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Highlights

What we have learned from COVID-19 pandemic?

Dynamic COVID-19 pandemic with evolution of viral variants

The emerging outbreak SARS-CoV-2 infection that had been reported in Wuhan since December 1st, 2019[1,2] has caused unprecedented COVID-19 pandemic after the century of 1918 Influenza pandemic.[3] Like 1918 influenza pandemic, the sequelae of COVID-19 are so pervasive as to affect all aspects of life including health, economics, finances, education, politics, business, and social activities globally.[4] More importantly, COVID-19 pandemic is intractable to be prevented because of high dynamic and capricious biological property characterized by several surges of pandemic with emerging viral variants evolving from the wild type descended from the original outbreak in China, the D614G mutant preponderating in the first surge of pandemic around the Europe,[5] the B.1.1.7 mutant circulating in UK responsible for the second surge and third surge[6,7] until P.1.5.3. and P1 from African and Brazil, respectively,[8–10] that would probably contribute to the third and fourth surge of ongoing pandemic. The evolution of viral variants of SARS-CoV-2 occurring in successive surges of COVID-19 pandemic have further proved the high possibility that the occurrence of second and third surge of influenza pandemic was mainly due to the emerging mutants as well although the official name of virus had not been ascertained at that time until 1940.[11,12]

It is now difficult to be sure of whether the viral variants of influenza causing the second and third surge of pandemic were more transmissible and more likely to predispose infected individual to have severe disease than the wild type responsible for the first surge in 1918 but the empirical data on COVID-19 pandemic in 2020 have shown such a tendency of higher transmission and severer disease as proven in this special issue using the epidemic model and big data analytics. Due to the evolution of viral variant, it is imperative to elucidate how COVID-19 pandemic was transmitted from the initial outbreak of SARS-CoV-2 from Wuhan, China to inter-continental and global transmission evolving from first to third surge of COVID-19 pandemic.

Regarding the mode of transmission, although both infectious diseases are pandemic global transmission routes and types of cluster infection for further causing community-acquired outbreaks in 1918 at War I would be completely different from the corresponding issues in 2020 featuring with high profiles of international connections on all aspects of life. Cluster infections in 1918 were widely seen in barracks due to the War I whereas those occurring in COVID-19 pandemic have been seen in a variety of public gatherings.[3] Compared with 1918 influenza pandemic, the evolution of cluster infections into large-scale community-acquired outbreaks in COVID-19 pandemic becomes more complex and may need to develop new epidemic methods and approaches to model various kinds of cluster infections like household, cruise ship, religion gathering, recreation center and so on, and also various extents of community-acquired outbreaks at country and global scale.

Progressive property of multistate COVID-19 associated with treatment and medical capacity

In addition to learning contact and transmission model on population level from SARS-CoV-2 infection, the unique feature of COVID-19 disease on individual level is pertaining to its progressive property from mild, moderate, and severe form until death or recovery, which is not only determined by treatment modality but also subject to individual immune response.[13,14] However, the extent of severity and the corresponding treatment modalities following clinical guideline would affect the allocation of hospital beds and intensive care (ICU) beds.

The clinical progression of COVID-19 can be classified into the risk states of low (no and low oxygen supplement), medium- (non-invasive ventilator and high oxygen supplement), and high- (ECMO and invasive ventilator) risk states until the outcomes of recovery or death.[15] While the

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medical care of oxygen supplement is sufficient low- and medium-risk patients, intensive care is required for patients at high risk state. Moreover, therapies should be tailored by these risk states to have optimal outcomes. For the low- and medium-risk patients, antiviral therapies such as remdesivir is required to reduce viral load. For high-risk patients, anti-inflammatory therapies such as dexamethasone plays major role in modulating the immune response to reduce the severity of cytokine storm.[13,16,17] How to provide clinical management model for the optimal allocation of medical capacity should be learned from the country experiencing in early period of COVID-19 pandemic such as Italy in order not to collapse health and medical care system.

Beside the concern over medical capacity, whether it is effective to provide the optimal care and treatment for different severity of COVID-19 disease to reduce deaths from COVID-19 and accelerate the recovery need to be evaluated. In addition to standard care following clinical guideline, a series of randomized controlled trial have been conducted to demonstrate how to improve effectiveness using antiviral therapy compared with standard care.[16–22] However, these randomized controlled trials may throw light on whether the antiviral therapy of interest is effective in treating COVID-19 but may not elucidate how it works in reducing deaths and facilitating recovery. So doing requires a better understanding of natural disease progression of COVID-19 until death and recovery on individual level. The better use of the control group derived from a series of randomized controlled trials may form the comparator for evaluating the efficacy of anti-viral therapy, using the severity of COVID-19 disease as a surrogate endpoint, playing the complementary role with the results based on randomized controlled trials.

Containment measures of infection control over COVID-19

As far as containment measures are concerned, although NPIs like lockdown, isolation, and quarantine had been already operated in 1918 these measures used in COVID-19 pandemic are more diversified and may vary with time, place, and population. Moreover, evaluation of the effectiveness of these NPIs may need to take into account different scenarios from low-risk infection area such as Taiwan to high-risk infection area such as the countries with explosive epidemics.

The NPIs from the conventional approaches of quarantine and isolation to the lockdown at different scale have been implemented in the epicenter of first pandemic period in China.[23] With the propagation of COVID-19 pandemic, the NPI of lockdown has also been used to contain the outbreak in countries such as Italy and USA.[24–26] Stemming from this ultimate form of NPIs, a series of containment measures including the conventional approach of border control involved with quarantine and isolation, restriction on mass gathering, closure of school, limitation on medical accessibility, and ban on a series of social activities have been implemented to reduce the risk of clustered events and community-acquired outbreak. The effectiveness of these NPIs in reducing reproductive number of COVID-19 by 17.5% to more than 35% were estimated, depending on the extent of its implementation.[27]

Although NPIs have been proved as effective measures in containing the spread of COVID-19, the societal and economic impact incurred by these containment measures render its implementation a difficult decision. For a better understanding of the effectiveness of NPIs to reach an informed decision making, scenarios taking into account the combination of a series of NPIs and the force of COVID-19 transmission in community is required. In addition to the implementation of NPIs for containing COVID-19, vaccination against SARS-CoV-2 infection and anti-viral therapy for treating COVID-19 cannot be overemphasized.

Systematic approaches to elucidate and evaluate COVID-19 pandemic and interventions

In spite of numerous researches on COVID-19 published previously, there is short of serials articles that are offered for studying all of lessons learning from COVID-19 pandemic indicated above by giving a global and dynamic epidemiological profile of COVID-19 pandemic from the origin of outbreaks to recent surge of pandemic, a panorama lens for analyzing and evaluating relevant containment measures and vaccine, and economic consideration of the impacts of COVID-19 and evaluation of relevant interventions. Neither is a special issue to enshrine all relevant contexts into a unified framework covering (1) natural infectious process resulting from the spread and transmission of SARS-CoV-2 and the disease progression after onset of symptoms; (2) containment measures on NPIs, vaccine, and antiviral therapy for the alteration of natural course from infection to disease; (3) evidence-based evaluation of all these interventions; and (4) economic evaluation of interventions and of global burden of COVID-19.

The authors began with a historical overview of 1918 influenza pandemic in contrast to the current COVID-19 pandemic with respect to the origin of outbreak, the chronological order on a series of surges of pandemic, and successive pandemics after 1918 with different subtypes of influenza contrasted with two kinships of SARS-CoV-2, SARS and MERS, before COVID-19 pandemic. Such a comparison prompts and inspires all of authors involved in this special to propose a comprehensive study framework for navigating how to integrate four parts with each other to give a concise review of each theme as seen in the accompanying article in this special issue.

Evidence-based findings from transmission to disease and prevention of COVID-19 pandemic

Based on the proposed study framework and the concise overview, this special issue produces ten corresponding original articles providing evidence-based findings on each of theme. This special issue provides a new insight into the new patterns of household infection, cluster infection, and new patterns of community-acquired outbreaks in parallel with the evolution of viral on the spread of SARS-CoV-2, which had heralded from the original outbreak in China until evolved into three surges of pandemic contained by effective NPIs implemented in 2020, and vaccine uptake from 2021 onwards. Based on Taiwan data, the risk of household infection as high as 44.4% in the year 2020. This figure increased to 58.3% in the second surge of pandemic period of the year 2021, most likely due to the introduction of B.1.1.7 viral variant.

Most importantly, these ten original articles provide a new insight into a series of new findings on emerging infectious disease revealing from COVID-19 pandemic after the application of epidemic modelling and big data analytics to data on COVID-19 pandemic from January 2020 to April 2021 to decipher the patterns of COVID-19 transmission across global countries and regions. On the basis of the case load of COVID-19 and time for containing epidemic, those patterns of outbreaks in global countries and areas were categorized into five categories, labelled as

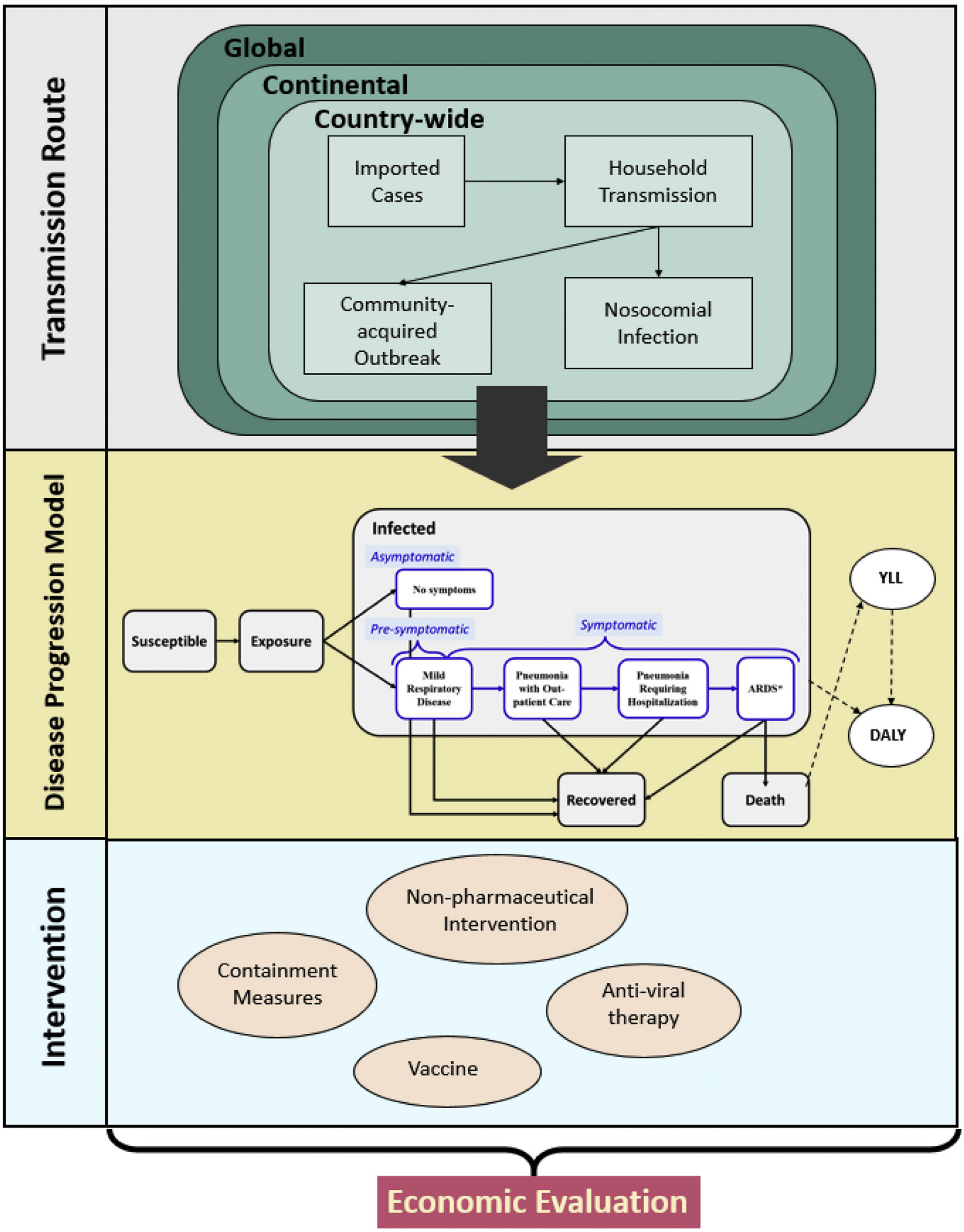

Figure 1 Systematic framework for studying emerging infectious disease on COVID-19.

"controlled epidemic", "mutant propagated epidemic", "propagated epidemic", "persistent epidemic" and "long persistent epidemic" after taking into account the time required to contain the outbreak. Such a classification will be helpful in assessing the overall effectiveness implemented in each countries and area and shed light on the timing of lifting social distancing.

The measures for the containment of COVID-19 outbreak including a series of NPIs, such as border control, lockdown, quarantine and isolation, social distancing, and mitigation strategies. On the basis of reported COVID-19 cases in Italy and Israel, a computer simulation deign was applied to assess the NPIs required to contain the outbreak in different pandemic periods. Support by the empirical data, the extent of isolation and quarantine up to 90% is required to curb the epidemic curve. For the scenario of vaccination distribution, the confinement measures of 17% can reach the goal of containing outbreak.

In addition to the dynamics of COVID-19 transmission in population, the clinical evolution of COVID-19 in respect to a continuum of disease spectrum till recovery and death was elucidated in this special issue. By using the COVID-19 disease progression model, a quantitative index was developed to inform the optimal medical resource allocation for caring and triaging COVID-19 patients.

On the basis of the COVID-19 clinical course, the efficacy of antiviral therapy and the needs of medical care were evaluated. The economical appraisal on the impact of COVID-19 and the mass vaccination programs for the COVID-19 pandemic was assessed. By applying a Bayesian sequential synthesis design to integrate the information of observational study and randomized controlled study, the significant efficacy of remdesivir therapy in reducing the risk of COVID-19 death and increasing the odds of discharge by 31% and 10% were estimated.

The vaccination distribution has been a major public health strategy for the containment of COVID-19 pandemic since the end of 2020. Focusing on three major vaccines, AZD1222, mRNA-1273, and BNT162b2, this special issue assessed the cost-utility and cost-benefit of this strategy. The results show that with vaccination distribution up to 70% coverage, the mass vaccination strategy was demonstrated to dominate no vaccination in spite of the type of vaccine was used. The results of cost-benefit analysis suggest that investing USD $1 earlier in vaccine may return hundreds of USD$ when value of statistical life was taken into account.

Given the great impact of COVID-19 pandemic on human society that have taken place for more than a year, its global burden was assessed by translating into economic measurement in this special issue. This disease burden of COVID-19 was estimated as US$591 billion and US$2368 billion based on Hedonic wage method and contingent valuation method, respectively. A large variation on the impact of COVID-19 across countries and areas under different Human Development Index ranging from US$0.001 billion to US$691.4 billion was observed. This variation was further elucidated by using a machine learning categorization in this special issue.

In summary, we propose a systematic framework and evidence-based evaluation for emerging infectious disease based on real world data learning from COVID-19 pandemic after the century of 1918 influenza pandemic as shown in Fig. 1 in this special issue. All contexts of this special issue not only build up a benchmark for elucidating transmission route and disease progression of such a high contagious emerging infection disease but also provide evidence-based approaches and findings for guiding and navigating policy-making on containing pandemic given a panorama profile including epidemic, disease progression, clinical management and treatment, medical capacity for accommodating surges of pandemic, economic evaluation of intervention, and global burden of disease.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;**382**:1708—20.
2. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;**382**:1199—207.
3. Morens DM, Taubenberger JK, Fauci AS. A Centenary tale of two pandemics: the 1918 influenza pandemic and COVID-19, Part I. *Am J Publ Health* 2021;**111**(6):1086—94.
4. Barro RJ, Ursúa JF, Weng J. The coronavirus and the great influenza pandemic: lessons from the "Spanish flu" for the coronavirus's potential effects on mortality and economic activity. *NBER Work Pap* 2020:w26866. Available at: http://www.nber.org/papers/w26866.
5. European Center for Disease Prevention and Control (ECDC). *Risk related to spread of new SARS-CoV-2 variants of concern in the EU/EEA 2020*. Available at: https://www.sanitainformazione.it/wp-content/uploads/2020/12/valutazione-del-rischio.pdf.
6. Funk T, Pharris A, Spiteri G, Bundle N, Melidou A, Carr M, et al. Characteristics of SARS-CoV-2 variants of concern B. 1.1. 7, B. 1.351 or P. 1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. *Euro Surveill* 2021;**26**(16):2100348.
7. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B. 1.1. 7 in England. *Science* 2021;(6538):372.
8. Mascola JR, Graham BS, Fauci AS. SARS-CoV-2 viral variants—tackling a moving target. *J Am Med Assoc* 2021;**325**(13):1261—2.
9. Triggle CR, Bansal D, Ding H, Islam MM, Farag EABA, Hadi HA, et al. A comprehensive review of viral characteristics, transmission, pathophysiology, immune response, and management of SARS-CoV-2 and COVID-19 as a basis for controlling the pandemic. *Front Immunol* 2021;**12**:631139.
10. Eurosurveillance Editorial Team. Updated rapid risk assessment from ECDC on the risk related to the spread of new SARS-CoV-2 variants of concern in the EU/EEA—first update. *Euro Surveill* 2021;**26**(3):2101211.
11. Taubenberger JK. The origin and virulence of the 1918 "Spanish" influenza virus. *Proc Am Phil Soc* 2006;**150**(1):86.
12. Barclay W, Openshaw P. The 1918 Influenza Pandemic: one hundred years of progress, but where now? *Lancet Respir Med* 2018;**6**(8):588—9.
13. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. *N Engl J Med* 2020;**383**:1757—66.
14. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al. Immunology of COVID-19: current state of the science. *Immunity* 2020;**52**(6):910—41.
15. World Health Organization. *WHO R&D blueprint novel Coronavirus: COVID-19 therapeutic trial synopsis*. Geneva, Switzerland: World Health Organization; 2020. Available from:

https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis.
16. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med* 2020;**383**(19):1813—26.
17. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *J Am Med Assoc* 2020;**324**(13):1307—16.
18. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;**382**:1787—99.
19. Chen CP, Lin YC, Chen TC, Tseng TY, Wong HL, Kuo CY, et al. A multicenter, randomized, open-label, controlled trial to evaluate the efficacy and tolerability of hydroxychloroquine and a retrospective study in adult patients with mild to moderate coronavirus disease 2019 (COVID-19). *PloS One* 2020;**15**:e0242763.
20. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med* 2020;**383**:2030—40.
21. Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: a randomized-controlled trial. *Clin Infect Dis* 2020:ciaa1009.
22. Omrani AS, Pathan SA, Thomas SA, Harris TRE, Coyle PV, Thomas CE, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. *EClinicalMedicine* 2020;**29**:100645.
23. Lau H, Khosrawipour V, Kocbach P, Mikolajczyk A, Schubert J, Bania J, et al. The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China. *J Trav Med* 2020;**27**(3):taaa037.
24. Bertuzzo E, Mari L, Pasetto D, Miccoli S, Casagrandi R, Gatto M, et al. The geography of COVID-19 spread in Italy and implications for the relaxation of confinement measures. *Nat Commun* 2020;**11**:4264.
25. Ren X. Pandemic and lockdown: a territorial approach to COVID-19 in China, Italy and the United States. *Eurasian Geogr Econ* 2020;**61**(4—5):423—34.
26. Gatto M, Bertuzzo E, Mari L, Miccoli S, Carraro L, Casagrandi R, et al. Spread and dynamics of the COVID-19 epidemic in Italy: effects of emergency containment measures. *Proc Natl Acad Sci USA* 2020;**117**:10484—91.
27. Brauner JM, Mindermann S, Sharma M, Johnston D, Salvatier J, Gavenčiak T et al. Inferring the effectiveness of government interventions against COVID-19. Science 2021; 371(6531).

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