Author's response to reviews

Title: Highly-cited estimates of the cumulative incidence and recurrence of vulvovaginal candidiasis are inadequately documented

Authors:

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Author's response to reviews: see over
Dear Ms Rada:

I am submitting a revised version of the manuscript “Highly-cited estimates of the cumulative incidence and recurrence of vulvovaginal candidiasis are inadequately documented” for consideration in BMC Womens Health.

I appreciate the feedback provided by the four distinguished reviewers and have made numerous revisions to the manuscript in response. A detailed accounting of these revisions follows this covering letter; the reviewers’ original comments are in bold. Two references are specific to my responses to the reviewers, and these are indicated through use of square brackets. The other references are those which are found in the manuscript itself.

Please note that my co-author, Patricia A. Buffler, passed away on 26 September, which was prior to my receipt of the reviewers’ feedback. While it is standard for all authors to approve the version of a manuscript sent to a journal, in this case only I was available to do so.

I look forward to hearing from the editors soon.

With best regards,

Sujit D Rathod, MSc PhD
Reviewer #1: Betsy Foxman

Reviewer's report:
The authors purport to trace the origin of commonly cited estimates of the cumulative incidence of vulvovaginal candidiasis in the literature. After tracing them to clinical opinion of two clinicians, they suggest that the existing population-based studies (which they suggest but do not state are not commonly cited) are fatally flawed because these studies depend on self-report of medical history. They further assert that the cumulative incidence cannot be estimated accurately from the existing population-based studies. They do not cite any studies that estimated the incidence based on self-reported physician diagnosis in a short time period (e.g., Sex Transm Dis. 2000 Apr;27(4):230-5.) where effects of recall are likely to be low.

The reviewer is correct that these studies were not cited. I will now reference the two population-based studies of the prevalence of vulvovaginal candidiasis: “Since Sobel’s estimate was published there have been two population-based studies of the prevalence of recurrent vulvovaginal candidiasis, both of which found that approximately 8% of women are affected by RVVC.(3,68) These studies – though the most rigorous available – must be interpreted with caution, as few of the women recruited opted to participate, there was evidence that recall of past diagnoses diminished over time, and the criteria the participants’ physicians used to make the diagnoses were unknown.”

While listed as a ‘debate,’ I was unclear as to what were the terms of the debate, and what the issues of interest are. Yes, physician diagnosis of VVC is a problem- most US physicians do not have laboratory capability in their offices to confirm diagnosis using a wet mount, and culture for VVC is not definitive as Candida is a common inhabitant of the vaginal microbiota. However, the totality of all the studies they reviewed suggest that VVC occurs and recurs frequently.

The Reviewer’s rebuttal here demonstrates that the points made in this paper are, indeed, debatable. I welcome a counter-argument supporting the notion that these widely reported figures are reasonable estimates.

As described in this Debate, the studies I describe either cite unsupported data on the incidence or recurrence of vulvovaginal candidiasis or use measurement methods that are acknowledged – by this reviewer among others - to be inaccurate. Accordingly, it is not possible to determine to what extent the estimates presented in the literature are accurate.

The estimates are undoubtedly imprecise, but they present no evidence to suggest they are off by an order of magnitude.

It is possible that these estimates derived from actual studies are off by an order of magnitude. In the words of Sobel: “Vulvovaginal candidiasis is not a reportable disease, and prevalence estimates have relied mainly on self-reported history of physician diagnosis. This multiplies errors because it relies on the participant’s memory, as well as the accuracy of physician diagnosis. Regrettably, vulvovaginal candidiasis is routinely diagnosed without benefit of microscopy or culture, and in as many as half of the cases so diagnosed, the women may be
uninfected or have other conditions.”[1]

In response to Reviewer #1 and Reviewer #3, I have referenced additional primary sources with regard to the inaccuracy of self- or physician-diagnosed vulvovaginal candidiasis.

On page 6 the authors state that women inappropriate diagnosis VVC, as do their clinicians, because the literature cites erroneous estimates. However, the estimates from a random digit dialing survey conducted shortly after treatment was made available over the counter (in 2000) are essentially the same as from a similar study published in 2013. This does not support their assertion that women are over diagnosing as are physicians because of an erroneous literature.

I have revised this paragraph so that it is clear I am proposing a hypothesis rather than making an assertion: “One may posit that over time these estimates have fostered an impression among clinicians that women with vaginitis have a high probability of having vulvovaginal candidiasis, so much so that many clinicians dispense with confirmatory tests and rely on syndromic diagnoses. Then, in the words of Sobel: ‘Misdiagnosis by clinicians inevitably results in incorrect self-diagnosis by patients.’(4) – a finding which has been confirmed.(77) These misdiagnoses will continue to manifest themselves in research data which rely on self-reported recall of self- or physician-diagnosed vulvovaginal candidiasis.”

On page 7 the authors state “the commonly cited incidence and recurrence figures were not derived from empiric investigation.” This is an issue not limited to VVC, but why this is important is entirely unclear.

I believe that it is important for the epidemiologic data presented in peer-reviewed literature – whether relating to vulvovaginal candidiasis or any other health condition - to be empirically supported, and for biases in those data to be acknowledged. Given that there are methods known to confirm a diagnosis vulvovaginal candidiasis - such as the diagnostic guidelines from the US Centres of Disease Control which are cited in this manuscript – investigators can avail themselves of the methods to make accurate measurements rather than continue to rely on self-report.

There are empiric investigations, such as those by Geiger et al., and Foxman et al., in the literature. These the authors dismiss these as estimates are based on self-reported history of physician diagnosis. One can argue that self-reported history of physician diagnosis either over- or under- estimates the burden of VVC, as treatment is available without prescription over the counter. However, the authors do not make either of these arguments.

The Reviewer is arguing that error in physician misdiagnosis can be in either direction. This point is implicit in the statement: “In the absence of laboratory-confirmation of Candida in women with vulvovaginal candidiasis-associated symptoms, both self-diagnosis and clinical diagnosis are known to be of low accuracy.(3,9)”
The proposed solution seems quite naïve: why would anyone fund such a study unless there was already a suggestion of significant burden?

Certainly there is enough anecdotal evidence to suggest a “significant burden”. Funding of a study such as that proposed in the paper is contingent on the magnitude of incidence and recurrence of vulvovaginal candidiasis being unknown, which is the argument I have made in this paper.

How will they obtain a representative population for study that is compliant for follow-up that has a better response rate than the studies they dismiss?

There is a wealth of literature concerning the conduct of research studies, and it is outside the scope of this paper to detail the recommendations regarding recruitment and retention of study participants.

Further, why are more accurate incidence and recurrence estimates required?

The purpose of this paper was to highlight that there are no reliable estimates of incidence and recurrence of vulvovaginal candidiasis. I wish to let the reader decide whether this is a concern.
Reviewer #2: Macit Ilkit
Reviewer's report:
This paper was an excellent review of many aspects of Candida vaginitis. In addition, I suggest mentioning the need for further studies and proposing a few directions for these studies.

I have outlined the design of a proposed study in the penultimate paragraph: “Population-based cohort studies are essential for providing reasonable estimates of the incidence and recurrence of vulvovaginal candidiasis. A study of this nature requires: 1) a population-based survey of women to identify prevalent infections; 2) prospective follow-up of an initially unaffected cohort for at least one year; 3) laboratory testing for the presence of Candida species upon report of vulvovaginal candidiasis-associated symptoms; and 4) exclusion of Candida as an ‘innocent bystander’ (i.e. when symptoms are a consequence of another condition).(4)”
Reviewer #3: Ana Paula Sampaio Carvalho
Reviewer's report:
Rathod and Buffler present in their manuscript “Highly-cited estimates of the cumulative incidence and recurrence of vulvovaginal candidiasis are inadequately documented” the analysis of the cited estimates of the cumulative incidence of VVC. The authors present their observations about three main sentences:
1- 75% of women will experience an episode of vulvovaginal candidiasis in their lifetimes
2- 50% of initially infected women will experience at least a second episode
3- 5-10% of all women experience recurrent vulvovaginal candidiasis

Discretionary Revisions
The manuscript addresses an important problem and is well argued

I appreciate this feedback.

however, the authors spend too much time detonating these sentences and not debating the subject with other published data.

I agree it would be ideal to contrast these widely-cited figures with those available from more robust research studies. Unfortunately, it does not appear that such studies have been conducted.

In the discussion section once more the authors point other studies mainly in a critical point of view. Is there no reliable study?

Indeed, in this paper I have argued that there is no reliable study.

I have refined the argument further now in response to Reviewer #1 and Reviewer #3. I discuss the two population-based studies of self-reported physician diagnosed vulvovaginal candidiasis, and argue that they lack reliability: “Since Sobel’s estimate was published there have been two population-based studies of the prevalence of recurrent vulvovaginal candidiasis, both of which found that approximately 8% of women are affected by RVVC.(1,2) These studies — though the most rigorous available — must be interpreted with caution, as few of the women recruited opted to participate, there was evidence that recall of past diagnoses diminished over time, and the criteria the participants’ physicians used to make the diagnoses were unknown.”

Further evidence of the absence of reliable studies is the continued citation of the undocumented figures. Surely if more robust studies existed, their findings would be reported widely.
Reviewer #4: Cathy Watson
Reviewer’s report:
- Major Compulsory Revisions
  *None identified
- Minor Essential Revisions
  1. The authors assert that Sobel is often erroneously cited for the statement that 5-10% of all women experience RVVC. This is misleading, as Sobel himself cites this figure his later highly cited Lancet publication (Sobel 2007), using Foxman et al. 1998 as his source (see below), of which he was a co-author. “The infection - caused by Candida spp affects 70–75% of women at least once during their lives, most frequently young women of childbearing age. 40–50% of women will experience a recurrence. 5–8% of adult women have recurrent vulvovaginal candidosis, defined as four or more episodes every year.” (Sobel 2007). Clarification of the authors’ assertion is requested.

It is not clear that the report from Foxman et al (1998) can be used to support the estimate of the recurrent vulvovaginal candidosis figure.[2]

Further, many authors continue to cite Sobel’s publications prior to his Lancet paper.

2. The statement “...both self-diagnosis and clinical diagnosis are known to be of low accuracy” is supported by two secondary references. It would be more appropriate to use primary references such as Nyrijesy et al. 1997.

I thank the reviewer for this suggestion. I have added primary references to support this statement. “In the absence of laboratory-confirmation of Candida in women with vulvovaginal candidiasis-associated symptoms, both self-diagnosis and clinical diagnosis are known to be of low accuracy.(4,73–76)”

3. The sentence “The literature on vulvovaginal candidiasis continues to report these unsupported estimates for the burden of vulvovaginal candidiasis among all women, leading women experiencing abnormal vaginal discharge and their respective medical practitioners to be more likely to make syndromic diagnosis of VVC” makes an unfounded association between the literature and the subsequent predictor of diagnostic behaviour. It is well supported in the literature that self-diagnosis and diagnosis without mycological confirmation are inaccurate, and that VVC is often over-diagnosed without evidence. However, it is unlikely that most women are aware of and influenced in their self-diagnosis by knowledge of the estimates in the literature. It is also possible that clinician misdiagnosis may be impacted by lack of confidence in diagnosing other vaginal conditions such as vulval vestibulodynia or vulval dermatitis rather than by being influenced by inaccurate citations of VVC in the literature. I would suggest that this section be re-worked to modify this unfounded association.

I have re-worked this paragraph so that it is clear I am proposing a hypothesis rather than making an assertion: “One may posit that over time these estimates have fostered an impression among clinicians that women with vaginitis have a high probability of having vulvovaginal candidiasis, so much so that many clinicians dispense with confirmatory tests and rely on syndromic diagnoses.
Then, in the words of Sobel: ‘Misdiagnosis by clinicians inevitably results in incorrect self-diagnosis by patients.’ (3) – a finding which has been confirmed. (4) These misdiagnoses will continue to manifest themselves in research data which rely on self-reported recall of self- or physician-diagnosed vulvovaginal candidiasis.”

- Discretionary Revisions / general comments

4. The recommendations proposed are fair but ambitious! A representative sample of the population would be challenging to obtain, and the lack of information from non-responders would bias the analysis. This is likely reflect in the high number of epidemiological studies using self-reported diagnosis of VVC.

I agree – it is certainly more challenging to conduct more robust studies, but that has not proven to be a barrier in many other areas of health research.

In this paper, I have argued that the current methods used to measure the population-level incidence and recurrence of vulvovaginal candidiasis are inadequate. I wish to let the reader decide whether this is a concern.

5. The fourth recommendation “exclusion of Candida as an innocent bystander’ refers presumably to asymptomatic vaginal colonisation of Candida spp. It is not proven that asymptomatic colonisation is always ‘innocent’ as several authors have documented the significance of asymptomatic colonisation such as the likelihood of developing post-antibiotic symptomatic vaginal candidiasis (e.g. Pirotta & Garland 2006) and yeast colonisation is a necessary precursor to symptomatic VVC (e.g. Beigi et al. 2004).

I have clarified this point: “and 4) exclusion of Candida as an `innocent bystander (i.e. when symptoms are a consequence of another condition).’ (3)”

It is still possible, as the reviewer has described, for the Candida spp. to develop into vulvovaginal candidiasis in the future.

6. In the Discussion section, the authors bring in new material and references that contribute to the background of the argument. This may be more appropriate in the previous section.

I will be happy to consider moving material and references from the Discussion to the Background, and welcome specific recommendations to this end.
References
