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Authors' reply

"One hand cannot tie up a bundle of wood." This African proverb highlights the need for complementary efforts to achieve important tasks. The comments from Fernando Kemta Lekpa and colleagues on our Article[1] underscore the challenge of COVID-19 diagnosis in symptomatic people testing negative for SARS-CoV-2 by both antigenic rapid diagnostic tests (RDTs) and RT-PCR. The authors suggest integrating clinical and radiographical features into the COVID-19 diagnostic algorithm for low-resource settings. Specifically, they believe chest CT could have an added screening value when there is strong clinical suspicion of COVID-19 but negative RT-PCR or RDT results.

The use of chest CT for COVID-19 diagnosis has been extensively assessed and is reported to have 87% sensitivity and 43% specificity—test characteristics no better than most RT-PCR assays and RDTs.[2] Although chest CT could potentially detect lower respiratory tract disease in symptomatic patients with negative upper respiratory tract testing, it is better used to help classify COVID-19 disease as mild, moderate, or severe. Because of its low specificity, ionising radiation, and limited availability, we do not believe chest CT should be added to COVID-19 screening and diagnostic algorithms in low-resource settings. However, we agree with Lekpa and colleagues that COVID-19 antibody tests have an important place in screening algorithms for people testing negative by RDT and RT-PCR, and we included antibody testing in our algorithm for asymptomatic patients.[1] We also agree that if there is ongoing strong suspicion for COVID-19, clinicians can request up to three RDTs or RT-PCR tests to increase the probability of detecting SARS-CoV-2, especially in patients with low viral load in very early or later phases of the disease. If subsequent tests are negative and strong clinical suspicion for COVID-19 disease remains, we believe these patients should be treated as though they have COVID-19. Treatment should then be adapted to symptom severity based on pulse oximeter readings or chest CT findings, where available. Pulse oximetry is a proxy measure of arterial oxygenation, a prognostic indicator, and recommended for inpatient and remote monitoring of patients with confirmed or possible COVID-19 to identify silent hypoxaemia and limit risk of significant deterioration.[3] We believe pulse oximetry is a more practical risk-stratification tool for confirmed or possible COVID-19 patients, especially in low-resource settings. Those with pulse oximetry levels lower than 92% should be managed as severe COVID-19 disease, per WHO guidelines.[4] Low-cost pulse oximeters could supplement management of patients with negative RDT and RT-PCR results in low-income and middle-income countries, with added prognostic and monitoring value, higher availability, and lower cost than chest CT.

We declare no competing interests.

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1 Boum Y, Fai KN, Nicolay B, et al. Performance and operational feasibility of antigen and antibody rapid diagnostic tests for COVID-19 in symptomatic and asymptomatic patients in Cameroon: a clinical, prospective, diagnostic accuracy study. *Lancet Infect Dis* 2021; published online March 25. https://doi.org/10.1016/S1473-3099(21)00132-8.

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4 WHO. COVID-19 clinical management: living guidance. Geneva: World Health Organization; January, 2021.

Bell's palsy and SARS-CoV-2 vaccines—an unfolding story

Following the documentation of a case of Bell's palsy associated with vaccination,[1] we were contacted by patients and colleagues from Canada, Australia, Europe, the UK, and United Arab Emirates. Questions raised were whether mRNA vaccine recipients are at increased risk of developing Bell's palsy, and what to recommend to individuals with a history of Bell's palsy.

In their Comment, Al Ozonoff and colleagues[2] considered key statistical and epidemiological aspects of SARS-CoV-2 vaccine trial safety data regarding the onset of facial paralysis. Here, we offer a different interpretation of their findings and statistical consideration of risks associated with mRNA and non-mRNA SARS-CoV-2 vaccines.

Despite geographical and seasonal variations,[3,4] the generally agreed incidence of Bell's palsy is 15–30 cases each year per 100 000 population. Ozonoff and colleagues[2] rightly state that the predicted 12-month (annual) incidence of Bell's palsy inferred from mRNA vaccine trials is higher than that reported during the 2-month observation period of these studies. They concluded that the observed incidence of Bell's palsy in the mRNA vaccine arms was 3·5 to seven times higher than expected in the general population. However, safety data were collected for participants with a median follow-up of 2 months after the second dose; therefore, the data refer to an overall observation period of approximately 12 weeks from dose one. Given this, and considering Bell's palsy as the possible outcome of individual doses, the observed incidence in the mRNA vaccine trials would be roughly 1·5 to three times higher than in the general population (table).

The numerical imbalance reported with mRNA vaccine trials was not

	Expected occurrence during mRNA vaccine trials (recipients)	Actual occurrence during mRNA vaccine trials (recipients)	Actual occurrence during mRNA vaccine trials (doses)
Rate per 100 000*	~3 to 7 cases (15–30 cases per year)	~21 cases (89 cases per year)	~10 cases (44 cases per year)
Ratio	1:14 285 to 1:28 570	1:5000	1:10 000

*Rate per 100 000 recipients for the second and third columns and per 100 000 doses for the fourth column.

Table: **Expected and actual rates of Bell's palsy in COVID-19 mRNA vaccine trials**

seen in the Oxford-AstraZeneca and Johnson & Johnson phase 3 studies using more traditional virus-based technology. Examination of adverse event data from the Yellow Card scheme in the UK and from the EU EudraVigilance database might help clarify this matter. As of March 21, the Yellow Card-reported frequency of facial paralysis or paresis and facial nerve disorder after any dose was close to 23 per million with the Pfizer-BioNTech vaccine and 13 per million with the Oxford-AstraZeneca vaccine. Excluding reports of facial paralysis cross-listed with cerebrovascular accident, EudraVigilance data indicate a much higher frequency of facial paralysis after the Pfizer-BioNTech vaccine than after the Oxford-AstraZeneca vaccine (497 *vs* 56 cases or 13·6 *vs* 4·1 per million doses as of April 3). The risk of developing facial paralysis could be two to three times higher in individuals receiving mRNA vaccines than in those receiving traditional vaccines. These findings should be considered when selecting a vaccine for patients with a history of Bell's palsy.

We declare no competing interests.

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1 Colella G, Orlandi M, Cirillo N. Bell's palsy following COVID-19 vaccination. *J Neurol* 2021; published online Feb 21. https://dx.doi.org/10.1007%2Fs00415-021-10462-4.

2 Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. *Lancet Infect Dis* 2021; **21:** 450–52.

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4 Erdur H, Ernst S, Ahmadi M, et al. Evidence for seasonal variation of Bell's palsy in Germany. *Neuroepidemiology* 2018; **51:** 128–30.

Authors' reply

We thank Nicola Cirillo and Richard Doan for their careful consideration of our Comment[1] and the available safety data from the recent mRNA vaccine trials. They are correct to call attention to the follow-up period for reporting safety events as important to interpret event rates appropriately. We have three points in response.

First, data reported in the US Food and Drug Administration briefings suggest risk of Bell's palsy is greatest within 1 month of a second vaccine dose. Page 43 of the Pfizer briefing notes "from dose 1 through 1 month after dose 2, there were three reports of Bell's palsy in the vaccine group and none in the placebo group".[2] According to page 42 of the Moderna briefing,[3] three cases of Bell's palsy occurred 32, 28, and 27 days after vaccination (presumably first dose) versus one case that occurred 17 days after injection in the placebo group. Using an abbreviated follow-up period of 2 months after the first dose—ie, 1 month after the second dose—there are six Bell's palsy cases reported in the combined vaccine groups versus one case in the combined placebo groups, with a denominator of approximately 5664 person-years in each group. Thus we observe annualised incidence rate in the vaccine group of roughly 106 cases per 100 000 population, again 3·5–7·0 times the expected background rate of 15–30 cases per 100 000 population per year.

Second, although risk of a vaccine-associated event begins after the first dose of vaccine is received, this risk increases substantially after the second dose.[2,3] Our original calculation does not fully account for the month of observation between first and second doses, but the authors' assumption of 12 weeks observation might be overly conservative since it assumes constant risk over 3 months of follow-up. A weighting function applied to observation time would offer a more sophisticated analysis. A nuanced interpretation of these safety data must await availability of complete datasets from both trials.

Third, the greater than three-fold increase in Bell's palsy incidence observed in EudraVigilance when comparing mRNA vaccines to other vaccines adds to the evidence that mRNA vaccines impose higher risk of Bell's palsy than other vaccines based on different platforms, alongside ongoing work to identify likely mechanisms.[4] We agree this evidence might be a consideration for clinicians when advising patients with a history of Bell's palsy on the choice of vaccine to receive.

In conclusion, we appreciate attention to these data and clarification of an important point in our original Comment. The available data remain consistent with a more than three-fold increase in risk for Bell's palsy within 1 month of a second vaccine dose.

OL is a named inventor on patents relating to vaccine adjuvants and human in-vitro systems that model vaccine action. AO and EN declare no competing interests.

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1 Ozonoff A, Nanishi E, Levy O. Bell's palsy and SARS-CoV-2 vaccines. *Lancet Infect Dis* 2021; **21:** 450–52.

For **adverse event data reported through the Yellow Card scheme** see https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions

For the **EudraVigilance database** see http://www.adrreports.eu/en/index.html

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