Journal of Hospital Infection 90 (2015) 186–195

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Review

French recommendations for the prevention of 'emerging extensively drug-resistant bacteria' (eXDR) cross-transmission☆

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ARTICLE INFO

Article history:
Received 2 February 2015
Accepted 7 April 2015
Available online 24 April 2015

Keywords:
Carbapenemase-producing Enterobacteriaceae (CPE)
Extensively drug-resistant bacteria (XDR)
Multidrug-resistant bacteria (MDR)
Vancomycin-resistant enterococci (VRE)

SUMMARY

Controlling the spread of multi- or extensively drug-resistant bacteria (MDR or XDR) includes a dual strategy for reducing antibiotic prescriptions and preventing their spread from patient carriers. Standard precautions are applicable to all health professionals caring for any patients; additional barrier precautions (isolation) are recommended for patients carrying transmissible infectious diseases or MDR bacteria in sporadic or epidemic situations. Moreover, additional precautions may be required for populations at particular risk of infection or colonization by emerging XDR (eXDR), defined in our country as carbapenemase-producing Enterobacteriaceae and vancomycin-resistant enterococci. Our ability to detect and identify eXDR carriers early and ensure their follow-up, through effective communication between all those involved, is a significant challenge for controlling their spread. Thus, the French High Committee for Public Health has updated and standardized all French existing recommendations concerning the prevention of the cross-transmission of these bacteria, and these recommendations are summarized in this review. The recommendations are based on scientific and operational knowledge up to 2013. Different preventive strategies are recommended for patients found to be carrying eXDR and those who are considered to be at risk of having eXDR because of a history of contact. The local context, the experience of the infection control team, the different times at which detection of eXDR takes place (during admission, hospitalization, etc.) and the

☆ These recommendations were presented in part at the 9th Healthcare Infection Society International Conference, November 16th–18th, 2014, Lyon Convention Center, France.

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http://dx.doi.org/10.1016/j.jhin.2015.04.002

epidemiological situation (sporadic cases, clusters, outbreaks, widespread epidemic) must be included in risk assessments that in turn inform the control measures that should be applied in each clinical circumstance.

Introduction

The spread of multidrug-resistant (MDR) bacteria in Europe and in France over the last five years represents a health emergency at the dawn of the post-antibiotic era.[1—7] The European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) have included bacterial resistance to antibiotics in their priorities. Hygiene measures have been proven to be effective in limiting cross-transmission of MDR bacteria.[8] Their application has contributed to a reduction in the incidence of certain bacteria in French health institutions, such as the meticillin-resistant *Staphylococcus aureus* (MRSA).[9,10] By contrast, extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-E), such as *Escherichia coli*, have spread in hospitals and in the community over the last decade.[11]

In 2009, the French Ministry of Health asked the Safety Patient Committee (CSSP) of the High Council for Public Health (HCSP) to publish national recommendations for controlling the spread of highly resistant bacteria (vancomycin-resistant enterococcus (VRE) and carbapenemase-producing Enterobacteriaceae (CPE)] from repatriates.[12] Thereafter there were reports of NDM-1 CPE spread in Europe after being imported from India in August 2010, and recognition that there was a foreign link in 80% of CPE episodes in France (75% of which were cases of medical repatriation and 17% patients hospitalized abroad within the last year).[13—15] Thus it was identified that the scope of the recommendations needed to be broadened to include patients with a history of hospital stays abroad without direct repatriation and to reflect legal notices published by the French Ministry of Health in 2010 and 2012.[16]

Other considerations in developing the revised 2013 guidelines were: (i) the changing epidemiology of MDR bacteria in France (including the increasing number of cases of CPE with no links to hospital stays abroad); (ii) new experience of the infection control management of MDR bacteria occurring as sporadic or clustered cases and in wider epidemic settings; and (iii) recognition that the control measures recommended in the 2010 guidelines were not always interpreted in the same way by institutions and infection control practitioners, and sometimes conflicted with other sources of guidance available in France.[17—22]

This article summarizes the updated 2013 French national guidelines to identify and control the spread of emerging extensively drug-resistant bacteria (eXDR) and emphasizes the main strategies for isolation and screening eXDR patients and their contacts.

Methods

Composition of the working group

A national working group was formed including health professionals in hospital hygiene, infectious diseases, microbiology and public health. Various regional co-ordinating centres for infection control, resistance surveillance networks, and national health institutions were represented. The working group's expertise was also based on interviews with expert laboratories from the national reference centre (CNR) for resistance to antibiotics and from the ECDC.

Methodology for the preparation of data sheets and recommendations

A review of the international recommendations and literature was conducted between July and September 2012. The review of international recommendations concerning strategies for controlling eXDR epidemics was performed based on exploring the websites of French, European and worldwide health organizations, the websites of French, European, and worldwide specialist societies. The review of the literature was conducted on PubMed and involved research combining MeSH terms or predefined keywords. Publications from January 2005 to August 2012 were included in the review. The abstracts from 1500 articles were read; from these, 219 full articles were requested. Fifty-one of these articles contained sufficient details of preventive measures and were used to inform the development of this guidance.[23—73]

French recommendations to control the spread of eXDR bacteria

Definition of emerging extensively drug-resistant bacteria (eXDR)

Extensively drug-resistant (XDR) bacteria are defined here as being sensitive to only one or two classes of antibiotics. Magiorakos *et al.* have published an international expert proposal for interim standard definitions for acquired resistance in multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria that is quite different from the definition used in these French recommendations.[74,75] In France, the term 'emerging XDR (eXDR)' is used to describe multidrug-resistant bacteria that present an emerging infection control challenge widely in our country.

The French guideline targets CPE and VRE as the main eXDR screening targets in patients with a history of hospitalization in hospitals abroad (medical repatriations and hospitalizations within the previous year). This choice is based on two observations: (i) the limited sporadic or epidemic spread of these two eXDR in France at that time, and (ii) these bacteria belonging to the commensal gastrointestinal tract flora are therefore likely to be carried for a long time and can potentially spread in hospitals and in the community.

Opportunistic saprophytic bacteria, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, were not considered as eXDR bacteria by the 2013 French working group, even though MDR strains may also be imported after hospital stays abroad,

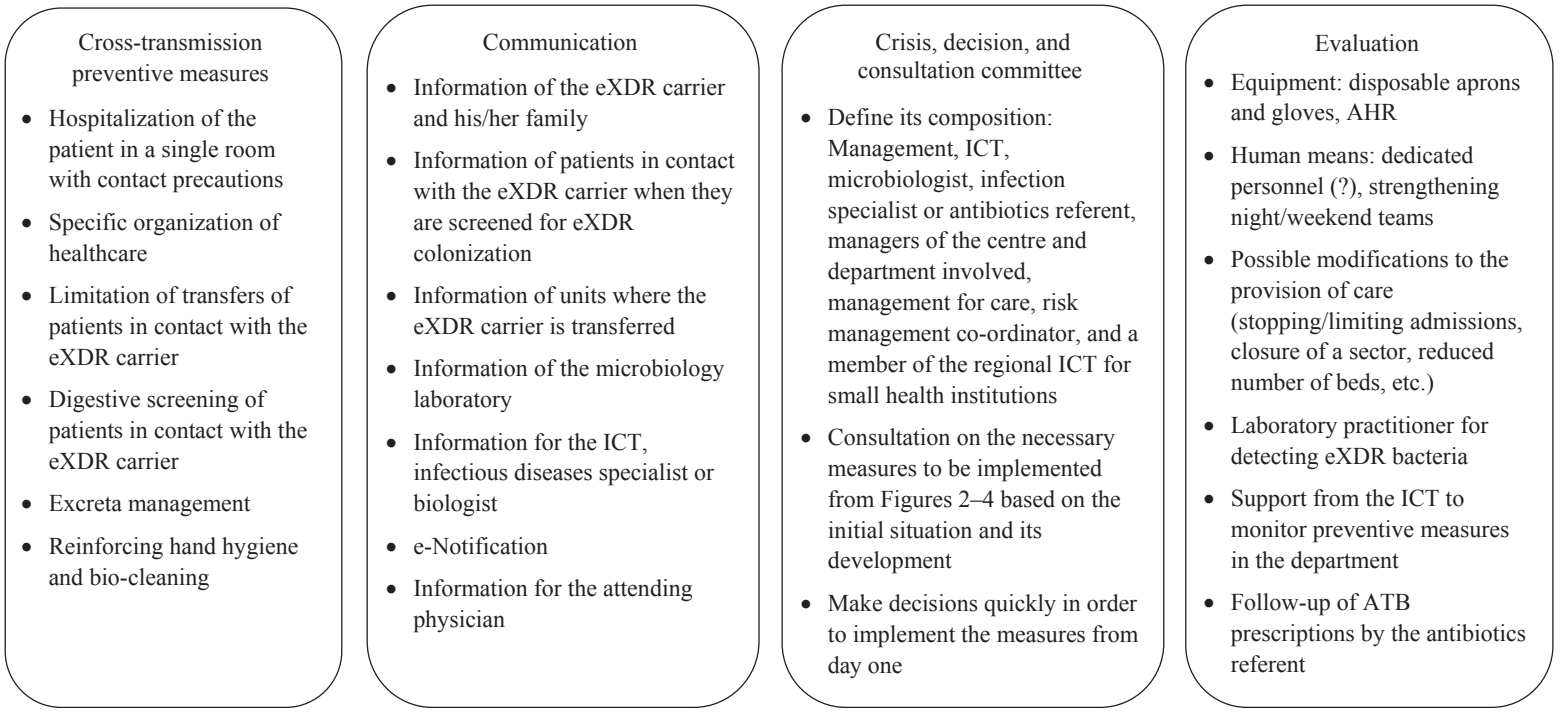

Figure 1. General measures to be applied when an emerging extensively resistant (eXDR) bacterium is identified. ICT, infection control team; ATB, antibiotic; AHR, alcohol hand rub; HIS, hospital information system.

because it was considered that the risks posed by such bacteria were largely confined to specialist units such as intensive care units.[75] Other MDR bacteria that are already endemic in France (e.g. MRSA, ESBL-producing Enterobacteriaceae) were also not considered as eXDR bacteria.

Definition of target patients in France

The new 2013 French guidelines to control the spread of eXDR identify patients who must be hospitalized in a single room with contact precautions until the results of a rectal swab looking for CPE and VRE gastrointestinal tract carriage are available:[75]

- Direct repatriates as inpatients from an overseas health institution abroad for a hospital stay or repeated sessions (excluding consultations). These repatriated patients are defined as patients transferred from abroad by medical repatriation or by an insurance company, directly or indirectly, from a healthcare facility situated in a country other than France. A French legal note requires insurance companies to promptly notify the regional health authorities of all repatriation operations in order to identify patients suspected of carrying eXDR bacteria. However, it seemed necessary for these data also to be communicated by the health authorities to the hospital infection control teams (ICTs), in real time, in order to ensure that control measures and screening are implemented immediately.
- Patients with a history of hospitalization abroad within the previous year whatever the medical or surgical wards and particularly in highly specific care sectors (organ transplant service, complex surgery, etc.).
- Patients with past medical history of eXDR carriage.
- Patients with a history of contact with eXDR patients.

Definition of contact patients in France

A contact patient is a patient exposed to an eXDR bacteria carrier. To date, there are no precise definitions available in the literature. Contact patients are defined in France as patients for whom inpatient care has involved sharing paramedical and/or medical healthcare workers with one or more carrier patients, where there has been direct contact between the healthcare workers and patients. This includes both the current hospitalization and previous hospitalizations

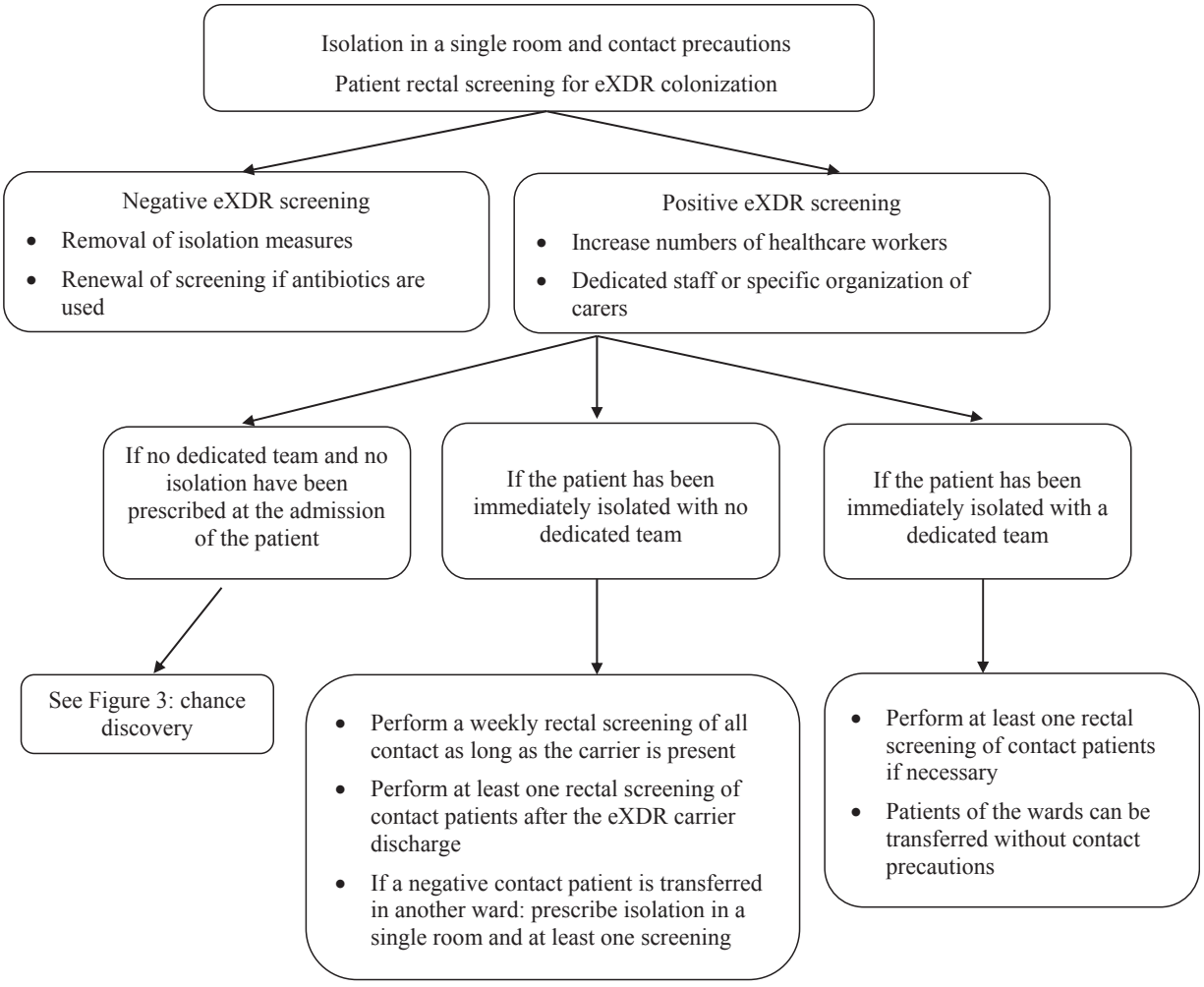

Figure 2. Recommendations to detect emerging extensively resistant (eXDR) bacteria at the hospital admission of a patient hospitalized abroad within the previous year.

where exposure to an eXDR carrier is known or highly suspected.

Screening and microbiological diagnosis of eXDR bacteria

The eXDR bacteria included in these guidelines are Enterobacteriaceae which produce all types of carbapenemase [class A (KPC and GES), class B (VIM, NDM, and IMP), and class D (OXA-48)], as well as *E. faecium* which acquired the genes (*vanA* or *vanB*) for glycopeptide resistance. Only molecular methods can identify the carbapenemase-encoding genes in Enterobacteriaceae and those encoding VanA or VanB in *E. faecium*. The majority of laboratories do not have these molecular tools. The guidelines define a procedure enabling all medical laboratories to identify as quickly as possible the isolates of Enterobacteriaceae and *E. faecium* that are likely to produce carbapenemase enzymes or exhibit VanA/VanB resistance, respectively. Applying and interpreting the methods occurs according to the recommendations by the Antibiogram Committee of the French Society of Microbiology (CASFM). The CASFM information letter on the detection of carbapenemases is accessible on the French Society of Microbiology website.[76] Gastrointestinal carriers are identified through testing for the eXDR bacteria in stools or rectal swabs. It is recommended that swabs are checked visually for the presence of faecal matter, and that separate swabs are used for screening for CPE and VRE. High-performance swabs must be used, along with a multipurpose collection and transport system that maintains the viability of bacteria for up to 48 h at room and refrigerator temperature. Where only one swab is received, it is recommended that the swab be inserted into a tube containing 200 μL sterile water. Stools, rectal swabs, or aliquots of the suspension are plated in selective agars suitable for the search for CPE and VRE, respectively, and incubated for 24 or 48 h.

To date, there are no selective media suitable for detecting all CPE. Medical laboratories can use a selective medium if available, enabling the search for third-generation cephalosporin (3GC)-resistant Enterobacteriaceae (with the exception of strains producing OXA-48 alone, the CPE strains are 3GC-resistant). Each sample can be cultured on a quarter plate, and an ertapenem (ERT) disk is placed in the centre of the inoculum. It is highly likely that the colonies growing close to the ERT disk will be CPE. Laboratories that detect such strains and

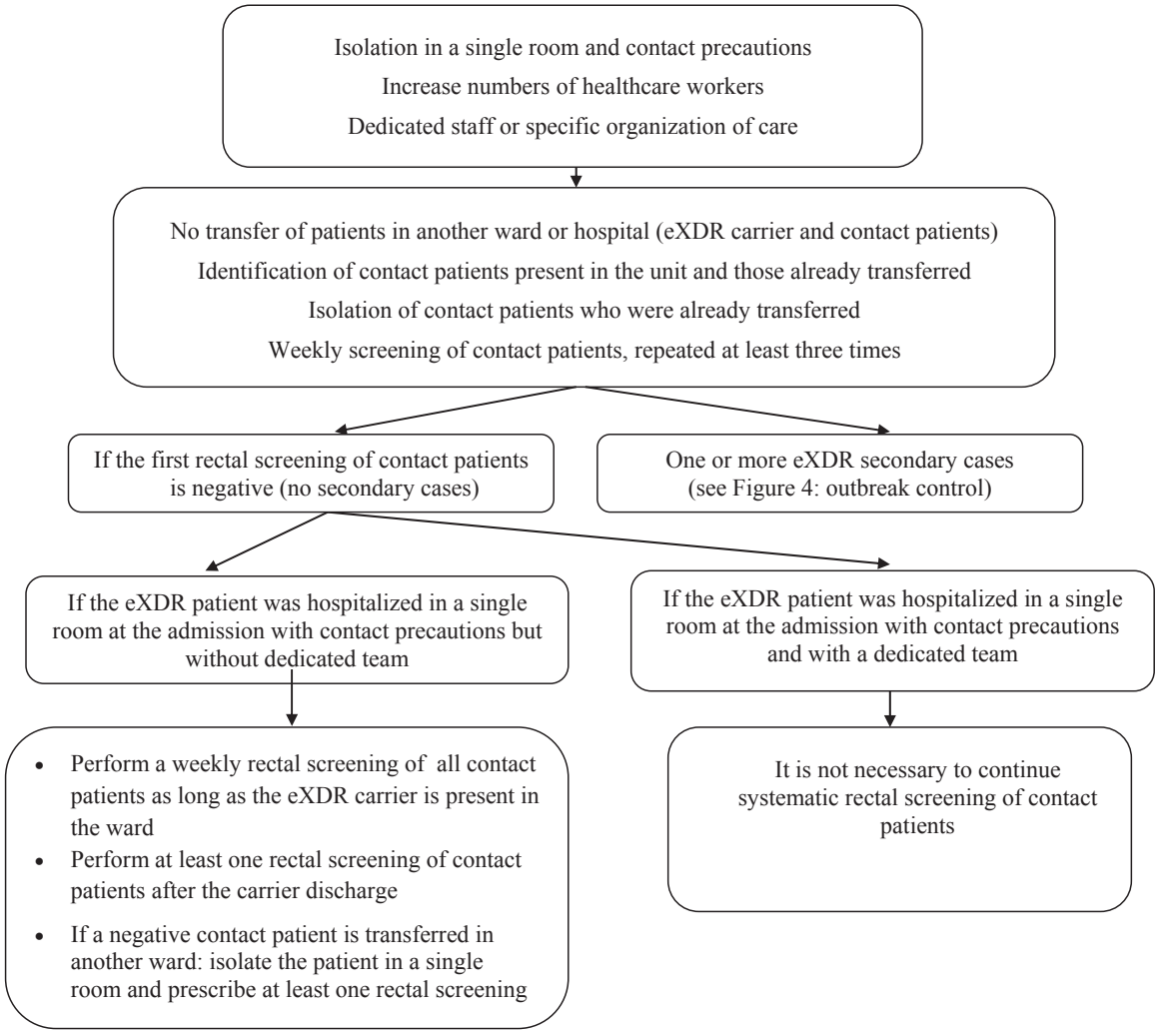

Figure 3. Recommendations to control the spread of emerging extensively resistant (eXDR) bacteria when detected from a clinical sample during hospitalization.

Box 1
Recommendations for the control of emerging extensively resistant (eXDR) bacteria spread in an epidemic situation (outbreak)

- Activation of the local epidemic control plan
- Stopping transfers of eXDR carriers and contact patients
- Temporarily stopping admissions
- Cohorting of carriers, contact patients, and newly admitted patients into three different sectors with dedicated staff, respectively
- Weekly rectal screening of contact patients
- Screening of contact patients who were already transferred to another institution
- Electronic alert to identify readmissions

The epidemic is considered to be controlled if, since the detection of the last carrier:

- eXDR carriers, contact patients and newly admitted patients are cared for by different staff in different cohorts
- At least three weekly rectal screenings of contact patients already hospitalized are negative

that do not have the capability to confirm carbapenemase production themselves must refer isolates to a competent laboratory with which it has established operational links, or to the CNR. Rapid tests such as the CARBA-NP test may be used.[77]

Selective media for the reliable detection of VRE are available, and should be used by medical laboratories. However, isolates must be identified to species level, and the MIC values of vancomycin and teicoplanin determined; only *E. faecium* strains that are confirmed to be resistant to vancomycin and/or teicoplanin are deemed to be eXDR. Strains exhibiting the VanC resistance phenotype do not spread in an epidemic way and do not require contact isolation. Laboratories that cannot adequately characterize the resistance phenotypes of enterococci must refer their isolates to a competent regional or national laboratory. Any identified CPE or VRE should be reported to the regional and national health authorities via a web notification.

Prevention of eXDR bacteria sporadic and epidemic cross-transmission

The general precautions recommended to prevent transmission of eXDR are summarized in Figure 1. Different levels of control are applied according to whether or not a patient has been shown to have an eXDR, and the likely timing of acquisition (Figures 2, 3; Box 1). Implementation of these requires healthcare institutions to ensure that there is adequate provision of the basic facilities listed in Table I; locally, the ICT has a key role in this.

Various levels of risk of transmission are defined for contact patients (Box 2), and screening programmes are based around these risks. There are two objectives in screening for secondary cases: (i) to provide an overview of transmission which may have already been established in cases where an eXDR carrier has been discovered by chance, and (ii) to ensure that, without a clinical team dedicated to the care of the eXDR carrier, secondary spread to other patients does not occur. Many studies demonstrate the importance of screening contacts in controlling eXDR epidemics.[29,49,56,63,78] However, the optimal time period between repeated screenings is unknown. The French guidelines recommend systematically screening contact patients weekly until one week after the discharge of an eXDR patient in acute care units, and every 15 days in physical medicine and rehabilitation (PMR). No screening is

Table I
Risk assessment of emerging extensively drug-resistant (eXDR) bacteria spread by cross-transmission related to different hospital and patient criteria

Criteria	Risk assessment
Type of care	Characteristics of patients and burden of cares
Pressure of colonization	Number of eXDR patients in a ward or unit
Organization	Ratio between healthcare workers and patients. Leadership and collective organization.
Observance of hygiene guidelines	Universal precautions, particularly hand hygiene, wearing of gloves, excreta elimination, and safety. Isolation (quality of the information, use of dedicated medical device or systematic disinfection after each use). Quality and frequency of environmental cleaning and disinfection.
Ward architecture	Number of single rooms. Possibility of creating different separation (cohort). Number of individual toilets and washing basins. Use of shower rinse basins to disinfect basins in patient room.
Transmission risk levels	Delay of isolation of the eXDR patient in a single room and prescription of precaution measures. Number of patients in contact with the eXDR carrier.
Expertise	Infection control team visibility and availability to inform all healthcare workers and to perform direct evaluation of prevention practices. Healthcare workers' experience in managing outbreak.

Box 2
Emerging extensively drug-resistant bacteria (eXDR) spread: control and screening strategies according to different levels of risk

Low risk of cross-transmission:

Patient in isolation precaution at the admission

Recommendations:

- Perform rectal screening on all patients in contact with the carrier by a rectal swab, weekly.
- Perform rectal screening on all patients in contact with the carrier before transfer to another ward or hospital. Screening should be repeated at least once after they have been transferred.
- Perform at least one post-exposure rectal screen on all contact patients who are still hospitalized after the carrier has been discharged.
- After discharge from hospital, detect and perform rectal screening to all patients who were in contact with the carrier, when they are rehospitalized.

Intermediate risk of cross-transmission:

The patient was not detected at the hospital admission. The carriage of eXDR has been detected from a clinical sample after few hospital days. No contact isolation was prescribed at the admission.

Recommendations:

- List all the patients who were in contact with the carrier.
- Perform rectal screening on hospitalized patients and send a letter to inform discharged patients of the situation and the need to declare that they have been in contact with a carrier during the last hospitalization.
- Do not transfer patients in contact with the carrier until the epidemiological situation has been assessed (except emergency). If so, patient should be transferred with isolation precautions in a single room and three-weekly rectal screening should be performed.
- If no secondary cases have been identified after three screenings among all patients who were in contact with the carrier, the risk of cross-transmission becomes low.

High risk of transmission

Several secondary cases have been identified (outbreak).

Recommendations:

As long as the epidemiological situation is not controlled:

- Perform three rectal screens of all patients who were in contact with the carriers.
- Do not transfer patients who were in contact with the carriers.
- Staff must be particularly vigilant for the risk of positive screenings in contact patients exposed to antibiotic treatment.
- It is recommended to dedicate nurse and medical staff in three different cohorts to separate newly admitted patients, exposed patients and patients with eXDR.

recommended in long-term care facilities or at home. Each contact patient without three negative screenings must be identified when he or she is rehospitalized in acute care or in PMR, and their eXDR risk reassessed.

The literature and local clinical experience show that cases of cross-transmission can occur despite standard precautions and solely prescribing contact precautions.[25,38,48,78,79] Systematic application of contact precautions by all healthcare workers throughout the day, night, and weekend is difficult to achieve.[15] Cohorting of affected patients, with dedicated healthcare workers, encourages observance for contact precautions. No randomized studies have been conducted comparing dedicated and non-dedicated staff, but several quasi-experimental studies show a positive impact of dedicated staff to control cross-transmission at hospital, regional, or national levels.[21,25,38,49,61,78,80,81]

Detection of a patient at risk of eXDR bacteria carriage

Two measures are recommended to facilitate the identification of these patients in all health institutions. On an administrative level this involves adding the 'medical repatriation' category into the documentation for the patient's hospital admission, and on a clinical level it involves remembering the importance of specific questioning about hospitalization abroad at the time of admission. In an epidemic situation exhaustive screening of patient contacts is required (current and those transferred to another facility or discharged home) together with cohorting of patients into three distinct areas (cases, contacts, and patients who are neither cases nor contacts) (Boxes 1 and 2).

Comparison of international guidelines on multidrug-resistant bacteria

In response to the growing threat of CPE spread in healthcare systems, several guidance documents have been published internationally providing recommendations for the implementation of multimodal infection control interventions to prevent the spread of CPE in acute healthcare facilities. Guidelines, such as those from the US Centers for Disease Control and Prevention (CDC) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), are mainly based on prior guidelines for prevention and control of multidrug-resistant micro-organisms and on expert opinion.[82,83] At the same time, many European countries have addressed the spread of CPE by creating new or modified guidelines based on strategies for other MDR bacteria, or by creating national task forces to develop local or national strategies.[61,84–86] However, there has been little or no co-operation between countries, and consequently there is no harmonization of approaches taken, even in neighbouring countries.[87] The present French recommendations are particularly comprehensive in that they include courses of action tailored for use in sporadic and epidemic settings in acute care and long-term care facilities.

Difficulties in implementing the guidelines

Isolation measures are a common approach to prevent the spread of high impact micro-organisms including various MDR bacteria. Some institutions interpret 'isolation' as a 'quarantine type' separation of the patient, who is not allowed to leave the isolation room. Other institutions isolate patient bedspace within a multi-bed room, and others will designate a

single room for the patient, but allow him or her to move around the hospital freely, with only healthcare workers encouraged to wear gloves and gowns during patient care. There are substantial differences with respect to the staffing levels available to manage isolated patients between different healthcare settings. For instance, if a patient is in a single room for isolation purposes, the staff-to-patient ratio may not necessarily be increased and therefore less time remains for patient care activities.[88] Some of the recommendations about patient isolation are likely to be impracticable in many European countries because of constraints on resources (availability of single rooms, bringing in extra staff, use of dedicated staff for isolated patients), and there is no advice as to how to prioritize the various demands on resources. Many hospitals in Europe rely on agency staff to maintain safe staff levels. Such staff may not be appropriate for the care of eXDR patients, because they may be less likely to comply with the procedures set out in the guidance. Moreover, they may be a possible vector of spread of these bacteria if they are also working in other healthcare settings.

Conclusion

Several different French guidelines have been produced in recent years to prevent the spread of MDR bacteria, including CPE and VRE. In July 2013 a new document was produced that has harmonized all the existing guidelines on the prevention of the transmission of eXDR. These were relayed in January 2014 by a legal notice of the French Ministry of Health. All the tools currently used to fight the threat posed by eXDR bacteria in all healthcare settings are described in these guidelines. Although there will inevitably be some epidemiological differences in eXDR between countries, we believe that efforts should be made to harmonize guidance between countries as much as possible to ensure that there is a co-ordinated approach to the threat that eXDR present to modern medicine.

Appendix. National Working Group

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Funding sources
None.

Conflict of interest statement
None declared.

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