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CovMT: an interactive SARS-CoV-2 mutation tracker, with a focus on critical variants

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The number of confirmed SARS-CoV-2 cases worldwide has now reached around 100 million, with 2·1 million reported deaths[1] and more than 450 000 SARS-CoV-2 genomes already sequenced. It is vital to keep track of mutations in the genome of SARS-CoV-2, especially in the spike protein's receptor binding domain (RBD) region, which could potentially impact disease severity and treatment strategies.[2–4] In the wake of a recent increase in cases with a more infective variant featuring an RBD mutation (N501Y, B.1.1.7) in the UK, countries worldwide are concerned about the spread of this or similar variants. Increasing sequencing efforts and user-friendly mutation tracking systems are needed for timely tracking of SARS-CoV-2 variants.

We developed a COVID-19 virus mutation tracker system (CovMT; appendix) based on SARS-CoV-2 isolate genomes deposited to GISAID to track the worldwide sequencing efforts and the evolution of the mutational landscape of this virus. CovMT, which is updated daily, summarises mutations from more than 450 000 isolates into groups of generic virus clades, lineages, and more specific mutation sets we call mutation fingerprints. These summaries, with metadata of location, date of sampling, and patient disease severity information, when available, at the continent and country levels, are accessible from the main page of the CovMT system (appendix).

For **CovMT** see https://www.cbrc.kaust.edu.sa/covmt

See **Online** for appendix

For **GISAID** see http://gisaid.org

CovMT also provides a timeline history of SARS-CoV-2 variants related to mutations in the RBD region of the spike protein. As of the end of January, 2021, the spread of N501Y, B.1.1.7 variants has been detected in SARS-CoV-2 isolate genomes from nearly 60 additional countries using CovMT (appendix). Nonsynonymous mutations in the RBD region have a high potential to be linked to increased binding efficiency, increased infectivity, and the potential to evade antibodies.[2–4] To track all similar variants, we ranked mutations in the RBD region based on their appearance in the number of isolate genomes in CovMT. The CovMT timeline (appendix) shows that N501Y, S477N, N439K, and L452R mutations can now be detected in more than 41 700, 23 300, 9700, and 2000 isolates, respectively. An important RBD mutation, E484K, which probably allows the virus to evade existing antibodies,[5] was originally recorded in Denmark during March, 2020, and is now on the rise in South Africa[5] since October, 2020. More than 510 isolates show triple mutations (K417N, E484K, and N501Y, lineage B.1.351) in South Africa, with some isolates now detected in the UK and 22 other countries. We observed that the UK variant (B.1.1.7) has also acquired the E484K mutation (appendix). A more recent variant, P.1, with E484K and N501Y RBD mutations, appeared in four travellers arriving in Japan from Brazil on Jan 2, 2021. The P.1 variant now appears in six other countries. Timelines and lineage history of each of the top ten most common RBD mutations can be explored at CovMT.

With a particular focus on critical mutations in the RBD region of the spike protein, and with an option to seamlessly accrue the clinical metadata, including disease severity, we believe that CovMT will be useful for scientists, the general public, and authorities to explore country-specific information.

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Estimates of anti-SARS-CoV-2 antibody seroprevalence in Iran

Iran was among the first countries outside China to report a large outbreak of COVID-19, but the transmission dynamics across the country have largely remained unknown due to the scarcity of serological, epidemiological, and genomic data. One of the main barriers

has been the fact that Iran's Ministry of Health and Medical Education (MoHME) stopped releasing province-level data on the number of confirmed COVID-19 cases from March 22, 2020, onward. Furthermore, provincial data on the number of confirmed COVID-19-related deaths were never released. Instead, MoHME reports the percentage change in the number of cases with respect to previous days as an indicator of the state of the epidemic in each province and colour-codes them from blue (low incidence) to yellow (medium incidence), orange (high incidence), and red (very high incidence).

Despite the significant implications of understanding the Iranian epidemic for the country and the Eastern Mediterranean region as a whole, research investigations have largely been hindered due to the lack of epidemiological data on the number of cases and deaths, age-stratified and sex-stratified data, both at the national and province level, and seroepidemiological analysis.[1] The study by Hossein Poustchi and colleagues,[2] sponsored by MoHME and carried out by the then Deputy Minister of Research and Technology of the Ministry of Health Reza Malekzadeh and his team, to measure SARS-CoV-2 antibody seroprevalence in the general population across 18 cities of Iran was the first systematic investigation into the geographical spread of COVID-19 across the country nearly a year after the first two cases were reported in Qom on Feb 19, 2020. Their analysis showed greatly varied levels of exposure in different cities, with some reaching very high levels (>50% in Qom and Rasht) by late April to early June.

Before the study by Poustchi and colleagues, we did a similar province-level analysis using seasonal all-cause mortality data to estimate the excess mortality in all 31 provinces of Iran from winter to summer, 2020.[3] Our findings corroborate the results by Poustchi and colleagues (appendix p 1), with an overall significant correlation (R^2=0·67 and p<0·001; appendix p 2). Our results further suggest that most provinces would continue to have a two to four times increase in exposure until the end of summer (Sept 21, 2020), with Qom and Golestan reaching approximately 57% (95% CI 44–69) population-level exposure.[3]

In the absence of more recent serology or province-level data, our estimates provide the most recent indicator of prevalence. This comparison is of immediate epidemiological importance as it highlights areas with the largest epidemic growth, which require the most immediate interventions. The continued availability of province-level data would be of paramount public health importance in a country that is facing such a heavy toll from COVID-19.

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Hossein Poustchi and colleagues[1] reported SARS-CoV-2 antibody seroprevalence in the general population and high-risk occupational groups across 18 cities in Iran. However, there are several major concerns regarding their study design, analysis, and results.

First, although appendix 2 of the Article mentions cities as clusters, it is unclear how these clusters were selected. The inverse of the selection probability of individuals, which is a function of probability of cluster selection and unknown here, should be used as weights in the analyses.[2]

Second, the sample size calculation has errors. In the design effect formula, n is calculated as $\sum m^2 / \sum m = 1180{\cdot}2$ (where m is the cluster size)[3] but not the number of clusters (n=18), as mentioned in appendix 2. Also, the intracluster correlation (δ) of 0·05 is too high for large clusters (such as those encountered in the study by Poustchi and colleagues), without any supporting references. Furthermore, it is unclear whether the seroprevalence (p) of 0·15 refers to the general population or high-risk groups, and again no references are given on the reported value.

Third, the bootstrap procedure described in appendix 2 mimics simple random sampling and does not consider clustering in the design, leading to too narrow confidence intervals (CIs). In fact, the appropriate bootstrapping procedure for cluster designs would draw the cluster units rather than individual units with replacement. Alternatively, one can use cluster-robust standard errors.[4] The CIs are also narrow due to uncertainties in the sensitivity and specificity estimates. A Monte-Carlo bias analysis from an appropriate probability distribution of sensitivity and specificity can be used for overcoming this problem.[5]

Fourth, a seroprevalence of 72·6% for Rasht city seems to be an overestimate and inconsistent with

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