# Recommendations for the optimal introduction of novel antibiotics to treat uncomplicated gonorrhoea in the face of increasing antimicrobial resistance: a case study with zoliflodacin

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**! Other zoliflodacin abstracts at IUSTI 2024 !**

**- Oral Zoliflodacin for Treatment of Uncomplicated Gonorrhoea in High-Risk Populations: Subgroup Analyses of a Global Phase 3 Randomised Controlled Clinical Trial,** by Luckey A *et al.*
*Oral presentation*
*Session 16B. Clinical Management*
*Thu Sep 19 2024, 16:00 - 17:30*

**- Descriptive analysis of sexually transmitted infections risk factors among participants included in the global zoliflodacin Phase 3 clinical trial,** by Luckey A *et al.*
*Poster 304.*

## BACKGROUND

There were an estimated 82.4 million [47.7 million-130.4 million] new cases of gonorrhoea in 2020, the majority in low- and middle-income countries (LMICs)[1,2]. Introduction of future new antibiotics to address this public health need will require an optimised strategy to ensure sustained, affordable access balanced with antibiotic stewardship. The investigational, first-in-class antibiotic, zoliflodacin, given as a single oral dose for uncomplicated urogenital gonorrhoea, recently demonstrated non-inferiority to ceftriaxone plus azithromycin and safety in a Phase 3 randomised controlled trial [3,4]. This has the potential, pending regulatory approval, to help address the threat of untreatable gonorrhoea, as levels of antimicrobial resistance (AMR) to current first-line treatments increase. The workshop aimed to explore evidence generation in order to develop introduction strategies for future new gonorrhoea treatments.

## METHODS

The Global Antibiotic Research & Development Partnership (GARDP) convened an expert meeting during the 2023 STI and HIV World Congress to:

- describe **local challenges,** focusing on South Africa and Thailand to programmatic adoption of future new antibiotics for the treatment of gonorrhoea infection
- discuss **key implementation questions** about the introduction of future new oral treatments (such as zolifodacin) in low- and middle-income countries (LMICs)
- Propose **recommendations** that could inform guidelines and policy change.

## RESULTS

### CONTEXT/LOCAL ENVIRONMENT

**IDENTIFIED CHALLENGES**

- Lack of comprehensive population-level epidemiological and AMR surveillance data
- Inappropriate use of antibiotics and contribution to the development of AMR
- Lack of rapid point-of-care diagnostic tests (POCTs) that allow identification of *N. gonorrhoeae* and susceptibility to antibiotics
- Lack of diagnostics to detect treatment failures
- Timely development of susceptibility testing methods for new drug
- Identification and treatment of partners

**IMPLEMENTATION QUESTIONS**

- How do countries identify patients most in need?
- What is/are the use case(s) for the new treatment? For example:
  - limited to second-line treatment (clinical and/or microbiological failures)?
  - used for first-line where proportion of isolates of ceftriaxone-resistant gonococci is high (e.g. ≥ 5%)?
  - used only for treating people from high-risk groups and their partners?

**RECOMMENDATIONS**

- Need to strengthen surveillance to support the current syndromic management approach and to identify specific population groups in need
- Investigation of novel diagnostic implementation to improve stewardship
- Additional local AMR studies to support surveillance
- Understanding the local implementation of guidelines and the patient pathway to help inform introduction of new treatments
- Explore expedited partner therapy strategies and effectiveness

### GUIDELINE/POLICY

**IDENTIFIED CHALLENGES**

- Insufficient evidence available to definitively support a decision on when to introduce a new antibiotic or combination regimen
- Threshold of 5% resistant isolates at which to update guidelines has not been empirically established

**IMPLEMENTATION QUESTIONS**

- When is it optimal to introduce a new treatment into the guidelines?
- Do treatment combinations need to be investigated and, if so, which ones?
- Which populations would benefit most from the introduction of a new treatment (e.g., partners of those receiving second-line treatment, high risk groups, etc.)?
- What additional data is needed to support decision-making for inclusion into guidelines?
- What is a suitable threshold of AMR to justify a change in first line treatment?

**RECOMMENDATIONS**

- Modelling of various resistance-minimising strategies:
  - the predicted time to emergence and rate of transmission of resistance to the new drug, using different introduction strategies
  - outcomes to be monitored following introduction in different population groups
  - the advantages and disadvantages of using an antibiotic like zoliflodacin as part of a combination therapy
- Studying the efficacy of a new drug like zoliflodacin compared to alternative treatment options for ceftriaxone-resistance
- Confirm appropriate prevalence threshold of resistance to current treatments that would necessitate a switch in first-line treatment
- Looking at historical data on discontinued antibiotics due to a guideline change

### SUSTAINABILITY

Evidence on the health benefit, economic value and preferences and values in the general and in high-risk populations to the introduction of a new agent.

## CONCLUSION

Expert recommendations included:

- generation of evidence for supporting uptake of new treatments into the guidelines
- additional AMR studies to support surveillance
- investigation of implementation of novel diagnostic approaches to improve stewardship
- better understanding of preferences and values among the population in need
- modelling the emergence of *N. gonorrhoeae* resistance and transmission under different new treatment introduction conditions

Research needs to be population- and region-specific to inform whether to introduce a new antibiotic immediately to provide an oral option that will help reduce the selective pressure on the rate of development of ceftriaxone resistance, or to limit the introduction of the new antibiotic until diagnostic and surveillance capacity increases; and to determine the best options for stewardship within an equitable public health approach.

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**References:**

1. World Health Organization. Gonorrhoea (Neisseria gonorrhoeae infection). https://www.who.int/news-room/fact-sheets/detail/gonorrhoea-(neisseria-gonorrhoeae-infection). Accessed 25 September 2023.
2. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
3. Luckey A, Broadhurst H, Daram P, Delany-Moretlwe S, de Vries HJC, Kittiyaowamarn R, Lewis D, Mueller JP, O'Brien S, Richardson MA, Srinivasan S, Taylor SN, Unemo M, Hook E, for the zoliflodacin Phase 3 study group. Oral zoliflodacin is non-inferior to a combination of ceftriaxone and azithromycin for treatment of uncomplicated urogenital gonorrhoea: results of a large global Phase 3 randomised controlled trial. Abstract number 01099 (oral presentation; ESCMID Global, April 2024, Barcelona, Spain.