Reviewer’s report

Title: Is the tide turning again for cephalosporin resistance in Neisseria gonorrhoeae in Europe? Results from the 2013 European surveillance

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Reviewer: Maira Goytia

Reviewer's report:

In the manuscript “Is the tide turning again for cephalosporin resistance in Neisseria gonorrhoeae in Europe? Results from the 2013 European surveillance”, by M. J. Cole, G. Spiteri, S. Jacobsson, R. Pitt, V. Grigorjev and M. Unemo, the authors hypothesize that trends of increased resistance to cephalosporins are reverting. Reversion of antimicrobial resistance in N. gonorrhoeae is a controversial hypothesis that the authors propose to answer using thorough epidemiological analysis from the Euro-GASP (European Gonococcal Antimicrobial Surveillance Programme). In the manuscript, and through the analysis of epidemiological data from 2 time periods (2013 vs 2009-2010), the authors show a tendency of decreased resistance levels in cephalosporins (ceftriaxone and cefixime) and azithromycin.

Although, many of the odds ratio and percentages obtained in the several comparisons are not statistically significant, these values show a tendency that can only be further assessed by future epidemiological analysis of this kind. In the manuscript, the authors conclude that the observed trends of decreased resistance levels in cephalosporins and azithromycin might be temporary and that renewed increased resistance is likely to be observed in the future.

This important study highlights the potential long-term positive impact of surveillance programs on gonococcal antimicrobial resistance. The authors conclude that the Euro-GASP and treatment guidelines to limit increase in resistance levels to antimicrobials in N. gonorrhoeae are efficient and need to be sustained and emphasized.

At this point, I must note that I am affected by the suggestion that decreased resistance to antimicrobials in N. gonorrhoeae could be more than a temporary trend. The constant increase of antimicrobial resistance in N. gonorrhoeae is a major public health problem worldwide with the glooming possibility of “untreatable gonorrhea” (Ohnishi M et al., 2011, AAC). Hence, I am troubled to suggest that the trend could be reverting, as of now. Indeed, a misleading message could be presented to the greater public, leading to several consequences (changes in behavior, impairing the importance (and funding) of programs to combat antimicrobial resistance such as Euro-GASP, GISP or GASP-LAC). This manuscript will open wide discussions among scientists and/or ID and STD doctors.

The methods are well-described, complete and concise. Declarations on data
collection, statistical analysis, ethical approval, limitations of the study and conflict of interest are clearly stated. Peer-reviewed work is correctly referenced and collaborators are acknowledged. The data used in this study were collected by the Euro-GASP, from several European countries participating in the program. The Euro-GASP has developed a formal and standardized protocol for strain collection and antimicrobial susceptibility testing with several layers of quality assurance and control, to obtain comparable data across the program. The tables and figures appear to be genuine, from original data collected by the Euro-GASP and compiled by the authors. The tables and figures are precisely labeled and annotated. This manuscript is well-written, concise and presents data and conclusions in a rational and coherent manner. No major editorial modifications are needed.

I support the publication of this manuscript, with minor modifications stated below.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

1. l. 205: The authors point out that in the population of men who have sex with men (MSM) the level of resistance to ciprofloxacin is lower than in heterosexual men or women. This is a tendency not observed in studies conducted in the US. In studies focusing in ciprofloxacin resistance in the US, the literature suggests that levels of resistance in MSM are greater than in the heterosexual population (See Del Rio C et al, 2011, MMWR 60(26):873-77; Hook 3rd EW, et al., 2013, MMWR, 62(06):103-06; Goldstein E et al., Emerg Inf Dis, 2012, 18(8):1290-97; Kirkcaldy RD et al., 2013, Ann Int Med 158(5 Pt 1):321-28). How would the authors discuss these observations and relate them to their observations?

2. Different patterns of antimicrobial resistance levels (quinolones vs cephalosporins) are observed for the populations studied (MSM vs heterosexual men), could the authors expand their hypotheses on these observations?

3. l. 230: The authors could provide suggestions to overcome the problems of “lack of identification and under-reporting of treatment failures” as these issues observed worldwide would benefit from starting an open discussion among public health officials, and fundamental and clinical researchers.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. It is unclear in the abstract whether the 7 ceftriaxone resistant isolates are also resistant to cefixime (although this point is clarified in the main text).

Suggestion: “Seven (0.4%) isolates displayed ceftriaxone resistance (in addition to cefixime resistance) compared to three and ten isolates in 2012 and 2011, respectively.”

2. Similarly, it is unclear in the abstract if the number of isolates reported relate to the total (1994) or the subset (93) number of isolates for the ciprofloxacin and azithromycin resistance levels.
Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)
No major compulsory revisions are needed.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I, Maira Goytia, PhD, declare that I have no competing interests.