ECDC
POLICY BRIEFING

Last-line antibiotics are failing: options to address this urgent threat to patients and healthcare systems

Summary

The emergence and spread of highly-resistant bacteria, especially those resistant to 'last-line' antibiotics, such as carbapenems and colistin, is a grave public health concern and a threat to patient safety and economies in Europe and globally. When last-line antibiotics are no longer effective, this means that there is no antibiotic left with which to treat a patient, making such infections in children and adults potentially fatal. Resistance to last-line antibiotics also compromises the effectiveness of life-saving medical interventions such as cancer treatment and organ transplantation. Therefore, it is imperative that we contain the spread of these highly resistant bacteria now, particularly since the antibiotic pipeline is empty for the development of new antibiotics and will likely remain so for years to come.

Patients who are infected with bacteria resistant to antibiotics are more likely to develop complications and up to three times more likely to die from the infection [1]. It is estimated that the global burden of deaths could reach 10 million each year by 2050 if no action is taken[1] [2]. This poses serious challenges to the functioning of healthcare systems and represents high economic costs to society.

This briefing aims to draw the attention of policymakers to examples of measures that can be taken at national and local levels to halt the spread of these highly resistant bacteria. Case studies illustrating successful implementation of such measures, with positive outcomes, will also be highlighted.

The issue

The emergence and rapid global spread of highly resistant bacteria, especially those resistant to last-line antibiotics, is a significant threat to patients, healthcare systems and the economy. Antibiotics such as carbapenems and colistin are considered 'last-line' because they are the only antibiotics that still work when treating infections with bacteria that are resistant to all other antibiotics.

The spread of these highly resistant bacteria is at very different stages in European countries (Figures 1 and 2), and outbreaks of carbapenem-resistant bacteria have been reported from several EU Member States [3,4]. Colistin is the antibiotic of choice when carbapenems no longer work and human consumption of colistin almost doubled in Europe between 2010 and 2014; in particular in countries that report high levels of carbapenem resistance [6]. Now resistance to colistin is spreading as well.

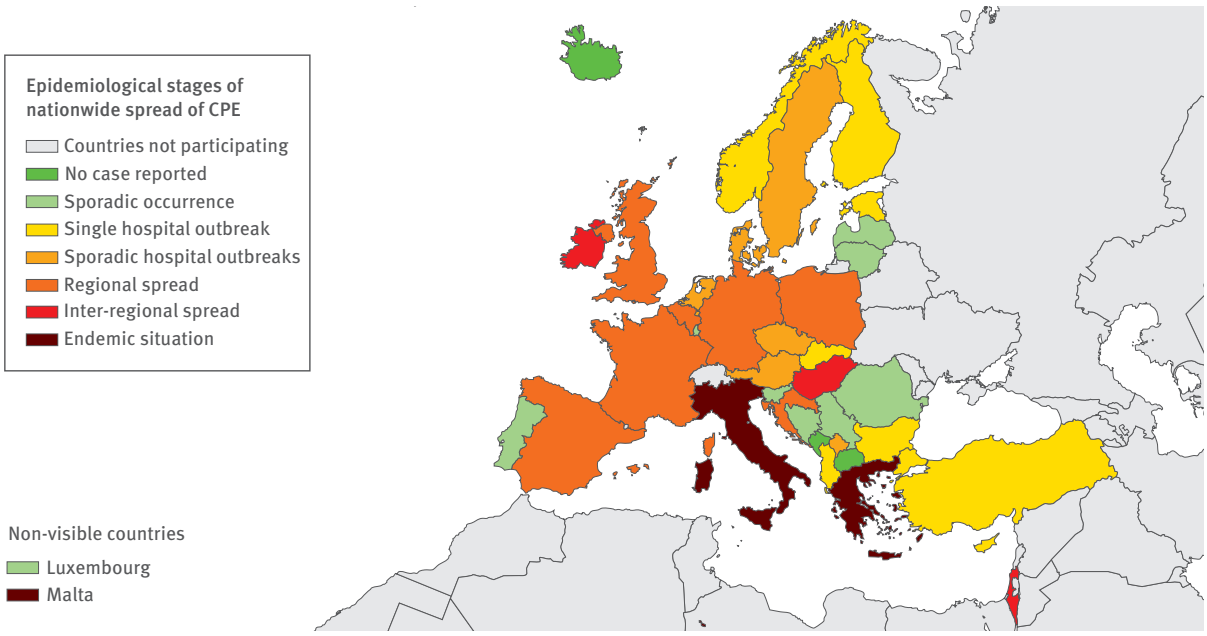
Only concerted worldwide measures, including improved infection prevention and control in hospitals and other healthcare settings, as well as more prudent use of antibiotics, can offer a long-term solution.

Implications of inaction

Poor patient outcomes, higher morbidity and mortality, and higher costs and length of hospital stay are associated with infections caused by highly resistant bacteria. These bacteria therefore pose a threat to patient safety [5]. High mortality rates, ranging from 26% to 44% [6,7], are directly associated with having an infection with these highly

[1] The morbidity and mortality estimates of the impact of resistance are based on projections for all antimicrobial agents and not just antibiotics.

Figure 1. Occurrence of carbapenemase-producing Enterobacteriaceae[2] in 38 European countries, using an epidemiological scale indicating the level of national spread, 2013



resistant bacteria. In a study from Israel, patients infected with these bacteria were four times more likely to die from the infection than patients infected with bacteria that were not resistant [8].

Hospitals spend, on average, an additional EUR 10 000 to 40 000 to treat each patient infected with resistant bacteria in Europe and North America. The associated impact of lost economic output due to reduced labour efficiency, prolonged sickness and death are likely to double this figure [1].

Globally, about 700 000 deaths each year[3] are estimated to be attributed to resistant infections, including not only strains of common bacterial infections, but also HIV, tuberculosis and malaria [9]. If current infection and resistance trends are not reversed, it has been suggested that the global burden of deaths could reach 10 million every year by 2050 [2]. This would also affect Europe's economy and could result in a reduction of the European GDP by between 1% and 4.5% by 2050 [10].

What can be done?

A multi-level strategy is important to curb the entry and spread of these highly resistant bacteria in hospitals. This is outlined in the European Union (EU) Council Recommendation on patient safety, including the prevention and control of healthcare associated infections [5]. Examples of measures to prevent the spread of highly resistant bacteria are:

1. Creating a national multidisciplinary taskforce made up of experts in the field with political support is essential. This taskforce will create policy, collect data and intervene when necessary at the national and hospital level.

2. Ensuring that hospitals have an adequate ratio of appropriately trained infection control practitioners (ICPs) to beds. A ratio of 1 ICP per 250 beds [11] has been the standard; newer evidence may support a ratio of 1 ICP per 100 beds [12,13]. There is a wide variation of the ratio of ICPs to beds in hospitals across Europe [14].

3. Active screening of 'at-risk' patients upon admission to a hospital is an effective method to detect whether patients are carrying highly resistant bacteria. This is crucial for the prevention of spread in hospitals [15], because when a patient is found to be a carrier of highly resistant bacteria, infection prevention measures can be immediately implemented [16,17]. This can only be done in conjunction with timely reporting of positive results by the microbiological laboratory. This measure is especially relevant to EU Member States because there is increased mobility of patients between countries for the receipt of healthcare [18].

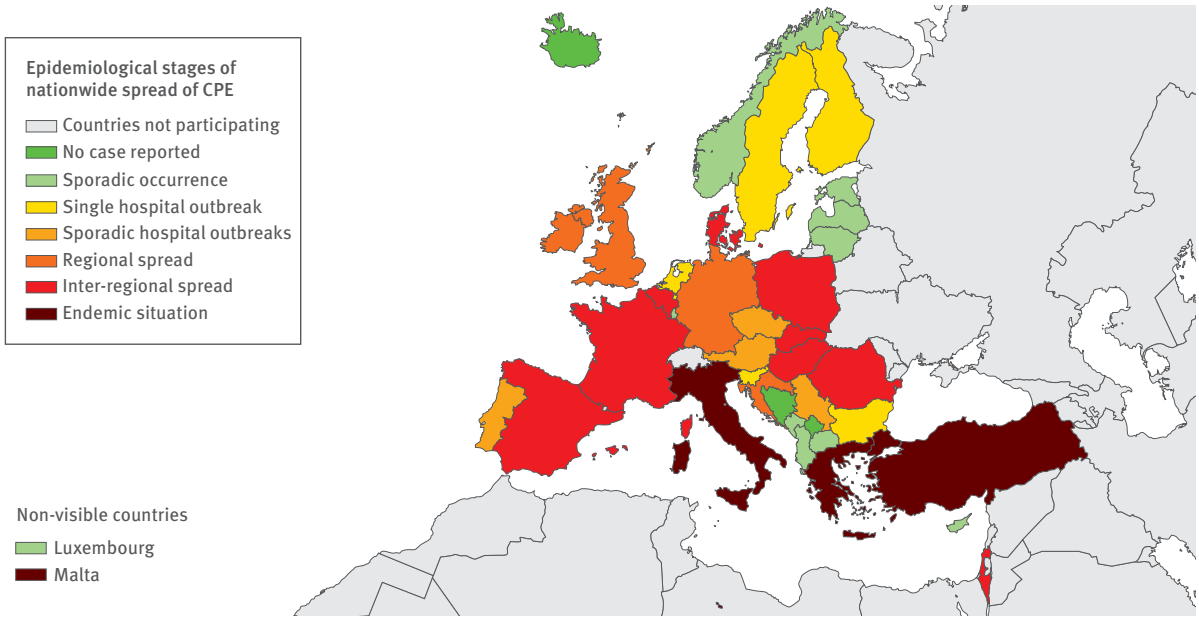
'Active screening should be done for all patients who are at-risk of being carriers of these highly-resistant bacteria. Controlling antibiotic resistance should focus on the implementation of both infection control and antibiotic stewardship in hospitals and in long-term care facilities', Andreas Voss (MD,PhD) Professor of Infection Control, Radboud University Medical Centre, Nijmegen, the Netherlands.

4. Isolation of patients who are carriers of highly-resistant bacteria, ideally in single rooms or alternatively in separate areas such as 'cohort wards', is an important measure to contain the spread of these bacteria [14,16]. In 2012, the median percentage of hospital beds that were in single

[2] Carbapenemase-producing Enterobacteriaceae are highly resistant bacteria that are resistant to carbapenems due to the production of an enzyme – carbapenemase.

[3] The morbidity and mortality estimates of the impact of resistance are based on projections for all antimicrobial agents and not just antibiotics.

Figure 2. Occurrence of carbapenemase-producing Enterobacteriaceae in 38 European countries, using an epidemiological scale indicating the level of national spread, 2015



rooms was only 9.9% on average for Europe and was under 5% in eight EU/EEA countries [6].

5. Hand hygiene is the 'single most important measure' to prevent transmission of bacteria in hospitals, according to the World Health Organization [19,20]. The cost of hand hygiene promotion is less than 1% of the cost of taking care of patients with healthcare-associated infections [19]. There is wide variation in the consumption of alcohol-based hand rub for hand hygiene in hospitals across Europe [14]. Compliance with correctly performed hand hygiene needs to be continuously monitored and supported through education and audit.

The EU Council Recommendation on prudent use of antimicrobial agents in human medicine [21] emphasised that controlling antibiotic resistance can only be achieved through a combination of infection prevention and control measures, as well as prudent use of antibiotics. A 'One Health' approach is important to ensure close cooperation between human and veterinary medicine to reduce the use of last-line antibiotics in food-producing animals [22] [23].

Useful ECDC resources:

Rapid risk assessment: Carbapenem-resistant Enterobacteriaceae [4]

Rapid risk assessment: Plasmid-mediated colistin resistance in Enterobacteriaceae [23]

Systematic review of the effectiveness of infection control measures to prevent the transmission of CPE through cross-border transfer of patients. Stockholm: ECDC; 2014

Case studies

1. Active screening to control a large hospital outbreak in the Netherlands [24]

In a hospital in the Netherlands, a large outbreak of highly resistant bacteria that was inadequately controlled for two years, triggered a hospital-wide outbreak containment strategy, which included:

- defining categories of patients who were at risk of being carriers of highly-resistant bacteria
- active screening of at-risk patients
- pre-emptive isolation of at-risk patients upon admission
- prompt assistance for outbreak support from the National Institute of Health and the Environment and the hospital's Department of Medical Microbiology.

The implementation of active screening of at-risk patients for highly resistant bacteria in this hospital was a cornerstone measure in the successful control of this outbreak. Furthermore, other healthcare facilities in the region were informed and advised to screen for carriage of highly resistant bacteria when patients had been admitted to the hospital affected during the outbreak period.

2. Measures taken to control a local outbreak on a hospital ward in Greece [25]

On a ward in a Greek hospital, a multifaceted infection control intervention was implemented over a three-year period to control the spread of highly resistant bacteria.
This programme consisted of:

- active screening of all patients for these highly resistant bacteria on admission to the ward
- weekly screening of all patients who were negative on admission

- placement of all patients who were carriers in either single rooms or cohort wards
- dedicated nursing staff
- use of contact precautions
- monitoring of compliance with hand hygiene.

This intervention led to a significant decrease in infections caused by highly resistant bacteria. Eighteen months after implementation of the intervention, the prevalence of patients that were carriers of these bacteria had dropped from 12.3% to 0%. The success of this intervention at a local level shows that results can be achieved even in a country with overall high levels of resistance.

3. A strategy to control a nationwide outbreak in Israel [26]

In Israel, the Ministry of Health launched a multifaceted intervention at national level to contain the spread of highly resistant bacteria occurring in hospitals across the country.

This nationwide intervention consisted of three main components:

- Mandatory reporting of all patients who were carriers of highly resistant bacteria to public health authorities
- Mandatory isolation of hospitalised carriers in either single rooms or a cohort ward
- Creation of a multidisciplinary professional taskforce reporting directly to the Ministry of Health. This taskforce had statutory authority to collect data directly from hospitals and intervene to control outbreaks. Within this framework, all microbiology laboratories were required to adhere to guidelines for uniform standards of detection and reporting.

In acute care hospitals in Israel, the monthly incidence of infections with highly resistant bacteria decreased from 55.5 to 11.7 cases per 100 000 patient-days within a year. Furthermore, compliance with this intervention prevented new cases arising.

Commitment at the highest political level, as well as the dedication and cooperation of policymakers and healthcare professionals, made this intervention a success.

Sources

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Suggested citation: European Centre for Disease Prevention and Control. Last-line antibiotics are failing: options to address this urgent threat to patients and healthcare systems. Stockholm: ECDC; 2016.

Catalogue number: TQ-06-16-176-EN-N
ISBN: 978-92-9193-997-8
DOI: 10.2900/866735

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