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.

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used instead of case fatality ratio.[2,3] A ratio is a comparison of two similar quantities. Ratios have no dimensions and can take any value; a ratio of 1 means the two quantities being compared are equal to each other. The case fatality ratio is the ratio of deaths (numerator) to identified cases (denominator), and is usually expressed as percentage.[2,3] As clearly described by Kelly and Cowling,[1] a rate has a time dimension (ie, time^{-1}); it expresses changes in one quantity over a time period. Risk, however, is the probability associated with an adverse outcome that is likely to occur in the future during follow-up. Like ratios, risk has no dimensions but, unlike ratios, risk is confined to values between 0 and 1.

From a scientific standpoint, these terms acquire different meanings depending on the variables being measured in the relevant study designs. In the context of the COVID-19 pandemic, case fatality ratios are obtained from cross-sectional studies, whereas risk estimates are obtained from prospective cohort studies. The infection rate is calculated by counting new infections in equally spaced time intervals (eg, daily or weekly). This growth rate reflects the speed and scale of new cases and can be used to monitor the effects of preventive interventions.

Thus, in scientific research, these terms do not always align with their usual English language semantics and should not be used interchangeably. Ratio, rate, and risk have different meanings that are based on the variable being measured in the relevant study designs. It is hoped that future publications will use the terms appropriately, in line with the context.

I declare no competing interests

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Implication of SARS-CoV-2 evolution in the sensitivity of RT-qPCR diagnostic assays

Since the initial outbreak of COVID-19 and identification of a novel enveloped RNA betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reports suggest the virus might be evolving, albeit at a lower rate than influenza viruses.[1–3] Nevertheless, in light of the rapid and pandemic-scale spread of COVID-19, mutations in SARS-CoV-2 raise new diagnostic challenges, including the redesign of the oligonucleotide sequences in use in RT-qPCR assays to circumvent potential primer–sample mismatches.

We report an analysis of all high-coverage SARS-CoV-2 genome sequences (1825 in total) deposited in the Global Initiative on Sharing All Influenza Data (GISAID) database[4] as of March 30, 2020. We aligned the sequences against the reference sequence obtained from the Wuhan seafood market pneumonia virus isolate, Wuhan-Hu-1 (NC_045512). Subsequently, we annotated in the alignments the binding sites of 33 oligonucleotides developed by different centres and shared by WHO[5] for use in the RT-qPCR detection of SARS-CoV-2 from human samples. We then calculated the nucleotide diversity (π)[6] in the binding region of each oligonucleotide (figure).

The analysis revealed that 79% (26 of 33) of the primer binding sites used in the RT-qPCR assays were mutated in at least one genome. The substitution of three nucleotides (GGG substituted to AAC) at the beginning of the binding site of the forward primer designed by the Chinese National Institute for Viral Disease Control and Prevention in the gene encoding for the nucleocapsid phosphoprotein was of relevance. The AAC variant was in 14% (258 of 1825) of the genomes isolated and sequenced in 24 different countries (Australia, Belgium, Brazil, Chile, China, Czech Republic, Denmark, England, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Mexico, the Netherlands, Peru, Portugal, Spain, Switzerland, the USA, Vietnam, and Wales).

Notwithstanding the possibility of sequencing errors, the fact that some variants were consistently found in different sequencing experiments at independent test sites suggests that these genetic variants are true variants. Moreover, the observation that at least one of the previously designed primers is now likely to be ineffective at detecting up to 14% of the virus variants in circulation strengthens the need to continue optimising the oligonucleotides in use in assays being developed. Oligonucleotide optimisation will be facilitated by global sharing of SARS-CoV-2 genomes and the frequently updated reports on sequence analysis that are available on the GISAID[4] website.

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We acknowledge all authors originating and submitting the sequences used in this Correspondence (appendix).

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See Online for appendix

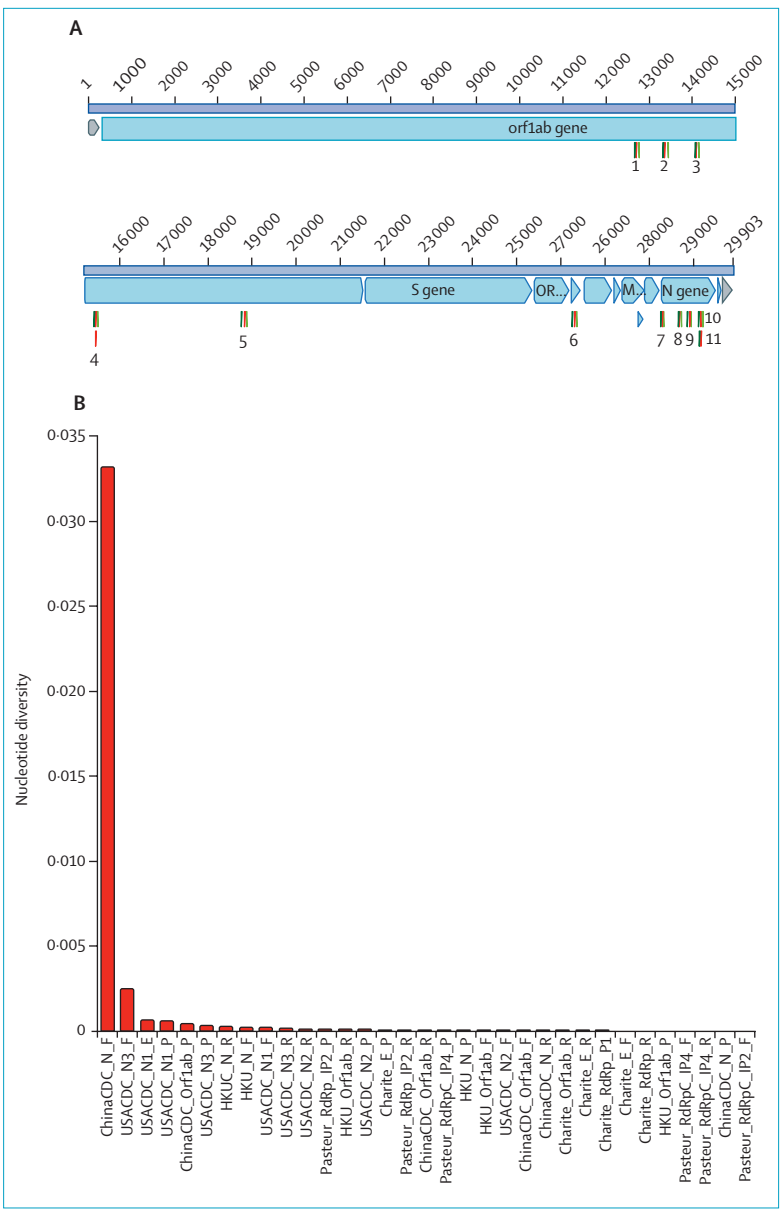

***Figure*: Genomic position and nucleotide diversity in the binding sites of oligonucleotides in use in RT-qPCR diagnostic assays across 1825 SARS-CoV-2 genomes isolated from humans in different countries**
(A) Graphical representation of a SARS-CoV-2 genome (29 903 nucleotides, NC_045512), showing genes (blue) and oligonucleotide primer binding sites (forward primers in dark green, reverse primers in light green, and double-dye oligonucleotide probes in red). (1) Pasteur_RdRp_IP2, (2) ChinaCDC_Orf1ab, (3) Pasteur_RdRp_IP4, (4) Charité_RdRp, (5) HKU_Orf1ab, (6) Charité_E, (7) USACDC_N1, (8) USACDC_N3, (9) ChinaCDC_N, (10) HKU_N, and (11) USACDC_N2.[5] (B) Nucleotide diversity (π) in the binding sites of the oligonucleotides in use in RT-qPCR diagnostic assays across 1825 SARS-CoV-2 genomes isolated from humans in different countries. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

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COVID-19 and essential pregnant worker policies

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The Article by Nan Yu and colleagues[1] provides timely information to inform policies concerning essential pregnant workers. In past epidemics (eg, H1N1 influenza, Middle East respiratory syndrome, and severe acute respiratory syndrome), pregnant women and their offspring have been at increased risk of morbidity and mortality.[2] By contrast, the maternal, fetal, and neonatal outcomes reported by Yu and colleagues were surprisingly good. When considering this study, it is important to note that all of the women were full-term (≥37 weeks) and underwent caesarean section within 3 days of presentation. Prompt delivery allowed for experimental treatment in all women; all patients received antiviral treatment, including ganciclovir, oseltamivir, interferon, and Arbidol (ie, umifenovir) tablets. Traditional Chinese medicine, such as Jinye Baidu granules or Lianhuaqingwen capsules, or both, was also administered to four of seven women, and five of seven received the steroid methylprednisolone. Because the safety of these interventions during pregnancy is not established, infection in the first, second, or early third trimester, without immediate delivery, might not lead to similar favourable outcomes. For example, in a case series on nine pregnant women with a larger range of gestational ages and severe cardiopulmonary disease attributed to COVID-19, seven of nine died.[3] Although the worse outcomes of this non-systematic series do not establish risk, they do highlight that low risk should not be assumed in the absence of multicentre databases to study pregnancy-related outcomes.

Furthermore, although only one newborn baby was found to have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the study by Yu and colleagues,