

Antimicrobial resistance (AMR) and spread of New Delhi Metallo- β -Lactamase (NDM) in Italy: A call for policymakers

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Antimicrobial resistance (AMR) occurs when microorganisms such as bacteria, viruses, fungi and parasites change in ways that render the medications used to cure the infections they cause ineffective [1]. AMR is a significant global public health concern [2]. Low-quality medicines, wrong prescriptions and poor infection prevention and control, as well as lack of government commitment and poor surveillance are also hindering the control of antimicrobial drug resistance [1, 3]. As AMR undermines the achievement of the UN's Sustainable Development Goals, the World Health Organization (WHO) called for a coordinated action among all countries worldwide, giving a special role to their governments [2, 4]. According to the European Centre for Disease Prevention and Control (ECDC) country visit to Italy in 2017, the Antimicrobial resistance (AMR) situation in Italian hospitals and regions poses a major

public health threat to the country. The levels of *carbapenem-resistant Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* have now reached hyper-endemic levels and, together with *meticillin-resistant Staphylococcus aureus* (MRSA), this situation causes Italy to be one of the Member States with the highest level of resistance in Europe [5, 6]. Recently, a large outbreak of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant *Enterobacteriaceae* (CRE) has been reported from the Tuscany region in Italy, where 9 Tuscan hospitals notified, from 1 November 2018 to 23 May 2019, a total of 350 cases, including those related to asymptomatic carriers. As a consequence, all hospitals in Tuscany have strengthened prevention and control measures against this infection [7]. NDM is a metallo-beta-lactamase able to hydrolyse almost all beta-lactams, including carbapenems [8]. Since its first description

KEY WORDS: Antibiotic resistance, Antimicrobial resistance (AMR); carbapenem resistance; Enterobacteriaceae; epidemiology; New Delhi-Metallo-beta_Lactamases; public health; surveillance.

in 2008 from a *Klebsiella pneumoniae* strain isolated from a patient repatriated to Sweden after hospitalisation in New Delhi, India, NDM-positive strains have been identified worldwide, with the highest prevalence in the Indian subcontinent, causing healthcare-associated outbreaks worldwide [5].

Risk factors for acquisition of carbapenemase-producing CRE, including those producing NDM, include recent admissions to healthcare facilities, especially in regions with a high CRE prevalence, residence in long-term care facilities, surgical procedures and indwelling devices, as well as intensive care therapy and long duration of hospitalization [9, 10]. Since its first identification in 2009, the prevalence of the *bla*_{NDM} gene has continuously increased worldwide [11]. *Klebsiella pneumoniae* and *Escherichia coli* are the predominant carriers of *bla*_{NDM} [8], but the source of infection remains unknown [12]. This outbreak in Italy is one of remarkable importance, because NDM-producing carbapenem-resistant Enterobacteriaceae (CRE) are not susceptible to some of the new beta-lactam/beta-lactamase inhibitor combinations such as ceftazidime-avibactam and meropenem-vaborbactam, thus reducing the treatment options. Furthermore, as *Klebsiella Pneumoniae* carbapenemase (KPC)-producing CRE is already endemic in Italy and Tuscany is a highly touristic area, therefore the risk for spread to European healthcare facilities of NDM-producing CRE from the current outbreak is high [12]. For this reason, as suggested by ECDC [5], Italian stakeholders should timely take actions to prevent transmission in healthcare facilities

for preventing transmission from CRE-positive patients and preventing spread of CRE in specific wards/units, as well as they should take actions to prevent cross-border spread. The Tuscany region has implemented a specific epidemiological surveillance. According to its Agenzia Regionale di Sanità (ARS) data, between November 2018 and 27 October 2019, NDM producing CREs have been identified in the blood of 129 patients and the rate of mortality in patients with sepsis was as 33% [13].

Tuscany has an effective antibiotic resistance monitoring system (SMART network) [14], but in Italy systems for surveillance of AMR at regional level are only in place in a few regions. Indeed, there are two sentinel networks at national level, named AR-ISS and MICRONET, but there is an unequal, geographical distribution of the hospital laboratories that participate in AR-ISS and MICRONET, which are mostly located in the northern regions, despite the fact that AMR prevalence is acknowledged to be highest in the central and the southern regions of the country. Moreover, as highlighted by the ECDC Report, at local hospital level, surveillance of AMR tend to be unstructured and lacking focus in the keys areas of interest, and not all hospitals have an on-site microbiology laboratory supported by a microbiologist, as well as not all microbiology units of laboratories are run by a medical doctor. The different accreditation system of laboratories among Italian regions, furthermore, hinders the process of building up an effective comprehensive monitoring system at national le-

Competing interests - none declared.

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Cite this article as - Nucera G. Antimicrobial resistance (AMR) and spread of New Delhi Metallo- β -Lactamase (NDM) in Italy: A call for policymakers. *J Health Soc Sci.* 2019;4(3):297-300

DOI 10.19204/2019/ntmc1

Received: 30/10/2019

Accepted: 05/11/2019

Published: 15/11/2019

vel [5]. This complicates the implementation of the recent guidelines suggested by ECDC and requires prompt action by Italian policy-makers. Otherwise, the first Italian National Action Plan on Antimicrobial Resistance (PNCAR) 2017–2020 [15], which represents

the tool needed to implement the Italian strategy, could be ineffective.

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Journal of Health and Social Sciences*

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