Review Article

An Outlook on the COVID-19 Infection Magnitude in Pakistan and Potential Factors Contributing to Low Mortality Rates

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Abstract

Background: COVID-19 has severely affected some countries with a high mortality rate than others. In Pakistan, its mortality rate is lower (2.06%) than neighboring countries and even economically advanced countries. Here we discuss the distinct characteristic of the Pakistani population that might have contributed to this lower mortality.

Methods: COVID-19 mortality data were collected from December, 2019 to July, 2020 and studied for population age spectrum, health facilities, immunization profiles, physical activity, and obesity from Pakistan and other countries.

Results: Lower COVID-19 related mortality rate was observed in Pakistan (2.06%) as compared to France (18.02%), Italy (14.45%), UK (14.01%), Spain (9.56%), the USA (4.71%), and Iran (4.77%). Small proportion (3.5%) of the elderly population (>65 years of age), exposure to different viral antigens, a higher rate of BCG vaccination, better physical activity practices, and lower obesity prevalence in Pakistani population as compared European and North American population may contribute to lower COVID-19 related mortality rate.

Conclusions: Multiple factors may have contributed to this lower mortality rate in Pakistan. Our observations may facilitate clinicians to identify individuals who may have low risk to COVID-19 related deaths. Comrehensive studies are warrented to address it further.

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Introduction:

Several epidemics in the past two decades have been caused by the viruses of the family Coronaviridae; Severe Acute Respiratory Syndrome (SARS) in China in 2002 and 2003, and the Middle East Respiratory Syndrome (MERS) in the Middle East in 2012. The disease caused by SARS Coronavirus 2 (SARS-CoV-2) is the most recent outbreak that originated in Wuhan, China, in December 2019 and presented with severe pneumonia of unknown origin. World Health Organization (WHO) named this novel Coronavirus disease 2019 as "COVID-19" on February 11, 2020. Soon it got spread across the world and on March 11, 2020, WHO declared it a pandemic and advised the precautionary strategies[1-3].

The SARS-CoV-2 has emerged as the most infectious human Coronavirus[4]. It primarily spreads through infectious respiratory droplets and affects alveolar cells. The virus enters host cells through its spike protein by binding to Angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 receptors are present on several human cells including multiple epithelial cell types across the respiratory tract, macrophages, alveolar epithelial type II cells in the parenchyma, pneumocytes,

and intestine cells[5-7]. After it enters the cells, the viral RNA and proteins multiply and assemble into new viral particles that leave the cells via exocytosis and infect other cells[8]. The viral production stresses the endoplasmic reticulum that leads to cell death. However, the underlying mechanism of infection is still unknown[7].

COVID-19 is a highly contagious disease and difficult to control because the infectious agent (SARS-CoV-2) has a reproductive rate (R_0) as high as 7[9] and a short incubation period of 5-6 days (WHO). The incubation period can differ amongst individuals and the difference in viral load reflects in the varying time required for the presentation of symptoms. The clinical spectrum of COVID-19 ranges from mild symptoms which could be handled at home, to severe lung disease which could be managed at the hospital with/without ventilator assistance. About 80% of the patients remain asymptomatic or develop mild symptoms. Initially, the virus affects respiratory epithelial and alveolar cells, later it may spread to the digestive tract. This virus may also affect the urogenital, central nervous, and circulatory systems[10]. The damage to lung cells reduces the pulmonary surfactant production that causes acute respiratory distress syndrome (ARDS); characterized by rapid onset of widespread inflammation in the lungs, leading to inefficient gaseous exchange across the surface and eventually cellular death. The severity of the infection and duration of the incubation period may depend upon several factors such as immunological strength, age, and prevailing health conditions.

COVID-19 mortality rates

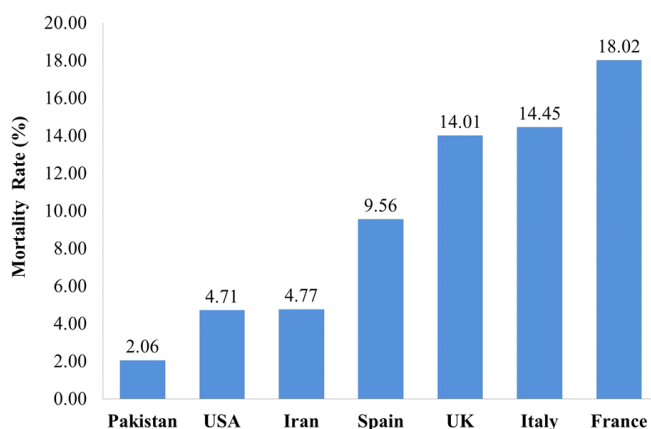COVID-19 mortality rates in countries from Europe,

North America, and Asia were obtained from various databases[11-13] (Figure1). Selected countries from Europe (UK, France, Spain, and Italy) and North America (USA) have reported more causalities than those from Asia (Pakistan and Iran), from December 2019 to July 2020. Higher mortality rates are noted in France (18.02%), Italy (14.45%), and UK (14.01%) than in Pakistan (2.06%) and Iran (4.77%).

Figure 2 shows the pattern of COVID-19 mortality rates for the initial 14 weeks from the first reported case in these selected countries. Low mortality rates after 4 weeks of this outbreak were noted in Italy (6.81%), Spain (3.07%), France (1.69%), and the UK (0.48%). However, these rates rose significantly after 8 weeks (12.79%, 10.19%, 11.02%, and 12.46% respectively). Whereas a high mortality rate was reported in the USA (17.14%) after 4 weeks, and later it decreased after 8 weeks (2.62%). This change in the pattern of mortality rates can be accredited to government policies and pub-
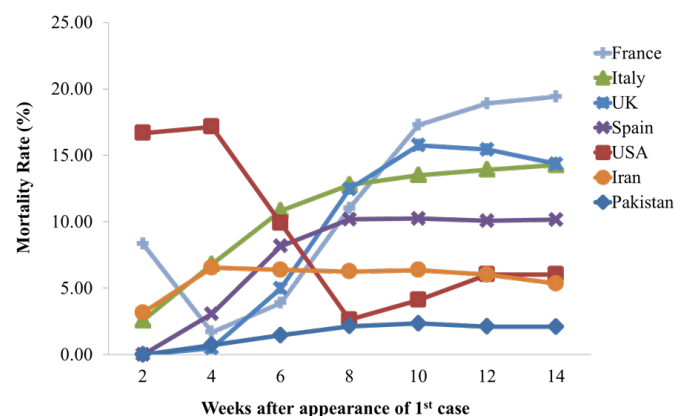

Figure 2: *Pattern of COVID-19 mortality rates for the initial 14 weeks in selected countries from Europe, North America, and Asia[11-13].*

lic attitudes towards the disease. Pakistan had a lower mortality rate as compared to these countries throughout the pandemic, regardless of the increase in the number of cases.

A potential association between COVID-19 mortality and healthcare resource availability is recently reported[14]. UK, France, Spain, Italy, and the USA have more advanced healthcare systems than Pakistan. However, this disparity in the healthcare system does not explain the low COVID-19 related mortality rate in Pakistan. Here, we discuss potential reasons for this low mortality rate in Pakistan.

Figure 1: *COVID-19 associated mortality rates in selected countries from Europe, North America, and Asia[11].*

Factors that may contribute to lower COVID-19 mortality in Pakistan

On June 18, 2020, 160,118 COVID-19 cases were reported in Pakistan and 158,641 in France. Of these cases, COVID-19 associated deaths were 3,093 in Pakistan and 29,603 in France[11]. Despite having an equal number of COVID-19 cases in both countries, Pakistan had ~10 times lower mortality rate than France. A comparison of pattern and outcome of COVID-19 in Pakistan and its neighboring countries reported the lowest case fatality rates (proportion of deaths amongst symptomatic cases within a defined population) in Pakistan (2.1%) than Iran (6.1%), China (5.5%), India (3.3%), and Afghanistan (2.6%)[15]. Mortality analysis of COVID-19 first 100 deaths in the Pakistani population showed that the majority of these individuals were males (75%), within the age group of 60-69 years and hypertension was the most frequent comorbidity (67%)[16]. Since no vaccines or therapeutic agents are available for COVID-19 infected cases, this lower mortality in Pakistan can be attributed to inherent factors such as population age spectrum, general immunity of the population against antigens, genetics, and immunological differences.

1. Population age spectrum

Age matters in the development or progression of any disease because it affects significantly the immune system. The immune system of elderly people slowly responds due to loss of immune cells, thymus degeneration, lower receptor variety on lymphocytes, and lesser cell-to-cell communications leading to delayed response[17,18]. Aged people also produce a more severe inflammatory response for increased concentration of pro-inflammatory cytokines such as tumor necrosis factor and may develop autoimmune disorders[19]. Therefore, elderly people are more vulnerable to any infection than adults[20,21].

Several comorbidities of increasing age are obesity, diabetes, hypertension, and heart diseases. These complications occur because of several underlying factors that can lead to immune system dysfunction, which further increases susceptibility to infections[22]. The risk of severe illness from COVID-19 may also increase with age[12]. Older people are most vulnerable to COVID-19 infection and have a high mortality risk.

Studies showed that the population age spectrum may explain the variations in mortality across countries. A substantial proportion of the population is above the age of 65 years in Italy (22.6%), the UK (18.2%), Spain (19.4%), and the USA (15.8%). Conversely, a very small proportion (3.5%) of the Pakistani population falls in this old age category (Figure 3). A recent meta-analysis also reported a significant association between older age ($\geq$ 65 years) and high mortality risk from COVID-19 infection[23]. Taken together, a relatively smaller proportion of the Pakistani population is at high mortality risk for COVID-19 infection and this is could be a reason for low mortality in Pakistan.
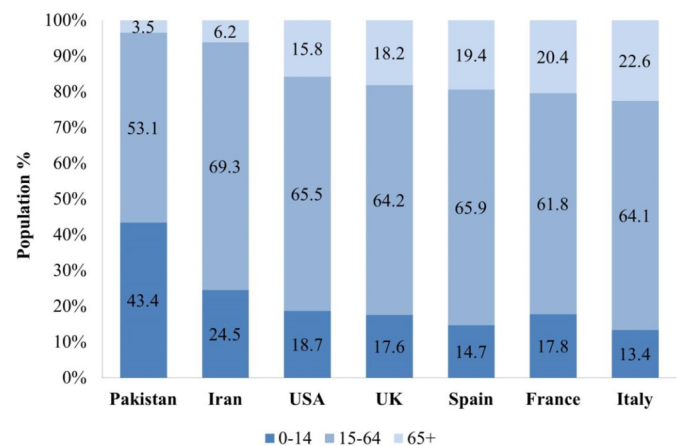

Figure 3: *Population age spectrum in selected countries from Europe, North America, and Asia*[15,24].

2. Differences in immune landscape

Immunity is a multifaceted phenomenon and depends upon several factors including earlier pathogens exposure, nutrition, vaccination, age, gut microflora, environmental, and heredity factors[25-27]. Innate immunity develops rapidly and is crucial for the detection and elimination of pathogens in the early stages of life. Adaptive immunity develops slowly by the interplay between T and B lymphocytes. Upon exposure to a new antigen, the receptors on B and T cells rearrange and generate a diverse stock of receptors capable of identifying potential pathogens and get rid of them 28. The diversity of antigenic exposure strengthens adaptive immunity.

The climatic conditions in Pakistan are temperate and the various seasonal deviations support the growth of diverse microbial species. The majority of the Pakistani population is infected with some microbial/infectious diseases during their lifetimes such as flu, cholera,

typhoid fever, malaria, dysentery, diphtheria, whooping cough, tetanus, mumps, measles, smallpox, and viral hepatitis[24]. This diverse antigen exposure may trigger the immune response to generate lymphocytes and increase the infection-fighting capabilities of the body. The overall exposure of the Pakistani population to infectious disease is higher than other populations from the USA, the UK, France, Italy, and Spain 29. This may have contributed to higher immunity in the Pakistani population. The better sanitary conditions and a hygienic lifestyle may have influenced lesser adaptive immunity in developed countries.

Different diseases are reported to have disproportionate effects on different populations[30,31,32,33]. The genetic variability may lead to a difference in the immune system factors deployed against a pathogenic attack. This difference in the immunological landscape could be one of the potential reasons for the Pakistani population to show a better immunological response and lower mortality against COVID-19 than the USA, UK, France, Italy, and Spain.

3. Cross-protection upon vaccination

Each country develops vaccine programs based on prevalent antigens and related diseases. Bacillus Calmette-Guerin (BGC), Oral Polio Vaccine (OPV), Inactivated Polio Vaccine (IPV), Rotavirus vaccine, Pneumococcal vaccine, and Measles vaccine are commonly offered in Pakistan[34]. The government of Pakistan administers these vaccines within 15 months after birth under the "Expanded Programme on Immunisation" (http://www.epi.gov.pk/immunisation-schedule/).

BCG is a live attenuated vaccine and induces nonspecific cross-protection against pathogens[35]. BCG-vaccinated individuals showed a reduced risk of developing acute lower respiratory tract infections as compared to non-vaccinated ones[36]. An association between BCG administration and reduced COVID-19 related mortality is reported[37]. Lower mortality rates are observed in countries with universal and long-standing BCG administration policies than those with no universal BCG policy. Pakistan has over 90% coverage of this vaccine[38]. This might have influenced the lower mortality rates in Pakistan than in developed countries where tuberculosis is not a common disease.

4. Physical activity

Regular physical activities have a profound effect on the immune system[39]. Exercise enhances immune surveillance because it makes substantial hemodynamic changes e.g. increases in cardiac output, vasodilation, and blood flow[40]. Regular exercise may help combat the disease by boosting immune systems and preventing comorbidities (obesity, diabetes, hypertension, and heart diseases)[41]. Exercise mobilizes the immune cells, enhances immune surveillance, and reduces the chance of pathogens to cause disease. Other benefits of exercise include immune cell metabolic reprogramming and anti-inflammatory signaling[42].

People with physical activities and tough routine life are generally observed to be less affected by infection because of their active immune system[43]. Lack of physical activity or a sedentary lifestyle can make a person more susceptible to COVID-19 related complications. Figure 4 demonstrates the comparison between various countries[44]. The arduous lifestyle has helped the Pakistani population in developing an agile immune system which could be a contributing factor in lower COVID-19 related deaths in the country.
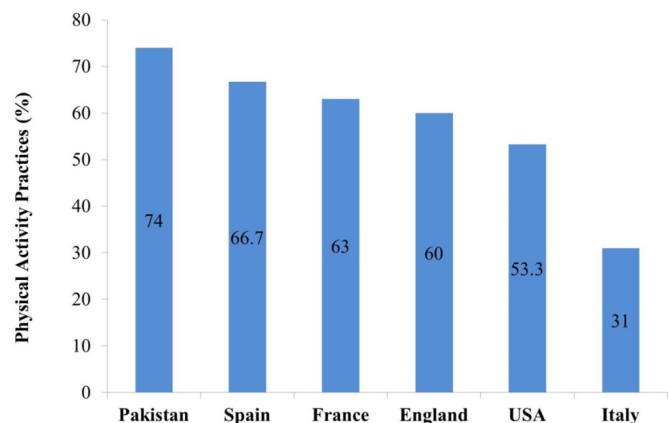

Figure 4: *Physical activity practices in selected countries from Europe, North America, and Asia (https://www.euro.who.int/en/health-topics/disease-prevention/physical-activity/data-and-statistics/physical-activity-fact-sheets).*

5. Obesity

Obesity is a serious health issue worldwide. European and American populations have a significantly higher prevalence of obesity than the Pakistani population 45 (Figure 5). Low socioeconomic conditions can attribute to this in the Pakistani population. This imparts a

laborious lifestyle, hence lower obesity prevalence.

Obesity affects pulmonary functions and decreases expiratory reserve volume and lung functional capacity 46. It increases the severity of viral respiratory infections; Influenza A and H1N1. By analogy to these viral respiratory infections in the past, obesity plays an important role in COVID-19 transmission and severity 47. As obesity increases the risk of developing COVID-19 infection 48, it may also increase the risk of COVID-19 related mortality. However, the association between obesity and the disease is still unclear.
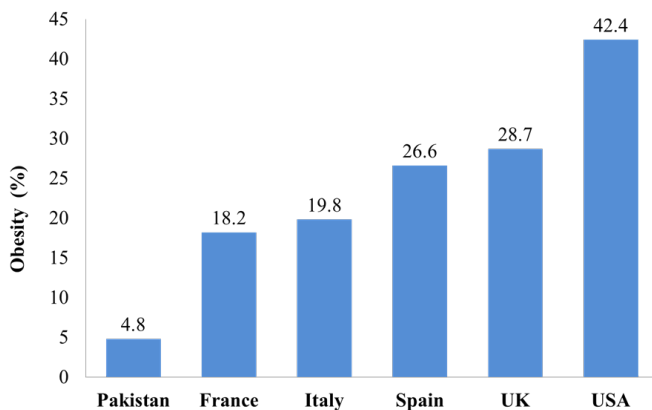

Figure 5: *Prevalence of obesity in selected countries from Europe, North America, and Asia (WHO).*

6- Hypertension medication

Hypertension is a common disease worldwide. Angiotensin Receptor Blockers (ARBs) and ACE inhibitors (ACE-Is) are commonly used for the treatment of hypertension worldwide. ARBs also show a protective effect against inflammation[49] and protect the lungs from severe acute respiratory syndromes, including those caused by a coronavirus[50]. As ARBs block the ACE receptors, fewer binding sites will be available to the SARS-CoV-2 virus and therefore the severity of the infection will be less in hypertensive patients taking these drugs[51]. A hospital-based study on hypertensive COVID-19 infected patients demonstrated that ACE-Is or ARB usage is linked with lower mortality risk in comparison to non-users[52].

7. Herd immunity

The development of immunity against a viral pathogen is a complex multi-step process. Initially, the body acts against the virus by the non-specific innate response. It is followed by an adaptive immune response, where the body produces specific antibodies against the viral pathogen. If both responses are strong enough, they may prevent progression to severe illness and may even prevent it from causing symptoms. It can also prevent re-infection from the same virus[53]. The development of immunity can be measured by the presence of specific antibodies in the blood.

The concept of herd immunity states; if a threshold of population inhabitants achieves immunity against the disease; it breaks the chain of transmission. This threshold depends upon the basic reproductive rate (R_0) of the virus. The R_0 value for SARS-CoV-2 varies from 2 to 7 in different countries. Assuming, an R_0 estimate of 3, the herd immunity threshold will be $\sim$ 67% of the population. This suggests that the infection will decline once the proportion of individuals with gained immunity to SARS-CoV-2 in the population exceeds 0.67[9].

The National Institute of Blood Diseases Pakistan has claimed that Pakistan is moving towards achieving herd immunity against SARS-CoV-2 (www.thenews.com.pk /print/690377, July 22, 2020). Pakistani population is effectively fighting against the disease and the impact is being observed in the COVID-19 positivity rate daily (number of confirmed cases divided by the number of tests) which has dropped to 8.6% on July 20, 2020, from 22.4% reported on June 4, 2020,[15]. This may be attributed to the aforementioned factors. Further, Pakistan has not imposed a complete lockdown at any stage of this pandemic. The first COVID-19 case in Pakistan was reported on February 26, 2020. By that time, Pakistan had already started taking precautionary measures due to serious conditions in neighboring countries, China and Iran. Instead of complete lockdown, the Pakistani government opted for social distancing and smart lockdown policy, in which the areas with a higher number of cases were sealed whereas other areas were open with restricted movement and precautionary measures. Due to which the asymptomatic patients had been in contact with healthy individuals, promoting viral propagation in the population. The preliminary results of a study by the National Institute of Blood Diseases, Pakistan show 40% of the Karachi (Pakistan) population has developed antibodies against SARS-CoV-2. Hence, the Pakistani population may develop herd

immunity soon.

It is worth mentioning here, that the observations made in this review are based on First; the data about overall mortality or case fatality rates (proportion of deaths amongst symptomatic cases) were compared. The infection fatality rate (proportion of deaths among the infected individuals) is still unknown. However, the infection fatality rate is likely to be lower than case fatality rates. Second; Higher mortality rates are noted among elderly individuals with several comorbidities worldwide, hence, it is difficult to comment whether these individuals died with COVID-19 or died from COVID-19. Third; Several individuals may have died in their homes without any report of being infected. Therefore, one needs to be cautious while interpreting these findings due to the above observations. A futuristic approach can be to collect the annual death rates data in each of these countries and then measure the excess deaths observed in 2020 as COVID-19 related mortality.

Conclusion:

Coronaviruses have caused epidemics earlier and recently COVID-19 has emerged as a pandemic worldwide. This infectious agent (SARS-CoV-2) is highly contagious, spread before an individual develops symptoms, and caused high morbidity worldwide. Pakistan, despite having less advanced health care systems, suffered significantly lower fatalities than many countries. Multiple factors may have contributed to this lower mortality rate, including a lower proportion of the elderly population than western countries, immunological differences, vaccination, sufficient physical activity, and lower obesity prevalence. These population dynamics might have helped in better survival against the infection. Our observations may facilitate clinicians to identify individuals who may have low risk to COVID-19 related deaths. Comrehensive studies are warrented to address it further.

Acknowledgments:

References:

1. Ramadan N, Shaib H. Middle East respiratory syndrome coronavirus (MERS-CoV): A review. Germs. 2019; 9(1):35-42. doi: 10.18683/germs.2019.1155.

2. Deng SQ, Peng HJ. Characteristics of and public health responses to the coronavirus disease 2019 outbreak in China. J Clin Med 2020; 9(2):575. doi: 10.3390/jcm9020575.

3. Dhama K, Sharun K, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaicumpa W, Bonilla-Aldana DK, Rodriguez-Morales AJ. Coronavirus disease 2019–COVID-19. Clin Microbiol Rev 2020; 33(4):e00028-20. doi: 10.1128/CMR.00028-20.

4. Paules CI, Marston HD, Fauci AS. Coronavirus infections—more than just the common cold. JAMA 2020; 323(8):707-708. doi: 10.1001/jama.2020.0757.

5. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun 2020; 526(1):135-140. doi: 10.1016/j.bbrc.2020.03.044.

6. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med 2020; 14(2):185-192. doi: 10.1007/s11684-020-0754-0.

7. Boopathi S, Poma AB, Kolandaivel P. Novel 2019 coronavirus structure, mechanism of action, antiviral drug promises and rule out against its treatment. J Biomol Struct Dyn 2020; 1-10. doi: 10.1080/07391102.2020.1758788.

8. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14(8):523. doi: 10.1038/nrmicro.2016.81.

9. Randolph HE, Barreiro LB. Herd Immunity: Understanding COVID-19. Immunity 2020;

52(5):737-41. doi: 10.1016/j.immuni.2020.04.012.

10. Zhang Y, Geng X, Tan Y, Li Q, Xu C, Xu J, et al. New understanding of the damage of SARS-CoV-2 infection outside the respiratory system. Biomed Pharmacother 2020; 110195. doi: 10.1016/j.biopha.2020.110195.

11. Worldometer. (n.d.). Current world population. Retrieved January 16, 2020, from https://www.worldometers.info/

12. Centers for Disease Control and Prevention (2020). Coronavirus Disease 2019 (COVID-19).Retrieved from https://www.cdc.gov/coronavirus/2019-ncov/index.html

13. Government of Pakistan, COVID-19 database. Retrieved from https://covid.gov.pk/stats/pakistan

14. Ji Y, Ma Z, Peppelenbosch MP, Pan Q. Potential association between COVID-19 mortality and health-care resource availability. Lancet Glob Health 2020; 8(4):e480. doi: 10.1016/S2214-109X(20)30068-1.

15. Roser M, Ritchie H, Ortiz-Ospina E, Hasell J. "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. 2020; Retrieved from: 'https://ourworldindata.org/coronavirus'

16. Chaudhry A, Ikram A, Baig MA, Salman M, Ghafoor T, Hussain Z, et al. Mortality Analysis of COVID-19 Confirmed cases in Pakistan. MedRxiv 2020; doi: 10.1101/2020.06.07.20121939.

17. Goronzy JJ, Weyand CM. Ageing, autoimmunity and arthritis: T-cell senescence and contraction of T-cell repertoire diversity–catalysts of autoimmunity and chronic inflammation. Arthritis Res Ther 2003; 5:225. doi: 10.1186/ar974.

18. Qi Q, Liu Y, Cheng Y, Glanville J, Zhang D, Lee J-Y, et al. Diversity and clonal selection in the human T-cell repertoire. Proc Natl Acad Sci USA 2014; 111(36):13139-44. doi: 10.1073/pnas.1409155111.

19. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, et al. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc 2013; 14(12):877-82. doi: 10.1016/j.jamda.2013.05.009.

20. Dowling DJ, Levy O. Ontogeny of early life immunity. Trends Immunol 2014; 35:299-310. doi: 10.1016/j.it.2014.04.007.

21. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 2015; 282:20143085. doi: 10.1098/rspb.2014.3085.

22. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: JACC health promotion series. J Am Coll Cardiol 2018; 72(14):1622-39. doi: 10.1016/j.jacc.2018.08.2141.

23. Parohan M, Yaghoubi S, Seraji A, Javanbakht MH, Sarraf P, Djalali M. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. Aging Male 2020; 1-9. doi: 10.1080/13685538.2020.1774748.

24. Government of Pakistan, Pakistan Bureau of Statistics 2020. Retrieved from www.pbs.gov.pk/

25. Schmid-Hempel P. Variation in immune defence as a question of evolutionary ecology. Proc Biol Sci 2003;270:357-66. doi: 10.1098/rspb.2002.2265.

26. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R. Bacterial community variation in human body habitats across space and time. Science 2009; 326:1694-7. doi: 10.1126/science.1177486.

27. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell 2012; 148(6):1258-70. doi: 10.1016/j.cell.2012.01.035.

28. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immunol 2010; 125(2):S33-S40. doi: 10.1016/j.jaci.2009.09.017.

29. Roome T, Khan S. Communicable infections in Pakistan: a battle to confront. J Dow Uni Health Sci 2014; 8(2): 41-42.

30. Dowd JB, Palermo T, Chyu L, Adam E, McDade TW. Race/ethnic and socioeconomic differences in stress and immune function in The National Longitudinal Study of Adolescent Health. Soc Sci

Med 2014; 115:49-55. doi: 10.1016/j.socscimed. 2014.06.011.

31. Nédélec Y, Sanz J, Baharian G, Szpiech ZA, Pacis A, Dumaine A, et al. Genetic ancestry and natural selection drive population differences in immune responses to pathogens. Cell 2016; 167(3):657-669.e21. doi: 10.1016/j.cell.2016.09.025.

32. Hayward JA, Tachedjian M, Cui J, Cheng AZ, Johnson A, Baker ML, et al. Differential evolution of antiretroviral restriction factors in pteropid bats as revealed by APOBEC3 gene complexity. Mol Biol Evol 2018; 35(7):1626-37. doi: 10.1093/molbev/msy048.

33. Coussens LM, Zitvogel L, Palucka AK. Neutra-lizing tumor-promoting chronic inflammation: a magic bullet? Science 2013; 339:286-91. doi: 10.1126/science.1232227.

34. Government of Pakistan, Expanded program on immunization 2020. Retrieved from http://www.epi.gov.pk/immunisation-schedule/

35. Covián C, Fernández-Fierro A, Retamal-Díaz A, Díaz FE, VASQUEZ AE, Lay MK-L, et al. BCG-induced cross-protection and development of trai-ned immunity. Implication for vaccine design. Fro-nt Immunol 2019; 10:2806. doi: 10.3389/fimmu.2019.02806.

36. Stensballe LG, Nante E, Jensen IP, Kofoed P-E, Poulsen A, Jensen H, et al. Acute lower respiratory tract infections and respiratory syncytial virus in infants in Guinea-Bissau: a beneficial effect of BCG vaccination for girls: community based case–control study. Vaccine 2005; 23(10):1251-7. doi: 10.1016/j.vaccine.2004.09.006.

37. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. Med Rxiv 2020. doi: 10.1101/2020.03.24.20042937.

38. Iqbal NT, Hussain R. Non-specific immunity of BCG vaccine: a perspective of BCG immunothe-rapy. Trials Vaccinol 2014; 3:143-9. doi: 10.1016/j.trivac.2014.08.002.

39. Shephard RJ. Development of the discipline of exercise immunology. Exerc Immunol Rev 2010; 16:194-222. PMID: 20839500.

40. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the regulation of immune functions. Prog Mol Biol Transl Sci 2015; 135:355-80. doi: 10.1016/bs.pmbts.2015.08.001.

41. Jakobsson J, Malm C, Furberg M, Ekelund U, Svensson M. Physical Activity During the Coronavirus (COVID-19) Pandemic: Prevention of a Decline in Metabolic and Immunological Fun-ctions. Front Sports Act Living 2020; 2:57. doi: 10.3389/fspor.2020.00057.

42. Campbell JP, Turner JE. Debunking the myth of exercise-induced immune suppression: redefining the impact of exercise on immunological health across the lifespan. Front Immunol 2018; 9:648. doi: 10.3389/fimmu.2018.00648.

43. Romeo J, Wärnberg J, Pozo T, Marcos A. Physical activity, immunity and infection. Proc Nutr Soc 2010; 69:390-9. doi: 10.1017/S0029665110001795.

44. Dietz W, Santos-Burgoa C. Obesity and its Impli-cations for COVID-19 Mortality. Obesity 2020; 28(6):1005. doi: 10.1002/oby.22818.

45. World Health organization, Obesity and overweight 2020. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

46. Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev 2020; 21(6). doi; 10.1111/obr.13034.

47. Cai Q, Chen F, Wang T, Luo F, Liu X, Wu Q, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Diabetes Care 2020; 43(7): 1392-1398. doi: 10.2337/dc20-0576.

48. Gao F, Zheng KI, Wang X-B, Sun Q-F, Pan K-H, Wang T-Y, et al. Obesity is a risk factor for greater COVID-19 severity. Diabetes Care 2020; 43(7):e72-e74. doi: 10.2337/dc20-0682.

49. De Araújo L, Nagaoka M, Borges D, Kouyoumdjian M. Participation of hepatic α/β-adrenoceptors and AT1 receptors in glucose release and portal hypertensive response induced by

adrenaline or angiotensin II. Braz J Med Biol Res 2018; 51(12). doi: 10.1590/1414-431X20187526.

50. Saavedra JM. COVID-19, angiotensin receptor blockers, and the brain. Cell Mol Neurobiol 2020; 40(5):667-674. doi: 10.1007/s10571-020-00861-y.

51. Rico-Mesa JS, White A, Anderson AS. Outcomes in patients with COVID-19 infection taking ACEI/ARB. Curr Cardiol Rep 2020; 22:1-4. doi: 10.1007/s11886-020-01291-4.

52. Peng Y, Meng K, Guan H, Leng L, Zhu R, Wang B, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020; 48:E004-E. doi: 10.3760/cma.j.cn112148-20200220-00105.

53. WHO Coronavirus (COVID-19) Dashboard 2020. Retrieved from https://covid19.who.int/