PEER REVIEW HISTORY

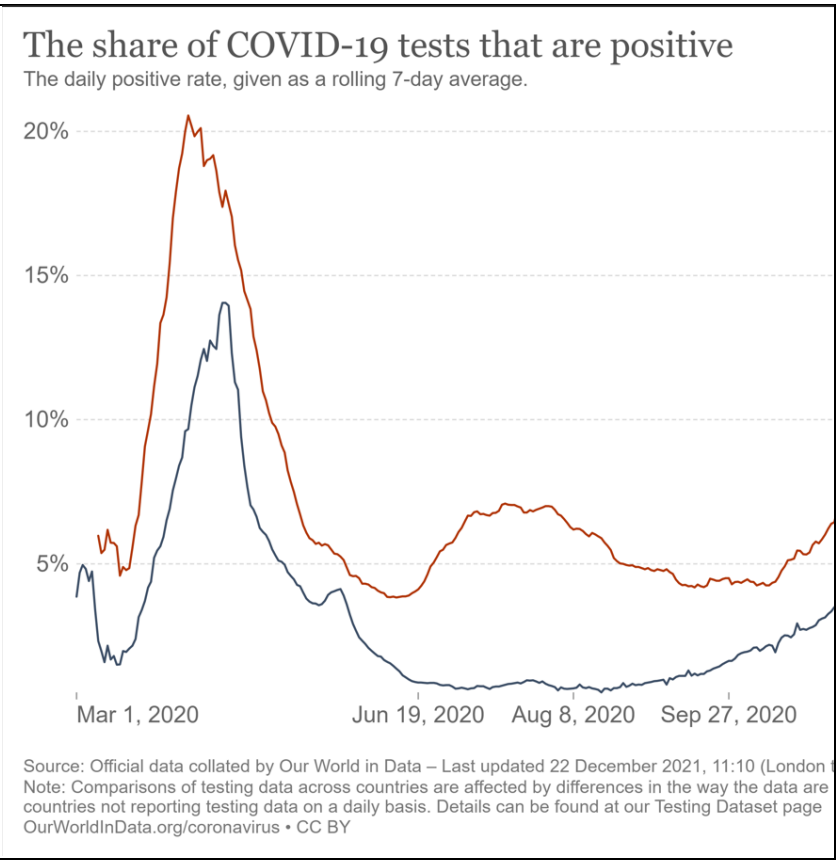
ARTICLE DETAILS

TITLE (PROVISIONAL)	Diagnostic Yield of Screening for SARS-CoV-2 among Patients Admitted to Hospital for Alternate Diagnoses: An Observational Cohort Study
AUTHORS	Davis, Philip; Rosychuk, Rhonda; Hau, Jeffrey P; Cheng, Ivy; McRae, Andrew; Daoust, Raoul; Lang, Eddy; Turner, Joel; Khangura, Jaspreet; Fok, Patrick T.; Stachura, Maja; Brar, Baljeet; Hohl, Corinne

VERSION 1 – REVIEW

REVIEWER	P Lephart Michigan Medicine, Pathology - Clinical Microbiology
REVIEW RETURNED	22-Dec-2021

GENERAL COMMENTS	This article represents a high-quality assessment of universal COVID screening across a wide geographical region and demographically diverse population. However, I believe the authors have misunderstood a key component of the IDSA recommendations for universal screening and how it should be interpreted in the context their study. I do not believe the 2% and 10% decision points recommended by the IDSA refer to incident rates of new cases per 100,000 population or, as was noted in this article, the 2% threshold alone would have required a daily rate of over 6 million new cases of active disease which is clearly not reasonable. Instead, given the articles they reference, I believe they are referring to the prevailing SARS-CoV-2 diagnostic yield as opposed to a population prevalence of disease. With that interpretation, it would be revealing to compare the ranges of incident COVID-19 cases per 100,000 with a 7-day average daily positive SARS-COV-2 testing rate. A review of SARS-CoV-2 testing data over the relevant time frame shows Canada eclipsing the 10% threshold for approximately 2 weeks in mid-April and dipping below 2% positivity from early June through early October. Including 7-day average positive SARS-COV-2 diagnostic rates over the time frame of the study would more appropriately place the authors data in the context of the IDSA universal testing thresholds. Otherwise, the multivariable analysis of factors associated with positive SARS-CoV-2 NAATs as presented demonstrates the importance of asymptomatic screening in high-risk populations and in those with certain COVID-19 compatible symptoms. It is this reviewer's recommendation that this article could be approved given revisions to address the application of the IDSA guidelines and inclusion of overall SARS-CoV-2 diagnostic yield data over the course of this study.

REVIEWER	Ed Gracely Drexel University College of Medicine
REVIEW RETURNED	04-Feb-2022

GENERAL COMMENTS	The authors have attempted to determine the yield from COVID testing of individuals admitted for reasons other than COVID. They used reasonable methods and overall the study is pretty straightforward. The biggest issue with studies like this is that they quickly become outdated. Would the yield today in the era of Omicron be the same as with earlier strains? That seems unlikely, but there is no way to assess how much the newer strains would change the results. Table 2: Is the first column truly univariate (that is, no adjustment for anything?) or is it a limited multivariate analysis with adjustment for age and sex? The p-value for health care worker seems very small for a wide CI that almost reaches 1. Please check that this is correct. Figure 3: With such small percentages, the CI should be asymmetrical, as is seem with COPD, but the others are not. Please check the calculations. Likewise for figure 2 -- I don't use a simple percentage +/- 1.96 SE for any CI for percentages. There are more accurate methods. Edit p 13 line 31. "that" --> "than" on the right. Writing suggestion. You key result is buried in a longer paragraph on the bottom of page 9. I would make "Of 3,113 patients admitted

	without COVID-19 " start a new paragraph.

VERSION 1 – AUTHOR RESPONSE

1. **Reviewer: 1**
   This article represents a high-quality assessment of universal COVID screening across a wide geographical region and demographically diverse population. However, I believe the authors have misunderstood a key component of the IDSA recommendations for universal screening and how it should be interpreted in the context their study. I do not believe the 2% and 10% decision points recommended by the IDSA refer to incident rates of new cases per 100,000 population or, as was noted in this article, the 2% threshold alone would have required a daily rate of over 6 million new cases of active disease which is clearly not reasonable. Instead, given the articles they reference, I believe they are referring to the prevailing SARS-CoV-2 diagnostic yield as opposed to a population prevalence of disease. With that interpretation, it would be revealing to compare the ranges of incident COVID-19 cases per 100,000 with a 7-day average daily positive SARS-COV-2 testing rate. A review of SARS-CoV-2 testing data over the relevant time frame shows Canada eclipsing the 10% threshold for approximately 2 weeks in mid-April and dipping below 2% positivity from early June through early October. Including 7-day average positive SARS-COV-2 diagnostic rates over the time frame of the study would more appropriately place the authors data in the context of the IDSA universal testing thresholds. Otherwise, the multivariable analysis of factors associated with positive SARS-CoV-2 NAATs as presented demonstrates the importance of asymptomatic screening in high-risk populations and in those with certain COVID-19 compatible symptoms.

   We agree wholeheartedly with Dr. Lephart's concern that the IDSA testing thresholds do not make sense as published, and that there may have been an error. We reviewed the latest published IDSA guidelines, and ***the IDSA does in fact base their recommended testing thresholds on prevalence of diseas,****[1] and not on test positivity. The IDSA has not updated their recommendations, nor have they published any retraction or correction. Rather than assuming, that the IDSA meant something other than what they have written and published, we think it is important to develop the evidence base in this area, which could inform a revision of their guidelines. To facilitate this, we have followed this reviewer's excellent recommendation to present our data on test positivity over the study period and have provided some edits to the text.*

2. It is this reviewer's recommendation that this article could be approved given revisions to address the application of the IDSA guidelines and inclusion of overall SARS-CoV-2 diagnostic yield data over the course of this study.

   We agree and included a graphical representation of the test positivity over the study period (see new Figure 2). While we did not feel comfortable revising our interpretation of the IDSA recommendations in our paper, because we have verified that our interpretation is correct, we absolutely agree with this astute reviewer and have recommended that the IDSA urgently revise their threshold (Discussion section, 4th paragraph).

3. **Reviewer: 2**
   The authors have attempted to determine the yield from COVID testing of individuals admitted for reasons other than COVID. They used reasonable methods and overall the study is pretty straightforward.

   Thank you.

4. The biggest issue with studies like this is that they quickly become outdated. Would the yield today in the era of Omicron be the same as with earlier strains? That seems unlikely, but there is no way to assess how much the newer strains would change the results.

   Thank you and we agree. We have added this aspect, and our plan to repeat the study in a new dataset to the Limitations section (Discussion, last paragraph).

Our study was performed before the era of Omicron. We intend to repeat the study with the data from different variants in the future. However, we believe our methods remain constant and can be shared across jurisdictions for local adoption. A very practical application of our work is being developed at one of the CCEDRRN hospitals, our findings are informing an economic decision analytic model to determine when the hospital should stop universal testing of all its admissions.

5. Table 2: Is the first column truly univariate (that is, no adjustment for anything?) or is it a limited multivariate analysis with adjustment for age and sex?

   The first column of Table 2 is truly univariate (no adjustment for any a priori variables).

6. The p-value for health care worker seems very small for a wide CI that almost reaches 1. Please check that this is correct.

   Thank you for your suggestion, we corrected the p-value.

7. Figure 3: With such small percentages, the CI should be asymmetrical, as is seem with COPD, but the others are not. Please check the calculations. Likewise for figure 2 -- I don't use a simple percentage +/- 1.96 SE for any CI for percentages. There are more accurate methods.

   Thank you for your suggestion. We updated our 95% CI using the Exact method.

8. Edit p 13 line 31. "that" --> "than" on the right.

   Thank you for your suggestion. We have corrected this error.

9. Writing suggestion. You key result is buried in a longer paragraph on the bottom of page 9. I would make "Of 3,113 patients admitted without COVID-19 " start a new paragraph.

   We have made this change.

VERSION 2 – REVIEW

REVIEWER	P Lephart Michigan Medicine, Pathology - Clinical Microbiology
REVIEW RETURNED	25-Apr-2022

GENERAL COMMENTS	I thank the authors for addressing the concerns with the IDSA's recommendations directly in their discussion and also in the inclusion of their study group's asymptomatic positivity rate over the time period of the study. I do think Figure 2 would be more powerful if shown with two lines; (1) the asymptomatic rate from your study(already shown) and (2) the overall disease prevalence (including symptomatic disease) either across Canada as a whole or for the sites in the study. The IDSA states that they "assessed studies that reported prevalence of COVID-19 among asymptomatic individuals in the community and determined that the prevalence may range from <1 to 10%" and then uses these asymptomatic rates as thresholds that should be used to guide further asymptomatic testing. It seems to this reviewer that it would be more useful, particularly to those sites not performing asymptomatic screening (and thus unaware of a local rate) to instead use the local symptomatic rate as a guide to where "hot spots" are and when asymptomatic screening would be worthwhile, assuming there is a link between the two rates. Therefore, it would be interesting to see what you study sites (or Canada's) overall prevalence rate was when your asymptomatic rates eclipsed the IDSA's 20 missed cases

	per 1,000 patients (>2% in March, 2020) and whether the rise in rates you note at the end of the study period mirrored a rise in symptomatic prevalence.

REVIEWER	Ed Gracely Drexel University College of Medicine
REVIEW RETURNED	12-Apr-2022

GENERAL COMMENTS	The authors have responded to my questions, but a few details need attention. In table 2, I asked, "Is the first column truly univariate (that is, no adjustment for anything?)". The authors replied that it was truly univariate. Perhaps I should have clarified that the reason for my question is that the table footnote refers to "Final model determined by including variables with a p-value of p<0.20 during the sex and age adjusted analysis.." Where is the sex and age adjusted analysis? is that a third analysis that is not shown? Please clarify. Also, you never refer to table 2 in the text. Please do so.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
The authors have responded to my questions, but a few details need attention.

In table 2, I asked, "Is the first column truly univariate (that is, no adjustment for anything?)". The authors replied that it was truly univariate. Perhaps I should have clarified that the reason for my question is that the table footnote refers to "Final model determined by including variables with a p-value of p<0.20 during the sex and age adjusted analysis.." Where is the sex and age adjusted analysis? is that a third analysis that is not shown? Please clarify.

Thank you for your comment. The first column of Table 2 is truly univariate, we decided not to show the sex and age adjusted analysis.

Also, you never refer to table 2 in the text. Please do so.

Thank you for letting us know, and this is now reflected in the manuscript.

Reviewer: 1
I thank the authors for addressing the concerns with the IDSA's recommendations directly in their discussion and also in the inclusion of their study group's asymptomatic positivity rate over the time period of the study. I do think Figure 2 would be more powerful if shown with two lines; (1) the asymptomatic rate from your study(already shown) and (2) the overall disease prevalence (including symptomatic disease) either across Canada as a whole or for the sites in the study. The IDSA states that they "assessed studies that reported prevalence of COVID-19 among asymptomatic individuals in the community and determined that the prevalence may range from <1 to 10%" and then uses these asymptomatic rates as thresholds that should be used to guide further asymptomatic testing. It seems to this reviewer that it would be more useful, particularly to those sites not performing asymptomatic screening (and thus unaware of a local rate) to instead use the local symptomatic rate as a guide to where "hot spots" are and when asymptomatic screening would be worthwhile, assuming there is a link between the two rates. Therefore, it would be interesting to see what you study sites (or Canada's) overall prevalence rate was when your asymptomatic rates eclipsed the IDSA's 20 missed cases per 1,000 patients (>2% in March, 2020) and whether the rise in rates you note at the end of the study period

Thank you for your comment. We would like to clarify that Figure 2 is not our study groups' asymptomatic positivity rate over time, but rather the positivity rate of all our eligible study patients over time, which includes symptomatic and asymptomatic patients across all study sites in Canada. We have changed the title of Figure 2 to make this more clear. We also have a smaller study population, especially asymptomatic patients, we are not certain if we will be able to illustrate a clear difference in disease prevalence between asymptomatic and symptomatic patients.

VERSION 3 – REVIEW

REVIEWER	P Lephart Michigan Medicine, Pathology - Clinical Microbiology
REVIEW RETURNED	01-Jul-2022

GENERAL COMMENTS	Thank you for your responses to my comments. I have no further concerns.

REVIEWER	Ed Gracely Drexel University College of Medicine
REVIEW RETURNED	01-Jul-2022

GENERAL COMMENTS	Previous review: In table 2, I asked, "Is the first column truly univariate (that is, no adjustment for anything?)". The authors replied that it was truly univariate. Perhaps I should have clarified that the reason for my question is that the table footnote refers to "Final model determined by including variables with a p-value of p<0.20 during the sex and age adjusted analysis.." Where is the sex and age adjusted analysis? is that a third analysis that is not shown? Please clarify. You replied: Thank you for your comment. The first column of Table 2 is truly univariate, we decided not to show the sex and age adjusted analysis.

VERSION 3 – AUTHOR RESPONSE

Response:
Getting there. But we still need a few minor clarifications. First of all, the footnote to table 2 should say, " with a p-value of p<0.20 during the sex and age adjusted analysis (not shown),"... to clarify that this is not the analysis in the table.

Also, I notice that the text says, "The initial multivariable logistic regression model to identify factors associated with a positive NAAT considered candidate variables with a p-value cut-off point of 0.20 based on the Wald test from univariable analyses..." This appears to reference only the univariable analyses, NOT the age/sex adjusted ones. Please clarify.

Thank you for your suggestion. We have corrected the footnote to Table 2 to say univariable analyses rather than sex and age adjusted analysis.

VERSION 4 – REVIEW

REVIEWER	Ed Gracely Drexel University College of Medicine
REVIEW RETURNED	06-Jul-2022

GENERAL COMMENTS	OK. Assuming you did not use the sex and age adjusted analysis for

	anything, only the univariable analysis, (as now stated in text and table) the paper is OK.