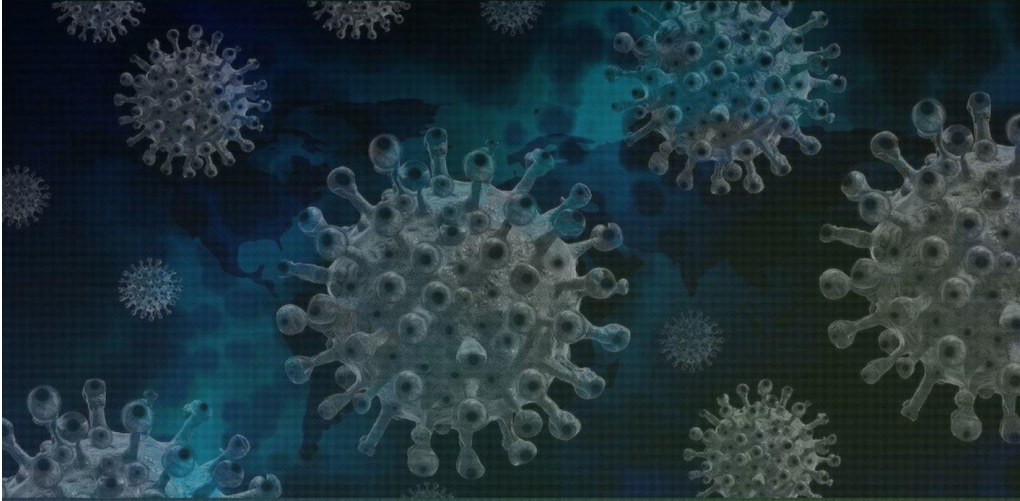


Mario Coccia



COVID-19 PANDEMIC CRISIS

Analysis of origins, diffusive factors and problems of lockdowns and vaccinations to design best policy responses

Vol.2



KSP BOOKS

COVID-19

Pandemic Crisis

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problems of lockdowns and vaccinations to
design best policy responses

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Mario Coccia

Research Director at National Research Council of Italy

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COVID-19 Pandemic Crisis: Analysis of origins, diffusive factors and problems of lockdowns and vaccinations to design best policy responses Vol.2

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Preface

The Coronavirus Disease 2019 (COVID-19) is still circulating in 2022 with new variants (e.g., Delta and Omicron) that generate socioeconomic issues in countries. This contribution endeavors to clarify the origin of novel coronaviruses, factors determining the transmission dynamics of COVID-19 and the effects of non-pharmaceutical and pharmaceutical interventions of containment in society. These basic aspects of COVID-19 pandemic crisis can improve the preparedness of countries to cope with next pandemic threats and the negative effects of their socio-economic impact.

This book is designed for policymakers and general readers that wish to clarify critical aspects of COVID-19 and that wish to expand their knowledge on these areas. Studies that I include here are integrated with cases study and empirical analyses underpinned in real contexts of nations. In particular, this book concentrates on selected topics of particular relevance to problems of COVID-19 pandemic crisis, and which meet the needs of the intended audience.

The book is divided in four interrelated parts.

- The first part of this book focuses on likely origin of the viral agent the SARS-CoV-2 causing the COVID-19 (Chapter 1).

- The second part focuses on environmental, demographic, and geographical factors that influence the spread of COVID-19 in society (Chapters 2-3).

- The third part describes the effects of non-pharmaceutical interventions of governments to cope with COVID-19 pandemic, when appropriate drugs and treatments lack (Chapter 4) and clarifies the manifold aspects and effects of vaccination campaign in economy and society (Chapters 5-6-7-8).

- The final part of the book explains some general approaches and concepts that can improve the preparedness of countries to prevent and/or to cope with pandemic impacts (Chapter 9).

However, no single book could hope to cover adequately all aspects of this multi-disciplinary field of inquiry, such as infectious diseases and their effects in economies and society, and here it is not the intention to attempt to cover all aspects of COVID-19 pandemic crisis. It is regrettable but inevitable therefore that some topics are excluded or given only limited coverage. I hope that readers, such as clinicians, policymakers, etc., dealing with infectious diseases like COVID-19 and other similar viral agents are able to see this text as a general overview to understand the complex and different factors associated with COVID-19 global pandemic crisis.

This book's strengths and weaknesses are the responsibility of author.

Mario Coccia

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2023

Introduction

In the presence of Coronavirus Disease 2019 (COVID-19), environmental, social and medical sciences have to clarify factors determining the diffusion and the best policy responses to cope with COVID-19 and prevent next pandemic crisis.

The COVID-19 is still circulating in 2022 with new variants (e.g., Delta and Omicron) that generate socioeconomic issues in countries (Coccia, 2022; 2021, 2021a, 2021b, 2021c). In 2020, during the first wave of the COVID-19 pandemic, countries applied non-pharmaceutical measures of containment and technological exaptation of existing drugs (Ardito *et al.*, 2021; Coccia, 2021, 2021a, 2021b, 2021c, 2022a, 2022d). Instead, from 2021 onwards, countries have implemented vaccination campaigns to cope with the negative effects of subsequent waves of COVID-19 (Coccia, 2021c, 2022d; Our World in Data, 2022). Fundamental questions in this research field to face next pandemic crisis are: How to stop the diffusion of novel viral agents? What is the best policy response? Is it a general or partial lockdown? And what are the effects of containment policies on socioeconomic system? How to improve the

preparedness of nations to cope with next pandemic impacts? These questions are main scientific issues that have been inadequately addressed in social studies, yet they offer exciting entry points into the current discussion of COVID-19 pandemic crisis and in particular to prepare countries to next environmental threats (Coccia, 2021d, 2021e, 2022b).

As a matter of fact, in 2021 and 2022, the most applied health policy worldwide is the administration of new types of vaccines based on viral vector, protein subunit and nucleic acid-RNA (Coccia, 2022c). The vaccination plans have the potential goal to reduce the diffusion of COVID-19, to relax non-pharmaceutical measures and maintain low basic reproduction number, but an important problem is whether these novel types of vaccines are really effective to reduce high numbers of COVID-19 related infected individuals and deaths between countries to control and/or eradicate the pandemic diffusion and to reduce negative effects in society. Akamatsu *et al.* (2021) argue the vital role of governments to implement an efficient campaign of vaccination to substantially reduce infections in society and avoid the collapse of healthcare system. Shattock *et al.* (2021) argue that a rapid vaccination rollout can allow the sooner relaxation of non-pharmaceutical interventions, but emerging viral variants of SARS-CoV-2 create new scenarios and problems for epidemic control. Shattock *et al.* (2021) also find that a gradual phased relaxation can substantially reduce population-level morbidity and mortality and that faster vaccination campaign can offset the size of pandemic wave, allowing more flexibility for non-pharmaceutical control measures to be relaxed sooner. In fact, in some countries, vaccination campaigns have been rapidly implemented, with a high number of doses administered in a brief period (Ali & Altaf, 2021; Cylus *et al.*, 2021). In other countries, the rollout of vaccinations has been a slower process. These differences among countries are due to manifold economic and institutional factors (Bontempi *et al.*, 2021; Bontempi & Coccia, 2021; Coccia, 2018a, 2018b, 2018d, 2019, 2019a; Cocca & Bellitto, 2018, 2018a; Coccia & Finardi, 2013; Coccia & Rolfo, 2000; DeRoo *et al.*, 2020). Economic factors, such as high public investments, are basic aspects for

effective vaccination campaigns to cope with COVID-19 (Durmus, 2021). Some research suggests that higher-income countries perform better than low-income ones in vaccinating their citizens. The rollout of vaccinations is also associated with sociocultural factors, such as living conditions, education and religious beliefs, communication, etc. (Coccia, 2018a, 2018b). In this context, political and administrative factors are relevant aspects for crisis management of pandemic threats, but they are hardly known (Coccia, 2018, 2021e; Kluge *et al.*, 2020). A number of studies argue that good governance can support policy responses against COVID-19 pandemic (Cylus *et al.*, 2021; Kluge *et al.*, 2020; Sagan, 2021). Janssen & van der Voort (2020) highlight the key role of agile and adaptive governance in crisis management of COVID-19. However, Aschwanden (2020, 2021) raised many doubts about the achievement of herd immunity with current vaccination, which is a “false promise” because of manifold factors affecting transmission dynamics of COVID-19 (Coccia, 2021b, 2021c).

In this context of uncertain policy responses and effects of COVID-19, the presentation of new results and new knowledge in these fields of research are basic to improve the governance of countries to design an effective strategy to prevent future epidemics similar to COVID-19 that generate health and socioeconomic issues for nations and globally (Coccia, 2021c). In fact, it is more and more necessary to provide new knowledge and findings to support policy makers and reduce their bounded rationality to support effective and timely policy responses in the presence of new waves of COVID-19 pandemic and similar epidemics of new viral agents.

The purpose of this book is to provide a collection of new studies to clarify some of the topics just mentioned, focusing on critical aspects of COVID-19 in an interdisciplinarity perspective. In particular, *what this book adds to current studies* is main results about:

- determinants in the emergence of biological agents to improve aspects connected with public health and biosecurity

Introduction

- underlying relationships between infected people and environmental, demographic, and geographical factors that influenced COVID-19 spread
- role of high expenditures in health sector and a lower exposure of population to air pollution, regardless a higher percentage of population aged more than 65 years, to mitigate average COVID-19 fatality rate
- effects of restriction policies on level of COVID-19 mortality and on dynamics of economic growth in countries
- optimal level of vaccination between countries and main effects on the level of COVID-19 infections and mortality

Finally, the book shows some approaches to support decision making for crisis management to cope with COVID-19 pandemic crisis and emergencies of infectious diseases of similar viral agents.

Overall, then, the studies presented in this book show main aspects of the evolution of problems associated with the COVID-19 and of the improvement of preparedness in countries to cope with next pandemic impacts. Social studies, like the present book, are a vital tool that can complement studies of biology and medicine in contexts of interdisciplinary perspective of the ecology of COVID-19 that can explain critical relationships underlying infectious diseases in interaction with environment and society and how novel diseases and containment polices affect economy and society.

This book endeavors to clarify challenges and hardly known effects of COVID-19 and of the control measures that can help policy makers to develop effective regulations to support healthcare sector and to reduce risk factors associated with future epidemics similar to the COVID-19.

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2023

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1

Determinants in the emergence of viral agents: The SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared in late 2019 ([Anand *et al.*, 2021](#); [Bontempi *et al.*, 2021](#); [Bontempi & Coccia, 2021](#); [Coccia, 2021, 2021a](#)). One of the main questions in science and society is if the origins of SARS-CoV-2 is due to natural event of spillover from wildlife or associated with human activity of scientific research ([Andersen *et al.*, 2020](#); [Boni *et al.*, 2020](#); [Frutos *et al.*, 2021; 2022](#); [Relman, 2020](#); [Sachs *et al.*, 2020](#); [Segreto *et al.*, 2021](#); [Wolfe *et al.*, 2007](#)). [Bloom *et al.* \(2021\)](#) argue that initially information provided by Chinese scholars does not clarify if the cause is due to a natural (zoonotic) spillover of bats through an intermediate host or a possible lab incident. The latter hypothesis may be associated with Mojiang mine (China)

Determinants in the emergence of viral agents: the SARS-CoV-2

incident in 2012 when six miners died with an unexplained viral pneumonia (cf., [Rahalkar & Bahulikar, 2020](#)). Frutos et al. (2022) discuss about pros and cons factors of the natural origin of the unexplained viral pneumonia in Wuhan (China) over 2019. In this context, Sirotkin & Sirotkin (2020) argue that the etiology of this novel coronavirus is hardly known because the intermediate host for completing a natural zoonotic jump is not identified, and the application of research techniques of gain-of-function¹ of viral serial passage is one of the possible sources of this novel coronavirus. In fact, the molecular analyses of specimens raise further questions that suggest further investigations of origins of SARS-CoV-2 and factors of risk associated with gain-of-function research (Sirotkin & Sirotkin, 2020). Relman (2020) maintain that to avoid next pandemics like COVID-19, it is important to unravel the origins of SARS-CoV-2. Sirotkin & Sirotkin (2020) also argue that the origin of SARS-CoV-2 plays an important aspect to develop effective drugs and apply appropriate treatments. Overall, then, COVID-19 is still circulating in 2021 with mutations of the novel coronavirus but the origins of SARS-CoV-2 are still unknown.

The present study confronts this problem here by developing a meta-analysis to clarify, whenever possible, the origins of SARS-CoV-2 considering the two principal hypotheses given by a natural spillover and factors associated with human activity in research laboratories². This study is part of a large research project directed to explain the origins of SARS-CoV-2, factors determining transmission dynamics of COVID-19 and best practices to design effective policy

1 Gain-of-function research (GoF research) applies techniques that genetically alter an organism (e.g., viruses) to improve the biological functions of gene products.

2 For scientific activity within research laboratories see: [Ardito et al., 2021; 2005a, 2008, 2016, 2019d, 2019e, 2019g](#); [Coccia and Benati, 2018](#); [Coccia and Cadario, 2014](#); [Coccia and Rolfo, 2000, 2008](#); [Pagliari and Coccia, 2021](#).

Methodology

The deductive approach of this study is as follows.

Firstly, the social and health phenomenon observed is the COVID-19 that is still circulating with mutations of the novel coronavirus (SARS-CoV-2)³ and generating continuous infections and deaths in manifold countries (Johns Hopkins Center for System Science and Engineering, 2021).

Secondly, multiple working hypotheses about possible origins of the SARS-CoV-2, based on literature, are proposed (Coccia, 2018):

Hypothesis 1. Natural (zoonotic) spillover from of the novel coronavirus from bats through intermediate host

Hypothesis 2. The application of scientific research for science advances (and consequently lab accident)

Thirdly, the proposed hypotheses are tested by metanalysis and statistical evidence to accept or reject them. In particular:

- The first hypothesis is assessed with estimates of the probability of occurrence used for big natural disasters that generate a lot of fatalities, considering COVID-19 pandemic as a natural disaster (USGS, 2021).

The second hypothesis is analyzed with the approach of *backward chaining*: an inference method used in many artificial intelligence applications (Russell & Norvig, 2010). Backward chaining starts with proposed hypothesis and works backwards from consequent facts to antecedent events to assess if any data supports any of these consequents (Figure 1).

³ WHO considers the following variants of concern: Beta, Gamma, Delta and Delta Plus; Variants of interest (Lambda and Mu) and manifold variants under monitoring (ECDC, 2021).

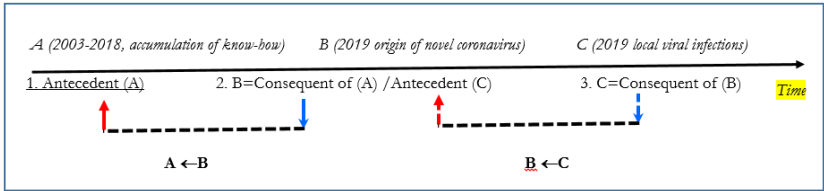


Figure 1. Backwards changing to explain the emergence of the novel viral agent

- Fact (consequent C): The novel virus was first identified in the Chinese city of Wuhan in December 2019
- (B=antecedent of C and consequent of A): the existence of laboratories in Wuhan able to apply scientific research of gain-of-function to support science advances in virology
- (A=antecedent of B). If Chinese lab located in Wuhan has technical know-how to support science advances in coronavirus. In fact, one of the most important approaches to explain scientific development is the theory of the accumulation of knowledge (Science, 1965). The cumulative theory states that scientific development is due to a gradual growth of knowledge based on a sum of facts accumulated by scholars, institutions and other subjects (Haskins, 1965; Seidman, 1987).

In this context of the accumulation of knowledge, basic and applied sciences evolve and converge creating discoveries and path-breaking innovations (Coccia & Wang, 2016; Coccia & Finardi, 2012, 2013; Coccia & Bellitto, 2018; Coccia, 2018b, 2018c; 2020a, 2020b, 2020e, Haskins, 1965)⁴. Therefore, discoveries are driven by an activity of accumulation in science and this approach of the evolution of science is irreversible and can never go back (Science, 1965).

Accumulation of knowledge in this specific field of research is measured with total document results (articles, conference papers, conference reviews, book chapters, short surveys, letters, etc.) before the emergence of SARS-CoV-2 in 2019: i.e., from 2005 (first year) to 2018 in Scopus (2021), which is a

⁴ The scientific development is also associated with the evolution of technology (cf., Ardito *et al.*, 2021; Calabrese *et al.*, 2005; Coccia, 2014, 2015, 2017a, 2017c, 2017d, 2019a, 2019b, 2020d).

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multidisciplinary database that allows scientometrics analysis to explain characteristics of science and scientific research. Data under study to support the hypothesis are:

- Number of publications using as keywords in search documents of Scopus (2021): bat and SARS-CoV from 2005 to 2018 period
- Journals on which these studies are published
- Affiliations of these publications
- Funding sponsors of publications and scientific research
- Leading countries in these specific studies
- Key papers on these topics and vital subjects

Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

- *Hypothesis 1.* Origin of SARS-CoV-2 with natural (zoonotic) spillover from bats through an intermediate host

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has generated from December 2019 to November 2021 more than 5,210,000 deaths worldwide (Johns Hopkins University, 2021). This novel coronavirus and COVID-19 pandemic are assumed to be a natural disaster. U.S. Geological Survey (USGS) assesses natural disasters forecasting life loses. USGS (2021) calculates probability estimates for the occurrence of earthquake, hurricane, flood, and tornado disasters with 1,000 fatalities per event in the United States for 1 year exposure times (Table 1).

Table 1. *Forecasting Life Losses with Natural Disasters*

Disaster	1,000 fatalities per event	
	Exposure time	
	1 year	2 years
	Probability of occurrence %	≈Probability of occurrence %
Earthquakes	1.0	2.0
Hurricanes	6.0	12.0
Floods	0.4	0.8
Tornadoes	0.6	1.2
Arithmetic mean of all disasters	2.0	4.0

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The average probability of occurrence of a big natural disaster that generates in 2 years 1,000 fatalities is roughly 4.0%; *mutatis mutandis* a natural disaster that generates over 2 years almost 5,000,000 fatalities is infinitely small (i.e., probability of occurrence is almost 0%) or impossible event. This basic analysis leads to reject the hypothesis of natural spillover of the novel coronavirus from bats to worldwide society.

□ *Alternative Hypothesis 2. Application of scientific research to coronaviruses for science advances*

The second hypothesis is analyzed with the approach of *backward chaining*:

- November-December 2019. Fact (consequent C): the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first identified in the Chinese city of Wuhan in December 2019. At the end of 2019, medical professionals in Wuhan (China) were treating cases of pneumonia that had an unknown source (Backer *et al.*, 2020; Li *et al.*, 2020; Public Health England, 2020; Riou & Alhaus, 2020). Days later, researchers confirmed that the illnesses (called COVID-19) were caused by a new coronavirus (SARS-CoV-2).
- 2018 year (fact B as antecedent of C): in Wuhan (China) there is a principal laboratory able to support science advances in virology: Wuhan Institute of Virology Chinese Academy of Sciences (CAS), that was founded in 1956. It is the only institute in the country focused exclusively on carrying out fundamental research in general virology. Its research has expanded from general virology to encompass clinical related virology and research on emerging disease (WIV, 2021). Fact B as antecedent of C is also a main consequent of A.
- 2005-2018 (A is antecedent B). This period, before the emergence of the novel coronavirus, has a lot of scientific research concerning the relationship between bats and SARS-CoV as detected with an in-depth search in Scopus (2021). At global level from 2005 (first year available) to 2018, there are 133 document results in this specific topic. The leading laboratories to perform scientific research on

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these specific topics are Chinese Academy of Sciences, Wuhan Institute of Virology-Chinese Academy of Sciences and The University of Hong Kong (Figure 2). These studies have been published in international journals, such as Journal of virology, Mbio, Archives of biology and Journal of general Virology (Figure 3). Instead, the most important funding sponsors of these studies are in figure 4, such as National Institute of Allergy and Infectious Diseases, National Institutes of Health, National Natural Science Foundation of China, U.S. Department of Health and Human Services, Chinese Academy of Sciences and Ministry of Science and

Technology of the People's Republic of China. Finally, the proactive countries in the studies on these topics are in figure 5.

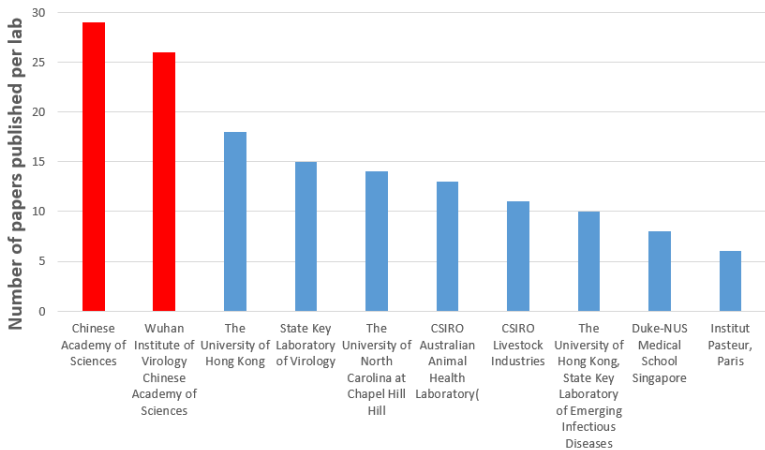


Figure 2. Leading top 10 laboratories in performing scientific research on SARS-CoV from 2005 to 2018.

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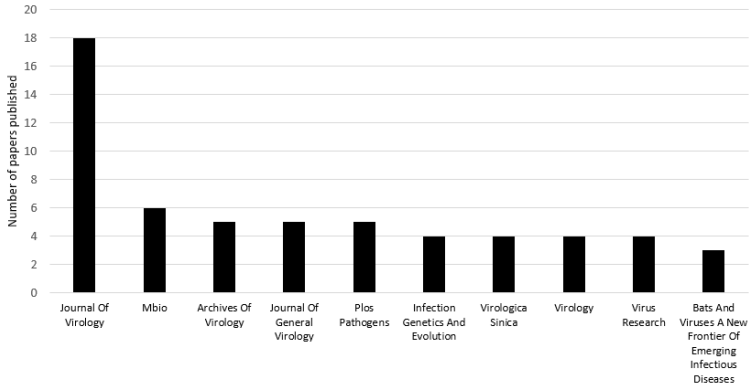


Figure 3. Top 10 journals publishing scientific research on SARS-CoV from 2005 to 2018.

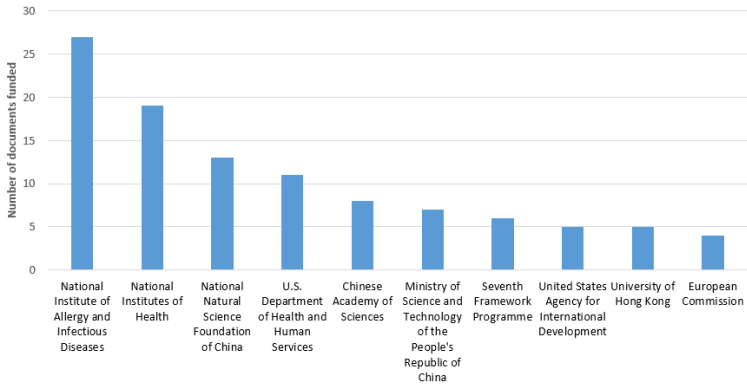


Figure 4. Top 10 funding sponsor of scientific research on SARS-CoV from 2005 to 2018.

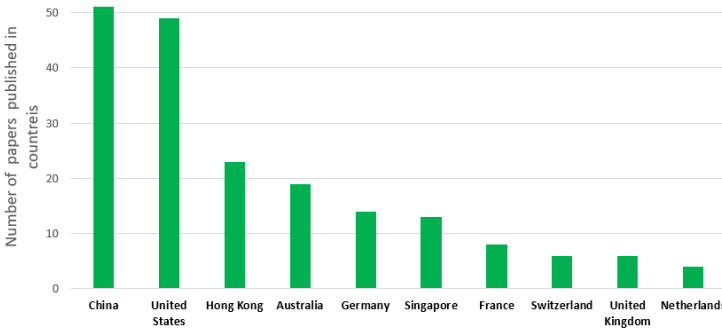


Figure 5. Top 10 countries performing scientific research on SARS-CoV from 2005 to 2018.

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A focus on scientific research concerning bat and SARS-CoV over 2005-2018 period in Wuhan Institute of Virology-Chinese Academy of Sciences (Scopus, 2021), which is in the epicenter city of COVID-19 shows that has 26 papers published on international journals (e.g., Journal of General Virology, Journal of Virology, Virologica Sinica, Archives of Virology, BMC Evolutionary Biology, Bats and Viruses-A New Frontier of Emerging Infectious Diseases, etc.). The 26 paper represents 20% of total publications over 2005-2018. If we consider also Chinese Academy of Science, having 29 papers, The University of Hong Kong with 28 papers (with State Key Laboratory of Emerging Infectious Diseases) and State Key Laboratory of Virology (Center for Emerging Infectious Diseases, Wuhan Institute of Virology-WIV) with 15, in China there is more than 74% of scientific research in these topics over 2005-2018. These studies at WIV are done mainly in collaboration with Chinese Academy of Sciences, CSIRO Australian Animal Health Laboratory, CSIRO Livestock Industries, Duke-NUS Medical School Singapore, East China Normal University, University of Chinese Academy of Sciences, etc.

Main funding sponsors of these studies are: Ministry of Science and Technology of the People's Republic of China, National Institutes of Health, Chinese Academy of Sciences, National Institute of Allergy and Infectious Diseases, National Natural Science Foundation of China, U.S. Department of Health and Human Services, Fogarty International Center, Commonwealth Scientific and Industrial Research Organisation, European Commission and National Research Foundation Singapore (cf., Appendix A).

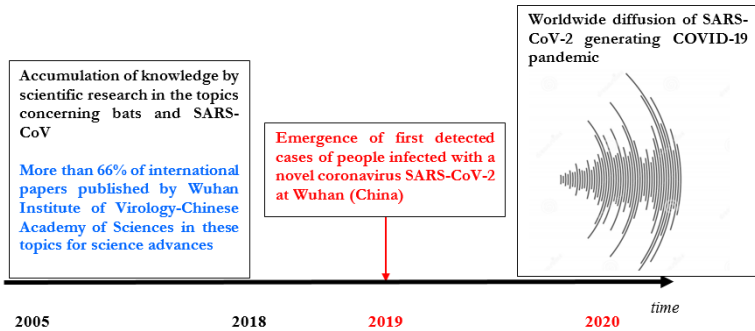


Figure 6. Chronology of events associated with COVID-19 pandemic shock

Overall, the leading role worldwide of Wuhan Institute of Virology Chinese Academy of Sciences in the research on bat and SARS-CoV to produce science advances suggests that this laboratory has accumulated technical knowledge and know-how over 2005-2018 period to support a gradual growth of knowledge in fundamental research in this field of research (Figure 6). Hence, this backward reasoning seems to support the hypothesis that the novel coronavirus may be originated with a process of accumulation of knowledge (2005-2018=13 years) in a specific place over time and space with research directed to science advances.

Discussion

Relman (2020) argues that: “A deliberative process for investigating the origins of this pandemic must be representative of all relevant disciplines, expertise, and stakeholders; must achieve political neutrality, scientific balance, and access to all relevant information and samples; and must operate with transparency and independent oversight. Without these features, it will not be credible, trustworthy, or effective”. In this context, the findings of the study here suggest that natural spillover of the novel coronavirus is a rare or impossible event, whereas the creation of a novel coronavirus with a research activity to produce science advances is a reasonable hypothesis because of the accumulation of knowledge in this specific research filed in

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the principal laboratories over 2005-2018 period. In particular, the hypothesis of a (natural) zoonotic spillover from bats, through an intermediate host to humans, is a rare event because some scholars wrongly compare nature to an engineer. Jacobs (1977) argues that this is a misleading comparison because unlike natural evolution, the engineers work with a conceived plan to achieve goals (products) with their endeavors. Moreover, engineers work to produce a new product using specific materials and equipment designed to achieve the task. Relman (2020) argue that the explanation of the origin of SARS-CoV plays a vital role in forecasting future pandemics. If the hypothesis of natural spillover from bats is true with strong evidence of the casual event of SARS CoV- 2 passing directly from bat to human, or by an intermediate host, then efforts of prevention must be directed to improve the management of the interactions between bats (and in general wildlife) and human (cf., Latinne *et al.*, 2020). Daszak *et al.* (2020) argue that to prevent the next epidemic and pandemic like COVID-19, research and investment of nations⁵ should focus on:

- 1) surveillance among wildlife to identify the high-risk pathogens they carry
- 2) surveillance among people who have contact with wildlife to identify early spillover events
- 3) improvement of market biosecurity regarding the wildlife trade.

However, if the novel coronavirus is created by scholars by research for science advances and then "SARSCoV-2 escaped from a lab" (Relman, 2020) causing a pandemic crisis, critical aspects of prevention are the improvement of biosecurity in laboratory testing of hazardous pathogens. A further comparative meta-analysis of two hypotheses shows that natural spillover of SARSCoV-2 (that is generating high numbers of COVID-19 related infections and deaths in two years) is almost an impossible event (using the analogy with

⁵ Effective R&D investments of nations in the activity of prevention of infectious diseases is associated with economic development and good institutions; see Coccia, 2005, 2017, 2017b, 2018a, 2019c, 2019f, 2021g.

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the probability of occurrence of other natural disasters; cf., [USGS, 2021](#)), whereas manifold studies shows that there have been several high-profile accidents in research laboratories worldwide ([Ménard & Trant, 2020](#)). In fact, Hellman et al. (1986) examining almost 600 accidents between 1966 and 1984, found that 13% of accidents occurred in research labs and 2% in fabrication rooms. Van Noorden (2013), with a survey from Nature and UCLA of about 2,500 scientists, reveals that 30% of interviewed reported having witnessed a severe lab injury. Another study in Canadian chemistry and biology labs reports that 15% of scholars surveyed had at least one injury ([Ayi & Hon, 2018](#)). Simmons et al. (2018) found that lab accidents represented 18.4% of the total incidents reported at Iowa State university. In fact, the support of the hypothesis of human factors in the origins of SARS-CoV-2, and likely accident lab and consequential diffusion in society, leads to basic aspects of improving the technical guidelines at all levels for biosafety of laboratories conducting testing of hazardous pathogens similar to SARS-CoV-2 that generate pandemic crisis (Figure 7).

<p>Hypothesis 1</p> <p><i>Natural spillover from bats through an intermediate host of the novel coronavirus</i></p>	<p>Hypothesis 2</p> <p><i>Process of research for science advances and lab accident with consequential spatial-temporal diffusion</i></p>
<p>Probability of occurrence of a natural event generation with more than 5,200,000 deaths</p>	<p>Probability of a lab accident</p>
<p>≈ 0%</p>	<p>≈ 13-30%</p>

Figure 7. Comparative probability of proposed hypotheses based on a meta-analysis.

Ménard & Trant (2020, p.18) maintain that factors determining lab accidents can be due to: "risks associated with the materials or equipment being used, risks related to the skills, knowledge and choices of the research personnel doing the study, characteristics or qualities of the PI and the research lab in which the research is occurring and risk factors arising from the departmental or institutional level".

Hence, *a priori* the epidemic/pandemic, in responding to a

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constant pandemic threat of novel viral agents in future, the international communities must reinforce surveillance and proper biosafety procedures in public and private institutes of virology that study viruses and new viruses to avoid that may be accidentally spread in surrounding environments with damages for population and vegetation. In this context, international collaboration among scientists is a basic aspect to address these risks and support decisions of policymakers to prevent lab accidents and threats for future pandemics that create huge socioeconomic issues worldwide (National Health Commission of The People's Republic of China , 2020)⁶. Yuan *et al.* (2020) argue that in China, information of lab safety should be internally linked to the national intelligent syndromic surveillance system, which could help different levels of organizations to better coordinate and allocate resources for targeted investigations and interventions to improve the biosafety of labs at the greatest need and facilitate more comprehensive surveillance of risk for disease outbreak (Jia & Yang, 2020).

A posteriori in the initial phase of the epidemic/pandemic, prevention and preparedness of pandemic threats have to directed to design and implement strategic actions given by improvements of the early warning systems in the international community using existing infrastructure to ensure rapid detection of suspected cases in humans based on reliable international laboratories that receive all the data and clinical specimens needed for an accurate evaluation of an emergence of pandemic risk for applying timely containment operations al local and global level (Coccia, 2021d, 2022).

Conclusion

The origins of novel viral agents associated with future epidemics/pandemics pose, more and more, serious questions and policy responses to security, biosecurity and public health of nations (Relman, 2020). A pandemic like COVID-19 can occur at any time with little warning; any delay in detecting

⁶ Some accidents can be also due to terrorism activity (Coccia, 2018d).

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and sharing novel virus samples; and in developing, producing, distributing, or administering a therapeutic or vaccine could result in significant additional morbidity and mortality, and deterioration of socioeconomic systems (Coccia, 2020c, 2021a, 2021e, 2021i; Huang *et al.*, 2021). The findings of the study here suggest that natural spillover of the novel coronavirus is a rare or impossible event, whereas the creation of a viral agent with a research activity to produce science advances is a reasonable hypothesis because of the accumulation of knowledge in specific research fields of principal laboratories worldwide. Although this study has provided interesting results about the origin of SARS-CoV-2, that are of course tentative, it has several limitations. First, a limitation of the study is the lack of data about specific scientific activity of laboratory testing for hazardous pathogens also because of information that are classified for national security. Second, not all possible confounding factors that affect the origins of this novel coronavirus are taken into consideration and in future these factors deserve to be analyzed for supporting results here. Third, the lack of integration of data to find parents additional genome sequences of coronaviruses and measurements of SARS-CoV-2 evolution under a variety of defined conditions. Future research should consider these aspects, new data, when available, and when possible, to examine also other factors associated with the origins of this novel coronavirus. Despite these limitations, the results presented here suggests the critical aspect of the accumulation of scientific knowledge that is a main factor to support science advances in the field of virology for the creation of novel viral agents (Wu *et al.*, 2016; Zhang & Holmes, 2020). However, there is need for much more detailed research in these topics and this study encourages further investigations that should be collaborative between scholars of different disciplines and nations to have access to relevant information and to design appropriate policy responses to prevent similar pandemic both if the novel coronavirus has a natural spillover from wildlife and if it is due to scientific research for science advance and consequential laboratory accident.

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Overall, then, different factors of the origins of SARS-CoV-2 are not only related to medicine but also to other social, political and economic aspects, as well as leadership in international system, play a critical role to clarify the truth and to improve the preparedness of countries to prevent similar pandemic or to control negative impact of pandemic crisis on public health, economy and society (cf., Coccia, 2019, 2020a; Coccia, 2021f; 2021h). To conclude, Relman (2020) argues that: “A deliberative process for investigating the origins of this pandemic must be representative of all relevant disciplines, expertise, and stakeholders; must achieve political neutrality, scientific balance, and access to all relevant information and samples; and must operate with transparency and independent oversight.... A more complete understanding of the origins of COVID-19 clearly serves the interests of every person in every country on this planet. ... it will lead to more effective responses to this pandemic, as well as efforts to anticipate and prevent the next one. It will also advance our discussions about risky science”.

Appendix

Publications concerning bats and SARS-CoV from 2015 to 2018 period.

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2

Environmental, demographic, and geographical factors affecting the diffusion of COVID-19: A case study

Introduction

This chapter has two goals. The first is to explain the main factors determining the diffusion of COVID-19 that is generating a high level of deaths. The second is to suggest a strategy to cope with future epidemic threats with of accelerated viral infectivity in society.

Coronavirus disease 2019 (COVID-19) is viral infection that generates a severe acute respiratory syndrome with serious clinical symptoms given by fever, dry cough, dyspnea, and pneumonia and may result in progressive respiratory failure and death. Kucharski *et al.* (2020) argue that COVID-19 transmission declined in Wuhan (China) during late January, 2020 (WHO, 2019, 2020, 2020a; nCoV-2019 Data Working Group, 2020). However, as more infected individuals arrive in international locations before control measures are applied, numerous epidemic chains have led to new outbreaks in different nations worldwide (Xu & Kraemer Moritz, 2020; Wang *et al.*, 2020; Wu *et al.*, 2020). An outbreak of COVID-19 has led to more than 13,900 confirmed deaths in Italy and

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more than 51,000 deaths worldwide as of April 1st, 2020 (Johns Hopkins Center for System Science and Engineering, 2020; cf., Dong *et al.*, 2020). Understanding the prime factors of transmission dynamics of COVID-19 in Italy, having the highest number of deaths worldwide, is crucial for explaining possible relationships underlying the temporal and spatial aspects of the diffusion of this viral infectivity. Results here are basic to design a strategy to prevent future epidemics similar to COVID-19 that generates health and socioeconomic issues for nations and globally.

Currently, as people with the COVID-19 infection arrive in countries or regions with low ongoing transmission, efforts should be done to stop transmission, prevent potential outbreaks and to avoid second and subsequent waves of a COVID-19 epidemic (European Centre for Disease Prevention and Control, 2020; Quilty & Clifford, 2020; Wells *et al.*, 2020). Wells *et al.* (2020) argue that at the very early stage of the epidemic, reduction in the rate of exportation could delay the importation of cases into cities or nations unaffected by the COVID-19, to gain time to coordinate an appropriate public health response. After that, rapid contact tracing is basic within the epicentre and within and between importation cities to limit human-to-human transmission outside of outbreak countries, also applying appropriate isolation of cases (Wells *et al.*, 2020). The case of severe acute respiratory syndrome outbreak in 2003 started in southern China was able to be controlled through tracing contacts of cases because the majority of transmission occurred after symptom onset (Glasser *et al.*, 2011). These interventions also play a critical role in response to outbreaks where onset of symptoms and infectiousness are concurrent, such as Ebola virus disease (WHO, 2020b; Swanson *et al.*, 2018), MERS (Public Health England, 2019; Kang *et al.*, 2016) and other viral diseases (Hoang *et al.*, 2019; European Centre for Disease Prevention and Control, 2020a). Kucharski, *et al.* (2020) claim that the isolation of cases and contact tracing can be less effective for COVID-19 because infectiousness starts before the onset of symptoms (cf., Fraser *et al.*, 2004; Peak *et al.*, 2017). Hellewell *et al.* (2020) show that effective contact

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tracing and case isolation is enough to control a new outbreak of COVID-19 within 3 months, but the probability of control decreases with long delays from symptom onset to isolation that increase transmission before symptoms. However, it is unclear if these efforts will achieve the control of transmission of COVID-19. In the presence of COVID-19 outbreaks, it is crucial to understand the determinants of the transmission dynamics of this viral infectious disease for designing strategies to stop or reduce diffusion, empowering health policy with economic, social and environmental policies. This study focuses on statistical analyses of association between infected people and environmental, demographic and geographical factors that can explain transmission dynamics over time, and provide insights into the environmental situation to prevent and apply, *a priori*, appropriate control measures (Camacho *et al.*, 2015; Funk *et al.*, 2017; Riley *et al.*, 2003). In particular, this study here can explain, whenever possible, factors determining the accelerated viral infectivity in specific regions to guide policymakers to prevent future epidemics similar to COVID-19 (Cooper *et al.*, 2006; Kucharski *et al.*, 2015). However, there are several challenges to such studies, particularly in real time. Sources may be biased, incomplete, or only capture certain aspects of the on-going outbreak dynamics.

Data and study design

The complex problem of viral infectivity of COVID-19 is analysed here in a perspective of reductionist approach, considering the geo-environmental and demographic factors that we study to explain the relationships supporting the transmission dynamics (cf., Linstone, 1999). In addition, the investigation of the causes of the accelerated diffusion of viral infectivity is done with a philosophical approach *sensu* the philosopher Vico (Flint, 1884). In particular, the method of inquiry is also based on Kantian approach in which theoretical framework and empirical data complement each other and are inseparable. In this case the truth on this phenomenon,

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Data and their sources

This study focuses on $N=55$ Italian cities that are provincial capitals. Sources of data are The Ministry of Health in Italy for epidemiological data (Ministero della Salute, 2020), Legambiente (2019) for data of air pollution deriving from the Regional Agencies for Environmental Protection in Italy, il Meteo (2020) for data of weather trend based on meteorological stations of Italian province capitals, The Italian National Institute of Statistics for density of population concerning cities under study (ISTAT, 2020).

Measures

The unit of analysis is main Italian provincial cities. In a perspective of reductionism approach for statistical analysis and decision making, this study focuses on the following measures.

- Pollution: total days exceeding the limits set for PM_{10} (particulate matter 10 micrometres or less in diameter) or for ozone in the 55 Italian provincial capitals over 2018. This measure is stable over time and the strategy of using the year 2018, before the COVID-19 outbreak in Italy, is to include the health effects of exposures to pollutants, such as airborne particulate matter and ozone (Brunekreef *et al.*, 2002). In fact, days of air pollution within Italian cities are a main factor that has affected health of population and environment (Legambiente, 2019).

- Diffusion of COVID₁₉. Number of infected from 17 March, 2020 to April 2020 (Ministero della Salute, 2020). Infected are detected with COVID-19 tests according to following criteria:

- Have fever or lower respiratory symptoms (cough, shortness of breath) and close contact with a confirmed COVID-19 case within the past 14 days; OR

- Have fever and lower respiratory symptoms (cough, shortness of breath) and a negative rapid flu test

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- Meteorological indicators are: average temperature in °C, Moisture %, wind km/h, days of rain and fog from 1st February to 1 April, 2020 (il [Meteo](#), 2020).

- Interpersonal contact rates: a proxy here considers the density of cities (individual /km²) in 2019 ([ISTAT](#), 2020).

Data analysis and procedure

This study analyses a database of $N=55$ Italian provincial capitals, considering variables in 2018-2019-2020 to explain the relationships between diffusion of COVID₁₉, demographic, geographical and environmental variables.

Firstly, preliminary analyses of variables are descriptive statistics based on mean, std. deviation, skewness and kurtosis to assess the normality of distributions and, if necessary to fix distributions of variables with a *log*-transformation.

Statistical analyses are also done categorizing Italian provincial capitals ($N=55$) in groups as follows:

- Hinterland cities
- Coastal cities

Categorization in:

- Windy cities
- Not windy cities

Categorization in:

- Cities of North Italy
- Cities of Central-South Italy

Categorization in:

- Cities with >100 days per year exceeding the limits set for PM₁₀ or for ozone
- Cities with <100 days per year exceeding the limits set for PM₁₀ or for ozone

Categorization in:

- Cities with ≤ 1000 inhabitant/km²
- Cities with > 1000 inhabitant/km²

Categorization in:

- Cities with ≤ 500 inhabitant/km²
- Cities with 500-1500 inhabitant/km²
- Cities with > 1500 inhabitants/km²

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Secondly, the bivariate and partial correlation verifies relationships (or associations) between variables under study, and measures the degree of association. After that the null hypothesis (H_0) and alternative hypothesis (H_1) of the significance test for correlation is computed, considering two-tailed significance test.

Thirdly, the analysis considers the relation between independent and dependent variables. In particular, the dependent variable (number of infected people across Italian provincial capitals) is a linear function of a single explanatory variable given by total days of exceeding the limits set for PM_{10} across Italian province capitals. Dependent variables have in general a lag of 1 years in comparison with explanatory variables to consider temporal effects of air pollution predictor on environment and population in the presence of viral infectivity by COVID19 in specific cities of Italy.

The specification of the linear relationship is a *log-log* model is:

$$\log y_t = \alpha + \beta \log x_{t-1} + u \tag{1}$$

α is a constant; β = coefficient of regression; u = error term

y = dependent variable is number of infected individuals in cities

x =explanatory variable is a measure of air pollution, given by total days of exceeding the limits set for PM_{10} or ozone in cities

This study extends the analysis with a multiple regression model to assess how different indicators can affect diffusion of COVID-19. The specification of the linear relationship is also a *log-log* model as follows:

$$\log y_t = \alpha + \beta_1 \log x_{1, t-1} + \beta_2 \log x_{2, t-1} + u \tag{2}$$

y = dependent variable is number of infected individuals in cities

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x_1 = explanatory variable is a measure of air pollution, given by total days of exceeding the limits set for PM₁₀ or ozone in cities

x_2 = density of cities, inhabitants /km²

In addition, equation [2] is performed using data of infected at $t=17^{\text{th}}$ March, 2020 in the starting phase of growth of the outbreak in Italy, and the at $t+16\text{days}=1^{\text{st}}$ April, 2020 in the phase of maturity of viral infectivity during lockdown and quarantine to assess the magnitude of two explanatory variables in the transmission dynamics of COVID-19. The estimation of equation [2] is also performed using hierarchical multiple regression, a variant of the basic multiple regression procedure that allows to specify a fixed order of entry for variables in order to control for the effects of covariates or to test the effects of certain predictors independent of the influence of others. The R^2 changes are important to assess the predictive role of additional variables. The adjusted R-square and standard error of the estimate are useful as comparative measures to assess results between models. The F -test evaluates if the regression model is better than using only the mean of the dependent variable. If the F value is very small (e.g., 0.001), then the independent variables reliably predict the dependent variable.

Moreover, the linear relationship is also specified with a quadratic model as follows:

$$y_t = \alpha + \beta x_{t-1} + \beta (x_{t-1})^2 + u \quad (3)$$

the goal is to apply an optimization approach, to calculate the minimum of equation [3] that suggests the maximum number of days in which cities can exceed the limits set for PM₁₀ or ozone. Beyond this critical estimated limit, there are environmental inconsistencies of air pollution associated with meteorological conditions that can trigger a take-off of viral infectivity with damages for health of population and economic system (cf., Coccia, 2017c, 2017d). The max number of days in which cities can exceed the limit set for air pollution that minimizes the number of people infected, before the take-off of epidemic curve, can also suggest

Environmental, demographic, and geographical factors affecting the diffusion... implications of proactive strategies and critical decision to cope with future epidemics similar to COVID-19 in society. Ordinary Least Squares (OLS) method is applied for estimating the unknown parameters of relations in linear regression models [1-3]. Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

Descriptive statistics of variables in *log* scale, based on Italian province capitals ($N=55$), have normal distribution to apply appropriate parametric analyses.

Table 1. Descriptive statistics of Hinterland and Coastal Italian province capitals

	Days exceeding limits set for PM ₁₀ or ozone 2018	Infected 17 th March 2020	Infected 1 st April 2020	Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020	Rain Days Feb-Mar 2020	Fog Days Feb-Mar 2020
<i>Hinterland cities N=45</i>									
Mean	80.40	497.00	1929.69	1480.11	9.11	68.31	8.02	4.81	4.14
Std. Deviation	41.66	767.19	2265.86	1524.25	2.20	7.68	3.69	2.38	3.13
<i>Coastal cities N=10</i>									
Mean	59.40	171.30	715.80	1332.80	10.61	74.40	11.73	5.10	3.25
Std. Deviation	38.61	164.96	522.67	2463.04	2.20	7.38	2.60	2.71	3.68

Table 1 shows that hinterland cities have and average higher level of infected individuals than coastal cities. Hinterland cities have also a higher air pollution (average days per years) than coastal cities, in a context of meteorological factors of lower average temperature, lower average wind speed, lower rain days and lower level of moisture % than coastal cities.

Table 2. Descriptive statistics of windy and not windy of Italian province capitals

	Days exceeding limits set for PM ₁₀ or ozone 2018	Infected 17 th March 2020	Infected 1 st April 2020	Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020	Rain Days Feb-Mar 2020	Fog Days Feb-Mar 2020
<i>Low windy cities N=41</i>									
Mean	84.32	536.20	2036.15	1517.41	9.05	68.23	7.30	4.56	4.18
Std. Deviation	43.31	792.84	2333.72	1569.70	2.12	7.50	2.77	2.33	2.94
<i>High windy cities N=14</i>									
Mean	53.93	149.57	750.86	1265.64	10.36	72.89	12.77	5.75	3.39
Std. Deviation	25.87	153.55	640.02	2108.31	2.43	8.37	3.46	2.56	4.00

Table 2 shows that cities with low intensity of wind speed (7.3km/h) have an average higher level of infected individuals than windy cities (average of 12.77km/h). Cities with lower intensity of wind speed have also a higher level of air pollution (average days per years), in a meteorological context of lower average temperature, lower rain days, lower level of moisture % and a higher average days of fog.

Table 3. Descriptive statistics of Northern and Central-Southern Italian province capitals

	Days exceeding limits set for PM ₁₀ or ozone 2018	Infected 17 th March 2020	Infected 1 st April 2020	Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020	Rain Days Feb-Mar 2020	Fog Days Feb-Mar 2020
<i>Norther cities N=45</i>									
Mean	80.51	515.60	1968.4	1448.00	9.05	69.40	7.89	4.80	4.31
Std. Deviation	42.67	759.18	2230.4	1538.10	1.97	7.61	3.15	2.42	3.06
<i>Central-Southern cities N=10</i>									
Mean	58.90	87.60	541.5	1477.30	10.88	69.50	12.31	5.15	2.50
Std. Deviation	32.36	129.98	735.2	2424.50	2.92	9.64	4.44	2.52	3.65

Table 3 shows that cities in the central and southern part of Italy have, during the COVID-19 outbreak, a lower number of infected than cities in North Italy. This result is in an environment with lower air pollution (average days per years),

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 higher average temperature, higher average wind speed,
 higher rain days and lower level of moisture %.

Table 4. Descriptive statistics of Italian provincial capitals according to days exceeding the limits set for PM₁₀

	Days exceeding limits set for PM ₁₀ or ozone			Density inhabitants/km ²	Temp °C	Moisture %	Wind km/h	Rain Days	Fog Days
	Infected 17 th March 2018	Infected 1 st April 2020	2020						
<i>Cities with >100days exceeding limits set for PM₁₀ N=20</i>									
Mean	125.25	881.70	3124.75	1981.40	9.19	71.30	7.67	4.80	4.88
Std. Deviation	13.40	1010.97	2905.18	1988.67	1.46	7.63	2.86	2.57	2.65
<i>Cities with <100days exceeding limits set for PM₁₀ N=35</i>									
Mean	48.77	184.11	899.97	1151.57	9.49	68.34	9.28	4.90	3.47
Std. Deviation	21.37	202.76	708.32	1466.28	2.62	7.99	4.15	2.37	3.44

Table 4 confirms previous results considering cities with >100days exceeding limits set for PM₁₀ or ozone: they have, versus cities with less than 100 days, a very high level of infected individuals, in an environment of higher average density of population, lower average intensity of wind speed, lower average temperature with higher average moisture % and days of fog.

Table 5. Descriptive statistics of Italian provincial capitals according to density per km² (2 categories)

	Days exceeding limits set for PM ₁₀ or ozone			Density inhabitants/km ²	Temp °C	Moisture %	Wind km/h	Rain Days	Fog Days
	Infected 17 th March 2018	Infected 1 st April 2020	2020						
<i>Cities with ≤1000 inhabitant/km² N=30</i>									
Mean	64.37	248.37	960.97	510.77	10.01	69.61	9.28	4.08	3.75
Std. Deviation	39.25	386.95	951.26	282.11	1.95	10.30	4.41	2.37	3.40
<i>Cities with >1000 inhabitant/km² N=30</i>									

>1000 inhabitant/km ² N=25									
Mean	91.24	665.08	2606.60	2584.40	8.63	69.19	7.99	5.80	4.26
Std. Deviation	40.24	919.70	2717.57	2000.63	2.40	3.59	2.79	2.17	3.03

Table 6. Descriptive statistics of Italian provincial capitals according to density per km² (3 categories)

	Days exceeding limits set for PM ₁₀ or ozone 2018	Infected 17 th March 2020	Infected 1 st April 2020	Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020	Rain Days Mar 2020	Fog Days Feb-Mar 2020
<i>Cities with <1000 inhabitant/km² N=17</i>									
Mean	52.82	116.12	567.12	312.76	9.88	71.12	9.52	4.44	4.41
Std. Deviation	36.87	128.13	466.49	161.34	2.12	8.91	5.73	2.79	3.79
<i>Cities with 500-1000 inhabitant/km² N=22</i>									
Mean	84.32	430.91	1519.50	951.32	9.04	68.50	8.37	4.34	3.75
Std. Deviation	37.28	476.29	1018.07	277.77	2.65	9.17	2.33	2.06	2.99
<i>Cities with >1000 inhabitant/km² N=16</i>									
Mean	91.19	789.00	3182.75	3355.44	9.33	68.86	8.26	6.03	3.84
Std. Deviation	43.29	1103.03	3239.96	2151.27	1.81	4.32	2.79	2.19	3.03

Tables 5-6 show results considering categorization of cities per density of population/km². Results reveal that average number of infected individuals increases with average density of people/km², but with an arithmetic growth, in comparison to geometric growth of number of infected individuals with other categorizations of cities. These findings suggest that density of population per km² is important for transmission dynamics but other factors may support acceleration of viral infectivity by COVID-19 rather than high probability of interpersonal contacts in cities.

In short, results suggest that among Italian province capitals:

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- Number of infected people is HIGHER in: Cities with >100 days exceeding limits set for PM₁₀ or ozone, located in hinterland zones having a low average intensity of wind speed and lower temperature in °C.

Table 7. Correlation

N=55	Log Days exceeding limits set for PM ₁₀ or ozone 2018	Log Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020
Log Infected 17 March, 2020					
Pearson Correlation	.643**	.484**	-.117	.005	-.377**
Sig. (2-tailed)	.001	.001	.397	.970	.005
N=55	Days exceeding limits set for PM ₁₀ or ozone 2018	Density inhabitants/km ² 2019	Temp °C Feb-Mar 2020	Moisture % Feb-Mar 2020	Wind km/h Feb-Mar 2020
Log Infected 1 April, 2020					
Pearson Correlation	.620**	.552**	-0.247	0.049	-0.281*
Sig. (2-tailed)	0.001	0.001	0.069	0.720	0.038

Note: **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

Table 7 shows association between variables on 17th March and 1st April, 2020: a correlation higher than 62% (p -value<.001) is between air pollution and infected individuals, a lower coefficient of correlation is between density of population and infected individuals ($r=48-55\%$, p -value<.001). Results also show a negative correlation between number of infected individuals and intensity of wind speed among cities ($r= -28$ to -38% , p -value <0.05): this effect is due to the role of wind speed that cleans air from pollutants that are associated with transmission dynamics of viral infectivity.

Table 8. Partial Correlation

<i>Control Variables</i>		<i>Log Infected 17 March, 2020</i>	<i>Log Infected 1 April, 2020</i>
Temp °C	<i>Pearson Correlation</i>		
Moisture %			
Wind km/h			
Feb-Mar 2020			
	<i>Log Days exceeding limits set for PM₁₀ or ozone 2018</i>	0.607	.602
	<i>Sig. (2-tailed)</i>	.001	.001
	<i>N</i>	50	50

Table 8 confirms the high correlation between air pollution and infected individuals on 17th March and 1 April, 2020, controlling meteorological factors of cities under study ($r>60\%$, $p\text{-value}<.001$).

Table 9. Partial correlation

<i>Control Variables</i>		<i>Log Infected 17 March, 2020</i>	<i>Log Infected 1 April, 2020</i>
<i>Log Density inhabitants/km² 2019</i>	<i>Pearson Correlation</i>		
	<i>Log Days exceeding limits set for PM₁₀ or ozone 2018</i>	0.542	.496
	<i>Sig. (2-tailed)</i>	.001	.001
	<i>N</i>	52	52
<i>Log Days exceeding limits set for PM₁₀ or ozone 2018</i>	<i>Pearson Correlation</i>		
	<i>Log Density inhabitants/km² 2019</i>	0.279	.385
	<i>Sig. (2-tailed)</i>	.041	.004
	<i>N</i>	50	50

Partial correlation in table 9 suggests that controlling density of population on 17th march and 1st April 2020, number of infected people is associated with air pollution ($r\geq 50\%$, $p\text{-value}<.001$), whereas, controlling air pollution the correlation between density of population in cities and infected individuals is lower ($r=27\text{-}38\%$, $p\text{-value}<.001$). The reduction

Environmental, demographic, and geographical factors affecting the diffusion... of r between infected individuals and air pollution from 17th March to 1st April, and the increase of the association between infected people and density of people in cities over the same time period, controlling mutual variables, suggests that that air pollution in cities seems to be a more important factor in the initial phase of transmission dynamics of COVID-19 (i.e., 17th March, 2020). In the phase of the maturity of transmission dynamics (1st April, 2020), with lockdown that reduces air pollution, the role of air pollution reduces intensity whereas human-to-human transmission increases.

Table 10. Parametric estimates of the relationship of Log Infected 17 March and 1 April on Log Days exceeding limits set for PM₁₀ and Log Density inhabitants/km² 2019 (hierarchical regression)

	Model 1A Step 1: Air pollution	Model 2A, Step 2: Interpersonal contacts	Model 1B Step 1: Air pollution	Model 2B, Step 2: Interpersonal contacts
	log Days exceeding limits set for PM ₁₀ , 2018	log Days exceeding limits set for PM ₁₀ , 2018	log Days exceeding limits set for PM ₁₀ , 2018	log Days exceeding limits set for PM ₁₀ , 2018
log infected 17th March, 2020			log infected 1st April, 2020	
Constant α	-1.168	-2.168	Constant α	2.171**
(St. Err.)	(1.053)	(1.127)	(St. Err.)	(.827)
Coefficient β_1	1.526***	1.266***	Coefficient β_1	1.129***
(St. Err.)	(0.250)	(.272)	(St. Err.)	(.196)
Coefficient β_2		.309*	Coefficient β_2	
(St. Err.)		(.148)	(St. Err.)	
F	37.342***b	22.059* **c	F	33.158***b
R ²	0.413	0.459	R ²	.385
ΔR^2 .	0.413	0.046	ΔR^2 .	.385
ΔF	37.342***	4.388*	ΔF	33.158***
				1.089 (.851) .847*** (.206) .335** (.111) 23.604* **c .476 .091 9.028**

Notes: *** p -value < 0.001; ** p -value < 0.01; * p -value < 0.05; b = predictors: log Days exceeding limits set for PM₁₀; c = predictors: log Days exceeding limits set for PM₁₀, 2018 year; Log Density inhabitants/km² 2019.

These findings are confirmed with hierarchical regression that also reveals how air pollution in cities seems to be a driving factor of transmission dynamics in the growing phase of COVID-19 (17th March, 2020). In the phase of the maturity of transmission dynamics (1st April, 2020), the determinant of air pollution is important to support infected population but

Environmental, demographic, and geographical factors affecting the diffusion... reduces intensity, whereas the factor of human-to-human transmission increases, *ceteris paribus* (Table 10). This result reveals that transmissions dynamics of COVID-19 is due to human-to-human transmission but the factor of air pollution-to-human transmission of viral infectivity supports a substantial growth.

Table 11. Parametric estimates of the relationship of Log Infected 1st April, 2020 on Log Density inhabitants/km² 2019, considering the groups of cities with days exceeding limits set for PM₁₀ or ozone

↓DEPENDENT VARIABLE	Model cities with <100 days exceeding limits set for PM ₁₀ or ozone, 2018	↓DEPENDENT VARIABLE	Model cities with >100 days exceeding limits set for PM ₁₀ or ozone, 2018
	Log Density inhabitants/km ² 2019		Log Density inhabitants/km ² 2019
<i>log</i> infected 1 April, 2020		<i>log</i> infected 1 April, 2020	
Constant α (St. Err.)	4.501 (.801)	Constant α (St. Err.)	1.425 (1.624)
Coefficient β_1 (St. Err.)	0.303* (0.122)	Coefficient β_1 (St. Err.)	0.856*** (0.223)
R ² (St. Err. of Estimate)	0.158 (.828)	R ² (St. Err. of Estimate)	0.450 (.803)
F	6.207*	F	14.714***

Note: Explanatory variable: Log Density inhabitants/km² in 2019; *** p-value<0.001; * p-value<0.05.

Table 11 shows results of the transmission dynamics of COVID-19 considering the interpersonal contacts, measured with density of population in cities understudy. In short, results suggest that density of population explains the number of infected individuals, increasing the probability of human-to-human transmission. However, if we decompose the sample to consider the cities with ≤ 100 days exceeding limits set for PM₁₀ or ozone and with >100 days exceeding limits set for PM₁₀ or ozone, then the expected increase of number of infected individuals is higher in cities having more than 100 days exceeding limits set for PM₁₀ or ozone. In particular,

- Cities with ≤ 100 days exceeding limits set for PM₁₀, an increase of 1% in density of population, it increases the expected number of infected by about 0.30%

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- Cities with >100 days exceeding limits set for PM₁₀, an increase of 1% in density of population, it increases the expected number of infected by about 1.43%!

The statistical output of table 11 is schematically summarized as follows:

	Cities with ≤100 days exceeding limits set for PM ₁₀	Cities with >100 days exceeding limits set for PM ₁₀
Density of population	0.30 (<i>p</i> <0.05)	1.43 (<i>p</i> <0.001)
<i>F</i>	6.207 (<i>p</i> <0.05)	14.714 (<i>p</i> <0.001)
<i>R</i> ²	15.8%	45%

In short, the coefficient of regression in cities with >100 days exceeding limits set for PM₁₀ is much bigger than the coefficient in cities with ≤100 days exceeding limits set for PM₁₀, suggesting that air pollution-to-human transmission is definitely important to explain the transmission dynamics of COVID-19. The policy implications here are clear: COVID-19 has reduced transmission dynamics on population in the presence of lower level of air pollution and specific environments with lower intensity of wind speed. Hence, the effect of accelerated transmission dynamics of COVID-19 cannot be explained without accounting for the level of air pollution and geo-environmental conditions of the cities.

Table 12. Parametric estimates of the relationship of Infected 1st April, 2020 on days exceeding limits set for PM₁₀ (simple regression analysis, quadratic model)

Explanatory variable	Response variable: Infected 1 April, 2020			<i>F</i> (sign.)
	<i>B</i>	St. Err.	<i>R</i> ² (St. Err. of Estimate)	
Days exceeding limits set for PM ₁₀	-35.32	32.26	0.38 (1693.91)	15.89(0.001)
(Days exceeding limits set for PM ₁₀) ²	0.39*	0.194		
Constant	1438.81	1080.89		

Note: * *p*-value=0.057

A main question for environmental policy is: What is the maximum number of days in which cities can exceed the

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limits set for PM₁₀ or ozone per year, before that the combination between air pollution and meteorological condition triggers a take-off of viral infectivity (epidemic diffusion) with damages for health of population and economy in society?

The function based on table 12 is:

$$y = 1438.808 - 35.322x + 0.393x^2$$

y = number of infected individuals 1st April, 2020

x = days exceeding limits of PM₁₀ or ozone in Italian provincial capitals

The minimization is performed imposing first derivative equal to zero.

$$Dy / x = y' = -35.322 + 0.786x = 0$$

$x = 35.32 / 0.786 = 44.94 \sim 45$ days exceeding limits of PM₁₀ or ozone in Italian provincial capitals.

This finding suggests that the max number of days in which Italian provincial capitals can exceed per year the limits set for PM₁₀ (particulate matter 10 micrometres or less in diameter) or for ozone, considering the meteorological condition is about 45 days. Beyond this critical point, the analytical and geometrical output suggests that environmental inconsistencies because of the combination between air pollution and meteorological conditions trigger a take-off of viral infectivity (epidemic diffusion) with damages for health of population and economy in society.

Discussion

Statistical analyses for $N=55$ Italian provincial capitals confirm the significant association between high diffusion of viral infectivity and air pollution. Studies show that the diffusion of viral infectivity depends on the interplay between host factors and the environment (Neu & Mainou, 2020). In this context, it is critical to understand how air quality can affect viral dissemination at national and global level (Das & Horton, 2017). Many ecological studies have examined the association between the incidence of invasive pneumococcal

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disease and respiratory virus circulation and various climatic factors (McCullers, 2006; Jansen *et al.*, 2008). These studies show that in temperate climates, the epidemiology of invasive pneumococcal disease has a peak incidence in winter months (Dowell *et al.*, 2003; Kim *et al.*, 1996; Talbot *et al.* 2005). Brunekreef and Holgate (2002) argue that, in addition to climate factors, the health effects of air pollution have been subject to intense investigations in recent years. Air pollution is ubiquitous in manifold urban areas worldwide of developed and developing nations. Air pollution has gaseous components and particulate matter (PM). The former includes ozone (O₃), volatile organic compounds (VOCs), carbon monoxide (CO) and nitrogen oxides (NO_x) that generate inflammatory stimuli on the respiratory tract (Glencross *et al.*, 2020). Of these pollutants, PM has a complex composition that includes metals, elemental carbon and organic carbon (both in hydrocarbons and peptides), sulphates and nitrates, etc. (Ghio *et al.*, 2012; Wooding *et al.*, 2019).

Advanced countries, such as in Europe, have more and more smog because of an unexpected temperature inversion, which trap emissions from the city's coal-burning heating stoves and diesel powered buses near ground-level in winter. The ambient pollution mixes with moisture in the air to form a thick, foul-smelling fog that affect the health of people in the city (Wang *et al.*, 2016; Bell *et al.*, 2004). The exposure to pollutants, such as airborne particulate matter and ozone, generates respiratory and cardiovascular diseases with increases in mortality and hospital admissions (cf., Langrish & Mills, 2014). Wei *et al.* (2020) analyse the effect of heavy aerosol pollution in northern China—characterized by long-duration, high PM_{2.5} concentrations and wide geographical coverage—that impacts on environmental ecology, climate change and public health (cf., Liu *et al.*, 2017, 2018; Jin *et al.*, 2017). The biological components of air pollutants and bio aerosols also include bacteria, viruses, pollens, fungi, and animal/plant fragments (Després *et al.*, 2012; Fröhlich-Nowoisky *et al.*, 2016; Smets *et al.*, 2016). Studies show that

Environmental, demographic, and geographical factors affecting the diffusion... during heavy aerosol pollution in Beijing (China), 50%-70% of bacterial aerosols are in sub micrometre particles, 0.56-1 μm (Zhang *et al.*, 2019; cf., Zhang *et al.*, 2016). As bacteria size typically ranges from 0.5 to 2.0 μm (Després *et al.*, 2012), they can form clumps or attach to particles and transport regionally between terrestrial, aquatic, atmospheric and artificial ecosystems (Smets *et al.*, 2016). Moreover, because of regional bio aerosol transportation, harmful microbial components, bacterial aerosols have dangerous implications on human health and also plantation (cf., Van Leuken *et al.*, 2016). Harmful bio aerosol components—including pathogens, antibiotic-resistant bacteria, and endotoxins—can cause severe respiratory and cardiovascular diseases in society (Charmi *et al.*, 2018). In fact, the concentration of microbes, pathogens and toxic components significantly increases during polluted days, compared to no polluted days (Liu *et al.*, 2018). In addition, airborne bacterial community structure and concentration varies with pollutant concentration, which may be related to bacterial sources and multiplication in the air (Zhang *et al.*, 2019). Studies also indicate that microbial community composition, concentration, and bioactivity are significantly affected by particle concentration (Liu *et al.*, 2018). To put it differently, the atmospheric particulate matter harbours more microbes during polluted days than sunny or clean days (Wei *et al.*, 2016). These studies can explain one of the driving factors of higher viral infectivity of COVID-19 in the industrialized regions of Nord Italy, rather than other part of Italy (Tables 1-6). In fact, viable bio aerosol particles and high microbial concentration in particulate matter play their non-negligible role during air pollution and transmission of viral infectivity (Zhang *et al.*, 2019). For instance, airborne bacteria in $\text{PM}_{2.5}$ from the Beijing-Tianjin-Hebei regions in China revealed that air pollutants are main factors in shaping bacterial community structure (Gao *et al.*, 2017). Xie *et al.* (2018) indicate that total bacteria concentration is higher in moderately polluted air than in clean or heavily polluted air. Liu *et al.* (2018) show that bacterial concentration is low in moderately or heavily pollution in $\text{PM}_{2.5}$ and PM_{10} , whereas

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the pathogenic bacteria concentration is very high in heavy and moderate pollution. Sun *et al.* (2018) study bacterial community during low and high particulate matter (PM) pollution and find out that predominant species varied with PM concentration. In general, bio aerosol concentrations are influenced by complex factors, such as emission sources, terrain, meteorological conditions and other climate factors (Zhai *et al.*, 2018). Wei *et al.* (2020) also investigate the differences between inland and coastal cities in China (Jinan and Weihai, respectively) to explain the influence of topography, meteorological conditions and geophysical factors on bio aerosol. Results suggest that from clean days to severely polluted days, bacterial community structure is influenced by bacterial adaptation to pollutants, chemical composition of pollutants and meteorological conditions (cf., Sun *et al.*, 2018). Moreover, certain bacteria from Proteobacteria and Deinococcus-Thermus have high tolerance towards environmental stresses and can adapt to extreme environments. As a matter of fact, bacilli can survive to harsh environments by forming spores. Moreover, certain bacteria with protective mechanisms can survive in highly polluted environments, while other bacteria cannot withstand such extreme conditions. In particular, bacteria in the atmosphere to survive must withstand and adapt to ultraviolet exposure, reduced nutrient availability, desiccation, extreme temperatures and other factors. In addition, in the presence of accumulated airborne pollutants, more microorganisms might be attached to particulate matter. Thus, in heavy or severe air pollution, highly toxic pollutants in PM_{2.5} and PM₁₀ may inhibit microbial growth. Numerous studies also indicate the role of meteorological conditions in pollution development that creates appropriate conditions for microbial community structure and abundance, and viral infectivity (Jones & Harrison, 2004). Zhong *et al.* (2018) argue that static meteorological conditions may explain the increase of PM_{2.5}. In general, bacterial communities during aerosol pollution are influenced by bacterial adaptive mechanisms, particle composition, and meteorological conditions. The particles could also act as carriers, which have complex adsorption and

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toxicity effects on bacteria (Wei *et al.*, 2020). Certain particle components are also available as nutrition for bacteria and the toxic effect dominates in heavy pollution. The differences in bacterial adaptability towards airborne pollutants cause bacterial survival or death for different species. Groulx *et al.* (2018) argue that microorganisms, such as bacteria and fungi in addition to other biological matter like endotoxins and spores comingle with particulate matter (PM) air pollutants. Hence, microorganisms may be influenced by interactions with ambient particles leading to the inhibition or enhancement of viability and environmental stability (e.g., tolerance to variation in seasonality, temperature, humidity, etc.). Moreover, Groulx *et al.* (2018) claim that in the case of microbial agents of communicable disease, such as viruses, the potential for interactions with pollution may have public health implications. Thus, the variation in bacterial community structure is related to different pollution intensities. Wei *et al.* (2020) show that *Staphylococcus* increased with PM_{2.5} and became the most abundant bacteria in moderate pollution. In heavy or severe pollution, bacteria, which are adaptable to harsh environments, increase. In moderate pollution, the PM_{2.5} might harbour abundant bacteria, especially genera containing opportunistic pathogens. Therefore, effective measures should control health risks caused by bio aerosols during air pollution, especially for immunocompromised, elderly and other fragile individuals. This may explain the high mortality of certain individuals having previous pathologies because of COVID-19 in Italy that has the mortality rate (the percentage of deaths compared to the total of those who tested positive for COVID-19) of about 80% in individuals aged > 70 years with comorbidities as of April 1st, 2020 (Istituto Superiore Sanità, 2020; cf., WHO, 2020c). Papi *et al.* (2006) also indicate that chronic obstructive pulmonary disease (COPD) was significantly exacerbated by respiratory viral infections that cause reduction of forced expiratory volume in 1s (FEV₁) and airway inflammation (cf., Gorse *et al.*, 2006). Ko *et al.* (2007) report that the most prevalent viruses detected during acute exacerbations of COPD in Hong Kong were the influenza A

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virus and coronavirus. They indicate that among patients with a mean age of more than 75 years, mean FEV₁ was 40% of predicted normal and the FEV₁/FVC (forced vital capacity) ratio was reduced to 58% of normal. De Serres *et al.* (2009) also suggested that the influenza virus frequently causes acute exacerbations of asthma and COPD. Moreover, the study by Wei *et al.* (2020) argues that air pollution in coastal city Weihai in China was slightly lower than the inland city of Jinan. This study supports our results that the viral infectivity by COVID-19 is higher in hinterland cities rather than coastal cities in Italy. Wei *et al.* (2020, p.9) also suggest that different air quality strategies should be applied in inland and coastal cities: coastal cities need start bio aerosol risk alarm during moderate pollution when severe pollution occurs in inland cities.

Other studies have reported associations between air pollution and reduced lung function, increased hospital admissions, increased respiratory symptoms and high asthma medication use (Simoni *et al.*, 2015; Jalaludin *et al.*, 2004). In this context, the interaction between climate factors, air pollution and increased morbidity and mortality of people and children from respiratory diseases is a main health issue in society (Darrow *et al.*, 2014). Asthma is a disease that has been associated with exposure to traffic-related air pollution and tobacco smoke (Liao, 2011). Many studies show that exposure to traffic-related outdoor air pollutants (e.g., particulate matter PM₁₀ with an aerodynamic diameter ≤ 10 μm , nitrogen dioxide NO₂, carbon monoxide CO, sulfur dioxide SO₂, and ozone O₃) increases the risk of asthma or asthma-like symptoms (Shankardass *et al.*, 2009; Weinmayr *et al.*, 2010). Especially, current evidence indicates that PM₁₀ increases cough, lower respiratory symptoms and lower peak expiratory flow (Ward & Ayres, 2004; Nel, 2005). Weinmayr *et al.* (2010) provide strong evidence that PM₁₀ may be an aggravating factor of asthma in children. Furthermore, asthma symptoms are exacerbated by air pollutants, such as diesel exhaust, PM₁₀, NO₂, SO₂, and O₃ and respiratory virus, such as adenovirus, influenza, parainfluenza and respiratory syncytial virus (Jaspers *et al.*, 2005; Murdoch and Jennings, 2009;

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Murphy *et al.*, 2000; Wong *et al.*, 2009). The study by Liao *et al.* (2011) confirms that exacerbations of asthma have been associated with bacterial and viral respiratory tract infections and air pollution. Some studies have focused on the effect of meteorology and air pollution on acute viral respiratory infections and viral bronchiolitis (a disease linked to seasonal changes in respiratory viruses) in the first years of life (Nenna *et al.*, 2017; Ségala *et al.*, 2008; Vandini *et al.*, 2013, 2015). Carugno *et al.* (2018) analyse respiratory syncytial virus (RSV), the primary cause of acute lower respiratory infections in children: bronchiolitis. Results suggest that seasonal weather conditions and concentration of air pollutants seem to influence RSV-related bronchiolitis epidemics in Italian urban areas. In fact, airborne particulate matter (PM) may influence the children's immune system and foster the spread of RSV infection. This study also shows a correlation between short- and medium-term PM₁₀ exposures and increased risk of hospitalization due to RSV bronchiolitis among infants. In short, manifold environmental factors—such as air pollution levels, circulation of respiratory viruses and colder temperatures—induce in longer periods of time spent indoors with higher opportunities for diffusion of infections between people. In fact, in Italy the high diffusion of viral infectivity by COVID-19 in North of Italy is in winter period (February–March, 2020). Studies also show that air pollution is higher during winter months and it has been associated with increased hospitalizations for respiratory diseases (Ko *et al.*, 2007a; Medina-Ramón *et al.*, 2006). Moreover, oscillations in temperature and humidity may lead to changes in the respiratory epithelium which increased susceptibility to infection (Deal *et al.*, 1980). Murdoch & Jennings (2009) correlate the incidence rate of invasive pneumococcal disease (IPD) with fluctuations in respiratory virus activity and environmental factors in New Zealand, showing how incidence rates of IPD are associated with the increased activity of some respiratory viruses and air pollution. Another side effect of air pollution exposure is the association with the incidence of mumps. Hao *et al.* (2019) explore the effects of

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short-term exposure to air pollution on the incidence of mumps and show that exposure to NO₂ and SO₂ is significantly associated with higher risk of developing mumps. Instead, Yang *et al.* (2020) analyse the relationship between exposure to ambient air pollution and hand, foot, and mouth diseases (in short, HFMDs). Results show that the exposure of people to SO₂, NO₂, O₃, PM₁₀ and PM_{2.5} is associated with HFMDs. Moreover, the effect of air pollution in the cold season is higher than in the warm season. Shepherd & Mullins (2019) have also analysed the relationship between arthritis diagnosis in those over 50 and exposure to extreme air pollution in utero or infancy. Results link early-life air pollution exposure to later-life arthritis diagnoses, and suggest a particularly strong link for Rheumatoid arthritis (RA)¹. Sheperd & Mullins (2019) also argue that exposure to smog and air pollution in the first year of life is associated with a higher incidence of arthritis later in life. These findings are important to explain complex relationships between people, meteorological conditions, air pollution and viral infectivity because millions of people continue to be exposed to episodes of extreme air pollution each year in cities around the world.

Air pollution, immune system and genetic damages

The composition of ambient particulate matter (PM) varies both geographically and seasonally because of the mix of sources at any location across time and space. A vast literature shows short-term effects of air pollution on health, but air pollution affects morbidity also in the long run (Brunekreef & Holgate, 2002). The mechanism of damages of air pollution on health can be explained as follows. Air pollutants exert their own specific individual toxic effects on the respiratory and cardiovascular systems of people; in addition, ozone, oxides of nitrogen, and suspended particulates have a common

¹ Rheumatoid arthritis is a chronic inflammatory disorder in which the body's immune system attacks its joints, and is one of the most common autoimmune diseases (Cooper & Stroehla, 2003). Moreover, rheumatoid arthritis is a major cause of disability that reduces patient's lifespan by 15-20% from the onset of the illness (Myllykangas-Luosujärvi *et al.*, 1995; *cf.*, Chang *et al.*, 2016; De Roos *et al.*, 2014; Farhat *et al.*, 2011; Jung *et al.*, 2017).

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About the respiratory activity, the adult lung inhales approximately 10-11,000 L of air per day, positioning the respiratory epithelium for exposure to high volumes of pathogenic and environmental insults. In fact, respiratory mucosa is adapted to facilitate gaseous exchange and respond to environmental insults efficiently, with minimal damage to host tissue. The respiratory mucosa consists of respiratory tract lining fluids; bronchial and alveolar epithelial cells; tissue resident immune cells such as alveolar macrophages (AM), dendritic cells, innate lymphoid cells and granulocytes; as well as adaptive memory T and B lymphocytes. In health, the immune system responds effectively to infections and neoplastic cells, with a response tailored to the insult, but must tolerate (i.e., not respond harmfully to) the healthy body and benign environmental influences. A well-functioning immune system is vital for a healthy body. Inadequate and excessive immune responses generate diverse pathologies,

Environmental, demographic, and geographical factors affecting the diffusion... such as serious infections, metastatic malignancies and autoimmune conditions (Glencross *et al.*, 2020). In particular, immune system consists of multiple types of immune cell that act together to generate (or fail to generate) immune responses. In this context, the explanation of relationships between ambient pollutants and immune system is vital to explain how pollution causes disease, and how pathology can be removed. Glencross *et al.* (2020) show that air pollutants can affect different immune cell types, such as particle-clearing macrophages, inflammatory neutrophils, dendritic cells that orchestrate adaptive immune responses and lymphocytes that enact those responses. In general, air pollutants stimulate pro-inflammatory immune responses across multiple classes of immune cell. Air pollution can enhance T helper lymphocyte type 2 and T helper lymphocyte type 17 adaptive immune responses, as seen in allergy and asthma, and dysregulate anti-viral immune responses. In particular, the association between high ambient pollution and exacerbations of asthma and chronic obstructive pulmonary disease (COPD) is consistent with immunological mechanisms. In fact, diseases can result from inadequate responses to infectious microbes allowing fulminant infections, inappropriate/excessive immune responses to microbes leading to more (collateral) damages than the microbe itself, and inappropriate immune responses to self/environment, such as seems to be in the case of COVID-19. Glencross *et al.* (2020) also discuss evidence that air pollution can cause disease by perturbing multicellular immune responses. Studies confirm associations between elevated ambient particulate matter and worsening of lung function in patients with COPD (Bloemsma *et al.*, 2022), between COPD exacerbations and both ambient particulate matter and ambient pollutant gasses (Li *et al.*, 2022) and similarly for asthma exacerbations with high concentration of ambient pollutants (Orellano *et al.*, 2017, Zheng *et al.*, 2015). In short, the associations between ambient pollution and airways exacerbations are stronger than associations with development of chronic airways diseases. Glencross *et al.* (2020) also argue that ambient pollutants can directly trigger

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cellular signalling pathways, and both cell culture studies and animal models have shown profound effects of air pollutants on every type of immune cell studied. In addition to the general pro-inflammatory nature of these effects, many of studies suggest an action of air pollution to augment Th2 immune responses and perturb antimicrobial immune responses. This mechanism also explains the association between high air pollution and increased exacerbations of asthma – a disease characterized by an underlying Th2 immuno-pathology in the airways with severe viral-induced exacerbations. Moreover, as inhaled air pollution deposits primarily on the respiratory mucosa, potential strategies to reduce such effects may be based on vitamin D supplementation. Studies show that plasma levels of vitamin D, activated by ultraviolet B, are significantly higher in summer and fall than winter and spring, in a latitude-dependent manner (Barger-Lux & Heaney, 2002). Since the temperature and hour of sun are dependent upon the latitude of population residence and influenced by urban/rural residence, Oh *et al.* (2010) argue that adequate activated vitamin D levels are also associated with diminished cancer risk and mortality (Lim *et al.*, 2006; Grant, 2002). For instance, breast cancer incidence correlates inversely with the levels of serum vitamin D and ultraviolet B exposure, which are the highest intensity in summer season. These relationships of vitamin D and cancer risk are not limited to breast cancer, but are also relevant to colon, prostate, endometrial, ovarian, and lung cancers (Zhou *et al.*, 2005).

In the context of this study and considering the negative effects of air pollution on human health and transmission dynamics of viruses, summer season may have twofold effects to reduce diffusion of viral infectivity:

- 1) hot and sunny weather increases temperature and improves environment that can reduce air pollution, typically of winter period, and as result alleviate transmission of viral infectivity by COVID-19 (Ko *et al.*, 2007a; Medina-Ramón *et al.*, 2006; Wei *et al.*, 2020; Dowell *et al.*, 2003; Kim *et al.*, 1996; Talbot *et al.* 2005);

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2) sunny days and summer season induce in population a higher production of vitamin D that reinforces and improves the function of immune system to cope with viral infectivity of COVID-19.

Overall, then, statistical analysis, supported by relevant studies in these research topics, reveals that accelerated transmissions dynamics of COVID-19 is also to air pollution-to-human transmission in addition to human-to-human transmission.

Strategies to prevent future epidemics similar to COVID-19

At the end of 2019, medical professionals in Wuhan (China) were treating cases of pneumonia cases that had an unknown source (Li *et al.*, 2020; Zhu & Xie, 2020; Chan *et al.*, 2020; Backer *et al.*, 2020). Days later, researchers confirmed the illnesses were caused by a new coronavirus (COVID-19). By January 23, 2020, Chinese authorities had shut down transportation going into and out of Wuhan, as well as local businesses, in order to reduce the spread of viral infectivity (Centers for Disease Control and Prevention, 2020; Public Health England, 2020; Manuell & Cukor, 2011). It was the first in the modern history of several quarantines set up in China and other countries around the world to cope with transmission dynamics of COVID-19. Quarantine is the separation and restriction of movement of people who have potentially been exposed to a contagious disease to ascertain if they become unwell, in order to reduce the risk of them infecting others (Brooks *et al.*, 2019). In short, quarantine can generate a strong reduction of the transmission of viral infectivity. In the presence of COVID-19 outbreak in North Italy, Italian government has applied the quarantine and lockdown from 11 March, 2020 to 13 April, 2020 for all Italy, adding also some holidays thereafter. In fact, Italy was not able to prevent this complex problem of epidemics and has applied quarantine as a recovery strategy to lessen the health and socioeconomic damages caused by COVID-19. Millions of people have been quarantined for the first time in Italy and is

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one of the largest actions in the history of Italy. In addition, Italy applied non-pharmaceutical interventions based on physical distancing, school and store closures, workplace distancing, to avoid crowded places, similarly to the COVID-19 outbreak in Wuhan (cf., [Prem et al., 2020](#)). The benefits to support these measures until April, 2020 are aimed at delaying and reducing the height of epidemic peak, affording health-care systems more time to expand and respond to this emergency and, as a result reducing the final size of COVID-19 epidemic. In general, non-pharmaceutical interventions are important factors to reduce the epidemic peak and the acute pressure on the health-care system ([Prem et al., 2020](#); [Fong et al., 2020](#)). However, [Brooks et al. \(2019\)](#) report: “negative psychological effects of quarantine including post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. Some researchers have suggested long-lasting effects. In situations where quarantine is deemed necessary, officials should quarantine individuals for no longer than required, provide clear rationale for quarantine and information about protocols, and ensure sufficient supplies are provided. Appeals to altruism by reminding the public about the benefits of quarantine to wider society can be favourable”.

This strategy, of course, does not prevent future epidemics similar to the COVID-19 and it does not protect regions from future viral threats. Nations, alike Italy, have to apply *proactive strategies* that anticipate these potential problems and works to prevent them, reducing the health and economic impact in society.

Suggested proactive strategies to prevent future epidemics similar to COVID-19

[Daszak et al. \(2020\)](#) argue that to prevent the next epidemic and pandemic similar to COVID-19, research and investment of nations should focus on:

- 1) surveillance among wildlife to identify the high-risk pathogens they carry

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2) surveillance among people who have contact with wildlife to identify early spillover events

3) improvement of market biosecurity regarding the wildlife trade.

In addition, high surveillance and proper biosafety procedures in public and private institutes of virology that study viruses and new viruses to avoid that may be accidentally spread in surrounding environments with damages for population and vegetation. In this context, international collaboration among scientists is basic to address these risks, support decisions of policymakers to prevent future pandemic creating potential huge socioeconomic issues worldwide (cf., [Coccia & Wang, 2016](#))². In fact, following the COVID-19 outbreak, The Economist Intelligence Unit (EIU) points out that the global economy may contract of about by 2.2% and Italy by -7% of real GDP growth % in 2020 ([EIU, 2020](#)). Italy and other advanced countries should introduce organizational, product and process innovations to cope with future viral threats, such as the expansion of hospital capacity and testing capabilities, to reduce diagnostic and health system delays also using artificial intelligence, and as a consequence new ICT technologies for alleviating and/or eliminating effective interactions between infectious and susceptible individuals, and finally of course to develop effective vaccines and antivirals that can counteract future global public health threat in the presence of new epidemics similar to COVID-19 ([Chen et al, 2020](#); [Wilder-Smith et al., 2020](#); [Riou & Althaus, 2020](#); [Yao et al., 2020](#); cf., [Coccia, 2015, 2017, 2019, 2020](#))³.

² Socioeconomic shocks can lead to a general increase of prices, high public debts, high unemployment, income inequality and as a consequence violent behaviour ([Coccia, 2016, 2017, 2017a](#)).

³ For additional studies about science and technology, cf., [Coccia, 1999, 2003, 2005, 2005a, 2005b, 2005c, 2006, 2008, 2009, 2010, 2010a, 2010b, 2010c, 2011, 2012, 2012a, 2012b, 2012c, 2012d, 2013, 2014, 2014a, 2014b, 2014c, 2014d, 2014e, 2014f; 2015, 2015a, 2015b, 2015c; 2016, 2016a, 2016b, 2017, 2017a, 2017b, 2017c, 2017d, 2017e, 2017f, 2017g; 2018, 2018a, 2018b, 2018c, 2018d, 2018e, 2018f, 2018g, 2018h, 2018i, 2018l, 2018m, 2018n; 2019, 2019a, 2019b, 2019c, 2019d, 2019e, 2019f, 2019g, 2019h, 2019i, 2019l, 2019m, 2019n, 2019o, 2019p; Coccia, 2020, 2020a, 2020b, 2020c, 2020d, 2020e, 2020f](#),

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This study here shows that geo-environmental factors of accelerated diffusion of COVID-19 are also likely associated with high air pollution and specific meteorological conditions (low wind speed, etc.) of North Italy and other Northern Italian regions that favour the transmission dynamics of viral infectivity. North Italy is one of the European regions with the highest motorization rate and polluting industrialization (cf., [Legambiente, 2019](#)). In 2018 in 55 provincial capitals the daily limits for PM₁₀ or ozone were exceeded (i.e., 35 days for PM₁₀ and 25 for ozone). In 24 of the 55 Italian province capitals, the limit was exceeded for both parameters, with negative effects on population that had to breathe polluted air for about four months in the year with subsequent health problems. In fact, the cities that last year passed the higher number of polluted days are Brescia with 150 days (47 for the PM₁₀ and 103 for the ozone), followed by Lodi with 149 (78 for the PM₁₀ and 71 for the ozone),—these are two cities with severe COVID-19 outbreak—, Monza (140), Venice (139), Alessandria (136), Milan (135), Turin (134), Padua (130), Bergamo and Cremona (127) and Rovigo (121). These provincial capitals of the River Po area in Italy have exceeded at least one of the two limits just mentioned. The first city not located in the Po valley is Frosinone (Lazio region of the central part of Italy) with 116 days of exceedance (83 for the PM₁₀ and 33 for the ozone), followed by Genoa with 103 days, Avellino a city close to Naples in South Italy (Campania region with 89 days: 46 for PM₁₀ and 43 for ozone) and Terni with 86 (respectively 49 and 37 days for the two pollutants). Many cities in Italy are affected by air pollution and smog because of traffic, domestic heating, industries and agricultural practices and with private cars that continue to be by far the most used means of transportation (more than 39 million cars in 2019). In fact, a major source of emissions of nitrogen oxides into the

2020g, 2020h, 2020i; Coccia and Bellitto, 2020; Coccia and Benati, 2018, Coccia and Bozeman, 2016; Coccia et al., 2015; Coccia and Finardi, 2012, 2013; Coccia et al., 2012; Coccia and Rolfo, 2002, 2008, 2009; Coccia and Wang, 2015, 2016; Coccia and Watts, 2020.

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atmosphere is the combustion of fossil fuels from stationary sources (heating, power generation) and motor vehicles. In ambient conditions, nitric oxide is rapidly transformed into nitrogen dioxide by atmospheric oxidants such as ozone (cf., [Brunekreef & Holgate, 2002](#)). In Italy, the first COVID-19 outbreak has been found in Codogno, a small city of the Lodi area, close to Milan. Although local lockdown as red zone on February 25, 2020, the Regional Agency for Environmental Protection showed that concentrations of PM_{10} beyond the limits in almost all of Lombardy region including the red zone (i.e., $82 \text{ } \mu\text{g}/\text{m}^3$ of air measured in Codogno). The day after, February 26, 2020, the mistral wind and then the north wind swept the entire Po valley, bringing to Lombardy region a substantial reduction in the average daily concentrations of PM_{10} , which almost everywhere were lower than 50 micrograms of particulate matter/ m^3 of air.

Hence, high concentration of nitrogen dioxide, a noxious gas, particulate air pollutants emitted by motor vehicles, power plants, and industrial facilities in North Italy seems to be a platform to support diffusion of viral infectivity ([Groulx et al., 2018](#)), increase hospitalizations for respiratory virus bronchiolitis (cf., [Carugno et al., 2018](#); [Nenna et al., 2017](#)), increase asthma incidence ([Liao et al., 2011](#)) and damage to the immune system of people ([Glencross et al., 2020](#)). Transmission dynamics of COVID-19 has found in air pollution and meteorological conditions of North Italy an appropriate environment and population to carry out an accelerated diffusion that is generation more than 13,000 deaths and a huge number of hospitalizations in a short period of time.

An *indirect effect* of quarantine and lockdown in Italy is the strong reduction of airborne Nitrogen Dioxide Plummets and PM_{10} over Norther of Italy. The maps by ESA (2020) show concentrations of nitrogen dioxide NO_2 values across Italy before the quarantine and lockdown in February, 2020 and during the quarantine and lockdown in March, 2020. The reduction in NO_2 pollution is apparent in all North Italy (Po Valley). Hence, the measures taken to cope with the COVID-19 outbreak (closure of schools and the reduction of traffic),

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the study suggests that environmental inconsistencies because of the combination between air pollution and meteorological conditions trigger a take-off of viral infectivity (epidemic diffusion) with damages for health of population and economy in society. Italy must design and set up necessary measures to drastically reduce the concentrations of pollution present and improve air quality in cities. Italy not has to respect Legislative Decree 155/2010 that establishes a maximum number of 35 days / year with concentrations higher than 50 $\mu\text{g} / \text{m}^3$. As a matter of fact, the quarantine and other non-pharmaceutical interventions can reduce the impact of viral infectivity in the short term, but to prevent future epidemics similar to COVID-19, Italy and advanced nations have more and more to sustain a sustainable growth. The environmental policy has to be associated with sustainable technologies that reduce air pollution improving the quality of air and environment for population to cope with future viral threats (cf., Coccia, 2005, 2006, 2018; Coccia & Watts, 2020)⁴. Italy must support, more and more, sustainable mobility as engine of socioeconomic change and redesign cities for people using an urban planning that improves public respiratory health. Moreover, in the presence of the association between air pollution, climate⁵ and viral infectivity. Italy and other advanced nations have to immediately reduce the motorization rate of polluting machines with a transition to new electric vehicles, generating a revolution in society. It is basic to encourage sustainable mobility, by enhancing local, urban and commuter public transport with electric vehicles and creating vast Low Emission Zones within cities. Italy has to launch a real sustainable growth roadmap with the aim of

4 cf. for dynamics of technological and economic change in society the studies by Coccia (2005a, 2005b, 2008, 2008, 2009, 2015a, 2017e, 2017f, 2017g, 2018a, 2019a, 2019b, 2019c, 2019d; Coccia and Finardi, 2012; Coccia & Rolfo, 2008).

5 Some studies show that in addition to human-to-human contact, ambient temperature is an important factor in the transmission and survival of coronaviruses (Zhu *et al.*, 2020) as well as temperature variation and humidity may also be important factors affecting the COVID-19 mortality (Ma *et al.*, 2020)

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complete zero emissions in all socioeconomic system. Some studies done in the past show the causality of the reduction of air pollution on health benefits. For instance, Pope (1989) describes the case of a labour dispute that shut down a large steel mill in the Utah Valley for 14 months in 1987. Toxicological studies of particulate matter collected before, during, and after the strike, in the Utah Valley case, provide strong evidence of a causal relation between exposure to ambient particulate matter and mortality and morbidity. Ambient particulate matter concentrations as well as respiratory hospital admissions were clearly decreased during the strike, increasing to prestrike levels after the dispute ended (Pope, 1989; cf., the reduction of mortality described by Pope, 1996). Another example includes the reductions in acute-care visits and hospital admissions for asthma in Atlanta (GA, USA), in conjunction with reduced air pollution due to traffic restrictions taken during the 2000 Olympic games (Friedman, 2001).

Concluding remarks

The intensity of human interactions with Earth systems has accelerated in recent decades, because of urban development, population growth, industrialization, deforestation, construction of dams, etc., with changes in physical, biological, and chemical processes in soils and waters. In particular, human activity, driven by a high level of world population that is about eight billion (U. S. Census Bureau 2020), has induced changes to Earth's surface, cryosphere, ecosystems, and climate that are now so great and rapid, advancing the geological epoch of Anthropocene (Crutzen & Stoermer, 2000; Foley *et al.*, 2013). The beginning of the Anthropocene at around 1780 AD marks the beginning of immense rises in human population and carbon emissions as well as atmospheric CO² levels (Ellis *et al.*, 2013). The scale of carbon emissions associated with industrial activity is leading to a rise in atmospheric greenhouse gases at a rate unprecedented and gradual rise in carbon dioxide (Glikson, 2013; Coccia, 2014a). In this era of Anthropocene, the health

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effects of air pollution have been subject to intense study in recent years. Exposure to airborne particulate matter and ozone has main health effects associated with increases in mortality and hospital admissions for respiratory and cardiovascular diseases (Kampa & Castanas, 2008; Hoek *et al.*, 2013). The idea that air pollution episodes have a detrimental effect on health is now rarely contested, and acute exposures to high concentrations of air pollutants exacerbate cardiopulmonary disorders in human population worldwide (Langrish & Mills, 2014).

This study shows that factors determining the diffusion of epidemics similar to COVID-19 are due to manifold elements, in addition to human-to-human transmission, given by:

1. *General factors* that are the same for all locations and associated with innate biological characteristics of the viruses, incubation time, effects on infected and susceptible people, etc.

2. *Specific factors* that are different for each location and even for each individual, such as level of air pollution over time and space, meteorological conditions of specific location, season, density of areas, economic wealth, cultural characteristics (religious habits, food culture, etc.), organization and efficiency of healthcare sector, facilities and equipment in health sector, immune system of people, average age of population, sex of people, etc.

The main results of the study here, based on case study of COVID-19 outbreak in Italy, are:

- The acceleration of transmission dynamics of COVID-19 in North Italy has a high association with air pollution of cities measured with days of exceeding the limits set for PM₁₀ or ozone

- Cities having more than 100 days of air pollution (exceeding the limits set for PM₁₀), they have a very high average number of infected individual (about 3,100 infected), whereas cities having less than 100 days of air pollution, they have a lower average number of infected (about 900 infected individuals)

- Hinterland cities with higher number of average days exceeding the limits set for PM₁₀ have a very high number of

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infected people on 1st April, 2020 (arithmetic mean is about 2,000 infected, with average polluted days more than 80), than coastal cities also having days of exceeding the limits set for PM₁₀ or ozone (arithmetic mean about 700 infected, with average polluted days about 60). In fact, coastal cities have an average higher intensity of wind speed (about 12 km/h) than hinterland cities (8 km/h) and statistical analysis reveals a negative coefficient correlation between number of infected and intensity of wind speed ($r = -28$ to -38% , p -value < 0.05): in fact, wind speed and other elements clean air from pollutants that are associated with transmission dynamics of viral infectivity.

○ Air pollution in cities under study seems to be a more important predictor in the initial phase of transmission dynamics (on 17th March 2020, $b_1 = 1.27$, $p < 0.001$) than human-to-human transmission ($b_2 = 0.31$, $p < 0.05$). In the second phase of the transmission dynamics of viral infectivity, air pollution reduces intensity (on 1st April, 2020 $b'_1 = .85$, $p < 0.001$) also because of indirect effect of lockdown and human-to-human transmission slightly increases ($b'_2 = 0.34$, $p < 0.01$): *This result reveals that accelerated transmissions dynamics of COVID-19 is due to mainly air pollution-to-human transmission in addition to human-to-human transmission.*

○ To minimize future epidemics similar to COVID-19, the max number of days per year in which Italian provincial capitals can exceed the limits set for PM₁₀ (particulate matter 10 micrometres or less in diameter) or for ozone, considering their meteorological conditions, is about 45 days.

Hence, high concentration of nitrogen dioxide, a noxious gas, particulate air pollutants emitted by motor vehicles, power plants, and industrial facilities in North Italy seems to be a platform to support diffusion of viral infectivity (Groulx *et al.*, 2018), increase hospitalizations for respiratory virus bronchiolitis (cf., Carugno *et al.*, 2018; Nenna *et al.*, 2017), increase asthma incidence (Liao *et al.*, 2011) and damage to the immune system of people (Glencross *et al.*, 2020). Beelen *et al.* (2013) report the need to draw attention to the continuing effects of air pollution on health. A socioeconomic strategy to prevent future epidemics similar to the COVID-19 is also the

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reduction of pollution with fruitful environmental and health effect by the rationalization of manufacturing industry in a perspective of sustainable development, de-industrializing polluting activities in the geographical development of current capitalism. De-industrialization of polluting industries and sustainable development impose often huge social costs in the short term on people, households, and families but they have long-run benefits for human societies. Studies show that public and environmental health policy interventions are necessary and have the potential to reduce morbidity and mortality across Europe (cf., [Raaschou-Nielsen et al., 2013](#)). In fact, the improvements in air quality have been accompanied by demonstrable benefits to human health. Pope *et al.* (2009) reported that PM_{2.5} concentrations fell by a third from the early 1980s to the late 1990s across major US metropolitan areas, with each 10 µg/m³ reduction associated with an increase in life expectancy of 0.61 years. Because of health problems of polluting industrialization, Wei *et al.* (2020) suggest different air pollution regulations in regions having varied geographical and climatic conditions, and different bio aerosol pollution. In particular, Wei *et al.* (2020) suggest that different air quality strategies should be applied in inland and coastal cities, e.g., coastal cities also need start bio aerosol risk alarm during moderate pollution when severe pollution occurs in inland cities. Guo *et al.* (2019) argue that in recent years, haze pollution is a serious environmental problem affecting cities, proposing implications for urban planning to improve public respiratory health. In short, the long-term benefits of sustainable economic development are basic for the improvement of environment, atmosphere, air quality and especially health of populations ([Blackaby, 1978](#); [Bluestone & Harrison, 1982](#); [Pike, 2009](#)).

Overall, the, these findings here are consistent with correlational studies and indicate that health effects of air pollution exposure can span decades and extend beyond cardiopulmonary systems affecting diffusion of epidemics similar to COVID-19. Hence, it is important to reinforce evidence related to air pollution and inter-related factors of the transmission dynamics of virus similar to COVID-19, and

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helps policy makers to develop proactive regulations for the control of environment, air pollution, polluting industrialization and prevention of the diffusion of viral infectivity. The complex problem of epidemic threats has to be treated with an approach of dissolution: it means to redesign the strategies and protocols to cope with future epidemics in such way as to eliminate the conditions that caused accelerated diffusion of COVID-19, thus enabling advanced nations to do better in the future than the best it can do today (Ackoff & Rovin, 2003, pp.9-10; Bundy *et al.*, 2017). This study reveals interesting results of transmission dynamics of COVID-19 given by the mechanism of air pollution-to-human transmission that in addition to human-to-human transmission seems to have accelerated diffusion of epidemics in Italy. However, these conclusions are tentative. There are several challenges to such studies, particularly in real time. Sources may be incomplete, or only capture certain aspects of the on-going outbreak dynamics; there is need for much more research in to the relations between viral infectivity, air pollution, meteorological factors and other determinants, when the COVID-19 outbreak is over. Overall, then, in the presence of polluting industrialization of cities and air pollution -to-human transmission of viral infectivity, this study must conclude that a comprehensive strategy to prevent future epidemics similar to COVID-19 has also to be designed in environmental and socioeconomic terms, that is in terms of sustainability science and environmental science, and not only in terms of biology, healthcare and health sector.

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3

The relation between health expenditures, air pollution and fatality rate of COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is an influenza caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared in late 2019 (Coccia, 2020). COVID-19 pandemic is still circulating in 2021 with variants that continue to generate high numbers of COVID-19 related infected individuals and deaths in manifold countries worldwide (Johns Hopkins Center for System Science & Engineering, 2021; CDC, 2021). Seligman *et al.* (2021) show some characteristics of people that are significantly associated with COVID-19 mortality, such as: " mean age 71.6 years, 45.9% female, and 45.1% non-Hispanic white ... disproportionate deaths occurred among individuals with nonwhite race/ethnicity (54.8% of deaths ... $p < 0.001$), individuals with income below the median (67.5% . . . $p < 0.001$), individuals with less than a high school level of education (25.6% ... $p < 0.001$), and veterans (19.5% ... $p < 0.001$)". In this context, the fundamental question is which economic and environmental factors of countries can reduce

Relation between health expenditures, air pollution and fatality rate of COVID-19 mortality of COVID-19 and as a consequence reduce the negative impact of COVID-19 pandemic crisis in society (cf., [Anser et al., 2020](#)). The study here confronts this question by developing a global analysis based on more than 160 countries to explain, whenever possible, the factors determining a lower rate of COVID-19 mortality between countries worldwide. In particular, the main goal of this study is to clarify health, economic and environmental factors that have reduced fatality rate of the COVID-19 in society. The development of this study flows from a recognition that current literature does not clarify the complex economic, social and institutional factors that can mitigate the mortality of COVID-19 between countries. The assumptions of this study are that wealth of nations, healthcare spending and air pollution are factors associated with fatality rate of COVID-19 between countries. Lessons learned from this study can support effective and proactive strategies for reducing fatality rates of infectious diseases in the presence of future epidemics similar to the COVID-19. This study is part of a large research project that investigates factors determining the transmission dynamics of the COVID-19 pandemic and socioeconomic effects of the COVID-19 pandemic crisis in society to cope with future epidemics with appropriate policy responses (cf., [Coccia, 2020, 2021](#)).

Theoretical framework

Manifold studies focus on different aspects of COVID-19 pandemic crisis (cf., [Hu et al., 2021](#); [Tian et al., 2021](#)). [Asirvatham et al. \(2020\)](#) estimate an adjusted case fatality rate of COVID-19 in India considering some factors of urban environment and population. Results suggest that urban population and population aged more than 60 years were associated with increased adjusted case fatality rate. In this context, healthcare interventions directed to test elderly, people with comorbidities (e.g., having diabetes, cardiovascular diseases, cancer, etc.) and urban population are critical public policies to constrain negative effects of COVID-19 pandemic in society. [Siddiqui et al. \(2020\)](#) also

Relation between health expenditures, air pollution and fatality rate of COVID-19 analyze the impact of COVID-19 pandemic in India and show that: “low public health expenditure combined with a lack of infrastructure and low fiscal response implies several challenges to scale up the COVID-19 response and management. Therefore, an emergency preparedness and response plan is essential to integrate into the health system of India”. Ahmed *et al.* (2020) focus on demographic, socioeconomic, and lifestyle health factors of countries to explain different COVID-19 effects in society. Ahmed *et al.* (2020) suggest that health expenditure per capita has a positive relation with case recovery; in addition, countries with high average age of population and high percentage of urban population have also a high fatality of COVID-19 pandemic in society. In this research field, Kavitha & Madhavaprasad (2020) maintain that preventive health care measures and policies of social distancing applied on a vast portion of population can constraint the spread of COVID-19. Lyanda *et al.* (2020) argue that reinforcing public health sector and epidemiological surveillance programs can both reduce the spread of COVID-19 and prevent unnecessary deaths of this infectious disease. The role of health expenditure is also investigated by Gaffney *et al.* (2020, p. 396) that maintain how: “the United States’ underfunded public health infrastructure, fragmented medical care system, and inadequate social protections impose particular impediments to mitigating and managing the outbreak... While the United States has a relatively generous supply of Intensive Care Unit beds and most other health care infrastructure, such medical resources are often unevenly distributed or deployed, leaving some areas ill-prepared for a severe respiratory epidemic”. González-Bustamante (2021) shows that in South America the social pressure on healthcare system affects interventions of governments to constrain the diffusion of COVID-19. In China, Jin & Qian (2020) analyze: “the Chinese public-health expenditure at national and provincial levels ..., and then compare it with the expenditures of other countries. The results show that: (1) the level of public-health expenditure in China is relatively low and far lower than that in developed countries; (2) Chinese governments have not paid enough

Relation between health expenditures, air pollution and fatality rate of COVID-19 attention to the prevention and control of major public-health emergencies, which may be an important reason for the outbreak of COVID-19; (3) Chinese public-health expenditure shows a fluctuating growth trend, but the growth rate is so slow that it is lower than that of GDP and fiscal expenditure; (4) although the Chinese government inclines the public-health expenditure to the poor provinces in central and western regions, the imbalance and inequity of public-health resource allocation are still expanding among provinces; (5) there is a lot of waste of resources in the public-health system, which seriously reduces the efficiency of public-health expenditure in China. Therefore, the Chinese government should improve the quantity and quality of public-health expenditure in the above aspects". Kapitsinis (2020) investigates the diffusion of the novel coronavirus in nine European countries and pinpoints that health investments play a vital role to alleviate mortality rate of the COVID-19. Instead, Barrera-Algarín *et al.* (2020) show that in Europe, a lower level of government health investments per capita is associated with high numbers of COVID-19 deaths per million inhabitants; in general, a high mortality of COVID-19 is also due to low health expenditure associated with high income inequality. Finally, Perone (2021) analyzes Italy and shows that health care efficiency is one of the factors associated with the reduction of fatality rate; moreover, population aged 70 years and above, and concentration of air pollutants are positively associated with fatality rate in society.

Overall, then, current literature shows that economic system and interventions of public policy in specific countries (e.g., India, China, the USA, Italy, etc.) have generated different effects of the evolution of COVID-19 pandemic in society. However, *what is hardly known* is to explain and generalize at global level which economic and environment factors of countries can lower mortality of COVID-19 in society to design effective and proactive strategy to constrain future epidemics similar to COVID-19.

Materials and methods

This study has the primary objective to explain factors determining a lower fatality rate of the COVID-19 between countries. Results can explain and generalize, whenever possible, vital characteristics of countries for designing an effective and proactive strategy to limit negative impact of future COVID-19 pandemic crisis and similar epidemics.

Sample and working hypothesis

The study is based on a sample of 161 countries that is categorized in two sub-samples according to the level of Gross Domestic Product (GDP) per capita (wealth of individuals) of nations is higher/lower than arithmetic mean of the sample $N=161$, to compare groups having similar socioeconomic framework.

The main working hypothesis of this study is that high GDP per capita and healthcare spending, and low air pollution are factors associated with reduction of the fatality rate of COVID-19 between countries.

Measures

The measures for statistical analyses are:

- *Number of COVID-19 infected individuals (%)* is measured with confirmed cases of COVID-19 on 14 December 2020 divided by population of countries under study. Source of data: Johns Hopkins Center for System Science and Engineering (2021).
- *Number of COVID-19 deaths* is measured with fatality rate (%) of COVID-19 given by deaths on 14 December 2020 divided by total infected individuals in countries. Source of data: Johns Hopkins Center for System Science and Engineering (2021).
- *Wealth of population* is measured with Gross Domestic Product (GDP) per capita, Purchasing Power Parity (PPP-current international U.S. dollars \$) in 2019 (last year available in dataset). GDP per capita is gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product

Relation between health expenditures, air pollution and fatality rate of COVID-19 taxes and minus any subsidies not included in the value of products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Source of data: World Bank (2020).

- The expenditures in health sector are measured by:

a) Level of current health expenditure expressed as a percentage of GDP in 2017 (last year available in dataset). Estimates of current health expenditures include healthcare goods and services consumed during each year. Although this indicator does not include capital health expenditures (e.g., buildings, machinery, IT and stocks of vaccines for emergency or outbreaks), it is a main proxy of investments in health sector; in fact, countries having higher levels of health expenditures as percentage of GDP also tend to have a higher level of Research and Development expenditure (% of GDP)¹: bivariate correlation, using data of 2017, shows a positive coefficient equal to $r=.45$ (p -value 0.01, $N=115$ countries), whereas regression analysis with log-log model reveals that a 1% increase in the Research and Development expenditure (% of GDP), it increases expected current health expenditure (% of GDP) of .14% (p -value .001; coefficient R^2 indicates that about 20% of the variation of health expenditure can be attributed linearly to Research and Development expenditure; cf., Coccia, 2012, 2018). Source of data: World Bank (2020a);

b) Domestic general government health expenditure per capita, PPP (current international \$) in 2017 (last year available): Public expenditure on health from domestic sources per capita expressed in international dollars at purchasing power parity (PPP time series based on ICP2011 PPP). Source of these data is also World Bank (2020b).

- Elderly are measured with population aged 65 years and above as a percentage of the total population (population

¹ Gross domestic expenditures on research and development (R&D), expressed as a percent of GDP, include both capital and current expenditures in the four main sectors: business enterprise, government, higher education and private non-profit. R&D covers basic research, applied research, and experimental development.

Relation between health expenditures, air pollution and fatality rate of COVID-19 here counts all residents regardless of legal status or citizenship in 2019, last year available). Source: World Bank (2020c). Population aged 65 and above is an important factor in infectious diseases because many studies show negative effects of COVID-19 on health of old people (Cohen-Mansfield, 2020; Perone, 2021).

- Air pollution in environment is measured by percent of population exposed to ambient concentrations of PM_{2.5} that exceed the World Health Organization (WHO) guideline value in 2017 (last year available). In particular, it indicates the portion of a country's population living in places where mean annual concentrations of PM_{2.5} are greater than 10 micrograms per cubic meter, the guideline value recommended by the WHO as the lower end of the range of concentrations over which adverse health effects due to PM_{2.5} exposure have been observed. Source: World Bank (2020d). In this context, studies reveal that areas with frequently high levels of air pollution — exceeding safe levels of ozone or particulate matter — had higher numbers of COVID-19 related infected individuals and deaths (Coccia, 2020, 2021, 2021a; Martelletti & Martelletti, 2020). Moreover, high concentrations of particulate air pollutant induce serious damages to the immune system of people, weakening human body to cope with infectious diseases of (new) viral agents and other diseases (Glencross *et al.*, 2020).

- Containment measures against the spread of COVID-19 are assessed with total days of lockdown across countries in the year 2020 (Coccia, 2021b). Tobias (2020, p. 2) states that: “Lockdown, including restricted social contact and keeping open only those businesses essential to the country's supply chains, has had a beneficial effect”. Flaxman *et al.* (2020) show that lockdowns seem to have effectively reduced transmission of the COVID-19. Atalan (2020) argues that countries can start lockdown when there is an acceleration of daily confirmed cases beyond a critical threshold and can end it when there is a strong reduction of Intensive Care Unit (ICU) admissions (cf., Chaudhry *et al.*, 2020). Source: COVID-19 pandemic lockdowns (2021).

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a) 3.3. Data analysis procedure

The sample of $N=161$ countries is divided in two sub-samples (group 1 and 2) having similar socioeconomic conditions for a comparative analysis as follow:

□ group 1: countries with a Gross Domestic Product per capita higher than arithmetic mean of the sample

□ group 2: countries with a Gross Domestic Product per capita lower and/or equal than arithmetic mean of the sample

Firstly, data are analyzed with descriptive statistics of variables given by arithmetic mean (M) and standard deviation (SD), doing a comparative analysis between two groups of countries just mentioned. In addition, the normality of the distribution of variables, to apply correctly parametric analyses, is analyzed with skewness and kurtosis coefficients; in the presence of not normal distributions, variables are transformed in logarithmic scale to have normality.

Secondly, follow-up investigation is the Independent Samples t -Test that compares the means of two independent groups in order to determine whether there is statistical evidence that the associated population means are significantly different. The assumption of homogeneity of variance in the Independent Samples t Test -- i.e., both groups have the same variance -- is verified with Levene's Test based on following hypotheses:

$H_0: \sigma_1^2 - \sigma_2^2 = 0$ (population variances of group 1 and 2 are equal)

$H_1: \sigma_1^2 - \sigma_2^2 \neq 0$ (population variances of group 1 and 2 are not equal)

The rejection of the null hypothesis in Levene's Test suggests that variances of the two groups are not equal: i.e., the assumption of homogeneity of variances is violated. If Levene's test indicates that the variances are equal between the two groups (i.e., p -value large), equal variances are assumed. If Levene's test indicates that the variances are not equal between the two groups (i.e., p -value small), the assumption is that equal variances are not assumed.

After that, null hypothesis (H'_0) and alternative hypothesis (H'_1) of the Independent Samples t -Test are:

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H'_0 : $\mu_1 = \mu_2$, the two population means are equal in countries with a higher and lower level of GDP per capita

H'_1 : $\mu_1 \neq \mu_2$, the two population means are not equal in countries having a higher and lower level GDP per capita

Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

The arithmetic mean (M) of the GDP per capita in 2019 of the sample ($N=155$ valid countries and 6 missing values) is $M=\$22,794$; as consequence the two groups for a comparative analysis are:

□ Countries with a Gross Domestic Product per capita in 2019 $> \$22,794$, $N=58$ countries

□ Countries with a Gross Domestic Product per capita in 2019 $\leq \$22,794$, $N=98$ countries

Table 1. Descriptive statistics

Description of variables	Countries with a Gross Domestic Product per capita in 2019 $\leq \$22,794$		Countries with a Gross Domestic Product per capita in 2019 $> \$22,794$	
	M	SD	M	SD
- Cases/population, % 2020	0.81	1.11	2.39	1.66
- Fatality rate, % 2020	2.28	1.57	1.68	0.88
- GDP per capita PPP (\$), 2019	\$8,538.85	\$6,035.58	\$446,634.61	\$20,215.07
- Health expenditure (% of GDP), 2017	5.97	2.12	7.59	2.77
- General government health expenditure per capita, PPP (\$), 2017	\$243.72	\$260.29	\$2,323.90	\$1,373.42
- Population aged 65 years and above as a percentage of population, 2019	5.83	3.85	15.07	6.41
- PM _{2.5} air pollution, population exposed to levels exceeding WHO guideline value (% of total), 2017	97.70	11.95	72.34	38.23
- COVID-19 pandemic lockdowns (days), 2020	55.26	51.22	96.71	85.79

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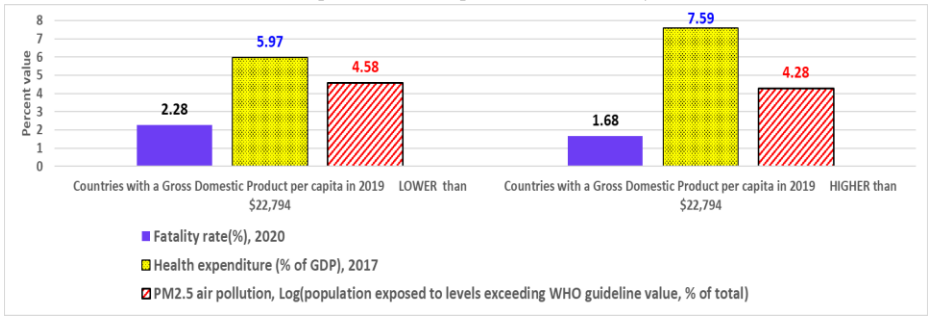


Figure 1. *Fatality of COVID-19, health expenditure and population exposed to high levels of air pollution in countries with GDP per capita higher/lower than \$22,794. Note: log scale of PM_{2.5} air pollution is to have comparable numbers in the bar graph*

Table 1 shows that fatality rate is lower in richer countries (1.68%) that have an average GDP per capita more than \$46,600, a high level of health expenditure of roughly 7.6% of GDP, a high level of government health expenditure of about \$2,300 per capita, a lower exposure of population to levels exceeding PM_{2.5} air pollution according to WHO guidelines, and finally a longer period of lockdown, regardless a higher percentage of population aged 65 years and above and a higher incidence of confirmed cases on population in these countries (cf., Figure 1).

Table 2 shows the Independent Samples *t* Test, as follow-up inspection, to assess the significance of the difference of arithmetic mean between groups of countries under study. The *p*-value of Levene's test is significant, and we have to reject the null HP of Levene's test and conclude that the variance in the groups under study is significantly different (i.e., equal variances are not assumed), except lockdown (days) that has *p*-value < .06 and equal variances are assumed. Table 2 reveals a statistically significant difference of arithmetic mean between groups having GDP per capita lower than \$22,794 (group 1) and higher than \$22,794 (group 2) as indicated in table 1.

In particular, table 2 substantiates that:

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- There was a significant difference in average cases/population % between groups 1 and 2 ($t_{88.15} = -6.43, p < .001$)
- There was a significant difference in average fatality rate % between groups 1 and 2 ($t_{153.67} = 3.06, p < .01$)
- There was a significant difference in average GDP per capita between groups 1 and 2 ($t_{63.13} = -13.98, p < .001$)
- There was a significant difference in average health expenditure (% of GDP) between groups 1 and 2 ($t_{96.66} = -3.86, p < .001$)
- There was a significant difference in average government health expenditure per capita between groups 1 and 2 ($t_{59.48} = -11.41, p < .001$)
- There was a significant difference in average population aged 65 years and above as a percentage of total population between groups 1 and 2 ($t_{81.80} = -9.98, p < .001$)
- There was a significant difference in average population exposed to levels of PM_{2.5} air pollution exceeding WHO guideline value (% of total) between groups 1 and 2 ($t_{52.34} = 3.19, p < .01$)
- There was a significant difference in average days of COVID-19 pandemic lockdowns between groups 1 and 2 ($t_{70.00} = -2.03, p < .05$)

Table 2. Independent Samples Test

		Levene's Test for equality of variances		t-test for equality of Means				
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
Cases/population % 2020	•Equal variances assumed	17.462	0.001	-7.079	153.000	0.001	-0.016	0.002
	•Equal variances not assumed			-6.431	88.151	0.001	-0.016	0.002
Fatality rate % 2020	•Equal variances assumed	7.842	0.006	2.671	154.000	0.008	0.006	0.002
	•Equal variances not assumed			3.057	153.670	0.003	0.006	0.002
GDP per capita PPP (\$), 2019	•Equal variances assumed	46.016	0.001	-17.345	153.000	0.000	-38095.761	2196.380
	•Equal variances not assumed			-13.984	63.132	0.001	-38095.761	2724.193
Health expenditure (% of GDP), 2017	•Equal variances assumed	4.929	0.028	-4.127	154.000	0.001	-1.627	0.394
	•Equal variances not assumed			-3.859	96.660	0.001	-1.627	0.422

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not assumed								
General government health expenditure per capita, PPP (s), 2017	<ul style="list-style-type: none"> •Equal variances assumed •Equal variances not assumed 	163.442	0.001	-14.446	152.000	0.001	-2080.181	143.998
				-11.412	59.484	0.001	-2080.181	182.286
Population ages 65 years and above as a percentage of population, 2019	<ul style="list-style-type: none"> •Equal variances assumed •Equal variances not assumed 	21.540	0.001	-11.266	154.000	0.001	-9.244	0.821
				-9.975	81.803	0.001	-9.244	0.927
Log PM _{2.5} air pollution, population exposed to levels exceeding WHO guideline value (% of total), 2017	<ul style="list-style-type: none"> •Equal variances assumed •Equal variances not assumed 	59.944	0.001	4.311	148.000	0.001	0.518	0.120
				3.190	52.335	0.002	0.518	0.162
Log days COVID-19 lockdowns, 2020	<ul style="list-style-type: none"> •Equal variances assumed •Equal variances not assumed 	3.749	0.057	-2.030	70.000	0.046	-0.433	0.213
				-1.999	61.106	0.050	-0.433	0.217

Hence, findings suggest that fatality rate in richer countries (1.7%) is lower than medium-low income per capita countries (2.3%). Factors determining the mitigation of the fatality of COVID-19 in society can be due to a higher level of health expenditure of roughly 7.6% of GDP, higher level of government health expenditure per capita of about \$2,300, a lower exposure of population to levels exceeding PM_{2.5} air pollution according to WHO guidelines and a longer duration of lockdown, though countries with lower fatality rates have a higher percentage of population aged 65 years and above (considered as a risk group in population; cf., European Centre for Disease Prevention and Control, 2021)² and a higher incidence of confirmed cases in population. These statistical analyses provide important, very important results

² For instance, in this context, at 9 December 2020, fatality rate in Italy as a percentage of the age group was 3% (between people having 60-69 years), 10.2% (70-79 years), 19% (80-89) and finally about 23% in population aged > 90 years (ISS, 2020; cf., Perone, 2021).

Relation between health expenditures, air pollution and fatality rate of COVID-19 to explain factors associated with the effects of COVID-19 pandemic in society. In particular, an effective strategy to cope with global pandemic crisis has to be based on three main public policies:

- health policy with higher levels of healthcare expenditure as percentage of GDP directed to specific target of efficiency of overall healthcare sector

- environmental policies based on sustainability for reducing the exposure of population to air pollution

- and finally, a timely policy response based on containment and mitigation measures in a context of advanced economies.

Discussion and policy implications

Lau *et al.* (2021) argue that in the presence of a continuous global COVID-19 pandemic threat, actual confirmed cases appear vague numbers and suggest the mortality rate as the main indicator to evaluate the real effects of COVID-19 in society (cf., Antony *et al.*, 2020; Liu *et al.*, 2021). In this context, one of the goals of nations to cope with COVID-19 pandemic crisis is to mitigate the mortality rate (cf., Coccia, 2020a). Previous studies suggest that measures of containment, such as full lockdown, can reduce the human-to-human transmission dynamics of infectious diseases and negative effects of COVID-19 pandemic in society (Atalan, 2020; Prem *et al.*, 2020; Tobías, 2020).

However, these policy responses are necessary but, of course, not sufficient conditions to constraint a negative impact of pandemics in society because many countries with a longer duration of lockdown have also a very high fatality rate, such as Italy; as a consequence an additional inquiry is needed (Coccia, 2021b). *What this study adds to current studies* on the COVID-19 pandemic crisis, performing a global analysis of countries, is to explain, whenever possible, factors determining a lower rate of fatality between countries to support a comprehensive strategy to cope with future epidemics similar to COVID-19. In particular, this study confirms that GDP per capita, healthcare spending and air

Relation between health expenditures, air pollution and fatality rate of COVID-19 pollution are factors associated with fatality rate of COVID-19 across countries. Findings here can suggest general guidelines to mitigate fatality rates of future epidemics similar to COVID-19 as schematically summarized in the figure 2.

General guidelines to mitigate fatality rates of future epidemics similar to COVID-19

- Higher health expenditure $\geq 7.6\%$ of GDP
- Higher government health expenditure per capita $\geq \$2,000$
- Lower exposure of population to days exceeding levels of $PM_{2.5}$ air pollution (max 50 days per year)
- Timely application of containment policies
- Implementation of policies for sustainable development

Figure 2. Factors determining a mitigation of fatality rates of COVID-19 between countries to design general guidelines to constrain pandemic crises of novel viral agents similar to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that is the strain of the novel influenza that causes coronavirus disease 2019 (COVID-19).

Hence, follow-up materials to reduce fatality rates of COVID-19 have to be focused on structural public policies and appropriate policy responses to cope with a constant pandemic threat. Especially,

□ *Health Policy*

This study reveals that countries with lower fatality rates have a high level of health expenditure given by 7.6% of GDP and government health expenditure per capita of about \$2,300, whereas countries with higher fatality rates have a health expenditure of roughly 6% of GDP and very low government health expenditure per capita (a mere average value of about \$243 per inhabitants) that indicates a weak healthcare sector to cope with pandemics and also other diseases in society. Scholars, to reduce the risk factors of COVID-19 mortality, also consider socioeconomic, clinical, physical, biophysiological, and biochemical characteristics of people, which can be affected by the type of nutrition system, toxicity, and ecological footprint (Aljerf & Aljurf, 2020). Other scholars, such as Kapitsinis (2020), argue that investments in health sector are a critical public policy to mitigate mortality

Relation between health expenditures, air pollution and fatality rate of COVID-19 rate of COVID-19. In this context, countries should also support the expansion of hospital capacity and testing capabilities to reduce diagnostic delays of infectious diseases and foster new technology with the development of effective vaccines, antivirals and other innovative drugs that can counteract future public health threats of new epidemics similar to COVID-19 (Ardito *et al.*, 2021; Coccia, 2019, 2020).

□ *Environmental policy*

This study finds that sustainable environment plays a vital role for reducing the impact of COVID-19 in terms of COVID-19 related infected individuals and deaths; in particular, a low rate of fatality is associated with a low level of air pollution (cf., Coccia, 2020, 2020b, 2020c). In fact, average population exposed to levels exceeding WHO guideline value (% of total) is 72% in countries with a lower level of fatality rate, whereas in countries with a higher incidence of mortality of the COVID-19 is almost 98%! Coccia (2020, 2021) shows that number of infected people was higher in Italian cities with >100 days per year exceeding limits set for PM₁₀ or ozone. Copat *et al.* (2020), considering different studies about the relation between air pollution and the spread of COVID-19, suggest that PM_{2.5} and NO₂ can support the spread and lethality of COVID-19, but additional analyses are needed to confirm this relation concerning transmission dynamics of the SARS-CoV-2 (cf., Coccia, 2021). Coccia (2020), using a case study of Italy, explains that: “the max number of days that Italian provincial capitals can exceed per year the limits set for PM₁₀ (particulate matter 10 µm or less in diameter) or for ozone, considering the meteorological conditions, is about 48 days. Beyond this critical point, ... environmental inconsistencies, because of the combination between air pollution and meteorological conditions, trigger a take-off of viral infectivity (epidemic diffusion) with damages for health of population, economy and society” (cf. also Aljerf & Aljerf, 2020). In fact, days of air pollution, associated with climate change, affect the health of population and environment (Coccia, 2020; 2021). In this field of research, Carugno *et al.* (2018) analyze respiratory syncytial virus (RSV), the primary cause of acute lower respiratory infections in children:

Relation between health expenditures, air pollution and fatality rate of COVID-19 bronchiolitis. The study suggests that seasonal weather conditions and concentration of air pollutants seem to influence RSV-related bronchiolitis epidemics in Italian urban areas. In particular, airborne particulate matter (PM) may influence the children's immune system and foster the spread of RSV infection. This study also shows a correlation between short- and medium-term PM₁₀ exposures and increased risk of hospitalization because of RSV bronchiolitis among infants. Glencross *et al.* (2020) discuss that air pollution in the long run can cause diseases by perturbing multicellular immune responses, because areas with high air pollution are associated with increased exacerbations of asthma and novel influenza viruses (Coccia, 2020, 2020a, 2021). Moreover, in outdoor environment, studies suggest that the concentration of atmospheric pollutants is associated with the spread of SARS-CoV-2 (Coccia, 2020; Martelletti & Martelletti, 2020), but a high wind speed sustains clean days from air pollution, reducing whenever possible the spread of COVID-19 and other infectious diseases (cf., Coccia, 2020; Rosario *et al.*, 2020). To put it differently, a low wind speed in cities prevents the dispersion of air pollutants that can include bacteria and viruses, such as SARS-CoV-2, and can increase the incidence of COVID-19 in society, such as in some European regions (Coccia, 2020, 2021). Instead, in external environment, high wind speed supports the dilution and removal of the droplets, decreasing the concentration of viral agents in the air and the transmission dynamics of viral infectivity among people (cf., Coccia, 2020b, 2020c). In fact, Rosario *et al.* (2020, p. 4) also show that wind improves the circulation of air and also increases the exposure of the novel coronavirus to the solar radiation effects, a factor having a negative correlation in the diffusion of COVID-19. Guo *et al.* (2019) argue that haze pollution is a serious environmental problem affecting cities, proposing policies for urban planning that improve respiratory health of population. In addition, scholars argue that: “besides some high negative externalities associated with COVID-19 pandemic in the form of increasing death tolls and rising healthcare costs, the global world should have to know how to direct high mass carbon emissions and population

Relation between health expenditures, air pollution and fatality rate of COVID-19 growth through acceptance of preventive measures, which would be helpful to contain coronavirus pandemic at a global scale” (Anser *et al.*, 2020). In fact, Marazziti *et al.* (2021) point out that the activities of human society do not consider the long-term damages of climate change and of high air pollution that may increase in future more and more the diffusion of novel influenza viruses. Reilly *et al.* (2021) maintain that one of the main effects of the COVID-19 pandemic crisis on climate change can be its influence on national commitments to action, such as recovery funds directed to low carbon investments. As a matter of fact, improvements in air quality have been accompanied by demonstrable benefits to human health. In this perspective, countries should introduce organizational, product and process technologies directed to a sustainable development for the improvement of environment, atmosphere, air quality and especially public health of population to cope with future epidemics similar to COVID-19 and other diseases that generate cardiovascular and respiratory disorders in society (Amoatey *et al.*, 2020; Siafakas *et al.*, 2018).

□ *Public policy responses*

This study also shows that a lower mortality of COVID-19 is associated with countries having a timely application of lockdowns. The model by Balmford *et al.* (2020) reveals that countries with an immediate application of full lockdown reduced deaths compared to countries that delayed the application of this strong containment measure. Gatto *et al.* (2020) maintain that restriction to mobility and human interactions can reduce transmission dynamics of the COVID-19 by about 45%. In addition, Janssen & van der Voort (2020) show the utility of “smart lockdown” as policy responses based on suggested and not mandated mitigation measures that are focused on responsibility of individuals. In this context, new studies show that specific places have a high risk to be COVID-19 outbreaks (e.g., restaurants, gyms, stadium, discotheques, etc.; cf., Chang *et al.*, 2020); as a consequence, selected measures of containment (e.g., restricting maximum occupancy of specific places, social distancing and wearing of face masks) can be more effective interventions to constrain

Relation between health expenditures, air pollution and fatality rate of COVID-19 the spread of COVID-19, without deteriorating economic system, than policies based on uniformly reduction of the mobility of people (Chang *et al.*, 2020; cf., Coccia, 2021b; Renardy *et al.*, 2020). Studies also report that containment measures for COVID-19 pandemic crisis might affect mental health with: "disturbances ranging from mild negative emotional responses to full-blown psychiatric conditions, specifically, anxiety and depression, stress/trauma-related disorders, and substance abuse. The most vulnerable groups include elderly, children, women, people with pre-existing health problems especially mental illnesses, subjects taking some types of medication including psychotropic drugs, individuals with low socio-economic status, and immigrants" (Marazziti *et al.*, 2021). Simon *et al.* (2021) confirm that: "The negative capability well-being, mental health and social support impacts of the COVID-19 lockdown were strongest for people with a history of mental health treatment. Future public health policies concerning lockdowns should pay special attention to improve social support levels in order to increase public resilience".

In general, a continuous pandemic threat highlights fragility, vulnerability and weakness of ecosystem and society, and the difficulties of countries to cope with unforeseen crises. Hence, pandemic threats given by novel infectious diseases, such as the COVID-19, in the long run need timely policy responses of containment based on agility and adaptive governance of nations supported by efficient expenditures in health sector and sustainable policies for reducing air pollution (cf., Coccia, 2020, 2021). In the short run, efficient health systems can support the management of COVID 19 vaccinations to constrain current and future negative effects of pandemics in society (DeRoo *et al.*, 2020; Frederiksen *et al.*, 2020; Harrison & Wu, 2020). Evans & Bahrami (2020) pinpoint that super-flexibility can be an appropriate approach to cope with pandemic threats of current COVID-19 in which decision making of policymakers should be oriented to versatility, agility, and resilience. In short, this study, to reiterate, suggests that to constrain the negative impact in society of constant pandemic threats, nations have to apply public

Relation between health expenditures, air pollution and fatality rate of COVID-19 policies directed to increase expenditures in health sector and reduce the sources of air pollution for improving healthcare of population in a context of sustainable environment (Coccia, 2020; Sabat *et al.*, 2020, p. 917).

Conclusion observations and limitations

This statistical analysis here suggests that GDP per capita, healthcare spending and air pollution are factors associated with reduction of fatality rate of COVID-19 between countries. In particular, this new study here finds that countries with a low average COVID-19 fatality rates have high expenditures in health sector >7.5 (% of GDP), high health expenditures per capita $>\$2,300$ and a lower exposure of population to days exceeding safe levels of particulate matter ($PM_{2.5}$). Results of the study here also suggest that general guidelines for a global strategy to cope with pandemic threat have to be based on a public policy that supports health system with effective expenditures and investments, and an environmental policy directed to sustainability that reduces the exposure of population to air pollution. These public policies can induce a reduction of fatality rates in the presence of pandemics, regardless a higher incidence of confirmed cases and a higher percentage of elderly on total population.

In addition, results here can also suggest ambidexterity strategies of crisis management for more prosperous or less favored countries:

- Rich countries can focus in the short run on measures of containment of shorter duration because of a stronger healthcare sector based on high health expenditures (as % of GDP), whereas in the long run these countries should support environmental policies for reducing air pollution
- Developing countries have to focus in the short run on measures of containment of a longer duration because of a weak healthcare sector based on low health expenditures (as % of GDP) and in the long run have to support policies for enhancing health system and health of population.

These conclusions are, of course, tentative. A main concern is that there can be differences among countries belonging to

Relation between health expenditures, air pollution and fatality rate of COVID-19 the same group of developed and developing countries, having a similar level of GDP, because they can have different healthcare expenditures, institutional contexts and apply different strategies of pandemic management. In fact, despite the study here provides main findings to better design policy responses to pandemic threat, other confounding factors that influence variables under study here (e.g., institutional aspects, culture, religion, political system, structure of pharmaceutical industry, investments in hospital sector, in prevention, in medical personnel, etc.) need to be considered for more comprehensive analysis and policy responses of countries (cf., [Stribling et al., 2020](#)). The positive side of this study is a global analysis of more than 160 countries to generalize, whenever possible, findings here that are *prima facie* (i.e., accepted as correct until proved otherwise) to support appropriate policy responses at country level. However, future studies have also to focus on follow-up materials and questions investigating the role of different organizational and financing modes of healthcare systems and the allocation of financial resources between healthcare activities (e.g., preventive and curative care) or groups of healthcare providers (for example, hospitals and ambulatory centers) because can affect the health system capability of countries to cope with current and future pandemic crises. In fact, results here have also to be reinforced with much more follow-up investigation concerning detailed research into the relations between negative effects of pandemic threat in society, health systems, public health capacity and pandemic response of countries.

Overall, then, this study suggests that an effective strategy to reduce the negative impact of future pandemic threats, similar to COVID-19, in terms of fatality rates in society, has to be based on high expenditures (and investments) in health system and on policies of sustainable development to improve public health and overall ecosystem. To conclude, this study here could represent a starting point to analyze further socio-economic factors that may shape and support general guidelines for a global strategy to cope with future pandemic threats both in more prosperous and less favored countries.

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4

Effects of restriction policies on economic growth and mortality rate in COVID-19 pandemic crisis

Introduction

We are still in the throes of the pandemic of Coronavirus Disease 2019 (COVID-19), an infectious illness generated by new Severe Acute Respiratory Syndrome Coronavirus 2/SARS-CoV-2 (Bontempi et al., 2021; Bontempi & Coccia, 2021; Coccia, 2020, 2020a, 2020b, 2021; Johns Hopkins Center for System Science and Engineering, 2022; Vinceti et al., 2021). One of the fundamental problems to cope with pandemic crisis is the design and implementation of appropriate policy responses to reduce negative effects on health of people, healthcare sector and overall socioeconomic systems (Cf. also Coccia, 2020c, 2021a, 2021b, 2021c, 2021d, 2021e, 2021f, 2021g, 2021m; 2022, 2022a, 2022b, 2022c.). Nicoll & Coulombier (2009, p. 3ff) argue that health policies to cope with pandemic can be: a) Mitigation interventions are based mainly on nonpharmaceutical measures, such as social distancing, school closures, etc. with the aim to reduce transmission dynamics and social pressure on hospitals and healthcare

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sector (cf., [Moore et al., 2021](#)); b) Containment measures have the goal to interrupt transmission dynamics by efficient contact tracing (e.g., contact tracing apps on smartphone), quarantine and general lockdown, appropriate treatments with vaccines and vaccine certificates to circulate, etc. Countries can apply these policy responses with two main approaches: a) implementing high restrictions and strict containment policies, such as a prolonged period of full lockdowns, vaccine certificates and other compulsory measures of control in society; b) introducing low restrictions based on mitigation policies of brief period and little compulsory measures to respect the individual freedoms. The restrictions of countries can be measured with some indices, such as the stringency index ([Stringency Index, 2022](#)). This measure simply records restrictions and the strictness of government policies, but it does not provide information about the appropriateness of a country's response to reduce the negative effects of pandemic crisis in society. In particular, it is unknown if a higher score of the stringency index (or similar one) implies a better country's response than others lower on the index to cope with COVID-19 ([Hale et al., 2021](#); [Stringency Index, 2022](#)). However, whether higher levels of restrictions in society lead to a national strategy and country's response having the best effectiveness to cope with COVID-19 is a critical problem in science for appropriate preparedness and crisis management to reduce negative effects of current and next pandemics similar to COVID-19. The goal of this study is to develop a comparative analysis between countries having introduced a high or low level of restrictions to cope with COVID-19 pandemic crisis to assess if a policy response based on high compulsory measures is more effective to support a reduction of negative impact of COVID-19 on health of people and socioeconomic systems.

In particular, the idea here is to analyze if countries with high restrictions and compulsory measures have lower fatality rates of COVID-19 and better economic performances than countries having policy responses based on little restrictions. These results can provide main information to extend knowledge in these topics to improve the crisis management

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and design best practices and effective policy responses to cope with COVID-19 and similar pandemic crisis (cf., Coccia, 2019g, 2021c, 2022a, 2022b, 2022c). This study is part of a large research project to explain drivers of transmission dynamics of COVID-19 and design effective policy responses to cope with and/or to prevent pandemic threats in society (Coccia, 2020, 2020a, 2020l, 2020m, 2021, 2022a).

Theoretical framework

Studies of sociology of COVID-19 endeavor to assess the impact of COVID-19 crisis and related policies on socioeconomic systems of countries (Coccia, 2022; 2022a, 2022b). In general, crisis management of COVID-19 pandemic is based on a multi-level governance, combining both national, regional and urban strategies to provide, whenever possible, timely policy responses and improve safety in society (Anttiroiko, 2021). Taherinezhad & Alinezhad (2022) propose a relational two-stage model with desirable-undesirable variables to measure the efficiency of nations to cope with pandemic and assess the efficiency of nations during the evolution of epidemic. Studies show that on average policy responses in Europe in 2020 tend to apply less stringent interventions than countries in East Asia (Ritchie *et al.*, 2020). Anttiroiko (2021) analyzes how socioeconomic context, institutional arrangements, culture, and technology level can affect national responses to the pandemic in Eastern and Western countries. The study reveals that Asian countries applied policies with proactivity, whereas Western countries provide reactive policy responses against COVID-19 (cf., Coccia, 2021b, 2022a). Moreover, Anttiroiko (2021) highlights that Asian countries have applied with determination their policy responses to COVID-19 crisis in 2020 because of the early diffusion of pandemic that has supported learning processes and improved capabilities of crisis management. Instead, European countries have different culture, political systems and approaches to mitigate the negative impact of COVID-19 pandemic crisis on socioeconomic systems (Anttiroiko, 2021). Gupta *et al.* (2022) argue that nations to

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cope with the spread of COVID-19, they have imposed full lockdown that has negative effects on many sectors and overall economic system. In particular, manufacturing, agriculture, and the service sector have undergone a major slow down because of containment policies of lockdown that have disseminated negative effects on socioeconomic systems (cf., also [Oshakbayev et al., 2022](#)). [Salisu et al. \(2022\)](#) show that the negative impact of COVID-19 shock on real GDP is pervasive and more prevalent in the developed than emerging economies. [Yao et al. \(2022\)](#) analyze the factors that influence the COVID-19 pandemic in different countries. The findings suggest that countries with a higher democracy index have more deaths from COVID-19 in the initial phase of the pandemic, possibly due to low flexibility of governments and institutions to cope with unforeseen events with timely policy responses. Especially, [Yao et al. \(2022\)](#) show that the percentage of the population aged 65 years and above and health expenditure as a percentage of GDP were positively associated with countries' case fatality rates. This study suggests that the improvement of health system with increased hospital beds and healthcare workforce per capita should reduce case fatality rate (cf., [Coccia, 2021e](#)). [Han et al. \(2022\)](#) maintain that climate variables, air pollution, and socioeconomic factors are associated with COVID-19 transmission and affect policy responses of countries (cf., [Coccia, 2020a, 2020b, 2020c](#); [Coccia, 2021, 2021a, 2021f](#)). [Buechler et al. \(2022\)](#) show that stricter government restrictions and larger decreases in mobility (particularly retail and recreation) to cope with COVID-19 are most tightly linked to decreases in electricity consumption generating socioeconomic issues during the pandemic to manifold businesses. [Pedauga et al. \(2022\)](#) explore the sequence of reactions associated with shocks that arise from COVID-19 lockdowns. Findings reveal that a policy of lockdown generates different macroeconomic effects on sectors and firms. Full lockdowns negatively affect small and medium enterprises because of larger reductions in demand. [Kufel et al. \(2022\)](#) argue that initially, to cope with COVID-19 pandemic, governments introduced national lockdowns,

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which have impacted both energy consumption and economies. Results for some European countries confirm a negative impact of these non-pharmaceutical interventions and containment policies both on energy consumption and on business cycle. The reduction of restrictions in subsequent pandemic waves increased electricity consumption, which suggests movement out of the economic recession. Kirson *et al.* (2022) propose a model (that does not account for the Delta and other variants and improvements in COVID-19 treatments) that suggests how COVID-19 vaccines can be substantial sources of gains to US GDP and lives saved for lower COVID-19 infections (cf., Gächter *et al.*, 2022). Hence, COVID-19 pandemic crisis and the intensity of restriction policies of countries affect the dynamics of socioeconomic system such that Economic Outlook (2022) reveals that from October 2022 the prevision is a cut on global GDP growth forecast from 4.7% to 4.2%. One of the causes is the emergence of the Omicron variant that has lower damaging effects on health of people, but the disproportionate growth of global COVID-19 cases is inducing some countries to keep control measures and/or reduce restrictions slowly, feeding social insecurity, disruption of businesses and continuous constrains in economy. In this context, increasingly important aspects in social sciences are the evaluation of the effectiveness of policy responses of countries to cope with pandemic crisis in terms of reduction of COVID-19 related deaths and support of the recovery of socioeconomic system. Next section presents a methodology to clarify these issues to extend knowledge in this fields of research and improve future policy responses of countries to contain and/or prevent negative effects of pandemics on public health and economy.

Method

Sample

The sample is based on 12 main countries: Australia, Denmark, Finland, France, Germany, Greece, Italy, New Zealand, Norway, Portugal, Sweden and the United Kingdom

Measures for statistical analyses

– Stringency index is based on a composite measure of nine response indicators given by: school closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; international travel controls, etc. The index on any given day is calculated as the mean score of these nine metrics, each taking a value between 0 and 100. A higher score indicates a stricter response (i.e., 100 = strictest response). This index simply records the strictness of government policies, but it does not imply the appropriateness or effectiveness of a country's response to cope with COVID-19. A higher score does not necessarily mean that a country's response is 'better' than others lower on the index to reduce negative effects of pandemic crisis in society (Hale *et al.*, 2021; Stringency Index, 2022). Period January 2020 - January 2022.

– Quarterly gross domestic product total, percentage change, previous period, based on quarterly national accounts. Gross Domestic Product (GDP) is the standard measure of the value added created through the production of goods and services in a country during a certain period. It also measures the income earned from that production, or the total amount spent on final goods and services (less imports). While GDP is the single most important indicator to capture economic activity, it falls short of providing a suitable measure of people's material well-being for which alternative indicators may be more appropriate. This indicator is based on real GDP (also called GDP at constant prices or GDP in volume), i.e., the developments over time are adjusted for price changes. The numbers are also adjusted for seasonal influences. All the Organisation for Economic Co-operation and Development (OECD) countries compile their data according to the 2008 System of National Accounts. Sources: OECD Data (2022). Period 2020-2021: Q=Quarterly; 2020-Q1, 2020-Q2, 2020-Q3, 2020-Q4, 2021-Q1, 2021-Q2, 2021-Q3 and 2021-Q4

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– Current health expenditure (% of GDP). Level of current health expenditure expressed as a percentage of GDP. Estimates of current health expenditures include healthcare goods and services consumed during each year. This indicator does not include capital health expenditures such as buildings, machinery, IT and stocks of vaccines for emergency or outbreaks. ([The World Bank, 2022](#)). Period 2008-2018 (last year available)

– Population total 2020. Total population is based on the de facto definition of population, which counts all residents regardless of legal status or citizenship. The values are midyear estimates. Source: The World Bank ([2022a](#)).

– Vaccination is measured by percent share of people fully vaccinated against COVID-19 on 11 February 2022. Data refer to February 2022 but some countries, because of difficulty in the gather and transmission of information, can have data of January 2022. Of course, this small temporal gap of some countries does not affect the statistical analyses. The data here consider all types of COVID-19 vaccines used in different countries, such as vaccines by Johnson & Johnson, Oxford/AstraZeneca, Pfizer/BioNTech, Moderna, etc. ([Coccia, 2022c](#); [Mayo Clinic, 2021](#); [Ritchie et al., 2020](#)). Of course, every country is using a different combination of these COVID-19 vaccines to protect the population against COVID-19 and its variants. Source: Our World in Data ([2022](#)).

– COVID-19 deaths. Total number of deaths in February 2022. It indicates the severity of this new infectious disease in society. Source of data: Johns Hopkins Center for System Science and Engineering ([2022](#)).

– Fatality rate. Case Fatality Ratio % (on 11 February 2022). It indicates the severity of an infectious disease and evaluates the quality of health systems ([Coccia, 2021e](#); [Lau et al., 2021](#); [WHO, 2020](#); [Wilson et al., 2020](#)). Case Fatality Ratio (CFR) estimates the proportion of deaths among identified confirmed cases of COVID-19 and it is given by:

$$\text{Case Fatality Ratio (CFR)} \quad \text{\%} = \left(\frac{\text{Number of deaths from COVID-19}}{\text{Number of confirmed cases of COVID-19}} \right) \times 100$$

Angelopoulos *et al.* (2020) maintain that Case Fatality Ratios (CFRs) between countries are critical measures of relative risk that guide policymakers to decide how to allocate medical resource to cope with COVID-19 pandemic crisis. This study also calculates the mortality rate per 1000 people for a comparative analysis with CFRs to assess with accuracy the effects of policy responses of countries.

$$\text{Mortality rate per 1000 people} = \left(\frac{\text{Total number of deaths from COVID-19 at February 2022}}{\text{Total population in 2020}} \right) \times 1000$$

Source of data: Johns Hopkins Center for System Science and Engineering (2022).

Data analysis procedure

Firstly, the Stringency Index (2022) of the countries under study is used to categorize them in two sets:

- Group 1: Countries with a high level of restrictions and mandatory measures of control (measured with Stringency Index having an average value of about 63; 100 =strictest), such as Australia, France, Germany, Greece, Italy and Portugal.

- Group 2: Countries with a low level of restrictions and obligations in society to cope with COVID-19 (Stringency Index has an average value of 49): Denmark, Finland, New Zealand, Norway, Sweden and the United Kingdom.

Secondly, descriptive statistics given by arithmetic mean and standard error of the mean of variables (Quarterly GDP-Percentage change, Health expenditure % of GDP; Fully vaccinated people; Case Fatality Ratio % and Mortality per 1,000 people) is calculated for just mentioned two groups. Results show a preliminary comparative analysis of the effectiveness of countries policy responses based on a higher /lower score of the strictness of government policies on

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Thirdly, follow-up investigation on 12 countries is performed with bivariate Pearson correlation and partial correlation (controlling health expenditure as % of GDP) to assess the sample correlation coefficient, r , which measures the strength and direction of linear relationships between pairs of continuous variables under study. The strength can be assessed by these general guidelines:

$0.1 < |r| < 0.3$... small / weak correlation

$0.3 < |r| < 0.5$... medium / moderate correlation

$0.5 < |r|$ large / strong correlation

After that, the study performs the Independent Samples t -Test that compares the means of two independent groups to determine whether there is statistical evidence that the associated population means are significantly different. The assumption of homogeneity of variance in the Independent Samples t Test -- i.e., both groups have the same variance -- is verified with Levene's Test based on following statistical hypotheses:

$H_0: \sigma_1^2 - \sigma_2^2 = 0$ (population variances of group 1 and 2 are equal)

$H_1: \sigma_1^2 - \sigma_2^2 \neq 0$ (population variances of group 1 and 2 are not equal)

The rejection of the null hypothesis in Levene's Test suggests that variances of the two groups are not equal: i.e., the assumption of homogeneity of variances is violated. If Levene's test indicates that variances are equal between the two groups (i.e., p -value large), equal variances are assumed. If Levene's test indicates that the variances are not equal between the two groups (i.e., p -value small), the assumption is that equal variances are not assumed. After that, null hypothesis (H'_0) and alternative hypothesis (H'_1) of the Independent Samples t -Test are:

$H'_0: \mu_1 = \mu_2$, the two-population means are equal in countries having high and low restrictions.

$H'_1: \mu_1 \neq \mu_2$, the two-population means are not equal in

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Statistical analyses are performed with the Statistics Software SPSS® version 26.

Findings

The arithmetic mean (M) of the stringency index of countries under study generates the following categorization of countries in two groups for a comparative analysis:

- ❑ *Countries with a High level of restrictions and compulsory measures of control*, average stringency index over 2020-2022 (January) period = 62.97 (Std. Error .279)
- ❑ *Countries with a Low level of restrictions and compulsory measures of control*, average stringency index over 2020-2022 (January) period=49.01 (Std. Error .282)

Table 1. *Descriptive statistics*

Description of variables	Countries with HIGH restrictions		Countries with LOW restrictions	
	M	Std. Error Mean	M	Std. Error Mean
Stringency Index over 2020-2022 period	62.97	0.279	49.01	0.282
Quarterly GDP, Percentage change, 2020-2021	0.14	1.05	0.37	0.89
Current health expenditure % of GDP, 2008-2018	9.64	0.14	9.70	0.086
Mortality per 1000 people, February 2022	1.39	0.40	0.89	0.37
Fatality rates %, February 2022	0.82	0.17	0.43	0.12
Share of people fully vaccinated against COVID-19, February 2022	77.17	3.00	74.60	1.45

Note: M= arithmetic mean

Table 1 shows that countries with high restrictions and obligations in society (average stringency index of 62.97) have mortality per 1000 people and fatality rate (%) higher than countries with low restrictions and mandatory measures: 1.19 vs. 0.89 and 0.82 vs. 0.43, respectively. In addition, average quarterly GDP of countries with a high score of stringency index (high restrictions) is +0.14, 64% lower than countries with a low score of stringency index and low restrictions (that is +0.37). This finding reveals how compulsory measures block

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the operation of socioeconomic systems without reducing negative effects of COVID-19 pandemic crisis in society. Comparative analysis of these two groups of countries also shows that average health expenditure (% of GDP) is almost similar, whereas share of people vaccinated is higher, of course, in countries with high restrictions and compulsory measures that in some countries have been forces with immunity passports on work and vaccinations mandatory for adults that reduce individual freedoms generating a flawed democracy.

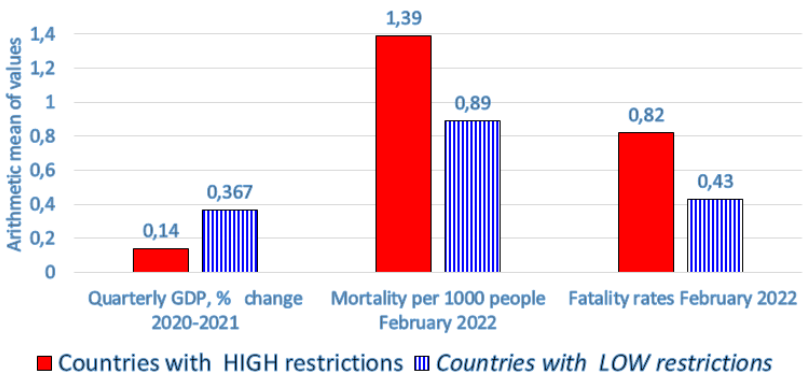


Figure 1. Comparative analysis of economic and health indicators between countries with high and low restrictions to cope with COVID-19

Figure 1 shows, *ictu oculi*, how countries with a high level of restrictions and compulsory measures have a deterioration of economic systems and a higher negative impact of pandemic in society. This result can be explained with the fact that restrictions and mandatory measures of control to cope with COVID-19 are not a sufficient strategy to reduce the negative impact of the novel coronavirus in society, because there are manifold factors that support the diffusion and mortality of this pandemic, also in countries having a high level of fully vaccinated people associate with high restrictions.

Table 2. Correlation

	Average Stringency Index 2020-2022	Average GDP Growth Q 2020-2021	Fatality Rate 11 Feb 2022	Total Mortality per 1000, 11 Feb 2022	Full Vaccinated people 11 Feb 2022
Pearson Correlation	1	-0.279	.795**	.543*	0.003

Notes: ** Correlation is significant at the 0.01 level (1-tailed). * Correlation is significant at the 0.05 level (1-tailed).

Table 2 shows a high positive correlation in sample between stringency index and fatality rate ($r=.80$, p -value .01) and total mortality ($r=.54$, p -value .05). These results are confirmed with partial correlation controlling average health expenditure (Table 3).

Table 3. Partial Correlation

<i>Control variable</i>	Pearson Correlation	Average Stringency Index 2020-2022	Average GDP Growth Q 2020-2021	Fatality Rate 11 Feb 2022	Total Mortality per 1000, 11 Feb 2022	Full Vaccinated people 11 Feb 2022
Average Health Expenditure 2008-2018	Average Stringency Index 2020/2022 Significance (1-tailed)	1	-0.262	0.796	0.614	-0.005
			0.218	0.002	0.022	0.494

Table 4. Independent Samples Test of countries with high vs. low restrictions.

		Levene's Test for equality of variances		t-test for equality of Means				
		F	Sig.	t	df	Sig. 2-tailed	Mean Difference	Std. Error Difference
Average GDP Growth Q 2020-2021	•Equal variances assumed	5.758	0.037	-1.152	10	0.276	-1.383	1.201
	•Equal variances not assumed			-1.152	5.01	0.301	-1.383	1.201
Fatality Rate, 11 Feb 2022	•Equal variances assumed	0.8	0.392	1.893	10	0.088	0.388	0.205
	•Equal variances not assumed			1.893	9.074	0.091	0.388	0.205
Total Mortality per 1000, 11 Feb 2022	•Equal variances assumed	0.069	0.798	0.91	10	0.384	0.497	0.546
	•Equal variances not assumed			0.91	9.939	0.384	0.497	0.546

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Full Vaccinated	•Equal variances								
People, 11 Feb 2022	assumed	1.489	0.25	0.77	10	0.459	2.567	3.334	
	•Equal variances								
	not assumed			0.77	7.222	0.466	2.567	3.334	

Independent Samples Test in table 4 suggests a similar arithmetic mean across countries with high and low restrictions (retain null hypothesis). This result may be due to small sample that reduces the consistency of this statistical analysis. However, in general, the statistical evidence above seems in general to support the hypothesis that elevated level of restrictions and obligations in society does not improve the management of COVID-19 pandemic compared to countries with little restrictions in terms of reduction of mortality and better functioning of economic system that shows a low average rate of quarterly growth (2020-2021 period) than countries having little compulsory measures.

Discussions

The critical findings of this study are that a strong policy of restrictions and obligations does not reduce negative effects of COVID-19 pandemic in society, whereas it seems to reduce the economic performance of countries in terms of low quarterly growth of GDP (average value over 2020-2021 period). This result can be explained with the fact that hard containment policies are not a sufficient strategy to reduce the negative impact of new coronavirus in society, because there are manifold factors that support the diffusion of the novel coronavirus and mortality of COVID-19. Many countries applied harsh and pervasive restrictions with the objective to reduce pandemic diffusion and support economic growth, but the evidence of this study shows that it is not a policy having effectiveness. Libman (2018) argues that governmental economic policy is one of the major factors influencing economic growth. However, the containment of COVID-19 pandemic crisis and growth performance depend not only on what policy measures the government decides to implement but also on how these policies are implemented such that inefficient regulatory measures can undermine also the most

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reasonable policy measures. Ball (2021) argues that Sweden adopted a more relaxed strategy that avoided lockdowns and people were treated with trust and openness about the measures being adopted. Initially, results suggested in 2020 that Sweden had much higher fatalities than surrounding countries (Ball, 2021), but in 2022 results in terms of low mortality related to COVID-19 and high economic growth of Sweden are better than other countries applying stringent measures of containment (Johns Hopkins Center for System Science and Engineering, 2022; Stringency Index 2022). The UK has also applied low restrictions to reduce the risk that strict policy responses would be unpopular and in 2022 economic performance is better and negative impact of COVID-19 is similar or lower than countries with more restrictions (Birch, 2021). Studies suggest that countries with manifold restrictions and obligations tend to generate complex and ambiguous rules, also because they are constantly changing with pandemic evolution, generating increasing confusion and social insecurity that damage people, organizations and overall socioeconomic systems (Gore, 1994). A prominent lesson to be learnt from the COVID-19 pandemic experience is how scientific advice feeds into political decision-making, and if it is based on the value of independence and transparency of that advice. In many countries, contradictory scientific recommendations have created confusion because many initial claims were subsequently proved to be false or misleading. Ball (2021, p. 9) argues that policy responses to cope with COVID-19 should be based on some requirements, such as:

- To establish credibility and generate trust
- Trust can only be generated by openness
- Openness requires recognition of uncertainty, where it exists
- The importance of precautionary measures should not be played down on the grounds that the risk is unproved
- The public should be trusted to respond rationally to openness
- Scientific investigation of risk should be open and transparent

— The advice and the reasoning of advisory committees should be made public

However, many of these tenets was disregarded during the COVID-19 pandemic by countries applying a lot of restrictions with ambiguity and inconsistency and delayed containment rules with the temporal evolution of pandemic, generating a low effectiveness to reduce negative effects in society (Coccia, 2021, 2022b). The COVID-19 pandemic shows how the effectiveness of scientific and technological interventions to support public policy is based on manifold social and institutional factors (Raleigh, 2020). In fact, policy responses of restrictions cannot be fully effective if people cannot afford to adhere to them (Green *et al.*, 2021). Effective response policies also depend on clear and honest communication, and an ability to overcome aspects of misinformation for compliance with restrictions (Ball, 2021). In general, efficient governance can support health system preparedness in the presence of turbulent scenarios given by pandemic crisis and new population needs. Moreover, countries with constant investment in health sector and preparedness can reduce mortality, morbidity and stress among the population as well as promote public health and economic recovery after pandemic crisis (Kluge *et al.*, 2020; Coccia, 2021b). Kapitsinis (2020) argues that investments in health sector are a critical public policy to mitigate mortality rate of COVID-19 and future pandemics. Hence, countries should support healthcare investments in the expansion of hospital capacity and R&D investments in innovative technology to develop effective vaccines, antivirals, innovative drugs and high-tech devices that can counteract future public health threats of new epidemics like COVID-19 (Ardito *et al.*, 2021; Coccia, 2017c, 2017d, 2019f, 2020)¹. Sagan *et al.* (2020) argue that

¹ For role of science, technology, research labs, leading firms and institutions for economic and social change see: Ardito *et al.*, 2021; Coccia, 2003, 2005, 2005a; Coccia, 2008, 2013, 2014, 2015, 2016, 2017, 2017a, 2017b, 2017c, 2017d, 2017e, 2018a, 2018b, 2018c, 2018d, 2018e, 2018f; Coccia, 2019, 2019a, 2019b, 2019c, 2019d, 2019e, 2019f; 2019g, 2019h, 2019i, 2019l, Coccia, 2020d, 2020e, 2020f, 2020g, 2020h, 2020i; Coccia, 2021h, 2021i, 2020l, 2020m; Coccia, 2022d; Coccia & Bellitto, 2018; Coccia & Benati, 2018;

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effective governance is a critical factor to a resilient response in the presence of crisis. Instead, bureaucratic rules directed to a high degree of control and restrictions over public and private life reduce individual liberties of people generating social, psychological and economic issues without reducing negative effect of pandemic in society (Chantler *et al.*, 2019; Cornell *et al.*, 2020; Dye & Mills, 2021; Phelan, 2020). Brown *et al.* (2021) suggest that the implementation of immunity passports, a main measure of restriction applied in many European countries, ought to be applied to maximize their benefit without reducing wellbeing of people. Kamin-Friedman & Peled Raz (2021) argue that green pass: “imposes restrictions on the movement of individuals who had not been vaccinated or who had not recovered, it is not consonant with solidarity and trust building. Implementing the Green Pass provision while advancing its effectiveness on the one hand, and safeguarding equality, proportionality, and fairness on the other hand may imbue this measure with ethical legitimacy despite involving a potential breach of trust and solidarity”. Saban *et al.* (2021) maintain that policymakers should use a balanced approach to protect public health, with minimum infringement on citizens' rights. Luster *et al.* (2021) maintain that: “the Green Pass policy raises practical, legal and ethical concerns.... any privileges or restrictions guided by one's COVID-19 immunization status must be designed with the utmost attention to prevent a disproportionate violation of the human rights of the non-vaccinated and the public at large”.

Overall then, restriction policies and compulsory measures are originated to cope with pandemic and support economic recovery, but some countries in Europe are using obligations to penalize people (such as without vaccination), reducing individual freedoms, increasing the discrimination between people in social, cultural and sporting activities, inducing tensions between different social groups, and as a

Coccia & Cadario, 2014; Coccia & Finardi, 2012, 2013; Coccia & Rolfo, 2000, 2008; Coccia & Watts, 2020; Coccia & Wang, 2015, 2016; Pagliaro & Coccia, 2021; Pronti & Coccia, 2020.

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consequence reducing perspective for sustaining economic growth (Kosciejew *et al.*, 2021; Waitzberg *et al.*, 2021; Wilf-Miron *et al.*, 2021). Gore (2004) argues that in contexts of uncertainty, governments tend to create administration's policies with inconsistencies, ambiguities and little transparency to reduce accountability to the people and the public interest (cf., Wilf-Miron *et al.*, 2021). Moreover, a persistent use of restriction policies, leveraging potential health risks, can lead to authoritarian rules that reduce individual freedoms and create socioeconomic problems, with low benefits to cope with COVID-19 pandemic (Wesołowski, 1990)². In general, Ball (2021) argues that the diversity of pandemic outcomes and responses throughout the world makes it hard to draw any general conclusions about how science, policy and society can and should interact (cf., Shattock *et al.*, 2022). Ball (2021, p. 9) also maintains that: "Politicians, ..., should not use science as a shield against making (or accepting responsibility for) difficult decisions, and should acknowledge that scientific advice is likely to be more effective when it is genuinely independent, autonomous and transparent. We cannot expect good public health to be valued and nurtured if political health is poor".

Conclusions

In the presence of a continuous global COVID-19 pandemic threat, one of the goals of nations is to mitigate mortality and support economic growth (cf., Coccia, 2020a, 2021e).

The results of this analysis here seem to be that:

□ a strict policy of many restrictions and obligations does not reduce negative effects of COVID-19 pandemic in society in terms of lower mortality per 1,000 people and a lower-case fatality rate than countries with little restrictions

² Wesołowski (1990) argues some axioms of the authoritarian regime, such as the state's power (state) is the fundamental mechanism of social integration and regulation; the state is an organism which stands above all other forms of social organization and exerts control over them; it uses violence when needed, etc.

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(findings here show 1.19 vs. 0.89 and 0.82% vs. 0.43%, for countries with high and low restrictions respectively)

□ countries with high restrictions and obligations reduce the economic performance in terms of lower average growth of quarterly Gross Domestic Product than countries with little restrictions (0.14% vs. 0.38%, for countries with high and low restrictions respectively).

Although this study has provided interesting results, that are of course tentative, it has several limitations. First, a limitation of the study is the lack of data in manifold countries. Second, not all the possible confounding factors that affect the policy responses and mortality of COVID-19 are taken into consideration and in future studies these factors deserve to be controlled for supporting results here. Third, the lack of integration of data with socioeconomic aspects of countries may influence the results of mortality and economic growth, making comparative analyses a problematic approach (Angelopoulos *et al.*, 2020; Coccia, 2018). Fourth, country-specific health investments may affect response policies of countries and have to be controlled in future development of this study. Thus, the generalization of this results should be done with caution.

Future research should consider new data and countries and to examine also other variables between countries to explain the interaction between policy responses, mortality and other socioeconomic factors. Hence, there is need for much more detailed research in these topics and this study encourages further investigations to clarify complex factors to design appropriate strategies cope with pandemic threat without damaging socioeconomic system. Results here have to be reinforced with much more follow-up investigation concerning a large sample of countries for detailed research into the relations between response policies, effects of pandemic in health of people and socioeconomic system.

Overall, therefore, the increase in mandatory measures may have little effectiveness in addressing the negative effects of the pandemic crisis and improving economic performance, also decreasing the individual freedoms that generate some abuses in democratic countries because of informally

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authoritarian rules applied in circumstances of social precariousness, fueling the fear of the pandemic in society. To conclude, it is worth raising the question whether in the presence of pandemic crisis, the uncontrolled implementation of health policies based on high restrictions and authoritarian rules by political authorities can generate more hazardous effects in society than new viral agents, restrictions that do not reduce negative the effects of COVID-19 pandemic in society, do not improve economic growth and direct nations towards a flawed democracy with socioeconomic issues of long run.

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5

Relation between COVID-19 vaccination and economic development of countries

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious illness caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared in late 2019 (Bontempi *et al.*, 2021; Bontempi & Coccia, 2021; Coccia, 2020, 2020a, 2020b, 2021). COVID-19 is still circulating in 2021 with mutations of the novel coronavirus that generate continuous COVID-19 infections and deaths in manifold countries (Johns Hopkins Center for System Science and Engineering, 2021; Vinceti *et al.*, 2021). High numbers of COVID-19 related infected individuals and deaths worldwide have supported the development of different types of vaccines based on viral vector, protein subunit and nucleic acid-RNA (Abbasi, 2020; MAYO CLINIC, 2021). The investigation of vaccination plans between countries is a crucial aspect to determine how the novel infectious disease can be controlled and/or eradicated in the population (Aldila *et al.*, 2021; Prieto Cruriel, *et al.* 2021). Vaccination has the potential effect to reduce the diffusion of COVID-19, to relax non-pharmaceutical measures and

Relation between COVID-19 vaccination and economic development of countries maintain low basic reproduction number, but an important point is to clarify the optimal levels of administering of vaccines between countries to reduce negative effects in society (Coccia, 2021a). Akamatsu *et al.* (2021) argue the vital role of governments to implement an efficient campaign of vaccination to substantially reduce infections in society, and avoid the collapse of healthcare system (cf., Coccia, 2021a, 2021b, 2022). Aldila *et al.* (2021) maintain that higher levels of vaccination rate can eradicate COVID-19 in population by approaching herd immunity to protect vulnerable individuals (cf., Anderson *et al.*, 2020; de Vlas & Coffeng, 2021; Randolph & Barreiro, 2020). Herd immunity indicates that only a share of population needs to be immune and therefore no longer susceptible to a viral agent (by overcoming natural infection or through vaccination) for controlling large outbreaks (Fontanet & Cauchemez, 2020). Scholars estimate the proportion of a population that needs to be vaccinated to support herd immunity, *ceteris paribus* (Redwan, 2021). The threshold level depends on basic reproduction number, R_0 —the number of cases, on average, spawned by one infected individual in an otherwise fully susceptible (Coccia, 2020; Kwok *et al.*, 2020). The index R_0 assumes that everyone is susceptible to virus, but the level changes as the epidemic evolves, since it depends on changes in susceptibility of the population, mitigation and restriction policies, circulation of variants, season, etc. (Aschwanden, 2020, 2021; Coccia, 2021a; Dashtbali & Mirzaie, 2021). Kwok *et al.* (2021) argue that the minimum proportion (%) of total population required to confer COVID-19 immunity change, such as it can be 5.66 in Kuwait and 85 in Bahrain. In this context, a fundamental problem in COVID-19 pandemic crisis is the detection of maximum level of vaccinated people between countries without compulsory actions on citizens and if the maximum level of vaccinated people changes according to the types of executives (e.g., mixed executives, monarchy, etc.). The natural acceptance of COVID-19 vaccines between countries can be a main proxy to assess the maximum level of consent in rich and democratic settings, whereas actions of nations for overcoming the max level of vaccinated people with

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autocratic interventions that reduce individual freedoms can show consequential socioeconomic issues.

This study in the presence of COVID-19 pandemic crisis can clarify some relations to design best practices of crisis management for vaccination plans directed to increase vaccinated people using rewards systems in democratic settings having little amount of oversight on public and private life rather than compulsory rules that reduces individual freedoms (cf., [Coccia, 2019g](#)). This study is part of a large research project to explain drivers of transmission dynamics of COVID-19 and design effective policy responses to cope with and/or to prevent pandemic threats in society ([Coccia, 2020, 2020a, 2020b, 2020c, 2021, 2021a, 2021b, 2021c, 2021d, 2021e, 2021f, 2021g, 2021h](#)).

Methods

Source and sample

The sample of this study is $N=150$ countries worldwide.

Measures for statistical analyses

– Vaccination is measured by percent share of people fully vaccinated against COVID-19 over September-October 2021. Data refer mainly to October 2021 but some countries, because of difficulty in the gather and transmission of information, provide data of September 2021, such as Algeria, Afghanistan, Turkmenistan, Madagascar, etc. The data here considers all types of COVID-19 vaccines used in different countries, i.e., vaccines by Johnson & Johnson, Oxford/AstraZeneca, Pfizer/BioNTech, Sinopharm/Beijing, Sinovac, Sputnik V and Moderna (Ritchie *et al.*, 2020). Of course, every country has been using a different combination of these COVID-19 vaccines to protect the population. Source: Our World in Data (2021).

– Gross Domestic Product (GDP) per capita in 2020. GDP per capita (constant 2010 US\$). GDP per capita is gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of products. It is calculated without

Relation between COVID-19 vaccination and economic development of countries making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in constant 2010 U.S. dollars. Source: The World Bank (2021).

– Democracy is measured using score of Freedom House Methodology. A country or territory is assessed considering indicators of political rights and civil liberties. The average of a country or territory’s political rights and civil liberties ratings is called the Freedom Rating, and the level determines the Freedom status given by:

- Free countries (1.0 to 2.5 Combined Average of the Political Rights and Civil Liberties)
- Partly Free (3.0 to 5.0)
- Not Free (5.5 to 7.0)

Source: Freedom House (2021, 2021a).

Model and data analysis procedure

– Level of economic development of countries is categorized using GDP per capita (constant 2010 US\$) in 2020 as follows (The World Bank, 2021):

- HIGH economic development >\$15,000
- MEDIUM economic development (\$2,000-14,999)
- LOW economic development < \$2,000

– Countries are also categorized using the typology of executives as follows (Norris, 2008):

- DIRECT Democracy
- PARLIAMENTARY Monarchy
- PRESIDENTIAL Republic
- MIXED Executives
- MONARCHY
- MILITARY State

Data are analyzed with descriptive statistics given by arithmetic mean and standard error of the mean, using the categorization of economic development, freedom status and type of executives between countries.

The normality of distributions of variables under study is checked with skewness and kurtosis coefficients and considering that some variables are not appropriate for

Relation between COVID-19 vaccination and economic development of countries parametric analyses, they are transformed in logarithmic scale for performing regression analysis.

After that, the analysis of simple regression applies quadratic models because they fit the scatter of data and detect nonlinear effects of relations understudy. The specification of *log-log* quadratic model is given by:

$$\bullet \log y_{i,t} = \alpha_0 + \beta_1 \log x_{i,t-1} + \beta_2 \log x_{i,t-1}^2 + u_{i,t} \quad (1)$$

where:

- $x_{i,t-1}$ = GDP per capita (constant 2010 US\$) in 2020
- $y_{i,t}$ = Share % of people fully vaccinated against COVID-19 over September-October 2021
- $u_{i,t}$ = Error term

country $i=1, \dots, n$; $t=time$

Remark 1: The square of GDP per capita in model [1] is introduced to consider the possibility of non-linear effects in the relation under study.

Remark 2: Model [1] has a time lag effect between explanatory (t-1) and dependent variable (t) to reduce the endogeneity of explanatory variable in model and provide reliable (estimated) parameters.

Finally, the optimization of the estimated relationships [1] is performed with the perspective of *maximization* of the equation [1] to find the maximum levels of share % of people fully vaccinated against COVID-19 in society. In particular, the estimated relationships [1] are objective functions of one (real) variable given by polynomial functions of second order. These estimated relations [1] are continuous and infinitely differentiable functions. The calculus applied on functional relation [1] provides the optimal levels of share % of people fully vaccinated against COVID-19 in countries. Model [1] is applied using the Freedom status per countries (Free, Partly Free or Not Free) and total number of countries ($N=150$).

Results are described in tables and presented in figures with the estimated relationships and optimal (max) level of

Relation between COVID-19 vaccination and economic development of countries share % of people fully vaccinated against COVID-19 in society.

Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

Table 1 shows that partially free and rich countries have a higher share of people fully vaccinated against COVID-19, whereas free countries having a medium level of GDP per capita have a higher share of vaccinated people than partially free and not free countries.

Table 1. Descriptive statistics of fully vaccinated people per level of GDP per capita and democracy, N=150 countries

Level of economic development using GDP per capita in 2020	Freedom Status	Fully vaccinated September - October 2021		
		N	Mean (%)	Std. Error
HIGH >\$15,000	▪ FREE	36	63.99	10.39
	▪ PARTLY FREE	3	66.63	11.99
	▪ NOT FREE	4	59.65	18.14
MEDIUM (\$2,000-14,999)	▪ FREE	24	38.31	20.28
	▪ PARTLY FREE	24	28.71	18.36
	▪ NOT FREE	17	23.22	19.19
LOW < \$2,000	▪ FREE	6	7.42	8.32
	▪ PARTLY FREE	22	4.28	5.41
	▪ NOT FREE	14	13.69	19.86

Table 2. Descriptive statistics of fully vaccinated per type of executives, N=150 countries

Type of Executives	Fully vaccinated September - October 2021		
	N	Mean (%)	Std. Error
DIRECT Democracy	2	63.05	2.25
PARLIAMENTARY Monarchy	21	52.01	5.34
PRESIDENTIAL Republic	39	27.21	3.78
MIXED Executives	78	31.32	3.06
MONARCHY	7	46.54	5.99
MILITARY State	3	8.97	3.37

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Table 2 shows that countries with monarchy and parliamentary monarchy have a higher share of people fully vaccinated against COVID-19 than countries having mixed executives and presidential republic.

Table 3. Regression analyses of people fully vaccinated in 2021 on GDP per capita 2020 in free, partly free and not free countries (log-log quadratic model [1])

	FREEDOM STATUS IN COUNTRIES (LEVEL OF DEMOCRACY)			TOTAL COUNTRIES
	FREE	PARTLY FREE	NOT FREE	
Constant α	-19.97***	-22.18***	-2.484	-18.66***
(St. Err)	(3.22)	(6.04)	(12.70)	(2.65)
Coefficient β_1	4.50***	5.049**	0.456	4.194***
(St. Err.)	(.70)	(1.534)	(3.03)	(.62)
Coefficient β_2	-.209***	-.243*	-.019	-.192***
(St. Err.)	(.037)	(.096)	(.179)	(.035)
R ²	.73	.65	.32	.67
(St. Err. of Estimate)	(.49)	(1.07)	(1.24)	(.904)
F	85.25***	42.17***	6.99**	144.95***

Note: Dependent (response) variable is: Share (%) of people fully vaccinated against COVID-19 in 2021 over September-October 2021 period. Explanatory variable is: Gross Domestic Product per capita in 2020. **Significance:** ***p-value<0.001; **p-value<0.01; *p-value<0.05

□ *FREE Countries*

• The estimated relationship of FREE countries, based on results of table 3, is:

$$j_{i,t} = -19.97 + 4.50w_{i,t-1} - 0.209 w_{i,t-1}^2$$

-
- The function is given by
-

$$j = -19.97 + 4.50 w - 0.209 w^2 \tag{2}$$

the necessary condition to maximize the function j is:

- $\frac{dj}{dw} = j'(w) = 4.50 - 0.418w = 0$

The first derivative equal to 0 is:

$$j'(w) = 0 \Rightarrow w^* = \frac{4.50}{0.418} = 10.76 \text{ level of GDP per capita (in log)} = \$47,098$$

Now if we replace w^* in equation [2], we have $j = 4.2525$ (in log scale) which is transformed by $e^j = 70.28\%$ = the max share of people fully vaccinable in free countries. The increase of this share beyond the maximum achievable level in free countries in general it needs the application of suitable rewards or policies of restriction associated with a high degree of control and regulation over public and private life of individuals that can generate social and economic issues, reducing the democratic environment and individual freedoms (Figure 1).

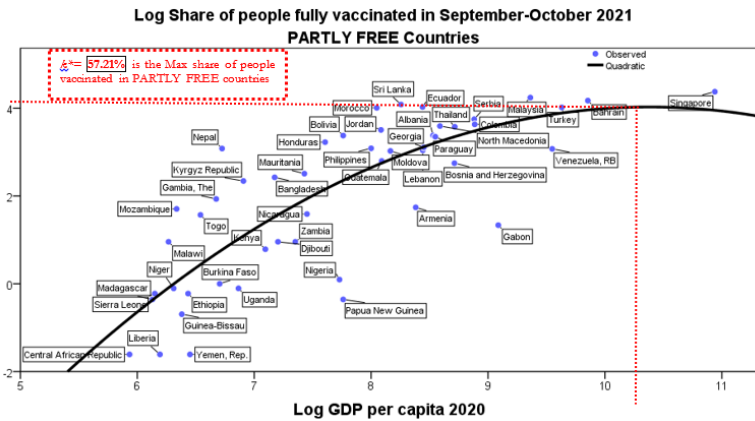


Figure 1. Relation of share of people vaccinated against COVID-19 (%) on GDP per capita in free countries based on quadratic model [1], with the maximum level of vaccinated people.

□ *PARTLY FREE Countries*

- The estimated relationship of FREE countries, based on results of table 3, is:

$$k_{i,t} = -22.18 + 5.049b_{i,t-1} - 0.243 b_{i,t-1}^2$$

- The function is given by

Relation between COVID-19 vaccination and economic development of countries

$$k = -22.18 + 5.049 b - 0.243 b^2 \tag{3}$$

the necessary condition to maximize the function k is:

$$\bullet \frac{dk}{db} = k'(b) = 5.049 - 0.486b = 0$$

The first derivative equal to 0 is:

$$k'(b) = 0 \Rightarrow b^* = \frac{5.049}{0.486} = 10.389 \text{ level of GDP per capita (in log)} = \$32,500.15$$

Now if we replace $b^*=10.389$ in equation [3], we have $k=4.04675$ (in \log scale) which is transformed by $e^k=57.21\%$ = the max share of people fully vaccinated in partially free countries. The increase of this share beyond the maximum achievable level in *partly free* countries in general it needs the application of appropriate rewards or additional interventions of control and regulation over public and private life that generate social and economic issues, reducing the democratic environment and individual freedoms further (Figure 1).

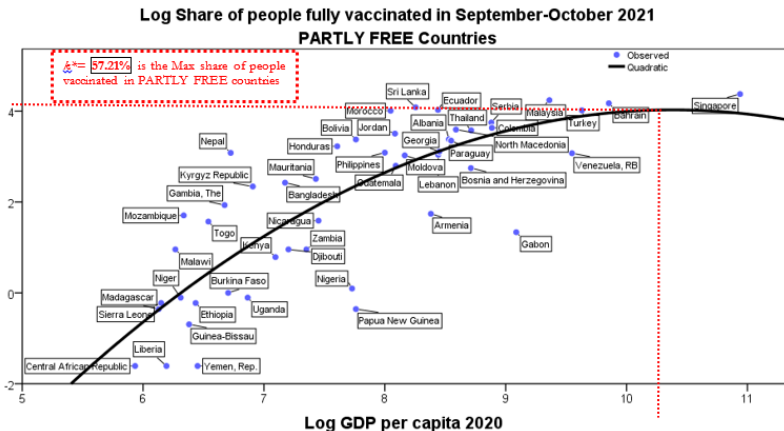


Figure 2. Relation of share of people vaccinated against COVID-19 (%) on GDP per capita in partly free countries based on quadratic model [1], with the maximum level of vaccinated people.

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□ *NOT FREE Countries*

• The estimated relationship in NOT FREE countries has not significant parameters as indicated in table 3 and we do not proceed with the approach of optimization because the results are misleading

□ *TOTAL Countries*

• The estimated relationship of total number of countries, based on results of table 3, is:

$$q_{i,t} = -18.66 + 4.194g_{i,t-1} - 0.192 g_{i,t-1}^2$$

• The function is given by

$$q = -18.66 + 4.194 g - 0.192g^2 \tag{4}$$

the necessary condition to maximize the function q is:

• $\frac{dq}{dg} = q'(g) = 4.194 - 0.384g = 0$

The first derivative equal to 0 is:

$$q'(g) = 0 \Rightarrow g^* = \frac{4.194}{0.384} = 10.922 \text{ level of GDP per capita (in log)} = \$55,374.53$$

Now if we replace g^* in equation [4], we have: $q = 4.2432$ (in \log scale) which is transformed by $e^q = 69.63\%$ = the max share of people fully vaccinated between all countries. The remaining share is associated with a natural hesitancy of people and individual freedoms typical of rich and democratic countries. In addition, as explained before, the increase of this share beyond the maximum level in countries, in general it needs the application of suitable rewards or restriction policies directed to a high degree of control and regulation over public and private life that generate social and economic issues, reducing the democratic environment and individual liberties of people (Figure 3).

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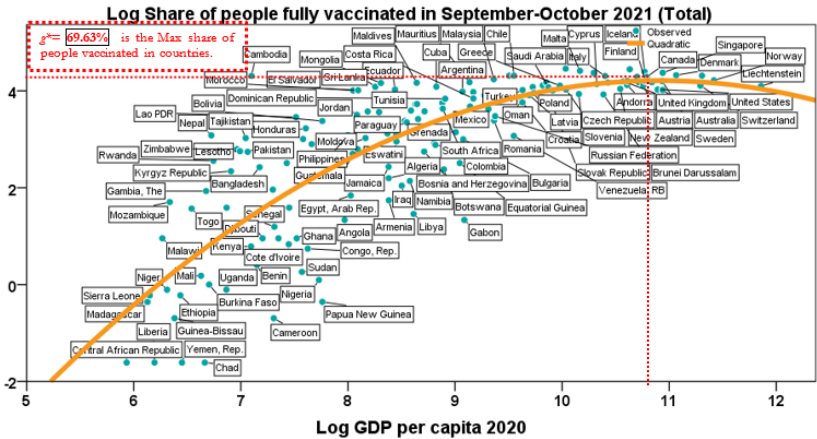


Figure 3. Relation of share of people vaccinated against COVID-19 (%) on GDP per capita in all countries ($N=150$) based on quadratic model [1], with the maximum level of vaccinated people.

- In general, the share of vaccinated against COVID-19 increases with the wealth of nations but it has a physiological maximum level of about 70% between countries at global level (in partly free countries is lower).

Discussions

Anttiroiko (2021) analyzes how socioeconomic context, institutional arrangements, culture, and technology level can affect policy responses to the pandemic crisis in Eastern and Western countries¹. Studies show that in average policy responses in Europe over 2020 tended to be less stringent than countries in East Asia (Ritchie *et al.*, 2020). Moreover, Anttiroiko (2021) highlights that Asian countries have applied with determination policy responses to cope with COVID-19 crisis because of the early diffusion of pandemic in their regions that has supported learning processes. Instead,

¹ For role of science and technology for economic and social change see: Ardito *et al.*, 2021; Calabrese *et al.*, 2005; Coccia, 2005; Coccia, 2008, 2014, 105, 2016, 2017a, 2017c, 2017d, 2018b, 2018c, 2019, 2019a, 2019b, 2019f; Coccia, 2020d, 2020e, 2020f, 2020g; Coccia and Cadario, 2014; Coccia and Finardi, 2012, 2013; Coccia and Rolfo, 2000, 2008; Coccia and Watts, 2020; Pagiario and Coccia, 2021.

European countries have different culture, institutions, political systems and approaches to cope with crises and have also to face with privacy and human rights issues, protests against governments for lockdown, restriction measures, vaccine passports, etc. (Coccia, 2005a, 2017, 2017b; 2018a, 2019c, 2019d, 2021; Coccia & Bellitto, 2018; Coccia & Benati, 2018) Findings here reveal that the share of vaccinated people against COVID-19 increases with the wealth of nations, but it has a physiological limit of about 70% between countries. One of the main issues is the vaccine hesitancy in a portion of population associated with individual freedoms of rich and democratic countries (cf., Verger & Peretti-Watel, 2021). Murphy *et al.* (2021) found that general adult populations of Ireland and the United Kingdom had vaccine hesitancy/resistance for 35% and 31% respectively. Schwarzingler *et al.* (2021) analyze the determinants of COVID-19 vaccine acceptance or refusal and suggest that highlighting the benefits in terms of herd immunity can reduce hesitation about COVID-19 vaccines (cf., Buttenheim & Asch, 2013; Echoru *et al.*, 2021; Kanyike *et al.*, 2021). In fact, COVID-19 vaccination is associated with levels of public trust in governments that have to be built and reinforced in the presence of situation of crisis management (cf., Soveri *et al.*, 2021; Vergara *et al.*, 2021). Abuza (2020) argues that the effectiveness of policies in the presence of biological threats is based on leadership and competence, rather than political regimes of countries. Some countries in Western world are stressing democratic society with restrictions to individual freedoms to increase the maximum share of people fully vaccinated (estimated here) by introducing green pass (or vaccine certificate or immunity certificate that here are used interchangeably), as a rule for entering certain businesses and public spheres and/or use public transport or to go to work (as in Italy); this bureaucratic tool is creating a hot debate and manifold socioeconomic issues (Brown *et al.*, 2021; Chantler *et al.*, 2019; Coccia, 2018d; Dye & Mills, 2021; Phelan, 2020). Brown *et al.* (2021) suggest that the implementation of immunity passports ought to be applied to maximize their benefit without reducing wellbeing of people. Saban *et al.*

(2021) maintain that policymakers should use a measured approach to protect public health, with minimum infringement on citizens' rights. Kamin-Friedman & Peled Raz (2021) argue that green pass: "imposes restrictions on the movement of individuals who had not been vaccinated or who had not recovered, it is not consonant with solidarity and trust building. Implementing the Green Pass provision while advancing its effectiveness on the one hand, and safeguarding equality, proportionality, and fairness on the other hand may imbue this measure with ethical legitimacy despite involving a potential breach of trust and solidarity". Luster *et al.* (2021) maintain that: "the Green Pass policy raises practical, legal and ethical concerns. ... any privileges or restrictions guided by one's COVID-19 immunization status must be designed with the utmost attention to prevent a disproportionate violation of the human rights of the non-vaccinated and the public at large. ... Green Pass policies might entrench existing discriminatory structures, ensuring equality is vital in moving forward. ... Despite the removal of the Green Pass in Israel, discussions continue regarding its modified reimplementation". Overall then, Green Pass or vaccine passport was originated to be an incentive to support vaccination plans, but some countries in Europe are using this bureaucratic tool to penalize people without vaccination, reducing individual freedoms, increasing the discrimination between people in social, cultural and sporting activities, fostering tensions between different social groups, and as a consequence reducing equity, trust and solidarity between people with consequential socioeconomic issues (Kosciejew *et al.*, 2021; Waitzberg *et al.*, 2021; Wilf-Miron *et al.*, 2021). In the presence of persistent green pass regime, protests and socioeconomic issues are opened up, which will support authoritarian rules to reduce individual freedoms leveraging potential health risks (cf., Wong, 1991). The side effects of this policy of restrictions in countries can be explained with two main aspects that are discussed in following sections.

□ Politics of fear

Hobbes (1996) maintains that having control over human fears meant holding power in the society. In general, the

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interaction between fear and politics is a main field of interest in science (Debiec & LeDoux, 2004; Robin, 2004). Gore (2004) argues that the politics of fear is directed to distort the political reality of a nation by creating fear in population that is disproportionate to actual dangers. In fact, in contexts of uncertainty, governments tend to create administration's policies with inconsistencies, ambiguities and little transparency to reduce accountability to the people and the public interest. Gore (2004) also argues that in specific circumstances: "there has been a disturbing willingness—even eagerness—to misrepresent the true nature of the policy involved and its real implications". In addition, Gore (2004) points out that the U.S. administration has used the politics of fear in economic policy for fiscal reforms; in many European countries, governments use the politics of fear based on COVID-19 pandemic to apply health policies that reduce individual freedoms and regulate the public and private life of people (cf., Wilf-Miron *et al.*, 2021). Gore (2004), square bracket added) also argued that: "[U.S.] administration uses fear of the problems of old age to contrive an illusory drug bill that essentially transfers billions from the people to the pockets of the large pharmaceutical companies". Governments can use fear for purposes that are not disclosed, then fear itself can quickly become a self-perpetuating and free-wheeling force that weakens national character, diverting attention from real threats and other problems, sowing confusion (Lupia & Menning, 2009). Hence, the intentional use of fear to manipulate the political process can create many vulnerabilities in population, nation and society.

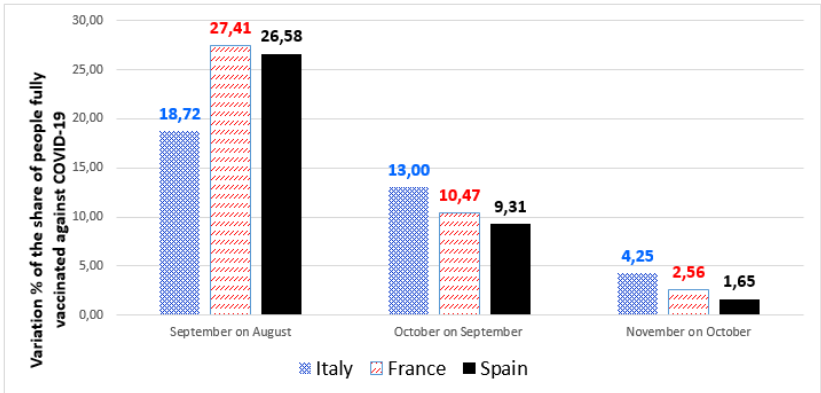


Figure 4. Percent variation (monthly) of the share of people fully vaccinated against COVID-19 in Italy and France (having Green Pass/vaccine passport regime) vs. Spain without green pass certificate from July to November 2021. **Note:** France introduced Green Pass on 21 July 2021; Italy on 6 August for museums, cultural places and events; 1st September for transportation of long distance; 15 October for all working places and 6th December 2021 also for urban transportation (subway, buses, etc.).

Prewitt (2004) think that institutional fear is a fundamental aspect of liberal thought and constitutional democracy. Arato (2004) argues that Hobbes formulated "a fear of the state of nature, of the war against all, is what drives us to establish something like the modern state". Finally, Arato (2004) shows the important role of "institutional fear" that underpins the social contract in liberal theory. In particular, Arato (2004), focusing on case study of the U.S.A., maintains that liberalism can produce a weak state having a poor regulation of emergency powers, such that the "emergency regime" tends to be constructed largely outside the Constitution generating problematic aspects in society (Prewitt *et al.*, 2004; Robin, 2004). A practical example is the COVID-19 pandemic crisis, and European countries to increase the max share of people vaccinated (as estimated here, beyond 70% of population) tend to apply politics of fear associated with informal authoritarian rules that stress constitutional principles (e.g., immunity passport), reduce the individual freedoms and create socioeconomic problems, with low benefits to cope with COVID-19 pandemic. In fact, figure 4 shows that the effects of Green pass regime, based on

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authoritarian rules, generate a moderate growth of vaccinations that disappears in the short-run, but it generates social issues for the reduction of individual freedoms, the increase of discrimination of people in social, cultural and sporting activities, the growth of tensions between different groups, reduction of equity, trust and solidarity too (Kosciejew *et al.*, 2021; Waitzberg *et al.*, 2021; Wilf-Miron *et al.*, 2021).

□ Strong leaders and authoritarian rules in democracies

The increase of vaccination in rich and democratic regions, by introducing restrictions and policies based on vaccine passport, is also associated with strong leaders having domestic and international support that can generate a substantial decline of democratic setting (Lavriča & Bieberb, 2021). This tendency of power in strong leaders, in the presence of crisis, is supported by a combination of social insecurity, cultural backlash and economic issues generated by pandemic crisis. To put it differently, the application of authoritarian rules in democratic systems is due to the emergence for strong leaders but also to social and economic insecurity that support authoritarian approaches that are exercised informally (Lavriča & Bieberb, 2021; cf., Coccia, 2019e). In fact, all political leaders guide restrictive interventions in a general framework in which they are considered "pragmatic reformers" and receive initially domestic and international support (Crowther 2017; Günay & Dzihic 2016; Vladislavljević 2019). Thus, the increasing public support to a strong political leader may be one of the causes of the rise in authoritarian rules in the Western countries in the presence of pandemic crisis, leveraging socioeconomic uncertainty and fear in society. These tendencies are generated in an institutional environment and countries having weaknesses of democratic institutions and balance of powers in the presence of emergencies and crisis.

Conclusions

Findings here reveal that the share of vaccinated against COVID-19 increase with the wealth of nations, but it has a physiological maximum level of about 70% between (rich and democratic) countries. In addition, monarchy and parliamentary monarchy have a higher share of people fully vaccinated against COVID-19 than mixed executives and presidential republic. Some countries in Western world are straining democratic society with restrictions to individual freedoms to increase the maximum share of people fully vaccinated (estimated here) by introducing restriction policies, vaccine certificate and penalties as a rule that create socioeconomic issues, such as discrimination of people in social activities, tensions between different groups, reduction of equity, trust, etc. (Brown *et al.*, 2021; Chantler *et al.*, 2019; Coccia, 2018a, 2021c; Dye & Mills, 2021; Koscieljew *et al.*, 2021; Waitzberg *et al.*, 2021; Wilf-Miron *et al.*, 2021). In particular, results here can explain some abuses in democratic countries based on a combination of the politics of fear and informally authoritarian rules² applied by a strong leader under circumstances of social insecurity.

Although this study has provided interesting results, that are of course tentative, it has several limitations. First, a limitation of the study is the lack of data about total vaccinations in manifold countries. Second, not all the possible confounding factors that affect the diffusion of vaccination are taken into consideration and in future these factors deserve to be controlled for supporting results here. Third, the lack of integration of data with cultural aspects may have influenced the results of vaccination across countries making comparative analyses a problematic approach (Angelopoulos *et al.*, 2020; Coccia, 2018). Fourth, country-specific health and social norms may affect the

² Wesolowski (1990) argues some axioms of the authoritarian regime, such as the state's power (state) is the fundamental mechanism of social integration and regulation; the state is an organism which stands above all other forms of social organization and exerts control over them; it uses violence when needed, etc.

vaccination and mitigation policies. Finally, the estimated relationships in this study focus on variables in specific months (based on recent data available) but an extension of the period under study is needed in future development of the research here. Thus, the generalization of this results should be done with caution. Future research should consider new data, when available, and when possible, to examine also other variables between countries to explain dynamic relationships under study over time and space and their interaction with vaccination, vaccine certificate, restriction policy and other social norms between countries. Despite these limitations, the results presented here suggests the maximum sustainable level of people vaccinated between rich and democratic countries (that is roughly 70%) and social and economic issues associated with the introductions of policy of restrictions and bureaucratic tools (e.g., immunity passport) to go beyond this limit using politics of fear and strong leaders. Hence, there is need for much more detailed research in these topics and this study encourages further investigations using lessons learned of COVID-19 pandemic crisis, also considering the interaction between effects of restrictions in societies and campaign of vaccination. Overall, then, many Western (democratic) countries are straining society with restrictions to individual freedoms to increase the maximum share of people fully vaccinated (with marginal results) by introducing vaccine passport and autocratic rules that impose restrictions to the movement of individuals who are not vaccinated, reducing equality and fairness between people. These aspects are applied using politics of fear and strong leadership nurtured by institutional context having weak democracy and vague separation of powers, when constitution expressly established that these functions have to be strong to address critical problem of abuse in democracy by our own rulers, our own political authorities who, if uncontrolled or made not accountable, can do great harm to society higher than (pandemic) crisis. To conclude, different factors between countries that are not only parameters related to medicine but also to social and political sciences can explain the effects of COVID-19 pandemic in society not only

Relation between COVID-19 vaccination and economic development of countries in terms of health but also in term of human and civil rights that should be accurately assessed to control future negative impact of pandemic crisis on public health, economy and society. It is worth raising the question whether our constitutional ordering of Western and democratic countries is still protecting us from fear and effective tangible democratic reduction that can became a hazardous process, similar to COVID-19 pandemic crisis, that direct future society towards *terra incognita* of uncertain social events.

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6

Optimal level of COVID-19 vaccinations to minimize infections

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared in late 2019 (Coccia, 2021). COVID-19 is still circulating in 2021 with mutations of the novel coronavirus that generate a constant pandemic threat in manifold countries with higher numbers of COVID-19 related infected individuals and deaths (Johns Hopkins Center for System Science and Engineering, 2021). Seligman *et al.* (2021) show some characteristics of people that are significantly associated with COVID-19 mortality, such as: " mean age 71.6 years, 45.9% female, and 45.1% non-Hispanic white... disproportionate deaths occurred among individuals with nonwhite race/ethnicity (54.8% of deaths ... $p < 0.001$), individuals with income below the median (67.5% . . . $p < 0.001$), individuals with less than a high school level of education (25.6% ... $p < 0.001$), and veterans (19.5% ... $p < 0.001$)".

The alarming levels of spread and severity of COVID-19 worldwide has supported the development of vaccines in 2020 based on messenger RNA vaccines, known as mRNA vaccines for high levels of protection by preventing COVID-19 among people that are vaccinated (Coccia, 2021a). The mRNA vaccines for COVID-19 are based on accumulated knowledge that the infective process itself is effective in raising an immune response and genetic engineering can be utilized to construct virus-like particles from the capsid and envelope proteins of viruses (Smoot, 2020; Coccia & Finardi, 2012). Moreover, mRNA vaccines eliminate a lot of phases in manufacturing process for the development of new drugs because rather than having viral proteins injected, the human body uses the instructions to manufacture viral proteins itself. In short, mRNA vaccines are produced and manufactured by chemical rather than biological synthesis, as a consequence the process of development is much faster than conventional vaccines to be redesigned, scaled up and mass-produced (Komaroff, 2020). Manifold public agencies for protecting and promoting public health through the control and supervision in the United Kingdom, the USA, Europe and other countries confirm that mRNA vaccines for COVID-19 can be effective and safely tolerated in population (Abbasi, 2020; Cylus *et al.*, 2021; Heaton, 2020; Jeyanathan *et al.*, 2020; Komaroff, 2020).

Because of the rapid spread of COVID-19 worldwide, understanding the significance of vaccination is crucial in determining how COVID-19 can be eradicated in the population (Aldila *et al.*, 2021). Vaccination has the potential to eradicate COVID-19, to relax nonpharmaceutical measures, maintaining low basic reproduction number, but it is an important and essential point to clarify the optimal strategy of administration of vaccines and widespread mass vaccinations to constrain COVID-19 pandemic and future variants in society (cf., Anser *et al.*, 2020). Akamatsu *et al.* (2021) argue that to cope with the infectious disease severity that increases considerably, governments have to implement an efficient campaign of vaccination to substantially reduce infections and mortality in society and also avoid the collapse of the

healthcare system. Aldila *et al.* (2021) argue that higher levels of vaccination rate can eradicate COVID-19 from the population. The final goal of a plan of vaccination is achieving herd immunity to protect vulnerable individuals (Anderson *et al.*, 2020; de Vlas and Coffeng, 2021, Randolph & Barreiro, 2020; Redwan, 2021). Herd immunity indicates that only a share of a population needs to be immune and as a consequence no longer susceptible (by overcoming natural infection or through vaccination) to a viral agent for epidemic control and to stop generating large outbreaks (Fontanet & Cauchemez, 2020). Scholars can estimate the proportion of a population that needs to be immune to support herd immunity. This threshold level depends on the basic reproduction number, R_0 —the number of cases, on average, spawned by one infected individual in an otherwise fully susceptible (Coccia, 2020; Kwok *et al.*, 2020). In particular, the formula for calculating the herd-immunity threshold is $1-1/R_0$ —it indicates that the more people who become infected by each individual who has the virus, the higher the proportion of the population that needs to be immune to reach herd immunity. The index R_0 assumes that everyone is susceptible to the virus, but the level changes as the epidemic proceeds, and it depends on changes in susceptibility of the population, mitigation policies, variants, etc. (Aschwanden, 2020, 2021). Kwok *et al.* (2021) estimated the R_t in different countries and a threshold for herd immunity in each country's population. The level of R_t ranges from 85% to 5.66% also because of measures of mitigation and containment to infectious disease and other factors, that if they are relaxed can move up herd-immunity threshold (Buss *et al.*, 2021). Rosen *et al.* (2021) describe socioeconomic and organizational factors associate with success of vaccination campaign in Israel as well as there are some aspects of misinformation and social dynamics that can reduce the effectiveness of a fruitful vaccination in population (cf., Prieto Cruriel, *et al.* 2021), and they can be divided into three major groups. Different models explain the spread and impact of COVID-19 considering social distancing and vaccination (Dashtbali *et al.*, 2021).

Optimal level of COVID-19 vaccinations to minimize infections

In this context, a key problem in current COVID-19 pandemic crisis is how herd immunity can be achieved with an effective vaccination campaign that supports a drastic reduction of numbers of COVID-19 related infected individuals and deaths. The study here confronts this problem here by developing a modelling and statistical analysis to explain, whenever possible, how change, at global level, optimal threshold that triggers a drastic reduction of COVID-19 infections and support herd immunity. Results can suggest best practices of optimization in the vaccination strategy, considering global data of more than 190 countries, in order to guide effective and timely policy responses that trigger the sharply reduction of confirmed cases in society for combatting the novel coronavirus and constraining negative effects of current COVID-19 pandemic crisis and future pandemics of similar infectious diseases in society. In fact, in the presence of COVID-19 pandemic crisis, it is more and more important to determine efficient strategies of vaccinations, rather than full lockdown that paralyze economic and social activities, to contain and/or prevent negative effects of pandemics on health people and economy (Coccia, 2021c). Lessons learned from this study could be of benefit to countries as they grapple to plan their COVID-19 vaccine programmes to reduce state of emergency of pandemic crisis and negative effects on socioeconomic system. This study is part of a large body of research directed to explain drivers of transmission dynamics of COVID-19 and design effective policy responses to cope with and/or to prevent pandemic threats (Coccia, 2021).

Materials and methods

Source and sample

The sample of this study is based on $N=192$ countries worldwide. Period under study is from March to May 2021, using data of vaccines and confirmed cases of COVID-19.

- **Measures**

- Doses of vaccines administrated $\times 100$ inhabitants on 15 March 2021, $N=114$ countries; on 14 April 2021 with $N=154$ countries, on 26 April 2021, $N=190$ countries . The number of countries tends to increase over time with the diffusion of vaccines across countries. Doses of vaccines refer to the total number of vaccine doses, considering that an additional dose may be obtained from each vial (e.g. six doses for Pfizer BioNTech® Comirnaty), whereas number of doses administered refers to any individual receiving any dose of the vaccine (cf., [Freed et al., 2021](#); [Oliver et al., 2020](#)). Source: Our World in Data ([2021](#)).

- Number of COVID-19 infected individuals (%) is measured with confirmed cases of COVID-19 divided by population of countries under study on 20 March 2021, $N=192$ countries, 25 April 2021, $N=192$ and 19 May 2021, $N=216$ countries. Source of data: Johns Hopkins Center for System Science and Engineering ([2021](#)).

Model and data analysis procedure

Firstly, data are analyzed with descriptive statistics of variables given by arithmetic mean (M) and standard error of the mean (SEM). In addition, the normality of the distribution of variables to apply correctly parametric analyses is analyzed with skewness and kurtosis coefficients. Variables of the doses of COVID-19 vaccines and confirmed cases are considered in two different periods of time because studies by Canada's National Advisory Committee on Immunization (NACI) show that Pfizer-BioNTech and Moderna vaccines started providing some level of protection 12 to 14 days after the first dose. By the time the second dose was administered —19 to 42 days after the first — the first shot was shown to be 92 per cent effective ([CBC, 2021](#); [CDC, 2021](#); [Rossman et al., 2021](#)).

Secondly, analysis of simple regression applies quadratic models because they fit the data scatter to detect nonlinear effects of relations under study.

The specification of model is given by:

$$y_{i,t} = \alpha_0 + \beta_1 x_{i,t-1} + \beta_2 x_{i,t-1}^2 + u_{i,t} \quad (1)$$

where:

○ $y_{i,t}$ = Number of COVID-19 infected individuals/population, dependent variable

○ $x_{i,t-1}$ = Doses of vaccines administrated \times 100 inhabitants, explanatory variable

○ $u_{i,t}$ = Error term

○ country $i=1, \dots, n$; $t=time$

Remark: Model [1] has a time lag effect between explanatory (t-1) and dependent variables (t) to logically include in the relations under study the period from the administration of vaccines doses to the level of protection in population and reduce the endogeneity for providing reliable (estimated) parameters.

Remark: The square of the doses of vaccines administrated \times 100 inhabitants in model [1] is introduced to consider, as hypothesized, the possibility of non-linear effects in the relation under study.

Thirdly, the optimization of the estimated relationship [1] is performed with the following perspective: the *maximization* of the equation [1] to find the optimal levels of doses of vaccines administrated \times 100 inhabitants that support a consequential drastic reduction of confirmed cases /population of COVID-19 over time to constraint negative effects of infectious disease in society and overcome pandemic crisis. In particular, the estimated relationships [1] are objective functions of one (real) variable represented by polynomial functions of an order higher than first order (*i.e.*, second order). These estimated relations [1] are continuous and infinitely differentiable functions. The calculus applied on functional relation [1] provides the optimal level of doses of vaccines administrated \times 100 inhabitants at the time t that reduces the spread of confirmed cases in society, and stop COVID-19 pandemic crisis for a general herd immunity.

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In order to decide the best strategy to prevent future pandemics using lessons learned from COVID-19, this study presents four scenarios, using global data in different periods:

Vaccination campaign and confirmed cases in March 2021

Vaccination campaign in March 2021 and confirmed cases in April 2021

Vaccination campaign and confirmed cases in April 2021

Vaccination campaign in April 2021 and confirmed cases in May 2021

Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

Table 1. Descriptive statistics

Variables	N	Mean	Std. Error
Doses vaccines per 100 inhabitants 15 March 2021	114	8.85	1.46
Doses vaccines per 100 inhabitants 14 April 2021	154	14.50	1.65
Doses vaccines per 100 inhabitants 26 April 2021	192	22.13	2.17
Confirmed Cases /population % 20 March 2021	192	2.57	0.23
Confirmed Cases /population % 25 April 2021	192	3.04	0.26
Confirmed Cases /population % 19 May 2021	216	2.95	0.003

N=number of cases (countries)

Case A: Vaccination campaign and confirmed cases of COVID-19 in March 2021

Table 2. Regression analyses of confirmed cases/population of 20 March on doses of vaccines on 15 March 2021 based on quadratic model [1]

Constant α	2.09***
(St. Err.)	(.38)
Coefficient β_1	.234***
(St. Err.)	(.05)
Coefficient β_2	-.002***
(St. Err.)	(.001)
R ²	.22
(St. Err. of Estimate)	(2.95)
F	16.43***
N	113

Note: Dependent variable is Confirmed cases/population (%) of 20 March 2021. Explanatory variable is doses of vaccines on 15 March 2021 per 100 inhabitants.

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Significance: *** p -value < 0.001

The estimated relationship, based on results of table 2, is:

$$z_{i,t} = 2.09 + 0.234h_{i,t-1} - 0.002 h_{i,t-1}^2$$

The polynomial function is given by

$$z = 2.09 + 0.234h - 0.002 h^2$$

the necessary condition to maximize is:

$$\frac{dz}{dh} = z'(h) = 0.234 - 0.004h = 0$$

The first derivative equal to 0 is:

$$z'(h) = 0 \Rightarrow h^* = \frac{0.234}{0.004} = 58.5 \text{ per 100 inhabitants}$$

$h^* = 58.5$ per 100 people indicates the optimal level of doses of vaccines, after that the function of confirmed cases has a sharply decrease that reduces the negative impact and diffusion of COVID-19 leading, whenever possible, to constraint the pandemic crisis in society.

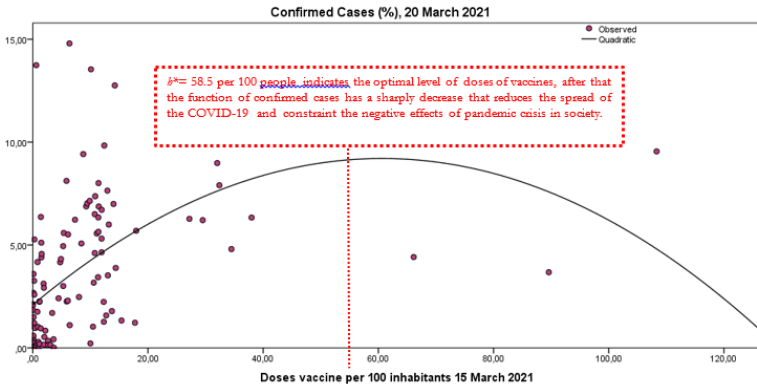


Figure 1. Relation of confirmed cases/population (%) of 20 March 2021 on doses of vaccines on 15 March 2021 based on quadratic model [1]

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□ *Case B: Vaccination campaign in March 2021 and confirmed cases in April 2021*

Table 3. *Regression analyses of confirmed cases/population (%) of 25 April on doses of vaccines on 15 March 2021 based on quadratic model [1]*

Constant α	2.47 ^{***}
(St. Err)	(.43)
Coefficient β_1	.281 ^{***}
(St. Err.)	(.05)
Coefficient β_2	-.002 ^{***}
(St. Err.)	(.001)
R ²	.23
(St. Err. of Estimate)	(3.35)
F	17.58 ^{***}
N	113

Note: Dependent variable is Confirmed cases/population (%) of 25 April 2021. Explanatory variable is doses of vaccines on 15 March 2021 per 100 inhabitants. Significance: *** p-value < 0.001

The estimated relationship, based on results of table 3, is:

$$y_{i,t} = 2.47 + 0.281x_{i,t-1} - 0.002 x_{i,t-1}^2$$

The function to optimize is given by

$$f = 2.47 + 0.281x - 0.002 x^2$$

the necessary condition to maximize is:

$$\frac{df}{dx} = f'(x) = 0.281 - 0.004x = 0$$

The first derivative equal to 0 is:

$$f'(x) = 0 \Rightarrow x^* = \frac{0.281}{0.004} = 70.25 \text{ per 100 inhabitants}$$

$x^* = 70.25$ per 100 people indicates the optimal level of doses of vaccines, after that the function of confirmed cases has a sharply decrease that reduces the negative impact and

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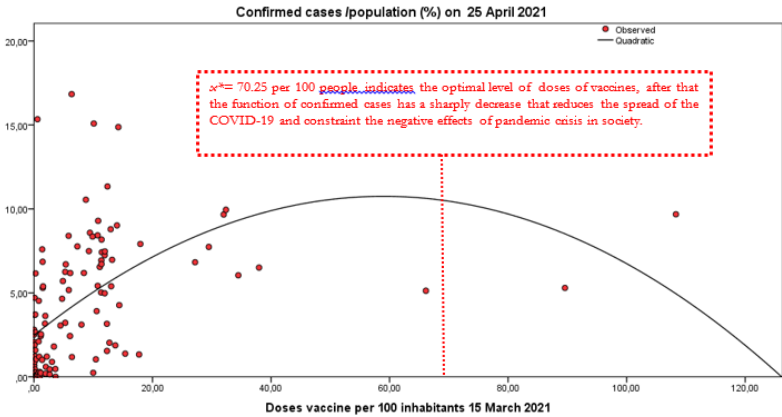


Figure 2. Relation of confirmed cases/population (%) of 25 April on doses of vaccines 15 March 2021 based on quadratic model [1]

□ Case C: vaccination campaign in April 2021 and confirmed cases in April 2021

Table 4. Regression analyses of confirmed cases/population (%) of 25 April on doses of vaccines on 14 April 2021 based on quadratic model [1]

Constant α	1.71 ***
(St. Err)	(.37)
Coefficient β_1	.197 ***
(St. Err.)	(.03)
Coefficient β_2	-.001 ***
(St. Err.)	(.000)
R^2	.28
(St. Err. of Estimate)	(3.23)
F	30.04 ***
N	153

Note: Dependent variable is Confirmed cases/population (%) of 25 April 2021. Explanatory variable is Doses of vaccines on 14 April 2021 per 100 inhabitants; Significance: *** p -value < 0.001

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The estimated relationship, based on results of table 4, is:

$$g_{i,t} = 1.71 + 0.234k_{i,t-1} - 0.002 k_{i,t-1}^2$$

The function is given by

$$z = 2.09 + 0.197k - 0.001 k^2$$

the necessary condition to maximize is:

$$\frac{dg}{dk} = g'(k) = 0.197 - 0.002k = 0$$

The first derivative equal to 0 is:

$$g'(k) = 0 \Rightarrow k^* = \frac{0.197}{0.002} = 98.5 \text{ per } 100 \text{ inhabitants}$$

$k^* = 98.5$ per 100 people indicates the optimal level of doses of vaccines, after that the function of confirmed cases has a sharply decrease that reduces the negative impact and diffusion of COVID-19 leading, whenever possible, to constraint the pandemic crisis in society.

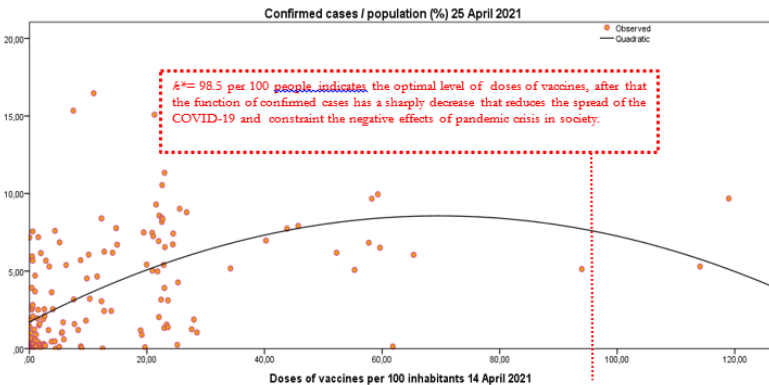


Figure 3. Relation of confirmed cases/population (%) of 25 April on doses of vaccines 14 April 2021 based on quadratic model [1]

□ Case D: Vaccination campaign in April and confirmed cases in May 2021

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Table 5. Regression analyses of confirmed cases/population of 19 May 2021 on doses of vaccines on 26 April 2021 based on quadratic model [1]

Constant α	.020 ***
(St. Err)	(.004)
Coefficient β_1	.001 ***
(St. Err.)	(.000)
Coefficient β_2	-.000005789 ***
(St. Err.)	(.000)
R^2	.11
(St. Err. of Estimate)	(.037)
F	12.16 ***
N	191

Note: Dependent variable is Confirmed cases/population of 19 May 2021. Explanatory variable is Doses of vaccines on 26 April 2021 per 100 inhabitants. Significance: ***p-value<0.001

The estimated relationship, based on results of table 5, is:

$$j_{i,t} = 0.02 + 0.001w_{i,t-1} - 0.000005789 w_{i,t-1}^2$$

The function to optimize is given by

$$j = 0.02 + 0.001w - 0.000005789 w^2$$

the necessary condition to maximize is:

$$\frac{dj}{dw} = j'(w) = 0.001 - 0.000011578w = 0$$

The first derivative equal to 0 is:

$$j'(w) = 0 \Rightarrow w^* = \frac{0.001}{0.000011578} = 86.37 \text{ per 100 inhabitants}$$

$w^* = 86.37$ per 100 people indicates the optimal level of doses of vaccines, after that the function of confirmed cases has a sharply decrease that reduces the negative impact and diffusion of COVID-19 leading, whenever possible, to constraint the negative societal effects of pandemic crisis in countries.

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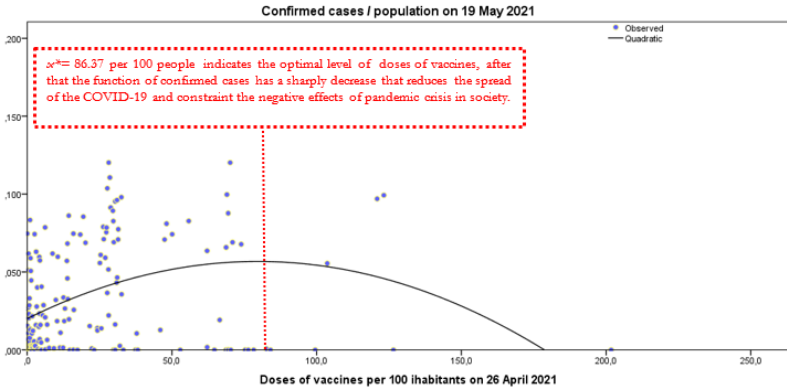


Figure 4. Relation of confirmed cases/population (%) of 19 May 2021 on doses of vaccines 26 April 2021 based on quadratic model [1]

Discussions

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that caused the Coronavirus Disease 2019 (COVID-19), as said, continues to be a constant pandemic threat in 2021 with mutations of novel coronaviruses¹, such that the state of emergency remains in manifold countries because of high numbers of COVID-19 related infected individuals and deaths in society. The COVID-19 pandemic crisis needs rapid pandemic responses in several areas, including health systems, development of new drugs and vaccine research associated with development, manufacturing, distribution, allocation, and administration (National Academy of Medicine, 2021, 2021a).

The main findings of statistical analysis and optimization can be summarized in the following table 6. In particular, the findings of this study reveal that a delay of vaccination plan in population, from March to April 2021, it moves forward the optimal level of doses administrated per 100 inhabitants, prolonging the state of emergency and exit from COVID-19 pandemic crisis with consequential damages and long-run deterioration of socioeconomic systems. Hence, the strategy

¹ WHO considers the following variants of concern: Alpha, Beta, Gamma and Delta; Variants of interest (Eta, Epsilon, Theta, Kappa) and manifold variants under monitoring, such as Iota and Zeta (ECDC, 2021).

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and optimal response to pandemic threats is, first start vaccination, first I can go out from emergency and crisis, synthesized with the acronym *FirstS*, *FirstO*: a timely start of the vaccination plan, it leads countries to anticipate the exit from the emergency and pandemic crisis.

Table 6. *Optimal level of vaccination based on relation of confirmed cases on doses of vaccines over time to constrain the diffusion of COVID-19*

Scenarios	Doses vaccines per 100 inhabitants administrated	Confirmed cases/population	Optimal* level of doses per 100 inhabitants that triggers the sharply decline of confirmed cases
A	15 March 2021	20 March 2021	58.50
B	15 March 2021	25 April 2021	70.25
C	14 April 2021	25 April 2021	98.25
D	26 April 2021	19 May 2021	86.37

A large number of factors can contribute to the success of implementing the optimal level of scenario A (Table 6), which is lower level of doses per 100 people than other scenarios, to maximize of the positive social impact, reducing confirmed cases, for achieving early the final goal of herd immunity and as a consequence to constrain negative socioeconomic effects. Rosen *et al.* (2021) indicate three groups for a case study of Israel, driven by a combination of facilitating factors and organizational synergies: a) extrinsic factors to health care (small size in terms of both area and population), a relatively young population, warm weather in December 2020, a centralized national system of government, and well-developed infrastructure for implementing prompt responses to large-scale national emergencies; b) health-system specific factors, such as the organizational, IT and logistical capacities of community-based health care providers, the availability of a cadre of well-trained, salaried, a tradition of effective cooperation between government, health plans, hospitals, and emergency care providers – particularly during national emergencies; and support tools and decision-making

frameworks to support vaccination campaigns; finally, c) specific factors to the COVID-19 vaccination effort: the mobilization of special government funding for vaccine purchase and distribution, timely contracting for a large amount of vaccines relative to population, the use of simple, clear and easily implementable criteria for determining who had priority for receiving vaccines in the early phases of the distribution process, a creative technical response that addressed the demanding cold storage requirements of the Pfizer-BioNTech COVID-19 vaccine, and well-tailored outreach efforts to encourage people to sign up for vaccinations and then show up to get vaccinated (cf., [McKee & Rajan, 2021](#)). [Sim et al. \(2021\)](#) analyze the response to the global coronavirus pandemic in Israel and the UK, showing the importance of factors influencing the early days of the rollout of vaccination and learning processes that can provide main lessons for other countries to plan COVID-19 vaccine programmes.

However, some rich countries are lacking several of these factors of governance, reducing the pace of vaccination to combat the spread of COVID-19. [Williams et al. \(2020\)](#) argue that effective responses to public health emergencies should rely on translating rapidly emerging research into timely, evidence-informed policies and best practices. Optimal strategies of vaccinations to pandemic shocks must have strong governance structures driven by adequate and effective leadership that engages with the communities, listens and adjusts to population needs. Efficient governance can support health system preparedness for performing efficient campaign of vaccinations in the presence of turbulent scenarios and new population needs. Moreover, countries with constant investment in health sector and preparedness can apply effective policy responses, vaccination-based, to reduce infections, mortality, morbidity and stress among the population as well as promote health of people and economic recovery ([Coccia, 2021f](#); [Kluge et al., 2020](#)). In general, efficient strategies of vaccinations have to be based on effective governance and technical capacity to respond in a short period of time to pandemic crisis ([Sagan et al., 2020](#); [Kluge et](#)

al., 2020). Sagan *et al.* (2020) consider a broad concept of governance that is not limited to health system alone but also directed to support other functions of nation and its government to work properly for strengthening health, economic and social systems in the presence of emergency. In general, crisis management of COVID-19 pandemic to implement effective vaccine programmes is based on effective multi-level governance, combining both national and local strategies to support vaccination campaign, achieve herd immunity and improve health safety in society (Anttiroiko, 2021; Ritchie *et al.*, 2020). Abuza (2020) argues that effective policy responses are due to leadership and competence, rather than regimes of countries.

Overall, then, in the presence of pandemic threat, mass vaccination is the most credible option to cope with the COVID 19 pandemic but it has to be applied properly and timely (DeRoo *et al.*, 2020; Frederiksen *et al.*, 2020; Harrison & Wu, 2020). The implementation of a mass vaccination campaign is a significant challenge for all countries globally because it is associated with manifold economic, socio-cultural and political-administrative factors. Economic factors are a relevant component since mass vaccination campaign involves enormous public investment to be organized (Ethgen *et al.*, 2019). The wealth of nations, in this sense, becomes a discriminating factor for success of vaccination plan. In fact, higher-income countries perform better than low-income ones in vaccine programmes of their citizens (Ataguba *et al.*, 2016). Other factors that affect vaccinations are socio-cultural factors, such house living conditions (Kusuma *et al.* 2010; Mitchell *et al.* 2009), education, religious beliefs (Soura *et al.* 2013), gender based inequity (Pande, 2003) and information (Logan *et al.* 2018). A vital role is due to good governance that provides effective organizational aspects of decision support for effective campaign of vaccinations (Glatman-Freedman & Nichols, 2012). Good governance has a whole range of positive effects on institutional change, organizational behavior, economic growth and as well as improvement of public services (Coccia, 2019, 2020a; Glatman *et al.*, 2010; Glatman-Freedman & Nichols, 2012; Kaufmann *et al.*, 1999). The ability

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to organize a vaccination campaign to cope with COVID-19 pandemic crisis can be compared to the organization of public service in a short period of time in a context of crisis management and factors described above play a critical role for achieve herd immunity (Coccia, 2020b, 2021b). In addition, country-level governance may also affect the infrastructure required for the successful implementation of vaccine programs, such as the ability to reach distant locations, to manage cold chain, to support safe disposal of used syringes and needles, and sustain training of human resources. In fact, country-level governance was found to be a stronger predictor of the initial introduction of new vaccines to poor African nations than healthcare-related financial indicators (cf., Glatman *et al.* 2010; Glatman-Freedman & Nichols, 2012).

Conclusions and prospects

COVID-19 and future epidemics of novel influenza viruses pose, more and more, a serious threat to national security and public health. An influenza pandemic can occur at any time with little warning; any delay in detecting a novel influenza strain; sharing of influenza virus samples; and in developing, producing, distributing, or administering a therapeutic or vaccine could result in significant additional morbidity and mortality, and deterioration of socioeconomic systems (Coccia, 2021). The global response to COVID-19 pandemic has pushed the studies for detecting factors and aspects for rapid pandemic response in several areas, including healthcare system, vaccine research, development, manufacturing, distribution, allocation, and administration of doses. These actions could support organizational behavior and human resources to improve preparedness efforts to advance R&D for efficient pandemic vaccines and timely public responses of vaccine plans to constrain the spread of pandemics similar to COVID-19. New strategies of vaccination campaign in the presence of severe pandemic threats have to be highly responsive, flexible, resilient, scalable, and more effective for reducing the impact of pandemic viruses and

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likely mutations. An efficient strategy of crisis management for pandemic threats can be based on three goals:

- Strengthen and diversify vaccine development, manufacturing, and supply chain;
- Promote innovative approaches and use of new technologies to detect, prevent, and respond to epidemics and pandemics; and
- Timely plan of vaccination to increase vaccine access and coverage across all populations in the presence of unforeseen pandemic of novel viral agents.

In this context, to adequately prepare for, prevent, detect, and respond to both epidemics and inevitable pandemics, it is important to reinforce the governance of countries, supporting pandemic preparedness efforts by collaborating with domestic and international stakeholders. In fact, execution of this strategic approach over the next ten years will require a better governance, innovative partnerships, financial investments, and efficient utilization of resources (U.S. Department of Health & Human Services, 2021). In short, policies of vaccination having agility and speed of responses have to be based on a better governance of countries that is a vital factor of crisis management to cope with new waves of COVID-19 and future epidemics/pandemics similar to COVID-19 (Chang *et al.*, 2020; Coccia, 2021d; Janssen & van der Voort, 2020; Renardy *et al.*, 2020). In the presence of a good governance, Evans & Bahrami (2020) pinpoint that countries can apply super-flexibility to cope with COVID-19 pandemic in which decision making is oriented to versatility, agility, and resilience.

In general, vaccine rollout plans have to face distribution and allocation hurdles, and new mutations of SARS-CoV-2, likely more transmissible and resistant to vaccines, can change the equation of herd-immunity and strategy of vaccinations, increasing the thresholds of immunization in population (Callaway, 2021; Dooling *et al.*, 2020; Vignesh *et al.*, 2020). A delay of the plan of vaccinations and of the achievement of optimal threshold within countries, it does not reduce transmission dynamics and it can foster

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emergence and diffusion of variants, such as in Brazil and India (ECDC, 2021; Mallapaty, 2021; Buss *et al.*, 2021; Whittaker *et al.*, 2021).

In short, the timely achievement of the optimal threshold of doses administered is basic, because a vaccination plan quickly and thoroughly can prevent new mutations of the novel coronavirus and constrain transmission dynamics in society and consequential socioeconomic issues (Akamatsu, 2021). In this context, non-pharmaceutical interventions continue to play a crucial part also during vaccination plans to stop/reduce the transmission paths and maximize the positive societal effects. Even though herd immunity is a difficult goal for manifold countries, the ability to vaccinate vulnerable people seems to be one of the vital factors for reducing hospitalizations, admission to Intensive Care Units and deaths from COVID-19 and similar infectious diseases (Jones & Helmreich, 2020). Engelbrecht & Scholes (2021) argue that COVID-19 can have a seasonal dependence and if herd immunity is not established by effective strategies of vaccination and/or vaccination has delayed diffusion for high demand that generates problems of production, recurring waves may generate additional health and socioeconomic issues.

Overall, then, findings here reveal that the optimal threshold by a timely vaccination can lead to a drastic reduction of COVID-19, though this novel infectious disease might not disappear in the short term. These results here can help policymakers to design satisfying goals to cope with current infectious diseases and to prevent future outbreaks of the COVID-19 and similar viral agents in future. Nevertheless, the proposed results are of course tentative because other factors should be included in future development of this study to design optimal strategy of vaccinations. A limitation of the study is the lack of data about doses administered and total vaccinations in manifold countries, mainly at the beginning of the year 2021, also for the difficulty of production and distribution of COVID-19 vaccines. Therefore, there is need for much more detailed research using updated data to further verify proposed relations between administration of

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vaccines and confirmed cases also in the presence of new mutation of the novel coronavirus between countries. To conclude, this study encourages further investigations for developing comprehensive analyses for supporting optimal strategies of vaccination plans, using lessons learned of COVID-19, also considering institutional and socioeconomic factors between countries, and not only parameters related to medicine to prevent future pandemics and/or to contain their negative impact on public health, economy and society.

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Optimal level of COVID-19 vaccinations to minimize infections

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7

Weaknesses of COVID-19 vaccinations in the total environment

Introduction

We are still in the throes in 2022 of negative socioeconomic effects of the pandemic of Coronavirus Disease 2019 (COVID-19), an infectious illness generated by (novel) mutant viral agent of the Severe Acute Respiratory Syndrome Coronavirus 2/SARS-CoV-2 (Bontempi *et al.*, 2021; Bontempi & Coccia, 2021; Coccia, 2020, 2020a, 2020b, 2021; Johns Hopkins Center for System Science and Engineering, 2022; Vinceti *et al.*, 2021; Cf. also Coccia, 2020c, 2021a, 2021d, 2021e, 2021f, 2021g, 2022). Initially, in 2020, countries apply non-pharmaceutical interventions (e.g., lockdown and quarantine) to cope with COVID-19 pandemic crisis; a later time, in 2021 and 2022, the most applied health policy worldwide is the administration of new types of vaccines based on viral vector, protein subunit and nucleic acid-RNA (Abbasi, 2020; Coccia, 2021g, 2022a, 2022b, 2022c; Mayo Clinic, 2021). The vaccination plans have the potential goal to reduce the diffusion of COVID-19, to relax non-pharmaceutical measures and maintain low basic reproduction number, but an important problem is whether

these novel types of vaccines are really effective to reduce high numbers of COVID-19 related infected individuals and deaths between countries to control and/or eradicate the pandemic diffusion and to reduce negative effects in society (Aldila *et al.*, 2021; Coccia, 2021a; Prieto Cruriel, *et al.* 2021; Saadi *et al.*, 2021). Akamatsu *et al.* (2021) argue the vital role of governments to implement an efficient campaign of vaccination to reduce infections in society, and avoid the collapse of healthcare system (cf., Coccia, 2021b, 2021c, 2022a). Shattock *et al.* (2021) argue that a rapid vaccination rollout can allow the sooner relaxation of non-pharmaceutical interventions, but emerging viral variants of SARS-CoV-2 create new scenarios and problems for epidemic control (Fontanet *et al.*, 2021; Papanikolaou *et al.*, 2021). Shattock *et al.* (2021) also find that a gradual phased relaxation can reduce population-level morbidity and mortality and that faster vaccination campaign can offset the size of pandemic wave, allowing more flexibility for non-pharmaceutical control measures to be relaxed sooner. Aldila *et al.* (2021) maintain that higher levels of vaccination rate can eradicate COVID-19 in population by approaching herd immunity to protect vulnerable individuals (cf., Anderson *et al.*, 2020; de Vlas & Coffeng, 2021; Randolph & Barreiro, 2020). However, Aschwanden (2020, 2021) raised many doubts about the achievement of herd immunity, which is a “false promise” because of manifold factors affecting transmission dynamics of COVID-19 (cf., Moore *et al.*, 2021). Seligman *et al.* (2021) analyze the COVID-19 pandemic in the United States and show that social determinants can affect COVID-19 mortality at the individual level. Results of demographics of deaths reveal a mean age of 71.6 years, 45.9% female, and 45.1% non-Hispanic white. They found that disproportionate deaths occurred among individuals with nonwhite race/ethnicity, individuals with income below the median, individuals with less than a high school level of education, and veterans (cf., Davies *et al.*, 2021; Wolf *et al.*, 2021). In general, substantial inequalities in COVID-19 mortality are due to racial/ethnic minorities and poor people having less education. Garber (2021) for the US case study maintains that mortality from

COVID-19 rises steeply with advancing age, in a pattern that parallels overall mortality. Age specific mortality rates increased in the US more for groups that already experienced greater mortality, such as non-Hispanic Black people, as reflected in projections of life expectancy at birth. Ackley *et al.* (2022), investigating the impact of the COVID-19 pandemic in the US, show that a significant percentage of excess deaths associated with the pandemic were not directly assigned to COVID-19. Across the U.S.A., the estimates of model indicate about 438,386 excess deaths occurred in 2020, among which 87.5% were assigned to COVID-19. Some regions of Mideast, Great Lakes, New England, etc. had the most excess deaths in large central metropolitan areas, whereas other regions (Southwest, Southeast, Rocky Mountains, Great Plains, etc.) reported the highest excess mortality in non-metropolitan areas. Stokes *et al.*, (2021) found that direct COVID-19 death counts in the US in 2020 are underestimated total excess mortality attributable to COVID-19. Racial and socioeconomic inequities in COVID-19 mortality also increased when excess deaths not assigned to COVID-19 were considered (cf., Stokes *et al.*, 2021a). Sanmarchi *et al.* (2021) argue that many countries experienced an increase in mortality during 2020. Several Latin American and East European countries exhibit a large gap between Excess Mortality (EM) and COVID-19 Confirmed Mortality (CCM), such as Mexico; other countries showed a moderate EM beyond CCM (e.g., Greece). Countries with negative EM also had extremely low CCM and were located in East Asia. Islam *et al.* (2021) point out that about one million excess deaths occurred in 2020 in many high-income countries. Age standardized excess death rates were higher in men than women in all countries. Excess deaths exceeded reported deaths from COVID-19 in many countries, indicating that determining the full impact of the pandemic on mortality requires assessment of excess deaths. Kiang *et al.* (2020) argue that the true number of deaths resulting from COVID-19, both directly and indirectly, is likely to be much higher, and correct analysis and evaluation of excess mortality are critical goals to understanding this pandemic and its effect on human life and overall society. In general, these studies

clearly show that the mortality of COVID-19 pandemic is a critical indicator associated with manifold factors (Barnard *et al.*, 2021; Garber, 2021; Islam *et al.*, 2021; Stokes *et al.*, 2021, 2021a; Woolf *et al.*, 2021). In this context, this study develops a statistical analysis to explain some relations between the level of vaccinations and mortality rate of COVID-19 between countries to clarify complex factors determining pandemic diffusion and negative impact in society. These results can support the design of best practices of crisis management to cope with current and future pandemic crisis similar to COVID-19 (cf., Coccia, 2019g). This study is part of a large research project to explain drivers of transmission dynamics of COVID-19 and design effective policy responses to cope with and/or to prevent pandemic threats in society (Coccia, 2020, 2020a, 2020l, 2020m, 2021, 2021m, 2022a).

Study design and methods

Sample

The total sample of this study is $N=151$ countries worldwide. For some statistical analyses based on different confounding factors, the sample can be lower for missing data of some variables.

Measures for statistical analyses

– Vaccination is measured by percent share of people fully vaccinated against COVID-19 over 11 January 2022. Data refer to January 2022 but some countries, because of difficulty in the gather and transmission of information, can have data of December 2021. Of course, this small temporal gap of some countries does not affect the statistical analyses based on a large sample >100 units. The data here consider all types of COVID-19 vaccines used in different countries, i.e., vaccines by Johnson & Johnson, Oxford/AstraZeneca, Pfizer/BioNTech, Sinopharm/Beijing, Sinovac, Sputnik V and Moderna (Ritchie *et al.*, 2020). Of course, every country has been using a different combination of these COVID-19 vaccines to protect the population. Source: Our World in Data (2022).

– Gross Domestic Product (GDP) per capita in 2020. GDP per capita (constant 2010 US\$). GDP per capita is gross domestic product divided by midyear population. GDP is the sum of gross value added by all resident producers in the economy plus any product taxes and minus any subsidies not included in the value of products. It is calculated without making deductions for depreciation of fabricated assets or for depletion and degradation of natural resources. Data are in constant 2010 U.S. dollars. Source: The World Bank (2022).

– Population Total 2020. Total population is based on the de facto definition of population, which counts all residents regardless of legal status or citizenship. The values are midyear estimates. Source: The World Bank (2022a).

– COVID-19 Deaths. Total number of deaths in January 2022. It indicates the severity of this novel infectious disease in socioeconomic systems. This study also calculates the mortality rate per 100 000 people for a comparative analysis between countries. Source of data: Johns Hopkins Center for System Science and Engineering (2022).

Model and data analysis procedure

Firstly, data are analyzed with descriptive statistics given by arithmetic mean and standard error of the mean. The normality of distribution of variables under study is checked with skewness and kurtosis coefficients and if distribution of variables is not normal, they are transformed in logarithmic scale for having normality and performing appropriate parametric analyses (Coccia, 2018).

This study focuses on the following ratio of COVID-19 deaths calculated for all countries:

$$= \left(\frac{\text{Mortality rate per 100 000 people}}{\text{Total population in 2020}} \right) \times 100\,000$$

(Total number of deaths from COVID-19 at January 2022)

Secondly, variables under study are analyzed with the bivariate Pearson Correlation that produces a sample correlation coefficient, *r*, which measures the strength and

direction of linear relationships between pairs of continuous variables, given by share of people fully vaccinated against COVID-19 and mortality rate (deaths / population $\times 100\ 000$) between countries. This study also calculates the partial correlation that indicates the strength and direction of a linear relationship between continuous variables just mentioned whilst controlling for the effect of GDP per capita.

Thirdly, the analysis of multiple regression is applied to predict the value of mortality rate (dependent or response variable) on the value of two explanatory variables: share of people fully vaccinated against COVID-19 and GDP per capita (independent variables or predictors).

The specification of *log-log* model is given by:

$$\log y_{i,t} = \alpha_0 + \beta_1 \log x_{i,t} + \beta_2 \log z_{i,t-1} + u_{i,t} \quad (1)$$

where:

- $y_{i,t}$ = Mortality rate of COVID-19 in January 2022.
 - $x_{i,t}$ = Share % of people fully vaccinated against COVID-19 in January 2022
 - $z_{i,t-1}$ = GDP per capita in 2020
 - $u_{i,t}$ = Error term
- country $i=1, \dots, n;$ $t=time$

Results of regression analysis are the R^2 and the standard error of the estimate, which determine how well regression model fits the data. R^2 value (also called the coefficient of determination) is the proportion of variance in the dependent variable that can be explained by independent variables. The *F*-ratio in the ANOVA table test whether the overall regression model is a good fit for the data. Unstandardized coefficients of partial regression indicate how much the dependent variable varies with an independent variable when the other independent variable is held constant and finally the statistical significance of each of the independent variables with *t*-test. Statistical analyses are performed with the Statistics Software SPSS® version 26.

Statistical analysis

Table 1 shows descriptive statistics and that variables with logarithmic transformation have a normal distribution (coefficients of skewness and kurtosis have values in the correct range) to perform appropriate and robust parametric analyses.

Table 1. *Descriptive statistics*

Variables	N	Mean	Std. Error of Mean	Skewness	Kurtosis
GDPPC 2020, GDP per capita \$	151	14,457.69	1,716.74	2.68	9.64
MOR2022, Mortality rate per 100 000 people (number)	151	111.43	9.75	1.33	1.69
VAC2022, Share % of people fully vaccinated	144	44.14	2.26	-0.13	-1.29
Log GDPPC2020	149	8.68	0.12	0.07	-0.90
LogMOR2022	151	3.82	0.13	-0.58	-0.68
LogVAC2022	144	3.40	0.09	-1.44	1.39

Table 2. *Bivariate correlation*

	Pearson Correlation	LogVAC2022	LogMOR2022
LogVAC2022		1	.646**
N		144	144

Note: MOR2022, Mortality rate per 100 000 people in 2022, VAC2022, Share % of people fully vaccinated in 2022; ** Correlation is significant at the 0.01 level (1-tailed).

The bivariate Pearson Correlation produces, in the sample of $N=144$ countries, a positive coefficient $r=.65$ ($p\text{-value}<0.01$), which indicates a strong correlation between mortality rate per 100 000 people and share % of people fully vaccinated. This finding is confirmed in table 3 with the partial correlation that indicates the moderate linear relationship between continuous variables just mentioned, controlling for the effect of GDP per capita ($r_{\text{partial}} = .44$, $p\text{-value}=.001$).

Table 3. *Partial correlation*

Control variable: GDPPC2020	Partial Correlation	LogVAC2022	LogMOR2022
	LogVAC2022	1	.443***
	N	135	135

Note: GDPPC 2020, GDP per capita; MOR2022, Mortality rate per 100 000 people in 2022; VAC2022, Share % of people fully vaccinated in 2022.

*** Correlation is significant at the 0.001 level (1-tailed).

Table 4. Regression analyses of mortality rate in 2022 on people fully vaccinated in 2022 (and GDP per capita 2020), log-log model [1]

	Simple Regression	Multiple regression
Constant α	0.754*	-0.542
(St. Err)	(0.325)	(0.665)
VAC ₂₀₂₂ , Coefficient β_1	0.917***	0.713***
(St. Err.)	(0.091)	(0.132)
GDPPC ₂₀₂₀ , Coefficient β_2	--	0.228*
(St. Err.)		(0.103)
R ²	.42	.43
(St. Err. of Estimate)	(1.23)	(1.22)
F	101.70***	52.80***

Note: Dependent (response) variable is: MOR₂₀₂₂, Mortality rate per 100 000 people in 2022; Explanatory variables are: VAC₂₀₂₂, Share (%) of people fully vaccinated against COVID-19 in 2022 and GDPPC₂₀₂₀, Gross Domestic Product per capita in 2020. Significance: *** p -value<0.001; p -value<0.05

Table 4 shows results of simple and multiple regression. Since results are similar, we describe estimated multivariate relationship based on Eq. [1] with two explanatory variables (i.e., Share % of people fully vaccinated against COVID-19 in 2022 and Gross Domestic Product per capita in 2020). The partial coefficient of regression β_1 of the model indicates that a 1% higher share of people fully vaccinated (controlling GDP per capita), increases the expected mortality rate of COVID-19 per 100 000 people by 0.7% (p -value < 0.001), whereas the partial coefficient of regression β_2 of the model indicates that a 1% higher level of GDP per capita (controlling share % of people fully vaccinated), increases the expected mortality rate of COVID-19 per 100 000 people by 0.2% (p -value < 0.05). F -test (the ratio of the variance explained by the model to the unexplained variance) is significant at 1 % (i.e., p -value < 0.001), such that overall regression model is a good fit for the data. R² of the model of multiple regression indicates that about 53% of the variation in mortality rate of COVID-19 can be attributed (linearly) to share (%) of people fully vaccinated against COVID-19 in 2022 and Gross Domestic Product per capita in 2020. Figure 1 shows regression line of COVID-19 deaths per 100 000 people on share of people vaccinated against COVID-19 (%) based on log-log model.

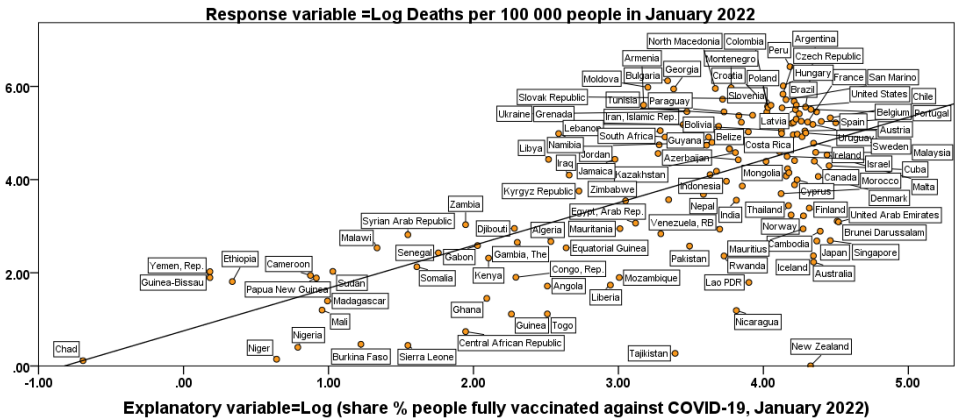


Figure 1. Relation of COVID-19 deaths per 100 000 people on share of people vaccinated against COVID-19 (%) based on log-log model.

Hence, these critical findings suggest that increasing the share of people vaccinated against COVID-19 is a necessary but not sufficient condition to mitigate the negative impact of COVID-19 in society in terms of reduction of mortality. In fact, the diffusion of the mutant novel coronavirus has complex aspects, and the increasing level of vaccinations seems not to a health policy enough to control the pandemic and reduce mortality because the transmission dynamics is driven by manifold environmental and socioeconomic factors that are discussed in the following section.

Discussions to explain the relation

The critical findings of this study are a strong correlation between mortality rate per 100 000 people and share % of people fully vaccinated against COVID-19 (also controlling for the effect of GDP per capita). This result can be explained with the fact that COVID-19 vaccinations are a necessary but not sufficient strategy to reduce the negative impact of the novel coronavirus in society, because there are manifold factors that support the diffusion and mortality of this pandemic, also in countries having an elevated level of fully vaccinated people.

Factors determining high mortality rates, though a high share of vaccinated people (factors to be considered when shaping general strategies to mitigate case fatality rates of future waves of COVID-19 and similar pandemics)

- High air pollution and exposure of population to days exceeding levels of PM_{2.5} air pollution (e.g., max 50 days of high levels of air pollution per year)
- Low wind speed, low temperature and high atmospheric humidity
- New SARS-CoV-2 variants of concern (e.g., Delta, etc.)
- Low health expenditure as % of GDP
- Low government health expenditure per capita
- Lower investments in innovative technology, such as high-tech medical ventilators
- Delayed application of containment policies
- Unsustainable policies for economic development
- High density and intensive commercial activity

Figure 2. Factors determining high mortality rates, though a high share of vaccinated people between countries. Factors to be considered to design general guidelines to constrain pandemic crises of novel viral agents like Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

Determinants of the pervasive diffusion of COVID-19 in society, which vaccinations cannot stop, are: new variants, high air pollution and density of people in cities, intensive commercial activities of countries, low investments in healthcare sectors and little new technology (such as non-invasive medical ventilation), etc.¹ (Figure 2).

□ *High level of air pollution*

Coccia (2020, 2021) finds out, based on a case study of Italy, that the number of infected people was higher in cities with >100 days per year exceeding limits set for PM₁₀ or ozone and cities located in hinterland zones (i.e., away from the coast). In hinterland cities (mostly those bordering large urban conurbations) with a high number of days exceeding PM₁₀ and ozone limits, coupled with low wind speed, the average

¹ For role of science, technology, research labs, leading firms and institutions for economic and social change see: Ardito *et al.*, 2021; Coccia, 2003, 2005, 2005a; Coccia, 2008, 2013, 2014, 2015, 2016, 2017, 2017a, 2017b, 2017c, 2017d, 2017e, 2018a, 2018b, 2018c, 2018d, 2018e, 2018f, 2019, 2019a, 2019b, 2019c, 2019d, 2018e, 2019f; 2018g, 2019h, 2019i, Coccia, 2020d, 2020e, 2020f, 2020g, 2020h, 2020i; Coccia, 2021h, 2021i, 2020l; Coccia, 2022d; Coccia & Bellitto, 2018; Coccia & Benati, 2018; Coccia & Cadario, 2014; Coccia & Finardi, 2012, 2013; Coccia & Rolfo, 2000, 2008; Coccia & Watts, 2020; Pagliaro & Coccia, 2021; Pronti & Coccia, 2020.

number of infected people in April 2020 more than doubled that of more windy coastal cities in Italy that had also exceeded the air pollution limits. These findings provide valuable insight into geo-environmental factors that may accelerate the diffusion of COVID-19 and similar viral agents. Studies show that sustainable environment plays a vital role for reducing COVID-19 related infected individuals and deaths; in particular, a low rate of fatality is associated with a low level of air pollution (cf., Coccia, 2020a, 2020b, 2020c). In fact, average population exposed to levels exceeding WHO guideline value (% of total) is 72% in countries with a lower level of fatality rate, whereas in countries with a higher incidence of mortality of the COVID-19 is almost 98%. Coccia (2020a; 2022b, 2022c) maintains that a proactive strategy to cope with future epidemics should concentrate on reducing levels of air pollution in hinterland and polluted cities. Copat *et al.* (2020), considering different studies about the relation between air pollution and the spread of COVID-19, suggest that PM_{2.5} and NO₂ can support the spread and lethality of COVID-19, but additional analyses are needed to confirm this relation concerning transmission dynamics and negative effects of the SARS-CoV-2 in society (cf., Coccia, 2021).

□ *Climate factors: low wind speed and temperature, high humidity*

Studies suggest that the concentration of atmospheric pollutants is a main driver of the spread of SARS-CoV-2 (Coccia, 2020a), but a high wind speed sustains clean days from air pollution, reducing whenever possible the spread of COVID-19 (cf., Coccia, 2020b, 2021, 2021a, 2021f; Caliskan *et al.*, 2020). To put it differently, a low wind speed in cities prevents the dispersion of air pollutants that can include bacteria and viruses, such as SARS-CoV-2, and can increase the incidence of COVID-19, such as in some European regions (Coccia, 2020a, 2020b, 2020c; 2021). Rosario *et al.* (2020, p. 4) suggest that wind improves the circulation of air and increases the exposure of the novel coronavirus to the solar radiation effects, a factor having a negative correlation in the diffusion of COVID-19. Nicastro *et al.* (2021) also analyze the spatial aspects of SARS-CoV-2 in response to UV light and

solar irradiation measurements on Earth. The results of study show that UV-B/A photons have a powerful virucidal effect on the single-stranded RNA virus of the COVID-19. Moreover, the solar radiation that reaches temperate regions of the Earth at noon during summers, it is a sufficient condition to inactivate 63% of virions in open-space concentrations in less than 2 minutes.

□ *High density of cities and intensive commercial activities*

Coccia (2020a, 2020b) showed, with a case study of Italy, that average number of infected individuals increases with average density of people/km². In fact, the density of population per km² is a principal factor for transmission dynamics of infectious diseases and studies confirm that high population density increases the probability of interpersonal contacts and viral transmission of COVID-19 in cities (Coccia, 2020a, 2021). Moreover, Bontempi & Coccia (2021) and Bontempi *et al.* (2021) find out that an intensive commercial activity, measured with the level of import and export, can be a main predictor of the diffusion of COVID-19 in society. In particular, the study suggests that total import and export of Italian provinces has a high association with confirmed cases over time (average $r > .78$, p -value $< .001$). Another study based on three large countries in Europe (Italy, France, and Spain) suggests the positive association between trade and pandemic diffusion. In general, international trade data is supposed to be a complex parameter of the transmission dynamics of the COVID-19 that includes many factors related to economic, demographic, environmental, and climate aspects.

□ *New SARS-CoV-2 variants of concern*

The novel coronavirus in environment and human ecosystem constantly changes through mutations. A new mutation generates a variant of the original virus of SARS-CoV-2. Fontanet *et al.* (2021) argue that in December 2020, an unexpected rise in reported COVID-19 cases was attributed to the emergence of new SARS-CoV-2 variants (Alfa, B.1.1.7) in the UK and (Beta, B.1.351) in South Africa. Both variants had a mutation in the receptor-binding domain of the spike protein

that is reported to increase transmission, ranging between 40% and 70%. Davies *et al.* (2021) show that Alpha variant (B.1.1.7) of SARS-CoV-2 is more transmissible than pre-existing variants. This study estimates that the hazard of deaths associated with B.1.1.7 is 61% higher than pre-existing variants. In short, analysis suggests that B.1.1.7 is not only more transmissible than previous SARS-CoV-2 variants but may also cause more severe illness. Other two variants of the novel coronavirus (SARS-CoV-2) that cause coronavirus disease 2019 (COVID-19) and subsequent health and socioeconomic problems are (Mayo Clinic, 2022):

- Delta (B.1.617.2). This variant is nearly twice as contagious as earlier variants and might cause more severe illness. The greatest risk of transmission is among unvaccinated people. People who are fully vaccinated can get vaccine breakthrough infections and spread the virus to others. However, it appears that vaccinated people spread COVID-19 for a shorter period than do unvaccinated people. While research suggests that COVID-19 vaccines are slightly less effective against the delta variant.

- Omicron (B.1.1.529). This variant might spread more easily than other variants, including delta. But it is not yet clear if omicron causes more severe disease. It is expected that people who are fully vaccinated can get breakthrough infections and spread the virus to others. However, the COVID-19 vaccines are expected to be effective at preventing severe illness. This variant also reduces the effectiveness of some monoclonal antibody treatments.

The alpha, gamma and beta variants of SARS-CoV-2 continue to be monitored but are spreading at much lower levels. The mu variant is also being monitored. Of course, these variants of the novel coronavirus change the transmissions dynamics and negative effects in society.

□ *Health investments and innovative technology of medical ventilators*

Coccia (2021e) reveals that countries with lower fatality rates have a high average level of health expenditure given by 7.6% of GDP and average government health expenditure per capita of about \$2,300, whereas countries with higher fatality

rates of COVID-19 have an average health expenditure of roughly 6% of GDP and very low government health expenditure per capita (a mere average value of about \$243 per inhabitants) that indicates a weak healthcare sector to cope with pandemics and also other diseases in society. In the context of COVID-19, a main technology to cope with a serious illness of people admitted in Intensive Care Units (ICUs) is mechanical ventilator (it is an artificial breathing device that is used for patients who are not able to breathe naturally due to a critical illness, such as COVID-19). Some of the most used products include positive and negative mechanical ventilators that are utilized in ICUs, neonatal care centers and ambulances. These devices consist of a hollow tube that is inserted into the patient's trachea to create a stable airway. They also assist in maintaining adequate levels of oxygen and carbon dioxide in the body to relieve respiratory distress, reverse respiratory muscle fatigue and initiate lung healing (IMARC, 2022). However, invasive ventilation can create problems to lung and infection in case of prolonged utilization, such as to treat COVID-19 patients. Ventilator-associated lung injury, sometimes referred to as ventilator-induced lung injury, is damage to the alveolar and / or small airways related to mechanical ventilation. Mechanisms include alveolar over distension and shear forces created by repeated opening and collapsing of the alveoli, leading to the release of inflammatory mediators that result in increased alveolar permeability and fluid accumulation. New technology is increasingly based on Non-Invasive Ventilation (NIV) that refers to the administration of ventilatory support without using an invasive artificial airway (endotracheal tube or tracheostomy tube). The use of NIV has markedly increased over the past two decades, and NIV has now become an integral tool in the management of both acute and chronic respiratory failure, in both the home setting and in the critical care unit. Non-invasive ventilation is an innovative technology that is generating a replacement for invasive ventilation, and its flexibility also allows it to be a valuable complement in patient management (Soo Hoo, 2020, 2010). New technology of NIV accurately measures patient's airway

pressure, moreover the respiratory abdominal sensor and transducer allow patient-triggered pressure assists with breath rate monitoring. New technology of NIV allows an adequate humidification to maintain airway clearance, optimize ventilation and improve patient comfort (in fact, normal functions of the nose and air passages of the respiratory tract are to warm, moisten and filter the inhaled gases before they reach the lungs. In normal respiration, the nasal mucosa and upper airways provide 75% of the heat and moisture supplied to the smaller airways and alveoli. By the time air reaches the alveoli, the inspired gas warms to 37°C at 100% relative humidity). In short, benefits of NIV are due to both the patient and the facility using it, such as cost-effective, no need for sedation, comfortable for the patient, intubation and airway skills not required and time-efficient for facility. In the presence of pandemic crisis some countries, such as Germany had a high number of medical ventilators: about 30,000 in 2020 ([Our World in Data, 2022a](#)) and though a population of 83.24 million, COVID-19 deaths (117 318) are lower than for instance Argentina that has 120 019 deaths with about 45 million of people ([The World Bank, 2022a](#); [Johns Hopkins Center for System Science and Engineering, 2022](#)). Other scholars, such as Kapitsinis (2020), argue that investments in health sector are a critical public policy to mitigate mortality rate of COVID-19. Hence, countries should support healthcare investments in the expansion of hospital capacity and R&D investments in innovative technology to develop effective vaccines, antivirals, innovative drugs and high-tech devices that can counteract future public health threats of new epidemics like COVID-19 ([Ardito et al., 2021](#); [Coccia, 2017c, 2017d, 2019f, 2020](#)).

Conclusive observations

Lau *et al.* (2021) argue that in the presence of a continuous global COVID-19 pandemic threat, the mortality rate is a main indicator to evaluate the real effects of COVID-19 in society (cf., [Liu et al., 2021](#)). In this context, one of the goals of nations to cope with COVID-19 pandemic crisis is to mitigate

mortality and case fatality rate (cf., Coccia, 2020a, 2021e). Initially, in 2020, countries apply non-pharmaceutical interventions (e.g., lockdown) to cope with COVID-19 pandemic crisis; a later time, in 2021 and 2022, the most applied health policy worldwide is the administration of vaccinations on a vast population (Coccia, 2022b). Findings here reveal that the increase of vaccinated people (%) against COVID-19 is not associated with a reduction of mortality of COVID-19 between countries because manifold factors can affect the complex dynamics of diffusion of COVID-19 pandemic in environment and society. Although this study has provided interesting results, that are of course tentative, it has several limitations. First, a limitation of the study is the lack of data about total vaccinations in manifold countries. Second, not all the possible confounding factors that affect the diffusion of vaccination and mortality of COVID-19 are taken into consideration and in future these factors deserve to be controlled for supporting results here. Third, the lack of integration of data with socioeconomic aspects of countries may influence the results of mortality, making comparative analyses a problematic approach (Angelopoulos *et al.*, 2020; Coccia, 2018). Fourth, country-specific health investments may affect the vaccination, management of healthcare and mortality of people and have to be controlled in future development of this study. Finally, the estimated relationships in this study focus on variables in specific months (based on recent data available) but an extension of the period under study is needed to reinforce results here. Thus, the generalization of this results should be done with caution.

Future research should consider new data, when available, and when possible, to examine also other variables between countries to explain the interaction between vaccination, mortality and other socioeconomic factors between countries. Despite these limitations, results presented here suggest that the vaccination is a health policy not enough to reduce mortality of COVID-19, control and stop the pandemic diffusion and subsequent negative effects in society. Hence, there is need for much more detailed research in these topics and this study encourages further investigations to clarify

complex factors driving pandemics in environment and ecosystems also considering the interaction between restrictions, vaccinations and general investments in healthcare. To conclude, varied factors between countries that are not only parameters related to medicine but also to social, economic and innovation studies can explain the mortality of COVID-19 pandemic in society and should be accurately considered to control future negative impact of pandemic crisis on public health, economy and society. Hence, results here have to be reinforced with much more follow-up investigation concerning detailed research into the relations between negative effects of pandemic in society, health system, public health capacity and pandemic response of countries.

Overall, then, this study suggests that an effective strategy to reduce the negative impact (in terms of mortality) of future pandemic threats similar to COVID-19, it has to be based on high investments in health system and design of comprehensive health, social and economic policy responses of crisis management, not only vaccination-based approach, considering that complex environmental and socioeconomic factors guide transmission dynamics of COVID-19 and negative effects in society. To conclude, this study here suggests analyzing further socio-economic factors that may shape and support general health strategy, beyond vaccinations, to cope with future pandemic crises by creating appropriate ecosystems and socioeconomic systems of countries that improve public health and overall wellbeing of people.

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8

COVID-19 in society between 2020 (without vaccinations) and 2021 (with vaccinations): A case study

Introduction

The novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the causative viral agent of the Coronavirus disease 2019 (COVID-19), an infectious disease that appeared in late 2019 ([Anand et al., 2021](#); [Coccia, 2020, 2020a, 2021](#)). COVID-19 is still circulating in 2021 with mutations of the novel coronavirus that generate a constant pandemic threat in manifold countries with higher numbers of COVID-19 related infected individuals and deaths ([Bontempi & Coccia, 2021](#); [Bontempi et al., 2021](#); [Johns Hopkins Center for System Science and Engineering, 2021](#)).

The alarming levels of spread and severity of COVID-19 worldwide has supported the development of vaccines in 2020 based on messenger RNA vaccines, known as mRNA vaccines for high levels of protection by preventing COVID-19 among people that are vaccinated ([Coccia, 2021a](#)). New mRNA vaccines for COVID-19 are based on accumulated knowledge that the infective process itself is effective in raising an

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immune response and genetic engineering can be utilized to construct virus-like particles from the capsid and envelope proteins of viruses (Smoot, 2020). These mRNA vaccines eliminate a lot of phases in manufacturing process for the development of new drugs because rather than having viral proteins injected, the human body uses the instructions to manufacture viral proteins itself. In short, mRNA vaccines are produced and manufactured by chemical rather than biological synthesis, as a consequence the process of development is much faster than conventional vaccines to be redesigned, scaled up and mass-produced (Komaroff, 2020). Manifold public agencies for protecting and promoting public health through the control and supervision in the United Kingdom, the USA, Canada, Europe and other countries confirm that mRNA vaccines for COVID-19 can be effective and safely tolerated in population (Abbasi, 2020; Cylus *et al.*, 2021; Heaton, 2020; Jeyanathan *et al.*, 2020; Komaroff, 2020).

Because of the rapid spread of COVID-19 worldwide, understanding whether and how the effects of COVID-19 in society change in the presence of vaccinations is a crucial aspect to eradicate infectious diseases in the population (Aldila *et al.*, 2021). Vaccination has the potential to keep low basic reproduction number, to relax nonpharmaceutical measures and to support the recovery of socioeconomic activities (cf., Anser *et al.*, 2020; Prieto Curiel *et al.*, 2021). Akamatsu *et al.* (2021) argue that to cope with infectious disease severity that increases considerably, governments have to implement an efficient campaign of vaccination to substantially reduce infections and mortality in society and also avoid the collapse of the healthcare system. Aldila *et al.* (2021) maintain that higher levels of vaccination rate can eradicate COVID-19 from the population. The final goal of a plan of vaccination is achieving herd immunity to protect vulnerable individuals (Anderson *et al.*, 2020; de Vlas & Coffeng, 2021, Randolph and Barreiro, 2020; Redwan, 2021). Herd immunity indicates that only a share of a population needs to be immune and as a consequence no longer susceptible (by overcoming natural infection or through vaccination) to a viral agent for epidemic control and to stop

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generating large outbreaks (Fontanet & Cauchemez, 2020; Rosen *et al.*, 2021).

However, other climatological, environmental, demographic, and geographical factors of the total environment can influence the spread of COVID-19 (Bashir *et al.*, 2020; Rosario *et al.*, 2020; Sahin, 2020; Sarmadi *et al.*, 2020). Zhong *et al.* (2018) argue that static meteorological conditions may explain the increase of bacterial communities in the presence of air pollution. Coccia (2020) reveals that, among Italian provincial capitals, the number of infected people was higher in cities having high air pollution, cities located in hinterland zones (i.e. away from the coast), cities having a low average intensity of wind speed and cities with a lower temperature (cf., Coccia 2020b, 2020c; 2021b). Rosario *et al.* (2020) also reveal that high wind speed improves the circulation of air and also increases the exposure of the novel coronavirus to the solar radiation effects, a factor having a negative correlation in the diffusion of COVID-19.

In this context, a key problem in current COVID-19 pandemic crisis is to assess the effects of COVID-19 related infected individuals and deaths, hospitalizations of people and admissions to Intensive Care Units with and without vaccinations. The study here confronts this problem here by developing a comparative analysis between the period April-May-June 2020 (without vaccinations) and April-May-June 2021 (with vaccinations) in Italy, which was the first European country to experience a rapid increase in confirmed cases and deaths of COVID-19 in 2020 and in 2021 is one of the countries with a widespread plan of vaccinations. The study here can provide critical results to clarify the dynamics of COVID-19 pandemic, effects of vaccinations in society and behavior of the novel Coronavirus in environment. Lessons learned from this study could be of benefit to countries to design strategies of health, environmental and social policy to cope with and/or to prevent pandemics similar to COVID-19. This study is part of a large body of research directed to explain drivers of transmission dynamics of COVID-19 and design effective policy responses of crisis management for

Materials and methods

The goal of this study is a comparative analysis of the effects of COVID-19 between April-May-June 2020 (without vaccination plan) and April-May-June 2021 (with vaccination plan) in Italy to assess differences and effects of the dynamics of this novel infectious disease in society.

Research question

How is the behavior of the COVID-19 in environment with or without vaccinations?

Are the effects of COVID-19 between April-May-June 2021 (with vaccination plan) lower than April-May-June 2020 without vaccination plan in Italy?

Research setting

The research setting is a case study of Italy, the first European country to experience a rapid increase of COVID-19 related infected individuals and deaths 2020 in which this novel coronavirus is still circulating in 2021 continuing to generate a higher number of infected individuals and deaths (Coccia, 2020, 2021). Moreover, Italy, on 20 June 2021 is one of the countries with widespread vaccinations having 76.11 doses of vaccines administered per 100 inhabitants, with a share of people fully vaccinated equal to 26% and share of people only partially vaccinated against COVID-19 also equal to 26 % (Our World in Data, 2021; Lab24, 2021).

Period, sample and source

The period under study is from 1st April to 15th June 2020 that is compared to the same period in 2021 in Italy, using daily data based on $N=76$ days in 2020 and $N=76$ days in 2021 for a total of $N=152$ cases for different variables. Source of epidemiological data under study is The Ministry of Health in Italy (Ministero della Salute, 2020).

Measures

The measures for statistical analyses are:

- *Number of daily COVID-19 infected individuals* is measured with confirmed cases of COVID-19 in population

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- *Number of daily COVID-19 swab tests* to verify the positivity to the novel coronavirus (confirmed case) by analyzing specimen of people (LabCorp, 2020).

- *Daily hospitalized people* are the hospitalized people (patients with different COVID-19 symptoms and patients in ICUs).

- *Daily admission to Intensive Care Units (ICUs)* is the number of recovery in ICUs of patients.

- *Number of daily COVID-19 deaths* is measured with total deaths per day in society

- *Daily Fatality rate* = ratio of deaths at (t) /confirmed cases at (t-14). The lag of about 14 days from initial symptoms to deaths is based on empirical evidence of some studies (Zhang et al., 2020).

Data analysis procedure

Firstly, the study calculates the daily contagiousness coefficient of COVID-19 in the period under study of 2020 and 2021, given by:

$$\frac{\text{Contagiousness coefficient of COVID – 19 at } t \text{ (CCV)} = \text{Confirmed cases at } t}{\text{swab tests at } t}$$

In order to eliminate from original time series y_t weekly seasonal variation, it is applied the method of moving averages (MM) considering the sub-period of length $r = 7$ days (a week), using the following formula for MM7:

$$y'_t = \frac{y_{t-3} + y_{t-2} + y_{t-1} + y_t + y_{t+1} + y_{t+2} + y_{t+3}}{r = 7 \text{ days}}$$

The new time series adjusted with averaging process is given by $y_t^* = \sum_t^s y'_t$ that tends to eliminate period to period weakly fluctuations and produces a much smoother series than original observations.

Data of daily hospitalization of people and admissions to ICUs are standardized as follows:

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$$\text{Daily hospitalization of people standardized} \\ \text{daily hospitalization of people (t)} \\ = \frac{\text{MM7 Contagiousness coefficient of COVID - 19 (t - 5)}}{\text{MM7 Contagiousness coefficient of COVID - 19 (t - 5)}}$$

$$\text{Daily admission ICUs standardized} \\ \text{daily admission ICUs (t)} \\ = \frac{\text{MM7 Contagiousness coefficient of COVID - 19 (t - 5)}}{\text{MM7 Contagiousness coefficient of COVID - 19 (t - 5)}}$$

The lag of about 5 days used to standardize these variables is based on an average period from diagnosis (initial symptoms and positivity to swab test) to the hospitalization and recovery in ICUs of patients as explained by specific studies (Faes *et al.*, 2020).

The sample of $N=152$ cases is divided in two sub-samples having similar temporal, health and societal conditions for a structural comparative analysis:

- group 1: data from 1st April to 15th June 2020, $N=76$
- group 2: data from 1st April to 15th June 2021, $N=76$

Secondly, Data are analyzed with descriptive statistics given by arithmetic mean (M) and Std. error of mean for a comparative analysis between two groups just mentioned.

Thirdly, follow-up investigation is the Independent Samples *t*-Test that compares the means of two independent groups in order to determine whether there is statistical evidence that the associated population means are significantly different. The assumption of homogeneity of variance in the Independent Samples *t* Test -- i.e., both groups have the same variance -- is verified with Levene's Test based on following statistical hypotheses:

$H_0: \sigma_1^2 - \sigma_2^2 = 0$ (population variances of group 1 and 2 are equal)

$H_1: \sigma_1^2 - \sigma_2^2 \neq 0$ (population variances of group 1 and 2 are not equal)

The rejection of the null hypothesis in Levene's Test suggests that variances of the two groups are not equal: i.e., the assumption of homogeneity of variances is violated. If Levene's test indicates that the variances are equal between the two groups (i.e., *p*-value large), equal variances are assumed. If Levene's test indicates that the variances are not

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equal between the two groups (i.e., p -value small), the assumption is that equal variances are not assumed.

After that, null hypothesis (H'_0) and alternative hypothesis (H'_1) of the Independent Samples t -Test are:

H'_0 : $\mu_1 = \mu_2$, the two population means are equal in 2020 and 2021

H'_1 : $\mu_1 \neq \mu_2$, the two population means are not equal in 2020 and 2021

Finally, trends of variables under study are visualized and analyzed for a comparative analysis of the impact of COVID-19 in Italy between 2020 (without vaccinations) and 2021 (with vaccinations). In particular, this study extends the statistical analysis with a regression model based on a linear relationship in which variables measuring the impact of the COVID-19 on health of people are a linear function of time in 2020 and 2021 period. The specification of linear relationship is given by a model using the time series y^*_t in 2020 and 2021:

$$\log y^*_t = \alpha + \beta t + u \quad (1)$$

y^*_t = measures of the impact of COVID-19 pandemic in society using MM7 of time series

t = time given by 2020 and 2021 period

u = error term

Ordinary Least Squares (OLS) method is applied for estimating the unknown parameters of linear model [1].

Statistical analyses are performed with the Statistics Software SPSS® version 26.

Results

Table 1 shows that confirmed cases in 2020 is about 4%, whereas in 2021 is 3.4%. Number of hospitalizations and ICUs of people, and deaths in 2020 has a slightly higher level, whereas fatality rate is lower in 2021 compared to 2021 likely because of a higher number of swab tests in 2021 that have

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detected more confirmed cases that increase the denominator of the ratio of fatality reducing the total value.

Table 1. *Descriptive statistics*

Description of variables	April-May-June 2020		April-May-June 2021	
	M	Std. Error Mean	M	Std. Error Mean
- Confirmed cases standardized	0.04	0.00	0.034	0.002
- Hospitalizations standardized	1270.45	191.07	854.010	84.281
- ICUs standardized	135.01	22.95	101.460	9.612
- Deaths	289.51	24.19	239.080	15.515
- Fatality rates	0.11	0.00	0.018	0.000

Note: M= arithmetic mean, N=76 days in 2020 and 76 in 2021

Table 2. *Independent Samples Test*

		Levene's Test for equality of variances		t-test for equality of Means				
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference
Confirmed cases 2020 vs. 2021	•Equal variances assumed	28.9	0.001	0.64	150.00	0.53	0.00	0.00
	•Equal variances not assumed			0.64	108.97	0.53	0.00	0.00
Hospitalizations 2020 vs. 2021	•Equal variances assumed	32.139	0.001	1.99	150.00	0.05	416.43	208.83
	•Equal variances not assumed			1.99	103.12	0.05	416.43	208.83
ICUs 2020 vs. 2021	•Equal variances assumed	27.08	0.001	1.35	150.00	0.18	33.55	24.88
	•Equal variances not assumed			1.35	100.52	0.18	33.55	24.88
Deaths 2020 vs. 2021	•Equal variances assumed	21.297	0.001	1.94	150.00	0.06	55.65	28.76
	•Equal variances not assumed			1.94	127.90	0.06	55.65	28.76
Fatality rates 2020 vs. 2021	•Equal variances assumed	74.863	0.001	48.80	150.00	0.001	0.09	0.00
	•Equal variances not assumed			48.80	78.70	0.001	0.09	0.00

Table 2 shows the Independent Samples *t* Test, as follow-up inspection, to assess the significance of the difference of

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arithmetic mean between groups of 2020 and 2021 under study. The p -value of Levene's test is significant, and we have to reject the null hypothesis of Levene's test and conclude that the variance in the groups under study is significantly different (i.e., equal variances are not assumed). Table 2 also shows t-test for Equality of Means that provides the results for the actual Independent Samples t Test. Results are convergent, except fatality rates. In particular, since p -value ≥ 0.5 , higher than fixed significance level $\alpha = 0.01$, we can accept the null hypothesis, and conclude that the mean of confirmed cases, hospitalizations of peoples, ICUs, and deaths in 2020 and 2021 is significantly equal: there is not a significant difference in mean between 2020 and 2021. Instead, for fatality rates, since p -value < 0.001 is less than chosen significance level $\alpha = 0.01$, we can reject the null hypothesis, and conclude that the mean in 2020 and 2021 is significantly different, likely for reasons mentioned for table 1.

Table 3. *Estimated relationships based on linear model of regression*

	Confirmed cases standardized		Hospitalizations standardized		ICUs standardized	
	2020	2021	2020	2021	2020	2021
Constant α	0.095***	0.065***	3776.09***	2089.60***	420.90***	243.34***
Coefficient β	-0.002***	-0.001***	-65.08***	-32.09***	-7.43***	-3.69***
Stand. Coeff. β	-0.90	-0.99	-0.86	-0.97	-0.82	-0.97
R ²	0.81	0.97	0.74	0.93	0.67	0.94
F-test	316.99***	2557.12***	215.57***	989.43***	151.34***	1229.56** *
	Deaths		Fatality rates			
	2020	2021	2020	2021		
Constant α	654.86***	466.71***	0.11***	0.02***		
Coefficient β	-9.26***	-6.05***	0.000021	-0.00008***		
Stand. Coeff. β	-0.97	-0.99	-0.80	.53		
R ²	0.94	0.97	0.01	0.48		
F-test	1143.21***	2525.92***	0.067	68.25***		

Notes: Explanatory variable: Case sequence (*time*)

Dependent variables: Hospitalizations standardized, Confirmed cases standardized, ICUs standardized, Deaths, Fatality rates

Significance: *** p -value < 0.001 , * p -value < 0.5

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Table 3 and figures 1-4 confirm, *ictu oculi*, previous results. In particular, simple regression analysis in table 3 shows, in average, a higher reduction in 2020 than year 2021 of the coefficients of regression of variables under study (p -value=.001, except fatality rate that in 2021 is not significant). The R^2 of regression models indicates that more than 47% and until to 97% of the variation in variables of the COVID-19 can be attributed (linearly) to time. F -test is significant with p -value <.001, except fatality rate in 2021.

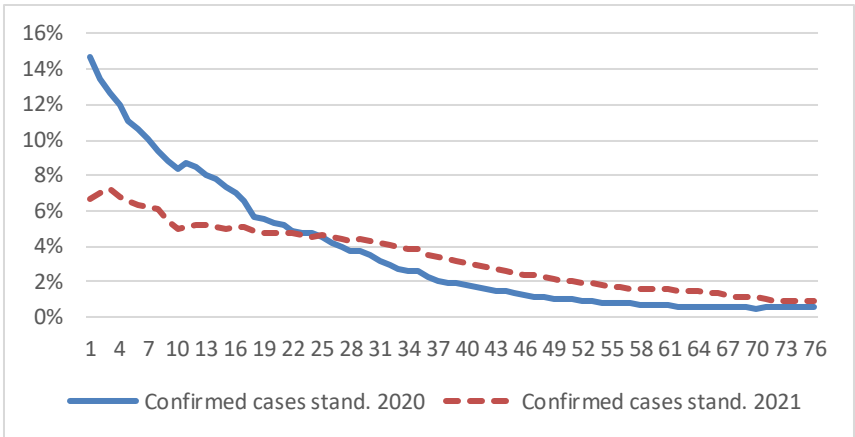


Figure 1. Trends of confirmed cases from April to June in 2020 and 2021, Italy

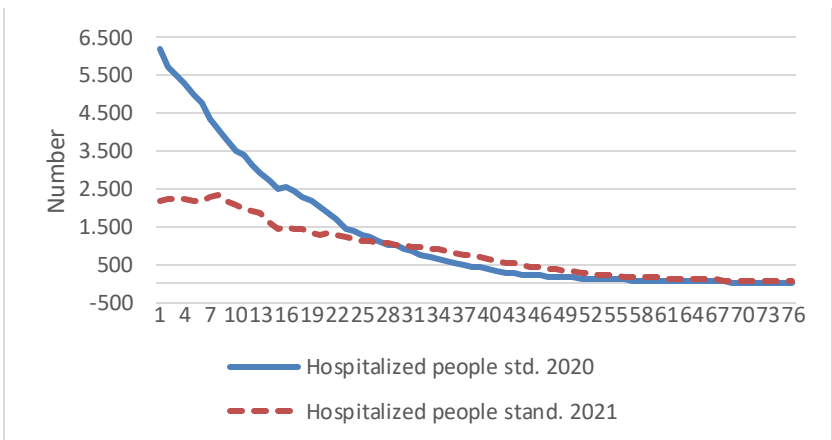


Figure 2. Trends of hospitalized people from April to June in 2020 and 2021, Italy

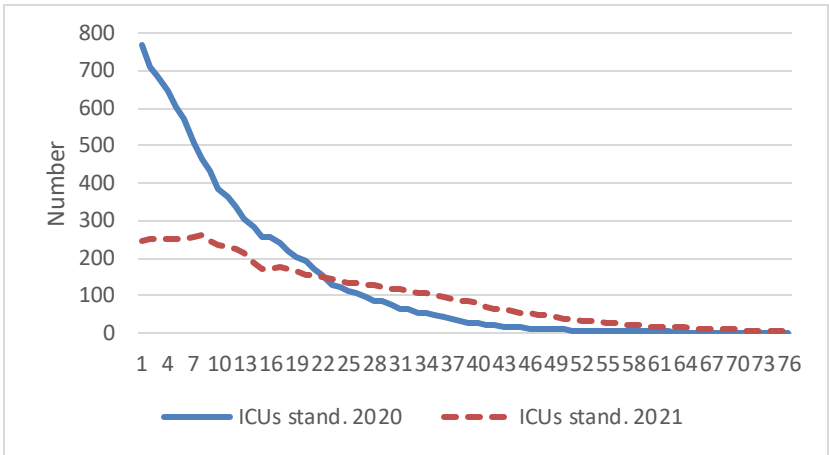


Figure 3. Trends of ICUs from April to June in 2020 and 2021, Italy

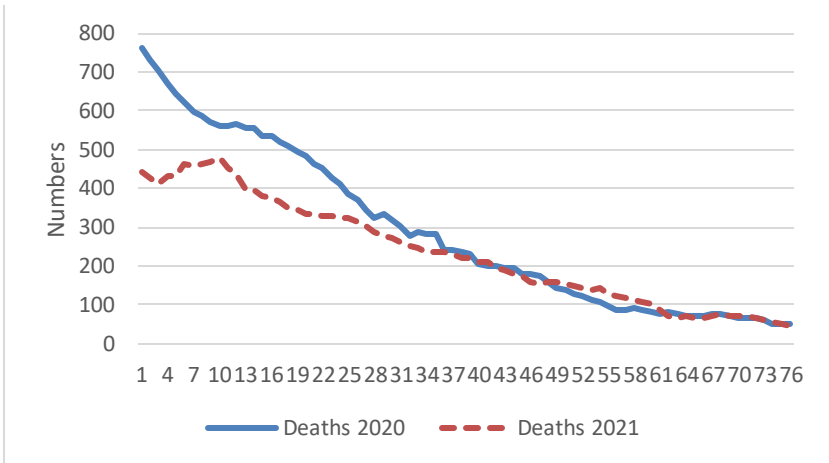


Figure 4. Trends of deaths from April to June in 2020 and 2021, Italy

Discussion of phenomena explained

One of the most crucial problems for the management of the COVID-19 pandemic crisis has been the effective implementation of vaccinations to constrain negative effects of pandemics in society. This study does not deal with effectiveness of vaccinations but it is a comparative analysis of the effects of COVID-19 in 2020 (without vaccinations) and

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2021 (with vaccinations) in the same socioeconomic system, given by Italy. Results reveal similar dynamics of COVID-19, regardless vaccinations. These findings suggest that other factors are associated with the dynamics of COVID-19, such as seasonality, that reduces the spread of the airborne disease of novel coronavirus over time and space and constrain the negative effects in society in the presence of specific conditions of total environment (atmosphere, biosphere and anthroposphere) in summer season.

In general, meteorological factors (e.g., temperature and humidity) play a well-established role in the seasonal transmission of respiratory viruses and influenza in temperate climates. Scholars analyze the sensitivity of COVID-19 to meteorological factors to explain how changes in the weather and seasonality may constrain COVID-19 transmission (Kerr *et al.*, 2021). In fact, studies report that the transmission of COVID-19 can be influenced by the variation of environmental factors associated with seasonality. Scholars suggest that the effects of seasonality on the influenza epidemic are associated with seasonal fluctuations connected with latitude in the North and South Hemisphere (Ianevski *et al.*, 2019; Shaman *et al.*, 2020). Recent studies point out the strong seasonal factor of COVID-19 because of environmental elements (Audi *et al.*, 2020; Moriyama *et al.*, 2020). The explanation of the role of seasonality in the spread of the COVID-19 pandemic is more and more important to design and implement appropriate public health interventions and plans of vaccination over time. The study by Liu *et al.* (2021, p.1ff) shows that the cold season in the Southern Hemisphere countries caused a $59.71 \pm 8.72\%$ increase of the total infections, whereas the warm season in the Northern Hemisphere countries contributed to a $46.38 \pm 29.10\%$ reduction. These results suggest that COVID-19 seasonality is more pronounced at higher latitudes, in the presence of larger seasonal amplitudes of environmental indicators are observed. Other studies have focused on temperature or humidity effects that might slow down transmission of the novel coronavirus (Karapiperis *et al.*, 2021; Rosario *et al.*, 2020). Byun *et al.* (2021) show that that manifold studies suggest an

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inverse relation between temperature and humidity and global transmission of SARS-CoV-2. In fact, COVID-19 tends to be temperature-sensitive and, as a consequence driven by a seasonal viral agent (cf., [Engelbrecht & Scholes, 2021](#)). The empirical evidence of these scholars seems to suggest that the novel coronavirus pandemic has just completed a full seasonal cycle, showing a negative correlation of the rate of diffusion with humidity and temperature: i.e. the SARS-CoV2 transmissibility tends to naturally decrease in summer seasons regardless vaccinations. Karapiperis *et al.* (2021) demonstrated that UV radiation is strongly associated with incidence rates, rather than mobility, suggesting that UV radiation is a seasonality indicator for COVID-19, irrespective of the initial conditions of the epidemic (cf., [Kumar *et al.*, 2021](#)). Many infectious diseases, such as endemic human coronaviruses, can be a seasonally recurrent infectious disease that varies over time and space ([Kronfeld-Schor *et al.*, 2021](#)).

Dbouk & Drikakis (2020) argue that epidemiologic models do not consider for the effects of climate conditions on the transmission dynamics of viruses, but a vital relationship between weather seasonality, airborne virus transmission, and pandemic disease exists over time. These scholars, applying fluid dynamics simulations, show that weather seasonality can induce two outbreaks of the COVID-19 pandemic worldwide. These two pandemic outbreaks per year are inevitable because are directly associated with weather seasonality based on temperature, relative humidity, and wind speed. Many studies, analyzing the role of climate and seasonality of pandemic diseases, have proposed an extension of the family of epidemiologic models with the introduction of seasonality transmission of SARS-CoV-2 ([Batabyal, 2021](#)).

Concluding observations and limitations

Currently, we know very little about relationships between novel coronavirus infections and environmental factors that can reduce virus spread, because of solar exposure and other climatological factors ([Coccia, 2020b, 2021b](#); [Rosario *et al.*, 2020](#)). Since the initial outbreaks worldwide, scholars analyze

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the seasonal dynamics of COVID-19 because results can be basic to better planning and preparedness to cope with the novel coronavirus disease (Byun *et al.*, 2021). This study reveals,–with a comparative analysis between the period April-May-June 2020 (without vaccinations) and April-May-June 2021 (with vaccinations) in Italy–, that the mean of confirmed cases, hospitalizations of people, admissions to ICUs and deaths in 2020 and 2021 is significantly equal, corroborating the seasonal behavior in the total environment of the COVID-19, which decreases regardless vaccinations. This result is basic for policy implications of crisis management. These findings can support the implementation of best practices of public health, based on seasons in the Northern and Southern Hemispheres, in which the COVID-19 and similar infectious disease pandemics unfold over time (cf., Coccia, 2021f). In fact, Danon *et al.* (2021) show that seasonal changes in transmission rate can affect the timing and size of the COVID-19 pandemic, shifting the peak into winter, with important implications for planning the healthcare capacity and also vaccinations.

What this study adds to current studies on the COVID-19 pandemic crisis is that the behavior of the novel coronavirus in the environment seems to be seasonal, regardless plans of vaccinations. This finding is critical to clarify transmission dynamics and support appropriate interventions of health policy to cope with virus spread and contain outbreaks of future infectious diseases. The understanding of the role of for seasonality is also a vital factor to mitigate socioeconomic issues. Policymakers and the public will need a deeper understanding of this factor associated with the COVID-19 and if a seasonality pattern for COVID-19 is confirmed, it can guide better health and social policies to cope with future infectious diseases similar to COVID-19. Kronfeld-Schor et al. (2021) argue that additional investigation should be directed to explain relationships between host immune seasonality warrants evaluation, weather and human behavior that may contribute to clarify dynamics of COVID-19 in terms of seasonality. A big challenge will be to predicting seasonality of

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infectious diseases directed to alleviate and/or prevent seasonal infectious diseases in complex, changing human-earth system. In particular, knowledge of other viral respiratory diseases suggests that the transmission of SARS-CoV-2 could be associated with seasonally varying environmental factors (e.g., temperature and humidity). Smit *et al.* (2021) argue that different studies suggest that climatic factors would reduce the viral transmission rate in places entering the boreal summer and the COVID-19 peak would coincide with the peak of the influenza season, increasing the burden on health systems. However, seasonality alone can be a main factor in transmission dynamics of COVID-19 but cannot be a sufficient element to curb the novel coronavirus transmission that requires multidisciplinary and timely intervention policies of short and long run, a scaled up health care capacity in the winter seasons, rather than summer period. In this perspective, the study here can provide main lessons learned from a comparative analysis that supports seasonal factors when formulating intervention strategies to cope with and/or prevent future pandemic diseases.

Overall, then, this statistical analysis here suggests that the reduction of the dynamics of COVID- seems to be associated with seasonality of the novel coronavirus that reduce the effects in the presence of favorable conditions of total environment in summer that constrain the spread of the airborne disease in society. These conclusions are, of course, tentative. A main concern is that there can be differences among countries according to their geographical position, climatological factors and also level of air pollution. Moreover, there can be a bias for detecting and reporting all COVID-19 data among different regions of the same nation. Finally, structure of population and characteristics of patients (e.g., ethnicity, age, sex, and comorbidities) may vary between regions affecting results. Although the study here provides main findings to better explain the behavior of COVID-19 in total environment to design policy responses to cope with pandemic threat, other confounding factors that influence variables under study here (e.g., institutional aspects, culture, investments in hospital sector, in prevention, in medical

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personnel, etc.) need to be considered for more comprehensive analysis.

To conclude, the evidence here suggests a strong seasonal effect of COVID-19, that if confirmed, will be more evident in subsequent months. The positive side of this study is that it proposes findings that are *prima facie* (i.e., accepted as correct until proved otherwise) to explain transmission dynamics of COVID-19 over time for appropriate policy responses of crisis management at country level. However, results have to be reinforced with much more follow-up investigations concerning relations between negative effects of pandemic in society, health system, climate factors to support effective policy responses to cope with pandemic diseases within and between countries.

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9

The prevention of pandemic impact similar to COVID-19

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which appeared in late 2019 (Coccia, 2020). COVID-19 and its variants have generated a pandemic with high numbers of infected individuals and deaths in manifold countries worldwide (Seligman *et al.*, 2021). In this context, it is basic to design strategies of crisis management to cope with/prevent pandemics of the COVID-19 and similar infectious diseases. The concept of strategy has a critical role in a framework of crisis management. Strategy is a current mode of cognition and action to enable the organization to take advantage of important opportunities or to cope with consequential problems and/or environmental threats in society, such as pandemics. Nations and their institutions have to prepare long-run strategies and specific plans of crisis management for pandemic threats to support the application of timely and effective processes of decision making to solve consequential problems in society. Strategies of crisis management should

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deal with pandemic threat before the emergence and, if necessary, cope with consequential problems and effects in society of the evolution of different pandemic waves (Groh, 2014). The main goal of these strategies is to reduce the risks of emergence of pandemics and solve the problems of pandemic threats and crises with effective and rapid decisions for reducing uncertainty and supporting as soon as possible the recovery of socioeconomic systems. In particular, strategies of countries for unforeseen pandemic crisis can be (Bundy *et al.*, 2017):

- *Responsive* based on the application of a previous plan of interventions ready to be used that endeavors to solve all consequential problems of pandemic crisis.
- *Preventive* based on the reduction of risk factors associated with the emergence of pandemics and the design of effective solutions for problems generated by a pandemic threat/crisis, pre-paring rapid strategic actions to stop or reduce negative effects in society in the short run.

The logical structure of these strategies of crisis management is based on following vital aspects:

- Analysis of the causes, risk factors and effects of pandemic threat (problem) in society, and possible solutions.
- Analysis of a limited number of variables associated with proposed solutions for achieving and sustaining specific goals given by the reduction of risk factors of the emergence of pandemics and negative effects in society.
- Analysis of different solutions to pandemic threats and crises and evaluation of pros and cons
- Choice of the satisfying solution in a context of limited rationally and turbulent environment of policymakers
- Application of the critical decision of problem solving for achieving the goals and evaluating expected results in a short period of time to refine and improve decision making with continuous learning processes.

Strategies of crisis management for on-going pandemic threats similar to COVID-19

Nicoll and Coulombier (Nicoll & Coulombier, 2009 p.3ff) show two main strategies to cope with pandemics:

- *Containment strategies* that endeavor to stop the diffusion of pandemics and epidemics in society. These interventions are directed to prevent vast chains of transmission and outbreaks, with public polices of quarantine and full lockdown associated with an accurate tracing of infections, isolation of infected people and timely treatments of patients.
- *Mitigation strategies* are based on social distancing, school closures, facemasks, etc. that endeavor to decrease the pandemic diffusion and the pressure of high hospitalization and admission to Intensive Care Units as well as protecting elderly and other people with high vulnerability (e.g., having cancer and other serious diseases).

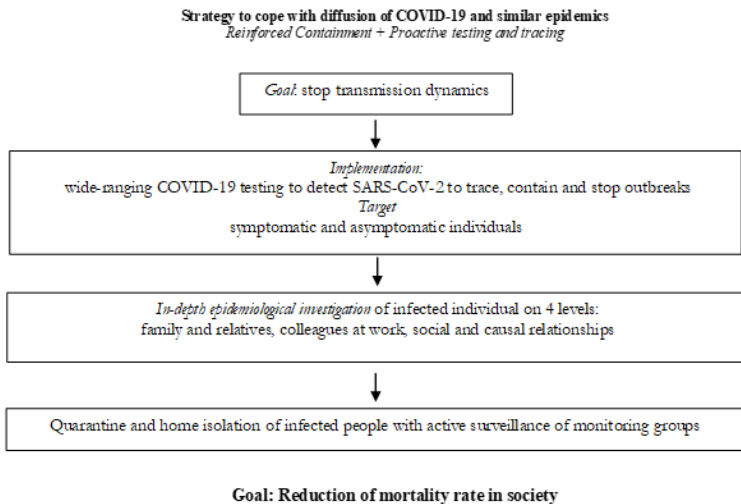


Figure 1. Strategic responses to cope with COVID-19 pandemic crisis and similar epidemics in future

In the presence of COVID 19 crisis and similar pandemics, many countries initially proposed a containment policy (quarantine and general lockdown) and subsequently

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mitigation measures, such as social distancing, disinfection of buildings, face masks, travel restrictions, etc. (Kucharski *et al.*, 2020; Walensky & DelRio, 2020). The study by Renardy *et al.* (2020) shows that a longer duration of lockdown that postpone the reopening of stores and the circulation of people does not decrease confirmed cases of infections and inter-related negative effects on public health, but longer duration of lockdown only defers these problems in a not too distant future. Instead, specific mitigation policies directed to diminish contacts among people can effectively lower the peak of pandemic waves and negative effects in society. Scholars also maintain that specific public places creating groups for social activities can generate a high risk of infections (e.g., pub, bar, etc.) (Chang *et al.*, 2020). A selected strategy to control the groups of people in these public places and the application of nonpharmaceutical measures of protection (e.g., facemasks) are more effective strategies to reduce confirmed cases than full lockdown of social and economic activities (Chang *et al.*, 2020).

In general, non-pharmaceutical measures are public health policies having the goals to lower the peak of pandemic wave and the high load on health system (Fong *et al.*, 2020; Prem *et al.*, 2020). However, Brooks *et al.*, (2020) report: “negative psychological effects of quarantine including post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma.”

Strategies for prevention of pandemics

Specific strategies can reduce risk factors of pandemic crises for preventing the emergence of pandemics and negative effects in society. This perspective focuses on health, environmental and instructional strategies.

Health strategies

Daszak *et al.*, (2020) highlight some critical aspects of strategies for prevention of pandemics, such as:

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- 1) control among wildlife to detect the transportation of dangerous pathogens
- 2) control the interaction between population and wildlife to detect as soon as possible spillover effects
- 3) control wildlife trade for enhancing biosecurity in domestic and international markets.

In addition, an intense activity of prevention has to be directed to control and appropriate application of biosafety protocols in public and private laboratories of virology that analyze viruses, pathogens and novel viral agents to minimize the possibility of accidental diffusion in environment and society with subsequent socioeconomic issues. The scientific collaboration among international laboratories plays a critical role to support the sharing of vital data and information for helping policymakers to apply plans to prevent/reduce the risk factors of future pandemics that can create socioeconomic issues worldwide (Coccia, 2020). This strategy of prevention can be driven by increasing levels of investments in health sector and R&D, as well as levels of health expenditure per capita. In fact, these preventive measures can control the emergence of pandemics and negative effects in society of future pandemics similar to COVID-19 (Coccia, 2020). In this context, Kapitsinis (2020) argues that investments in health sector are critical strategies to develop hospital efficiency in admissions of infected people, innovative treatments for novel infectious diseases and new technology driven by R&D labs supporting scientific advances directed to new vaccines, antivirals and other innovative drugs that can avoid and/or control future pandemic threats in countries (Coccia, 2020; Ardito *et al.*, 2021; Coccia, 2018; Coccia, 2019; Coccia, 2019a; Coccia & Watts, 2020).

Environmental strategies

Studies find that sustainable environment plays a vital role to reduce risk factors of epidemics and prevent pandemics similar to COVID-19; scholars maintain that a low rate of fatality is associated with a low level of air pollution in

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environment (Coccia, 2020; Coccia, and Watts, 2020; Coccia, 2020b; Coccia, 2021; Coccia, 2021a). Studies also show that countries with 72% of population exposed to levels exceeding WHO guideline value of air pollution have fatality rates of COVID-19 lower than countries with 98% population exposed to similar levels of air pollution. Coccia (2020) demonstrates that polluted cities should not exceed forty-eight days per year of air pollution, in the presence of climate conditions having little wind. In particular, when days of air pollution is higher than 100 days per year, the reduction of air quality and other factors can damage the health of population and support the acceleration of transmission dynamics of infectious diseases with consequential socioeconomic problems (Coccia, 2021; Coccia, 2021a).

Institutional strategies

Resilient systems to pandemic shocks must have strong institutions and governance driven by adequate and effective leadership that supports population needs. Efficient governance has to support preparedness to pandemic threats with constant investments in health system to reduce mortality, morbidity and stress among population, and promote economic recovery (Coccia, 2021; Coccia, 2021a; Coccia, 2021c; Klug *et al.*, 2020). Sagan *et al.* (2020) confirm that in Europe, a good governance in countries has played a critical role to support a resilient response of health system in the presence of COVID-19 pandemic crisis. In particular, Sagan *et al.*, (2020) consider a broad concept of governance, not limited to health system alone, that creates the institutional background to support economic and social systems of the nation and its government to work properly for preventing and/or coping with pandemic threats. Sagan *et al.*, (2020) pinpoint that the prevention of pandemic threats is also based on: 1) appropriate and effective governance of institutions and 2) skilled human capital with interdisciplinary technical capacity of crisis management to respond in a short period of time.

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Other factors for effective strategies to prevent and/or reduce risks of future pandemic crises can be:

- Leveraging operational levels based on medical personnel, epidemiologists, biologists, emergency managers, and other professionals for coping with the pandemic's threat.
- Creating a network of innovators with a great variety of expertise and capability in different fields to support policy decisions and their timely implementation (Jenkins-Smith *et al.*, 2018).
- Fostering academic institutions and leading scholars that play a vital role in supporting rational decisions of governments (Cairney, 2016; Weible *et al.*, 2020).
- Creating stable collaborations across different structures, such as academic and administrative institutions to accelerate learning process to prevent and/or to cope with pandemic threat/crisis (Crow *et al.*, 2018).

Overall, then, success or failure of strategies to prevent pandemic threats and crises depend on effective decision making in the presence of uncertainty, turbulent environment and highly restricted time (Coccia, 2021a). Studies show that general guidelines for a strategy to cope with pandemic threats have to support health expenditures and R&D investments for effective policy responses, and a policy directed to long-term sustainability that decreases air pollution and as a consequence negative effects on population and environment (Coccia, 2020; Coccia, 2021a; Coccia 2021b). Figure 2 shows these critical aspects for preventing and/or controlling the risk factors of future pandemics.

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General guidelines to mitigate fatality rates of future epidemics similar to COVID-19

- Higher health expenditure $\geq 7.6\%$ of GDP
- Higher government health expenditure per capita $\geq \$2,000$
- Policies of sustainable development to reduce air pollution (max 50 days per year)
- Timely application of selected containment policies in places and not general lockdown or quarantine

Figure 2. Factors determining a strategies to prevent negative effects of pandemic threats.

Finally, proposed ambidexterity strategies of crisis management for more prosperous or less favored countries are:

- *Rich countries* can focus in the short run on measures of containment of shorter duration because of a stronger healthcare sector based on high expenditures (as % of GDP), whereas in the long run these countries should support sustainable policies for reducing air pollution.
- *Developing countries* have to focus in the short run on measures of containment of a longer duration because of a weak healthcare sector based on low expenditures (as % of GDP) and in the long run they have to support public policies for enhancing health system and reducing air pollution.

Conclusions and prospect

Strategies of crisis management to prevent COVID-19 pandemic and similar epidemics are based on effective multi-level governance, combining both national, regional and urban strategies to provide timely policy responses for improving health safety in society (Anttiroiko, 2021). The experience of COVID-19 suggests that future infectious diseases of novel viruses can generate, more and more, a serious pandemic threat to public health of countries and their economies. New pandemics, similar to COVID-19, can emerge and spread rapidly and it is basic timely gathering and sharing of information and samples of novel viral agents for appropriate interventions to stop the emergence of epidemics. The preventive strategies have also to support the process of

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R&D directed to effective vaccines and subsequent production and distribution as soon as possible across countries to mitigate fatality rates and deterioration of economic growth and overall socioeconomic systems in the long run.

Nations have to design a crisis management team for managing strenuous situations given by pandemic threats and for making critical decisions to resolve, as far as possible, them. Successful crisis management teams understand the specificity of pandemic crisis and are thoroughly prepared for solving all problems and problematic situations. Moreover, in a crisis, leaders are expected to reduce uncertainty, providing an authoritative account of problems, solutions and difficulties. Moreover, leaders have to formulate a strategy and critical decisions to cope with pandemic crises that have to be accepted by other parties that have other positions and interests and are likely to suggest various alternative solutions and actions.

The global response to COVID-19 pandemic has pushed the boundaries on new and rapid pandemic responses in several areas, including healthcare system, vaccine research, health technologies, environment as well as development, manufacturing, distribution, allocation, and administration of innovative drugs and vaccines. These strategic actions of pandemic management have to trigger learning processes to support preparedness efforts of countries to advance timely public responses and efficient investments in R&D processes of innovative drugs and new pandemic vaccines (Ardito *et al.*, 2021; Coccia, 2019; Coccia & Watts, 2020).

Hence, strategies for pandemic threats have to be based on efficiency, flexibility, responsiveness and resiliency for decreasing negative effects of infectious diseases and in general of pandemics. Efficient crisis management in the presence of a pandemic threat is directed to three strategic goals:

- application of technological innovations and new technologies for improving actions to prevent the emergence of pandemics and/or to contrast vast diffusion of epidemics or pandemics
- acceleration of R&D of effective vaccines

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- finally, production on a vast scale of new vaccines and innovative drugs for countries worldwide to minimize socioeconomic issues and support recovery.

In the next years countries have to increase investments in equipment, organized infrastructures and education of human resources for improving preparedness activity to timely react in the presence of inevitable pandemics, also reinforcing international collaboration with key subjects for reducing negative effects on public health and economy (US Department of Health, 2021). Nations with international collaborations should also support scientific and technological paradigm shift to treat infectious diseases based on novel type of vaccines, such as messenger RNA vaccines, known as mRNA vaccines for high levels of protection by preventing diffusion of infection diseases in society. This new approach is different from classical approaches to vaccination. The scientific breakthrough of mRNA vaccines is founded on concept that the infective process itself is effective in raising an immune response and genetic engineering and biotechnologies can be utilized to construct virus-like particles from the capsid and envelope proteins of viruses. COVID-19 global pandemic crisis has accelerated the transition towards these innovative types of mRNA vaccines and leading companies in pharmaceutical sector are now focusing human and economic resources on vectored, subunit, RNA, and DNA platforms, respectively. The messenger RNA (mRNA) vaccines can jump the socioeconomic barriers of developing traditional vaccines, such as producing noninfectious viruses. Moreover, mRNA vaccines eliminate a lot of phases in manufacturing process for the development of these new drugs because rather than having viral proteins injected, the human body uses the instructions provided to manufacture viral proteins itself. mRNA molecules are also simpler to treat in labs than proteins. In short, mRNA vaccines are produced and manufactured by chemical rather than biological synthesis, as a consequence the process of development is much faster than conventional vaccines to be redesigned, scaled up and mass-produced. mRNA vaccines are being tested for other

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viral agents, such as Zika virus, and novel influenza, and as a consequence mRNA vaccine tools can be viable and quickly tailored for future epidemics similar to COVID-19.

Hence, in responding to constant pandemic threat of novel coronavirus in future, the international communities have to reinforce prevention and preparedness. In particular, nations and international organizations have to design and implement vital strategic actions, given by the improvement of the early warning system and timely containment operations. Moreover, the preparedness activities should reinforce the coordination of global science and research to accelerate the R&D and diffusion of effective pandemic vaccines and innovative antiviral drugs.

The strategic actions to prevent pandemic threats can be systematize as follows:

- Reinforce the early warning systems in the international community using existing infrastructures to ensure rapid detection of suspected cases in humans based on rapid and reliable international laboratories that receive all data and clinical specimens needed for an accurate evaluation of an emergence of pandemic risk
- Rapid containment policies to prevent that novel viruses increase the spread in human society or, whenever possible, delay its transmission dynamics in international community. New studies show that selected restrictions in specific places are better policy responses than full lockdown. Health policy should apply crisis management team and use global and regional stocks of antiviral drugs and other similar drugs to contain negative effects in society.
- Verify that all countries have designed and tested pandemic response plans and that international organizations are able to assume a leadership and provide clear guideline to coordinate nations during a pandemic. Developing countries having limited resources have to be supported in the development of pandemic plans to reduce gaps in basic capacities for

improving an equally and coordinated global response to a pandemic.

- Finally, nations should jointly invest and coordinate global R&D to produce pandemic vaccines and antiviral drugs that are rapidly and widely available as soon as the emergence of a pandemic and/or the diffusion of the novel virus. In particular, nations should identify priority research areas and foster funding to public- and private firms involved in R&D of innovative drugs. It is also important to gather and analyze more data on the use of established and new anti-viral drugs and vaccines for a safe administration of treatment and prophylaxis in all population. Foster partnerships among governments, regulatory authorities, universities, research laboratories, incumbent and new entrant firms can support R&D of novel drugs and in particular a timely vaccine manufacturing capacity that ensure equitable access across all nations. Moreover, R&D investments have to be directed to new vaccines conferring long-lasting protection against novel viruses and their variants. Finally, organizations and nations should foster scientific networks and laboratories to ensure that new scientific knowledge about an evolving pandemic and treatments has a rapid and wide-spread communication in real time worldwide.

These strategic actions have to achieve and sustain the main goal of reducing risk factors of epidemics and, in the presence of pandemics, providing whenever possible a vast immunological protection of people before they are exposed to a novel viral agents. Hence, the challenge is the environmental and social policies of prevention and the production of appropriate and safe vaccines that meet global needs shortly after the emergence of a pandemic to provide equitable access to all nations. In this context, nations have to support scientific institutions for R&D of new vaccines and the applications of new technologies that could prevent chains of trans-mission, increase vaccine supplies, timely vaccine delivery for a broad-spectrum and enduring protection against pandemics across population worldwide.

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These aspects are basic for a strategic approach to cope with pandemic threats and Evans & Bahrami (2020) suggest actions directed to super-flexibility and resilience (Janssen & Voort, 2020). Moreover, complex and unforeseen problems of pandemic crises should be treated with strategies of dissolution directed to eliminate sources of pandemic threats in society and improving the capacity of reaction of nations (Coccia, 2021a; Ackoff and Rovin, 2003; Coccia, 2021d). These strategies to prevent and cope with novel infectious diseases have to apply plans and decisions based on ecological rationality considering the specific context over time and space with a comparative evaluation of performance with leading countries applying alternative interventions. This comparative analysis can improve collective learning processes for effective decision making across countries in turbulent environments with pandemic crisis (Gigerenzer & Todd, 1999; Kahneman *et al.*, 1982).

In short, the development of these capacities can improve the world's ability collectively to defend itself against many emerging and epidemic-prone diseases. International experience for COVID-19 pandemic crisis has shown that well-planned public policies, scientific and economic coordination policies are effective interventions for reducing high-risk aspects during an outbreak.

Overall, then, a comprehensive strategy of crisis management for pandemic threats has to be based on environmental and socioeconomic factors, and new technology, and not only on parameters related to medicine, to help policymakers to evaluate manifold aspects to reduce institutional and social vulnerabilities to epidemics and design appropriate short-run and long-run plans to prevent and/or to contain the negative impact of future infectious diseases on public health, economy and society (Coccia, 2019; Coccia, 2015; Coccia & Bellitto, 2018). To conclude, in the presence of a constant pandemic threat, a comprehensive strategy to prevent future epidemics similar to COVID-19 has to be designed considering manifold factors of sustainability, environmental and socioeconomic sciences, and not only aspects related to life sciences, such as biology and medicine.

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Conclusion

This book here has tried to clarify some questions of COVID-19 pandemic to explain and generalize, as far as possible, some temporal and spatial aspects of the evolution of COVID-19 and effects of policy responses on socio-economic systems to improve the governance of countries to design an effective strategy to prevent future epidemics similar to COVID-19.

The results described in chapters suggest that the impact of COVID-19 and policy responses on health, social and economic systems depend on manifold factors, such as health investments, political systems of countries, level of governance, level of democracy, etc. The studies show that policymakers have had an unrealistic optimistic behavior that new waves of COVID-19 could not hit their countries and, especially, have, in general, a low organizational capacity to plan effective policy responses to cope with recurring COVID-19 pandemic crisis. As a result, inappropriate and delayed policy responses, and inefficient practices of crisis management to constrain the impact of new waves of COVID-19, associated with social and economic issues generated by previous effects of containment policies can again generate

Conclusion

negative effects on public health and, of course, socioeconomic systems.

The results show that extensive containment policies (i.e., national lockdowns) can create more damages than benefits in society and economic systems with uncertain effects on health of people.

Moreover, the positive effects of new COVID-19 vaccines to mitigate pandemic impact have been overvalued because of new variants of the novel coronavirus, vaccine hesitancy in society and other socio-economic problems. As a consequence, the complex problem of epidemic threats has to be treated and solved with interdisciplinary approaches in science, using, whenever possible the method of dissolution: it means to redesign the strategies and protocols to cope with future epidemics in such way as to eliminate the conditions that caused accelerated diffusion of COVID-19, thus enabling advanced nations to do better in the future than the best it can do today.

In this context, policy responses of containment need to be revised and focused mainly on specific places having a high risk to be COVID-19 outbreaks and never apply generalized interventions. In fact, new studies reveal that a minority of places (such as restaurants, gyms, etc.) can generate a large number of infections; as a consequence, selected containment measures in these places (e.g., restricting maximum occupancy, social distancing and compulsory wearing of facemask) are more effective policies than general lockdown and reduction of mobility. Moreover, some countries are stressing democratic society with restrictions to individual freedoms to increase the maximum share of people fully vaccinated by introducing green pass (or vaccine certificate or immunity certificate that here are used interchangeably) as a rule for entering in certain businesses and public spheres and/or use public transport or to go to work (as in Italy); this bureaucratic tool is creating a hot debate and manifold socioeconomic issues. Results here show that the effects of green pass regime, based on authoritarian rules, generate a moderate growth of vaccinations that disappears in the short-run, but it generates social issues for the reduction of

Conclusion

individual freedoms, the increase of discrimination of people in social, cultural and sporting activities, the growth of tensions between different groups, reduction of equity, trust and solidarity too. These policies applied are nurtured by institutional contexts having weak democracy and vague separation of powers, generating a critical problem of abuse by political authorities that if uncontrolled or made not accountable, can do great harm to society higher than (pandemic) crisis.

Hence, there are several challenges to such studies concerning COVID-19 pandemic and appropriate policy responses. Given the exponential growth of the literature in this research field, the next years should witness substantial progress in our understanding of infectious diseases in all its various guises and better clarify the effects of policies of containment and mitigation. On a broader plain, social studies have made great strides in developing a body of applied results that complements biological and medical studies to cope with future epidemics. There is every reason to suspect that this trend will continue, and the chapters in this volume strongly support that claim.

Overall, then, this book presents some new results of COVID-19 pandemic, whereas other topics need to be clarified. Especially, there is need for much more detailed research on how COVID-19 pandemic and similar epidemics evolve in the total environment and on long-run effects in society of strict containment policies and generalized vaccinations with new mRNA vaccines. These studies here and future knowledge can improve the governance and effectiveness on how treat patients, design policy responses, implement vaccination campaign with new drugs and apply new medical technologies directed to prevent and/or minimize the impact of future epidemics similar to the COVID-19 in society.

To conclude, this book can lay a foundation for the interdisciplinary studies to clarify complex aspects of the sources and effects of infectious diseases and related policy responses in human society.

COVID-19 Pandemic Crisis: Analysis of origins, diffusive factors and problems of lockdowns and vaccinations to design best policy responses Vol.2

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