Background and Objectives

- Antibiotic resistant bacteria are an established threat to global public health. Though resistance is a natural phenomenon, the current spread of resistance has been exacerbated in recent years due to inappropriate prescribing, treatment non-compliance, and agricultural overuse.2,3
- Carbapenem antibiotics have been widely used as last-line therapy for Gram-negative (GN) infections resistant to other antibiotics.1
  - Amongst GN bacteria, three – carbapenem resistant (CR) Enterobacteriaceae (including Escherichia coli and Klebsiella pneumoniae), Pseudomonas aeruginosa, and Acinetobacter baumannii – are recognised by the WHO as the highest ‘critical’ priority bacteria, requiring urgent innovative therapies to preclude widespread infection.4
  - In general, infections caused by resistant bacteria are associated with worse patient outcomes and greater economic costs than infections caused by susceptible bacteria.3
- We conducted this research to review and present the European experience of CR GN bacteria.

Results

Overall resistance rates

- Across EU/EEA member states, ten-year data for the four GN bacteria shows stable levels of carbapenem resistance for E. coli (<1%), P. aeruginosa (20%), and K. pneumoniae (8%), and a downward, but variable, trend in the proportion of CR Acinetobacter spp. (Figure 1). Note that data on CR Acinetobacter spp. have only been collected since 2012 (in response to concern about increasing prevalence).5
- In the EUS (France, Germany, Italy, Spain, UK), carbapenem resistance trends in E. coli and P. aeruginosa were similar to rates across the EU/EEA, though there was a marked increase in CR K. pneumoniae from 2009 (<2% to 8%) (Figure 1).5

Country-specific resistance rates

- Though resistance rates averaged across all countries in the EU/EEA give a broad sense of the level of resistance, this may obscure any inter-country variability. Figure 2 illustrates that the proportions of GN isolates that tested resistant were highly variable across the EU/EEA in 2016.6
- The call-out box on each map gives the carbapenem resistance rate in the highest resistance country.7

Figure 2. Country-specific carbapenem resistance rates in the EU/EEA in 2016, by bacteria.8

The number of isolates vs. the proportion carbapenem resistant

- High resistance rates do not necessarily translate into a high disease burden – if infections due to a highly resistant bacteria are very rare, the detrimental effect on society will be low.
  - Over the past five years, none of the species have exhibited both high resistance and high prevalence (Figure 3).9 Though carbapenem resistance rates in Acinetobacter spp. were high, the number of infections were relatively low. Conversely, carbapenem resistance in E. coli were very low, but the number of infections was far greater than for the other bacteria.

Figure 3. Comparison of the number of isolates tested vs. the proportion carbapenem resistant in the EU/EEA, 2012–2016.6

Mortality due to CR infections

- The literature search did not identify recent, high-quality systematic literature reviews analysing the attributable burden of CR GN infections in Europe. From reviews that used data from global sources, the following mortality rates were reported:
  - CR A. baumannii – 46% – Lemos et al., 2013.7
  - CR P. aeruginosa – 34% – Nathwani et al., 2014.10
  - CR K. pneumoniae – 41% – Ramos-Castañeda et al., 2018.9
  - CR E. coli – the search did not identify reviews reporting on the mortality attributable to CR E. coli.

Conclusions

- Rates of carbapenem resistance in GN bacteria are high in many parts of Europe, with eastern, southern, and Baltic countries most affected.6
  - The recent rise of CR bacteria is largely due to the dissemination of carbapenemases, enzymes capable of hydrolysing the antibiotic.
  - CR Acinetobacter spp. infections were associated with the highest mortality, though reviews using solely European data were not found.
  - Presently, highly resistant bacteria are not highly prevalent – this is prone to rapid change due to mutation or through gene transmission between bacteria.11
  - Should this happen, medicine will regress to a post-antibiotic era, meaning mortality from mild infections will rise, routine surgery will become highly unsafe, and the world will incur enormous economic costs.1,2
  - The insidious spread of CR GN bacteria in Europe emphasises the need for prudent antibiotic stewardship by physicians and patients, novel research by industry, and increased funding and streamlined regulatory approval for new antibiotics by decision makers and regulatory bodies.
  - High quality systematic literature reviews and meta-analyses on infection-associated mortality are required to fully illustrate the attributable disease burden of CR infections in Europe.