Prevention of Carbapenemase-producing Enterobacteriaceae (CPE) transmission in the Danish health care sector: Who should be screened for CPE and when? A systematic literature study

Degree Project in one year Master programme in medical microbiology, with specialization in infection prevention and control, 15 hp

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Abstract

Background

Carbapenemase-producing Enterobacteriaceae (CPE) cases increases every year in Denmark and the proportion of CPE positive cases with a travel history decreases. Several epidemiological links are found in the healthcare settings reflecting infection prevention and control (IPC) challenges and raising questions about whether the Danish screening tool identifies the right patients at the right time to timely establish relevant IPC measures.

Aim

To identify additional risk factors than described in the Danish CPE screening protocol in order to detect the Danish CPE positive patients and thereby reduce the risk of transmission and outbreaks.

Methods

A systematic literature search was conducted in PubMed, Embase and Cochrane Library during March 2022. Retrieved studies dealt with patients with laboratory confirmed CPE (colonization and/or infection) and associated risk factors with the aim to identify CPE colonized and/or infected patients and thereby prevent transmission and outbreaks. A systematic review was performed, and a selected group of studies providing knowledge of significant CPE risk factors in different countries with generalizable results were included.

Results

Nineteen studies were included. Antimicrobial therapy, especially broad-spectrum antibiotics, prior or current hospitalization and especially long hospitalization, travel history with or without hospitalization abroad were significant risk factors associated with CPE acquisition. Furthermore, comorbidities and invasive procedures were identified as risk factors for CPE acquisition, but without the possibility to identify specific comorbidities or invasive procedures associated with risk for CPE colonization and/or infection.

Conclusion

The results from this literature study can provide supplemental knowledge for developing a new additional algorithm for CPE screening of Danish inpatients and suggest further research.

Implications

This systematic literature review may be used as a supplement when revising the current Danish CPE screening protocol.

Background

Antimicrobial resistance is an increasing threat to global public health limiting our future capability to treat infections[1]. Due to a long-standing restrictive antibiotic policy and infection prevention and control (IPC) measures, the incidence in Denmark and other Scandinavian countries is still relatively low. However, in a globalized world microorganisms spread across borders and within countries[2]. Antimicrobial resistance surveillance is an important tool to follow trends, investigate transmission patterns and to guide interventions. Screening programs are a part of the surveillance and an important tool for early detection of carriers. Screening also provide information of potential clusters and outbreaks and important epidemiological knowledge that are used for interventions by the IPC teams.

Carbapenemase-producing organisms (CPO) are multi drug resistant organisms of special concern. Carbapenemases are enzymes that hydrolyse the most important antibiotics. Placed on transferable plasmids the carbapenemase genes spread between different groups of bacteria, often with additional resistance mechanisms, leaving none or only a few options of treatment.

In Denmark the Danish Health Authority and the State Serum Institute divided CPO into two main groups: Carbapenemase-producing Enterobacteriaceae (CPE), e.g. carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* and 'environmental' bacteria, e.g. carbapenemase producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii*[3,7].

The European Center of Disease Control (ECDC) published recommendations for IPC measures already in 2011 including CPE rectal screening at hospital admission, admission to specific wards, and during outbreaks[4]. The screening method, e.g. universal screening or risk-based screening, should be determined based on local prevalence, types of hospitals, capabilities of the laboratory and available resources and should be described in a National guideline[4].

In addition, the Centers for Disease Control and Prevention (CDC) classified CPE as "an immediate public health threat that requires urgent and aggressive action" in 2013[5].

In 2018 CPE became notifiable in Denmark and The Danish Health Authority published a national guideline on preventing the spread of CPO in Danish health care[7]. The guideline includes screening criteria for CPO and, in case of known or newly detected (laboratory confirmed) CPO, additional IPC measures are established[7]. Despite this effort, outbreaks occur within and between hospitals and other healthcare institutions and the number of CPO cases increases in Denmark every year and infections are associated with increased mortality and burden of disease with consequences for both the individual and society[4,6]. Timely identification of patients for whom supplementary IPC precautions are required is important to prevent transmission and outbreaks.

The Danish exposure-based targeted CPO-screening is based on 1) a risk factor questionnaire and 2) screen sampling for microbiological analyses.
According to the Danish national guideline all patients on admission are screened for CPO risk factors by interview and diagnostic sampling if

- they have previously been diagnosed with CPO,
- if they have had household contact with a CPO-positive person in the last 6 months,
- if they have received treatment in a hospital or clinic outside the Nordic countries in the last 6 months (lasting more than 24 hours or if an invasive procedure was performed) and/or,
- if they have stayed outside the Nordic countries in the last 6 months and received antibiotic treatment during their stay[7].

The admission screening interview should include additional questions and screen sampling if the patient in the past 6 months, in Denmark or abroad, has been admitted to a hospital ward with CPO outbreak, lived in nursing homes or similar institutions with CPO outbreak, stayed in places with poor hygienic conditions (e.g. war zones, refugee camps etc.) and/or has been dialyzed or received antineoplastic treatment[7].
In summary the primary screening interview focus on risk situations associated with exposure at home or nosocomial exposure in a healthcare facility outside the Nordic counties. The additional screening interview emphasizes nosocomial exposure in an outbreak healthcare setting in Denmark or abroad, special life circumstances (e.g. war etc.), and a few patient-related risk factors.
The sampling focus mainly on colonization in the intestinal, but also on possible infected or colonized sites. According to the guideline the following are sampled: feces or stool from rectum and in addition, any wounds, foreign body insertion sites, stoma if present, urine if the patient has urinary catheter, tracheal secretions if the patient is intubated and previous CPO sites[7].

Throughout the past decade travel abroad has been considered the main cause of CPE-cases in the Nordic countries. A study from Sweden, based on surveillance data from 2007-2013, concluded that 81% of the CPE cases had a travel history and among them 84% had been hospitalized abroad. The study also found that the transmission within Swedish hospitals was low[8]. A study from Norway, based on surveillance data from 2007-2014, found that 62% of the CPE-cases had a known travel history and/or hospitalization abroad and concluded that CPE in Norway mainly is imported[9]. A study from Finland, based on data from 2010-2013, also emphasized the significance of travel history and hospitalization abroad in relation to CPE cases found in Finland[10].

However, the Danish national surveillance from 2020 showed an increase in CPO cases in Denmark even though travel abroad decreased due to COVID-19. In 2019, 43% of the CPO positive persons reported travelling outside the Nordic countries, which decreased to 17% in 2020[6].
The majority of the CPO cases were CPE. In 2020, 288 CPO isolates were reported in 207 patients. Out of these 210 were CPE isolates from 183 patients. In 2019, 221 CPO isolates were reported in 187 patients and of these 194 isolates were CPE in 168 patients, showing that the number of CPE cases increased with 8,2% in 2020 compared to 2019. The number of outbreaks also increased from 16 in 2019 to 20 in 2020 involving another 65 patients in outbreaks in 2020 compared to 2019[6].
All epidemiological links were found in healthcare settings[6] reflecting IPC challenges and raising questions about whether the Danish screening tool identifies the right patients at the right time in order to timely establish relevant IPC measures. It also reveals a transition phase from having mainly travel imported CPE occurrence towards an endemic situation with other transmission patterns which should entail adjusted interventions.
In addition, a Danish study published in 2020 identified only one out of four patients with CPE by the Danish screening questionnaire[11], which also indicates that a revision of the Danish screening protocol is needed in order to detect the CPE carriers and thereby effectuating additional IPC precautions to prevent transmission and outbreaks.
There is international consensus that CPE screening and surveillance are important tools in controlling CPE transmission and reduce the risk of outbreaks[1,2,4,5]. The epidemiology and associated risk factors remain poorly understood and vary by geography, socio-demographic composition, local prevalence of CPE and antibiotic stewardship and further knowledge is needed.
The Danish national guideline on CPO prevention is about to be revised and it is thus relevant to examine recent literature. This study will only focus on CPE, since CPE comprise the largest proportion of CPO's and are of special concern because of the ability to cause clinical disease, increasing mortality and high potential to cause outbreaks in healthcare settings[4,7].

Aims

To identify additional carbapenemase-producing *Enterobacteriaceae* (CPE) risk factors than described in the Danish CPE screening protocol in order to detect Danish patients colonized and/or infected with CPE and thereby reduce the risk of transmission and outbreaks.

Methods

This systematic literature study was based upon the instructions for Master in medical science with focus on IPC, Gothenburg University and additional recommendations[12].

Literature search

A literature search was conducted electronically in PubMed, Embase and Cochrane Library during March 2022. The chosen databases are acknowledged as databases with mainly peer reviewed studies of good quality. As preparation for the study a preliminary wide search was conducted in Google Scholar during February and March 2022.

Key words for the search (free-text and Mesh terms - adjusted to each database) were 'mass screening', 'screening', 'screened', 'carrier state', 'asymptomatic carrier', 'carbapenemase', 'carbapenemase producing', 'Carbapenem-Resistant *Enterobacteriaceae*'. In Cochrane Library 'antibiotic resistance' and '*Enterobacteriaceae*' were added to widen the search and include more studies. These key words are summarized in table 1.

The selected keywords aimed to include all relevant studies within a suitable range and took into consideration that different terms are used for CPE. 'Risk factor/risk factors' as key words narrowed the search and excluded some relevant articles and were thereby not included in the keywords. Many results were displayed in Embase, including duplicates, however for maintenance of stringency the key words used in PubMed were kept in Embase (see table 1 and 2).

The literature search was limited to studies from 2017-2022 with the aim to emphasize recent literature studies and the newest knowledge within the field (see table 1 and 2).

Table 1: Key words

Database **N (total) = 1487**	**PubMed** **N = 489**	**Embase** **N = 945**	**Cochrane Library** **N = 53**
Key words	((((("**Mass Screening**" [Mesh:NoExp]) OR (**screening**[Title/Abstract])) OR (**screened** [Title/ Abstract])) OR ("**Carrier State**/ diagnosis"[Mesh])) AND ((**carbapenemase producing**[Title/Abstract]) OR ("**Carbapenem-Resistant Enterobacteriaceae**"[Mesh])). Filter: **5 years**.	((**mass screening** OR **screening**) OR (**disease carrier** OR **asymptomatic carrier**) OR **screened** [mp] OR **screening** [mp]) AND ((**carbapenemase producing Enterobacteriaceae** OR **carbapenemase**) OR **carbapenemase producing** [mp]). Filter: **5 years**.	((**carbapenemase producing**) OR (MeSH descriptor: [**Carbapenem-Resistant Enterobacteriaceae**] explode all trees)) OR ((((MeSH descriptor: [**Mass Screening**] this term only) OR ((**screening**):ti,ab,kw) OR ((**screened**):ti,ab,kw) OR (MeSH descriptor: [**Carrier State**] explode all trees)) AND (**antibiotic resistance***))) AND (**Enterobacteriaceae****)))). Filter: **5 years**.

** and **) Added to widen the search. Without this addition the search became very narrow with only a few results.*

Selection criteria

The study population includes patients on admittance or during hospitalization. The exposure is associated risk factors for CPE colonization and/or infection and the outcome is colonization and/or infection with CPE[13].

The type of studies is all quantitative peer reviewed original clinical studies that concerns CPE colonization and/or infection and any associated risk factors. Studies focusing on outcome, e.g. mortality or treatment are excluded. Laboratory testing methods are important but outside the scope

of this review and are thereby excluded unless they provide important knowledge in relation to risk factors. Studies concerning CPE among other multi-drug resistant organisms are included if it is possible to identify the proportion of CPE. The selection criteria are summarized in table 2.

Table 2: Selection criteria

	Inclusion criteria	Exclusion criteria
Type of studies	All quantitative Peer Reviewed original clinical studies	All studies that do not meet the inclusion criteria including unpublished literature
Period	Last 5 years (January 2017-March 2022)	All studies before 2017
Language	English	All other languages
Participants	Laboratory confirmed CPE cases (asymptomatic and infected) in humans	All others that do not meet med inclusion criteria.
Where?	Health care sector	Society, animals, environment (e.g. drinking water, rivers, wastewater, food).
Subjects	Any study that concern risk factors for CPE colonization and/or infection. Studies of CPE among other MDRO's.	Studies focused on outcome, e.g. mortality or treatment including microbiota. Articles about other MDRO's* without the possibility to identify the proportion of CPE. Laboratory diagnostics and testing methods and laboratory related epidemiology. CPE/CPO in organ transplants**.

*) MDRO = Multi Drug Resistant Organisms
**) Several very specific studies concerning organ transplants were found and should be researched individually.

Article selection and data extraction

All findings that fulfilled the inclusion criteria are reported in table 3. The studies were selected first by title (N=1487), then by abstracts (N=344) followed by full text reading (N=49). Several studies were found both in PubMed and Embase and duplicates were excluded (N=33). Unpublished literature, including conference abstracts with no available full text articles, was excluded, since the study method and quality is difficult to evaluate and it does not necessarily contain sufficient and reliable information, as the abstract can be based on unfinished studies. Recent studies of considerably large study populations and those considered the best possible quality with specific relevance for the research question are selected and included after full text reading (N=19).

Thirty full text read articles were excluded because they were specific for neonates or children in countries with significant differences in healthcare (N=3), emphasised prevalence, screening effectiveness, time and number of screens and not risk factors (N=15), focussed on CPE clearance (N=1), had problematic study design with low quality and/or lack of generalizability to Danish conditions, e.g. because of differences in healthcare setting, IPC precautions or similar (N=5), small study population or amount of cases (N=5), or were based on old data (N=1). This is summarized in table 3.

Table 3: Article selection and data extraction

Database N (total) = 1487	PubMed N = 489	Embase N = 945	Cochrane Library N = 53
Titles read **N (total) = 1487**	489	945	53
Abstracts read **N (total) = 344**	166	172*	6
Duplicates excluded	-	33**	-
Full text articles selected and read **N (total) = 49**	44	4	1
Reasons for exclusion of read articles	Emphasised prevalence, screening effectiveness, time, and number of screens. Low relevance for the research question. Not generalizable and transferable to Danish conditions. Small study population. Problematic study design and low quality. Very specific. Old data.	No full text article available. Not Peer Reviewed. As mentioned in the preceding column (PubMed).	*The only study selected for full text reading is included.*
Articles included **N (total) = 19**	17	1	1

**) Includes conference abstract, that are later excluded since no full text studies were available (= not peer reviewed).*
***) Chosen for full text reading. These articles were already chosen for full text reading in PubMed.*

Nordic countries are most comparable to Danish conditions both concerning prevalence, organization of health care and restrictive antibiotic policies. Only a few studies from Nordic countries were found, but high priority was given to include these studies. Neighboring European countries are also similar in several ways, but with differences in demographics and especially in antibiotic policies leading to a higher prevalence and differences in endemicity. Far East and overseas countries are included when the results were assessed relevant for the research question and germane to a Danish context. High prevalence countries can provide useful knowledge of risk factors since the number of cases in low prevalence settings are often too small to infer statistically significance. Therefore, studies from outside Scandinavia are included.

Quality assessment

The studies are assessed according to Grading of Recommendations Assessment, Development and Evaluation (GRADE)[12]. GRADE is a transparent systematic method to summarize evidence from multiple studies and one component is to rate the quality of each individual study based on internal validity (control of systematic bias), precision (reliability), and external validity (generalizability) [12]. The quality of each study are assessed as high quality, moderate quality, or low quality.

After rating each individual study, the overall evidence is assessed based on study design, study quality, generalizability, conformity, precision, and publication bias according to GRADE[12]. Randomized control trials (RCT) are considered the highest level of evidence, but difficult to perform and find, when studying identification of risk factors. The best available evidence are observational studies although they have a lower evidence score.

Retrospective design may lead to missing or imprecise data, but they are suitable for studying rare outcomes and long latency periods like CPE colonization. Prospective designs are difficult to perform on rare outcomes or exposures but may provide better quality of data on the primary exposure and confounding variables and are often less prone to bias, since the exposures are assessed before the outcome appears[14].

The study design is connected to the study quality and refers to internal validity, e.g. the possibility to control for confounders and other background factors[12], but also the size of the study population and selection of e.g. control groups. Even if studies include large study populations, the sample size can become small if the prevalence of cases are low. This can decrease the accuracy of the results. Multivariate analyses can upgrade the studies since multivariate analyses can adjust for confounders and provide strength to the statistical analyses. Confounding arises when two compared groups are not equal in terms of risk factors[14]. The results will only be considered significant if proved in multivariate analyses and not only in univariate or bivariate analyses. Matched case-controls are another way to control confounders already at the stage of data collection.

Logistic regression models are e.g. used for the calculation of Odds Ratio (OR) and these modulations increases the evidence. Different methods are used to test if the results occurred by chance, e.g. 95% Confidence Interval (CI) and p-value[14]. CI indicates the range within which the true effect lies with 95% certainty[14]. The wider the 95% CI is, the more uncertain the result is. Small sample sizes can lead to a wide 95% CI. The p-value indicates the probability of observing the given outcome or one that is more extreme, given that the null-hypothesis is correct[14]. If the p-value is < 0.05 the result is considered significant. Also, the p-value depends on the sample size and should be interpreted with caution. These tools are used to assess the precision of the study. Precision contains the assessment of whether the number of observations are too small for statistically significance[12]. Generalizability relates to external validity of the study[12]. This assessment is rated from the lowest to the highest, ‘unclear, possible’, ‘possible’, ‘acceptable’, ‘good’ and ‘very good’ respectively, assessing the transferability to a Danish context and relevance for the research question. Conformity refers to level of consistency between the studies analyzed[12] and publication bias refers to small studies from the same group of scientists[12] and can also be related to bias of ‘positive findings’ when an effect is observed.

Finally, the overall evidence is rated from very low, low, moderate to high:

- **Very low** - very little confidence in the estimated impact, the true effect is likely to differ significantly from the estimated effect.
- **Low** - the true effect might be markedly different from the estimated effect.
- **Moderate** – moderate confidence in that the true effect probably lies close to the results, with a possibility that it is significantly different.
- **High** – confidence in that the true effect is close to the estimated effect[12].

Ethical considerations

All included studies have been approved by an ethical committee or based on clear ethical considerations and personally identifiable information are anonymized. All studies obtained, based on the inclusion and exclusion criteria, are reported.

In general, four principles in medical ethics should always be considered. They are beneficence, non-maleficence (possible false positive or false negative results), justice (cost effectiveness) and autonomy and each of these can potentially be violated by screening programmes[15]. These are important principles in relation to all patients, but especially in relation to children, since children can experience the screen sampling as an assault, the psychological impact of isolation can be severe and they cannot themselves give consent to the screen sampling. This could also be the case with mentally disabled persons or other persons with similar challenges.

Each study does not describe the ethical considerations in detail, but when the study has been approved by a relevant ethical committee it is assumed, that these aspects have been taken into account.

Results

One of the aims was to present the newest data within the field. Nineteen recent studies, written in English, are included in this study: one study from 2022, four from 2021, six from 2020, four from 2019 and four from 2017. The included studies are observational studies: eight case-control studies, five cross sectional, one descriptive and case-control study and five exclusively descriptive studies. The nineteen selected studies were conducted in seventeen different countries: Nordic countries 4 (Denmark 2, Norway 1, Finland 1), Europe 6 (France 2, Belgium 1, Austria 1, Italy 1, Hungary 1), Overseas countries 4 (USA 2, Brazil 1, Australia 1), South East Asia 4 (Singapore 1, China 1, South Korea 1, Vietnam 1) and Middle East 1 (Lebanon).

The data form the selected studies are presented and summarized in alphabetical order (first author) in table 4 and the results are extracted further in the text.

Table 4: Data extraction of selected studies

	Author, year, title, journal, country	Aim	Study-design and data collection	Selection and description of study population and outcome measures	Results	Conclusions
1	Abramowich et al; 2020; **Infections due to CPB, clinical burden, and impact of screening strategies on outcome**. Médecine et maladies infectieuses. Belgium(16).	Identification of CPB risk factors, description of the clinical features, assessment of the impact of screening strategies on clinical outcome.	Descriptive monocentric study. Laboratory diagnostics and medical records.	88 patients - all patients (age >18) admitted, with hospitalization abroad < 6 month or previously known CPB. No controls. 72% male. Medium age 68. Risk screening at admission and screening of ICU patients every week. 41% colonized, 59% developed infection. 45% of all patients were diagnosed during admission at ICU. 69% of all cases were hospital-acquired.	Out of 88 patients 80% had underlying chronic condition. Risk factors: recent invasive medical device (94% of patients), antibiotic therapy (82%), travel abroad (17%), and hospitalization (> 50%).	The study suggests screening of all ICU patients and patients at risk admitted to other wards.
2	Aung et al; 2021; **Epidemiology and Transmission of CPE in a Health Care Network of an Acute-Hospital and Its Affiliated Intermediate- and Long-Term-Care Facilities (LTCF) in Singapore**. American society for Microbio. Singapore(17).	Identification of intra and inter-facility transmission events and facility type-specific CPE risk factors in acute-care hospital (ACH) and its inter-mediate-term and long term care facilities (LTCF).	Serial cross-sectional monocentric study. Laboratory diagnostics and medical records.	5,357 adult patients. All inpatients in LTCF. Hospitalization > 48 hours in ACH were included, randomly selected. 55% from ACH, 45% from LTCF were screened: 56 patients with CPE. Median length of admission prior to screening: 10 days in ACH, 22 days in LTCF. Median age: 73. 54% male. Patients in ACH had more co-morbidities. Participation rate 87%. Serial screening during a 6 weeks period in June and July 2014-2016 of patients admitted to ACH and LTCF. 50-80% of patients from ACH were transferred to LTCF.	CPE prevalence in ACH 1.3%, 0.7% in ILTCFs. 4 times as likely that patients in the ACH are CPE colonized compared to LTCF. Significant risk factors for CPE colonisation in ACH are hospital admission >3 weeks, penicillin use, proton pump inhibitor use, dementia, connective tissue disease, prior CRE carriage in the ACH. For ILTCFs, presence of wounds, respiratory procedures, VRE carriage, and CRE carriage showed significant association.	Risk factors varies between facilities. The study showed inter-facility transmission but did not find evidence for transmission between ACT and LTCF. The study suggests targeted screening and CPE screening when long stayers are transferred from the ACH to ILTCFs.
3	Barbadoro et al; 2021; **Carriage of CRE in Adult Patients Admitted to a University Hospital in Italy**. Antibiotics. Italy(18).	To determine the prevalence of CPE in patients at admission and analyzation of selected associated factors.	Monocentric descriptive surveillance study and matched case-control. Laboratory diagnostic, surveillance data and medical records.	2478 adult patients screened on admission. 48 patients CPE positive (67% male, 56% > 65 years). Controls (same age, sex, hospital admission rate < 30 days, comorbidities as cases). Case-control ratio 1:1. Controls defined as not carrying CPE on admission. No controls had been in LTCF.	The study found a significant association between previous antibiotic use and hospital admission and CPE carriage on admission. Admission to ED was protective (83% controls and 52% of cases came from ED).	Screening patients at admission and improving infection control and screening programmes in hospitals. (CPE are endemic in Italy).

4	Cronin et al; 2017; **Risk factors for KPC-producing Enterobacteriaceae acquisition and infection in a health-care setting with possible local transmission: a case-control study**. Journal of Hospital Infection. Australia(19).	Identification of risk factors for KPC-Kp colonization and infection.	A matched case-control monocentric study. Laboratory diagnostic and medical records.	All hospitalized (>48 hours) adult patients with KPC-Kp colonization or infection. 34 cases of KPC-producing Enterobacteriaceae (including 31 KPC-Kp-cases) were matched with 136 controls. Controls were the next 4 patients admitted > 48 hours, following each case and without KPC-kp isolated from samples. 22 cases identified by clinical specimen and 12 from screening. No gender or age mentioned.	Risk factors: length of hospital stay >28 days in the past 12 months, prior VRE colonization, central venous catheter (CVC), gastrointestinal disease and invasive procedures, exposure to broad-spectrum antibiotics. Multivariate analysis showed 3 statistically significant risk factors length of hospital stay >28 days in the past 12 months, presence of a CVC and prior VRE colonization. Very few patients had overseas travel history.	Screening strategies targeting travellers can miss many cases. Patients admitted >28 days in the past 12 months, with CVC in situ, and known VRE colonization should be targeted for KPC screening. Screening should be considered if patients have been exposed to broad-spectrum antibiotics.
5	Fang et al; 2019; **Epidemiology and risk factors for CRE colonisation and infections: case-controlled study from an academic medical center in a southern area of China**. Fems. China(20).	To examine the prevalence, patient background and risk factors for CRE colonisation and infections and to clarify and identify genes that code for carbapenemases in Xiamen in China.	A monocentric case-control study. Laboratory diagnostic and medical records.	2875 inpatients hospitalized > 48 hours were screened for CRE. 47 CRE cases (median age 61, 72% male). Controls were randomly selected, negative for CRE, but positive for CSE, admitted in same unit as cases in the study period. CRE:CSE ratio 1:2. 38/47 KPC-2-carba. Controls matched cases in sex, age, demographics. *Klebsiella pneumoniae* was the main CRE isolate in 35/47. CRE were isolated from specimen in 37/47 CRE cases (possible infected cases).	Underlying conditions especially pulmonary diseases and antibiotics used prior to culture within 30 days represented key risk factors for acquisition of CRE. 83% (39/47) of cases were hospital-acquired.	Underlying conditions e.g. pulmonary diseases and antibiotics used < 30 days prior to culture represented key risk factors for CRE acquisition.
6	Hilliquin et al; 2017; **Risk factors for acquisition of OXA-48-producing Klebsiella pneumonia among contact patients: a multicentre study**. Journal of Hospital Infection. France(21).	Identification of risk factors for CPE acquisition among contacts of an index patient in non-cohorted populations.	A multicentre matched case-control study. Laboratory diagnostic and medical records.	51 secondary cases and 131 controls were included. All adults. Cases are secondary to CPE index patient and controls were also admitted at the same time and duration without acquisition of CPE. Cases: 59% male, mean age +/- SD: 70 +/- 18 years. 23/51 secondary cases were readmitted and previously known as carriers. 28/51secondary cases were identified in average 17 days (range 3-37 days) after admission. Controls remained negative, screened at least twice weekly.	Multivariate analysis: antimicrobial therapy during the exposure time, at least one invasive procedure, and geographical proximity were associated with acquisition.	Geographical proximity, invasive procedure, and antimicrobial therapy during exposure time were significantly associated with KP-OXA-48 acquisition.
7	Kim et al; 2020; **Risk Factors for CPE Infection or Coloni-**	Identification of risk factors for CPE	A monocentric case-control study.	All ICU patients (N=1176) were screened for CPE on admission and weekly. 45 CPE patients identified by screening or clinical	Multivariate analysis showed the following significant risk factors: pneumonia/chronic pulmonary	Importance of antibiotic stewardship, especially fluoroquinolone, in

	zation in a Korean Intensive Care Unit: A Case–Control Study. Antibiotics. South Korea(22).	infection and/or colonization.	Laboratory diagnostic and medical records.	cultures were included. Controls were randomly selected and did not acquire CPE during hospitalisation in the same period. Out of 45 CPE cases 13 patients were infected (average age 78, 62% male) and 32 were colonized (average age 73; 78% were male). 16 obtained CPE >48 hours after admission to ICU and were considered ICU acquired. 3,8% prevalence in ICU.	disease, previous use of fluoroquinolone, and previous use of a nasogastric tube were significant.	patients with pneumonia/ chronic pulmonary disease and using a nasogastric tube.
8	Lomont et al; 2022; **CPE and VRE faecium carriage in patients who have traveled in foreign countries: A single center 5-year prospective study**. American Journal of Infection Control. France(23).	Evaluation of the efficiency of the CPE/VRE-related French risk policy and the risk of spreading CPE/ VRE by patients who have stayed abroad without hospitalization.	A monocentric cross-sectional study. Laboratory diagnostic and medical records. Audits.	Patients who travelled abroad < 1 year before admission (N=1780) were screening and pre-emptively isolated. Median age 64 years, more men (60.6%) than women (39.4%). 59 carriers (3.3%) were detected: 44 carried only CPE, 12 only VRE, and 3 both. Median age 74 years, 68% men.	17 carriers were not hospitalized abroad, 16 carried only CPE and one only VRE. 9 of the 17 carriers without hospitalization abroad were involved in 18 readmissions during the study period, without cross-transmission. Patients who stayed abroad without hospitalization represented a true risk of spreading CPE/VRE.	35 occasions of cross-transmission would not have been detected if patients who travelled abroad without hospitalization were not screened.
9	Lusignani et al; 2020; **Infection control and risk factors for acquisition of CPE. A 5 year (2011–2016) case-control study**. Antimicrobial Resistance and Infection Control. Austria(24).	Investigate the epidemiology of CPE patients, microbiological characterization and explore CPE risk factors and evaluate current CPE IPC measures.	A monocentric case-control study. Laboratory diagnostic and medical records.	621,623 admitted patients, 75 with CRE carriage included. 58 CPE/75 CRE. Out of 58 CPE cases 47% were colonized, 53% infected. Median age of CPE patients: 48 years. Median length of ICU stay: 77 days. Case-control ratio 1:3. 177 matched controls (age, gender, hospitalization, admission close to a case patient). Current risk-based screening at admission did not identify 37 of the 58 CPE-positive patients. No CPE outbreaks occurred.	Risk factors by multivariate analysis: length of hospital admission > 20 days, hospital admission within the previous year, exposure to a healthcare facility in a country with high or unknown CRE prevalence < 3 months before admission, use of antibiotics > 10 days.	The overall CPE carriage rate in patients was very low. There is a need for an enlarged risk based targeted screening strategy.
10	Mathers et al; 2020; **Risk factors for KPC gene acquisition and clinical outcomes across multiple bacterial species**. Journal of Hospital Infection. USA(25).	To evaluate risk factors for CPE acquisition/ infection and associated clinical outcomes in the context of clonal, species-specific outbreaks.	A monocentric case-control study. Laboratory diagnostic and medical records.	20,817 inpatients in ACH or LTACH were screened. 303 KPCO cases (214 colonized, 89 with clinically confirmed infection), 5929 controls. Cases: first KPCO-positive culture > 48 h after admission. Controls: at least two negative screens (minimum 7 days apart) and no positive cultures. Median age of cases 59, 54% male, median length of stay in	Risk factors for KPCO acquisition: longer inpatient stay, transfusion, complex thoracic pathology, mechanical ventilation, dialysis, and exposure to carbapenems and β-lactam/β-lactamase inhibitors. Exposure to other KPCO-colonized patients was only a risk factor for acquisition in a single unit (direct	Healthcare exposures, antimicrobials and invasive procedures increased the risk of KPCO acquisition. IPC precautions can minimize KPCO transmission with patients from ACH to

				institution was 19 days prior to KPCO isolation.	patient-to-patient transmission did not play a major role).	LTCF. CPE guidelines may be more nuanced.
11	Moghnieh et al; 2021; **Epidemiology, risk factors, and prediction score of carbapenem resistance among inpatients colonized or infected with 3rd generation cephalonsporin resistant Enterobacterales**. Scientific reports. Lebanon(26).	Determination of the incidence and risk factors of CRE acquisition in inpatients and suggestion of a risk prediction score.	A monocentric matched case–control study. Laboratory diagnostic and medical records.	1538 inpatients with 3GCR Enterobacterales. 155 carbapenem resistant cases, mainly CPE (median age 66, 45% men) versus 155 carbapenem-sensitive 3GCR Enterobacterales (matched controls). 91/155 CRE cases were infected, 64/155 were colonized. Median length of stay after acquisition for cases: 12 days, controls 8 days.	Multivariate analysis: history of cerebrovascular disease, hematopoietic cells transplantation, presence of a chronic wound, endoscopy done during the 3 months before hospitalization, nosocomial site of acquisition of the organism in question, use of meropenem within past 3 months of CRE acquisition.	The proposed risk prediction score can help target surveillance screening for CRE among inpatients at the time of hospital admission and guide clinicians in the use of antibiotics (and on using anti-CRE therapy).
12	Predic et al; 2020; **Evaluation of patient risk factors for infection with CRE**. American Journal of Infection Control. USA(27).	To evaluate risk factors for CRE colonization/ infection and develop an algorithm for targeted CRE screening.	A monocentric matched case-control study. Laboratory diagnostic and medical records.	50 hospital acquired CRE adult patient cases (specimen collected > 48 hours after admission) and 100 CRE-negative matched controls. No significant difference between cases and controls regarding age or sex. Average age of cases 59. 28/50 were males. 30/50 CRE cases were infected and 20/50 were colonized.	Significant risk factors: use of fluoroquinolones and cephalosporins. In addition, undergoing an invasive procedure with a scope device. The significance of risk factors varied within the community-acquired and hospital-acquired cases.	Exposure to certain antimicrobials and invasive procedures with a scope device*. KPC-Kp are risk factors for CRE. It is necessary to focus on antimicrobial stewardship (CRE).
13	Räisänen et al; 2020; **Molecular epidemiology of CPE in Finland, 2012–2018**. European Journal of Clinical Microbiology & Infectious Diseases. Finland(28).	Reporting CPE data from national surveillance.	Descriptive register study. Laboratory diagnostic and surveillance data.	202 CPE positive patients (231 CPE strains) during 2012–2018. 57% were males, median age 56 years (range, 6 months – 98 years). No controls. 59% found by screening, 32% from clinical specimens, 9% information not available.	Travel or hospitalization abroad was reported in 91 patients, travel data were not available for 53 patients, 58 positive patients had no travel or hospitalization abroad. 52 strains were imported hospitalization abroad.	Travel abroad are a risk factor. 1/3 of the cases were not found by screening. The study suggests a possible hidden transmission in the healthcare settings.
14	Salomao et al; 2017; **CRE in patients admitted to the emergency department: prevalence, risk factors, and acquisition rate**.	To describe CRE prevalence in patients on ED-admission, to identify risk factors associated with colonization, and to determine the inci-	A monocentric cross-sectional survey. Laboratory diagnostic and medical records.	676 patients admitted to ED, 52% male. Patients were CRE screened < 24 hours after admission with two rectal swabs. Re-screening after 1 week. 46 patients were colonized with KPC. Mean age of cases 63 years (range 9-93). 45% were hospitalized for >1 week. 9 patients (18%) became colonized during their stay in ED. 6 cases	Multivariate analysis: Previous exposure to healthcare, liver disease, and use of antibiotics in the last month were factors significantly associated with colonization by CRE on admission to the ED.	The factors associated with CRE carriage allows to determine which population should be screened on admission and to establish contact precautions (isolation).

	Journal of Hospital Infection. Brazil(29).	dence of CRE acquisition during a stay in the ED.		(13%) had no previous exposure to healthcare in the past year. Cases were compared with those who were negative. Mean length of ED stay: 11.6 days.		
15	Samuelsen et al; 2017; **Molecular and epidemiological characterization of CPE in Norway, 2007 to 2014**. Plos One. Norway(9).	Analyzation of epidemiological, phenotypic and molecular characteristics of CPE in Norway, and to understand the molecular epidemiology.	Descriptive register study. Laboratory diagnostic and surveillance data.	53 CPE positive patients (59 CPE isolates). 44/53 were hospitalized patients. Patient age mean 63, median 66 years (range 3-96 years). No control group. 15% of isolates were obtained by fecal screening. The majority of CPE were isolated from urine (37%), blood culture (15%).	33 patients (62%) had known travel history and/or hospitalization abroad. 16 patients (30%) reported no travel or hospitalization abroad and for 4 patients (8%), no information was obtained. 8 cases were associated with secondary spread from imported cases.	CPE in Norway is mainly associated with travel. Targeted screening of patients with travel history and/or hospitalized abroad in high prevalence countries are important.
16	Skjøt-Arkil et al; 2019; **Carrier prevalence and risk factors for colonisation of multiresistant bacteria in Danish emergency departments: a cross sectional survey**. BMJ. Denmark(30).	Description of the carrier prevalence and demographic variation of four different multiresistant bacteria including CPE and analyzation of potential risk factors.	A multicenter cross-sectional survey. Interviews, laboratory diagnostic and medical records.	5117 adults (age > 18, median age 68 years, equal gender distribution) admitted at ED's > 4 hours, screening before 16 hours after admission. 4 CPE cases were identified, all men. 0,1 % CPE prevalence	Multivariate analysis was not carried out for CPE, since only 4 patients were identified. All 4 patients had been admitted to a hospital within the past 6 months, only one patient had been hospitalized outside Nordic countries and the same patient had received antimicrobial therapy abroad.	The current Danish screening program identify MRSA and CPE in fewer than 1:300 and 1:1250 patients. It's important to identify risk factors.
17	Tran et al; 2019; **High prevalence of colonisation with CRE among patients admitted to Vietnamese hospitals: Risk factors and burden of disease**. Journal of Infection. Vietnam(31).	Estimating prevalence and evaluating risk factors for CRE colonisation among inpatients (and to measure the CRE transmission and burden among new-born children in neonatal ICU).	A multicentre cross-sectional survey. Laboratory diagnostic and medical records.	2233 patients admitted to neonatal, paediatric and adult care were screened (63 wards in 12 hospitals). Patients included were admitted to or hospitalized in a participating hospital ward on the day of the CRE-point prevalence. 1165 (52%) were colonized with CRE. Mean CRE colonization rates increased from 13% on the day at admission to 89% at day 15 of hospital stay. CRE colonization increased on average 4.2% per day. ICU's had highest CRE colonisation rates.	Duration of hospital stay, HAI and treatment with a carbapenem were independent risk factors for CRE colonisation in multivariate analysis.	The study shows epidemic spread of CRE in Vietnam. Improvement in Vietnamese IPC strategies are urgent including implementation of a multimodal strategy.
18	Westerholt. et al; 2021; **Screening patients at admission to Copenhagen hospitals for carriage of resistant**	To determine the carrier prevalence and describe the phenotypic and genotypic characteristics of MRSA,	Descriptive register study Laboratory diagnostic, surveillance	2849 patients who had previous contact with healthcare systems abroad within 6 months (>24 hours or underwent invasive procedures during their stay) were screened upon admission for MRSA, VRE and CPO. 52% were male. Median age 54 years. No	The carrier prevalence for CPO was 1,5% upon admission to Copenhagen hospitals (patients with history of travel). Southern Europe, Asia and Africa were the main geographical regions.	Continued screening of all patients with previous contact with healthcare systems abroad is relevant upon admission to Danish hospitals.

	bacteria after contact with healthcare systems abroad, 2016–2019. International Journal of Antimicro. Agents. Denmark(32).	VRE and CPO in international travellers with contact to healthcare systems abroad.	data and medical records.	controls. 53 CPO isolates (42 isolates were CPE) from asymptomatic carriers.		
19	Zaha et al; 2019; **Recent Advances in Investigation, Prevention, and Management of HAIs: Resistant Multidrug Strain Colonization and Its Risk Factors in an ICU of a University Hospital**. BioMed Research International. Hungary(33).	To determine the spectrum of bacterial colonization individually among ICU patients' and to assess the predisposing risk factors for colonization.	Monocentric descriptive study. Laboratory diagnostic and medical records.	1971 patients (56% males mean age 65, 44% females mean age 70) sampled at admission to ICU (first 24 hours + after 7 days). The patients were admitted from other wards in the same hospital or referred from outside. 21% were CRE positive. 32% of the patients had been hospitalized in previous months, 75% have received antibiotics, 2.2% had chronic renal failure with regular dialysis. No controls.	Chronic liver disease and Carmeli's score were statistically significant risk factor in men. 7 days ICU stay increases the risk of CRE. For ESBL and CRE: 88% arrived at the ICU without being colonized. During the first 7 days of hospitalization 33% got infected with CRE.	It's important to identify and manage risk factors involved in the mechanism of colonization of patients with potentially multidrug-resistant pathogenic bacteria during hospitalization, especially in the ICU. Carmeli's score can be a helpful tool.

To present the data in the table in a clear manner only the first author is mentioned by name followed by et al and a reference citation and the following standard abbreviations are used, also in titles: Carbapenemase-producing bacteria (CPB), carbapenemase-Producing *Enterobacteriaceae* (CPE), Carbapenem-Resistant Enterobacterales (CRE), carbapenem-susceptible *Enterobacteriaceae* (CSE), *Klebsiella pneumoniae* carbapenemase (KPC), KPC-producing *Klebsiella pneumoniae* (KPC-Kp), KPC-producing organism (KPCO), Intensive Care Unit (ICU), Healthcare-Associated Infection (HAI), emergency department (ED), vancomycin resistant enterococci (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA).
Adult is defined as age > 18 years.
*) Endoscopic retrograde cholangiopancreatography, duodenal endoscope.

Sixteen studies indicate identification of risk factors for CPE (directly or indirectly) as the aim or a part of the aim and some studies also emphasize prevalence and secondarily identification of risk factors[16,17,18,19,20,21,22,23,24,25,26,27,29,30,31,33]. Three studies focus on surveillance data and secondarily on travel as a risk factor[9,28,32].

It appears like there is a slightly larger proportion of males in cases, but it is not possible to determine the overall gender distribution since some studies indicate the gender for the whole study population and some only for cases and one study does not mention gender.

Age is indicated by median age or mean age and vary in the different studies. Two studies does not mention the age of the study population, cases nor controls[19,31]. One study found a median age of 48 years for cases[24], another study identified a median age of 56 years[28], and two studies determined a medium age of 59 years[25,27]. Thirteen studies found a median age or mean age > 60 years[9,16,17,18,20,21,22,23,26,29,30,32,33].

Ten studies performed risk-based screening on admission[16,18,22,23,24,29,30,31,32,33] and three of these were admission to ICU and also involved screening every 7 days during hospitalization in ICU [16,22,33] and two studies screened both patients on admission and hospitalized patients[24,31].

Seven studies only screened inpatients, five of these indicated that screening were performed > 48 hours of hospitalization[17,19,20,25,27], one study only mention inpatients and not a time frame after admission[26] and another study screened secondary cases to an index patients[21], meaning that these patients must have been hospitalized already. Two surveillance studies does not provide detailed information about when the screenings were performed[9,28]. However these two countries have similar guidelines to the Danish guideline (Norway and Finland) and it is therefore likely to assume, that the majority are risk-based screenings performed on admission, but at the same time, they indicate cases found by clinical specimen which might refer to infections, probably found during hospitalization. Räisänen et al also indicate possible transmission in healthcare, most of these were probably not found on admission[28].

Five studies determined the proportion of colonized versus infected patients[16,22,25,26,27], but most studies do not have a clear distinction between colonized and infected cases, especially not in relation to associated risk factors (see table 4). Abramowitz et al did not observe any significant difference between colonized and infected patients in term of age, comorbidities, recent antimicrobial therapy, or recent stay in ICU[16].

Four out of five studies found a larger proportion of infected cases compared to colonized cases[16,24,26,27] while Mathers et al ascertained that 214 inpatients were colonized, while 89 had clinically confirmed infection[25]. Two out of the five studies conducted admission screening in ICU and screening every week during hospitalization in ICU[16,22]. One study performed risk-based

screening on admission and screening of inpatients[24] and two studies were performed on inpatients[26,27]. It would have been relevant to distinguish between colonization and infection on admission, of inpatients, and hospital-acquired CPE acquisition, but it is not possible to extract these data from all the studies.

Travel history and hospitalization abroad

Travel history and hospitalization outside Nordic countries is a central risk factor in the Danish National screening tool for CPE and six studies conducted in low or moderate prevalence countries identified travel history with or without hospitalization abroad as a risk factor by risk-based screening on admission[9,16,23,24,28,32].

Abramowicz et al determined that 17% of CPB cases had a travel history abroad[16]. The study population were ICU patients screened on admission with previous hospitalization abroad or known CPB carriage. ICU patients would often be admitted at ICU from other wards in the hospital but could also have initial admission at ICU. 69% of all cases were hospital-acquired, which could explain the low percentage of CPB cases with travel history abroad[16].

Lomont et al found that 41 patients colonized with CPE (out of 1780 screened patients with travel history < 1 year) had been hospitalized abroad. 20 CPE carriers had been abroad, but without hospitalization. The study concludes that patients with travel history, but without hospitalization, are a risk for spreading CPE[23], because the screening protocol does not include these patients.

Lusignani et al ascertained exposure to a healthcare facility in a country with high or unknown CPE prevalence 3 months prior to admission as an independent risk factor for CPE carriage[24]. Räisänen et al noticed that out of 231 CPE positive patients, 108 (63%) had travel and/or hospitalization history abroad[28] and Samuelsen et al found 62% of 53 cases with CPE were directly associated with travel or hospitalization abroad[9]. Westerholt et al evaluated the prevalence of multi drug resistant organisms, including CPE, and screened patients who had previous contact with healthcare systems abroad within the past 6 months before admission. Fifty-three CPO isolates were detected from 2349 screening results, 42 of these were CPE. The prevalence of CPO carriage with travel history was 1,5%, and showed that travel mainly from Asia, Africa and Southern Europe was associated with CPO and CPE carriage[32]. These geographic areas are areas with a different antibiotic policy than the Nordic countries. Skjøt-Arkil et al found four CPE cases in a study including 5117 patients. One patient had received treatment at a hospital or clinic outside Nordic countries[30] and Cronin et al found that very few KPC CPE cases had a history of overseas travel[19].

Previous hospitalization, hospitalization, and length of hospitalization

Eight studies conclude that previous hospitalization, hospitalization, and/or length of hospitalization is a risk factor for CPE acquisition[16,17,18,19,24,25,31,33]. Salomao et al screened patients within the first 24 hours after admission and found that previous exposure to healthcare in the last year is a risk factor for CRE acquisition[29] and Barbadoro et al also screened all patients on admission and ascertained that previous hospitalization in the past 30 days as a risk factor[18].

Abramowitz et al conducted risk-based screening on ICU patients at admission and once a week. 69% of all cases were hospital-acquired. Abramowitz et al concluded that hospitalization is a risk factor and ascertained that the median time between admission and CPB diagnosis was 8 days for infected patients and 6.5 days for colonized patients[16]. Zaha et al performed admission screening on all ICU patients and every week and ascertained that one-week admission at ICU increased the risk of CRE infection[33].

Aung et al found that hospitalization > 3 weeks is an independent risk factor for CPE colonization [17] and Cronin et al determined that hospital stay >28 days in the past 12 months are associated with KPC-Kp acquisition[19]. In both studies patients were screened > 48 hours of hospitalization.

Lusignani et al ascertained hospitalization > 20 days and hospitalization within the previous year as independent risk factors for CPE carriage and screened both patients on admission and hospitalized patients[24]. Tran et al performed a serial point prevalence study and screened all patients admitted or hospitalized on the point prevalence day and noticed that the prevalence of CRE colonization increased significantly during hospitalization, especially in neonatal ICU[31].

Antibiotic therapy

Fourteen studies conclude that antibiotic therapy is an independent risk factor for CPE acquisition[16,17,18,19,20,2122,24,25,26,27,29,31,33], but the variations in use of antibiotics in different countries must be considered in relation to the results. Antibiotic therapy was identified as a risk factor both in studies conducting admission screenings and screenings of inpatients.

Barbadoro et al ascertained a significant association between previous antibiotic use and CPE carriage on admission[18] and Salomao et al noticed that use of antibiotics in the last month is a risk factor for CPE colonization[29]. In both studies, admission screening was conducted.

Lusignani et al and Tran et al performed both admission screening and screening of inpatients[24,31]. Lusignani et al found use of antibiotics longer than 10 days as an independent risk factor for CPE carriage[24] and Tran et al ascertained treatment with carbapenem as a significant risk factor[31].

Three studies included only ICU patients with an expected extended exposure to broad-spectrum antibiotics because of critical illness. One of these studies performed risk-based admission screening and the other two conducted admission screening on all patients and in all three studies

screening was performed every seven days during hospitalization in ICU. Abramowicz et al found that 82% of CPB cases in ICU had received antibiotic therapy[16] and Kim et al determined use of fluoroquinolones as a significant risk factor for CPE[22]. Zaha et al does not investigate antibiotic therapy separately, but investigated Carmeli's score, which includes antibiotic treatment. Their evaluation of Carmeli's score for male patients showed association with CRE colonization[33].
Seven studies included inpatients. Cronin et al determined exposure to broad-spectrum antibiotics as a significant risk factor for KPC-Kp[19] and Predic et al found use of fluoroquinolones and cephalosporins as risk factors for CRE acquisition[27]. Mathers et al ascertained that exposure to carbapenems and β-lactam/ β-lactamase inhibitors were risk factors for KPCO acquisition[25]. Moghnieh et al found use of Meropenem within the last 3 months as a risk factor for CRE acquisition[26].
Aung et al mentioned penicillin as a risk factor for CPE colonization in ACH[17] and Fang et al concluded that antibiotics used prior to culture (< 30 days) is a risk factor for CPE acquisition[20]. Hilliquin et al studied the risk of CPE acquisition for secondary cases and ascertained that antimicrobial therapy during exposure time was a significant risk factor[21].

Comorbidities

The different studies identify different comorbidities presented in both studies conducting admission screening and studies that screened inpatients. VRE was identified as a risk factor in two studies[17,19]. Abramowicz et al determined that 80% of CPB cases had underlying chronic conditions and 51% had more than one[16], but the study population can be considered a high-risk population with critical illness (ICU patients). Specific comorbidities mentioned as risk factors in different studies are dementia and connective tissue disease in ACH[17], pulmonary disease[20,22], chronic wounds[17,26], cerebrovascular disease, hematopoietic cells transplantation, nosocomial site of acquisition[26], liver disease[29] and chronic liver disease in male patients[33].

Invasive procedures

Invasive procedures are mentioned as risk factors in eight studies[16,17,19,21,22,25,26,27]. Two of these are performed in ICU with admission screening and weekly screening during hospitalization in ICU and the rest of the studies conducted screening of inpatients.
A study found that 94% of CPB cases (N=88) were recently exposed to invasive medical device. The study population were ICU patients[16] and thereby a high-risk population with extended exposure to invasive medical device. Hillequin et al noticed that undergoing at least one invasive procedure is a risk factor for CPE acquisition in an outbreak ward[21] (possible transmission through healthcare professionals) and Predic et al determined that undergoing an invasive procedure with a scope device showed significance in relation to CRE[27]. Other procedures found to be significant

risk factors are respiratory procedures in LTCF[17], CVC[19], previous use of nasogastric tube (ICU patients)[22], transfusions and thoracic pathology, mechanical ventilation, dialysis[25], and endoscopy within the last 3 months before hospitalization[26].

Transfers and differences between health care facilities

The results from the studies did not find transfers and differences between health care facilities as risk factors for CPE acquisition. Aung et al ascertained that transmission within ACH was possible but did not find evidence of transmission from ACH to LTCF, although ACH was the main reservoir of CPE with higher prevalence[17]. Wards with higher prevalence increase the risk of CPE acquisition, but IPC precautions can reduce the risk of transmission. Barbadoro et al found ED protective against CRE acquisition, but it seems to be related to selection bias of controls. The study determined that previous admission to LTCF was not associated with CPE carriage[18].
ICU is mentioned in several studies as a risk ward, which might be associated with increased use of invasive devices, extended antimicrobial therapy, critical illness, and comorbidities.

Quality assessment

The quality of each individual study was assessed, and the rating of the individual studies are presented in table 5 and extracted in the following text. The quality assessment in table 5 is only an evaluation of the quality whereas studies with low quality should not be included in a systematic review[12]. The overall assessment and evidence evaluation are followed in the text.

Table 5: Quality assessment of each individual study

	Study	Internal validity (control of systematic bias)	Precision (reliability)	External validity (generali-zability)	Quality (low, moderate, high)
1	Abramowich et al; 2020 (16)	Retrospective. Monocentric study. CPE are included in CPB. Only ICU patients. No controls. Poor confounder adjustment. Possible transmission in ICU.	Descriptive statistics.	Acceptable	Moderate
2	Aung et al; 2021 (17)	Prospective. Monocentric. Randomly selected inpatients in LTCH and ACH. Patients in ACH had more comorbidities. Different length of admission between groups. Lack description of study population.	Multivariate analyses. Wide CI*, uncertainty in some results.	Good	Moderate
3	Barbadoro et al; 2021 (18)	Retrospective. Monocentric. Similar demographics (CC**). CC ratio 1:1. Possible selection bias. Lack description of own limitations.	Multivariate analyses.	Good	Moderate
4	Cronin et al; 2017 (19)	Retrospective. Monocentric. Matched CC. CC ratio: 1:4. Occurrence of KPC acquisition unknown (exposure until detection). Some controls might have been carriers (not all were screened).	Multivariate analyses. Wide CI.	Good	Moderate

5	Fang et al; 2019 (20)	Retrospective. Monocentric. CC ratio1:2. Randomly selected patients. Possible transmission in hospital. Level of risk factors not equal to expected level in the population.	Multivariate analyse. Wide CI.	Acceptable	Moderate
6	Hilliquin et al; 2017 (21)	Retrospective. Multicentre. Matched CC. Secondary cases might already have been colonized (species and type by PCR/connection to index case).	Multivariate analyses. No WGS***.	Good	High
7	Kim et al; 2020 (22)	Retrospective. Monocentric. Only ICU. Possible misclassification bias (not all tested by sensitive test method). Possible CPE among controls. Possible transmission in ICU.	Multivariate analyses.	Unclear, possible	Moderate
8	Lomont et al; 2022 (23)	Prospective. Monocentric. Screening bias: Unclear if all patients with travel history were screened. Some patients screened themselves.	Descriptive analyses.	Acceptable	Moderate
9	Lusignani et al; 2020 (24)	Retrospective. Monocentric. CC ratio 1:3. Matched CC. Mainly risk wards. Young study population (median age 48 years for cases).	Multivariate analyses.	Good	High
10	Mathers et al; 2020 (25)	Retrospective. Monocentric. CC ratio 1:19,5. Acquisition could have been close to transfers and then giving negative results. Sensitivity analysis made.	Multivariate analyses.	Very good	High
11	Moghnieh et al; 2021 (26)	Retrospective. Monocentric. Matched CC. Unclear how the patients were tested and in which wards.	Multivariate analyses.	Acceptable	Moderate
12	Predic et al; 2020 (27)	Retrospective. Monocentric. Matched CC. CC ratio 1:2. CRE: CPE cases are unknown. Mix of community- and hospital acquired. Confounder adjustment unclear.	Logistic regression.	Acceptable	Moderate
13	Räisänen et al; 2020 (28)	Retrospective. Possible inconsistence in patient swabbing.	Descriptive analyses.	Possible	High
14	Salomao et al; 2017 (29)	Prospective. Monocentric. CRE: CPE cases unknown. Possible bias in selection of controls.	Multivariate analyses.	Acceptable	Moderate
15	Samuelsen et al; 2017 (9)	Retrospective. Possible inconsistence in patients swabbing. Possible bias in false negative because of the media used.	Descriptive analyses.	Possible	Moderate
16	Skjøt-Arkil et al; 2019 (30)	Prospective. Multicenter. Only ED's, possible differences in other wards. Possible selection bias (not all ED patients were included, and the study does not include the Capital region).	Multivariate analyses. Big study population, small sample size.	Very good	Moderate
17	Tran et al; 2019 (31)	Prospective. Multicenter. Point prevalence in different amount of days. Cross transmission influences the results. Selection bias.	Multivariate analyses.	Possible	Moderate
18	Westerholt et al; 2021 (32)	Retrospective. Possible incomplete information. Real CPE acquisition time unknown.	Descriptive analyses.	Very good	High
19	Zaha et al; 2019 (33)	Retrospective. Monocentric. Only ICU. Possible bias in point ranking system and selection bias.	No multivariate analyses. No CI added to estima-ted Odds Ratio	Acceptable	Moderate

*) CI = 95% Confidence Interval
**) CC=Case-control
***) WGS =Whole genome sequencing

Fourteen studies have a retrospective design and five study designs were prospective.

CPE positive patients (colonized and/or infected) were defined as cases in eight studies [9,17,18,22,23,24,28,30]. Two studies focussed on carbapenemase-producing *Klebsiella pneumoniae* as cases[19,25], Hilliquin et al defined secondary OXA-48-producing *Klebsiella pneumoniae*-cases to

index patient as cases[21]. Eight studies presented the significant risk factors for a general group, e.g. CRE, CPO/CPB, which might provide some uncertainty, but all eight studies were assessed to provide valid results in relation to CPE[16,20,26,27,29,31,32,33]. The study populations are colonized and/or infected patients identified on admission or during hospitalization. Three studies focus only on ICU patients[16,22,33], one study emphasized ED patients[30], but most studies included different patient groups from different wards and mainly adults.

The control groups are differently selected, but all controls in the selected studies are assessed as valid control groups and comparable to cases, although the internal validity assessment did appoint some selection bias (table 5). Cases and controls are not expected to be completely comparable in terms of comorbidities, which might cause a confounding effect since comorbidities are considered risk factors for CPE acquisition.

Thirteen studies were monocentric and might not be representative in a wider perspective.

All selected studies include large study populations, although the sample size often becomes small because of relatively low prevalence of cases. The size of study populations varies and are selected differently which complicates comparison. Some are randomly chosen, and other studies describe specific inclusion criteria. Descriptive surveillance studies focus mainly on isolates.

The case-control ratio varies between the studies, but the analysis in each study is assessed reliable. Multivariate analyses have been performed in twelve studies (table 5), which have upgraded the studies. Logistic regression models are e.g. used for the calculation of Odds Ratio (OR) in several studies which increases the precision and evidence. Different methods are used to test if the results occurred by chance, such as CI and p-value, Chi-square (X^2) test, t-test and Fisher's Exact test etc[14]. One or several of these tests were used in all studies which adds strength to the reliability.

External validity relates to the generalizability of the study[12]. This assessment was rated from the lowest to the highest, 'unclear, possible', 'possible', 'acceptable', 'good' and 'very good' respectively, assessing the generalizability to a Danish context and relevance for the research question.

Fourteen studies were assessed with a moderate quality and five assessed as high quality (table 5). The quality define how well performed each study is but does not imply high evidence. A study could be of good quality, but with low evidential value[12].

The summarized evidence assessment is based upon study design, study quality, generalizability, conformity, precision, and publication bias according to GRADE[12], of which several aspects are presented above. The literature search did not identify any RCT's and the best available evidence are based on observational studies: eight case-control studies, five cross sectional, one descriptive and case-control study and five exclusively descriptive studies, although they are rated lower in

GRADE. All studies are considered consistent with each other, even though certain differences were ascertained. No publication bias was identified.

According to GRADE the overall evidence score for all the investigated risk factors are very low to low which implies that the true effect is likely to differ significantly from the estimated effect or that the true effect might be markedly different from the estimated effect.

Discussion

The findings in this systematic literature study mainly identify previous or current hospitalization and previous or current antimicrobial therapy, especially with broad spectrum antibiotics, as significant risk factors and the risk seems to increase with the length of hospitalization. Also comorbidities, and invasive procedures have an unmeasurable impact and travel abroad can be considered a risk factor in low prevalence countries.

These findings are in line with a systematic review and meta-analysis from 2018[34], that ascertained that **antibiotic treatment** is a risk factor documented in their meta-analysis. They also emphasize the impact of underlying conditions and use of invasive devices along with admission to ICU. Van Loon et al determined exposure to hospital care as a risk factor[34], whereas this current systematic literature review in addition provides knowledge of the **length of hospitalization**. The risk factor assessment made by Van Loon et al is based on 74 studies and the meta-analysis is based on 69 studies[34]. All these studies are different from the selected studies in the present systematic literature review. Nevertheless, the findings are in line with one-another, which gives strength to the reliability of the results.

The data in eight studies support previous or current hospitalization, and long hospitalization (the length varies in different studies) as risk factors for CPE acquisition and the subject should be investigated further to determine whether this should be integrated in the Danish national guideline. The current guideline indicates hospitalization abroad > 24 hours as a risk situation, but as previously mentioned the CPE cases increase every year and it is likely that the current algorithm does not identify the right patients at the right time[6,7,11].

The increased risk in health care can also be connected to transmission within the healthcare setting, e.g. because of problems with implementation or compliance with IPC precautions. Räisänen et al concludes that there is a hidden transmission in healthcare setting, since almost 1/3 of the CPE cases were not found by screening[28].

Hilliquin et al did not identify hospitalization duration as a significant risk in univariate analysis and multivariate analysis were therefore not performed[21]. This was probably due to the study population and the study design, because the cases were secondary cases to a CPE index patient and the controls were patients admitted at the same time and duration[21]. This study was performed in a

ward that must be considered as an outbreak ward with increasing risk of CPE acquisition and it is therefore not fit for studying the impact of length of hospitalization in general. The risk of acquiring CPE shortly after admission is more likely in an outbreak ward compared to a non-outbreak ward. Kim et al did ascertain previous admission to long term care facility (LTCF) as a significant risk factor in univariate analysis, but not identify it as a significant risk factor in the multivariate analysis[22]. A possible cause is, that the study population was only ICU patients that might not have had previous stay in LTCF. Kim et al found that 16 out of 45 CPE positive patients acquired CPE after admission to the ICU[22] and nosocomial transmission is therefore likely.
In general screening of inpatients will allow to study the association between the length of hospitalization and CPE acquisition.
All studies that found previous or current hospitalization and/or a certain length of hospitalization as a risk factor also found antibiotic therapy as a risk factor and it is likely that there is a correlation between these two factors, e.g. that the possibility of receiving antimicrobial therapy, especially broad spectrum antibiotics, is higher when the patients have been or are hospitalized.
General considerations are, that the true acquisition time for CPE colonization is always unknown when the first sample test is positive, since patients might have acquired CPE in past, and recent antibiotic therapy could simply reinforce an existing colonization rather than identify risk factors for recent acquisition. This could contribute with an inaccuracy. At the same time prior colonization are less probable in a low prevalence setting. The local prevalence is an important risk factor for CPE acquisition, and it is essential to be able to adjust for this when assessing CPE risk factors.
The detailed results concerning specific **antibiotic drugs** as a predisposing factor are inconsistent, but the results show consistency in identifying antibiotic therapy as a risk factor. This risk factor is probably associated with the fact that antibiotic therapy influences and destroys the natural microbiota which advantages the conditions of resistant microorganisms like CPE. When conducting this literature search several studies of microbiota as treatment were found and excluded, but it is an interesting subject, that should be investigated more as a part of a prevention programme.

Travel abroad was identified as a significant risk factor in six studies[9,16,23,24,28,32] and in addition, two studies did not find travel as a risk factor[19,30]. Travel history is considered an important risk factor in low prevalence countries where CPE are not endemic. Studies that ascertained travel history as a risk factor were performed in European countries, some with lower prevalence than others, but none of high prevalence countries in Europe were represented[2]. Also, a recent Dutch study based on data from 2017-2019 concluded that CPE remain low in the Netherlands and that recent hospitalization abroad is the main risk factor for acquisition of CPE[35], which is in line with older studies from the Nordic countries[8,,9,10].

Countries of origin of the studies mentioning travel history as a risk factor are Denmark, Norway, Finland, Belgium, Austria and France. France has a higher prevalence, but not compared to e.g. Spain and Italy[2]. Two studies from low prevalence countries (Denmark[30] and Australia[19]) could not demonstrate travel history as a risk factor. The Danish study did not have enough cases to identify risk factors and is therefore inconclusive in relation to travel abroad[30]. Cronin et al[19] investigated 34 cases matched with 136 controls and the finding might be connected to a small sample size and the fact that the study population was inpatients hospitalized > 48 hours. According to the findings in this systematic review history of travel abroad, including hospitalization abroad, poses a risk in low or moderate prevalence countries and are identified in risk-based admission screenings. However, a definite conclusion is not possible based on these findings, since the results of the studies vary and some studies are based on old data, despite being published from 2017 and forward. The study of Samuelsen et al[9] is e.g. based on surveillance data from 2007-2014 and much could have changed since. Second, the timeframe for screening patients with travel history varies and so do the number of screen swabs, which might have influenced the results.

Eight studies mention various **comorbidities** and it is not possible to identify a specific risk factor, but the findings can suggest that various comorbidities could be risk factors in relation to CPE acquisition [16,17,19,20,22,26,29,33]. No distinction was found between patients on admission or hospitalized patients in relation to comorbidities. The differences in the results might be connected to the fact that patients with different comorbidities are studied and therefore different comorbidities turn out significant. Different tools to assess the risk of comorbidities exist and such tools could be used to determine when the level of comorbidities could be valued as a risk factor for CPE acquisition.
VRE was identified as a risk factor in two studies[17,19]. The results of Aung et al[17] showed a wide 95% confidence interval (CI). VRE was identified as a risk factor with OR 16.42; 95% CI 1,52-177.48 indicating great uncertainty about the effect, and further research is needed. Also, prior VRE colonization (OR 6.0, 95% CI 1.6-23.2) presented by Cronin et al[19] indicates some uncertainty. These uncertainties are probably related to small sample sizes. In Denmark, there is an increasing level of VRE and no systematic national surveillance. In case VRE is a risk factor for CPE acquisition, increasing VRE could contribute to increasing CPE. The risk factors for VRE colonization and CPE colonization might be similar and the findings could also be related to confounding rather than VRE being a risk factor.

Eight studies ascertained various **invasive procedures** as significant risk factors[16,17,19,21,22,25,26,27], from which it seems possible to deduce invasive procedures in general as a risk factor. This is in line with Hilliquin et al[21], who found undergoing at least one invasive procedure as a risk for CPE

acquisition. It seems reasonable to consider the amount of invasive procedures performed during admission as a risk factor.

Some of the results are associated with uncertainty, probably due to small sample sizes, e.g. previous use of nasogastric tube (OR 10.7; 95% CI 3.0-38.7)[22], respiratory procedures in LTCF (OR 4.97; 95% CI 1.09-22.71)[17], undergoing an invasive procedure with a scope device (OR 4.57; 95% CI 1.31-16.02)[27] and further studies are needed.

Two out of eight studies were conducted in ICU with screening on admission and once a week during hospitalization in ICU. The rest of the studies conducted screening of inpatients and the influence of contact transmission in relation to invasive procedures should be investigated and compared with knowledge about colonization of e.g. catheters.

In this systematic review local **transfer** between health care facilities was not identified as a significant risk factor for CPE acquisition, but this study neither rules out nor identifies the risk associated with transfers within healthcare facilities. Aung et al ascertained that transmission within ACH was possible but did not find evidence of transmission from ACH to LTCF[17]. At the same time ACH patients hospitalized > 3 weeks were 2.7 times more likely to be CPE colonized than those with a shorter stay and LTCF's patients with length of stay < 3 weeks were 53% more likely to be colonized, which did suggest a possible colonization due to recent stay in ACHs[17]. Barbadoro et al determined that previous admission to LTCF was not associated with CPE carriage[18]. In another Italian study, all patients (N=1427) admitted to LTCF during 2014 were screened and the study found a CPE prevalence of 10,2%. Both previous admission to an intensive care unit (odds ratio: 4.04; 95% CI: 2.20-7.44; P < 0.001) and post-acute care hospitals (2.88; 1.74-4.77; P < 0.001) were significant risk factors in multivariate analysis[36]. In addition, a review from 2018 (American and Israeli)[37] also considers transfer as a risk and suggests that patients should be screened for CRE in the following situation: 1) at admission to a unit in cases of direct transfer from Long Term Acute Care facility (LTAC), 2) direct transfer from another hospital or from a LTCF with known endemicity, 3) direct transfer from a different ward in the facility, 4) hospitalization in ACH in the past 6 months, 5) functional dependency, 6) transfer from hospitals abroad from countries with known high endemicity and 7) prisoners. They recommend weekly screening for patients in ICU and LTAC, dependent elderly patients in medical non-ICU wards with high colonization pressure, dependent post-operative patients in surgical non-ICU wards with high prevalence, patients in hemato-oncologic units and patients in wards with high colonization pressure[37]. The endemic situation in USA and Israel is different from the Nordic countries but the suggestions can be used as inspiration. In Denmark, patients are often transferred from ward to ward within hospitals, between hospitals and across regions and outbreaks occurs across regions[6].

The findings in this systematic review were of very low to low evidence based on the overall GRADE quality assessment. However, the GRADE system has been developed to grade the evidence for different interventions/treatments and is thus more suitable for a research question where the PICO framework can be applied. In this systematic review PEO was found the most suitable frame when studying risk factors[13].

In general, it is problematic for observational studies to reach a high evidential score, which is a common challenge within this field, since observational studies are the best available. It is not possible to perform RCT's that can research risk factors. Of ethical reasons it is of course impossible to consciously expose or predispose randomized patients to CPE in order to study the outcome. The current systematic review can still provide supplemental knowledge within the field although the evidence is rated as very low to low.

In order to improve the overall assessment (evidence) more high quality studies like Mathers et al are needed and it would be good to conduct cohort studies, but these are both expensive, time consuming and often complicated to perform[14]. A prospective cohort study could for example study all patients receiving antibiotic therapy in a hospital and compare them with patients not receiving antibiotics and then investigate which patients acquired CPE and when.

This systematic literature study cannot alone provide the foundation for revising the Danish screening tool. However, it can be used as a supplement and highlight subjects for further research. This study suggests **adjusting the current screening protocol** and developing an **additional algorithm for CPE screening of Danish inpatients, especially long-term inpatients**. It could be advantageous to develop an automatic electronic algorithm, that would alert the clinicians when they should consider screening of the patient. In order to develop an additional algorithm further studies are needed about antimicrobial therapy and the duration of the treatment as well as duration of hospitalization, comorbidities and invasive procedures. Further Danish studies are needed, e.g. a study of risk factors in Danish CPE positive inpatients, an evaluation of our screening questionnaire as a follow up on the finding of Skjøt-Arkil[11,30] and also a cost-benefit analysis. It is important to evaluate the patient experiences by qualitative studies and the compliance and implementation of the guideline through observations, questionnaires, and interviews of health care professionals.

This systematic review does not provide knowledge about implementation and compliance with IPC guidelines and precautions. Health care professionals' knowledge and compliance with IPC precautions are essential to prevent transmission and outbreaks in Danish healthcare. Increasing focus on IPC education already in the basic health care educations are of vital importance creating the foundation for preventing spread of microorganisms in health care and thereby increasing patient safety. Full compliance with regular contact precautions would prevent most CPE

transmissions. Lomont et al[23] states that dedicated nursing staff is the most effective measure to avoid nosocomial transmission.
To provide further knowledge for revising the Danish screening protocol a meta-analysis of both risk factors and time of screening could contribute with important knowledge.
Dialyses and antineoplastic treatment are considered risk factors that should cause screening according to the current screening protocol[7]. This present systematic review did not find any support for keeping these two risk factors as a part of the screening protocol.

Multiple admission screens for CPE have important operational and financial implications[38]. Decisions concerning screening strategy must be based upon the local prevalence and epidemiology to set a relevant level of interventions according to the risk. In addition, ethical aspects should always be considered when implementing screening programmes and as mentioned previously four central principles in medical ethics are beneficence, non-maleficence (possible false positive or false negative results), justice (cost effectiveness) and autonomy[15].
The benefit is that early detection can reduce the risk of transmission and outbreaks by rapid intervention e.g. isolation and additional IPC precautions. The consequences of CPE colonization imply increased risk of invasive disease, especially if the person is or becomes immunosuppressed, and infections involves increased burden of disease and mortality.
In a wider perspective the benefit is to ensure the long-term antibiotic strategy through initial treatment with specific antibiotics and prevention of transmission in order to prevent widespread CPE in the population, which would limit our future possibilities to treat infections.
In relation to cost-effectiveness it is two-sided, since detection and management of outbreaks is costly economically (isolations are resource demanding), but screening programmes are costly as well, both concerning staff capacity, laboratory resources etc.
Screening can also provide a false security, since it is a momentary picture, which does not prevent the patients becoming positive later and in addition, because of the risk of false negative results[9,38]. False negative results could both be related to suboptimal laboratory sensitivity, poorly collected specimen and/or a 'masked' CPE carriage (present CPE below the detection limit)[38]. False positive screening results can cause unnecessary isolation and isolation can imply several disadvantages for the patient. A review found that isolation has a negative impact on patient mental well-being, e.g. depression, anxiety, and anger, and that the healthcare workers spent less time with patients in isolation affecting the patient safety negatively[39]. Being colonized with a resistant microorganism can also cause stigmatization, both in healthcare and in society, and at the moment there is no available treatment for CPE colonization and according to the Danish guideline CPE positive patients are considered life-long carriers in most cases[7]. And finally, patients have the right to

autonomy, including the right to refuse screening and especially patient groups unable to consent, e.g. mentally disabled, children or young persons < 18 years should be handled with care.

Limitations

It is a limitation that this study does not include assessment of the laboratory testing methods since these differences might influence the results. Also, it is a limitation that CPE/CPO in organ transplants was not included, and the subject should be further researched.

Although studies from the last 5 years are selected, some are based on data from previous years, which causes a delay between the data collected and the publication of data, emphasizing the importance of ongoing evaluation and updates of guidelines.

A systematic literature study is usually performed by several authors which allows re-assessment of the studies and discussions about the assessments. This study is performed by a single person under supervision, inclusion of additional authors might have contributed to a higher quality of the study.

Conclusions and implications

This systematic review identified mainly antimicrobial therapy with broad spectrum antibiotics, and previous or current hospitalization as significant risk factors for CPE acquisition, and indicated an association between long hospitalization and CPE acquisition. However, it was not possible to determine a specific length of hospitalization. The findings also indicate a possible correlation between antibiotic therapy and hospitalization and suggests further studies to identify **Danish inpatients** at higher risk of CPE colonization and/or infection, including patients without a travel history abroad.

Travel history abroad and hospitalization abroad were found as a significant risk factor in low prevalence countries emphasizing the importance of risk-based screenings on admission.

This study can neither rule out nor identify the risk associated with transfers within healthcare facilities and could not identify specific comorbidities or invasive procedures as risk factors for CPE colonization and/or infection. However, it was possible to conclude that comorbidities and invasive procedures in general constitute a risk for CPE acquisition.

This systematic literature study cannot alone provide the foundation for revising the Danish screening tool. However, it can be used as a supplement and highlight subjects for further research.

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