

1. Terms of reference, introduction and background

*“The emergence, in *N. gonorrhoeae*, of decreased susceptibility and resistance to the ‘last line’ cephalosporins,...is cause for concern. Gonorrhoea has the potential to become untreatable in the current reality of limited treatment options.... The loss of effective and readily available treatment options will lead to significant increases in morbidity and mortality, as the future could resemble the pre-antibiotic era when there was a risk of death from common infections....” [1, p4].*

In response to the increasing concern nationally and internationally about the development of cephalosporin resistant (Ceph-R) *N. gonorrhoeae* and to World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) action plans, the antimicrobial resistance in *Neisseria gonorrhoeae* subcommittee of the Scientific Advisory Committee of the Health Protection Surveillance Centre was convened. The sub-committee first met in May 2014.

The terms of reference of the sub-committee are as follows:

*To provide national guidelines for minimising the impact of antimicrobial resistance (AMR) in *N. gonorrhoeae*, including prevention, surveillance, clinical management, laboratory diagnosis and public health response.*

The sub-committee agreed that it would use the terms of reference for the group to frame these guidelines and that the main sources for the development of the guidelines would be the following documents:

1. Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*. [1].
2. Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe [2].
3. Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) Action Plan for England and Wales: Informing the Public Health Response [3].
4. Cephalosporin-resistant *Neisseria gonorrhoeae* Public Health Response Plan [4].

The Antimicrobial Resistance in *Neisseria gonorrhoeae* Sub-Committee of the Scientific Advisory Committee of the Health Protection Surveillance Centre met on six occasions, between 01/05/2014 and 25/08/2016. There was a four week consultation period in 2016. The organisations consulted with are outlined in Appendix 1.

These guidelines must be implemented in the context of the National Sexual Health Strategy [5], and in the context of broader national and regional strategies for sexual transmitted infection (STI) prevention and control. The guidelines should be reviewed and updated in five years, or earlier pending changes in surveillance data.

1.1 Responses to emergence of AMR in gonorrhoea

In 2014 WHO published its first global report on surveillance of antimicrobial resistance [6]. In this, *N. gonorrhoeae* was listed as one of nine bacteria of international concern.

“It is anticipated to be only a matter of time before gonococci with full resistance to the third generation extended spectrum cephalosporins emerge and spread internationally” [6, p29].

A “Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*” was published in 2012 [1]. This plan advocates the establishment of national STI guideline working groups and development, publication and dissemination of a national mitigation plan. Also in 2012, ECDC published its “Response plan to control and manage the threat of multidrug-resistant gonorrhoea in Europe” [2]. The plan details the response at European level and is designed as a guide for Member States when planning national interventions.

These plans have been developed in response to reports internationally of decreasing susceptibility to cephalosporins (especially oral cefixime) manifesting as clinical treatment failure. Clinical treatment failure with cefixime has been reported from Japan [7], Norway [8] and the United Kingdom (UK) [9]. In 2011, the first detected case of high-level resistance to injectable ceftriaxone, which also led to clinical treatment failure, was published [10].

In Ireland, in 2013, the first (three) cases of in-vitro cefotaxime resistance were reported [11]. One case had reduced susceptibility to ceftriaxone. All three cases were resistant to azithromycin and ciprofloxacin. Additionally, in 2015 Lynagh *et al.* reported two cases of gonorrhoea with a *N. gonorrhoeae* strain with high level azithromycin resistance (HL-AziR) (MIC >256mg/L) in Ireland [12]. There have been further cases reported in Ireland, and there is an ongoing outbreak of HL-AziR gonorrhoea in England [13, 14]. This first emerged in Leeds and the north of England in late 2014 [13]. It has since spread to the West Midlands and south of England, with 34 cases reported by April 2016 [14]. Initial cases were heterosexuals, but the later report suggested that there was evidence of HL-AziR spreading among men who have sex with men (MSM) by 2016. Therefore, the committee decided to also include epidemiological data on, and a protocol for surveillance of, HL-AziR in this report.

The WHO document “Global action plan to control the spread and impact of antimicrobial resistance in *Neisseria gonorrhoeae*” [1] recommends that to make a sustained difference in the continuing problem of multidrug-resistant *N. gonorrhoeae* infection, the following two overlapping goals must be met:

- broad-based control of drug resistance (prevention of the emergence of AMR in gonorrhoea).
- prevention of gonorrhoea;

Both should be approached in the wider context of global control of AMR.

1.2 Prevention of the emergence of AMR in gonorrhoea

Research in other jurisdictions indicates that indiscriminate antibiotic prescribing may be a problem [15]. Clinicians have a crucial role in preventing the spread of antimicrobial resistance through appropriate clinical management, partner notification services, and reporting cases of treatment failure [2].

In relation to use of antibiotics and appropriate management of cases of gonorrhoea WHO suggests the following strategies to reduce the emergence of AMR in *N. gonorrhoeae* [1].

- Early detection and diagnosis of gonococcal infections with appropriate treatment of cases and their partners;
- Advocacy for increased awareness on correct use of antibiotics among healthcare providers and among patients, particularly in key populations including MSM and sex workers;
- Appropriate selection of antibiotics for first-line treatment of gonorrhoea. Important considerations include:
 - high efficacy;
 - low cost;
 - acceptable toxicity;
 - microbial resistance that is unlikely to develop or can be delayed;
 - single dosage;
 - oral administration;
 - safety for use in women during pregnancy and lactation;
- Effective drug regulations and prescription policies;
- Research into and implementation of, as appropriate, alternative effective treatment antibiotic regimens for gonococcal infections.

The Irish College of General Practitioners (ICGP) has an e-learning module for GPs on STIs [16] which provides guidelines for clinicians working in primary care. This is an important resource for those working in primary care.

1.3 Gonorrhoea

Gonorrhoea is a STI caused by a Gram-negative bacterium *Neisseria gonorrhoeae*. It predominantly involves the mucosal surfaces of urethra, endocervix, rectum, pharynx and conjunctiva. There is a significant burden of gonococcal disease globally, with higher rates of infection in less developed countries in sub-Saharan Africa, Southeast Asia, Latin America and the Caribbean than in developed countries [17]. This public health problem is further compounded by the emergence and spread of antimicrobial resistance in *N. gonorrhoeae*, including third generation cephalosporin resistance [18].

In 2014, a total of 1,320 cases of gonorrhoea were reported in Ireland, giving a notification rate of 28.8/100,000 population. In the UK, a population-based study revealed prevalence rates amongst those aged 20 to 24 years to be 0.1% and 0.2% for men and women, respectively [19]. Gonorrhoea is also concentrated in certain core risk groups, such as MSM and young heterosexuals [20] and has been associated with deprivation and lower socioeconomic status [17, 21, 22]. In London in 2013, 65% of gonorrhoea cases were diagnosed in MSM, who constituted less than 2% of the London adult population. From 2010 to 2013, the number of gonorrhoea diagnoses in MSM increased three fold (rise of 222%) [22].

While more than 80% of genital site infections in men are symptomatic, up to 50% of women with endocervical infections can be asymptomatic [23]. Undetected or inadequately treated gonorrhoea can lead to complications such as prostatitis or epididymitis in men as well as salpingitis, pelvic inflammatory disease (PID), tubal infertility, or ectopic pregnancy in women. Gonorrhoea can also facilitate the transmission of HIV infection. Rates of human immunodeficiency virus (HIV) transmission in patients with gonorrhoea may be up to five times higher than in those without gonorrhoea [17].