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Title	COVID-19 screening of asymptomatic patients admitted through emergency departments in Alberta: a prospective study
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Reviewer 1	Corinne Hohl
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General comments (author response in bold)	ABSTRACT: 1. Components of the abstract are generally clear except the Methods section. In this the authors first state that only symptomatic patients were eligible for testing, yet that they extended testing. So, the added testing they did was on non-eligible patients? This is confusing. Please clarify what was done where. **We agree that adding the information of current eligibility for testing in the abstract is unnecessary and makes the whole section unclear. We modified the methods section as follows: Between April-9 and May-24, 2020, we screened for COVID-19 symptoms and tested for SARS-CoV-2 infection all consecutive patients admitted via emergency department (ED) to three Alberta hospitals. We assessed the rt-PCR positivity rate in those with and without COVID-19 symptoms, and the performance of symptom screening versus rt-PCR results on swab samples. We also summarized the provincial incidence of daily cases and effective reproductive number during the study period.** INTRODUCTION: 2. The introduction is clear and well written. **Thank you.** METHODS: 3. Did the authors obtain Ethics approval? In the results, this is called a "quality improvement study". However, this study is about something unknown, and should unlikely fall under the rubric of quality improvement. Please clarify. I am concerned that this study may be in conflict with the Helsinki declaration. **We obtained REB approval for this study and provided details in the acknowledgment section (page 10): Ethics approval: University of Calgary REB20-0689, issued on May 4, 2020. We have added the following statement to the methods (design paragraph, on page 4): We obtained institutional review board approval for this study with waiver of patient consent (University of Calgary REB20-0689).** 4. Were patients who did not meet their hospital's testing policy consented to the research study before study samples were taken? **Please see previous response; the University of Calgary REB approved the study with waiver of patient consent.** 5. How did you follow-up patients who tested negative? False negative tests have been reported, and thus it would have been important to understand whether any were re-tested subsequently, or developed respiratory symptoms in follow-up. No follow-up protocol is presented. **We tested asymptomatic people included in this study only upon admission via ED. We monitored these patients for symptoms during admission (see**

	response to point #7). Following negative testing, 26 people presented symptoms and were tested a second time; 7 a third time and 1 was tested 5 times. All tests were negative. We have added the following sentence to the result section: During admission, 26 asymptomatic patients developed symptoms possibly suggestive of COVID-19 and were tested a second time; 7 a third time and 1 patient was tested 5 times. All tests were negative. 6. Please describe your testing method. **Done: "Testing method: We used two swab kits for collecting samples: FLOQSwab and Universal Transport Medium for nasopharyngeal swabs, and APTIMA® Unisex or Multi-test Swab Specimen Collection Kit for throat swabs. We used a validated lab-developed real-time reverse transcriptase–polymerase chain reaction assay.[13]"** 7. Were all patients admitted, or were some released? Did you also include ED discharged patients in your study? **On page 4 ("Design and setting" section), we clarified that We did not include in this study people who were discharged from ED. We closely monitored for symptoms all asymptomatic study participants following the first test in the ED.** RESULTS: 8. Generally well written. **Thank you.** 9. No baseline characteristics are presented. This is lacking. **We have added the summary information on baseline age and sex after the description of the sample size (overall and by result of symptom screening): During the study period (April 9th to May 24th), 3,375 people (mean [SD] age 51 [21] years; 51% men) were hospitalized through the EDs in the three study sites, screened for symptoms and tested (65% via throat swab; 35% via a nasopharyngeal swab). Of these, 1,814 (54%) people were asymptomatic (mean [SD] age 55 years [22] and 51% men) and 1,561 had symptoms (mean age [SD] 47 [19] years, 51% men).** 10. Please present your results in two by two tables and add diagnostic test performance. **We have added a table summarizing the results (Table 2).** DISCUSSION: 11. Generally, well written. **Thank you.** 12. Please discuss your findings relative to other reports, for example the New York City data on asymptomatic women admitted for delivery had positive SARS-CoV-2 testing. Why did you find such differences? **We have added the following consideration on page 9: The prevalence of asymptomatic people varies across studies, which may be due to different underlying risks of community transmission but also to whether investigators considered only current symptoms or both current and**

	previous history of symptoms to define a person asymptomatic. In a recent report during an explosive epidemic in New York, as many as 15% of currently asymptomatic women admitted for delivery had positive SARS-CoV-2 testing.10 While a recent meta-analysis found a similar prevalence of asymptomatic rt-PCR positive people,24 positive swab results alone in currently asymptomatic people with unknown 4-week symptom history, may be due to the detection of non-viable virus and thus overestimate both the prevalence of asymptomatic people and the risk of asymptomatic transmission.[11]
Reviewer 2	Susan Lee
Institution	Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, Calif.
General comments (author response in bold)	Overall comments: 1) The authors have done a good job describing the results of screening asymptomatic patients admitted from the ED during the peak of Alberta's COVID-19 epidemic. My main concern is that based on the lower disease prevalence in Alberta, the actual expected number of positives would be extremely low (*see back-of-the-envelope calculation below) based on the number of patients tested, test sensitivity, and Alberta's epidemiology, the authors should be very careful that readers don't misinterpret the results to assume that protocolized assessment of symptoms without testing is effective in other contexts, as positivity rates are likely to vary based on disease prevalence. The main conclusion should be that in a low-prevalence environment, where the pre-test probability of COVID-19 is extremely low, testing for asymptomatic patients may be low-yield. If this point is adequately emphasized, this study does contribute valuable information and is important to share with the scientific community. *Per the authors, the Alberta epidemic peaked at 71.4/100,000, or about 0.071%. Assuming that asymptomatic, screened, admitted ED patients would roughly represent about 20% the risk of having COVID as the population (based on the authors' background review of ~20% of patients being asymptomatic), or about 0.014%. They tested 1841 patients, so we would expect 0.014% x 1841 = 0.26 positives in their cohort, or less than 1 person. In essence, due to good public health measures, which Alberta should be applauded for, their cohort was underpowered to detect any asymptomatic cases using their methodology. (Not the point of their article, but to get a true population asymptomatic prevalence, they would probably have needed to do something more like the Icelandic study of mass population testing) **We generally agree, and took two actions to acknowledge this important point: (1) we have added a table summarizing the screening performance (as requested by reviewer #1); (2) we have added the following statement to the discussion (limitation section): Second, given the relatively low degree of community transmission in Alberta with a peak of prevalent active cases at 0.071% of the population, our study may have been underpowered to detect asymptomatic cases. However, the true population prevalence of active cases may have been higher considering that during this study asymptomatic people as well as many symptomatic people were not tested in Alberta. Recent population-based screening data from Iceland indicate a prevalence of active cases that was over 10-fold higher at 0.8%, nearly half of whom were asymptomatic.[25]**

	The reviewer may be right (therefore we acknowledge this limitation); however, we do not know the true prevalence of active cases in Alberta (those who were tested and those who were not). Absence of asymptomatic testing and limited testing of symptomatic Albertans during that time may have led to underestimation of the true prevalence of active cases. If as high as in Iceland, we would have had 6 asymptomatic cases in our study sample. When we designed this study, we did not know. Abstract: 2) May be helpful to report that the Alberta peak of 71.4 cases per 100,000 is equivalent to 0.07%, especially since the introduction mentions asymptomatic rates in other settings (e.g. Iceland, which was described as a low prevalence at 1%) - people have difficulty translating cases per 100,000 into pre-test probability. **Done.** 3) page 3, line 40 – the study was underpowered to show that the screening process was effective, this conclusion should only be made when paired with "in a region with a low disease prevalence" (may be implied by strong 'public health containment', but would help to make it more explicit); better yet, don't need to conclude the screening process is effective, but rather state that additional testing to be low-yield when pre-test probability is extremely low. **We agree and have added "In a region with low disease prevalence, " and "low pre-test probability" to the abstract interpretation.** Introduction: Good background discussion and explanation of why detection of asymptomatic patients in the hospital setting would be beneficial **Thank you.** 5) The asymptomatic prevalence in various settings and transmission dynamics could be moved up from the discussion (page 8 line 34-44) into the introduction to provide more context **We have moved to the introduction the following: Studies in various settings have shown that 15-50% of people with positive rT-PCR were asymptomatic at testing.[4-6] Although pre-symptomatic spread has been described, the contribution of truly asymptomatic transmission remains unclear.[6]** 6) Examples of asymptomatic screening in other healthcare contexts might be useful, with particular attention to population disease rates or sick contacts in those settings: Rivett, et al, https://pubmed.ncbi.nlm.nih.gov/32392129/ Albalate, et al, https://pubmed.ncbi.nlm.nih.gov/32456944/ Al-Shamsi, et al, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254436/ **We have included all recommended papers to our reference list (8,9,12). We have added the following sentence to the introduction (end of second paragraph) to comment on ref #12: According to a recent report from the UK, 40% of asymptomatic staff who tested positive had symptoms >1 week before testing.[12]** 7) Mention of overall poor sensitivity of rt-PCR testing in asymptomatic patients would be helpful

	Vinh, et al, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267427/ Zitek, et al, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7234686/ **We agree this is an important point and these studies should be included in the reference list; since the introduction is already long, we have added the following considerations to the discussion: Fourth, although highly accurate, the sensitivity of the rt-PCR nasopharyngeal swabs, especially for asymptomatic screening, is not well described.[26,27]** Methods: 8) Unclear whether "we cannot exclude that exposure history" (page 5, line 20) means that these patients may have been classified as 'symptomatic'? Please clarify. **We specified that this statement referred to 'symptomatic' people only (manuscript page 4): "we cannot exclude that exposure history and other symptoms (e.g., gastrointestinal symptoms or loss of taste or smell) may have also been considered when determining who to test as new evidence emerged during the study".** 9) If the prevalence in Alberta peaked at around 71.4 cases per 100,000 – or around 0.07%, based on the description of the power calculation, this study was likely underpowered by the authors' own definitions. Unless the authors believe that asymptomatic ED admissions should have a higher positivity rate (if they do, they do not clearly indicate this). Maybe would be better to state that their study period was chosen when the epidemic was peaking, but never reached high-powered numbers, and also mention that nevertheless, the results are worth reporting because it shows testing characteristics of asymptomatic hospitalized patients in a low-prevalence environment. **Yes, we did believe that asymptomatic ED admissions would have had a higher rate of positive cases (1%), for several reasons, including that patients with COVID-19 have tended to have lower SES, a group at increased risk of COVID-19, and because patients sick enough to require hospitalization for other reasons might be less likely to acknowledge mild symptoms. We used methods to estimate a sample size based on margin of error around that estimate. We agree with the reviewer comment and have added the following sentence to the methods, statistical methods (manuscript page 5): Of note, we designed this study before the epidemic peak (the highest prevalence of active cases during the outbreak in Alberta).** 10) It's completely understandable given the context of the rapidly evolving pandemic that the study wasn't planned exactly a priori as written in the methods section, but it would be helpful to report which elements were pre-planned and which were determined post-hoc in the methods section. **We thank the reviewer for the helpful suggestions. We have addressed this concern by addressing comments #9 and #11.** 11) What was the follow-up protocol if any patients later developed symptoms? Results describe subsequent testing after they left the ED? How many needed subsequent testing and why? **We have added the following to the methods: "We did not include in this study people who were discharged from ED. We closely monitored for symptoms all asymptomatic study participants following the first test in the**

	ED." And the following to the results: "During admission, 26 asymptomatic patients developed symptoms possibly suggestive of COVID-19 and were tested a second time; 7 a third time and 1 patient was tested 5 times. All tests were negative." Results: 12) pg 7, line 17 – this is the first mention of it being a quality improvement study. Should be explained further in the methods section. What was the QI goal at the outset? What change was attempted to be made or measured? **Yes, this was part of a QI project aimed to assess the proportion of asymptomatic patients who test positive for COVID-19 who were admitted hospital. This was important as it was needed to inform appropriate use of PPE throughout the hospital. We have added the following sentence to the end of the introduction: "This study was part of a quality improvement project aimed at informing the appropriate use of personal protective equipment (PPE) and other in-hospital precautions, including isolation requirements, room assignments, and follow-up strategies for contact tracing."** 13) Authors describe in the methods using Table 1a to guide testing. Would be helpful to report how many were symptom-free, but answered 'yes' to the table 1b exposure questions **Unfortunately, this information is not available. As we were not testing asymptomatic patients routinely, this information was only used to guide IPC as to whether a patient needed to be isolated in hospital.** 14) Should report which patients had NP vs. throat swab as sensitivity can vary by site **We have added the following sentence to the results (page 6): "During the study period (April 9th to May 24th), 3,375 people (mean [SD] age 51 [21] years; 51% men) were hospitalized through the EDs in the three study sites, screened for symptoms and tested (65% via throat swab; 35% via a nasopharyngeal swab)"** 15) A more thorough description of the epidemiology characteristics of the Alberta COVID-19 infections (the positive cohort) during the study period would provide better context for the results. For example, how many cases were travel-related, associated with known-contacts vs. community spread. This has implications in interpreting the results - with stronger public health containment (i.e. lower community spread), the estimate of prevalence in the community might be even lower than the crude estimate based on cases per 100,000 population (making the study even more underpowered). **We agree this information would be useful, but it is not available to us.** 16) If the data are available, it would be interesting to see how many patients were picked up as "symptom positive" when the identified symptom was NOT what they presented with. (indicating that it's the protocol that helped 'catch' them rather than all that tested positive coming into the ED saying "hey, I think I have COVID") **We agree this information would be interesting, but unfortunately, this information is not routinely collected.**

	Discussion: 17) page 7 line 56 – it should be made explicitly clear that the processes described were sufficient in the context of hospital admission in a geographic region with low prevalence (i.e. where pre-test probability is extremely low) **We agree. We have added the suggested sentence to the first paragraph: " … in geographic regions where the prevalence of active cases (pre-test probability) is low, as it was in most regions of Canada during the first wave of COVID-19.22"** 18) page 9 line 28 – discussion identifies the key limitations of the study. More emphasis should be given to the low prevalence environment in Alberta. **We agree. We have added a limitation on page 8 to address this concern: Second, given the relatively low degree of community transmission in Alberta with a peak of prevalent active cases at 0.071% of the population, our study may have been underpowered to detect asymptomatic cases. However, the true population prevalence of active cases may have been higher considering that during this study asymptomatic people as well as many symptomatic people were not tested in Alberta. Recent population-based screening data from Iceland indicate a prevalence of active cases that was over 10-fold higher at 0.8%, nearly half of whom were asymptomatic.[25]** 19) Would be helpful for the authors to describe the pre-test probability of an asymptomatic patient presenting during the study period so the reader has a clearer understanding of just how rare a positive patient would be expected (see * in overall comments) **We assume the referee refers to the post-test probability, but we are not really sure. We have added the following sentence on page 7 (6-7 lines from the bottom of the page), when discussing the low yield of testing after negative screening result: "Even assuming a pre-test probability as high as 1% the post-test probability of a positive test in an asymptomatic person is very low, at 0.03%." If it refers to pre-test probability, then we believe we have responded to this in response to comments 1 and 9. If we have misunderstood your comment, please let us know.** 20) page 10, line 11 - I don't think the study is powered enough to confirm that the symptom assessment protocol was highly discriminatory. Perhaps just stating that it was sufficient in this context is a more suitable conclusion. **We agree and have modified the first part of the conclusion paragraph as follows: "In a region with a relatively low disease prevalence during the first wave of COVID-19, protocolized assessment of symptoms during the admission process was effective at ruling out patients with COVID-19 infection."** 21) Again, the final line in the conclusion (page 10, line 19) should state in the context of hospital admission when community transmission is minimal (or however the Alberta situation would best be described). **We have modified the second part of the conclusion paragraph as follows: "In such a setting, there may not be additive benefit to testing asymptomatic patients upon hospital admission."**