Multi-drug-resistant gonorrhea: a research & development roadmap to discover new medicines

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Summary points

- The number of gonorrhea cases is rising in many settings worldwide, and an increasing proportion are multidrug-resistant. The choice of antimicrobials that can be used for treatment of gonorrhea is very limited, and resistance has even been reported to extended-spectrum cephalosporins which are the mainstay of currently recommended antimicrobial therapy. Currently only three new chemical entities are in different stages of clinical development for treatment of gonorrhea
- In 2016 the Global Antibiotic Research and Development Partnership (GARDP) was launched by the World Health Organization and Drugs for Neglected Disease *initiative*, which hosts and provides governance for GARDP
- GARDP has worked together with experts from different regions to draft 'ideal' and 'acceptable' Target Product Profiles for the treatment of gonorrhea, reflecting medical need
- Amongst other activities to combat antimicrobial resistance, GARDP has developed a plan to meet the urgent need for new drugs to treat gonorrhea
- This research and development proposal includes, over the next seven years: exploring the introduction of a new clinical entity against gonorrhea; the identification of existing, suitable partner drugs; the recovery of previously abandoned, out-of-favor and withdrawn antibiotics, and the development of simplified treatment guidelines for the empiric management of sexually transmitted infections

Gonorrhea- a growing, worldwide disease burden

Gonorrhea is among the most common sexually transmitted infections (STIs), with an estimated 78 million new cases in 2012 [1]. Countries with good surveillance have reported increases, such as an 11% rise between 2014 and 2015 in the UK [2], a doubling of cases among MSM (men who have sex with men) in France between 2013 and 2015 [3], a 5% rise between 2013 and 2015 in the US [4], and an increase of 29-146% in almost all Australian states between 2010 and 2014 [5], all confirming longer trends. Decreasing condom use [6], increased urbanization and travel, poor infection detection rates, and inadequate or failed treatment [7] all contribute to this increase.

Gonorrhea affects high-, middle- and low-income countries. The African region has the highest rates of gonococcal infections worldwide, with 50 and 100 new infections per 1,000 women and men, respectively, every year [8]. In the US it is the second most frequently reported notifiable infectious disease, accounting for 395,000 cases in 2015, a 13% increase from 2014 [4]; in Canada a similar rise (15%) was reported.

Gonorrhea is a debilitating disease, which was responsible for an estimated 445,000 Years Lived with Disability (YLD) in 2015 [9].

Urogenital gonorrhea may be asymptomatic in 40% of men [10], and manifests most commonly as urethritis [11]. It is also asymptomatic in more than half of women [12]. In men, untreated urethral infection can lead to epididymitis, reduced fertility and urethral stricture. In women, when present, symptoms are non-specific and include abnormal vaginal discharge, dysuria, lower abdominal discomfort and dyspareunia. The lack of discernible symptoms [13] results in unrecognized and untreated infections, which can lead to serious complications. Overall, 10-20% of female patients develop pelvic inflammatory disease (PID) and consequently are at risk for infertility [14]. Pregnancy complications associated with gonorrhea include chorioamnionitis, premature rupture of membranes, preterm birth, ectopic pregnancies and spontaneous abortions [13, 15, 16]. Perinatal transmission occurs in 30-40% of cases, and occur predominantly in low- and middle income countries, where 3-15% of mothers are infected. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis (*ophthalmia neonatorum*). Such untreated conjunctivitis may lead to scarring and blindness.

Extra-genital infections are common in both sex, and frequently occur in the absence of urogenital infection [17, 18]. Rectal infections are usually asymptomatic but can manifest as rectal and anal pain or discharge. Pharyngeal infections are mostly asymptomatic, but mild sore throat and pharyngitis may occur. Although bacterial concentrations are generally lower than in other infection sites, the pharynx is thought to be a favorable site for resistance emergence due to acquisition of resistance traits from commensal *Neisseria* spp. [19]. Disseminated gonococcal infections with gonococcal arthritis also occur. Because they are frequently asymptomatic, extra-genital infections often remain untreated, despite their key role in disease transmission.

Co-infection with other major STIs -HIV, Herpes Simplex Virus, *Chlamydia trachomatis*, *Mycoplasma genitalium* and syphilis - are common and may result in synergistic effects on transmission and disease severity .

Almost all antibiotic classes used against gonorrhea lost their efficacy because of resistance [20]. Sulfonamides, penicillins, early-generation cephalosporins, tetracyclines, macrolides and fluoroquinolones can no longer be relied upon. The extended-spectrum cephalosporins (ESCs, *i.e.* cefixime and ceftriaxone), which represent the last remaining option for first-line empirical monotherapy, are also under threat, with resistance reported worldwide [7, 21-24]. The WHO Gonococcal Antimicrobial Surveillance Programme (GASP) found that resistance is spreading especially in Asia, North America, Europe, Latin America and the Caribbean, and Australia, with

large data gaps in Africa and Central Asia [25]. Reports of treatment failures with ESC are on the increase [26-38] and the first case of treatment failure with a dual therapy has recently been reported . Fluoroquinolone, high-level azithromycin and cephalosporin resistance has now been found in several countries [19, 39-41].

N. gonorrhoeae displays extraordinary genetic versatility to achieve AMR, allowing horizontal gene transfer events with nonpathogenic *Neisseria* species that reside in different anatomical sites, particularly the pharynx [42-44].

The acquisition of multiple AMR traits, except perhaps for fluoroquinolone [45], does not appear to affect biological fitness, resulting in the persistence of strains that are multidrug (MDR) or extensively drug-resistant (XDR) even in the absence of antimicrobial selection pressure [45-47]. In the context of gonorrhea, MDR denotes resistance to current guideline treatments [48, 49] including oral ESC plus resistance to two or more of macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides and carbapenems. XDR denotes resistance to both oral and intramuscular ESCs or resistance to one type of ESC and spectinomycin, with resistance to three or more of macrolides, fluoroquinolones, penicillins, tetracycline, aminoglycosides and carbapenems [48, 49]. The WHO recommends adapting treatment guidelines in areas with over 5% resistance.

Most patients are managed in the community, and because of limited diagnostic access and capabilities, in many settings gonorrhea treatment is empiric (*i.e*., symptom-based, without identification of the causative organism or definition of its antimicrobial susceptibility profile) and syndromic, in accordance with the WHO guidance [50]. Treatment is based on the presence of easily recognized signs (*e.g*. urethral or vaginal discharge), and the provision of antibiotics that deal with the majority of, or the most serious, organisms responsible for the syndrome. With increasing resistance to ESC monotherapy, several countries have now adopted combination therapy with ESC plus azithromycin [51, 52]. However, whether dual therapy actually delays resistance emergence is not supported by strong evidence [53], and strains resistant to either ESC or azithromycin are already in circulation [26-36, 38]. In some regions of Africa and Latin America, less costly fluoroquinolones are still recommended, although they have been removed from WHO guidelines, and extensive resistance has been described [54-57].

Effective treatment of pharyngeal infections (regardless of resistance) is more difficult than treatment of uro-genital infections; while the average cure rate for urogenital infection is 96%, outcomes drop to 79 and 84% (males and females) for oropharyngeal infections [58, 59]. This may relate to insufficient drug exposure in the latter site. Worryingly, these infections most probably act as a reservoir and persistence of pathogens at these sites jeopardize global efforts to slow the spread of resistant gonorrhea.

Insufficient research and development (R&D) for an urgent public health threat

As a disease that is not usually deadly but affects millions, gonorrhea control initiatives lack sufficient coordination and investment. With increasingly limited treatment options in the wider context of AMR there is now growing concern that the threat of untreatable gonorrhea will become reality. In February 2017, the WHO listed *N. gonorrhoeae* among 'High Priority' pathogens for R&D of new antibiotics [60]. While hospital-acquired pathogens may have figured highest on the list, due to the mortality they cause, *N. gonorrhoeae* was notably included because infections are extremely widespread, cause substantial morbidity with a significant health cost for countries, can affect pregnant women and their babies, and develops AMR at a particularly rapid pace. Gonorrhea was also listed by the CDC (US Centers for Disease Control and Prevention) in the top 'Urgent Threat' category of 18 drug-resistant threats to the United States [61], and is included in similar AMR priority lists in the UK and Canada.

The current pipeline for gonorrhea treatments is relatively empty, with only three new chemical entities in various stage of clinical development. Two of these candidates are also being developed for other indications.

Solithromycin (Cempra Inc.) is an oral fluoroketolide with activity against Gram-positive and fastidious Gram-negative bacteria, including *N. gonorrhoeae, M. genitalium* and *C. trachomatis* [62-64]. It targets three different prokaryotic ribosomal sites and showed good efficacy in a Phase 2 study [65], with a 100% efficacy for genital, oral, and rectal sites of infection in men and women. A phase 3 trial is on-going.

Zoliflodacin (Entasis Therapeutics) is a first-in-class spiropyrimidinetrione topoisomerase II inhibitor with activity against several pathogens, including *N. gonorrhoeae*, and *C. trachomatis* [66, 67]. Zoliflodacin has been shown to be highly effective *in vitro* against a large collection of geographically and genetically diverse *N. gonorrhoeae* isolates [68] Results from a Phase 2 trial showed high efficacy on urogenital infections (98-100% microbiological cure rate, dependent on dose; clinicaltrials.gov n° NCT02257918). Over 90% of participants were male.

Gepotidacin (GlaxoSmithKline) is another bacterial topoisomerase II inhibitor, a novel triazaacenaphthylene with good *in vitro* activity against a wide range of drug-resistant bacteria, including MRSA (methicillin-resistant *Staphylococcus aureus*), ESBL (extended-spectrum β-lactamases)-producing *Enterobacteriaceae*, and *N. gonorrhoeae* [69]. A Phase 2 trial was recently completed and 96.7% and 94.8% cure rate were achieved with 1500 mg and 3000 mg respectively (clinicaltrials.gov n° NCT02294682). Like previously, over 90% of the participants were male.

A global surveillance plan is outlined by Wi et al. in parallel with this R&D proposal [70]

The spread and incidence of gonococcal AMR is of great concern, and has outpaced the development of new medicines, raising the prospect of untreatable gonorrhea [71, 72]. A business-as-usual scenario will prevent achievement of the Global Health Sector STI Strategy's target, approved by the World Health Assembly in 2016, of a 90% reduction of the incidence of gonorrhea by 2030. The frequency of asymptomatic infections, the rapidly changing antimicrobial susceptibility patterns, the variety of AMR mechanisms, and, paradoxically, progress against HIV

(resulting in a reduced use of condoms) make the control of AMR gonorrhea particularly challenging.

Commercial drug development for infectious diseases suffers from 'market failure'. There are multiple reasons for this, relating to how antibiotics are prescribed and sold, but also because stewardship initiatives may be diametrically at odds with the race against the 'patent clock' to recoup development costs. Finally there is competition from cheap generics, and the increasing need to combine with other drugs, which brings formulation, costs, regulatory and profitability challenges. Thus, there is an urgency to replenish the antibiotic drug discovery pipeline. In the shorter term, for gonorrhea, there is a need to advance, prioritize and evaluate the three new molecules in the clinical pipeline, investigate new antimicrobial combinations, and re-consider use of existing antibiotics. For both new and existing drugs, there is a lack of clinical efficacy data on oropharyngeal infections,.

The unmet treatment needs can be summarized as:

- No sustainable therapeutic option for MDR and XDR gonorrhea
- No evidence-based, sufficiently effective treatment for extra-genital infections, particularly oropharyngeal infections
- No evidence-based treatment for complications arising from initial urogenital infections

An R&D proposal for gonorrhea

At the sixty-eighth World Health Assembly in 2015 the WHO adopted the Global Action Plan on Antimicrobial Resistance. One of the Plan's initiatives was the launch of the Global Antibiotic Research and Development Partnership (GARDP; www.gardp.org) in May 2016 [73]. GARDP is hosted and governed by the Drugs for Neglected Diseases *initiative* (DND*i*), and has set up several programs aimed at developing new treatments in the short- to medium term for STIs, neonatal sepsis, and an antimicrobial memory recovery initiative. The latter aims to retrieve drugs and drug candidates (and associated expertise) whose use or development were halted in the past for reasons that no longer apply (*e.g.* Pharma portfolio considerations).

To better define the essential characteristics of new treatments for gonorrhea, and efficiently steer R&D activities, GARDP and the WHO convened an international STI expert panel in mid-2016, who agreed on a Target Product Profile (TPP; **Error! Reference source not found.**). The requirements were split for short- and long- term targeted treatment, with each being further divided between 'ideal' and 'acceptable' profiles. Based on the needs identified above, and in line with the consensus TPP, GARDP has developed a comprehensive R&D strategy that is broken down into four complementary components.

	Short-term (up to 5 years)		Long-term (up to 10 years)	
	Ideal	Acceptable	Ideal	Acceptable
Indication	**(First line) treatment of uncomplicated, uro-genital gonorrhea**	**(First line) treatment of uncomplicated, uro-genital gonorrhea**	**(First line) treatment of uro-genital gonorrhea (susceptible and**	**(First line) treatment of uro-genital gonorrhea (susceptible and MDR)**

	(susceptible and MDR) **First line treatment of extra-genital gonorrhea (ano-rectal and oro-pharyngeal)**	**(susceptible and MDR)**	**MDR, complicated and uncomplicated)** **First line treatment of extra-genital gonorrhea (ano-rectal and oro-pharyngeal)** **Treatment of *Chlamydia* infections**	
Activity against co-infecting STI pathogens	***Chlamydia trachomatis***		***Chlamydia trachomatis, Mycoplasma genitalium***	***Chlamydia trachomatis***
Patient population	**Adults and adolescents (aged 10-19 years)**		**Adults, children and adolescents**	
Clinical efficacy	**97% (95% CI, 95-100)**	**95% (95% CI, 90-100)**	**97% (95% CI, 95-100)**	**95% (95% CI, 90-100)**
Activity against ESC and macrolide-resistant NG strains	**Yes**		**Yes**	
Mechanism of action (target site, -cidal vs static; broad-spectrum vs narrow spectrum)	**Bactericidal/static** **Intracellular activity** **No cross resistance**	**Bactericidal/static** **-** **Limited cross-resistance**	**Unique mechanism** **Bactericidal/static** **Intracellular activity** **No cross resistance**	**Bactericidal/static** **-** **Limited cross-resistance**
Safety and tolerability	**Well tolerated in pregnancy and lactation** **No patient monitoring required post treatment**	**-** **Minimal outpatient monitoring required post treatment**	**Well tolerated in pregnancy and lactation** **No patient monitoring required post treatment**	**-** **Minimal outpatient monitoring required post treatment**
Contra-indications	**None**	**Pregnancy and lactation**	**None**	**Pregnancy and lactation**
Drug-Drug Interaction profile	**None**	**Minimal**	**None**	**Minimal**
Route of Administration / formulation	**Oral/IM, separated combination**		**Fixed-dose combinationfor orals**	**Co-packaged loose combination**
Dosing Schedule	**Single dose**	**Multiple doses**	**Single dose**	**Multiple doses**
Treatment duration	**One day**	**Up to 5 days**	**Up to 3 days**	**Up to 5 days**
Stability	**Heat stable, 3-year shelf-life in climatic region IV[a]**	**Heat stable, 3-year shelf-life**	**Heat stable, 3-year shelf-life in climatic region IV**	**Heat stable, 3-year shelf-life**
Cost (price /day of therapy)	**Equivalent to current treatment regimens**		**Equivalent to current treatment regimens**	
Time to patient availability	**5 years**	**7 years**	**7 years**	**10 years**

Table 1: Consensus Target Product Profile (TPP) developed by the gonorrhea expert group. IM: intramuscular injection. MDR, multidrug-resistant; STI, sexually transmitted infection; ESC, extended-spectrum cephalosporin; NG, *Neisseria gonorrhoeae*; IM, intramuscular injection, IV, intravenous injection. [a]Hot tropic/humid climate, simulated with 30ºC and 65% relative humidity.

Component 1: Accelerate the development of a New Chemical Entity

As part of this first component GARDP will seek to accelerate development and registration of one new molecule for the treatment of uncomplicated gonorrhea and in particular to support the conduct of late development activities (i.e. phase 3 and 4 trials). GARDP also aims to work with the patent holders to optimize the profile of the molecule along the lines of the TPPs.

To support access, stewardship, and conservation of the molecule, and keeping in mind the necessity to integrate it within existing guidelines, GARDP would then investigate possible combinations of the new molecule with existing antibiotics. *In vitro* studies would be initiated to investigate synergies, antagonisms and activity against other STIs.

Finally, GARDP will seek to explore the clinical efficacy of the new clinical entity, alone or in combination, on 1) extra-genital gonorrhea, and 2) patients co-infected with other STIs. This may entail investigating increased dosage or multiple dose regimens, conducting additional PK/PD (pharmacokinetic/pharmacodynamic) investigations and gathering additional clinical data through subsequent trials in high-risk groups.

Component 2: Evaluate the potential of existing antibiotics and their combinations

Several existing antibiotics have shown good anti-gonococcal properties *in vitro*, and for some, in patients: gentamicin, kanamycin, ertapenem and fosfomycin. However, their efficacy remains to be confirmed in randomized clinical trials. Adequate PK/PD studies for these antibiotics are lacking, and more data are needed on their MIC (minimum inhibitory concentration) and the relationship between the MICs, PK/PD and clinical outcomes. More data are also required for their utility in treating extragenital and complicated infections. Other antibiotics have been abandoned but may deserve further investigation. The aminocyclitol spectinomycin was commercialized in the 1960s as a specific treatment for gonorrhea. Resistance rapidly emerged in some settings [74-76] and spectinomycin use was discontinued. But resistance is currently rare worldwide [20] and spectinomycin retains excellent activity against most gonococcal isolates. It is used in some European countries, China and South Korea, but its availability in other regions is limited.

GARDP will aim at better understanding the opportunities and liabilities of existing drugs, and seek to identify optimal combinations through *in vitro* work. Clinical efficacy of these combination(s) will be confirmed through trials involving groups with high STI burdens, and sites in different countries that represent varied patterns of resistance.

Component 3: Explore co-packaging and development of Fixed Dose Combinations

Management of STIs often entails the co-administration of two or more antibiotics in order to cover all possible etiological agents. Co-packaged products or fixed-dose combinations thus offer many practical advantages such as facilitating control over prescription, distribution and administration of antibiotic combinations and reduce production costs. In addition, such combinations may increase compliance and this may help to limit the emergence of AMR. Finally

fixed drug combination and/or co-packaging offer a clear advantage in terms of stewardship. As part of this third component, GARDP will explore combinations and/or co-packaging for the optimal combinations of new and/or existing antibiotics identified through the first two components.

Component 4: Support the development of simplified treatment guidelines and foster conservation

To ensure appropriate use of new treatments, GARDP and WHO will work with pharmaceutical companies, regulators and other stakeholders to ensure the newly developed antibiotics/combinations are globally accessible while at the same time used in an appropriate manner. The partners will support the development of evidence-based, regional/national treatment guidelines. This may entail the conduct of observational studies and resistance surveys, in collaboration with WHO, to inform the integration of optimal combinations in STI guidelines. It may also involve observational studies to support the use of developed treatments in vulnerable populations (*e.g*. pregnant women and adolescents). GARDP will also work with partners to promote the appropriate use of new treatments by health care providers and patients by educating key stakeholders, supporting the conduct of pilot implementation studies and monitoring of treatment use and emergence of resistance.

Conclusions

The number of gonococcal infections is rapidly rising worldwide. Most worryingly, *N. gonorrhoeae* is an important member of the bacterial community that spreads AMR. Just three new clinical entities are in various stages of clinical development for treatment of gonorrhea today, in a therapeutic area that lacks a strong commercial interest. GARDP, a joint initiative founded by the WHO and DND*i*, has begun to document ideal and acceptable profiles of antimicrobials for gonorrhea treatment. Four R&D routes have been outlined that require donor support: introduction of a new molecule for gonorrhea, identification of ideal combination partners among existing antibiotics, formulation of new fixed drug combinations and establishment of a stewardship framework for the distribution and use of the new treatments. GARDP intends to work with its partners and other stakeholders to complete this roadmap and bring one new treatment to clinical practice by 2023.

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