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Viral Shedding Kinetics and Transmission of Emerging SARS-CoV-2 Variants—Critical Components of Study Design

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When responding to the COVID-19 pandemic, public health entities have had to use available data to rapidly develop policies to reduce transmission, including determining duration of isolation and evaluating interventions such as masking to reduce transmission. Mathematical models often can be used to evaluate interventions when data are sparse, assuming that key parameters are known. SARS-CoV-2 shedding kinetics (corresponding to within-host virus proliferation, peak, and clearance stages) and its association with disease progression and onward transmission inform models that can be used to evaluate the effectiveness of prevention strategies. Jung et al,[1] in a timely composite analysis of 2 intensive longitudinal studies in South Korea, shed light on this association.

The first study (March 2020 to November 2021) tracked secondary transmission from health care workers, patients, and caregivers, stratified by vaccination status, and found that secondary transmission from fully vaccinated infected individuals was less common than from unvaccinated and partially vaccinated ones.[1] Vaccinated individuals received the ChAdOx-nCoV-1, BNT162b2, or mRNA-1273 vaccines. The second study[1] (July to August 2021) attempted to culture virus daily from mildly symptomatic individuals, finding that although viral load was similar across groups, unvaccinated and partially vaccinated individuals shed culturable virus longer than vaccinated individuals. The different duration of culturable virus between groups in the second study provides a plausible mechanism for patterns in secondary transmission noted in the first. Detecting these differences in transmission and viral shedding may not have been possible without strong study designs.

The studies by Jung and colleagues[1] highlight key design components for viral shedding kinetics studies, including (1) universal and intensive longitudinal sampling of individuals, (2) testing viral load with a continuous and standardized scale, and (3) assessing viral viability. First, before detection, sampling should occur frequently enough to facilitate

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estimating the day that an individual's infection began (ie, day 0), and screening should include individuals regardless of symptom status. One potential limitation of the viral shedding kinetics study by Jung et al[1] is that it enrolled only mildly symptomatic patients, missing shedding from asymptomatic individuals and failing to account for potential differences in infectiousness during presymptomatic periods across variants.

Second, after a positive test result, frequent sampling of individuals is necessary to detect differences among groups (eg, by vaccination status or variant). Care should also be given to the type of test and choice of sampling site (or sites) because of potential tissue tropism and/or methodologic constraints. As opposed to qualitative test results, it is also helpful to measure viral dynamics on a quantitative and continuous scale. Jung et al[1] used cycle threshold (Ct) values converted to viral load so that different stages of infection and individual heterogeneity could be more readily assessed across studies. Peak viral load varies among individuals[2] and by SARS-CoV-2 variant,[3] yet the factors that cause this heterogeneity remain unclear.

Third, evaluation of mitigation strategies relies on understanding the ability to infect others; however, neither molecular nor antigen tests are perfectly correlated with infectivity. Therefore, measures of viral viability, such as culturability, are useful, as are simultaneous evaluations of secondary transmission rates to correlate with the viral shedding kinetics. Finally, although constrained by many factors, timely analysis and dissemination of results are critical in informing response to an ongoing pandemic.

Transmissibility through the different phases of viral shedding (proliferation, peak, and clearance) and its dependence on immune status and the variant involved can inform individual clinical decisions as well as public health mitigation strategies, such as testing. Test-based strategies that fail to detect infections in the proliferation phase may be ineffective at preventing onward transmission, whereas understanding test characteristics in the clearance phase is crucial for optimizing end-of-isolation guidelines. A short proliferation period can facilitate presymptomatic transmission (if peak is close to symptom onset), and mitigation strategies to prevent variants with such characteristics would have to rely on early detection through frequent screening or broad mitigation strategies. For instance, mathematical modelers were able to use early reports of viral kinetics[4] to quickly evaluate strategies to prevent presymptomatic spread, such as masks.[5] Alternatively, peak and clearance phase characteristics determine the appropriate tests (eg, nucleic acid amplification vs antigen tests) and isolation periods for a given context. Not only are the proliferation, peak, and clearance phases useful for informing public health decisions, but they also facilitate comparisons across populations and variants.

A study[2] using ancestral strain through Delta variant samples collected from a professional sports league estimated faster clearance times for vaccinated individuals, which is consistent with the findings of Jung et al,[1] in which the duration of culturable virus was shorter for fully vaccinated persons. Replication of the results in different countries and among variants suggests a general pattern. However, athletes are not representative of the general population; complementary future studies would prioritize people who are at increased risk for SARS-CoV-2 infection (eg, frequent exposures) or severe COVID-19 (eg, older

individuals with more comorbidities) or who have various immune states (eg, based on vaccination as well as prior infection and duration from each). Expanding the reach of viral shedding studies would increase their value.

Viral shedding studies allow updates to important epidemiologic parameters when new SARS-CoV-2 variants emerge. Early data from the Omicron wave, including repeated virus isolation data from Japan[6] and longitudinal Ct values of samples from sports leagues,[3] indicate infectious periods within the range found for the Delta variant. Alternatively, Omicron peak viral RNA appeared lower (higher Ct value) than Delta in that study,[3] which hints that any enhanced transmissibility from Omicron may be attributable to factors other than levels of viral shedding itself. Other complicating factors—even other within-host processes—such as body site–specific tropisms or cellular interactions (eg, receptor-binding affinity), could explain these differences. Potential reductions in antigen test sensitivity with new variants, such as Omicron, create similar complications.[7] Despite such challenges, these approaches could be used against future variants, with a goal of translating changes in within-host dynamics, such as immune escape or faster proliferation at the start of infections, to differences in transmission at the population level.

Knowledge about viral shedding critically informs multiple prevention strategies that must be deployed early as novel viral pathogens emerge. Prepositioned study platforms (eg, household and health care settings) would ideally allow rapid collection of samples and data on emergent pathogens, while allocating necessary laboratory resources to quickly evaluate methods for assessing the pathogen (eg, test sensitivity and viral culture methods) and process the numerous samples. Strengthening public health infrastructure, fostering multidisciplinary partnerships, and building off existing research activities may enable such platforms.

Understanding viral shedding leads to a better understanding of infectiousness profiles, leading, in turn, to better parameterization of the mathematical models that inform prevention guidance. Thus, with timely analysis and dissemination, rich longitudinal data can inform rapid public health responses to outbreaks or pandemics. In the case of Jung et al,[1] the primary methods—estimating illness onset (using symptom onset or, ideally, with universal testing regardless of symptoms), frequent sampling of positive individuals, quantitative viral measures, and assessment of viral viability—are what make these studies useful.

Collecting and sharing high-quality pathogen shedding kinetics data quickly and combining them with secondary transmission data, where feasible, could improve public health outcomes by informing modeling and refining key decision-making before widespread transmission of novel SARS-CoV-2 variants and other pathogens occurs.

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