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.

	Acinetobacter	*Klebsiella*	*Pseudomonas*	*Stenotrophomonas*
CREDIBLE-CR trial[1]				
All-cause mortality*	49% (19/39)	21% (6/28)	18% (2/11)	67% (2/3)
Detected resistance†	3% (1/36)	0% (0/27)	0% (0/12)	0% (0/5)
SIDERO-CR study[5]				
Detected resistance	10% (38/368)	2% (12/720)	1% (2/262)	0% (0/217)
GA, USA, surveillance				
Detected resistance	8% (9/108)	6% (5/89)	0% (0/69)	0% (0/29)
Heteroresistance	59% (64/108)	30% (27/89)	9% (6/69)	48% (14/29)

All-cause mortality data are from the CREDIBLE-CR trial.[1] Detected resistance data (minimum inhibitory concentration >4 μg/mL) are from the CREDIBLE-CR trial[1] or SIDERO-CR study,[5] or were generated by disk diffusion assay on carbapenem-resistant isolates from GA, USA, according to Clinical and Laboratory Standards Institute guidance. Heteroresistance data were established by population analysis profile to identify minority resistant subpopulations within an isolate. *All-cause mortality data for *Klebsiella*, *Pseudomonas*, and *Stenotrophomonas* spp are for patients who did not have *Acinetobacter* spp coinfection. †Data not available for all isolates in the CREDIBLE-CR trial.

***Table*: All-cause mortality and cefiderocol non-susceptibility among carbapenem-resistant pathogens**

We surveyed for cefiderocol heteroresistance among carbapenem-resistant bacteria collected in the Georgia Emerging Infections Program, GA, USA, including *Acinetobacter baumannii* (2012–15), *Klebsiella* spp (2011–15), *Pseudomonas aeruginosa* (2015–16), and *Stenotrophomonas maltophilia* (2018–21; appendix p 1). By standard disk diffusion AST, the vast majority of isolates were classified as susceptible to cefiderocol, consistent with the CREDIBLE-CR trial and the SIDERO-CR surveillance study of 1873 carbapenem non-susceptible, Gram-negative pathogens.[1,5] However, sensitive testing by population analysis profile identified cefiderocol heteroresistance in each pathogen, with particularly high rates in *Acinetobacter* (table; appendix pp 1, 4). Importantly, these data indicate that cefiderocol heteroresistance was present in the USA before clinical approval of this drug by the US Food and Drug Administration in 2019. The frequency of heteroresistance was far greater than that of detected resistance for all four pathogens and was similar to the all-cause mortality rate, suggesting that heteroresistance might have contributed to cefiderocol treatment failure in the CREDIBLE-CR study.

Hallmarks of heteroresistance are the resistant subpopulation increasing in frequency with antibiotic treatment and decreasing in frequency after removal from the drug. We observed both effects in a representative carbapenem-resistant *A baumannii* isolate (appendix pp 3, 5). In the CREDIBLE-CR study, the minimum inhibitory concentration of some isolates exposed to cefiderocol increased after treatment, which might be consistent with heteroresistance.[1]

CREDIBLE-CR involved isolates from 16 countries and SIDERO-CR involved those from 52 countries, with similar frequencies of detected cefiderocol resistance (by standard AST) as observed in our research, suggesting that the GA, USA, isolates are representative. Therefore, the widespread and undetected cefiderocol heteroresistance among carbapenem-resistant pathogens observed here might explain the discordance between this drug's excellent susceptibility profile in vitro and its association with increased patient mortality.

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1 Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis* 2021; **21:** 226–40.
2 Band VI, Satola SW, Smith RD, et al. Colistin heteroresistance is largely undetected among carbapenem-resistant Enterobacterales in the United States. *mBio* 2021; **12:** e02881–20.
3 Band VI, Crispell EK, Napier BA, et al. Antibiotic failure mediated by a resistant subpopulation in *Enterobacter cloacae*. *Nat Microbiol* 2016; **1:** 16053.
4 Band VI, Satola SW, Burd EM, Farley MM, Jacob JT, Weiss DS. Carbapenem-resistant *Klebsiella pneumoniae* exhibiting clinically undetected colistin heteroresistance leads to treatment failure in a murine model of infection. *mBio* 2018; **9:** e02448–17.
5 Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of Gram-negative bacilli collected worldwide in 2014 to 2016. *Antimicrob Agents Chemother* 2018; **62:** e01968–17.

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Structured serological testing is an essential component to investigating SARS-CoV-2 reinfection

We read with interest Belén Prado-Vivar and colleagues' findings of suspected severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection

in a 46-year-old man in Ecuador.[1] As reported elsewhere,[2] Prado-Vivar and colleagues describe a more severe symptomatic course during the second infection than during the first. Understanding factors associated with potential reinfection might enable early decision-making for the clinical management of suspected cases. Reporting of such cases, supported by sequencing, including whole-genome sequencing (WGS), as presented by Prado-Vivar and colleagues, or Sanger sequencing, and preferably viral cell culture, is necessary to identify reinfection rather than prolonged viral shedding. Although a vital step, WGS requires retention of the initial sample and a biosafety 3 laboratory, is resource intensive,[2] and samples with very low viral loads might not be successfully sequenced, limiting its use as a high-throughput tool.

By comparison, serological testing is increasingly widely available, yet in cases of reinfection has so far provided little insight into whether the risk of reinfection correlates in any way with an inability to produce an effective humoral response. Prado-Vivar and colleagues' patient was IgM-reactive, IgG-negative on a lateral flow assay, with presumably an assigned significance of at least an initial response to SARS-CoV-2.[1] Other reported cases of reinfection have likewise described serology at initial presentation as IgM only, negative, or not tested.[2] Our experience with lateral flow assays suggests that early IgM-only positive results should be interpreted with caution: six of 12 health-care workers tested in a delayed case identification programme[3] underwent retesting with both an anti-nucleocapsid (anti-NP) IgG and an anti-receptor binding domain (anti-RBD) IgG assay and had a seronegative result (appendix pp 3–4). Conversely, among patients who had a documented IgG response (both anti-NP and anti-RBD), we found three cases of possible reinfection, albeit they were not substantiated by WGS (appendix pp 3–4).

We therefore strongly advocate use of a structured approach to reporting serological data alongside WGS when exploring reinfection. When high Ct values, as reported by Prado-Vivar and colleagues, are thought to correlate with low viral burden, it is possible that the initial infection could simply lack sufficient stimulation of germinal centre reactions to generate isotype-switching and lasting, detectable antibody production.[4] To delineate any relevance of primary infection viral burden on isotype switch, we must allow for inter-IgG class variability and consider the impact on assay selection; anti-NP IgG assays can identify previous exposure, but it is anti-RBD IgG assays that might provide further information through correlation with neutralising activity, and expression of these antibodies might be discordant.[5] Standardising reporting of serological data for reinfection cases might help characterise the role of the humoral response in cases of reinfection, and it would appear doing so with an anti-RBD IgG assay could have greater utility.

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1 Prado-Vivar B, Becerra-Wong M, Jose Guadalupe J, et al. A case of SARS-CoV-2 reinfection in Ecuador. *Lancet Infect Dis* 2020; published online Nov 23. https://doi.org/10.1016/S1473-3099(20)30910-5.
2 Iwasaki A. What reinfections mean for COVID-19. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30783-0.
3 Pallett SJC, Rayment M, Patel M, et al. Point-of-care serological assays for delayed SARS-CoV-2 case identification among health-care workers in the UK: a prospective multicentre cohort study. *Lancet Resp Med* 2020; **8:** 885–94.
4 Baumjohann D, Preite S, Reboldi A, et al. Persistent antigen and germinal center B cells sustain T follicular helper cell responses and phenotype. *Immunity* 2020; **38:** 596–605.
5 Rosadas C, Randell P, Khan M, McClure MO, Tedder RS. Testing for responses to the wrong SARS-CoV-2 antigen? *Lancet* 2020; **396:** e23

Regulatory approval of COVID-19 vaccine for restricted use in clinical trial mode

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Covaxin is India's first indigenous vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), developed through a collaboration between Bharat Biotech and the National Institute of Virology, which is a branch of the Indian Council of Medical Research, the Indian official authority for medical research. The development team isolated a strain of SARS-CoV-2 from patients with asymptomatic infection and developed a vaccine on a Vero cell-line manufacturing platform to deliver the inactivated coronavirus strain. On Jan 3, 2021, the vaccine was granted approval "for restricted use in emergency situation in public interest as an abundant precaution, in clinical trial mode",[1] which raised several concerns across the scientific society.[2]

There is an urgency and a feeling of moral obligation to get the vaccine to the public as early as possible, based on large-scale evidence on its safety and efficacy. However, the approval of a partly studied vaccine through an accelerated process on the basis of results from phase 1 and 2 clinical trials[3] and incomplete data on the

See **Online** for appendix