sufficient to draw a sound conclusion on the absorption of azithromycin during the initial stage of an infectious disease. The low serum concentrations of ciprofloxacin reported by Ramirez appeared not to be explained by the infectious state of the patients, since they were low on all measurement days.<sup>28</sup>

Second, most PK studies in healthy volunteers were performed while the antimicrobial concentrations had reached steady state, rather than after a dose on the first day of treatment.<sup>33</sup>

Third, the non-comparison studies, regarding amoxicillin, ampicillin, ciprofloxacin and enoxacin, were not designed to draw any conclusions on the bioavailability of

orally administered antimicrobial agents. The primary aim of these studies was to assess their target attainment in the acutely ill phase. Yet, none of the studies defined the target to be attained. Also, the studies on  $\beta$ -lactam antibiotics<sup>22, 25</sup> did not comment on the duration that the serum concentrations were above the MIC.

### **Strengths and limitations**

To the best of our knowledge, this is the first study that systematically reviewed the bioavailability of orally administered antibiotics during the initial phase of infection in non-ICU patients in accordance with the PRISMA statement. A major strength of our systematic review is that we had a very broad and thorough search strategy, and three title and abstract screening reviewers, reducing the risk that articles have been missed. Our systematic review is also subject to several limitations. Because we included studies that used very heterogeneous methods, study endpoints and outcome measurements, we were not able to pool the data and process them in a meta-analysis. Also, most of the included studies were dated from 1975 to 1995. It is uncertain whether the used laboratory methods to measure the antibiotic serum concentrations were sensitive enough to present reliable results. Most studies did not report whether their method for antibiotic concentration measurement was validated (*table 2*). Finally, it is possible that relevant pharmacokinetic data have not been published. For example, studies sponsored or performed by a pharmaceutical company are less likely to be published, regardless of the results.<sup>33</sup>

### **Future research**

Our findings showed that knowledge of the bioavailability of orally administered antibiotics during the acute phase of a febrile illness in non-ICU patients is scarce. In previous studies the PK of antibiotics in a broader sense, so not only bioavailability, but also clearance and volume of distribution, has been mainly investigated in healthy volunteers and in critically ill patients.<sup>8-10, 34</sup> Non-ICU patients cannot be automatically equated with the latter, as systemic infection might profoundly alter the PK of antibiotics depending on its severity.<sup>34</sup> For example, in critically ill infectious patients an increased volume of distribution is often seen, due to capillary permeability negatively impacting exposure.<sup>7-10</sup> And in terms of clearance, as stated before, both toxic antibiotic serum concentrations and subtherapeutic antibiotic serum concentrations can be seen, depending on the perfusion alterations of the kidney. Especially in cases of augmented renal clearance both the area-under-the-concentration-time curve as well as the percentage of time of a dosing interval the antibiotic concentration is above the minimum inhibitory concentration will be lower.<sup>7-10</sup> In addition, the results from critically ill patients do not learn anything about bioavailability of antibiotics, as

antibiotics are almost always administered intravenously in these patients. The same accounts for patients newly admitted to a general ward with an acute infection. This reluctance to administer antibiotics orally from the beginning of a course proves that clinicians are not a priori convinced that the acute phase of an infection does not alter bioavailability, neither in ICU patients nor in non-ICU patients, even if the gastrointestinal tract of the patient is intact. The two studies on ciprofloxacin<sup>27, 29</sup> and the one study on clarithromycin<sup>26</sup> in which the same patients in the febrile and afebrile phase of infection were compared, suggest that bioavailability is not altered during the initial phase of infection. Although these results are promising concerning the possibility to switch from IV to oral therapy within the first 24 hours of treatment, the value of these studies is limited due to their small number of included patients (respectively n=12, 7 and 12). For the other orally administered antibiotics evidence is completely lacking whether febrile illnesses influences the extent of bioavailability.<sup>21-25, 28</sup> If febrile illnesses do have an effect on the bioavailability of orally administered antibiotics, it is likely that there are clinical consequences of oral administration: reduced bioavailability could lead to insufficient serum concentrations, negatively affecting clinical outcome and the risk of development of antibiotic resistance, while increased bioavailability might increase the risk of toxicity.<sup>12, 35, 36</sup> We therefore believe that current and new oral antimicrobial agents should be tested in non-ICU patients during the acute phase of febrile illness as well, and not only in healthy volunteers or during the convalescent state.

## Conclusion

There is a clear knowledge gap regarding the bioavailability of widely used orally administered antibiotics during the initial phase of a systemic infection in non-ICU patients, as only a few, mostly small, studies could be identified on this matter that generally had a high risk of bias. Although from a theoretical perspective there does not seem to be a reason not to start early oral antibiotic therapy in febrile patients without gastrointestinal problems, this gap needs to be covered to indeed provide the evidence that an early switch (within 24 hours of start of therapy) still ensures high enough antibiotic concentrations for effective treatment. Therefore, well-designed and large enough studies on this specific topic are warranted so that it can be elucidated whether patients can benefit from the advantages of the IV-to-oral switch earlier than nowadays.

## List of abbreviations

<b>AUC</b>	Area-under-the-plasma-concentration-time curve
<b>C<sub>max</sub></b>	Maximum serum concentrations
<b>C<sub>peak</sub></b>	Peak concentrations
<b>C<sub>serum</sub></b>	Serum concentrations
<b>C<sub>through</sub></b>	Through concentrations
<b>CYP</b>	Cytochrome P450
<b>F</b>	Bioavailability
<b>ICU</b>	Intensive Care Unit
<b>IV</b>	Intravenously
<b>MIC</b>	Minimum inhibitory concentration
<b>NOS</b>	Newcastle-Ottawa Quality Assessment Scale
<b>PK</b>	Pharmacokinetics
<b>PK/PD</b>	Pharmacokinetics/pharmacodynamics
<b>PPK</b>	Population pharmacokinetics
<b>T<sub>max</sub></b>	Time of achieving maximum serum concentrations

**Supplementary data**  
Table 1: PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 Appendix Table 2, 3.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Table 2, 3.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	Not applicable

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, 7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
<b>DISCUSSION</b>			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 2: Search strategy Ovid MEDLINE

Ovid MEDLINE(R) ALL <1946 to July 21, 2020>			
Search history sorted by search number ascending			
#	Searches	Results	Type
1	anti-bacterial agents/ or amoxicillin/ or ampicillin/ or azithromycin/ or ciprofloxacin/ or clarithromycin/ or clindamycin/ or erythromycin/ or erythromycin estolate/ or erythromycin ethylsuccinate/ or floxacillin/ or fluoroquinolones/ or levofloxacin/ or norfloxacin/ or ofloxacin/ or roxithromycin/ or trimethoprim, sulfamethoxazole drug combination/ or (amoxicillin or ampicillin or azithromycin or ciprofloxacin or clarithromycin or clindamycin or erythromycin or erythromycin estolate or "erythromycin ethylsuccinate or floxacillin" or fluoroquinolones or levofloxacin or norfloxacin/ or ofloxacin or roxithromycin or trimethoprim or quinolone* or cotrimoxazol or macrolide* or metronidazol* or antibiotics or antimicrobial).ti,ab,kf,rn.	642546	Advanced
2	pharmacokinetics.fs. or exp pharmacokinetics/ or exp area under curve/ or exp absorption/ or (Pharmacodynamic* or pharmacodynamic* or PK or "pk/PD" or PPK or tmax or cmax or AUC or bioavailability or "area under the curve" or "drug level" or absorption or half-life or "Therapeutic range" or "Drug exposure" or ((serum or plasma or blood) adj5 (concentration or level* or sample*))).ti,ab,kf.	1757881	Advanced
3	exp C-Reactive Protein/ or exp FEVER/ or febrile.mp. or exp BACTEREMIA/ or (bacteremia or bacteraemia).ti,ab,kf. or exp SEPSIS/ or exp Systemic Inflammatory Response Syndrome/ or SIRS.ti,ab,kf. or qsofa.ti,ab,kf. or exp Leukocytosis/ or ((acute* adj ill*) or convalescence).ti,ab,kf.	272396	Advanced
4	1 and 2 and 3	3480	Advanced
5	exp Infant, Newborn/ or (exp animals/ not humans/) or (mice or mouse or rat or rats or pig or pigs or dog or dogs).ti. or case reports.pt. or exp Neutropenia/	7582665	Advanced
6	4 not 5	2212	

Table 3: Search strategy Embase

Embase Classic+Embase <1947 to 2020 July 22>			
Search history sorted by search number ascending			
#	Searches	Results	Type
1	*antibiotic agent/ or *amoxicillin/ or *ampicillin/ or *azithromycin/ or *ciprofloxacin/ or *clarithromycin/ or *clindamycin/ or exp **erythromycin estolate"/ or *erythromycin/ or exp **erythromycin ethylsuccinate"/ or *flucloxacillin/ or **quinolone derivative"/ or *moxifloxacin/ or *norfloxacin/ or *ofloxacin/ or *roxithromycin/ or *otrimoxazole/ or (amoxicillin or ampicillin or azithromycin or ciprofloxacin or clarithromycin or clindamycin or erythromycin or "erythromycin estolate" or "erythromycin ethylsuccinate" or flucloxacillin or floxacillin or fluoroquinolones or levofloxacin or norfloxacin or ofloxacin or roxithromycin or trimethoprim or quinolone* or cotrimoxazol or macrolide* or metronidazol* or antibiotics or antimicrobial).ti,ab,kw,tn.	660495	Advanced
2	exp *pharmacokinetics/ or **"area under the curve"/ or *exp absorption/ or (Pharmacodynamic* or pharmacodynamic* or PK or "pk/PD" or PPK or tmax or cmax or AUC or bioavailability or "area under the curve" or "drug level" or absorption or half-life or "Therapeutic range" or "Drug exposure" or ((serum or plasma or blood) adj5 (concentration or level* or sample*))).ti,ab,kw.	2182791	Advanced
3	exp leukocytosis/ or exp C reactive protein/ or exp fever/ or exp bacteremia/ or (bacteremia or bacteraemia).ti,ab,kw. or SIRS.ti,ab,kw. or qsofa.ti,ab,kw. or febrile.mp. or exp sepsis/ or exp "systemic inflammatory response syndrome"/ or ((acute* adj ill*) or convalescence).ti,ab,kw.	825637	Advanced
4	1 and 2 and 3	6125	Advanced
5	exp newborn/ or ((exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/) or case report/ or exp Neutropenia/	10488229	Advanced
6	4 not 5	3799	

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## CHAPTER 6:

# The effect of the acute phase of infection on absorption of and exposure to orally administered antibiotics in non-critically ill, hospitalized patients

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## Abstract

**Objectives:** During the acute phase of infection, intravenous (IV) antibiotics are preferred to ensure adequate systemic exposure. To assess whether adequate exposure may also be achieved with oral antibiotics, we investigated exposure to oral antibiotics and probability of target attainment (PTA) during the acute phase of infection and after defervescence.

**Methods:** We enrolled hospitalized, non-critically ill febrile patients treated with IV antibiotics other than amoxicillin or ciprofloxacin. The study consisted of two visits: when patients had received <24h IV treatment, and when patients had become afebrile. On both visits, patients received one additional dose of 750mg amoxicillin, or 500mg ciprofloxacin, depending on the presumed infection, after which serial blood samples were obtained. Primary endpoint was the ratio of the AUC during the febrile and the afebrile phase. The AUCs were considered to be equivalent when the ratio of the mean AUCs and its 90%-CI was contained within the acceptance interval of 80-125%. Secondary endpoint was PTA.

**Results:** 44 patients (15 amoxicillin, 29 ciprofloxacin) completed both study visits. The median time between both study visits was 65.8h (range 33.8-427.4). The ratio of the mean AUCs (visit 1/2) was 97% (90%-CI of 80-117%) for amoxicillin and 112% (90%-CI of 108-116%) for ciprofloxacin. The PTA for amoxicillin and ciprofloxacin did not differ between both phases and was adequate to treat common pathogens.

**Conclusions:** The acute phase of infection in non-critically ill febrile patients does not influence the exposure to, or PTA of, orally administered amoxicillin and ciprofloxacin. This might justify earlier IV-to-oral switching.

## Introduction

Intravenously (IV) administered antibiotics are preferred over orally administered antibiotics during the acute phase of a systemic infection to ensure adequate antibiotic exposure.<sup>1, 2</sup> Even for antibiotic agents that are known to have good bioavailability physicians are reluctant to treat serious infections orally, because of the belief that the systemic response to an infection may alter the absorption, distribution, metabolism and/or clearance of antibiotics.<sup>3, 4</sup>

In critically ill patients it has indeed been demonstrated that acute infection-induced pathophysiological changes lead to an increase of volume of distribution and augmented or impaired renal clearance.<sup>3, 5, 6</sup> Data on bioavailability, however, are scarce and contradictory and may not apply to non-critically ill patients.<sup>4, 7</sup> In a recently published systematic review, the very limited number of available studies on this topic suggested that the bioavailability of orally administered antibiotics in non-critically ill patients was not altered during the acute phase.<sup>8-11</sup> Yet, included studies were small and had a high risk of bias. Consequently, sound evidence is lacking whether adequate antibiotic levels can be reached in the systemic circulation when antibiotics are administered orally during the initial stage of an infectious illness.

As a consequence, in hospitalized febrile patients who require IV antibiotic treatment it is recommended to switch to oral therapy only when the patient has been treated intravenously for at least 48-72 hours and is recovering.<sup>12</sup> Switching to oral therapy has been shown to lower the length of hospital stay, the risk of new infections and healthcare costs, without compromising clinical outcome.<sup>13</sup> The cut-off duration of 48-72 hours of IV therapy is however arbitrary. Patients may therefore be unnecessarily exposed to prolonged IV treatment.

The primary aim of this study was therefore to compare the exposure to orally administered amoxicillin and ciprofloxacin in hospitalized non-critically ill patients during the acute phase of infection and after defervescence, to determine whether the acute phase of infection has an effect on antibiotic exposure after oral administration. A secondary aim was to compare probability of target attainment. This knowledge contributes to assessing the possibility of an earlier IV-to-oral switch therapy, in order to gain the benefits of the switch as soon as possible.

## Methods

### Study design and setting

The EXPO-AB study was a multicentre, prospective intervention study. Non-critically ill, febrile patients treated with IV antibiotics were recruited from August 2019 to December 2021 on the general wards of three acute care hospitals in Amsterdam, the Netherlands: OLVG West, a large non-academic teaching hospital; and the Amsterdam University Medical Centres, locations VUmc and AMC, two academic teaching hospitals. Ethical approval for the EXPO-AB study was given by the Medical Ethical Committee of the Amsterdam University Medical Centres, location AMC. All included subjects signed informed consent. The trial is registered at the Netherlands Trialregister (NTR): NL7782.

### Study procedures and data collection

Non-critically ill patients were defined as patients admitted to a general, non-ICU ward. Patients were eligible for inclusion if they were aged  $\geq 18$  years and were diagnosed with an acute febrile illness, with a body temperature  $\geq 38.3^{\circ}\text{C}$  measured at least once since admission, and in need of IV antibiotics therapy. Furthermore, patients had to be able to take medication orally, defined as the absence of abdominal pathology that may alter absorption, like vomiting, severe diarrhoea, malabsorption syndrome, short bowel syndrome, severe gastroparesis, continuous nasogastric suction, ileus, or history of resection surgery of the gastrointestinal tract, i.e. esophagectomy, pylorus-preserving pancreaticoduodenectomy. The decision to start IV antibiotics and the choice of antibiotics were at the discretion of the treating physician, following local guidelines. The IV therapy had to be other than amoxicillin or ciprofloxacin, but prescribed for an indication for which amoxicillin or ciprofloxacin is a registered treatment, for instance community-acquired pneumonia or urosepsis.<sup>14, 15</sup> This enabled us to safely investigate exposure to oral amoxicillin and ciprofloxacin without affecting standard patient care for the febrile illness. Patients were excluded when they had an glomerular filtration rate of  $<30\text{mL/min}$  estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation<sup>16</sup>, or were diagnosed with liver cirrhosis, active hepatitis or liver failure, to exclude a gross effect of altered clearance on antibiotic exposure. Patients were also excluded if they were neutropenic ( $<1000/\mu\text{L}$ ), were treated with chemotherapy within the past 28 days, were pregnant, or when they had a history of alcohol or drug abuse.

The study consisted of two visits: visit 1 ("Febrile phase"), when patients were febrile (temperature  $\geq 38.3^{\circ}\text{C}$  measured at least once since admission) and had

received less than 24h empiric IV treatment; and visit 2 ("Afebrile phase"), when patients were recovering from their infectious illness and were afebrile (temperature < 38.3°C) for at least 24 hours, or when they qualified for an IV-to-oral switch.<sup>17</sup> In addition to the IV antibiotic treatment, at both study visits the subjects received a single oral dose of amoxicillin 750mg, if the presumed infection at that moment was a registered indication for amoxicillin, or ciprofloxacin 500mg, if the infection was a registered indication for ciprofloxacin.<sup>14, 15</sup> Thereafter, a maximum of four blood samples were obtained per study visit to measure the antibiotic plasma concentrations: three samples randomly during the first four hours after administration, focusing on the absorption part of the concentration-time curve, and one sample around 6h and 8h for respectively amoxicillin and ciprofloxacin. The time of drug administration and blood sample collection were carefully documented.

Demographic results, medical history, co-medication, vital parameters and body temperature were documented by the coordinating investigator and plasma creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), albumin and bilirubin were measured on both study visits.

### Sample handling

The blood samples were obtained in heparinized tubes either via an intravenous catheter or by direct venipuncture and immediately transferred on dry ice to the laboratory of the Department of Hospital Pharmacy & Clinical Pharmacology of the Amsterdam UMC or to the Clinical Chemistry Laboratory of the OLVG, where they were centrifuged and stored at -80°C until analysis. Total and unbound amoxicillin and ciprofloxacin concentrations were analysed using a validated LC-MS/MS method. Unbound concentrations were measured in a random selection of 20% of the samples. For amoxicillin total and unbound concentrations, the lower limit of quantification (LLQ) was 0.5mg/l with an accuracy of 96.7% and a precision of 14.1%. The higher limit of quantification (HLQ) was 40 mg/l with an accuracy of 104% and a precision of 7.8%. For the corresponding parameters for ciprofloxacin we refer to De Vroom et al.<sup>18</sup>

### Endpoints

Primary endpoint was the ratio of the mean area-under-the-plasma-concentration versus time curve (AUC) of the febrile and afebrile phase, for both amoxicillin (AUC<sub>0-8</sub>) and ciprofloxacin (AUC<sub>0-12</sub>). The secondary endpoints were the ratios of

the mean maximum plasma concentrations ( $C_{max}$ ) and the difference in probability of target attainment (PTA) of the febrile and afebrile phase. For amoxicillin, target attainment was defined as exceeding the minimum inhibitory concentration (MIC) during more than 50% of a dosing interval of eight hours. MIC's used for this purpose were the EUCAST epidemiological cut-off (ECOFF) values for *Streptococcus pneumonia* (0.06mg/L), *Streptococcus pyogenes* (0.06mg/L) and *Haemophilus influenzae* (2.0mg/L).<sup>19</sup> For ciprofloxacin PTA was defined as achieving an  $AUC_{0-24}/MIC$  ratio  $\geq 125$ , considering ECOFF values of *Escherichia coli* (0.064mg/L) and *Pseudomonas aeruginosa* (0.5mg/L).<sup>19</sup> The  $AUC_{0-24}$  for ciprofloxacin was pragmatically obtained by multiplying the  $AUC_{0-12}$  by 2. Target attainment was deemed sufficient when PTA was  $>90\%$ .<sup>20, 21</sup>

### **Population pharmacokinetic modelling**

Individual  $AUC_{-}$ ,  $C_{max}$  and PTA values of amoxicillin and ciprofloxacin were calculated using a population pharmacokinetic (PPK) model developed with nonlinear mixed-effects modelling (NONMEM) (Version 7.3(ICON Development Solutions, Hanover, MD, USA)). Detailed methodological information on model development is presented in the appendix. In short, first a structural PPK model was developed. Next, a covariate analysis was performed in which patient demographics and pathophysiological factors were tested for their correlation with the identified PK parameters from the structural model, which yielded the final model. Last, the validity and robustness of the model was tested by performing a visual predictive check (VPC) and a bootstrap analysis.

### **Sample size calculation and statistical analysis**

$AUC_{0-8}$  for amoxicillin and  $AUC_{0-12}$  for ciprofloxacin were considered to be equivalent when the ratio of the mean AUCs in the febrile and afebrile phase was contained within the acceptance interval of 80-125%, which was adapted from the bioequivalence criteria.<sup>22</sup> In order to achieve 90% power at a 5% significance level, 13 patients were required per study visit for amoxicillin, assuming a mean  $AUC_{0-\infty}$  of 22.6 mg\*h/L and a standard deviation of 4.9.<sup>23</sup> We aimed to include 15 patients. For ciprofloxacin, 32 patients were required, considering a mean  $AUC_{0-\infty}$  of 11.05 mg\*h/L and a standard deviation of 3.99.<sup>11, 24</sup> Patients who started the study but in whom zero concentration-time measurements were collected in either the febrile or afebrile phase of the illness were considered non-evaluable for the endpoint measurements and were to be replaced by additional patients. PK data of these patients collected in one of both phases were used for the development of the PPK model.

Baseline categorical patient characteristics were summarized by presenting numbers and percentages. Continuous baseline characteristics were summarized by presenting the mean and standard deviation or the median and minimum to maximum ranges, as appropriate.

The ratio of the mean AUC and mean C<sub>max</sub> was obtained by logarithmic transformation of the AUC and C<sub>max</sub> data, followed by a paired T-test and logarithmic back transformation.<sup>22</sup> Differences in PTA were illustrated by descriptive statistics. These statistical analysis were performed in IBM SPSS Statistics for Windows, version 26.0.

## Results

### Patient characteristics

A total of 52 participants were included in the study: 19 receiving amoxicillin, of whom 15 patients completed both study visits, and 33 receiving ciprofloxacin, of whom 29 patients completed both study visits. The intended sample size of 32 patients for ciprofloxacin was not achieved due to slow inclusion resulting from the corona pandemic. The reasons of the patients to discontinue the study were discomfort and possible side effects (n=3); early discharge or transferal to another hospital (n=3); and one patient died due to the underlying febrile illness. In addition, one patient in the ciprofloxacin arm was switched to oral ciprofloxacin by the treating physician before visit 2.

The patient characteristics of the patients that completed both study visits are presented in table 1, the characteristics of all included patients are presented in the Supplementary table S1.

The majority of patients who received amoxicillin were empirically diagnosed with community-acquired pneumonia and of ciprofloxacin with a complicated urinary tract infection or an intra-abdominal infection. The median time between both study visits was 47.3h (range 43.7-185.7h) for amoxicillin and 67.1h (33.8-427.4h) for ciprofloxacin. The wide range was caused by the variety of underlying diseases, causing some patients to be infectious for a prolonged period, e.g., in case of disseminated streptococcal infection or endocarditis, which was diagnosed after the first study visit.

Table 1: Patient characteristics

	amoxicillin (n=15)			ciprofloxacin (n=29)		
<b>Age (years)</b>	67 (21-80)			65 (18-87)		
<b>Gender (m)</b>	12 (80%)			13 (49%)		
<b>Height (cm)</b>	175 (157 - 195)			168 (1.55 – 1.89)		
<b>Weight (kg)</b>	77.9 (53.3-121)			79.9 (45-130)		
<b>BMI</b>	23.8 (18.8-40.9)			27.2 (18.0-39.3)		
<b>Presumed site of infection at admission</b>	11 respiratory tract infection 4 urinary tract infection			18 urinary tract infection 8 Intra-abdominal infection 3 bone/joint infection		
<b>Definitive site of infection</b>	9 respiratory tract infection 4 urinary tract infection 1 gastrointestinal infection 1 disseminated streptococcal infection			16 urinary tract infection 8 Intra-abdominal infection 1 bone/joint infection 3 skin and soft tissue infection 1 endocarditis		
<b>Time between both study visits<sup>a</sup></b>	47.3h (43.7-185.7)			67.1h (33.8-427.4)		
	<b>BL</b>	<b>SV1</b>	<b>SV2</b>	<b>BL</b>	<b>SV1</b>	<b>SV2</b>
<b>Body temperature (°C)</b>	38.9 (38.3 – 40.5)	37.2 (36.6-38.6)	36.7 (36-37.8)	39 (38.3-40)	37.2 (36.1-40.5)	36.7 (0.47)
<b>Antipyretic use</b>	12 (80%)	12 (80%)	8 (53%)	21 (72%)	22 (76%)	18 (62%)
<b>Plasma creatinine (µmol/L)</b>	82 (47-176)	98 (47-176)	84 (40-152)	90 (42-145)	86 (42-145)	75 (41-143)
<b>eGFR (CKD-EPI) (ml/min/1.73m2)</b>	78 (31-131)	78 (31-131)	89 (32-139)	63 (44-129)	65 (44-129)	74 (40-154)
<b>AST (U/L)</b>	30 (16-52)	25 (16-75)	31 (17-159)	27 (12-118)	26 (12-119)	32 (9-119)
<b>ALT (U/L)</b>	19 (11-51)	19 (11-137)	27 (12-96)	23 (10-134)	23 (10-134)	29 (5-140)
<b>GGT (U/L)</b>	40 (13-178)	41 (13-194)	42 (19-269)	38 (16-1267)	39 (16-913)	66 (19-574)
<b>Albumin (g/L)</b>	35 (30-43)	35 (28-43)	33 (25-42)	37 (28-45)	36 (28-45)	34 (20-38)
<b>Bilirubin (µmol/L)</b>	9 (3-29)	9 (3-29)	5 (3-9)	11 (2-555)	11 (2-555)	6 (2-470)

Data are presented as number (%) or median (range).

<sup>a</sup>The wide range was caused by the variety of underlying diseases, causing some patients to be infectious for a prolonged period, e.g., in case of disseminated streptococcal infection or endocarditis. Most SV1 results were the laboratory results from baseline. In case no recent (<24h) results were available, (new) blood samples were obtained for SV1.

Abbreviations: BMI, body mass index; BL, baseline; SV1, study visit 1; SV2, study visit 2; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase

### Population pharmacokinetic analysis

For the PPK analysis the blood samples of all subjects were included, which yielded a total of 121 amoxicillin and 219 ciprofloxacin plasma samples for analysis. Of these, 67 and 115 samples were obtained at study visit 1, of which 53 and 88 samples were obtained during the first four hours after administration, and 54 and 104 samples at study visit 2, of which 43 and 80 samples were obtained during the first four hours after administration. The measured total antibiotic plasma concentrations are presented in figure 1 and 2 for amoxicillin and ciprofloxacin respectively. Less than 2% of samples were below the LLQ, for which we imputed the value of LOQ/2. The total and unbound plasma concentrations of both amoxicillin and ciprofloxacin were strongly correlated, both  $r$ : 0.99, 95%-CI 0.98 – 0.99, indicating linear plasma protein binding. We therefore used total plasma concentrations to build the PPK model.

Detailed information of the PPK model development is presented in the appendix (Supplementary tables S2 and S3). In short, the PK of amoxicillin was best described by a one-compartment model, using logarithmic transformed data with non-linear absorption (Michaelis-Menten model) and an absorption lag time ( $T_{lag}$ ). Interindividual variability (IIV) could be estimated for clearance (CL) and interoccasion variability for maximum absorption rate ( $V_{max}$ ). Multivariate analyses showed that CKD-EPI was significantly associated with CL. The VPC plot (figure 1) showed that the final model was able to predict the range of observed amoxicillin concentrations without bias and was therefore valid to be used for the  $AUC_{0-8}$ ,  $C_{max}$  and PTA calculations.

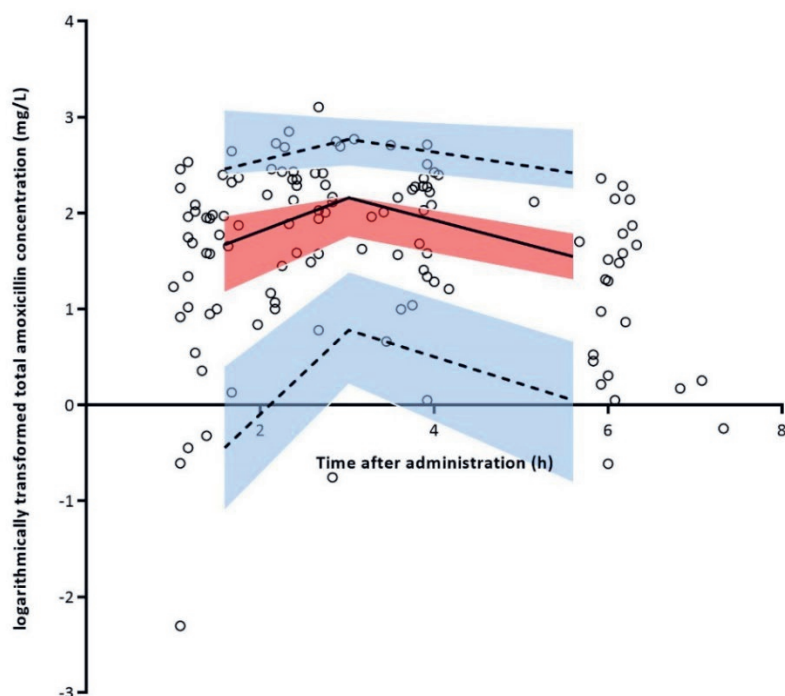
The PK of ciprofloxacin was best described by a one-compartment model, using first order absorption, a  $T_{lag}$  and first order elimination, without logarithmic transformation of the data. IIV could be estimated for CL and volume of distribution ( $V_d$ ). Multivariate analyses showed that body temperature was significantly associated with  $V_d$  and CKD-EPI with CL. The VPC plot (figure 2) showed adequate fit of the final model predicting the vast majority of observed ciprofloxacin concentrations without bias and was therefore valid to be used for the  $AUC_{0-12}$ ,  $C_{max}$  and PTA calculations.

### Amoxicillin and ciprofloxacin AUC and $C_{max}$ equivalence

Results of the calculated AUC and  $C_{max}$  values of visit 1 versus visit 2 are presented in table 2. The before after slope line plots in figure 3A and 3B show the individual changes in AUC from SV1 to SV2 for amoxicillin and ciprofloxacin respectively. The ratios of the mean  $AUC_{0-8}$  of orally administered amoxicillin and

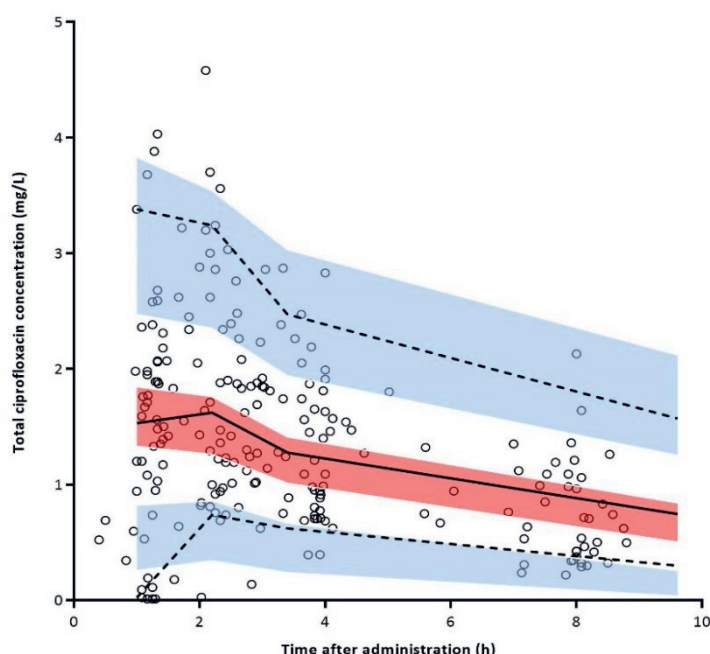
the mean  $AUC_{0-12}$  of orally administered ciprofloxacin were respectively 97% (90%-CI 80-117%) and 112% (90%-CI 108-116%), and therefore equivalent between the febrile and afebrile phase of infection. For the ratios of the mean  $C_{max}$ , this only accounted for ciprofloxacin: 111% (90%-CI 106-117%). Patients who received amoxicillin had a slightly lower mean peak concentration when they were febrile compared to when they were afebrile, with a 90%-CI that did not meet the equivalence criteria (ratio 94%, 90%-CI 71-124%).

**Figure 1. VPC plot amoxicillin**



Visual predictive check (VPC) for logarithmically transformed total amoxicillin concentrations versus time based on 1,000 simulations of the final model. The black open circles are the observed concentrations. The solid line represents the median and the dashed lines the 5<sup>th</sup> and 95<sup>th</sup> percentiles of the observed data. The red shaded area is the 95% confidence interval (CI) of the model-predicted median and the blue shaded areas are the 95% CIs of the model-predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles. The solid and dashed lines run within their respective shaded areas, thereby demonstrating adequate fit of the model.

Figure 2. VPC plot ciprofloxacin



Visual predictive check (VPC) for the total ciprofloxacin concentrations versus time based on 1,000 simulations of the final model. The black open circles are the observed concentrations. The solid line represents the median and the dashed lines the 5<sup>th</sup> and 95<sup>th</sup> percentiles of the observed data. The red shaded area is the 95% confidence interval (CI) of the model-predicted median and the blue shaded areas are the 95% CIs of the model-predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles. In the 5<sup>th</sup> percentile (lower blue shaded area) there is a minor overestimation of observed concentrations with Time after administration <2h and a minor underestimation at the end of the dosing interval. The overestimation was likely to be caused by 3 observed concentrations that were <LOQ and which were imputed with a value of LOQ/2, which the final model cannot predict. Overall, these model misspecifications are small and all other solid and dashed lines run within their respective shaded areas demonstrating sufficient fit of the model.

**Table 2. AUC and Cmax of amoxicillin and ciprofloxacin during the febrile and afebrile phase of infection**

	Febrile	Afebrile	Ratio	90%-CI
<b>amoxicillin</b>				
<b>AUC<sub>0-8</sub> (mg*h/L)</b>	34.79 (1.64)	36.0 (1.59)	97%	80-117%
<b>Cmax (mg/L)</b>	8.86 (1.56)	9.45 (1.42)	94%	71-124%
<b>ciprofloxacin</b>				
<b>AUC<sub>0-12</sub> (mg*h/L)</b>	10.74 (1.46)	9.58 (1.40)	112%	108-116%
<b>Cmax (mg/L)</b>	1.82 (1.34)	1.63 (1.29)	111%	106-117%

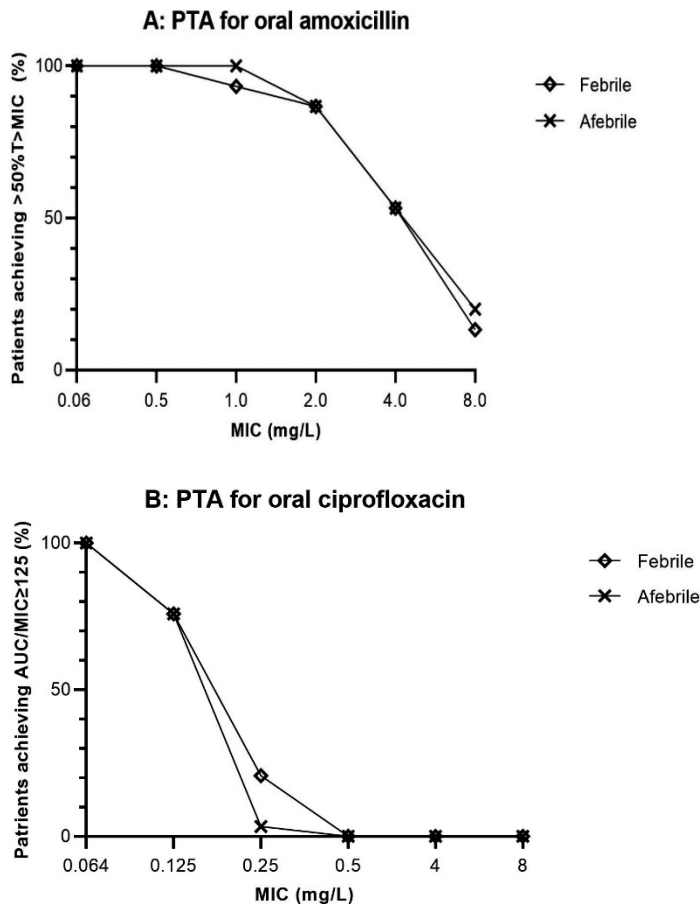
Data are presented as mean with standard deviation unless otherwise indicated. Abbreviations: AUC, area under the plasma concentration time curve; Cmax, maximum plasma concentration; 90%-CI, 90% confidence interval.



### Pharmacokinetic/Pharmacodynamic target attainment

Figures 4A and 4B show the PTA for amoxicillin and ciprofloxacin. For amoxicillin, assuming MIC's of 0.06mg/L and 2.0 mg/L, the PTA was 100% and 86.7% respectively for both the febrile and the afebrile phase. For ciprofloxacin, assuming MIC's of 0.064mg/L and 0.5mg/L, the PTA was respectively 100% and 0% for both the febrile and the afebrile phase.

Figure 4: PTA for oral amoxicillin and ciprofloxacin



A: Probability of target attainment (PTA) for oral amoxicillin 750mg, defined as achieving an amoxicillin plasma concentration above the MIC during half of the dosing interval (50%T>MIC); B PTA for oral ciprofloxacin 500mg, defined as achieving an AUC<sub>0-24</sub>/MIC ratio  $\geq 125$  (calculated AUC<sub>0-12</sub> multiplied by 2).

PTA was calculated for a range of MIC's, for the febrile phase and the afebrile phase separately.

## Discussion

With this study we have shown that the exposure to orally administered amoxicillin and ciprofloxacin is not different during the acute phase of infection as compared to the afebrile phase in hospitalized, non-critically ill patients. We were able to develop a valid PPK model for both amoxicillin and ciprofloxacin, as was shown by the VPC plots and bootstrap results, enabling reliable calculation of individual AUC, Cmax and PTA values. In addition, we have shown that for both phases the probability of pharmacokinetic/pharmacodynamics (PK/PD) target attainment is high for amoxicillin in case of microorganisms with an MIC  $\leq 1.0$  mg/L and for ciprofloxacin in case of microorganisms with an MIC  $\leq 0.064$  mg/L. These results suggest that from a pharmacokinetic point of view reluctance for oral administration of amoxicillin and ciprofloxacin during the acute phase of infection is not necessary.

To our knowledge this is the first population pharmacokinetic study investigating the absorption of and resulting exposure to oral antibiotics in non-critically ill patients.<sup>8</sup> Studies regarding antibiotic exposure have predominantly been performed in critically ill patients using IV antibiotics, as the gastrointestinal tract is usually impaired or not accessible in that population.<sup>4</sup> In our previously reported systematic review, we showed that only three studies truly addressed the absorption of and exposure to oral ciprofloxacin and clarithromycin during the febrile and afebrile phase of infection in non-critically ill patients.<sup>8</sup> Although these studies also concluded that the exposure was not altered during the acute phase of infection, they had a small sample size and used now outdated laboratory and pharmacokinetic methodology to assess the AUC and Cmax, questioning the reliability and generalizability of the results.<sup>9-11</sup>

Our PPK model showed that the absorption of amoxicillin was best described by nonlinear saturable absorption (Michael Menten kinetics), confirming previous studies.<sup>25-27</sup> No significant effect of the acute phase of infection on PK parameters could be found as study visit was tested as a categorical covariate. Although the mean Cmax was numerically slightly lower during the acute phase of infection, the wide 90%-CI (71-124%) indicates that the sample size may have been too small to accurately measure Cmax (non)equivalence. In addition, Cmax is not the PK/PD target in case of amoxicillin. For ciprofloxacin, which followed first order absorption as previously described<sup>28</sup>, higher body temperature was significantly associated with lower Vd. This might lead to increased peak concentrations, as was confirmed by the (non-significant) higher Cmax of ciprofloxacin on study visit 1 (ratio of mean Cmax: 111%). This did not result in a different AUC between both study visits. As both drugs follow first order elimination and no association was identified between

body temperature and CL, indeed no effect of the febrile phase on AUC was expected.

When comparing our PPK modeling results with those of studies performed in critically ill<sup>21, 24, 29, 30</sup> and burn patients<sup>31</sup>, creatinine clearance was likewise associated with CL of both amoxicillin<sup>29, 31</sup> and ciprofloxacin<sup>21, 24, 30</sup>. The IIV of CL was lower in our study population, suggesting that exposure is more predictable in non-critically ill patients, also in the acute phase of infection. Therefore, the acute phase of infection only had a marginal effect on the PK of the investigated antibiotics in non-critically ill patients. This in contrast with critically ill patients, where CL and Vd may differ considerably between patients: decreased and increased CL, and increased Vd are observed due to (extremely) decreased or (extremely) increased renal function, altered fluid balance and organ support.<sup>6</sup>

Based on our results, the recommended oral dosing regimen of amoxicillin 750mg t.i.d. would suffice during the acute phase of most infections for which amoxicillin is the preferred treatment. This is in line with the PK/PD simulation study of de Velde and colleagues performed in healthy volunteers.<sup>25</sup> Most amoxicillin-susceptible microorganism have an MIC <2mg/L and the PTA for amoxicillin was only just below 90% for microorganisms with an MIC of 2mg/L (Figure 3).<sup>19</sup> For ciprofloxacin the PK/PD target was not sufficiently attained for microorganisms with an MIC of >0.064mg/L, also not during the afebrile phase. In previous studies it was already shown that a ciprofloxacin dose of 500mg b.i.d. is often not enough to attain the PK/PD target of  $AUC_{0-24}/MIC > 125$  for bacteria with MIC values >0.125 mg/L, nor for ciprofloxacin 750mg b.i.d. in case of difficult to treat infections such as *Pseudomonas aeruginosa* (MIC=0.5mg/L).<sup>21, 28, 32, 33</sup> These results suggest that if oral treatment is initiated during the acute phase of infection, rapid microbiological test results should be used as a basis for potential dose adjustments to ensure that sufficient bacterial killing can be achieved, or a higher ciprofloxacin starting dose should be considered.<sup>28, 32</sup>

### Strength and limitations

This is the first study investigating population pharmacokinetics during the acute phase of infection in non-critically ill febrile patients, in a group of patients covering a wide range of ages, renal function and infectious diseases. Our results therefore provide new and relevant data applicable to the majority of hospitalized, febrile patients. Furthermore, patients were their own control, which eliminated residual variation between the febrile and afebrile phase. Also, the time of administration and blood sampling were carefully registered. A limitation is that special patient

populations, for example patients with severe renal impairment or neutropenic patients, were excluded. Although it is to be expected that equivalent exposure also accounts for these patients, this was not investigated. Our results can therefore not be automatically extrapolated to these patients. In addition, although the first study visit was performed within the first 24h of initiation of IV antibiotics, the body temperature in most of our patients had already declined, albeit not normalized, at that time. This may have limited the power to identify associations between PK parameters and body temperature. Also, the primary focus of the study was to investigate exposure, for which we investigated single administrations only instead of repeated dosages. Our results on PTA for the investigated antibiotics, especially ciprofloxacin, are therefore lower than those reported after multiple dosing and at steady-state.<sup>28, 32</sup> This is caused by the fact that we were forced to multiply the  $AUC_{0-12}$  of ciprofloxacin by two to estimate  $AUC_{0-24}$  (assuming b.i.d. dosing). Nonetheless, even when presenting a worst-case scenario, our results showed that exposure to ciprofloxacin was sufficient to treat common infections (e.g. *Escherichia coli*). A final limitation is that we focused on the PTA for ciprofloxacin 500mg, instead of 750mg which is used for difficult to treat infections including *Pseudomonas aeruginosa*. However, simulations using the developed PPK model showed that with 750mg ciprofloxacin the PTA to effectively treat *Pseudomonas aeruginosa* (MIC = 0.5mg/L) infections was still insufficient (PTA=0%).

## Conclusion

With this study we have shown that the differences in antibiotic exposure (AUC) between the febrile and afebrile phase of infection is contained within the acceptance interval of 80-125% in hospitalized non-critically ill infectious patients. In addition, the PK/PD target was equally attained during both phases and sufficient to treat common pathogens. Herewith, we have provided a pharmacokinetic base for an IV-to-oral switch within 48h of IV therapy for a large patient population, as our study population was heterogeneous in age, febrile illness and renal function. The next step is to actually shorten the IV treatment duration. Next to increasing patient comfort, an earlier switch may (further) reduce length of hospital stay and healthcare costs.

## Supplementary data

### Methods

#### Population pharmacokinetic model building

##### *Structural Model*

For the structural model, both one- and two compartment models were tested using both logarithmic and untransformed data. The PPK models were parameterized in terms of first order absorption rate constant ( $K_a$ ) or zero order absorption rate constant or nonlinear, Michaelis-Menten, absorption (with parameters maximum absorption rate ( $V_{max}$ ) and amount associated with 50% of  $V_{max}$  ( $K_m$ )), clearance (CL), volume of distribution ( $V_d$ ) and -if applicable- intercompartment clearance ( $Q$ )). Also transit compartment models were tested to describe the absorption phase of amoxicillin and ciprofloxacin. Between-patient (IIV) and interoccasion variability (IOV) were estimated for identified PK parameters using exponential equations. Occasion in this respect was defined as a study visit. Residual variability was modelled with additive or proportional models or a combination of both. Goodness-of-fit was judged by both the goodness-of-fit plots and the precision of the parameter estimates. Goodness-of-fit was created using Pirana and Xpose (version 4.3.2, Niclas Jonsson and Mats Karlsson, Uppsala, Sweden). Whether addition of a parameter to the model statistically significantly improved the fit was determined with the likelihood ratio test. A p-value below 0.05 in a Chi-squared-distribution, corresponding to a decrease of 3.8 units in the objective function value (OFV), was considered statistically significant.

##### *Covariate model*

To explain IIV and IOV, covariates were tested in a two-step approach. In the first step all different covariates were introduced to the structural model separately (univariate analysis) and tested for their statistical significance, improvement of goodness of fit plots and a reduction in estimates for IIV, IOV and/or residual variability. Covariates that were considered included: age, weight, body temperature and CKD-EPI (continuous variables); the presence of fever within 24h of the study visit, sex, presence of gastro-intestinal or intra-abdominal comorbidity and use of cardiovascular drugs and calcium carbonate (binary variables). A p-value of  $<0.05$ , determined with the likelihood ratio test, was considered statistically significant during this step of the analysis. In the second step, all covariates selected during the first step were included in the model, yielding the intermediate model. A backward elimination procedure, followed by a forward addition procedure was subsequently used (multivariate analysis). A covariate was retained during this step of model development if exclusion during the backward

elimination procedure resulted in a statistically significant worsening of the fit and addition during the forward addition procedure resulted in a statistically significant improvement of the fit, again determined with the likelihood ratio test. A p-value  $<0.01$ , corresponding to an increase of 6.63 units in the OFV, was applied for this purpose to correct for the multiple testing phenomenon. This yielded the final model.

#### *Model Robustness and Predictive Performance*

Visual predictive checks (VPC, 1000 simulations) were performed with the final model to analyse the models' capacity to predict the range of observed amoxicillin and ciprofloxacin concentrations. In addition, a bootstrap analysis was performed to test the robustness of the final PPK model, in which the dataset was resampled and fitted to the model 1000 times.

After these evaluation steps of the final model, individual  $C_{max}$ , % $FT > target$  and AUC values were calculated based on the PPK models' empirical Bayes parameter estimates.

## **Results**

### **Population pharmacokinetic analysis**

#### *Amoxicillin*

The PK of amoxicillin was best described by a one-compartment model, using logarithmic transformed data with non-linear Michaelis-Menten absorption and an absorption lag time ( $T_{lag}$ ).

Because all samples were obtained at least 60 minutes after oral amoxicillin administration,  $K_m$  could not be estimated precisely and was therefore fixed to a value of 286, based on data from de Velde and colleagues.<sup>1</sup> IIV could be estimated for CL and IOV could be estimated for  $V_{max}$ . The PPK results of amoxicillin are presented in table 2.

Hundred percent of covariate data was available. After univariate analysis, eGFR and age were statistically significantly associated with CL; eGFR with  $V_d$ ; and body temperature with  $V_{max}$ . After multivariate analysis, the association between eGFR and CL remained, based on the criteria for statistical significance as well as on an improvement of goodness of fit plots. In addition, the estimate for IIV of CL decreased from 72.1 to 27.1%. Given the logarithmic transformation of the data, residual variability was modelled with an additive error model and was estimated to be 0.38 mg/L for the final model.

The VPC plots are presented in figure 1 in the main text. The figure shows that the final model was able to predict the range of observed amoxicillin concentrations without bias, as the simulated 95% confidence intervals (CI) correspond well with the measured concentrations. The bootstrap estimations were similar to the estimates from the final model, indicating the stability of the model. However, the bootstrap analysis showed that the 95% CI of the association between CKD-EPI on CL contained 0, indicating a >5% chance that an association between CKD-EPI and amoxicillin CL was not present (table 2). Since amoxicillin is a predominantly renally cleared drug, making the identified association biologically highly plausible, it was decided to retain this covariate-PK parameter association. A lack of power likely contributed to the observed wide confidence interval.

### *Ciprofloxacin*

The PK of ciprofloxacin was best described by a one-compartment model, using first order elimination and first order absorption and a  $T_{lag}$ , without logarithmic transformation of the data. IIV could be estimated for CL and Vd. PPK results of ciprofloxacin are presented in table 3.

Hundred percent of covariate data was available. After univariate analysis, eGFR, plasma creatinine, age, body temperature and fever were statistically significantly associated with CL; weight, age, body temperature and fever with Vd; weight, age, gender and gastrointestinal comorbidity with  $T_{lag}$ . After multivariate analysis the association between eGFR on CL and body temperature on Vd remained based on the criteria for statistical significance as well as on an improvement of goodness of fit plots. In addition, the IIV of CL and Vd decreased relative to the structural model respectively from 54.4% to 39.6% and from 28.5% to 28.1%, while residual variability decreased from 38% to 37%.

The VPC plots are presented in figure 2 in the main text. The figure shows that the final model was sufficiently able to predict the range of observed ciprofloxacin concentrations without bias, as the simulated 95% CI correspond well with the majority of the measured concentrations. In the 5<sup>th</sup> percentile (lower blue shaded area) there is a minor overestimation of observed concentrations with Time after administration <2h and a minor underestimation at the end of the dosing interval. The overestimation was likely to be caused by three observed concentrations that were below the lower limit of quantification (LOQ) and which were imputed with a value of LOQ/2, which the final model cannot predict. The bootstrap estimations were similar to the estimates from the final model, indicating the robustness of the model.

**Supplementary Table 1: Patient characteristics, all included patients**

	<b>amoxicillin (n=19)</b>			<b>ciprofloxacin (n=33)<sup>a</sup></b>		
<b>Age (years)</b>	68 (21-88)			67 (18-88)		
<b>Gender (m)</b>	15			16		
<b>Height (cm)</b>	174 (157 - 195)			168 (1.55 – 1.89)		
<b>Weight (kg)</b>	77.9 (51.5-121)			79.9 (45-130)		
<b>BMI</b>	23.1 (18.3-40.9)			27.2 (18.0-39.3)		
<b>Presumed site of infection at admission</b>	15 respiratory tract infections 4 urinary tract infections			19 urinary tract infections 1 respiratory tract infections 10 intra-abdominal infection 3 bone/joint infection		
	<b>BL (n=19)</b>	<b>SV1 (n=19)</b>	<b>SV2 (n=15)</b>	<b>BL (n=33)</b>	<b>SV1 (n=33)</b>	<b>SV2 (n=29)</b>
<b>Body temperature</b>	38.9 (38.3–40.5)	37.2 (36.1-38.6)	36.7 (36-37.8)	39 (38.3-40)	37.2 (35.6-40.5)	36.7 (0.47)
<b>Antipyretic use</b>	15 (78.9%)	15 (78.9%)	8 (53%)	22 (66.7%)	23 (69.7%)	18 (62%)
<b>Plasma creatinine (μmol/L)</b>	91 (47-176)	91 (47-176)	84 (40-152)	90 (42-166)	86 (42-191)	75 (41-143)
<b>eGFR (CKD-EPI) (ml/min/1.73m<sup>2</sup>)</b>	72 (31-131)	78 (31-131)	89 (32-139)	63 (36-129)	65 (31-129)	74 (40-154)
<b>AST (U/L)</b>	30 (16-52)	28 (16-75)	31 (17-159)	26 (12-118)	26 (12-119)	32 (9-119)
<b>ALT (U/L)</b>	19 (9-51)	19 (9-137)	27 (12-96)	23 (9-134)	22.5 (8-134)	29 (5-140)
<b>GGT (U/L)</b>	40 (13-178)	39 (13-194)	42 (19-269)	39 (16-1267)	41.5 (16-913)	66 (19-574)
<b>Albumin (g/L)</b>	36.5 (30-44)	36.5 (28-44)	33 (25-42)	36.5 (28-45)	35.5 (28-45)	34 (20-38)
<b>Bilirubin (μmol/L)</b>	9 (3-29)	9 (3-29)	5 (3-9)	11 (2-555)	11 (2-555)	6 (2-470)

Data are presented as number (%) or median (range).

Abbreviations: BMI, body mass index; BL, baseline; SV1, study visit 1; SV2, study visit 2; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transferase

Supplementary Table 2. Parameter estimates and bootstrap analysis of amoxicillin

	Structural model		Final model		Bootstrap of final model	
Fixed effects	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	95% CI
Vmax (mg/h)	1050	7.0	963	13.2	936	564-1731
Km (mg)	286 fixed		286 fixed		286 fixed	
Tlag (h)	0.93	5.0	0.92	5.5	0.91	0.65-1.01
V (L)	55.9	9.6	53.8	11.2	53.8	42.0-69.4
CL (L/h)	14.6	17.5	15.0	11.7	14.9	11.1-19.4
<b>Between-subject variability (%CV)</b>						
CL	72.1	18.4	27.1	36.8	26.4	8.8-89.7
<b>Interoccasion variability (%CV)</b>						
Vmax	146	20.9	143	20.4	132	61.2-294
<b>Residual Variability</b>						
Additive error (mg/L)	0.37	11.3	0.38	13.2	0.37	0.26 – 0.45
<b>Covariates</b>						
eGFR (CKD-EPI) (ml/min/1.73m <sup>2</sup> ) on CL			1.28	33.9	1.24	-0.37-2.06

Abbreviations: Vmax, maximal absorption rate; Km, amount corresponding to 50% Vmax; Tlag, absorption lag time; V, volume of distribution; CL, clearance; CV, coefficient of variation ( $\sqrt{\exp(\omega^2)-1}$ ); eGFR, estimated glomerular filtration rate; Temp, temperature; RSE, relative standard error; 95% CI, 95% confidence interval

Shrinkage in the final model for between-subject variability in CL was 28% and for inter-occasion variability in Vmax 0.1% for occasion (=study visit) 1 and 29% for occasion 2. Shrinkage for residual variability was 17%.

Individual CL was estimated as:  $CL = 15 * (CKD-EPI/72)^{1.28} * \exp(\eta)$ , where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.071

Individual Vmax was estimated as:  $Vmax = 963 * \exp(\kappa)$ , where  $\kappa$  is the interoccasion random effect with population mean 0 and variance 1.11.

**Supplementary Table 3. Parameter estimates and bootstrap analysis of ciprofloxacin**

	Structural model		Final model		Bootstrap of final model	
Fixed effects	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	95% CI
Ka (mg/h)	2.88	25	2.89	23.2	3.11	1.97 – 32.4
Tlag (h)	0.39	2	0.39	1.6	0.39	0.37 - 0.82
V (L)	243	7	245	7.4	245	213 - 284
CL (L/h)	38.3	9	36.0	7.8	35.9	29.4 - 42.4
<b>Between-subject variability (%CV)</b>						
V	28.5	20	28.1	19	27.3	11.7 - 38.7
CL	54.4	12	39.6	14.2	38.0	16.0 – 51.7
<b>Residual Variability</b>						
Proportional error (%)	38	9	37	9.7	37	30 – 45
<b>Covariates</b>						
eGFR (CKD-EPI) (ml/min/1.73m <sup>2</sup> ) on CL			0.93	24.1	0.94	0.49 - 1.41
Temp on V			-6.41	40.9	-6.33	-11.3 - - 2.75

Abbreviations: Ka, absorption rate constant; Tlag, absorption lag time; V, volume of distribution; CL, clearance; CV, coefficient of variation ( $\sqrt{\exp(\omega^2 - 1)}$ ); eGFR, estimated glomerular filtration rate; Temp, body temperature; RSE, relative standard error; 95% CI, 95% confidence interval

Shrinkage in the final model for between-subject variability in V and CL was 19% and 19% respectively. Shrinkage for residual variability was 8.2%.

Individual CL was estimated as:  $CL = 36 * (CKD-EPI/70)^{0.93} * \exp(\eta)$ , where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.15

Individual V was estimated as:  $V = 245 * (Temp/37)^{-6.41} * \exp(\eta)$ , where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.076.

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## CHAPTER 7:

# Population pharmacokinetic/pharmacodynamic target attainment of ceftriaxone 2 grams once daily in non-critically ill hospitalized adult patients

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## Abstract

**Background:** Pharmacokinetic/pharmacodynamic (PK/PD) target attainment of ceftriaxone is compromised in patients with severe infection due to infection-induced pathophysiological changes. This has been demonstrated in ICU patients and in non-ICU hospitalized patients in sub-Saharan Africa. Insufficient data is available on whether this also accounts for non-ICU patients in a high-income country setting. Therefore, we do not know whether they are adequately treated with the currently recommended dosing regimen of 2g q24h.

**Methods:** We performed a multicentre population pharmacokinetic (PPK) study in hospitalized non-ICU adult patients empirically treated with intravenous ceftriaxone, to assess the probability of target attainment (PTA) of 2g q24h. During both the acute phase of infection (i.e. first 24h of treatment) and during convalescence, a maximum of four random blood samples were obtained per patient for ceftriaxone total ( $CEF_T$ ) and unbound ( $CEF_U$ ) concentration measurements. PTA was calculated by PPK modelling using non-linear mixed effect analysis and was defined as the percentage of patients of which the  $CEF_U$  exceeded the minimum inhibitory concentration (MIC) during more than 50% of the first dosing interval of 24 hours (50%  $fT > MIC$ ). Monte Carlo simulations were performed to determine PTA for different estimated glomerular filtration rates (eGFR; CKD-EPI) and MIC's. PTA >90% was considered adequate.

**Results:** Forty-one patients provided 252  $CEF_T$  and 253  $CEF_U$  concentrations. The median eGFR was 65ml/min/1.73m<sup>2</sup> (5<sup>th</sup>-95<sup>th</sup> percentile 36-122). With the recommended dose of 2g q24h, PTA >90% was achieved for bacteria with an MIC ≤2mg/L. Simulations showed that PTA was insufficient for an MIC of 4mg/L in case the eGFR was 122ml/min/1.73m<sup>2</sup> (PTA 56.9%) and for an MIC of 8mg/L regardless of eGFR.

**Conclusion:** The PTA of 2g q24h ceftriaxone dosing is adequate for common pathogens during the acute phase of infection.

## Introduction

Ceftriaxone is used as empiric antibiotic treatment in hospitalized patients for a variety of conditions.<sup>1, 2</sup> Both national and international guidelines recommend an empiric dosing regimen of 2 grams per 24 hours (2g q24h).<sup>3, 4</sup> Ceftriaxone has time-dependent bacterial killing activity, and its activity is thus dependent on the duration of time the unbound concentration exceeds the MIC (%fT>MIC). Its pharmacokinetic properties – being hydrophilic, and renally cleared<sup>(5)</sup> – however compromise the exposure to ceftriaxone during the acute phase of infection.<sup>(6-8)</sup> In ICU patients it was convincingly demonstrated that acute infection-induced pathophysiological changes such as increased or Augmented Renal Clearance (ARC) and increased volume of distribution decreased ceftriaxone systemic exposure, thereby lowering the probability of pharmacokinetic/pharmacodynamic (PK/PD) target attainment (PTA).<sup>7, 9-12</sup>

Bos and colleagues also reported underexposure to ceftriaxone 2g q24h in severely ill, non-ICU hospitalized patients in sub-Saharan Africa, possibly caused by similar pharmacokinetic (PK) changes.<sup>13</sup> Whether this also accounts for non-ICU, hospitalized patients in a high-income country setting is unknown, as studies in this population are lacking, while severity of illness, underlying diseases, as well as nutritional- and hydration status may differ considerably from those of patients in Africa. Consequently, we do not know whether non-ICU, hospitalized patients in a high-income country setting are adequately treated with the currently recommended dosing regimen.

The aim of this study was therefore to investigate the PTA for ceftriaxone during the acute phase of infection in non-ICU, hospitalized patients in a high-income country setting treated with 2g q24h.

## Materials and Methods

### Study design and setting

This was a prospective observational population pharmacokinetic (PPK) sub-study of the EXPO-AB study. The EXPO-AB study was a multicentre prospective intervention study, investigating the oral absorption of and systemic exposure to two single doses of amoxicillin or ciprofloxacin administered in addition to IV antibiotic treatment - during the febrile phase of infection and during convalescence, respectively, - in non-critically ill hospitalized patients.<sup>14</sup> From the EXPO-AB study population, we identified patients empirically treated with IV

ceftriaxone. Study patients were recruited from August 2019 to December 2021 on the general wards of three hospitals in the Netherlands: OLVG West, Amsterdam, a large non-academic teaching hospital; and the Amsterdam University Medical Centres, locations VUmc and AMC, two large academic teaching hospitals. Ethical approval for the EXPO-AB study was obtained from the Medical Ethical Committee of the Amsterdam University Medical Centre, location AMC. All patients provided written informed consent to use plasma samples obtained for the EXPO-AB study for additional research. The trial is registered at the Netherlands Trialregister (NTR): NL7782.

### **Study procedures and data collection**

EXPO-AB study patients were eligible for inclusion in the current sub-study if they were treated with IV ceftriaxone 2g q24h as part of standard patient care. Other inclusion criteria as defined in the EXPO-AB study were age  $\geq 18$  years, and presence of an acute febrile illness, defined as a body temperature of  $\geq 38.3$  degrees Celsius measured at least once during admission. Patients were excluded when they had to be admitted to an ICU, had an estimated glomerular filtration rate (eGFR)  $< 30$  ml/min using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation<sup>15</sup>, had liver cirrhosis, active hepatitis or liver failure, when they were neutropenic (neutrophil counts  $< 1000/\mu\text{l}$ ), were treated with chemotherapy within 28 days prior to the study, were pregnant at the time of inclusion or when they had a history of alcohol or drug abuse.

The EXPO-AB study consisted of two visits: visit 1 ("Febrile phase"), when patients were febrile (body temperature  $\geq 38.3^\circ\text{C}$  measured at least once during admission) and were within the first 24h of IV ceftriaxone treatment; and visit 2 ("Afebrile phase"), when patients were recovering from their infectious illness and were afebrile (temperature  $< 38.3^\circ\text{C}$ ) for at least 24 hours, or when they qualified for an IV-to-oral switch<sup>16</sup> according to their treating physician. At both study visits the subjects received a single oral dose of amoxicillin 750mg or ciprofloxacin 500mg for the purpose of the main study. At both visits a maximum of four blood samples were obtained according to the protocol of the EXPO-AB study<sup>14</sup>, in which ceftriaxone could be measured besides amoxicillin and ciprofloxacin. This resulted in complete random sampling for the current ceftriaxone PPK sub-study. The timing, dose and infusion rate of all ceftriaxone administrations and the timing of blood sample collections were documented carefully.

Demographic and clinical data, which included age, gender, weight, length, BMI, presence of fever within 24h of study visit, and body temperature were assessed on both study visits by the coordinating investigator, and plasma creatinine,

albumin, and bilirubin were also measured on both visits. The GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>15</sup>

### Sample handling and quantification

Blood samples were obtained in heparinized tubes either via an intravenous catheter or by direct venepuncture and transferred to the laboratory of the Department of Hospital Pharmacy & Clinical Pharmacology of the Amsterdam UMC or to the Clinical Chemistry Laboratory of the OLVG on dry ice, where they were directly centrifuged and stored at -80°C until analysis. Unbound (CEFu) and total (CEFT) ceftriaxone plasma concentrations were analysed using a validated LC-MS/MS method in the laboratory of the Amsterdam UMC. The lower limit of quantification (LLQ) was 0.1 mg/l with an accuracy of 117.5% and a within- and between-assay variability of 4,7% and 12,7%. The higher limit of quantification (HLQ) was 50 mg/l with an accuracy of 100.4% and a within- and between-assay variability of 2,7% and 9,4%.

### Endpoints

The primary endpoint was target attainment during the acute phase of infection, defined as a CEFu that exceeded the minimum inhibitory concentration (MIC) during more than 50% (i.e. >12h) of the first 24 hours of IV ceftriaxone treatment (50% fT>MIC). This parameter was subsequently used to calculate the probability of target attainment (PTA) during the acute phase of infection, being the percentage of patients that attained 50% fT>MIC during the first 24 hours of IV ceftriaxone treatment. A PTA of 90% following the 2g q24h dosing regimen was considered sufficient.<sup>17</sup> The secondary endpoint was target attainment during the acute phase of infection defined as 95% fT>MIC during the first 24 h of IV ceftriaxone treatment. A percentage of 95% was chosen over 100% as the latter would be impossible to attain given the infusion rate of 30 minutes of the first administration. PTA was also calculated with this secondary endpoint. MIC's used to calculate target attainment were the clinical breakpoints as provided by EUCAST for susceptibility to ceftriaxone of commonly encountered causative pathogens: *Streptococcus pneumonia* (0,5 mg/L), *Enterobacterales* (1 mg/L) and *Staphylococcus aureus* (8 mg/L).<sup>3</sup>

### **Population pharmacokinetic model development**

A population PK (PPK) model was developed based on measured  $CEF_U$  and  $CEF_T$  plasma concentrations from samples collected during both study visits. Nonlinear mixed-effects modelling (NONMEM) (Version 7.3, ICON Development Solutions, Hanover, MD, USA) was used for model development. The First Order Conditional Estimation method with interaction was used throughout the data analysis.

#### *Structural Model*

For the structural model, both one- and two compartment models were tested with either logarithmic or untransformed data to describe the unbound ceftriaxone ( $CEF_U$ ) data, together with both linear and nonlinear protein binding models for description of total ceftriaxone ( $CEF_T$ ) data as described earlier.<sup>13</sup> Ceftriaxone observed concentrations in mg/L were converted to mmol using a molar mass of 554.6 g/mol.<sup>18</sup> Estimated PK parameters were clearance (Cl) of  $CEF_U$ , volume of distribution (V) of  $CEF_U$ , the maximum binding capacity (Bmax) of  $CEF_U$ , and the  $CEF_U$  concentration at which albumin binding is half maximal (Km). Between-patient (BPV) and inter-occasion variability (IOV) were estimated for identified PK parameters using exponential equations. Occasion in this respect was defined as a study visit. Residual variability was modelled with additive or proportional error models or a combination of both. Goodness-of-fit was judged by both the goodness-of-fit plots and the precision of the parameter estimates. Goodness-of-fit plots were created using Pirana and Xpose (version 4.3.2, Niclas Jonsson and Mats Karlsson, Uppsala, Sweden). Whether addition of a parameter to the model statistically significantly improved the fit was determined with the likelihood ratio test. A p-value <0.05 in a Chi-squared-distribution was considered statistically significant, corresponding to a drop in objective function (OFV) of 3.8 with one degree of freedom.

#### *Covariate model*

To explain BPV and IOV, covariates were tested in a two-step approach. In the first step all different covariates were introduced to the structural model separately and tested for their statistical significance, improvement of the fit and the extent of BPV and/or IOV that was explained by the introduced association. In addition, the identified PK parameter-covariate association needed to be biologically plausible. Covariates that were considered were: age, weight, body temperature at study visit, eGFR, bilirubin and albumin plasma concentration (continuous variables); the presence of fever within 24h of the study visit, study visit itself and sex (categorical variables). A p-value of <0.05, determined with the likelihood ratio test, was considered statistically significant during this step of the analysis. Observed concentrations of albumin in g/L were converted to mmol/L using a molar mass of

69,000 g/mol for albumin. Observed concentrations of bilirubin in  $\mu\text{mol/L}$  were also converted to  $\text{mmol/L}$ .

In the second step, all covariates selected during the first step were included in the model, yielding the intermediate model. A backward elimination procedure (multivariate analysis), followed by a forward addition procedure was subsequently used to develop the final model. A covariate was retained in the model if exclusion during the backward elimination procedure resulted in a statistically significant worsening of the fit and if addition during the forward inclusion procedure resulted in a statistically significant improvement of the fit, again determined with the likelihood ratio test. A p-value  $<0.01$  was applied for this purpose to correct for the multiple testing phenomenon, corresponding to a change in OFV of 6.63 with one degree of freedom. This yielded the final model.

For some covariates data were missing, defined as no value available within 24 hours before or after sample collection. If  $<10\%$  of data for a covariate were missing, missing values were imputed with the median value of the concerning patient or with the median value of the population if all data for that covariate were missing for the concerning patient. If  $\geq 10\%$  of data for a covariate were missing, concentration-time data from the concerning patient were ignored during estimation of the PK parameter-covariate association as described earlier, yielding estimation of a missing data-parameter for the concerning association(19), which has no further pharmacokinetic meaning.

#### *Model Robustness and Predictive Performance*

Prediction corrected visual predictive checks (VPC) were performed with the final model, stratified for  $\text{CEU}$  and  $\text{CEF}_T$  (1000 simulations each) to analyse the model's capacity to predict the range of observed ceftriaxone concentrations. In addition, a bootstrap analysis was performed to test the robustness of the final PPK model, in which the dataset was resampled and fitted to the model 1000 times. After these evaluation steps of the final model, attainment of the endpoints 50%  $\text{fT} > \text{MIC}$  and 95%  $\text{fT} > \text{MIC}$  during the first 24h of ceftriaxone IV treatment was assessed for every patient. For this purpose individual  $\text{CEU}$  plasma concentration-time values were estimated with the empirical Bayes estimates of the PK parameters of the final model to obtain the time within the first 24 h of treatment that the  $\text{CEU}$  concentration was above a certain MIC. If the time above that MIC within the first 24h of treatment exceeded 12h or 22.8h, then the 50% $\text{fT} > \text{MIC}$  respectively 95% $\text{fT} > \text{MIC}$  was attained.

### Monte Carlo simulations

Monte Carlo simulations were performed with the final and internally validated model to predict the PTA for a ceftriaxone 2g q24h dosing regimen administered to patients in three renal function categories: the study population's observed median CKD-EPI-estimated GFR and its 5<sup>th</sup> -95<sup>th</sup> percentile. For each eGFR-category, 1000 patients were simulated. Based on the simulation results, the PTA for 50%fT>MIC was calculated for various MIC's during the first 24h of IV ceftriaxone treatment.

### Statistical analysis

Baseline categorical patient characteristics were summarized by presenting numbers and percentages. Continuous baseline characteristics were summarized by presenting the mean and standard deviation or the median and minimum to maximum ranges, as appropriate. These analyses were performed using R (Version 4.0.3).

## Results

### Patient characteristics

A total of 41 patients were included in the study. Blood samples could be obtained on both study visits from thirty-three patients. Four patients were already discharged before the second study visit and the other four patients were no longer treated with ceftriaxone on the second study visit. Clinical and demographic characteristics are shown in table 1. The majority of patients were presumptively diagnosed with a respiratory tract infection, an urinary tract infection or an intra-abdominal infection. The median eGFR at baseline was 65ml/min/1.73m<sup>2</sup> (5<sup>th</sup> -95<sup>th</sup> percentile 36-122ml/min/1.73m<sup>2</sup>). All patients received ceftriaxone 2g with an infusion rate of 30 minutes.

### Population pharmacokinetic analysis

The blood samples that were obtained on both study visits yielded a total of 253 ceftriaxone plasma samples that were used for the PPK analysis: 253 CEF<sub>U</sub> (concentration range 0.448 mg/L to 119 mg/L) and 252 CEF<sub>T</sub> (range 3.25 mg/L to 232 mg/L). The median unbound fraction was 16% (range 7.3% - 51.3%). There were seven outliers with an unbound fraction over 65%, caused by one patient who was diagnosed with cholangitis (without signs of liver cirrhosis, active hepatitis or liver failure) and severe hyperbilirubinemia (470-555 µmol/L). Figure 1A and 1B

show  $CEF_U$  plotted against  $CEF_T$  and the unbound fraction plotted against  $CEF_T$ , respectively, to demonstrate nonlinearity of protein binding.

**Table 1 Baseline characteristics of the study population (N=41)**

<b>Age (years)</b>	67 (18-88)		
<b>Female</b>	16 (39%)		
<b>Weight (kg)</b>	78.8 (18.8)		
<b>BMI (kg/m<sup>2</sup>)</b>	26.3 (18-40.9)		
<b>Presumed site of infection at admission</b>	12 respiratory tract infection 20 urinary tract infection 7 intra-abdominal infection 2 bone/joint infection		
<b>Time between study visits (h)</b>	67.0 (33.8-185.7)		
	<b>Baseline (n=41)</b>	<b>SV1 (n=41)</b>	<b>SV2 (n=33)</b>
<b>Body temperature (°C)</b>	38.9 (38.3- 40.5)	37.3 (35.6-40.5)	36.85 (35.9-37.8)
<b>Plasma creatinine (μmol/L)</b>	90 (45-176)	87 (45-191)	80 (40-152)
<b>eGFR (CKD-EPI) (ml/min/1.73m<sup>2</sup>)</b>	64 (31-132)	65 (31-132)	86 (32-154)
<b>Albumin (g/L)</b>	36 (28-45)	35 (28-45)	33 (25-45)
<b>Bilirubin (μmol/L)</b>	10 (2-555)	10.5 (2-555)	5.5 (2-470)

Data are presented as number (%), mean (SD) or median (range)

Abbreviations: BMI, body mass index; BL, baseline; SV1, study visit 1; SV2, study visit 2; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration

### *Structural model*

The PK of ceftriaxone was best described by an one-compartment model with non-linear protein binding, without logarithmic transformation of the data. BPV could be estimated for  $CEF_U$  CI and V and Bmax. In addition, IOV could be estimated for  $CEF_U$  CI and Bmax. The PPK results of the structural ceftriaxone model are presented in table 2.

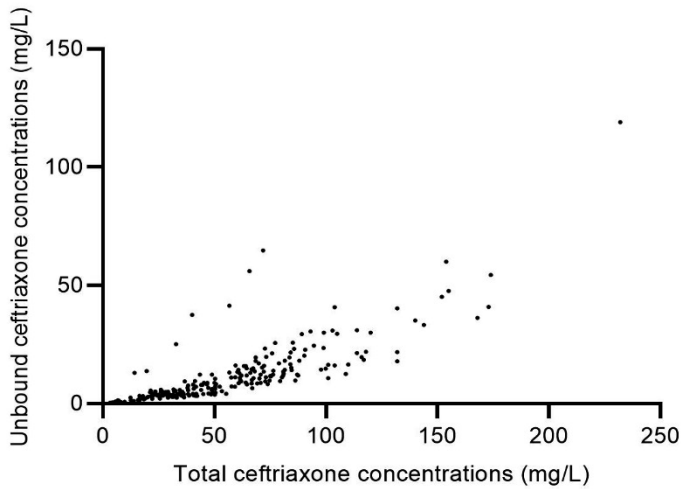
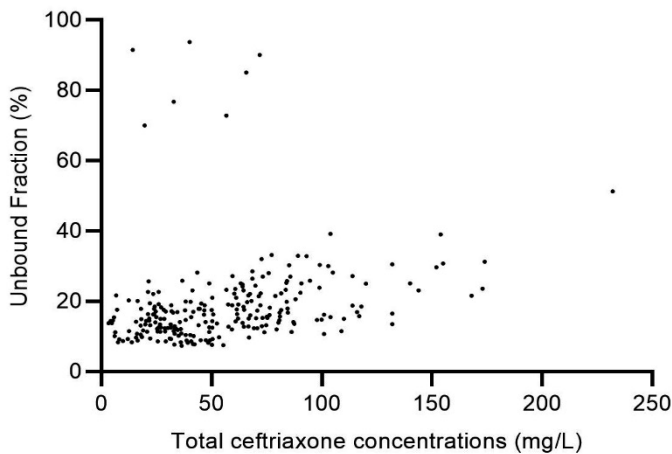
### *Covariate model*

The albumin concentrations of six patients were missing on either the first or second study visit, which accounted for <10% of the albumin data. The missing

data was therefore imputed with the median albumin concentration of the concerning patient measured during the study period. For bilirubin, 22.9% of data was missing. Therefore, a missing data-parameter was estimated. For all other covariates all data was available. After univariate analysis, eGFR (CKD-EPI), age and body temperature were statistically significant associated with CEF<sub>U</sub> CI; bilirubin and fever with CEF<sub>U</sub> V; and albumin and bilirubin with B<sub>max</sub> and K<sub>m</sub>. After multivariate analysis, the association between eGFR (CKD-EPI) and CEF<sub>U</sub> CI remained, explaining 27.8% of BPV in CEF<sub>U</sub> CI. Also the associations between albumin and B<sub>max</sub> and between bilirubin and B<sub>max</sub> remained, explaining 79.5% of BPV in B<sub>max</sub>. As a reflection of the latter two associations, the unbound fraction vs albumin and bilirubin is presented in figure 2A and figure 2B respectively. Residual variability was modelled with a proportional error model and was estimated to be 13.8% (CEF<sub>U</sub>) and 13.0% (CEF<sub>T</sub>) for the final model.

#### *Model robustness and predictive performance*

The goodness of fit plots are presented in figure 3 and the VPC plots are presented in figure 4A and 4B. The figures show adequate goodness-of-fit and that the final model was able to predict the range of the observed CEF<sub>U</sub> and CEF<sub>T</sub> concentrations without bias, as the simulated 95% confidence intervals in figure 4 correspond well with the measured concentrations. The bootstrap estimations were similar to the estimates from the final model, indicating the robustness of the final model (table 2).

**Figure 1A: ceftriaxone unbound concentration versus total ceftriaxone concentration****Figure 1B: ceftriaxone unbound fraction versus total ceftriaxone concentration**

A: covariate relationship between the unbound fraction of ceftriaxone and albumin. The unbound fraction non-linearly increases with a decreasing albumin concentration. B: covariate relationship between the unbound fraction of ceftriaxone and bilirubin. The unbound fraction non-linearly increases with an increasing bilirubin concentration. The seven outliers with an unbound fraction over 65% belong to one patient diagnosed with cholangitis with severe hyperbilirubinemia (470-555  $\mu\text{mol/L}$ ).

**Table 2. Population Pharmacokinetic parameter estimates and bootstrap analysis of ceftriaxone**

	Structural		Final		Bootstrap	
	<i>Estimate</i>	<i>RSE (%)</i>	<i>Estimate</i>	<i>RSE (%)</i>	<i>Estimate</i>	<i>95% CI</i>
<b>Fixed effects</b>						
CEF <sub>U</sub> Cl (L/h)	7.64	8.1	7.19	7.5	7.21	6.25 – 8.22
CEF <sub>U</sub> Vd (L)	85.1	11.1	86.5	12.3	85.75	70.65 – 106.87
Bmax (mmol/L)	0.228	7.9	0.275	8.6	0.271	0.231 – 0.333
Km (mmol/L)	0.0284	9.2	0.0289	9.6	0.029	0.024 – 0.036
<b>Between-patient variability (%CV)</b>						
CEF <sub>U</sub> Cl	50.5	12.1	42.2	10.8	41.6	30.8 – 51.8
CEF <sub>U</sub> Vd	66.6	15.8	67.9	14.2	65.8	42.3 – 89.8
Bmax	40.4	39.7	18.2	29.0	16.8	5.3 – 28.3
Correlation Cl-V	0.79	28.9	0.93	25.1	0.92	0.90 – 1.0
<b>Inter-occasion variability (%CV)</b>						
CEF <sub>U</sub> Cl	25.2	23.1	22.8	16.5	22.5	14.5-32.1
Bmax	12.9	31.9	15.1	29.4	14.4	5.0 – 28.3
<b>Residual variability (%)</b>						
Proportional error CEF <sub>U</sub>	13.8	17.0	13.8	16.7	13.4	9.5 – 17.6
Proportional error CEF <sub>T</sub>	13.0	19.4	13.0	18.9	12.6	9.0 – 17.1
<b>Covariate effects</b>						
eGFR (CKD-EPI) on CEF <sub>U</sub> Cl	-	-	0.746	13.0	0.73	0.55 -0.95
Albumin on Bmax	-	-	1.38	20.5	1.31	0.69 – 1.88
Bilirubin on Bmax	-	-	-0.24	35.7	-0.23	-0.38 – -0.057
Parameter when bilirubin is missing <sup>a</sup>	-	-	0.980	4.7	0.990	0.89 -1.08

Parameter estimates with relative standard error (RSE) or 95% confidence interval (95% CI).

For model-building purposes, observed concentrations of  $CE_{U_i}$  and  $CE_{T_i}$  were converted from mg/L into mmol/L by dividing observed concentrations by the molar mass of ceftriaxone of 554.6 g/mol and observed concentrations of albumin were converted from g/L into mmol/L by the molar mass of albumin of 69,000 g/mol. Observed concentrations of bilirubin were converted from  $\mu\text{mol/L}$  to mmol/L. <sup>a</sup>This missing covariate data parameter was incorporated since 22.9% of bilirubin data was missing. Individual PK parameter were estimated by the final model as follows:

$$- CE_{U_i} Cl = 7.19 * (CKD-EPI/72)^{0.746} * \exp^{\eta+\kappa}$$

where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.164 and where  $\kappa$  is the interoccasion random effect with population mean 0 and variance 0.051.

$$- CE_{U_i} Vd = 86.5 * \exp^{\eta}$$

where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.379.

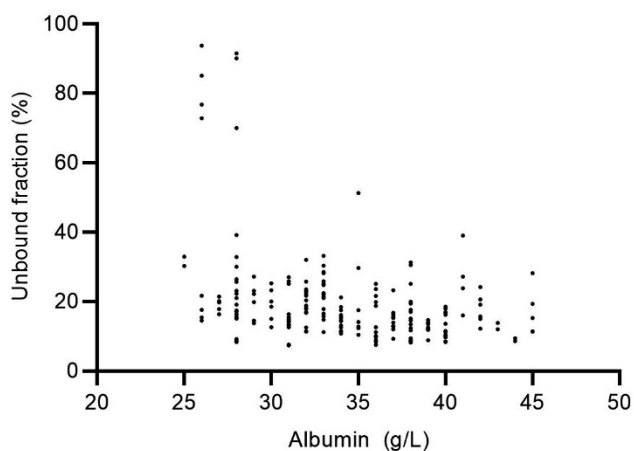
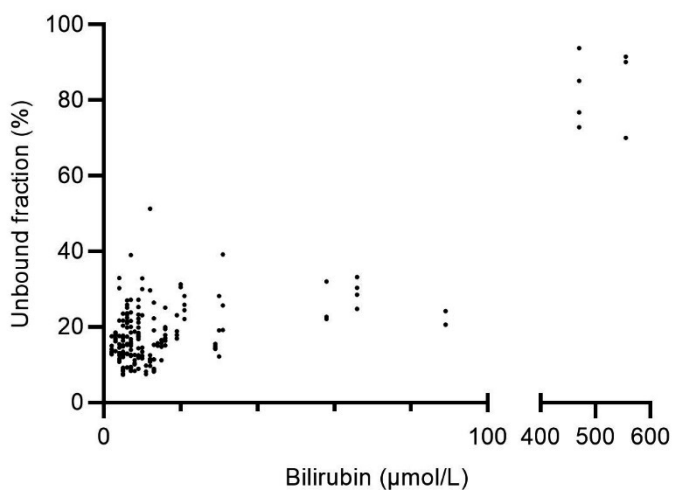
$$- Bmax = 0.275 * (Bilirubin/0.006)^{(-0.240*MISS)} * 0.980^{(1-MISS)} * (Albumin/0.52)^{1.38} * \exp^{\eta+\kappa}$$

where  $\eta$  is the interindividual random effect with population mean 0 and variance 0.0326 and where  $\kappa$  is the interoccasion random effect with population mean 0 and variance 0.023. MISS is an indicator variable that is 0 when bilirubin covariate data is missing and 1 when bilirubin covariate data is present.

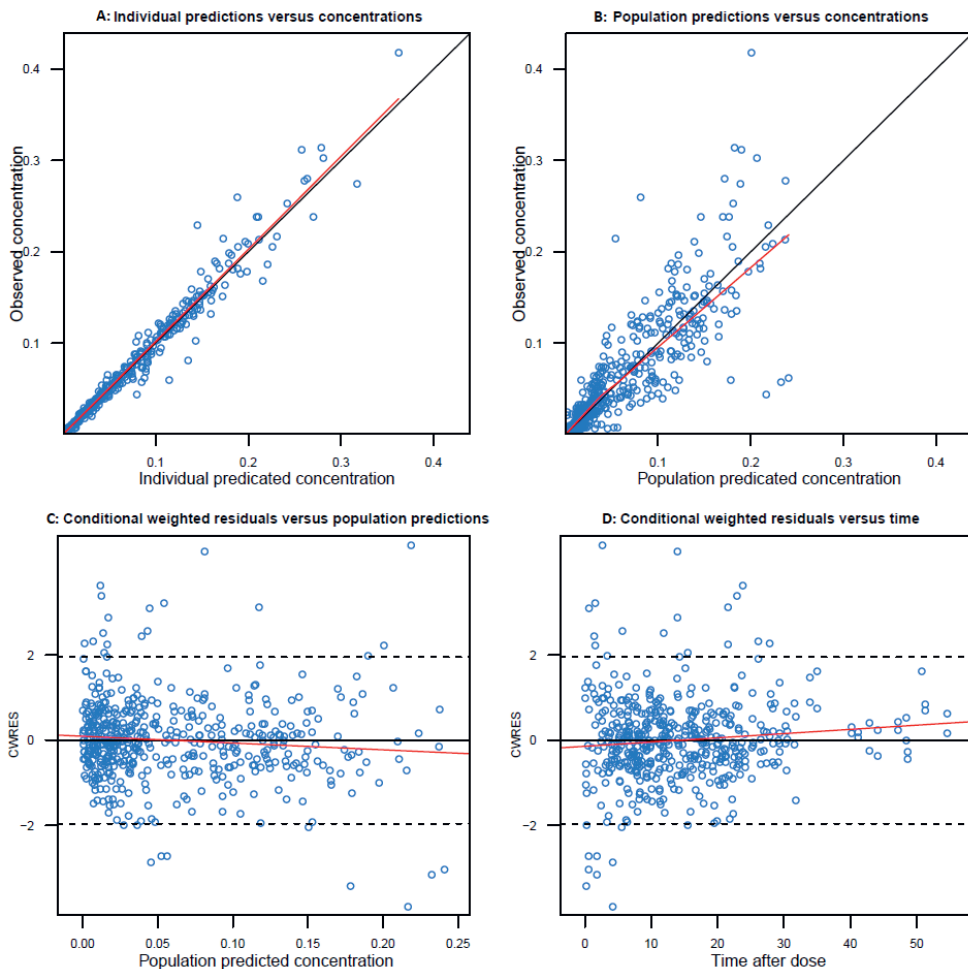
$CE_{T_i}$  was estimated by the final model as  $CE_{U_i} + ((CE_{U_i} * Bmax) / (CE_{U_i} + Km))$ .

Abbreviations:  $CE_{U_i}$ , unbound concentration ceftriaxone;  $CE_{T_i}$ , total concentration ceftriaxone; Bmax; maximum albumin binding capacity of ceftriaxone; Km,  $CE_{U_i}$  concentration at which albumin binding is half maximal; Cl, clearance; V, Volume of distribution; CV, coefficient of variation, eGFR (CKD-EPI), glomerular filtration rate estimated using the CKD-EPI equation.

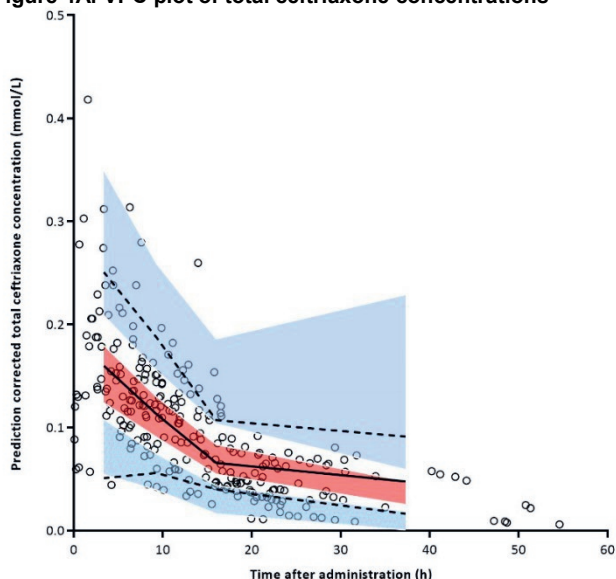
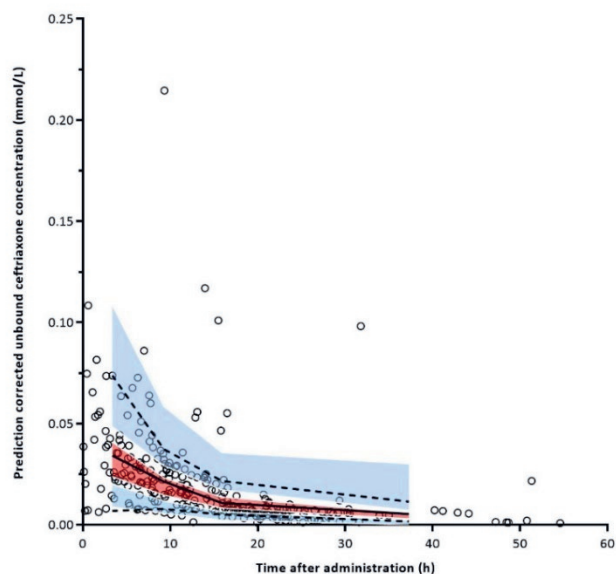
Shrinkage for between-patient variability on  $CE_{U_i}$  Cl,  $CE_{U_i}$  V and Bmax was 7.1%, 6.2% and 21% respectively for the final model. Shrinkage for inter-occasion variability on  $CE_{U_i}$  Cl was 22% on occasion 1 and 29% on occasion 2 and on Bmax was 29% on occasion 1 and 49% on occasion 2.

**Figure 2A: Unbound fraction versus albumin****Figure 2B: Unbound fraction versus bilirubin**

In figure 2B the unbound fraction was calculated by  $\text{CEF}_U/\text{CEF}_T \times 100\%$ . Both figures illustrate non-linearity of protein binding. The seven outliers with an unbound fraction over 65% belong to one patient diagnosed with cholangitis with severe hyperbilirubinemia (470-555  $\mu\text{mol/L}$ )

**Figure 3: Goodness of fit plots for total and unbound ceftriaxone concentrations**

Each dot is a data point, the red line represents the trend line and the solid black line is the line of identity in figures A and B and the line  $y=0$  in figures C and D. The dotted black lines in figures C and D mark  $\pm 2$ . All plots show a random pattern around the black lines, indicating unbiased fit of the model. Abbreviations: CWRES = conditional weighted residuals.

**Figure 4A: VPC plot of total ceftriaxone concentrations****Figure 4B: VPC plot of unbound ceftriaxone concentrations**

Prediction corrected visual predictive check (VPC) for the total (figure 4A) and unbound (figure 4B) ceftriaxone concentrations versus time after ceftriaxone administration based on 1,000 simulations. The black circles are the prediction corrected observed data. The solid line represents the median and the dashed lines the 5<sup>th</sup> and 95<sup>th</sup> percentiles of the prediction corrected observed data. The red shaded area is the 95% CI of the model-predicted median and the blue shaded areas are the 95% CIs of the model-predicted 5<sup>th</sup> and 95<sup>th</sup> percentiles. The solid and dashed lines run within their respective shaded areas, thereby demonstrating adequate fit of the model.

### Probability of target attainment during first 24h of treatment

Figure 5A and 5B show the PTA of respectively 50% and 95%  $fT > MIC$  for ceftriaxone 2g q24. The PTA (50%  $fT > MIC$ ) of the 41 included patients was 100%, 100% and 68.3% and PTA (95%  $fT > MIC$ ) was 100%, 92.7% and 19.5% for MIC values 0.5, 1 and 8 mg/L, respectively.

Of these 41 patients, 14 patients received the second ceftriaxone dose at least 24h after the first one, as prescribed by the treating physician. Twenty-one patients received a second dose within 12-24h after the first administration and 6 patients received a second dose already within 12h of the first administration. These deviations from what was prescribed were caused by practical reasons considering the routine time windows of nurses' antibiotic administration rounds, which often resulted in drug administration early in the morning following the day of ceftriaxone initiation. From that moment on a dosing interval of 24h was more accurately adhered to. As a result, time above MIC during the first 24h of iv ceftriaxone treatment, and thus PTA, is higher than would have been observed when an exact dosing interval of 24h would have been used between the first and second administration for all patients.

For patients who had their second dose at least 12h after the first one ( $n=35$ ), the 50%  $fT > MIC$  endpoint could be assessed for the 2g q24h dosing regimen without an flattering effect caused by a second dose that was administered too early, i.e. if their individually estimated CEFu at 12h after the first administration was greater than the MIC, the target was attained. PTA in these 35 patients was 100%, 100% and 42.9% for MIC values of 0.5, 1 and 8mg/L respectively.

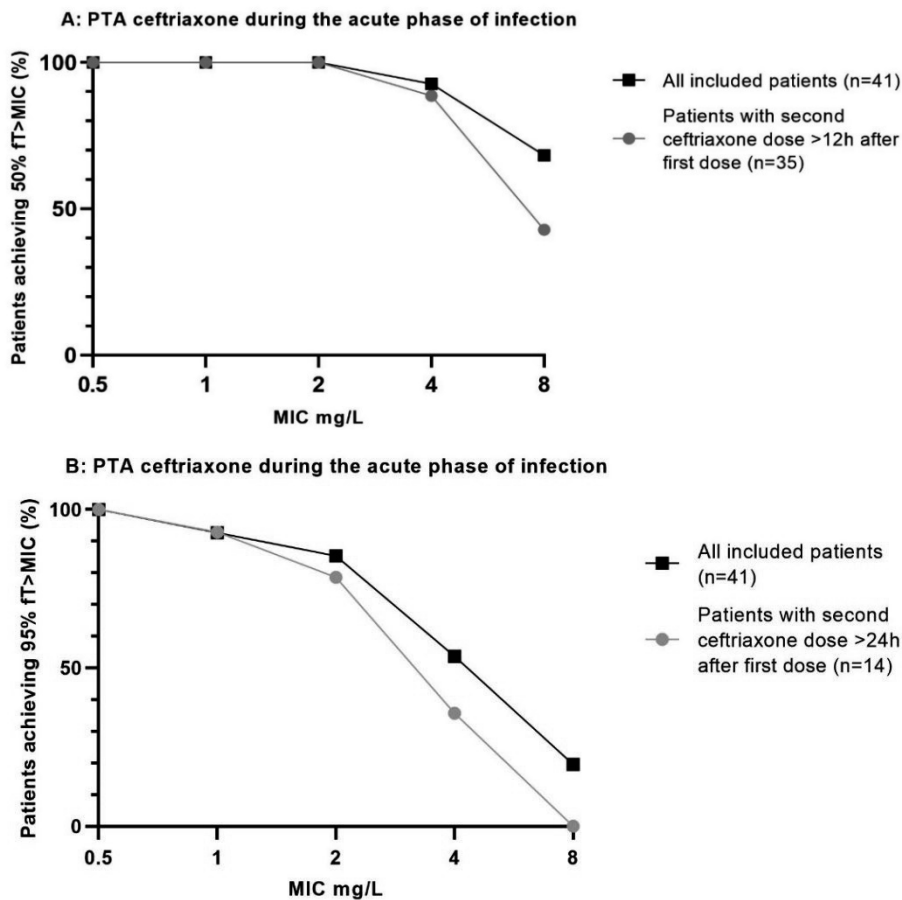
For patients who had their second dose at least 24h after the first one ( $n=14$ ), the 95%  $fT > MIC$  endpoint could be assessed for the 2g q24h dosing regimen without the flattering effect caused by a second dose that was administered too early and PTA in these patients was 100%, 92.9% and 0% for MIC values of 0.5, 1 and 8mg/L respectively. Restricting the PTA analyses to the patients who received their second dose after at least 12h respectively 24 h only marginally affected the PTA, especially for the lower MIC values (fig 5A and 5B).

### Monte Carlo simulations

The PTA (50%  $fT > MIC$ ) calculated based on the Monte Carlo simulations for three different eGFR values (the median CKD-EPI-estimated GFR measured in the study population and its 5<sup>th</sup> -95<sup>th</sup> percentile: 36, 65 and 122ml/min/1.73m<sup>2</sup> was above 90% for bacteria with an MIC  $\leq 2$ mg/L regardless of eGFR (figure 6). Assuming an MIC of 4mg/L, the PTA was 98.5%, 92.5% and 56.9% for

respectively eGFR of 36, 65 and 122ml/min/1.73m<sup>2</sup>. For bacteria with an MIC of 8mg/L the PTA was insufficient (<90%) regardless of eGFR.

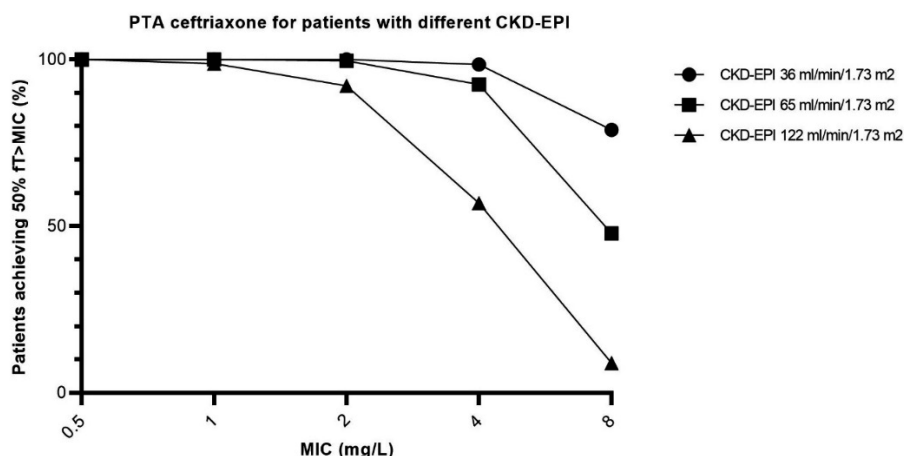
Figure 5: Observed PTA for ceftriaxone during the acute phase of infection



A: Probability of target attainment (PTA) for ceftriaxone, with target attainment defined as achieving a ceftriaxone plasma concentration above the MIC during at least 12h of the first 24h of treatment (50%T>MIC). PTA was calculated for a range of MICs. Line with squares represents PTA of all 41 included patients; line with dots represents PTA for the 35 patients who received their second dose after at least 12h of the first dose.

B: PTA for ceftriaxone, with target attainment defined as achieving a ceftriaxone plasma concentration above the MIC during at least 22.8h of the first 24h of treatment (95%T>MIC). PTA was calculated for a range of MICs. Line with squares represents PTA of all 41 included patients; line with dots represents PTA for the 14 patients who received their second dose after at least 24h of the first dose.

**Figure 6: Simulation based PTA for ceftriaxone during the acute phase of infection for patients with different estimated creatinine clearance**



Probability of target attainment (PTA) for ceftriaxone, with target attainment defined as achieving a ceftriaxone plasma concentrations above the MIC during at least 12h of the first 24h of treatment (50%T>MIC).

PTA was calculated based on Monte Carlo simulations for a range of MICs and for patients with different levels of renal function, based on the observed median estimated GFR and 5th -95th percentile of the study population. 1000 simulations per eGFR category were performed. Line with dots represents eGFR of 36ml/min/1.73m<sup>2</sup>; line with squares eGFR of 65ml/min/1.73m<sup>2</sup>; line with triangles eGFR of 122ml/min/1.73m<sup>2</sup>.

## Discussion

With this study we have demonstrated that the vast majority of non-ICU hospitalized febrile patients in a high-income country setting who receive empiric ceftriaxone treatment in the acute phase of infection are adequately treated with the recommended dose of 2g q24h. Substantial risk for PTA<90% was only shown for bacteria with an MIC of 4mg/L when renal function is not impaired and in case of an MIC ≥8 mg/L. Using ceftriaxone 2g q24h as empiric therapy seems therefore to be adequate for common infections, with the exception of *Staphylococcus aureus* infections.<sup>20</sup>

Our PPK model showed that the PK of ceftriaxone was best described using a one-compartment model with non-linear protein binding and first order elimination. BPV could be estimated for Cl, Vd and Bmax, IOV for Cl and Bmax and covariate associations were found between eGFR and CEF<sub>0</sub> Cl, between albumin and Bmax and between bilirubin and Bmax. The former two associations are similar in the PPK model described in ICU patients and in and non-ICU hospitalized patients in

sub-Saharan Africa.<sup>13, 21</sup> The association between bilirubin and Bmax has also been observed in ICU patients and can be explained by the fact that bilirubin competitively binds to albumin, decreasing the binding capacity for ceftriaxone.<sup>22</sup>

PTA in our study population was high compared to what was reported in severely ill non-ICU patients in sub-Saharan Africa<sup>13</sup> In these patients, the PK/PD target of 50% $fT > MIC$  was only sufficiently attained for microorganisms with an MIC  $\leq 0.25$  mg/L when using ceftriaxone 2g q24h.<sup>13</sup> Our study population had higher Vd and Bmax and lower CI values as well as lower estimated BPV in these parameters than the non-ICU patients in sub-Saharan Africa, probably because compared to those patients our patients had a higher BMI, had normal albumin values and a lower eGFR, of which the latter mainly contributes to the increased PTA of CEF<sub>U</sub>.<sup>23</sup> The non-ICU patients in sub-Saharan Africa had a median BMI of 18.9 kg/m<sup>2</sup>, hypoalbuminemia and a median creatinine clearance of 91 mL/min with large variability (range of 4-261 mL/min), suggesting that they were more severely ill.<sup>13</sup> In addition, they were younger and therefore more at risk for developing augmented renal clearance.<sup>9</sup> These patient characteristics and PK differences may explain why subtherapeutic ceftriaxone exposure occurred more often in those patients than in our study population.

In healthy volunteers and mouse models the PK/PD target of 40-50%  $fT > MIC$  was shown to be sufficient, whereas often 100%  $fT > MIC$  is targeted in ICU patients.<sup>24-26</sup> As the optimal PK/PD target in non-ICU hospitalized patients has yet to be defined, both targets were investigated. Our reported patient characteristics (rapid normalization of body temperature, normal albumin values and less variable eGFR between patients, table 1), suggest that the average hospitalized non-ICU patient in a high-income country setting seems to be less severely ill during the acute phase of infection than ICU patients and may therefore be less subjected to PK changes. We also showed that the PK estimates in our study population did not differ considerably between the acute phase of infection and convalescence. The comparability of the PK between both phases is also illustrated by the observation that no time varying covariates, such as body temperature or the presence of fever within 24h of the study visit, could be identified and that the covariates that were identified hardly explained any IOV in CI and Bmax. Together, this may suggest that the ICU target of 100%  $fT > MIC$  is perhaps not necessary in less severely ill patients, justifying the chosen primary endpoint of this PPK study,  $fT50\% > MIC$ .<sup>25</sup> In addition, even with a PK/PD target of 95%  $> MIC$ , the currently recommended dose would still be sufficient for common infections caused by bacteria with an EUCAST breakpoint MIC  $\leq 1$  mg/L, such as *Streptococcus pneumoniae* and *Enterobacterales*.

### Strengths and limitations

This was the first study investigating population pharmacokinetics and PTA of ceftriaxone in a group of hospitalized, non-ICU patients in their acute phase of infection in a high-income country setting covering a wide range of ages, renal function and infectious diseases. As a result, our study provides a sound pharmacokinetic evidence base for the recommended empiric dosing regimen of 2g q24h for this patient group. Another strength is that we used CEF<sub>U</sub> concentrations for the PPK model and PTA calculations. Given the nonlinearity of protein binding of ceftriaxone, CEF<sub>T</sub> plasma concentrations are not representative for CEF<sub>U</sub>, the pharmacologically active compound,<sup>21, 27</sup> with lower CEF<sub>T</sub> concentrations in case of hypoalbuminemia and hyperbilirubinemia due to lower B<sub>max</sub>. Regarding limitations, as the present study was an observational sub-study of the EXPO-AB study, we did not have influence on the administration times of ceftriaxone. As a result, only 14 patients actually received their second ceftriaxone administration  $\geq 24$ h after the first one and 35 patients after  $>12$ h. Our endpoints, 50%fT $>$ MIC and 95%fT $>$ MIC in the first 24h dosing interval, could therefore only be truly measured in these 35 and 14 patients respectively. The other patients received a second ceftriaxone dose within the first 24h of treatment, of whom 6 even within the first 12h, flattering the likelihood that 50%fT $>$ MIC and especially 95%fT $>$ MIC within the first 24h would be attained. Whether this is an accurate reflection of clinical practice in other hospitals is unknown, but likely. Restricting the PTA analyses to the patients who received their second dose after at least 12h respectively 24 h only slightly affected the results, and did even not so for MIC values  $\leq 1$ mg/L (figure 5). To further generate insight in the PTA of 2g q24h ceftriaxone, we also performed Monte Carlo simulations using the final and internally validated PPK model.

### Conclusion

PTA for ceftriaxone during the acute phase of infection in non-ICU, hospitalized patients in a high-income country setting treated with 2g q24h is sufficient to treat common pathogens with an MIC  $\leq 2$  mg/l. Substantial risk for underexposure was only shown for bacteria with an MIC of 4mg/L when renal function is not impaired, and in case of an MIC  $\geq 8$  mg/L regardless of renal function.

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## CHAPTER 8:

# General discussion and recommendations

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## Part I: Optimizing the measurement of the QI ‘Guideline-adherent therapy’

Measuring guideline-adherence of antimicrobial therapy usually requires manual chart review, which can therefore be very time-consuming. This often results in the evaluation of a relatively small number of patients and a low frequency of analysis. A more efficient method to evaluate the appropriateness of antimicrobial use is therefore urgently needed. In the first part of this thesis we investigated the possibilities of using the Electronic Medical Record (EMR) to more efficiently measure guideline adherence of antimicrobial therapy. Antimicrobial Stewardship Programmes (ASP) have shown their value in contributing to appropriate antimicrobial therapy and improving patient outcomes.<sup>1, 2</sup> Unfortunately, limited funding and personnel often restrict their effectiveness.<sup>3</sup> Information Technology (IT), and specifically the use of data retrieved from the EMR, is gradually gaining ground in supporting ASP, as it has the potential to facilitate interventions by increasing ASP’s scope and efficiency.<sup>4, 5</sup>

We demonstrated that using the patient screening functionality in EPIC and ChipSoft software, which does not require implementation of additional tools or efforts by the prescriber, already resulted in broadening the A-team’s scope. This functionality enabled us to obtain a list of all patients on antimicrobials, broken down per hospital department, during a self-set time frame. While this functionality was formerly mainly used for the hospital-inpatient setting, with little adjustments we were able to use it for the hospital-outpatient setting as well. This relatively simple screening-method made it therefore possible to perform a Point-Prevalence Survey (PPS) in the hospital-outpatient setting, which had received little attention before, investigating guideline adherence of all antimicrobial prescriptions for prophylaxis and therapy (**Chapter 2**).<sup>6</sup> This enabled the A-team to initiate targeted interventions, as we identified clear opportunities for quality improvement.

Although this screening method reduces time to identify eligible patients for a PPS in both the inpatient and the outpatient setting, the actual PPS still requires manual chart review. We demonstrated that by incorporating mandatory indication registration in the antimicrobial order form, manual chart review is no longer necessary for a global assessment of antimicrobial guideline adherence regarding both empiric therapy and total duration of therapy (**Chapters 3 and 4**). We used an antimicrobial order form that can be incorporated in the EMR software without the need of a third-party vendor, a method that can be used by all EMR using EPIC and ChipSoft software. In addition, by structuring the order form by means of aligning the selectable indications with those of the antimicrobial guidelines, we showed the possibilities of standardized data collection: an automated assessment

of appropriate antimicrobial use on the local level, which enables benchmarking on the regional or national level.<sup>7</sup>

However, several points have to be made. First, our described methods do only apply to hospitals that use EMR and in particular Epic and ChipSoft. We believe that the screening functionality can be used by these hospitals. However, to get started institution-specific programming is still needed, which requires IT-directed time, effort, and possibly additional funding.<sup>8</sup> We should therefore keep in mind that the generalizability of our findings is probably restricted to middle- and high income countries where sufficient resources are available. That being said, the use of IT in healthcare and Antimicrobial Stewardship has shown to be of worth.<sup>5, 9</sup> Low- and middle income countries (LMIC) would likewise benefit of a structured electronic documentation and assessment of antimicrobial use (and health registry in general), as these are the countries with the highest resistance rates.<sup>10</sup> Currently these countries are advised to implement ASP interventions in a stepwise approach, building on existing structures and reporting,<sup>11</sup> which mostly means without the use of IT systems. To increase the efficacy of ASP in those countries where it is most needed, we should strive for LMIC policy makers to invest in the implementation of local IT systems and the education of IT personnel in healthcare.

In addition to this, the described methods may considerably reduce the workload for A-teams in the long term, as screening of eligible patients, or manual chart review to retrieve the indication of antimicrobial prescriptions are no longer required, enabling to evaluate the quality of antimicrobial use on a large scale. However, time still needs to be invested in the initiation of the project (including supervising the IT, defining endpoints for analysis and constructing a syntax for repeated analysis) and also in the validation of the extracted datasets. Although the first requires a one-time investment, the latter does not. The error rates of our extracted datasets were mainly caused by wrongly selected indications by physicians that did not match with what they had documented in the patient record. To identify and limit this error rate, time is needed to repeat the validation regularly - for example annually - as the error rate might fluctuate over time. This can however be limited to a small random sample of records, minimizing the time investment.

Interestingly, during the validation of our datasets we noted that the extent and duration of electronically prescribed antimicrobials were in general correctly extracted from the EMR. This implicates that the used technology is reliable and that its main challenge lies in the reliability of physicians' selection of the

indications. Human errors are unfortunately inevitable. It is to be expected however that accuracy increases with habituation, education and feedback.<sup>12</sup> This will minimize the error rate (as we saw in Hospital A in chapter 3), and will put our described method in its full strength. Steve Jobs once said: “It’s not a faith in technology. It’s faith in people”, meaning that what’s important is that you have a faith in people, that they’re basically good and smart, and if you give them tools, they’ll do wonderful things with them. After writing this thesis, I could not agree more.

Finally, we deliberately performed the PPS in the hospital-outpatient setting to explore additional targets for improvement (**Chapter 2**), as this setting has received little attention so far. We found clear targets for quality optimization in this setting, with approximately 40% of the prescriptions that did not adhere to the guideline, mainly due to the inappropriate use of amoxicillin-clavulanic acid.<sup>13</sup> Nevertheless, we limited the mandatory indication registration to the inpatient setting only. In hindsight, it should have been implemented in the outpatient setting as well, enabling also an automated assessment of guideline adherence in the hospital-outpatient setting.

### **Future perspectives**

To further improve the quality of prescribing it would be interesting to link patient characteristics (i.e. allergy, renal function), microbiological results and guidelines to the mandatory indication registration in the EMR, enabling not only to give tailored recommendations whenever an antimicrobial agent is prescribed, but also offering opportunities for a more thorough quality assessment. Catho and colleagues already published a study protocol for a trial investigating the impact of computerised decision support with audit and feedback on antibiotic use, in which physicians receive decision support with regard to the choice of antimicrobial therapy based on the indication entry and local guidelines.<sup>14</sup> Regarding other aspects of appropriate antibiotic use, Dutey-Magni and colleagues showed that it is feasible to extract antimicrobial consumption, indication of prescriptions, timing of conversion of intravenous to oral therapy and microbiological culture sampling<sup>15</sup>, enabling measuring several quality indicators at the same time. If efficacy and efficiency can be shown, we should aim for a structured IT implementation that is similar between hospitals globally, as it would enable benchmarking the results not only locally or nationally, but also internationally. Altogether, the use of IT in ASP is still in its infancy, but the possibilities are promising.

## Part II: Optimizing the QI “IV to oral switch”

In the second part of this thesis we investigated the possibility of safely shortening the currently recommended duration of IV therapy in non-critically ill patients admitted to general wards. A major barrier for an earlier switch, within 48 hours of therapy, is the perception that the systemic reaction to an acute infection might alter the pharmacokinetics of and thereby the exposure to antibiotics.<sup>16</sup> This has been demonstrated for critically ill patients admitted to the intensive care unit, who are at risk for changes in absorption and first pass mechanism, and for developing augmented renal clearance and increased volume of distribution, which may result in lower antibiotic exposure.<sup>17</sup> The uncertainty whether such pharmacokinetic changes also account for non-critically ill patients currently makes clinicians reluctant to consider an earlier switch to oral antibiotics with a further reduction in length of hospital stay and healthcare costs and increased patient comfort.<sup>2</sup>

We have demonstrated that there is a knowledge gap regarding absorption of and exposure to oral antibiotics under febrile circumstances in the general patient population (**chapter 5**). In our systematic review we showed that there were surprisingly few pharmacokinetic studies on orally administered antibiotics, like  $\beta$ -lactams, quinolones and macrolides, during the initial phase of infection in non-critically ill hospitalized patients, while we had broad search criteria and no restrictions in year of publishing. The studies had in general a high risk of bias, did not provide sufficient information to compare the exposure to oral antibiotics in febrile and afebrile patients, and had small sample sizes. The only three studies, two on ciprofloxacin and one on clarithromycin, that compared the pharmacokinetics of febrile patients with those of clinically recovered patients suggested that exposure was not altered in these patients. The recommendation to evaluate the possibility to switch to oral antibiotics after 48 to 72 hours seems therefore to be arbitrary, but sound evidence is lacking.

We have provided such evidence by performing population pharmacokinetic studies on the absorption of and exposure to oral administered amoxicillin and ciprofloxacin (**chapter 6**) and the exposure to IV administered ceftriaxone (**chapter 7**) during the acute phase and the afebrile phase of infection in hospitalized non-critically ill patients. We demonstrated that the exposure to the oral antibiotics was equivalent between the febrile and afebrile phase and showed that the probability of target attainment was similar between both phases and sufficient to treat common infections. In addition, we showed that the acute phase of infection did not affect the pharmacokinetics of IV administered ceftriaxone. Ceftriaxone exposure achieved during the first 24 hours of infection was adequate to effectively kill common bacteria with an MIC  $\leq 2$ mg/L. Herewith, we have provided evidence

regarding pharmacokinetics during the acute phase of infection in a general patient population: non-critically ill, febrile hospitalized patients seem to be less subjected to acute infection-induced pathophysiologic changes affecting pharmacokinetics of antibiotics than critically ill patients. Our findings thus imply that from a pharmacokinetic point of view, there seems to be no good reason for non-critically ill patients not to switch earlier to oral antibiotics.

However, before implementing an earlier oral switch, there are several points to consider. First, although we investigated a heterogeneous group of patients in terms of age, renal function and infectious illness, it should be noted that the majority of patients rapidly recovered and had already normalizing body temperatures within 24h of initiation of the IV antibiotics. Therefore, it can be presumed that the non-critically ill hospitalized patients we investigated were not severely ill. It is to be expected that more severely ill patients are more likely subjected to pharmacokinetic changes leading to antibiotics underexposure, as was shown in severely ill patients admitted to the general wards of a hospital in Mozambique, who seemed to be more at risk for developing augmented renal clearance.<sup>18</sup> Our findings should therefore only be extrapolated to similarly ill patients. In our opinion this still covers a large group of patients, as we believe that the investigated patient population reflects the average non-critically ill hospitalized patient in a high income country setting.

Second, although we found equivalent and sufficient antibiotic exposure, we did not investigate whether an earlier switch would also be beneficial for clinical outcome. It is to be expected that a shortened IV treatment results in reduction of hospital length of stay and thereby the risk of developing nosocomial infections like catheter-related bacteraemia and phlebitis, and improvement of patient comfort and mobility.<sup>2, 16, 19</sup> However, in order to tackle any misperceptions of prescribers that IV antibiotics are superior to oral antibiotics, evidence regarding the benefits of switching earlier to oral antibiotics should first become available. Evidence on antibiotic exposure alone may be not convincing enough to gain enough acceptance for a new treatment strategy, which is needed to increase the chances of successful implementation.

### **Future perspectives**

Now that we have provided pharmacokinetic evidence that the currently recommended IV-to oral switch moment is arbitrary and that equivalent antibiotic exposure is reached during the acute phase of infection and the afebrile phase, the next step is to shorten the IV treatment duration for those patients rapidly showing signs of convalescence of disease. Convalescence of disease can be evaluated

after 24 hours, when patients have received at least one IV antibiotic dose, instead of the current 48-72 hours, using the same IV-oral switch criteria.<sup>27</sup> In order to accomplish this, we need to gain broad acceptance, both nationally and locally, not only from prescribers but also from other stakeholders: leaders and patients. As we mentioned above, we believe that this requires an additional study investigating the benefits of an earlier switch. In our opinion such a study could best be done by means of a cluster randomized trial. This way, the new strategy is implemented as standard patient care enabling habituation and it also allows the evaluation of possible benefits of an earlier switch under real-world conditions. The earlier switch can be monitored or supervised by local A-teams who already monitor a timely IV-to-oral switch. We believe that length of hospital stay should be the primary endpoint of the study. Schuts et al. showed that most evidence regarding the benefits of an early switch is available on length of hospital stay. In addition, length of hospital stay indirectly reflects clinical, safety and costs outcomes, relevant to all involved parties. To conduct such a study, I would like to pass on the baton to my successor.

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# ADDENDUM

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## Summary

Due to the widespread (mis)use of antimicrobials, antimicrobial resistance rates have accelerated, leading worldwide to increased morbidity, mortality and healthcare costs. In order to curb antimicrobial resistance, Antimicrobial Stewardship Programmes (ASPs) have been developed globally to measure and subsequently improve appropriate use of antimicrobials and minimizing unintended consequences. To guide the activities of Antimicrobial Stewardship teams (A-teams), international guidelines have been developed that encompass, amongst others, recommendations of appropriate antibiotic use at the patient level, based on quality indicators (QIs). In this thesis, we focus on optimizing the QI's 'Guideline-adherent therapy' and 'Intravenous (IV) to oral therapy switch'.

### **Part I: Optimizing the measurement of the QI 'Guideline-adherent therapy'**

The evaluation of whether antibiotics are prescribed according to the guideline requires manual patient chart review, which can be very time-consuming. This often results in the evaluation of a relatively small number of patients and few opportunities for analysis. To support A-team's activities and increase their effectiveness, a more efficient method to evaluate the appropriateness of antibiotic use is urgently needed. In the first part of this thesis we investigated the possibilities of using the Electronic Medical Record (EMR) to more efficiently measure guideline adherence of antibiotic therapy.

In **Chapter 2** we showed that the patient screening functionality of the Electronic Medical Record (EMR) can be used to support the performance of a point-prevalence survey (PPS, a method to evaluate the appropriateness of antibiotic use) in the outpatient clinic. This functionality was formerly mainly used for the hospital-inpatient setting. With little adjustments we were able to use it for the hospital-outpatient setting as well, which had received little attention before. We found that 40% of the outpatient prescriptions did not adhere to the guideline. This was mainly caused by unnecessarily (not indicated) prophylaxis prescribed after surgery or another intervention and by inappropriate (indicated, but prescribed not according the guideline) antibiotic therapy. Therapeutic antibiotics for skin-and-soft tissue infections, respiratory tract infection and ear-nose-throat infections were most frequently inappropriately prescribed. Amoxicillin-clavulanic acid was the most frequently inappropriately prescribed antimicrobial agent. We showed here that antibiotics prescribed at the hospital outpatient clinics warrant ASP attention as well.

While this screening functionality reduced the time needed to identify eligible patients for a PPS, the actual PPS still required manual chart review.

In **Chapter 3** we showed the feasibility of using the EPD for an automated evaluation of antibiotic guideline-adherence. This (partly) would make manual chart review redundant, and making larger scale evaluation of antibiotic prescriptions possible. We implemented a mandatory indication registration tool in the medication prescribing software of the EPD in three hospitals. The selectable indications were aligned with those of the national antibiotic guidelines, enabling benchmarking the results on regional and national level. In our study we focused on the evaluation of empiric antibiotics prescribed for respiratory and urinary tract infections, in patients admitted to general (i.e., non-ICU) wards. We extracted all antibiotic prescription data from the EMR. In a sample of the extracted data we evaluated whether the selected indications matched the indications that were written in the case notes. We saw a miss-match in 3.3% to 21.8% of the evaluated prescriptions, caused by the incorrect selection of the indication by prescribers. Regarding appropriate antibiotic use, a considerable variation in guideline adherence was seen between the hospitals. This provided clear targets for local A-teams. Feasibility to use this approach was thus shown, with caveat that initial local validation and, if indicated, optimization of the datasets are necessary to ensure accuracy of the extracted data.

In **Chapter 4** we showed that an automated evaluation of the total antibiotic therapy duration is feasible as well, using the same method as described in chapter 3. Evaluation of therapy duration was formerly limited to the duration of antibiotic use during hospital admission, without including the post-discharge period. We showed that the total antibiotic therapy duration can be retrieved from the EPD by merging the inpatient prescriptions with consecutively prescribed outpatient antibiotics. In a sample of the extracted data, we evaluated whether the total antibiotic therapy duration and the selected indications matched with what was documented in the case notes. The total therapy duration was accurately extracted in 96% of the evaluated prescriptions. The selected indication did not match the indication documented in the patient records in 17% of cases, due to inaccurate indication selection by prescribers. On average, in 44% of patients treatment was continued post-discharge, accounting for 60% (standard deviation 19%) of their total length of therapy (LOT). Guideline non-adherence due to excessive treatment duration varied from 10% to 50% per indication, showing possibilities for quality improvement. Feasibility of this approach was thus shown with the same caveat as described in chapter 3.

## Part II: Optimizing the QI “IV to oral switch”

It is currently recommended to evaluate an antibiotic IV-to-oral therapy switch 48-72 hours after initiation of IV treatment. The main reason why oral therapy is not administered during the first 48-72 hours of infection is the assumption that the systemic response to an infection may alter the pharmacokinetics of antibiotics, which may lead to insufficient systemic antibiotic exposure. This has been demonstrated in critically ill patients and in severely ill, non-ICU hospitalized patients in sub-Saharan Africa, but whether this also accounts for non-critically ill patients is unknown. In the second part of this thesis we investigated the possibility of safely shortening the currently recommended duration of IV therapy in non-critically ill patients admitted to general wards, by investigating the pharmacokinetics of antibiotics in these patients.

In **chapter 5** we showed that there is a knowledge gap regarding the effect of the initial phase of infection on the exposure of oral antibiotics in non-ICU patients. This was investigated by means of a systematic review. Our review identified 9 studies on 6 antibiotics, which had generally a high degree of bias and did not provide sufficient information to compare antibiotic exposure in febrile versus afebrile patients. One study on clarithromycin and two on ciprofloxacin were the only studies that investigated systemic antibiotic exposure in patients when they were febrile and after convalescence, enabling a proper comparison. These studies suggested that exposure was not different in these patients. Unfortunately, these studies included a very limited number of patients. Our review thus shows that insufficient evidence exists to draw a sound conclusion on whether or not the exposure to antibiotics is altered in the febrile phase relative to the afebrile phase in non-ICU patients.

In **chapter 6** we showed that the exposure to and efficacy of oral antibiotics in patients admitted to the general wards are comparable between febrile and afebrile patients. By means of a population pharmacokinetic study, the EXPO-AB study, we investigated whether the febrile phase of infection influenced the exposure to orally administered amoxicillin and ciprofloxacin compared to the afebrile phase of infection. Patients that were treated with IV antibiotics (other than amoxicillin and ciprofloxacin) received an additional single tablet of these oral antibiotics within 24h of initiation of the IV treatment, and when they were afebrile. Amoxicillin and ciprofloxacin blood concentrations were measured during both phases, enabling building a Population Pharmacokinetic model. The results showed that antibiotic exposure was equivalent in the febrile and the afebrile phase. In addition, we showed that that for both phases the probability of attaining the effective pharmacokinetic/ pharmacodynamix (PK/PD) “bacterial killing” target was sufficient

to treat common infections. These results suggest that from a pharmacokinetic point of view, hesitations to orally administer amoxicillin and ciprofloxacin during the febrile phase of infection is not necessary in non-ICU patients.

In **chapter 7** we showed that the currently recommended IV ceftriaxone dose results in sufficient antibiotic exposure for effective therapy, in the majority of patients admitted to general wards. Although ceftriaxone is globally widely used in hospitalized patients, to date it is unknown whether adequate antibiotic exposure is achieved with the recommended dose during the acute phase of infection in non-critically ill patients. We therefore investigated whether the currently recommended dosing regimen of 2 grams every 24h is sufficient for PK/PD target attainment in patients hospitalized to general wards. The study was performed in patients that were included in the EXPO-AB study (chapter 6) and were treated with IV ceftriaxone. A population pharmacokinetic model was build. The results showed that the recommended dose of 2g per 24h was sufficient to treat common infections. The recommended dose was only insufficient for bacteria with a high “minimal inhibition concentration” for ceftriaxone, especially in patients of whom the renal function is not impaired. This study has provided evidence regarding the pharmacokinetics of ceftriaxone during the acute phase of infection in a general patient population. In addition, we have provided a sound pharmacokinetic evidence base for the recommended empiric dosing regimen of 2g per 24h for these patients.

## Nederlandse samenvatting

Door veelvuldig (onjuist) gebruik van antibiotica is het percentage resistente bacteriën geleidelijk toegenomen. Dit leidt tot mondiale toename van morbiditeit, mortaliteit en zorgkosten. Om de antibioticaresistentie binnen de perken te houden, zijn er wereldwijd Antimicrobial Stewardship Programma's (ASP's) tot stand gebracht. Het doel van ASP's is het monitoren en, waar nodig, het verbeteren van correct antibiotica gebruik om daarmee ongewenste consequenties te minimaliseren. Om de activiteiten van Antimicrobial Stewardship teams (A-teams) te begeleiden zijn er internationale richtlijnen opgesteld. Hierin staan onder andere aanbevelingen voor juist antibioticagebruik, gebaseerd op kwaliteitsindicatoren die geassocieerd zijn met reductie van antibioticaresistentie, zorgkosten en mortaliteit. In dit proefschrift focussen we op het optimaliseren van de kwaliteitsindicatoren "antibioticatherapie conform de richtlijn" en "de intraveneuze (IV) naar orale therapie switch".

### **Deel I: Het optimaliseren van de meetmethode van de kwaliteitsindicator: "antibioticatherapie conform de richtlijn"**

Om te meten of antibiotica conform de richtlijn worden voorgeschreven is handmatige beoordeling van het patiëntendossier nodig, wat veel tijd in beslag neemt. Dit resulteert vaak in de beoordeling van een relatief klein aantal patiënten op een beperkt aantal momenten. Om A-teams te ondersteunen en hun effectiviteit te vergroten, is een efficiëntere meetmethode om juist gebruik van antibiotica te evalueren nodig. In het eerste deel van dit proefschrift onderzochten we de mogelijkheden om het elektronisch patiëntendossier (EPD) te gebruiken om op efficiëntere wijze te meten of antibiotica volgens de richtlijn werden voorgeschreven.

In **hoofdstuk 2** hebben we laten zien dat de patiënten-screening functionaliteit van het EPD gebruikt kan worden ter ondersteuning van een puntprevalentie meting (een methode om correct antibioticagebruik te beoordelen) op de polikliniek. Deze functionaliteit werd voorheen alleen gebruikt in klinische setting. Met kleine aanpassingen kon deze methode ook worden gebruikt in de poliklinische setting, waar tot nu toe nauwelijks metingen werden verricht. We zagen dat 40% van de poliklinische antibiotica voorschriften niet volgens de richtlijn was. Dit werd voornamelijk veroorzaakt door onnodig (niet geïndiceerd) voorgeschreven antibioticaprofylaxe na een chirurgische ingreep of een interventie anderszins, alsook door onjuist (wel geïndiceerd, maar niet conform de richtlijn zonder goede reden) voorgeschreven antibioticatherapie. Antibioticatherapie voor huid- en weke

delen infecties, luchtweginfecties en keel-neus-oor infecties werd het vaakst onjuist voorgeschreven, en met name het middel amoxicilline-clavulaanzuur. Met dit onderzoek hebben we laten zien dat daarom antibioticagebruik in de polikliniek ook aandacht van A-teams behoeft.

Hoewel deze screeningsmethode de identificatie van patiënten die in aanmerking komen voor een puntprevalentiemeting versnelt, is voor de daadwerkelijke meting vooralsnog handmatige beoordeling van het patiëntendossier noodzakelijk.

In **hoofdstuk 3** hebben we laten zien dat het EPD de mogelijkheid biedt om de beoordeling of antibiotica volgens de richtlijn is voorgeschreven automatisch uit te voeren. Dit maakt een handmatige beoordeling van patiëntendossiers (deels) overbodig, waardoor er op grotere schaal antibiotica voorschriften beoordeeld kunnen worden. Hiervoor hebben we in drie ziekenhuizen een verplichte indicatieregistratie voor antibiotica aanvragen in het EPD geïmplementeerd. De selecteerbare indicaties hebben we gelijkgetrokken met de indicaties zoals deze zijn opgenomen in de landelijke antibioticarichtlijnen. Dit maakt het benchmarken van juist antibioticagebruik op regionaal of nationaal niveau mogelijk. Voor dit onderzoek hebben we ons beperkt tot de beoordeling van empirisch voorgeschreven middelen voor luchtweg- en urineweginfecties, bij patiënten die liggen opgenomen op de verpleegafdelingen. We hebben alle data over voorgeschreven antibiotica geëxtraheerd uit het EPD. Middels een steekproef hebben we beoordeeld of de geselecteerde indicatie op het orderformulier, overeenkomt met de notitie in het dossier. Hieruit bleek dat in 3,3% tot 21,8% de geselecteerde indicatie niet overeenkwam met de notitie, doordat de voorschrijver in het aanvraagformulier een verkeerde indicatie had geselecteerd. Bij de beoordeling van juist antibioticagebruik zagen we een aanzienlijke variatie in het percentage correct gebruik tussen de ziekenhuizen. Dit maakte individuele, gerichte acties voor lokale A-teams mogelijk. Hiermee hebben we laten zien dat het EPD gebruikt kan worden voor het efficiënter meten van juist antibioticagebruik. Wel is lokale validatie, en indien nodig optimalisatie, van de dataset nodig om te beoordelen of de geëxtraheerde data kloppen.

In **hoofdstuk 4** hebben we laten zien dat een geautomatiseerde beoordeling van de duur van de totale antibiotica kuur ook mogelijk is met de methode uit hoofdstuk 3. Beoordeling van de kuurduur werd voorheen vaak beperkt tot de kuurduur tijdens een klinische opname, niet rekening houdend met ontslagmedicatie. In onze studie zagen we dat de totale kuurduur weergegeven kan worden door klinische antibiotica kuren te koppelen aan aansluitend voorgeschreven poliklinische (ontslag) antibiotica. Van een steekproef hebben we beoordeeld of de kuurduur en de indicatie overeenkwamen met de patiëntnotitie. Hieruit bleek dat in

96% van de gevallen de kuurduur exact klopte. Echter, in 17% kwam de geselecteerde indicatie niet overeen met de indicatie in de notitie, ook hier door een onjuiste selectie van de indicatie door de voorschrijver. Gemiddeld werd bij 44% van de patiënten de antibioticakuur na ontslag voortgezet. De behandelduur na ontslag besloeg 60% van de totale behandelduur. De totale kuurduur was in 10% tot 50% van de voorschriften, afhankelijk van de indicatie, volgens de richtlijn te lang. Dit toont de mogelijkheden van deze methode voor kwaliteitsverbetering, onder hetzelfde voorbehoud als beschreven in hoofdstuk 3.

## **Deel II: Het optimaliseren van de kwaliteitsindicator “IV-orale switch”**

Het huidige advies luidt dat de switch van intraveneuze (IV) therapie (per infuus) naar orale therapie (tabletten) geëvalueerd dient te worden 48-72 uur na start van de IV therapie. De voornaamste reden waarom orale therapie niet binnen de eerste 48-72 uur wordt gestart berust op de veronderstelling dat de systemische reactie op een infectie mogelijk de farmacokinetiek van antibiotica verandert. Dit zou leiden tot onvoldoende blootstelling aan antibiotica om effectief te zijn. Dit is vastgesteld bij patiënten op de Intensive Care (IC) en bij ernstig zieke niet-IC-patiënten opgenomen in sub-Sahara Afrika. Of dit ook geldt voor niet-IC patiënten opgenomen in hoge inkomenslanden, is onbekend. In het tweede deel van dit proefschrift onderzochten we de mogelijkheid om de geadviseerde IV antibiotica therapieduur bij patiënten op verpleegafdelingen te verkorten door de farmacokinetiek in deze patiëntengroep in kaart te brengen.

In **hoofdstuk 5** hebben we laten zien dat er weinig bekend is over de blootstelling aan antibiotica tijdens de initiële fase van de infectie bij niet-IC patiënten. Dit hebben we onderzocht met een systematisch literatuuronderzoek, waarbij we 9 studies vonden over 6 verschillende antibiotica. Deze studies hadden in het algemeen een hoog risico op bias en leverden onvoldoende informatie op om de blootstelling aan orale antibiotica te vergelijken tussen patiënten met en zonder koorts. Eén studie over claritromycine en twee studies over ciprofloxacin onderzochten de blootstelling aan orale antibiotica bij patiënten in periodes met én zonder koorts. Dit maakt in opzet een goede vergelijking mogelijk. Deze studies suggereerden dat koorts geen nadelig effect heeft op de biologische beschikbaarheid van antibiotica. In deze studies werd echter een klein aantal patiënten onderzocht. Onze review laat dus zien dat er onvoldoende wetenschappelijk bewijs is om een conclusie te kunnen trekken over de invloed van koorts op de blootstelling aan antibiotica bij niet-IC patiënten.

In **hoofdstuk 6** hebben we laten zien dat de blootstelling aan, en effectiviteit van, orale antibiotica bij patiënten opgenomen op de verpleegafdelingen vergelijkbaar zijn wanneer zij koorts hebben en wanneer zij weer koortsvrij zijn. Dit hebben we onderzocht met een populatie farmacokinetiek studie: de EXPO-AB studie. Hierin keken we of de acute, ofwel febrile, fase van infectie invloed had op de blootstelling aan oraal toegediende amoxicilline en ciprofloxacin ten opzichte van de koortsvrije fase. In de studie kregen patiënten die met IV antibiotica (anders dan amoxicilline of ciprofloxacin) werden behandeld, één extra antibioticum tablet toegediend binnen 24 uur na start van de IV behandeling, en opnieuw wanneer zij koortsvrij geworden waren. Tijdens beide fases werden de amoxicilline en ciprofloxacin concentraties in het bloed gemeten. Hiermee werd een populatie farmacokinetisch model gebouwd. De resultaten lieten zien dat de blootstelling vergelijkbaar was tussen de febrile en de koortsvrije fase. Daarnaast zagen we dat de kans op het behalen van het effectieve farmacokinetische/farmacodynamische (PK/PD) “bacterial killing” target vergelijkbaar was tussen de twee fases en voldoende hoog voor het behandelen van veel voorkomende infecties. Deze resultaten suggereren dat behandeling met orale antibiotica tijdens de acute fase van infectie bij niet-IC patiënten vanuit farmacologisch oogpunt veilig lijkt.

In **hoofdstuk 7** hebben we laten zien dat de huidige geadviseerde IV ceftriaxon dosering voldoende is voor effectieve behandeling bij de meerderheid van de patiënten op de verpleegafdelingen. Hoewel ceftriaxon wereldwijd een veelgebruikt antibioticum is bij klinische patiënten, was het niet bekend of de systemische blootstelling bij deze groep adequaat is tijdens de acute fase van infectie. Daarom hebben we onderzocht of de huidige geadviseerde dosering van 2 gram per 24 uur voldoende is om de PK/PD target te behalen bij patiënten op de verpleegafdeling. De studie werd uitgevoerd bij de patiënten die meededen aan de EXPO-AB studie (hoofdstuk 6) en behandeld werden met IV ceftriaxon. Er werd opnieuw een populatie farmacokinetisch model gebouwd. We zagen dat de geadviseerde dosering van 2 gram per 24 uur voldoende hoog was om veel voorkomende infecties te behandelen. De dosering is echter onvoldoende om bacteriën aan te pakken met een hoge “minimale inhibitie concentratie”- waarde, met name wanneer de nierfunctie van de patiënt normaal is. Met deze studie hebben we de farmacokinetiek van ceftriaxon tijdens de acute fase van infectie bij een algemene, niet-IC patiënten-populatie in kaart gebracht. Daarnaast hebben wetenschappelijke onderbouwing geleverd voor het huidige doseeradvies van ceftriaxon 2 gram per 24 uur.

## List of publications

### This thesis

**van den Broek, A.K.**, van Hest, R. M., Lettinga, K. D., Jimmink, A., Lauw, F. N., Visser, C. E., & Prins, J. M. (2020). The appropriateness of antimicrobial use in the outpatient clinics of three hospitals in the Netherlands. *Antimicrobial Resistance & Infection Control*, 9(1), 1-9. doi: 10.1186/s13756-020-0689-x. PMID: 32087756

**van den Broek, A. K.**, Prins, J. M., Visser, C. E., & van Hest, R. M. (2021). Systematic review: the bioavailability of orally administered antibiotics during the initial phase of a systemic infection in non-ICU patients. *BMC infectious diseases*, 21(1), 1-11. doi: 10.1186/s12879-021-05919-w. PMID: 33743592

**van den Broek, A.K.**, Beishuizen, B. H., Haak, E. A., Duyvendak, M., Ten Oever, J., Sytsma, C., van Triest, M., Wielders, C.C.H. & Prins, J. M. (2021). A mandatory indication-registration tool in hospital electronic medical records enabling systematic evaluation and benchmarking of the quality of antimicrobial use: a feasibility study. *Antimicrobial Resistance & Infection Control*, 10(1), 1-10. doi: 10.1186/s13756-021-00973-0. PMID: 34217361

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**van den Broek, A.K.**, Visser, C. E., Veenstra, J., van den Berg, B.T.J., Prins, J.M. & van Hest, R. M. (2022). The effect of the acute phase of infection on absorption of and exposure to orally administered antibiotics in non-critically ill, hospitalized patients. *Journal of Antimicrobial Chemotherapy*, accepted for publication

### Submitted for publication

**van den Broek, A.K.**, van Schip, A., Visser, C.E., Bos, J.C., Prins, J.M., Hest, R.M. (2022). Population pharmacokinetic/pharmacodynamic target attainment of ceftriaxone 2 grams once daily in non-critically ill hospitalized adult patients

**Other**

Hodiamont, C. J., **van den Broek, A.K.**, de Vroom, S. L., Prins, J. M., Mathôt, R. A., & van Hest, R. M. (2022). Clinical Pharmacokinetics of Gentamicin in Various Patient Populations and Consequences for Optimal Dosing for Gram-Negative Infections: An Updated Review. *Clinical Pharmacokinetics*, 1-20.

PMID: 35754071

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## PhD portfolio

**Name PhD student:** Annemieke Kaniki van den Broek  
**PhD period:** 2018-2022  
**Name PhD supervisor:** Prof. dr. J.M. Prins

General courses	Year	ECTS
E-BROK	2018	1.5
Practical Biostatistics	2019	1.4
Clinical Epidemiology: Randomized Controlled Trials	2019	0.6
Clinical Epidemiology: Systematic Review	2019	0.7
Amsterdam World of Science	2019	0.7
Endnote	2019	0.1

Specific courses	Year	ECTS
Infectious Diseases	2018	1.3
Advanced Topics in Biostatistics	2021	2.1
Teach the Teacher: the 6Step	2020	1,0
NONMEM	2020	2.0

Seminars, workshops and master classes	Year	ECTS
Dutch Antibiotic Stewardship Masterclass	2019	1.0
Nationale SWAB A-team meeting	2018-2021	0.6

Poster presentations	Year	ECTS
European Congress of Clinical Microbiology And Infectious Diseases	2019	0.5
European Congress of Clinical Microbiology And Infectious Diseases	2022	0.5
European Congress of Clinical Microbiology And Infectious Diseases	2022	0.5
Scientific Spring Meeting KNVM & NVMM	2022	0.5

<b>Presentations</b>	<b>Year</b>	<b>ECTS</b>
Nationale SWAB A-team meeting	2019	0.5
RCI Refereeravond antimicrobial stewardship	2021	0.5
Dutch Pharmacology Day (cancelled due to COVID)	2020	0.5

<b>(Inter)national conferences</b>	<b>Year</b>	<b>ECTS</b>
Infectious diseases symposium Amsterdam	2019-2021	0.75
European Congress of Clinical Microbiology And Infectious Diseases	2021-2022	1.5
SWAB middagsymposium	2018-2021	0.5
Dutch Pharmacology Day	2021	0.5

<b>Other</b>	<b>Year</b>	<b>ECTS</b>
Clinical pharmacologist in training	2019-2021	25
Antimicrobial Stewardship Team member Amsterdam UMC	2018-2022	2.0
CureVac Harold study	2021	6.4

<b>Teaching</b>	<b>Year</b>	<b>ECTS</b>
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#### **Lecturing**

Clinical pharmacology: bachelor's students	2020	0.25
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#### **Supervising**

Master's thesis Aleid Breuning: SARS-CoV-2 antibody response in asymptomatic patients	2020	1.5
Pharmacy students: How to perform a Point Prevalence Survey?	2018-2022	0.5
Pharmacist in training: Anne van Schip	2021	1.5

<b>Parameters of Esteem</b>	<b>Year</b>
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#### **Grants**

Travel grant All&I	2022
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## About the author

Annemieke Kaniki van den Broek was born in Mwanza, Tanzania, on June 18<sup>th</sup> 1992. When she was four years old, she moved to Helmond, the Netherlands, where she grew up with her parents Jacques and Eliza, together with her sisters Marlies and Ineke and her brother Hans. She was a dancer (ballet, jazz, hip-hop) and won several championships (Dutch, European and World) with her hip-hop team “Young and Extreme”. In 2010 she completed her Athenaeum education at dr.- Knippenbergcollege Helmond, after which she moved to Amsterdam to study medicine at the University of Amsterdam. During her studies she went back to her roots, Sengerema, Tanzania, where her mother was born. Here she did an elective clinical internship in Tropical medicine in the hospital where her father worked as clinical officer in charge in the ‘80’s. She finished her scientific Masters’ internship at the department of Endocrinology of the Amsterdam UMC, supervised by prof. Fliers, which resulted in a long-lasting enthusiasm for science. In 2017 she graduated cum laude from the University of Amsterdam, after which she worked for 8 months as Internal Medicine resident in MC Slotervaart, Amsterdam. In April 2018, she started her PhD trajectory at the department of Infectious diseases of the Amsterdam UMC, supervised by prof. dr. Jan Prins, dr. Reinier van Hest and dr. Caroline Visser, resulting in this thesis. During her PhD she completed the training to be a clinical pharmacologist. In addition, she volunteered to aid in the integration of refugees (‘newcomers’). In October 2022 she started her residency Internal Medicine at Ziekenhuis Amstelland – Amsterdam UMC, which she will continue to do so for at least six years.



Annemieke currently lives with her partner Pim and their son Louka in Muiden. Next to her love for her family (and for medicine), she loves hiking, running, bikepacking, ice-skating and convincing her friends and colleagues to do these activities with her and Pim (or other less active social activities).

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Lieve Eem, je hebt me een enorm warm welkom gegeven de eerste dag dat ik aan de slag ging, waarvoor dank! Jammer genoeg kunnen we niet meer samen naar huis reizen en komen we elkaar niet meer spontaan tegen in de Haarlemmerstraat. Gelukkig zal ik je in de toekomst nog vaak genoeg zien als burgemeester van Amsterdam.

Lieve Thomas, dank voor al je gevraagde en ongevraagde adviezen, gezelligheid, VO2 max competitie en voor het zijn van mijn Disney buddy. Well, come to think of it. Kid, honestly I could go on and on.

Lieve SAAF, mijn laatste jaren heb ik voornamelijk met jullie gespandeerd. D3 – of zeg maar gerust mijn promotietraject an sich - would not be the same without you en dat weten jullie.

Suus, je bent uniek. Ik ben blij dat ik vanaf dag 1 een mede sportfanaat had, met wie ik ook nog eens kon borrelen, schaatsen en NONMEM-nooben. Aaf, mijn vraagbaak, luisterend oor dag in dag uit, mede harry, twilight, bridgerton lover. Je bent een fantastisch persoon! Allebei: you do you, altijd!

Lieve Sanne, van het slootje naar het AMC. De koffie zal niet hetzelfde smaken zonder jou. Dankjewel voor de gezelligheid gedurende de afgelopen 5 jaren!

Mijn lieve vrienden: OG's, SLW, krullenbolliës, geneeskunde vrienden.

Dank voor jullie gezelligheid, de spiegel die jullie mij voorhouden wanneer ik weer eens onzeker ben, de drankjes, dansjes, sportactiviteiten, vertrouwen en meer!

Sil, dank voor het verbeteren van mijn Nederlandse samenvatting.

Kim (Blekkenhorst, reclame), dank voor het prachtig ontwerp van de kافت en huisstijl! Je hebt mijn roots en de oorspronkelijke kافت van mijn vader beeldig geïllustreerd.

Mijn paranimfen, dankjulliewel dat jullie er altijd voor me zijn en voor jullie bereidheid om mij bij te staan tijdens mijn verdediging!

Lieve Flo (Floor), co-buddy, sport-buddy, nieuwjaarsduik-buddy, promotie-buddy, klinische farmacologie-buddy, algeheel-buddy. We lopen nagenoeg hetzelfde traject, alleen jij bij de kinder. Vanaf dag 1 was jij er voor mij om al mijn verhalen, onzekerheden, problemen, mijlpalen aan te horen en te aanschouwen. Ik kan niet wachten tot je mijn buurvrouw wordt!

Lieve Margereth (Margot), van p1a(llerbeste), naar Amsterdamse/Muidense yuppen. Wat hebben we veel meegemaakt he? Dankjewel voor jouw vriendschap (bijna 18 jaar and counting) en je bijdrage aan mijn allereerste artikel. Geef een econometrist data en ze maakt er een mooi tabel van. De vraag is of ie in de smaak valt bij andere artsen, maar dat terzijde.

En dan, save the best for last:

Familie: Jullie zijn allen een motivator geweest voor het volgen van een promotietraject en hebben mij gemaakt tot de persoon die ik nu ben en waar ik trots op ben.

Lieve vader, vijf jaar geleden heb je het eerste stokje overgedragen, nu ik – wat carrière betreft – nagenoeg volledig in jouw voetsporen loop is het tijd om het tweede stokje over te dragen. Dankjewel dat je de weg voor mij vrij hebt gemaakt om het behalen van een doctorstitel na te streven. Mijn basis voor het worden van een goede arts is gelegd doordat je ons enerzijds overal mee naartoe hebt genomen (Sengerema hospital, het KIT en het tropenmuseum, dienstritjes in Helmond en Eindhoven) en anderzijds omdat je ons nagenoeg nooit naar de huisarts hebt meegenomen. De diagnose aanstelleritis werd veelvuldig gesteld, waardoor ik toen al leerde om hoofd- van bijzaken te onderscheiden. Dankjewel!

Lieve mama, jij bent mijn grootste motivator. Je hebt me laten inzien hoe belangrijk studeren is. Jij bent de sterkste vrouw die ik ken en bezit alle eigenschappen van een goede onderzoeker: nieuwsgierig, optimistisch, enthousiast en veerkrachtig – en dat allemaal in het kwadraat. De weg die jij hebt af gelegd, van Sengerema naar de roltrappen van Dar es Salaam en naar Stiphout en alles ertussenin,

hebben jou nooit tegengehouden om door te gaan met een glimlach. Ik ben blij dat ik een fractie van deze eigenschappen bezit. Dankjewel voor jouw steun wanneer het even te veel wordt, jouw kookkunsten wanneer we daar zin in hebben en gewoon het thuis zijn, bij jou. Nakupenda sana, Ahsante sana, Kushukuru, Emienza

Lieve Lies, jij droomt, letterlijk, als geen ander. Jouw enthousiasme voor promoveren, het niet denken in hokjes en het streven naar perfectie is op mij overgewaaid. Ik hoop dat mijn proefschrift die van vader evenaart in jouw ogen!

Lieve lens, jij bent niet kapot te krijgen, zelfs niet door het syndroom van Lemiere. Dankzij jouw mentale en fysieke kracht !! (en ok, ook een beetje door de Nederlandse gezondheidszorg en de antibiotica). Jij bent de reden dat ik graag wilde promoveren bij het A-team, infectieziekten, resulterend in een fantastisch promotietraject.

Lieve Hans, samen in de klas op de basisschool, middelbare school en in de collegebanken. Alles samen, met af en toe een pauze. Pole pole, samen tot aan de eindstreep. Dankzij jou weet ik hoe ik mijn hoofd koel moet houden tijdens zeer stressvolle situaties, wat het werken nu een stuk makkelijker maakt.

Allerliefste Pim, waar te beginnen.. Bij het begin dan maar? De eerste date heb ik helaas moeten afzeggen, omdat ik net met een nieuw co-schap zou beginnen de volgende dag, chirurgie nota bene. Was dit het moment dat je dacht, dit ruwe diamant dient geslepen te worden, of was dat pas bij het aanschouwen van my heart will go on met gestijlde haren? En geslepen heb je. Van toen tot nu heb jij altijd aan mijn zij gestaan, mij aangemoedigd, mij (zelf)vertrouwen gegeven en mij laten inzien dat ik alles kan bereiken wat ik zou willen. Tegenslagen horen erbij en perfectie bestaat niet (let je zelf ook op?). Naast dat de haren los gingen, ben ik ook gaan loslaten. Het resultaat: rust. Mieksie wasn't built in one day en had Pimmetje nodig om dat in te zien. Dankjewel dat je me de ruimte hebt gegeven om deze ontwikkeling door te maken, om mijn dromen na te jagen en voor al het andere wat buiten het bestek van dit boekje gaat. Big time, long time, every time.

En dan, teamwork makes the dream work. Louka, lieve kleine Louka, jij bent alles.

