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for any treatment group even more questionable. Moreover, the high proportion of female participants (predictor of severe adverse drug reactions) might bias the results. Last, although it is stated that adherence was good, no data are shown to support it. Altogether, in my view, before embarking on a large-scale clinical trial, the data should be further critically evaluated including analysis of the pharmacokinetic results (not presented) in the context of efficacy and safety.

I declare no competing interests.

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### Authors' reply

We thank Enrica Alteri for her Correspondence. Although it is true that the small group sizes do not permit intergroup comparisons, all active groups showed a clear antiparasitic effect (mean 79–85% in the intention-to-treat population), including the short 2-week regimen. We consider the efficacy rates high enough to make it worth assessing these alternative regimens in a phase 3 trial, even the short regimen with an apparently lower effect (79%). Since the difference in efficacy versus placebo is greater than 75%, the group with the best safety profile can be selected. We therefore consider the results for the 2-week benznidazole monotherapy group to be particularly promising, since this shortened duration could substantially facilitate adherence to treatment. Adherence was good in our study, shown by the low rate of permanent

discontinuation due to adverse events (7%).<sup>1</sup> Most patients in all groups had adverse events, and although the rate of temporary interruption seems higher in the group receiving 300 mg for 2 weeks, the sample size does not allow confirmation of whether this is a significant difference compared with the other active groups. Importantly, this reflects the fact that patients were able to pause and, once adverse events resolved, resume and complete treatment, resulting in blood parasitological clearance. The longer treatment duration in the other groups resulted in prolonged adverse events, making permanent discontinuation the only alternative for several patients. For patients discontinuing permanently due to adverse effects, the mean duration of treatment was 23 days. Results of a pharmacokinetic analysis will be presented in a future publication; these and others<sup>2</sup> suggest that the different treatment schemes in BENDITA show acceptable amounts of drug exposure within the range of the existing standard treatment. Although several participants had liver function abnormalities (liver enzymes more than three times the upper limit of normal), which is expected in this class of drugs,<sup>3</sup> this was only considered an adverse event of special interest when alanine aminotransferase or aspartate aminotransferase concentrations exceeded eight times the upper limit of normal.<sup>4</sup>

We noted the high proportion (70%) of female participants as a potential source of bias; however, random allocation resulted in a similar distribution of men and women in the treatment groups. More generally, strategies are needed to increase treatment rates for men with Chagas disease. Larger clinical studies would provide the evidence needed to establish whether shortened benznidazole regimens could contribute to reducing the public health burden of this neglected disease.

We declare no competing interests.

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### SARS-CoV-2 rapid antigen detection tests

We read with interest the Personal View by Rosanna Peeling and colleagues,<sup>1</sup> who discuss the benefits and limitations of SARS-CoV-2 antigen rapid detection tests (Ag-RDTs) for scaling up diagnostic capacities in different settings. As recent evaluations suggest, Ag-RDTs can reliably detect patients during the initial infective phase of COVID-19 (when patients have high viral loads).<sup>2,3</sup> Fewer data are available for the use of these tests to identify asymptomatic carriers, such as before attending gatherings related to education, work, or travel.<sup>4,5</sup> As the authors emphasise, the screening of asymptomatic individuals in low-prevalence settings is hampered by imperfect specificity.<sup>1</sup> The dilemma that most detected cases represent false positives rather



Published Online  
May 4, 2021  
[https://doi.org/10.1016/S1473-3099\(21\)00249-8](https://doi.org/10.1016/S1473-3099(21)00249-8)

	Cutoff	Total	True negatives	False positives	Specificity
Manufacturer instructions	≥1.0	773	706	67	91.3 (89.1–93.2)
Testing positive samples twice	≥1.0	767	725	42	94.5 (92.6–96.0)
Using a higher cutoff level	≥3.0	773	756	17	97.8 (96.4–98.7)
Testing positive samples twice and using a higher cutoff level	≥3.0	767	761	6	99.2 (98.2–99.7)

Data are n or % (95% CI), unless otherwise indicated.

**Table:** Specificity of an automated fluorescence immunoassay for SARS-CoV-2 antigen in RT-PCR-negative asymptomatic individuals according to testing strategy



Published Online  
May 4, 2021  
[https://doi.org/10.1016/S1473-3099\(21\)00206-1](https://doi.org/10.1016/S1473-3099(21)00206-1)

than true infections might require a two-tier approach with molecular confirmation,<sup>1</sup> affecting the practicality and acceptance of such a strategy. Here we suggest alternative strategies to optimise the use of Ag-RDTs in asymptomatic populations with low positivity likelihood.

From September, 2020, to January, 2021, we evaluated an Ag-RDT to screen asymptomatic individuals before surgery or childbirth. 773 people were tested in parallel with STANDARD F COVID-19 Ag fluorescence immunoassay (SD Biosensor, Gyeonggi-do, South Korea) and a commercial RT-PCR (COVID-19 Genesig; Primerdesign, Chandler's Ford, UK)<sup>2</sup> using separate nasopharyngeal swabs, following the manufacturers' instructions. The antigen assay was read with an automated device (F2400; SD Biosensor), which provides a quantitative immunofluorescence index. All individuals tested negative by RT-PCR; however, 67 samples (8.7%) were initially positive by the Ag-RDT (table). We examined alternatives to improve test accuracy in our population. First, we repeated the Ag-RDT of positive samples using the same dilution buffer to calculate the average index, resulting in a reduction of false positives to 42 (5.5%). Second, we raised the cutoff for positivity from 1.0 (recommended by the manufacturer) to 3.0, on the basis of a receiver operating characteristic (ROC) curve which demonstrated optimum diagnostic performance

at a cutoff of 3.36 (100% sensitivity; 98.5% specificity). To perform the ROC analysis, 30 RT-PCR-positive samples from patients with early COVID-19 from a previous study were included.<sup>3</sup> This approach reduced false positives to 17 (2.2%), and specificity increased significantly (table). The combination of both strategies showed the highest specificity (99.2%; table).

Although further studies are necessary to confirm our results, the presented data suggest that the dilemma of imperfect specificity of Ag-RDTs in asymptomatic populations can be diminished significantly by evaluating testing protocols that maintain the capacity of getting rapid results while increasing the accuracy of the tests.

We declare no competing interests. We thank Gabriel Pizarro for technical assistance.

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## SARS-CoV-2 rapid antigen detection tests

I read with interest the Personal View by Rosanna Peeling and colleagues<sup>1</sup> on the performance of rapid antigen detection tests (Ag-RDTs) across different SARS-CoV-2 prevalence settings. The authors elegantly show that the negative predictive value (NPV) increases with decreasing disease prevalence and conclude that “for asymptomatic individuals in low prevalence settings, for travel, return to schools, workplaces, and mass gatherings, Ag-RDTs with high negative predictive values can be used with confidence to rule out infection”.<sup>1</sup> However, the clinical interpretation of NPVs requires attention.

Independent evaluation of different Ag-RDTs has shown that their sensitivity ranges between 70% and 90% (lower confidence limits 50–80%) in symptomatic individuals,<sup>2</sup> but it deteriorates remarkably (<50%) in asymptomatic close contacts,<sup>3</sup> in those with low nasopharyngeal viral loads,<sup>2</sup> and in paediatric patients.<sup>4</sup> By contrast, the NPV is excellent (>97%) in all instances,<sup>2–4</sup> which has led most investigators to conclude that a negative Ag-RDT might reliably rule out the infection in low-prevalence settings.<sup>1,4</sup>

Predictive values are inherently dependent on disease prevalence and, as such, they can be misleading. When the probability of the disease is low, the NPV of any diagnostic test is high, irrespective of its sensitivity (figure). Assuming a disease prevalence of 2.5%, an Ag-RDT with