**Analysis**

Could Expanding the COVID-19 Case Definition Improve the UK’s Pandemic Response in The Vaccination Era?

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| **KEY MESSAGES*** **There is a wide range of symptoms associated with COVID-19.**
* **Many patients with COVID-19 do not experience the UK official case-defining symptoms initially, or ever, and other symptoms often manifest earlier.**
* **Limiting the case definition and symptomatic testing to those with only the ‘official’ symptoms will miss, or delay the identification of, many COVID-19 cases. This is a major concern for interrupting transmission.**
* **We evaluate the potential opportunities and challenges of expanding: the clinical case definition; the criteria for self-isolation; and eligibility for symptomatic testing - asking whether these could improve the UK’s pandemic response in the vaccination era.**
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**Contributors and sources**

The authors have broad experience and direct involvement in COVID-19 responses. Alex Crozier has expertise in developing and troubleshooting diagnostic assays and improved COVID-19 testing programmes for sports organisations. Dr Jake Dunning is a Senior Research Fellow in the Epidemic diseases Research Group Oxford (ERGO) at the University of Oxford and formerly a National Incident Director for COVID-19 at Public Health England. Dr Selina Rajan is a Public Health Specialist Registrar who has supported the Public Health England regional response, including managing outbreaks in care homes and educational institutions, and has also contributed extensively to the COVID-19 Health Systems Response Monitor produced by the European Observatory on Health Systems and Policies in partnership with the World Health Organisation. Professor Malcolm G Semple is a professor of outbreak medicine and child health and consultant physician in paediatric respiratory medicine, and a member of NERVTAG and regularly attends SAGE COVID-19. Professor Iain Buchan is a public health physician data scientist, Dean of Liverpool’s Institute of Population Health, and researcher leading the evaluation of the Liverpool community testing pilot. Professor Martin McKee is research director of the European Observatory on Health Systems and Policies, and a member of Independent SAGE.

Drawing on scientific evidence and our combined field experience, we aim to evaluate the potential opportunities and challenges of expanding the clinical case definition and the criteria for self-isolation and symptomatic testing eligibility, and ask whether this could help improve the UK’s pandemic response in the vaccination era.

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**Patient involvement**

No patients were involved in the writing of this manuscript

**Conflicts of Interest**

We have read and understood [BMJ policy on declaration of interests](http://static.www.bmj.com/sites/default/files/attachments/resources/2011/07/bmjpolicyondeclarationofinterestsmarch2014.pdf) and have the following interests to declare: IEB and MGS received grant funding from the UK Department of Health and Social Care to evaluate LFT in the Liverpool pilot. IEB reports fees from AstraZeneca as Chief Data Scientist adviser via Liverpool University outside the submitted work. MGS is Chair of the Infectious Disease Scientific Advisory Board and a minority shareholder in Integrum Scientific LLC, Greensboro, NC, USA, a company that has interests in COVID-19 testing but not with lateral flow technology, and reports grants from the NIHR, the Medical Research Council, and the Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool.

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**Standfirst**

*Alex Crozier and colleagues evaluate the potential opportunities and challenges of expanding the clinical case definition, linked to self-isolation and symptomatic testing, and ask whether this could help improve the UK’s pandemic response in the vaccination era.*

In the COVID-19 pandemic, the British public have 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 UK case-defining symptoms are just a few of many described by those infected with SARS-CoV-2.2,3,4,5 Many mild-to-moderate cases 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 onset7,8,9,10,11 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, un- 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 hospitalisations and deaths.18 Therefore, improvements in transmission control are 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 COVID-19 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%), asthenia (weakness and/or fatigue) (63%), myalgia (63%), rhinorrhoea (60%), gustatory dysfunction (54%) and sore throat (53%).20 Up to half of cases don’t present with any UK case-defining symptom: loss of taste or smell (70%), cough (63%), or fever (45%) loss of taste or smell (70%), cough (63%), or fever (45%).3,21 So, UK cases are less likely to seek symptomatic testing and self-isolate. While this may reduce the volume of testing, it is likely to impede control of transmission. Critically, unofficial symptoms often manifest earlier.9 In a recent population-based study in Arizona, USA, the most commonly-reported first symptoms were sore throat (19.0%), headache (15.5%), cough (12.7%), runny nose/cold-like symptoms (12.1%) and fatigue (12.0%).22 These unofficial symptoms are more common in school-age children16 and younger people,17 who now account for an even greater proportion of transmission because older people are vaccinated.

WHO2 and CDC4  already include 9 and 11 more case-defining symptoms than the UK, respectively. Greater testing capacity is now available to address a wider case definition in the UK, particularly with rapid antigen tests, yet these are only officially available to people without symptoms.23,24 Some people with wider symptoms, however, may use asymptomatic testing facilities.25 Symptomatic testing with RT-PCR meanwhile is open only to those declaring a high temperature, a new continuous cough, or a loss/change in sense of smell.

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 experiencing symptoms throughout infection (persistently asymptomatic), becoming infectious before symptoms manifest (pre-symptomatic), or having only unofficial or subtle symptoms (pauci-symptomatic). Persistently asymptomatic cases likely account for less than 20% of infections, and they may be 3-25 times less likely than those with symptoms to pass on the virus.7,8,9,10,11 Real-world evidence suggests pre-symptomatic and (official and unofficial) symptomatic cases drive transmission more than asymptomatic cases.7,8,9,10,11 It seems counter-intuitive, therefore, to have no official UK guidance on wider COVID-19 symptoms, or to offer different testing routes for those with ‘official’ symptoms vs no symptoms, with nothing in-between. Meanwhile, people with unofficial symptoms might bypass to rules to get a test – legitimising this choice could be helpful.

There have been concerns over testing capacity, false negative rapid tests, and non-compliance with self-isolation.23,24 However, the benefits of identifying more cases sooner are likely to be significant. 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 and waste capacity. Indeed, NERVTAG28 and SAGE29 in September 2020 considered data from the First Few Hundred Study30 and COVID Symptom Study App to reason against expanding symptomatic testing eligibility. 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 and/or one-dosed, 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 REACT selected chills (all ages), headache (5–17 years), appetite loss (18–54 and 55+ years), and muscle aches (18–54 years) as jointly and positively predictive of RT-PCR positivity together with the ‘official’ four 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 a wider symptom definition captured cases a day earlier than the current definition, on average,31 a critical time-difference for preventing onwards 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, the ‘official’ symptom combination (cough, dyspnoea, fever, anosmia/ageusia) identified only 69% of symptomatic cases (requiring 47 tests per case identified), while the combination with the highest coverage (fatigue, anosmia/ageusia, 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 re-open society.

**Implementing an Updated Clinical Case Definition**

Expanding the case definition would likely increase testing demand 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 (based on background prevalence, epidemiological history, and clinical presentation) and the performance of the test,34,35 there is likely to be a substantial net-reduction in transmission if more symptomatic cases are identified and isolate sooner.

The initial UK 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 Delta variant and the potential evolution of more transmissible and/or vaccine resistant variants means that, even with vaccination, further waves of cases, hospitalisations, and deaths may ensue.18 Mitigating waves, and potentially enduring transmission,36 requires agile intervention to minimise the risks of vaccine escape variants, long-COVID, further NHS disruption and further harms from restrictions. To realise the benefits of a wider case definition it will be necessary to revise testing and self-isolation policies.

Recognising RT-PCR capacity is limited, and quick turnaround is vital, we suggest targeting this capacity dynamically, guided by continuous review of symptoms, transmission patterns, variants, vaccination uptake, and circulation of other respiratory viruses. A data-driven approach could be taken to optimise identification of infections by varying testing eligibility based on symptoms and contexts.37 Age-specific pre-test probability (based on number and type of symptoms, epidemiological history, and local prevalence) could direct actions (RT-PCR and self-isolation; rapid antigen testing; or no action). Higher risk individuals (e.g., with specific or numerous symptoms and/or known contacts) could be referred for RT-PCR testing, while lower-risk individuals (e.g., with fewer than two non-specific symptoms) are referred for rapid antigen testing, ideally at a test site,38,39 and not required to isolate if test negative.

Only half the public correctly identify the official COVID-19 symptoms,40 therefore any change would have to be accompanied by better communication. This is particularly important now when there is a large rapid antigen testing capacity, the usefulness of which is constrained by a lack of clarity on how best to use it.23 Intelligence-led adaptation of the test, trace, and isolate system could make an important contribution to UK COVID-19 responses while we wait for direct COVID harms to abate as all eligible adults become fully vaccinated.

**Test, Trace, and Isolate in the Vaccination Era**

Given the heterogeneity in SARS-CoV-2 transmission,8,14,15 where fewer than 20% of cases may account for more than 80% of transmission, re-opening society ahead of maximum vaccination coverage requires more identification and self-isolation of infectious cases to contain emerging clusters. To achieve this, the UK’s 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 (forwards/backwards) contact tracing,14 effective symptom monitoring,41 and prompt contact-testing42 can also reduce transmission.13 Repeat testing of contacts may usefully replace isolation of asymptomatic contacts.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 are also key. Testing uptake among symptomatic individuals has been low, and engagement with testing and isolation has been lowest in the communities with the highest SARS-CoV-2 prevalence and gravest COVID-19 consequences.23,24,40 Effective support to isolate is key to controlling transmission.46,47 To make the most of an expanded case definition, public health and NHS systems need to integrate more at/across local and national levels48,49, enabling nimbler, more equitable targeting of test-trace-isolate50,51 and surge vaccination.52

An immediate adaptation could be the introduction of rapid antigen tests for symptomatic testing,39 enabling contact tracing days sooner than possible with RT-PCR tests, with rapid test negative individuals also tested by RT-PCR to mitigate false negatives. Adapting testing to patterns of symptoms would require a human advisor or AI chatbot to interact with the symptomatic individual ordering a test. In this way, tests may be better directed, advice could be given to isolate and talk to contacts straight away, and then isolation support-needs identified. International experiences show that cluster-based approaches can improve responses.49,53

Vaccinations alone are unlikely to end the pandemic. New, more transmissible and (partially) vaccine-resistant variants may spread through susceptible populations with high hospitalisation rates. Inequalities in vaccination are also shifting the burdens to the most disadvantaged, who are also the most harmed by COVID-19 restrictions. To reopen society with greater alacrity and fairness, transmission control must improve. This starts with a fuller case definition and rests on adaptive, locally-grounded, and intelligence-led public health responses.

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