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.

Brain, Behavior, and Immunity xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

One size does not fit all – Patterns of vulnerability and resilience in the COVID-19 pandemic and why heterogeneity of disease matters

Luba Sominsky[a,*], David W. Walker[a], Sarah J. Spencer[a,b]

[a] School of Health and Biomedical Sciences, RMIT University, Melbourne, VIC, Australia
[b] ARC Centre of Excellence for Nanoscale Biophotonics, RMIT University, Melbourne, VIC, Australia

A new decade has started with the emergence of a novel zoonotic coronavirus, now termed COVID-19, and also known as 2019-nCoV or severe acute respiratory syndrome coronavirus (SARS)-CoV-2 (Zhu et al., 2020). Originating in December 2019 in Wuhan, Hubei province, China, with a cluster of patients presenting with pneumonia, COVID-19 has quickly spread not only throughout China, but also throughout the world. As of March 11, 2020, with nearly 125,000 cases and more than 4000 fatalities in 118 countries and territories, COVID-19 has been declared as a pandemic by the World Health Organisation (WHO) (WHO, 2020b, March 11).

1. Who is (not) getting sick and why is this important

Of the six previously known coronavirus species, only two other strains – SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) – are zoonotic in origin and have been associated with high risk of severe outcomes and mortality, estimated at case-fatality ratio of approximately 11% and 34%, respectively (WHO, 2003, 2019). Similar to SARS-CoV and MERS-CoV, COVID-19 causes respiratory symptoms that are often severe, with current estimates of case-fatality ratio of 3%-4%, although lower estimates should be considered as more global information comes into light (Wilson et al., 2020). While the epidemiology of COVID-19 still unravels and much remains to be learnt, what already appears to be unusual in the case of this and other coronaviruses, is the population at risk. While the most vulnerable population to suffer severe outcomes of respiratory viruses other than coronaviruses are typically older adults, people suffering from chronic medical conditions, and children, in the case of COVID-19 there have so far been no fatalities in children aged 0–9 years of age in China. The disease incidence in children also seems to be lower than in the rest of the population; estimated at 2.4% of all reported cases in people under the age of 18, according to the WHO-China Joint Mission report based on 55,924 laboratory-confirmed cases (WHO, 2020a). Preliminary statistics from Italy's outbreak of COVID-19, currently the second most affected country outside of China with the highest case-fatality ratio to date of approximately 7%, similarly suggest children are not likely to be at high risk of severe disease (EpiCentro, 2020). It appears that COVID-19 infections in children have occurred during the early stages of the pandemic (Liu et al., 2020), but they are reported with less frequency and children do not become as sick.

Although the current pandemic is arguably too new to have produced reliable statistics on population demographics on the world stage, the emerging pattern of resilience to severe outcomes of COVID-19 in children is puzzling considering what we know of other viruses, such as influenza and measles. In the case of influenza, children aged < 5 years are more likely to suffer severe outcomes of both seasonal and pandemic influenza (Ruf and Knuf, 2014). Unvaccinated young children are also at highest risk of measles and its severe outcomes, including death (Lo Vecchio et al., 2019). However, SARS-CoV, MERS-CoV, and now COVID-19 are strikingly less common and less severe in children than in adults (Zimmermann and Curtis, 2020). It is likely that a milder representation of the disease in young children results in decreased reporting and testing, thus leading to under-sampling and the possibility that disease incidence is similar in children to adults (Dong et al., 2020). However, this potential under-sampling in itself points to a decreased illness severity and an overall resilience to the disease in children.

Several reasons have been proposed to try and explain this resilience, one of which is a potential for certain immunity due to the commonality of other human coronaviruses in children (Zhang et al., 2018). This reasoning, however, does not explain why the elderly who are also at high risk of infection with human coronaviruses, are not immune. Another potential reason for decreased severity of the disease in children is that pre-existing chronic medical conditions such as cardiovascular diseases may predispose adults to more severe outcomes (Guan et al., 2020; Wu and McGoogan, 2020). In this regard, angiotensin-converting enzyme 2 (ACE2) that plays role in cardiovascular disease, has been identified as a functional receptor of SARS-CoV and SARS-CoV-2 (Wrapp et al., 2020), and its potential immaturity in children has been proposed to underlie the reduced disease severity (Dong et al., 2020), but there is currently no supporting evidence to substantiate this claim. There is also a possibility that differences in the maturity of the immune system underlie the different immune responses to an infection. As such, activation of the innate immune

* Corresponding author.
E-mail address: luba.sominsky@rmit.edu.au (L. Sominsky).

https://doi.org/10.1016/j.bbi.2020.03.016
Received 18 March 2020; Accepted 18 March 2020
0889-1591/

system in the early phase of SARS-CoV infection has an important role in the control viral replication (Chen et al., 2010). In the elderly, the innate immune system is less efficient and its ability to respond to infections is diminished, resulting in greater vulnerability of older adults to severe outcomes of infectious diseases (Boe et al., 2017). It is thus plausible that the immune system in the young is more effective in responding to COVID-19, reducing its severity. However, neither of these possibilities really explain why children seem relatively immune (or at least resilient) to COVID-19 but not to influenza or measles and this question is essential to answer. This apparent resilience of children to COVID-19 brings up important ideas that are necessary for the research and medical communities to properly address, and not only in relation to the current pandemic. One is that responses to disease are heterogeneous within a population. Two is that we should be exploiting the causes of this heterogeneity to help patients recover more quickly.

2. One size does not fit all

The idea that responses to disease are heterogeneous within a population is well-acknowledged in the epidemiological community. However, is not one that is particularly well integrated in basic biomedical science research. For decades, if not centuries now, fundamental science has worked with the broad assumption that male mouse and rat models of young-adult age in the absence of a life history of neuroimmune challenge (Pittman, 2019) are necessary and sufficient to understand all of mammalian physiology.

We also routinely work with how a treatment affects the mean response of a population. Admittedly, there are numerous road blocks to approaching things differently. There is significant cost in both monetary terms and in time in assessing an outcome in both sexes at various stages of hormonal peaks at multiple ages across the lifespan and on the background of a wealth of life experiences. The logistics of “thinking outside the mean” are also complicated and costly. An individual response well-outside the mean could indicate that this single animal or human patient holds the cure to the next viral outbreak, or could just indicate pipetting error or a random variation that is physiologically meaningless for a workable part of the population. The latter issue indicates a particular importance of rigorous statistical approaches in the analysis of our own scientific work and in the assessment of work by others (Makin and Orban de Xivry, 2019). A limited sample-size, for instance, may be insufficient to provide valuable information in some cases, but may shed light on critical details in other circumstances when the sample is inherently limited. With appropriate experimental and statistical controls in place, it is therefore essential to start focusing on individual populations of vulnerability and resilience.

In addition to children, pregnant women also represent a vulnerable population at risk for viral infections, with increased risk of complications in influenza, including the 2009 influenza H1N1 pandemic (Siston et al., 2010), varicella virus, measles and the severe foetal consequences of Zika virus (reviewed in (Racicot and Mor, 2017)). Interestingly, and in line with the pattern of COVID-19 producing milder symptoms in children, there is currently no evidence for increased risk of severe outcomes of COVID-19 in pregnant women. We should note, though, that this evidence is based on limited data, while reports from SARS-CoV, MERS-CoV and from other respiratory infections suggest these conclusions are premature and pregnant women could be at risk of a severe course of COVID-19 (Rasmussen et al., 2020). If, however, pregnancy proves to provide some protection from disease severity, it could offer unique opportunities for the development of therapeutic solutions. It would also be essential to see whether COVID-19 during pregnancy has longer-term implications for the offspring, similar to neurodevelopmental impacts of maternal influenza and other infections (Meyer et al., 2007).

As mentioned above, the elderly and those suffering from chronic medical conditions are also at high risk of severe disease outcomes, and, as such, the unique characteristics of these populations should always be considered when attempting to extrapolate scientific discoveries and their therapeutic applications. This approach is at the heart of a personalised (individualised) medicine approach, where patients’ therapies are targeted based on their genetic differences, along with their unique lifestyles and other environmental factors (Conti et al., 2010). The current COVID-19 pandemic and its epidemiology is yet another reminder there is no ‘one size fits all’ when it comes to all aspects of scientific research, including experimental design, statistical analyses and therapeutic implications.

3. Conclusions on COVID-19 for the psychoneuroimmunology community

A major focus of the field of psychoneuroimmunology is on understanding disease vulnerability and resilience throughout the lifespan. The emerging epidemiology of COVID-19 indicates distinct effects of age on disease severity. While the global research community is focusing now on finding the ways to halt the spread of the virus and prevent its reoccurrence, this pandemic is an important reminder to all biomedical scientists of the wide implications their research may have. To deliver replicable, translatable and robust outcomes, we must consider the heterogeneity of a disease in a population, and to capitalise on both vulnerability and resilience in our search for basic mechanisms and for clinically-relevant health applications.

Acknowledgement

SJS was supported by funding from a National Health and Medical Research Council Career Development Fellowship II (APP1128646).

References

Boe, D.M., Boule, L.A., Kovacs, E.J., 2017. Innate immune responses in the ageing lung. Clin. Exp. Immunol. 187, 16–25.

Chen, J., Lau, Y.F., Lamirande, E.W., Paddock, C.D., Bartlett, J.H., Zaki, S.R., Subbarao, K., 2010. Cellular immune responses to severe acute respiratory syndrome coronavirus (SARS-CoV) infection in senescent BALB/c mice: CD4+ T cells are important in control of SARS-CoV infection. J. Virol. 84, 1289–1301.

Conti, R., Veenstra, D.L., Armstrong, K., Lesko, L.J., Grosse, S.D., 2010. Personalized medicine and genomics: challenges and opportunities in assessing effectiveness, cost-effectiveness, and future research priorities. Med. Decis. Making 30, 328–340.

Dong, Y., Mo, X., Hu, Y., Qi, X., Jiang, F., Jiang, Z., Tong, S., 2020. Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China, e20200702.

EpiCentro, I.S.d.S., 2020. Epidemia COVID-19, Aggiornamento nazionale 12 marzo 2020. Available online at: https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_12-marzo-2020.pdf.

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S.C., Du, B., Li, L.J., Zeng, G., Yuen, K.Y., Chen, R.C., Tang, C.L., Wang, T., Chen, P.Y., Xiang, J., Li, S.Y., Wang, J.L., Liang, Z.J., Peng, Y.X., Wei, L., Liu, Y., Hu, Y.H., Peng, P., Wang, J.M., Liu, J.Y., Chen, Z., Li, G., Zheng, Z.J., Qiu, S.Q., Luo, J., Ye, C.J., Zhu, S.Y., Zhong, N.S., China Medical Treatment Expert Group for, C., 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med.

Liu, W., Zhang, Q., Chen, J., Xiang, R., Song, H., Shu, S., Chen, L., Liang, L., Zhou, J., You, L., Wu, P., Zhang, B., Lu, Y., Xia, L., Huang, L., Yang, Y., Liu, F., Semple, M.G., Cowling, B.J., Lan, K., Sun, Z., Yu, H., Liu, Y., 2020. Detection of Covid-19 in Children in Early January 2020 in Wuhan, China. N. Engl. J. Med.

Lo Vecchio, A., Krzysztofiak, A., Montagnani, C., Valentini, P., Rossi, N., Garazzino, S., Raffaldi, I., Di Gangi, M., Esposito, S., Vecchi, B., Melzi, M.L., Lanari, M., Zavarise, G., Bosis, S., Valenzise, M., Cazzato, S., Sacco, M., Govoni, M.R., Mozzo, E., Cambriglia, M.D., Bruzzese, E., Di Camillo, C., Pata, D., Graziosi, A., Sala, D., Magurano, F., Villani, A., Guarino, A., Galli, L., Group, S.M.S., 2019. Complications and risk factors for severe outcome in children with measles. Arch Dis Child.

Makin, T.R., Orban de Xivry, J.J., 2019. Ten common statistical mistakes to watch out for when writing or reviewing a manuscript. Elife 8.

Meyer, U., Yee, B.K., Feldon, J., 2007. The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? Neuroscientist 13, 241–256.

Pittman, Q.J., 2019. How to make a better mouse for brain behavior and immunity. Brain Behav. Immun. 76, 1–2.

Racicot, K., Mor, G., 2017. Risks associated with viral infections during pregnancy. J. Clin. Invest. 127, 1591–1599.

Rasmussen, Sonja A., Smulian, John C., Lednicky, John A., Wen, Tony S., Jamieson, Denise J., 2020. Coronavirus disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. American Journal of Obstetrics and Gynecology. https://doi.org/10.1016/j.ajog.2020.02.017.

Ruf, B.R., Knuf, M., 2014. The burden of seasonal and pandemic influenza in infants and children. Eur. J. Pediatr. 173, 265–276.

Siston, A.M., Rasmussen, S.A., Honein, M.A., Fry, A.M., Seib, K., Callaghan, W.M., Louie, J., Doyle, T.J., Crockett, M., Lynfield, R., Moore, Z., Wiedeman, C., Anand, M., Tabony, L., Nielsen, C.F., Waller, K., Page, S., Thompson, J.M., Avery, C., Springs, C.B., Jones, T., Williams, J.L., Newsome, K., Finelli, L., Jamieson, D.J., Pandemic H1N1 Influenza in Pregnancy Working Group, 2010. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. JAMA 303, 1517–1525.

WHO, 2003. World Health, Organization – Consensus Document on the Epidemiology of Severe Acute Respiratory Syndrome (SARS). World Health Organization, Geneva.

WHO, 2019. World Health Organization - MERS-CoV situation update from the Eastern Mediterranean Region. Available online at:. World Health Organization. http://applications.emro.who.int/docs/EMRPUB-CSR-241-2019-EN.pdf.

WHO, 2020. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) Available online at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.

WHO, 2020, March 11. World Health Organization, Coronavirus disease 2019 (COVID-19) Situation Report – 51. World Health Organization.

Wilson, N., Kvalsvig, A., Barnard, L.T., Baker, M.G., 2020. Case-fatality risk estimates for COVID-19 calculated by using a lag time for fatality. Emerg. Infect. Dis. 26.

Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S., McLellan, J.S., 2020. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 367, 1260–1263.

Wu, Z., McGoogan, J.M., 2020. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA.

Zhang, S.F., Tuo, J.L., Huang, X.B., Zhu, X., Zhang, D.M., Zhou, K., Yuan, L., Luo, H.J., Zheng, B.J., Yuen, K.Y., Li, M.F., Cao, K.Y., Xu, L., 2018. Epidemiology characteristics of human coronaviruses in patients with respiratory infection symptoms and phylogenetic analysis of HCoV-OC43 during 2010–2015 in Guangzhou. PLoS ONE 13, e0191789.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu Gao, G.G.F., Tan, W., China Novel Coronavirus Research, 2020. A novel coronavirus from patients with pneumonia in China, 2019. N. Engl. J. Med. 382, 727–733.

Zimmermann, P., Curtis, N., 2020. Coronavirus infections in children including COVID-19: an overview of the epidemiology, clinical features, diagnosis, treatment and prevention options in. Children Online First.