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.

Medical Hypotheses 144 (2020) 110238

Contents lists available at ScienceDirect

Medical Hypotheses

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

Letter to Editors

Second wave of Covid-19 is determined by immune mechanism

ARTICLE INFO

Keywords:
Covid-19
Innate immunity
Epidemic curve

ABSTRACT

A second wave of new severe acute respiratory syndrome coronavirus 2 (Covid-19) cases is widely feared. In fact resurgence of cases has been clearly observed in several countries that had seen flattening of the epidemic curve. In general, relaxation of community control measures is almost always blamed for the resurgence of cases. In this letter, the author describes an immunological explanation for the double-peaked epidemic curve of new viral diseases including Covid-19. According to this hypothesis, a second wave of cases is due to the effective innate immunity in some of the population. These individuals may later develop clinical disease upon repeated exposure. This theory claims that a double-peaked pattern of new cases in a new viral epidemic is intrinsically determined by the pattern of pathogen interaction with the host. According to this hypothesis, relaxation of the community control measures is not responsible; at least in part, for resurgence of cases.

There has been a great concern over resurgence of covid-19 cases among communities. Fears over a “second wave” of the pandemic are wide spread. A double-peaked epidemic curve has been reported in the famous “Spanish flu” pandemic [1]. In the current Covid-19 pandemic, a recurring rise of the incidence rate has been observed in several countries. In Japan, a crisp two-peak incidence curve is clear [2]. Similar trends are reported from other countries.

The notion of epidemics that normally have two peaks of new cases over time is widely accepted [3]; although epidemiologists have not characterized this pattern as an established model. In general, the resumption of international travel or the relaxation of the community control measures are almost always blamed for the resurgence of the disease incidence.

In this letter, this author suggests that a double-peaked epidemic curve is an intrinsic feature of viral outbreaks. According to this hypothesis, immune response to viral exposure in different individuals determines the spread pattern in the community.

The two principal divisions of the immune response to pathogens are the innate and the adaptive immunity. Both divisions play a major role in the body response to viral exposure. Innate immune response includes natural killer (NK) cells, complement and interferon systems of proteins and the immunoglobulin A (IgA) secreted in several body fluids [4–6]. Adequate innate immune response may clear the virus at the point of entry. On the contrary, adaptive immune response requires initial viral replication. Intracellular viral particles are presented to $CD8^+$ T lymphocytes in conjunction with class-I MHC antigens. Consequently, virus-specific cytotoxic $CD8^+$ T lymphocytes develop and expand in a monoclonal population. Both effective and memory cells develop during this process.

Healthy individuals who are exposed to a minor viral load potentially clear the virus at the point of entry. According to this assumption, a viremic stage is aborted and an adaptive immune response does not developed. In such a case, immune evasion [5] does not occur. Such individuals do not have adequate memory cell population and remain susceptible to repeat infection. On the contrary, individuals who passed through a viremia stage possibly pass into a clinical or subclinical infection which entails the development of an adaptive immune response and the generation of memory cells. These individuals potentially develop protective immunity; the effectiveness of which is beyond the scope of this letter.

The current hypothesis presumes the presence of a sector in the community of healthy individuals who have the effective innate immune machinery to clear the virus at the point of entry in the respiratory tract. With continued societal activity, these individuals are repeatedly exposed to a new viral inoculation each time they socially interact with undiagnosed patients or carriers. Each exposure poses a binomial risk of developing a clinical disease because one exposure does not grant any degree of immunity against future exposures. With the passage of time, the probability of getting a clinical disease state increases as the number of independent exposures increases.

On a community level, exposed individuals can be categorized into two classes. People who clear the virus at the point of entry will not develop an adaptive immune response to any significant degree. The pattern of disease in this particular sector is one of slow steady accumulation of new cases over long time. The second class of people are those who experience a viremic stage upon a single incidence or a few times of virus exposure. Together with the development of clonal virus-specific $CD8^+$ T lymphocytes, these individuals will experience subclinical or clinical viral illness and are responsible for the early rise in the epidemic curve.

Assuming the above hypothesis is true; a viral epidemic curve will show an early upstroke corresponding to persons who pass into viremia upon initial exposure to the virus followed by a second slower rise due to cases who develop the disease after repeated process of inoculation and clearance at the point of entry. It is fairly reasonable to assume that the latter group of patients may be the healthier individuals who will have lower case-fatality rate. Together with the notion of the covid-19 cases getting milder with time, objective evidence from Japan indicates that the second peak in incidence is not accompanied with a corresponding peak in fatality [2].

The implications of this hypothesis are medically and socially relevant. According to this theory, resurgence of a viral outbreak is

https://doi.org/10.1016/j.mehy.2020.110238
Received 1 August 2020; Received in revised form 18 August 2020; Accepted 30 August 2020
Available online 02 September 2020

intrinsically determined by the nature of the virus interaction with the host. Relaxation of the community measures or “reopening” of the economy may not be blamed for a second rise in incidence rates. The theory also provides one explanation for the possible observation of decreased case-fatality over time.

In conclusion, the author describes an immunological explanation for a double-peaked epidemic curve of Covid-19 and other new viral diseases.

Declaration of Competing Interest

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Martini M, Gazzaniga V, Bragazzi NL, Barberis I. The Spanish Influenza Pandemic: a lesson from history 100 years after 1918. J Preventive Med Hygiene 2019;60(1):E64–7.
[2] WHO coronavirus disease (COVID-19) dashboard. Geneva: World health organization; 2020 [1 August 2020]; Available from: https://covid19.who.int/region/wpro/country/jp.
[3] Xu S, Li Y. Beware of the second wave of COVID-19. Lancet (London, England) 2020;395(10233):1321–2.
[4] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate. Immunity 2006;124(4):783–801.
[5] Lei X, Dong X, Ma R, Wang W, Xiao X, Tian Z, et al. Activation and evasion of type I interferon responses by SARS-CoV-2. 2020;11(1):3810.
[6] Zielecki F, Weber M, Eickmann M, Spiegelberg L, Zaki AM, Matrosovich M, et al. Human cell tropism and innate immune system interactions of human respiratory coronavirus EMC compared to those of severe acute respiratory syndrome coronavirus. J Virol 2013;87(9):5300–4.

Osama Hussein*
Surgery Department, Mansoura University Oncology Center, Egypt
E-mail address: osamahussein@mans.edu.eg.

* Address: Mansoura University Oncology Center, Mansoura 35516, Egypt.