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Could expanding the covid-19 case definition improve the UK's pandemic response?

Alex Crozier and colleagues evaluate the potential opportunities and challenges of expanding the symptom list linked to self-isolation and testing as vaccines are rolled out

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During the covid-19 pandemic the British public has been instructed: "If you have a high fever, a new continuous cough, or you've lost your sense of smell or taste or its changed, self-isolate and get a test."[1] Yet these symptoms are just a few of many described by those infected with SARS-CoV-2.[2-5] Many people with mild-to-moderate disease don't have these symptoms (initially), and other symptoms often manifest earlier.[3,6] Most spread is from symptomatic cases around the time of symptom onset,[7-11] and interrupting transmission depends on early identification and isolation of contagious individuals.[12,13] The narrow UK case definition therefore limits this detection, restricting the effectiveness of the test, trace, and isolate programme.[8,14,15]

As vaccination progresses and social mixing increases, infections are now highest among young, unvaccinated, or partially vaccinated people, who are also more likely to experience 'unofficial' symptoms.[16,17] Variants are adding further to transmission, as predicted, with potential for another wave of hospital admissions and deaths.[18] Improvements in transmission control are urgently needed. Here, we build on calls to broaden the UK's covid-19 case definition,[5,19] analysing the potential to improve self-isolation and symptomatic testing guided by a case definition fit for the vaccination era.

Updating the UK's clinical case definition

The European Centre for Disease Prevention and Control described a breadth of symptoms associated with mild-to-moderate covid-19, the most commonly reported being headache (70%), nasal obstruction (68%), weakness or fatigue (63%), myalgia (63%), rhinorrhoea (60%), gustatory dysfunction (54%), and sore throat (53%).[20] Many infected people do not present with the symptoms used in the UK case definition: loss of taste or smell, a cough, or fever which, before vaccination rollout were reported by 70%, 63%, and 45% of symptomatic cases, respectively.[3,21] While restricting access to symptomatic testing to those with "official" symptoms may control the volume of testing, this narrow definition is now likely to impede control of transmission.

Critically, unofficial symptoms often manifest earlier.[9] In a recent population based study in Arizona, US, the most commonly reported first symptoms were sore throat (19%), headache (16%), cough (13%), runny nose or cold-like symptoms (12%), and fatigue (12%).[22] These symptoms are more common in school age children[16] and younger people,[17] who now account for an even greater proportion of transmission because older people are vaccinated.

The World Health Organization[2] and Centers for Disease Control and Prevention[4] already include nine and 11 more case defining symptoms, respectively, than the UK. Greater testing capacity is now available to accommodate a wider case definition in the UK, particularly with rapid antigen tests. However, rapid tests are officially being used only for self-testing (at home or at testing centres) by people without symptoms,[23,24] although some people with wider symptoms may also be using them.[25] Symptomatic testing using reverse transcription polymerase chain reaction (RT-PCR) tests meanwhile is open only to those declaring a high temperature, a new continuous cough, or a loss or change in sense of smell, and to confirmed contacts of RT-PCR positive cases.

The UK's narrow clinical case definition impedes not only the identification of cases but also the understanding of SARS-CoV-2 transmission. Although infected individuals without symptoms can clearly pass on the virus,[26] the characterisation of asymptomatic infection and transmission has been poor.[3] It is important to distinguish between those not experiencing symptoms throughout infection (persistently asymptomatic), becoming infectious before symptoms manifest (presymptomatic), or having only unofficial or subtle symptoms (pauci-symptomatic). Persistently asymptomatic cases probably account for less than 20% of infections, and these people may be 3-25 times less likely than those with symptoms to pass on the virus.[7-11]

Real world evidence suggests presymptomatic and (official and unofficial) symptomatic cases drive transmission more than asymptomatic cases.[7-11] It seems counterintuitive, therefore, to have no official UK guidance on wider covid-19 symptoms, or to offer different testing routes for those with official symptoms and those with no symptoms, with nothing in- between. People with unofficial symptoms can bypass the rules to get a test—legitimising this choice could be helpful.

Concerns have been raised over testing capacity, false negative rapid test results, and non-compliance with self-isolation.[23,24] However, the benefits of identifying more cases sooner are likely to be substantial. The Scientific Advisory Group for Emergencies (SAGE) recommended "prioritising rapid testing of symptomatic people is likely to have a greater impact on identifying positive cases and reducing

transmission than frequent testing of asymptomatic people in an outbreak area."[27]

Testing people with a single, non-specific symptom could, of course, overwhelm or waste capacity. Indeed, September 2020 government advisory groups[28 29] considered data from the First Few Hundred Study[30] and Covid Symptom Study App to reason against expanding eligibility for symptomatic testing. The data suggested expanding the definition would decrease symptom specificity from 97% to 94% while only marginally increasing symptom sensitivity from 85% to 95%. However, more recent evidence on symptom combinations warrants reconsidering the case definition, especially since vaccination means the population most likely to be infected and transmit will now be younger or partially immunised, and so less likely to experience severe disease or official symptoms.

Combinations of symptoms could be used to help identify more cases sooner without overwhelming testing capacity. An age stratified approach derived from the React study selected chills (all ages), headache (5–17 years), appetite loss (≥18 years), and muscle aches (18–54 years) as jointly predictive of positive RT-PCR results, together with the official symptoms.[5] The authors concluded that triage based on these symptoms would identify more cases than the current approach, at any level of testing.

The Virus Watch cohort suggested that using a wider symptom definition captured cases a day earlier than the current definition, on average,[31] a critical time difference for preventing transmission. The Covid Symptom Study App was used to identify optimal symptom combinations for capturing most cases with fewest tests, and found that within three days of symptom onset, dyspnoea plus the official symptom combination (cough, fever, loss of smell or taste) identified only 69% of symptomatic cases and required 47 tests for each case identified.[32] The combination with the highest coverage (fatigue, loss of smell or taste, cough, diarrhoea, headache, sore throat) identified 96% of symptomatic cases (requiring 96 tests per case identified).[32] This combination of symptoms would increase the number of cases captured by symptomatic testing by over a third, and would likely result in earlier identification of many cases,[22] potentially containing transmission more as we reopen society.

Implementing an updated clinical case definition

Expanding the case definition is likely to increase demand for testing and numbers self-isolating. The system-wide effects would be complex, requiring careful implementation.[33] Any change must neither overwhelm NHS Test and Trace nor impede existing symptomatic testing. Instructions such as "isolate if you have case defining symptoms, regardless of test status" must not lose clarity despite more complex lists of symptoms. Potential harms from false negative or positive results need mitigation. While it is essential to consider the pre-test probability of infection (based on background prevalence, epidemiological history, and clinical presentation) and the performance of the test used,[34 35] a substantial net reduction in transmission is likely if more symptomatic people are identified and isolate sooner.

The UK's decision to adopt a narrow case definition was based on ease of communication, avoiding confusion with other infections, and preserving testing capacity. This situation is now different—testing capacity is high. The emergence of the delta variant and the potential evolution of more transmissible or vaccine resistant variants means that, even with vaccination, further waves of cases, hospital admissions, and deaths may ensue.[18] Mitigating these waves, and the potential for enduring transmission,[36] requires agile intervention to minimise the risks of vaccine escape variants, long covid, further NHS disruption, and harms from restrictions. To realise the benefits of a wider case definition it will be necessary to revise policies for testing and self-isolation.

Since RT-PCR capacity is limited, and quick turnaround is vital, we suggest dynamic targeting of RT-PCR testing, guided by continuous review of symptoms, transmission patterns, variants, vaccination uptake, and circulation of other respiratory viruses. Routinely collected data could be used to adapt testing eligibility, access, and communications systematically and quickly.[37–39] Communication is particularly important considering that only half the public can correctly identify the existing official covid-19 symptoms.[40] Data intensive, intelligence-led adaptation of the test, trace, and isolate system could make an important contribution to the UK's pandemic responses while we wait for the vaccination programme to progress as far as possible and for covid-19 to abate.

Refining test, trace, and isolate

Given the heterogeneity in SARS-CoV-2 transmission,[8 14 15] whereby fewer than 20% of cases may account for more than 80% of transmission, reopening society ahead of maximum vaccination coverage requires better identification and self-isolation of infectious cases to contain emerging clusters. To achieve this, the NHS Test and Trace system must increase the proportion of cases tested (and isolated) early in their infection and trace more contacts before onwards transmission. Early, active case finding combined with enhanced contact tracing (including backwards to identify source of infection),[14] effective symptom monitoring,[41] and prompt contact testing[42] can also reduce transmission.[13] Repeat testing of contacts may usefully replace isolation for those without symptoms.[43 44] Viral sequencing can also help trace clusters back to their source,[45] as well as targeting resources to identify and contain more transmissible or vaccine resistant variants. Hyper-local approaches—involving communities at neighbourhood or street level, in faith groups, and other local contexts—are also vital.

Testing uptake among people with symptoms has been low, and engagement with testing and isolation has been lowest in communities with the highest prevalence of SARS-CoV-2 and the gravest consequences from covid-19.[23 24 40] Effective support, including prompt financial help, during self-isolation is the key to controlling transmission.[46 47] To make the most of an expanded case definition, public health and NHS systems must integrate more at both local and national levels,[48–50] enabling nimbler, more equitable targeting of test-trace-isolate resources[51 52] and surge vaccination.[53] In addition, combinations of RT-PCR and rapid antigen tests may be helpful in reducing delays between symptom onset, testing, self-isolation, and initiation of contact tracing.[39]

Vaccinations alone are unlikely to end the pandemic. New, more transmissible and (partially) vaccine resistant variants may spread through susceptible populations causing high hospital admission rates. Inequities in vaccination are also shifting the burden of disease and disruption to the most disadvantaged communities, who are also harmed most by covid-19 restrictions. To reopen society with greater speed and fairness, control of transmission must improve. This starts with an expanded and more context appropriate case definition and rests on adaptive, locally grounded, and information-led public health responses.

Key messages

- Covid-19 is associated with a wide range of symptoms
- Many patients do not experience the UK's official case defining symptoms, initially, or ever, and other symptoms often manifest earlier

- Limiting the symptomatic testing to those with these official symptoms will miss or delay identification of many covid-19 cases, hampering efforts to interrupt transmission
- Expanding the clinical case definition of covid–19, the criteria for self-isolation, and eligibility for symptomatic testing could improve the UK's pandemic response
- Dynamic targeting based on data could avoid overloading resources

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