

Analysis proposals for test-negative design and matched case-control studies during widespread testing of symptomatic persons for SARS-Cov-2

Jan P Vandenbroucke^{1,2,3}, Elizabeth B Brickley¹,
Christina M.J.E. Vandenbroucke-Grauls⁴, Neil Pearce¹

(1) Departments of Medical Statistics, Non-communicable Disease Epidemiology and Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

(2) Department of Clinical Epidemiology, Leiden University Medical Center, The Netherlands

(3) Department of Clinical Epidemiology, Aarhus University, Denmark

(4) Department of Medical Microbiology and Infection Prevention, Amsterdam UMC, The Netherlands

Corresponding Author:

Jan P Vandenbroucke, Leiden University Medical Center, Dept. Clinical Epidemiology, PO Box 9600, 2300 RC Leiden, The Netherlands, E-mail: J.P.Vandenbroucke@lumc.nl,

Summary

Over the next weeks an increasing number of countries will be expanding testing of symptomatic persons for infection with SARS-CoV-2. It is important to consider the most efficient ways to collect information that will allow us to understand and manage the COVID-19 pandemic. Therefore, we propose two types of case-control studies that can be carried out in test-settings for symptomatic persons. The first, the 'Test-negative case-control design' (TND) is the easiest to set up, since all symptomatic persons will be tested; it only demands collecting information from these persons, some of which will already be collected routinely. The second, standard matched case-control studies (CC) demands that at least one person who accompanies the symptomatic persons to the test facilities is asked for the same information. We will first summarize the TND and explain how it may be added to large-scale testing of persons with signs and symptoms. The TND can show differences in risk factors between symptomatic persons with SARS-CoV-2 (who suffer from COVID-19) and persons with other respiratory infections. However, factors that are risk factors of equal magnitude for both COVID-19 and other respiratory infections will not be identified by the TND. Thus, secondly, we discuss the option of adding standard matched case-control studies (separately for the SARS-CoV-2 test-positives, and for the test-negatives) by asking persons who accompany the symptomatic persons to the test facilities to become controls. Those case-control studies give a contrast between COVID-19 patients and matched persons from the general population. We also provide suggestions for other types of matched and non-matched population controls. Such studies can help distinguish between exposures that are risk factors for both COVID-19 and other respiratory infections, and exposures that are risk factors for just COVID-19 (or just for other respiratory infections). We conclude that incorporating the test-negative design into on-going testing efforts can be useful in itself, but it would be more useful with the addition of the matched case-control designs which will lead to a 'triangulation' of evidence. Health authorities should urgently consider setting up such case-control studies to learn more about the risk factors for symptomatic SARS-CoV-2 infection in the COVID-19 pandemic.

The situation of Coronavirus disease 2019 (COVID-19) is moving fast, and it is not surprising that different countries are in different stages, both in terms of the pandemic, and in terms of their response to it. Widespread testing is a key part of monitoring an epidemic.[1, 2] Ideally, this should involve random/representative population samples, rather than just testing of those with symptoms.[3] However, most countries are currently focussing on testing those with symptoms, since this maximises the chance of identifying and isolating patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in order to reduce onward transmission and to inform further treatment if required. There is much that can be learnt about COVID-19, even if only symptomatic people are tested. However, more may be learnt by conducting formal test-negative and matched case-control studies obtaining some additional information on all of those tested and their accompanying persons. In this paper, we describe these study designs, and how they can enhance understanding of risk factors for symptomatic SARS-CoV-2 infection in the COVID-19 pandemic.

Essence of the Test-Negative Case-control Design (TND)

Test-negative case-control studies[4-9] are studies based on persons who undergo testing because they present with signs and symptoms that may point to a particular disease. The cases are those who test positive for the disease, and the controls are those who test negative - the test-negatives will have another reason for their signs and symptoms, most likely another viral disease. [8] These 'cases' and 'controls' usually come from a particular geographical population, but this may not be explicitly defined, because not everyone in a particular area may present for testing (and some people may come from outside of the area for testing).

TNDs involve comparing the odds of a given intervention (e.g. vaccine receipt) or a given risk factor (e.g., smoking) among symptomatic participants who test positive compared those who test negative. Given certain assumptions described in the literature,[8] it can produce effect estimates (odds ratios) which are generalizable to the broader general population. The approach has most commonly been used for assessing vaccine effectiveness[4] or for identifying risk factors for antibiotic resistance,[5, 10] but has also been applied to estimate risk factors in circumstances in which 'diagnostic suspicion bias' was suspected, for example in studies on oral contraceptives and venous thrombosis, and on aspirin use and Reye syndrome.[8]

Test-negative designs are an expedient way to obtain quick answers to important questions. An additional advantage is that, by design, they protect against some forms of bias which are otherwise difficult to control. People who get tested for a disease will not usually be representative of all those who have the disease (unless everyone in the population is tested) - usually, they are more likely to have severe symptoms, and more likely to seek medical help. This help-seeking behaviour is in turn affected by many factors such as age, gender, socioeconomic status, access to health care, proximity to testing facilities, severity of symptoms, type of personality (degree of hypochondria), and in certain settings also insurance coverage. The idea of the test-negative design is that the same selective forces that lead individuals to be tested will operate on both those who test positive and those who test negative. Thus, there has been substantial discussion of this study design,[4-9] and it is generally agreed that it can produce valid effect estimates under the assumption that the selection forces are similar for the test-positives (the cases) and the test-negatives (the controls).

Reasons for thinking about the TND in the COVID-19 pandemic

Given that large numbers of people are being tested in the population, additional insights into the risk factors for COVID-19 can be gained by collecting the same information on symptomatic individuals who test positive and those who test negative, i.e. by ‘adding on’ a test-negative case-control study. Specific risk factors for COVID-19 will be present more often in those symptomatic individuals who test positive for SARS-CoV-2 than in than those who test negative.

Because the test-negatives belong to the same source population (i.e. people who would come for testing if they had symptoms of Covid-19) as the test-positives and had the same motivation to be tested, this may give timely and locally relevant insight into the course of the epidemic in different types of communities (urban, rural), in communities where there are many cases, as well as in communities where there are few cases.

Direct comparisons of ‘test-positives’ to ‘test-negatives’ (comparison TND in the Figure) involve a (test-negative) case-control study which can yield insight into specific risk factors for becoming infected and symptomatic with SARS-CoV-2: these may include age, sex, race/ethnicity, socioeconomic factors (e.g. income, education), occupational exposures (e.g. healthcare workers performing aerosol-generating procedures, delivery drivers, teachers), contact patterns (e.g. household exposure to confirmed case, travel histories, childcare responsibilities), geographic residence (e.g. urban versus rural), behavioural factors (e.g. shopping locations, smoking), medical risk factors (e.g. immunodeficiency), and genetic factors (from the swabs taken for viral diagnosis, these will also contain nasal or buccal cells).

We like to emphasize that it is not necessary that *all* test sites ask for *all* this information. Some of this information might already be routine. If a sufficient number of test sites test large numbers of people, *different* types of information may be asked at *different* testing sites – so as not to burden the test sites and to be able to answer several questions at once, and to be able to adapt short questionnaires to evolving questions. Some risk factors may be immediately important for local decisions, others more widely or more theoretically. In principle, the questions might be parcelled up between test-sites, provided that each (group of) test-sites that uses one particular set of questions is sufficiently large. The data can be analysed just like any other case-control study, although additional consideration should be given to assessing various possible interpretation issues arising because both the cases and controls represent a subgroup of the general population.[8]

Critical reflections on the interpretation and feasibility of the TND in the COVID-19 pandemic

As with any other TND study, there are several aspects which need to be considered critically.

Most importantly, the TND involves a comparison between persons who test positive for SARS-CoV-2 and persons who test negative but who have similar signs and symptoms. Usually therefore the test-negatives will have another reason for their similar signs and symptoms - most likely they will have another respiratory infection, by another virus. There will be some exposures (e.g. overcrowding) which increase the risks both of COVID-19 and of other respiratory infections. It follows that the TND can only identify those risk factors that are either totally distinct or clearly different in magnitude from the risk factors for illnesses that that can manifest with similar symptoms (e.g. other viral infections, bacterial infections, or possibly allergies). So if, for example,

living in over-crowded conditions equally increased the risks both of COVID-19 and of other respiratory infections, then the proportions living in overcrowded conditions would be similar in the test-positives (cases) and the test-negatives (controls); on the other hand, if male sex was a risk factor for symptomatic SARS-CoV-2 infection, but not for other respiratory infections, then more of the test-positives than the test-negatives would be male.

An additional consideration is seasonality; it is not yet known how the incidence of SARS-CoV-2 infections over the calendar year will evolve. Seasonality may also affect the mixture of pathogens causing the symptoms in the test-negative group. Influenza and respiratory syncytial viruses peak in winter months as compared to, for example, parainfluenza viruses which peak in spring and autumn months.[11] Although this is an area of great uncertainty, it is possible that in summer months, there might not be sufficient test-negative controls. The design and analyses options might then be limited to a contrast between the test-positive and their accompanying persons. However, as the seasonality is different around the globe, a TND which is not possible in one hemisphere will become possible in the other.

Adding standard case-control studies by asking the accompanying persons as a ‘matched’ population control group

A TND can potentially identify risk factors for COVID-19 that differ from those for other respiratory infections, either in kind or in magnitude, but will not identify risk factors that the test-positives and test-negatives have in common. On the other hand, comparing test-positives with a general population control group will tell us about risk factors for Covid-19, but does not tell us which factor is specific for SARS-CoV-2 rather than respiratory infections in general. The ideal situation is to have both comparisons. This strategy has been advocated and applied as an extension of TNDs of antibiotic resistance[5, 10]. This experience leads us to propose a similar strategy for studies on COVID-19.

Depending on the type of testing facilities, many of the persons who go for COVID-19 testing will be accompanied by other persons (think of drive-thru testing facilities), who may be household members, relatives or friends. Thus, it may be expedient to immediately ask an accompanying person to volunteer the same information (e.g. completing a short exposure questionnaire) at the time of testing the person with symptoms – this may in practice be done before the test result is known. These persons are members of the general population, and should not have Covid-19 symptoms (they may in some instances, but in general they should not be accompanying if they do). If at least one accompanying person is asked for the same information as the symptomatic persons, this has the potential to allow further evaluation of risk factors (e.g. BMI, school attendance) or non-pharmaceutical interventions (e.g. social distancing adherence and the use of mouth caps) this leads to a comparison with the general population; a particular benefit is that these risk factors may influence the risk of exposure to a range of respiratory pathogens and would therefore be difficult to detect in a TND.

Note that in a separate heading below (***“Other general population control groups”***), we offer ideas for other general population control groups that may fit better in other settings. Here we continue

discussing the design with the ‘accompanying persons’, which might be on the one hand very feasible in several settings, but is on the other hand methodologically more complex.

For both the test-positives (COVID-19 cases) and the test-negatives (controls who are persons with other respiratory infections), the accompanying person can be seen as a ‘matched’ population control – usually they will be a spouse, sibling or close friend. This matched approach has been widely used in epidemiology, and the strengths and weaknesses have been extensively discussed.[12, 13] Briefly, using friends, siblings or spouses as matched population controls, has the advantage of logistic convenience, plus it may indirectly ‘match’ for various risk factors (e.g. socioeconomic status, availability of health care, health seeking behaviour). The case and control become similar in many respects. However, as with any other pair-matched case-control study, this problem is removed by conducting a pair-matched analysis – essentially the matched analysis focusses on the subgroup of case-control pairs where the case and control differ with respect to the exposure under study, i.e. a pair-matched analysis is an analysis of the ‘difference’ that *remains* between cases and their controls despite them being made more equal by the matching.

This strategy will lead to two case-control data sets as represented in the Figure: test-positives with their accompanying persons (comparison Case Control-A in the Figure), and test-negatives with their accompanying persons (comparison Case Control-B in the Figure).

Comparison CC-A enables us to study directly the differences in risk factors between a person with COVID-19 and a control person without respiratory symptoms. Thus, in this analysis all risk factors that increase the risk of COVID-19 (some of which will also be risk factors for other respiratory diseases) will be seen to differ between cases and controls.

Comparison CC-B enables us to directly assess risk factors for the other respiratory pathogens (e.g. influenza virus) that could be causing symptoms similar to those of COVID-19.

A comparison of the findings from the TND with comparison CC-A and comparison CC-B will then enable us to assess which risk factors are specific to COVID-19 and which are risk factors for respiratory infections (including with SARS-CoV-2) in general. If these studies were all perfect, one would be able to calculate the results of any one contrast from the two others, e.g., the results of comparison CC-A should logically follow from combining the results of the TND comparison and CC-B (so if the odds ratio for male sex is 1.0 in the TND, but is 2.0 in comparison CC-B, then it also should be 2.0 in comparison CC-A). In reality there might be differences due to sampling and/or unknown factors, e.g. the selection factors for the test-positives and their accompanying persons may be different from those for the test-negatives and their accompanying persons. Thus, although it would be sufficient in theory to only conduct the TND) and comparison CC-A (the matched case-control study for test-positives), it is also valuable to conduct comparison CC-B (the matched case-control study for the test-negatives), which enables us to carry out additional checks for potential biases. If data are collected at the time of testing the symptomatic person, data of test-positives, test-negatives and their accompanying persons will be collected simultaneously.

Critical reflections on the interpretation of case-control studies with accompanying persons as matched controls

There are potential issues with respect to having accompanying persons as matched controls. The use of 'friend' controls leaves the choice of the control to the case and not to the investigator.- In an ideal matched analysis, the investigator controls the matching. As noted above, "friend controls" may be quite similar to the cases; in addition, they may have some possible inherent biases [see pages 119-20 in [13]], for example 'popularity' of certain persons, that extroverts are more often mentioned as friends, close similarities of behaviour, etc. We should stress again, however, that the problem is not that the cases and controls are made 'too similar' - this problem applies to all matched case-control studies and is addressed by taking the matching into account in the analyses.[12] Rather, the problem is that they may be made similar in ways that the investigator cannot control.

A second issue is that the accompanying persons of the test positives in the CCA comparison might be as yet asymptomatic carriers of SARS-CoV-2. A common reflex might be to want to know this and to remove these persons from the analysis. Apart from involving logistically difficult additional testing of the accompanying persons, it is not necessary. This can be illustrated by considering a hypothetical study. Suppose we could identify the population (a subgroup of the general population) which would come for testing if they had symptoms. Ideally, one would then test all of this population and we would estimate the risk of infection in this population, and in various subgroups. In the population (P) there might be a certain number of people (T) who tested positive. Note that the population denominator (P) includes both people who currently have symptomatic infections and people who don't – it is just the total population 'at risk'. The risk of having a symptomatic infection is then T/P . If we compare two subgroups who are exposed or not-exposed to a particular factor, their risks might be T_1/P_1 and T_0/P_0 respectively, and the risk ratio (the ratio of these two proportions) would indicate the relative risk of symptomatic Covid-19 infection in the exposed and non-exposed (e.g. if the RR was 2.0 then the exposed would be twice as likely as the non-exposed to have symptomatic Covid-19 infection).

A case-control study involves studying all of the 'cases' (i.e. T) and a sample of the population which generated them (P). Thus, provided that the controls are a representative sample of the source population P (i.e. everyone who would have come for testing if they had symptoms – which is a reasonable assumption to make since they came with someone who was being tested), then the odds ratio for Covid-19 infection in the case-control study will estimate the risk ratio in the population (P) which generated the cases (T). Of course, a small number of the controls may have asymptomatic Covid-19 infection, and would have tested positive if they had been tested. But this is not a problem – they would have been part of the denominator (P) if a full population survey had been conducted, and they are therefore eligible to be selected as controls. This is analogous to the case-cohort (case-base) design which is a commonly used design for case-control studies .[14, 15]

In sum, the case-control comparisons focus on *symptomatic* disease. For studies of risk factors for *asymptomatic* disease other designs would be necessary. The focus on symptomatic disease is warranted because symptomatic disease might be the beginning of a cascade of increasing disease severity, and risk factors for being infected without symptoms are likely different from risk factors

for symptomatic infection (e.g., males and older people do more often have symptomatic infections).

Despite the methodological complexities, comparisons CC-A and CC-B add greatly to the information that is gained from the TND. In the TND, persons are self-selected because of signs and symptoms, and because of their tendency or ability to seek medical care. For example, those with very severe symptoms will almost always seek medical care; however, amongst people with less severe symptoms, hypochondriacs will more often seek care than other people; this, however is the same regardless of the underlying reason for the signs and symptoms. Thus, all are self-selected and that self-selection will be similar. As such, the TND has great potential, except for the aforementioned problem that risk factors that increase the risk both of COVID-19 and the other respiratory pathogens in the same way will not differ between the test-positives (cases) and the test-negatives (controls). In contrast, the control selection in comparison CC-A and CC-B is a friend, or spouse or household member control which will make persons more similar in age, occupation, obesity, perhaps gender. In case of spouses, gender will mostly be opposite, which does not matter in a matched analysis, and can be advantageous even for gender related risk factors [16]). Of course, always keeping in mind the mentioned drawback that the matching process is not under control of the investigator, this enables us to identify risk factors which apply to both COVID-19 and to other respiratory pathogens.

This creates a ‘triangulation’ situation[17] with information about specific differences in risk factors between symptomatic SARS-CoV-2 infected test-positives and test-negatives with similar signs and symptoms, and two matched case-control studies of test-positives and test-negatives with their accompanying persons, respectively. While the TND has its potential biases[4, 9], so have case-control studies with ‘friend controls’, [page 119-20 in[13]] but the ways the controls are selected, and the potential biases are largely different.

Additional possibilities

There are some additional possibilities which should be noted briefly.

Firstly, we would note that, again if resources allow, follow-up could be organized for both test-positives and negatives of the TND (by email, apps, internet, phone, or record linkage), as well as for the accompanying persons. This would allow to follow the epidemic more closely and help to answer hypotheses that have arisen from patient observations: that males, smokers, or the obese are more often in need of ICU, or that NSAIDs and ACE-inhibitors aggravate the course of the disease. For accompanying persons, the follow-up can be used to further explore whether the risk factors measured at the time of testing predict the subsequent development of symptoms that may be due to COVID-19 infections – at which time they may be asked to be tested. This might shed light on transmission and the incidence of infection in the community.

Secondly, at some test sites where there are plenty of resources one might proceed to also test the accompanying persons, which might yield additional insights:

- The accompanying person of those tested positive may give an immediate insight into whether household contacts or close friends are also infected. This would yield actionable clinical information regarding the need to self-isolate and also gives crude insight into the infectiousness of the agent,

similar to a household transmission study. In addition, as the median incubation period for SARS-CoV-2 has been estimated to be 5 days [18]), the companion testing may identify (presently) asymptomatic SARS-CoV-2 infections and provide rough estimates of the prevalence of asymptomatic carriers in the community they come from. Interestingly, the subgroup of accompanying persons who are very close contacts of the test-positive person but who test negative might give clues for factors that determine resistance to infection.

- The accompanying person of test-negatives may be of particular interest if they are test-positive, since that may point to the possibility of a 'false negative' in the original test-negative person. Current evidence suggests that the viral load of SARS-CoV-2 is highest near the beginning of symptom onset and may wane over time.[19, 20] Therefore, delays to seeking testing after symptom onset could lead to a higher likelihood of false negatives as the amount of virus shed may decrease during the course of the disease.

Other general population control groups

The above reflections were all written for settings with an accompanying person, because this seemed most feasible in many situations, in particular with widespread drive-thru testing. However, many alternatives for population control selection can be envisaged. For example:

- if patients are referred for testing by General Practitioners, the most natural control persons will be a sample from these general practices; this sample could be matched to the practice of the referring GPs, or alternatively weighted according to the size of the referring GP practices.

- if patients present directly in hospital, a control group of non-respiratory out- or inpatients might be constructed to represent the catchment population of the hospital; such patient controls used to be common in pharmacoepidemiology[21]

- in countries where large scale and detailed databases exist (e.g., Scandinavian countries) much information might be obtained by sampling controls from these databases. If the controls are a random sample (possible with broad age restriction) of the general population, matching is not necessary and a single population control group can be used. This was done in a test-negative design for antibiotic resistance.[10] Non-matching has the advantage that all characteristics can be studied in their naturally occurring frequencies. Additional urgent questionnaires might be mailed by government mailboxes.

- in countries where insurance and/or prescription data are the main source of epidemiologic information, sampling of controls might be done via insurance or other third party payers (for example Medicare and Medicaid and group insurance schemes in the US).

Discussion

An ideal approach for monitoring the pandemic and determining the risk factors for COVID-19 would involve random/representative population sampling.[3] In addition to molecular testing (nose

and/or throat swabs) to identify acute infections, serologic assays should be used to identify recent infections, which will facilitate understanding of risk factors, herd immunity, and the extent of asymptomatic transmission in the broader population.[22]

However, in the initial surveillance efforts that are being developed in this unfolding pandemic, population-based testing remains limited by laboratory capacity (i.e., due to unprecedented demands for reagents and trained technicians), funding and political will. The first thoughts of decision makers in several countries are to facilitate testing for people with minimal to more overt symptoms who became ill recently, either in order to isolate, or in order to know which treatment trajectory is necessary if symptoms worsen.[1, 2] This is what is being done by facilitating the availability of tests to general practitioners, by ‘drive-thru’ testing, testing at supermarkets, etc.

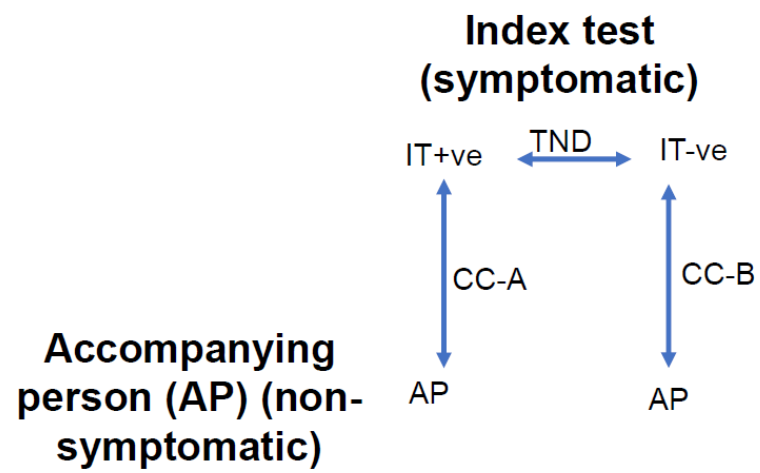
The situation with COVID-19 remains urgent, and it is important that the best possible use is made of information collected in the process of widespread testing of symptomatic persons. Therefore, there may be research and public health benefits in employing a test-negative case-control design preferably with the matched case-control studies added to it (with or without adding follow-up, and with or without extending the testing to accompanying persons). Still, such collection of information has to be as ‘light’ as possible, in order not to disturb the primary medical aim: to test people for their own benefit and for controlling the epidemic. This proposed collection of data can be done with minimal extra effort, it would roll along with the epidemic, and can potentially yield important information at much less cost, and with greater ease, than doing genuinely random population repeated sampling and testing. The latter approach may be the gold standard, but the test-negative design may be a more affordable and practical alternative until genuine random population testing becomes possible. Adding case-control studies with general population comparison groups may create a ‘triangulation’ situation[17] for inferences about local as well as general factors that drive the pandemic. Likewise, any follow-up or testing ‘add-ons’ will lead to better understanding. Finally, having the infrastructure for a test-negative design already established in different settings may be a valuable base for evaluating interventions’ effectiveness against SARS-CoV-2 infection as novel vaccines and other measures that limit transmission (e.g. face masks) become available. Public health authorities should urgently consider setting up formal ‘test-negative case-control studies’ and matched case-control studies with accompanying persons, or other matched or non-matched population controls, to learn more about the risk factors for symptomatic SARS-CoV-2 infection in the COVID-19 pandemic.

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Figure

Test-negative design (TND): compares IT+ve with IT-ve

Matched case-control study A (CC-A): compares IT+ve with their APs

Matched case-control study B (CC-B): compares IT-ve with their APs