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The Evolving Usefulness of the Test-negative Design in Studying Risk Factors for COVID-19

To the Editor:

In a recent paper in this journal,[1] we described how to use the test-negative design as an efficient tool for identifying risk factors for COVID-19. In the early period of the pandemic, almost all tested persons were symptomatic, which led to the proposal of using an ancillary population-based control group—in addition to the test-negative controls—because it is likely that different respiratory diseases share common risk factors.

As the COVID-19 pandemic has progressed, the testing situation has changed: more and more persons without symptoms are being tested. This obviates the necessity of an additional population control group and may make it possible to disentangle the risk factors for becoming infected with SARS-CoV-2 from the risk factors for becoming diseased with COVID-19.

The inclusion of persons without symptoms in test-negative design studies will facilitate investigation of social factors (e.g., occupation, remote work status, socioeconomic status, risk tolerance, and personal activities) that increase risks of exposure and infection, with or without subsequent development of symptoms. It will also allow comparisons of the relative effectiveness of interventions (e.g., masks, vaccines) against the different endpoints of infection and disease, which is of high relevance to decision-making regarding public policies. In contrast, test-negative design studies that are restricted to symptomatic persons will primarily bring to light biologic/clinical factors (e.g., sex, age, immunosuppression, asthma, and pregnancy) associated with developing symptomatic disease after infection.[1,2]

For the application of the test-negative design to study risk factors in situations where testing includes symptomatic as well as non-symptomatic persons, the reason for testing is important to record and account for in analysis and inference. The analysis can be stratified into three groups: participants tested due to presence of symptoms consistent with COVID-19, participants tested due to contact with a case (e.g., as a result of contact tracing), and participants tested as a precautionary measure to manage risk while engaging in activities in which close contact is inevitable, such as travel or work.

In the stratum for whom the reason for testing is "having symptoms," the interpretations from of our previous paper apply. Symptomatic cases and controls can be enrolled from the test-positives and test-negatives and compared to each other, and more can be learned by triangulating the findings with an additional population control group.[1] Adjusting for severity has been advocated because of potential noncollapsibility[3]; however, such problems are usually trivial.[4] In the stratum of persons who are tested because of a recent contact, without having symptoms, it is not necessary to add an additional population control group as such a test-negative design in fact refers to transmission risk factors in the community. For example, a test-negative design may elucidate which family member situations (e.g., parent-to-child) lead to infections more often; alternatively, if the close contact is a co-worker or friend who tested positive, the test-negative design might become more detailed in the sense of asking test-positives versus test-negatives how close the contact was, which may lead to some refinements in general precautions (e.g., meetings in open air vs. closed rooms). If the contact is instead a warning by for example a phone application, this will be unexpected, and the reasons leading to test positivity will likely not be obvious, but this may lead to an inquiry about general risk situations (i.e., participating in certain activities) of those testing positive versus negative. Similar inferences will be possible in test-negative design analyses of persons being tested as a precautionary measure.

In summary, increasingly people are being tested for a variety of reasons; it is therefore necessary to control for reason for testing in the analysis, which may enrich the application of the test-negative design as a tool for identifying risk factors for SARS-CoV-2 infection and COVID-19 disease.

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