

TACKLING THE RISE OF DRUG-RESISTANT GONORRHEA

Partnership to develop new drug

The spread and incidence of drug-resistant gonorrhea is rapidly outpacing the development of new drugs; without action the world faces a nightmare scenario of untreatable gonorrhea.

A new partnership agreement between the not-for-profit Global Antibiotic Research and Development Partnership (GARDP) and Entasis Therapeutics to develop a new drug, zoliflodacin, specifically to treat gonorrhea, hopes to provide a solution.

GARDP is a joint initiative of the World Health Organization (WHO) and the Drugs for Neglected Diseases initiative (DNDi), which provides GARDP's governance.

GONORRHEA – A GLOBAL PUBLIC HEALTH CRISIS

The rising prevalence of bacterial sexually transmitted infections (STIs) is a major global public health concern. The World Health Organization (WHO) estimates that there are approximately 357 million new cases of curable STIs every year, including 78 million cases of gonorrhea.¹

Gonorrhea (sometimes known as “the clap”) is caused by the bacterium *Neisseria gonorrhoeae* or gonococcus. A commonly transmitted bacterial STI, it can infect women’s reproductive organs including the cervix, uterus, and fallopian tubes; as well

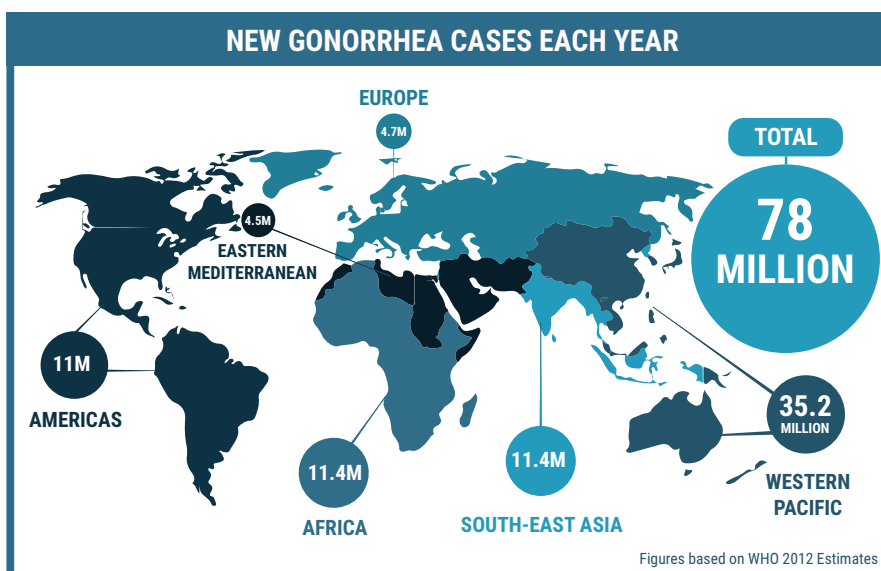
as the urethra, rectum, mouth, throat, and eyes of both men and women. If left untreated, complications arising from it can lead to infertility, particularly in women. Pregnancy complications include ectopic pregnancies and spontaneous abortions.

In up to 40% of cases, predominantly in low and middle-income countries, mothers can pass the infection to their unborn children at delivery.² This can result in neonatal conjunctivitis which, if left untreated, can lead to scarring and blindness.

Gonorrhea can also increase the risk of contracting and transmitting HIV in men and women. It affects every region of the world, with worrying increases recorded in recent years. The highest rates are in Africa, where every year, there are approximately 50 and 100 new infections per 1,000 adult women and men, respectively.³

Gonorrhea is the second most frequently reported infectious disease in the USA with 395,000 recorded cases in 2015.^{4*} In 2014, more than 66,000 cases were recorded across the EU, with nearly 60% coming from the UK.⁵

The WHO global health strategy on STIs has a specific objective to reduce incidence of gonorrhea by 90% by 2030.⁶



* The US Centers for Disease Control (CDC) estimates that actual numbers are more than 800,000 cases each year

GROWING DRUG-RESISTANCE TO ANTIBIOTICS USED TO TREAT GONORRHEA

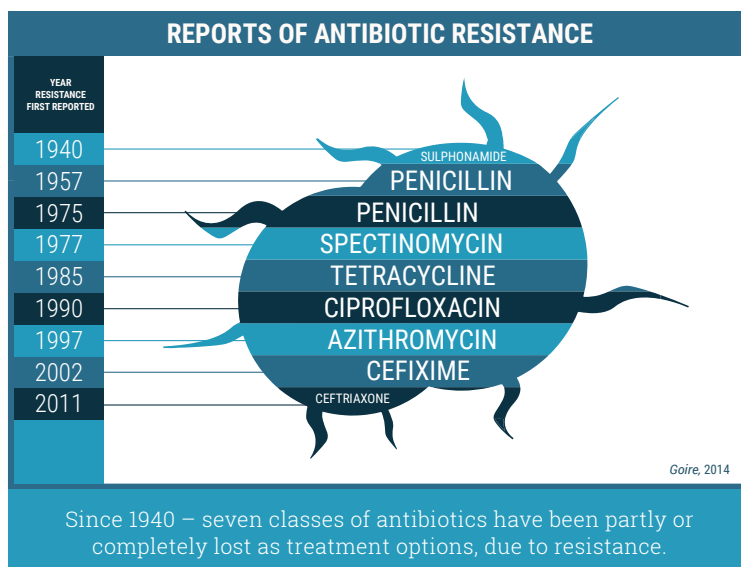
Since the 1940s gonorrhoea has developed resistance to antibiotics used to treat it. In July 2017, the WHO released data showing alarmingly high levels of drug-resistance to antibiotics used to treat gonorrhoea across the world. In a survey of 77 countries, 97% reported recorded instances of drug resistance to ciprofloxacin, 81% increasing resistance to azithromycin, and 66% to the current last-resort treatment: the extended-spectrum cephalosporins (ESCs) oral cefixime or injectable ceftriaxone.⁷

WHO guidelines state that when treatment failure rates or antibiotic resistance levels reach 5%, treatment guidelines for gonorrhoea must be adapted.

The data, which shows that more than 50 countries reported resistance to cefixime, and more rarely to ceftriaxone, led the WHO to update global treatment recommendations in 2016. Now doctors, when needing to use these already last-resort options, must administer two different antibiotics: an injection of ceftriaxone and an oral dose of azithromycin. As surveillance of resistance is extremely limited in some areas – particularly in parts of Africa, Asia, and the Middle East – it is expected that the actual rates of resistance to these last-resort treatments are much higher than reported.

Gonorrhoea is listed by the WHO as a “high” priority for research and development (R&D) of new antibiotics. It is also listed as a top “urgent” threat by the US Centers for Disease Control (CDC) and features on similar lists in the UK and Canada.

Yet, there are few drugs currently in clinical development, reflecting the scientific and medical challenges of developing novel antibiotics against drug-resistant gonorrhoea. Since antibiotic resistance develops and can spread rapidly, R&D for new antibiotics has to continuously “bear fruit” to maintain a robust pipeline of drug candidates to prevent the advent of untreatable infections.



The need to reserve new antibiotics for the patients with drug-resistant infections exacerbates profitability issues created by the relatively short time frame in which antibiotics are administered. As a consequence, many pharmaceutical companies see less value in investing in antibiotics compared to drugs for other therapeutic areas.

GARDP AND ENTASIS PARTNERSHIP TO CO-DEVELOP ZOLIFLODACIN

Zoliflodacin is an entirely new class of antibiotic, and the only new potential candidate in clinical development that has specifically been developed to treat gonorrhoea. The drug has shown promising signs with a Phase II study, sponsored by NIAID, showing cure rates of up to 100% for urogenital infections in the per protocol population.

In one of its first R&D projects and its first licensing deal with a company, GARDP has entered a partnership with Entasis to co-develop zoliflodacin in Phase III clinical trials. These are planned in countries potentially including South Africa, Thailand, the USA and a European country.

Stewardship

Stewardship – the effort to ensure that antibiotics are effectively conserved, and appropriately used, to both maximise their current efficacy and their chances of being available in the future – is essential to the fight against drug-resistance. At the same time, drugs must be affordable and available to those who need them. As such, promoting effective stewardship is intrinsic to the GARDP strategy.

If the trials are successful, it is hoped that zoliflodacin will offer a significant opportunity to provide a pilot case study in how to introduce antibiotics into the market to ensure appropriate use. Through its pharmaceutical management programme, GARDP is committed to work on cost and affordability.

The fact that the drug has been specifically developed to treat gonorrhoea will greatly help in this regard, as it will not be prescribed to treat numerous diseases.**

Work will be carried out with the WHO and relevant countries, to build on and develop appropriate access and stewardship plans, including through post Phase III studies and licensing agreements, to develop appropriate stewardship clauses and sublicences.

** Under the terms of the agreement, Entasis may later develop it for other indications, subject to clinical studies. Importantly, to ensure stewardship to better control its use, this would be strictly restricted to hospital settings.

The US National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), also plans to support pharmacological studies on the drug as part of the development programme. The trials are expected to start in the second half of 2018, and to last for 18 months. If successful, the process of registering zoliflodacin with the US Food and Drug Administration (FDA) and others would be expected towards the end of 2020.

THE TERMS OF THE PARTNERSHIP

The DNDi/GARDP and Entasis Collaboration Agreement for the development of a new treatment for uncomplicated gonorrhoea, includes the licensing of existing and future intellectual property to enable development and registration.

Under the terms of the agreement, GARDP is responsible for the pharmaceutical activities and clinical trials including financing, managing, and coordinating Phase III trials to demonstrate safety and efficacy of zoliflodacin in patients infected with gonorrhoea, including clinical safety, pharmacovigilance, and drug registration in the countries where it has licensing rights.

For its part, Entasis will work with GARDP on the clinical trial development strategy to ensure successful registration, and is responsible for sharing all necessary information on the drug for the purposes of its development into Phase III, for registering the drug in its territories, for post-marketing pharmacovigilance in those countries, and maintaining a worldwide patient safety database.

Entasis currently hold patents on the active pharmaceutical ingredient (API) for zoliflodacin. Under the agreement, to ensure global access, Entasis has granted GARDP an exclusive and

royalty-free license, (for use in the treatment of gonorrhoea) with sublicensing rights for manufacturing worldwide and for the sale and/or distribution in 168 countries or territories.

In relation to any new intellectual property rights generated during the development process, Entasis and GARDP have agreed to grant certain royalty-free exclusive licensing rights to each other, with the right to sublicense to enable registration and manufacturing.

Both Entasis and GARDP will share the data needed to obtain marketing approval to register the drug.

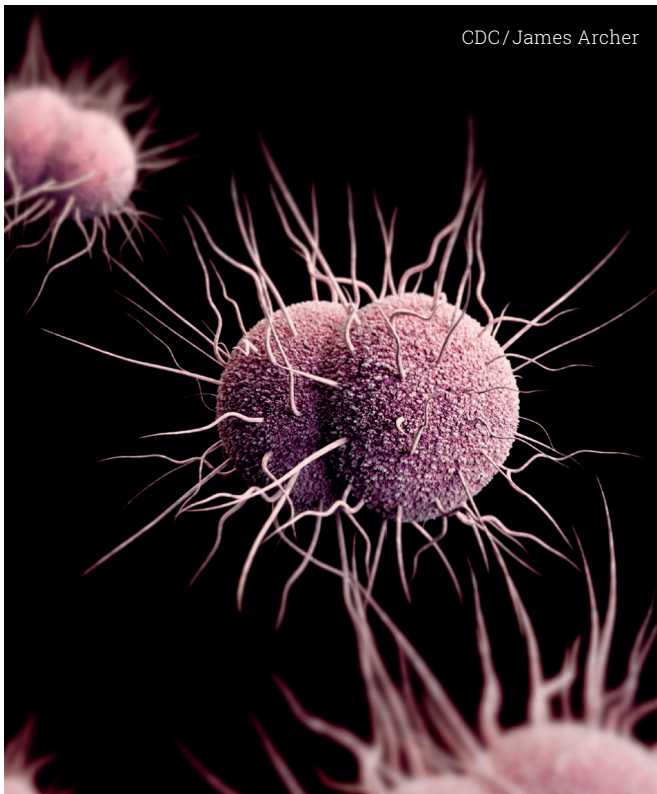
Both parties have committed to supply and distribute the drug product in their respective territories on an equitable and affordable basis and to work together to streamline manufacturing processes to enhance efficacy and cost effectiveness.

Entasis territories

Australia | Austria | Belgium | Bulgaria | Canada | China | Croatia | Cyprus | Czech Republic | Denmark | Estonia | Finland | France | Germany | Greece | Hong-Kong | Hungary | Iceland | Ireland | Israel | Italy | Japan | Latvia | Liechtenstein | Lithuania | Luxembourg | Malta | Monaco | Netherlands | New Zealand | Norway | Poland | Portugal | Russia | Singapore | Slovakia | Slovenia | South Korea | Spain | Sweden | Switzerland | Taiwan | United States of America | United Kingdom

GARDP territories

GARDP's license covers 168 countries or territories in the rest of the world. This includes the entirety of Sub-Saharan Africa. It also covers most of Eastern Europe, the Middle East and North Africa, South-East Asia and Central and South America. Argentina, Brazil, and Mexico are GARDP territories provided national partnerships at country level are developed and which include a contribution of resources to the development programme.



Computer-generated 3D image of drug-resistant *Neisseria gonorrhoeae* bacteria.

GOING FORWARD

As its first product partnership agreement, GARDP sees this as an excellent opportunity to provide a pilot model for key aspects of tackling drug-resistance, notably global access and stewardship – from which lessons can be learnt for the public health community at large. It aims to adapt a specific approach for each of its programmes, notably through its community-based approach.

Antimicrobial resistance is recognised as a global crisis by the WHO and the G20, with calls for new mechanisms to develop new treatments. In June 2017, the G20 held the first ever Health Ministers' meeting which called for "broadening the voluntary financial support" for initiatives, including GARDP, which "reinvigorate research and development in science and industry for antimicrobials."

“ The rise of antimicrobial resistance is a severe threat that is rendering more and more life-saving medicines useless. WHO together with DNDi has set up GARDP as a proactive initiative, within a larger global response, that can bring new products into the R&D pipeline. ”

– Dr Margaret Chan, former Director-General, World Health Organization

GARDP

Launched in May 2016 by the World Health Organization (WHO) and the Drugs for Neglected Diseases *initiative* (DNDi), GARDP aims to develop and deliver new treatments for bacterial infections where drug resistance is present or emerging, or for which inadequate treatment exists.

Zoliflodacin is one of GARDP's first R&D projects, and its first partnership agreement with a company. GARDP is currently operating within DNDi, which provides GARDP's governance.

References:

- ¹ Antibiotic-Resistant Gonorrhoea on the Rise, New Drugs Needed – World Health Organization (WHO), 2017
- ² Multi-Drug Resistant Gonorrhoea: A Research and Development Roadmap to Discover New Medicines – Alirol et al, 2017
- ³ Globally Sexually Transmitted Infection Surveillance 2015 – WHO, 2016
- ⁴ Sexually Transmitted Disease Surveillance 2015 – the US Centers for Disease Control (CDC), 2016
- ⁵ Gonorrhoea – Annual Epidemiological Report 2016 [2014 data] – The European Centre for Disease Control (ECDC), 2016
- ⁶ Global Health Sector Strategy on Sexually Transmitted Infections 2016-2021 – WHO, 2016
- ⁷ Antibiotic-Resistant Gonorrhoea on the Rise, New Drugs Needed – WHO, 2017
- ⁸ Global Action Plan to Control the Spread and Impact of Antimicrobial Resistance in *Neisseria gonorrhoeae* – WHO, 2012