Antimicrobial resistance in *Neisseria gonorrhoeae* (NG) and pharmacokinetic/pharmacodynamic (PK/PD) considerations

**Magnus Unemo and George Drusano**

**WHO CC for Gonorrhoea and other STIs**
Department of Laboratory Medicine, Örebro University Hospital, Sweden

**Institute for Therapeutic Innovation**
College of Medicine, University of Florida, Orlando, FL, USA
Accumulation of NG antimicrobial resistance (AMR) determinants ⇒ treatment excluded in >80 years – only ceftriaxone (± azithromycin) left!
Evidence of first international spread of ceftriaxone resistance in NG

- **2015-onwards**: Strain with resistance to ceftriaxone initially reported in Japan, followed by Australia, Canada, Denmark, France, Ireland, UK, China, Singapore, Cambodia....
- **2018**: UK and Australian isolates of the same strain
  - resistance to ceftriaxone plus high-level resistance to azithromycin

‘Man Has World’s Worst Super-gonorrhoea’,
BBC News, (28 March 2018)

Two new cases of resistant gonorrhoea in UK
BBC News (9 Jan 2019)
Countries with reported decreased susceptibility/resistance to ceftriaxone in NG, WHO GASP/GLASS 2015-16 vs. 2017-18

23.8% of countries (11.1% of countries ≥5%)

30.8% of countries (8.8% of countries ≥5%)

Unemo et al. Sex Health. 2019

Unemo et al In review
Verified treatment failures with ceftriaxone (CRO; 250-1000 mg) ⇒ increase surveillance!

<table>
<thead>
<tr>
<th>Country (No.; country of infection), year</th>
<th>(CRO , f_{T&gt;\text{MIC}}), hours (median)²</th>
<th>Site of failure</th>
<th>Final successful treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (n=2; Australia), 2007²⁸</td>
<td>41.4-50.3</td>
<td>Pharynx</td>
<td>CRO 500 mg×1/ CRO 1 g×1</td>
</tr>
<tr>
<td>Japan (n=1; Japan), 2009⁹</td>
<td>0</td>
<td>Pharynx</td>
<td>Noneb</td>
</tr>
<tr>
<td>Sweden (n=1; Japan), 2010¹⁰</td>
<td>15.6-32.8</td>
<td>Pharynx</td>
<td>CRO 1 g×1</td>
</tr>
<tr>
<td>Australia (n=1; Australia), 2010²⁹</td>
<td>41.3-49.9</td>
<td>Pharynx</td>
<td>AZM 2 g×1</td>
</tr>
<tr>
<td>Slovenia (n=1; Serbia), 2011²⁶</td>
<td>24.3</td>
<td>Pharynx</td>
<td>CRO 250 mg×1 plus AZM 1 g×1</td>
</tr>
<tr>
<td>Australia (n=2; Australia), 2011²⁷</td>
<td>41.3-49.9</td>
<td>Pharynx</td>
<td>CRO 1 g×1 plus AZM 2 g×1/</td>
</tr>
<tr>
<td>Sweden (n=3; Sweden), 2013-14²⁵</td>
<td>32.8-41.3</td>
<td>Pharynx</td>
<td>CRO 1 g×1</td>
</tr>
<tr>
<td>UK (n=1; Japan), 2014³⁵</td>
<td>24.3</td>
<td>Pharynx</td>
<td>CRO 1 g×1 plus AZM 2 g×1</td>
</tr>
<tr>
<td>France (n=1; France), 2017¹⁹</td>
<td>6.6</td>
<td>Pharynx</td>
<td>Lost to follow up</td>
</tr>
<tr>
<td>UK (n=1; Thailand), 2018²²</td>
<td>24.3</td>
<td>Pharynx</td>
<td>ETP 1 g×1, 3 days</td>
</tr>
<tr>
<td>UK (n=1; UKᵀ), 2018²¹</td>
<td>15.6</td>
<td>Rectum, Urogenital</td>
<td>ETP 1 g×1, 3 days</td>
</tr>
</tbody>
</table>

CRO even at 1 g×1 dose does not cure occasional cases (observed also in PK/PD modeling and Hollow Fibre Infection Model, in manuscript)

Modified from Unemo et al. Sex Health. 2019
WHO GASP – Limitations (improvements in progress)

- **Limited number of countries**, particularly in WHO African and Eastern Mediterranean Regions
- **Low number (<100/year) and suboptimal representativeness of isolates** in many countries (geographically, from all risk groups, sexes and anatomical sites)
- **Use of disc diffusion methods in some regions** – introduce MIC determination (agar dilution or Etest)!
- **Lack of standardised global QA (QCs and EQA)** – introduce 2016 WHO reference strains (Unemo et al. JAC. 2016; currently updated) and validated EQA!
- **Lack of harmonised global clinical breakpoints** for decreased susceptibility or resistance (most use EUCAST or CLSI)
- **No/limited clinical and epidemiological data of patients** (Euro-GASP and US GISP exceptions) CDC/WHO and WHO GLASS support improvements!
- **Limited surveillance of treatment failures, antimicrobial use (especially for STIs), AMR determinants, and genome sequencing** (introduced in some GASPs)
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- Limited surveillance of treatment failures, antimicrobial use (especially for STIs), AMR determinants, and genome sequencing (introduced in some GASPs)

Additionally lacking (partly caused present AMR situation)

- Limited understanding of the dynamic interaction between NG and antimicrobials (during their different concentration-time profiles) and in different infection sites, and about ideal dosing for effective NG kill + suppression of AMR amplification – antimicrobial PD (integrating microbiology and pharmacology)!
- For new antimicrobials, we need to avoid the same fate by improved PK/PD knowledge before antimicrobials are introduced for treatment (study kill and AMR suppression, ideal dosing, prediction of AMR, predisposition to AMR, resistance evolution and fitness of AMR strains)

(Euro-GASP and US GISP exceptions) CDC/WHO and WHO GLASS support improvements!
Optimising treatments for sexually transmitted infections: surveillance, pharmacokinetics and pharmacodynamics, therapeutic strategies, and molecular resistance prediction

Arlene C Seña, Laura Bachmann, Christine Johnston, Teodora Wi, Kimberly Workowski, Edward W Hook III, Jane S Hocking, George Drusano, Magnus Unemo

Global and national surveillance
- Expand and improve Neisseria gonorrhoeae antimicrobial resistance surveillance
- Develop antimicrobial resistance surveillance for Mycoplasma genitalium
- Monitor clinical treatment failures
- Inform treatment guidelines

Detection and diagnostic methods
- Develop sensitive rapid POC tests for detection of STIs
- Develop rapid POC tests for antimicrobial resistance prediction to guide individualised therapies
- Implement M. genitalium macrolide resistance testing before treatment
- Identify novel antimicrobial resistance determinants
- Promote newer technologies (eg, whole genome sequencing)

Research and public health initiatives
- Update treatment guidelines and syndromic management protocols
- Promote antimicrobial stewardship for STIs
- Provision of education and resources
- Promote STI research, especially POC tests, and new drug and vaccine development

Antimicrobials and therapeutic regimens
- Determine PK-PD parameters
- Explore single-dose monotherapies vs combination vs multiple-dose therapies
- Conduct modelling to assess resistance suppression
- Develop and investigate novel therapeutic agents

Figure 3: Key priorities for STI treatment optimisations

STI Treatment Optimizations expert workshop 2018 hosted by STI CTG (NIAID/DMID funded), Washington, USA
Pharmacokinetic considerations regarding the treatment of bacterial sexually transmitted infections with azithromycin: a review

Table 1. Comparative pharmacokinetics of antimicrobials commonly used for treatment of STIs

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Activity</th>
<th>Bioavailability (%)</th>
<th>Tmax (h)</th>
<th>Serum t1/2 (h)</th>
<th>V (L/kg)</th>
<th>Protein binding (%)</th>
<th>Predominant excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin¹⁹,²⁰</td>
<td>bacteriostatic</td>
<td>37 (oral)</td>
<td>2–3</td>
<td>68</td>
<td>31.1</td>
<td>concentration dependent: 51% at 0.02 μg/mL to 7% at 2 μg/mL</td>
<td>bile/faeces</td>
</tr>
<tr>
<td>Ceftriaxone²¹</td>
<td>bactericidal</td>
<td>100 (im)</td>
<td>2–3</td>
<td>6–8; im: 8.2²²</td>
<td>0.19²³</td>
<td>83–96</td>
<td>bile/faeces (44% of dose)</td>
</tr>
<tr>
<td>Doxycycline²¹</td>
<td>bacteriostatic</td>
<td>~100 (oral)</td>
<td>2–3</td>
<td>12–16</td>
<td>50</td>
<td>82–93</td>
<td>urine (30%–65% of dose)</td>
</tr>
<tr>
<td>Ciprofloxacin²¹</td>
<td>bactericidal</td>
<td>60–70 (oral)</td>
<td>1–2</td>
<td>5</td>
<td>3.2</td>
<td>20–40</td>
<td>urine (40%–50% of dose)</td>
</tr>
<tr>
<td>Cefixime²¹,²⁴</td>
<td>bactericidal</td>
<td>40–50 (oral)</td>
<td>2–6</td>
<td>3–4</td>
<td>1.1</td>
<td>70</td>
<td>urine (50% of dose)</td>
</tr>
</tbody>
</table>

Ceftriaxone:
Why work so well (injected, very bactericidal, good urine levels and bioavailability)?
- Low Vd (suboptimal cell penetration), high protein binding, poorly distributed into gyn. tissue, low levels in PMNLs and extravascular space…..
Pharmacokinetic considerations regarding the treatment of bacterial sexually transmitted infections with azithromycin: a review

Fabian Yuh Shiong Kong\textsuperscript{1*}, Patrick Horner\textsuperscript{2,3}, Magnus Unemo\textsuperscript{4} and Jane S. Hocking\textsuperscript{1} JAC. 2019

Table 2. Relative concentrations of antimicrobials in saliva compared with plasma\textsuperscript{38,42,88,90,105,106}

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Protein binding (%)</th>
<th>Saliva:plasma ratio\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>7–51\textsuperscript{b}</td>
<td>Conc dependent 6</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&lt;30</td>
<td>0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>50</td>
<td>0.9</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>32</td>
<td>healthy, 0.8; sick, 1.4</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>20–40</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefixime</td>
<td>65</td>
<td>0.2</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>85</td>
<td>0.2</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>82–93</td>
<td>0.1</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>83–96?</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Penicillin V</td>
<td>80</td>
<td>0 (not detected)</td>
</tr>
</tbody>
</table>

Saliva conc.: limited association with cure of pharyngeal gonorrhoea!
Pharyngeal gonorrhoea (asymptomatic, ↑ treatment failures and AMR emergence?)

- High saliva flow rate, swallowing and epithelial cell surface (with most bacteria attached) is replaced in ~3 hours ⇒ concentration in saliva is rarely reflecting efficacy?
- Where is gonococcal infection possible (found, e.g., intracellularly in tonsils, in cellular debri in tonsillar crypts, in tonsillar exudate, and in saliva)?
- How differs antimicrobial distribution by tissue type?
- Usually asymptomatic (↓ inflammation) ⇒ ↓ penetration of antimicrobial

**Legend**

1. Uvula
2. Tongue
3. Posterior pharyngeal wall
4. Soft palate
5. Posterior tonsillar pillar
6. Anterior tonsillar pillar
7. Tonsils

Modified from slide by Fabian Kong
Pharmacokinetic Determinants of Penicillin Cure of Gonococcal Urethritis

HAROLD W. JAFFE,† ARNOLD L. SCHROETER, GLADYS H. REYNOLDS, AKBAR A. ZAIDI, JOHN E. MARTIN, JR., AND JAMES D. THAYER

7-10 h of serum total PCG concentration above 3-4×MIC required for cure
- Initially extended to other antimicrobials/classes (serum conc 4×MIC_{90} ≥10 h after Cmax)!
Monte Carlo simulation ($fT_{\text{MIC}}$ of ≥20-24 h required for cure with ceftriaxone)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>median a</th>
<th>lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>65.4</td>
<td>32.6</td>
<td>&gt;90</td>
</tr>
<tr>
<td>0.03</td>
<td>56.9</td>
<td>28.3</td>
<td>&gt;90</td>
</tr>
<tr>
<td>0.06</td>
<td>48.5</td>
<td>23.9</td>
<td>&gt;90</td>
</tr>
<tr>
<td>0.125</td>
<td>40.3</td>
<td>19.6</td>
<td>83.3</td>
</tr>
<tr>
<td>0.25</td>
<td>31.6</td>
<td>15.4</td>
<td>65.8</td>
</tr>
<tr>
<td>0.5</td>
<td>23.1</td>
<td>11.1</td>
<td>49.8</td>
</tr>
<tr>
<td>1</td>
<td>14.6</td>
<td>5.32</td>
<td>34.4</td>
</tr>
<tr>
<td>2</td>
<td>6.05</td>
<td>0.0</td>
<td>20.3</td>
</tr>
<tr>
<td>4</td>
<td>0.0</td>
<td>0.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

- Ceftriaxone (CRO) MIC 0.25-2 mg/L: lower 95% CI 0-15.4 h for currently identified ceftriaxone-resistant strains ⇒ **1 g will not cure all cases internationally!**
Knowledge lacking regarding PK/PD for gonorrhoea treatment?

- **No detailed knowledge of nearly anything (considering all sites)?**
  - PK/PD efficacy drivers and their parameters (e.g. exact $fT_{>MIC}$ for CRO) for both NG kill and AMR suppression (can differ!)
  - Bacterial burden at different sites (some information available)
  - Mutational and transformational frequency (and donors) to AMR
  - Step size of AMR
  - Exposures to optimize bacterial cell kill rate and extent
  - Exposures to optimize AMR suppression
  - Infection site concentration (penetration, intra-/extracellular ratio, protein-binding, inflammation….in infected sites)

- **Dual (combination) therapy (extremely complex to understand)**

- **Frequently treat gonorrhoea + concomitant STI(s)/other infection AND in anogenital tract as well as in the complex pharynx**

Compiled from many slides from George Drusano
For gonorrhoea in different sites:
• Determine + optimise the PK/PD drivers
• Evaluate efficacy (bacterial kill) PLUS AMR suppression, while limiting side effects
• Single- vs. multiple-dose regimens (Monotherapy vs. dual therapy)
Pharmacokinetic/pharmacodynamic considerations for new and current therapeutic drugs for uncomplicated gonorrhoea – challenges and opportunities

Ursula Theuretzbacher¹, Lindley Barbee², Kristie Connolly³, George Drusano⁴, Prabha Fernandes⁵, Edward Hook⁶, Ann Jerse⁷, John O'Donnell⁸, Magnus Unemo⁹, Françoise Van Bambeke¹⁰, Brian VanScy¹¹, Peter Warn¹², Brian J. Werth¹³, François Franceschi¹⁴, Emilie Alirol¹⁴

International gonorrhoea PK/PD expert workshop organised by Global Antibiotic Research and Development Partnership (GARDP)
Table 1. Future areas for PK/PD research on drugs for gonorrhoea

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>Study relevance of intracellular location and antibiotic concentrations, local factors e.g. biofilm, protein binding, bacterial burden, clumping, influence of commensals, immune system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant antibiotic concentration</td>
<td>Which concentrations to use for modelling; do serum concentrations reflect the concentrations required at urogenital, rectal and pharyngeal sites of infection?</td>
</tr>
<tr>
<td>PK/PD index</td>
<td>Adapt PK/PD indices that consider single and multiple dose regimens and the requirement for sterilization</td>
</tr>
<tr>
<td>Strain-dependent factors</td>
<td>Define impact of strain variability on modelling and clinical cure</td>
</tr>
<tr>
<td>HFIM</td>
<td>Validate and explore HFIM with old antibiotics and correlate the results with known clinical outcome, explore new knowledge such as PK input, consider strain-specific factors</td>
</tr>
<tr>
<td>In-vivo models</td>
<td>Develop in-vivo models for infections other than cervical gonorrhoea, expand studies and correlate the results with known clinical outcome of old antibiotics</td>
</tr>
<tr>
<td>Clinical breakpoints</td>
<td>Provide information to reassess clinical breakpoints, define failure thresholds</td>
</tr>
<tr>
<td>Dosing regimens</td>
<td>Explore different dosing regimens: single dose, multiple dose and combination therapy</td>
</tr>
<tr>
<td>Resistance</td>
<td>Integrate the goals of fast killing with minimised emergence of resistance</td>
</tr>
<tr>
<td>Research environment</td>
<td>Intensify international collaborative actions and research efforts</td>
</tr>
</tbody>
</table>
Hollow Fibre Infection Model (HFIM)

- **Hollow Fibre Infection Model** for NG, for simulation of real gonococcal infection and PK/PD, efficacy (single and multiple dose and ideal dose), and AMR emergence and suppression (different doses)

- (PK/PD driver, bacteriostatic/bactericidal, time-/concentration-dependent, rate of bacterial killing, post-antibiotic effect when it falls below MIC, etc.)

![Diagram of Hollow Fibre Infection Model](image)

*Figure 4: Cross-section of a hollow fiber cartridge. The test organism is retained in the small volume outside the fiber while nutrient broth and drug circulate through the insides of the fiber. Small molecules such as drugs can freely cross the fiber along with nutrients and waste products, bacteria and cells cannot cross the fiber.*

*Figure 5: The hollow fiber two compartment model. Test organisms are retained in the hollow fiber cartridge. The central reservoir is continuously re-circulating the nutrient broth. Drug is added to the central reservoir and the elimination kinetics are controlled by the addition of diluent to the central reservoir. The volume in the central reservoir is kept constant.*
Relationship between Gepotidacin Exposure and Prevention of On-Therapy Resistance Amplification in a *Neisseria gonorrhoeae* Hollow-Fiber *In Vitro* Infection Model

Brian D. VanScoy, Nicole E. Scangarella-Oman, Steven Fikes, Sharon Min, Jianzhong Huang, Karen Ingraham, Sujata M. Bhavnani, Haley Conde, Paul G. Ambrose
HFIM at WHO CC, Sweden – in collaboration with GARDP (Francois Franceschi, Renata Da Costa, Seamus O’Brien (Emilie Alirol earlier)) and George Drusano (David Brown, Arnold Louie)

Standardised and quality-assured HFIM based on geographically, temporally and genomically diverse WHO NG reference strains (n=16), including strains causing failures with previous and current treatments
Pharmacodynamic evaluation of ceftriaxone single dose therapy (0.125-1 g) to eradicate ceftriaxone-susceptible and ceftriaxone-resistant *Neisseria gonorrhoeae* strains in a dynamic Hollow Fibre Infection Model for gonorrhoea

In manuscript

Magnus Unemo¹*, Daniel Golparian¹, Joakim Oxlencork², Francois Francesch¹³, Fabian Kong⁴, David Brown⁵, Arnold Louie⁵, George Drusano⁵, Susanne Jacobsson¹

Based on ceftriaxone (CRO) human serum concentrations:
- 125 mg – 1 g effectively eradicate highly susceptible strains
- 500 mg eradicates all except high-level resistant strains (MIC≥1 mg/L)
- 1 g eradicates all susceptible and resistant strains

Pharynx: PK parameters? ⇒ Extremely limited data! ⇒ Best guess?

Not for distribution or Tweet!
Human Pharmacokinetics and Distribution in Various Tissues of Ceftriaxone

F. Fraschini, P.C. Braga, G. Scarpazza, F. Scaglione, O. Pignataro, G. Sambataro, C. Mariani, G.C. Roviaro, F. Varoli, G. Espositi

Table III. Mean serum and tissue concentrations of ceftriaxone after a single 1-gram intramuscular injection

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Mean concentration (μg/g) at the following times (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Lung (n = 13)</td>
<td>12.5 (1)</td>
</tr>
<tr>
<td>Nasal mucosa (n = 30)</td>
<td>21.0 (6)</td>
</tr>
<tr>
<td>Tonsil (n = 30)</td>
<td>10.2 (6)</td>
</tr>
<tr>
<td>Middle ear mucosa (n = 30)</td>
<td>6.03 (6)</td>
</tr>
<tr>
<td>Mean serum concentration (μg/ml) (n = 7)r</td>
<td>61.3</td>
</tr>
</tbody>
</table>

n = Number of patients/tissue specimens.

Explaining the Poor Bacteriologic Eradication Rate of Single-Dose Ceftriaxone in Group A Streptococcal Tonsillopharyngitis: A Reverse Engineering Solution Using Pharmacodynamic Modeling

Jeffrey L. Blumer, PhD, MD*‡; Michael D. Reed, PharmD*‡; Edward L. Kaplan, MD§; and George L. Drusano, MD||

Ceftriaxone 500 mg single dose to children (2-12 years) scheduled for elective tonsillektomi (tonsillar ceftriaxone protein binding 89.1%)
Pharmacodynamic evaluation of ceftriaxone single dose therapy (0.125-1 g) to eradicate ceftriaxone-susceptible and ceftriaxone-resistant *Neisseria gonorrhoeae* strains in a dynamic Hollow Fibre Infection Model for gonorrhoea

Based on ceftriaxone (CRO) human plasma concentrations:
- 125 mg – 1 g effectively eradicate highly susceptible strains
- 500 mg eradicates all except high-level resistant strains (MIC≥1 mg/L)
- 1 g eradicates all susceptible and resistant strains

Based on CRO pharyngeal (i.e., tonsil) concentrations:
- 500 mg do not eradicate resistant strains (MIC≥0.5 mg/L)
- 1 g eradicates all except high-level resistant strains (MIC≥1 mg/L)

Not for distribution or Tweet!

- Substantially more failures estimated with 500 mg and 1 g, because many patients do not reach sufficient CRO $fT_{>\text{MIC}}$!

Not for distribution or Tweet!
Pharmacodynamic evaluation of dosing, bacterial kill and resistance suppression for zoliflodacin against *Neisseria gonorrhoeae* in a dynamic Hollow Fiber Infection Model

Susanne Jacobsson¹, Daniel Golparian¹, Joakim Oxlèbark², Emilie Alirol³, François Franceschi³, Tomas N Gustafsson⁴, David Brown⁵, Arnold Louie⁵, George Drusano⁵, Magnus Unemo¹*

We are grateful to Entasis (John Mueller, John O’Donnell, Alita Miller)

An international zoliflodacin phase 3 RCT, enrolling adults with uncomplicated gonorrhoea and comparing a zoliflodacin 3 g single oral dose to a dual therapy of ceftriaxone and azithromycin, is ongoing.
NG WHO F and WHO X in dose-range HFIM experiments (n=2) of zoliflodacin single oral dose of 0.5-8 g (followed 7 days)

(A) Growth controls

(B) Zoliflodacin 0.5 g

(C) Zoliflodacin 1 g

(D) Zoliflodacin 2 to 8 g

0.5-1 g doses: Too limited exposure + AMR amplification (GyrB target mutations)

Design based on ZOLI 3 g PK parameters (AUC24, Tmax, T1/2, protein-binding); linear PK assumed for other doses

Jacobsson et al. Front Pharmacol. 2021
NG WHO X reference strain in dose-fractionation HFIM experiments (n=2) simulating zoliflodacin single oral dose of 1, 2, 3 and 4 g given as equally divided doses q12 h and q8 h over 24 h

(A) Zoliflodacin 1 to 4 g, q12 h

(B) Zoliflodacin 1 to 4 g, q8 h

Jacobsson et al. Front Pharmacol. 2021
Population PK/PD modeling parameter values for the HFIM zoliflodacin study with NG reference strains WHO F (WHO X)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_a$ (L)</td>
<td>1076 (1066)</td>
<td>1022 (1081)</td>
<td>65.16 (274.4)</td>
</tr>
<tr>
<td>CL (L/hr)</td>
<td>116.7 (119.2)</td>
<td>105.6 (116.6)</td>
<td>13.11 (28.12)</td>
</tr>
<tr>
<td>$K_{ss}$ (hr$^{-1}$)</td>
<td>1.142 (1.163)</td>
<td>1.086 (1.407)</td>
<td>0.07051 (0.4059)</td>
</tr>
<tr>
<td>$K_{ss}$ (hr$^{-1}$)</td>
<td>0.5602 (1.206)</td>
<td>0.5987 (1.680)</td>
<td>0.06005 (0.9231)</td>
</tr>
<tr>
<td>$K_{kill}$ (hr$^{-1}$)</td>
<td>4.524 (20.74)</td>
<td>4.722 (18.11)</td>
<td>0.2418 (5.846)</td>
</tr>
<tr>
<td>$K_{kill}$ (hr$^{-1}$)</td>
<td>1.519 (3.256)</td>
<td>1.502 (3.661)</td>
<td>0.03657 (1.374)</td>
</tr>
<tr>
<td>$C_{50s}$ (mg/L)</td>
<td>0.2507 (0.7454)</td>
<td>0.2885 (0.6349)</td>
<td>0.04692 (0.3133)</td>
</tr>
<tr>
<td>$C_{50r}$ (mg/L)</td>
<td>0.4334 (1.520)</td>
<td>0.4491 (1.059)</td>
<td>0.03111 (1.276)</td>
</tr>
<tr>
<td>$H_s$ (---)</td>
<td>1.581 (8.494)</td>
<td>1.490 (4.963)</td>
<td>0.2066 (5.870)</td>
</tr>
<tr>
<td>$H_r$ (---)</td>
<td>4.377 (11.68)</td>
<td>4.013 (13.07)</td>
<td>0.7291 (5.976)</td>
</tr>
<tr>
<td>POPMAX (CFU/mL)</td>
<td>$5.981 \times 10^5 (2.665 \times 10^5)$</td>
<td>$9.913 \times 10^6 (9.149 \times 10^6)$</td>
<td>$4.601 \times 10^6 (2.896 \times 10^6)$</td>
</tr>
<tr>
<td>IC2 (CFU/mL)</td>
<td>$6.723 \times 10^5 (2.922 \times 10^5)$</td>
<td>$7.851 \times 10^5 (2.471 \times 10^5)$</td>
<td>$1.535 \times 10^5 (2.352 \times 10^5)$</td>
</tr>
<tr>
<td>IC3 (CFU/mL)</td>
<td>$6.405 (8.080)$</td>
<td>$9.912 (5.478)$</td>
<td>$4.143 (7.135)$</td>
</tr>
</tbody>
</table>

$V_a$, apparent volume of the central compartment; CL, clearance; $K_{ss}$ and $K_{ss}$, rate constants of growth for the susceptible and resistant population, respectively; $K_{kill}$ and $K_{kill}$, rate constants of kill for the susceptible and resistant population, respectively; $C_{50s}$ and $C_{50r}$, concentrations of zoliflodacin at which the kill rate is half maximal for the susceptible and resistant population, respectively; $H_s$ and $H_r$, Hill's constants for the susceptible and resistant populations, respectively (unitless); POPMAX, maximal population size; CFU, colony forming units; IC2 and IC3, sizes of the total and resistant populations, respectively, at therapy initiation.

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Predicted-Observed regressions for zoliflodacin concentrations, total NG burden and resistant NG burden, respectively for the pre-Bayesian regression (panels A-C) and for the Bayesian regressions (panels D-F) for WHO F

(A) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis

(B) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis

(C) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis

(D) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis

(E) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis

(F) Zoliflodacin versus *N. gonorrhoeae* Hollow Fiber Model Analysis
Predicted-Observed regressions for zoliflodacin concentrations, total NG burden and resistant NG burden, respectively for the pre-Bayesian regression (panels A-C) and for the Bayesian regressions (panels D-F) for WHO X

(A) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

(B) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

(C) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

(D) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

(E) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

(F) Zoliflodacin versus *N. gonorrhoeae* WHO X - Hollow Fiber Model Analysis

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Zoliflodacin Resistance Suppression
Model-Based Dose Identification

• Employing the parameter vector identified in the previous slide, we calculated that a dose > 1 g and < 2 g will suppress resistance emergence

• This is not enough!

• We must examine also NG strains potentially predisposed to resistance emergence

• We must then use a population PK parameter vector and covariance matrix to perform a Monte Carlo simulation to identify a dose that would attain the resistance-suppression exposure for a large proportion of the target population

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Simulations for zoliflodacin single dose compared to the same total dose given half the dose twice 12 hours apart and one-third the dose three times 8 hours apart (WHO X reference strain)

(A) Experiment #1 1 g once  
Experiment #2 0.5g twice  
Experiment #3 0.333 g three times

(B) Experiment #1 2 g once  
Experiment #2 1g twice  
Experiment #3 0.556 g three times

(C) Experiment #1 3 g once  
Experiment #2 1.5g twice  
Experiment #3 1 g three times

(D) Experiment #1 4g once  
Experiment #2 2g twice  
Experiment #3 1.333g three times

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Zoliflodacin Exposure Profile to Optimize Rate of Kill

- Daily administration always produces the most rapid rate of kill
- This advantage dissipates as the dose escalates
- Rate of kill approaches a maximal rate
- The REAL advantage is that one need not worry about adherence with subsequent doses
- The impact of exposure on kill rate and resistance suppression is the real reason to perform this mathematical modeling exercise!

Jacobsson et al. Front Pharmacol. 2021
HOWEVER, for new antimicrobials we also need to predict AMR emergence, fitness and spread and consider mutations potentially causing AMR OR predisposing for AMR emergence:

Pharmacodynamic evaluation of zoliflodacin treatment of Neisseria gonorrhoeae strains with pre-existing and in vitro selected GyrB mutations using a dynamic Hollow Fibre Infection Model (HFIM)

Susanne Jacobsson¹, Daniel Golparian¹, Joakim Oxelbark², Francois Franceschi³, David Brown⁴, Arnold Louie⁴, George Drusano⁴, Magnus Unemo¹*

We are grateful to Entasis (John Mueller, John O’Donnell, Alita Miller)
Conclusions

- Surveillance of AMR (including genome sequencing), treatment failures, and antimicrobial consumption needs to be expanded globally
- Exceedingly limited PK/PD data regarding treatment of gonorrhoea exist
- Appropriate PK data for all infection site, particularly pharynx, including inter-patient variance for these PK data (population modelling!) are urgently needed
- Determine and subsequently optimise the PK/PD drivers and doses for bacterial kill and AMR suppression (while avoiding serious adverse effects)
- Improve understanding of single- vs. multiple dose (potential benefits depends on PK/PD drivers for the specific antimicrobial) and monotherapy vs. dual therapy (for gonorrhoea AND gonorrhoea+other infection)
- PK studies (and extragenital infections) should ideally be included in all treatment trials