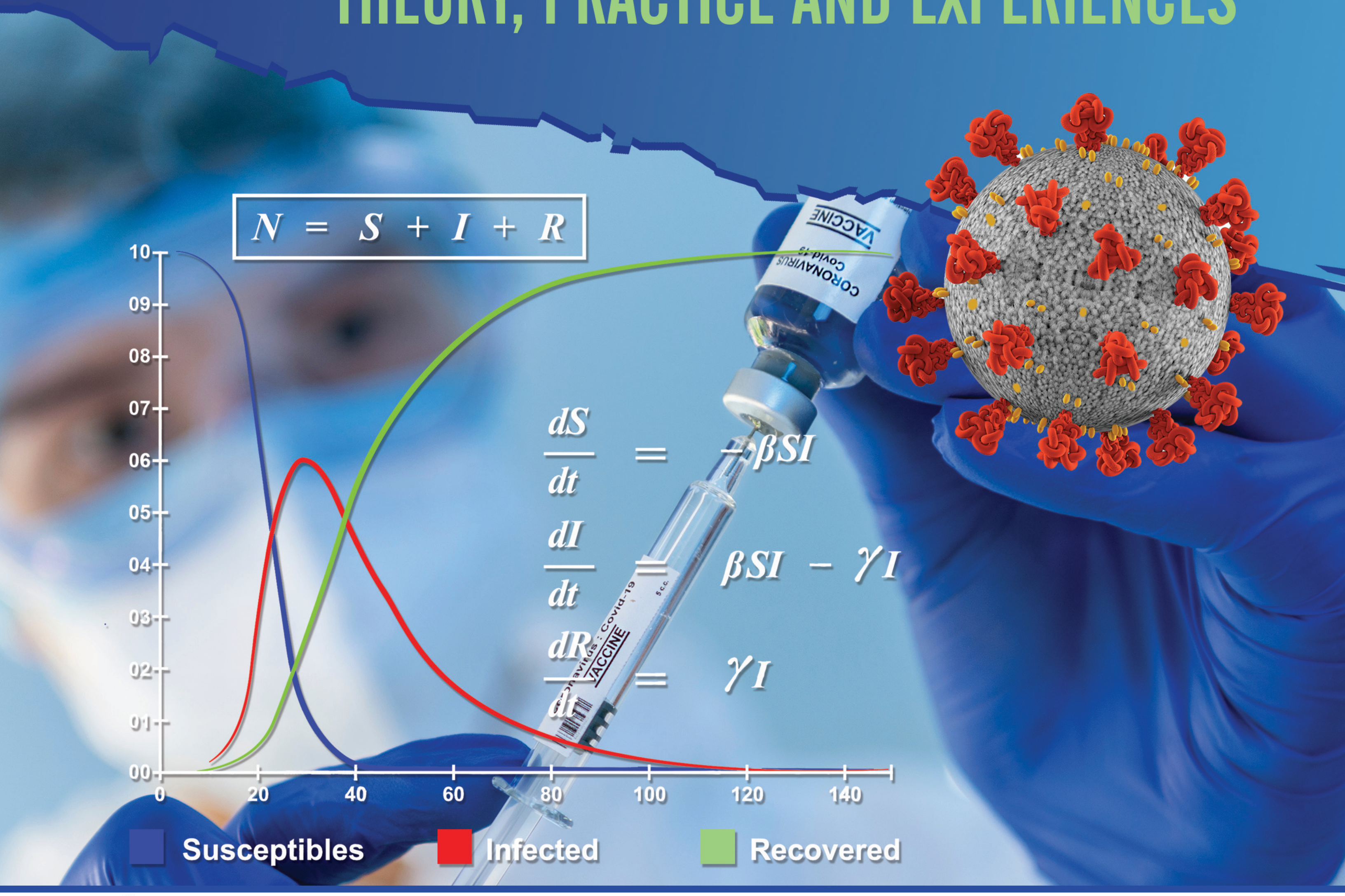
MOVING FROM COVID-19

MATHEMATICAL MODELS TO VACCINE DESIGN: THEORY, PRACTICE AND EXPERIENCES



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Editor:
Andrés Fraguela-Collar

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Moving from COVID-19
Mathematical Models to Vaccine Design: Theory, Practice and Experiences

Edited by

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Moving from COVID-19 Mathematical Models to Vaccine Design: Theory, Practice and Experiences

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Contents

FOREWORD I

Living and coping with COVID 19, the second pandemic of the millennia after the 2009 influenza pandemic, has posed unprecedented challenges. The world has dealt with pandemics before. Human history has been shaped by diseases that present themselves as epidemic, endemic or pandemic diseases. We have registered pandemics since well before the Christian era, and surely, although no registries are available, they have always accompanied humankind. Some remarkable pandemics, that changed the course of history were the Black Plague in the 14th century that killed a great proportion of the European population, and the Spanish Influenza, that occurred little more than a century ago in 1918-19, and killed well over 40 million people, although some scholars say the number of deaths might have reached more the 100 million.

Circumstances have changed and the world is quite different from what it used to be just a few decades ago. Knowledge, technology and communications have developed in an unprecedented speed in human history in the last century and especially in the last four decades. While these are great achievements, they also pose new challenges. Lifestyles have changed and the world faces global threats such as climate change, overpopulation, undernourishment, non-communicable diseases, the emergence of new potentially pandemic infectious diseases such as COVID-19, and many others that have pushed together the global community in efforts to deal with them in a coordinated fashion. Common targets such as the Sustainable Development Goals prove that leaders all over the world are concerned about the future of human kind, although not all to the same extent.

These efforts, however, have been insufficient, and COVID-19 has shown that much more than meetings, nice documents and good intentions are needed to face current challenges. ConfrontingCOVID-19 has risen several questions that need yet to be answered by scientists as well as politicians. For instance, what was the origin of SARS-CoV-2; how can we deal with health inequities such as differential access to vaccines, or why many governments and country leaders disregarded the World Health organization’s recommendations.

In this very complicated scenario, any attempt to better understand and cope with COVID-19are welcome. This book will surely provide vast and comprehensive knowledge about the pandemic and its development, and the best ways to confront it.

Editor and author, Andrés Fraguela Collar, has brought together several contributors, from different Mexican institutions as well as from highly renowned institutions from other countries in a great effort to try to understand COVID-19.

In chapter 1, readers will find a very thorough and challenging description of the mathematical modelling of pandemics in general and of COVID-19, in particular.

Chapter 2 will guide them through key issues about the epidemiology of infectious diseases. They will get a comprehensiveview from chapter 3 about what was known at the time the book was written about how SARS-CoV-2 does its damage, how we, human beings, experience the disease and where were the possible treatment options at that moment.

Chapter 4 is devoted to mathematical modelling of epidemics. Chapter 5 will offer readers avery interesting discussion about the importance of data analysis, and the challenges faced when dealing with something new like COVID-19.

Chapter 6 deals with the epidemic progression of the diseases in a non-homogeneous population. Those who love Mathematics will enjoy this chapter. Chapter 7 leads the reader through the very important subject of social inequities and their role in the propagation of infectious diseases.

Chapter 8 will update the reader on the statistical approach to understand the severity and fatality of COVID-19.

Chapter 9 is devoted to the Cuban experience, on immunotherapy and the role played by mathematical models of disease progression at the individual level.

Chapter 10 and last explains in a very comprehensive manner many aspects of vaccine development and the challenges it poses.

Throughout the book, the reader will find many graphs, tables and formulas, and a very extensive bibliography in each chapter.This book is an example of a multidisciplinary endeavor. It is no easy reading for those who do not have statistical or mathematical background, but anyhow it will be highly enjoyable for any reader and particularly for those familiar with mathematical concepts and methods.

COVID-19 is evolving in many senses, and it is a challenge to health systems, and at the individual level, to both clinicians and researchers. Modelling it has proved to be a very difficult task and as we learn more about it, we discover that there are yet many things to unveil. With this disease, human kind is walking in unchartered territory.

I recommend the reader to follow on new every day developments, to stick to basic publichealth messages which have proven to be the best defense against the disease and to have in mind that this will not be the last pandemic we will face. There is a very high probability of a new pandemic in the future, although we do not know when or how it will occur. As someone said “the clock is ticking, but we do not know what time it shows...”

Enjoy this book, as it contributes to better understand COVID-19.

Pablo Kuri-Morales
Independent Health Consultant

FOREWORD II

Mathematical modeling of infectious diseases has a long history of being used as a tool to study the mechanisms by which a disease can spread within communities, to predict the direction of an outbreak in a population and to evaluate the effectiveness of therapeutic interventions (*e.g*., vaccination programs) to control an epidemic. These mathematical models derive from basic theories, the collection of statistical data or both, and they help to define parameters for a variety of infectious diseases, and to estimate the effects of the different interventions.

The appearance of a new human viral infection which causes the disease known as COVID-19, constitutes both a challenge and a test to the usefulness and relevance of mathematical modeling. This coronavirus known as SARS-CoV-2 emerged suddenly in South Asia and rapidly disseminated around the globe. It represents a significant concern because, very few times before, the population of the whole world had to face a disease of such pandemic proportions, that has exposed the lack of preparedness of the health care systems to handle thousands of patients and the limited therapeutic interventions to counteract such disease. Fortunately, rapid action in the development of effective vaccines worldwide and the accelerated emergency approval of these therapeutics has let different countries to combat this disease, increasing survival and reducing the death toll.

Current and emerging problems during the pandemic, and the effectiveness of the vaccine platforms developed to cope with it, will define the future of outbreak control. For example, it is unknown whether this novel coronavirus will establish itself in an endemic form or will it eventually die out. Furthermore, the appearance of variants (also known as mutations in the viral genome of SARS-CoV-2) that increase the capacity of the virus to cause disease (*e.g*., transmissibility), might increase the capacity of the virus to overcome vaccine protection. Therefore, continuous monitoring of the pandemic is required, not only to evaluate vaccine distribution and coverage, but also to follow up individuals who were infected by SARS-CoV-2, since they could be carriers viral variants that might disseminate through the population.

Mathematical modelling can help decide which interventions to avoid and which to test, or can predict epidemic or pandemic patterns, as well as help understanding the impact of vaccination programs. In this book entitled: “Moving from COVID-19 Mathematical Models to Vaccine Design: Theory, Practice and Experiences”, the authors provide a perspective on how to attack a present problem in public health with mathematical tools, that can guide the decision making related to COVID-19 epidemiology and vaccine production and distribution. But why is this book different from others already published on mathematical modelling? First, the authors of this book are from different countries that are significantly affected by the disease. Second, the book presents a balance set of basic and applied chapters describing topics from disease progression and prevention to those models that could be used in different scenarios. The aim of the book is to present the COVID-19 pandemic as a complex public health problem, that requires the participation of multidisciplinary and interdisciplinary groups of experts to tackle the problems associated with the disease, and demonstrate the role mathematical and computational modeling had during the course and evolution of the pandemic.

The book is divided into 10 chapters. Chapters 1, 4 and 6 introduce mathematical and computational models that can be used to study the COVID-19 pandemic and understand the epidemiology of the disease. Chapters 2 and 3 describe the epidemiology and present the clinical manifestations associated with the disease. Chapter 5 discusses the importance of data science as a tool for COVID-19 informatics. Chapter 7 presents an important aspect of the pandemic that has to do with the impact in populations that lack proper health services or present pre-existing health conditions. Chapter 8 is an overview of the statistical methods that can be used to understand COVID-19 morbidity and mortality. Chapter 9 discusses the impact mathematical modeling and statistics can have in the treatment of COVID-19 patients. Finally, chapter 10 is an overview of all the experimental vaccines available to combat the COVID-19 pandemic. I hope this book becomes a referent for current and future generations of investigators interested in mathematical modeling and infectious diseases, and provides additional tools to understand the current pandemic.

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FOREWORD III

The pandemic of COVID-19, caused by the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2), has shaken up our societies, with an intensity and effects not suffered by humanity for a long time. To date, there have been registered millions of deaths associated to COVID-19, and hundreds of millions of confirmed cases all around the world. Moreover, this pandemic has triggered not only a deep and global health crisis, but also an economic and social (without mentioning psychological, educational, *etc*.) crisis like never seen before.

In order to endure and overcome this major tribulation, the different human communities, guided by their respective administrations and governments, have been put to the test in multiple and severe ways, under the direct effects of the disease, and the performance of several therapeutical and non-pharmaceutical interventions and mitigation measures. Among others, we could mention: the severity of symptoms and disease evolution in serious and critical cases (including assisted ventilation), and the long-term effects; the lack of effective treatments, specially in the first stages; unstoppable death tolls and incidence rates, with increasing numbers of hospitalizations that press and even saturate the health care national systems; hygiene or sanitary measures (frequent hand washing, not touching the face, the generalized use of disinfection products, the use of masks, gloves, and glasses, *etc*.); the use of detection tests (as PCR); quarantines, home isolation and confinements; the implementation of severe social distancing and isolation measures (indeed curfews in some cases); mobility, travel, circulation and gathering restrictions, and closure of borders; reduction or suspension of nonessential activities, with loss of millions of jobs and increasing unemployment rates; total or partial closure of colleges and universities and the unequal and frequently improvised performance of on-line education; campaigns for tracing possible cases; vaccination programs; the psychological effects on mental health in the community; *etc*.

Hence, this picture entailed the scientific community to face to an unprecedented challenge, in order to appropriately assess and advise health authorities and decision-makers. Such a kind of complex phenomena appeals to multidisciplinary and interdisciplinary groups of experts to take their part in order to reach a comprehensive approach, able to deal with the many relevant and multifactorial aspects of COVID-19, as illness and as pandemic. Of course, topics as the epidemiological and clinical aspects of the disease are central, but not the unique ones. Other matters require to be understood, as the SARS-CoV-2 virology, or the COVID-19 pathophysiology and immunology; the study of temporal evolution of infected individuals and their contagiousness; the lack of preparedness of the health care systems and the rapid reaction in Medicine research, including the development and access to vaccines; the population heterogeneity and the effects of mobility and human behavior in the spread of the disease; the role of health and social inequities; *etc*.

In this context, the appearance of scientific works, which organize and summarize a great part of the scientific job carried out, is of great value. In particular, if the subject is approached from a comprehensive and multidisciplinary perspective, considering the individual and collective levels, and their temporal and spatial evolution, the biological, socioeconomic, technological aspects, *etc*., and its consequences for the societies in which it occurs, as the current work does. In addition, the case of this scientific work is especially interesting, since it highlights the role that Mathematical and Computational Modeling can play together with other related areas such as Data Science and Statistics, when dealing with this type of multidisciplinary phenomenon, for which is an excellent reference for researchers and decision makers on how to deal with this type of problem.

Based on all that has been said above, I hope that this book will help researchers and decision makers to better understand and evaluate the situations that can arise in the context of a complex problem such as that caused by the COVID-19 pandemic and the way to face it.

Victoriano Gabriel Covarrubias Salvatori
Head of the Council of Science and Technology of the State of Puebla
Puebla, Mexico

PREFACE

This book is a multidisciplinary work, dedicated to the current problems around the COVID-19 pandemic and which has been carried out by a group of specialists from various scientific institutions in Mexico, United Kingdom, Spain, France, Russia, Cuba, Belgium and India.

Although the book does not exhaust the subject, it is however the result of the authors' effort to convey, to a certain extent, a comprehensive approach. Therefore, although not all possible points of view and relevant matters are addressed, which make up the multidisciplinary dimension of the research that has been carried out around the COVID-19 pandemic and its associated virus SARS-CoV-2 with its variants of concern, those that have proven to be essential and accessible to the authors' competence and resources have been included.

The first chapter aims to give a comprehensive view of results from different scientific perspectives that have been useful for building and studying epidemiological mathematical models for COVID-19. The conclusions and predictions provided by these results, have been the source of key recommendations to decision-making in several countries.

In later chapters, the problem is approached from the epidemiological and from the clinical point of view which together encompass its individual and societal dimensions. As in all health problems both points of view are essential although their methods and analytical tools are different. However, both approaches complement each other to provide the understanding of the measures that contribute to solving problems and their negative effects, which is indispensable for a global approach to the problem. Mathematical modeling, to different degrees and at different times, is present in both approaches.

The epidemiology of COVID-19 requires analyzing and dealing with large volumes of data, through mathematical and statistical models, which allow studying the problem of transmission as a complex problem, by means of theoretical and computational resources. All these conceptual and operational tools are present in the book under a general and global approach.

The exclusive epidemiological perspective, is however insufficient. Clinical aspects such as: pathophysiology, clinical manifestations, pharmacological treatment of COVID-19, among others, are also essential for understanding and coping with this disease. Chapters 2 and 3 attempt to provide a panoramic view of the epidemiological and clinical components of this multifaceted problem.

Chapters 4 and 5 attempt to advance in the direction of the modeling of epidemics and pandemics, by presenting and discussing techniques and procedures for analyzing and modeling data analysis, thus providing the conceptual and practical bases to solve or minimize the undesirable effects of the pandemic.

Chapters 4 and 6 introduce the reader to the modeling of epidemics through the use of mathematical models. Different perspectives and uses of the models are presented. Chapter 6 in particular is devoted to the study of the effect of population heterogeneity in the process of spread of COVID-19, which is essential for the study of the pandemic, and surprisingly relegated in the available literature, as compared with other topics. “Data Science” is addressed in chapter 5, and shows the process of transforming data into information, using standard procedures with a rich recent development. Data Science is an indispensable tool for a full understanding of the ways in which COVID-19 manifests itself, and the different interpretations.

Population heterogeneity is revealed not only by territorial distribution and demographic factors associated with different social groups, but also by existing social inequalities and biological factors that characterize the response of different individuals to COVID-19 such as age, sex, pre-existing comorbidities, *etc*. Chapters 7 and 8 are devoted to the study of these two interesting topics.

The scientific and methodological approach associated with the study of the presence of “social inequalities” in the evolution of the pandemic, provides essential methods to assess the influence of context in morbidity and mortality associated with COVID-19. Chapter 7 addresses this problem from a conceptual, methodological and practical point of view, showing examples of specific cases.

Chapters 8 and 9 combine quantitative measurement and a qualitative approach to assess and understand the severity, fatality, and impact (both short and long term) of a pandemic with explicit application to COVID-19.

In particular, for a better understanding of the impact of immunotherapy protocols with their modeling aspects, the Cuban protocol, implemented during the pandemic, is shown and developed as an example, of the role and application of mathematical and statistical models.

Chapter 10 addresses a fundamental strategy for the control and elimination of the pandemic, namely the production and application of vaccines. Two key problems are included:

- The conception, production and laboratory evaluation, through clinical trials in its various phases, including the extent and duration of immunity and protection, all encompassed by the clinical aspects of the problem.

- The massive application of strategies to control the disease, to anticipate new mutations and variants, and to build risk perception among the general population. This chapter shows the progress attained on an essential issue with a prospective view to curb and ultimately eradicate the pandemic.

At the end of the book we have included an appendix with a series of graphs, duly selected, that show relevant data on how the COVID-19 pandemic has evolved in different regions and countries of the world. Concretely, this group of charts show the time series of the rolling 7-day average of number of daily new confirmed COVID-19 cases and deaths in the countries with the largest number of accumulated confirmed cases of COVID-19 in the world, and some specific regions (the whole World, the European Union, and the continents of Asia, Europe, North America, South America, and Africa). These plots constitute a simplified snapshot of the pandemic, that would be useful to quickly summarize the whole picture.

The topics covered in the book will undoubtedly be useful for specialists from different areas who have been involved, either in scientific research or daily work, with the COVID-19 pandemic. Doctors from different specialties, epidemiologists, chemists, biologists, pharmacologists, immunologists, microbiologists, mathematicians, computer scientists, sociologists and specialists in data analysis, among others will be clear beneficiaries of the messages conveyed by the book.

It will also be useful to any reader who, without being a specialist in any of these areas, wants to have an overview of the extensive work that has been carried out, during the little more than a year and a half that has elapsed since the beginning of the pandemic today. The book provides a very complete picture of the meaning scope of multidisciplinary scientific work aimed at a common goal.

I must express deserved recognition and gratitude to all who, in one way or another, have made possible the final result of this multidisciplinary work, on a subject that is of fundamental importance for all humanity.

In the first place, our gratitude to all the authors, many of whom were immersed in their professional daily work of caring for COVID-19 patients in intensive care rooms in hospitals or in laboratories dedicated to the creation of vaccines and immunotherapeutic treatments, while they wrote their chapters.

We also want to thank the Council of Science and Technology of the State of Puebla (CONCYTEP) in Mexico and, in particular, the Head of the Council, Dr. Victoriano Gabriel Covarrubias Salvatori, who, on behalf of the State Government, provided his support for the fulfillment of this work.

Our thanks to the Scientific Directorate of the HM Hospitales of Spain, Research Foundation who provided us with an extensive database of their COVID-19 patients, which has been of great help in obtaining some of the results presented in this book.

A special recognition to Dr. Moisés Soto Bajo, for the valuable work done in the revision and composition of the book.

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Dedication:

In memory of those who died as a result of the COVID-19 pandemic,

To all people, especially children, who have lost a loved one due to the pandemic,

To healthcare workers who have been on the front lines caring for COVID-19 patients,

To the scientists around the world, whose work has been the striking force that will ultimately control this pandemic.

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CHAPTER 1

An Approach to COVID-19: Current Results, Perspectives and its Study with Mathematical and Computational Modeling Tools

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Abstract. This chapter presents the COVID-19 pandemic as a complex problem, which has resulted in multidisciplinary and interdisciplinary research of unprecedented magnitude at the international level. In particular, the important role that mathematical and computational modeling has played throughout the different phases of the evolution of the pandemic is analyzed. Some of the most notorious achievements and difficulties in obtaining results with the use of mathematical

Andrés Fraguela-Collar (Ed.)

models and computational simulations are discussed, and some proposals are presented about relevant and still pending tasks.

Key words: COVID-19, epidemiological model, sensitivity analysis, bifurcations, parameter identification, controllability, stabilization.

1 INTRODUCTION

1.1 Importance

Today, mathematical and computational modeling is an indispensable tool for the study of complex systems and phenomena. Mathematical Epidemiology and its application to the study of the COVID-19 pandemic has been a relevant example of the usefulness of this tool.

In this chapter, we analyze and conceptualize some aspects of the pandemia from different perspectives, according to its relevance when studying and representing mathematically this phenomenon. We summarize relevant, and basically quantitative information about "model calibration and assessment".

We also review the mathematical and computational models which have been used to describe the pandemia and the main results they have yielded. This text has been written in such a way that the congruence between the first analysis phase and the second conceptual synthesis phase of modeling could be easily perceived, that, although arising in a disordered way, underlie all modeling processes.

Finally, without any pretensions to being exhaustive, we show some fundamental results achieved with these models until now, and we identify some relevant problems and suggest possible strategies for their solution from the perspective of mathematical and computational modeling.

This summary, dedicated to such a wide and complex topic, necessarily has to be brief, schematic, and incomplete. Consequently, the matter is developed without the deep insight devoted to different topics in the remaining chapters of the book, to which readers are redirected to deepen into each corresponding topic.

Therefore, the goal of this chapter is, on the one hand, to offer a review of the scientific work in relation to the COVID-19 pandemic, having as backbone the mathematical and computational modeling; and on the other hand, to show the close link between scientific results achieved along a widespread multidisciplinary research, the demands of the decision making in different stages of the pandemic, and the proposing and resolution of problems by using mathematical and computational models.

In this chapter, we will review from a methodological point of view, how mathematical models for the study of COVID-19 have evolved, based on basic principles. With the modeling of the phenomenon as a directing vector, relevant aspects will be discussed and how they have been taken into consideration. Among others, we can mention the inclusion of NPI (non-pharmaceutical interventions); population heterogeneity, including vulnerability and variability of human behavior; the effect of mobility; mitigation measures; the intra-domiciliary, extra-domiciliary and intra-hospital dynamics; limited immunity, after recovery from the disease, or as a result of the application of vaccines; vaccination strategies; the genetic variability of the virus and its characteristics regarding the transmission and severity of the disease, etc.

Despite the large number of important results that have been obtained so far, we will show that there are still many nonminor problems that require an answer. We will also discuss the need for new ideas to deal with them; on the one hand, to obtain models that better represent the dynamics of COVID-19, and on the other, a more in-depth qualitative analysis of the models is needed.

Frequently, using very particular models, general conclusions have been drawn only from numerical simulations, which reproduce certain incidence data in the study areas. In addition, on many occasions, to carry out numerical simulations, the information required by the models is used, which does not even correspond to the place where the results are applied. In this context, in addition to obtaining new results of a general nature, the qualitative study would allow to encompass and confirm a large number of results of this type.

With the support of more complete and reliable databases and numerical simulations of

CHAPTER 2

Epidemiology of COVID-19

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Abstract. In the last days of December 2019, in a seafood market in Wuhan, China, an outbreak of pneumonia of unknown origin was identified and later reported to the World Health Organization (WHO) regional office through the International Health Regulations for its dissemination to WHO member countries. The WHO declared the outbreak of a Public Health Emergency of International Concern (PHEIC) on January 30th, and on March 11th, 2020, the WHO Director-General declared it a pandemic. Today, it has been spread to more than 200 countries. The SARS-CoV-2 pandemic could be considered the health event with the greatest impact worldwide in the last 100 years. As of March 11th, 2021, one year later, more than 17 million cases and 2,615,018 deaths have been registered. The clinical picture caused by SARS-CoV-2 ranges from mild to severe forms. Some require hospitalization and, in some cases, even treatment in Intensive Care Units is needed

Andrés Fraguela-Collar (Ed.)

due to multiorgan disease. Medium and long-term sequelae are still under investigation. The pandemic has affected health services in Mexico and all over the world, not only due to the hospital reconversion for the care of patients with COVID-19 in the face of the emergency, but also because the care of patients with other conditions has been delayed with a negative impact on the physical and mental health of populations. Likewise, it has deranged several social activities such as travel, commerce, and education.

Key words: Severe acute respiratory syndrome, antigens, antibodies, COVID-19, coronavirus, epidemic, epidemiology, fatality, mortality, outbreak, pandemic, PHEIC, population, preventive measures, SARS-CoV-2, spike protein, vaccines, zoonosis.

1 INTRODUCTION

1.1 Importance

It is essential to establish the origin and to follow the evolution of a pandemic to identify the factors that could allow to define health public actions and interventions for the containment and mitigation of such events. This knowledge can also help to prevent or reduce the frequency of new pandemics.

1.2 Preliminaries

Epidemics and pandemics have accompanied man throughout the history of mankind. The Spanish influenza pandemic in 1918, known as “the mother of pandemics” claimed the lives of more than 50 million people. In 1957-1958 and 1968, there were two other major epidemics also due to influenza viruses, the A virus (H2N2) and the influenza A virus (H3N2), respectively. The 1918-1919 pandemic is the benchmark against which all other epidemics and pandemics are compared, due to the unprecedented number of victims [1].

Various factors favor the emergence and reemergence of pathogens, as well as their spread, including population growth, the increase in disorganized urbanization, international travel, human migratory movements, and climate change [2, 3].

In this century, various threats to global public health have occurred, of which 70-80% are related to emerging or reemerging diseases of zoonotic origin (transmitted from animals to humans): SARS-CoV in 2003, influenza A(H5N1) virus in 2004, influenza A(H1N1) virus in 2009, MERS-CoV from the Middle East in 2012, influenza A(H7N9) virus in 2013, Ebola virus and the Zika virus in 2014, among others [4]. In this 21st century, the first virus that triggered the alarm of the World Health Organization (WHO) was the Severe Acute Respiratory Syndrome (SARS) coronavirus in 2003 in China [5]. In 2009, a less deadly pandemic than the 1918 pandemic was the result of a combination of genetic changes in the virus, and was the first pandemic of this century, caused by the influenza A (H1N1) virus, with Mexico as its epicenter. Worldwide, an estimated 151,700 to 575,400 deaths were caused by infection with influenza A(H1N1)pdm09 (2009 H1N1 Pandemic) virus during the first year that the virus circulated [6]. Later, this virus became a seasonal virus and to date circulates globally and is currently part of the composition of seasonal influenza vaccines [7].

2 CORONAVIRUSES OF PUBLIC HEALTH IMPORTANCE

Coronaviruses are an extensive family of viruses, some of which can cause diseases in humans (zoonoses), ranging from the common cold to severe clinical pictures. such as those caused by the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) identified in 2003. In 2012, another coronavirus of importance to public health that causes the Middle East Respiratory Syndrome (MERS-CoV), was identified in Saudi Arabia. In 2019, the SARS-CoV-2 coronavirus that causes COVID-19 emerged [8–10]. Although the three coronaviruses identified in 2003, 2012, and 2019, have had an impact on public health, there are large differences in the number of cases, deaths, and fatality rates (Fig. 1).

CHAPTER 3

COVID-19 Pathophysiology, Clinical Manifestations, and Drug Treatment

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Abstract. COVID-19 is caused by a single-stranded RNA encapsulated betacoronavirus, known as SARS-CoV-2, implicated in the pandemic that started in China in 2019. Viral replication consists of five stages that culminate in the release of the new virion. The exaggerated inflammatory response of COVID-19 is characterized by an elevation of acute phase reactants such as C-reactive protein and ferritin. It is associated with an unfavorable clinical course, intensified

Andrés Fraguela-Collar (Ed.)

by abnormal activation of the protein complex called the inflammasome. When the immune response does not control the virus, lung tissue damage occurs that leads to the massive release of proinflammatory cytokines, producing acute respiratory failure syndrome. Vascular permeability is increased; interaction with coagulation factors develops disseminated intravascular coagulation and multiorgan failure. Up to 33% of cases can be asymptomatic. Clinical manifestations can be mild or severe and involve various organs and systems. Among the most commonly affected are: respiratory, cardiovascular, renal, and hematological and coagulation systems. Among the most representative laboratory data are: elevation of inflammatory markers (CRP, inflammatory cytokines, tumor necrosis factor), high levels of D-Dimer, elevation of troponin I, lymphopenia, thrombocytopenia, alteration of liver enzymes and kidney function. There are risk factors and comorbidities that contribute to the severity of the clinical picture (mainly cardiovascular and metabolic diseases): diabetes mellitus, high blood pressure, obesity, chronic lung diseases, cancer, and chronic kidney failure. There are also other genetic factors associated with the host's immunopathogenesis and response to SARS COV-2 infection. There are various imaging methods that allow adequate identification and involvement of the pulmonary and cardiovascular systems with great sensitivity and specificity (computed tomography and echocardiography). The pandemic imposed decisions with very little information regarding what may be useful as a therapeutic strategy. This uncertainty applies to the treatment indicated in the prevention phase, as well as to the different stages of severity of the disease. In many cases, treatments were applied without having gone through a trial phase but only with the theoretical support of its probable benefit. However, over time, controlled studies showed that they did not provide any benefit and that they could even have a deleterious effect. Other therapies still in use have shown contradictory results in the different clinical trials where they were tested. Very few therapeutic options have shown undisputable benefit so far. The only ones that can modify the presentation or course of the disease are vaccines, which have also been developed in record time and in controlled trials, and all those that have been approved showed a decrease in the risk of infection and in the risk of presenting a severe manifestation of the disease.

Key words: Angiotensin-converting enzyme, acute respiratory distress syndrome, asymptomatic infection, Beta-coronavirus, cardiovascular system, clinical manifestations, Caspase 1, Coronavirus, COVID-19, cytokine storm, dyspnea, echocardiography, Ferritin, hemo-phagocytosis, hypoxia, inflammation immune system, inflammasome, inflammatory response, Interleukin 6, lympho-histiocytosis, micro-angiopathy, Procaspase, Protein C, RNA, SARS-CoV-2, thrombosis, T lymphocytes, viral replication, respiratory failure.

1 INTRODUCTION

1.1 Importance

This chapter provides a comprehensive overview of three crucial aspects related to COVID-19 and its causal agent SARS-CoV-2. In the first place, it exposes the mechanisms of viral damage of SARS-CoV-2, its biochemical components, the inflammatory response it triggers, as well as the thrombotic phenomena it causes, all of which are essential to understand the pathophysiology of COVID-19. It also reviews the clinical manifestations of COVID-19 across a wide spectrum of clinical conditions, including both asymptomatic and mild and severe symptomatic forms. This is of great importance to provide early and adequate medical care and to achieve the highest possible reduction in mortality. Finally, it summarizes the scientific evidence supporting the therapeutic options available so far, all of them aimed at mitigating the systemic inflammation produced by cytotoxic damage and preventing related complications.

1.2 Preliminaries

COVID-19 is caused by the SARS-CoV-2 virus and until July 2021 it has caused more than 3.8 million deaths worldwide. Although the majority of patients do not require hospitalization, a minority present with severe illness with acute respiratory distress syndrome. Currently, more information is known about the transmission and clinical presentation of patients with SARS-CoV2

CHAPTER 4

Modelling Epidemics: a Perspective on Mathematical Models and Their Use

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Abstract. In this text, we look at several mathematical models that have been constructed during the present pandemic to address different issues of importance to public health policies about epidemic scenarios and their causes. We start by briefly reviewing the most basic properties of the classic Kermack-McKendrick model and then proceed to look at some generalizations and their applications to contact structures, co-circulation of viral infections, growth patterns of epidemic curves, characterization of probability distributions and passage times necessary to parametrize the compartments that are added to the basic Kermack-McKendrick model. All of these examples revolve around the idea that a system of differential equations is constructed from

Andrés Fraguela-Collar (Ed.)

a specific epidemiological problem, has as a central and main theoretical and conceptual support the epidemiological, medical, and biological context that motivates its construction and analysis.

Key words: Mathematical models, COVID-19, Mathematical epidemiology, COVID population dynamics

1 INTRODUCTION

1.1 Importance

Here, we argue on the importance of theoretical and conceptual perspectives in modelling the COVID-19 pandemic. Fitting equations to data without a sound perspective on the biological feasibility of the model will provide a statistically significant fit but will also fall short of providing useful information for the management, mitigation, and eventual control of the epidemic.

1.2 Preliminaries

The epidemic of SARS-CoV-2 that started in late December 2019 in Wuhan, China, and became a pandemic by late January 2020, is still with us. Mathematical models have been used since the very early days to forecast and inform public health strategies and decisions geared to control or, at least, mitigate the impact of the epidemic. Epidemic models became a notoriety both in the academic, public health and popular realms. The epidemics of infectious diseases are social phenomena whose dynamics are strongly influenced by the inherent heterogeneity of human populations regarding age, gender, genetic profiles, physiology, preferences, education, socioeconomic level, religion, customs, etc. All of these factors induce high variability and uncertainity on the disease transmission process. To confront the epidemic, a large number of modellers used variants of the family of so-called Kermack-McKendrick models. The Kermack-McKendrick models were first published in a series of papers in early decades of the XX century. These models are compartmental in nature and follow the fate of the individuals in the population where an infectious disease is present. One of the equations follows the prevalence of the disease, which, in the most classical SIR model, describes a bell-shaped curve with a unique maximum and where both initial growth and final decline are exponential in nature. This model originally was used to describe the bubonic plague epidemic [1]. Anderson G. McKendrick was a Scottish medical practitioner born at the end of the XIX century. He worked in Sudan and India where he learned mathematics by himself [2]. As a result from this experience, he published a first version of his now famous model [3], which later in his life was further developed with the help of W.O. Kermack in a series of landmark papers. In 1927, William O. Kermack and McKendrick started a series of papers entitled Contributions to the Mathematical Theory of Epidemics that together constitute the fundamental background of mathematical epidemiology [1, 4–7]. Infectious diseases are transmitted through contacts between susceptible and infectious individuals. The models that we will comment on in the following sections assume that all individuals are exactly equal and can be unequivocally classified into distinct classes that correspond to their physiological disease status: susceptible, exposed, infectious, recovered, quarantined, etc. During this long pandemic of SARS-CoV-2, many papers have been published where many more compartments are added to the basic transmission model (hospitalized, asymptomatically infected, presymptomatically infected, isolated individuals and so on). This increase in the number of compartments gives the illusion of realism but at the price of increasing the number of parameters -two per new compartment- thus requiring either estimating all parameters or assigning values to some of them for the purpose of inference, simulation, forecast and prediction. Modelling has to deal with two problems, one is lack of identifiability, the other, overfitting. Many of the parameter values are taken from the medical and epidemiological literature and assumed to be true. This form of "parameter reduction" does not necessarily diminish the sensitivity of the model solutions to variations in these parameter values. Mathematical models are tools to study natural phenomena. Models can certainly be used to predict, but they can also be used to explain and understand the mechanisms and causes of a given natural phenomenon. Kermack-McKendrick models are excellent strategical tools of this type. Their objective is then not so much to forecast incidence, or number of deaths and hospitalized individuals, for example,

CHAPTER 5

Data Science: A Useful Tool for Understanding SARS-CoV-2 Information Facts

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Abstract. By the end of 2019, a local pneumonia outbreak in Wuhan, China, was determined to be caused by a novel form of coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which, since then, has spread worldwide thus becoming the most important public health issue of the beginning of the 21^{st} century. As a response, governments and health organizations started collecting data about this disease for analyzing it, trying to draw conclusions that could lead to a better understanding of it, and eventually to alleviate its effects. Through the analysis of the available data, our area of interest has to do with finding possible correlations

Andrés Fraguela-Collar (Ed.)

among the variables related to COVID-19 cases which could give some insights. For example, which factors make a given patient to present an aggravated form of this illness, or even a higher risk of dying? Does the level of poverty make some people prone to get ill? What about the place where people live in? These and other questions can be answered based on the analysis of the available data. In this chapter, we give a brief introduction to Data Science (DS), a field of Artificial Intelligence (AI), and present some data analysis using publicly available COVID-19 data sets provided by the Mexican government. This allows us to show how AI tools and techniques can help us to better understand some aspects of this kind of situation, and in this way, hopefully helping health officials and providers to create better health policies and services and succeeding in their goal: saving lives.

Key words: Artificial Intelligence, Bayesian Network, COVID-19, Database, Data Science, Decision Tree, Entropy, Epidemiology, Health, Information, Knowledge, Pandemic, SARS-CoV-2, Workflow

1 INTRODUCTION

1.1 Importance

This chapter highlights the potential impact of Data Science, as a branch of Artificial Intelligence, in unveiling relevant associations related to COVID-19. Data Science provides tools to find meaningful associations from large databases, which can later be tested with more specific analytical techniques. A better understanding of the causation web around this disease is a key factor to design and implement strategies to cope with the pandemic.

1.2 Preliminaries

Ipsa scientia potestas est. This phrase means “knowledge itself is power”. It appears in Meditationes Sacræ[1], which was written by Sir Francis Bacon (1561-1626), and is of an astonishing relevance at the present time. In fact, this was not the first time humankind realized that knowledge is worth, frequently even more than wealth. Other ancient references exist in this same sense, which confer great importance to knowledge.

But, what is knowledge, and is it really as important as we think? How is knowledge related to information and data? There is not a unified consensus on how these concepts are related, since each source assumes slightly different points of view, and even their definitions are constructed cross-reference to the other ones. For example, as stated in the Merriam-Webster dictionary [2], knowledge, information, and data are defined as:

Knowledge:

1. The fact or condition of knowing something with familiarity gained through experience or association.
2. The range of one's information or understanding.
3. The fact or condition of having information or of being learned.

Information:

1. Knowledge obtained from investigation, study, or instruction.
2. A signal or character (as in a communication system or computer) representing data.
3. Something (such as a message, experimental data, or a picture) which justifies change in a construct (such as a plan or theory) that represents physical or mental experience or another construct.

Data

1. Factual information (such as measurements or statistics) used as a basis for reasoning, discussion, or calculation.
2. Information in digital form that can be transmitted or processed.

CHAPTER 6

Epidemic Progression in a Heterogeneously Distributed Population

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Abstract. The chapter is devoted to a compartmental epidemiological model of infection progression in a space-distributed multipatch population with communication between the patches due to the movement of individuals. The subpopulations inside the patches consist of different groups with respect to the intensity of disease transmission both within and between groups. The heterogeneity of the population and its transfer between the patches influence the rate of epidemic

Andrés Fraguela-Collar (Ed.)

progression, the final size of the epidemic, and the number of infected individuals.

Key words: COVID-19 epidemiology, heterogeneous population, multipatch model

1 INTRODUCTION

1.1 Importance

Heterogeneous populations with subpopulations differing in the rate of disease transmission are described with compartmental epidemiological models. Basic reproduction number (BRN), the final size of epidemic, and the maximal current number of infected individuals are determined. It is shown that BRN is not sufficient to determine the epidemic progression in a heterogeneous population. Multipatch models for spatially distributed populations are considered.

1.2 Epidemiological Situation

In the beginning of the second year of the COVID-19 pandemic, we can identify several consecutive stages of its progression. The initial stage with the exponential growth of the number of infected individuals was followed by the next stage characterized by the alternation of more or less strict measures of social distancing and their relaxation, and by the quarantine of the infected individuals. In the absence of vaccines and efficient antiviral drugs against SARS-CoV-2 infection, these were the only available measures to restrain the epidemic progression together with basic sanitary measures such as masks and personal hygiene.

It became clear in early 2020 that a relatively high proportion of severe cases and mortality rates distinguish the coronavirus disease from the annual influenza epidemic for which collective immunity is reached after several weeks after the epidemic peak followed by the epidemic decay. This scenario is impossible for the COVID-19 pandemic because the public health system and, particularly, intensive care units become rapidly saturated and incapable of dealing with the flow of COVID and other patients. Public authorities use measures of social distancing to balance between uncontrolled epidemic growth and economic losses due to reduced activity.

As a result of this strategy accepted throughout the world, according to the official statistics by March 2021, there were about 120 million of total cases of infection, and about 2.6 million of deaths, although these data can be strongly underestimated (at least for infected) due to the large number of asymptomatic and unregistered cases. The total number of cases largely varies between the countries: 5-10% in Europe and USA, and much less in China and some other Asian countries. According to recent estimates, the number of deaths in the USA is about 15% more in 2020 compared to the previous year, with this increase related to the COVID-19 pandemic. A similar death rate increase can be expected in a number of European countries, but, as for the number of infected individuals, it can be substantially less in some Asian countries. There can be many reasons for such large disparities, but it is unclear which of them are the most influential.

The third stage of the epidemic started in January 2021 with the beginning of the vaccination campaign. By the middle of March, the vaccination was barely beginning[1] and the essential decrease in the number of newly infected individuals can only be expected after several months. Since the number of vaccines remains insufficient, the vaccination strategy adopted in many countries consists in the priority vaccination of more vulnerable elderly people and more exposed groups of the population, such as medical workers.

One of the important questions which determines the further evolution of the epidemiological situation concerns the duration of the immunity of the recovered and vaccinated individuals. In the case of recovered individuals, the level of antibodies and their persistence strongly depend on the severity of the disease [1–3]. Secondary coronavirus infections can be related to weak immunity or virus mutations. Reliable statistics on the number of repeated infections is not available, but it remains probably quite limited. The duration of immunity after vaccination is now estimated by 6 months (validity of vaccination certificates), but it can be eventually longer with an inter-individual

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[1] `https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html`

CHAPTER 7

Social Inequalities in COVID-19

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Abstract. Social inequalities have become an essential component of the health situation analysis. Health statistics are incomplete if its basic indicators are not linked to socioeconomic, sociodemographic, or sociocultural strata. The evaluation of health systems' performance must include global indicators along with their distribution in social strata.

The COVID-19 pandemic has not affected all countries to the same extent. Global statistics of both, confirmed cases and deaths portray wide differences among countries.

Recent reports show wide differences associated with stratification criteria such as skin color or ethnic groups, sex, age, education, socioeconomic condition, and geographic area. The web of interactions between individual and contextual factors also influences the development of the new

Andrés Fraguela-Collar (Ed.)

pandemic.

This chapter lays the conceptual basis for measuring social inequalities in health and presents a basic set of the most common indices. It underscores the fact that a metric choice is not only technical, but to a great extent depends on ethical and political considerations. We document social inequalities in several health indicators associated with COVID-19 using public data or information retrieved from recently published papers.

The first section of this chapter lays the conceptual foundations for measuring health inequalities. The second one exposes selected results and findings in different settings, and a brief analysis of the application of the inequality indices.

Key words: Concentration, COVID-19, dispersion, entropy, health disparity, health indicators, indices, inequities, right to health, social inequality, stratifying variables.

1 INTRODUCTION

1.1 Importance

This chapter provides methodological guidelines to measure social inequalities in the expression of COVID-19 indicators, and general suggestions for the use and interpretation of indices. It also includes illustrative applications and discussion of recent relevant examples. This will encourage the routine inclusion of inequalities to describe and monitor the current pandemic.

1.2 Preamble

The COVID-19 pandemic, which at the time of writing this text - April 1, 2021 - has already claimed the lives of 2.82 million people out of a total of about 129 million cases worldwide, does not affect all countries to the same extent, nor is it homogeneously distributed within a country. This lack of homogeneity has many causes. Some are natural: mortality is much higher in people over 60 years of age, and in those with associated comorbidities, such as high blood pressure and chronic obstructive respiratory disease, regardless of their age. Health personnel in direct contact with patients are at greater risk. There are also recent indications that a certain genetic predisposition could be involved in an increased risk of poor outcome [1]. It is not possible to eradicate these causes.

Other causes, however, are related to unjust orders that imply lack of access to quality health services, precarious living conditions, and low perception of risk. Several of these causes are passed down from one generation to another.

The differences between the two causes, the natural and unavoidable, and the contextual and avoidable, mark a distinction between inequalities (or simple differences) and inequities (or unjust inequalities). This distinction between just and unjust, between avoidable and inevitable, imposes a marked attribute of subjectivity on the study of inequalities, which is added to the intrinsic difficulties of description or analysis, when choosing a metric.

To evaluate the design and implementation of coping strategies, monitoring the classic health indicators of incidence, cumulative incidence, or mortality is not enough. It is necessary to study the distribution of these indicators according to relevant population groups. The performance evaluation of a health system, to put it in statistical language, does not reduce to measures of position, but must also include measures of dispersion. Nor is it possible to limit oneself to negative indicators . Positive indicators such as access to a reliable diagnosis, vaccination, and quality health services that guarantee a better prognosis and better evolution of the disease must be included.

Along with the pandemic, an infodemic has been unleashed in the world that, although it generates considerable benefits in the cognitive order, also carries with it high levels of disinformation and a great danger denounced by the World Health Organization (WHO) itself [2].

The vast theme evoked by the title of this chapter can be considered from three related, but essentially different, approaches. One of them is the impact of social inequality on the severity of the pandemic. This approach would explain at least part of the large gaps between countries and why some have performed better than others. A second focus is on the foreseeable consequences

CHAPTER 8

Statistical Approaches to Understand COVID-19 Severity and Fatality

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Abstract. Statistical methods are essential tools for confronting the current COVID-19 pandemic. These include approaches for quantifying the health impacts of the pandemic, methods for identification of patterns, or risk stratification, for estimating the risk of individuals to become infected, and of patients to die, and important clues on how to approach prediction models in a comprehensive way. The purpose of this chapter is to review basic statistical concepts related to characterization of COVID-19 severity and provide an application of a real scenario related to the identification of predictors of COVID-19 fatality in evolving databases. Some other statistical descriptions and comments are made of problems drawn from real situations.

Andrés Fraguela-Collar (Ed.)

Key words: COVID-19, Statistics, Epidemiology, Prediction models, Health impact, Stratification, Severity, Fatality, Cuba

1 INTRODUCTION

1.1 Importance

Several approaches play an essential role in confronting the COVID-19 pandemic, among them are sociological and mathematical approaches. It is also important to emphasize the role of statistics in helping countries, societies, and the international community to understand and confront this pandemic in an efficient and sustainable manner.

1.2 Preliminaries

Statistics is a methodological discipline with roots in probability and mathematics. Statistics focuses on the variability of data, aiming to explaining it with statistical concepts and based on the knowledge of a particular context. The analysis of individual units (e.g. only one country) or situations (e.g. only developing countries) only offer a limited description of the issue. Statistics needs to use data from different units and from different situations so that inferences can be made from what has been observed, although with a certain level of uncertainty. Solutions to problems like the COVID-19 pandemic are in general based on comparisons.

Statisticians must understand well the context (e.g. biomedicine, sociology) on which statistical methods will be applied, as well as the complementary methodological disciplines that are available for a particular discipline. For example statistics often coincide with epidemiological methods to address medical research, such as the COVID-19 pandemic. Statistical thinking is key in facing the COVID-19 pandemic, and a correct calculation and interpretation of statistical and epidemiological indicators is necessary when characterizing the evolution of the outbreak, the prediction of future outcomes, and to inform the efficient allocation of healthcare resources to mitigate current and future COVID-19 related burdens.

The purpose of this chapter is to review the basic statistical concepts related to the characterization of COVID-19 severity, and provide an application of a real scenario related to the identification of predictors of COVID-19 fatality in evolving databases.

2 BASIC STATISTICS APPLIED TO COVID-19 SEVERITY

2.1 Confirmed Cases, Severity, and Recovery or Death

When dealing with an outbreak of a new infectious agent it is priority to understand its severity as a main indicator of fatality. While at the individual level, severity is assessed by the gravity of signs and symptoms, at the population level, fatality ratios are calculated to assess the severity of disease and, when calculated for specific population subgroups, identify vulnerable groups and prioritize healthcare allocation of resources. Fatality rates can be calculated accounting for deaths among all infected individuals (infection fatality ratio, IFR) or deaths among confirmed cases (case fatality ratio, CFR). At the onset of the COVID-19 outbreak, only CFR could be calculated as only cases derived from surveillance systems and/or severe cases from reporting hospitals were available. Mild cases not seeking healthcare attention are common, and so is the proportion of asymptomatic individuals. These unaccounted cases introduce an important bias in CFR estimates stemming from the preferential ascertainment of severe cases, and delayed reporting, [1], and hinder the comparison of the infection severity across populations.

Underreporting is a particularly important issue in COVID-19 due to the magnitude of the crisis and the overloaded testing capacity of the health systems across the world [2]. As the pandemic evolves and testing becomes more available, CFR estimates will be more reliable but, especially when comparing populations, the limitations of the use of CFR should be acknowledged and methods to increase comparability should be applied, for example, by introducing time in the calculation by using a lag-time since first case reported in the country to avoid insufficient testing and delayed reporting [3]. Furthermore, it is advisable to report the period during which deaths

CHAPTER 9

Understanding the Impact of Cuban Immunotherapy Protocols During COVID-19 Disease: Contributions from Mathematical Modeling and Statistical Approaches

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Abstract. Cuban protocols to treat patients with COVID-19 include interferon alpha 2B and anti-inflammatory therapy at different moments of the progression of the disease. Here, we present the results obtained using a mathematical model to study the immunopathology associated with COVID-19. Model simulations reproduce the clinical observations for the antiviral and

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anti-inflammatory therapies and provide explanations for their efficacy from an immunological point of view. In addition, we present new data and statistical analysis of the clinical use of itolizumab, a humanized anti-CD6 antibody that reduces the secretion of multiple inflammatory cytokines. Authors concluded that the timely use of itolizumab can reduce the probability of death while its late prescription might not significantly reduce COVID-19 morbidity and mortality.

Key words: COVID-19, mathematical modeling, statistical analysis, itolizumab, interferon alpha 2B

1 INTRODUCTION

1.1 Importance

We develop a mathematical model for the dynamics of the immune response associated with COVID-19. Model results help to understand the effect of immunotherapies used in Cuban protocols on this infectious disease, and predict the best treatment strategies. We also present new clinical data for the use of itolizumab, a Cuban anti-inflammatory therapy. Statistical analysis of its efficacy in Cuban patients is in agreement with mathematical model predictions.

1.2 Preliminaries

COVID-19 is an acute respiratory disease caused by a highly pathogenic novel coronavirus SARS-CoV-2. The widely reported symptoms of COVID-19 are extremely variable, ranging from minimal symptoms to significant hypoxia with acute respiratory distress syndrome (ARDS) and multiorgan failure, which could be fatal [1].

COVID-19 is not a clear-cut disorder, but a gradually evolving pathology, characterized by a series of stages sustained by different molecular mechanisms. Earliest analyses of people with coronavirus in China suggested that it might not be the virus alone that damages the lungs and kills, but an overactive immune response might also contribute [2]. The disease can hence be divided into different phases including a respiratory and a proinflammatory stage [3].

Type I Interferons (IFNs) play a primary role in the inhibition of viral replication through the coordination of antiviral immune responses and modulation of inflammatory responses. The type I IFN response in SARS patients was observed to be deregulated in patients that experienced adverse outcomes and severe disease [4]. In addition, the viral infection can lead to an excessive immune reaction in some patients, which is a hyperinflammatory state, known as cytokine release syndrome or cytokine storm [1].

Even though the exact immune mechanisms of COVID-19-mediated pathogenesis are still under investigation [5], we propose a mathematical model to explain the role of the innate and adaptive immune response in the outcome of the disease. We also present new data and statistical analyses of the clinical use of itolizumab, a humanized anti-CD6 antibody that reduces the secretion of multiple inflammatory cytokines.

2 MATHEMATICAL MODEL PRESENTATION

The immune response induced by COVID-19 involves several cells and molecules that play different roles depending on the stage of viral infection. The first response against the virus is mediated by components of the innate immune response, where the antigen presenting cells (APCs) have an important role in processing virus antigens and secreting Type I IFN that directly acts in inhibiting virus replication inside infected cells. This process helps to control virus expansion, but the total or partial elimination of the virus depends on the magnitude of this response. The second response is mediated by components of the adaptive immune response, where CD8+ T cells play a crucial role. These cells arrive to the site of infection with a time delay after virus entry to the system, differentiating into cytotoxic T cells after antigen recognition and interleukin-6 (IL-6) signaling. Cytotoxic T cells are able to kill infected cells and finally eliminate the virus from the system. In patients with deficiency in types of immune response, the presence of a higher virus load

CHAPTER 10

Vaccines Against SARS-CoV-2. Eradicating COVID-19

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Abstract. A year after the COVID-19 pandemic started, a global effort to develop vaccines and make them available to the public, has prompted a turning point in the history of vaccine development. The post-COVID era has accelerated the efforts to bring novel platform vaccine technologies such as nucleic acid or viral-vectored vaccines, which were proved to offer safety, efficacy, and speed in development and production, but have restricted records in the clinic. To date, five candidate vaccines have been approved for emergency use by different regulatory agencies

Andrés Fraguela-Collar (Ed.)

across the world, after demonstrating their robust immunogenicity response and efficacy against SARS-COV-2 infection. We summarize and analyse the progression of those vaccines with major research development and results in peer-reviewed journals.

Key words: COVID-19, SARS-CoV-2, vaccines, viral vectors, adenovirus, RNA vaccines, DNA vaccines, pandemic.

1 INTRODUCTION

1.1 Importance

Despite advances in many directions, from epidemiologic control to specific treatments, prevention based on immunization is the cornerstone of the strategy to cope with the pandemic. This chapter highlights its importance and exposes the uncertainties and challenges still remaining after more than one year of worldwide efforts towards safe and effective vaccines.

1.2 Preliminaries

Severe Acute Respiratory Syndrome coronavirus 2 (SARS-Cov2) is the newly discovered virus responsible for coronavirus disease 2019 (COVID-19). The COVID-19 outbreak reported in late 2019, emerged in the city of Wuhan (Hubei, China) and spread fast all over the world, making it a new public health concern [1, 2]. On 11 March 2020, the World Health Organization (WHO) officially had to consider the global COVID-19 outbreak as a pandemic due to the high number of cases continuing to disseminate at a remarkable pace in many worldwide territories.

Since the beginning of the COVID-19 pandemic, many effective measures have been taken in place to prevent the disease transmission, but most of these measures are not sustainable and have caused major disruptions to the economy as well as social and psychological issues. The ability of the virus to propagate in either symptomatic or asymptomatic patients made the control of the disease is a real challenge for the authorities, and vaccination is the most important tool to protect against COVID-19 [3, 4].

The development of a new vaccine usually takes at least 10-15 years and needs to be evaluated for safety, immunogenicity, and efficacy in humans before it is licensed for use. An initial preclinical phase is conducted to identify a suitable target antigen. Both *in vitro* and *in vivo* evaluations will be performed to assess the ability of the new candidate to induce an effective immune response. The clinical phase intends to establish the safety and efficacy of a new vaccine in humans prior to its being licensed by regulatory agencies and getting into the clinic.

During a global health emergency, the development of a new vaccine must be accelerated to prevent and control the disease without compromising on safety. The COVID-19 vaccine has shown how fast a new candidate development can be achieved when sufficient resources are made available. With the recent COVID-19 pandemic, a new era in vaccinology using nucleic acid or viral vector technology has contributed to setting a fast-track development.

In this chapter, we highlight the different strategies that were introduced to develop a new COVID-19 vaccine since the start of the race for an effective and safe vaccine. We describe the current vaccines developed under different platforms and analyse the vaccines approved for emergency use based on results in peer-reviewed journals.

2 VACCINE DEVELOPMENT PROCESS

The development of a new vaccine is a result of a long process which involves several stages from laboratory research to regulatory submission for clinical trials. Regulatory agencies classify the process of the development of a new vaccine into preclinical (*in vitro* and *in vivo* animal tests) and clinical (clinical trials in humans) stages.

The preclinical phase is a requirement to take a new vaccine candidate from the laboratory to humans. The first step is exploratory and consists of the generation of the antigen that might induce an immune response and help to prevent the disease. A new antigen can be characterized

Appendix: COVID-19 in charts

In this appendix we present some charts which represent in some sense the evolution of the pandemic COVID-19. These graphics were retrieved on September 7, 2021 from the web page Our World in Data[1]. The raw data on confirmed cases and deaths for all countries is sourced from the COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University[2].

The first and second group of figures show the time series of the number of daily new confirmed COVID-19 cases and deaths, respectively (their rolling 7-day average). Please note that the number of confirmed cases is lower than the number of actual cases, because of limited testing, and the number of confirmed deaths may not be an accurate count of the real number of actual deaths from COVID-19, due to limited testing and challenges in the attribution of the cause of death. Note also that these factors have been changing with time as new information about COVID-19 were available.

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[1] [Hannah Ritchie, Edouard Mathieu, Lucas Rodés-Guirao, Cameron Appel, Charlie Giattino, Esteban Ortiz-Ospina, Joe Hasell, Bobbie Macdonald, Diana Beltekian and Max Roser (2020) - "Coronavirus Pandemic (COVID-19)". Published online at OurWorldInData.org. Retrieved from: `https://ourworldindata.org/coronavirus` [Online Resource]].

[2] [Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Inf Dis. 20(5):533–534. doi: 10.1016/S1473-3099(20)30120-1], `https://github.com/CSSEGISandData/COVID-19`.

Andrés Fraguela-Collar (Ed.)

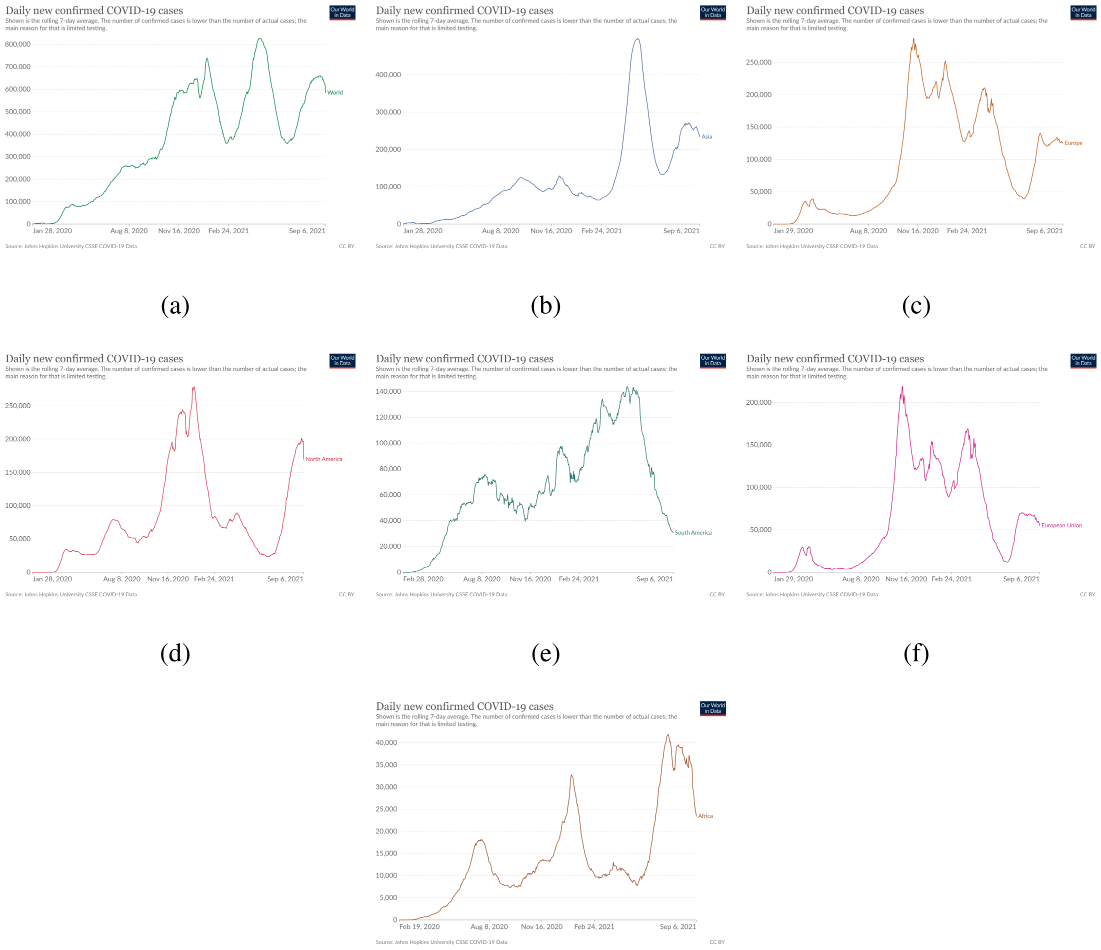

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Figure 1: Daily new confirmed COVID-19 cases for different regions. (a) World, (b) Asia, (c) Europe, (d) North America, (e) South America, (f) European Union, (g) Africa

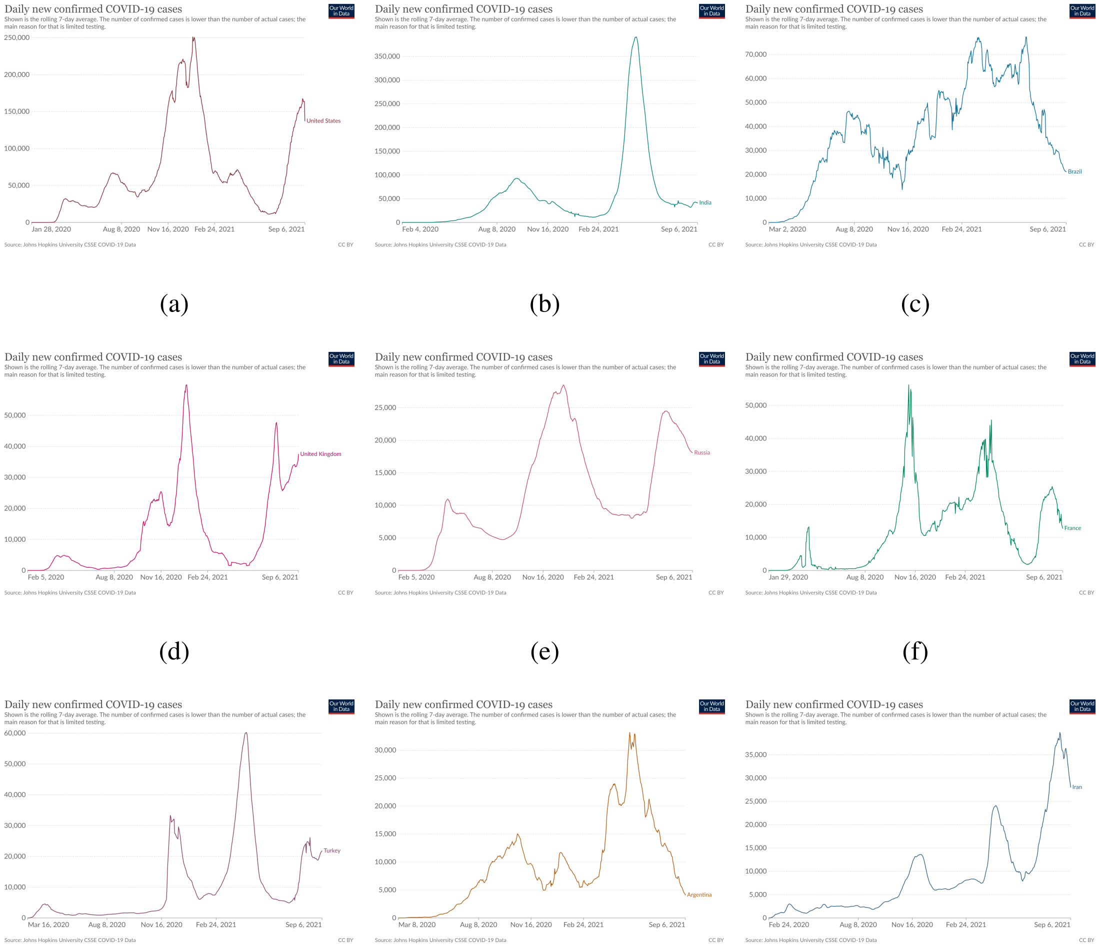

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Figure 2: Daily new confirmed COVID-19 cases for different countries. (a) United States, (b) India, (c) Brazil, (d) United Kingdom, (e) Russia, (f) France, (g) Turkey, (h) Argentina, (i) Iran

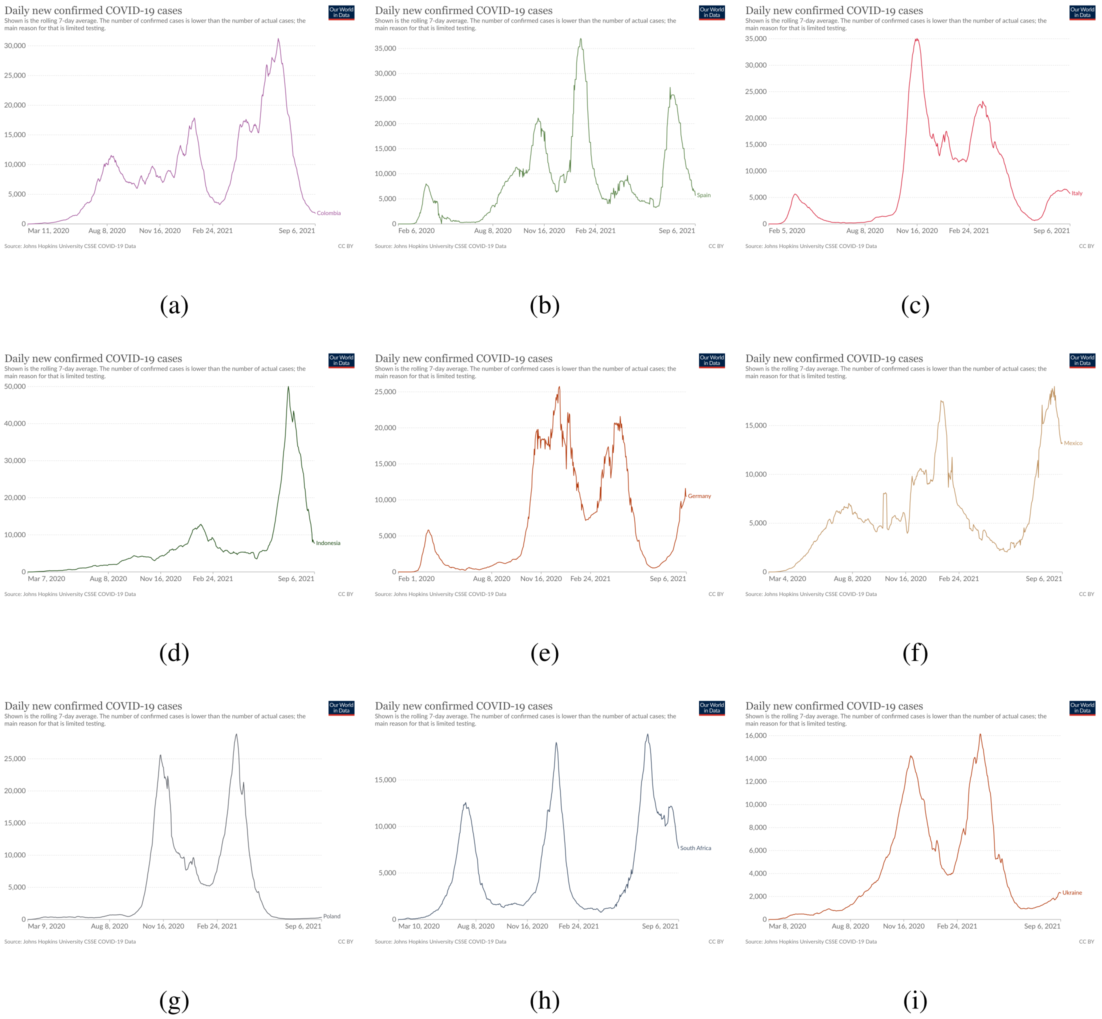

Figure 3: Daily new confirmed COVID-19 cases for different countries. (a) Colombia, (b) Spain, (c) Italy, (d) Indonesia, (e) Germany, (f) Mexico, (g) Poland, (h) South Africa, (i) Ukraine

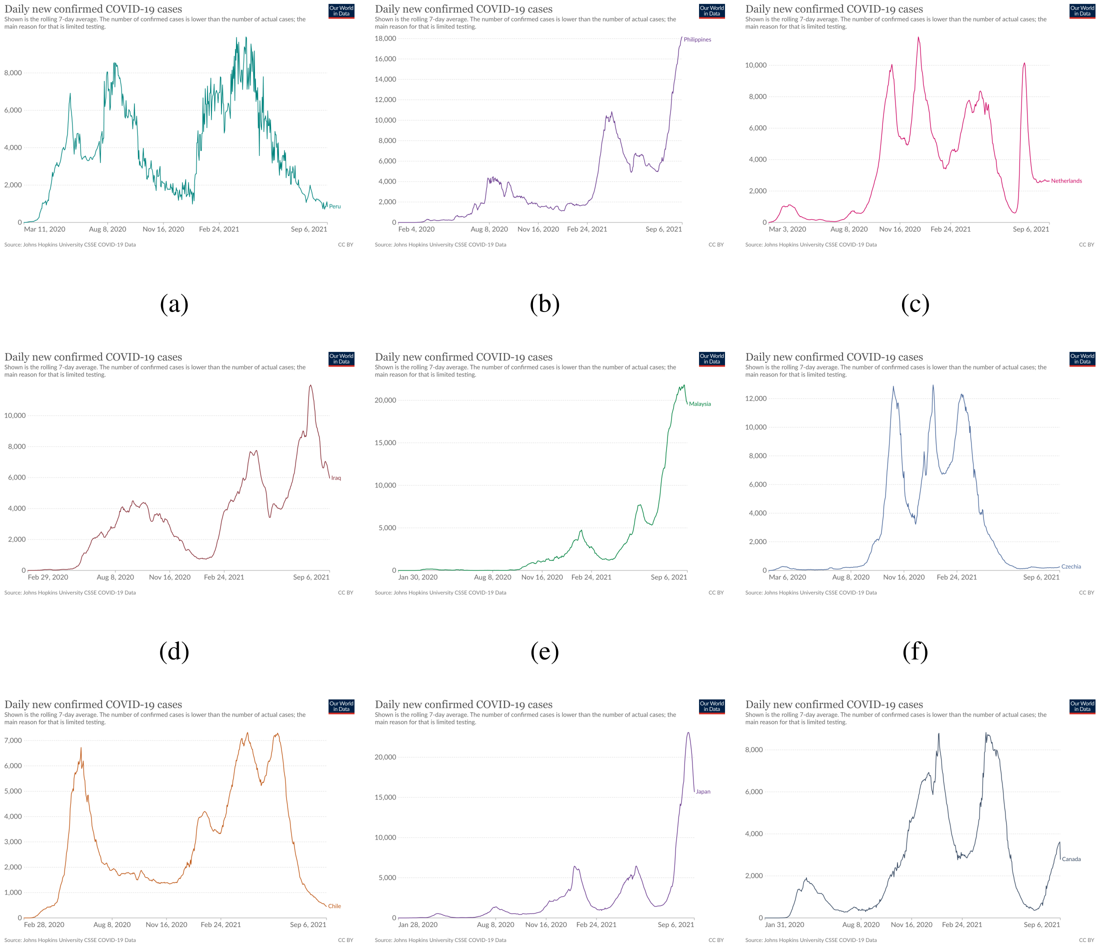

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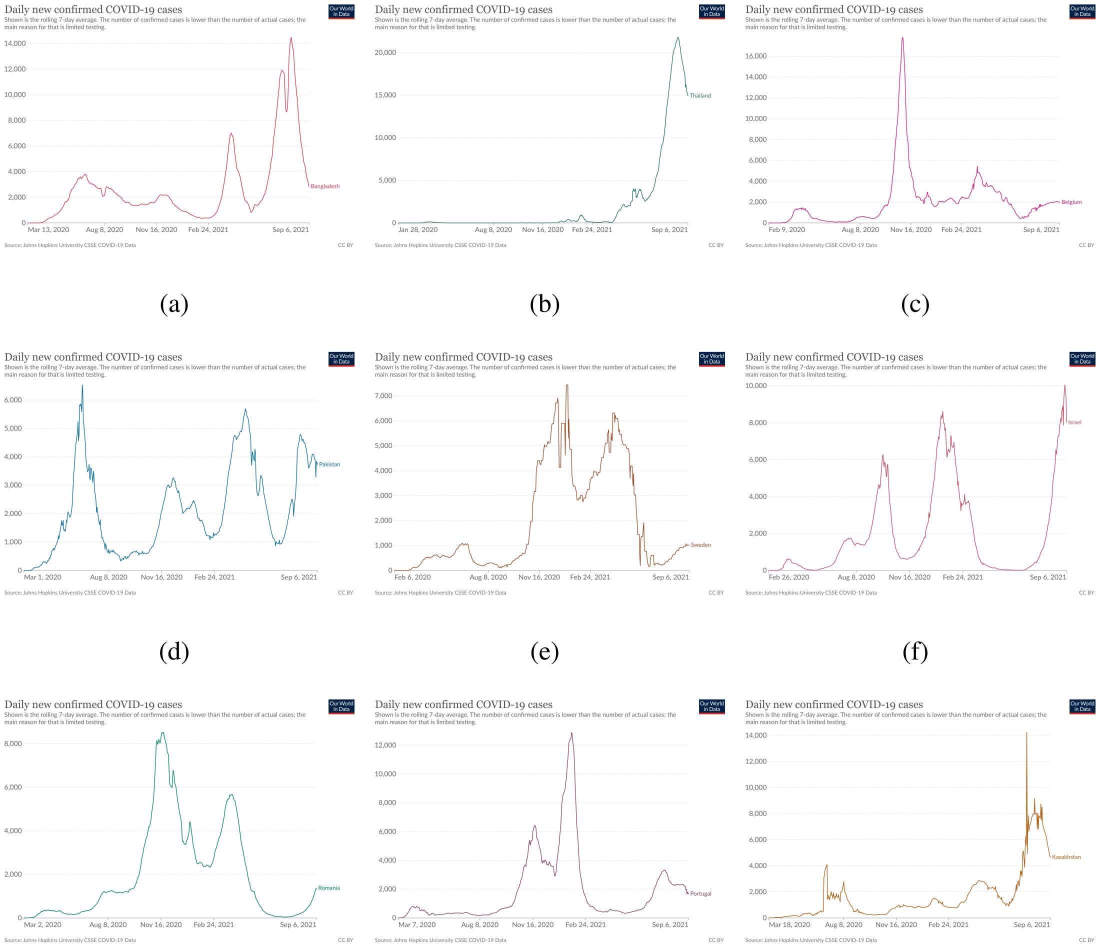
Figure 4: Daily new confirmed COVID-19 cases for different countries. (a) Peru, (b) Philippines, (c) Netherlands, (d) Iraq, (e) Malaysia, (f) Czechia, (g) Chile, (h) Japan, (i) Canada



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(g) (h) (i)

Figure 5: Daily new confirmed COVID-19 cases for different countries. (a) Bangladesh, (b) Thailand, (c) Belgium, (d) Pakistan, (e) Sweden, (f) Israel, (g) Romania, (h) Portugal, (i) Kazakhstan

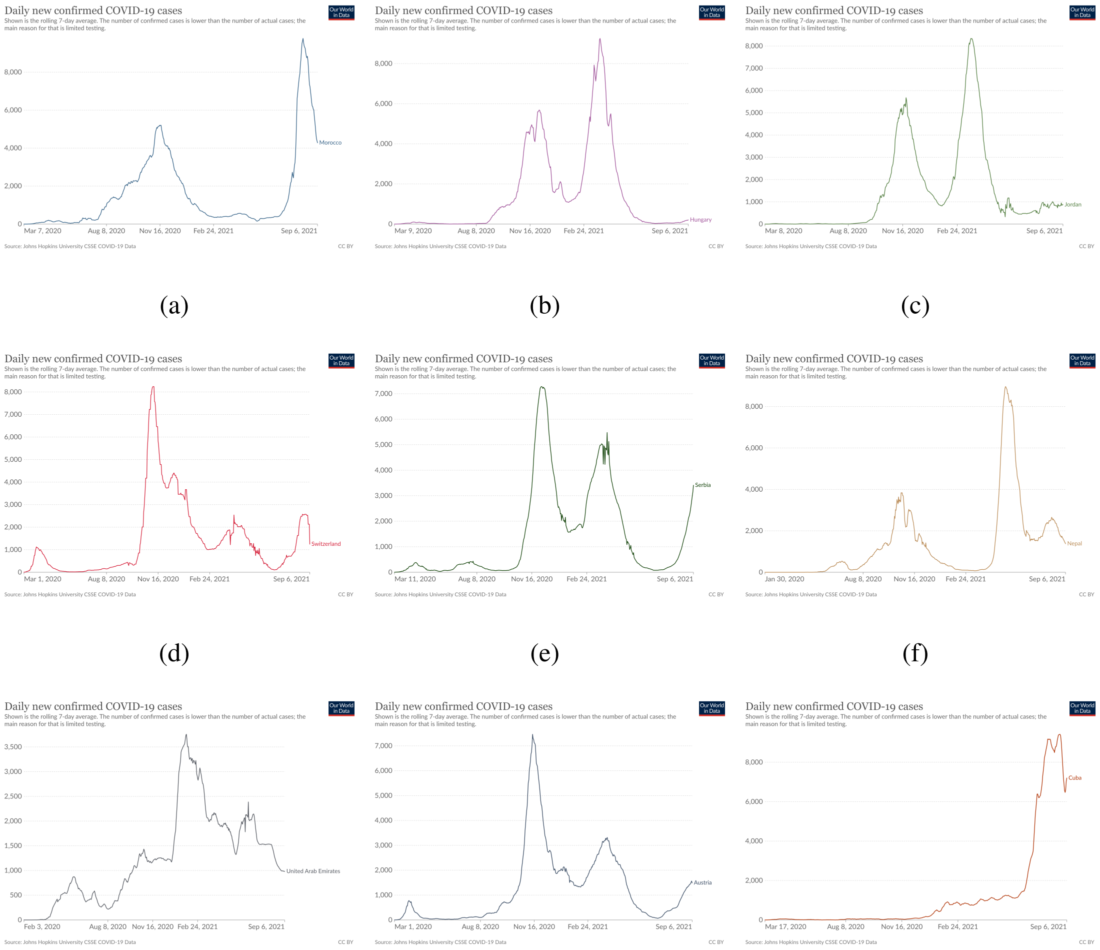

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Figure 6: Daily new confirmed COVID-19 cases for different countries. (a) Morocco, (b) Hungary, (c) Jordan, (d) Switzerland, (e) Serbia, (f) Nepal, (g) United Arab Emirates, (h) Austria, (i) Cuba

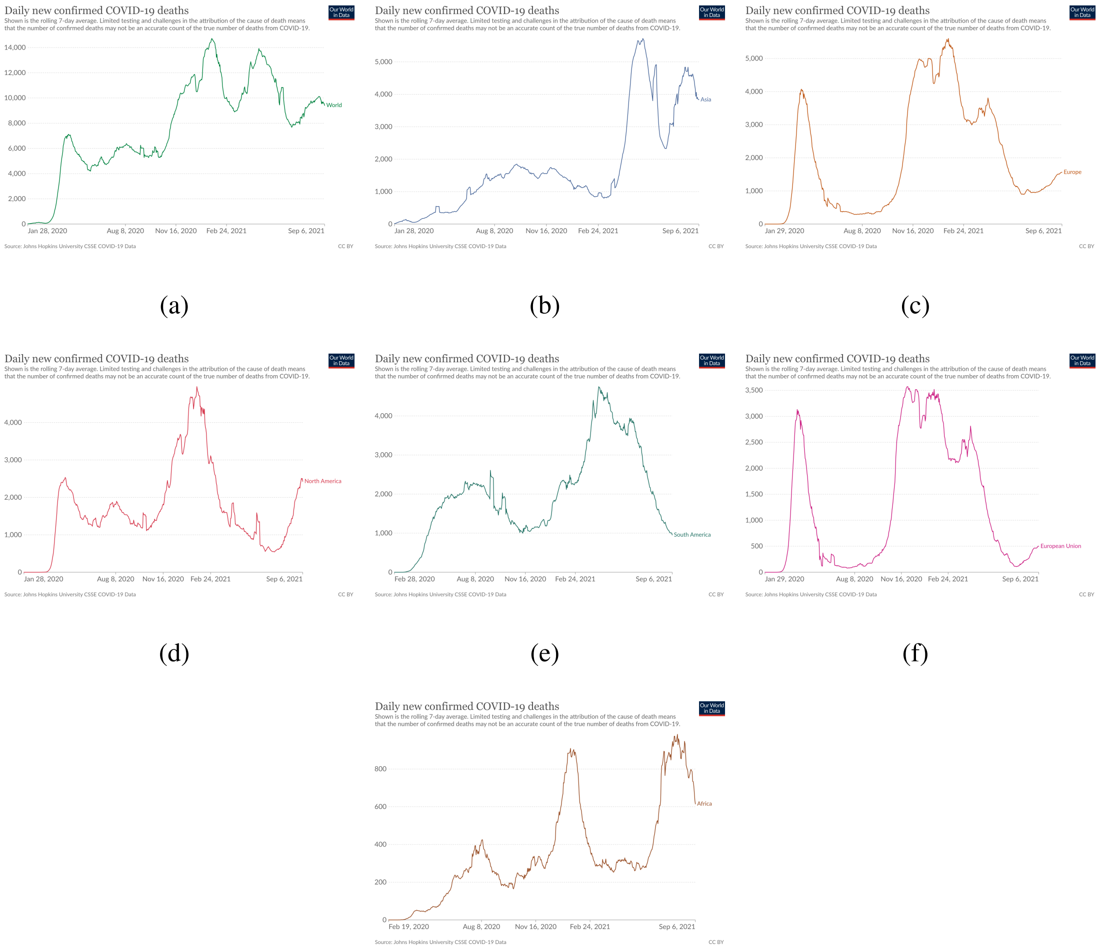

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Figure 7: Daily new confirmed COVID-19 deaths for different regions. (a) World, (b) Asia, (c) Europe, (d) North America, (e) South America, (f) European Union, (g) Africa

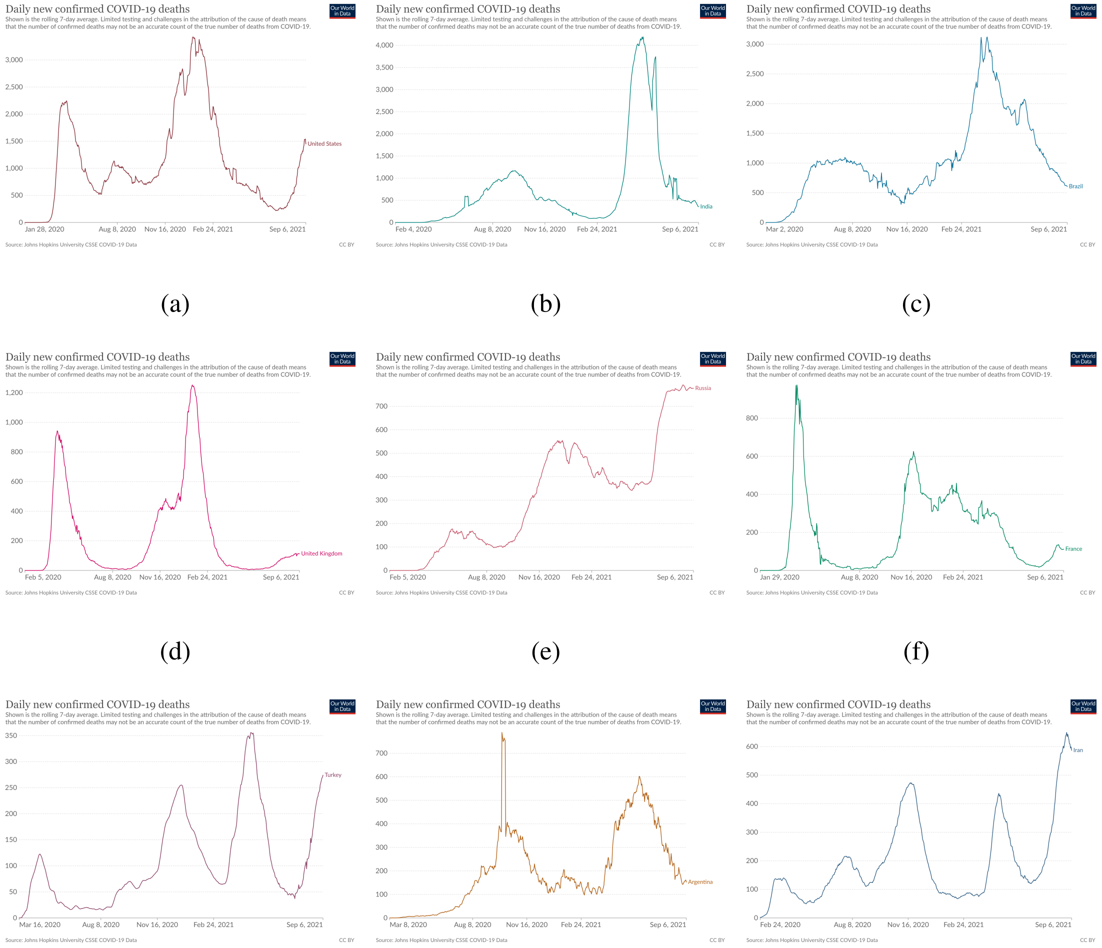

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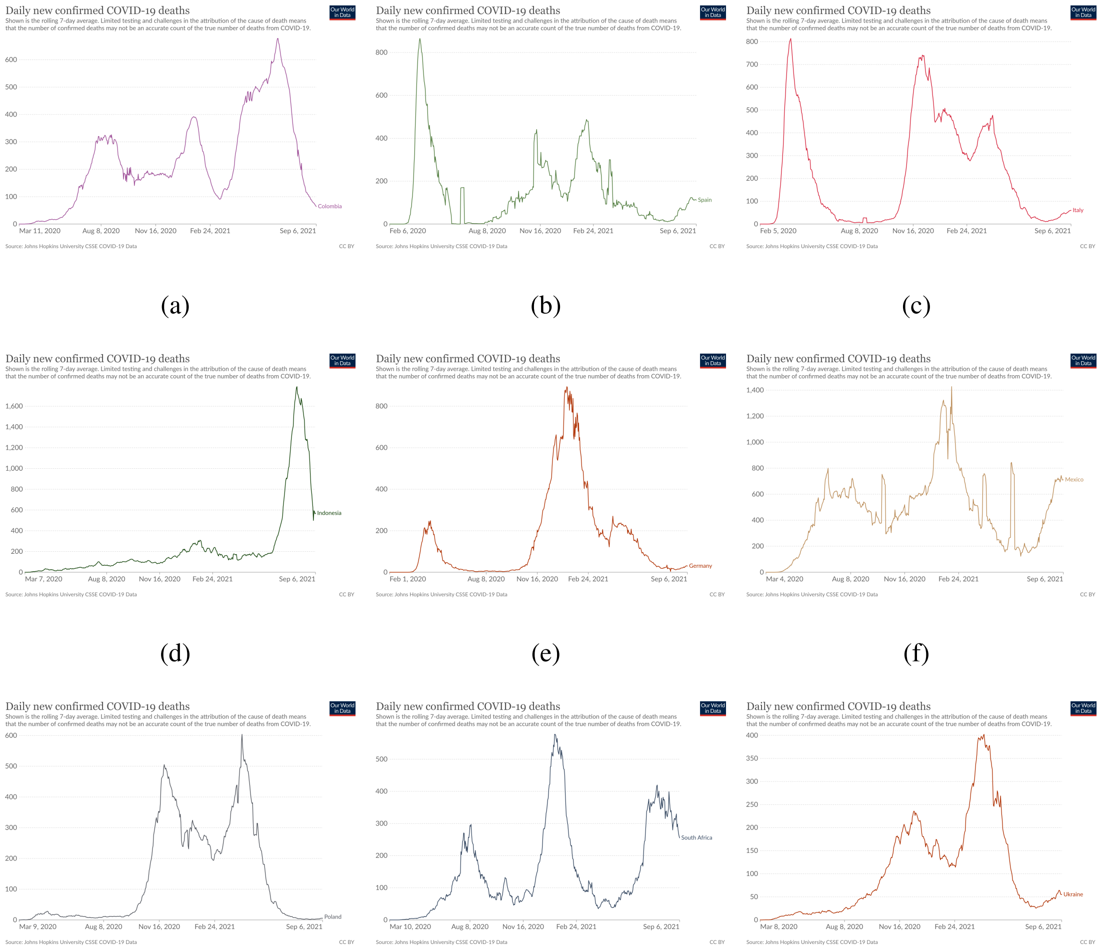
Figure 8: Daily new confirmed COVID-19 deaths for different countries. (a) United States, (b) India, (c) Brazil, (d) United Kingdom, (e) Russia, (f) France, (g) Turkey, (h) Argentina, (i) Iran



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(g) (h) (i)

Figure 9: Daily new confirmed COVID-19 deaths for different countries. (a) Colombia, (b) Spain, (c) Italy, (d) Indonesia, (e) Germany, (f) Mexico, (g) Poland, (h) South Africa, (i) Ukraine

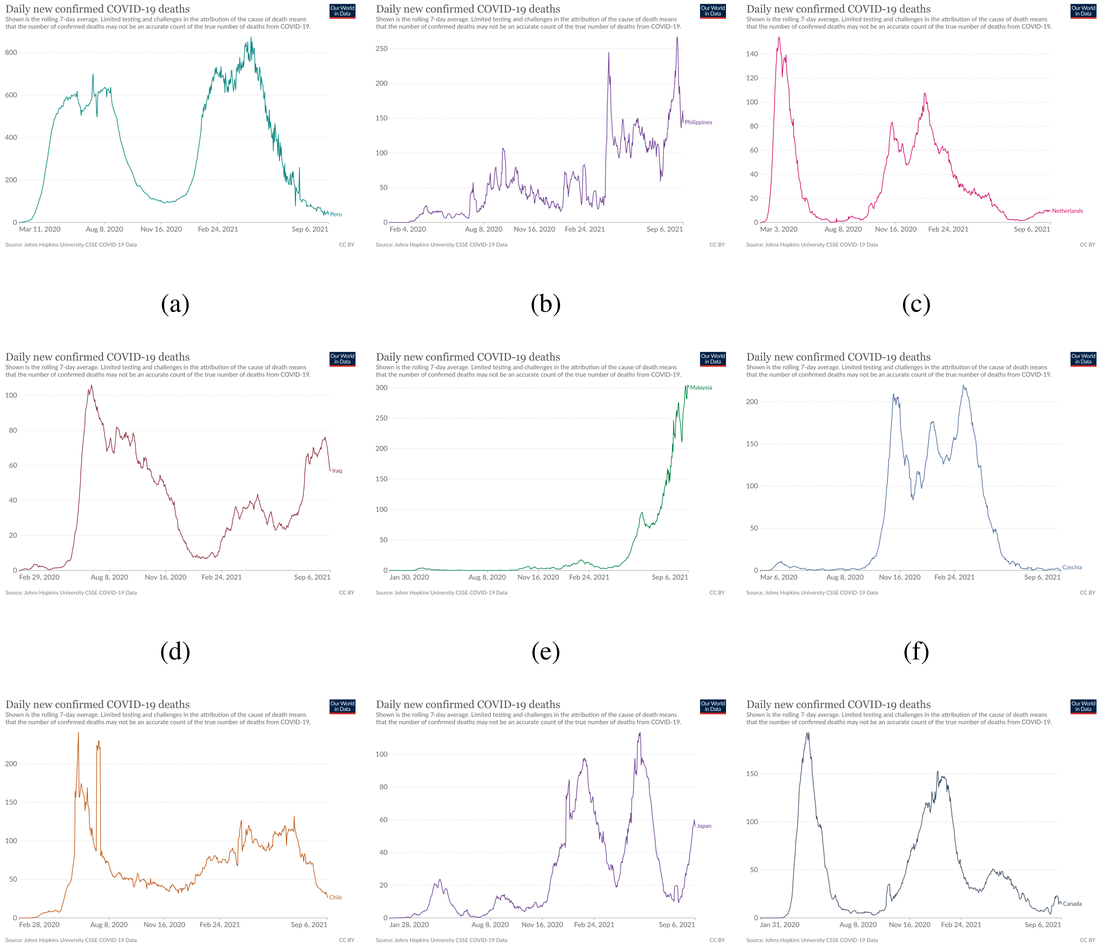

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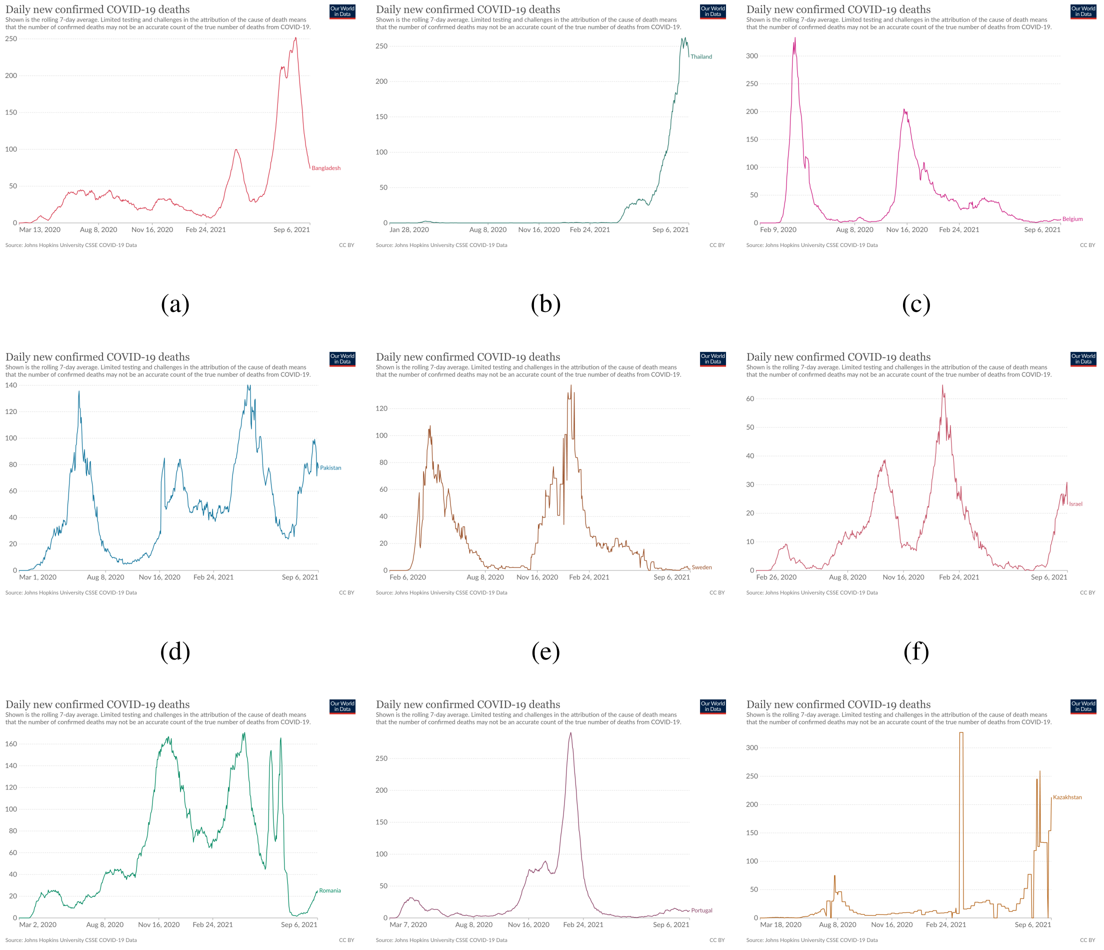
Figure 10: Daily new confirmed COVID-19 deaths for different countries. (a) Peru, (b) Philippines, (c) Netherlands, (d) Iraq, (e) Malaysia, (f) Czechia, (g) Chile, (h) Japan, (i) Canada



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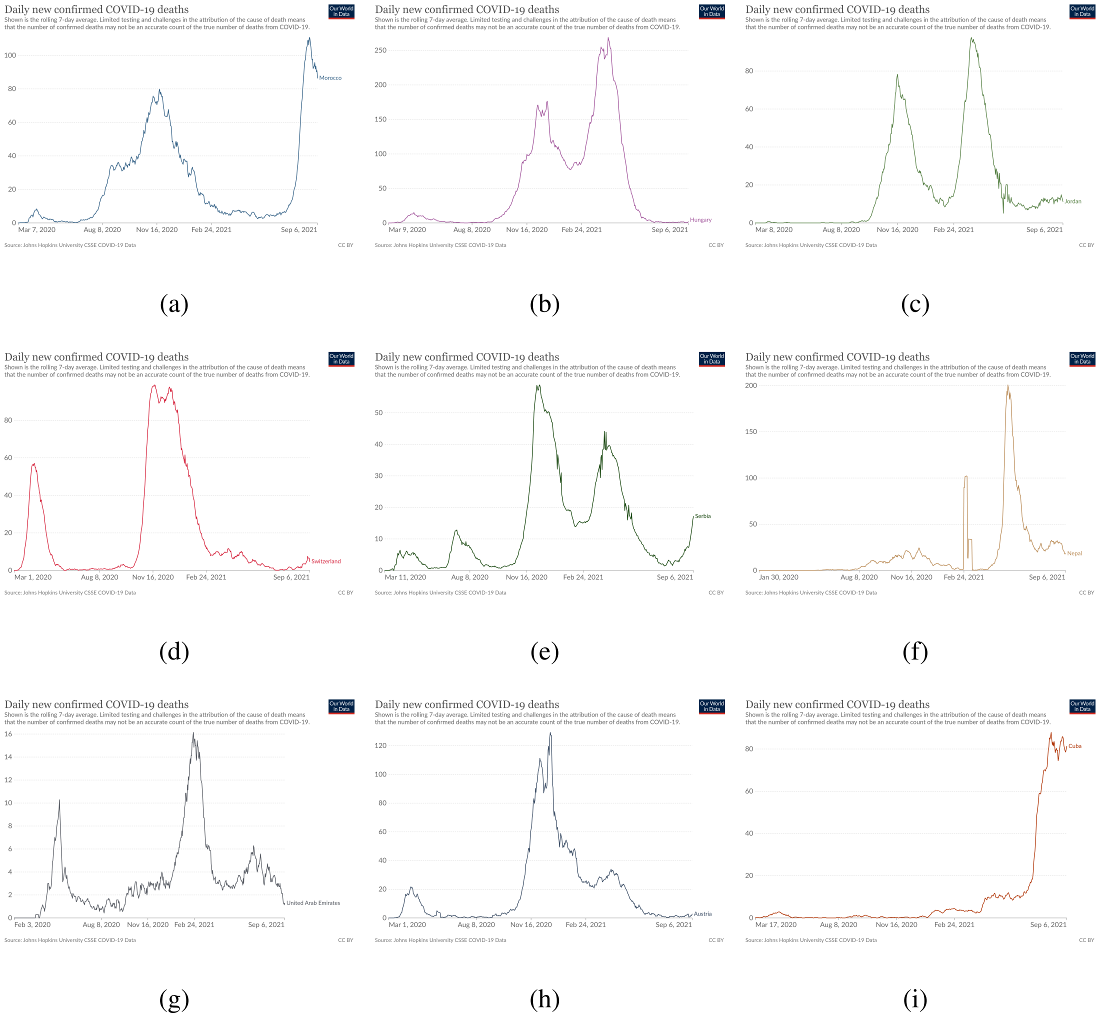
(g) (h) (i)

Figure 11: Daily new confirmed COVID-19 deaths for different countries. (a) Bangladesh, (b) Thailand, (c) Belgium, (d) Pakistan, (e) Sweden, (f) Israel, (g) Romania, (h) Portugal, (i) Kazakhstan



(a) (b) (c)

(d) (e) (f)

(g) (h) (i)

Figure 12: Daily new confirmed COVID-19 deaths for different countries. (a) Morocco, (b) Hungary, (c) Jordan, (d) Switzerland, (e) Serbia, (f) Nepal, (g) United Arab Emirates, (h) Austria, (i) Cuba

SUBJECT INDEX

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Andrés Fraguela Collar is a research professor of applied mathematics at the Autonomous University of Puebla (Mexico). He received his Ph.D. degree and the Habilitation of the Doctorate in Science from Lomonosov State University and the Institute of Mathematics V.A. Steklov of the Russian Academy of Sciences. He is the author of more than 140 original theoretical and applied research papers, including book chapters and books, on topics that involve Functional Analysis and Differential Equations and their applications in epidemiology, neuroscience, cardiology and some industry problems. Dr. Fraguela has participated in 48 multidisciplinary research projects, more than 200 presentations at international conferences and has been an editor and reviewer in several scientific journals. He has been a distinguished visitor of the Complutense University of Madrid, Associate Professor at the M.V. Lomosov State University, Senior Scientific Collaborator of the Institute of Mathematics V.A. Steklov and Chair of Excellence of the National Council of Science and Technology of Mexico.