

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Antimicrobial stewardship and infection prevention interventions targeting healthcare associated <i>Clostridioides difficile</i> and carbapenem-resistant <i>Klebsiella pneumoniae</i> infections: A scoping review.
<b>AUTHORS</b>	Okeah, Bernard; Morrison, Valerie; Huws, Jaci

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Hsu, Li Yang National University Health System, Singapore
<b>REVIEW RETURNED</b>	16-Dec-2020

<b>GENERAL COMMENTS</b>	<p>This work is a scoping review looking at interventions to control <i>Clostridium difficile</i> and drug-resistant <i>Klebsiella pneumoniae</i>, two rather distinct and unrelated organisms. I have a number of comments:</p> <ol style="list-style-type: none"><li>1. It is unclear why these 2 organisms were chosen together, as opposed to addressing them separately or including other organisms.</li><li>2. Although the authors mention that they have searched for interventions addressing <i>Klebsiella pneumoniae</i>, what they mean is drug-resistant (carbapenem-resistant) <i>Klebsiella pneumoniae</i>, as <i>K. pneumoniae</i> per se is a human commensal and opportunistic pathogen. It is probable that a significant number of papers are missed, as the number of papers selected was small, and control of drug-resistant <i>K. pneumoniae</i> tends to be included among interventions addressing drug-resistant Enterobacteriaceae such as <i>E. coli</i> in general.</li><li>3. The key outcome of this review seems to be condensed into the acronym ESCAPE-BIN, but the broad categories are well known and have been used elsewhere.</li><li>4. One of the objectives of this work was to assess if behavioral theory had been applied to interventions against these organisms. The authors used the lack of mention of behaviour change in hand hygiene as an example, but because they did not review the interventions separately, but rather how these were used against just two organisms, they have missed the bulk of publications on behaviour change theory in hand hygiene, for example.</li></ol>
-------------------------	---

<b>REVIEWER</b>	Vaughn, V University of Michigan
<b>REVIEW RETURNED</b>	29-Dec-2020

**GENERAL COMMENTS**

This article represents a scoping review of studies to reduce klebsiella and c. diff. It is extremely well written, and the methodology is rigorous. Overall, I think it adds to the existing literature and provides a good review of existing interventional studies. I have a few major concerns that slightly temper my enthusiasm. First, I found the inclusion criteria confusing. Second, I worry that the number of articles searched is quite low for such a broad topic and likely limited the study substantially (perhaps to only positive findings—which could bias the findings). Finally, I really enjoyed the new ESCAPE-BIN mnemonic, but believe that the article could be enhanced by describing what this mnemonic adds to existing frameworks for stewardship and infection prevention.

**Major concerns:**

1. The inclusion criteria are a little confusing. It originally states that studies evaluating CDI or klebsiella were included but then mentions outcomes of antibiotic use were also allowed (in Table 1). However, I suspect if outcomes of antibiotic use were included the number of studies would be MUCH larger. Also, those findings don't seem to be reported. Would rephrase/explain how antibiotic use as an outcome was or was not included.
2. 814 articles is a very refined search for such a scoping and large topic. After reviewing MESH terms, I worry that this is actually a very low number and may have excluded some studies. There are many studies that don't mention c diff explicitly but have it as a secondary outcome with antibiotic use as a primary outcome. I can already think of a few studies that I think would meet inclusion criteria but are not found here (e.g., <https://pubmed.ncbi.nlm.nih.gov/27498601/>, <https://pubmed.ncbi.nlm.nih.gov/29790913/>). Because c diff is so rare, it is often included as a secondary outcome. Your search method may have only retrieved those studies that actually found an effect on c diff instead of the large numbers of underpowered or negative studies.
3. Discussion: I like the ESCAPE-BIN acronym and find it a useful conceptualization. However, I think the manuscript could benefit from discussing what this acronym adds to other taxonomies for stewardship (e.g., CDC core elements of stewardship, IDSA/SHEA stewardship guidelines)

**Minor Concerns:**

1. Title: suggest renaming to explain this is focused on klebsiella and CDI only, not all antibiotic resistance.
2. Abstract: repetitive information in design and setting.
3. Would change Clostridium to Clostridioides throughout.
4. Intro: define DALY
4. Intro: would explain why you were so interested in behavioral theory applications and Kotters in particular.
5. No kappa (or similar statistic) included for inter-reviewer reliability in article selection/inclusion.
6. Flow diagram could be improved by adding reasons for exclusion. This is consistent with PRISMA recommendations, "reasons for exclusions at each stage."
7. Really appreciated the tables and their visual representations. Might be helpful to notate which were statistically significant, or is that implied by an arrow up or down?
5. Would review throughout to ensure you use infection prevention and antibiotic stewardship correctly. They seemed to sometimes

	be used interchangeably when their definitions are distinct. E.g., introduction, “The review focused on infection prevention interventions aimed at curbing transmission of <i>C. diff</i> and/ or <i>Klebsiella pneumoniae</i> or optimizing the use of antimicrobials in healthcare settings.” Here, would be more appropriate to say “infection prevention or antibiotic stewardship interventions” or just “interventions”
--	--

### VERSION 1 – AUTHOR RESPONSE

#### REVIEWERS' COMMENTS AND ACTIONS TAKEN

REVIEWER 1 COMMENTS	ACTIONS TAKEN	PAGES
1. It is unclear why these 2 organisms were chosen together, as opposed to addressing them separately or including other organisms.	<p>The justification has been added under the rationale.</p> <p>Words inserted: “In this scoping review, the focus is on healthcare associated <i>Clostridioides difficile</i> and CRKP infections. <i>Clostridioides difficile</i> is the single most leading cause of nosocomial diarrhea globally primarily linked with the use of antibiotics that disrupt the stability of gut microbiota allowing the pathogenic bacteria to flourish [28]–[30]. On the other hand, <i>Klebsiella pneumoniae</i> also ranks amongst the top three leading causes of neonatal sepsis in resource limited settings [31], [32] with some strains known to produce extended-spectrum B-lactamases (ESBL) associated with multi-drug resistance to carbapenems and colistin [33]. More often, cultures obtained from patient environments, stools, water, and blood have been shown to contain <i>Klebsiella pneumoniae</i> [33] and <i>Clostridioides difficile</i>. Studies show that approximately 25% of patients in England, Australia, and the United States of America get colonized by CRKP during their hospitalization period [33]–[35]. Patient-to-patient transmission of CRKP accounts for an estimated</p>	2-3

	52% of the cases identified in healthcare settings [36].”	
2. Although the authors mention that they have searched for interventions addressing Klebsiella pneumoniae, what they mean is drug-resistant (carbapenem-resistant) Klebsiella pneumoniae, as K. pneumoniae per se is a human commensal and opportunistic pathogen. It is probable that a significant number of papers are missed, as the number of papers selected was small, and control of drug-resistant K. pneumoniae tends to be included among interventions addressing drug-resistant Enterobacteriaceae such as E. coli in general.	Revised to show the focus was on interventions primarily targeting carbapenem-resistant K. pneumoniae and C. difficile. Interventions targeting other organisms such as E. coli that would have some impact on either C. difficile or CRKP were excluded and this was to allow for comparison across interventions with an almost similar design and focus. However, this scoping review equally acknowledges the fact that interventions targeting a specific organism would generally have an impact on other pathogens responsible for healthcare associated infections.	Throughout the paper
3. The key outcome of this review seems to be condensed into the acronym ESCAPE-BIN, but the broad categories are well known and have been used elsewhere.	The three outcomes for this scoping review have now been more clearly described to include: Mapping out the interventions, describing intervention outcomes, and assessing the application of behaviour-based evidence	3, 4, 13, 14, & 15
4. One of the objectives of this work was to assess if behavioral theory had been applied to interventions against	Addressed in detail in the discussion. “Generally, application of current behaviour change evidence appears to be either limited or not reported across IP and AMS	13 & 14

<p>these organisms. The authors used the lack of mention of behaviour change in hand hygiene as an example, but because they did not review the interventions separately, but rather how these were used against just two organisms, they have missed the bulk of publications on behaviour change theory in hand hygiene, for example.</p>	<p>interventions targeting C. difficile and CRKP in healthcare settings, hence, the need for further exploration.”</p>	
<p>REVIEWER 2 COMMENTS</p>	<p>ACTIONS TAKEN</p>	<p>PAGES</p>
<p>1. The inclusion criteria are a little confusing. It originally states that studies evaluating CDI or klebsiella were included but then mentions outcomes of antibiotic use were also allowed (in Table 1). However, I suspect if outcomes of antibiotic use were included the number of studies would be MUCH larger. Also, those findings don't seem to be reported. Would rephrase/explain how antibiotic use as an outcome was or was not included.</p>	<p>We apologise that the reviewer found these confusing. The inclusion criteria have now been revised and clarified and the outcomes specified as follows (see page 4 of the document): “Antimicrobial use associated with C. difficile or CRKP, adherence to IP and AMS guidelines, and associated risk for the targeted pathogens.”</p>	<p>4</p>

<p>2. 814 articles is a very refined search for such a scoping and large topic. After reviewing MESH terms, I worry that this is actually a very low number and may have excluded some studies. There are many studies that don't mention c diff explicitly but have it as a secondary outcome with antibiotic use as a primary outcome. I can already think of a few studies that I think would meet inclusion criteria but are not found here (e.g., <a href="https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fpubmed.ncbi.nlm.nih.gov%2F27498601%2F&amp;data=04%7C01%7Cv.morrison%40bangor.ac.uk%7C0dc063112c644b8b8eaf08d8b894b673%7Cc6474c55a9234d2a9bd4ece37148dbb2%7C0%7C0%7C637462296157400370%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Iik1haWwiLCJXVCI6IjMn0%3D%7C3000&amp;sdata=YjO8kMg6fzpD49LsDum9ad%2FsHrtTqu9mK3vCA6J5rNQ%3D&amp;reserved=0">https://eur01.safelinks.protection.outlook.com/?url=https%3A</a></p>	<p>Whilst we agree with the reviewer that studies exist where <i>C. difficile</i> is examined as a secondary outcome, the review presented here was purposively limited to studies that primarily focussed on <i>C. difficile</i> or CRKP in healthcare settings. This was to allow for comparison across the interventions with regards to the impact of the interventions and the application of current behaviour change evidence hence the refined eligibility criteria outline on page 4. The two suggested studies would not therefore meet the inclusion criteria as they did not primarily focus on <i>C. difficile</i> or CRKP in healthcare settings. This limitation has been acknowledged on page 15 of the scoping review.</p>	<p>4 &amp; 15</p>
--	---	-------------------

<p>%2F%2Fpubmed.ncbi.nlm.nih.gov%2F29790913%2F&amp;data=04%7C01%7Cv.morrison%40bangor.ac.uk%7C0dc063112c644b8b8eaf08d8b894b673%7Cc6474c55a9234d2a9bd4ece37148dbb2%7C0%7C0%7C637462296157400370%7CUnknown%7CTWFPbGZsb3d8eyJWljoiMC4wLjAwMDAiLCJQljoiV2luMzliLCJBTiI6Ik1haWwiLCJXVCi6Mn0%3D%7C3000&amp;sdata=ffDJ%2FR%2FNVDOE510NcxZkYwpqNd0OS1FhuHo0pGK1H4I%3D&amp;reserved=0)</p> <p>. Because c diff is so rare, it is often included as a secondary outcome. Your search method may have only retrieved those studies that actually found an effect on c diff instead of the large numbers of underpowered or negative studies.</p>		
<p>3. Discussion: I like the ESCAPE-BIN acronym and find it a useful conceptualization. However, I think the manuscript could benefit from discussing what this acronym adds to other taxonomies for stewardship (e.g., CDC core elements of stewardship, IDSA/SHEA</p>	<p>We are pleased that this reviewer likes our acronym and agree it needed further consideration in terms of other taxonomies. The acronym has now been linked to the CDC core elements and described</p>	<p>14</p>

stewardship guidelines)		
<b>MINOR CONCERNS</b>	<b>ACTIONS TAKEN</b>	<b>PAGES</b>
1. Title: suggest renaming to explain this is focused on klebsiella and CDI only, not all antibiotic resistance.	The title has been revised accordingly	1
2. Abstract: repetitive information in design and setting.	This has been revised so as to remove repetition	1
3. Would change Clostridium to Clostridioides throughout.	Clostridioides difficile (C. difficile) has now been used throughout the document	
1. Intro: define DALY	Now defined on page 2	2
2. Intro: would explain why you were so interested in behavioral theory applications and Kotters in particular.	This explanation has been provided in the rationale -highlight in text or copy and paste wording here?	2-3
3. No kappa (or similar statistic) included for inter-reviewer reliability in article selection/inclusion.	N/A	
4. Flow diagram could be improved by adding reasons for exclusion. This is consistent with PRISMA recommendations, "reasons for exclusions at each stage."	We agree and have addressed this omission- reasons for exclusion have been added	Supplementary file 1
5. Really appreciated the tables and their visual representations. Might be helpful to notate which were statistically significant, or is that implied by an arrow up or down?	Done: The arrows represent statistically significant changes, legend updated to reflect this	location



<p>6. Would review throughout to ensure you use infection prevention and antibiotic stewardship correctly. They seemed to sometimes be used interchangeably when their definitions are distinct. E.g., introduction, “The review focused on infection prevention interventions aimed at curbing transmission of C. diff and/ or Klebsiella pneumoniae or optimizing the use of antimicrobials in healthcare settings.” Here, would be more appropriate to say “infection prevention or antibiotic stewardship interventions” or just “interventions”</p>	<p>amended/clarified throughout the document to consistently show the focus was on antimicrobial stewardship and infection prevention interventions</p>	
--	---	--

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	Vaughn, V University of Michigan
<b>REVIEW RETURNED</b>	27-Apr-2021

<b>GENERAL COMMENTS</b>	<p>This article represents a scoping review of studies to reduce klebsiella and c. diff. The reviewers have responded well to my prior concerns. The inclusion criteria now make more sense as do the reasons for including behaviour change theories. The remainder of my concerns are minor.</p> <p>Concerns:</p> <ol style="list-style-type: none"> <li>1. Would also state that you did not assess risk of bias as a limitation.</li> <li>1. Abstract: “mapped out” is a bit colloquial. Suggest rewording</li> <li>2. Abstract: Would just say 22/04/2020 through 30/09/2020 rather than updated</li> </ol>
-------------------------	--

	<p>3. Was eligibility studied published between 2010 and 2019? Why then was the review updated 30/09/2020? Shouldn't it include studies published before 30/9/2020?</p> <p>4. Results: you repeat twice, that three interventions target klebsiella in neonatal populations (lines 40-46, page 5)</p> <p>5. You said "N/A" to my concern that inter-rater reliability in article selection/inclusion was not reported, please explain? If not captured, or no dual review, that should be listed as a limitation</p>
--	--

<b>REVIEWER</b>	Carrara, Elena Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
<b>REVIEW RETURNED</b>	14-May-2021

<b>GENERAL COMMENTS</b>	<p>The authors undertook a significant effort in attempting a literature review of AMS and IPC interventions to target CDI and CR-Kp. The review methodology (search strategy, inclusion/exclusion) has been undertaken in accordance with PRISMA guidelines, even though some arbitrary choices (i.e. limiting the inclusion timeline to last 10 years, not restricting by study design..) might be arguable and would deserve a bit of discussion. My major concern with this research is that the main point of the whole review seems to be missed by the authors. Several SRs with similar inclusion criteria have already been published, but a practical focus on behaviour change theories might actually be the real added value of this research. In the light of this aim, the authors mention at the beginning some relevant frameworks (ESCAPE_BIN, COMB), but my feeling is that this kind of analysis is not really the core of the review, but just partially addressed as a component of the discussion (this same observation has been made also by Reviewer 2, and I think that the authors should more extensively review the manuscript under this indication). The actual results are presented as a very detailed and descriptive summary of included studies, but I am afraid that this very precise and detailed description does not provide to the reader a real sense of what is published.</p> <p>More specific comments on the text:</p> <ul style="list-style-type: none"> <li>- in general the whole paper needs some revision of the terminology (abbreviations in the abstract are not spelled out consistently AMR/AMS? quasi experiment/al line 37 pag 1 line 55 pag 3; pag 5 line 31);</li> <li>-a reference to the COMB model is mentioned as a strength in the first page, but then is not really assessed in the rest of the paper (again only mentioned in the discussion, while an analysis of the studies' interventions with a focus on this framework would be more helpful to the reader);</li> <li>- Introduction (and the paper in general) would probably benefit of being shortened a bit (paragraph 1 of the introduction line 5-line 24 can be probably removed as a whole);</li> <li>- pag 3 line 8 refers to a very high percentage of CR-Kp colonised patients, reference to this sentence does not seem to refer to this number (please, check);</li> <li>- Methods pag 3 line 35-42 can also be removed;</li> <li>- Narrative detailed of eligibility plus a table (table 1 )seems a bit redundant to me, I suggest choosing one of the two;</li> <li>- pag 6 line 36: I am unsure that adding grey literature can actually limit the publication bias that much;</li> <li>- pag 6 line 44: who checked the 20% of the studies?</li> </ul>
-------------------------	---

	<p>- pag 4 line 48-55: consider moving this very detailed description in the supplemental material?</p> <p>- pag 5 line 18-25: I suggest removing this paragraph, since everything is already correctly detailed in the PRISMA flow-chart;</p> <p>- Results: in general I suggest shortening all the descriptive part, and trying to condensate in a more detailed table. Table 2 and 3 are a good start, but much more information could be summarized in those tables, rather than listing the number of studies and all the reference in detail in the text;</p> <p>The remaining part of results and discussion might benefit a revision under the idea that I highlighted in the beginning (stronger focus on ESCAPE-BIN, COM-B, behaviour change, interaction of ASP and IPC...).</p>
--	---

## VERSION 2 – AUTHOR RESPONSE

### Actions taken on reviewers' comments

REVIEWER 1 COMMENTS	ACTIONS TAKEN	PAGES
<p>1. The spelling of the name of co-author in ScholarOne system is different from the main document. Kindly amend accordingly. ScholarOne system: Morrison, Val Main document: Valerie Morrison</p>	<p>We appreciate that the reviewer has highlighted this. When we pull the details of the co-author through the ScholarOne system, the details retrieved are incomplete and unfortunately this cannot be edited from our end. We have written to the editor about this to help with adding the correct details for the co-author.</p>	N/A
<p>2. Would also state that you did not assess risk of bias as a limitation.</p>	<p>This is now included as a limitation</p>	16
<p>3. Abstract: "mapped out" is a bit colloquial. Suggest rewording</p>	<p>We have replaced "mapped out" with "assessed".</p>	1
<p>4. Abstract: Would just say 22/04/2020 through 30/09/2020 rather than updated</p> <p>5. Was eligibility studied published between 2010 and 2019? Why then was the review updated 30/09/2020? Shouldn't it include studies published before 30/9/2020?</p>	<p>We have revised the section to read as: "The databases searched include MEDLINE, PubMed, Web of Science, and CINAHL between 22/04/2020 and 30/09/2020"</p>	1 & 4

6. Results: you repeat twice, that three interventions target klebsiella in neonatal populations (lines 40-46, page 5)	We have deleted the repetition in this section.	5
7. You said "N/A" to my concern that inter-rater reliability in article selection/inclusion was not reported, please explain? If not captured, or no dual review, that should be listed as a limitation	We have included this as a limitation.	15
	ACTIONS TAKEN	PAGES
1. The authors undertook a significant effort in attempting a literature review of AMS and IPC interventions to target CDI and CR-Kp. The review methodology (search strategy, inclusion/exclusion) has been undertaken in accordance with PRISMA guidelines, even though some arbitrary choices (i.e. limiting the inclusion timeline to last 10 years, not restricting by study design..) might be arguable and would deserve a bit of discussion. My major concern with this research is that the main point of the whole review seems to be missed by the authors. Several SRs with similar inclusion criteria have already been published, but a practical focus on behaviour change theories might actually be the real added value of this research. In the light of this aim, the authors mention at the beginning some relevant frameworks (ESCAPE_BIN, COMB), but my feeling is that this kind of analysis is not really the core of the review, but just partially addressed as a component of the discussion (this same observation has	<p>We do appreciate the reviewer's feedback and concern about the inclusion criteria not being restricted to study design. However, this scoping review aimed at and gaining a broader understanding of the topic including the designs used to study the interventions.</p> <p>About strengthening the behaviour change component in the review, we have now included some additional analysis on behavioural theory using the COM-B elements under the results and discussion sections.</p>	14

<p>been made also by Reviewer 2, and I think that the authors should more extensively review the manuscript under this indication). The actual results are presented as a very detailed and descriptive summary of included studies, but I am afraid that this very precise and detailed description does not provide to the reader a real sense of what is published.</p>		
<p>2. in general the whole paper needs some revision of the terminology (abbreviations in the abstract are not spelled out consistently AMR/AMS? quasi experiment/al line 37 pag 1 line 55 pag 3; pag 5 line 31);</p>	<p>We have revised the terminology used in the paper for consistency</p>	
<p>3. a reference to the COMB model is mentioned as a strength in the first page, but then is not really assessed in the rest of the paper (again only mentioned in the discussion, while an analysis of the studies' interventions with a focus on this framework would be more helpful to the reader);</p>	<p>We have included more analysis under the results synthesis and discussion</p>	<p>14</p>
<p>4. Introduction (and the paper in general) would probably benefit of being shortened a bit (paragraph 1 of the introduction line 5-line 24 can be probably removed as a whole);</p>	<p>We have revised this sentence</p>	<p>2</p>
<p>5. pag 3 line 8 refers to a very high percentage of CR-Kp colonised patients, reference to this sentence does not seem to refer to this number (please, check);</p>	<p>We have checked and updated the references</p>	<p>3</p>
<p>6. Methods pag 3 line 35-42 can also be removed;</p>	<p>We have removed the section as recommended</p>	<p>3</p>

7. Narrative detailed of eligibility plus a table (table 1 )seems a bit redundant to me, I suggest choosing one of the two;	We have revised the narrative description to removed the details that are provided in the table.	3-4
8. pag 6 line 36: I am unsure that adding grey literature can actually limit the publication bias that much;	We have revised this sentence	4
9. pag 6 line 44: who checked the 20% of the studies?	This has now been clarified, the reviewers exchanged their extracted data for checking.	4
10. pag 4 line 48-55: consider moving this very detailed description in the supplemental material?	We have moved the detailed description and included it under supplementary file 2	Supplementary file 2
11. pag 5 line 18-25: I suggest removing this paragraph, since everything is already correctly detailed in the PRISMA flow-chart;	We have removed this description as recommended	5
12. Results: in general I suggest shortening all the descriptive part, and trying to condensate in a more detailed table. Table 2 and 3 are a good start, but much more information could be summarized in those tables, rather than listing the number of studies and all the reference in detail in the text;	Whilst we agree with the reviewer on the need to summarise the detailed descriptive part of the results, the included studies were very diverse and important details would be lost. We also worry that having all the details in one table would mean a complex and extended table that would be difficult to understand, hence, our decision to capture these details in the description. Secondly, we were also keen on highlighting the behavioural aspects of the interventions which could only be achieved through the descriptions considering that behaviour change was not explicitly stated in most of the papers.	N/A
13. The remaining part of results and discussion might benefit a revision under the idea that I highlighted in the beginning (stronger focus on ESCAPE-BIN, COM-B, behaviour change, interaction of ASP and IPC...).	We have provided additional analysis and discussion around behaviour change in the results and discussion sections	14-16