GLOBAL ANTIBIOTIC RESEARCH AND DEVELOPMENT PARTNERSHIP

Developing new antibiotic treatments, promoting responsible use, and ensuring access for all

A joint WHO/DNDi initiative incubated by DNDi in support of the Global Action Plan for Antimicrobial Resistance

GONORRHOEA EXPERT MEETING

Drugs for Neglected Diseases *initiative* offices,
Geneva, Switzerland / 27-28 June 2016

DNDi
Drugs for Neglected Diseases *initiative*

World Health Organization

Background

The mission of the Global Antibiotic Research and Development Partnership (GARDP) is to develop new antibiotic treatments that address antimicrobial resistance, and to promote their responsible use for optimal conservation, while ensuring equitable access for all in need. The Partnership is a joint initiative of the Drugs for Neglected Diseases *initiative* (DND*i*) and the World Health Organization (WHO) in support of the Global Action Plan for Antimicrobial Resistance. Launched in May 2016, the Partnership is now in its incubation, or start-up phase, hosted by DND*i*. Until the end of 2017, the Partnership will build up its team, establish a legal entity, and set out its long-term strategy and roadmap. In addition, the Partnership aims to have at least two projects that address urgent global health needs ready for implementation by the end of 2016, and two more by the end of 2017.

GARDP will work closely with all stakeholders in the field of antibiotic research and development (R&D) – including pharmaceutical and biotechnology companies, start-ups, other product development partnerships, academia, civil society, and health authorities – from countries of all income levels – to develop new antibiotic treatments.

It will address global public health and specific needs of low- and middle-income countries; target products that industry will likely not develop due to lack of profitability or other reasons; pilot the use of alternative incentive models that de-link the cost of R&D from volume-based sales and price of antibiotics, which support conservation of and access to new antibiotics; and ensure that new antibiotic treatments developed by the Partnership are affordable to all in need.

The Global Antibiotic R&D Partnership (GARDP) was launched in 2016, and has secured over 2.5M of the targeted 3M EUR seed funding from the Federal Ministry of Health of Germany, The Netherlands' Ministry of Health Welfare and Sports, the South African Medical Research Council, the United Kingdom Department for International Development, the Swiss Federal Office of Public Health, and Médecins Sans Frontières. It involves complementary roles by the WHO and DND*i*. The process is on track to have an independent organization within two years. A first scientific consultation took place in February 2016 hosted by the Institut Pasteur, where ideas for 10 projects were submitted, presented, and discussed with over 40 scientists.

Objectives of the Gonorrhoea Expert Meeting

1. To review and evaluate the needs, progress and development of new and effective treatment options for gonorrhoea
2. To identify the current barriers and hurdles to the development of effective new drugs for gonorrhoea and propose potential solutions
3. To develop a roadmap for the development and introduction of new treatment for gonorrhoea (including laboratory diagnosis to support treatment)

Targeted Outcomes

1. Consensus on the current state of affairs of development of new medicines for sexually transmitted infections (STIs), and to identify the gaps and main challenges
2. Clarification on public, private, and political interests in the development of new treatments for gonorrhea
3. Roadmap for the way forward for new gonorrhoea treatment development

Summary

Gonorrhoea caused by *Neisseria gonorrhoeae* is a common, sexually transmitted bacterial disease with about 78 million new cases occurring annually. If left untreated, or unsuccessfully treated, it can lead to serious complications and permanent *sequelae* affecting both adults in their prime and children. Gonorrhoea resistance is a public health concern. Antimicrobial resistance has regularly appeared and expanded with every release of new classes of antibiotics. The spread and incidence of gonococcal antimicrobial resistance (AMR) is alarming, rapidly outpacing the development of new medicines, with the frightening prospect of untreatable gonorrhoea. 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 gonorrhoea by 2030.

In the framework of the implementation of the WHO Global Action Plan on Antimicrobial Resistance, WHO and DND*i* have gathered experts on gonorrhoea to understand and formulate the medical needs and highlight barriers for the development of new and effective treatment for the disease. This expert meeting comprised gonorrhoea specialists from Asia (China, India and The Philippines), the Americas (USA, Brazil and Canada), Africa (Zimbabwe and South Africa), Europe (Sweden and Switzerland), and Australia.

In response to the threat of multi-drug resistant *Neisseria gonorrhoeae,* and the emerging resistance to the extended spectrum cephalosporins, last-line treatment options, the global WHO Gonococcal Antimicrobial Surveillance Programme (GASP) was revitalized in 2009 to monitor resistance pattern in *N. gonorrhoeae*, and inform treatment guidelines. Despite efforts to improve antimicrobial susceptibility monitoring*,* surveillance for gonococcal AMR is currently suboptimal and faces many challenges, especially in the highest-burden countries. Around 60 countries report. There is also growing concern about obtaining sufficient numbers of viable and representative gonococcal isolates. Moreover, AMR data are not comparable across countries and are of questionable validity due to varied laboratory methodology and interpretative criteria, as well as limited quality assurance mechanisms. In addition, one of the most reliable assays (antibiotic Etest® strips or agar-dilution methods) for measuring MIC (minimum inhibitory concentration) determination are expensive or unavailable or, in the case of agar-dilution, labour-intensive and technically complex. In addition, critical alerts and other data are often not shared until published in an academic journal, which compromises the timely detection of emerging resistance.

In spite of whole-pathogen-genome sequencing (WGS) programmes put in place in the USA, Canada, and Europe, genetic determinants for gonorrhoea AMR are often not clear, precluding the widespread implementation of molecular methods both for diagnosis and antimicrobial resistance (AMR) even in high-income countries. New WHO *N. gonorrhoeae* treatment guidelines have just been released, based on available evidence and antimicrobial resistance patterns. It was identified that new treatment options are urgently needed and that national AMR monitoring should be strengthened to inform national treatment recommendations.

On the drug discovery front, the clinical pipeline is insufficient, with, after the loss of delafloxacin in 2015 at Phase III, three new compounds in different stages of clinical trial evaluation. Another important issue is that (as for other indications) introducing *combinations* of novel NCEs (new chemical entities) – now preferred over monotherapy to delay the emergence and spread of AMR – is complicated with respect to trial design and regulatory hurdles, especially with regard to bacterial infections.

Exciting work was done showing that decreased susceptibility to clusters of antibiotics is associated with a small set of bacterial efflux pumps; targeting those could revive many older drug classes. Recently an extensively drug resistant ('XDR') *N. gonorrhoeae* strain was described with AMR against six classes of

antibiotics, and exhibiting susceptibility only to spectinomycin. Mapping out regional resistance patterns may guide rational treatment options. However, such 'stewardship' policies cannot provide long-term solutions, and new medicines are urgently needed. In order to guide drug discovery the meeting experts agreed on a set of go/no-go criteria to guide drug development, with Target Product Profiles (TPPs) for addressing both short- and longer-term needs for new gonorrhoea treatments.

Meeting Report

The global burden of gonorrhoea; surveillance and goals

For 2012, there were estimated 357 million new cases of the main curable STIs (sexually transmitted infections; Chlamydia, gonorrhoea, syphilis, trichomoniasis, [Newman, 2015]), predominantly in Asia, the Americas and Africa; 78 million of these were gonorrhoea. Persistent gonococcal infections can lead to serious complications in adults, children, and unborn babies. Co-infection with HIV is common, and treating gonococcal urethritis in these patients reduces the HIV RNA load in semen [Cohen, 1997]. In the 2013 Global Burden of Disease Study that was published in The Lancet [Global Burden of Disease Study, 2015], gonorrhoea was estimated to cause 225,000 YLDs (years lived with disability). As with many other infectious diseases, there are serious concerns, articulated by the WHO and others, over the spread of resistant gonococcal *N. gonorrhoeae* strains and ultimately untreatable gonorrhoea. In 2012, the WHO launched a *Global action plan to control the spread and impact of antimicrobial resistance in Neisseria gonorrhoeae* [World Health Organization, 2012]. Its key points included advocacy, STI prevention and control, surveillance (AMR and treatment failure), rational drug use, capacity building, and increased R&D. Since 1935, seven drug classes against gonorrhoea have been discovered and most have been partially or completely lost to resistance (Fig. 1). There have now been several reports of resistance against ceftriaxone as well. In 1990, the WHO introduced the global surveillance network for gonococcal antimicrobial susceptibility [World Health Organization, 1990], which was revitalized in 2009 as the Gonococcal Antimicrobial Surveillance Programme (GASP) and over 60 countries in six regions monitor AMR. There are concerns over the fact that less than half of the 108 countries surveyed, especially in high burden countries, are not monitoring gonococcal antimicrobial resistance and trends of resistance are often not determined. In fact, fewer countries now test due to the loss of capacity to isolate *N. gonorrhoeae* and due to limited resources. Many participating GASP countries have reported high rates of resistance in *N. gonorrhoeae* isolates resistant to quinolones, such as ciprofloxacin, and there are several countries reporting high rates of resistance to azithromycin. Since 2009, 46 countries have reported decreased susceptibility to extended-spectrum cephalosporins. Data on the susceptibility of *N. gonorrhoeae* to extended-spectrum cephalosporins were reported by 49 countries in 2012 and/or 2013, with 59% (29 of 49) countries reporting decreased susceptibility in 2012/2013. GASP found resistance was spreading (over 2009-13) especially in Asia, N. America, Europe, and Australia (with large data gaps in Africa and Central Asia preventing an assessment of the situation in those regions). More detailed region-by-region data and trends were presented [WHO Global STI surveillance report 2015].

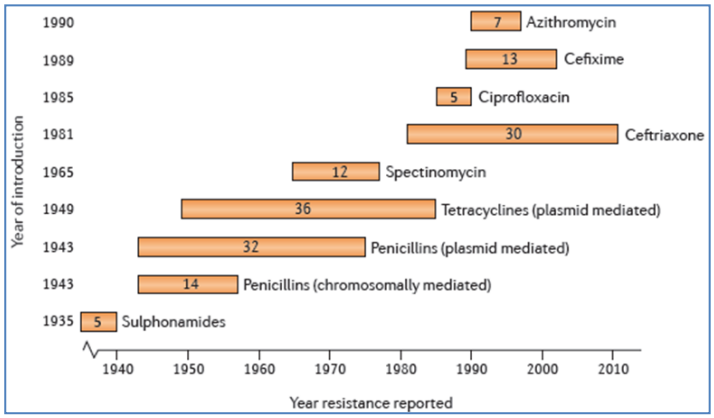

Figure 1 New drugs and their loss to resistance, from [Goire, 2014]

The WHO has recently released its recommendations for the treatment of gonorrhoea [World Health Organization, 2016]. It was strongly recommended that local resistance data should determine the choice of therapy (both for dual and single therapy). Dual therapy should be used in the absence of up-to-date, local and high-quality AMR data that support use of any single therapy, and where antimicrobial resistance surveillance in key populations is lacking. In the rapidly changing resistance landscape, treatment options are becoming limited. Another problem is that many countries do not provide combinatorial treatments; in Africa and Latin America, quinolones are still frequently used although these are not in the WHO guidelines, and high prevalence resistance has been described [Deguchi, 1997; Lagace-Wiens, 2012]. This is because it is very difficult to change treatment guidelines quickly. Another major factor is disseminating the new guidelines in the field, with physicians not informed of the extent of AMR in a given region.

WHO is strengthening GASP to ensure that valid and comparable data are available. New WHO gonococcal reference strains [Unemo, 2016b], with characterization against 23 antimicrobials, and reference genome sequences have been updated for external quality assurance and for reference in diagnostic and treatment development. There is a need to make these strains widely accessible; they are held by a few laboratories and are difficult to acquire. Also, shipping them to national laboratories in different countries is costly. WHO is also enhancing GASP in sentinel countries to ensure that valid and comparable data are collected. It was also noted by the participants that in spite of spreading AMR, recruitment of study participants remains a challenge due to restrictions in inclusion criteria and inclusion of sufficient number of patients with AMR pathogens, as local resistance prevalence remains often around 5%. Systematically recalling patients is also inconvenient, when cure rates are approximately 90-95%.

Treatment options: how to make 'older drugs' last longer by better understanding resistance, and dynamically adapting to the changing resistance landscape

There are widespread concerns over gonorrhoea treatment, with loss of the option for increased doses of ceftriaxone, and resistance against both drugs in dual combinations, which are moreover unaffordable in many countries. Recently, the first failure with dual therapy (ceftriaxone plus azithromycin), verified to be caused by an 'XDR' strain, was described with resistance against ceftriaxone, cefixime, azithromycin, penicillins, tetracyclines, and fluoroquinolones – though still susceptible to spectinomycin [Fifer, 2016].

A list of current and **alternative dual regimens** was also presented.

Current treatment recommendations:

1	Ceftriaxone 250 mg x 1	plus	Azithromycin 1 gram x 1
2	Cefixime 400 mg x 1	plus	Azithromycin 1 gram x 1
3	Sepctinomycin 2 grams x 1	plus	Azithromycin 1 gram x 1

In case of treatment failure:

1	Ceftriaxone 500 mg / 1 gram x 1	plus	Azithromycin 2 gram x 1
2	Cefixime 800 mg x 1	plus	Azithromycin 2 gram x 1
3	Sepctinomycin 2 grams x 1	plus	Azithromycin 2 gram x 1
4	Gentamicin 240 mg	plus	Azithromycin 2 gram x 1
5	Gemofloxacin 320 mg x 1	plus	Azithromycin 2 gram x 1

A discussion took place regarding 'recycling' old or previously discarded antimicrobials: spectinomycin, gentamicin, ertapenem, and fosfomycin. It is crucial to gather more data regarding these drugs, including efficacy for rectal and pharyngeal infections, pharmacokinetics/pharmacodynamics, MIC, relationships between MIC and treatment outcome, *etc*. Most of these medicines are not 'ideal' but they could be

utilized in combination therapy with other medicines. An overview was presented of **active clinical trials** to evaluate repurposed old antimicrobials or novel antimicrobials for uncomplicated gonorrhoea:

- **Gentamicin intramuscular** (Ongoing; Phase III [Aim: 718 participants]): Gentamicin 240 mg versus ceftriaxone 500 mg; (azithromycin 1 g added to both arms)
- **Solithromycin oral** (Ongoing; Phase III [Aim: 300 participants]): Open-label, randomized, multi-centre (Culture/NAATs: 7/21 days). Solithromycin 1 g versus ceftriaxone 500 mg + azithromycin 1 g; Phase II data recently published [Hook, 2015].
- **AZD0914 oral** (Completed; Phase II [Aim: 180 participants]): Open-label, randomized, multi-centre (Culture: 6 days)
  AZD0914 2 g (n=70) and AZD0914 3 g (n=70) versus ceftriaxone 500 mg (n=40) – Results to be presented in Sept. 2016
- **Gepotidacin oral** (Ongoing; Phase II [Aim: 60 participants]): Open-label, randomized, multi-centre, dose-ranging (Culture: 4-8 days), Gepotidacin 1.5 g and gepotidacin 3 g

The Phase III delafloxacin trial was terminated due to an unacceptable number of treatment failures.

A number of projects are advancing in the preclinical segment of the pipeline. These include new derivates/analogues of earlier developed antimicrobials: eravacycline, omadacycline, tigecycline, dalbavancin, SM-295291 and SM-369926 (carbapenems), aminomethyl spectinomycin, solithromycin (CME-101), avarofloxacin (JNJ-Q2) and sitafloxacin (DU-6859); and other novel compounds [Unemo, 2015; Unemo, 2014]:

- Single/Dual-target topoisomerase inhibitors:
  - VXc-486 (VT12-008911)
  - gepotidacin (GSK2140944)
  - zoliflodacin (ETX0914, AZD0914)
- Pleuromutilins
  - *e.g*. Lefamulin (BC-3781)
- Non-β-lactam PBP2 inhibitors
- Boron-containing inhibitor AN3365
- LpxC inhibitors
- FabI inhibitors
  - *e.g*. FAB001 (MUT056399))
- Efflux pump inhibitors
- Defensins, immune modulators, or therapeutic vaccine (LL-37, IDR1, immunobodies [Fc], factor H-Fc immunotherapeutic molecule)

Key characteristics of particularly the three antimicrobial agents in clinical trial evaluation (solithromycin, zoliflodacin, and gepotidacin), including references, were presented. Prioritization of these molecules is partly guided by their modelled propensity to generate AMR strains [Basarab, 2015; Foerster, 2015].

It was strongly emphasized that clinical studies must also examine efficacy and PK/PD in extra-genital loci, particularly the pharynx.

The oral solithromycin Phase II and ongoing Phase II trials were reviewed. The NIAID (National Institute of Allergy and Infectious Diseases) has contributed to increase the additional inclusion of women and

adolescents in its Phase III trial. A Phase I for the same drug is ongoing to specifically measure the genito-urinary and pharyngeal, and rectal PK; sampling from these sites is non-standard in Phase I trials. For an ongoing Phase II trial with gepotidacin (GSK2140944), technical support was provided by NIAID. It was emphasized that rapid molecular tests are essential to monitor AMR, but remains to be a challenge due to varied genetic determinants for resistance and mechanism of resistance are also evolving. Once genetically defined, as for ciprofloxacin and *gyrA*, existing hardware such as any real-time PCR machine can be used [Hemarajata, 2016]; a study is planned for Summer 2016. In collaboration with Southern Research, the NIAID has set up a platform that includes 96 CDC (Centres for Disease Control and Prevention) *N. gonorrhoeae* isolates and six control antibiotics. So far, eight candidate products were tested. Dose-response experiments were performed in the mouse model of gonorrhoea infection, using cefixime and ceftriaxone as standards. The goal is to model PK/PD, to guide trial dosing patients.

The history and rationale of treatment guidance was reviewed to change treatment when AMR exceeds 5%, or treatment efficacy below 95% (*e.g*. with a CI interval starting at 90 or 95%). With regards to repurposing old medicines, a case was made to revisit old (1961) spectinomycin, even though AMR was selected in mid-1990s when it was frequently used, and although the medicine is expensive in most countries. Spectinomycin should not be used with pharyngeal infections (poor efficacy). Neither should gentamicin or fosfomycin, because they have not been evaluated for this anatomical site. On the plus side, gentamicin and fosfomycin are cheap and widely available, and all three antimicrobials have a rather unique MoA (mode of action). The big problem is that the original clinical studies are old, low-quality, and non-standard. For instance, they were limited geographically, evaluated few anatomical sites (no pharyngeal infections), participants' HIV status was not reported, and MIC analysis was lacking.

Two combination trials were described ([Kirkcaldy, 2014]; gentamicin + azithromycin and gemifloxacin + azithromycin). Efficacy was excellent but there were tolerability concerns, which also resulted in substantial numbers of adverse events among participants (gastrointestinal upset, vomiting).

It was noted that 65% of *N. gonorrhoeae* isolates was susceptible *in vitro* to all tested antimicrobials that are in use in the USA. There was a suggestion to rotate first-line agents every couple of months; however, such a frequency is at odds with the slow implementation of new US guidelines (a year) – a situation that is likely not better in other countries. Furthermore, this is not a realistic scenario because there are not multiple effective first-line treatments. However, if novel antimicrobials are licensed this might become a realistic scenario again. Another suggestion for discussion was to increase the cephalosporin dosing, or increase exposure by *i.m*. injection followed by oral dosing. But modelling suggests such an approach might not work for 1 g ceftriaxone (*p.o.*) as it will fail to maintain suitable MIC thresholds. The merits of various combination treatments were discussed.

Key for the overall management of AMR is better and rapid detection of MDR strains; strengthening the GASP network, and evaluating additional combinations. Drug synergy studies need to be standardized.

In the wrap-up discussion, agreement was reached that studying new drug combinations is required as a short-term solution; in this area the development of FDCs (fixed-dose combinations) of existing off-patent drugs might represent the low-hanging fruit. But for the longer term, NCEs are a must. One of the problems is the handing over of leads from academic groups to industry, as the latter is unfamiliar with this therapeutic area and lacks expertise. To further the development of new gonorrhoea medicines, the best the community can do is prepare sound lead packages that correspond to the TPP (see below), exert advocacy, appeal to the pharmaceutical industry's social responsibility and co-develop medicines using DND*i*'s pioneering PDP (Product Development Partnership) model.

General R&D considerations for new medicines against gonorrhoea

Beyond AMR surveillance and appropriate (dual) treatment it is important to 'sell' the importance of gonorrhoea and overcome the stigma of STIs, as well as overcoming widespread misperceptions among both patients and care providers. The main R&D hurdles are the rejection by industry portfolio managers of gonorrhoea projects as representing negative value; regulatory hurdles both for combinations and approving extra-genital labels; and pregnancy/lactating safety issues. On the 'push' side are collaborative research networks, specific incentives and soliciting pharmaceutical industry's goodwill. A significant problem in trials is the low percentage of enrolled patients among those that are eligible. Many decline, often for lack of time (participation interferes with work or childcare), while extra-genital infection, use of other antibiotics, or co-infection with HIV also result in non-eligibility. The wisdom of excluding HIV-carriers was disputed (especially as so many patients are co-infected), and a set of desirable medicine properties (TPP elements) was listed. For future studies, evaluation of efficacy at extra-genital sites will be crucial, as is the inclusion of female patients and MSM (men who have sex with men). Enrollment is not expected to become easier in the future.

Current activities in drug discovery [Unemo, 2014]

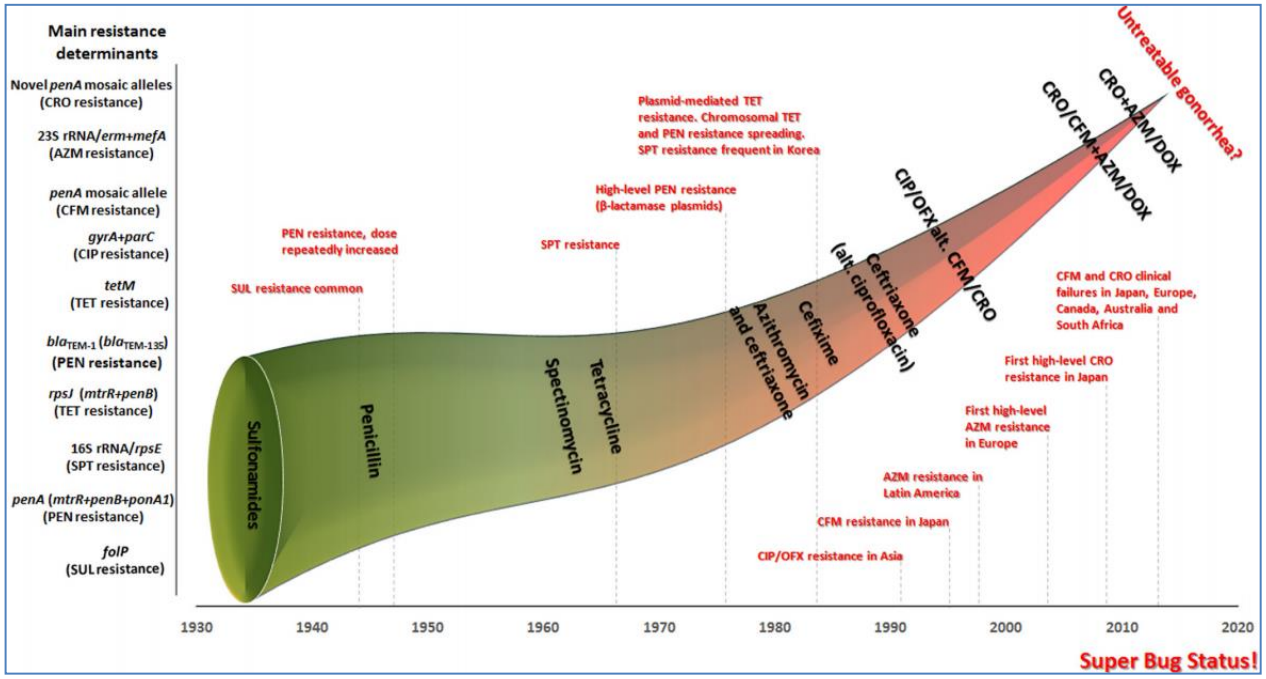

Figure 2 History of discovered and recommended antimicrobials and evolution of resistance in Neisseria gonorrheae [Unemo, 2014]

Figure 2 presents a recent view on the history of resistance in gonorrhoea and the narrowing options and pipeline for treatment ([Unemo, 2016a; Unemo, 2014]). Following the drop-out of delafloxacin in 2015 due to treatment failures associated with resistance mediated by GyrA mutations, there are now three new candidate medicines in the clinical pipeline. It is clear that each of these new medicines (if registered!) is likely to be compromised by the development of resistance. Already, resistance against one of the three, solithromycin, was demonstrated [Golparian, 2012]. The other molecules are zoliflodacin (AZD0914, ETX0914; targeting GyrB), and gepotidacin (GSK2140944; GyrA).

As alternatives, adjunctive therapies could be considered that potentiate the activity of existing antibiotics, and vaccines. One participant questioned investing resources in gonorrhoea vaccines. There are many excellent vaccines against viruses but very few against bacteria (the latest tuberculosis vaccine is about a century old) and virtually none against eukaryotic pathogens.

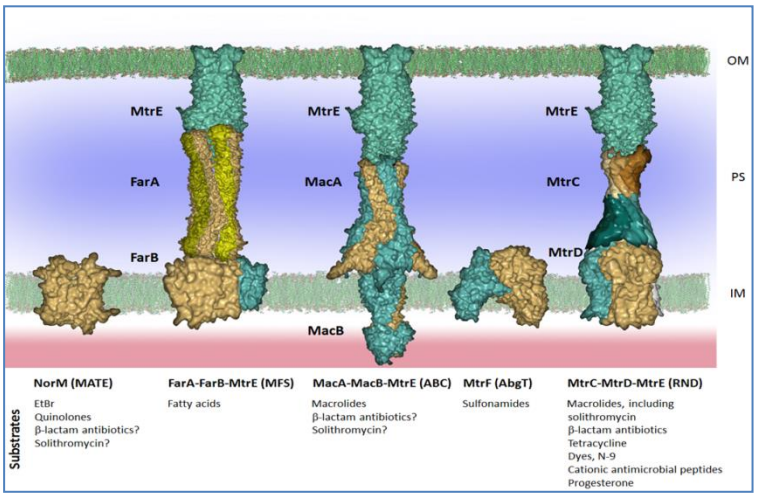

Figure 3: Gonococcal efflux pumps and antimicrobial substrates (Shafer et al. 2016, in press).

As an example of 'adjunctive' therapies, the MtrCDE drug efflux system was presented (Fig. 3). It was shown [Veal, 2002] that this efflux system contributes to β-lactam and macrolide resistance and is essential for the survival of gonococci. The contribution of the MtrCDE system to antibiotic resistance was also demonstrated in an animal model [Jerse, 2003]. A MtrCDE inhibitor could thus resuscitate several classes of previously discarded antibiotics. Gonococcal efflux pumps have been described for a wider set of antimicrobial compounds. This was again illustrated with HO41 [Golparian, 2014], and new antimicrobials such as zoliflodacin and solithromycin (fluoroketolide; [Foerster, 2015]), and genetically, by modulating expression of the MtrR and MtrE operons.

Near-term priorities: the 'low-hanging fruit'

In order to engage industry, speakers advocated estimating magnitude of the present and future market size so as to help buy-in from key stakeholders. Diagnostic capabilities are to be expanded to cover both symptomatic and asymptomatic infections. A detailed overview was provided of preclinical and clinical studies that are to be conducted to provide packages for the various phases of drug discovery. For certain countries, speakers encouraged to explore the feasibility for detectable biomarkers in urine or saliva to test for treatment compliance. Another recommendation was to prioritize medicines that have multiple microbial targets (like the artemisinins, for malaria); this could clearly delay the emergence of AMR. There is a place for both oral and parenteral formulations, and medicines that have bactericidal rather than bacteriostatic efficacy, as well as an ability to accumulate in both bacterial and eukaryotic cells at acidic pH. *In vivo* studies ought to demonstrate efficacy against extra-genital infection. A pragmatic (pharmacoeconomic) argument was made for new *N. gonorrhoeae* medicines to also target other (Gram-negative) bacteria, to expand market potential but also to ensure wholesalers would stock the product: the '*defined spectrum'* concept. As there is not (yet) much concern over *Chlamydia trachomatis* resistance, a medicine against this pathogen could be co-administered. A paediatric formulation is desired (suspension, or syrup) with adapted dosing, in regimens that are simple and short. The medicine should be stable (zone IVb compliant) and cheap. Safety in pregnancy is important, but it was realized that this assessment is a long-term one as it is not typically addressed in trials, but post-market from databases with inadvertent exposure cases. Yet it was proposed that the repro-toxicology study package is frontloaded preclinically.

Diagnostics: status and progress

Several diagnostic approaches support treatment and monitoring AMR. Agar dilution, Etest®, Disk diffusion and molecular testing are used differently in high-, middle-, and low-income countries. The Agar dilution test is the 40-y old gold standard but is technically complex, requiring strict quality control. Etest® strips are easier and more reproducible, but expensive, and not available or difficult to obtain for some antibiotics. In Canada (as in many other high-income countries), gonorrhoea is mostly (70%) diagnosed with NAAT (nucleic acid amplification testing, *e.g.* PCR). Note that this assay does not detect resistance; a perverse effect of NAAT is that fewer samples are available for AMR testing.

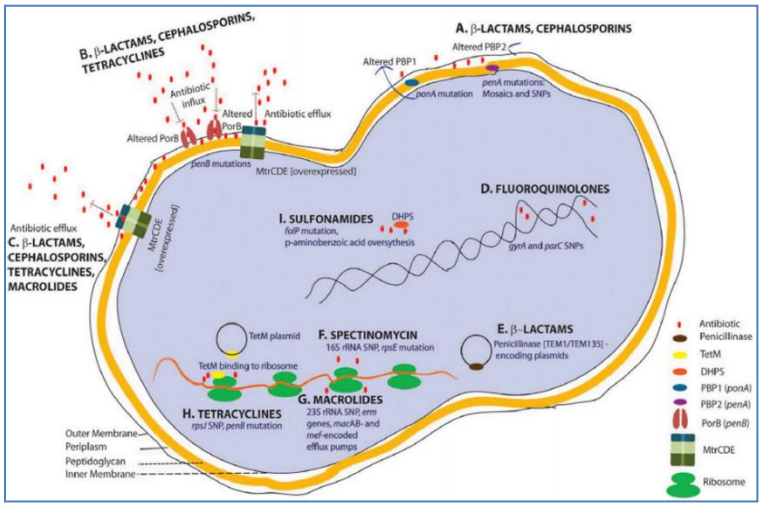

Figure 4 Mode of action of drugs against gonorrhea [Dillon, 2015]

The development of molecular (PCR-based) approaches that combine gonorrhoea diagnosis and AMR determination is hampered by the genetic complexity of resistance (Fig. 4; although some specific point mutations have been identified), and the regional variability of AMR mutations. Thus, a plethora of assays has been reported for ciprofloxacin resistance, centred on the *gyrA* and *parC* genes; however, the approach for cephalosporin resistance is much less clear. NML (National Microbiology Laboratory)-Canada is in the process of setting up a Web-based repository of AMR-associated mutations. The problem remains that probably multiple genomic sites need to be queried in an AMR-decisive PCR-assay using equipment that is not accessible to low-income countries.

Subsequently, whole-genome-sequencing (WGS) was discussed, a technology that is increasingly feasible and accessible with, *e.g.*, the MiniION hand-held sequencer in relatively advanced development. Using this approach, phylogenetic trees were built and overlaid with AMR phenotypes. Gonorrhoea WGS capacity is also widespread in the USA; again it is critical to associate data with robust phenotypic characterization. However, even with these robustly assessed, their relationships are still poorly understood; moreover roll-out of analysis equipment will suffer from even higher hurdles than those for 'simple' PCRs that target individual SNPs. The need to better understand the fitness costs for AMR was emphasized. As noted earlier, it is a struggle to rationally adjust treatment guidelines with regional AMR patterns; when penicillin was discarded in 1985, most isolates around Atlanta were still susceptible to the medicine.

Diagnostics in surveillance, and the management of antibiotics may differ in high- and low-income settings. Three approaches were presented to manage symptomatic STI patients [Aral, 2006]:

- Etiology-based management relies on identifying causative microorganisms or detecting specific antibodies (costly, technically complex laboratory diagnosis, trained personnel, quality assurance programmes, infrastructure)
- Clinical diagnosis-based management is rapid, inexpensive, and requires less infrastructure than etiology-based management (inaccurate, misses multiple infections, under-treatment/overtreatment)
- Syndromic management is based on the recognition of clinical signs and symptoms. It is inexpensive, can be standardized and used by a variety of healthcare workers (issues are overtreatment, lack of local data, inconsistencies in implementation, inadequate monitoring)

A group discussion took place for recommendations for low-, lower-middle, upper-middle- and high-income countries, guided by scenario descriptions for Burundi, Indonesia, South Africa, and the United Kingdom. The outcome of this discussion is presented below:

Scenario 1: Low-Income Country

Key issues:

- Need to define if gonorrhoea is a problem within the country
- Conduct AMR survey through national reference laboratory (target: men with urethral discharge)
- Conduct etiology survey for syndromes where gonorrhoea is a known cause

How:

- Need to strengthen reference laboratories to undertake gonococcal susceptibility testing
- Rely on Etest® or antibiotic-impregnated discs to determine antimicrobial susceptibility and increase the phenotypic testing
- If molecular capability is high at reference laboratory, consider genetic AMR screening
- At district level, increase laboratory capacity for gonococcal susceptibility in selected labs which could be used to support surveillance
- At clinic level, await rapid tests for *N. gonorrhoeae* – until then, motivate staff to help in national AMR surveys

Useful comments in discussion:

- Surveillance should be used to improve syndromic management
- Better to focus getting more female partners of men with urethral discharge treated (e.g. patient-delivered partner therapy) rather than building diagnostics in clinic (*e.g.* microscopy)
- Buying and maintaining freezers to keep isolates is a major challenge
- Possibility of leveraging GeneXpert to help with gonorrhoea surveys and gonorrhoea AMR testing – currently cost of reagents is too high
- Advocacy to lower cost of Etest®; open lines of communication with all product manufacturers

Scenario 2: Lower-Middle Income Country

Key issues:

- Sporadic AMR surveillance occurring – quality very variable
- University partnerships need to be improved – often small *ad hoc* AMR projects are undertaken but these do not get into the national surveillance database
- Need to improve quality of AMR surveillance

How:

- Several reference labs may be present in the country – focus on those that may be there to strengthen reference laboratories to undertake gonococcal susceptibility testing (*i.e.* do not spend resources on setting up new capacity)
- Improve surveillance methodology (*e.g.* numbers of patients recruited in each survey)
- Aim to establish surveillance of early warning indicators (*e.g.* MSM, sex workers)
- If molecular capability is high at reference laboratory, consider genetic AMR screening
- Ensure a QA programme is in place – or establish one if needed
- At district level, increase laboratory capacity for gonococcal susceptibility in selected labs which could be used to support surveillance
- Need to understand how to better motivate staff to help in national AMR surveys

Useful comments in discussion:

- Check quality of generics in use in country
- Review antimicrobial stewardship programmes in the country
- Possibility of leveraging GeneXpert to help with gonorrhoea surveys and gonorrhoea AMR testing – currently cost of reagents is too high

Scenario 3: Upper-Middle Income Country

Key issues:

- Many have good national (*e.g.* South Africa – NICD in Johannesburg) or regional reference laboratories (*e.g.* Brazil – one in each of 5 regions; 27 states with variable lab capacity)
- Need to improve quality of AMR surveillance
- Need to establish surveillance of early warning indicators (*e.g.* MSM, sex workers)
- Need to strengthen private-public laboratory networks
- Need to generate more data on STI cases seen in private sector (approximately 50% in South Africa, 30% in Brazil)

How:

- Encourage private practitioners to engage in surveillance – issue of bias discussed if private practitioners volunteer
- Ministry of Health could pay for the surveillance testing in private practice so that patients do not need to pay and private practitioners may feel more engaged in surveillance exercises
- Strengthen existing provincial/state reference laboratories, where required, to undertake gonococcal susceptibility testing (*i.e.* do not spend resources on setting up new capacity)
- Improve surveillance methodology (*e.g.* numbers of patients recruited in each survey)
- If molecular capability is high at reference laboratory, consider genetic AMR screening – perhaps whole genome sequencing in a few countries with high quality national reference laboratories
- Ensure a QA programme is in place – or establish one if needed
- Need to understand how to better motivate staff to help in national AMR surveys

Useful comments in discussion:

- Increase notification of urethral discharge cases and gonorrhoea cases through making them notifiable – Ministries of Health could make this happen through national policy changes
- Review antimicrobial stewardship programmes in the country
- Possibility of leveraging GeneXpert to help with gonorrhoea surveys and gonorrhoea AMR testing – currently cost of reagents are too expensive.

Scenario 4: High-Income Country

Key issues:

- Many countries rely on molecular diagnostics to diagnose gonorrhoea and gonococcal culture is not commonly performed on a routine basis
- Need to increase number of gonococcal isolates available for AMR surveillance/reporting
- AMR-related mutations detection through molecular methods is possible but is still not routinely performed in most countries

How:

- Rely on E tests or antibiotic-impregnated discs to determine antimicrobial susceptibility and increase the phenotypic testing
- If molecular capability is high at reference laboratory, undertake genetic AMR screening for patient care
- Whole genome sequencing should be possible in several countries; however, likely to remain a research tool for most countries over the next 5 years but could yield useful information – will require substantial bioinformatics support

Useful comments in discussion:

- Need to strengthen private-public laboratory networks
- Need to generate more data on STI cases seen in private sector

Stewardship discussion

Based on the mandate provided by Resolution WHA68.7 at the World Health Assembly in May 2016, options were discussed for establishing a global development and stewardship framework to support the

development, control, distribution, and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines, and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access. A UN High-Level meeting on AMR is scheduled in September 2016 that will chart the way forward, but developing a global framework on appropriate use, R&D, and access is likely to take a number of years. The concept of sustainable access was introduced at the meeting (innovation + access + stewardship). It was accepted that GARDP will need to go beyond the traditional PDP approach, especially considering its broad geographical and country income contexts and varying TPPs. At a practical level, GARDP **could consider** the following: *i*) hosting an incentive mechanism; *ii*) responsible and fair licensing and pricing with potentially some market segmentation; *iii*) supporting registration in priority countries; *iv*) phase IV and implementation studies; v) promoting policy change with the support of WHO; and *vi*) promoting and supporting the set-up of a Global Drug Facility (GDF)-type procurement mechanism for certain specialized antibiotics. Practical measures could also be implemented at country level ranging from training, building local capacity in key areas, monitoring studies with pilot programmes, and use of appropriate packaging. Further work needs to be done on how engagement with local private practitioners can support sustainable access.

Several additional ways were addressed by which appropriate use could be fostered for any new medicine developed by GARDP. If a new gonorrhoea treatment is developed in cooperation with a private company and is protected by patents, the agreement with the company will have to govern the division of markets. A number of options were discussed where the market would be divided between GARDP and the developer/patent holder: segmentation by country, by indication, or along private/public markets. Pricing decisions are also important: the problem with setting the price for patients too low is that there is a risk of excessive uptake, and product diversion; too high a price prevents access. Differential packaging may be needed for patients in public and private markets. Packaging and labelling should also be designed specifically to foster appropriate use. Stewardship also includes updating the treatment guidelines and training healthcare providers.

TPP discussion

As pointed out earlier, TPPs are living documents that reflect present patient needs for a given disease. (The FDA has recently issued draft guidelines on this topic.) They must be sufficiently specific to guide preclinical and clinical drug discovery. The gonorrhoea TPPs reviewed at this meeting were divided into short- and longer term needs (beyond 5 years). There was some initial discussion on how to appropriately formulate entries. For instance, it was decided that stewardship recommendations, such as not to use with respiratory tract co-infection, are important but do not belong in the TPP. 'Safety in pregnancy' is a valid goal but is not conclusively addressed during development; the TPP requirements translate this into a 'no red flags' in the preclinical repro-toxicology package. There was also some concern over ambiguous language, such as '*must have a different mechanism of action*'. Some might interpret that as '*must not hit the same target*', *e.g*. should not inhibit the same enzyme. But a compound that inhibits an 'old' enzyme through a different site, where the host cannot tolerate mutations (acquire resistance) would be perfectly fine. In an age where we see a 'renaissance' in phenotypic HTS activity directly on pathogens [Wells, 2015], and where target deconvolution is often deferred, a less ambiguous (and much more pragmatic) requirement would simply be that new molecules work on all (known) resistant strains. This is the language used in TPPs and TCPs (compounds) for malaria [Burrows, 2013] and neglected diseases [Katsuno, 2015]. Below is the consensus TPP for gonorrhoea treatment as agreed on in the meeting:

	Ideal (up to 5 years short-term)	Acceptable (up to 5 years short-term)	Ideal (5-10 years long-term)	Acceptable (long-term)
Indication	First line treatment of uncomplicated NG Urogenital, anorectal and oro-pharyngeal	First line treatment of uncomplicated NG Urogenital and anorectal	First line treatment of uncomplicated NG Urogenital, anorectal and oro-pharyngeal	First line treatment of uncomplicated NG Urogenital and anorectal
Activity against co-infecting STI pathogens	CT		CT, MG, and incubating TP	
Patient population	Adults and adolescents	Adults, children and adolescents	Adults, children and adolescents	Adults 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, ESC and azithromycin	Yes, ESC and azithromycin	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 No patient monitoring required post treatment	- Minimal outpatient monitoring required post treatment	Safe 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, fixed-dose combination (FDC)	Oral/IM, loose combination	Oral, fixed-dose combination (FDC)	Oral/IM, loose combination
Dosing Schedule	Single dose	Multiple doses	Single dose	Multiple doses
Treatment duration		Maximum 3 days		Maximum 3 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	3 years	5 years	7 years	10 years

Next Steps

Based on this meeting, GARDP could propose to develop a strategy and project proposal around the following:

1) Conduct, with no delay, a scoping exercise to identify potential drug candidates (existing, off-patent, and NCEs) that correspond to the key elements in the TPPs
2) Based on the above, develop a short- to medium-term project based on possible scenarios, such as:
   - accelerating one or more of the NCEs in the pipeline through Phase III, registration, and Phase IV / pilot implementation (in a range of geographical locations based on public health need)
   - development of (possibly fixed-dose) combination treatments that may also include one or more of the NCEs in development
   - expansion of indication to cover extra-genital sites
   - improved guidelines of the empiric management of STIs where drug-resistant gonorrhoea is a problem
3) Develop a sustainable access pilot project for the global introduction of new treatments, including licensing, stewardship, and access
4) Pilot, with the support of other actors, an alternative incentive mechanism to promote the development, conservation, and access of a NCE for gonorrhoea such as a small market entry reward and / or an advanced purchasing commitment tied to a procurement facility
5) Explore a longer-term drug screening project for STIs
6) Conduct advocacy and resource mobilization for more public funded R&D for STIs

Conclusions

As for other infectious diseases, alarming multi-drug resistance is on the rise in *N. gonorrhoeae*, rapidly outpacing drug discovery. A concerted effort is required to better manage the use of existing medicines, and feeding the pipeline with innovative NCEs. Much of these efforts can be coordinated in the more general fight against AMR. Gonorrhoea can be considered a neglected field of R&D, despite the fact that some new medicines are in the pipeline. A concerted effort by all actors will be required to address this need and ensure a public health approach is taken.

Attendees

Name	Affiliation	Country based
Adele Schwartz Benzaken	Ministry of Health	Brazil
Aparna Narendrula	Global Antibiotic R&D Partnership/DND*i*	Switzerland
Carolyn Deal	NIH/NIAID	USA
Christelle Elias	WHO	Switzerland
David Lewis	Western Sydney Sexual Health Centre	Australia
Edward W. Hook III	University of Alabama at Birmingham	USA
Francis Ndowa	Independent Consultant	Zimbabwe
Gabrielle Landry	Global Antibiotic R&D Partnership /DND*i*	Switzerland
Gail Bolan	Centers for Disease Control and Prevention	USA
Ian Askew	WHO	Switzerland
James Kiarie	WHO	Switzerland
Jean-Pierre Paccaud	Global Antibiotic R&D Partnership/DND*i*	Switzerland
Magnus Unemo	WHO Collaborating Centre, Orebro University Hospital	Sweden
Manju Bala	Vardhman Mahavir Medical College & Safdarjung Hospital	India
Marc Sprenger	WHO	Switzerland
Maria Luiza Bazzo	Federal University of Santa Catarina	Brazil
Matthew Golden	University of Washington	USA
Manica Balasegaram	Global Antibiotic R&D Partnership/DND*i*	Switzerland
Monica Lahra	WHO Collaborating Centre, South Eastern Area Laboratory Services & Prince of Wales Hospital	Australia
Pauline Berra	Global Antibiotic R&D Partnership/DND*i*	Switzerland
Peter Beyer	WHO	Switzerland
Ranmini Kularatne	Centre for HIV & STIs, National Institute for Communicable Diseases	South Africa
Rob Hooft van Huijsduijnen	Consultant (Rapporteur)	Switzerland
Teodora Wi	WHO	Switzerland
William Shafer	Emory University	USA
Xiang-Shen Chen	National Center for STD Control, Chinese Academy of Medical Sciences & Peking Union Medical College	China

Abbreviations:

AMR, antimicrobial resistance; DND*i*, Drugs for Neglected Diseases *initiative*; CDC, Centers for Disease Control and Prevention; FDC, fixed-dose combination; MIC, minimum inhibitory concentration; NCE, new chemical entity; *N*. *gonorrhoeae*, *Neisseria gonorrhoeae*; NAAT, nucleic acid amplification testing; NIAID, National Institute of Allergy and Infectious Diseases; MNL, National Microbiology Laboratory; GDF, Global Drug Facility; PK, pharmacokinetics; PD, pharmacodynamics; PDP, Product Development Partnership; STI, sexually transmitted infections; TPP, Target Product Profile; WHO, World Health Organization

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