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EDITORIAL

Return to work for healthcare workers with confirmed COVID-19 infection

Healthcare facilities face uncertainty deciding when healthcare workers (HCWs) with confirmed SARS-CoV-2 can return to work because of the risk of infection for both staff and patients. Infection control and return to work policies must be balanced with potential HCW shortages. As of May 2020, The United States Centers for Disease Control and Prevention (US-CDC) recommends two strategies for HCW return to work: either a testing-based approach with two negative nasopharyngeal swabs taken 24 h apart; or a non-testing-based approach based on symptom resolution [1]. Whereas, Public Health England (PHE) recommends HCWs return after 7 days from symptom onset, provided clinical improvement has occurred and the HCW has been afebrile for 48 h [2]. Differences in recommendations create confusion for workers and employers who commonly lack a clear understanding of the underlying scientific evidence and rationale.

Several surrogate markers for non-infectivity are available: viral culture, detection of viral genetic material (such as real-time polymerase chain reaction (RT-PCR)), serologic assay and symptom resolution. The isolation of live virus on cell culture is considered the gold standard for determining infectivity. Animal studies show a correlation between infectivity and viral culture for certain viruses, but not specifically SARS-CoV-2. For example, a 2015 study on the infectivity of H1N1 influenza in ferrets demonstrated that detection of high viral culture titres from infected animals correlated with transmission to other healthy animals [3]. However, viral cultures are impractical due to technical challenges, time required and potential exposure of laboratory personnel. Understanding how other tests or surrogate markers relate to viral culture positivity may inform the potential period of infectivity.

RT-PCR of nasopharyngeal, nasal or oropharyngeal swabs with detection of viral RNA is most widely used for diagnosing SARS-CoV-2 infection but has limitations. The detection rate of RT-PCR for SARS-CoV-2 varies by the site sampled, with at least one study finding much lower sensitivity in nasal and pharyngeal swabs compared to lower respiratory specimens [4]. Furthermore, there may be poor correlation between persistently positive RT-PCR results after symptomatic recovery and infectivity. The median duration of RT-PCR positivity has been reported to be 20 days with the longest seen being 37 days [5]. However, in a study of nine mild SARS-CoV-2 patients, none had positive viral culture once the viral load fell below 10^6 copies/ml despite positive RT-PCR up to Day 28 [6]. This suggests that RT-PCR may overestimate the window of infectivity and waiting for two consecutive negative RT-PCR results may unnecessarily exclude HCWs from work. Nucleic acid amplification tests, which are commercially available as point of care test, employ similar principles of viral detection and are therefore subject to similar limitations.

Symptom resolution plus a proscribed time-off work based on epidemiological estimates of the infectious period is another approach. Similar to PHE, the US-CDC suggests excluding HCW from work until 'at least 3 days have passed since recovery…and, at least 10 days have passed since symptoms first appeared' [1]. Therefore, the earliest time HCWs would return to work is 7 days following symptom onset as per PHE, which corresponds to one recent estimate of the infectious period [7]. While this approach is intuitively appealing, empirical data demonstrating non-infectivity for HCWs who meet the US-CDC or PHE benchmarks are largely lacking. The recent Wölfel *et al.* study of nine patients showed live viral isolation was not successful beyond Day 8 of symptoms onset [6]. The authors suggested that using symptom resolution beyond Day 10, combined with less than 10^6 viral RNA copies/ml of sputum can be used to predict low residual risk of infectivity [6]. However, the study was small, and the patients had mild symptoms; thus, it is unclear if these results can be extrapolated to other populations with differing clinical courses. Another issue is that the symptomatology of SARS-CoV-2 infection is evolving, with increasing evidence for viral transmission among asymptomatic or pre-symptomatic patients [7], making it challenging to apply symptom resolution principles to these individuals.

Serological evidence may also be informative but is not currently part of most return to work policies. Serologic studies have reported that patients seroconvert between 7 and 14 days post onset of symptoms [6,8]. Wölfel *et al.* found that no viruses can be cultured after Day 7 of symptom onset at which time only 50% of their subjects had seroconverted, with other patients taking up to Day 14 to seroconvert [6]. This suggests that seroconversion can occur a few days after cessation of infectivity [6]. Serological assays for SARS-CoV-2 is an area of active

research and development although current tests face several limitations. The sensitivity and specificity of the commercially available serologic assays vary by testing method (e.g. quantitative ELISA, qualitative lateral flow assay, neutralization assay) and manufacturer. Currently many test kits lack external validation and may have potential cross-reactivity to other human coronaviruses. However, this may improve soon with government oversight and approval. Even though the false-positive rate of serological testing has been a concern for use in diagnosis, in the context of testing a HCW who was a confirmed case by other methods, the likelihood of a false-positive test would be low given the high pre-test probability of SARS-CoV-2. Despite laboratory studies having demonstrated the ability of SARS-CoV-2 antibodies from convalescent patient sera to neutralize pseudovirion *in vitro* [9], it is still unclear if such immunity is functional or long-lasting. However, these unknowns should not affect return to work decisions when using the presence of antibody response as a surrogate marker for cessation of infectivity. The biggest limitation of using serology is in its application to HCWs who may be non-seroconvertors or weak seroconvertors (meaning their immune response may be below the limit of detection for testing kits), which has been estimated to be as high as 16.7% for IgG at 42-day follow-up in one study [10].

Based on the available evidence, testing HCWs post SARS-CoV-2 infection with RT-PCR is the most conservative approach. Two consecutive negative swabs would ensure that viral shedding has ceased, although this will likely overestimate the period of infectivity. Limitations would include delaying return to work, which could be problematic if all available HCWs are needed for clinical care, as well as the cost and resources required for testing. Serology is likely the next most conservative strategy, with seropositivity used to infer non-infectivity. A symptoms-only policy is the least conservative but may be appropriate when resources are scarce, or testing is not possible. A pragmatic approach may be to use a combination of serologic testing and cessation of clinical symptoms to assist HCW return to work in a way that protects their patients, especially those vulnerable, and colleagues thereby limiting furlough of HCWs during a pandemic.

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