

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of antimicrobial dressings in England and the association with published clinical guidance: interrupted time series analysis
AUTHORS	Hussey, Louise; Stocks, Susan; Wilson, Paul; Dumville, Jo C.; Cullum, Nicky

VERSION 1 – REVIEW

REVIEWER	Kevin Selby University of Lausanne, Switzerland
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	<p>Thank you for the opportunity to review this paper describing the rapid adoption of antimicrobial wound dressings in the absence of evidence. Please note that I have limited knowledge of wound dressings, and so can primarily comment on the form of the article and the research methods. My main critique of this paper would be that the title and abstract are not adequately supported by the actual results of the paper. The paper describes: 1. rapid adoption of antimicrobial wound dressings, and 2. decreased use after the publication of guidelines. I fail to see how this justifies the title "routine data to identify opportunities to increase value", an idea also placed prominently in the abstract despite not being supported by the results.</p> <p>Other feedback on abstract:</p> <p>-> if the objectives and conclusions are shortened, there should be room to include the change in time trends before and after 2010, to me a critical part of this study</p> <p>Strengths and limitations summary:</p> <p>-> I don't understand the meaning of "Methods using these data show how new products can be adopted...". Which methods?</p> <p>Overall: the article could benefit from editing to shorten.</p> <p>Introduction:</p> <p>-> Would be helpful to also have context regarding the expected impact of published guidance. Also, are any data available regarding the marketing of antimicrobial dressings?</p> <p>-> Wouldn't use the word 'qualitative', given that there was no qualitative data collection</p> <p>Methods:</p> <p>-> I would consider moving the list of key publications to the methods section, as this is not a result of the current study. Instead, the authors are using an interrupted time series to describe the effect of an intervention.</p> <p>-> Please provide justification for not requiring ethics approval</p> <p>-> Given that your 'search' was not systematic, I wouldn't describe it in the methods. The table itself might be more appropriate for supplementary materials.</p>
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	<p>-> please include why $p < 0.1$ was used for some statistical comparisons</p> <p>Results:</p> <p>-> For figures 1 and 2, it might be helpful to have an additional curb that represents the total prescriptions and expenditures</p> <p>-> I find it misleading to talk of a '38-fold increase' in silver dressings when they were only available shortly before the study period. By definition they will start from almost zero.</p> <p>-> page 9, the authors speculate several time about reasons for reductions. Given that they only have secondary quantitative data sources available, I would remove these comments.</p> <p>Discussion:</p> <p>-> Do the authors have any knowledge of how these dressings were marketed? I agree that antibiotics dressings have an intuitive appeal</p> <p>-> Any knowledge of positive anecdotal experiences or endorsement by key opinion leaders in these fields?</p> <p>-> I appreciated the discussion page 14 about the wider context of de-implementation, with options like formulary restriction. I didn't understand, however, the phrase "This may suggest that strategies seeking to influence..."</p> <p>-> beyond costs, are there risks of patient harm and resistance with these products?</p>
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REVIEWER	Eddy Lang University of Calgary
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	<p>The premise underlying this paper is that health care systems can explore administrative data on purchasing and relate that to clinical practice guidelines to identify opportunities for increased value and reduced waste in resource allocation. The example they focus on deals with antibiotic dressings that have seen a fairly remarkable increase in utilization. They then correlate with clinical practice guidelines which are noted to fail to demonstrate and evidence for silver product and antimicrobial impregnated dressing types.</p> <p>I think the paper is valuable and will stimulate thought and reflection on ways to seek opportunities to achieve cost savings in healthcare. I would raise the following points for consideration.</p> <p>The title of the paper is perhaps a bit far-reaching and creates expectations that are not delivered. The example provided is useful but the suggestion that such instances abound is unsupported.</p> <p>While referred to in the limitations sections I think more can be said about the monochromatic nature of the data. The increase in dressing utilization might have in theory, although unlikely been related to trends in trauma, population aging trends, trauma etc.</p> <p>I think it is important not to confound absence of evidence that supports the benefit of an intervention and an evidence base that cannot confirm equivalence between less costly options and more popular and pricey ones. Issues around patient preference, adherence to skin, frequency of dressing changes is not all that well addressed.</p> <p>It would be of value for the authors to link their methodology to Choosing Wisely campaigns that are emerging internationally.</p>
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VERSION 1 – AUTHOR RESPONSE

<p>Reviewer 1</p>	<p>My main critique of this paper would be that the title and abstract are not adequately supported by the actual results of the paper. The paper describes: 1. rapid adoption of antimicrobial wound dressings, and 2. decreased use after the publication of guidelines. I fail to see how this justifies the title "routine data to identify opportunities to increase value", an idea also placed prominently in the abstract despite not being supported by the results.</p>	<p>The title of the manuscript has been changed to reflect the results of the paper</p>	<p>The use of antimicrobial dressings and the association with published clinical guidance: interrupted time series analysis</p>	<p>01/01/2002</p>
	<p>Other feedback on abstract: 1. if the objectives and conclusions are shortened, there should be room to include the change in time trends before and after 2010, to me a critical part of this study</p>	<p>The abstract has been edited to include the results of the ITS and the change in trend before and after 2010.</p>	<p>During the year of the SIGN intervention (2010) there was a significant reduction in the use of silver but there was no consistent ongoing reduction from 2011 to 2015.</p>	<p>2/17-19</p>

2. I don't understand the meaning of "Methods using these data show how new products can be adopted...". Which methods?

This point in the 'Strength and limitations' has been re-written

Techniques such as interrupted time series analysis of prescribing data can be used to explore and illustrate the relationship between treatment choice and the contemporaneous availability of evidence about clinical and cost effectiveness.

03/04/2006

	<p>Overall: the article could benefit from editing to shorten.</p>	<p>The article has been edited to remove text, however there has also been information added to address reviewers' comments</p>	<p>NA</p>	
	<p>Introduction:</p> <p>Would be helpful to also have context regarding the expected impact of published guidance. Also, are any data available regarding the marketing of antimicrobial dressings?</p>	<p>Text added to give context regarding possible impact of published guidance.</p> <p>We could find no relevant information on the marketing of antimicrobial dressings.</p>	<p>In addition to these analyses, we also present this antimicrobial use and cost data in the context of contemporaneously available systematic review findings and other clinical guideline recommendations to examine whether trends may reflect any resulting change in practice.</p> <p>NA</p>	<p>05-Aug</p>

	<p>Wouldn't use the word 'qualitative', given that there was no qualitative data collection</p>	<p>The word 'qualitatively' has been removed</p>	<p>In addition to these analyses, we also qualitatively present this antimicrobial use and cost data in the context of contemporaneously available systematic review findings and other clinical guideline recommendations to examine whether trends may reflect any resulting change in practice.</p>	<p>05-Jun</p>
	<p>Methods:</p> <p>I would consider moving the list of key publications to the methods section, as this is not a result of the current study. Instead, the authors are using an interrupted time series to describe the effect of an intervention.</p>	<p>We have left the table of key publications in the results section as this is where we feel it fits best, however we are happy to move to either methods</p>	<p>NA</p>	

		section or appendices if this is preferred editorially		
	Please provide justification for not requiring ethics approval	A statement has been added at the end of the methods section	Ethical approval was not required as this study is based on secondary analysis of freely available PCA information	07/03/2005
	Given that your 'search' was not systematic, I wouldn't describe it in the methods.	Although the examination of key publications was not systematic it did still involve a search with certain parameters which we felt warranted some description in the Methods. This has been edited to make it shorter.	<p><i>Identification of relevant guidelines and systematic reviews</i></p> <p>Firstly we located key national guidelines relevant to the use of wound dressings in the community; these were clinical practice guidelines for complex wounds such as leg ulcers, foot ulcers and pressure ulcers (venous leg ulcers are the most prevalent complex wounds in the community setting) (15). We restricted our search to recognised UK-based producers of high quality, evidence-based guidelines who follow a transparent, rigorous process of guideline production – i.e. The National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and relevant professional bodies such as the Royal Colleges. Secondly we searched for relevant Cochrane systematic reviews which follow a rigorous and transparent process and they are freely available and highly accessed in the UK (in 2017 Cochrane reviews collectively had 2,136,922 full-text downloads in the UK alone) (16). Recommendations regarding the use of antimicrobial dressings were detailed in the published clinical guidance.</p>	06/01/2009

	<p>The table itself might be more appropriate for supplementary materials</p>	<p>As stated above, we have felt the table of key publications in the results section as this is where we feel it fits best, however we are happy to move to either methods section or appendices if this is preferred editorially</p>	<p>NA</p>	
	<p>Please include why $p < 0.1$ was used for some statistical comparisons</p>	<p>The p value simply shows how likely it is that there is a difference between the measured value for a variable and its comparison group if the null hypothesis is true (it is the statistical interaction between the 2 groups). So it is what comes out of the regression model. Rather than state the actual P values we used 3</p>	<p>We used 3 categories just to make it easier to read so if labelled:</p>	<p>6/25-29</p>

	<p>categories just to make it easier to read so if labelled:</p> <p>$p < 0.001$ then is as it reads $p < 0.05$ is less than 0.05 but greater than $0 > 0.001$ $p < 0.1$ is less than 0.1 but greater than 0.05</p> <p>If the editor prefers we can show the actual p values for all the comparisons.</p>	<p>$p < 0.001$ then is as it reads</p> <p>$p < 0.05$ is less than 0.05 but greater than $0 > 0.001$</p> <p>$p < 0.1$ is less than 0.1 but greater than 0.05</p>	
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	<p>For figures 1 and 2, it might be helpful to have an additional curb that represents the total prescriptions and expenditures</p>	<p>We understand the potential benefits of adding additional curves to Figures 1 and 2, however have decided not to add these as it creates a more complicated picture that would require another level of explanation covering areas (such as the frequent use of cheap and frequently changed gauze dressings at the beginning of the study period) outwith and not relevant to the subject covered in the paper. Because of this we decided to include Figure 3 which illustrates how the expenditure and use of</p>	<p>NA</p>	
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		antimicrobial dressings changes with time as a proportion of total wound dressings.		
	I find it misleading to talk of a '38-fold increase' in silver dressings when they were only available shortly before the study period. By definition they will start from almost zero.	As the actual figures appear in the text this additional illustrative interpretation has been removed	Whilst iodine dressings have been prescribed relevantly consistently between 1998 and 2006, during the same period the quantity of silver dressings prescribed increased from 143,600 to 5,485,684 (a 38 fold increase).	Jul-16

Page 9, the authors speculate several times about reasons for reductions. Given that they only have secondary quantitative data sources available, I would remove these comments.

These comments have been removed

This pattern was significantly different from the annual decrease in use of non-antimicrobial dressings, which continuously declined from 2005 to 2015 (Table 2 and comparing panels B and D in Appendix 1). ~~The reasons for this reduction in non-anti-microbial dressing use are not obvious from these data and are considered further in the discussion.~~

Comparing use of antimicrobial and non-antimicrobial dressings in the post-intervention period (from 2011 to 2015) we observe increasing expenditure on non-antimicrobials dressings with decreased use (by quantity). ~~Again reasons for this increased cost with reducing use are not obvious from these data and are considered further in the discussion.~~

Oct-22

				Oct-30
	<p>Discussion:</p> <p>Do the authors have any knowledge of how these dressings were marketed? I agree that antibiotics dressings have an intuitive appeal Any knowledge of positive anecdotal experiences or endorsement by key opinion leaders in these fields?</p>	<p>We could not find research data on the marketing of antimicrobial dressings. However text has been added citing findings from a paper examining how research evidence is used to support claims made in advertisements for wound care products (1)</p>	<p>Research showing how evidence is used to support claims made in product advertisements within two wound care journals found just 35% of claims about the benefits of a product cited supporting evidence. When these sources of evidence were investigated the cited evidence did not support the claim being made in 56% of cases</p>	13/30-32, 14/1

I appreciated the discussion page 14 about the wider context of de-implementation, with options like formulary restriction. I didn't understand, however, the phrase "This may suggest that strategies seeking to influence..."

The text has been changed to clarify the statement

This may suggest that **any action aimed at implementing evidence-based guidance within** community nursing may **benefit from being** more focused on the type of change necessary to generate a reduction in specific prescribing practices.

13/15-17

Beyond costs, are there risks of patient harm and resistance with these products?

As stated in the introduction, the European Regulatory Framework requires that the manufacturers demonstrate that new devices (including dressings) are safe and fit for purpose. There is little evidence regarding the toxicity of the absorption of silver ions but it is suggested that health risks are low. Silver resistance in bacteria has been identified and regularly isolated from clinical environments (2). The VULCAN trial did not report any adverse events caused by the use of silver dressings (3)

We have not made any changes to the text: whilst an interesting area we didn't feel it was a relevant topic of discussion in this paper.

Reviewer 2	The title of the paper is perhaps a bit far-reaching and creates expectations that are not delivered. The example provided is useful but the suggestion that such instances abound is unsupported.	The title of the manuscript has been changed to reflect the results of the paper	The use of antimicrobial dressings and the association with published clinical guidance: interrupted time series analysis	01/01/2002
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While referred to in the limitations sections I think more can be said about the monochromatic nature of the data. The increase in dressing utilization might have in theory, although unlikely been related to trends in trauma, population aging trends, trauma etc.

Text has been added

Our analysis of wound care prescribing is limited by the available data. **Temporal changes in dressing use and expenditure may also be influenced by demographic and epidemiological factors (e.g. an ageing population and the rise in chronic diseases such as diabetes).**

14/19-21

	<p>I think it is important not to confound absence of evidence that supports the benefit of an intervention and an evidence base that cannot confirm equivalence between less costly options and more popular and pricey ones.</p>	<p>We would agree however we do not believe we are confounding these issues. The burden of using costly products over less costly ones (if there is no evidence of a difference in clinical outcomes) are other alternative treatments foregone. Indeed, we and others (see ref 5) would argue that the only rational response to this type of scenario is to restrict use of the more costly practices that do not have evidence of benefit as they place the largest burden on the healthcare system.</p>	<p>NA</p>	
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	<p>Issues around patient preference, adherence to skin, frequency of dressing changes is not all that well addressed.</p>	<p>Text has been added to address this issue</p>	<p>Patient preference may also play a part in dressing selection. Research has shown that healing time was ranked by patients as the most important factor (compared to other factors such as dressing change frequency and pain).</p>	<p>14/20-22</p>
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	<p>It would be of value for the authors to link their methodology to Choosing Wisely campaigns that are emerging internationally.</p>	<p>Text linking to the Choosing Wisely campaign has been added</p>	<p>Choosing Wisely is a global initiative to address issues such as patient and clinician preferences and making better decisions about care with the aim that this will help avoid tests, treatments or procedures that are unlikely to be of benefit. Choosing Wisely UK is led by the Academy of Medical Royal Colleges and as yet does not encompass nursing as a profession or have any guidance focused on the management of complex wounds.</p>	<p>13/22-26</p>
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VERSION 2 – REVIEW

REVIEWER	Kevin Selby University of Lausanne
REVIEW RETURNED	12-Apr-2019

GENERAL COMMENTS	<p>For the most part the authors have adequately responded to my requests. I think they misunderstood my comment about a $p < 0.1$. I don't mind that they used ranges. It's just that $p < 0.05$ is typically considered statistically significant, so using a $p < 0.1$ is somewhat misleading, especially in the context of multiple comparisons.</p>
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	I leave it to the editors to decide whether their list of guidelines should remain a 'result' or be moved to the supplementary materials.
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VERSION 2 – AUTHOR RESPONSE

I think they misunderstood my comment about a $p < 0.1$. I don't mind that they used ranges. It's just that $p < 0.05$ is typically considered statistically significant, so using a $p < 0.1$ is somewhat misleading, especially in the context of multiple comparisons.

We apologise for misunderstanding. We did discuss how to present the P values before the first submission as our original plan was to simply state the P values for all the comparisons. However this made the table rather large and, potentially too complicated to distinguish the P values for the interrupted time series (ITS) analysis from the confidence intervals for the changes in usage or costs (trends). Consequently we decided to just identify those with lower P values. Using a cut-point for dichotomising significant or not-significant is increasingly recognised as incorrect or, at the least, poor academic practice (as discussed here)

<https://amstat.tandfonline.com/doi/abs/10.1080/00031305.2016.1154108#.XOUV2aR7IPY>).

If one chooses to do this, the choice of cut-point is arbitrary, therefore we made the decision to use 0.1 for a practical reason. Most P values were very large and it seemed misleading to group a P value of 0.07 into this "non-significant" group. We would be happy to alter the table to show the actual P value for each comparison if the editor or reviewer recommends this.

I leave it to the editors to decide whether their list of guidelines should remain a 'result' or be moved to the supplementary materials.

We have left the table of key publications in the results section as this is where we feel it fits best. Part of the process in conducting this study (and therefore described in the methods) was to carry out a search within certain parameters to identify the relevant key evidence and clinical guidance. Therefore the outcome of this search is included in the results section. However, we are happy to move to either the methods section or appendices if this is preferred editorially.