



World Health
Organization



**Guidelines for the
prevention and control
of carbapenem-resistant
Enterobacteriaceae,
Acinetobacter baumannii and
Pseudomonas aeruginosa
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ABBREVIATIONS AND ACRONYMS

AMR	antimicrobial resistance
CDC	Centers for Disease Control and Prevention (Atlanta, USA)
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CP	carbapenemase-producing
CPE	carbapenemase-producing Enterobacteriaceae
CRAB	carbapenem-resistant <i>Acinetobacter baumannii</i>
CRE	carbapenem-resistant Enterobacteriaceae
CRPsA	carbapenem-resistant <i>Pseudomonas aeruginosa</i>
DNA	deoxyribonucleic acid
EMBASE	Excerpta Medica Database
EPOC	Effective Practice and Organisation of Care (group)
ESBL	extended-spectrum beta-lactamases
GDG	Guidelines Development Group
GLASS	Global Antimicrobial Resistance Surveillance System
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAI	health care-associated infection
ICU	intensive care unit
IHR	International Health Regulations
IPC	infection prevention and control
ITS	interrupted time series
LMICs	low- and middle-income countries
LTCFs	long-term care facilities
PCR	polymerase chain reaction
PICO	Population (P), intervention (I), comparator (C) and outcome(s) (O)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SDG	Sustainable Development Goals
USA	United States of America
WASH	water, sanitation and hygiene
WHO	World Health Organization

GLOSSARY OF TERMS

Acute health care facility: A setting used to treat sudden, often unexpected, urgent or emergent episodes of injury and illness that can lead to death or disability without rapid intervention. The term *acute care* encompasses a range of clinical health care functions, including emergency medicine, trauma care, pre-hospital emergency care, acute care surgery, critical care, urgent care, and short-term inpatient stabilization.

Alcohol-based handrub: An alcohol-based preparation designed for application to the hands to inactivate microorganisms and/or temporarily suppress their growth. Such preparations may contain one or more types of alcohol and other active ingredients with excipients and humectants.

Antimicrobial resistance surveillance of invasive isolates: Major antimicrobial resistance surveillance systems focus on data from invasive isolates. According to the European Antimicrobial Resistance Surveillance Network (<https://ecdc.europa.eu/en/publications-data/ears-net-reporting-protocol-2017>) and the USA National Healthcare Safety Network (https://www.cdc.gov/nhsn/pdfs/pscmanual/11psc_aucurrent.pdf), eligible specimens to identify invasive isolates include cerebrospinal fluid and blood specimens.

Carbapenem resistance (including carbapenemase-producing [CPI]): Carbapenem resistance among Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* may be due to a number of mechanisms. Some strains may be innately resistant to carbapenems, while others contain mobile genetic elements (for example, plasmids, transposons) that result in the production of carbapenemase enzymes (carbapenemases), which break down most beta-lactam antibiotics, including carbapenems. Frequently, CP genes are

co-located with other resistance genes, which can result in cross-resistance to many other antibiotic drug classes (1-3). Thus, while carbapenem-resistant strains of these pathogens are frequently CP (CP-Enterobacteriaceae [CPE], CP-A. *baumannii*, CP-P. *aeruginosa*), they may have other carbapenem resistance mechanisms that make them equally difficult to treat and manage clinically. Thus, the term “carbapenem-resistant Enterobacteriaceae” includes all strains that are carbapenem-resistant, including CPE. For this reason, infection and prevention control actions should focus on all strains of carbapenem-resistant Enterobacteriaceae, *A. baumannii* and *P. aeruginosa*, regardless of their resistance mechanism. Adequate infection prevention and control measures are essential in both outbreak and endemic settings (4).

Cohorting: The practice of grouping together patients who are colonized or infected with the same organism in order to confine their care to one area and prevent contact with other susceptible patients. Cohorts are created based on clinical diagnosis, microbiological confirmation with available epidemiology and the mode of transmission of the infectious agent. Cohorting is defined according to the United States Centers for Disease Control and Prevention (CDC) *Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings* 2007 (5).

Contact precautions: Measures intended to prevent the transmission of infectious agents, which are spread by direct or indirect contact with the patient or the patient environment. These include: ensure appropriate patient placement; use of personal protective equipment, including gloves and gowns; limit the transport and movement of patients; use disposable or dedicated patient-care equipment; and prioritize the cleaning and disinfection of rooms. Contact precautions are

defined according to the CDC *Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007* (5).

Grading of Recommendations Assessment, Development and Evaluation (GRADE): An approach used to assess the quality of a body of evidence and to develop and report recommendations.

Health care facility: For the purpose of these guidelines, a health care facility includes any type of acute care facility, secondary or tertiary care facilities, long-term care facilities and rehabilitation centres.

Health care-associated infection (also referred to as “nosocomial” or “hospital-acquired infection”): An infection occurring in a patient during the process of care in a hospital or other health care facility, which was not present or incubating at the time of admission. Health care-associated infections can also appear after discharge.

Health care-associated infection point

prevalence: The proportion of patients with one or more active health care-associated infections at a given time point.

Health care-associated infection incidence:

The number of new cases of health care-associated infections occurring during a certain period in a population at risk.

Low- and middle-income countries: WHO Member States are grouped into four income groups (low, lower-middle, upper-middle and high) based on the World Bank list of analytical income classification of economies for the fiscal year, which is based on the *Atlas* gross national income per capita estimates (released annually in July). For the current 2017 fiscal year, low-income economies are defined as those with a gross national income per capita of US\$ 1005 or less in 2016; middle-income economies are those with a gross national income per capita of more than US\$ 1045, but less than US\$ 12 235; high-income economies are those with a gross national income per capita of US\$ 12 236 or more. (Lower-middle- and upper-middle-income economies are separated at a gross national income per capita of US\$ 4125.)

Multimodal strategy: A multimodal strategy comprises several elements or components (three or more; usually five) implemented in an integrated way with the aim of improving an outcome and changing behaviour. It includes tools, such as bundles and checklists, developed by multidisciplinary teams that take into account local conditions. The five most common components include: (1) system change (availability of the appropriate infrastructure and supplies to enable infection prevention and control good practices); (2) education and training of health care workers and key players (for example, managers); (3) monitoring infrastructures, practices, processes, outcomes and providing data feedback; (4) reminders in the workplace/communications; and (5) culture change within the establishment or the strengthening of a safety climate. It is important to note the distinction between a multimodal strategy and a bundle. A bundle is an implementation tool aiming to improve the care process and patient outcomes in a structured manner and is often used as an operational tool in the context of multimodal strategies. Multimodal strategies are a more comprehensive implementation approach.

Patient isolation: Patients should be placed in single-patient rooms when available. When single rooms are in short supply, patients who are infected or colonized with the same resistant pathogen can be placed in the same room together (cohorted). Adapted definition according to the CDC *Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings 2007* (5).

Patient zone: Contains the patient and his/her immediate surroundings. This typically includes all inanimate surfaces that are touched by or in direct physical contact with the patient, such as the bed rails, bedside table, bed linen, infusion tubing, bedpans, urinals and other medical equipment. It also contains surfaces frequently touched by health care workers during patient care, such as monitors, knobs and buttons, and other “high frequency” touch surfaces. This is according to the definition included in the *WHO guidelines on hand hygiene in health care* (6). Contamination is also likely in toilets and associated items (7).

DECLARATIONS OF INTEREST

In accordance with WHO policy, all members of the GDG were required to complete and submit a WHO Declaration of Interest form before each meeting, declaring conflicts of interest in the last three to four years. External reviewers and experts who conducted the systematic reviews were also required to submit a Declaration of Interest form. The secretariat then reviewed and assessed each Declaration. In the case of a potential conflict of interest, the reason was presented to the GDG.

According to the policy of the WHO Office of Compliance, Risk Management and Ethics, the biographies of potential GDG members were posted on the internet for a minimum of 14 days before formal invitations were issued. The guidance of this Office was also adhered to and included undertaking a web search of all potential members to ensure the identification of any possibly significant Declarations of Interest.

The procedures for the management of declared conflicts of interests were undertaken in accordance with the WHO *guidelines for declaration of interests* (WHO experts). When a conflict of interest was considered significant enough to pose any risk to the guideline development process or reduce its credibility, the experts were required to openly declare such a conflict at the beginning of the Technical Consultation. However, the declared conflicts were considered irrelevant on all occasions and they did not warrant any exclusion from the GDG. Therefore, all members participated fully in the formulation of the recommendations and no further action was taken.

The following interests were declared by GDG members and external experts:

- Nalini Singh reported a WHO consultancy from 15 September 2014 to 16 January 2015 for the development of standards of antimicrobial resistance surveillance systems (total amount, approximately US\$ 55 000)
- Folasade Ogunsola reported being the chairman of a scientific review committee of an AstraZeneca research trust fund for Nigerian scientists (US\$ 3000 per year for three years, completed in 2016); having received US\$ 4000 from AstraZeneca in 2014 for travel; and a CDC foundation grant for infection and prevention control curriculum development and needs assessment (approximately US\$ 148 000 for the period 2016-2017).
- Petra Gastmeier declared that her institution received financial contributions from companies producing alcohol-based handrubs (Bode, Schülke, Ecolab, B Braun, Lysoform, Antiseptica, Dr Schumacher and Dr Weigert) to support the German national hand hygiene campaign (approximately Euros 60 000 between 2014 and 2015).
- Kalisvar Marimuthu declared membership of the National Infection Prevention and Control Committee of Singapore.

EXECUTIVE SUMMARY

Introduction

Health care-associated infections (HAI) are one of the most common adverse events in care delivery and both the endemic burden and the occurrence of epidemics of HAI are a major public health problem. HAI have a significant impact on morbidity, mortality and quality of life and present an economic burden at the societal level. However, a large proportion of these infections is preventable by effective infection prevention and control (IPC) measures (8-10).

Carbapenem-resistant gram-negative bacteria, namely, carbapenem-resistant Enterobacteriaceae (CRE) (for example, *Klebsiella pneumoniae*, *Escherichia coli*), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPsA), are a matter of national and international concern as they are an emerging cause of HAI that pose a significant threat to public health (1). These bacteria are difficult to treat due to high levels of antimicrobial resistance (AMR) and are associated with high mortality. Importantly, they have the potential for widespread transmission of resistance via mobile genetic elements (11).

Rationale for the development of CRE-CRAB-CRPsA guidelines

Since the publication of an expert consensus document on the core components for infection prevention and control by the World Health Organization (WHO) in 2009 (12), threats posed by epidemics, pandemics and AMR have become increasingly evident as ongoing universal challenges and they are now recognized as top priorities for action on the global health agenda. Effective IPC is the cornerstone of such action to control AMR and the spread of multidrug-resistant pathogens, such as CRE-CRAB-CRPsA. This is emphasized by the International Health Regulations (IHR), which identify effective IPC as a key strategy for dealing

with public health threats of international concern. More recently, the United Nations Sustainable Development Goals (SDGs) highlighted the importance of IPC as a contributor to safe, effective high-quality health service delivery, particularly those related to water, sanitation and hygiene (WASH) and quality and universal health coverage. In 2016, WHO released the updated *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13). These new guidelines form a key part of WHO strategies to prevent current and future threats, strengthen health service resilience and help combat AMR. During the guideline development process and the many detailed discussions by the Guideline Development Group (GDG) members, it became clear that the specific threat posed by infections due to CRE-CRAB-CRPsA required specific attention, including having clear, practical IPC guidelines on how best to manage this rapidly emerging problem. CRE-CRAB-CRPsA infections are particularly notable because they are associated with high morbidity and mortality, as well as the potential to cause outbreaks and contribute to the spread of resistance. Furthermore, it was recognized that colonization with CRE-CRAB-CRPsA precedes or is co-existent with CRE-CRAB-CRPsA infection almost universally. Thus, early recognition of CRE-CRAB-CRPsA colonization is likely to help identify patients most at risk of subsequent CRE-CRAB-CRPsA infection. This will also allow the earlier introduction of IPC measures in health care settings to prevent pathogen transmission to other patients and the hospital environment. For this reason, it was agreed that a key priority should be the development of WHO IPC guidelines specifically targeting the prevention and control of colonization and infection with CRE-CRAB-CRPsA in health care settings.

Objectives

The objectives of the guidelines are to provide:

- evidence-based recommendations on the early recognition and specific required IPC practices and procedures to effectively prevent the occurrence and control the spread of CRE-CRAB-CRPsA colonization and/or infection in acute health care facilities;
- an evidence-based framework to help inform the development and/or strengthening of national and facility IPC policies and programmes to control the transmission of CRE-CRAB-CRPsA in a variety of health care settings.

The recommendations included in these guidelines build upon the overarching IPC standards set by the WHO publication *Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)* and, in this context, they are meant to align with fundamental IPC principles and to strengthen their uptake.

Target audience

The CRE-CRAB-CRPsA guidelines are intended to support IPC improvement at the health care facility and national level, both in the public services and private sector. At the facility level, the main target audience is local IPC teams and/or professionals in charge of planning, developing and implementing local IPC programmes. This includes senior managers (for example, chief executive officers) and, ultimately, all health care workers providing patient care. At the national level, this document provides guidance primarily to policy-makers responsible for the establishment and monitoring of national IPC programmes and the delivery of AMR national action plans within ministries of health.

The guidelines are also relevant for national and facility safety and quality leads and managers, regulatory bodies and allied organizations, including academia, national IPC professional bodies, non-governmental organizations involved in IPC activity and civil society groups.

The guidelines focus primarily on acute health care facilities. However, the core principles and practices of IPC to be applied as a control measure against the emergence and spread of CRE-CRAB-CRPsA are common to any facility where health care is delivered. Therefore, these guidelines should also be implemented with some adaptations by primary

and long-term care facilities (LTCFs) as they develop and review their IPC programmes.

Although legal, policy and regulatory contexts may vary, these guidelines are relevant to both high- and low-resource settings.

Methods

The guidelines were developed following the methods outlined in the 2014 WHO *handbook for guideline development (14)*. The development process included six main stages: (1) identification of the PICO (Population/Participants, Intervention, Comparator, Outcome/s) question (an approach commonly used to formulate research questions); (2) performing a systematic review for the retrieval of the evidence; (3) developing an inventory of national and regional IPC action plans and strategic documents; (4) assessment and synthesis of the evidence; (5) formulation of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; and (6) writing of the guidelines and planning for the dissemination and implementation strategies.

The development of the guidelines involved the formation of four main groups to guide the process: the WHO Guideline Steering Group, the GDG, the Systematic Reviews Expert Group and the External Peer Review Group. The WHO Steering Group identified the primary critical outcomes and topics, formulated the research questions and identified the systematic review teams, the guideline methodologist and members of the GDG. The GDG included international experts in IPC and infectious diseases, public health, researchers and patient representatives, as well as country delegates and stakeholders from the six WHO regions.

The systematic review assessed the following research question: *What is an effective approach to preventing and controlling the acquisition of and infection with CR and/or CRAB and/or CRPsA among inpatients in health care facilities?* Studies with no time limit applied and conference abstracts from the last five years (2012-2016) were included. Search terms included three concepts: (1) carbapenemase/carbapenem resistance; (2) core IPC measures; and (3) CRE and/or CRAB and/or CRPsA (that is, CRE-CRAB-CRPsA) colonization and/or infection rates.

The CRE-CRAB-CRPsA literature review used the risk of bias criteria developed for the Cochrane Effective Practice and Organization of Care (EPOC) reviews. Based on the systematic reviews, the GDG formulated recommendations using the GRADE approach. Finally, the GDG identified research gaps and implications for research. Additionally, a review of the guidelines was conducted by the WHO Public Health Ethics Consultation Group and feedback was incorporated accordingly.

Recommendations

The 2016 *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)* provided an initial foundation for the development of the recommendations for the prevention and control of CRE-CRAB-CRPsA. The GDG evaluated the relevance of the core components, together with the evidence emerging from the new systematic review specifically on CRE-CRAB-CRPsA. It identified eight key recommendations that apply to the facility level and which can be used to improve the development of national policy on the prevention and control of CRE-CRAB-CRPsA transmission and infection across health sectors.

The eight recommendations are summarized in Table 1, including the strength of each recommendation and the quality of the supporting evidence. Of note, the numbered list of IPC recommendations included in the guidelines is not intended to be a ranking order of the importance of each recommendation. As countries and facilities implement the recommendations (or undertake actions to review and strengthen their existing IPC programmes), they may decide to prioritize specific components depending on the context, previous achievements and identified gaps, with the long-term aim to build a comprehensive approach as detailed across all eight recommendations.

Guideline implementation

The successful implementation of these guidelines is dependent on a robust implementation strategy and a defined and appropriate process of adaptation and integration into relevant regional, national and facility-level policies and strategies. These CRE-CRAB-CRPsA guidelines should be integrated with the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)* and the national action plans for AMR. Such IPC implementation is crucial for the achievement of strategic objective 3 of the AMR Global Action Plan adopted by all Member States at the World Health Assembly in 2015. Support by national decision-makers, key stakeholders, partner agencies and organizations is also critical to enable effective implementation and to address research gaps (as outlined in the guidelines), particularly in limited resource settings.

Table 1. Summary of recommendations for the prevention and control of CRE, CRAB and CRPsA

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
Recommendation 1: Implementation of multimodal IPC strategies		
<p>The panel recommends that multimodal IPC strategies should be implemented to prevent and control CRE-CRAB-CRPsA infection or colonization and that these should consist of at least the following:</p> <ul style="list-style-type: none"> • hand hygiene • surveillance (in particular, for CRE) • contact precautions • patient isolation (single room isolation or cohorting) • environmental cleaning 	<ul style="list-style-type: none"> • The evidence supporting this recommendation showed that multimodal strategies comprised of several elements implemented in an integrated way were used as the intervention in most studies. The use of multimodal strategies is also strongly recommended as the most effective approach to successfully implement IPC interventions in the 2016 <i>WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level</i>. • Most studies were from settings with a high prevalence of CRE-CRAB-CRPsA. Nevertheless, the GDG considered that the IPC principles outlined in this recommendation were equally valid in all prevalence settings. • While the control of large outbreaks was recognized to be very costly, these studies were all conducted in high-to-middle-income countries. Thus, there are concerns regarding the cost implications and the affordability of outbreak control in settings with limited resources. • Although the scope of the evidence review and this recommendation address acute care facilities, it is equally critical that all types of health care facilities apply similar IPC principles for the control of CRE-CRAB-CRPsA. • Implementing this recommendation may be complex in some health systems as it requires a multidisciplinary approach, including executive leadership, stakeholder commitment, coordination and possible modifications to workforce structure and process in some cases. Facility leadership should clearly support the IPC programme aimed at preventing the spread of CRE-CRAB-CRPsA by providing materials and organizational and administrative support through the allocation of a protected and dedicated budget, according to the IPC activity plan. Such an approach was considered to be consistent with Core component 1 in the <i>WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level</i>. • Good quality microbiological laboratory support is a very critical factor for an effective IPC programme and implementation of this recommendation. • Education/training and monitoring, auditing and feedback are critical to the success of a multimodal strategy. Emphasis should be placed on these when implementing multimodal interventions and their specific components, particularly in the context of an IPC programme. • Each component of the multimodal strategy included in this recommendation is also the focus of additional stand-alone recommendations. Remarks and details of each component are provided in the dedicated sections of the guidelines. 	<p><i>Strong recommendation, very low to low quality of evidence</i></p>

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
Recommendation 2: Importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA		
<p>The panel recommends that hand hygiene best practices according to the <i>WHO guidelines on hand hygiene in health care</i> should be implemented.</p>	<ul style="list-style-type: none"> • The evidence for the high beneficial impact of good hand hygiene compliance has been reviewed previously in sufficient detail and therefore the WHO recommendations on hand hygiene in health care should be followed (see <i>WHO guidelines on hand hygiene in health care</i>). Effective implementation strategies have been developed, tested and are now used worldwide. Practical approaches to implement these strategies at the facility level are described in the <i>WHO guide to implementation</i> and associated toolkit (http://www.who.int/infection-prevention/tools/hand-hygiene/). It is important to use these approaches and resources and adapt them to the local context. • Hand hygiene compliance and the appropriate use of alcohol-based handrub are very dependent on appropriate product placement and availability. Adequate resources are therefore necessary to ensure these features are met. • It is important to monitor hand hygiene practices through the measurement of compliance according to the approach recommended by WHO 	<p><i>Strong recommendation, very low quality of evidence.</i></p>
Recommendation 3: Surveillance of CRE-CRAB-CRPsA infection and surveillance cultures for asymptomatic CRE colonization		
<p>The panel recommends that:</p> <p>a) surveillance of CRE-CRAB-CRPsA infection(s) should be performed; and</p> <p>b) surveillance cultures for asymptomatic CRE colonization should also be performed, guided by local epidemiology and risk assessment. Populations to be considered for such surveillance include patients with previous CRE colonization, patient contacts of CRE colonized or infected patients and patients with a history of recent hospitalization in endemic CRE settings.</p>	<p><i>Surveillance for CRE-CRAB-CRPsA infection/s</i></p> <ul style="list-style-type: none"> • Surveillance of CRE-CRAB-CRPsA infection is essential (that is, clinical monitoring of signs and symptoms of infection, as well as laboratory testing and identification of carbapenem resistance among potential CRE-CRAB-CRPsA isolates from clinical samples). • Laboratory testing and identification of carbapenem resistance among potential CRE-CRAB-CRPsA isolates may not be available or routine in some settings (for example, LMICs), but should now be considered as routine in all microbiology laboratories to ensure the accurate and timely recognition of CRE-CRAB-CRPsA. Surveillance of CRE-CRAB-CRPsA infection allows a facility to define the local epidemiology of CRE-CRAB-CRPsA, identify patterns and better allocate resources to areas of need. <p><i>Surveillance cultures for asymptomatic CRE colonization</i></p> <ul style="list-style-type: none"> • Information regarding a patient's CRE colonization status does not (yet) constitute routine standard of care provided by health systems. However, in an outbreak or situations where there is a high risk of CRE acquisition (for example, possible contact with a CRE colonized/infected patient or endemic CRE prevalence), CRE colonization status should be known. Information regarding CRE colonization status could potentially have important beneficial effects on the empiric antibiotic treatment plan for screened patients who subsequently develop potential CRE infection. • This recommendation should always apply in an outbreak situation and also, ideally in endemic settings. However, the GDG extensively discussed the best approach to surveillance cultures of asymptomatic CRE colonization in a high CRE prevalence (endemic) setting, particularly in low-income settings where resources and facilities are limited and the actual appropriate improvement of IPC infrastructures and best practices may deserve prioritization over surveillance. The GDG agreed that there is no one single best approach, but instead the decision should be guided by the local epidemiology, resource availability and the likely clinical impact of a CRE outbreak. 	<p><i>Strong recommendation, very low quality of evidence.</i></p>

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
	<ul style="list-style-type: none"> • Surveillance screening should be based on patient risk assessment (that is, patients who are at a higher risk of CRE acquisition and the potential risk that these patients pose to others in their environment). The following patient risk categories should be considered: <ul style="list-style-type: none"> – patients with a previously documented history of CRE colonization or infection; – epidemiologically-linked contacts of newly-identified patients with CRE colonization or infection (this could include patients in the same room, unit or ward); – patients with a history of recent hospitalization in regions where the local epidemiology of CRE suggests an increased risk of CRE acquisition (for example, hospitalization in a facility with known or suspected CRE); – based on the epidemiology of their admission unit, patients who may be at increased risk of CRE acquisition and infection (for example, immunosuppressed patients and those admitted to intensive care units (ICUs), transplantation services or haematology units, etc.). • Surveillance culture of feces or rectal swabs or perianal swabs (in rare clinical situations, for example neutropenic patients) were considered the best methods in descending order of accuracy. However, it was recognized that rectal swabs were often considered to be the most suitable clinical specimen in many health care situations for practical reasons. A minimum of one culture was considered necessary, although additional cultures may increase the detection rate. • Surveillance cultures should be performed as soon as possible after hospital admission or risk exposure, processed and reported promptly to avoid delays in the identification of CRE colonization. It was not possible to identify the optimal frequency of testing after admission due to limited and heterogeneous evidence; however, several studies included a regular screening timetable (for example, weekly or twice-weekly) following the initial on-admission screening. <p><i>Additional remarks</i></p> <ul style="list-style-type: none"> • Recommended surveillance activities could involve potential harms or unintended consequences for the patient with ethical implications (for example, a sense of cultural offensiveness or stigma associated with obtaining a rectal swab or providing a stool (fecal) specimen or discrimination of colonized or infected patients). Mitigation measures were included in the “values and preferences” section, as well as important references in this field. • The evidence available on surveillance cultures for CRAB and CRPsA colonization concluded that it was not sufficiently relevant to extend the recommendation to these two microorganisms. In particular, the value of active surveillance for CRAB and CRPsA colonization, while sometimes beneficial, depends on the clinical setting, epidemiological stage (for example, outbreak) and body sites. Optimal microbiological methods for CRAB and CRPsA surveillance cultures for colonization require further research. 	

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
Recommendation 4: Contact precautions		
<p>The panel recommends that contact precautions should be implemented when providing care for patients colonized or infected with CRE-CRAB-CRPsA.</p>	<ul style="list-style-type: none"> • “Contact precautions” include: (1) appropriate patient placement; (2) use of personal protective equipment, including gloves and gowns; (3) limiting transport and movement of patients; (4) use of disposable or dedicated patient-care equipment; and (5) prioritizing cleaning and disinfection of patient rooms (see Glossary). The use of patient isolation is addressed in Recommendation 5. • Contact precautions should be considered as a standard of care for patients colonized or infected with CRE-CRAB-CRPsA in the vast majority of health systems. • Health care worker education regarding the principles of IPC and monitoring of contact precautions is crucial. • In some circumstances, depending on the individual risk assessment of some patients, pre-emptive isolation/cohorting and the use of contact precautions may be necessary until the results of surveillance cultures for CRE-CRAB-CRPsA are available. This was considered to be an important consideration for patients with a history of recent hospitalization in regions where the local epidemiology of CRE suggests an increased risk of CRE acquisition (see Recommendation 3: patient risk categories). • Clear communication regarding a patient’s colonization/infection status is important, that is, flagging the medical chart. • Applying contact precautions could involve potential unintended consequences for the patient (for example, patient frustration or discomfort during treatment with contact precautions). Mitigation measures were included in the “values and preferences” section, as well as important references in this field. Furthermore, it was recognized that occupational health issues associated with the use of some personal protective equipment (for example, latex gloves) should also be taken into consideration for health care workers. 	<p><i>Strong recommendation, very low to low quality of evidence</i></p>
Recommendation 5: Patient isolation		
<p>The panel recommends that patients colonized or infected with CRE-CRAB-CRPsA should be physically separated from non-colonized or non-infected patients using (a) single room isolation or (b) by cohorting patients with the same resistant pathogen.</p>	<ul style="list-style-type: none"> • It was noted that there is an inconsistency in the use of the terms “isolation” and “cohorting” in some settings. For the purposes of these guidelines, the following standard definitions were used: <ul style="list-style-type: none"> – Isolation: patients should be placed in single-patient rooms (preferably with their own toilet facilities) when available. When single-patient rooms are in short supply, patients should be cohorted. – Cohorting: the practice of grouping together patients who are colonized or infected with the same organism to confine their care to one area and prevent contact with other patients. • The purpose of isolation is to separate colonized/infected patients from non-colonized/non-infected patients. • The strongest evidence for the effectiveness of patient isolation was among patients with CRE colonization/infection. It was the panel’s view that this recommendation was also likely to be effective to prevent cross-transmission among patients colonized or infected with CRAB and/or CRPsA. 	<p><i>Strong recommendation, very low to low quality of evidence</i></p>

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
	<ul style="list-style-type: none"> • Patient isolation could be associated with some potential harms and negative unintended consequences (for example, social isolation and psychological consequences, such as depression or anxiety). Mitigation measures were included in the “values and preferences” section, as well as important references in this field. The preference is for colonized/infected patients to be managed in single rooms where possible. Cohorting is reserved for situations where there are insufficient single rooms or where cohorting of patients colonized or infected with the same pathogen is a more efficient use of hospital rooms and resources. Patient isolation should always apply in an outbreak situation. Isolation in single rooms may not be possible in endemic situations, particularly in low-income settings where resources and facilities are limited. • There is evidence and clinical experience to support the use of dedicated health care workers to exclusively manage isolated/cohorted patients, although there may be some feasibility issues. 	<p><i>Strong recommendation, very low to low quality of evidence</i></p>
<p>Recommendation 6: Environmental cleaning</p>		
<p>The panel recommends that compliance with environmental cleaning protocols of the immediate surrounding area (that is, the “patient zone”) of patients colonized or infected with CRE-CRAB-CRPsA should be ensured.</p>	<ul style="list-style-type: none"> • The optimal cleaning agent for environmental cleaning protocols of the immediate surrounding area of patients colonized or infected with CRE-CRAB-CRPsA has not yet been defined. Three CRE-CRAB-CRPsA studies used hypochlorite (generally a concentration of 1000 parts per million [ppm]) as an agent to undertake environmental cleaning. • Appropriate educational programmes for hospital cleaning staff are crucial to achieve good environmental cleaning. • The use of multimodal strategies to implement environmental cleaning was considered essential. This includes institutional policies, structured education and monitoring compliance with cleaning protocols. • Assessment of cleaning efficacy by performing environmental screening cultures for CRE-CRAB-CRPsA was noted to be worthwhile in some settings (Recommendation 7). • In some outbreak situations, temporary ward closures were necessary to allow for enhanced cleaning. 	<p><i>Strong recommendation, very low quality of evidence</i></p>
<p>Recommendation 7: Surveillance cultures of the environment for CRE-CRAB-CRPsA colonization/contamination</p>		
<p>The panel recommends that surveillance cultures of the environment for CRE-CRAB-CRPsA may be considered when epidemiologically indicated.</p>	<ul style="list-style-type: none"> • Correlation of environmental surveillance culture results to the rates of patient colonization/infection with CRE-CRAB-CRPsA should be undertaken with caution and depends on an understanding of the local clinical epidemiological data and resources. • Based on expert opinion (and only limited available data), surveillance cultures of the general environment were considered most relevant to CRAB outbreaks. Outbreaks of CRPsA colonization/infection among patients appeared to be more commonly associated with environmental CRPsA contamination involving water and waste-water systems, such as sinks and taps (faucets). 	<p><i>Conditional recommendation, very low quality of evidence</i></p>

Formal recommendation	Key remarks from the GDG*	Strength of recommendation and quality of evidence**
Recommendation 8: Monitoring, auditing and feedback		
The panel recommends monitoring, auditing of the implementation of multimodal strategies and feedback of results to health care workers and decision-makers.	<ul style="list-style-type: none"> Monitoring, auditing and feedback of IPC interventions are a fundamental component of any effective intervention and especially important for strategies to control CRE-CRAB-CRPsA. Appropriate training of staff who undertake monitoring and feedback of results is crucial. All components of the multimodal strategy intervention should be regularly monitored, including hand hygiene compliance. Monitoring, auditing and feedback of multimodal strategies are a key component of all IPC educational programmes. IPC monitoring should encourage improvement and promote learning from experience in a non-punitive institutional culture, thus contributing to better patient care and quality outcomes. 	<i>Strong recommendation, very low to low quality of evidence</i>

CRE: carbapenem-resistant Enterobacteriaceae; CRAB: carbapenem-resistant *Acinetobacter baumannii*; CRPsA; carbapenem-resistant *Pseudomonas aeruginosa*; HAI: health care-associated infection/s; AMR: antimicrobial resistance; IPC: infection prevention and control; GDG: Guidelines Development Group.

* More detailed remarks can be found in each section dedicated to specific recommendations.

** Quality of evidence was classified as high, moderate, low, or very low according to factors that include the study methodology, consistency and precision of the results, and directness of the evidence (15).

1. BACKGROUND

Health care-associated infections (HAI) are one of the most common adverse events in care delivery and both the endemic burden and the occurrence of epidemics are a major public health problem. HAI have a significant impact on morbidity, mortality and quality of life and represent an economic burden at the societal level. However, a large proportion of HAI are preventable and there is a growing body of evidence to help raise awareness of the global burden of harm caused by these infections (8, 9), including strategies to reduce their spread (10).

Infection prevention and control (IPC) is a universally relevant component of all health systems and affects the health and safety of both people who use services and those who provide them. Driven by a number of emerging factors in the field of global public health, there is a need to support Member States in the development and strengthening of IPC capacity to achieve resilient health systems, both at the national and facility levels. These factors are closely related to the aftermath of recent global public health emergencies of international concern, such as the 2013-2015 Ebola virus disease outbreak and the current review of the International Health Regulations (IHR), together with the World Health Organization (WHO) action agenda for antimicrobial resistance (AMR) and its lead role in implementing the associated Global Action Plan.

There is a worldwide consensus that urgent action is needed by all Member States to prevent and control the spread of antimicrobial-resistant microorganisms. Following the endorsement of the Global Action Plan to Combat AMR, all Member States committed to develop their national action plans by the World Health Assembly 2017, with the inclusion of IPC as one of the five objectives. International experts, including the AMR Strategic

and Technical Advisory Group highlighted the urgent need for WHO to have a strong leadership role, including the development of guidelines and implementation packages on targeted procedures to contain the spread of specific microorganisms.

In a recent formal WHO meeting for the development of guidelines on core components of IPC programmes, experts recommended that priority should be given to carbapenem-resistant gram-negative bacteria, a problem of emerging concern, which poses a significant public health threat in both high- and low-to-middle-income countries. No specific international evidence-based guidelines are currently available on IPC best practices and procedures to prevent and control carbapenem-resistant gram-negative bacteria and the experts considered that there is an urgent need for such guidance.

1.1 Epidemiology and burden of disease of carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPsA)

Carbapenem-resistant gram-negative bacteria, namely, CRE (for example, *Klebsiella pneumoniae*, *Escherichia coli*), CRAB and CRPsA, are an emerging cause of HAI that pose a significant threat to public health (1). These bacteria are difficult to treat due to high levels of AMR and are associated with high mortality. Importantly, they have the potential for widespread transmission of resistance via mobile genetic elements (11). While some strains are innately resistant to carbapenems, others contain mobile genetic elements (for example, plasmids, transposons) that result in the production of carbapenemase enzymes (carbapenemases), which break down most beta-lactam antibiotics, including carbapenems. Frequently, these carbapenemase-

producing (CP) genes are co-located on the same mobile element with other resistance genes, which can result in co-resistance to many other antibiotic drug classes (1-3). Notably, these carbapenemase-encoding mobile genetic elements can be readily transmitted between intestinal bacteria (11). Thus, while carbapenem-resistant strains of these pathogens are frequently CP (CP-Enterobacteriaceae [CPE], CP-*A. baumannii* and CP-*P. aeruginosa*), they may have other carbapenem resistance mechanisms that make them equally difficult to treat and manage clinically. For this reason, IPC actions should focus on all strains of CRE, CRAB and CRPsA, regardless of their resistance mechanism. Adequate IPC measures are essential in both outbreak and endemic settings (4).

During the last decade, there has been an alarming global increase in the incidence and prevalence of carbapenem-resistant gram-negative bacteria. In Europe, the population-weighted mean percentage of invasive isolates resistant to carbapenems in 2015 was 17.8% for *P. aeruginosa*, 8.1% for *K. pneumoniae* and 0.1% for *E. coli* (16). Increasing trends of invasive isolates of carbapenem-resistant *K. pneumoniae* were observed from 2012-2015, particularly in Croatia, Portugal, Romania and Spain. Countries with the highest rates of carbapenem-resistant *K. pneumoniae* included Greece, Italy and Romania (16). Among 27 countries reporting resistance results for more than 10 *A. baumannii* isolates, 12 had percentage rates of carbapenem resistance of 50% or higher (17). According to a point prevalence survey of HAI and antimicrobial use in Europe, 18 of 28 countries reported CRE and three countries reported HAI with more than 20% of resistant isolates, with the highest percentage (39.9%) in Greece (18). In the United States of America (USA), 49.5% of *A. baumannii*, 19.2% of *P. aeruginosa*, 7.9% of *K. pneumoniae* and 0.6% of *E. coli* invasive isolates submitted to the National Healthcare Safety Network were resistant to carbapenems in 2014 (19).

According to the 2014 global report on AMR, carbapenem-resistant *K. pneumoniae* were reported from all WHO regions, although only 37% of Member States could provide data (20). This included two regions with some countries reporting up to 50% of *K. pneumoniae* resistant to carbapenems. There was some variation in the reported geographical spread of CRE and carbapenemase genes. Identified high-prevalence

areas and countries included Greece, Israel, Italy, North Africa, Turkey, the USA and the Indian subcontinent (20). In particular, a rapid international spread of *K. pneumoniae* CPE due to the clonal expansion of certain strains (that is, clonal complex 258) has been observed since its discovery in the USA in 1996 (21). Of notable concern, human isolates harbouring the MCR-1 gene, which confers resistance to colistin, a powerful antimicrobial considered as the last line of defense against CRE, have been reported recently across hospitals in the Asia/Pacific region, Europe, Latin America and North America (22).

Carbapenem-resistant gram-negative bacteria are highly transmissible and have a high potential to cause outbreaks in health care settings. Following the worldwide dissemination of CRE, a range of outbreaks have occurred across different global regions in acute care settings, as well as in long-term care (23-29). In Europe, several large hospital outbreaks have occurred in the Czech Republic, France, Germany, Greece, Italy, Spain and the United Kingdom, particularly of carbapenem-resistant *K. pneumoniae* (30). A comparison of the epidemiological stages (that is, sporadic cases, hospital outbreaks, regional spread, endemicity) of CPE and CRAB in Europe in 2013 suggested that CRAB had a broader dissemination (31). Outbreaks of CRAB have been found to be mainly transmitted via the hands of health care workers, contaminated equipment and the health care environment (32, 33). Similar outbreaks of CRPsA have also been reported, including an association with contaminated medical devices (3, 34, 35).

Outbreaks of carbapenem-resistant gram-negative bacteria have been found to be highly costly. For example, a cost evaluation of a CPE outbreak occurring across five hospitals in the United Kingdom estimated a cost of approximately 1.1 million euros over 10 months (36).

Mortality and clinical outcomes associated with carbapenem-resistant gram-negative bacteria can be severe. A meta-analysis evaluating the number of deaths attributable to CRE infections found that 26-44% of deaths across seven studies were attributable to carbapenem resistance. Among these, the number of deaths among CRE-infected patients was two-fold higher than those attributed to carbapenem-susceptible Enterobacteriaceae (37). An observational study in seven Latin American countries found that the attributable mortality

was significantly higher in patients with CPE bloodstream infections than those where the pathogens were carbapenem-susceptible (38). The European Centre for Disease Control and Prevention also reported mortality ranging from 30-70% and above 50% in patients with CRE bloodstream infections (30). One meta-analysis found that patients with CRPsA bacteremia had 3.07 higher odds of death compared to those with carbapenem-susceptible *P. aeruginosa* bacteremia (95% confidence interval [CI]: 1.60-5.89) (39). Another meta-analysis found a significant association between carbapenem resistance and mortality among *A. baumannii* patients (adjusted odds ratio: 2.49; 95% CI: 1.61-3.84) (40).

1.2 Rationale for developing recommendations to prevent and control colonization and/or infection with CRE-CRAB-CRPsA

The Guidelines Development Group (GDG) was particularly concerned about the burden of illness associated with infection and colonization due to CRE-CRAB-CRPsA and considered the development of IPC guidelines as an urgent priority to stop the spread of these microorganisms. The reasons for this included:

- CRE-CRAB-CRPsA infection is associated with high morbidity and mortality (see section 1.1);
- CRE-CRAB-CRPsA transmission is associated with a high potential to cause outbreaks (see section 1.1);
- one key mechanism of carbapenem resistance among CRE-CRAB-CRPsA is a mobile resistance gene that can be readily transmitted between various intestinal bacterial species, resulting in an additional acquisition of resistance (see section 1.1);
- long-term consequences of CRE-CRAB-CRPsA acquisition can be severe, that is, the duration of colonization (and subsequent risk for infection) can be lengthy, which can also have potentially substantial psychological and management implications for colonized patients (41);
- there is currently a lack of effective treatments available for (1) patients infected with CRE-CRAB-CRPsA and (2) those colonized with CRE-CRAB-CRPsA (that is, de-colonization);
- CRE-CRAB-CRPsA are highlighted as the top critical priority pathogens in the WHO publication *Prioritization of pathogens to guide discovery, research and development of new*

antibiotics for drug-resistant bacterial infections (42);

- the cost impact of CRE-CRAB-CRPsA colonization/infection on health care systems is high and potentially threatening to the stability of the health care system in both the short and long term; IPC is critical to control these costs and resource implications (36).

The GDG also emphasized that the focus on the prevention and control of CRE-CRAB-CRPsA should be seen in the context of the broader priority to implement effective IPC for the prevention of all HAI and the strengthening of health care service delivery. Threats posed by epidemics, pandemics and AMR have become increasingly evident as ongoing universal challenges and they are now recognized as top priorities for action on the global health agenda. Effective IPC is the cornerstone of such action. This is emphasized by the IHR, which identify effective IPC as a key strategy for preparedness and response to public health threats of international concern. Furthermore, the United Nations Sustainable Development Goals (SDG) highlight the importance of IPC as a contributor to safe and effective high-quality health service delivery, particularly those related to water, sanitation and hygiene (WASH) and quality universal health coverage.

The 2016 evidence-based *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13) and key principles of standard and transmission-based precautions (5) provide a foundation for the development of an effective IPC programme and related practices. Efforts should be made to implement these core components and key principles. The recommended best practices and procedures to prevent and control CRE-CRAB-CRPsA included in this guideline strongly build upon these core component recommendations.

Although not included in the scope of these guidelines, antimicrobial stewardship or “coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration” also play an important role in the prevention of CRE-CRAB-CRPsA and have been referenced in other CRE-CRAB-CRPsA guidance documents (43, 44). Antimicrobial stewardship interventions have been

linked to decreased rates of antimicrobial resistance and improved patient outcomes (43).

1.3 Scope and objectives of the guidelines

The overarching question that defines the purpose of these CRE-CRAB-CRPsA guidelines is:

What is an effective approach to preventing and controlling the acquisition of and infection with CRE-CRAB-CRPsA among inpatients in health care facilities?

Target audience

The CRE-CRAB-CRPsA guidelines are intended to support IPC improvement at the health care facility and national level, both in the public and private sectors. At the facility level, the main target audience are the IPC leads and focal persons (that is, professionals in charge of planning, developing and implementing local facility IPC programmes) and senior managers (for example, chief executive officers) and, ultimately, all health care workers providing patient care. At the national level, this document provides guidance primarily to policy-makers responsible for the establishment and monitoring of national IPC programmes and the delivery of AMR national action plans within ministries of health.

The guidelines are also relevant for national and facility safety and quality leads and managers, regulatory bodies and allied organizations, including academia, national IPC professional bodies, non-governmental organizations involved in IPC activity and civil society groups.

The guidelines focus primarily on acute health care facilities. However, the core principles and practices of IPC to be applied as a countermeasure to the emergence and spread of CRE-CRAB-CRPsA, are common to any facility where health care is delivered. Therefore, the key principles of these guidelines should also be implemented by primary care and LTCFs as they develop and review their IPC programmes while taking the local setting into account.

While legal, policy and regulatory contexts may vary, these guidelines are relevant to both high- and low-resource settings.

Objectives and scope of the guidelines

The primary objective of these guidelines is to provide evidence- and expert consensus-based recommendations on the early recognition and specific required IPC practices and procedures to effectively prevent the occurrence and control the spread of CRE-CRAB-CRPsA colonization and/or infection in acute health care facilities. They are also intended to provide an evidence-based framework to inform the development and/or strengthening of national and facility IPC policies and programmes to control the transmission of CRE-CRAB-CRPsA in a variety of health settings. The recommendations can be adapted to the local context based on information collected ahead of implementation and thus influenced by available resources and public health needs.

The CRE-CRAB-CRPsA guidelines are based on the foundation provided by the 2016 *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)*, with the aim to specifically describe best practices and procedures to prevent and control the spread of CRE-CRAB-CRPsA in health care. The GDG evaluated the relevance of these components, together with the evidence emerging from systematic reviews, and developed the recommendations listed in this document, which are meant to align with fundamental IPC principles and to strengthen their uptake.

It is essential to note that the numbered list of IPC recommendations included in these guidelines are by no means intended to be a ranking order of the importance of each component. As countries and facilities implement the recommendations (or undertake actions to review and strengthen their existing IPC programmes), they may decide to prioritize specific components depending on the context, previous achievements and identified gaps, with the long-term aim to build a comprehensive approach as detailed across all eight recommendations in the guidelines.

2. METHODS

2.1 WHO guidelines development process

The guidelines were developed according to the requirements described in the *WHO handbook for guideline development (14)* and a planning proposal approved by the WHO Guidelines Review Committee.

The development process included six main stages: (1) identification of the PICO (Population/ Participants, Intervention, Comparator, Outcomes) question, an approach commonly used to formulate research questions; (2) the conduct of two systematic reviews for the retrieval of the evidence using a standardized methodology; (3) development of an inventory of national and regional IPC action plans and strategic documents; (4) assessment and synthesis of the evidence; (5) formulation of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach; and (6) writing of the guidelines and planning for the dissemination and implementation strategies.

The development process included also the participation of four main groups that helped guide and greatly contributed to the overall process. The roles and functions are described herein.

WHO Guideline Steering Group

The WHO Guideline Steering Group was chaired by the coordinator of the WHO IPC Global Unit in the Department of Service Delivery and Safety. Participating members were also from the Antimicrobial Resistance Secretariat, the Water, Sanitation and Hygiene (WASH) Unit, and the IPC focal points at the WHO Regional Office for the Americas and the Regional Office for the Eastern Mediterranean.

The Steering Group contributed to the initial planning document for the development of the guidelines, identified the primary critical outcomes and topics and formulated the research questions. The Group identified systematic review teams, the guideline methodologist, the members of the GDG and the external peer reviewers. The GDG chair and the IPC Global Unit coordinator supervised the evidence retrieval, syntheses and analysis, organized the GDG meetings, prepared or reviewed the final guideline document, managed the external peer reviewers' comments and the guideline publication and dissemination. The members of the WHO Steering Group are presented in the Acknowledgements section.

WHO Guidelines Development Group

The WHO Guideline Steering Group identified 24 external experts, country delegates and stakeholders from the six WHO regions to constitute the GDG (also referred to as “the panel”). This was a diverse group representing various professional and stakeholder groups, such as IPC, clinical microbiologists, epidemiologists, public health and infectious disease specialists and researchers. Geographical representation and gender balance were also considerations when selecting GDG members. Members of this group appraised the evidence that was used to inform the recommendations, advised on the interpretation of the evidence, formulated the final recommendations while taking into consideration the 2016 *WHO Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)*, and reviewed and approved the final CRE-CRAB-CRPsA guideline document. The GDG members are presented in the Acknowledgements section.

External Peer Review Group

The Group was composed of five technical experts with high-level knowledge and experience in IPC, AMR, patient safety and health management, including field implementation, and a patient representative. The Group was geographically balanced to ensure views from both high- and low- and middle-income countries (LMICs); no member declared a conflict of interest. The primary focus was to review the final guideline document and identify any inaccuracies or errors and comment on technical content and evidence, clarity of language, contextual issues and implications for implementation. The Group ensured that the guideline decision-making processes incorporated values and preferences of end-users, including health care professionals and policy-makers. Of note, it was not within the remit of this Group to change the recommendations formulated by the GDG. All reviewers agreed with each recommendation and some suggested selected editing changes. The members of the WHO External Review Peer Group are presented in the Acknowledgements section.

Research question/PICO

The specific PICO question was developed by the WHO secretariat based upon feedback and discussion by the GDG responsible for the 2016 *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)*. The main research question underlying this work was:

What is an effective approach to preventing and controlling the acquisition of and infection with CRE and/or CRAB and/or CRPsA among inpatients in health care facilities?

For each intervention, the PICO question was formulated as follows:

Population: patients of any age admitted to an inpatient health care facility including acute health care facilities, secondary or tertiary health care facilities, LTCFs and rehabilitation centres.

Intervention: any IPC measure (single measures or part of a multimodal strategy) implemented to contain CRE-CRAB-CRPsA transmission in the inpatient setting (for example, screening policies, contact precautions, hand hygiene interventions, environmental cleaning). We excluded studies exclusively dealing with bacterial isolate collection and identification, susceptibility testing, basic

science or animal models, treatment, prophylaxis, stewardship, or duodenoscopes/endoscopes.

Comparator: regular care practices with no specific IPC intervention.

Outcome: CRE-CRAB-CRPsA transmission within the inpatient facility measured by the incidence or prevalence of acquisition of colonization and/or infection with these organisms

2.2 Evidence identification and retrieval

According to the guidelines development plan approved by the WHO Guidelines Review Committee, a literature systematic review and an inventory of national and regional IPC action plans and strategic documents were conducted.

Literature systematic review

The systematic review followed the guidelines development plan approved by the WHO Guidelines Review Committee as well as the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (45).

Search strategy

The following databases were searched:

1. MEDLINE
2. Excerpta Medica Database
3. Cumulative Index to Nursing and Allied Health Literature
4. Global Index Medicus
5. Cochrane Library
6. Outbreak Database

Abstracts from the following international conference were also retrieved:

- Interscience Conference on Antimicrobial Agents and Chemotherapy and the American Society of Microbiology Microbe;
- European Congress of Clinical Microbiology and Infectious Diseases;
- Infectious Diseases Society of America Annual Scientific Meeting (ID-Week);
- International Conference on Prevention and Infection Control.

No time delimiters were used for the study selection, although conference abstract searches were restricted to the last five years (2012-2016). Languages included were English, French, German, Italian, Portuguese and Spanish. The search terms used were adapted to each database, but always based on a combination of three concepts:

1. carbapenemase/carbapenem resistance;
2. core IPC measures;
3. CRE and/or CRAB and/or CRPsA (CRE-CRAB-CRPsA) colonization and/or infection rates (that is, primary outcomes).

All steps of the systematic review concerning references retrieved from electronic databases were performed using the DistillerSR® systematic review software (Evidence partners, Ottawa, Canada). References retrieved from conferences were manually screened using the same inclusion/exclusion criteria. Removal of duplicates was performed before title and abstract screening using Endnote and the algorithm provided by the Distiller SR® software or removed manually.

Screening and data extraction

Using a standardized screening form, two reviewers reviewed all titles and abstracts retrieved from electronic databases and conference abstract sites. Disagreements between reviewers were resolved by discussion and a third reviewer as necessary. Studies were not considered when the title and abstract clearly indicated that the study did not meet the inclusion criteria (see PICO question above). If a study passed the title screening, but an abstract was not available, it was passed to the full-text screening level. If a report of the same study was duplicated in several records, the most recent peer-reviewed publication was included.

Full-text eligibility of all studies was independently conducted by two reviewers with reasons for exclusion annotated and tracked in Distiller (for example, “not about CRE-CRAB-CRPsA”). The primary reason for excluding studies was if the article did not meet the defined eligibility criteria (see PICO question above). Conflicts and uncertainties about whether to include or exclude a reference were discussed with another investigator of the team until consensus was reached.

Two reviewers independently performed data extraction of all included studies using a standardized data extraction form and any uncertainties about extracted data were discussed with the team.

Risk of bias assessment and evaluation of the evidence

All included studies were assessed against design-specific Effective Practice and Organization of Care (EPOC) entry and quality criteria

(<http://epoc.cochrane.org/epoc-specific-resources-review-authors>). Eligible EPOC study designs included randomized controlled trials, non-randomized controlled trials, controlled before-after and interrupted time series (ITS) studies with sufficient data to statistically assess before-after trends. When studies appeared to be potentially of EPOC standard, but there were insufficient published data to be certain, study authors were contacted to seek additional relevant information. Based on both the published data and the authors’ responses to the data request (as well as additional data analyses as needed), these studies were again assessed as to whether they were of EPOC or non-EPOC standard.

For potential ITS studies, the following four entry criteria were deemed necessary for a study to be classified as EPOC.

1. Clearly defined time points when the intervention(s) occurred.
2. At least three data points before the main intervention and three after.
3. Objective measurement of performance/provider behaviour of health/patient outcome(s) in a clinical situation (for example, CRE-CRAB-CRPsA detection in clinical cultures and/or screening swabs).
4. Relevant and interpretable data presented or obtainable. Preferred results included change in slope (that is, the trend in pre- compared to post-intervention periods) and level (that is, the immediate change after intervention implementation) in outcome prevalence or incidence.

The risk of bias among ITS studies was assessed using the ITS-specific Cochrane checklist including:

- intervention independent of other changes;
- shape of the intervention effect pre-specified;
- intervention unlikely to affect data collection;
- knowledge of the allocated interventions adequately blinded during the study;
- incomplete outcome data adequately addressed;
- study free from selective outcome reporting;
- study free from other risks of bias.

For EPOC-compatible studies, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

(<http://www.gradeworkinggroup.org/#pub>)

evidence profiles were created assessing:

1. study limitations;
2. inconsistency of results;

3. indirectness of evidence;
4. likelihood of publication bias;
5. number of participants;
6. quality.

Risk of bias assessments using the EPOC framework were conducted by two reviewers. Disagreements were resolved by consensus or consultation with the project's senior author and/or methodologist if no agreement could be reached. Studies not meeting the EPOC study design criteria ("non-EPOC studies") were not formally assessed and their quality was considered very low.

An evaluation of the overall body of the evidence was conducted using the GRADE system and according to specific outcomes, including a synthesis of results and quality of evidence assessment. Evidence was synthesized descriptively. It was not possible to perform a meta-analysis due to the wide range of intervention packages and outcomes assessed and a large degree of heterogeneity in study designs and methods used in the included studies. Quality of evidence was assessed in terms of study limitations, consistency and precision of results, the directness or applicability of summary estimates, and the risk of publication bias (46, 47). It was classified as high, moderate, low or very low according to these factors (15).

Inventory of national and regional IPC action plans and strategic documents

A methodology and data capture approach was developed for the inventory to identify, record and analyse regional and national documents addressing guidelines related to the management of CRE-CRAB-CRPsA infections and/or colonization, including a web search and expert consultation. The approach covered all six WHO regions (African Region, Region of the Americas, Eastern Mediterranean Region, European Region, South-East Asia Region and the Western Pacific Region). WHO regional focal points and GDG members were requested to provide input on existing documents from countries and regional offices. For documents with no existing translation in English, French, Spanish, German, Italian or Portuguese, contacted experts were asked to summarize the key points presented in the documents.

A summary of the inventory's findings is reported in Appendix 2.

Evidence appraisal and development of recommendations by the GDG

The results of the systematic review and regional inventory were presented at a GDG meeting held on 1-2 March 2017. The standardized methodology including the PICO question, GRADE framework and EPOC criteria were described. The GDG also evaluated the relevance of the 2016 *WHO Guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13) as a foundation for the development of these recommendations for the prevention and control of CRE-CRAB-CRPsA.

Recommendations were then formulated by the GDG based on the quality of the evidence, the balance between benefits and harms, values and preferences (for example, those of patients, health care workers, and policy-makers), resource implications (for example, at the national and facility level) and acceptability and feasibility. These were assessed through discussion among members of the GDG. The strength of recommendations was rated as either "strong" (the panel was confident that the benefits of the intervention outweighed the risks) or "conditional" (the panel considered that the benefits of the intervention probably outweighed the risks). For some recommendations, the GDG decided that the strength of the recommendation should be strong despite limited available evidence and its very low to low quality. These decisions were based on consideration of the magnitude of effects reported in the included studies and expert opinion consensus. The methodologist provided guidance to the GDG in formulating the wording and strength of the recommendations. Full consensus (100% agreement) was achieved for the text and strength of each recommendation.

The draft chapters of the guidelines containing the details of the recommendations were then prepared by the IPC Global Unit team and circulated to the GDG members for final approval and/or comments. All relevant suggested changes and edits were incorporated in a second draft. The second draft was then edited and circulated to external peer reviewers and the draft document was revised to address all relevant comments. Based on the reviewers' comments, the discussion was also expanded in some cases after the main GDG meeting via email or teleconferences. When this was necessary, feedback and final approval

was gathered from all GDG members. Additionally, a review of the guidelines was conducted by the WHO Public Health Ethics Consultation Group. The group recommended greater discussion of potential harms (for example, psychological suffering among patients identified as colonized or infected), unintended consequences (for example, discrimination) with ethical implications and potential mitigation measures. To address this feedback, suggestions from the reviewers were added. Furthermore, key principles and lessons from guidance on ethical considerations for other infectious diseases were assessed and incorporated accordingly.

3. EVIDENCE-BASED RECOMMENDATIONS ON MEASURES FOR THE PREVENTION AND CONTROL OF CRE-CRAB-CRPsA

3.1 Recommendation 1: Implementation of multimodal infection prevention and control strategies

The panel recommends that multimodal IPC strategies should be implemented to prevent and control CRE-CRAB-CRPsA infection or colonization and that these should consist of at least the following:

- hand hygiene
- surveillance (particularly for CRE)
- contact precautions
- patient isolation (single room isolation or cohorting)
- environmental cleaning

(Strong recommendation, very low to low quality of evidence)

Rationale for the recommendation

- Multimodal strategies comprising several elements were used as the intervention in most studies. The recommendation includes those elements included in the reviewed studies that were most strongly supported by evidence and were implemented in an integrated way.
- Among 11 studies evaluating the impact of an IPC intervention on CRE infection or colonization, 10 assessed a multimodal intervention (28, 48-56). Nine of the 10 reported a significant reduction in CRE outcomes post-intervention, thus demonstrating the significant impact of the multimodal intervention (28, 48, 49, 51-56).
- Among five studies evaluating the impact of an IPC intervention on CRAB infection or colonization, four assessed a multimodal intervention (50, 57-59). Three of the four reported a significant reduction in CRAB outcomes after the intervention, thus demonstrating the significant impact of the multimodal intervention (50, 57, 59).
- Among three studies evaluating the impact of an IPC intervention on CRPsA infection or colonization, all assessed a multimodal intervention (58, 60, 61). Two reported a significant reduction in CRPsA outcomes after the intervention, thus demonstrating the significant impact of a multimodal intervention (60, 61).
- Due to the different methodologies, interventions and outcomes measured, no meta-analysis was performed.
- The quality of the evidence was low for the most clinically important outcomes (that is, CRE infection, CRAB infection or colonization and CRPsA infection) and very low for all other CRE-CRAB-CRPsA outcomes.
- Despite the limited available evidence and its very low to low quality, the GDG unanimously recommended that an IPC programme consisting of multimodal strategies to prevent and control the acquisition of and infection with CRE-CRAB-CRPsA should be in place in all acute health care facilities and that the strength of this recommendation should be strong. This decision was based on the:
 - large effect of CRE-CRAB-CRPsA infection/colonization reduction reported in 13 of the 17 studies that assessed multimodal interventions for CRE-CRAB-CRPsA;

- panel’s conviction that the existence of such a multimodal IPC programme is necessary to control CRE-CRAB-CRPsA colonization/infection, which is consistent with the reviewed evidence that led to the development and the content of the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)* where the use of multimodal strategies is strongly recommended as the most effective approach to successfully implement IPC interventions;
- evidence and international concern about the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

- The GDG recognized that most studies were from settings with a high prevalence of CRE-CRAB-CRPsA. Nevertheless, it considered that the IPC principles outlined in this recommendation were equally valid in all prevalence settings.
- The GDG noted that while the control of large outbreaks was recognized to be very costly, these studies were all conducted in high-to-middle-income countries. Thus, there are concerns regarding the cost implications and the affordability of outbreak control in settings with limited resources.
- Although the scope of the evidence review and this recommendation address acute care facilities, the GDG considered it equally critical that all types of health care facilities apply similar IPC principles to the control of CRE-CRAB-CRPsA.
- The GDG recognized that some components of the recommended multimodal intervention could involve potential harms (for example, psychological suffering among isolated patients) or unintended consequences (for example, discrimination of colonized/infected patients) with ethical implications. These were discussed with an ethics review group and considerations resulting from this discussion and mitigation measures were included in the “values and preferences” section, as well as important references in this field.
- The GDG recognized that implementing this recommendation may be complex in some health systems as it requires a multidisciplinary approach, including executive leadership, stakeholder commitment, coordination and possible modifications to workforce structure and process in some cases. Facility leadership should clearly support the IPC programme aimed at preventing the spread of CRE-CRAB-CRPsA by providing materials and organizational and administrative support through the allocation of a protected and dedicated budget, according to the IPC activity plan. Such an approach was considered to be consistent with Core component 1 in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)*.
- The GDG identified that good quality microbiological laboratory support is a very critical factor for an effective IPC programme and implementation of this recommendation.
- The GDG considered that environmental cleaning was especially important in the area immediately surrounding the patient, that is, the “patient zone” (see Recommendation 6) (61).
- Education/training and monitoring, auditing and feedback are critical to the success of a multimodal strategy. Emphasis should be placed on these when implementing multimodal interventions and their specific components, particularly in the context of an IPC programme.
 - Education/training: Eight of 11 CRE studies mentioned supporting education and training (48-55). Among these, seven reported a significant reduction in CRE outcomes (48, 49, 51-55). Four of five CRAB studies mentioned education and training (50, 57-59), of which three reported a significant reduction in CRAB outcomes (50, 57, 59). All three CRPsA studies mentioned education and training (58, 60, 61), of which two reported a significant reduction in CRPsA outcomes (60, 61).
 - Monitoring, auditing and feedback: See Recommendation 8 for more details.
- Daily patient bathing with chlorhexidine was part of the intervention in a limited number of studies which reported mixed or inconsistent findings (two of 11 CRE; two of five CRAB and none of the three CRPsA studies) (50, 51, 62). However, the GDG considered that it was associated with an insufficient level of evidence to be formally recommended for CRE-CRAB-CRPsA.

Background

Emerging problems with CRE-CRAB-CRPsA infections and colonization are known to increase health care costs, usage of broad spectrum (and sometimes toxic) antimicrobial agents and to be associated with high rates of morbidity and mortality. IPC programmes are known to be effective in controlling many HAI, including those due to CRE-CRAB-CRPsA. However, the details of their effectiveness have sometimes been difficult to define due to differences in health care systems, the nature of various outbreaks and differences related to the background endemicity of CRE-CRAB-CRPsA. In consideration of these issues, the GDG explored the evidence captured within a systematic review to identify the impact of IPC interventions to reduce infection rates and colonization due to CRE-CRAB-CRPsA.

Summary of the evidence

The purpose of the evidence review was to evaluate the effectiveness of IPC interventions in acute health care facilities to prevent and control CRE-CRAB-CRPsA-related patient outcomes. Primary outcomes varied as follows:

- eleven studies included CRE-related patient outcomes, that is, incidence of CRE infection, CRE bloodstream infection, prevalence of CRE infection and incidence of CRE infection or colonization (28, 48-56, 63);
- five studies included CRAB-related patient outcomes, that is, incidence of CRAB infection, incidence of CRAB infection or colonization and incidence of CRAB and CRPsA colonization (50, 57-59, 62);
- Three studies included CRPsA-related patient outcomes, that is, incidence of CRPsA infection and incidence of CRAB and CRPsA colonization (58, 60, 61).

All included studies were of ITS design from countries in the Americas Region (four of 11 CRE, three of five CRAB and one of three CRPsA studies), Eastern Mediterranean Region (four of 11 CRE, none of three CRAB and three CRPsA studies), European Region (two of 11 CRE, none of five CRAB and one of three CRPsA studies), and the Western Pacific Region (one of 11 CRE, two of five CRAB and one of three CRPsA studies).

CRE: Among the 11 studies evaluating the impact of an IPC intervention on CRE infection or colonization, 10 assessed a multimodal intervention (28, 48-56). Nine of the 10 reported

a significant reduction in CRE outcomes after the intervention as demonstrated by a significant reduction in slope (that is, trend; range: -0.01 to -3.55) (28, 50, 51, 53-56) and/or level (that is, immediate change; range: -1.19 to -31.80) (28, 48, 51, 54-56) after the intervention.

All included contact precautions as a component of their multimodal strategy. In addition, nine of 10 studies included active patient surveillance (for example, rectal swab collection among at-risk patients on admission and weekly, as well as contact screening, apart from one study that assessed expanded active surveillance as a stand-alone intervention), monitoring, auditing and feedback (for example, feedback to leadership and health care workers), and patient isolation. Six of 10 included hand hygiene; four of 10 included education and antibiotic stewardship; three of 10 included enhanced environmental cleaning and flagging of positive patients in the electronic medical record; two of 10 included daily chlorhexidine gluconate baths (one study that assessed chlorhexidine gluconate baths as a stand-alone intervention was excluded); and one of 10 included a rotation of dedicated staffing to the cohort to prevent work overload, environmental surveillance cultures, creation of a multidisciplinary IPC taskforce and intensive care unit (ICU) closure.

Four studies showed a significant reduction both in slope (post-intervention trend: -0.32 to -3.55) and level (immediate change after intervention implementation: -1.19 to -31.80) in the incidence of CRE infection per 10 000 patient-days (28, 54-56). These studies used a multimodal approach of strict contact precautions, enhanced active surveillance (for example, using rectal culture samples from the ICU and step-down unit patients on admission and weekly), contact screening, cohorting for positive cases with dedicated staff and equipment, environmental and staff hand cultures, hand hygiene enforcement, carbapenem prescribing restriction, medical record flagging and an infected patient database to identify readmissions and regular reporting to hospital management and public health authorities.

CRAB: Among the five studies evaluating the impact of an IPC intervention on CRAB infection or colonization, four assessed a multimodal intervention (50, 57-59). Three of the four reported a significant reduction in CRAB outcomes after the intervention as demonstrated by a significant reduction in slope (that is, trend; range: -0.01

to -4.81) (50, 57, 59) and/or post-intervention level (that is, immediate change; -48.86) (50). Among these four studies, all included contact precautions, hand hygiene, education and monitoring, auditing and feedback as components of their multimodal strategy. In addition, three of four included active patient surveillance, patient isolation and enhanced environmental cleaning, two of four included education, and one of four included environmental surveillance cultures, flagging of positive patients in medical records, daily chlorhexidine gluconate baths, antibiotic stewardship and multidisciplinary task force meetings. One study (50) showed both a significant reduction in slope (that is, trend; -4.81) and level (that is, immediate change; -48.86) in the incidence of CRAB infection or colonization per 10 000 patient-days. Enfield et al (50) used a multimodal approach of monitoring, auditing and feedback, pre-emptive isolation for all patients, enhanced staff education on contact precautions, patient and staff cohorting, enhanced antibiotic stewardship, enhanced active surveillance of all patients (wound and respiratory samples) twice weekly and screening of all those in the ICU, chlorhexidine baths, limiting public access to rooms and common areas and environmental cleaning.

CRPsA: Among the three studies evaluating the impact of an IPC intervention on CRPsA infection or colonization, all assessed a multimodal intervention. Two reported a significant reduction in CRPsA outcomes as demonstrated by a significant reduction in slope (that is, trend; -1.36) (61) and/or post-intervention level (that is, immediate change; -0.02) (60). All three studies included active patient surveillance, contact precautions, and monitoring, auditing and feedback as components of their multimodal strategy. In addition, two of three included enhanced environmental cleaning, environmental surveillance cultures and antibiotic stewardship, and one of three included patient isolation, hand hygiene, education, ward closure and removal of automatic urine collection machines.

The GDG considered the overall quality of the evidence as very low to low given the medium to high risk of bias in the study design and implementation and the indirectness of evidence (that is, varying intervention packages, populations and outcomes measured). For some specific outcomes with fewer studies and data points measured, the imprecision of results lowered the quality of evidence.

Additional factors considered when formulating the recommendation

Values and preferences

The GDG recognized that this recommendation may have the following potentially important implications:

- Implementing the multimodal strategy might have workload implications for health care workers and other staff and this may affect morale unless managed with consideration and appropriate education (64).
- Patients who are colonized/infected with CRE-CRAB-CRPsA may suffer discrimination in the quality of their health care unless appropriate management structures are put in place. Unless managed with consideration and appropriate education, this may have an emotional impact on the morale of patients colonized/infected with CRE-CRAB-CRPsA. For this reason, health systems should give special consideration to the important management and education aspects related to CRE-CRAB-CRPsA.
- It was acknowledged that the literature review did not include studies directly addressing some of these issues. However, based on their extensive clinical experience, the GDG panel members universally supported these considerations regarding patient and staff values.

These aspects are examined in more detail in the next chapters of these guidelines. Despite these issues, the GDG considered the importance of restricting the spread of CRE-CRAB-CRPsA to be of such priority that this recommendation was supported unanimously.

Although no study was found on patient values and preferences with regards to this recommendation, the GDG was confident that patients and the public are strongly supportive of IPC programmes to control CRE-CRAB-CRPsA given the morbidity and mortality risks due to these pathogens. Furthermore, health care providers and policy-makers across all settings are likely to be in support of CRE-CRAB-CRPsA IPC programmes to reduce the harm caused by HAI and AMR due to these pathogens and to achieve safe, quality health service delivery in the context of universal health coverage.

Additionally, principles and lessons from guidance on ethical considerations in public health for other infectious diseases can also be taken into account

(42, 65-67). In brief, these guidance documents describe the following key values:

- public health necessity (for example, public health powers are exercised under the theory that they are necessary to prevent an avoidable harm);
- reasonable and effective means (for example, there must be a reasonable relationship between the public health intervention and achievement of a legitimate public health objective);
- proportionality (for example, the human burden imposed should not be disproportionate to the expected benefit);
- social justice, distributive justice and equity (for example, the risks, benefits and burdens of public health action are fairly distributed, thus precluding the unjustified targeting of already vulnerable populations);
- solidarity and the common good (for example, infectious diseases increase the risks of harm for entire populations; we can all gain from societal cooperation and strong public health facilities to reduce the threat of infection);
- effectiveness (for example, public health officials have the duty to avoid doing things that are not working and implement evidence-based measures that are likely to lead to success);
- trust, transparency and accountability (for example, public health officials should make decisions that are responsive, evidence-based and disclosed in an open manner);
- autonomy (for example, guaranteeing individuals the right to make decisions on their own lives, including health care and treatment options);
- participation (for example, public health officials have the responsibility to involve the public and patients);
- subsidiarity (for example, decisions should be made as close as possible to the individual and community);
- reciprocity (for example, health care workers deserve benefits in exchange for running risks to treat those with infectious diseases, such as actions to minimize these risks by providing a reliable supply of protective equipment).

In relation to the prevention and control of CRE-CRAB-CRPsA, these values can be considered for each of the multimodal strategy components described in the subsequent recommendations. Careful judgement should be used to decide which ones are most relevant according to each specific context and how they can be used to articulate related obligations. Promoting these values requires the active cooperation of multiple individuals and

entities who share responsibility for the prevention and control of CRE-CRAB-CRPsA.

Resource implications

The GDG was confident that the recommendation can be accomplished in all countries. However, it did acknowledge that there will be particular resource implications for low- and middle-income countries (LMICs), most notably, limited access to qualified and trained IPC professionals and inadequate microbiology laboratory capacity. At present, a defined career path for IPC does not exist in some countries, thus restricting health care workers' professional development. Furthermore, human resource capacity is often limited, especially with respect to available doctors and other trained health care professionals. Many countries with experience of implementing IPC programmes, including data from high- and middle-income countries, indicate that it is feasible and effective. However, in settings with limited resources, there is a need for prioritization based on local/regional needs to determine the most important, feasible and effective approaches.

Finally, the GDG agreed that not all countries will have adequate resources and expertise to fully support all aspects of this recommendation when executed to its fullest extent. Although the available evidence is largely limited to high- and middle-resource settings, the panel believes that the resources invested are worth the net gain, irrespective of the context. Thus, the provision of secured budget lines will be important to support the full implementation of the recommendation.

Acceptability

The GDG was confident that key stakeholders are likely to find this recommendation acceptable, while recognizing that it requires widespread and executive support, as well as specific actions for stakeholder engagement. The need for effective advocacy to assist in moving forward the acceptance of the recommendation was noted.

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- Additional well-designed research studies, especially from LMICs, as the available evidence focuses on high-income countries that may be difficult to apply more broadly. In particular, a situation analysis of current CRE-CRAB-CRPsA

prevention and control measures in LMICs could provide a baseline for assessing guideline implementation.

- Impact and ideal composition of multimodal strategies, including minimum standards for IPC training and studies on cost-effectiveness to determine adequate budgeting for CRE-CRAB-CRPsA control activities.
- Patients' perceptions, understanding and acceptance of the implementation of these IPC multimodal strategies
- Impact of an effective IPC programme in support of strategies to improve hygiene and IPC in the community.

3.2 Recommendation 2: Importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA

The panel recommends that hand hygiene best practices according to the *WHO guidelines on hand hygiene in health care* should be implemented (6).

(Strong recommendation, very low quality of evidence)

Rationale for the recommendation

- Among CRE studies, six of 11 included hand hygiene (for example, education, auditing of compliance and enforcement) as part of their assessed intervention (48-51, 54, 55). Five of the six reported a significant reduction in CRE outcomes after the intervention (48, 49, 51, 54, 55).
- Among CRAB studies, four of five included hand hygiene as part of their assessed intervention (50, 57-59). Three of the four reported a significant reduction in CRAB outcomes after the intervention (50, 57, 59).
- Among CRPsA studies, one of three included hand hygiene as part of their assessed intervention (58). This study did not report a significant reduction in CRPsA outcomes after the intervention.
- Despite the limited available evidence and its very low quality, the GDG unanimously recommended to emphasize the importance of appropriate hand hygiene compliance in the control of CRE-CRAB-CRPsA and that the strength of this recommendation should be strong. This decision was based on the:
 - panel's conviction that good hand hygiene compliance is fundamental to all multimodal IPC interventions, which is consistent with the substantial reviewed evidence on the impact of hand hygiene to reduce HAIs and AMR that led to the development and content of the *WHO guidelines on hand hygiene in health care* (6) and the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13);
 - evidence and international concern about the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

- The GDG considered that the evidence for the high beneficial impact of good hand hygiene compliance has been reviewed previously in sufficient detail and therefore the WHO recommendations on hand hygiene in health care should be followed (see *WHO guidelines on hand hygiene in health care* (6)). Effective implementation strategies have been developed, tested and are now used worldwide (68, 69) and practical approaches to implement these strategies at the facility level are described in the *WHO guide to implementation and associated toolkit* (<http://www.who.int/infection-prevention/tools/hand-hygiene/>). The GDG highlighted the importance of using these approaches and resources and adapting them locally.
- The GDG recognized that hand hygiene compliance and the appropriate use of alcohol-based handrub are very dependent on appropriate product placement and availability as noted in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13). Adequate resources are therefore necessary to ensure these features are met.
- The GDG emphasized the importance of monitoring hand hygiene practices through the measurement of compliance according to the approach recommended by WHO (7).

Background

Appropriate hand hygiene compliance is considered fundamental to all good IPC programmes and the control of cross-transmission of many pathogens, including CRE-CRAB-CRPsA (see *WHO guidelines on hand hygiene in health care* (6)). The general evidence to support hand hygiene implementation as part of effective IPC programmes to prevent HAI and AMR has been previously summarized in the

WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13) and associated documents (70).

Summary of the evidence

In this section, we examine the evidence that included hand hygiene as part of the intervention to prevent and control CRE-CRAB-CRPsA-related

patient outcomes. Included studies assessing hand hygiene were of ITS design from countries in the Americas Region (three of 11 CRE, three of five CRAB and one of three CRPsA studies), Eastern Mediterranean Region (one of 11 CRE, none of five CRAB and three CRPsA studies), European Region (one of 11 CRE, none of five CRAB and three CRPsA studies) and the Western Pacific Region (one of 11 CRE, one of five CRAB and none of three CRPsA studies). Hand hygiene was often described as the auditing of hand hygiene practices and supervision and feedback of results, rather than education on hand hygiene alone.

CRE: Six of 11 CRE studies included hand hygiene as part of a multimodal approach (48-51, 54, 55). Primary outcomes were the incidence of CRE infection (three of six), CRE bloodstream infection (two of six), the prevalence of CRE infection (one of six) and the incidence of CRE infection or colonization (one of six), including one study with two reported outcomes. Five of the six reported a significant reduction in CRE outcomes post-intervention, including significant slope (that is, trend; range: -0.09 to -3.55) and level estimates (that is, immediate change; range: -1.19 to -31.80) (48, 49, 51, 54, 55).

CRAB: Four of five CRAB studies included hand hygiene as part of a multimodal approach. Primary outcomes were the incidence of CRAB infection (one of four), CRAB infection or colonization (two of four) and CRAB and CRPsA colonization (one study) (50, 57-59). Three of the four reported a significant reduction in CRAB outcomes post-intervention, including significant changes in slope estimates (that is, trend; range: -0.01 to -4.81) and one significant change in the level estimate (that is, immediate change; -48.86) (50, 57, 59).

CRPsA: One of three CRPsA studies included hand hygiene as part of a multimodal approach (58). In this study, the primary outcome was the incidence of CRAB and CRPsA colonization. No significant reduction in CRPsA outcomes was reported post-intervention.

The GDG considered the overall quality of the evidence as very low. Hand hygiene was not an intervention component in all studies and it was evaluated only as part of a multimodal strategy and the GRADE assessment was undertaken by pathogen (that is, CRE, CRAB or CRPsA) and outcome (for example, incidence

of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection and/or colonization, etc.), rather than according to specific interventions alone.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention as this was not the focus of the literature review. However, this topic has been extensively reviewed previously (see *WHO guidelines on hand hygiene in health care* (6)). In particular, patients' points of view regarding the importance of good hand hygiene practices during health care delivery have been explored in many surveys over the past 10 years. Results clearly showed that patients highly value visible compliance with this key preventive measure and consider it as a marker of high quality care (71, 72). In a number of studies, active patient participation in hand hygiene improvement strategies was also included and tested, for example, patients were encouraged to ask health care workers to practice hand hygiene when appropriate (73). Although these experiences have not always led to positive results in terms of improved hand hygiene compliance (74), the GDG was confident that the typical values and preferences of health care providers, policy-makers and patients would favour this intervention. Health care providers, policy-makers and health care workers are likely to place a high value on this recommendation.

Resource implications

The GDG was confident that the resources are worth the expected net benefit from following this recommendation, while recognizing that the procurement of alcohol-based handrub will require a certain level of resources and materials. It was also noted that the implementation of hand hygiene multimodal improvement strategies requires adequate human resources and expertise for local development and adaptation, as well as infrastructures and equipment for execution, although some solutions may likely be low cost.

Feasibility

The GDG was confident that this recommendation can be accomplished in all countries. However, the panel noted that feasibility would hinge on the presence of IPC programmes, IPC expertise

and the availability of materials and equipment to assist in appropriate local adaptation.

Acceptability

The GDG was confident that key stakeholders are likely to find this recommendation acceptable.

Research gaps

The GDG discussed the need for further research related to this recommendation, including:

- the exact relative contribution of good hand hygiene to preventing and controlling CRE-CRAB-CRPsA infection/colonization;
- effective and feasible measures to monitor hand hygiene compliance among health care workers in limited resource settings.

3.3 Recommendation 3: Surveillance of CRE-CRAB-CRPsA infection and surveillance cultures for asymptomatic CRE colonization

The panel recommends that:

- a) surveillance of CRE-CRAB-CRPsA infection(s) should be performed, and
- b) surveillance cultures for asymptomatic CRE colonization should also be performed, guided by local epidemiology and risk assessment. Populations to be considered for such surveillance include patients with previous CRE colonization, patient contacts of CRE colonized or infected patients and patients with a history of recent hospitalization in endemic CRE settings.

(Strong recommendation, very low quality of evidence)

Rationale for the recommendation

Surveillance for CRE-CRAB-CRPsA infection/s

- Given the clinical importance of CRE-CRAB-CRPsA infection(s), the GDG considered that regular ongoing active surveillance of infections was required.

Surveillance cultures for asymptomatic CRE colonization

- Only limited evidence was available for undertaking surveillance cultures for colonization with CRAB and CRPsA. Thus, the GDG decided that this recommendation should focus on CRE surveillance for colonization (see *Additional remarks* below).
- The GDG recognized that colonization with CRE usually precedes or is co-existent with CRE infection. Thus, early recognition of CRE colonization helps to identify patients most at-risk of subsequent CRE infection, as well as allowing the earlier introduction of IPC measures (especially those indicated in Recommendation 1) to prevent CRE transmission to other patients and the hospital environment.
- Among CRE studies, 10 of 11 included active patient surveillance (for example, rectal swab collection among at-risk patients on admission and weekly, contact screening) as part of their assessed intervention (28, 48-53, 55, 56, 63). Eight of the 10 reported a significant decrease in CRE outcomes post-intervention (28, 48, 49, 51-53, 55, 56).
- Among CRAB studies, three of five included active patient surveillance as part of their assessed intervention (50, 57, 58). Two of the three reported a significant decrease in CRAB outcomes post-intervention (50, 57).
- Among three CRPsA studies, all included active patient surveillance as part of their assessed intervention (58, 60, 61). Two studies reported a significant decrease in CRPsA outcomes post-intervention (60, 61).
- Despite the limited available evidence and its very low to low quality, the GDG unanimously agreed that this recommendation should be strong. This decision was based on the:
 - panel’s conviction about the benefit of surveillance as a key core component to prevent and control CRE-CRAB-CRPsA, which is consistent with the reviewed evidence that led to the development and content of the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13) where surveillance is already the object of a strong recommendation;
 - evidence and international concern about the burden and impact of CRE-CRAB-CRPsA infection and CRE colonization (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

Surveillance for CRE-CRAB-CRPsA infection/s

- The GDG unanimously agreed that surveillance of CRE-CRAB-CRPsA infection is essential (that is, clinical monitoring of signs and symptoms of infection and laboratory testing and identification of carbapenem resistance among potential CRE-CRAB-CRPsA isolates from clinical samples).
- The GDG recognized that laboratory testing and identification of carbapenem resistance among potential CRE-CRAB-CRPsA isolates may not be available or routine in some settings (for example, LMICs). However, given the current situation, the panel unanimously agreed that testing for carbapenem resistance in these pathogens should now be considered as routine in all microbiology laboratories to ensure the accurate and timely recognition of CRE-CRAB-CRPsA.

- The GDG highlighted that the surveillance of CRE-CRAB-CRPsA infection allows a facility to define the local epidemiology of CRE-CRAB-CRPsA, identify patterns and better allocate resources to areas of need. Reviewing laboratory results over a specified period of time and looking at the demographics, exposures and locations of patients can help a facility to understand where, when and which patients are becoming ill in order to better prevent and control infections.

Surveillance cultures for asymptomatic CRE colonization

- The GDG recognized that information regarding a patient's CRE colonization status does not (yet) constitute routine standard of care provided by health systems. However, in an outbreak situation or situations where there is a high risk of CRE acquisition (for example, possible contact with a CRE colonized/infected patient or endemic CRE prevalence), CRE colonization status should be known. The surveillance culture results for the identification of CRE colonization may not have an immediate benefit to the screened patient, but instead they may contribute to the overall IPC response to CRE. It was also noted that information regarding CRE colonization status could potentially have important beneficial effects on the empiric antibiotic treatment plan for screened patients who subsequently develop potential CRE infection.
- The GDG believes that this recommendation should always apply in an outbreak situation and ideally, also in endemic settings. However, the panel extensively discussed the best approach to surveillance cultures of asymptomatic CRE colonization in a high CRE prevalence (endemic) setting, particularly in low-income settings where resources and facilities are limited and the actual appropriate improvement of IPC infrastructures and best practices may deserve prioritization over surveillance. The panel agreed that there is no one single best approach, but instead the decision should be guided by the local epidemiology, resource availability and the likely clinical impact of a CRE outbreak.
- The GDG believes that surveillance screening should be based on patient risk assessment (that is, patients who are at a higher risk of CRE acquisition and the potential risk that these patients pose to others in their environment). The following **patient risk categories** should be considered:
 - patients with a previously documented history of CRE colonization or infection;
 - epidemiologically-linked contacts of newly-identified patients with CRE colonization or infection (this could include patients in the same room, unit or ward);
 - patients with a history of recent hospitalization in regions where the local epidemiology of CRE suggests an increased risk of CRE acquisition (for example, hospitalization in a facility with known or suspected CRE);
 - based on the epidemiology of their admission unit, patients who may be at increased risk of CRE acquisition and infection (for example, immunosuppressed patients and those admitted to ICUs, transplantation services or haematology units, etc.).
- The GDG noted that surveillance cultures of fecal material were the preferred approach for the identification of CRE colonization. Regarding sample collection, culture of feces/rectal swabs or perianal swabs in rare clinical situations (for example, neutropenic patients) were considered the best methods in descending order of accuracy. However, it was recognized that for practical reasons, rectal swabs were often considered to be the most suitable clinical specimen in many health care situations. A minimum of one culture was considered necessary, although additional cultures may increase the detection rate.
- The GDG noted that surveillance cultures should be performed as soon as possible after hospital admission or risk exposure and that they should be processed and reported promptly to avoid delays in the identification of CRE colonization. The GDG was unable to identify the optimal frequency of testing after admission due to limited and heterogeneous evidence and noted that several studies included a regular screening timetable (for example, weekly or twice-weekly) following the initial on-admission screening.

Additional remarks

- The GDG recognized that undertaking the recommended surveillance activities could involve potential harms or unintended consequences for the patient (for example, a sense of cultural offensiveness or stigma associated with obtaining a rectal swab or providing a stool (fecal) specimen or discrimination

of colonized/infected patients) with ethical implications. These were discussed with an ethics review group and considerations resulting from this discussion and mitigation measures were included in the “values and preferences” section, as well as important references in this field.

- The GDG noted that several studies had identified the benefits of real-time medical record alerts regarding the CRE colonization/infection status of patients, particularly the improved identification of high-risk patients, and that such alerts helped direct appropriate IPC surveillance and containment efforts.
- The GDG also considered the evidence available on surveillance cultures for CRAB and CRPsA colonization and concluded that it was not sufficiently relevant to extend the recommendation to these two microorganisms. In particular, it was noted that the value of active surveillance for CRAB and CRPsA colonization, while sometimes beneficial, depends on the clinical setting, epidemiological stage (for example, outbreak) and body sites. It was also recognized that the optimal microbiological methods for CRAB and CRPsA surveillance cultures for colonization require further research.
- Additionally, the Global Antimicrobial Resistance Surveillance System (GLASS) recommends the inclusion of carbapenem-resistant *E coli*, *K. pneumoniae* and *Acinetobacter* species among national AMR surveillance targets (<http://www.who.int/antimicrobial-resistance/en/>).

Background

Surveillance of CRE-CRAB-CRPsA infection and surveillance cultures of asymptomatic CRE colonization allow the early introduction of IPC measures to prevent transmission to other patients and the hospital environment. The general evidence to support surveillance as a key element to prevent HAI and the cross-transmission of pathogens has been previously summarized in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Summary of the evidence

In this section, we examine the evidence that included surveillance as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient colonization/infection outcomes.

Included studies assessing active patient surveillance were of ITS design from countries in the Americas Region (five of 11 CRE, two of five CRAB and one of three CRPsA studies), Eastern Mediterranean Region (three of 11 CRE, none of five CRAB and three CRPsA studies), European Region (two of 11 CRE, none of five CRAB and one of three CRPsA studies) and the Western Pacific Region (none of 11 CRE, one of five CRAB and one of three CRPsA studies). Active patient surveillance for asymptomatic colonization was often described as rectal swab collection among at-risk patients (that is, those housed in the ICU or step-down unit) on admission and weekly or biweekly, as well as contact screening.

CRE: Ten of 11 CRE studies included active patient surveillance as part of their assessed multimodal approach (apart from one study that assessed expanded surveillance as a stand-alone intervention (28, 48-53, 55, 56, 63). Primary outcomes were the incidence of CRE infection (seven of 10), CRE bloodstream infection (two of 10), prevalence of CRE infection (one of 10) and incidence of CRE infection/colonization (one of 10), including one study with two reported outcomes. In addition, studies assessed active surveillance of target populations, including high-risk patients, such as those in the ICU (nine of 10), contacts (eight of 10) and those with a history of recent hospitalization (seven of 10). Nine of 10 studies screened patients for CRE colonization on admission and seven of 10 screened patients at least weekly or every other week. Eight of the 10 studies reported a significant reduction in CRE outcomes post-intervention, including a significant change in slope (that is, trend; range: -0.01 to -2.39) and level estimates (that is, immediate change; range: -1.19 to -25.33) (28, 48, 49, 51-53, 55, 56).

CRAB: Three of five CRAB studies included active patient surveillance as part of a multimodal approach (50, 57, 58). Primary outcomes were the incidence of CRAB infection or colonization (two of three) and the incidence of CRAB and CRPsA colonization (one of three). Two of the three studies reported a significant reduction in CRAB outcomes post-intervention, including significant changes in slope estimates (that is, trend; range: -0.01 to -4.81) and one significant

change in the level estimate (that is, immediate change; -48.86) (50, 57).

CRPsA: All three CRPsA studies included active patient surveillance as part of a multimodal approach (58, 60, 61). The primary outcomes were the incidence of CRPsA infection (two of three) and the incidence of CRAB and CRPsA colonization (one of three) (58, 60, 61). Two studies reported a significant reduction in CRPsA outcomes post-intervention, including one significant change in the slope estimate (that is, trend; -1.36) and one significant change in the level estimate (that is, immediate change; -0.02) (60, 61).

The GDG considered the overall quality of the evidence to be very low. The approach to surveillance often varied between studies. Thus, it was assessed only as part of a multimodal strategy and the GRADE assessment was undertaken for CRE by outcome (for example, incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection/colonization), rather than according to specific interventions alone.

Additional factors considered when formulating the recommendation

Values and preferences

The GDG recognized that there may be concerns about adverse events with obtaining a rectal swab in some clinical scenarios (for example, neutropenic patients, neonates). In such cases, a stool specimen/fecal culture may be obtained or, if not available, a perianal swab.

The GDG also recognized that occasionally there may be other unintended social concerns and consequences in some settings, such as a sense of cultural offensiveness or stigma associated with obtaining a rectal swab or providing a stool specimen/fecal culture and eventually, patient identification as colonized by CRE. In rare situations, this may result in patient refusal to provide the surveillance culture. Appropriate patient communication and efforts to maintain patient dignity and respect should be ensured to mitigate possible misconceptions, including the training of health care workers to increase their awareness of these potential issues.

The panel recognized that the identification of CRE colonization, while potentially beneficial

to the patient and the nature of the health care response(s), could also result in inappropriate patient discrimination if the health facility did not have adequate management structures in place to ensure routine clinical care, regardless of colonization status. The panel recognized that this important, potential ethical concern needed to be balanced against the major ethical issues and clinical impact associated with likely widespread CRE transmission if surveillance cultures were not performed. Confidentiality of the data and patient colonization or infectious status should be maintained and shared only through the appropriate channels to minimize potential discrimination.

Although no study was found on patient values and preferences with regards to this intervention (as it was not the focus of the literature review), the panel was confident that overall, the typical values and preferences of patients and health care workers would be supportive of surveillance cultures. The panel also considered that most health care providers and patients in the vast majority of settings are likely to place a higher value on the information regarding colonization with CRE than the above-listed concerns, given the potentially serious health implications of CRE infection.

However, the GDG considered that a patient risk assessment is an important component of a surveillance programme as screening efforts should be focused on “high-risk” patient populations as indicated in the recommendation and in the related remarks, particularly those at risk of CRE acquisition.

Furthermore, the GDG considered that developing a robust communication and information sharing strategy regarding a patient’s CRE colonization status is crucial. This is particularly valid for inter-facility patient transfers as it was noted that many published CRE outbreaks had occurred in facilities where knowledge of an individual patient’s previous surveillance culture results had not been adequately communicated to the receiving health care facility and subsequent CRE transmission had occurred.

Other shared lessons on ethical considerations of surveillance can be found in the *WHO discussion paper on addressing ethical issues in pandemic influenza planning* (65) as well as in other public health ethics guidance (66, 67).

Resource implications

The GDG recognized that there are financial implications related to surveillance cultures for colonization. However, the GDG considered that these resources are worth the expected net benefit, although this benefit may vary between settings, depending on resources available.

The GDG also recognized that financial and technical support are needed in some settings to strengthen laboratory capacity in order to both undertake appropriate testing for carbapenem resistance and to be able to provide adequate and timely testing of clinical and surveillance culture specimens. In addition, enhanced efforts and training related to the laboratory analysis and interpretation of microbiological results may be required in some settings. Epidemiological and clinical skills are also required to adequately respond to the surveillance culture results. Appropriate treatment should also be available for CRE-CRAB-CRPsA.

Feasibility

The GDG was confident that this recommendation can be accomplished in all countries, but it acknowledged that the above-mentioned resource implications can pose challenges as to its feasibility. The recommendation is likely to require adaptation or tailoring to the cultural setting. Moreover, continuous education to support adequate surveillance may be difficult and challenging in some countries, particularly where there is a low availability or lack of knowledgeable professionals able to teach IPC. In addition, efficient and effective surveillance for both CRE-CRAB-CRPsA infection and CRE colonization requires adequate data collection and an appropriate management infrastructure. For example, the GDG acknowledged that surveillance may be more laborious in systems using paper-based medical records compared to electronic medical records.

Acceptability

The GDG was confident that key stakeholders are likely to find this recommendation acceptable.

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including the following topics.

- Ideal schedule for CRE surveillance cultures of colonization, as well as for settings where CRE is rare and endemic.

- Most cost-effective approach to CRE surveillance, in particular for limited resource settings.
- Optimal cost-effective laboratory methods for CRE surveillance, including isolate characterization (for example, identification of the genotypes).
- Identification of appropriate methods and definitions to accurately identify clearance of colonization and inform strategies for the discontinuation of active surveillance. This may also have important implications for the morale of CRE-colonized patients as some hope of clearing their CRE colonization may be important to both their future health care and likelihood of future discrimination. Moreover, patients who are no longer carriers, but are nevertheless hospitalized in carrier cohorts due to non-identification of clearance, may be at risk of re-acquisition of CRE.
- Risk factors for prolonged colonization and acquisition of new CRE strains.
- Global and national epidemiology of CRE-CRAB-CRPsA infection/s. This is required to assist with an accurate assessment of patients related to their likely risk of colonization with these pathogens, including an understanding of country prevalence data. It was noted that such open disclosure may be associated with some political concerns in some regions. The GDG believed that further reflection and better approaches are required to optimize communication regarding this issue with the aim to achieve transparency, while avoiding alarm.
- Optimal methods for surveillance for asymptomatic colonization with CRAB and CRPsA. It was noted that the value of screening for CRAB and CRPsA, while sometimes beneficial, depended on the clinical setting, epidemiological stage (for example, sporadic cases versus outbreak, etc.) and the local epidemiology of CRAB and CRPsA.
- Importantly, the linkage between the availability of surveillance culture results for asymptomatic colonization with CRE-CRAB-CRPsA and the implementation of effective IPC interventions for effective containment.
- Relevance of approaches to surveillance used for extended-spectrum beta-lactamases (ESBL)-producing *Klebsiella* spp. for CRE screening.
- Patient values and preferences concerning the implementation of surveillance cultures for asymptomatic colonization with CRE and communication strategies.

3.4 Recommendation 4: Contact precautions

The panel recommends that contact precautions should be implemented when providing care for patients colonized or infected with CRE-CRAB-CRPsA.

(Strong recommendation, very low to low quality of evidence)

Rationale for the recommendation

- Among the 11 CRE studies, 10 studies included contact precautions as part of their assessed intervention, while the remaining study included contact precautions as a component of their baseline (pre-intervention) strategy (28, 48-56). Nine of the 10 reported a significant reduction in CRE outcomes post-intervention (28, 48, 49, 51-56).
- Among the five CRAB studies, four studies included contact precautions as part of their assessed intervention, while the fifth study included contact precautions in their baseline (pre-intervention) strategy (50, 57-59). Three of the four studies reported a significant reduction in CRAB outcomes (50, 57, 59).
- Among the three CRPsA studies, all included contact precautions as part of their assessed intervention (58, 60, 61). Two reported a significant reduction in CRPsA outcomes post-intervention (60, 61).
- Despite the limited available evidence and its very low to low quality, the GDG unanimously agreed that the strength of this recommendation should be strong. This decision was based on the:
 - inclusion of contact precautions in the IPC guidelines and strongly recommended to be made available, implemented and taught to health care workers at the national and facility levels as part of Core component 2 of effective IPC programmes in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13);
 - panel’s concerns regarding the known ready transmissibility of CRE-CRAB-CRPsA by direct or indirect contact with the patient or the patient environment and the proven efficacy and practical applicability of this intervention in reducing transmission of other similar multidrug-resistant pathogens;
 - evidence and international concern about the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

- In line with other key and internationally recognized guideline documents, the GDG defined “contact precautions” in these guidelines as: (1) ensuring appropriate patient placement; (2) use of personal protective equipment, including gloves and gowns; (3) limiting transport and movement of patients; (4) use of disposable or dedicated patient-care equipment; and (5) prioritizing cleaning and disinfection of patient rooms (see *Glossary*) (5). The use of patient isolation is addressed in Recommendation 5.
- The GDG noted that contact precautions should be considered as a standard of care for patients colonized/infected with CRE-CRAB-CRPsA in the vast majority of health systems.
- It was recognized that health care worker education regarding the principles of IPC and monitoring of contact precautions is crucial.
- The GDG recognized that in some circumstances, depending on the individual risk assessment of some patients, pre-emptive isolation/cohorting and the use of contact precautions may be necessary until the results of surveillance cultures for CRE-CRAB-CRPsA are available. This was considered to be an important consideration for patients with a history of recent hospitalization in regions where the local epidemiology of CRE suggests an increased risk of CRE acquisition (see Recommendation 3: patient risk categories).
- Clear communication regarding a patient’s colonization/infection status is important (that is, flagging the medical chart).
- The GDG recognized that applying contact precautions could involve potential unintended consequences for the patient (for example, patient frustration or discomfort during treatment with contact precautions). These were discussed with an ethics review group and considerations resulting from this discussion and mitigation measures were included in the “values and preferences” section, as well as important references in this field. Furthermore, it was recognized that occupational health issues associated with the use of some personal protective equipment (for example, latex gloves) should also be taken into consideration for health care workers.

Background

Contact precautions are an important fundamental component of the IPC measures necessary to control HAI and other infections. Contact precautions are part of transmission-based precautions and are included in the list of the IPC guidelines strongly recommended to be made available, implemented and taught to health care workers at the national and facility levels as part of Core component 2 of effective IPC programmes (13). These precautions include measures intended to prevent the transmission of infectious agents spread by direct or indirect contact with the patient or the patient environment. These include: (1) ensure appropriate patient placement; (2) use personal protective equipment, including gloves and gowns; (3) limit transport and movement of patients; (4) use disposable or dedicated patient-care equipment; and (5) prioritize cleaning and disinfection of patient rooms (5). The general evidence supporting their implementation is summarized in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Summary of the evidence

In this section, we examine the evidence that included contact precautions as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient outcomes.

Studies assessing contact precautions were of ITS design from countries in the Americas Region (four of 11 CRE, three of five CRAB and two of three CRPsA studies), Eastern Mediterranean Region (three of 11 CRE, none of five CRAB and three CRPsA studies), European Region (two of 11 CRE, none of five CRAB and three CRPsA studies) and the Western Pacific Region (one of 11 CRE, one of five CRAB and one of three CRPsA studies). The intervention related to contact precautions was often not described in detail, but some studies described it as health care workers' education on contact precautions and the auditing of compliance with contact precautions.

CRE: Ten of the 11 CRE studies included contact precautions as part of a multimodal approach, while the remaining study included contact precautions only in the baseline (pre-intervention) strategy (28, 48-56). The primary outcomes were CRE infection (seven of 10), CRE bloodstream infection (two of 10), prevalence of CRE infection

(one of 10), and the incidence of CRE infection or colonization (one of 10), including one study with two reported outcomes. Nine of the 10 studies reported a significant reduction in CRE outcomes after the intervention including significant changes in slope estimates (that is, trend; range: -0.01 to -3.55) and level estimates (that is, immediate change; range: -1.19 to -31.80) (28, 48, 49, 51-56).

CRAB: Four of the five CRAB studies included contact precautions as part of a multimodal approach, while the fifth study included contact precautions only in their baseline (pre-intervention) strategy (50, 57-59). The primary outcomes were the incidence of CRAB infection (one of four), incidence of CRAB infection and colonization (two of four) and the incidence of CRAB and CRPsA colonization (one of four). Three of the four studies reported a significant reduction in CRAB outcomes post-intervention, including significant changes in slope estimates (that is, trend; range: -0.01 to -4.81) and a significant change in the level estimate (that is, immediate change; -48.86) (50, 57, 59).

CRPsA: All three CRPsA studies included contact precautions as part of a multimodal approach (58, 60, 61). The primary outcomes were the incidence of CRPsA infection (two of three) and the incidence of CRAB and CRPsA colonization (one of three). Two reported a significant reduction in CRPsA outcomes after the intervention including one significant change in the slope estimates (that is, trend; -1.36) and one significant change in the level estimate (that is, immediate change; -0.02) (60, 61).

The GDG considered the overall quality of the evidence to be very low to low. The approach to contact precautions often varied between studies. It was assessed only as part of a multimodal strategy and the GRADE assessment was undertaken by pathogen (that is, CRE, CRAB or CRPsA) and outcome (for example, incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection and/or colonization, etc.), rather than according to specific interventions alone.

Additional factors considered when formulating the recommendation

Values and preferences

No study was found on patient values and preferences with regards to this intervention as

this was not a component of the literature search strategy. Nevertheless, the GDG recognized that some patients and their relatives may have concerns about the appearance of health care workers using personal protective equipment and may not feel at ease. Appropriate patient education and communication about the importance of contact precautions to avoid the spread of CRE-CRAB-CRPsA to others should be undertaken. Health care workers should be trained to be able to cope with potential misconceptions of contact precautions and to communicate with patients in the best way possible. For health care workers, occupational health issues associated with the use of some protective equipment (for example, latex gloves) should also be taken into consideration. However, the GDG was confident that health care providers, health care workers, policy-makers and patients in all settings are likely to be supportive of the recommendation since the evidence supports the fact that the intervention is linked to improved patient outcomes and protects the health workforce. When feasible, consideration should be given to attribute priority services and priority allocation of dedicated health care personnel and resources to patients who are subject to contact precautions in order to mitigate their frustration, discomfort and potential harm.

Resource implications

The GDG recognized that the application of contact precautions required an increase in resource usage (for example, gowns and gloves), as well as the need for their appropriate disposal and associated costs. The GDG also recognized that the use of contact precautions was often associated with some inconvenience and increase in workload to health care workers managing patients colonized/infected with CRE-CRAB-CRPsA. It was noted that the use of gloves could occasionally be associated with some occupational exposure issues, such as cutaneous reactions. When implementing contact precautions, technical expertise is required for the overall coordination and programme management, which may pose some difficulties in LMICs. Other shared lessons on ethical considerations of personal protective equipment can be found in the *WHO discussion paper on addressing ethical issues in pandemic influenza planning* (65), as well as in other public health ethics guidance (66, 67).

Despite these concerns, the GDG was confident that the resources required are worth the expected net benefit from following this recommendation.

Feasibility

The GDG was confident that this recommendation can be implemented in all countries, while acknowledging that this may pose some challenges in LMICs.

Acceptability

The GDG was confident that key stakeholders are likely to find this recommendation acceptable, especially since it is consistent with the approved *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- Resource planning and optimization regarding the use of gowns and gloves (that is, predicting usage patterns to allow an adequate supply of provisions).
- Efficacy and cost-effectiveness of various types of material used to make gowns. For instance, are disposable gowns superior to non-disposable gowns? Despite the lack of evidence, experts on the GDG agreed that both disposable gowns and non-disposable gowns (with adequate washing) could be used.
- Identification of when contact precautions should appropriately be ceased among patients colonized/infected with CRE-CRAB-CRPsA.
- Qualitative research to understand the factors facilitating success for implementation, including the identification of barriers and challenges.
- Guidance on which patients to prioritize for the implementation of contact precautions in resource-limited settings (for example, those most likely to transmit infection, type of care provided).
- Patient values and preferences concerning the implementation of contact precautions.

3.5 Recommendation 5: Patient isolation

The panel recommends that patients colonized or infected with CRE-CRAB-CRPsA should be physically separated from non-colonized or non-infected patients using

- a) single room isolation; or**
- b) cohorting patients with the same resistant pathogen.**

(Strong recommendation, very low to low quality of evidence)

Rationale for the recommendation

- Among 11 CRE studies, nine included patient isolation as part of their assessed intervention (28, 48-55). Eight of the nine reported a significant reduction in CRE outcomes after the intervention (28, 48, 49, 51-55).
- Among the five CRAB studies, three studies included patient isolation as part of their assessed intervention (50, 57, 59). All three studies reported a significant reduction in CRAB outcomes.
- Among three CRPsA studies, one included patient isolation as part of the assessed intervention and reported a significant reduction in CRPsA outcomes post-intervention (61).
- Despite the limited available evidence and its very low to low quality, the GDG unanimously agreed that the strength of this recommendation should be strong. This decision was based on the:
 - inclusion of patient isolation as an essential element of contact precautions to be used for patients with CRE-CRAB-CRPsA colonization/infection as they represent an increased risk for contact transmission (5, 13);
 - panel’s concerns regarding the known ready transmissibility of CRE-CRAB-CRPsA and the proven effectiveness of patient isolation/cohorting in reducing transmission of other similar multidrug-resistant pathogens;
 - evidence and international concern regarding the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

- It was noted that there is an inconsistency in the use of the terms “isolation” and “cohorting” in some settings. For the purposes of these guidelines, the following standard definitions (5) were used:
 - Isolation: patients should be placed in single-patient rooms (preferably with their own toilet facilities) when available. When single-patient rooms are in short supply, patients should be cohorted.
 - Cohorting: the practice of grouping together patients who are colonized/infected with the same organism to confine their care to one area and prevent contact with other patients.
- The purpose of isolation is to separate colonized/infected patients from non-colonized/non-infected patients.
- The GDG noted that while the strongest evidence for the effectiveness of patient isolation was among patients with CRE colonization/infection, it was the panel’s view that this recommendation was also likely to be effective to prevent cross-transmission among patients colonized/infected with CRAB and/or CRPsA.
- The GDG noted that patient isolation could be associated with some potential harms and negative unintended consequences (for example, social isolation and psychological consequences, such as depression or anxiety). These were discussed with an ethics review group and considerations resulting from this discussion and mitigation measures were included in the “values and preferences” section, as well as important references in this field. In summary, the GDG believed these could be minimized with appropriate management and that the advantages of patient isolation in terms of preventing cross-transmission of CRE-CRAB-CRPsA outweighed these concerns.
- The preference is for colonized/infected patients to be managed in single rooms where possible. Cohorting is reserved for situations where there are insufficient single rooms or where cohorting of patients colonized or infected with the same pathogen is a more efficient use of hospital rooms and resources. The GDG believes that patient isolation should always apply in an outbreak situation. Isolation in single rooms may not be possible in endemic situations, particularly in low-income settings where resources and facilities are limited.
- The GDG noted that there is evidence and clinical experience to support the use of dedicated health care workers to exclusively manage isolated/cohorted patients, although the panel recognized there may be some feasibility issues (see *Resource implications and Feasibility*).

Background

Patient isolation is an important component of contact precautions and aims to prevent the transmission of infection between patients by physically separating them in single rooms or by cohorting. The general evidence to support patient isolation as an effective IPC intervention to prevent HAI and the cross-transmission of pathogens has been previously summarized in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Summary of the evidence

In this section, we examine the evidence on patient isolation or cohorting as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient outcomes.

Studies assessing patient isolation were of ITS design from countries in the Americas Region (four of 11 CRE, two of five CRAB and one of three CRPsA studies), Eastern Mediterranean Region (two of 11 CRE, none of five CRAB and three CRPsA studies), European Region (two of 11 CRE, none of five CRAB and three CRPsA studies) and the Western Pacific Region (one of 11 CRE, one of five CRAB and none of three CRPsA studies). The intervention of patient isolation was often described as single room isolation when available, otherwise cohorting or geographical separation.

CRE: Nine of the 11 CRE studies included patient isolation as part of a multimodal approach (28, 48-55). The primary outcomes were CRE infection (six of nine), CRE bloodstream infection (two of nine), prevalence of CRE infection (one of nine) and the incidence of CRE infection or colonization (one of nine), including one study with two reported outcomes. Eight of the nine studies reported a significant reduction in CRE outcomes after the intervention, including significant changes in slope estimates (that is, trend; range: -0.01 to -3.55) and level estimates (that is, immediate change; range: -1.19 to -31.80) (28, 48, 49, 51-55).

CRAB: Three of five CRAB studies included patient isolation as part of a multimodal approach (50, 57, 59). The primary outcomes were the incidence of CRAB infection (one of three) and the incidence of CRAB infection and colonization (two of three). All three studies reported a significant reduction in CRAB outcomes post-intervention, including a significant change in slope estimates (that is, trend; range: -0.01 to -4.81) and a significant change in

the level estimate (that is, immediate change; -48.86) (50, 57, 59).

CRPsA: One of three CRPsA studies included patient isolation as part of a multimodal approach (61). The primary outcome was the incidence of CRPsA infection. The study reported a significant reduction in CRPsA outcomes after the intervention including a significant change in the slope estimate (that is, trend; -1.36) (61).

The GDG considered the overall quality of the evidence to be very low to low. The approach to patient isolation often varied between studies. It was assessed only as part of a multimodal strategy and the GRADE assessment was undertaken by pathogen (that is, CRE, CRAB or CRPsA) and outcome (for example, the incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection and/or colonization, etc.), rather than according to specific interventions alone.

Additional factors considered when formulating the recommendation

Values and preferences

The GDG recognized that patient isolation could occasionally be associated with some potentially negative unintended consequences, including a sense of stigma and psychological impact on isolated patients. In addition, some patients may feel some social isolation and have psychological consequences, such as depression or anxiety when managed in a single room (64). Appropriate patient communication and efforts to maintain patient dignity and respect should be emphasized to mitigate potential misconceptions. This may require specific communication training for some health care workers. In cases of prolonged isolation where morale may be affected, patients should be provided with psychological support. Similarly, it was noted that there may be a negative impact on some health care workers who manage such patients in isolation rooms, including a sense of stress and reduced morale. The GDG considered that these issues should be openly recognized and can be adequately addressed if managed appropriately.

It was also recognized that the implementation of this recommendation was likely to have a potential impact on single room availability in hospitals, a need for increased staffing and

equipment availability, and an increase in budget allocation for the purchase of disposable protective equipment and the cost of disposal. In some cases, single room and cohort isolation have been shown to be associated with a reduced standard of medical care if not well managed (64).

Nevertheless, it was the panel's view that each of these concerns should be addressed and could be minimized or abolished with an appropriate management structure.

In conclusion, the GDG considered that each of these issues could be minimized with appropriate management and that the advantages of patient isolation in terms of preventing the cross-transmission of CRE-CRAB-CRPsA outweighed these concerns. When feasible, consideration should be given to providing priority services to patients who are subject to isolation or cohorting and priority allocation of dedicated health care personnel and resources in order to mitigate psychological consequences and other potential harm.

Other shared lessons on ethical considerations of patient isolation can be found in the *WHO guidance on ethics of tuberculosis prevention, care and control* (42) and the *WHO discussion paper on addressing ethical issues in pandemic influenza planning* (65), as well as in other public health ethics guidance (66, 67). These guidance documents emphasize that the goal (as it relates to patient isolation) should be to protect public health while minimizing human rights violations and ethical concerns. Thus, the "public health necessity" and "distributive justice" (see description of ethical concepts in Recommendation 1) of isolation should be ensured and monitored.

Resource implications

It was recognized that patient isolation may have considerable resource implications, including the need for single rooms. This is particularly relevant in LMICs where single rooms are often scarce. Therefore, the use of patient isolation may impact on the health facility infrastructure. Single room isolation can increase health care worker workload. However, the cohorting of patients colonized/infected with the same pathogen may ease some workload issues in certain circumstances. A reliable implementation of this recommendation is also likely to require adequately trained IPC staff.

The GDG was confident that the resources necessary to separate infected/colonized patients

from those who are non-infected/colonized are worth the expected net benefit from following this recommendation.

Feasibility

The GDG was confident that this recommendation can be implemented in most countries, although some support may be required in LMICs. Moreover, the panel acknowledged that the implementation of this recommendation should be undertaken with care and sensitivity to be feasible and to avoid misunderstanding and increased suffering by some patients.

Acceptability

The GDG acknowledged that awareness-raising actions are needed regarding the risks of CRE-CRAB-CRPsA spread and the burden of related patient outcomes to be acceptable to health care facility senior managers who may need to take decisions on increasing the number of single rooms and other resources. Overall, the GDG was confident that key stakeholders are likely to find this recommendation acceptable.

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- cost-effectiveness and practicality of isolation and cohorting of patients with CRE-CRAB-CRPsA, particularly in LMICs or other settings where there are competing needs;
- transmission dynamics of CRE-CRAB-CRPsA and the identification of differences between these three groups of pathogens;
- benefit of dedicated health care worker staff to exclusively manage isolated/cohorted patients;
- benefit of increased bed spacing on CRE-CRAB-CRPsA acquisition in settings where opportunities for isolation/cohorting are limited;
- identification of when patient isolation should be appropriately ceased among patients colonized or infected with CRE-CRAB-CRPsA;
- Patient values and preferences concerning the implementation of patient isolation for CRE-CRAB-CRPsA colonization/infection.

3.6 Recommendation 6: Environmental cleaning

The panel recommends that compliance with environmental cleaning protocols of the immediate surrounding area (that is, the “patient zone”) of patients colonized or infected with CRE-CRAB-CRPsA should be ensured.

(Strong recommendation, very low quality of evidence)

Rationale for the recommendation

- Among the 11 CRE studies, three included environmental cleaning as part of their assessed intervention (49, 50, 53). Two of the three studies reported a significant reduction in CRE outcomes after the intervention (49, 53).
- Among the five CRAB studies, three included environmental cleaning as part of their assessed intervention (50, 57, 59). All three reported a significant reduction in CRAB outcomes after the intervention.
- Among the three CRPsA studies, two included environmental cleaning as part of their assessed intervention (60, 61). Both studies reported a significant reduction in CRPsA outcomes after the intervention.
- Despite the limited available evidence and its very low quality, the GDG unanimously agreed that the strength of this recommendation should be strong. This decision was based on the:
 - known role of environmental contamination in facilitating the transmission of CRE-CRAB-CRPsA and other similar multidrug-resistant pathogens to patients;
 - panel’s recognition that environmental cleaning is known to be an effective intervention in reducing the transmission of other multidrug-resistant pathogens that are similar to CRE-CRAB-CRPsA;
 - evidence and international concern regarding the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2);
 - the fact that a clean and hygienic environment is considered one of the core components of effective IPC programmes according to the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Remarks

- According to the definition included in the *WHO guidelines on hand hygiene in health care* (6), the “patient zone” contains the patient and his/her immediate surroundings. Typically, this includes all inanimate surfaces that are touched by or in direct physical contact with the patient, such as the bed rails, bedside table, bed linen, infusion tubing, bedpans, urinals and other medical equipment. It also contains surfaces frequently touched by health care workers during patient care, such as monitors, knobs and buttons and other “high frequency” touch surfaces. Contamination is likely also in toilets and associated items (7).
- The optimal cleaning agent for environmental cleaning protocols of the immediate surrounding area of patients colonized/infected with CRE-CRAB-CRPsA has not yet been defined. Three CRE-CRAB-CRPsA studies used hypochlorite (generally a concentration of 1000 parts per million [ppm]) as an agent to undertake environmental cleaning (50, 53, 61).
- The GDG noted that appropriate educational programmes for hospital cleaning staff are crucial to achieve good environmental cleaning.
- The use of multimodal strategies to implement environmental cleaning was considered essential. This includes institutional policies, structured education, and monitoring compliance with cleaning protocols (75, 76).
- Assessment of cleaning efficacy by performing environmental screening cultures for CRE-CRAB-CRPsA was noted to be worthwhile in some settings (Recommendation 7).
- The GDG noted that in some outbreak situations, temporary ward closures were necessary to allow for enhanced cleaning (48, 61).

Background

The general evidence to support environmental cleaning (and maintenance of the built environment) as an effective IPC intervention to prevent HAI and cross-transmission of pathogens has been previously summarized in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level* (13).

Summary of the evidence

In this section, the evidence that included cleaning as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient outcomes was examined.

Studies assessing environmental cleaning were of ITS design from countries in the Americas Region (one of 11 CRE, two of five CRAB and none of three CRPsA studies), Eastern Mediterranean Region (one of 11 CRE, none of five CRAB and three CRPsA studies), European Region (one of 11 CRE, none of five CRAB and one of three CRPsA studies) and the Western Pacific Region (none of 11 CRE, one of five CRAB and one of three CRPsA studies). The intervention of environmental cleaning was often described as “enhanced”, for example, increasing frequency of cleaning, changing the cleaning solution and auditing of practices and feedback.

CRE: Three of the 11 CRE studies included environmental cleaning as part of a multimodal approach (49, 50, 53). The primary outcomes were CRE infection (one of 10), CRE bloodstream infection (one of 10) and the incidence of CRE infection or colonization (one of 10). Two of the three studies reported a significant reduction in CRE outcomes after the intervention including significant change in slope estimates (that is, trend; range: -0.09 to -0.91) (49, 53).

CRAB: Three of the five CRAB studies included environmental cleaning as part of a multimodal approach (50, 57, 59). The primary outcomes were the incidence of CRAB infection (one of three) and the incidence of CRAB infection and colonization (two of three). All three studies reported a significant reduction in CRAB outcomes after the intervention including a significant change in slope estimates (that is, trend; range: -0.01 to -4.81) and a significant change in the level estimate (that is, immediate change; -48.86) (50, 57, 59).

CRPsA: Two of the three CRPsA studies included environmental cleaning as part of a multimodal approach (60, 61). The primary outcomes were the incidence of CRPsA infection. Both reported a significant reduction in CRPsA outcomes after the intervention including a significant change in the slope estimate (that is, trend; -1.36) and a significant change in the level estimate (that is, immediate change; -0.02) (60, 61).

The GDG considered the overall quality of the evidence to be very low. The approach to environmental cleaning often varied between studies. It was assessed only as part of a multimodal strategy and the GRADE assessment was undertaken by pathogen (that is, CRE, CRAB or CRPsA) and outcome (for example, the incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection/colonization, etc.), rather than according to specific interventions alone.

Additional factors considered when formulating the recommendation

Values and preferences

Although there was no study identified on patient values and preferences with regards to this recommendation, the GDG considered that environmental cleaning was likely to have positive implications since most patients and their families prefer hospitals that are demonstrably clean.

Resource implications

The GDG recognized that strengthening environmental cleaning is likely to have resource implications depending on the cleaning product used and in terms of an increased workload for cleaners and potentially enhanced degradation to some vinyl and other surfaces in hospitals.

However, the panel considered that most cleaning products, including hypochlorite, are generally low cost and that salaries for hospital cleaners are also often relatively low. The panel noted that some cleaning agents (for example, hydrogen peroxide), while seemingly effective, can be disruptive to hospital workflow and bed utilisation given the time and equipment required for their use. It was noted that while a number of studies cited the effective use of hypochlorite, it could be associated with occupational health issues unless used according to the correct instructions.

The GDG acknowledged that some LMICs may face basic water, sanitation and hygiene challenges. However, a sufficient and reliable water supply is essential to support basic cleaning. Furthermore, shared hospital items (for example, furniture) should be made of easily cleanable material and should be maintained without any damage that may impede adequate cleaning.

The GDG was confident that this recommendation can be implemented in all countries in the long term, including in limited resource settings, and that the resources required will be worth the net benefit, despite the costs incurred. Implementing a clean and safe environment is a fundamental prerequisite to effective IPC and quality of care. There is a need for institutions to provide the necessary physical and educational resources in order to meet this recommendation.

Feasibility

The GDG believed that this recommendation is feasible in most health care settings, given an appropriate allocation of resources and executive leadership. The panel considered the benefit from this recommendation to be worthwhile in terms of reducing the risk of CRE-CRAB-CRPsA colonization/infection.

Acceptability

The GDG was confident that key stakeholders are likely to find the recommendation acceptable.

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- optimal cleaning agent and method in terms of efficacy, cost-effectiveness, simplicity of use and availability (particularly in LMICs);
- the optimal cleaning protocol, particularly in LMICs where clean water may be scarce;
- standardization of the definition of “enhanced” cleaning (this was described in the evidence in a heterogeneous manner) and its efficacy and effectiveness compared to regular environmental cleaning;
- CRE-CRAB-CRPsA survival time or persistence in the environment;
- effectiveness of cleaning protocols for high-risk items, such as bedpans and urinals;
- optimal educational approach regarding environmental cleaning practices;
- most accurate monitoring indicators for environmental cleaning.

3.7 Recommendation 7: Surveillance cultures of the environment for CRE-CRAB-CRPsA colonization/contamination

The panel recommends that surveillance cultures of the environment for CRE-CRAB-CRPsA may be considered when epidemiologically indicated.

(Conditional recommendation, very low quality of evidence)

Rationale for the recommendation

- Among the 11 CRE studies, only one included environmental surveillance cultures as part of their assessed intervention and reported a significant reduction in CRE outcomes post-intervention (55).
- Among the five CRAB studies, only one included environmental surveillance cultures as part of their assessed intervention and reported a significant reduction in CRAB outcomes after the intervention (59). In addition, one study monitored environmental contamination after cleaning using an adenosine triphosphate (ATP) bioluminescence assay as part of their intervention and found a significant reduction in CRAB outcomes after the intervention (50).
- Among the three CRPsA studies, two included environmental surveillance cultures as part of their assessed intervention and reported a significant reduction in CRPsA outcomes post-intervention (60, 61).
- The panel noted that environmental contamination with CRE-CRAB-CRPsA is commonly associated with increased rates of patient colonization and infection with these pathogens, particularly CRAB and CRPsA. All studies used environmental surveillance cultures to monitor the efficacy of hospital cleaning, which was one of the key elements of their multimodal IPC interventions.
- The evidence was not uniform, of very low quality, and appeared to be strongest for CRAB and CRPsA, rather than CRE. Thus, the GDG considered surveillance cultures of the environment to be a conditional recommendation.

Remarks

- The panel noted that the correlation of environmental surveillance culture results to the rates of patient colonization/infection with CRE-CRAB-CRPsA should be undertaken with caution and depends on an understanding of the local clinical epidemiological data and resources.
- Based on expert opinion (and only limited available data), surveillance cultures of the general environment were considered most relevant to CRAB outbreaks. Outbreaks of CRPsA colonization/infection among patients appeared to be more commonly associated with environmental CRPsA contamination involving water and waste-water systems, such as sinks and taps (faucets).
- Epidemiology, microbiological laboratory capacity and available resources should be evaluated when considering the implementation of this recommendation, hence its “conditional” attribution.

Background

Although environmental contamination with CRE-CRAB-CRPsA is commonly observed when patients are colonized and/or infected with these pathogens, the exact attribution of the environmental contamination to the clinical problem is not always clear, except as a marker of the thoroughness of hospital cleaning. However, environmental surveillance may be a potentially useful measure to assess the level of contamination and the efficacy of cleaning in the surroundings of patients colonized or infected with CRE-CRAB-CRPsA. Considering these issues, the GDG explored the evidence related to the role of environmental surveillance cultures as part of the interventions

used to control CRE-CRAB-CRPsA within the systematic review performed as a background to these guidelines.

Summary of the evidence

In this section, the evidence that included environmental surveillance as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient outcomes is examined.

Included studies assessing environmental surveillance were of ITS design from countries in the Americas Region (none of 11 CRE, one of five CRAB and one of three CRPsA studies), Eastern Mediterranean Region (one of 11 CRE, none of

CRAB and three CRPsA studies), European Region (none of 11 CRE, none of five CRAB and three CRPsA studies) and the Western Pacific Region (one of 11 CRE, none of five CRAB and one of three CRPsA studies). Environmental surveillance was often described as environmental cultures implemented together with enhanced environmental cleaning.

CRE: One of 11 CRE studies included environmental surveillance as part of a multimodal approach (55). The primary outcome was the incidence of CRE infection. This study reported a significant reduction in CRE infection after the intervention, including a significant change in slope (that is, trend; -0.32) and level estimates (that is, immediate change: -3.93).

CRAB: One of five CRAB studies included environmental surveillance as part of a multimodal approach (59). The primary outcome was the incidence of CRAB infection. The study reported a significant reduction in CRAB infection post-intervention, including a significant change in slope estimate (that is, trend; -0.09). In addition, one study monitored environmental contamination after cleaning using an adenosine triphosphate bioluminescence assay (but not culture) as part of their intervention and also found a significant reduction in CRAB infection and colonization (50).

CRPsA: Two of three CRPsA studies included environmental surveillance as part of a multimodal approach (60, 61). Both primary outcomes were the incidence of CRPsA infection. These studies reported a significant reduction in CRPsA outcomes after the intervention, including one significant change in the slope estimate (that is, trend; -1.36) and in the level estimate (that is, immediate change; -0.02).

The GDG considered the overall quality of the evidence to be very low. The approach to surveillance cultures of the environment often varied between studies. It was assessed only as part of a multimodal strategy as it was not an intervention component in all studies and the GRADE assessment was undertaken by pathogen (that is, CRE-CRAB-CRPsA) and outcome (for example, the incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection and/or colonization, etc.), rather than according to this specific intervention alone. Furthermore, the GDG noted that

surveillance cultures of the environment were a component in few studies and the efficacy of the recommendation appeared to vary depending on the responsible pathogen and the epidemiological context. For this reason, the GDG considered this recommendation to be conditional.

Additional factors considered when formulating the recommendation

Values and preferences

The GDG was confident that the typical values and preferences of patients, health care workers, health care providers and policy-makers would favour hospital-based environmental surveillance when linked to environmental cleaning and the timely feedback of results to stakeholders.

Resource implications

The GDG recognized that the collection and microbiological testing of environmental cultures can require a specialized approach and that capacity-building may be required in some health care settings, especially in LMICs. The GDG also recognized that the purpose of environmental cultures was almost universally to inform hospital cleaning initiatives, but capacity-building in cleaning techniques and training may be required to achieve optimal cleaning.

Under certain circumstances, the GDG believed that the additional financial resources required for environmental surveillance cultures are worth the expected net benefit from following this recommendation. However, the GDG recognized that its implementation may be resource-intensive, particularly in LMICs. It was also noted that there will be significant implications regarding available human resources, microbiological/laboratory support, information technology and data management systems for the implementation of this recommendation. Furthermore, laboratory quality standards must be considered as these will affect the outcome of surveillance data and interpretation. Despite these potential resource implications, the GDG regarded the function of environmental surveillance cultures as important under certain conditions.

Feasibility

While feasibility is likely to vary substantially in different settings, the GDG was confident that this recommendation can be accomplished in all countries. However, local human resources

(including technical capacities) and laboratory capacity will need to be evaluated and addressed, particularly in LMICs. Additional education will likely be required to help standardize the audit and surveillance process across all countries.

Acceptability

The GDG was confident that key stakeholders are likely to find this conditional recommendation acceptable when applied under the appropriate circumstances. Of note, a priority assessment is required to adequately evaluate environmental surveillance and take decisions.

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- the most optimal sampling methods to accurately identify environmental contamination with CRE-CRAB-CRPsA and the appropriate laboratory processing of cultures to maximize the identification of these pathogens from such specimens;
- the most cost-effective approaches to surveillance cultures for CRE-CRAB-CRPsA.

3.8 Recommendation 8: Monitoring, auditing and feedback

The panel recommends monitoring, auditing of the implementation of multimodal strategies and feedback of results to health care workers and decision-makers.

(Strong recommendation, very low to low quality of evidence)

Rationale for the recommendation

- Among the 11 CRE studies, nine included monitoring, auditing and feedback (for example, feedback of results to leadership and health care workers) as part of their assessed intervention (28, 48, 50-56). Eight of the nine reported a significant reduction in CRE outcomes (28, 48, 51-56).
- Among the five CRAB studies, four included monitoring, auditing and feedback as part of their assessed intervention (50, 57-59). Three of the four reported a significant reduction in CRAB outcomes (50, 57, 59).
- Among the three CRPsA studies, all included monitoring, auditing and feedback as part of their assessed intervention (58, 60, 61). Two reported a significant reduction in CRPsA outcomes (60, 61).
- Despite the limited available evidence and its very low quality, the GDG unanimously agreed that the strength of this recommendation should be strong. This decision was based on the:
 - panel’s conviction regarding the benefit of monitoring, auditing and feedback as a key IPC core component to prevent and control CRE-CRAB-CRPsA, which is consistent with the reviewed evidence that led to the development and content of the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)* where these processes are already the object of a strong recommendation;
 - evidence and international concern regarding the burden and impact of CRE-CRAB-CRPsA colonization/infection (in particular, see epidemiological data in section 1.1 and specific reasons for developing these recommendations in section 1.2).

Remarks

- The GDG considered that the monitoring, auditing and feedback of IPC interventions are a fundamental component of any effective intervention and especially important for strategies to control CRE-CRAB-CRPsA.
- Appropriate training of staff who undertake monitoring of the implementation of multimodal strategies and the feedback of results is crucial.
- All components of the multimodal strategy intervention should be regularly monitored, including hand hygiene compliance.
- Monitoring, auditing and feedback of multimodal strategies are a key component of all IPC educational programmes.
- The GDG agreed that IPC monitoring should encourage improvement and promote learning from experience in a non-punitive institutional culture, thus contributing to better patient care and quality outcomes.

Background

The general evidence to support the monitoring, auditing and feedback of IPC interventions as an effective practical recommendation to prevent HAI and cross-transmission of pathogens has been previously summarized in the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (13)*.

Summary of the evidence

In this section, the evidence that included monitoring, auditing and feedback as part of the intervention to prevent and control CRE-CRAB-CRPsA-related patient outcomes is examined.

Studies assessing monitoring, auditing and feedback were of ITS design from countries in the Americas Region (four of 11 CRE, three of five CRAB and

two of three CRPsA studies), Eastern Mediterranean Region (two of 11 CRE, none of five CRAB and three CRPsA studies), European Region (two of 11 CRE, none of five CRAB and three CRPsA studies) and the Western Pacific Region (one of 11 CRE, one of five CRAB and one of three CRPsA studies). The intervention of monitoring, auditing and feedback was often described as the monitoring of IPC practices and feedback to both hospital and regional leadership, as well as directly to health care workers.

CRE: Nine of the 11 CRE studies included monitoring, auditing and feedback as part of a multimodal approach (28, 48, 50-56). The primary outcomes were CRE infection (six of 10), CRE bloodstream infection (two of 10), prevalence of CRE infection (one of 10) and incidence of CRE infection or colonization (one of 10), including one study with two reported outcomes. Eight of the nine studies reported a significant reduction in CRE outcomes post-intervention, including significant changes in slope (that is, trend; range: -0.01 to -3.55) and level estimates (that is, immediate change; range: -1.19 to -31.8) (28, 48, 51-56).

CRAB: Four of the five CRAB studies included monitoring, auditing and feedback as part of a multimodal approach (50, 57-59). The primary outcomes were the incidence of CRAB infection (one of four), incidence of CRAB infection and colonization (two of four) and incidence of CRAB and CRPsA colonization (one of four). Three of the four studies reported a significant reduction in CRAB outcomes after the intervention, including a significant change in slope estimates (that is, trend; range: -0.01 to -4.81) and in the level estimate of (that is, immediate change; -48.86) (50, 57, 59).

CRPsA: All three CRPsA studies included monitoring, auditing and feedback as part of a multimodal approach (58, 60, 61). The primary outcomes were the incidence of CRPsA infection (two of three) and the incidence of CRAB and CRPsA colonization (one of three). Two reported a significant reduction in CRPsA outcomes after the intervention including one significant change in the slope estimate (that is, trend; -1.36) and one significant change in the level estimate (that is, immediate change; -0.02) (60, 61).

The GDG considered the overall quality of the

evidence to be very low to low. Although monitoring and feedback was a common component of most CRE-CRAB-CRPsA studies, the approach often varied between studies and the GRADE assessment was by outcome (for example, the incidence of infection, incidence of bloodstream infection, prevalence of colonization, incidence of infection and/or colonization, etc.), rather than according to this specific intervention alone.

Additional factors considered when formulating the recommendation

Values and preferences

Although no study was identified on patient or health care worker values and preferences regarding monitoring, auditing and feedback, this was the key focus of the literature review. However, the GDG was confident that both health care workers and patients in all settings would place a high value on this recommendation. The GDG was also of the unanimous view that education and practical training on appropriate approaches for accurate monitoring, auditing and feedback of IPC interventions would be welcomed in all health care settings.

Other shared lessons on ethical considerations of monitoring can be found in the *Guidance on ethics of tuberculosis prevention, care and control* (42) and the *WHO discussion paper on addressing ethical issues in pandemic influenza planning* (65). In particular, an effective monitoring system should also consider the extent to which ethical considerations have been incorporated into formal policies.

Resource implications

The GDG was confident that the resources required to undertake effective monitoring, auditing and feedback are worth the expected net benefit and that implementing this recommendation is likely to reduce overall health care costs.

Feasibility

The GDG was confident that this recommendation is feasible in all health care settings.

Acceptability

The GDG was confident that key stakeholders are likely to find this recommendation acceptable as it is consistent with evidence previously summarized in the *WHO guidelines on core*

components of infection prevention and control programmes at the national and acute health care facility level (13).

Research gaps

The GDG discussed the need for further research in several areas related to this recommendation, including:

- monitoring, auditing and feedback of critical IPC aspects beyond that of hand hygiene (despite its importance), especially related to CRE-CRAB-CRPsA in areas such as environmental cleaning and disinfection and isolation/cohorting initiatives;
- feedback to patients and caregivers;
- more innovative, reliable methods of monitoring beyond traditional approaches, for example, electronic monitoring and feedback.

4. GUIDELINE IMPLEMENTATION AND PLANNED DISSEMINATION

The overall aim of this guideline is to improve the quality and safety of health care and the outcome of patients accessing health services, as well as the safety of health care workers, in the context of national and local action plans to prevent or reduce the spread of AMR. The emergence of CRE-CRAB-CRPsA and their rapid spread in several countries is considered to be one of the most alarming problems in the global health agenda related to AMR. Adoption of these guidelines in the form of national and local policies and their translation into practice at the facility level are therefore essential. Their integration within existing approaches to IPC and AMR surveillance and control is crucial.

National commitment to IPC and the implementation of IPC programmes, including the core components recommended in recently issued WHO guidelines (13) and their integration within the national action plans for AMR, are fundamental to the success of the CRE-CRAB-CRPsA guidelines. This is crucial for the achievement of strategic objective 3 of the AMR Global Action Plan adopted by all Member States at the World Health Assembly in 2015. It is key that national IPC programmes support the local programmes by several means, including setting national standards, fostering the training and recruitment of IPC staff, facilitating regular

provision of IPC supplies, supporting the availability of adequate infrastructures and a clean environment, and the development of coordination activities with the local IPC team and other IPC-related programmes.

Guideline implementation

The successful implementation of the recommendations in these CRE-CRAB-CRPsA guidelines is dependent on a robust implementation strategy and a defined and appropriate process of adaptation and integration at the facility level, as well as inclusion in regional and national strategies. Implementation effectiveness will be influenced by existing health systems in each country, including available resources, the existing capacity and policies and a strong coordination mechanism at the national or sub-national level. The support of key stakeholders, partner agencies and organizations is also critical.

Specific details that need to be considered to adequately implement these CRE-CRAB-CRPsA guidelines are frequently addressed within these guidelines under “Remarks” and “Additional factors considered when formulating the recommendation” for each recommendation. The key points for each recommendation are summarized below in Table 2.

Table 2. Recommendation resource implications and feasibility considerations

Recommendation	Resource implications and feasibility considerations
<p>1. Implementation of IPC multimodal strategies</p> <p>Strong recommendation</p>	<ul style="list-style-type: none"> • Multimodal strategies can be complex and require a multidisciplinary approach including executive leadership, stakeholder commitment, coordination, local champions or role models and possible modifications to workforce structure and process. Preventing or controlling the spread of CRE-CRAB-CRPsA should be advocated for as a priority patient safety issue and response to AMR. • Human resource capacity including trained IPC professionals, dedicated IPC budgets and good quality microbiological laboratory support are critical to effective IPC programmes. • Most data on IPC programme implementation come from high- and middle-income countries. However, the panel believed that the resources invested for IPC programmes are worth the net gain, irrespective of context. In settings with limited resources, prioritization should be based on local/regional needs.
<p>2. Importance of hand hygiene compliance for the control of CRE-CRAB-CRPsA</p> <p>Strong recommendation</p>	<ul style="list-style-type: none"> • Practical approaches to hand hygiene improvement and implementation should be considered according to the WHO recommendations (http://www.who.int/infection-prevention/tools/hand-hygiene/) with appropriate local adaptation. • Hand hygiene compliance and the use of alcohol-based handrub are influenced by appropriate product placement and availability. Thus, it is critical to ensure that these adequate resources are in place.
<p>3. Surveillance cultures for asymptomatic CRE colonization and surveillance of CRE infection</p> <p>Strong recommendation</p>	<ul style="list-style-type: none"> • Laboratory testing and identification of carbapenem resistance among potential CRE-CRAB-CRPsA isolates may not be available or routine in limited resource settings. However, given the threat represented by AMR spread, the panel believed that testing for carbapenem resistance in these pathogens should now be considered as routine in all microbiology laboratories to ensure the accurate and timely recognition of CRE-CRAB-CRPsA. For this reason, enhanced efforts and training related to laboratory testing, analysis and interpretation of results may be required. • To support surveillance, enhanced training on epidemiological methods and appropriate data collection and management infrastructure may also be required. • Information regarding a patient's CRE colonization status does not (yet) constitute routine standard of care provided by health systems. However, in an outbreak or high-risk situation, it was determined that CRE colonization status should be known and such information considered an important patient safety issue. This may not have an immediate benefit to the screened patient, but instead it will contribute to the overall IPC response to CRE. • In some limited resource settings, the improvement of IPC infrastructure and best practices may deserve prioritization over surveillance. The panel agreed that there is no one single best approach, but instead the decision should be guided by local epidemiology, resource availability and the likely clinical impact of a CRE outbreak. • The panel noted that although surveillance cultures of fecal material were preferred for the identification of CRE colonization, rectal swabs may be a more practical clinical specimen to collect in many health care situations. • There is growing evidence of the role of genotyping and whole genome sequencing of CRE isolates. Integrating this information into the epidemiological investigation of outbreaks is valuable to decide upon the consequent actions needed for their control. However, some questions remain unanswered, including the criteria that accurately define when a patient is no longer colonized with CRE. The panel believed that at least two consequent negative cultures should be available in order to consider a patient no longer colonized.

Recommendation	Resource implications and feasibility considerations
4. Contact precautions Strong recommendation	<ul style="list-style-type: none"> • The application of contact precautions involves an increase in workload to health care workers managing these patients, including technical expertise for their overall coordination and programme management. • The application of contact precautions requires an increase in resource usage (for example, gowns and gloves), as well as the cost for their appropriate disposal. It was noted that the use of gloves could occasionally be associated with some occupational exposure issues, such as cutaneous reactions.
5. Patient isolation Strong recommendation	<ul style="list-style-type: none"> • The preference is for colonized/infected patients to be managed in single rooms where possible. Cohorting is reserved for situations where there are insufficient single rooms or where cohorting of patients colonized/infected with the same pathogen is a more efficient use of hospital rooms and resources. However, the panel believed that patient isolation should always apply in an outbreak situation. • The use of dedicated health care workers to exclusively manage isolated/cohorted patients is recommended when feasible, although the panel acknowledged that this may be challenging in limited resource settings. • Patient isolation should be undertaken with care and sensitivity to avoid misunderstanding and increased suffering by some patients.
6. Environmental cleaning Strong recommendation	<ul style="list-style-type: none"> • Strengthening environmental cleaning could have resource implications depending on the type of cleaning product used. Most cleaning products, including hypochlorite, are generally low cost. Some cleaning agents (for example, hydrogen peroxide), while seemingly effective, can be disruptive to hospital workflow and bed utilization given the time and equipment required for their use. Products should be used according to correct instructions to prevent occupational health issues. • There may be an increased workload for hospital cleaners, although their salaries are often relatively low. • Some limited resource settings may face basic WASH challenges. A sufficient and reliable water supply is essential for basic cleaning. • All furniture should be easily cleanable as damaged furniture can prevent adequate cleaning. Environmental cleaning could also potentially lead to the enhanced degradation of some vinyl and other surfaces in hospitals.
7. Surveillance cultures of the environment for CRE-CRAB-CRPsA colonization/contamination Conditional recommendation	<ul style="list-style-type: none"> • Environmental surveillance cultures may be resource-intensive in terms of human resources and laboratory, information technology and data management infrastructures. The GDG believed that the resources invested are worth the net gain in certain conditions, particularly for CRAB outbreaks. • The collection and microbiological testing of environmental cultures can require a specialized approach necessitating capacity-building, particularly in limited resource settings. • Additional education will likely be required to help standardize the cleaning techniques and surveillance methods.
8. Monitoring, auditing and feedback	<ul style="list-style-type: none"> • Appropriate training of staff who undertake monitoring of the implementation of multimodal strategies and the feedback of results is crucial. • The GDG agreed that IPC monitoring should encourage improvement and promote learning from experience in a non-punitive institutional culture, thus contributing to better patient care and quality outcomes.

Recommendation 1

The success of this recommendation clearly depends on the implementation of the IPC Core component 5 that is related to multimodal strategies as the best approach to practically implement an IPC intervention (13). A multimodal strategy indicates the “how” to implement IPC interventions and consists of several of elements or components (three or more; usually five) implemented in an integrated way with the aim of improving an outcome and changing behaviour. It often includes tools that facilitate the organization of the work and the execution of care processes and tasks, such as bundles and checklists or standard operating procedures. Multidisciplinary teams that are able to take into account and influence local conditions are key to develop and lead the implementation of multimodal strategies. The identification and involvement of champions or role models (that is, individuals who actively promote the components of the strategy and their associated evidence-based practices within an institution) has been shown to be very effective in several cases. Implementation of the multimodal strategy indicated in this recommendation requires the organizational coordination of activities within the facility and across teams and departments (for example, infection control, microbiology, infectious diseases, etc.) and strong support by senior management. Preventing or controlling the spread of CRE-CRAB-CRPsA should be considered as a priority patient safety issue. Thus, developing or strengthening a patient safety culture within the facility should be an essential focus of the multimodal strategies in response to AMR, including outbreak situations.

Recommendation 2

Improvement of hand hygiene compliance at the point of care can be achieved by implementing the WHO strategy and using the WHO toolkit or other similar multimodal strategies (<http://www.who.int/infection-prevention/tools/hand-hygiene/en/>). The key components of the WHO hand hygiene improvement strategy (77) are:

- 1. System change:** ensuring that the necessary infrastructure is in place to allow health care workers to practice hand hygiene. This includes two key elements: (1) access to a safe, continuous water supply, soap and towels; and (2) readily accessible alcohol-based handrub at the point of care.
- 2. Training/education:** providing regular training on

the importance of hand hygiene to all health care workers, based on the “My 5 moments for hand hygiene” approach and the correct procedures for handrubbing and handwashing.

- 3. Evaluation and feedback:** monitoring hand hygiene practices and infrastructure, together with related perceptions and knowledge among health care workers, while providing performance and results feedback to staff.
- 4. Reminders in the workplace:** prompting and reminding health care workers about the importance of hand hygiene and the appropriate indications and procedures for its optimal performance.
- 5. Institutional safety climate:** creating an environment and the perceptions that facilitate awareness raising about patient safety issues, while guaranteeing consideration of hand hygiene improvement as a high priority at all levels. This should include active participation at both the institutional and individual levels, an awareness of the individual and institutional capacity to change and improve (self-efficacy), and partnership with patients and patient organizations.

Recommendation 3

Sample collection for the surveillance of CRE colonization and reporting of results should be done as soon as possible after hospital admission or risk exposure. Some experts even believe that screening of high-risk patients should be undertaken in the emergency department when it is clear that they require hospital admission. However, even with prompt screening, there is an inevitable delay between sample collection and obtaining laboratory results. Thus, for patients considered to be at potentially high risk of CRE infection or colonization, pre-emptive patient isolation may need to be considered in some circumstances until surveillance results become available. The GDG considered such actions and information as an important patient safety issue. For this reason, the GDG believed that there was no need to obtain formal written patient consent for each screening culture, as long as a robust system was in place to routinely explain to patients the CRE prevention and control programme and its importance. However, it is important to recognize that such surveillance programmes may be associated with additional financial costs in terms of the microbiological cultures, the subsequent need for patient isolation and the equipment required. Nevertheless, these costs are universally considered

to be worthwhile if they help to avoid a CRE outbreak as these types of outbreaks are well known to be very costly to contain. The GDG recognized the growing evidence of the role of genotyping and whole genome sequencing of CRE isolates and the value of integrating this information into the epidemiological investigation of outbreaks to help orient the consequent actions needed for their control. Nevertheless, some questions remain unanswered, including the criteria that accurately define when a patient is no longer colonized with CRE. Practical issues such as “*how many negative surveillance cultures truly mean a patient is no longer colonized*” remain uncertain, yet they can have substantive practical implications in terms of patient management both in outbreak and endemic settings. According to expert opinion, the GDG noted that at least two consequent negative cultures should be available in order to consider a patient no longer colonized; other protocols addressing surveillance guidance among other CRE prevention and control measures also exist (78).

Recommendations 4 and 5

The GDG recognized that an adequate and continuous availability of patient rooms and equipment/supplies are needed for the successful implementation of contact precautions and that the cost of this infrastructure and materials (including their disposal) was a critical consideration that requires careful planning, including resource availability. In some cases, it was noted that important details, such as what material is optimal for some equipment (for example, gowns), remain currently uncertain and require further research. Of note, the education and training of staff regarding these recommendations is critical for their successful and reliable implementation, as well as appropriate communication of their importance to patients.

Recommendations 6 and 7

Adequate routine cleaning of health care facilities is a fundamental pillar of good IPC, yet it may not always be undertaken as rigorously as it should be or as it is assumed to be. For CRE-CRAB-CRPsA control, good cleaning is critical. Nevertheless, the optimal cleaning agent has not yet been totally defined. The GDG noted that ensuring appropriate regular cleaning should not be considered as “enhanced” cleaning, but instead it should comprise the careful execution of standard cleaning protocols with special attention to the

“patient zone”. Furthermore, the GDG recognized that the evidence demonstrating the value of environmental screening cultures related to their impact on improved environmental cleaning standards and activities was limited.

Recommendation 8

Monitoring, auditing and feedback is a fundamental aspect of any IPC intervention to demonstrate compliance and thus link it to the outcomes intended to be improved. These guidelines highlight the need to monitor the multimodal strategy (Recommendation 1) and the implementation of each specific recommendation. Standardized national or international tools should be used as much as possible (for example, hand hygiene compliance monitoring according to the method recommended by WHO; hand hygiene self-assessment framework:

http://www.who.int/gpsc/country_work/hhsa_framework_October_2010.pdf?ua=1).

Although compliance with the recommendations should demonstrate the effect of these CRE-CRAB-CRPsA guidelines, the GDG recognized that some important topics that are likely to impact on their success may have not been discussed in this document and these need to be considered in the context of monitoring, auditing and feedback. In particular, the importance of good antimicrobial stewardship programmes to ensure appropriate antimicrobial prescribing to minimize the emergence of CRE-CRAB-CRPsA and the “selective pressure” that inappropriate prescribing can play in the problems associated with CRE-CRAB-CRPsA colonization and infection.

Guideline dissemination

The guidelines will be made available online and in print, together with all supplementary and additional information. They will also be accessible through the WHO library database and the web pages of the WHO IPC Global Unit, the WHO Antimicrobial Resistance Secretariat and the WHO Department of Service Delivery and Safety.

Active dissemination will then take place through a number of mechanisms including (not exclusively):

- The Global IPC Network and the WHO *Save Lives: Clean Your Hands* and *Safe Surgery Saves Lives* global campaigns;
- The WHO AMR coordination mechanisms, including the Newsletter;

- WHO collaborating centres;
- WHO stakeholders and collaborators (for example, other Service and Delivery Units, WASH unit, Emergency Response programme);
- WHO regional and country offices, ministries of health, nongovernmental organizations (including civil society bodies);
- Other United Nations agencies;
- Professional associations;
- Professional national and international societies.

Consideration will be given to the role of regional dissemination workshops and other international conferences and meetings, depending on successful resource mobilization.

The use of social media within the context of mobile health technologies will also be explored as a mechanism to supplement conventional dissemination approaches.

The guidelines will be translated into all official United Nations languages as soon as possible. Third-party translations into additional non-United Nations languages will be encouraged, complying with WHO guidance on translations. A short summary of the guidelines will be made available in print and online.

Technical support for the adaptation and implementation of the guidelines in countries will be provided at the request of ministries of health or WHO regional or country offices.

The IPC teams at all three levels of WHO will continue to work with all stakeholders and implementers to identify and assess the priorities, barriers and facilitators to guideline implementation. The team will support the efforts of stakeholders to develop guideline adaptation and implementation strategies tailored to the local context. Adaptation of the recommendations contained in the guideline is an important prerequisite to successful uptake and adoption to ensure the development of locally appropriate documents that are able to meet the specific needs of each country and its health service. However, modifications to the recommendations should be justified in an explicit and transparent manner.

Dissemination through the scientific literature is considered crucial for the successful uptake and adoption of the recommendations and WHO and members of the Systematic Reviews Expert

Group aim to develop a number of papers for publication in peer-reviewed journals.

Evaluation of the recommendations

Implementation of these CRE-CRAB-CRPsA guidelines can be measured in a number of ways and an evaluation framework will be developed by the WHO IPC Global Unit in collaboration with stakeholders involved in the guideline development. Lessons learned from the dissemination and implementation of these guidelines will be reviewed in the development of the evaluation strategy. Mechanisms will be explored to track:

- The number of countries that incorporate the CRE-CRAB-CRPsA guidelines in their facility and national IPC and AMR programmes. At present, no monitoring system exists that can collect this information in a comprehensive manner on a routine basis, but this will be actively explored.
- The number of print copies and downloads from the WHO website as an indicator of interest in the guideline.
- The number of requests for technical assistance from Member States.
- Requests relating to adaptation and translations.

Review and update of the recommendations

Informed by the evaluation approach, WHO will establish a review period for these guidelines every 3-5 years.

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APPENDICES

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Appendix 2: Inventory of national and regional guidelines

An inventory of regional and national guidance documents related to the management of CRE-CRAB-CRPsA infections/colonization was identified and analysed, including a web search and expert consultation. The approach covered all six WHO regions (African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region). WHO regional focal points and GDG members were requested to provide input on existing documents from countries and regional offices. For documents with no existing translation in English, French, German, Italian, Portuguese or Spanish, experts were asked to summarize the key points presented. The aim was to learn from and compare with the identified guidance documents,

while acknowledging that they significantly range in scope and evidence base, thus highlighting the need for the development of international evidence-based guidelines for the management of CRE-CRAB-CRPsA.

In total, 34 guidance documents were identified, including 30 national and four regional documents (1-34). Twenty-six (76%) did not report the methods for their guidance development. Two (6%) reported an expert consultation process only, five (15%) reported an expert consultation process and a literature review, and two (6%) reported both a literature review and a grading of evidence. Fourteen (38%) included suggestions for implementation strategies (for example, suggested roles, organizational and strategy planning processes and tools). Twenty-one (62%) were specific to CRE/CPE compared to all gram-negative bacteria.

Table. Overall characteristics of identified guidance documents

Characteristic	N=34 (%)
Scope of guidance	
National guidance documents	30 (88)
Regional guidance documents	4 (12)
Methods for guidance development	
None reported	25 (74)
Consultation only	2 (6)
Consultation and literature review	5 (15)
Literature review and grading of evidence	2 (6)
Included implementation strategies*	14 (41)
Focus of guidance	
CRE/CPE	20 (59)
Resistant gram-negative bacteria	14 (41)

* For example, suggested roles, organizational and strategy planning processes and tools.

The publication year ranged between 2012 and 2014 among the seven guidance documents that reported a literature review. The origin of publications included the European Region (five; 71%), the Western Pacific Region (one; 20%) and an international working group (one; 20%) (2-8). Across all guidance documents, there was an emphasis on a multifaceted approach (namely, screening, contact precautions, patient isolation, cohorting, hand hygiene, cleaning and the built environment). Such a multimodal strategy is strongly recommended in the *WHO guidelines on*

core components of infection and prevention and control programmes at the national and acute health care facility level (35).

The 2014 European Society of Clinical Microbiology and Infectious Diseases guidelines for the management of infection control measures to reduce the transmission of multidrug-resistant gram-negative bacteria in hospitalized patients used the most robust evidence-based methods, including a comprehensive systematic review and the GRADE approach to formulate recommendations (2).

These guidelines include detailed recommendations by pathogen group and epidemiological setting, including endemic and epidemic (that is, outbreak). Common strategies with strong recommendations across the pathogens included hand hygiene and contact precautions for endemic settings, and hand hygiene, contact precautions, active surveillance and isolation for epidemic settings.

Among the remaining guidance documents that reported a literature review (six), all recommended screening and patient isolation and five (83%) recommended cohorting, hand hygiene, environmental cleaning, inter-facility communication protocols and stewardship. Three (50%) recommended medical record alerts or real-time laboratory notification protocols and two (33%) recommended education. According to the *WHO guidelines on core components of infection and prevention and control programmes at the national and acute health care facility level (35)*, all guidance documents recommended strategies relevant to the core components on surveillance and multimodal strategies and five (83%) recommended strategies relevant to the core components of IPC programmes, guidelines and the built environment.

The publication year ranged between 2009 and 2017 among the 27 guidance documents that reported no literature review. The origin

of publications included the European Region (16; 59%), the Region of the Americas (nine; 33%), the South-East Asia Region (one; 4%) and the Western Pacific Region (one; 4%) (1, 9-34). Twenty-five (93%) recommended screening, contact precautions and hand hygiene. Twenty-four (89%) recommended patient isolation, 20 (74%) recommended environmental cleaning, 18 (67%) recommended cohorting and 15 (56%) recommended stewardship. Less than half recommended inter-facility communication protocols (13; 48%), education (12; 44%), medical record alerts or real-time laboratory notification protocols (11; 41%) and chlorhexidine (six; 22%). According to the *WHO guidelines on core components of infection prevention and control programmes at the national and acute health care facility level (35)*, all recommended strategies relevant to the core component on multimodal strategies, 25 (93%) recommended strategies relevant to the core component on surveillance, and 20 (74%) recommended strategies relevant to the core component on the built environment.

A comprehensive list of *selected* national CRE guidelines can be found at: <https://ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/carbapenem-resistant-enterobacteriaceae>, accessed 26 October 2017.

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