Monte Carlo simulations of pharmacodynamic target attainment of ceftriaxone, ertapenem, fosfomycin, and gentamicin for the treatment of uncomplicated anogenital gonorrhea. A substudy of the NABOGO RCT.

Abstract

Introduction: The increasing rates of gonococcal antimicrobial resistance to many treatment options such as penicillins, sulphonamides, tetracyclines as well as last line option cephalosporins make Neisseria gonorrhoeae (Ng) a multidrug resistant organism. The aim of this project was to predict the efficacy of the alternative antimicrobial agents ertapenem, fosfomycin, and gentamicin along with the first-line choice ceftriaxone for the treatment of uncomplicated gonorrhea.

Methods: Blood samples were collected from 60 healthy volunteers and 61 gonorrhea participants of the NABOGO study (NCT03294395), who received either 500 mg ceftriaxone ,1000 mg ertapenem, or 5mg/kg gentamicin intramuscularly or 6 g fosfomycin orally. Subsequently four blood samples were taken at approximately T=0.5, 1.5, 5, 24, hours. Population pharmacokinetic (PK) models were developed and used to simulate the time course of drug exposure using stochastic Monte Carlo simulations (MSC).

Results: Typical clearance (and inter-patient variability) was 0.817 (17.5%), 1.65 (26.9%), 19.7 (21.5%) L h^{-1} for ceftriaxone, ertapenem, and fosfomycin respectively. The mean elimination rate constant for gentamicin was 0.0143 (50%) h^{-1}. The probability of target attainment (PTA) at a MIC value of 1 mg/L amounted to 96.4% for ertapenem. Fosfomycin reached 100% PTA up to a MIC of 2 mg/L. The PTA for ceftriaxone and gentamicin reached a value of respectively 97.8% and 100% at MIC 0.5 mg/L with the current dosing.

Conclusion: The study revealed, both through clinical efficacy trials and MCS, that the decline of ceftriaxone susceptibility levels can be managed using the antimicrobial ertapenem as an alternative first-line therapy for gonorrhea. Gentamicin showed intermediate efficacy. Unlike in the clinical trial, fosfomycin simulations showed promising efficacy, though further research is required using a more frequent dosing regimen to reach optimal serum concentrations. Ceftriaxone simulations were consistent with the primary clinical results of clearance of *N. gonorrhoeae*.

Introduction

Gonorrhea is one of the most common sexually transmitted diseases with, according to the World Health Organization, 87 million new cases worldwide each year, mostly among people aged 15 – 49 years (1,2). Due to the rising spread of resistant strains, the annual lifetime medical costs of 133.4 million dollar and the potential increases in medical costs, gonorrhea has become a major public health concern(3). Gonorrhea is spread to the genitals, rectum or throat through sexual contact and can lead to serious complications including severe reproductive health complications such as pelvic inflammatory disease (PID), and tubular factor infertility, if left untreated(4). It is also associated with an increased risk of HIV acquisition and transmission. Just like many other gram-negative pathogens the bacterium Neisseria gonorrhoeae, that causes this infection, has become resistant to commonly used antimicrobial drugs(1,3).

Ceftriaxone 500 mg intramuscularly as a single dose is the recommended first-line treatment for gonorrhea(5).
Since there are no alternative treatment options for gonorrhea, it is necessary to investigate the efficacy and safety of alternative antimicrobials.

Ertapenem, like the current treatment ceftriaxone, belongs to the so-called beta-lactam antibiotics and the MIC of resistant N. gonorrhoeae strains have been proven to be much lower for ertapenem(6). Therefore, it is likely to be effective in treating extended-spectrum cephalosporin-resistant gram-negative bacteria such as N. gonorrhea(7). In addition, ertapenem has also been proven to be effective against other extended spectrum beta-lactamase (ESBL) producing gram-negative bacteria. Ertapenem is generally administered through intramuscular injection; however, this mode of administration has not yet been registered in Europe.
Another alternative antimicrobial agent useful in the treatment of gonorrhea might be fosfomycin. The relatively old and “forgotten” antibiotic fosfomycin has a broad spectrum of in vitro activity and can function as a safe and potential option in a time of increasing prevalence of multi-drug resistant bacteria. Due to its relatively low use, and unique mechanism of action, resistance to fosfomycin continues to be rare(8).
Gentamicin, an aminoglycoside, is a widely used antimicrobial used to treat various types of bacterial infections including PID, urinary tract infections and pneumonia among others(9,10). It has also been useful for treating bacteria resistant to other antimicrobials. Aminoglycoside treatment is associated with nephro- and ototoxicity(9). The effect of a single dose of gentamicin has led to a transient rise in creatinine in earlier studies(11). However, persistent impairment and other adverse clinical events were rare.

From 2017 to 2020 the NABOGO double-blind randomized clinical non-inferiority trial (RCT) was conducted, evaluating the efficacy of ceftriaxone (n=103), along with ertapenem (n=103), fosfomycin(n=38), and gentamicin(n=102) as treatment alternatives for anogenital Ng (12). The primary outcome was the proportion of patients with successful treatment of anogenital gonorrhea, defined as a NAAT-negative test-of-cure (TOC) of the primary anatomical site of infection in each study arm 7-14 days after treatment. The primary endpoint in the ceftriaxone, ertapenem, fosfomycin, and

gentamicin arm was observed in 100%, 99%, 93%, and 12% of the patients with anogenital gonorrhea, respectively. In patients with pharyngeal gonorrhea, the primary endpoint was observed in 90% of the patients treated with ceftriaxone, 88% with ertapenem, and 26% with gentamicin(12).

PPK analysis

Analyzing pharmacokinetic (PK) data using the software NONMEM® has emerged as an important tool to integrate data, acquiring pharmacokinetic knowledge, and aiding the decision-making regarding drug dosing regimens(13). It provides information regarding the population mean value of PK parameters and the distribution of these parameters i.e., the interindividual variability (IIV) calculated from observations in that specific population based on maximum-likelihood estimates using stochastics methods. Quantifying these IIVs of the model parameters clearance (Cl), volume of distribution (V), and absorption rate constant (Ka) is critical to the ability to describe the pharmacokinetics of a typical individual within a population as accurately as possible. After a drug is administered it traverses through a biological system undergoing four essential processes of absorption, distribution, metabolism, and excretion. The absorption is significantly impacted by the solubility of an antimicrobial agent as well as its volume of distribution which, in turn, is influenced by the extent of plasma protein binding by the antibiotic(14). The primary plasma binding protein for most antibiotics is albumin. Only the free, unbound drug distributes into the extravascular space and is responsible for pharmacological activity and/or side effects(14). Antimicrobial activity is related to antimicrobial exposure over a dosing interval relative to the minimal inhibitory concentration (MIC). The MIC is the lowest concentration, typically stated in milligrams per liter (mg/L), at which an antimicrobial agent can inhibit the growth of a specific microorganism. It functions as a static threshold value that varies depending on the pathogen and can be determined by evaluating the growth and antibiotic-induced kill profile over time(1,5).

Estimating pharmacokinetic population parameters and their respective IIVs will help understand the dose-exposure-response relationships relative to a range of values for the susceptibility of gonococcal strains. Consequently, providing answers on appropriate drug regimens needed to treat gonorrhea under changing antimicrobial resistance based on the drug's pharmacodynamic index using Monte Carlo simulations (MCS). Combining pharmacokinetic data of these alternative antibiotics, based on plasma drug concentration data, with antimicrobial susceptibility data will help predict their treatment efficacy.

The aim of this study was to assess the population pharmacokinetics of the alternative antimicrobials: ertapenem, fosfomycin, gentamicin, along with current first-line treatment ceftriaxone thereby investigating the extent to which simulated patients achieved the required pharmacodynamic exposure targets, relative to the MIC required to treat gonorrhea, through PK modeling and simulations. Thus, keeping pace with antimicrobial resistance by providing answers on treatment efficacy and safety of these alternative drugs and perhaps extend current treatment protocol with successful alternative options.

Materials and methods

Sample collection and analysis

The data used to develop the population PK models for each antibiotic came from the NABOGO RCT and the Nabogo substudy(12). See Figure 1. The patients enrolled in the NABOGO RCT received either ceftriaxone or one of three experimental antimicrobials with treatment success as an endpoint in each study arm. The antimicrobial agents ceftriaxone 500 mg, ertapenem 1000 mg, and gentamicin dose of 5 mg kg^{-1} with a maximum of 400 mg (divided over two separate injections) were administered by intramuscular injection. Fosfomycin 6g was administered orally. See Table 1. The fosfomycin arm was terminated early following an interim analysis revealing <60% efficacy. Due to low participation of NABOGO participants in the PK analysis we impleneted a NABOGO substudy. In this substudy, we recruited healthy volunteers who received similar doses of these antimicrobials. Gentamicin was not included in the substudy due to its potentially serious side effects such as nephrotoxicity and ototoxicity. In the NABOGO RCT, one blood sample was collected at two or three random time points distributed over the following options: 0.5, 1, 2, 4, 6, 8 or 24h after treatment administration. In the NABOGO substudy, four blood samples were taken at approximately T=0.5, 1.5, 5, 24, hours after administration.

Total plasma drug concentrations of the antibiotics were assayed in the clinical laboratory of the pharmacology department by liquid chromatography coupled to mass spectrometric detection. Between- and within day variation of the measured plasma concentrations was 1.5% in the concentration range of 0.4 to 10 mg/ml.
Along with the plasma concentrations, creatinine, albumin, and alanine aminotransferase (ALAT) serum concentrations were measured.
The following data were recorded for each patient: identification number (ID), dose administered, date, time, total plasma concentrations at specific times, creatinine concentration, albumin and ALAT on drug admission, bodyweight (BW), length, age, and sex.

Data analysis

The total plasma concentration data were analyzed using nonlinear mixed effects modelling (NONMEM) software. Pirana was used as a graphical interface for NONMEM. The post evaluation analysis of individual plots and model diagnostics of NONMEM output was performed using the R-studio software package “Xpose”.
The pharmacokinetic data was used to estimate the set of PK parameters along with the interindividual variability, and residual unidentified random effects(15). The pharmacokinetic analyses including the final parameter estimates, consecutive analysis, as well as covariate modelling, were performed using the First Order Conditional Estimation (FOCE) algorithm.
Concentration versus time profiles were described with compartment models. Estimated PK parameters included rate of absorption (Ka), volume of distribution (V) and clearance (CL). As bioavailability (F) could not be estimated V and CL reflect the “apparent” parameters (V/F and CL/F).

Interindividual variability of the pharmacokinetic parameters were estimated using log-normal distributions with mean zero and ω^2 variance. Residual variability was estimated using a proportional and residual error with additive and combined error structures with mean of zero and variance σ_1^2(16). The oral bioavailability including a term for variability was investigated during fosfomycin PK/PD modeling.
In the population PK analysis, it was determined whether IIV could be explained by specific patient characteristics or covariates. The covariate influence on the PK parameters were originally examined by plots of the individual parameter against various clinical characteristics. Then, stepwise forward inclusion method was used to incorporate selected covariates to the basic structural model. Following, the linear relationship was assessed centering the median value of the covariate within the studied population.
After finalization of the structural model, covariate model screening was performed to identify covariates that significantly explain IIVs in the population PK parameter and thereby improving the model's predictive performance i.e., closer determination of individual measurement values(17). Eventually providing dosing recommendations based on the pharmacokinetic effect of a particular condition e.g., creatinine, age, gender bodyweight etc.
Although covariates can only explain a small fraction of the variation between predicted values, covariate parameters were included in the model if the decrease in the Objective function value (OFV) was at least 3.84 for one degree of freedom ($P< 0.05$)(18). The likelihood ratio test on the differences in the OFV was used to statistically compare the models. The plasma concentration data of all four drugs were best described using a one compartmental model.
The effect of using fixed estimates of parameters was also examined.

Model evaluation and validation

The models were evaluated by visual inspection of the goodness of fit plots. Thereby inspecting the plots of the measured concentrations versus individual (IPRED) and population predictions (PRED), conditional weighted residuals (CWRES) vs. PRED and CWRES vs. time.
To analyze the stability and robustness of the model and determine the confidence intervals of the final population model parameters bootstrap analysis (n=1000) was performed. The predictive performance of the final PK model was evaluated through a Visual Predictive Check (VPC) in which the different percentiles of the observed data were compared to the percentiles of the simulated data, grouped together within bins. This internal validation visualizes the median model prediction and the variability between patients and within patients (5th and 95th percentiles).

PK/PD properties

The relationship between the required exposure to an antibiotic i.e., the time (T) the free drug concentration remains above the MIC, and the clinical efficacy differs between antibiotics. Exposure to antibiotics can be concentration- or time-dependent(19). Optimizing antibiotic exposure increases the therapeutic impact thereby reducing the risk of antimicrobial resistance(20). The pharmacological information regarding the PD target of the used antimicrobials, resulting in maximal activity and minimal toxicity to

treat gonorrhea has not yet been extensively studied. Most antibiotics that have been reintroduced due to the decrease in new antimicrobial agents are still being reassessed. Defining the correct PK/PD index needed to maximize clinical efficacy while minimizing the risk of toxicity is critical to determine the optimal antibiotic dosing regimen in which patients achieve the required target needed to treat gonorrhea(21).

PD targets associated with maximum therapeutic efficacy of the antibiotics investigated in this study are shown in Table 1 and were preclinically defined based on animal or in-vitro models reported in scientific literature(22). The efficacy of the time-dependent antimicrobials ceftriaxone, ertapenem, and fosfomycin are associated with free drug concentrations remaining above the MIC for respectively 80%, 40%, and 70% of the dosing interval. Given that all regimens consisted of one dose only this equates to 19.2, 9.6, and 16.8 hours respectively based on a 24-hours interval. The efficacy of the concentration-dependent gentamicin is associated with a free drug maximum concentration to MIC ratio of 10 or higher(23). This, in addition to drug specific properties and antimicrobial activity associated with treatment efficacy, along with the extent of plasma protein binding were critically examined before the simulations were performed. The protein binding values for each antimicrobial, also shown in Table 1, were used to correct total plasma concentration measurements for protein binding. The 1,000 simulated concentration-time profiles per antimicrobial were then used to predict the probability of target attainment (PTA).

Probability of target attainment

The probability of target attainment was calculated based on 1,000 simulations using the final population PK models. The PTA vs. MIC curves show the percentage of the probability of patients reaching a predefined PK/PD target relative to different bacterial minimum inhibitory concentrations (MICs). This will assist in determining the optimal plasma concentration values and support dose recommendations within a patient population.

PTA analyses are used to determine the susceptibility breakpoints and play a key role in the optimization and justification of dosage regimens using simulations. It can also be used to recommend specific dosing in subpopulations like infants or elderly patients(25). Based on the EMA guidelines, dosing regimens to treat pathogens with MICs of the pathogen at the upper end of the wild-type distribution are considered efficacious when provided a PTA > 90% based on the selected PD-target(25).

Results

Patients and samples

Blood samples of 60 volunteers from the Nabogo substudy and 61 gonorrhea patients who participated in the NABOGO study were collected. The characteristics of the volunteer and patient group are displayed in Table 2. For ceftriaxone samples from 22 volunteers and 17 patients were available. For ertapenem samples from 20 volunteers and 21 patients were collected. For fosfomycin samples from 18 volunteers were collected and for gentamicin samples from 23 patients were collected.
Two samples from volunteers who received fosfomycin had concentrations below the limit of detection. In the PK analysis these samples received the concentration value of the limit of detection. The pharmacokinetic profiles of the volunteers did not differ significantly from the gonorrhea patients.

Pharmacokinetic analysis

The time profiles of plasma concertation of all the antibiotics were best described by a one-compartment model.

The population PK model for ceftriaxone estimated a population mean value of 0.817 L/h for CL and the V amounted to 9.49 L. The estimated Ka was equal to 1.77 h^{-1} (Table 3a). The IIV parameter on V did not give a significant improvement in the model fit, hence this value could not be estimated.
For ertapenem average CL was 1.65 L/h, Ka was 0,958 h^{-1}, and V was 9.42 L (Table 3b). IIV could be estimated for Ka and CL as the correlation between V and CL was high. Hence, both variance terms of these parameters could not be individually estimated. For Fosfomycin CL was 19.7 L/h, Ka was 0,119 h^{-1}, and V was 14.2 L (Table 3c).
The basic goodness of fit plots in Figure 2a-d show a decent fit of the model to the data. The individual ertapenem plots used for comparison and closer inspection of the predictions are shown in Figure 3.
The population PK model for gentamicin was developed using a published one-compartment model with first-order elimination and its parameterization described in Lent-Evers et al(24). The elimination rate constant (K_E) in this model is calculated using the following formula:

$$K_E = K_{NR} + K_R \cdot CL_{CR} \quad (1)$$

In which the elimination rate constant K_E is described as a function of nonrenal clearance (K_{NR}) and renal clearance (K_R) as a function of creatinine clearance (CL_C). The single gentamicin plasma concentrations following a single intramuscular dose were implemented in this model without parameter estimation. The value for the absorption rate (K) was added to the model and fixed based on earlier studies through which values above 3 h^{-1} produced a relatively better fit than values below 3 h^{-1} to describe the rate in which gentamicin was absorbed intramuscularly, (9).
The PK parameter estimates of the final models are included in Table 3d.

The inclusion of several covariates led to a statistically significant improvement of the fit of the data. Especially BW on CL in the ceftriaxone model and BW on V in the ertapenem model. The effect of the covariate creatinine clearance on CL led to a significant decrease in OFV in the ertapenem model as well. The covariate effects were not included in the models and must be further investigated using additional data. The VPC plots of the final models are shown in Figure 4. The results of the bootstrap analyses for ceftriaxone, ertapenem, and fosfomycin are shown in Table 3a-c.

Probability of target attainment

The PD targets evaluated for the single dose administration for ceftriaxone, ertapenem, fosfomycin, and gentamicin were 80% fT>MIC, 40%f T>MIC, 70% fT>MIC, and Cmax/ratio≥ 10, respectively(19). The measured total drug concentrations were converted to free fraction prior to simulations based on plasma protein binding found in literature (Table 2).

PTA vs. MIC-curves

The PTA as a function of MIC for the studied antimicrobials are illustrated in Figure 5. The curves were used to investigate the percentage of patients achieving associated pharmacodynamic target following drug administration at different MIC values ranged from 0.03125-16 mg/L for all four antimicrobials.

Ertapenem simulations provided a PTA-value of 96.4% up to a MIC-value of 1mg/L. In-vitro studies showed that ceftriaxone-resistant isolates (MIC=0.5-4 mg/L) had ertapenem MICs of 0.016 to 0.064 mg/L(7). The PTA-value exceeding 90% at the MIC breakpoint indicates that ertapenem might be a potential therapeutic agent in the treatment of ceftriaxone-resistant gonorrhea.

To examine whether sufficient plasma concentrations are achieved with the current treatment, PTA versus MIC profiles were also determined for ceftriaxone. Ceftriaxone reached sufficient PTA at MIC ≤ 0.5 mg/L.

Ng isolates tested against fosfomycin showed MICs ranging from ≤1 to 32 mg/L demonstrating full susceptibility at MIC 4 mg/L and lower(23,26). Fosfomycin simulations allowed a PTA of 100% to be obtained for a MIC-value up to 2 mg/L. The probability of simulated patients attaining the target Cmax/MIC≥ 10 after administering gentamicin was higher than 90% at a MIC value of 0.5 mg/L and lower. Strains with a MIC≥ 1 mg/L resulted in the probability of target attainment below the accepted value after administration of gentamicin.

Discussion

Given the paucity of effective anti-gonococcal agents, novel strategies to treat N. gonorrhoeae are urgently needed. Over the past decades Ng has developed resistance to nearly every drug used to treat the infection, including sulfonamides, penicillin, tetracycline, and fluoroquinolones(27). This led to the current recommended treatment supporting ceftriaxone monotherapy(28).
Based on in vitro studies, ertapenem, fosfomycin, and gentamicin have been suggested as potential alternative treatment options(6,23,26). To assess and explore their antimicrobial efficacy against Ng population PK models were developed allowing the performance of MCS thereby evaluating the PTA for a range of MIC values.
Based on the obtained PTA vs. MIC profiles for each of the alternative antimicrobials, treatment outcome was predicted based on the relationship between the MIC and PD target. The PTA vs. MIC profile for ertapenem showed PTA values above 90% for a MIC of 1 mg/L or lower indicating antimicrobial efficacy against ceftriaxone-resistant strains. The results also showed that ceftriaxone could possibly be used in isolates with a MIC-value higher than the EUCAST resistance breakpoint 0.125 mg/L as the curves predicted PTAs greater than 90% up to MIC of 0.5 mg/L. Moreover, increasing the ceftriaxone dose could extend the duration of time during which ceftriaxone plasma concentration exceeds the MIC-value. Gentamicin showed moderate efficacy against Ng exceeding 90% PTA up to an MIC of 0.5 mg/L. The simulations performed with the fosfomycin model showed promising activity against Ng allowing PTA >90% to be reached up to a MIC-value of 2 mg/L. Its unique mechanism of action and promising in vitro activity makes it an attractive option to treat Ng.

Although our MCS demonstrated efficacy of fosfomycin against Ng, in the RCT the fosfomycin arm was terminated after an interim analysis, due to low clinical efficacy. The explanation for these contradictory results of fosfomycin reaching PD targets based on the model predictions while leading to treatment failure among gonorrhea patients in the NABOGO RCT remains uncertain(27).
Very little information is available for the PK/PD indices of fosfomycin as relatively few in-vitro studies have been done to study PK/PD properties of the drug(22). Based on time-kill assays, fosfomycin is considered to have time dependent activity in N. gonorrhea isolates and resistance has not been observed (22,27). Its time-dependent mechanism of activity and limited post-antibiotic effect implies the requirement of a more frequent dosing regimen to reach adequate serum concentrations.
Further studies are needed to identify its activity against Ng after oral administration of multiple doses. Hereby providing further justification of the PK/PD index and establishing susceptibility breakpoints for Ng to predict the optimal fosfomycin dose to treat gonorrhea. (29).

Nonetheless, the predictions of the ceftriaxone, ertapenem, and gentamicin models were in line with the results of the NABOGO RCT. This particularly confirms the clinical test results of ertapenem through model predictions implying clinical efficacy against Ng. The same applies for gentamicin as an alternative option, for example in low- and middle-

income countries where weak drug supply chains fail to make antibiotics consistently available, despite its low efficacy against pharyngeal gonococcal infections.

As for the PTA, this needs to be supported by PD data in which the correlation between reaching the target attainment and treatment success is examined. The results of the NABOGO RCT showed a very high rate of treatment failure in pharyngeal gonorrhea infections indicating suboptimal concentrations being reached in pharyngeal gonorrhea patients(28). Due to the pharynx being home to naturally occurring related bacteria of the Neisseria species, this can lead to colonization by commensal species and resistant strains. This makes it an important site for resistance emergence. In addition, the anatomical characteristics of the pharynx can hinder the drug penetration in this site(30). More information is needed about the degree of antimicrobial agents penetrating the mucous membrane of the pharynx, the pharmacokinetic properties, and the presence of inflammatory cell infiltration.
It is crucial to shed light on why many antimicrobial agents appear to reach suboptimal concentrations in tonsillar and other oropharyngeal tissue. Carrying out future studies focused on patients with pharyngeal gonorrhea and thereby performing more accurate simulations can help determine the optimal plasma concentrations and site-specific targets needed to treat this type of gonorrhea. This can result in a reduced risk of gonorrhea transmission and antimicrobial resistance.

In the population PK analysis only a limited amount of IIV could be explained by patient characteristics. This may be caused by the relatively small number of healthy volunteers, which was a small homogenous population with few outliers in terms of covariates. Most of the volunteers had similar weight, age, and renal function. Also, a limited number of samples were available from patients enrolled in the NABOGO RCT reducing the power in the covariate analysis.

The degree to which antibiotics bind to plasma proteins plays a major role in the rate of diffusion between plasma and tissue and thereby influences the clearance and volume of distribution of the drug(31,32). As the free drug concentration correlates with therapeutic effect, total drug plasma concentrations measured in this study were converted to free drug concentrations based on plasma protein binding extent found in literature. However, the extent of plasma protein binding is highly variable and can be altered by many factors, including stress, liver, or kidney disfunction(31). Measuring free drug concentrations with adequate precision and accuracy can be more time- and resource-intensive but will lead to more accurate PTA vs. MIC profiles and a more accurate correlation between susceptibility patterns and treatment outcomes.

Apart from genetic mutations leading to increased drug resistance of N. gonorrhoeae there are several factors that play an important role in the development of resistant strains such as overuse of antibiotics, underdosing of antibiotics, unrestricted access to (poor quality) antimicrobials and the inappropriate selection of antibiotics(33). Until effective alternative treatment options are available, responsible antimicrobial use and stewardship should be promoted along with other key properties to prevent sexually transmitted infections worldwide such as safe sex practices and early diagnoses.

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In conclusion, our MCS have confirmed that alternative antimicrobials are available for the treatment of gonococcal in the future when resistance to ceftriaxone may increase. The efficacy of ertapenem was shown to be optimal whereas gentamicin may have shortcoming efficacy, as in the RCT trial it exhibited reduced pharyngeal efficacy. However, based on the PTA profile, gentamicin could serve as an alternative if ertapenem is not available. In the MCS fosfomycin showed promising activity but needs further investigation using a more frequent dosing regimen to reach optimal serum concentrations.

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Tables and Figures

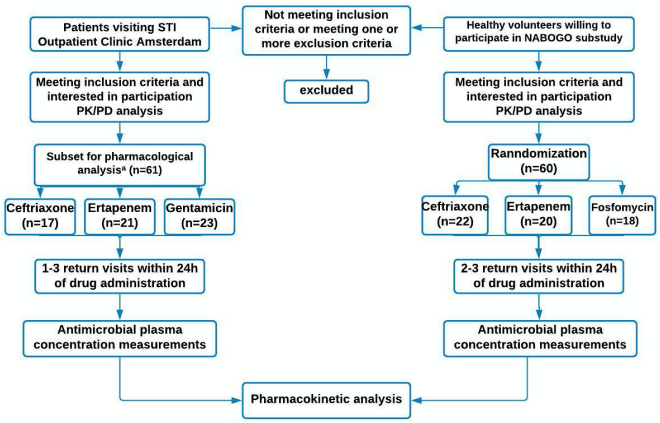

Figure 1. Flowchart illustrating the study design and the flow of participants (patients and volunteers) through the multi-arm trials.
[a] The fosfomycin arm had been discontinued on advice of the DSMB based on low efficacy prior to the additional PK study

Table 1. Administered antibiotics and the PK/PD indices associated with antimicrobial activity and plasma protein binding(5,7,8,10,34)

Antimicrobial	Dose	PK/PD index	PD target associated with optimal bacterial killing and/or clinical outcome	Plasma protein binding (%)
Ceftriaxone	500 mg IM	% fT > MIC	80% fT> MIC	83-96%
Ertapenem	1000 mg IM	% fT > MIC	40% fT> MIC	84-96%
Fosfomycin	6000 mg PO	% fT > MIC	70% fT>MIC	3%
Gentamicin	5 mg/kg IM	Cmax/MIC ratio	Ratio ≥ 10	30%

Abbreviation: IM, intramuscular. PO, per os. PK/PD, pharmacokinetic/pharmacodynamic. MIC. Minium Inhibitory Concentration. Cmax, maximum concentration.

Table 2. Patient characteristics including P values for continuous variables (Mann-Whitney test) and for categorial variables (chi-square test) respectively (11).

Demographics	Volunteers n (%) or median (IQR)	Gonorrhea patients n (%) or median (IQR)	P-value
	N=60	N=61	-
Sex (%) Male Female	 20 (33.3) 40 (66.7)	 56 (92) 5 (8)	<0.001
Age (years)	25 [24-27]	34 [26-41]	<0.001
HIV (%)	0 (0)	0 (0)	-
Weight (kg)	71 [62-82]	77 [68-82]	0.019
Length (cm)	173 [168-180]	183 [176-185]	<0.001
BMI (kg/m^2)	23 [21-25]	23 [21-25]	0.524
Creatinine (µmol/L)	74 [67-83]	80 [68-89]	0.148
Creatinine clearance (ml/min/1.73m^2)	113 [102-134]	127 [104-143]	0.058
ALAT (U/L)	20 [15-25]	-	-
Albumin (g/L)	46 [44-50]	-	-
Medication (%) • Ceftriaxone • Ertapenem • Fosfomycin • Gentamicin	 22 (36.7) 20 (33.3) 18 (30) -	 17 (27) 21 (34) - 23 (39)	-
Samples per AB (#) • Ceftriaxone • Ertapenem • Fosfomycin • Gentamicin	 4 4 4 -	 2 2 - 2	-

Abbreviation: HIV, Human immunodeficiency virus. BMI, Body Mass Index. ALAT, ALanine AminoTransferase.

Estimated population PK parameters

Table 3a. The pharmacokinetic parameter estimates from the final ceftriaxone model

Ceftriaxone 500 mg IM					*Bootstrap analysis*
PK parameter	*Estimate*	*RSE (%)*	*CI (5-95%)*	*Shrinkage*	*Medians (95%CI)*
CL (L h^{-1})	*0.817*	*5*	*0.74-0.89*	*-*	*0.818 (0.75-0.90)*
V (L)	*9.49*	*3*	*8.88-10.10*	*-*	*9.53 (8.95-10.24)*
Ka (h^{-1})	*1.77*	*9*	*1.45-2.09*	*-*	*1.79 (1.50-2.24)*
IIV CL (%)	*17.5*	*18*	*-*	*31.8%*	*16.9 (9.80-22.4)*
IIV V (%)	*Block*	*-*	*-*	*-*	*-*
IIV Ka (%)	*41.8*	*20*	*-*	*23.3%*	*40.2 (22.1-56.8)*
Prop. RE	*0.182*	*11*	*0.141-0.223*	*-*	*0.182 (0.14-0.24)*
Add. RE	*0**	*-*	*-*	*-*	*-*
Total				*19%*	*-*

*Fixed Add. RE
Abbreviation: PK, Pharmacokinetic. CL, Clearance. V. Volume of distribution. Ka, Absorption rate constant. Prop. RE, Proportional Residual Error. Add. RE, Additive Residual Error. RSE, Relative Standard Error. CI, Confidence Interval.

Ertapenem 1000 mg IM					*Bootstrap analysis*
PK parameter	*Estimate*	*RSE (%)*	*CI (5-95%)*	*Shrinkage*	*Medians (95%CI)*
CL (L h^{-1})	*1.65*	*4.7*	*1.49-1.80*	*-*	*1.63 (1.52-1.85)*
V (L)	*9.42*	*3.1*	*8,84-10,0*	*-*	*9.28 (8.58-9.87)*
Ka (h^{-1})	*0.958*	*11*	*0.742-1.17*	*-*	*0.93 (0.767-1.20)*
Corr CL-V	*0.299*	*57.2*	*0.036-0.63*	*-*	*0.30*
IIV CL (%)	*26.9*	*33*	*-*	*27%*	*25.2 (8.94-45.39)*
IIV V (%)	*NA**	*-*	*-*	*-*	*-*
IIV Ka (%)	*57.3*	*12*	*-*	*9%*	*56 (38.7-69.8)*
Prop. RE	*0.152*	*11*	*0.120-0.184*	*-*	*0.14 (0.11-0.17)*
Add. RE	*0*	*-*		*-*	*-*
Total				*30%*	*-*

Table 3b. The pharmacokinetic parameter estimates from the final ertapenem model
Abbreviation: PK, Pharmacokinetic. CL, Clearance. V. Volume of distribution. Ka, Absorption rate constant. Prop. RE, Proportional Residual Error. Add. RE, Additive Residual Error. RSE, Relative Standard Error. CI, Confidence Interval.

Table 3c. The pharmacokinetic parameter estimates from the final fosfomycin model

Fosfomycin 6g PO					*Bootstrap analysis*
PK parameter	*Estimate*	*RSE (%)*	*CI (5-95%)*	*Shrinkage*	*Medians (95%CI)*
CL (L h^{-1})	*19.7*	*8*	*16.6-22,80*	*-*	*19.6 (17.2-22.9)*
V (L)	*14.2*	*17*	*9.38-19.0*	*-*	*14.0 (10.0-19.3)*
Ka (h^{-1})	*0.119*	*7*	*0.103-0.135*	*-*	*0.12 (0.10-0.13)*
IIV CL (%)	*21.5*	*42*	*-*	*27%*	*21.2 (5.7-33.4)*
IIV V (%)	*-*	*-*	*-*	*-*	*-*
IIV Ka (%)	*16.9*	*39*	*-*	*33%*	*15.9 (3.23-32.9)*
Prop. RE	*0.367*	*11*	*0.296-0.456*	*-*	*0.36 (0.30-0.45)*
Add. RE	*0.8*	*23*	*0.443-1157*	*-*	*0.75 (0.24-1.15)*
Total	*-*	*-*	*-*	*10%*	*-*

Abbreviation: PK, Pharmacokinetic. CL, Clearance. V. Volume of distribution. Ka, Absorption rate constant. Prop. RE, Proportional Residual Error. Add. RE, Additive Residual Error. RSE, Relative Standard Error. CI, Confidence Interval.

Table 3d. The pharmacokinetic parameter estimates from the final gentamicin model (22)

Gentamicin 5mg/kg IM*				
Theta	*Estimate*	*RSE (%)*	*CI (5-95%)*	*Shrinkage*
Kelr	*0.0143*			
KNR (Lh^{-1})	*0.0118*	*-*	*-*	*-*
TVKR (L h^{-1})	*0.0025*	*-*	*-*	*-*
V (l/kg)	*0.33*	*-*	*-*	*-*
IIV KNR (%)	*50.0*	*-*	*-*	*-*
IIV KR (%)	*50.0*	*-*	*-*	*-*
IIV V (%)	*33.2*	*-*	*-*	*-*
Prop. RE (sd)	*0.1*	*-*	*-*	*-*
Add. RE (sd)	*0*	*-*	*-*	*-*

* With a maximum 400 mg (in two doses)
Abbreviation: PK, Pharmacokinetic. CL, Clearance. V. Volume of distribution. Ka, Absorption rate constant. Prop. RE, Proportional Residual Error. Add. RE, Additive Residual Error. RSE, Relative Standard Error. CI, Confidence Interval.

Goodness of fit plots of the final population PK models

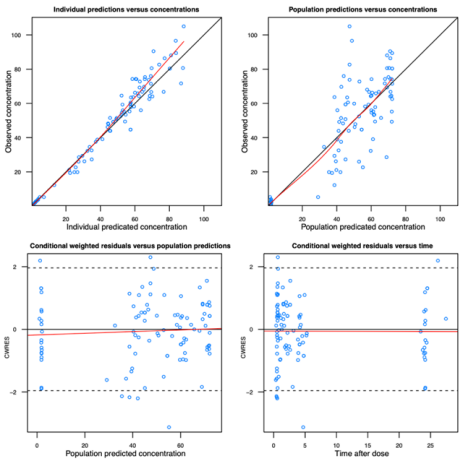

Figure 2A. GOF plots of the final population PK model for ertapenem

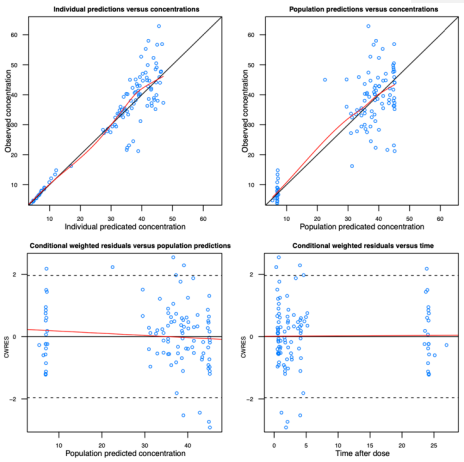

Figure 2B. GOF plots of the final population PK model for ceftriaxone

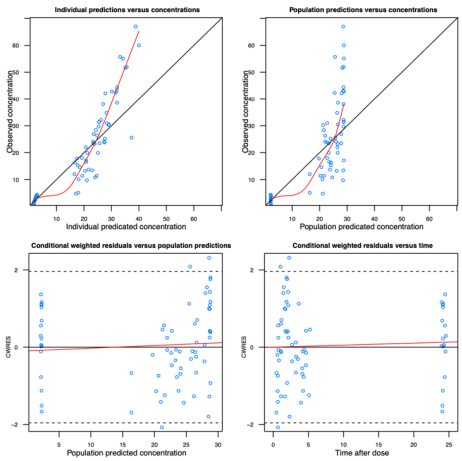

Figure 2C. GOF plots of the final population PK model for fosfomycin

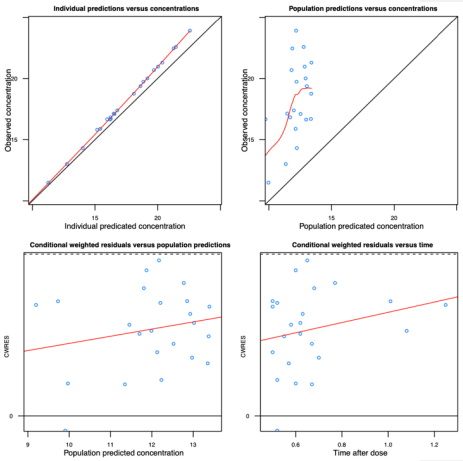

Figure 2D. GOF plots of the final population PK model for gentamicin

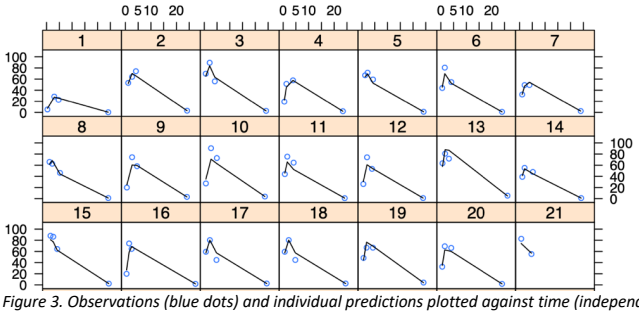

Figure 3. Observations (blue dots) and individual predictions plotted against time (independent variable) for every individual in the ertapenem group. Plots were used for comparison and closer inspection of the predictions.

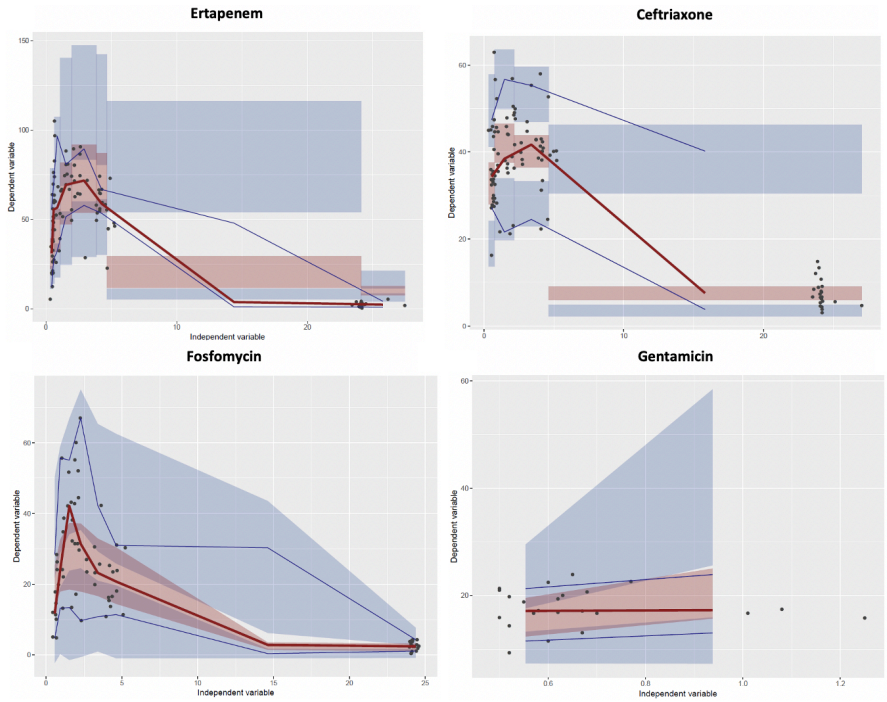

Figure 4. Visual predictive check plots of the final model for ertapenem, ceftriaxone, fosfmocyin, and gentamicin. The 95th and 5th percentiles of the predicted concentrations are represented by blue lines. The blue shaded areas represent the 95% CI for the predicted percentiles. The red line within the red shaded regions, displaying the 95% CI, represents the 50th percentiles.

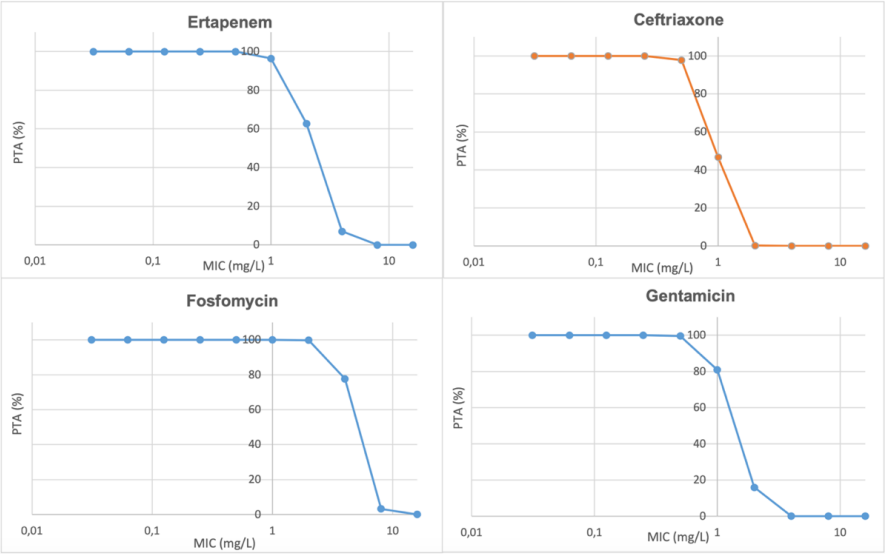

Figure 5. Probability of target attainment curves for the studied alternative antimicrobials and current last-line option ceftriaxone