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CHAPTER

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Guesstimating the COVID-19 burden: what is the best model?

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1. Introduction

Since the outbreak of the COVID-19 pandemic, countries across the globe have attempted various mitigation measures to curb the spread of the virus. There has been significant underreporting in countries which employ only a symptom-based algorithmic testing approach for COVID-19, focusing exclusively on health-conscious people who present to government-approved testing facilities. Such an approach results in a volunteer bias and ultimately contributes to distortion of COVID-19 data due to limited number of tests being conducted in a country, hence underestimating the overall case count (Silverman et al., 2020). It has increasingly become evident that access to population-level data is an essential feature of any nation's ability to flatten the curve, by adopting a testing—retesting—contact tracing approach. However, this model has rarely been followed in Pakistan, due to lack of information and access to affordable, large-scale testing methods.

Emerging research on COVID-19 transmission illustrates how asymptomatic infections within a country may be much higher than the number of polymerase chain reaction (PCR) reported cases (Bendavid et al., 2020). Seroprevalence findings from a large-scale census in Pakistan from April to July 2020 indicated 17.7 times higher prevalence as compared to traditional PCR government testing within the same time frame (Javed et al., 2020). Hence, an effective approach to pandemic response would involve a synergistic model encompassing both PCR testing and mass-level screening via serologic test kits in order to capture the true extent of the disease within the population. This approach has significant implications in guiding public health policies by increasing the country's testing capacity via cost-effective methods.

As research demonstrates that the extent of silent transmission of COVID-19 in a population may not be captured by an exclusively PCR-focused testing methodology, the most

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successful way to conduct massive level testing is through serologic tests as they minimize the need for hospital settings, reduce the pressure on an already overwhelmed health system, and assess the true prevalence of the disease.

2. Mass testing and screening model

Mass-level, population-based serologic testing has demonstrated groundbreaking results in assessing the true prevalence of COVID-19, as opposed to PCR-based positivity rates used by most governments to report official figures (which are unable to capture the proportion of asymptomatic yet positive cases within the general population). Pakistan has faced an issue of limited testing capacity focused exclusively on symptom-based PCR tests which severely underestimated the true prevalence of the disease within the population. In such a context, where official data on COVID-19 cases fail to capture the true extent of transmission, it is important for governments to redirect resources toward increasing countries' testing capacities and strengthening primary health systems.

The figures emerging from the ongoing by the government, the proportion tested positive from the total number of people tested is termed as the positivity rate of COVID-19 infections, which is very different from the total prevalence of COVID-19 within a population. The positivity rate only encapsulates the total number of positive cases among symptomatic individuals or contacts of COVID-19 positive cases tested divided by the total number of PCR tests conducted, which excludes asymptomatic cases from being reported in official figures (Martinez et al., 2020). Hence, the positivity rate is not an appropriate indicator to determine the true extent of the disease as it fails to capture the proportion of positive cases within the general, low-risk population including asymptomatic carriers, who can only incidentally be identified via a mass-screening model. In contrast to PCR tests, serologic tests are based on the qualitative, as well as titers of IgM and IgG, generated by the body in response to an SARS-CoV-2 infection (Ravi et al., 2020). Serologic tests can detect asymptomatic carriers and assess past exposure, whereas PCR has a high false-negative rate, especially when the viral load is low, giving it a false assurance while continuing to unknowingly spread the infection. According to growing research on seroprevalence findings across the world, scientists suggest that COVID-19 screening via antibody kits can be a critical mechanism for disease surveillance, therapeutics, and reopening of offices and public spaces (Abbasi, 2020). FDA also issued guidance allowing the use of serology tests for COVID-19 screening combined with the existing approach of PCR testing in a synergistic model, to ensure that the true prevalence of infections is captured within a country (West et al., 2020).

Evidence shows that one of the most effective pandemic response strategies for curbing the spread of COVID-19 takes into account data generated from large-scale seroprevalence studies to inform epidemic parameters (Bendavid et al., 2020). On a policy level it is essential to conduct seroprevalence studies to build an accurate database on COVID-19 cases, as opposed to the official statistics which only capture the symptomatic cases who present for PCR testing, as this distorts the data due to volunteer bias.

3. Cross-country comparisons

Even with COVID-19 vaccines in development, with some having reached the authorization phase, they cannot adequately cater to the sheer number of rising COVID-19 cases globally at least until late 2021, as the first priority would be to administer vaccines to frontline workers and high-risk populations. Therefore, it is important to focus on scaling up the diagnostic process rather than depending solely on vaccines to bring the pandemic to an end. Countries need to opt for a prevention-based approach by incorporating mass-screening and testing among the low-risk, asymptomatic population, and reassess the effectiveness of focusing exclusively on a PCR testing methodology for mass-level screening. A lot can be learned from the various approaches adopted by different countries around the world, as there are several factors to consider while designing effective public policy guidelines for a successful pandemic response strategy. While most countries are focusing on testing people with overt symptoms to identify patients with COVID-19 infections, a more strategic approach would involve random sampling to accurately follow the extent of infections within a population (Vandenbroucke et al., 2020). Although it is difficult to make completely accurate comparisons of the prevalence of COVID-19 infections between countries due to data gaps and potential ecological fallacies, if done carefully there is a lot to gain from cross-country analyses of nonpharmaceutical interventions undertaken.

There are a range of factors which explain why some countries fared better in terms of crisis response compared to others. These factors include COVID-19 diagnostic tools used, intensity of testing and contact tracing, lockdown measures implemented, coordinated efforts toward implementing national COVID-19 response strategies, and collaboration between private and public sectors toward crisis management. Hence, a more reliable conclusion can be achieved through an investigation of epidemiological analyses of interventions different countries have implemented toward reopening public spaces. All these are integral measures which can contribute to informing a robust, country-specific pandemic response policy.

Countries which were hit the hardest by the pandemic, including China, the United States, and Spain, began conducting seroprevalence studies on the general population to trace the silent transmission of COVID-19 infections among asymptomatic cases. Such seroprevalence studies provide insights about past as well as current infections in the population, as opposed to PCR tests which solely detect current infections, which is a limitation for designing epidemiological guidelines. The most successful strategy among countries which were able to curb the spread of COVID-19 infections was the speed and intensity of testing, mass screening, and contact tracing. Learning from their experiences of the coronavirus that causes SARS, governments in China, Hong Kong, Taiwan, Singapore, South Korea, followed by Australia and New Zealand (Baker et al., 2020) took early and decisive action toward screening as well as social distancing and implementing phased lockdown. South Korea implemented one of the most successful models of intensive mass testing and contact tracing, and managed to control the spread of the virus without the need for a total lockdown. Similarly, Taiwan also avoided a complete lockdown, yet achieved the lowest population infection rates recorded (Pearce et al., 2020). Hence policy-makers in Pakistan can learn from these examples to devise a context-specific strategy in curbing the spread of infections in the country and deploying cost-effective measures of mass-level testing and screening.

4. Limitations of PCR testing

While PCR tests have been considered the gold standard for COVID-19 testing across the world, it is important to note that the selection of sample and site of testing plays a major role in accuracy of the results (Wang, Kang, et al., 2020, Wang, Xu, et al., 2020, Wang, Yao, et al., 2020). As per the paper published in a peer-reviewed journal *JAMA*, even the "gold standard" PCR kits can have an accuracy ranging from 32% (pharyngeal swab) to 63% (nasal swab) depending on the technique of sample collection, the site, and the phase of the disease (Wang, Kang, et al., 2020, Wang, Xu, et al., 2020, Wang, Yao, et al., 2020). PCR testing can have high false negatives during the asymptomatic period and may miss out people who do have the disease, who could potentially infect others with the false assumption that they are safe because the viral load in their body may be too low to be detected by the PCR tests. While PCR testing has a high specificity for SARS-CoV-2, the sensitivity depends on the timing of onset of symptoms (Pearl, 2019), the bodily fluid tested, and the assay used (Corbin et al., 2017; Vandenbroucke et al., 2020).

Although many PCR kits have been developed and used by the World Health Organization (WHO), the Centers for Disease Control (CDC), as well as many private companies, there are growing concerns about accuracy of the test results. For example, many false-negative results have been reported in China using PCR tests, at rates as high as 20%–40% despite onset of clinical symptoms. Hence, PCR test results must be interpreted carefully, as it has been proven that antibodies against SARS-CoVs are developed even by reduced amount of antigens in the body (Aziz et al., 2020). On the other hand, Enzyme-linked immunosorbent assay (ELISA) technology demonstrates high sensitivity and specificity for diagnosing COVID-19 antibodies, even among asymptomatic individuals (Nicol, 2020) but this also requires lengthy protocols and availability of expensive lab equipment (Augustine et al., 2020; Aziz et al., 2020). In comparison, serologic tests offer a more cost-effective approach for mass-level testing and screening, as they are portable point-of-care devices which can be used outside of laboratory or hospital settings.

It is clear that solely relying on PCR testing is insufficient to document the window of infections, as they only capture active infections, whereas antibody tests allow for identification of silent transmission of infections as asymptomatic cases do not go undetected (Augustine et al., 2020). This has important epidemiological implications for policy-makers in planning for crisis response. Given the limitations of PCR tests, random sampling has proved to be the ideal method of capturing the prevalence of infections in any country. Resource-constrained nations such as Pakistan often face logistical challenges such as limited hospital capacity, funding, and lack of a coordinated national response for crisis management. Hence to counter these issues, policy-makers often focus on directing resources toward increasing testing capacity for the most vulnerable populations who are at higher risk of contracting the disease, as well as those symptomatic cases who willingly present to facilities for testing (Vandenbroucke et al., 2020). Given that majority of people who present to facilities for testing would be those who are health conscious or are symptomatic, the COVID-19 cases reported in official government statistics would yield biased numbers as it cannot be categorized as a random sample. Hence we propose that randomized, mass-scale testing should be implemented to accurately trace the virus trends within the general population.

5. Serologic tests

In contrast to PCR tests, serologic tests rely upon on the qualitative detection of IgM and IgG generated by the body in response to an SARS-CoV-2 infection. IgM is usually the first antibody type generated by the body in response to a COVID-19 infection, followed by IgG which then replaces IgM as the predominant antibody in the blood. IgM and IgG combat infections by targeting specific antigens on the surface of the virus. Serologic antibody tests not only detect confirmed COVID-19 cases, they can also reveal asymptomatic carriers of the disease before they are aware that they are infected and actively spreading the infection to others around them. Research demonstrates that many asymptomatic carriers of COVID-19 infection may unwittingly spread the virus to more vulnerable members of society such as immunocompromised patients and people above 50 years of age as well as those with underlying chronic diseases (Wang, Kang, et al., 2020). Hence, antibody kits offer a reliable alternative to detecting COVID-19 infections which would otherwise not be detected by a PCR test when the viral load is low. This is because antibody kits depend upon detecting the response of the body rather than detecting the virus or antigen itself, which allows antibody kits to detect exposure to COVID-19 before the onset of symptoms (Javed et al., 2020). Moreover, seroprevalence studies can allow us to assess the prevalence of the disease rather than just the incidence as indicated through PCR testing of symptomatic individuals.

Serologic tests also provide results within 15 min, compared to PCR test results which can take up to 24–48 h after patient sample is taken. This faster turnaround time of results is crucial for tracking the transmissibility of COVID-19 among a population, so that policy measures can be implemented quickly to contain the outbreak. Therefore, widespread serologic testing is required to ensure that most of the population is screened for COVID-19, so the findings can then be used to better detect infection fatality rate and decide for public policy guidelines (Anguelov et al., 2020).

6. Insights from South Asia

Many countries in the developing world are currently facing large data deficits in terms of their official number of COVID-19 cases reported. Seroprevalence findings from a large-scale census conducted on a dense, urban, working population in Pakistan from April to July 2020 indicated that by July 6, 2020, 4.11 million people in Pakistan had been infected with COVID-19, which was 17.7 times higher than the official number of 231,818 symptom-based PCR cases reported by the government within the same time frame (Javed et al., 2020). This is because asymptomatic carriers of the virus had not been presenting at government-approved facilities for PCR tests; hence this testing methodology failed to capture the true prevalence of the disease within the Pakistani population. As a result, most asymptomatic carriers are underreported in official COVID-19 figures leading to vast gaps in the data. Given that Pakistan is facing an issue of limited testing capacity focused exclusively on symptom-based PCR tests, there is a need to conduct seroprevalence studies to determine the true extent of the disease via serologic tests.

At the same time, several questions arise regarding the varying incidence of disease between neighboring South Asian countries. While Pakistan fared better in terms of lower number of COVID-19 deaths, India's COVID-19 mortality rate was one of the highest in the world. Even after factoring in the differences in population density and geographical area, the mortality rate per million population in India is much higher compared to Pakistan. There are various reasons why our disease methodology is different from India's. It could be due to different immunity levels, varying testing methodology adopted, or different levels of exposure to the virus. The initial findings from the seroprevalence data in Pakistan show a high prevalence of humoral, adaptive immunity (specific to COVID-19 or cross-reactivity to previous SARS) in the Pakistani population, which is different from innate immunity.

7. Trace, test, and treat model of South Korea

South Korea led the way in implementing a unique COVID-19 testing model of contact tracing and mass screening, which enabled the country to curb the spread of infections without imposing a complete lockdown in all public spaces. This kind of pandemic response strategy was deemed as the most effective approach in slowing down the spread of the virus implemented by South Korea, followed by Singapore, Vietnam, and Taiwan. Mass screening was followed by isolating the infected individuals as well as contacts of positive cases. This was combined with redirecting resources toward increasing testing capacity, to ensure that asymptomatic cases do not go undiagnosed. South Korea's experience with the 2015 Middle East respiratory syndrome (MERS) led them to identify the need to implement a mass-screening model for early detection of COVID-19 cases among the asymptomatic population (Balilla, 2020). As a result, South Korea was one of the few countries which was able to identify the true prevalence of COVID-19 infections relatively earlier in the course of the pandemic compared to other nations.

Pakistan can benefit from the approach implemented by South Korea for tracing COVID-19 cases. Epidemiological analyses predict that the number of COVID-19 cases in Pakistan is manyfold higher than the official numbers reported by government statistics, which means that health-care facilities would be unable to cater to the sheer number of patients requiring urgent medical attention (Raza, 2020). Hence, we suggest that the mass testing and contact tracing approach should be followed for detection of asymptomatic cases, while isolating the most vulnerable members of the population, including people above 50 years of age as well as those with comorbidities.

8. Sero-prevalence findings from Pakistan

Although literature indicates that asymptomatic infections within a population may be manyfold higher than the number of PCR reported cases (Shakiba et al., 2020), large-scale, seroprevalence studies within low-risk populations have rarely been conducted in Pakistan. Hence, in order to expand the database of COVID-19 infections in the country, the first of its kind, mass-level (census) seroprevalence study was conducted on a random sample of 24,210

individuals from various workplaces in metropoles of Pakistan from April to July 2020. The seroprevalence study was conducted using USFDA EUA and CE approved serologic test kits with a sensitivity of 95.3% and specificity of 98.7% for IgG, and a sensitivity of 86.48% and specificity of 95.18% for IgM (Wanzhou et al., 2020), with a false-positive rate ranging from 2% to a maximum of 7% (Bendavid et al., 2020), due to nonspecific immunity and nonspecific protection to COVID-19. This indicates that serologic testing kits can effectively be used as cost-effective measures for conducting mass screening among asymptomatic individuals, who would otherwise not present at a government-approved PCR testing facility. Consequently, the official number of confirmed cases severely underrepresents the full extent of COVID-19, as they fail to capture the proportion of the population who are asymptomatic carriers and are actively spreading the infection to more vulnerable members of society.

In Pakistan, there is an urgent need to bridge the large data deficit between the actual numbers of COVID-19 cases using serologic tests, compared to only those individuals presenting to government-approved facilities for PCR testing. Given this gap in data, Pakistan's first 100% census seroprevalence study was conducted across various major cities of Pakistan using the IgG/IgM Test Kit (Colloidal gold) with follow-up and sequential testing after every 15–20 days (Javed et al., 2020). The sample size included an adult, working population aged 18–65 years, recruited from dense, urban workplaces including factories, corporates, restaurants, media houses, schools, banks, health-care providers in hospitals, and families of positive cases across various cities in Pakistan, including Karachi, Lahore, Multan, Peshawar, and Quetta (Javed et al., 2020). This was the first of its kind, large-scale, cross-sectional study conducted among the low-risk, urban, and working population. The seroprevalence study results showed both past and current COVID-19 infections within the study population. The results indicated that 90% of the sample which tested positive were asymptomatic carriers of the infection, who would otherwise have never presented for PCR testing at a government-approved facility and would have continued to spread the infection to others around them.

The study results revealed a total of 17.5% COVID-19 positive cases from a sample size of 24,210 individuals (Javed et al., 2020). Most of these included current infections at 11.5%, while 6% were past infections and had recovered. From the sample of 24,210 individuals recruited in the study, a total of 8937 registered employees were screened from factories and corporate offices, out of which 15.2% tested positive. Specifically, 7.2% tested IgM positive, while 4.8% tested IgG positive and 3.2% were combined IgM and IgG positive. "This prevalence can be extrapolated to the one million registered working population of Karachi, meaning at least 152,000 infected cases in Karachi alone, with 104,000 being exposed as of 6th July [sic] 2020, who were unaware and spreading infection to people around them" (Javed et al., 2020).

These findings can be applied to the remaining urban workforce of Pakistan with similar demographics, between the ages of 18–65 years. Given a base population of 61.7 million registered workers (Shaikh, 2019), within this age range, "assuming that 36% live in urban areas with similar workplace dynamics (22.21 million), it can be extrapolated that 4,110,381 (4.11 million) from the working population were infected with COVID-19 as of 6th July [sic] 2020" (Javed et al., 2020). Within the same time frame, the official statistics reported 1,420,623 (Ministry of National Health Services Regulations and Coordination, 2020) symptom-based COVID-19 tests across Pakistan. If these results are extrapolated to all tests

conducted on symptomatic individuals, given the false negativity of PCR especially when viral load is less and a 30% prevalence of test positivity among individuals who have symptoms, at least 426,187 people were infected with COVID-19 in Pakistan by July 6, 2020. "Overall, from a sample of 24,210 individuals screened, 17.5% tested positive, with 7% IgM positive, 6.0% IgG positive and 4.5% combined IgM and IgG positive. The study results revealed that if these findings were extrapolated to the rest of the urban, working population with similar demographics, 4.11 million individuals in Pakistan were infected with COVID-19 by 6th July [sic] 2020, as opposed to 231,818 cases quoted by the official figures" (Javed et al., 2020).

The seroprevalence study revealed groundbreaking results regarding the spread of COVID-19 infections within the Pakistani population. Results indicated that 90% of the population who tested COVID-19 positive (screened via serologic tests) were asymptomatic carriers of the disease, who would otherwise have not presented at a PCR testing facility due to their nonexistent or mild symptoms. This was the first of its kind, large-scale census conducted on the general, urban population of Pakistan, which indicated that the total number of COVID-19 positive cases is 17.7 times higher than symptom-based PCR reported figures. While the study showed "sero-prevalence of 17.5% at workplaces, the newly emergent cases at 6 weeks had an incidence rate of 7%" (Javed et al., 2020). These results have important implications for shaping the pandemic response policy in Pakistan, as it shows the prevalence of the disease to be manyfold higher than the official confirmed cases reported by government-approved facilities. Although the study results are restricted to Pakistan's dense, urban, adult, working population, it can still provide useful insights for formulating public health and policy guidelines. However, before the study results can be conclusive, there is a need to conduct a household, multistage, cluster random survey in order to find the true extent of COVID-19 in Pakistan.

Based on the results of this seroprevalence study, given that there are 535,914 confirmed COVID-19 cases reported in the official government statistics as of January 26, 2021, and a total of 7,722,829 tests conducted on symptomatic patients, we can extrapolate that currently 6.32 million individuals are infected with COVID-19 in Pakistan, which is 11.8 times higher than the numbers reported in the official statistics. Therefore, if a similar seroprevalence study is replicated keeping in mind the updated numbers of COVID-19 statistics as of January 26, 2021, it becomes clear that while the data deficit has reduced due to increased numbers of PCR tests being conducted in January 2021 compared to July 2020, there is still a large gap in the seroprevalence data which needs to be bridged in order to improve public policy guidelines.

9. Conclusion

While the highest burden of disease during the COVID-19 pandemic was initially observed in countries across Europe and North America, the rates of transmission rapidly increased in developing countries in South Asia over the course of the pandemic. At the same time, huge underreporting biases were witnessed especially in resource-constrained countries such as Pakistan, due to limited testing capacity and low number of tests conducted

per million population. Hence any epidemiological comparison between countries needs to take into account this systematic bias of underreported figures (Biswas et al., 2020), which would need to include data that go beyond the case count captured by official reports. If asymptomatic infections continue to go undetected by the diagnostic tools used by a country, this gap in data would reduce the effectiveness of crisis response policies developed (Anguelov et al., 2020).

Taking Pakistan as a case study for underreporting of COVID-19 cases, we propose that countries which use a synergistic model encompassing both PCR testing and mass-level screening via serologic test kits are better equipped to capture both the incidence as well as the prevalence of COVID-19. No effective strategy for curbing the spread of the virus can be formulated without access to authentic data on the disease burden; hence the mass-screening model allows even asymptomatic carriers of the virus to be identified which will help in designing better epidemiological models and allow for efficient policymaking decisions on a national level.

While most countries initially focused on a purely symptom-based approach for detecting COVID-19 cases, evidence shows that asymptomatic cases are likely to constitute a major proportion of all infections, especially among the younger population demographic in South Asian countries (Anguelov et al., 2020). Knowing the ratio of symptomatic to asymptomatic infections is a critical factor which defines the kind of pandemic response policy undertaken by a country, and would therefore allow early detection and action toward curbing the spread of the disease (Anguelov et al., 2020). Hence, an approach which combines PCR testing as well as mass-level screening within a government framework can ensure that better public policy guidelines are implemented to curtail the spread of the virus. Employing large-scale testing to trace and isolate asymptomatic cases who might unknowingly pass the virus to more vulnerable members of the population has proved to be a vital strategy in containing the spread of infections. Compared to all other COVID-19 diagnostic tools, serologic tests are deemed as the most cost-effective model of mass-screening. This approach also takes into account the fact that developing countries such as Pakistan have lower income per capita compared to developed nations; therefore we cannot use a cost-intensive model for diagnosis, but rather a more affordable point-of-care model that was successfully employed by South Korea, China, and Taiwan.

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