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# Epidemiology of infections caused by polymyxin-resistant pathogens

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ABSTRACT

Confronting the storm of carbapenemase-producing Gram-negative pathogens and thus facing the threat of untreatable infections, the medical community revived colistin. Not long since its re-introduction and despite the fact that resistance to colistin at least in *Escherichia coli* is rare, chromosomally-mediated colistin resistance in metallo-β-lactamase-producing *Klebsiella pneumoniae* strains was reported in 2004 from Greece. Subsequent studies revealed the highest predominance in Italy (38%) and Greece (26%), with colistin-resistant (Col-R) strains frequently carrying a carbapenemase. On the other hand, the international prevalence of Col-R *Acinetobacter baumannii* varied, predominantly in Southern Europe and Southeast Asia, with rates exceeding 80% in Italy and Greece. Risk factors have mainly incriminated the selective pressure of excess consumption of colistin both in animals and humans. In November 2015, emergence of plasmid-mediated colistin resistance due to the *mcr-1* gene was reported from China, mostly in community-derived *E. coli* strains. As of 1 September 2016, the *mcr-1* gene was detected in 35 countries worldwide in livestock/retail meat and in human sources from 29 and 22 countries, respectively. Heavy usage of polymyxins in animals has been incriminated as the reservoir of the *mcr-1* gene. Therefore, it is imperative that: (i) polymyxins are banned as growth promoters and for prophylaxis in animals; (ii) targeted surveillance plus molecular epidemiology is performed in hospitals; (iii) carriers or patients infected with isolates harbouring both *mcr-1* and carbapenemase genes are strictly isolated; (iv) susceptibilities are based on exact colistin minimum inhibitory concentration (MIC) determination; and (v) rational use of colistin is audited in hospitals.



## 1. Introduction

Infections due to multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) Gram-negative bacteria, particularly in critically ill patients in intensive care units (ICUs), nowadays represent a major threat worldwide. *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* producing various carbapenemases are the commonest implicated pathogens, mostly causing bacteraemia and ventilator-associated pneumonia [1]. Mortality rates, particularly in carbapenemase-producing *K. pneumoniae* (CPKP), reached 75% in some series and were attributed both to virulence and to the lack of appropriate antimicrobial therapy [1–3]. In November 2015, the European Centre for Disease Prevention and Control (ECDC) reported the highest endemic situation of Enterobacteriaceae producing carbapenemase from three countries, i.e. Greece, Italy and Turkey (Fig. 1) [4]. Therefore, polymyxins, which are antibiotics from the 1960s that possess promising in vitro activity against formerly XDR pathogens [1], were revived in the 2000s as a last-line therapeutic option. It was expected that the ever-increasing resistance to carbapenems would lead to the excessive consumption of polymyxins (Fig. 2) [5]. Not long since the re-introduction of colistin into clinical practice, the emergence of colistin-resistant (Col-R) strains, particularly in CPKP isolates, was reported [6–8]. Based on the underlying resistance mechanisms, colistin resistance in Gram-negative organisms, as reported until November 2016, was considered as chromosomally mediated and therefore not transmissible [9]. Unfortunately, in November 2015, plasmid-mediated resistance was reported for the first time and was attributed to a new *mcr-1* gene, thus creating a real threat [10].

Owing to the much greater experience with colistin, only this compound will be reviewed herein.

## 2. Epidemiology

### 2.1. Chromosomally-mediated colistin resistance in Gram-negative organisms

#### 2.1.1. K. pneumoniae

Among the Enterobacteriaceae, *K. pneumoniae* is the species most commonly involved in resistance development to colistin, whereas resistance in other species is rarely reported [9]. The first report of

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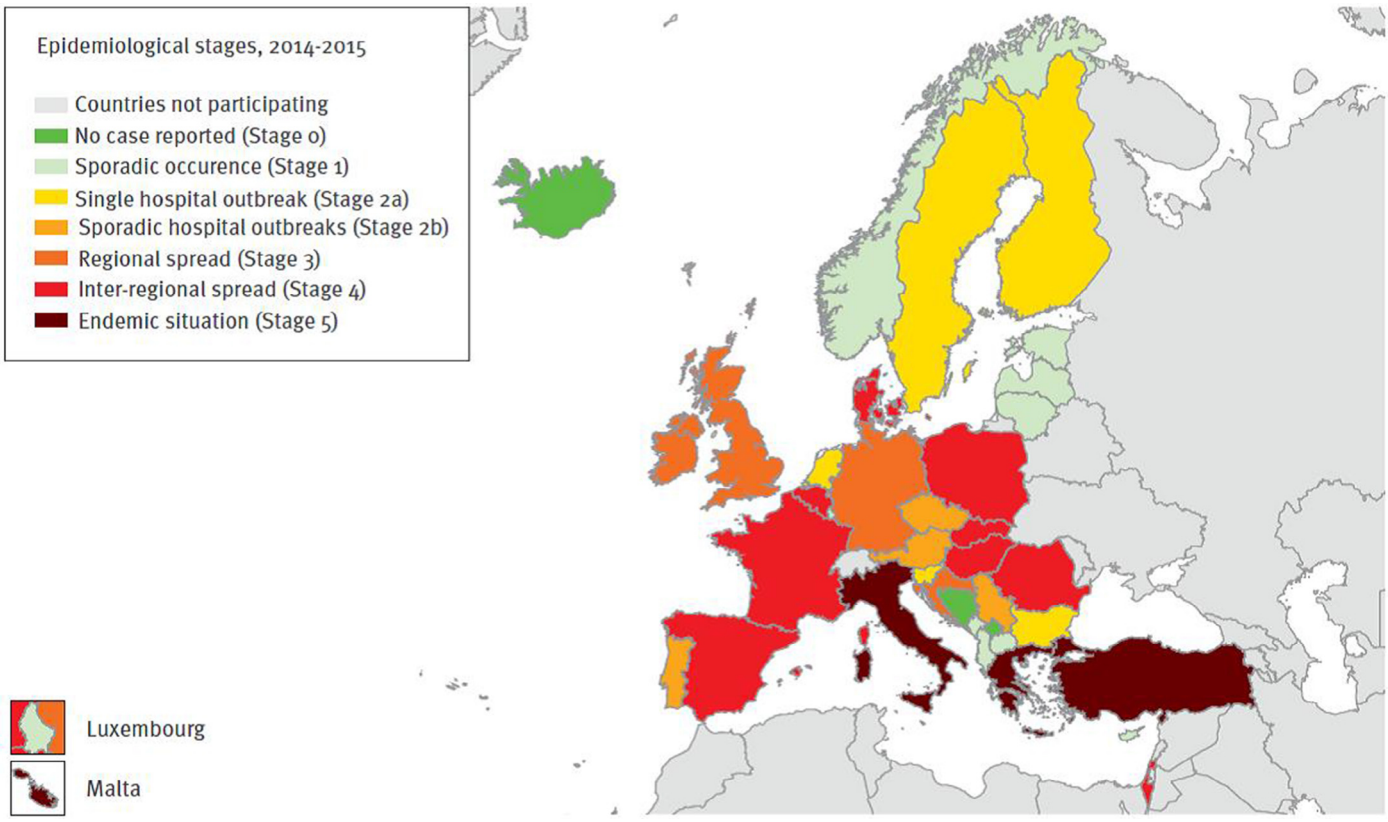


**Fig. 1.** Occurrence of carbapenemase-producing Enterobacteriaceae (*Klebsiella pneumoniae* and *Escherichia coli*) as assessed by national experts from 38 European countries, May 2015. Reproduced from the European Centre for Disease Prevention and Control (ECDC) [4].

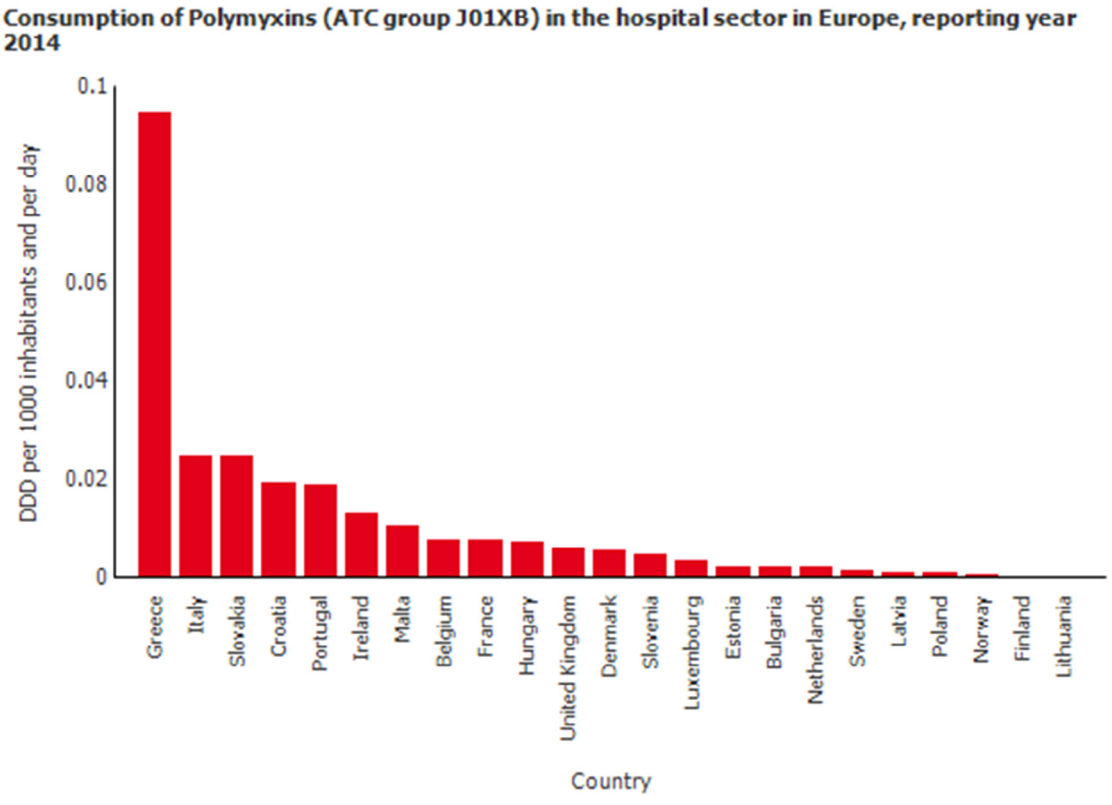


**Fig. 2.** Trends in consumption of polymyxins from several European countries, reporting year 2014. ATC, Anatomical Therapeutic Chemical classification system; DDD, defined daily doses. Reproduced from the European Centre for Disease Prevention and Control (ECDC) [5].