Multidrug-resistant *Neisseria gonorrhoeae*: implications for future treatment strategies

In an observational study, Helen Fifer and colleagues[1] describe the successful propagation of a high-level azithromycin-resistant clone of *Neisseria gonorrhoeae* in the UK. Shortly after publication of the Article, Public Health England reported on a man who had acquired multidrug-resistant *N gonorrhoeae*.[2] This isolate of *N gonorrhoeae* showed high-level resistance to azithromycin as well as to the last remaining recommended first-line antibiotic (ceftriaxone),[3] necessitating the use of a broad-spectrum carbapenem antibiotic (ertapenem), which is typically used for severe multidrug-resistant infections.

The study by Fifer and colleagues[1] and the report by Public Health England[2] add to the growing literature describing the worldwide increase in antibiotic-resistant *N gonorrhoeae* and might herald the movement towards large-scale use of recycled classes of broad-spectrum antimicrobials, including carbapenems and fosfomycin.[3] In the absence of the mass availability of a new drug for *N gonorrhoeae* in the near future,[3] an increase in ceftriaxone resistance might lead to consideration of routine use of carbapenems, given their high in-vitro activity and history of safety and tolerability. However, the implications of a shift to a carbapenems such as ertapenem as first-line empirical therapy for *N gonorrhoeae* are manifold.

In the USA, where nearly 470 000 cases of *N gonorrhoeae* were reported by the Centers for Disease Control in 2016, a change to ertapenem as standard treatment could result in up to 470 000 additional doses of carbapenems administered annually. With an estimated 4·6 million inpatient days of carbapenems prescribed in 2012,[4] a change to ertapenem as standard therapy for *N gonorrhoeae* could thus increase the total annual use of carbapenems in the USA by up to 10%. Furthermore, most carbapenem prescribing starts in inpatient settings,[5] where patients are often older with more comorbidities, and a switch to receipt of these drugs in healthy individuals could support a greater selection pressure on non-target pathogen microbial flora, in particular carbapenemase-producing Enterobacteriaceae, within people in the community.[6]

Although few therapeutic options are available for gonorrhoea, the implications of broad administration of historically reserved antimicrobial classes should be carefully considered, particularly in the community setting. Further reflection is required on how broad administration might shape transmission, infection, and management of common pathogens. With the gradual erosion of effective antimicrobials across bacterial species, simple antibiotic recommendations no longer exist, and weight must be given to the potential effect of selection of antibiotic resistance across all exposed organisms, or *N gonorrhoeae* might indirectly pave the way for the emergence of other untreatable infections.

YG has received consulting fees from GlaxoSmithKline. All other authors declare no competing interests.

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4CMenB safety and persistence of protection are unsatisfactory

A systematic review and meta-analysis of the multicomponent meningococcal serogroup B vaccine (4CMenB) in *The Lancet Infectious Diseases* by Maria Elena Flacco and colleagues[1] concludes "4CMenB has an acceptable short-term safety profile". We consider this statement, based on ten randomised trials and eight follow-on extension trials, as overoptimistic for many reasons. The trialists were in financial ties with the vaccine manufacturer, who funded all the trials, a condition notoriously associated with exaggeration of benefits or underestimation of risks of the sponsor's drug.

Only 30% of trials accurately reported allocation concealment and 10% were double blinded: intervention effect estimates seem to be exaggerated in trials with inadequate or unclear (*vs* adequate) allocation concealment (ratio of ORs 0·93) and absence of or unclear double blinding is associated with a 13% exaggeration of intervention effects.[2] Average bias is driven by trials with subjective outcomes (different from mortality).[2]

An indication of these biases is that some researchers deemed several adverse effects as unrelated in the 4CMenB groups (eg Kawasaki

disease and febrile convulsions) in their studies. These decisions are questionable, since randomisation should ensure the best comparability between the study groups and control of the confounding factors, and therefore allows definition of a causal relationship between treatment and observed effects.[3] Even not questioning the trialists' conclusions, in 7209 individuals, 4CmenB showed 5·4 (95% CI 3·8–7·4) per 1000 potentially vaccine-related acute serious adverse events, with a significantly higher risk than control vaccines (OR 4·36; 95% CI 1·05–18·10).[1] 4CMenB has a separate schedule of administration to other routine vaccinaton. Therefore, in a birth cohort of 500 000 people per year (the approximate number in Italy), an excess of about 2700 serious adverse events would occur, including 208 cases (95% CI 43–608) of Kawasaki disease, 277 (76–710) of juvenile arthritis (which might require long-term disease-modifying antirheumatic drugs treatments), and 485 (195–1000) febrile convulsions, probably underestimated according to our other calculations.[4]

Furthermore, if correctly compared with no intervention (not with routine vaccinations administered separately), in a population of 500 000 individuals 4CMenB would produce 370 000 injection-site pain events, plus other local adverse events. Moreover, 4CMenB would be associated with systemic adverse events (eg, sleepiness, unusual crying, and fever with temperature >38·5°C) in up to 92% of children (this value includes the background rate of events).

Assuming, optimistically, that the current Italian 4CMenB vaccine schedule of four inoculations could prevent 87% of annual cases lifelong, the number of theoretically preventable invasive meningococcal B disease cases would be 58 of the 67 cases per year that occurred before the introduction of 4CMenB vaccination programmes, avoiding three to five deaths and about 16 sequelae in survivors. This benefit should be weighed against the abovementioned adverse effects, a number-needed-to-vaccinate of 34 480 injections to avoid one meningococcal B disease,[5] and a disproportionate opportunity cost, even assuming lifelong protection. Instead, after the primary course, Flacco and colleagues state that "a booster dose is required to prolong the protection against strain M10713, and the immunogenicity against strain NZ98/254 remains suboptimal".[1] We think the term suboptimal is an understatement for the small proportion of patients (35%) in whom immunogenicity persisted after 6 months.

Therefore, the Italian Health Ministry, who considers the universal offer of 4CMenB vaccination free of charge a priority, should provide more clear information on the potential serious adverse events for citizens deciding whether to be vaccinated.

The views expressed by this authors are their own and do not necessarily represent those of their organizations.

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Authors' reply

We thank Alberto Donzelli and Piergiorgio Duca for their correspondence that contributes to a valuable scientific debate on the instruments and policies to control meningococcal B disease. Briefly, three concerns are raised: (1) the studies included in our meta-analysis[1] are biased or at high risk of bias; (2) the cost-benefit profile of 4CMenB is questionable; thus (3) the information provided by the Italian Ministry of Health should change.

On the first point, we partly agree: the fact that all trials were sponsored by the manufacturer is undoubtedly a limitation.[2] We reported this issue three times in our discussion, where we also affirmed that "additional studies, preferably non-industry sponsored, are needed to support the long-term safety and efficacy of 4CMenB".[1] However, it's likely that only the manufacturing company has the resources to test an unlicensed vaccine on infants or children, which is why most interventional head-to-head randomised controlled trials are industry sponsored.[3] Also, the direction of bias caused by quality issues in vaccine trials is still uncertain and far from being simply described by an OR=0·93 or a 13% effect exaggeration,[2,4] and an in-depth analysis of the potential correlation with vaccination of all serious adverse events is, rather than a sign of bias, a universally adopted procedure to substantially enhance the validity of results.

Concerning the second point, our meta-analysis was not intended to be, neither could it be given the complexity, a cost-utility analysis, which we certainly welcome, but which must be properly done and cannot consist of some simple computations and inferences on sparse numbers of adverse events (Kawasaki disease and juvenile arthritis) assumed to be singularly significantly higher among vaccinees, although they were not. If our conclusions are to be

overoptimistic, Donzelli and Duca's computations are certainly overly pessimistic.

Finally, we cannot comment on the information provided by the Italian Ministry of Health, as Donzelli and Duca are making a generic claim. Although we do agree that clear information should always be provided to citizens, 4CMenB vaccine is not one of the vaccines that have been made compulsory for all residents younger than 16 years, and the Ministry of Health is correctly waiting until further evidence is available from both randomised controlled trials and large observational studies.

We declare no competing interests.

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HIV outbreak in Pakistan

Since 2004, the distribution of HIV incidence in Pakistan has developed from high-risk groups to concentrated epidemics. According to an estimate by UNAIDS, Pakistan contains approximately 130 000 people living with HIV.[1] Several factors, including low literacy, high poverty, and unsafe blood transfusions have made Pakistan more vulnerable to HIV spread than other countries.[1] Lapses in basic health facilities have worsened the situation. In March, 2018, another HIV outbreak was reported in a village near to Kot Momin, Sargodha, situated in central Punjab 175 km from Lahore. Initially, the unusual disease was mistakenly diagnosed either as hepatitis B or C or tuberculosis at basic health units in the area. However, patients were not recovering after treatment for these diseases. Ultimately, the patients were referred to the District Headquarter Hospital in Sargodha where they were diagnosed with AIDS. Initially, 35 (1·29%) of 2717 inhabitants of the village were diagnosed with HIV.[2] Such a high prevalence of HIV cases in a small village alarmed the Punjab AIDS Control Program and provincial authorities, motivating them to take prompt initiatives.

Most residents of rural areas of Pakistan are uneducated on the possible reasons for HIV spread. One of the reasons might be the use of contaminated syringes. Unqualified health practitioners are filling the gap in these areas left by the government's failure to cater to the health-care needs of residents. Additionally, barbers contribute to the spread of HIV by the reuse of razors. Extramarital affairs, sexual intercourse with sex workers, particularly male and transgender individuals, injection drug use, and same-sex relationships are possible reasons for the HIV/AIDS spread in rural Pakistan. Being a conservative Muslim society, people in Pakistan might be hesitant to discuss their sexual practices. A demographic survey in Pakistan showed that only half of the studied population had heard of HIV/AIDS.[3] Another survey reported that only 38% of men and 22% of women were aware that use of condoms prevents transmission of HIV.[4] In Kot Momin, different villages within a 10–12 km radius are connected socially. Thus, nearby localities should be screened too. The government should lead awareness programmes in collaboration with NGOs for the general population. Similarly, barbers and unqualified health practitioners in rural areas should be trained to avoid any future epidemic.

We declare no competing interests.

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Early detection of Lassa fever: the need for point-of-care diagnostics

Peter Okokhere and colleagues' description[1] of acute kidney injury as a notable complication of Lassa fever reinforces previous evidence on the benefits of early ribavirin therapy to further underscore the importance of early diagnosis. However, reliable early detection of Lassa fever has proven challenging. As Thomas Geisbert suggests in his Comment,[2] point-of-care diagnostics that provide rapid results at the primary and community level could play a part in addressing this bottleneck.

Of the 1849 patients suspected to have Lassa fever on the basis of case definition during the current Nigerian outbreak, three-quarters did not have Lassa fever once tested.[3]