PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	HIV and syphilis testing for women and heterosexual men aged above 25 years in the Netherlands: possibilities for targeted testing at Sexual Health Centers
AUTHORS	Willemstein, Inge; Götz, Hannelore; Visser, Maartje; Heijne, Janneke

VERSION 1 – REVIEW

REVIEWER	Richard Muhindo Makerere University
REVIEW RETURNED	19-Mar-2023

GENERAL COMMENTS	Expect for line 40, in the introduction, where man is used instead of men, this is a well written paper with public health implications regarding STI and HIV prevention programs

REVIEWER	Christina Schumacher Johns Hopkins University School of Medicine, Pediatrics
REVIEW RETURNED	24-Mar-2023

GENERAL COMMENTS	This paper addresses and interesting and appropriate question - among sexual health clinic patients who are heterosexual (i.e., women and men who have sex with women only) and older (> 25 years) can targeted HIV/syphilis testing be targeted towards a subset of these patients. For populations (such as the one included in this study) where disease is rare and when resources may be limited, targeted testing is certainly an appropriate prevention strategy. For HIV in particular, where success of several high-impact interventions has led to decreasing incidence, questions about how best to focus interventions for maximum impact is important in this and other settings. For this, I think the question is important, relevant and useful to the field. To answer this question, the authors sought to develop a prediction model to inform a targeted testing strategy among older heterosexuals. In particular, I thought Table 3 to be the most useful data presented and showed the efficiency of symptoms and partner notification as heuristic for testing, though substantial number of diagnoses were still missed when only these two criteria were used. The proportion of missed diagnoses was substantially improved when adding age as criteria, but the proportion tested increased from 2% to 55%, and the criteria with the fewest missed infection required testing ~75% of patients, which begs the question, is this really still targeted testing? Were interactions investigated as predictors– for example age and sex/gender? Including interactions may improve prediction without increasing the proportion tested quite as much. Relatedly, something I think would be interesting for

	the authors to address in the discussion a little more is how many missed infections is acceptable? If resources preclude not being able to test all comers, than perhaps developing criteria to truly perform targeted testing AND not miss any diagnoses is not (yet) attainable. Perhaps targeted testing could be done, but better/different information is needed from medical records to develop better prediction criteria (and the authors may be able to speculate as to what this might be.) Without costing information, it's hard to say, though because of the expense of lifetime treatment for HIV, nearly all HIV interventions are found to be cost effective. Perhaps the better framing would be, what is the optimal strategy? My main comment, however, are related to the methodology that I think need to be addressed: The methods as presented do not conform to current literature on appropriate methods for the development of prediction models, and I suggest the analyses be revised accordingly, or if not possible, the limitations more thoroughly discussed. For example: 1) the use of backwards stepwise regression for predictor selection; 2) rarity of outcome which both limits the number of prediction variables that can be included and likely precluded development of training dataset and internal model validation. I suggest referring to the TRIPOD checklist (which should be included in addition or in lieu of the STROBE statement), and a recent journal article written by the editors of several respiratory journals that is a useful discussion of appropriate development and reporting for prediction models that I think will be helpful to the authors when revising their manuscript (See; Leisman DE et al. Development and Reporting of Prediction Models: Guidance for Authors From Editors of Respiratory, Sleep and Critical Care Journals. Crit Care Med 2020 May; 48(5): 623-633. doi: 10.1097/CCM.0000000000004246)

REVIEWER	Tiffany Renee Phillips Melbourne Sexual Health Centre
REVIEW RETURNED	29-Jun-2023

GENERAL COMMENTS	Thank you for the opportunity to review this important work examining predictors for HIV/Syphilis among heterosexuals in the Netherlands to direct targeted testing strategies. The manuscript is well written and the analysis is sound. I have no major concerns and minor feedback below. -I think you could consider describing in Methods which symptoms qualify as "HIV/syphilis specific"—it would make it clearer how you define this variable as well as make it more obvious why you didn't separate HIV and syphilis symptoms as two distinct variables (there is overlap with some general symptoms, ie fever and swollen lymph nodes etc). I see you provide a good rational for including them together in the limitation which is helpful.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Expect for line 40, in the introduction, where man is used instead of men, this is a well written paper with public health implications regarding STI and HIV prevention programs

We thank the reviewer for this comment; we adjusted man to men (page 5, line 22).

Reviewer #2

This paper addresses and interesting and appropriate question - among sexual health clinic patients who are heterosexual (i.e., women and men who have sex with women only) and older (> 25 years) can targeted HIV/syphilis testing be targeted towards a subset of these patients. For populations (such as the one included in this study) where disease is rare and when resources may be limited, targeted testing is certainly an appropriate prevention strategy. For HIV in particular, where success of several high-impact interventions has led to decreasing incidence, questions about how best to focus interventions for maximum impact is important in this and other settings. For this, I think the question is important, relevant and useful to the field.

We thank the reviewer for highlighting the relevance of our research question.

To answer this question, the authors sought to develop a prediction model to inform a targeted testing strategy among older heterosexuals. In particular, I thought Table 3 to be the most useful data presented and showed the efficiency of symptoms and partner notification as heuristic for testing, though substantial number of diagnoses were still missed when only these two criteria were used. The proportion of missed diagnoses was substantially improved when adding age as criteria, but the proportion tested increased from 2% to 55%, and the criteria with the fewest missed infection required testing ~75% of patients, which begs the question, is this really still targeted testing?

We are happy that the reviewer brought this up. This is important in the discussion. We have added to the discussion section page 11, lines 213-215: "Also, when adding all of these significant determinants to targeted testing, most participants would still have been tested (74%). This raises the question whether you would be able to calling this targeted testing".

Were interactions investigated as predictors– for example age and sex/gender? Including interactions may improve prediction without increasing the proportion tested quite as much.

For all significant determinants that remained in the final model, we investigated interactions by adding interaction terms to all univariate regressions separately (see page 7, lines 71-74). This also included age and sex. For any significant interaction we performed stratified analyses (supplemental tables S1 & S2). In the result section of this manuscript we described the results of these analyses. Since we already investigated interactions, we did not add anything new to the manuscript.

Relatedly, something I think would be interesting for the authors to address in the discussion a little more is how many missed infections is acceptable? If resources preclude not being able to test all comers, than perhaps developing criteria to truly perform targeted testing AND not miss any diagnoses is not (yet) attainable. Perhaps targeted testing could be done, but better/different information is needed from medical records to develop better prediction criteria (and the authors may be able to speculate as to what this might be.)

We thank the reviewer for this comment. We agree with the reviewer that targeted testing scenarios may have been improved if additional and more specific clinical data were used for this study. Unfortunately, we are bound to the limits of the surveillance data. On page 10, lines 163-167 we added this to the limitations of our study: "First, we were limited to variables as available in SOAP data. More detailed clinical data may have had improved the results of the regression model and the application of possible targeted testing scenarios in clinical practice."

Without costing information, it's hard to say, though because of the expense of lifetime treatment for HIV, nearly all HIV interventions are found to be cost effective. Perhaps the better framing would be, what is the optimal strategy?

Thanks for this addition. We added to the discussion about cost evaluation "To find the optimal strategy, HIV and syphilis treatment costs should also be included in these evaluations" (page 11, line 224-226).

My main comment, however, are related to the methodology that I think need to be addressed:

The methods as presented do not conform to current literature on appropriate methods for the development of prediction models, and I suggest the analyses be revised accordingly, or if not possible, the limitations more thoroughly discussed. For example: 1) the use of backwards stepwise regression for predictor selection; 2) rarity of outcome which both limits the number of prediction variables that can be included and likely precluded development of training dataset and internal model validation. I suggest referring to the TRIPOD checklist (which should be included in addition or in lieu of the STROBE statement), and a recent journal article written by the editors of several respiratory journals that is a useful discussion of appropriate development and reporting for prediction models that I think will be helpful to the authors when revising their manuscript (See; Leisman DE et al. Development and Reporting of Prediction Models: Guidance for Authors From Editors of Respiratory, Sleep and Critical Care Journals. Crit Care Med 2020 May; 48(5): 623-633. doi: 10.1097/CCM.0000000000004246)

We apologize for the confusion caused. In our study we did not aim to develop a clinical prediction model as referred to in the cited article. We performed a statistical logistic regression model in order to find possible determinants associated with a HIV/syphilis diagnosis. These could be used for targeted testing guidelines, rather than an overall clinical prediction rule intended to inform clinicians as meant in the cited paper. To avoid further confusion, we change the wording throughout the manuscript from 'determinants predictive for HIV and syphilis diagnosis' to 'determinants of HIV and syphilis diagnosis'.

However, following this comment, we did add a clarification in the discussion section (page 10, lines 187-189 "Finally, it should be noted that the results of our study might be different when evaluating future years, based on possible differences in population and/or STI testing policy. Therefore continuous evaluation remains needed").

Reviewer #3

Thank you for the opportunity to review this important work examining predictors for HIV/Syphilis among heterosexuals in the Netherlands to direct targeted testing strategies.
The manuscript is well written and the analysis is sound. I have no major concerns and minor feedback below.

We thank the reviewer for the positive remarks.

-I think you could consider describing in Methods which symptoms qualify as "HIV/syphilis specific"—it would make it clearer how you define this variable as well as make it more obvious why you didn't separate HIV and syphilis symptoms as two distinct variables (there is overlap with some general symptoms, ie fever and swollen lymph nodes etc). I see you provide a good rational for including them together in the limitation which is helpful.

Unfortunately, in the Dutch national surveillance data of Sexual Health Centers (SOAP) that we use for this analyses, HIV/syphilis-specific symptoms is one variable and could therefore not be separated in this study as two distinct variables. We clarified this in the method section "(e.g. weight loss, fever, ulcers, swollen lymph nodes)" on page 6, line 52-53 and added to the limitation section on page 10, line 163-165 "First, we were limited to variables as available in SOAP data. For example,

HIV/syphilis-specific symptoms is one combined variable. We do note that clinical symptoms of recent HIV infection and early syphilis infection do overlap, so a clinical distinction would not be possible"

VERSION 2 – REVIEW

REVIEWER	Tiffany Renee Phillips Melbourne Sexual Health Centre
REVIEW RETURNED	03-Aug-2023

GENERAL COMMENTS	The authors have adequately addressed the reviewers concerns