Novel Therapies Targeting Drug-Resistant Gonorrhea

ASM Microbe

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ENTASIS THERAPEUTICS
Innovative Antibacterials

Speaker notes

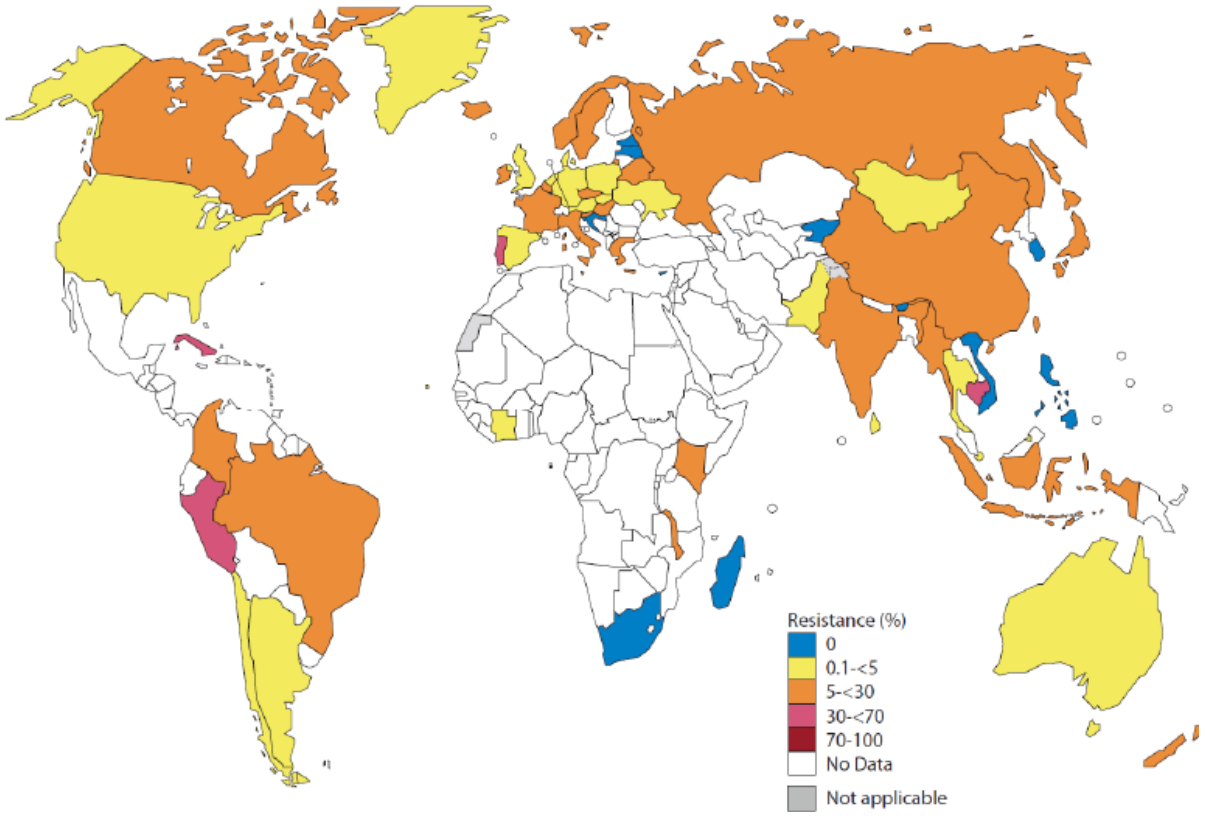
- Only discussing novel antibacterial agents
- Not discussing biologicals, vaccines or non-traditional approaches (e.g., phages)
- Talk excludes known classes or derivatives from recent Phase 3 clinical trials or ongoing trials (e.g., NABOGO)
- Only used publicly available information
- “Novel” is subjective call of the speaker

Agenda

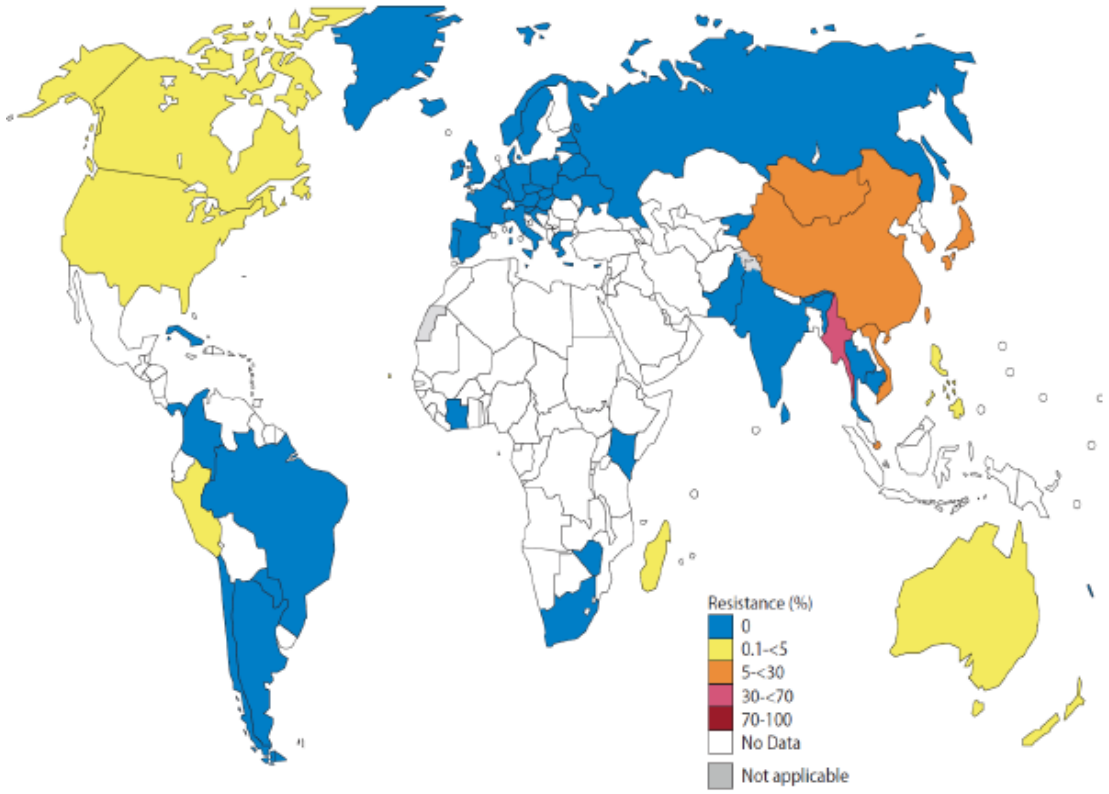
- Spread of gonococcal resistance and attributes of novel agents
- Profiles for novel compounds
- Clinical development teachings
- Key takeaways

New therapies for drug-resistant gonorrhea are urgently needed

50/62 (80.6%) countries - resistance to azithromycin (30 countries ≥ 5%)



15/63 (23.8%) countries - DS/R to ceftriaxone (7 countries ≥ 5%)



Unemo et al *WHO GASP 2015-2017 -an observational study emphasizing essential global actions*

Slide courtesy of Seamus O'Brien (GARDP)

Attributes of new agents

- Novel chemotype
- Novel mode of action
- Orally bioavailable
- Active against clinical isolates resistant FQs, ESCs and macrolides
- No pre-existing resistance
- Hollow-fiber infection model (Brian VanScoy, ICPD)
  - PD driver analysis
  - Dosage regimen
  - Resistance suppression (combination studies)
- PK/PD from *N. gonorrhoeae* or surrogate pathogen murine infection model
- Option for multiple dosing

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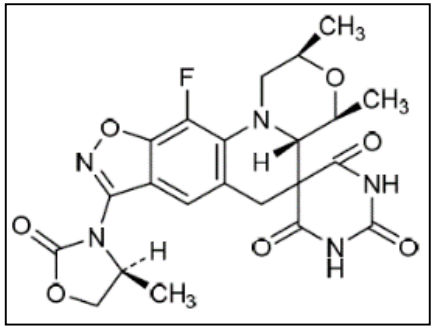
Profiles of Novel Compounds

Compound Name	Development	Drug class	Target
Zoliflodacin (ETX0914)	Phase 2	Spiropyrimidinetrione	DNA gyrase (GyrB)
Gepotidacin (GSK2140944)	Phase 2	Triazaacenaphthyleen	DNA gyrase/ topoisomerase
Lefamulin (BC-3781)	Phase 1	Plueromutilin	50S ribosome; peptidyl transferase center
SMT-571	Lead optimization	Novel chemotype	Cell division
Debio 1453	Lead optimization	FabI inhibitor	FabI

Zoliflodacin is a first-in-class antibiotic



Basarab, G. *et al*. Nature Scientific Reports; Sept. 2015

Indication: Uncomplicated gonorrhea
Formulation: granules for oral suspension in sachet
Predicted dosage: 3 g single dose

Mechanism of action

- First drug candidate from a new class of antibiotics
- Distinct mode of action on DNA gyrase

In vitro activity

- MIC_{90} values for *N. gonorrhoeae*: 0.125 - 0.25 mg/L.
- ≥ 1400 isolates tested, including XDR and MDR isolates (US, EU, China)
- No pre-existing resistance

Clinical experience

- As of today, 6 studies have been completed and 327 individuals have been exposed
- Very good safety profile
- High cure rates at urogenital and rectal site during Phase 2 trial
- GARDP-sponsored global Phase 3 initiation anticipated in 2019

Zoliflodacin has the best microbiological profile against contemporary clinical isolates of *N. gonorrhoeae*

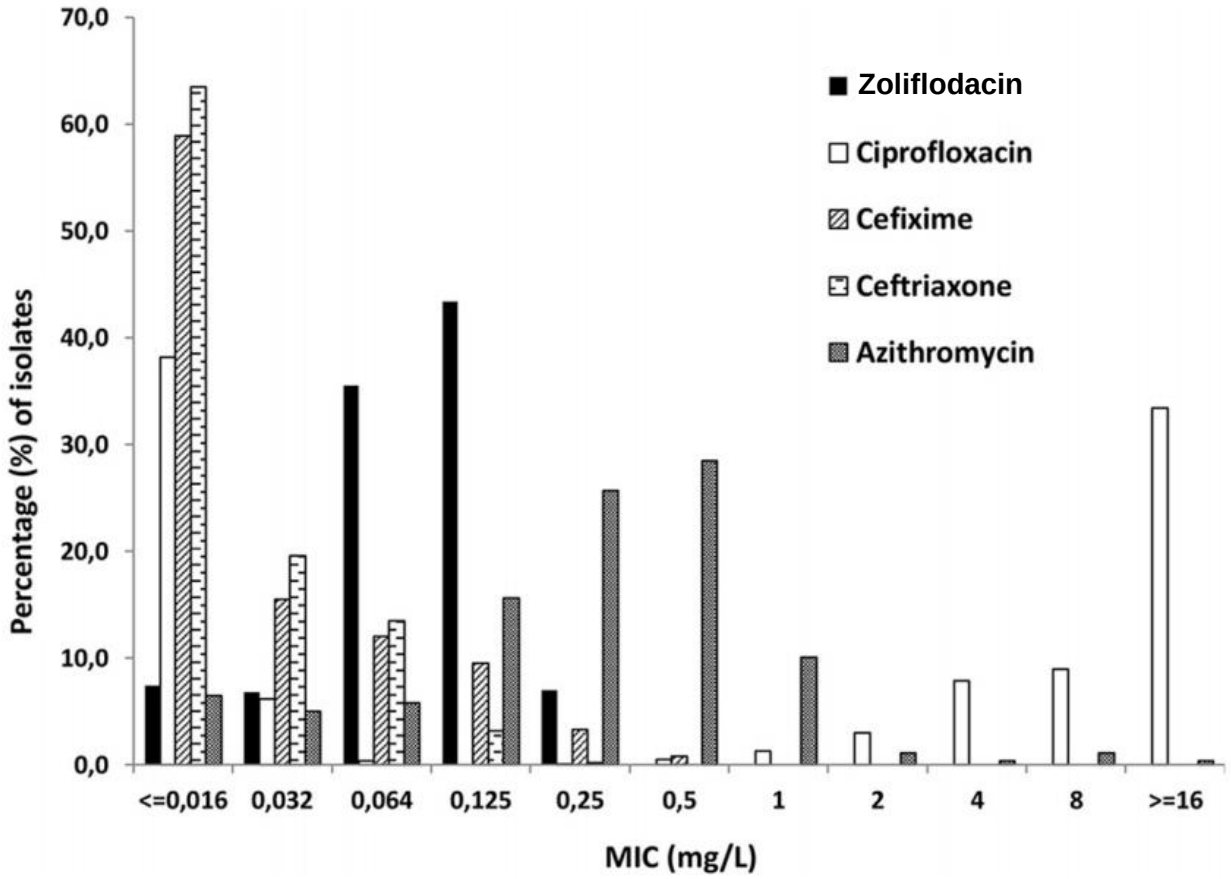
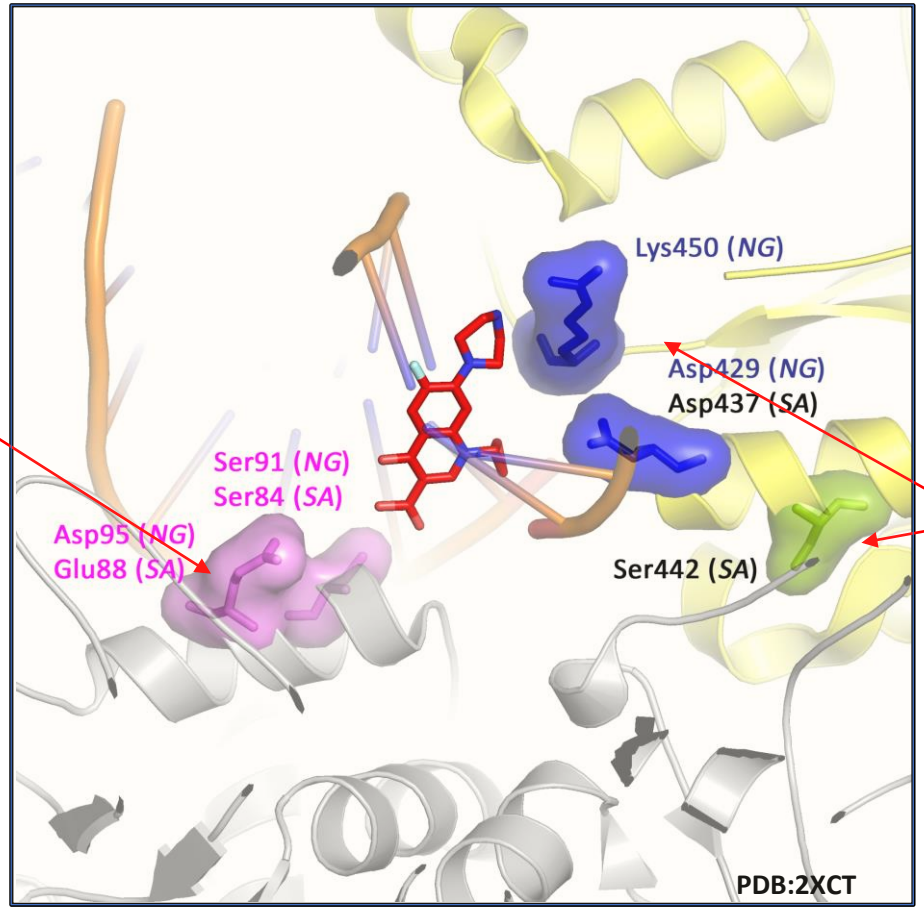


FIG 1 MIC (mg/liter) distributions for the novel DNA topoisomerase II inhibitor ETX0914, the fluoroquinolone ciprofloxacin, cefixime, ceftriaxone, and azithromycin for 873 consecutive clinical *Neisseria gonorrhoeae* isolates obtained in 21 European countries from 2012 to 2014. Note that for azithromycin, only 565 isolates were included, i.e., all isolates with exact MICs available.

Unemo, M et al., Antimicrob. Agents Chemother. 59: 6053, 2015

Zoliflodacin targets a “traditional” antibacterial mechanism in a novel way

Key interaction points for fluoroquinolones on Gyrase A



Zoliflodacin touch-points on Gyrase B

Nature Scientific Reports 5, 11827, 2015
Front. Microbiol. 6, 1377, 2015
Antimicrob. Agents Chemother. 59(3), 1478, 2015

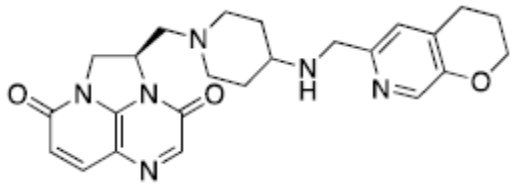
Zoliflodacin: Successful Clinical Proof-of-Concept[1]

	Microbiological Efficacy[2]	
Anatomic site	**Zoliflodacin (3 g)**	**Ceftriaxone**
Urogenital	47/47 (100%)	21/21 (100%)
Pharyngeal	7/9 (77.8%)	4/4 (100%)
Rectal	6/6 (100%)	3/3 (100%)

- Positive Phase 2 trial results support progression to Phase 3
- Baseline MIC range (0.008-0.25 mg/L)
- Treatment failures were not associated with resistance to zoliflodacin
- Zoliflodacin was generally well tolerated at clinically effective doses
- Phase 3 trial planned to initiate in 2019

1) Taylor et al. N Engl J Med 2018; 379:1835-1845
2) Represents results for the per-protocol population

Gepotidacin (GSK2140944)



Indication: Uncomplicated urogenital gonorrhea
Formulation: Capsules

Mechanism of action

- Dual targeting mechanism of action (GyrA & ParC)
- Binds a novel site distinct from quinolones

In vitro activity

- MIC_{90} for *N. gonorrhoeae*: 0.5-1 mg/L

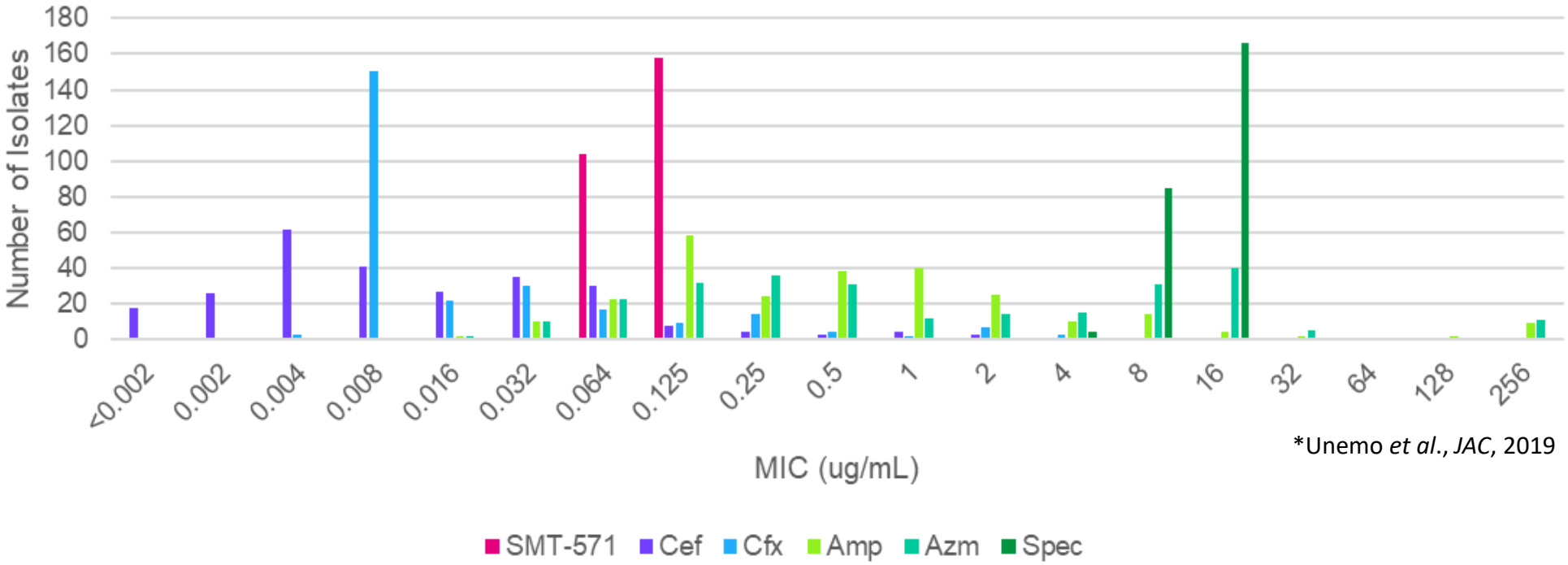
Clinical experience

- US-based Phase 2 trial completed in 2016
- Emergence of resistance to gepotidacin observed in 2 of 3 treatment failures (MSM; all FQ^R)
  - ParC D86N Baseline MIC 1.0 mg/L
  - ParC D86N GyrA A92T ToC MIC ≥ 32 mg/L
- Future clinical options: achieve higher PK/PD magnitudes and suppress resistance emergence
  - Guided by hollow fiber infection model (see VanSoy, B. et al., ASM ESCMID 2018)

Taylor, S. et al., CID. 67:504, 2018
Jacobsson, S. et al., J Antibac. Chem. 73:2072, 2018
Scangarella-Oman et al., Antimicrob. Agents Chemo. 62:1, 2018

SMT-571 – Summit Therapeutics

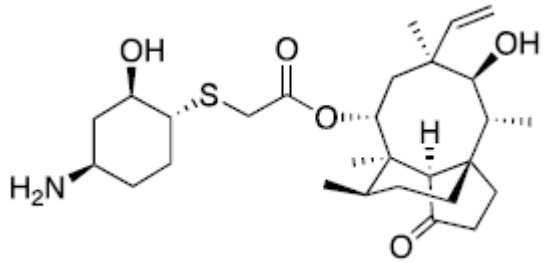
- SMT-571 is the lead from a new antibiotic class to treat *Neisseria gonorrhoeae*
- A targeted spectrum antibiotic with excellent activity across 262 clinical isolates*
- Novel mechanism of action with a low potential for resistance development



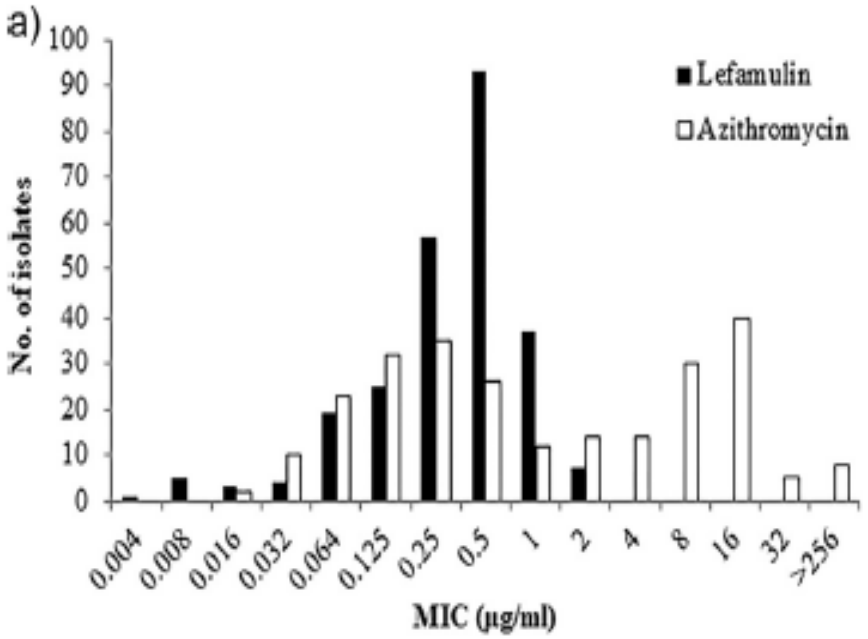
*Unemo *et al.*, *JAC*, 2019

Slide courtesy of Paul Meo (Summit)

Lefamulin (BC-3781) – Novel pleuromutilin class

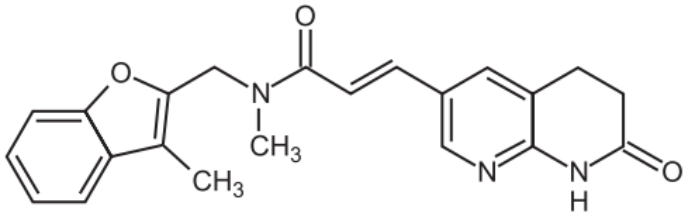


- Inhibits bacterial protein synthesis
- Distinct binding mode to peptidyl transferase center of the 50S ribosomal subunit
- Potent activity against gonococcal isolates; MIC_{90} 1.0 mg/L
- No cross resistance to other antimicrobials including azithromycin



Jacobsson, S. et al, Antimicrob. Agents Chemo. 61:1, 2017

FabI – Debiopharm/Nobelex



Debio 1452/AFN-1452

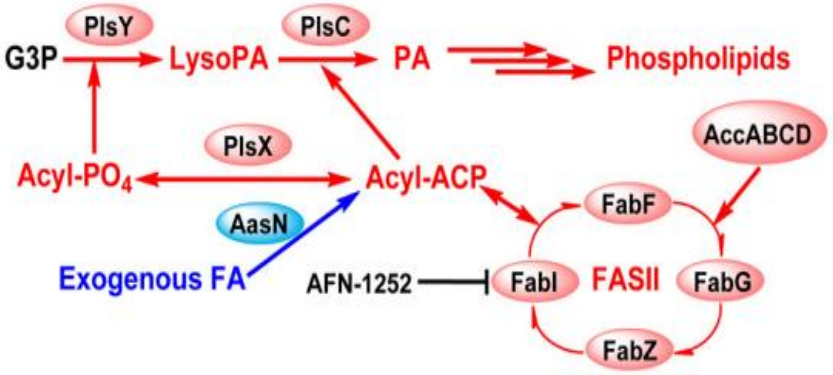
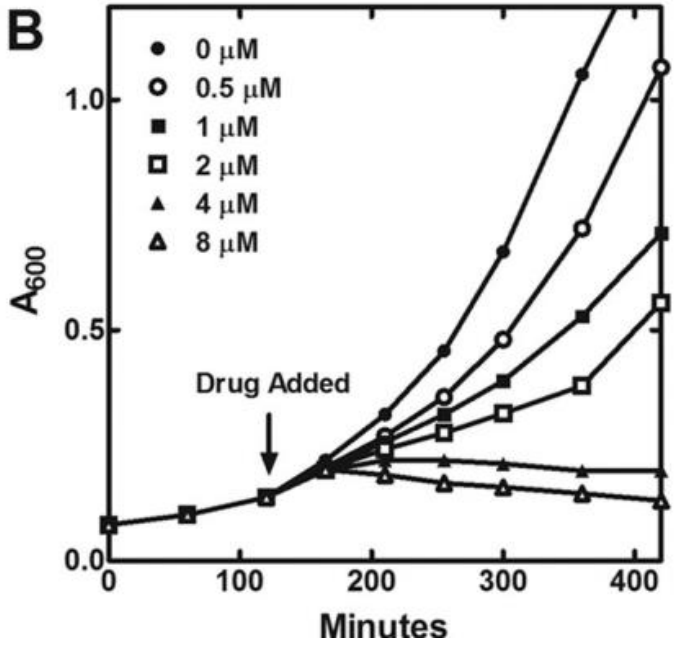


FIGURE 7. **Fatty acid and phosphatidic acid synthesis in *Neisseria***

Yao et al., J. Biol. Chem. 291:171, 2016



- Dose-dependent inhibition of *Neisseria* growth and fatty acid synthesis in vitro
- Inhibition of *Ng*FabI cannot be bypassed by exogenous fatty acid supplementation in vitro

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Development learnings….dose selection

Target attainment in gonorrhea is challenging to assess

- Predictive animal infection and HF models to assess pharmacodynamics (e.g., PD driver, dosing regimen, resistance suppression)
- PK/tissue penetration data at site of infection to inform exposure/response relationships
- Small dose-finding trials (Phase 2) for preliminary indication of efficacy
- Gathering data in high-risk groups (MSM; FSW)

Development learnings….trial design

- Selection of experienced trial sites
- Aim for higher enrollment of women & adolescents
- Consideration of multi-dose regimens
- Is the 95% clinical efficacy target too rigid?

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The takeaways…..

- Current R&D pipeline targeting new *anti-N. gonorrhoeae* therapeutics is small; small number agents in clinical trials
- Focus on exposure/response relationship
  - Advance understanding of pre-clinical in vitro and in vivo pharmacology to guide clinical dose, exposure, duration and resistance emergence
  - Tissue levels of drugs at sites of infection; patient PK variability
  - Consider alternative dosing regimens; multi-dose treatment
- Future clinical plans & trial design guided by recent development learnings

Taylor, S. et al., CID 67:504, 2018; Chen, M. et al., Lancet ID, 2019; Hook, E. et al., STI 46:279, 2019

Thank you!

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