

GUIDELINE

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Dutch guideline for the prevention and control of multidrug-resistant organisms in the hospital setting, 2024 update

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Abstract

The emergence of multidrug-resistant organisms (MDROs) represents a significant challenge for global healthcare systems. The Netherlands maintains one of the lowest antimicrobial resistance rates in the world, attributed to prudent antibiotic use and effective infection prevention and control policies in healthcare settings. This report presents an updated national guideline for the infection prevention and control of MDROs in hospitals, developed by the Dutch Collaborative Partnership for Infection Prevention Guidelines (SRI). Using a multidisciplinary approach and evidence-based frameworks such as AGREE-II and GRADE, the guideline addresses the definition of MDRO, risk assessment and recommendations for MDRO screening, isolation and infection prevention measures, source and contact tracing, discontinuation of isolation measures, and organization of care. It incorporates new evidence, and other aspects such as patient perspectives, sustainability, costs, and organizational factors, providing practical recommendations to mitigate MDRO transmission. This update aims to strengthen national infection control practices and sustain the Dutch low antimicrobial resistance levels.

Keywords Guidelines, Infection control, Cross infection, Evidence-based practice, Microbial Drug Resistance, Transmission

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Introduction

Antimicrobial resistance is rising to alarmingly high levels worldwide, leading to increased medical costs, prolonged hospital stays, and higher morbidity and mortality rates [1]. The Netherlands remains one of the countries with the lowest antimicrobial resistance rates in clinical isolates across Europe [2]. For instance, the prevalence of vancomycin-resistant *Enterococcus faecium* (VRE) in blood cultures is substantially lower in the Netherlands, at 0.5%, compared to the European Union /European Economic Area (EU/EEA) population-weighted mean percentage of 19.8% in 2023 [2]. Similarly, the prevalence of carbapenem-resistant Enterobacterales remains low, with 0.1% for *Escherichia coli* and 0.4% for *Klebsiella pneumoniae* versus 0.3–13.3% across the EU [2]. Only the prevalence of third-generation cephalosporin-resistant Enterobacterales has increased in recent years in the Netherlands, with resistance in *E. coli* rising from 6.1 to 8.0% and in *K. pneumoniae* from 7.6 to 10.2% over the past 10 years [2, 3]. However, it remains below the EU average (2023: 16.2% for *E. coli* and 34.8% for *K. pneumoniae*) [2].

The low prevalence of antimicrobial resistance in the Netherlands is largely attributed to the prudent and restrictive use of antibiotics [4], and effective infection prevention and control (IPC) policies in healthcare settings. These measures are guided by national guidelines and overseen by the Dutch Health and Youth Care Inspectorate (IGJ). The first Dutch guideline for multidrug-resistant organisms (MDRO) was published in 2005 and updated in 2012 as part of a planned revision [5, 6]. However, no further revisions have been made since 2012, highlighting the need to update the MDRO guideline. New insights, such as revised MDRO criteria and updated IPC measures, should be incorporated.

From 1981 to 2017, the Dutch Working Party on Infection Prevention (Werkgroep Infectie Preventie [WIP]) was responsible for developing national IPC guidelines to reduce nosocomial infections and the transmission of pathogens in healthcare settings [7, 8]. After the dissolution of the WIP, a new infrastructure was established, and in 2021, the Dutch Ministry of Health, Welfare and Sport (VWS) launched the Dutch Collaborative Partnership for Infection Prevention Guidelines (Samenwerkingsverband Richtlijnen Infectiepreventie [SRI][9]), a new guideline organization dedicated to developing evidence-based IPC guidelines [8]. During the interim period, no revisions were made to the existing WIP guidelines. The SRI has since published its first set of guidelines online, including the guideline for MDRO [10].

The SRI guideline on MDROs outlines IPC measures in specialist medical care settings—primarily hospitals—to

prevent the transmission of MDROs, excluding methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant tuberculosis (MDR-TB), as these are addressed in separate SRI guidelines. The guideline is intended for healthcare professionals involved in the care of patients with MDROs and those responsible for developing and implementing local IPC policies. The guideline was developed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence-to-Decision Framework, which allows clinical questions to be addressed using evidence from systematic literature reviews, supplemented by expert opinions and additional literature [11, 12]. In this paper, we describe the methodology, results and recommendations of the MDRO guideline developed by the SRI.

Methods

The guideline was developed following recommendations from established manuals on guideline development, including the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) [11–13].

Guideline development group

A multidisciplinary Guideline Development Group (GDG) with a balanced range of expertise was formed. The GDG consisted of representatives from the Dutch Society of Medical Microbiology (NVMM), the Dutch Society of Internal Medicine (NIV), the Dutch Society of Dermatology and Venereology (NVDV), the Dutch Society of Infection Prevention and Control in the healthcare setting (VHIG), the National Institute for Public Health and the Environment (RIVM), the Dutch Association of Elderly Care Physicians and Social Geriatricians (Verenso), the Dutch Nursing Association (V&VN), the Patient Federation Netherlands (PFNL) and the Netherlands Society of Occupational Medicine (NVAB). The GDG held regular meetings with support from a guideline methodologist [8].

Key questions

During the preparatory phase, the GDG consulted relevant stakeholders to gather input on the challenges faced in the care of patients with MDROs. Additional feedback was collected from stakeholders during an invitational conference. Recommendations from the previous guideline [5, 6] were also reviewed to identify areas for potential revisions. Based on these inputs, the GDG prioritized the challenges and formulated draft key questions, which were subsequently finalized.

Evidence review and grading

The clinical questions focused on the effectiveness of various IPC aspects. Comprehensive searches were conducted in Embase, Ovid/Medline, and Cinahl to identify relevant studies published in English. These databases were searched up to date as stated in each review protocol (see Additional files). Studies were selected based on their design, study population, and interventions.

For each clinical question, the data were summarized and evaluated using the GRADE methodology, which categorizes the quality of evidence as high, moderate, low, or very low [8, 11, 12, 14, 15]. If the GDG determined that the evidence was insufficient in a particular area, further research to address identified knowledge gaps could be recommended.

Guideline recommendations

When formulating guideline recommendations, the GDG used conclusions from the systematic literature review to answer the clinical questions. However, these conclusions were not always directly applicable as practical recommendations. Therefore, the evidence-to-decision framework required the GDG to consider other aspects, such as patient perspectives, sustainability, preferences, costs, and organizational aspects [8, 12]. These considerations, often based on expert opinion or literature not included in the systematic literature review, were explicitly and systematically documented, presenting arguments both in favour and against various IPC measures [11, 12]. Recommendations were thus based on a combination of the scientific conclusions from the systematic literature review (if applicable) and additional considerations. The quality of evidence and the weight of the additional considerations influenced the strength of each recommendation.

Results

The key questions and recommendations were structured into six distinct modules.

Module I: definition of multidrug-resistant organisms (MDRO)

Various definitions of MDRO exist in the international literature. In 2012, an international group of experts proposed interim standard definitions for “multidrug-resistant”, “extensively drug-resistant”, and “pan drug-resistant” bacteria to enhance global uniformity [16]. These definitions have been criticized for being overly broad and for assigning equal weight to all antimicrobial classes. In 2017, the World Health Organization (WHO) published a list of resistant bacteria that should be prioritized for the development of new antibiotics [17].

Although widely used to guide IPC measures globally, this WHO list was not initially intended for that purpose. Recently, an update of the list was published, but again, primarily focused on research and development [18].

Since 2005, a context-specific definition for MDRO has been developed, tailored to the Dutch healthcare system. This approach built on the aforementioned international publications and focused on more pragmatic criteria. According to this definition, MDROs are characterized by three core criteria: (a) the microorganism causes disease, (b) it has acquired antimicrobial resistance that hampers (empirical) therapy, and (c) it has the potential to spread if transmission-based precautions are not implemented [5].

To further establish consensus, in 2021, the Dutch Society of Medical Microbiology (NVMM) consulted its members to define which microorganisms should be classified as MDROs based on these criteria. Potential MDROs were assessed by medical microbiologists, with microorganisms primarily transmitted outside healthcare settings (e.g., *Streptococcus pneumoniae*, *Salmonella* spp., and *Neisseria gonorrhoeae*) excluded. Consensus that a microorganism met all three criteria provided a solid rationale for the GDG to designate it as an MDRO.

The GDG based its recommendations largely on the previous national guideline [6], expert opinion, and consensus, while also considering additional factors such as the clinical impact of limited treatment options on patient outcomes, the organism's transmissibility, and the effectiveness of IPC measures. These factors informed decisions regarding the classification of MDROs and the implementation of screening, isolation, and other IPC interventions.

Evidence and rationale for the recommendations

Based on the abovementioned considerations, a list of microorganisms classified as MDRO has been compiled and presented in Table 1. One new pathogen, *Candida auris*, is added to the updated MDRO list [6]. Given the high prevalence of antifungal resistance [19–23], the rapid resistance development [24, 25], and the lack of consensus on antifungal susceptibility testing and clinical breakpoints [26], *C. auris* is classified as an MDRO in all cases, regardless of susceptibility test results. Conversely, some microorganisms previously classified as MDROs are no longer considered as such. For example, Enterobacterales resistant to aminoglycosides and fluoroquinolones are no longer defined as MDROs, as these organisms do not significantly hinder treatment with standard therapies.

Plasmid-mediated AmpC beta-lactamase-producing Enterobacterales Plasmid-mediated AmpC beta-lactamase-producing Enterobacterales were not classified as MDRO in the previous national guideline [6], primarily due to the absence of reported outbreaks in the Netherlands and the low prevalence of plasmid-mediated AmpC beta-lactamase Enterobacterales. Additionally, differentiating between chromosomal and plasmid-mediated AmpC beta-lactamase production was challenging with the laboratory methods available at the time [27]. However, advancements in diagnostic techniques since the 2012 guideline have prompted a reassessment of whether plasmid-mediated AmpC beta-lactamase-producing Enterobacterales meet the criteria for MDRO classification.

While plasmid-mediated AmpC beta-lactamase-producing Enterobacterales meet the first two core criteria (disease causation and obstruction of standard therapy), it was unclear if they also met the third criterion (transmissibility). A systematic literature review was conducted to explore the following question in addressing this issue: *Are outbreaks caused by E. coli, K. pneumoniae, Klebsiella oxytoca, or Proteus mirabilis with a plasmid-encoded AmpC beta-lactamase (without extended-spectrum beta-lactamase or carbapenemase) observed in healthcare facilities, if only basic IPC measures are implemented?* See Additional file 1 for the corresponding Population, Intervention, Comparison, and Outcomes (PICO) question, summary of the literature, results, and evidence tables. Three studies were included in the literature analysis [28–30]. The GDG concluded that available data from these studies did not justify classifying Enterobacterales with a plasmid-encoded AmpC gene as MDRO requiring additional IPC measures. The literature suggests that the spread of these bacteria in specialized medical care settings has been minimal. Furthermore, a surveillance study in the Netherlands reported a decrease in the carriage of these microorganisms among hospitalized patients from 2013 to 2016, even without additional IPC measures [31]. Consequently, the GDG concludes that plasmid-mediated AmpC beta-lactamase-producing Enterobacterales do not currently meet the criteria for classification as MDRO. However, given the dynamic nature of hospital-associated bacteria and the unpredictable evolution of microbial trends, there remains a possibility that successful Enterobacterales strains with plasmid-encoded AmpC genes could emerge. Therefore, ongoing surveillance in hospitals is essential to detect any potential rise of such strains.

Recommendation 1

Consider the following microorganism as MDRO:

Table 1 An overview of microorganisms defined as MDRO

Microorganism	Resistance (mechanism) ¹
Enterobacterales	ESBL
Enterobacterales	Carbapenem ² or carbapenemase
Enterobacterales group II ³	Aminoglycosides ⁴ + fluoroquinolones ⁵ + sulfamethoxazole/trimethoprim
<i>Acinetobacter baumannii-calcoaceticus</i> complex ⁶	Aminoglycosides ⁴ + ciprofloxacin or levofloxacin
<i>Acinetobacter baumannii-calcoaceticus</i> complex ⁶	Carbapenemase ⁷
<i>Pseudomonas aeruginosa</i>	≥3 of the following: Tobramycin or amikacin Carbapenem ⁸ or carbapenemase Piperacillin Ceftazidime Fluoroquinolones
<i>Enterococcus faecium</i>	Vancomycin or vanA gene or vanB gene + penicillin-group
<i>Candida auris</i> ⁹	Regardless of resistance ¹⁰

In specific settings, such as neonatology or haematology, local policies may define MDRO differently, often due to specific antimicrobial prophylaxis. During outbreaks of resistant pathogens not yet classified as MDROs, additional infection prevention measures may be necessary

ESBL = extended-spectrum beta-lactamase

¹ Resistance is determined based on clinical breakpoints (see <https://www.eucast.org/>)

² For *Proteus* spp., *Providencia* spp., *Serratia marcescens* and *Morganella morganii* imipenem is not considered

³ Includes *Citrobacter freundii*, *Enterobacter* spp., *Klebsiella aerogenes*, *Hafnia alvei*, *Morganella morganii*, *Providencia* spp., *Serratia marcescens*, and other Enterobacterales typically carrying chromosomal AmpC

⁴ Resistance to gentamicin or tobramycin or amikacin; for *S. marcescens* tobramycin and amikacin are not considered [76, 77]

⁵ Resistance to ciprofloxacin, norfloxacin, or levofloxacin

⁶ Includes *Acinetobacter calcoaceticus*, *A. baumannii*, *A. pittii*, and *A. nosocomialis*

⁷ The *bla*_{OXA-51} gene is not considered a carbapenemase gene, as it is an intrinsic chromosomal resistance gene. If the laboratory cannot detect relevant carbapenemase genes or carbapenemase production, resistance to imipenem and/or meropenem should be determined based on clinical breakpoints

⁸ Excluding ertapenem

⁹ See WHO fungal priority pathogens list

¹⁰ Susceptibility testing is always indicated

Recommendation 2

Do not classify Enterobacterales with a plasmid-mediated AmpC gene as MDRO. Monitor in hospital settings for increases based on phenotype to detect nosocomial transmission of Enterobacterales with a plasmid-mediated AmpC gene, and implement outbreak management measures to control outbreaks

Module II: risk assessment for screening of MDRO and recommendations for MDRO selection per risk

For the past 20 years, Dutch hospitals have implemented a risk-based screening policy for asymptomatic MDRO carriage upon admission [6]. This policy (search and destroy/control) targeted known MDRO carriers, patients who had been hospitalized in another Dutch healthcare setting with an outbreak within the past two months during an ongoing outbreak, and patients who had been hospitalized in a foreign healthcare setting within the past two months, as they were all considered at higher risk for MDRO carriage. These patients were screened upon admission and (pre-emptively) isolated while awaiting culture results to reduce patient-to-patient transmission. Since 2015, it has also been recommended to additionally screen individuals residing in refugee centers, although this recommendation was based on limited evidence [32]. Patients treated in foreign healthcare settings were screened for Gram-negative MDRO, while the recommendation to screen individuals from refugee centers did not specify which MDRO to screen for.

The previous national MDRO guideline [6], international guidelines, and relevant scientific articles were reviewed to evaluate whether the current risk groups still have an increased risk of MDRO carriage. This review also aimed to determine whether potential new risk groups, such as travelers without healthcare-related contacts, should be added, taking into account the (low) background prevalence of MDROs in the Netherlands.

Evidence and rationale for the recommendations

Foreign healthcare setting Several recent studies have examined the risk of MDRO carriage associated with recent admissions to foreign healthcare settings, all of which support the inclusion of hospitalization abroad as a risk factor. See Additional file 2 for an overview of studies from primarily low-endemic MDRO countries that report the prevalence of MDRO carriage among patients treated in foreign hospitals or otherwise provide data on this risk factor. Based on this data, the GDG recommends maintaining the current risk assessment, which includes recent admission to a healthcare facility abroad for Gram-negative MDRO. However, the GDG also recommends screening for VRE for this group, given the currently low prevalence of VRE in the Dutch population [33] and the occasionally high carriage rates within this risk group (Additional file 2). Additionally, screening for *C. auris* is recommended as *C. auris* is an emerging pathogen caus-

ing outbreaks of invasive healthcare-related infections worldwide, including in Europe [21, 22].

Refugee shelters In recent years, several studies have investigated the prevalence of MDRO among asylum seekers and refugees. See Additional file 2 for an overview of studies reporting MDRO prevalence among individuals residing in refugee centres. Compared to the background prevalence in the Netherlands, a higher prevalence of MDRO was observed in individuals living in or recently staying at refugee centres. For this reason, the GDG recommends screening individuals who have resided in a refugee centre within the past two months for at least ESBL-producing Enterobacterales and carbapenemase-producing or carbapenem-resistant Enterobacterales (CPE/CRE). The GDG does not recommend screening this group for multidrug-resistant *P. aeruginosa*, resistant *A. baumannii-calcoaceticus* complex, or *C. auris* due to a lack of evidence.

Patients recently traveling abroad (without healthcare contact) Traveling abroad is often cited as a risk factor for MDRO carriage. A recent systematic review of 22 studies concluded that the risk of acquiring an MDRO depends on the travel destination and the use of antibiotics during the trip. The highest rates of MDRO carriage were observed after travel to South Asia (median 71%), followed by North Africa (median 41%), with ESBL-producing *E. coli* being the most found. Although CPE was found in only a few cases, the culture methods used were not always aimed at detecting it [34]. A study by Wuerz, which included 15 studies, also showed an increased prevalence of ESBL-producing Enterobacterales among travellers, particularly if fluoroquinolones were used during the trip [35]. The duration of MDRO carriage acquired during travel is generally short, ranging from a median of 30 days [36] to 1–2 months [37], although this can vary depending on the clone.

Based on this data, the GDG concludes that patients who have recently travelled to Asia (including Turkey) and/or Africa have an increased risk of carrying ESBL-producing Enterobacterales and possibly CPE or CRE. The GDG advises healthcare facilities to be vigilant for possible ESBL-producing Enterobacterales and CPE/CRE carriage in travellers from these regions and leaves it to the local healthcare facility, whether to include this group in the risk assessment.

Risk assessment in the outpatient setting The risk assessment is indicated upon or shortly before admission to a healthcare facility, not during outpatient clinic visits [38]. However, in some outpatient settings, invasive procedures are performed. Additionally, there are outpatient departments that can be considered clinical departments based on the patient population or type of care provided (such as dialysis and oncology day centres). In these cases, the risk of MDRO transmission may be higher or have a larger impact, making a risk assessment necessary. The GDG considers it the responsibility of the healthcare facility to determine which outpatient departments are classified as “clinical” depending on the invasiveness of the procedures performed or the characteristics of the patient population.

Recommendation 3

Conduct following risk assessment upon or shortly before admission to a healthcare facility, as well as during visits to outpatient clinics that the healthcare facility designates as clinical departments:

1. Determine if the patient is a known carrier of an MDRO and implement appropriate infection control measures
 2. Screen for carriage of all MDROs listed in Recommendation 1 in patients who meet the following criteria:
 - Patients who stayed in a healthcare facility abroad for more than 24 h within the last two months
 - Patients who stayed in a healthcare facility abroad for less than 24 h within the last two months and underwent an invasive procedure
 - Patients who stayed in a healthcare facility abroad between two and twelve months ago and underwent an invasive procedure
 3. Screen for MDRO carriage in patients transferred from another Dutch healthcare facility with an ongoing MDRO outbreak. Screen for the specific MDRO causing the outbreak
 4. Screen for extended-spectrum beta-lactamase-producing Enterobacterales (ESBL-E) and carbapenemase-producing or carbapenem-resistant Enterobacterales (CPE/CRE) in patients who have resided in a refugee center within the past two months
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Module III: Isolation and infection prevention measures

While standard precautions apply to all patient interactions (regardless of their MDRO status), the GDG considers them insufficient to prevent MDRO transmission; therefore, additional organism-specific measures are recommended. While substantial evidence supports these additional measures to prevent MDRO transmission, many studies assessed bundled strategies. These strategies typically combine interventions such as specific personal protective equipment (PPE), single-room or isolation settings, and environmental disinfection. This bundling complicates assessment of the effectiveness of individual interventions. Furthermore, many studies are conducted during outbreaks, often lacking control groups and are prone to performance bias.

To provide recommendations on which IPC measures should be taken to prevent MDRO transmission, specified by each MDRO, the GDG considered most

recommendations from the previous national MDRO guideline [6], along with international guidelines and expert opinions. A systematic review of the literature was conducted to assess the scientific evidence supporting the need for terminal disinfection of patient rooms when a patient is infected with or colonized by ESBL-producing *E. coli*. Another systematic review was performed to determine if additional IPC measures are necessary in the outpatient setting.

Evidence and rationale for the recommendations

Isolation and infection prevention measures in the inpatient setting Table 2 provides an overview of the isolation and additional IPC measures for each MDRO in the inpatient setting, while Additional file 3 details the evidence and rationale behind these recommendations.

In summary, alongside standard precautions such as hand hygiene according to the WHO's 5 Moments [39], healthcare workers are advised to wear gowns and gloves when in direct contact with patients or their immediate environment in all cases of MDRO. This practice reduces the risk of contaminating hands and clothing, which could otherwise contribute to the transmission of MDRO.

For the *A. baumannii-calcoaceticus* complex and *C. auris*, the use of a surgical mask is recommended during patient care. In the case of *A. baumannii-calcoaceticus* complex, this is recommended due to insufficient evidence to revise the recommendation from the previous national MDRO guideline [5, 6]. For *C. auris*, a surgical mask is recommended because much remains unknown about the transmission routes of this emerging microorganism.

A. baumannii-calcoaceticus complex and *C. auris* are the only microorganisms for which an isolation room with an anteroom and specific air management (e.g., ventilation control) is recommended. *A. baumannii-calcoaceticus* complex can potentially spread via airborne transmission [40, 41]. For *C. auris*, although the exact transmission route is not yet fully understood and airborne transmission is unlikely, current literature indicates that it can spread easily and cause outbreaks in healthcare settings [22]. The presence of an anteroom may improve adherence to infection control measures. For all other MDRO, the GDG advises using a single patient room with dedicated sanitary facilities. An exception is made for ESBL-producing Enterobacterales, for which isolation in a multiple-occupancy room may be permitted under certain conditions. This exception is supported by a recent cluster-randomized study that found no difference in ESBL-producing Enterobacterales infection risk between single and multiple-occupancy rooms [42]. However, the GDG still prefers single rooms

Table 2 an overview of the isolation and infection prevention measures described for each multidrug-resistant microorganism

Microorganism	Resistance	Patient room	Personal protective equipment			Terminal cleaning and disinfection after discharge, transfer, or death
			Gown	Surgical mask	Gloves	
Enterobacterales	ESBL	Single patient room with dedicated sanitary facilities Exception: A multiple-occupancy room is permitted if no single patient room is available, provided there is a 1.5-m space around the bed and dedicated sanitary facilities	Yes	No	Yes	Yes
Enterobacterales	Carbapenem or carbapenemase	Single patient room with dedicated sanitary facilities	Yes	No	Yes	Yes
Enterobacterales group II	Aminoglycosides + fluoroquinolones + sulfamethoxazole/trimethoprim	Single patient room with dedicated sanitary facilities	Yes	No	Yes	Yes
<i>Acinetobacter baumannii-calcoaceticus</i> complex	Aminoglycoside + ciprofloxacin or levofloxacin	Negative-pressure isolation room	Yes	Yes	Yes	Yes
<i>Acinetobacter baumannii-calcoaceticus</i> complex	Carbapenemase	Negative-pressure isolation room	Yes	Yes	Yes	Yes
<i>Pseudomonas aeruginosa</i>	≥ 3 of the following: Tobramycin or amikacin Carbapenem or carbapenemase Piperacillin Ceftazidime Fluoroquinolones	Single patient room with dedicated sanitary facilities	Yes	No	Yes	Yes
<i>Enterococcus faecium</i>	Vancomycin or <i>vanA</i> gene or <i>vanB</i> gene + penicillin-group	Single patient room with dedicated sanitary facilities	Yes	No	Yes	Yes
<i>Candida auris</i>	Regardless of resistance	Negative-pressure isolation room	Yes	Yes	Yes	Yes
High risk for MDRO carriage, regardless of type (e.g. a recent admission to a foreign healthcare facility)		Single patient room with dedicated sanitary facilities	Yes	No	Yes	Yes (if culture results are not yet available)

for ESBL-producing Enterobacterales to reduce contamination risk and improve adherence to infection control measures. If a single room is unavailable, contact isolation in a multiple-occupancy room may be allowed, provided a 1.5-m clearance around the bed and dedicated sanitary facilities.

Finally, terminal disinfection of a patient room following the discharge, transfer, or death of a patient with an MDRO infection or carriage is a widely accepted routine practice in Dutch hospitals. However, the necessity for terminal disinfection specifically for ESBL-producing *E. coli* is sometimes debated. In response to this debate, a systematic review of the literature was conducted to address the following question: *Is terminal disinfection of a patient room necessary after the discharge, transfer, or death of a patient infected with or carrying ESBL-producing Escherichia coli?* See Additional file 4 for the PICO criteria and the result of the search. Unfortunately, no studies meeting the PICO criteria were identified. Consequently, the GDG concluded that scientific evidence to support the de-implementation of terminal disinfection for ESBL-producing *E. coli* is currently lacking. Therefore, the recommendation remains unchanged from the previous national guideline: terminal disinfection (following cleaning) of the room is always recommended after the discharge, transfer, or death of a patient with any MDRO.

Recommendation 4

In the inpatient setting, when caring for or treating a patient with an MDRO (or a suspected MDRO) involving direct patient contact and/or contact with the patient's immediate environment, apply isolation and additional infection prevention measures as outlined in Table 2

Recommendation 5

Following the discharge, transfer, or death of a patient with an MDRO, including ESBL-producing *Escherichia coli*, perform terminal cleaning and disinfection of the patient room and the sanitary facility. This recommendation applies to single- and multi-occupancy patient rooms

Isolation and infection prevention measures in the outpatient setting It is unknown whether MDRO transmission occurs during outpatient visits. To address this research question, a systematic review of the literature was conducted. The GDG focused the literature search on evaluating the need for additional IPC measures specifically for VRE, CPE/CRE, and carbapenemase-producing or carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CP/CRAB). This selection was based on the potential risk of spread within healthcare facilities and the challenges of treating infections with limited antibiotic options. The review aimed to answer the following

question: *Are there outbreaks in outpatient clinics caused by vancomycin-resistant Enterococcus faecium, carbapenemase-producing or carbapenem-resistant Enterobacterales, or carbapenemase-producing or carbapenem-resistant Acinetobacter baumannii-calcoaceticus complex in the absence of additional measures beyond standard precautions?* See Additional file 5 for the PICO question, a summary of the literature and evidence tables.

The literature search yielded three outbreak studies [43–45] involving VRE and CPE/CRE in outpatient settings. Additionally, one observational study [46] described the risk of environmental contamination with VRE during outpatient visits. These outbreak studies indicate that CPE transmission can occur in outpatient clinics and have, in rare cases, initiated outbreaks in healthcare settings. Two studies describe extensive VRE contamination in dialysis units, which can lead to outbreaks. No studies were found regarding outbreaks of CP/CRAB in outpatient settings.

Despite the above findings, the GDG concluded that there is insufficient scientific evidence to support the routine implementation of additional IPC measures in outpatient clinics, as the transmission risk is generally lower than inpatient clinics. The GDG considered that contact and care moments in outpatient clinics are typically shorter and less intensive than inpatient settings. However, in situations where the outpatient clinic functions similarly to an inpatient unit—based on the type of care and/or patient population (e.g., dialysis and oncology day centers)—the GDG identified a higher risk and impact of transmission of VRE, CPE/CRE, and CP/CRAB. Therefore, additional IPC measures for these MDROs are indicated in such settings.

Recommendation 6

For patients with (suspected) vancomycin-resistant *Enterococcus faecium* (VRE), carbapenemase-producing or carbapenem-resistant *Enterobacterales* (CPE/CRE), or carbapenemase-producing, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex (CP/CRAB) in outpatient setting, additional infection prevention measures should be implemented if there is a high risk of transmission due to the nature of the care provided or if transmission would significantly impact the patient population

Module IV: source and contact tracing

Source and contact tracing are generally considered essential components of IPC policies. They provide insights into the potential spread of an MDRO, enabling early detection and helping prevent further transmission between patients. However, conducting these investigations requires additional resources, including materials, tools, and personnel, which leads to increased costs. Therefore, it is important to determine when and how

source and contact tracing should be implemented in cases of unexpected carriage or infection with an MDRO.

In developing considerations and recommendations, the GDG primarily focused on inpatient care.

To provide recommendations for conducting source and contact tracing, the GDG reviewed the previous national MDRO guideline [6], and supplemented it with expert opinion. Consideration was also given to the (low) background prevalence of MDRO in the Netherlands.

Evidence and rationale for the recommendations

In cases of an unexpected MDRO detection, the source and contact investigation follow the “ring principle”. This method starts by screening those with the highest risk of exposure, typically the patient’s roommates or immediate contacts. If another positive case is identified, the screening circle is widened to include patients at moderate or lower risk of exposure. The scope of screening is determined by infection control professionals, such as medical microbiologists or infection control practitioners [47]. Decisions regarding whether to implement additional isolation and IPC measures for close contacts while awaiting culture results are also made by these specialists as additional infection control measures may not always be necessary. Contact tracing and screening among healthcare workers is generally unnecessary, because MDRO carriage in staff rarely leads to transmission when standard precautionary measures are properly followed [48].

Exception policy for ESBL-producing *Escherichia coli* in non-outbreak situations In the previous national MDRO guideline, an exception was made for ESBL-producing bacteria, stating that contact tracing was not required for an unexpected ESBL case in non-outbreak situations, provided adequate surveillance was in place within the healthcare facility to detect any increase in cases [6]. The rationale at the time was that approximately 4% of the Dutch population carried ESBL-producing bacteria, making it challenging to identify nosocomial transmission, particularly because accurate typing methods were not yet widely available.

Although the prevalence of ESBL carriage in the Netherlands has remained stable at around 5% [49], the GDG has revised its recommendation on source and contact tracing. The previous policy remains valid for cases of unprotected contact with ESBL-producing *E. coli*, where contact tracing can be omitted if adequate surveillance is in place. However, for other ESBL-producing Enterobacterales, source and contact tracing is now recommended. This revision is due to the global dissemination of ESBL genes among virulent non-*E. coli* Enterobacterales lineages, which have increasingly spread within healthcare settings. In recent years, several outbreaks

involving ESBL-producing non-*E. coli* Enterobacterales have been reported in Dutch hospitals [50]. These non-*E. coli* ESBL-producing Enterobacterales pose a higher transmission risk than *E. coli* [42], and carriers also face an increased risk of infection [51]. As a result, source and contact tracing is recommended for all cases of unprotected contact.

Recommendation 7

Conduct source and contact tracing using the ring principle, targeting at least close contacts, when a patient who has been cared for without infection control measures is unexpectedly identified with an MDRO. For unexpected cases of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*, source and contact tracing can be omitted if adequate surveillance is implemented

It is not necessary to extend source and contact tracing to healthcare workers

Consult with an expert (e.g., medical microbiologist, or infection control practitioner) to determine whether additional isolation and infection prevention measures should be implemented for close contacts of the patient while awaiting the results of MDRO screening

If source and contact tracing indicate that transmission has occurred, initiate an investigation for a potential outbreak

Module V: discontinuation of isolation and infection prevention measures

Although infection prevention and isolation measures are essential to prevent MDRO transmission, they can reduce patient satisfaction, lower the quality of care provided, and increase healthcare workers’ workload [52–54]. Therefore, it is important to discontinue these measures once a patient is no longer an MDRO carrier. However, clear criteria for ending isolation remain lacking, and the previous guideline [6] did not specify the requirements needed to confirm MDRO clearance.

Evidence and rationale for the recommendations

The absence of clear criteria to determine when a patient is no longer an MDRO carrier raises important questions for clinical practice. To address these, a systematic review of the literature was conducted. The review aimed to answer the following question: *When can a patient with a previously detected MDRO be considered MDRO-free (i.e., after what duration and/or under what conditions)?* Details of the PICO framework, a summary of the literature, and evidence tables, can be found in Additional file 6. A systematic search was performed to provide evidence-based answers to the clinical question.

The literature search led to the inclusion of 15 studies [55–69]. The GDG noted significant variation in the reported duration of MDRO carriage across these studies. This variability can be partly explained by differences in diagnostic methods for detecting MDRO, variations in the number and locations of cultures collected, and the intrinsic characteristics of the microorganisms. Although

spontaneous loss of an MDRO often occurs within a few months, some individuals may carry MDRO for several years. Because the duration of carriage is unpredictable at the individual level, follow-up cultures are necessary to confirm MDRO clearance. Moreover, insights into the course of MDRO carriage have motivated recommendations regarding the optimal timing of follow-up cultures.

The literature shows that multiple cultures are needed to confirm the end of MDRO carriage reliably. Studies suggest using 1 to 3 negative cultures to define loss of carriage of ESBL-producing Enterobacterales and CPE/CRE. For VRE, 2 to 5 negative cultures are suggested. Misclassifying an MDRO carrier as MDRO-negative can increase the risk of an outbreak due to the premature discontinuation of isolation and IPC measures. The likelihood that a patient is correctly identified as MDRO-negative depends partly on the duration of carriage and the number of negative cultures obtained.

Given the very low level of evidence regarding the optimal timing and number of cultures, the GDG based its recommendations on insights from the literature and expert opinion. These recommendations take into account the risk of MDRO transmission within healthcare facilities and the potential for these organisms to cause infections that are difficult to treat with antibiotics.

For sampling sites, the GDG refers to the Dutch national guideline *Laboratory Detection of Multidrug-Resistant Organisms* [70], which generally includes rectal swabs or feces and, if applicable, clinical sites. *C. auris* is currently not included in the laboratory detection guideline. Pending a revision of this guideline, the GDG recommends following the guidance of Meijer et al. [71]: obtaining throat, nasal, and (peri-)anal swabs, along with additional swabs from the axilla, groin, and any other previously identified positive sites.

For patients known to be MDRO carriers who are likely to require readmission or future care, follow-up cultures are advised to confirm the clearance of MDRO carriage. Patients should be informed about the importance of these follow-up cultures and the process for obtaining them.

The GDG recommends follow-up cultures starting three months after the last positive culture to determine the loss of carriage of ESBL-producing Enterobacterales. The study with the largest number of patients [55] showed that after three months, 25% of the carriers have spontaneously lost the MDRO. The GDG considers the impact of incorrectly declaring loss of carriage for this MDRO type minimal. Therefore, the GDG advises confirming the end of carriage with two negative cultures taken on separate days, in line with common practice in studies and reflecting current practice in Dutch healthcare facilities. If the patient has received antibiotics to which the ESBL-producing Enterobacterales is

susceptible, the first culture should be obtained at least 48 h after the antibiotics have been discontinued.

For CPE/CRE, similar to ESBL-producing Enterobacterales, 25% of patients spontaneously lost the MDRO after three months, as reported in the previously mentioned study [55]. However, Oren et al. [72] reported that 45% of patients who initially tested negative for CPE/CRE had subsequent positive cultures. Due to the significant impact of the spread of CPE/CRE and based on the GDG's experience that individuals who test negative in the first year may remain carriers in subsequent follow-up cultures, the GDG advises that a CPE/CRE carrier should be considered MDRO-positive during the first year after the last positive culture, even if negative cultures are obtained. After one year, the likelihood of decolonization increases, and the end of carriage can be confirmed with two negative cultures, similar to the approach for ESBL-producing Enterobacterales. To minimize the risk of incorrectly declaring a patient MDRO-free, the GDG recommends that follow-up cultures (one set) be taken during the year following the end of carriage if the patient is admitted to a healthcare facility. If antibiotics to which CPE/CRE are susceptible have been administered, the first culture should be obtained at least 48 h after the antibiotics have been discontinued.

Long-term carriage for VRE is common, and the risk of VRE transmission in healthcare settings is high. The GDG recommends managing VRE carriers in a manner similar to CPE/CRE, considering them positive during the first year after the last positive culture, even if negative cultures are obtained. False-negative culture results are more common for VRE compared than for antimicrobial-resistant Enterobacterales. Current evidence suggests that the end of VRE carriage can be reliably confirmed ($\geq 95\%$) with five negative cultures, provided selective broth enrichment is used [73]. Sensitivity increases to 99.3% when molecular diagnostics and a selective broth enrichment step are used together [74]. If both a selective broth enrichment and polymerase chain reaction (PCR) are performed, the GDG advises establishing the end of carriage with three negative cultures. Additionally, the GDG recommends taking follow-up cultures (one set) during the first year after the end of carriage when the patient is admitted to a healthcare facility. If antibiotics susceptible to VRE have been given, the first culture should be taken at least 48 h after discontinuation of antibiotic therapy.

Other MDRO For multidrug-resistant group II Enterobacterales, multidrug-resistant *Pseudomonas aeruginosa*, resistant *Acinetobacter baumannii-calcoaceticus* complex and *C. auris*, the GDG is not aware of adequate studies on timing and number of cultures required to determine the end of carriage. However, since there is a need for

recommendations for these MDRO, the same reasoning was applied as for ESBL-producing Enterobacterales, CPE/CRE, and VRE. For multidrug-resistant group II Enterobacterales, the expected duration of carriage and the associated impact are considered like those for ESBL-producing Enterobacterales. Therefore, the GDG makes the same recommendation as for ESBL-producing Enterobacterales. For multidrug-resistant *Pseudomonas aeruginosa*, resistant *Acinetobacter baumannii-calcoaceticus* complex, and *C. auris*, GDG considers the risks and the sensitivity of detection methods to be comparable to CPE/CRE. Thus, the recommendations for the timing and number of cultures are the same as those for CPE/CRE.

Recommendation 8

When expecting readmission or future care, take follow-up cultures to demonstrate the end of MDRO carrier status based on the MDRO schedule outlined below. Cultures should only be collected if the patient has not received antimicrobials that suppress the growth of the relevant MDRO during and up to 48 h prior to the culture collection

ESBL-producing Enterobacterales (ESBL-E) and multidrug-resistant (MDR) group II Enterobacterales

Confirm the end of ESBL-E and MDR group II Enterobacterales carriage with two negative culture sets, collected on separate days, starting at least three months after the last positive culture

Carbapenemase-producing or carbapenem-resistant Enterobacterales (CPE/CRE)

Confirm the end of CPE/CRE carriage with two negative culture sets, collected on separate days, starting one year after the last positive culture

Take follow-up cultures (one culture set) if a patient is admitted to a healthcare institution in the first year after termination of carrier status to check for recurrences

Vancomycin-resistant Enterococcus faecium (VRE)

Confirm the end of VRE carriage with five negative culture sets, collected on different days, starting one year after the last positive culture. Three negative culture sets are sufficient if both a selective broth enrichment and PCR are used for detection

Take follow-up cultures (one culture set) if a person is admitted to a healthcare institution in the first year after the end of carriage to check for recurrences

Multidrug-resistant P. aeruginosa and resistant Acinetobacter baumannii-calcoaceticus complex

Confirm the end of multidrug-resistant *P. aeruginosa* and resistant *A. baumannii-calcoaceticus* complex carriage with two negative culture sets, collected on separate days, starting one year after the last positive culture

Take follow-up cultures (one culture set) if a person is admitted to a healthcare institution in the first year after the end of carriage to check for recurrences

Candida auris

Confirm the end of *Candida auris* carriage with two negative culture sets collected on separate days, starting one year after the last positive culture

Take follow-up cultures (one culture set) if a person is admitted to a healthcare institution in the first year after the end of carriage status to check for recurrences

Module VI: organization of care

The Netherlands is recognized for having a significantly lower MDRO prevalence compared to many other countries [1, 2]. In order to preserve this low prevalence, there are essential organizational requirements for managing patients with a suspected or confirmed MDRO infection or carrier status.

Healthcare facilities must ensure safe care by implementing transparent IPC policies and clearly communicating MDRO status to care providers and patients. Patient MDRO status should be shared with care providers and explained to patients. Outbreaks require a coordinated response by an outbreak management team, including isolation, contact tracing, and reporting to public health authorities. In addition to managing outbreaks, institutional MDRO policies should carefully balance IPC with the individual care needs, behaviour, and well-being of patients. Special consideration is required for the impact of prolonged isolation or restrictions, ensuring patient well-being is preserved while safeguarding public health.

To support epidemiology and regional/national outbreak management, outbreaks must be reported in accordance with the Public Health Act. Healthcare institutions must notify the Health and Youth Care Inspectorate of incidents as specified in the Healthcare Quality Act. In the event of an MDRO outbreak, the Health and Youth Care Inspectorate emphasizes the importance of early reporting to the Healthcare-associated Infections and Antimicrobial Resistance Monitoring Group (SO-ZI/AMR), a national advisory body dedicated to providing timely national monitoring and risk assessment of nosocomial outbreaks [50].

Surveillance of MDRO

National/regional Building on organizational efforts to manage MDROs, effective surveillance is important for monitoring and controlling their spread. In the Netherlands, national surveillance is conducted by the RIVM for CP/CRAB and carbapenemase-producing *Pseudomonas aeruginosa*. Additionally, sharing information about MDRO spread within healthcare institutions is encouraged through regional healthcare networks to facilitate earlier detection and prevent transmission.

Specialist medical care Under the current risk assessment, some MDRO carriers may not be identified promptly within specialist medical care. However, it is important to recognize the early spread of MDROs. Medical microbiologists and IPC experts are responsible for implementing an effective surveillance system that includes monitoring MDROs through clinical cultures and routine screening swabs, investigating potential epi-

demiological links, and performing typing when needed. Additional methods, such as screening all currently hospitalized patients at a certain point in time (point prevalence study), or screening patients with a prolonged hospital stay (e.g. 7 or 10 days), may enhance early detection and outbreak prevention.

At present, not all resistant microorganisms are categorized as MDROs. However, some resistant organisms may eventually meet the criteria and be classified as such. The plasmid AmpC-producing *Klebsiella* spp. (except *K. aerogenes*), *E. coli* and *P. mirabilis* are not currently designated as MDROs. Nevertheless, hospitals should implement surveillance to detect the emergence of new, successful AmpC gene-carrying Enterobacterales. This can be done, for example, by monitoring the presence of ESBL-negative isolates of these species with a cefotaxime and/or ceftazidime MIC ≥ 8 ug/ml in clinical cultures.

Recommendation 9

Share information about the spread of MDROs within the healthcare institution nationally and regionally
Establish a surveillance system to detect the early spread of MDROs

Epilogue

In 2021, the Ministry of Health, Welfare, and Sport launched a new initiative called the Dutch Collaborative Partnership for Infection Prevention Guidelines (Samenwerkingsverband Richtlijnen Infectiepreventie, SRI) [8, 9]. The SRI is a collaboration among various key stakeholders to develop, maintain, and manage high-quality infection prevention and control (IPC) guidelines with broad support. One of the first guidelines published by the SRI was the guideline for IPC of multidrug-resistant organisms (MDROs) for hospitals.

The previous national MDRO guideline served as the foundation for this new version. A key improvement was that the updated guideline was developed in line with the recommendations from The Appraisal of Guidelines for Research and Evaluation (AGREE-II) [13]. This is a highly structured, transparent, and informative system for assessing the quality of evidence used in guideline development. Evidence-based guidelines are generally recognized for improving the effectiveness and quality of care, reducing variations in healthcare practices, and minimizing costly and avoidable adverse events [13].

Unfortunately, there is often limited availability of high-quality graded evidence to support strong recommendations in IPC. A recent review by Mitchell et al. [75] evaluated 31 national and international IPC guidelines published over the last decade, revealing that most recommendations were based on low-quality evidence. This is primarily because conducting randomized controlled trials in this area is often neither feasible nor ethical.

This lack of high-quality graded evidence presents a challenge for guideline developers. During the development of the MDRO guideline, the team systematically searched for relevant research to address the key questions posed. Some questions could be answered with the available evidence, while others could not be conclusively answered. The evidence-based methodology used in the guideline development process highlighted existing knowledge gaps. Consequently, the guideline development group (GDG) identified areas where scientific knowledge is limited, and further research is required to strengthen future recommendations (Additional file 7).

In the initial phases of the guideline development, the GDG consulted relevant professional organizations to gather input on the challenges encountered in caring for patients with MDROs. These consultations provided a comprehensive overview of challenges in the field, which were subsequently prioritized by the GDG to formulate draft key questions. While this structured approach ensured a focus on the most pressing issues, it also highlighted a wide range of challenges that extended beyond the scope of the clinical questions ultimately addressed in this guideline. Due to time and resource constraints, not all identified challenges could be addressed in this version of the guideline. This underscores the need for sustained efforts and sufficient resources to address the existing and new challenges in IPC.

As this guideline specifically focuses on medical specialist care, particularly hospitals, a separate guideline for prevention and control of MDRO in long-term care settings is currently under development by the SRI as a derivative of the hospital guideline and is scheduled for publication in 2025. This ensures that IPC measures are appropriately tailored to the distinct contexts and needs of both hospital and long-term care sectors.

To conclude, this guideline aims to provide recommendations on the definitions of MDRO and measures to prevent the transmission of MDRO in hospitals, thereby contributing to maintaining low levels of antimicrobial resistance in the Netherlands. However, additional research is essential to provide more precise answers to practical and unanswered questions in the future.

Abbreviations

AGREE-II	Appraisal of guidelines for research and evaluation II
CP	Carbapenemase-producing Acinetobacter baumannii-calcoaceticus complex
CPE	Carbapenemase-producing enterobacterales
CRAB	Carbapenem-resistant Acinetobacter baumannii-calcoaceticus complex
CRE	Carbapenem-resistant Enterobacterales
ESBL	Extended-spectrum beta-lactamase
EU/EEA	European Union/European Economic Area
GDG	Guideline development group
GRADE	Grading of recommendations assessment, development and evaluation
IGJ	Dutch health and youth care inspectorate (Inspectie Gezondheidszorg en Jeugd)

IPC	Infection prevention and control
MDR-TB	Multidrug-resistant tuberculosis
MDRO	Multidrug-resistant organisms
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NIV	Dutch society of internal medicine
NVAB	Netherlands society of occupational medicine
NVDV	Dutch society of dermatology and venereology
NVMM	Dutch society of medical microbiology
PCR	Polymerase chain reaction
PFNL	Patient federation Netherlands
RIVM	National Institute for public health and the environment
SO-ZI/AMR	Healthcare-associated infections and antimicrobial resistance monitoring group
SRI	Dutch collaborative partnership for infection prevention guidelines (Samenwerkingsverband Richtlijnen Infectiepreventie)
V&VN	Dutch nursing association
Verenso	Dutch association of elderly care physicians and social geriatricians
VHIG	Dutch society of infection prevention and control in the healthcare setting
VRE	Vancomycin-resistant <i>Enterococcus faecium</i>
VWS	Dutch Ministry of Health, Welfare, and Sport
WHO	World Health Organization
WIP	Dutch working party on infection prevention (Werkgroep Infectie Preventie)

Supplementary Information

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Supplementary Material 1
Supplementary Material 2
Supplementary Material 3
Supplementary Material 4
Supplementary Material 5
Supplementary Material 6
Supplementary Material 7

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Author contributions

AS and VW were equal contributors to the draft of the manuscript. AS, VW, EB, MT, JO, BV, PB, YR, JV, PM, RN, MK, AV, HG, BV and JS contributed to conceptualization, formal analysis, and writing and editing of the guideline. AS, MK, HG and BV provided methodological guidance and support. All authors read and approved the final manuscript.

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Declarations

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Consent for publication

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Competing interests

The authors declare no competing interests.

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