

## OPINION

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### **Additional information regarding the measures to control the spread of emergent highly-resistant bacteria (eHRB) recommended in the opinion of the French HCPH of 27 September 2016 in view of the emergence of a plasmid mediated (*mcr-1*) colistin resistance in *Enterobacteriaceae***

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On 4 August 2016, the High Council for Public Health (HCPH) received a referral from the General Directorate of Health (GDH) regarding measures to be taken about the emergence of a plasmid-mediated (*mcr-1*) colistin resistance in *Enterobacteriaceae*.

A national working group replied to the GDH's referral by drawing up and publishing two opinions regarding the definition of *mcr-1* carrying *Enterobacteriaceae* [1] and the laboratory microbiological detection methods [2].

In order to provide details of the application of preventive measures proposed in the first opinion [1] and of the recommendation of whether or not to carry out routine screening of contact patients for the presence of *mcr-1* in *Enterobacteriaceae*, the HCPH proposes the following measures within the framework of a self-referral.

#### **The HCPH points out the following:**

- The recommendations for the prevention of cross-transmission of emerging Highly-Resistant Bacteria (eHRB) published by the HCPH in 2013 [3,4] defined the eHRB as gut commensal bacteria that are able to spread according to limited sporadic or epidemic modes in France in hospitals or communities and that present multiple transferable resistance mechanisms. Unlike multi-resistant bacteria (MRB), these resistance mechanisms can, in the case of eHRB, extend to the latest types of antibiotics available.
- Taking into account international and French epidemiology at the time, the list of the eHRB drawn up in 2013 included *Enterobacteriaceae* that are carbapenem-resistant through the production of carbapenemases (CPE) and glycopeptide-resistant *enterococci* (GRE) (*E. faecium*).
- Patients targeted for routine digestive screening for carrying both of these eHRBs were patients who had been hospitalised for more than 24 hours abroad in the previous year, with or without direct repatriation, patients with a history of eHRB or contact patients of patients carrying eHRB who have been re-hospitalised.

- These recommendations provided that the list of eHRB could be revised according to the international epidemiological context of the emergence of new resistances to antibiotics.

**The HCPH notes the following:**

The emergence of colistin-resistant *Enterobacteriaceae* raises the question of into which of the existing categories (MRB or eHRB) the colistin-resistant strains by the expression of the *mcr-1/mcr-2* gene should be classified, bearing in mind that the measures to be set up to control their spread have a different organisational impact depending on how the strain is categorised:

- Although the plasmid-mediated colistin resistance was identified in different countries in extended-spectrum beta-lactamase-producing (ESBL) *Enterobacteriaceae*, it does not seem relevant to test for the frequent ESBL (clinical and gut isolates) routinely in search of those which carry the plasmid gene coding the resistance to colistin even though:
  - (i) the epidemiology of these strains and their spread in the community and in hospitals in France are not documented;
  - (ii) demonstrating this resistance routinely in laboratories is difficult;
  - (iii) as MRBs, ESBL are generally already subject to additional hygiene measures.
- To consider that any ESBL is a potential eHRB because it is potentially colistin-resistant, would mean applying to each identified ESBL the 2013 national recommendations for the care of patients at risk of carrying eHRB [3], thus setting up additional “contact” precautions such as defined by the French Society of Hospital Hygiene (SF2H) [5] until its colistin-resistant character by the expression of the *mcr-1/mcr-2* gene be invalidated.

**The HCPH indicates the circumstances in which colistin resistance must be identified while awaiting the results of national investigations into the prevalence of the phenomenon in France.**

As colistin resistance has also been identified in EPC strains, it is recommended [1] to test colistin resistance and to test for the presence of the *mcr-1* gene in any isolated EPC strain.

- either during routine screening when admitting a patient who has been hospitalised outside metropolitan France within the previous year, with or without direct repatriation,
- or in a sample for diagnostic purposes during hospitalisation in a clinical and therapeutic context requiring colistin.

**The HCPH underlines recommendations that have already been published [1]**

1) *For the precautions to be taken when caring for a patient proven to be carrying an *mcr-1/mcr-2*-positive enterobacterium:*

- Application of contact precautions whatever the resistance profile to 3<sup>rd</sup> generation cephalosporins (3GC) (i.e. ESBL strain), to penems (i.e. EPC strain) as well as to susceptible (“wild”) strains (Table 1) [1].

2) *For routine screening of *mcr-1/mcr-2* carried in the gut:*

- Screening strategies for patients being cared for by the same team (contact patients) as a case carrying an *mcr-1/mcr-2 enterobacteriaceae*, must be adapted to the strain’s resistance profile:
  - ✓ In case of CPE, the routine screening of all contacts must be organised with a search for colistin resistance;
  - ✓ In case of ESBL, routine screening of contacts for *mcr-1/mcr-2* is not recommended. However, routine screening may be decided in an uncontrolled epidemic situation when first line measures have failed.

**Table 1.** Summary of the guidelines of the French High Council for Public Health regarding the risk management of the spread of plasmid-mediated colistin resistance in *Enterobacteriaceae* [1].

Field concerned	Recommendation	
What type of patient should be routinely screened for plasmid-mediated colistin resistance?	<b>Recommendation 1</b>	<p>Test colistin resistance and for the presence of the <i>mcr-1</i> gene in any isolated CPE strain:</p> <ul style="list-style-type: none"> <li>• either during routine screening when admitting a patient who has been hospitalised outside metropolitan France within the previous year, with or without direct repatriation,</li> <li>• or in a sample for diagnostic purposes during hospitalisation in a clinical and therapeutic context requiring colistin.</li> </ul>
What additional hygiene precautions are to be taken?	<b>Recommendation 2</b>	<p>In the event of a CPE, apply the specific eHRB precautions, in addition to the standard precautions, presenting the <i>mcr-1</i> gene [3].</p> <p>If it is not a CPE, the 2009 recommendations of the SF2H “Cross-transmission: additional contact precautions” are to be applied [5].</p>
What should be done in the event of a plasmid-mediated colistin resistance?	<b>Recommendation 3</b>	<p>Report the case within the framework of the nosocomial infections provisions and send the strain to the National Reference Centre of resistance to antibiotics (for all strains carrying <i>mcr-1/mcr-2</i>, not solely the CPE).</p>
How can the epidemiological situation in France be determined?	<b>Recommendation 4</b>	<p>By undertaking national epidemiological studies on the prevalence of colistin resistance and on the presence of the <i>mcr-1</i> resistance gene in <i>Enterobacteriaceae</i> (whatever their antibiotic sensitivity profile) based on data from private and hospital pathology laboratories.</p> <p>These epidemiological studies could be coordinated by a national working group comprising experts from the HCPH, the French National Observatory for Epidemiology of Bacterial Resistance to Antimicrobials (ONERBA), the National Reference Centre of resistance to antibiotics (CNR Clermont-Ferrand) and the Public Health system in France.</p>

**These recommendations have been drawn up on the basis of knowledge available at the date of publication and are subject to modification in the event of new data being available.**

*Opinion drawn up by a group of experts, members or non-members of the HCPH, around the Expert Committee on the “Health System and Patient Safety” (CS-3SP). No conflict of interest has been identified.*

*The CS-3SP sat on 23 May 2017; 11 qualified members out of 18 qualified voting members were present, no conflict of interest was noted, the text was approved by 10 voting members, 1 abstention, 0 vote “against”.*

## References

1. Haut Conseil de la santé publique - French High Council for Public Health. Opinion of 27 September 2016 regarding the measures to be taken by health establishments with regard to an emerging plasmid-mediated (*mcr-1*) colistin resistance in Enterobacteriaceae.  
Available at <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=589> (consulted on 31/01/2017).
2. Haut Conseil de la santé publique - French High Council for Public Health. Opinion of 31 December 2016 regarding the microbiological diagnosis of resistant Enterobacteriaceae.  
Available at <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=589> (consulted on 31/01/2017).
3. Haut Conseil de la santé publique - French High Council for Public Health. Prevention of the cross-transmission of emerging Highly-Resistant Bacteria (eHRB). 10 July 2013.  
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4. Lepelletier D, Berthelot P, Lucet JC, Fournier S, Jarlier V, Grandbastien B for the National Working Group. French recommendations for the prevention of emerging extensively drug-resistant bacteria (eXDR) cross-transmission. *J Hosp Infect* 2015;90:186-195.
5. Société française d'hygiène hospitalière. Recommandations « Prévention de la transmission croisée : Précautions complémentaires contact ». 2009.  
Available at <http://sf2h.net> (consulted on 31/01/2017).

List of members of the Working Group set up to respond to this self-referral

Anne Berger Carbonne, Santé publique France  
Philippe Berthelot, CHU Saint-Etienne  
Richard Bonnet, CHU Clermont-Ferrand  
Céline Cazorla, CHU Saint-Etienne  
Christian Chidiac, HCPH  
Bruno Grandbastien, CHRU Lille  
Vincent Jarlier, groupe hospitalier Pitié-Salpêtrière, APHP  
Didier Lepelletier, HCPH  
Thierry Naas, CHU Bicêtre, APHP  
Marie-Hélène Nicolas-Chanoine, Hôpital Beaujon, APHP  
Patrick Plésiat, CHRU de Besançon  
Christian Rabaud, HCPH  
Pierre Tattevin, CHU Rennes  
Nathalie Van der Mee-Marquet, HCPH

Ann Pariente-Khayat, SG-HCPH

**Haut Conseil de la santé publique**

14 avenue Duquesne

75350 Paris 07 SP

[www.hcsp.fr](http://www.hcsp.fr)