PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The health service costs of treating venous leg ulcers in the UK: evidence from a cross-sectional survey based in the north west of England
AUTHORS	Urwin, Sean; Dumville, Jo C.; Sutton, Matt; Cullum, Nicky

VERSION 1 – REVIEW

REVIEWER	Ousey, Karen University of Huddersfield, Human and Health Sciences
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	Thank you for giving me the opportunity to review this clear and well presented paper. The information presented adds to the knowledge base and is especially relevant in light of the recent focus on the prevention and management of Leg Ulcers (LU) and information being released through the National Wound Care Strategy. It is interesting to note the debate surrounding the potential over estimation of previous published costs. I have 2 small comments for your consideration: Page 8, line 59 : should this: topic be topical? The use of antimicrobials is more expensive however I presume these leg ulcers were identified as being infected therefore the use of antimicrobials and antibiotics? Was there any data highlighting the amount of infected and non infected LUs?

REVIEWER	Vowden, Peter Bradford Teaching Hospitals NHS Foundation Trust, Department of Vascular Surgery
REVIEW RETURNED	30-Nov-2020

GENERAL COMMENTS	The Authors have attempted to estimate the prevalence and costs of venous leg ulcers among people in the community, based on a two-weeks cross sectional survey. Using unsubstantiated assumptions, the Authors have extrapolated their analysis to speculate what the national prevalence and annual costs of venous leg ulcer management might be at a national level. BMJ Open is a forum for publishing evidence-based research. Therefore, the Authors should limit their analysis to the findings from the cross-sectional survey. Notwithstanding this, there are issues with the methodology which raises questions about the validity of their findings. I have provided some comments for the Authors to address. 1. The title of the manuscript is misleading and should be amended to reflect the study design, in accordance with BMJ

	Open's Guidelines to Authors. A suggested title would be "Point prevalence and health service costs of treating venous leg ulcers in the UK: results from a two-week cross-sectional survey". 2. The Abstract should be revised in accordance with the comments below and restructured using the headings specified in BMJ Open's Guidelines to Authors. 3. The content of the Abstract requires changing after the Authors have amended their manuscript in accordance with the points below. 4. Introduction, page 4: There appears to be confusion about the content of the studies in references 7 and 8. The costs in reference 7 relate to the cost of managing newly diagnosed venous leg ulcers in clinical practice by the UK's NHS. Many of these patients are not included in the cohort studied in reference 8. The costs in reference 8 relate to the annual cost incurred by the NHS in 2012/13 and are quite different to the costs described in reference 7. This section needs to be amended. 5. 2.1 Study Design and Data: The Authors obtained resource use and prevalence data from cross-sectional surveys covering two-week periods in June/August 2015 in four community NHS locales and in July 2016 in a further five NHS community locals in the North West of England. Cross-sectional studies can be used to assess the prevalence of a health condition at the point of time the study is undertaken, but without any regard to the duration of the condition. Consequently, cross-sectional surveys are generally insufficient on their own to understand disease trends over time. Therefore, the Authors need to demonstrate that (1) the prevalence estimates based on two weeks in one year are representative of the whole year and (2) the patient population and prevalence estimates in the North West of England are representative of the whole country. In the absence of this, the Authors should limit the scope of their analysis to the boundaries of their study design, and not extrapolate their findings beyond what is reasonable and to a level at which there is considerable uncertainty. Publications should not be used as a forum to speculate estimates based on unfounded assumptions. 6. 2.1 Study Design and Data: The Authors used the study form described in reference 3 to capture data about each service user's current wound and its care. However, this form is somewhat limiting and only captures data pertaining to a patient's wound care in the previous seven days. Additionally, the types of comorbidities recorded are limited to specified conditions. While the form was developed for a point prevalence study, extrapolating the findings from data captured with this form to generate annual estimates is fraught with much uncertainty and a large margin of error which the Authors have not addressed. 7. 2.1 Study Design and Data: The Authors excluded patients from their analysis if their venous leg ulcer was not their most severe wound. This has the potential to underestimate the prevalence and cost calculations of venous leg ulcers. The Authors should include these excluded patients in their analysis, unless they can justify their exclusion, and uprate their prevalence and cost estimates accordingly. 8. 2.1 Study Design and Data: The survey form described in reference 3 only collected data on community activity. Consequently, the Authors used primary and secondary care resource use data from the patients who participated in the VenUS IV trial to estimate typical resource use/costs associated with managed venous leg ulcers. However, the VenUS IV trial screened 3,411 patients with a venous leg ulcer but only 457 patients were

	randomised to treatment. In other words, 87% of all the screened patients were excluded because their ulcer did not conform to the trial's inclusion criteria. Nevertheless, these excluded patients would have their venous leg ulcer managed in clinical practice and would utilise resources and incur corresponding health service costs. It is correct to use the resource use data from these 457 patients to compare the health economic impact of the interventions they received within the context of the trial. However, it is methodologically flawed to use resource use estimates from a sanitised, homogenous group of patients who fulfilled the inclusion criteria of the VenUS IV trial to estimate resource use associated with managing venous leg ulcers in clinical practice (i.e. outside of the trial), since these 457 patients are not representative of the wider population of patients with a venous leg ulcer who are managed in clinical practice. The resulting resource use and cost estimates are misleading at best and completely wrong at worst. 9. 2.2 Community Care Costs. The Authors assumed that dressings and bandages were changed at every visit by a community nurse. What about visits by/to healthcare assistants, practice nurses, tissue viability nurses etc.? 10. 2.2 Community Care Costs. Why were the number of visits based solely on the average number of community nurse visits. What about visits with other healthcare practitioners such as healthcare assistant, practice nurses, tissue viability nurse visits? 11. 2.5 Extrapolation of prevalence to a national level. For the reasons outlined above the Authors' estimate of national point prevalence for people in the community being treated for a venous leg ulcer is potentially erroneous and should be removed from the analysis unless the Authors can address all the aforementioned points. A calculation of this magnitude cannot be based on the Authors own unsubstantiated assumptions that (1) the point prevalence in the North West is similar to the rest of the UK and (2) the point prevalence over two-weeks in the summer is representative of every point of the year across the UK. Cross-sectional surveys were not designed to perform this type of extrapolation. 12. 2.5 Extrapolation of prevalence to a national level. The Authors reported that they estimated an annual period prevalence of venous leg ulcers using the incidence rate estimated by Petherick et al in reference 21 using THIN data. However, the incidence estimate in reference 21 is derived from a data set covering the period 1998-2006 and is thus at least 14 years out of date. The incidence of all wounds has increased substantially over the last 14 years, so the use of such an out of date incidence estimate can only lead to an erroneous result. 13. 2.6 Extrapolation of cost to a national level: For the reasons outlined above the Authors' estimate of the national cost of managing venous leg ulcers among people in the community is potentially erroneous and should be removed from the analysis unless the Authors can address all the aforementioned points. A calculation of this magnitude cannot be based on the Authors' speculation nor on their own unsubstantiated assumption that a snapshot two-week cost of wound care in the North West is similar to the rest of the year at all other points across the UK. 14. 3.1 Community survey data: summary statistics. What percentage and number of patients in the survey of 3,057 patients had a venous leg ulcer and were excluded from the analysis because this was not their primary (most severe) wound?

	15. Table 1 should be expanded to include data on patients whose venous leg ulcer was not their primary (most severe) wound. 16. To what extent can the Authors be confident that the data in Table 2 is not conflated with data from patients' other wounds? What is the margin of error? 17. Table 3 should be expanded to show the costs associated with different types of healthcare practitioners e.g. healthcare assistants, tissue viability nurses, practice nurses, district nurses, podiatrists, etc. 18. 3.3 Variation in Community Care Costs. The analysis in this section is misleading since it presents costs in isolation of cause and effect, and as such is potentially dangerous since readers can take away the wrong message. For example, a patient who received a honey dressing is expected to have their two-week community cost increased by £18.59 whereas a patient who received an iodine dressing is expected to have their two-week community cost reduced by £11.78. Does that mean patients should be given an iodine rather than a honey dressing? No, it does not – but the Authors have not considered whether the probability of healing among the patients who received a honey dressing is greater than those who received the iodine dressing or whether time to amelioration of the infection differs between the two dressings. In order words, the Authors have failed to put these findings into a clinical context and demonstrate what represents value for money to both the NHS and to the patient, but instead have provided a series of costs which in isolation of causal relationships can be misused and potentially lead to the wrong clinical decisions being made leading to poorer outcomes for patients. As such, section 3.3 and Table 4 should either be removed or modified, bearing in mind that what is important is presenting data that can be used to inform clinical decision making and improve patients' outcomes. 19. 3.4 Primary and Secondary Care Costs. This section is erroneous since it has not been estimated from the costs of managing venous leg ulcers in clinical practice, but from a homogenous cohort of patients who fulfilled the inclusion criteria of the VenUS IV trial, who are not representative of the whole venous leg ulcer population. This section should either be removed or revised using appropriate costings. 20. 3.5 Extrapolation of Prevalence and Costs. This section should be removed for all the reasons described above. In addition to the points above, prevalence of wounds cannot be estimated from incidence alone. Estimation of wound prevalence requires a combination of other inputs including (but not necessarily limited to) incidence of new wounds, recurrence of previously healed wounds, healing rates, time to healing and mortality rates (i.e. consideration needs to be given to what is flowing in and out of the prevalence pool). 21. The Authors need to estimate the margins of error in their analyses using bootstrapping or creating a probabilistic model. 22. Sensitivity analyses need to be performed to demonstrate the impact of changing the values of individual parameters on the results. 23. The Discussion in its currently form is largely irrelevant because the study is methodologically flawed. o Differences between the findings of different studies can arise for a range of reasons such as different study designs, different data sources, different patient populations etc. Furthermore, it appears the Authors are confused by the content of

	references 7 and 8 and have not recognised they are different studies using largely different patients. Reasons why one-year period prevalence estimates are substantially higher than point-prevalence estimates is outlined in “Calculating incidence rates and prevalence proportions: not as simple as it seems” by Spronk et al https://doi.org/10.1186/s12889-019-6820-3. o The work published by Phillips et al 2020 (Phillips CJ, Humphreys I, Thayer D, Elmessary M, Collins H, Roberts C, Naik G and Harding K (2020). Cost of managing patients with venous leg ulcers. Int Wound J, 17, 1074-1082.) should be included in the discussion section. 24. Reference 1 should read: Franks PJ, Morgan PA. Health-related quality of life with chronic leg ulceration. Expert Rev Pharmacoecon Outcomes Res. 2003;3(5):611-22. 25. General comments: o The paper makes reference to complex wounds and appears to classify all venous leg ulcers as “complex wounds” referring to the paper by Gray et al 2018 and Hall et al 2014 both of which define a complex wound as a “superficial-, partial- or full-thickness skin loss wound healing by secondary intention.” I question whether this actually defines a complex wound as this in effect includes every open wound from a simple laceration to a major traumatic wound. Both these papers are from the same author group. This is an inappropriate definition and is not in line with others in the literature, for example that by Suzuki et al (Suzuki K, Michael G and Tamire Y (2016). Viable intact cryopreserved human placental membrane for a non-surgical approach to closure in complex wounds. J Wound Care, 25, S25-S31.). The definition used by the authors would classify all venous leg ulcers as complex wounds which is clearly not always the case as many heal in a relatively short timeframe with simple compression and non-adherent dressings. o The levels of co-morbidity reported is far lower than I would have expected for either this age range or patients with VLU. Were the levels of co-morbidity reported by the nurses or were the patient’s actual co-morbidities as extracted from primary care records used? There is disparity between co-morbidity reported in the text and those in Table 1. o Although details on dressings were captured in the audit form there is no record of the number or size of the dressing used or any record of any tertiary dressings. Table 2 states that no dressing was recorded for 65 patients – therefore absolute maximum of 505 patients with complete records yet in section 3.3 it states 514 patients with complete information for covariate analysis. This needs clarification as there are also gaps in the compression system data outlined in Table 2. o Comments are made in relation to the use of antimicrobial dressing and the discussion suggests these were used inappropriately there is however no indication as to the indications for antimicrobial dressing selection such as wound deterioration, suspected infection or the presence of infection. Similarly, it is reported that 51 patients were on antibiotics but again there is no indication who prescribed these, whether their use was associated with a GP consultation, what type of antibiotic was prescribed or whether they were used in combination with an antimicrobial dressing. These data would be helpful to the reader and would put comments by the authors into context.

VERSION 1 – AUTHOR RESPONSE

Reviewer 2 Comment	Our Response
"*The Authors have attempted to estimate the prevalence and costs of venous leg ulcers among people in the community, based on a two-weeks cross sectional survey. Using unsubstantiated assumptions, the Authors have extrapolated their analysis to speculate what the national prevalence and annual costs of venous leg ulcer management might be at a national level. BMJ Open is a forum for publishing evidence-based research. Therefore, the Authors should limit their analysis to the findings from the cross-sectional survey.*"	It is accepted practice to extrapolate from cross-sectional data in modelling studies. For example, cross-sectional data are used widely in COVID-modelling work. We agree that to be useful, cross-sectional data must come from an appropriate sample. Our cross-sectional data come from a 2-week survey of all people treated by NHS community services from a population of almost 2 million people. To reassure ourselves of the appropriateness of extrapolating from this sample to calculate a national estimate over a year we required evidence that the **(i) the Greater Manchester population is not dissimilar from the rest of the UK in their risk and types of wounds** and (ii) **the two week period from which the data came is similar to the rest of the year (i.e., there is no evidence of seasonal variation in venous leg ulcer prevalence).** We have good evidence to believe that both our assumptions hold true. Firstly, we previously used the same approach to calculate the point prevalence of venous leg ulcers in Leeds (4 years earlier, different time of year). Our estimates were almost identical. *Leeds Study: Hall et al 2014 – ref 15 in paper) estimated a VLU point prevalence 0.29 per 10,000 (95% CI 0.25 to 0.33). Data collected 28 February to 13 March 2011. Data collected from community services, primary care services, mental health and learning disability services, acute services, prisons, care homes, hospices and private hospitals. Whilst data were collected across these services ~80% of participants were recorded as having wound care delivered by community teams, with 6.1% having the service delivering wound care recorded as primary care. Population size covered ~750,000.* *Manchester Study: Gray et al 2018 – ref 3 in paper) VLU point prevalence 0.32 per 10,000 (95% CI 2.9 to 3.4). Data collected in 2 week periods from June to August 2015 and July 2016. Data collected from community services only. Population size covered ~1.9 million.*

	We have searched the literature for further evidence of seasonal variation in leg ulcer incidence and found none, nor any biological basis for thinking that one might exist. We would also emphasise that we do not need to make some of the assumptions to use community-derived data that are required when using alternative data e.g., those from primary care. Previous work has used primary care data. This has the advantage of being longitudinal but the disadvantage of not capturing data on a large number of people with open wounds being treated by NHS community services and whose activity is frequently not reflected in primary care records. Part of the role of our analysis is to challenge the assumptions made in the previous work. In summary, cross-sectional data have some limitations but this is true of most data sources, including primary care. Our cross-sectional data were carefully collected for this specific purpose, and our estimates have been replicated at a different time of year and in a different place. We reject the claim that our assumptions are unsubstantiated and we have reflected on the limitations in the discussion. We can expand on this if required.
"The title of the manuscript is misleading and should be amended to reflect the study design, in accordance with BMJ Open's Guidelines to Authors. A suggested title would be "Point prevalence and health service costs of treating venous leg ulcers in the UK: results from a two-week cross-sectional survey".	We disagree since our methods clearly follow established guidance for cost-of-illness studies (references 10, 11 and 12) and we explicitly state this in the manuscript (design and study section paragraph 1). As noted above our Manchester prevalence data have already been published in BMJ Open (see http:// dx. doi.org/ 10. 1136/ bmjopen- 2017-019440). Comparison of our previously published study with this submission illustrates clearly the differences between the two pieces of work. In this submission our cross-sectional data form a part of a modelling exercise where these and additional data have been synthesised and costs considered. These studies are clearly different and the suggested change of title is not appropriate.
"The Abstract should be revised in accordance with the comments below and restructured using the headings specified in BMJ Open's Guidelines to Authors.	We are happy to change the structure of the abstract. We looked at the journal guidelines and also at other published papers in BMJ Open which gave us the impression of flexibility. We would happily follow editorial advice.

The content of the Abstract requires changing after the Authors have amended their manuscript in accordance with the points below."	We have not yet changed the abstract as we think the current structure maps to other examples in the journal so wait for further editorial advice once manuscript has been considered following this submission.
"Introduction, page 4: There appears to be confusion about the content of the studies in references 7 and 8. The costs in reference 7 relate to the cost of managing newly diagnosed venous leg ulcers in clinical practice by the UK's NHS. Many of these patients are not included in the cohort studied in reference 8. The costs in reference 8 relate to the annual cost incurred by the NHS in 2012/13 and are quite different to the costs described in reference 7. This section needs to be amended."	We did not mean to suggest that the studies used exactly the same data – rather that they both used *primary care data.* We have slightly re-phrased, as below and tracked in the manuscript: *'The mean cost (of staff time and wound care) of a venous leg ulcer per annum was estimated as £7600 in the UK at 2015/16 prices with community nursing time accounting for 78% of this cost [7]. Also using primary care data the annual cost (of staff time and treatments) of venous leg ulcer care attributable to the NHS in the UK was reported as £941 million, with a further £836 million attributable to unspecified leg ulcers [8].'*
"2.1 Study Design and Data: The Authors obtained resource use and prevalence data from cross-sectional surveys covering two-week periods in June/August 2015 in four community NHS locales and in July 2016 in a further five NHS community locals in the North West of England. Cross-sectional studies can be used to assess the prevalence of a health condition at the point of time the study is undertaken, but without any regard to the duration of the condition. *Consequently, cross-sectional surveys are generally insufficient on their own to understand disease trends over time. Therefore, the Authors need to demonstrate that:* *(1) the prevalence estimates based on two weeks in one year are representative of the whole year and* *(2) the patient population and prevalence estimates in the North West of England are representative of the whole country.* *In the absence of this, the Authors should limit the scope of their analysis to the boundaries of their study design, and not extrapolate their findings beyond what is reasonable and to a level at which there is considerable uncertainty. Publications*	We have addressed these issues as part of our response to the first point raised.

should not be used as a forum to speculate estimates based on unfounded assumptions."	
"2.1 Study Design and Data: The Authors used the study form described in reference 3 to capture data about each service user's current wound and its care. However, this form is somewhat limiting and only captures data pertaining to a patient's wound care in the previous seven days. Additionally, the types of comorbidities recorded are limited to specified conditions. While the form was developed for a point prevalence study, extrapolating the findings from data captured with this form to generate annual estimates is fraught with much uncertainty and a large margin of error which the Authors have not addressed."	As previously noted, we used cross-sectional data and data taken from care records about the number of visits in the preceding 7 days. Across the different areas and time periods over which our data were collected we saw nothing to suggest that this is not a reasonable approach to capturing visit data and we checked this extensively with those delivering the services. Again, these data have a distinct advantage over primary care data (which do not capture care delivered by community nursing services). We are strongly of the view that extraction and extrapolation of visit numbers from community-based care records have much to recommend them over alternative sources. We regard the point made about co-morbidity data as moot since we did not use them to calculate annual prevalence. We collected data on co-morbidities to help describe our wound care recipients and used broad headings. We only use comorbidities as a covariate when exploring variation in the total cost of VLUs over the two week period. We report 95% confidence intervals for our cost analysis to reflect uncertainty.
"Study Design and Data: The Authors excluded patients from their analysis if their *venous leg ulcer was not their most severe wound. This has the potential to* *underestimate the prevalence and cost calculations of venous leg ulcers. The Authors should include these excluded patients in their analysis, unless they can justify their exclusion, and uprate their prevalence and cost estimates accordingly."*	We did exclude a small number of patients as noted. We have addressed this issue in as a sensitivity analyse as noted on page 5 of the manuscript with corresponding results included on page 10. This results in a small increase in the point prevalence from 2.9 per 10,000 to 3.2 per 10,000.
"*2.1 Study Design and Data: The survey form described in reference 3 only collected data on community activity. Consequently, the Authors used primary and secondary care resource use data from the patients who participated in the VenUS IV trial to estimate typical resource use/costs associated with managed venous leg ulcers.*	It is important to emphasise important details about VenUS IV; the trial from which we took data for our modelling work. This was a pragmatic RCT, based in NHS community nursing services. It is one of the largest trials in people with venous leg ulcers ever conducted and had wide inclusion criteria to support recruitment of as representative a sample of participants as possible. Many people do not consent to be in trials, that is true, but this large RCT based in the relevant NHS services is an

However, the VenUS IV trial screened 3,411 patients with a venous leg ulcer but only 457 patients were randomised to treatment. In other words, 87% of all the screened patients were excluded because their ulcer did not conform to the trial's inclusion criteria. Nevertheless, these excluded patients would have their venous leg ulcer managed in clinical practice and would utilise resources and incur corresponding health service costs. It is correct to use the resource use data from these 457 patients to compare the health economic impact of the interventions they received within the context of the trial. However, it is methodologically flawed to use resource use estimates from a sanitised, homogenous group of patients who fulfilled the inclusion criteria of the VenUS IV trial to estimate resource use associated with managing venous leg ulcers in clinical practice (i.e. outside of the trial), since these 457 patients are not representative of the wider population of patients with a venous leg ulcer who are managed in clinical practice. The resulting resource use and cost estimates are misleading at best and completely wrong at worst."	extremely rich source of data in an area where, as noted, there is no perfect single source of data. We collected detailed resource use data on all ulcer-related NHS care including every GP visit and hospital visit (inpatient and outpatient). The specificity of these data is hugely important; whilst it does not mitigate limitations of representativeness, as the reviewer notes, it is not without value and should not be dismissed as suggested. In line with best practice, we used all our data cautiously, explicitly considering their strengths and weaknesses, and we believe we were transparent about their limitations. We can expand discussion of limitations as required. However we reject the claim that these data should just be discarded as they are not 'ideal.' As we have already indicated, taken collectively, we firmly believe our data have a distinct advantage for this work above primary care data. Our use of trial data of this type is common for cost modelling studies.
"*Community Care Costs. The Authors assumed that dressings and bandages were changed at every visit by a community nurse. What about visits by/to healthcare assistants, practice nurses, tissue viability nurses etc.?"*	We have counted all visits by all NHS staff but assumed, from a costing perspective, that these were by a community nurse (stated in the paper). Where there have been visits by healthcare assistants we will have over costed and where there have been visits from specialist nurses we will have under costed based on the time cost assigned to each visit. We know that visits from practice nurses and specialist nurses are relatively rare and the differences likely to be cancelled out. There are no complete datasets available relating to the primary and community care of leg ulcer patients, broken down by staff type. The approach we have taken is common in modelling and we have been clear about it. Further clarification can be added if required.
"Community Care Costs. The Authors assumed that dressings and bandages were changed at every visit by a community nurse. What about visits by/to healthcare assistants, practice nurses, tissue viability nurses etc.?"	See above

"2.2 Community Care Costs. Why were the number of visits based solely on the average number of community nurse visits. What about visits with other healthcare practitioners such as healthcare assistant, practice nurses, tissue viability nurse visits?"	See above
"Extrapolation of prevalence to a national level. For the reasons outlined above the *Authors' estimate of national point prevalence for people in the community being treated for a venous leg ulcer is potentially erroneous and should be removed from the analysis unless the Authors can address all the aforementioned points. A calculation of this* *magnitude cannot be based on the Authors own unsubstantiated assumptions that (1) the point prevalence in the North West is similar to the rest of the UK and (2) the point prevalence over two-weeks in the summer is representative of every point of the year across the UK. Cross-sectional surveys were not designed to perform this type of extrapolation."*	This point has been made previously and is addressed in responses we have given
"Extrapolation of prevalence to a national level. The Authors reported that they estimated an annual period prevalence of venous leg ulcers using the incidence rate estimated by Petherick et al in reference 21 using THIN data. However, the incidence estimate in reference 21 is derived from a data set covering the period 1998-2006 and is thus at least 14 years out of date. The incidence of all wounds has increased substantially over the last 14 years, so the use of such an out of date incidence estimate can only lead to an erroneous result."	The reason we use these incidence data is because they are the most recent reported incidence data for VLUs. It may be true that the ageing of the population over the last 14 years may be associated with an increased incidence of venous leg ulcers, although service developments and secondary prevention practices have also developed so we do not know the net effect. It is also important to note that we use the available (older) incidence data to explore the annual prevalence this would result in when combined with our robust point prevalence data. We do not present this annual prevalence as the 'definitive answer' rather we are considering what we can conclude using available data and how findings from different data sources and analyses compare.
"2.6 Extrapolation of cost to a national level: For the reasons outlined above the Authors' estimate of the national cost of managing venous leg ulcers among people in the community is potentially erroneous and should be removed from the analysis unless	This point has been made previously and is addressed in responses we have given.

the Authors can address all the aforementioned points. *A calculation of this magnitude cannot be based on the Authors' speculation nor on their own unsubstantiated assumption that a snapshot two-week cost of wound care in the North West is similar to the rest of the year at all other points across the UK."*	
"3.1 Community survey data: summary statistics. What percentage and number of *patients in the survey of 3,057 patients had a venous leg ulcer and were excluded from the analysis because this was not their primary (most severe) wound?"*	See above, inclusion of these people changes the point prevalence from 0.29 per 10,000 to 0.32 per 10,000 cascading this through the analysis makes minor changes that we now added
"Table 1 should be expanded to include data on patients whose venous leg ulcer was not their primary (most severe) wound."	We chose not to include a summary of these patients given the low numbers and the fact these had no substantial impact on the prevalence
"To what extent can the Authors be confident that the data in Table 2 is not conflated with data from patients' other wounds? What is the margin of error?"	The health care resource data presented in Table 2 are those used in the treatment of the venous leg ulcer. This is the reason we focused on people whose ulcer was the most severe wound – as resource use data were specific to the treatment of that wound only. We are very confident that the data relate to these wounds as questions in the survey explicitly ask the health care professional filling in the form to record treatment relating to this wound only. A further advantage of our bespoke data collection is that there were very few missing data. We do however, highlight the direction of possible error in costs if healthcare professionals cannot separate treatment for a particular wound. The limitations have to be treated in context of what is currently known and collected, especially as most wounds are treated in the community and not in primary care. Routinely collected data in the community do not exist to any great extent currently.
"Table 3 should be expanded to show the costs associated with different types of healthcare practitioners e.g. healthcare assistants, tissue viability nurses, practice nurses, district nurses, podiatrists, etc."	This point has been made previously and is addressed in responses we have given
"3.3 Variation in Community Care Costs. The analysis in this section is misleading since it presents costs in isolation of cause and effect, and as such is potentially dangerous since readers can take away the	A cost of illness study such as ours cannot be used to draw inference about causal relationships. Our analysis in Table 4 is showing variation in the cost of a VLU conditional on covariates included in

wrong message. For example, a patient who received a honey dressing is expected to have their two-week community cost increased by £18.59 whereas a patient who received an iodine dressing is expected to have their two week community cost reduced by £11.78. Does that mean patients should be given an iodine rather than a honey dressing? No, it does not – but the authors have not considered whether the probability of healing among the patients who received a honey dressing is greater than those who received the iodine dressing or whether time to amelioration of the infection differs between the two dressings. In order words, the Authors have failed to put these findings into a clinical context and demonstrate what represents value for money to both the NHS and to the patient, but instead have provided a series of costs which in isolation of causal relationships can be misused and potentially lead to the wrong clinical decisions being made leading to poorer outcomes for patients. As such, section 3.3 and Table 4 should either be removed or modified, bearing in mind that what is important is presenting data that can be used to inform clinical decision making and improve patients' outcomes."	the model. Highlighting variation of costs in a cost of illness study is in accordance with guidance (references 10, 11 and 12). We are careful not to make any claims about causality. To clarify, we show that patients with a honey dressing have a higher total cost relative to those with no dressings conditional on the covariates (age gender etc.) included in the model. As well as dressings we use a range of other covariates to explore associations; the purpose of this analysis is to illustrate the different drivers of cost. A related point is that there is **no evidence that any dressing is associated with improved health outcomes in people with venous leg ulcers (or any other wounds)** (https://doi.org/10.1002/14651858.CD012583.pub2). The citation is a Cochrane review (Dumville and Cullum are co-authors) with 78 studies (7014 participants) and a nested mixed treatment meta-analysis.
"Primary and Secondary Care Costs. This section is erroneous since it has not been estimated from the costs of managing venous leg ulcers in clinical practice, but from a homogenous cohort of patients who fulfilled the inclusion criteria of the VenUS IV trial, who are not representative of the whole venous leg ulcer population. This section should either be removed or revised using appropriate costings."	This point has been made previously and is addressed in responses we have given.
"Extrapolation of Prevalence and Costs. This section should be removed for all the reasons described above. In addition to the points above, prevalence of wounds cannot be estimated from incidence alone. Estimation of wound prevalence requires a combination of other inputs including (but not necessarily limited to) incidence of new wounds, recurrence of previously healed wounds, healing rates, time to healing and mortality rates (i.e. consideration needs to	The calculation of period prevalence requires data on both point prevalence and incidence. We combined our point prevalence estimate with incidence information available from the literature. This is standard epidemiological practice. The other factors noted here; healing, recurrence, death are all variations on whether someone has an ulcer (prevalence) or not and whether they should be considered in the numerator, denominator, both or neither.

be given to what is flowing in and out of the prevalence pool). *21. The Authors need to estimate the margins of error in their analyses using bootstrapping or creating a probabilistic model.* *22. Sensitivity analyses need to be performed to demonstrate the impact of changing the values of individual parameters on the results.* *23. The Discussion in its currently form is largely irrelevant because the study is methodologically flawed."*	We took the decision that the best way to tackle the "margin of error" issue was to estimate an 'exploratory' theoretical maximum annual prevalence for the UK extrapolated from our Manchester data. For all the reasons previously outlined, we maintain the opinion that our analysis is a firm advance on those using primary care data alone. We have indicated 95% confidence intervals throughout. Clearly given all the above we strongly disagree with the comment about our discussion. We believe our analysis is robust, transparent and defensible; albeit giving a result which diverges widely from Reviewer 2's previous estimate.
"Differences between the findings of different studies can arise for a range of reasons such as different study designs, different data sources, different patient populations etc. *Furthermore, it appears the Authors are confused by the content of references 7 and 8 and have not recognised they are different studies using largely different patients.* *Reasons why one-year period prevalence estimates are substantially higher than point-prevalence estimates is outlined in "Calculating incidence rates and prevalence proportions: not as simple as it seems" by Spronk et al https://doi.org/10.1186/s12889-019-6820-3."*	We agree that these are valid reasons why findings between studies can differ and therefore foster debate We have addressed the previous comment re reference 7 and 8 in that our main point is that both use primary care data. This has been checked through-out. We are aware of this paper highlighted by Reviewer 2 and consulted it during our analysis. A key conclusion of this paper in the difference between point and annual prevalence is: "*When calculating a 1 year period prevalence proportion, all existing episodes in a year contribute to the numerator. Whereas in a point-prevalence the existing episodes on an indicated date are summed."* We accounted for this when calculating our annual prevalence by using incidence proportions as stated previously.
"The work published by Phillips et al 2020 (Phillips CJ, Humphreys I, Thayer D, Elmessary M, Collins H, Roberts C, Naik G and Harding K (2020). Cost of managing patients with venous leg ulcers. Int Wound J, 17, 1074-1082.) should be included in the discussion section."	This has been added to the discussion
"Reference 1 should read: Franks PJ, Morgan PA. Health-related quality of life with chronic leg ulceration. Expert Rev Pharmacoecon Outcomes Res. 2003;3(5):611-22."	This has now been amended

"The paper makes reference to complex wounds and appears to classify all venous leg ulcers as "complex wounds" referring to the paper by Gray et al 2018 and Hall et al 2014 both of which define a complex wound as a "superficial-, partial- or full- thickness skin loss wound healing by secondary intention." I question whether this actually defines a complex wound as this in effect includes every open wound from a simple laceration to a major traumatic wound. Both these papers are from the same author group. This is an inappropriate definition and is not in line with others in the literature, for example that by Suzuki et al (Suzuki K, Michael G and Tamire Y (2016). Viable intact cryopreserved human placental membrane for a non-surgical *approach to closure in complex wounds. J Wound Care, 25, S25-S31.). The definition used by the authors would classify all venous leg ulcers as complex wounds which is clearly not always the case as many heal in a relatively short timeframe with simple compression and non-adherent dressings."*	Whether venous leg ulcers are classified as 'complex wounds' or 'open wounds' is a minor semantic point and not germane to the methods, analysis or interpretation of our research. The term "complex wound" is widely used in practice and peer-reviewed, published research (including in BMJ Open – see Gray et al, 2018).
"The levels of co-morbidity reported is far lower than I would have expected for either this age range or patients with VLU. Were the levels of co-morbidity reported by the nurses or were the patient's actual co-morbidities as extracted from primary care records used? There is disparity between co-morbidity reported in the text and those in Table 1."	This major point has been addressed previously Minor typos have been corrected.
"Although details on dressings were captured in the audit form there is no record of the number or size of the dressing used or any record of any tertiary dressings. *Table 2 states that no dressing was recorded for 65 patients – therefore absolute maximum of 505 patients with complete records yet in section 3.3 it states 514 patients with complete information for covariate analysis. This needs clarification as there are also gaps in the compression system data outlined in Table 2."*	Dressing costs only contribute to 14% of total cost therefore, the impact of considering the number, size or any tertiary dressing on the total cost will very minor. We use 514 patients with complete information on covariates (mentioned in the methods). Patients without a dressing have a cost coded as zero (the 65 patients noted by the reviewer) but may have costs for other components and are included in analysis. In other words, we do not exclude patients if they do not have a cost recorded for one of our categories. We have edited the text on page 5 paragraph 1 to make this clearer.

"Comments are made in relation to the use of antimicrobial dressing and the discussion suggests these were used inappropriately there is however no indication as to the indications for antimicrobial dressing selection such as wound deterioration, suspected infection or the presence of infection. *Similarly, it is reported that 51 patients were on antibiotics but again there is no indication who prescribed these, whether their use was associated with a* *GP consultation, what type of antibiotic was prescribed or whether they were used in combination with an antimicrobial dressing. These data would be helpful to the reader and would put comments by the authors into context."*	This point is based on the lack of clinical evidence for a benefit of anti-microbial dressings and in-line with current guidelines for venous leg ulcer care (reference 18 in paper), which do not recommend these dressings. Whilst it is also good to have extra information, details on the type and the healthcare professional who prescribes them bears little or no relevance on to the cost and prevalence of venous leg ulcers. We do not have details on the type of antibiotics. This is not the focus of the study.