Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

in those who do become infected despite vaccination, it would probably lead to lower infectiousness and less onward transmission. Hence, the authors compared the viral kinetics in breakthrough delta variant infections in vaccinated people with delta variant infections in unvaccinated people. They report that peak viral loads showed a faster decline in vaccinated compared with unvaccinated people, although peak viral loads were similar for unvaccinated and vaccinated people.

Although preventing severe disease and deaths remains the primary public health goal in the acute phase of the pandemic, and is still being achieved by available COVID-19 vaccines despite the emergence of the delta variant, addressing SARS-CoV-2 transmission is a crucial additional consideration. Reducing transmission is necessary to reduce virus circulation, reach herd immunity and end this tragic pandemic. This study confirms that COVID-19 vaccination reduces the risk of delta variant infection and also accelerates viral clearance in the context of the delta variant. However, this study unfortunately also highlights that the vaccine effect on reducing transmission is minimal in the context of delta variant circulation. These findings have immediate public health implications. Higher vaccination coverage rates need to be achieved because indirect protection from vaccinated to unvaccinated people remains suboptimal. The question of whether booster doses will improve the impact on transmission should be addressed as a top priority.[7] Research efforts should be directed towards enhancing existing vaccines or developing new vaccines that also protect against asymptomatic infections and onward transmission. Until we have such vaccines, public health and social measures will still need to be tailored towards mitigating community and household transmission in order to keep the pandemic at bay.

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Annelies Wilder-Smith
annelies.wilder-smith@lshtm.ac.uk

Department of Disease Control, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

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Remdesivir, on the road to DisCoVeRy

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Despite the availability of effective SARS-CoV-2 vaccines, improving care for patients with symptomatic infection remains relevant. Strategies to blunt the hyperinflammatory state that characterises severe COVID-19 include broad-spectrum immunosuppressive drugs such as corticosteroids, targeted immunomodulatory treatments such as tocilizumab or baricitinib, and direct-acting antivirals to reduce viral load.

In *The Lancet Infectious Diseases*, Florence Ader and colleagues[1] report results of the DisCoVeRy trial, the fifth large, randomised, controlled trial with the broad-spectrum antiviral drug remdesivir.[1] In this open-label study, 857 patients admitted to hospital with severe COVID-19 (oxygen saturation SpO_2 ≤94% or in need of supplemental oxygen or respiratory support) were randomly assigned to remdesivir plus standard of care or standard of care alone. There was no significant difference in the primary outcome, the odds of better clinical status defined on the WHO ordinal scale, at day 15 (odds ratio 0·98 [95% CI 0·77–1·25]; p=0·85). This finding remained consistent across all prespecified subgroup analyses, including duration of symptoms before admission or disease severity at random assignment. There was also no significant difference in 28-day mortality (0·93 [0·57–1·52]; p=0·77), and none of the time-to-improvement analyses showed any

significant benefit in favour of remdesivir. However, in an exploratory subgroup analysis of patients without mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at random assignment, the hazard for the composite endpoint of new mechanical ventilation, ECMO, or death was lower in the remdesivir group than in the standard-of-care group (hazard ratio [HR] 0·66 [95% CI 0·47–0·91]; p=0·010).

How do these findings compare to previous reports? In Spinner and colleagues' study[2] and in the participants in the ACTT-1 cohort who presented with moderate COVID-19 at admission,[3] remdesivir resulted in some benefit in predefined clinical outcomes compared with standard of care, particularly when treatment was started early after symptom onset. In patients with severe COVID-19, the ACTT-1 trial showed faster time to improvement with remdesivir, again especially when treatment began early after symptom onset.[3] However, enthusiasm was rapidly subdued by the results of the WHO Solidarity trial, which showed no effect of remdesivir on in-hospital mortality or time to discharge.[4] Importantly, systemic steroids were more frequently used in the Solidarity (47·6%) and DisCoVeRy (40%) trials than in the ACTT-1 trial (23%), which might explain some of the observed differences.

Although the absence of mortality benefit in Solidarity seems irrefutable, death is not the only relevant outcome. The results of DisCoVeRy are thus a valuable addition to the evidence to verify the effect of remdesivir on other clinically important endpoints. But will the negative findings of the DisCoVeRy trial finally settle the case for remdesivir, or do some of the study limitations leave some room for cautious optimism?

First, by comparing the clinical status at a fixed timepoint, the DisCoVeRy trial risked missing the optimal time to assess clinical benefit. 15 days might be too late to observe differences in patients who do not progress to mechanical ventilation and too soon in patients who do. Although time-to-event analyses aim to circumvent this problem, the commonly used time-to-improvement endpoint might also be contested in this case. The rationale behind the use of antiviral drugs is mainly to reduce the viral load and thereby mitigate disease progression rather than cause improvement. Therefore, time to deterioration might be a preferred endpoint. Indeed, Ader and colleagues[1] reported a lower hazard of mechanical ventilation, ECMO, or death in patients treated with remdesivir than in those treated with standard of care in a subgroup of patients who were not on mechanical ventilation at baseline. This finding is consistent with a post-hoc analysis of the ACTT-1 trial (HR for time to mechanical ventilation or death 0·67 [95% CI 0·52–0·87])[5] but inconsistent with a prespecified analysis in the Solidarity trial (rate ratio for initiation of mechanical ventilation or death 0·97 [95% CI 0·85–1·10]).

Second, there is inherent bias with an open-label design. The ordinal scale is prone to a degree of subjectivity, causing concern of a more optimistic interpretation of the clinical status of treated patients. On the other hand, with intravenous treatment, patients might be kept longer at the hospital to complete active treatment, as observed in both the Solidarity trial and the study by Spinner and colleagues.[2]

Last, median time from symptom onset to treatment initiation was 9 days (IQR 5–10) in the DisCoVeRy trial. This is similar to the other trials with hospitalised patients, and long after the peak in viral load will have passed in most patients. This might explain why no effect of remdesivir on viral clearance was seen in any of these studies.[6] As such, the DisCoVeRy results cannot deny or confirm a possible benefit in patients with rapidly progressive disease who present early or who are immunocompromised, the real-world clinical scenario in which remdesivir is most likely to still be considered.

In conclusion, remdesivir might have a clinically meaningful benefit in well selected patients that deserves further exploration. It will be important to compare its clinical effects with those of approved monoclonal antibodies. However, remdesivir's potential benefit in addition to steroids and other approved immunomodulators such as baricitinib and tocilizumab is highly uncertain. As findings from DisCoVeRy show an absence of effect on late clinical status and mortality, there is no reason to advocate remdesivir use outside of clinical trials.

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*Iwein Gyselinck, Wim Janssens
iwein.gyselinck@kuleuven.be

Respiratory Diseases, University Hospitals Leuven, BREATHE Research Group, Department CHROMETA, KU Leuven, 3000 Leuven, Belgium

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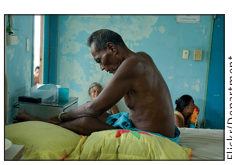
Sex-disaggregated tuberculosis data call for gender-equitable tuberculosis control

The call for more gender-equitable tuberculosis programming, informed by systematically collected and analysed sex-disaggregated and age-disaggregated data, has intensified in recent years.[1,2] Gender-equitable programming purposefully addresses inequities that are strongly affected by cultural and socially defined expectations, roles, responsibilities, norms, and power relationships based on sex, gender identity, or gender expression. For tuberculosis programmes, this means examining the intersectional gender context driving poor tuberculosis outcomes for men, women, and non-binary individuals (of all gender identities) and creating evidence-based strategies to address differential disease risk and service utilisation. The analysis of sex-disaggregated data to inform tuberculosis control efforts is fundamental in this regard, for how otherwise can funding for one of the world's top killers be targeted for maximum impact? What surprises us is that better use of sex-disaggregated data for programmatic improvements has not been made at the same rate as what we learn. In part, this might be due to insufficiently nuanced analysis of sex-disaggregated tuberculosis data. In *The Lancet Infectious Diseases*, the GBD 2019 Tuberculosis Collaborators address this issue in their Article summarising global, regional, and national sex differences in the global burden of tuberculosis by HIV status between 1990 and 2019.[3]

Sex-disaggregated data provide insight into gender-related tuberculosis burdens. First, the GBD study, like many others,[4] points to a greater overall tuberculosis burden faced by HIV-negative males than HIV-negative females. The authors reference previous studies pointing to men's delay in seeking health services and sometimes poorer treatment adherence compared with women. These findings reflect realities in many parts of the world and might be associated with male gender norms that inhibit care seeking and men's fear of income loss in contexts in which employers can easily terminate tuberculosis-infected workers.[5]

Second, tuberculosis infection risk and mortality are associated with negative health behaviours and risks that are strongly influenced by gender-related norms and practices that can differ for males and females. Notably, the authors show that, in 2019, the global all-age, population attributable fractions for tuberculosis deaths due to alcohol and smoking were 4·27 (95% uncertainty interval 3·69–5·02) times and 6·17 (5·48–7·02) times greater, respectively, for males than females. The data also show that in certain regions with high HIV prevalence, including southern and central sub-Saharan Africa, females generally experienced greater HIV and tuberculosis burden than males, with unsafe sex and intimate partner violence being significant contributors. This finding is not surprising given the well documented connections between intimate partner violence and women's HIV risk.[6] However, this study might be the first to draw attention to this association in the context of tuberculosis-related mortality and HIV and tuberculosis coinfection.

Third, HIV-positive women can face higher tuberculosis mortality rates than HIV-positive men depending on the sociodemographic context in which they live. An intriguing finding of this study[3] lies in the analysis of age-standardised tuberculosis mortality rates among HIV-positive individuals by sex and Socio-demographic Index (SDI) quintile. Between 1990 and 2019, males consistently had higher HIV and tuberculosis coinfection mortality than females in high and high-middle SDI quintiles. Yet the reverse was true,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