Reviewer's report

Title: Rapid evolution of fluoroquinolone-resistant Escherichia coli in Nigeria is temporally associated with fluoroquinolone use

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Reviewer: Stephen Baker

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The manuscript entitled “Rapid evolution of fluoroquinolone-resistant Escherichia coli in Nigeria is temporally associated with fluoroquinolone use” by Adebayo Lamikanra et al. attempts to assess and document the use of fluoroquinolone antimicrobials in Nigeria and the effect on commensal E.coli in this location. Performing such a study in a location such as this is challenging and due to study design, had inherent limitations, which cannot be avoided, such as the use of retrospective data and differences in sampling periods etc. The manuscript is, however, generally well written, with a good narrative and raises some interesting points and arguments. The authors rightly state that there is a paucity of data on fluoroquinolone resistance and its drivers in location such as this in Africa and the manuscript is worthy of publication. However, as the authors also discuss, the sample size is limited, the temporal sample collection and methodology is questionable and this reduces the overall impact of the article and should be considered in greater context in the discussion. To this end, whilst the author’s observation is entirely valid, the presented data is not exhaustive and clearly warrants further investigation, in terms of a prospective longitudinal study assessing more precise levels of antimicrobial usage and the effect of resistance in commensal organisms. As such I suggest that where the authors state that “More studies are needed to improve our understanding of the evolution and dissemination of quinolone resistance”, that they discuss how this should be tackled.

Other minor comments

Antimicrobial prescription rates were also monitored for the three decades in which resistance was studied.
- Would be better as “antimicrobial prescription practices were compared with antimicrobial resistance rates over a period spanning three decades”

Resistant haplotypes that predominate in sub-Saharan Africa appear to possess a fitness disadvantage, suggesting.
- Would benefit from the addition of the word Plasmodium

absence of antibacterial quinolone use.
- Antibacterial can be removed from this
Fluoroquinolones are stable, orally administrable, and now affordable. In the last decade, fluoroquinolones have become first- and second-line antibacterials of choice for acute respiratory, enteric and urinary tract infections as well as serious systemic infections such as bacteremia. Fluoroquinolones are also employed in combination with other antimicrobials to treat multidrug resistant TB. Additionally, their use and misuse in the informal sector, by unsanctioned providers and through self medication, is commonplace.

- is missing some required referencing

the primary target Mutations in the QRDRs of gyrA and parC are the most commonly documented quinolone resistance mechanisms, but resistance is also known to be conferred by mutations in the second topoisomerase gene, parE. Low-level resistance to the quinolones often evolves by acquisition of one resistance-conferring mutation or gene.

- is missing some required referencing

This study was exempted from review by the Institutional Review Board of Obafemi Awolowo University, Ile-Ife, Nigeria.

- I think this requires some clarification why as the study involves the sampling of individuals and the collection of retrospective data.

Prescription sheets were obtained with permission from the Obafemi Awolowo University Ile-Ife

- As above, there are some issues with using this information and some clarification is required about how this data was collected and what form it was in and if it was anonymous etc.

-In the results (line 177) the authors state an inhibition zone diameter of at least 10mm, I know that the methods outline the breakpoints etc. but easier if they add the resistnace/susceptible levels in brackets next to the zones.

None of those isolates are available for analysis

- this should be “were available” and needs a little clarification as to why.

Compared to E. coli K-12 strain MG1655, sixteen isolates showed a two-fold or greater upregulation in transcription of the outer membrane extrusion factor gene tolC.

- Whilst I see the benefit of using K-12 as a baseline, an additional control would be the use of a nalidixic acid sensitive local isolate. Clinical isolates do not behave the same way as lab strains and the increased activity of some of these strains may be curious to these isolates. I think it would be good to include some local sensitive isolates in this section and comment of the relationship to MIC/transcriptional effects of tolC.

The MLST section does not add anything to paper and can be removed.
This study allowed us to address the almost untestable question of population-level selective forces for quinolone resistance in bacteria within a malaria-endemic area.

- This sentence can be toned down or removed, as whether this is truly population level study and whether it can truly test the untestable is dubious.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests