GARDP
Strategy
Proposal

Sexually Transmitted Infections/Gonorrhea

GARDP STI/GONORRHEA STRATEGY

Contents

EXECUTIVE SUMMARY

The burden of Sexually Transmitted Infections (STIs) continues to be high. In 2012, WHO estimates that 357 million new cases of curable STIs occurred, including 78 million of gonorrhea. The risk of HIV transmission is increased by 3 to 5 fold in STI co-infected individuals, and STIs exhibit a high morbidity. For example, gonococcal infections are responsible for about half of all cases of Pelvic Inflammatory Diseases (PID). There are increasing concerns globally about the impact and speed of Antimicrobial Resistance (AMR) gonorrhea. Multi-drug resistant (MDR) and extensive- drug resistant (XDR) gonorrhea threatens richest and poorest countries alike, as the spread of gonococcal infections ignores geographical borders. While an increasing number of treatment failures to the last line of antibiotics are being reported, the pipeline remains desperately dry. There are however, a number of opportunities for GARDP to guide stewardship and access as well as R&D. This document describes the proposed actions to be implemented by GARDP to turn the tides in the fight against resistant gonorrhea.

INTRODUCTION

Disease burden

The rising prevalence of bacterial sexually transmitted infections (STI) continues to be a major public health concern globally. WHO estimates that in 2012, 357 million new cases of curable STI occurred, including 131 million new cases of chlamydia, 78 million of gonorrhea, 143 million of trichomoniasis, and 5.6 million of syphilis (1). The WHO regions most affected are the African region, the Western Pacific region and the Americas. The increase in STI incidence affects both low- and middle-income countries. For example, for 2015, Public Health England reports annual increases of 11% for gonorrhea and 20% syphilis (2). In Australia, the Kirby Institute has reported that between 2010 and 2014 the number of diagnoses of gonorrhea increased by 29‑146% across all States except one (3). This rise in the incidence of STI is compounded by the rapid spread of Antimicrobial Resistance (AMR).

Gonorrhea is one of the most common STI worldwide. The African region has the highest incidence rates of gonococcal infections in the world, with about 50 and 100 new infections per 1'000 women and men, respectively (4). It is the most frequent cause of urethral discharge in men, accounting for up to 85% of cases in South Africa, and up to 83% in Zimbabwe (5,6). In the US it is the second most frequently reported infectious diseases, accounting for 333,000 cases in 2013 (7). The Global Burden of Disease Study estimates that in 2013, gonorrhea was responsible for 225,400 Years Lived with Disability (YLD) per year (8).

There are serious concerns, articulated by the WHO and others, over the spread of resistant gonorrhea. *N. gonorrhoeae*, the etiological agent of gonorrhea, is evolving into a superbug and may soon become untreatable due to its resistance to all classes of antimicrobials available. This prompted the CDC to include *N. gonorrhoeae* as one of three organisms presenting an urgent threat (9). In 2012, the WHO launched a Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae* (10). Its key points included advocacy, STI prevention and control, surveillance, rational drug use, capacity building, and increased R&D to, e.g., identify new treatment alternatives.

Clinical manifestations

Gonococcal infections commonly manifest in men as urethritis. Symptoms of urethritis develop in 75% of the men within four to eight days of genital infection with *N. gonorrhoeae* and in 80 to 90% within two weeks (11). Urethral discharge (UD) is the most frequent presenting symptom, and is often undistinguishable from non-gonococcal urethritis (e.g. in *Chlamydia trachomatis* infections). Acute unilateral epididymitis can be a complication of gonococcal infection, although it is more common with *C. trachomatis* infections (12,13). Combined gonococcal and chlamydial infections of the epididymis are more frequent than epididymis infections cause by *N. gonorrhoeae* alone (14).

In women, gonococcal infections are often (≥50% of the cases) asymptomatic (18). Genital infections, in particular cervical infections, are the most common infections. When symptomatic, cervical infection typically manifests as vaginal pruritus and/or mucopurulent discharge. If left untreated, *N. gonorrhoeae* infections can ascend to involve the uterus and fallopian tubes, with dramatic consequences on reproductive health. Pelvic inflammatory

disease (PID) occurs in 10-20% of women with cervical gonorrhea and *N. gonorrhoeae* is thought to be a leading cause of PID worldwide (19). Given the high incidence of asymptomatic infections, PID can be the first presenting complaint. In pregnant women, the prevalence of gonococcal infections has been estimated at between 3 and 15 % in Low and Middle Income Countries (LMIC). Numerous past studies have highlighted a substantial prevalence (>50%) of penicillinase-producing strains (PPNG) (15). Pregnancy complications associated with urogenital gonorrhea include chorioamnionitis, premature rupture of membranes, preterm birth, ectopic pregnancies and spontaneous abortions (16–18). The risk of these complications in the setting of gonococcal infection has been reported as approximately two to five times greater than uninfected controls (16,19). Perinatal transmission occurs in 30 to 40 % of cases. Coinfection with *C. trachomatis* is frequent and mother-to-child HIV transmission is heightened in the presence of gonorrhea (20). Infants born to infected mothers have a lower mean birth weight, and can develop potentially blinding neonatal conjunctivitis, pharyngitis, arthritis, and gonococcemia (15,21).

Rectal and pharyngeal infections with *N. gonorrhoeae* occurs in both men and women but remain largely asymptomatic. Anorectal gonorrhea may be the only site of infection in up to 40% of men who have sex with men (MSM) (22,23). This observation is particularly concerning as gonococcal proctitis in MSM is associated with an approximately threefold increase in the risk of acquisition of HIV infection (24). Gonococcal proctitis cannot be distinguished from other infectious causes (e.g. Herpes simplex virus, Chlamydia and syphilis) of proctitis by symptoms alone. Gonococcal infection of the pharynx is usually acquired by oral sex exposure. A recent review found that prevalence among women and MSM in the US was 2.1% [0-29.6%] and 4.6% [0.5-16.5%] respectively (25). Oropharyngeal infections can occur also in the absence of urogenital infection (26,27). Although bacterial concentrations in the pharynx are generally lower than in the rectum or urogenital tract, the pharynx is thought to be a favorable site for the emergence of resistance. Worryingly, pharyngeal and anorectal infections are frequently asymptomatic (> 90%) and require screening with molecular assays to detect them.

Bacterial STIs such as gonorrhea, exhibit epidemiological synergy and may enhance the transmission of HIV by three to five times (28). The presence of HIV genetic material in urethral and semen specimens is significantly associated with gonococcal infection and effective treatment for gonorrhea significantly reduces the infectious inoculum (29,30). Men with gonorrhea are therefore an important group to target with effective antimicrobials therapies as part of the national HIV prevention strategies.

The looming threat of resistance

Since the 1940ies, most antibiotic classes used against gonorrhea have been partially or completely lost to resistance (31). Overuse and misuse of antibiotics and the widespread availability of counterfeit drugs with low levels of active compounds contributed to the development of resistances. Sulphonamides, penicillins, first generations cephalosporins, tetracyclines, macrolides and fluoroquinolones can no longer be relied upon. The extended-spectrum cephalosporins (ESCs), which represent the last remaining option for first line empirical monotherapy, are also under threat. During the last two decades, gonococcal strains exhibiting resistance to ESCs (i.e. cefixime and ceftriaxone) have emerged and spread worldwide (32–35). Since 2009, a total of 46 countries have reported decreased

susceptibility to ESC. The WHO Gonococcal Antimicrobial Surveillance Program (GASP) found resistance was spreading (over 2009-13) especially in Asia, North America, Europe, and Australia, with large data gaps in Africa and Central Asia preventing an assessment of the situation in those regions (36). Out of the 49 countries reporting data on drug susceptibility of *N. gonorrhoeae* in 2012- 2013, 29 (59%) reported decreased susceptibility to ESC. On the other hand reports of treatment failures are multiplying (37–40) and several countries have now revised their treatment guidelines to recommend dual therapy i.e. mainly ceftriaxone and azithromycin (41–43). The first case of treatment failure with this dual therapy has recently been reported (34).

N. gonorrhoeae has an extraordinary capacity to mutate and can do so either by altering directly its genetic material or by transformation (transfer of partial or whole genes from other bacteria). Other non-pathogenic *Neisseria* species (i.e. commensal species) are found in different human anatomical sites, particularly the pharynx. It is believed that repeated exposure to antibiotics led oral commensal *Neisseria spp* to develop resistance mutations which were in turn transferred to pathogenic *Neisseria spp*. For example, sulphonamide resistance in *N. meningitidis* is thought to have occurred as a result of horizontal DNA transfer from commensal *Neisseria* possessing mutations in the dihydropteroate synthase gene (44). Similarly, the acquisition by gonococci of ESC resistance appears to have emerged as a result of gene transfers from commensal *Neisseria spp.* The mosaic penA alleles, which are associated with elevated ESC MIC, appear to have evolved by DNA uptake and subsequent recombination of partial penA genes from commensal *Neisseria spp*. commonly residing in the oropharynx (i.e., *Neisseria sicca*, *Neisseria perflava*, *Neisseria cinerea*, *Neisseria polysaccharea* and/or *Neisseria flavescens*) into the gonococcal penA gene (45–47). Worryingly, *N. gonorrhoeae* can also acquire resistance genes from other bacterial genus, i.e. *Streptococcus* (48).

Of note, *N. gonorrheae* can use almost all mechanisms of bacterial resistance described so far, i.e. 1) antimicrobial destruction or enzymatic modification of antimicrobials, 2) target modification, 3) decreased uptake of antimicrobials, and 4) increased efflux of antimicrobials (31). The inherent properties of *N. gonorrheae* that allow it to acquire and retain resistance to several classes of antibiotics at the same time is particularly concerning. In *N. gonorrheae* most of the acquired or developed AMR mechanisms do not appear to cause significantly lower biological fitness, which results in the persistence of AMR or multidrug-resistance (MDR)/extensively drug-resistant (XDR) strains event in the absence of antimicrobials selection (49–51).

Current treatment options

The treatment of gonorrhea is largely empirical, and because of limited access to laboratory test to diagnose gonorrhea, most countries have adopted syndromic management in accordance with WHO global strategy for STI prevention and control. In the European region, USA, Canada, and Australia the greater availability of laboratory resources allows for the use of etiological diagnosis (52,53). Syndromic management is based on the identification of consistent groups of symptoms and easily recognized signs (e.g. UD, Genital Ulcer Disease (GUD), Vaginal Discharge (VD)), and the provision of treatment that will deal with the majority of, or the most serious, organisms responsible for producing a syndrome. This approach is cost-effective, allowing nurses to treat the majority of STI patients without

the need for laboratory-based diagnostics (54). In practice, UD in men is therefore managed with drugs that target uncomplicated gonorrhea PLUS drugs that target Chlamydia.

Single dose antimicrobial monotherapy has been the mainstay of gonococcal infections management for long. But in the face of increasing AMR, and in particular in view of the rise in the number of treatment failures with ESC, a number of countries have recently adopted a dual therapy in their treatment guidelines. In Canada, Europe, South Africa and Australia, where failure with monotherapy has been noticed, the recommended first-line treatment for uncomplicated, urogenital gonorrhea is Ceftriaxone (250 mg to 500 mg IM) + Azithromycin (1 to 2 g p.o.). The recently released WHO treatment guidelines for gonorrhea recommend that the treatment choice be based on local resistance data, and that first-line drugs achieve a minimum of 95% cure rates. However, when appropriate resistance surveillance data is not available, the guideline recommends dual therapy over monotherapy for people with gonorrhoea, irrespective of infection site (Ceftriaxone 250 mg IM + Azithromycin 1 g p.o. OR Cefixime 400 mg p.o. + Azithromycin 1 g p.o.). These regimens were recommended based on early clinical efficacy trials, PK/PD simulations, *in vitro* AMR surveillance and expert consultation. But the level of evidence supporting the use of these regimens is low. Besides, the cost of such a dual therapy is prohibitive for many countries and implementation in LMIC will prove challenging. In Africa and Latin America, fluoroquinolones are still frequently used although they have been removed from WHO guidelines and a high prevalence of resistance has been described (55,56). A study from Uganda showed that only 16% of gonococcal isolates were sensitive to the nationally-recommended first-line agent ciprofloxacin (57).

Effective treatment of pharyngeal infections is more difficult than treatment of uro-genital infections. A systematic review of therapeutic trials assessing treatment outcomes of 16,737 uncomplicated gonococcal infections reported an overall cure rate of 96.4% (58). However, when stratified by site of infection, cure rates were significantly lower in the oropharynx of both males (79.2%) and females (83.7%) compared with those observed at the urethra, cervix or rectum, irrespective of treatment regimen. The exact reason for this lower coverage of oropharyngeal infections is unknown but it is commonly believed that antimicrobials do not achieve high enough concentrations for a long enough period of time in the oropharynx as compared to the anogenital tract (58–60). Treatment of pharyngeal infections is however paramount. First because of the presumed role of the pharynx in the emergence of resistance. Second, because these infections most probably act as a reservoir of resistant *N. gonorrheae*. A study conducted in San Francisco suggests that transmission of strains with reduced susceptibility to ESC is associated with history of receptive oral sex as the only recent exposure (61). Pharyngeal infections are common, asymptomatic, and under-screened. Leaving them untreated further fuels the epidemic globally, and undermines efforts to contain the spread of resistances.

BOX1: Unmet gonorrhea treatment needs and gaps

- Lack of therapeutic options for multi-drug resistant (MDR) and extensive drug resistant (XDR) gonorrhea
- No evidence-based treatment for extra-genital infections
- No evidence-based treatment for complicated infections

GARDP GONORRHEA STRATEGY PROPOSAL

Overarching goal

The spread and incidence of gonococcal antimicrobial resistance (AMR) is alarming, rapidly outpacing the development of new medicines, with the frightening prospect of untreatable gonorrhea. This will put at risk the achievement of the target set by the Global Health Sector STI Strategy, approved by the World Health Assembly in 2016, of 90% reduction of the incidence of gonorrhea by 2030. The frequency of asymptomatic infections, the rapidly changing antimicrobial susceptibility patterns and the variety of resistance mechanisms make the control of resistant gonorrhea particularly challenging.

The absence of strong market incentives has resulted in a very weak pipeline, with only three companies (Entasis, Cempra and GSK) developing new antibiotics for gonorrhea. While each of these NCEs has the potential to overcome ESC-resistance, new resistances may emerge rapidly if these new molecules are introduced as monotherapies. In addition, development has so far focused on urogenital forms of the disease, and even if these NCEs have *in vitro* activity against Chlamydia, clinical studies are warranted before any recommendation can be made for their use in STIs case management. Finally, of the three compounds currently in the pipeline, two are also being developed for other indications (e.g. community acquired pneumonia), which foretell difficulties with regards to the stewardship framework.

Combinations of existing antibiotics are also being investigated but most efforts so far have focused on studying *in vitro* synergies and antagonisms. The only exception is the combination of gentamicin and azithromycin which has been evaluated in a phase 4 randomized controlled trial of patients with urogenital gonorrhea. A number of other existing antibiotics which exhibit anti-gonococcal activity deserve further investigations. As with NCEs, there is a clinical data gap with regards to efficacy in oropharyngeal infections and in Chlamydia infections.

To contain the spread of untreatable gonorrhea, it is essential that an alternative, complementary research and development agenda be designed to 1) ensure proper conservation of the new tools, 2) address extra-genital (and in particular oropharyngeal) gonorrhea and 3) match the overall framework of STIs case management (including syndromic management). GARDP will ensure that the above-mentioned gaps are filled by partnering with all key stakeholders involved in tackling gonococcal AMR to develop reliable and sustainable treatment options for the post-cephalosporins area.

Targeted outcome

The ultimate aim of the present proposal is to have, within 7 years-time, one treatment that

i) works against drug-sensitive and drug-resistant forms of the disease

ii) is suitable for integration into WHO-recommended STIs case management, including syndromic management

iii) works in both uro-genital and extra-genital (i.e. pharyngeal and anorectal infections)

Currently there are no dedicated programs targeting all three strategies, though there are efforts focused on developing and registering new treatments for uncomplicated, uro-genital gonorrhea.

The GARDP R&D strategy and project proposal will be guided by the consensus Target Product Profile (TPP) developed during the Gonorrhea expert meeting convened in June 2016 (table 2 in Annex). GARDP will look into a single-dose regimen for un-complicated, urogenital gonorrhea that would work in current resistant strains and which dosage could be adapted to also cover other STIs and extra-genital infections. Since the use of antibiotics combinations offers the theoretical advantage of preventing the emergence of resistance, and keeping in mind the necessity to protect new drugs while ensuring sustainable access, GARDP will look in particular into the development of combinations. Development of either fixed-dose combinations or co-packaged products will be explored. It would be essential to select combinations that are also active on *Chlamydia*, so that they may fit with the empirical management of STIs used by most countries.

How does the proposal fit into the overall Public Health approach?

The global response to multi-drug resistant gonorrhea will require collaborative, multi-sectorial actions. Key to the overall management of AMR will be the strengthening of the WHO Gonococcal Antimicrobial Surveillance Program (GASP), the development of molecular approaches that combine gonorrhea diagnosis and AMR determination, and the evaluation of new antibiotics and their combinations. The GARDP approach will be complementary to and synergistic with other efforts, in particular those promoted by WHO Global Action Plan to control and the spread and impact of AMR in *Neisseria gonorrheae*. The cornerstone of a public health approach to gonorrhea will be an affordable, short-course treatment that may be integrated easily in STIs case management, and that achieve high cure rates, irrespective of site of infection and pathogen resistance profile.

Proposed R&D Strategy

Based on the needs identified above, and in line with the consensus TPP, GARDP has developed a comprehensive R&D strategy that may be broken down in four complementary components.

Component 1: Accelerate the development of a New Chemical Entity

There are currently three New Chemical Entities (NCEs) in the clinical pipeline. Solithromycin is a novel oral fluoroketolide (macrolide) that has activity against most Gram-positive and fastidious Gram-negative bacteria, including *N. gonorrheae* and *C. trachomatis* (62,63). It binds to the bacterial ribosomes at 3 sites which result in potent bactericidal activity. A recently completed phase 2 study showed that all 59 patients receiving Solithromycin (1 or 1.2 g IM) were cured, including those with simultaneous pharyngeal and rectal gonorrheae (64). However, strain with *in vitro* elevated MIC values for solithromycin have been described (65) suggesting that solithromycin may not be used in monotherapy. Concerns have also been raised over solithromycin liver toxicity. A phase 3 study is on-going which will recruit 300 patients with uncomplicated gonorrhea. Of note, a number of trials have also been conducted in adolescents and pediatric patients (though for other indications, i.e. community-acquired pneumonia).

Zoliflodacin (also known as ETX0914) is a first-in-class drug (spiropyrimidinetrione) that inhibits bacterial topoisomerase II and shows *in vitro* antibacterial activity against several STI pathogens, including *N. gonorrheae*, *C. trachomatis* and *M. genitalium* (66,67). Zoliflodacin alone or in combination with azithromycin or ceftriaxone was highly effective against *N. gonorrheae*. A synergistic interaction with ciprofloxacin was also indicated *in vitro* (68). Finally Zoliflodacin MIC did not seem to correlate with MICs of previously or currently used antimicrobials, indicating absence of cross-resistance (69). Zoliflodacin is currently being developed by Entasis Therapeutics for uncomplicated urogenital gonorrhea only. Three clinical trials have been conducted so far (two phase 1 and one phase 2). Results from the phase 2 trial show high efficacy on urogenital infections (98-100% microbiological cure rate).

Gepotidacin is also an inhibitor of bacterial topoisomerases that has shown *in vitro* activity against a wide range of drug-resistant bacteria, including MRSA and ESBL-producing Enterobacteriaceae. Gepotidacin has also shown good *in vitro* activity against *N. gonorrhoeae* (70,71). It is being developed by GSK for several bacterial infections (pulmonary and skin infections), including gonorrhea. At least nine phase 1 studies have been conducted or are underway, including a thorough QT study and a study assessing PK-PD in healthy subjects with varying degrees of renal impairment.

As part of this first component GARDP intends to accelerate the development and registration of one NCE for the treatment of uncomplicated, uro-genital gonorrhea and in particular support the conduct of a late development trial(s). GARDP will work with the manufacturer to optimize the profile of the NCE and ensure that the formulation chosen is acceptable globally, and compatible with GARDP geographic reach and target clinical settings (i.e. tropical climates).

In order to ensure conservation of the NCE, and keeping in mind the necessity to integrate it in existing guidance, GARDP will investigate the possibility of combining the NCE with other

existing antibiotics (see component 2). This will entail conducting *in vitro* studies to investigate synergies, antagonisms and activity against other sexually-transmitted pathogens.

As part of this first component, GARDP will also seek to investigate the efficacy of the NCE on 1) extra-genital gonorrhea, and 2) patients infected with other STIs. This may entail investigating increased dosage or multiple dose regimens, conducting additional PK/PD investigations and gathering additional clinical data through subsequent trials in groups with high prevalence of oropharyngeal infections and/or Chlamydia co-infections (MSM and FSW).

Component 2: Evaluate the utility of existing antibiotics and their combinations for the treatment of gonorrhea

A number of existing antibiotics have shown good anti-gonococcal properties *in vitro*. Gentamicin, ertapenem, and fosfomycin are potentially interesting candidates, however, their efficacy remains to be confirmed in robust randomized clinical trials. PK/PD modeling and/or PK/PD studies for these antibiotics are lacking, and more data is needed on their MIC internationally and on the relationship between the MICs and clinical outcomes. More data is also warranted for their usefulness in the treatment of extra-genital and complicated infections. The aminocyclitol spectinomycin (2 g × 1 IM) was commercialized in the 1960s as a specific treatment for gonorrhea. Unfortunately, high-level resistance rapidly emerged (72–74) and spectinomycin was abandoned as a first-line empirical monotherapy for gonorrhea internationally. Currently resistance to spectinomycin is rare worldwide and the drug retains excellent activity against the majority of gonococcal isolates. It is being used to treat urogenital, uncomplicated gonorrhea in certain countries (i.e. China and Korea).

In addition to the above-mentioned antibiotics, further mapping of existing and potentially useful compounds needs to be undertaken as each of the above-mentioned antibiotics have drawbacks and may well fail in the short to middle term. For example, resistance to fosfomycin develops rapidly *in vitro* and the MIC of ertapenem is affected by the ESC resistance determinants (75). Safety issues have been noted in one trial investigating Gentamicin plus Azithromycin (76) and spectinomycin shows poor efficacy against pharyngeal infections (58). Several existing compounds for which published data may not be available could be of interest.

As part of this second component, GARDP will conduct a scoping exercise on existing antibiotics that could be suitable for inclusion in combination regimens that fit the TPP. The aim of this scoping exercise will be to identify molecules that

1) show bactericidal activity *in vitro* against *N. gonorrheae* (and also against *C. trachomatis*), in particular against ESC- and macrolide-resistant strains

AND

2) are minimally impacted by cross -resistance

AND

3) achieve a high Cmax/MIC ratio while retaining a good safety profile

OR

4) have successfully been used to empirically treat gonococcal infections, in particular after initial treatment failure

This scoping exercise will involve literature searches, contact with experts and approaching companies that have abandoned antibiotics development programs and may have interesting candidates in their compound libraries. This second component will link up with GARDP Antibiotics Memory Recovery initiative.

Optimal combinations of the candidate antibiotics identified through the scoping exercise will be investigated through *in vitro* studies to determine synergies and antagonisms, and to evaluate sensitivity to cross-resistance when this data is not available. Combinations with NCEs that are currently in development will also be investigated.

Clinical efficacy of the optimal combination(s) on urogenital infections will be confirmed through trials targeting groups with high STI burden. Care will be taken to involve sites in different countries to represent the variety of patterns of resistance. Efficacy on extra-genital infections will be investigated as a secondary outcome.

Component 3: Explore co-packaging of optimal antibiotics combination and development of Fixed Dose Combinations (FDC)

Most bacterial STIs are managed empirically and this 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 (FDCs) thus offers some practical advantages. From a stewardship perspective, co-packaging and/or FDCs also offer the advantage of facilitating control over prescription, distribution and administration of antibiotics combinations. Finally, FDCs can offer numerous advantages, including increased efficacy and/or better tolerance, better treatment adherence, lower costs of manufacturing, and simpler distribution.

Optimal combinations of NCEs and/or existing antibiotics will be identified through the first two components of the R&D strategy. Based on these optimal combinations, GARDP will aim to explore the feasibility and value of developing a co-package product FDC. In doing so GARDP will follow the following steps

1) Produce a Quality Target Product Profile for the co-packaged product/FDC to ensure the combination products have appropriate biopharmaceutical characteristics
2) Evaluate the possibility of securing access to the compounds intended to be included in the co-package product /FDC through licensing
3) Estimate feasibility and cost of developing the co-package product /FDC
4) Build up the clinical and pharmacological data and rationale for supporting co-packaging/FDCs registration

An oral FDC would be highly desirable given both the HIV risk associated with occupational needle stick injuries in countries with high HIV prevalence among STI patients and the over-treatment of patients and their partners inherent to syndromic management. However, an oral FDC may not be achievable and GARDP will also explore the development an injectable FDC or a co-packaged product.

Component 4: Support the development of simplified treatment guidelines for empiric management of STIs

While the development of new antibiotics / combinations is of outmost importance, it should go hand in hand with a sound access strategy and stewardship framework. GARDP will therefore need to go beyond the traditional PDP approach and work with WHO, pharmaceutical companies and regulatory authorities to ensure the newly developed antibiotics/combinations are globally accessible and that they are not "lost" to resistance within a few years after their introduction.

In order to secure access to developed treatment/combinations, GARDP will investigate both regulatory and public health pathways. Depending on the treatment/combination, registration may initially be pursued for uncomplicated gonorrhea and then expanded to include other relevant public health indications (e.g. other STIs). In some instances however (e.g. complicated gonorrhea), registration may not be an appropriate goal and GARDP will seek to obtain robust scientific evidence to support international and national guidelines change.

GARDP will

1) Work with national regulatory authorities to secure registration of developed antibiotics/combinations in high-burden countries while ensuring effective drug regulations and prescription policies are in place
2) With the support of WHO, and based on regional AMR data, develop evidence-based, regional treatment guidelines. This may entail the conduct of observational studies and resistance surveys, in collaboration with WHO, to inform the selection of optimal combinations in components 1 and 2, the selection of trial sites and the inclusion of treatment/combinations in STI guidelines. It may also involve observational studies to support the use of the existing and developed treatments/combinations in distinct populations (e.g. MSM, FSW, women, adolescents)
3) Promote the responsible use of new treatments by both health care providers and patients by educating key stakeholders, support the conduct of pilot implementation studies and monitoring of treatment use and emergence of resistance
4) Explore the possibility of rotating first-line treatments. If multiple effective first-line treatments were to become available, cycling of antibiotic combinations could be an important mechanism to prevent/delay the emergence of new resistance patterns globally.

CONCLUSION

It appears inevitable that ESC-resistant gonococcal strains with retained resistance determinants to previously recommended antimicrobials will spread internationally, possibly heralding an era of untreatable gonorrhea. This would be an exceedingly serious public health problem that would result in substantial morbidity and potentially jeopardize the fulfillment of several Sustainable Development Goals (SDG). Accordingly, a timely, decisive and multicomponent R&D strategy is required. GARDP has developed a 7 years proposal with the goal of developing one to two combinations to be integrated into the global action plan to combat the spread of drug-resistant gonorrhea. The goals and the objectives of the strategy, with details of each component, are summarized in table 1 below. Coordination with WHO, industrial partners, governments, and other key stakeholders will be crucial to procure these combinations as FDC, and at prices that are affordable to high burden countries.

	Priority level	Timing
Component 1 Accelerate the development of a New Chemical Entity (NCE)		
Accelerate development of an NCE for uncomplicated, urogenital gonorrhea (≥95% cure in urogenital sites irrespective of resistance profile)	1st	Medium-term
Optimize the formulation of the NCE for global use	1st	Short-term
Identify optimal combination(s) of the NCE with existing antibiotic(s) for proper conservation	2nd	Medium-term
Expand the NCE indication to extra-genital infections (≥95% cure in extra-genital sites)	3rd	Long-term
Expand the NCE indication to other STIs (e.g. Chlamydia)	3rd	Long-term
Component 2 Evaluate the utility of existing antibiotics and their combinations for the treatment of gonorrhea		
Identify optimal combinations of existing antibiotics for urogenital gonorrhea (*in vitro* studies)	1st	Short term
Confirm clinical efficacy of combinations on urogenital gonorrhea (95% cure irrespective of resistance profile)	1st	Medium-term
Generate local data on clinical efficacy and develop regional implementation plans	2nd	Long-term
Investigate clinical efficacy on extra-genital infections	3rd	Long term
Workstream 3 Foster the inclusion of treatments/combinations developed in Fixed Dose Combinations (FDC)		
Optimize formulations of antibiotics identified through WS1 and WS2 for inclusion in Fixed Dose Combination (FDC) or co-packaging	1st	Medium term
Secure scale up of manufacturing and GMP compliance	1st	Long-term
Build up the clinical and pharmacological dossier for FDC registration	2nd	Long-term
Workstream 4 Support the development of simplified treatment guidelines for empiric management of STIs and their complications		
Secure registration of treatments/combinations developed in WS1 and 2 in high burden countries	1st	Long term
Ensure treatments/combinations developed are included in WHO and national treatment guidelines	1st	Long term
Support pilot implementation studies and treatment use monitoring	3rd	Long-term

Table 1: Components and specific objectives of the GARDP R&D strategy on gonorrhea. Implementation of each component will be staged, depending upon funding.

REFERENCES

1. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS One. 2015;10(12):e0143304.
2. Infection report HIV-STIs Sexually transmitted infections and chlamydia screening in England, 2015. 2016.
3. Center for Disease Control and Prevention. HIV, viral hepatitis and sexually transmissible infections in Australia. Annual Surveillance Reports 2013 [Internet]. 2013. Available from: http://www.kirby.unsw.edu.au/surveillance/Annual-Surveillance-Reports
4. Report on global sexually transmitted infection surveillance 2013. 2014.
5. Takuva S, Mugurungi O, Mutsvangwa J, Machiha A, Mupambo AC, Maseko V, et al. Etiology and antimicrobial susceptibility of pathogens responsible for urethral discharge among men in Harare, Zimbabwe. Sex Transm Dis. 2014;41(12):713–7.
6. Mhlongo S, Magooa P, Müller EE, Nel N, Radebe F, Wasserman E, et al. Etiology and STI/HIV coinfections among patients with urethral and vaginal discharge syndromes in South Africa. Sex Transm Dis. 2010;37(9):566–70.
7. Sexually Transmitted Disease Surveillance 2013. Atlanta; 2014.
8. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
9. Antibiotic resistance threats in the United States, 2013 [Internet]. Current. Atlanta; 2013. Available from: http://www.cdc.gov/drugresistance/threat-report-2013/index.html
10. WHO. Global action plan to control the spread and impact of AMR in Neisseria gonorrhoeae. Geneva; 2012.
11. Harrison WO, Hooper RR, Wiesner PJ, Campbell AF, Karney WW, Reynolds GH, et al. A trial of minocycline given after exposure to prevent gonorrhea. N Engl J Med. 1979;300(19):1074–8.
12. Harnisch JP, Berger RE, Alexander ER, Monda G, Holmes KK. Aetiology of acute epididymitis. Lancet. 1977;1(8016):819–21.
13. Hawkins DA, Taylor-Robinson D, Thomas BJ, Harris JR. Microbiological survey of acute epididymitis. Genitourin Med. 1986;62(5):342–4.
14. Holmes KK, Berger RE, Alexander ER. Acute epididymitis: etiology and therapy. Arch Androl. 1979;3(4):309–16.
15. Laga M, Meheus A, Piot P. Epidemiology and control of gonococcal ophthalmia neonatorum. Bull World Health Organ. 1989;67(5):471–7.
16. Liu B, Roberts CL, Clarke M, Jorm L, Hunt J, Ward J. Chlamydia and gonorrhoea infections and the risk of adverse obstetric outcomes: a retrospective cohort study. Sex Transm Infect. 2013;89(8):672–8.
17. Donders GG, Desmyter J, De Wet DH, Van Assche FA. The association of gonorrhoea and syphilis with premature birth and low birthweight. Genitourin Med. 1993;69(2):98–101.

18. Maxwell GL, Watson WJ. Preterm premature rupture of membranes: results of expectant management in patients with cervical cultures positive for group B streptococcus or Neisseria gonorrhoeae. Am J Obstet Gynecol. 1992;166(3):945–9.

19. Ekwo EE, Gosselink CA, Woolson R, Moawad A. Risks for premature rupture of amniotic membranes. Int J Epidemiol. 1993;22(3):495–503.

20. Workowsky KA, Bolan GA, Center for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. Morb Mortal Wkly Rep Recomm Reports. 2015;64(RR-03):1–137.

21. Woods CR. Gonococcal infections in neonates and young children. Semin Pediatr Infect Dis. 2005;16(4):258–70.

22. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G, et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. Clin Infect Dis. 2005;41(1):67–74.

23. Schachter J, Moncada J, Liska S, Shayevich C, Klausner JD. Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men. Sex Transm Dis. 2008;35(7):637–42.

24. Craib KJ, Meddings DR, Strathdee SA, Hogg RS, Montaner JS, O'Shaughnessy M V, et al. Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. Genitourin Med. 1995;71(3):150–4.

25. Chan PA, Robinette A, Montgomery M, Almonte A, Cu-Uvin S, Lonks JR, et al. Extragenital infections caused by Chlamydia trachomatis and Neisseria gonorrhoeae: a review of the literature. Infect Dis Obstet Gynecol. 2016;5758387.

26. Koedijk FDH, van Bergen JEAM, Dukers-Muijrers NHTM, van Leeuwen AP, Hoebe CJPA, van der Sande MAB. The value of testing multiple anatomic sites for gonorrhoea and chlamydia in sexually transmitted infection centres in the Netherlands, 2006-2010. Int J STD AIDS [Internet]. 2012 Sep 1 [cited 2017 Jan 3];23(9):626–31. Available from: http://std.sagepub.com/lookup/doi/10.1258/ijsa.2012.011378

27. van Liere GAFS, Hoebe CJPA, Dukers-Muijrers NHTM. Evaluation of the anatomical site distribution of chlamydia and gonorrhoea in men who have sex with men and in high-risk women by routine testing: cross-sectional study revealing missed opportunities for treatment strategies. Sex Transm Infect [Internet]. 2014 Feb [cited 2017 Jan 3];90(1):58–60. Available from: http://sti.bmj.com/lookup/doi/10.1136/sextrans-2013-051248

28. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect. 1999;75(1):3–17.

29. Moss GB, Overbaugh J, Welch M, Reilly M, Bwayo J, Plummer FA, et al. Human immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion. J Infect Dis. 1995;172(6):1469–74.

30. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet. 1997;349(9069):1868–73.

31. Unemo M, Shafer WM. Antimicrobial resistance in Neisseria gonorrhoeae in the 21st century: past, evolution, and future. Clin Microbiol Rev. 2014;27(3):587–613.

32. Cámara J, Serra J, Ayats J, Bastida T, Carnicer-Pont D, Andreu A, et al. Molecular characterization of two high-level ceftriaxone-resistant Neisseria gonorrhoeae isolates detected in Catalonia, Spain. J Antimicrob Chemother. 2012;67(8):1858–60.

33. Ohnishi M, Golparian D, Shimuta K, Saika T, Hoshina S, Iwasaku K, et al. Is Neisseria gonorrhoeae initiating a future era of untreatable gonorrhea?: detailed characterization of the first strain with high-level resistance to ceftriaxone. Antimicrob Agents Chemother. 2011;55(7):3538–45.

34. Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D, et al. Failure of dual antimicrobial therapy in treatment of gonorrhea. N Engl J Med. 2016;374(25):2504–6.

35. Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant Neisseria gonorrhoeae in France: novel penA mosaic allele in a successful international clone causes treatment failure. Antimicrob Agents Chemother. 2012;56(3):1273–80.

36. Report on global sexually transmitted infection surveillance 2015. 2016.

37. Lewis DA, Sriruttan C, Müller EE, Golparian D, Gumede L, Fick D, et al. Phenotypic and genetic characterization of the first two cases of extended-spectrum-cephalosporin-resistant neisseria gonorrhoeae infection in south africa and association with cefixime treatment failure. J Antimicrob Chemother. 2013;68(6):1267–70.

38. Lewis DA, Sriruttan C, Coetzee J. Detection of multidrug-resistant gonorrhoea in the Gauteng province. 2012;27(4):199–200.

39. Golparian D, Ohlsson A, Janson H, Lidbrink P, Richtner T, Ekelund O, et al. Four treatment failures of pharyngeal gonorrhoea with ceftriaxone (500 mg) or cefotaxime (500 mg), Sweden, 2013 and 2014. Eurosurveillance [Internet]. 2014 Jul 31 [cited 2016 Sep 27];19(30):20862. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20862

40. Allen VG, Mitterni L, Seah C, Rebbapragada A, Martin IE, Lee C, et al. Neisseria gonorrhoeae treatment failure and susceptibility to cefixime in Toronto, Canada. JAMA. 2013;309(2):163–70.

41. Update to CDC's Sexually Transmitted Diseases Treatment Guidelines, 2010: Oral Cephalosporins No Longer a Recommended Treatment for Gonococcal Infections. MMWR Morb Mortal Wkly Rep. 2012;61(31):590–4.

42. Bignell C, Unemo M, European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS. 2013;24(2):85–92.

43. Bignell C, Fitzgerald M, Guideline Development Group, British Association for Sexual Health and HIV UK. UK national guideline for the management of gonorrhoea in adults, 2011. Int J STD AIDS. 2011;22(10):541–7.

44. Qvarnström Y, Swedberg G. Sulphonamide resistant commensal Neisseria with alterations in the dihydropteroate synthase can be isolated from carriers not exposed to sulphonamides. BMC Microbiol. 2002;2:34.

45. Ito M, Deguchi T, Mizutani K-S, Yasuda M, Yokoi S, Ito S-I, et al. Emergence and spread of Neisseria gonorrhoeae clinical isolates harboring mosaic-like structure of penicillin-binding protein 2 in Central Japan. Antimicrob Agents Chemother. 2005;49(1):137–43.

46. Ameyama S, Onodera S, Takahata M, Minami S, Maki N, Endo K, et al. Mosaic-like structure of penicillin-binding protein 2 Gene (penA) in clinical isolates of Neisseria

GARDP Gonorrhea R&D Strategy
version 2.1 of 28.02.2017

gonorrhoeae with reduced susceptibility to cefixime. Antimicrob Agents Chemother. 2002;46(12):3744–9.

47. Osaka K, Takahata M, Takakura T, Narukawa K, Endo K, Kiyota H, et al. Analysis of amino acid sequences of penicillin-binding protein 2 in clinical isolates of Neisseria gonorrhoeae with reduced susceptibility to cefixime and ceftriaxone. J Infect Chemother. 2008;14(3):195–203.

48. Cousin S, Whittington WLH, Roberts MC. Acquired macrolide resistance genes in pathogenic Neisseria spp. isolated between 1940 and 1987. Antimicrob Agents Chemother. 2003;47(12):3877–80.

49. Kunz AN, Begum AA, Wu H, D'Ambrozio JA, Robinson JM, Shafer WM, et al. Impact of fluoroquinolone resistance mutations on gonococcal fitness and in vivo selection for compensatory mutations. J Infect Dis. 2012;205(12):1821–9.

50. Warner DM, Shafer WM, Jerse AE. Clinically relevant mutations that cause derepression of the Neisseria gonorrhoeae MtrC-MtrD-MtrE Efflux pump system confer different levels of antimicrobial resistance and in vivo fitness. Mol Microbiol. 2008;70(2):462–78.

51. Warner DM, Folster JP, Shafer WM, Jerse AE. Regulation of the MtrC-MtrD-MtrE efflux-pump system modulates the in vivo fitness of Neisseria gonorrhoeae. J Infect Dis. 2007;196(12):1804–12.

52. Lee C, Chen D, Katz RL. Characteristics of nondepolarizing neuromuscular block: (I) post-junctional block by alpha-bungarotoxin. Can Anaesth Soc J [Internet]. 1977 Mar [cited 2014 Apr 29];24(2):212–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/139198

53. Global Strategy for the Prevention and Control of Sexually Transmitted Infections: 2006–2015, Breaking the chain of transmission [Internet]. Geneva; 2007. Available from: http://www.who.int/hiv/pub/toolkits/stis_strategy[1]en.pdf

54. Dallabetta GA, Gerbase AC, Holmes KK. Problems, solutions, and challenges in syndromic management of sexually transmitted disease. Sex Transm Infect. 1998;74 Suppl 1:S1-11.

55. Lagace-Wiens PRS, Duncan S, Kimani J, Thiong'o A, Shafi J, McClelland S, et al. Emergence of fluoroquinolone resistance in Neisseria gonorrhoeae isolates from four clinics in three regions of Kenya. Sex Transm Dis. 2012;39(5):332–4.

56. Deguchi T, Saito I, Tanaka M, Sato K, Deguchi K, Yasuda M, et al. Fluoroquinolone treatment failure in gonorrhea. Emergence of a Neisseria gonorrhoeae strain with enhanced resistance to fluoroquinolones. Sex Transm Dis. 1997;24(5):247–50.

57. Vandepitte J, Hughes P, Matovu G, Bukenya J, Grosskurth H, Lewis DA. High prevalence of ciprofloxacin-resistant gonorrhea among female sex workers in Kampala, Uganda (2008-2009). Sex Transm Dis. 2014;41(4):233–7.

58. Moran JS. Treating uncomplicated Neisseria gonorrhoeae infections: is the anatomic site of infection important? Sex Transm Dis. 1995;22(1):39–47.

59. Weinstock H, Workowski KA. Pharyngeal gonorrhea: an important reservoir of infection? Clin Infect Dis. 2009;49(12):1798–800.

60. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. Clin Infect Dis. 1995;20 Suppl 1:S47-65.

61. Bernstein KT, Marcus JL, Barry PM, Pandori MW, Buono S, Hess D, et al. Characteristics of males infected with common Neisseria gonorrhoeae sequence

types in the Gonococcal Isolate Surveillance Project, San Francisco, California, 2009. Am J Epidemiol. 2013;178(8):1289–95.

62. Roblin PM, Kohlhoff SA, Parker C, Hammerschlag MR. In vitro activity of CEM-101, a new fluoroketolide antibiotic, against Chlamydia trachomatis and Chlamydia (Chlamydophila) pneumoniae. Antimicrob Agents Chemother. 2010;54(3):1358–9.

63. Waites KB, Crabb DM, Duffy LB. Comparative in vitro susceptibilities of human mycoplasmas and ureaplasmas to a new investigational ketolide, CEM-101. Antimicrob Agents Chemother. 2009;53(5):2139–41.

64. Hook EW, Golden M, Jamieson BD, Dixon PB, Harbison HS, Lowens S, et al. A Phase 2 Trial of oral solithromycin 1200 mg or 1000 mg as single-dose oral therapy for uncomplicated gonorrhea. Clin Infect Dis. 2015;61(7):1043–8.

65. Golparian D, Fernandes P, Ohnishi M, Jensen JS, Unemo M. In vitro activity of the new fluoroketolide solithromycin (CEM-101) against a large collection of clinical Neisseria gonorrhoeae isolates and international reference strains, including those with high-level antimicrobial resistance: potential treatment op. Antimicrob Agents Chemother. 2012;56(5):2739–42.

66. Huband MD, Bradford PA, Otterson LG, Basarab GS, Kutschke AC, Giacobbe RA, et al. In vitro antibacterial activity of AZD0914, a new spiropyrimidinetrione DNA gyrase/topoisomerase inhibitor with potent activity against Gram-positive, fastidious Gram-Negative, and atypical bacteria. Antimicrob Agents Chemother. 2015;59(1):467–74.

67. Kohlhoff SA, Huband MD, Hammerschlag MR. In vitro activity of AZD0914, a novel DNA gyrase inhibitor, against Chlamydia trachomatis and Chlamydia pneumoniae. Antimicrob Agents Chemother. 2014;58(12):7595–6.

68. Foerster S, Golparian D, Jacobsson S, Hathaway LJ, Low N, Shafer WM, et al. Genetic resistance determinants, in vitro time-kill curve analysis and pharmacodynamic functions for the novel topoisomerase II inhibitor ETX0914 (AZD0914) in Neisseria gonorrhoeae. Front Microbiol. 2015;6:1377.

69. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High in vitro susceptibility to the novel spiropyrimidinetrione ETX0914 (AZD0914) among 873 contemporary clinical Neisseria gonorrhoeae isolates from 21 European countries from 2012 to 2014. Antimicrob Agents Chemother. 2015;59(9):5220–5.

70. Biedenbach DJ, Bouchillon SK, Hackel M, Miller LA, Scangarella-Oman NE, Jakielaszek C, et al. In vitro activity of gepotidacin, a novel triazaacenaphthylene bacterial topoisomerase inhibitor, against a broad spectrum of bacterial pathogens. Antimicrob Agents Chemother. 2016;60(3):1918–23.

71. Jones RN, Fedler KA, Scangarella-Oman NE, Ross JE, Flamm RK. Multicenter Investigation of Gepotidacin (GSK2140944) Agar Dilution Quality Control Determinations for Neisseria gonorrhoeae ATCC 49226. Antimicrob Agents Chemother. 2016;60(7):4404–6.

72. Ashford WA, Potts DW, Adams HJ, English JC, Johnson SR, Biddle JW, et al. Spectinomycin-resistant penicillinase-producing Neisseria gonorrhoeae. Lancet. 1981;2(8254):1035–7.

73. Stolz E, Zwart HG, Michel MF. Activity of eight antimicrobial agents in vitro against N. Gonorrhoeae. Br J Vener Dis. 1975;51(4):257–64.

74. Boslego JW, Tramont EC, Takafuji ET, Diniega BM, Mitchell BS, Small JW, et al. Effect

of spectinomycin use on the prevalence of spectinomycin-resistant and of penicillinase-producing Neisseria gonorrhoeae. N Engl J Med. 1987;317(5):272–8.

75. Unemo M, Golparian D, Limnios A, Whiley D, Ohnishi M, Lahra MM, et al. In vitro activity of ertapenem versus ceftriaxone against Neisseria gonorrhoeae isolates with highly diverse ceftriaxone MIC values and effects of ceftriaxone resistance determinants: ertapenem for treatment of gonorrhea? Antimicrob Agents Chemother. 2012;56(7):3603–9.

76. Kirkcaldy RD, Weinstock HS, Moore PC, Philip SS, Wiesenfeld HC, Papp JR, et al. The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea. Clin Infect Dis. 2014;59(8):1083–91.

77. Jerse AE, Wu H, Packiam M, Vonck RA, Begum AA, Garvin LE. Estradiol-treated female mice as surrogate hosts for neisseria gonorrhoeae genital tract infections. Front Microbiol. 2011;2(1):107.

78. Vonck RA, Darville T, O'Connell CM, Jerse AE. Chlamydial infection increases gonococcal colonization in a novel murine coinfection model. Infect Immun. 2011;79(4):1566–77.

79. Islam E a., Shaik-Dasthagirisaheb Y, Kaushic C, Wetzler LM, Gray-Owen SD. The reproductive cycle is a pathogenic determinant during gonococcal pelvic inflammatory disease in mice. Mucosal Immunol. 2016;9(4):1–14.

ANNEXES

	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 (sensitive and MDR) First line treatment of extra-genital gonorrhea (ano-rectal and oro-pharyngeal)	First line treatment of uncomplicated, uro-genital gonorrhea (sensitive and MDR)	First line treatment of uro-genital gonorrhea (sensitive and MDR, complicated and uncomplicated) First line treatment of extra-genital gonorrhea (ano-rectal and oro-pharyngeal) Treatment of chlamydia infections	First line treatment of uro-genital gonorrhea (sensitive and MDR) 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	Adults and adolescents	Adults, children and adolescents	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	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	Safe in pregnancy and lactation	-	Safe in pregnancy and lactation	-

	No patient monitoring required post treatment	Minimal outpatient monitoring required post treatment	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, loose combination	Oral/IM, loose combination	Fixed-dose combination (FDC)	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 region 4	Heat stable, 3-year shelf-life	Heat stable, 3-year shelf-life in region 4	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 2: Consensus Target Product Profile (TPP) developed by the gonorrhea expert group