Journal of
Social and Administrative Sciences
www.kspjournals.org
Volume 9 September 2022 Issue 3

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

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Abstract. The objective of this paper is to clarify, whenever possible, the determinants in the emergence of biological agents to improve aspects connected with public health and biosecurity. Case study of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is investigated to assess the likely emergence from a wildlife spillover and/or scientific research in labs with unexpected accident. Using a meta-analysis, results suggest that a natural spillover of SARS-CoV-2 that has generated more than 5.2 million of deaths, in analogy with natural disaster, seems to have a remote probability, instead a lab accident in the process of scientific research has a probability of occurrence of about 15-30%. These results here are important to support decision making of policymakers for global biosecurity strategies with appropriate responses to prevent the future diffusion of vital agents similar to SARS-CoV-2 in environment and society.
Keywords. Viral agent; Biological agent; SARS-CoV-2; Novel coronavirus; Zoonoses; Natural disaster; Lab accident; Laboratory biosafety; Biosecurity risks.
JEL. C52; L25; M14.

1. 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 and 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) incident in 2012 when six miners died with an unexplained viral pneumonia (cf., Rahalkar and 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 and Sirotkin (2020) argue that the etiology of this novel coronavirus is hardly known because the intermediate host for

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completing a natural zoonotic jump is not identified, and the application of research techniques of gain-of-function 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 and 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 and 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 laboratories . 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 responses to cope with and/or to prevent pandemic threats in society (Coccia, 2020, 2021b, 2021c, 2021i, 2021d, 2022).

2. 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) 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 and 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).

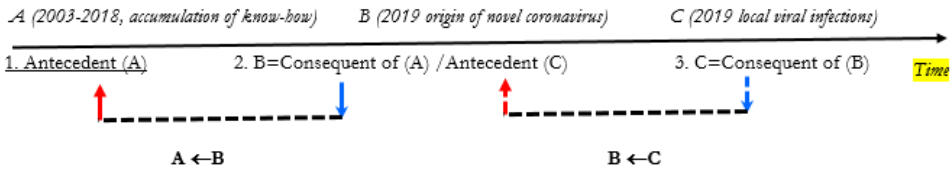

Figure 1. *Backwards changing to explain the emergence of the novel viral agent*

- 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 and Wang, 2016; Coccia and Finardi, 2012, 2013; Coccia an Bellitto, 2018;Coccia, 2018b, 2018c; 2020a, 2020b, 2020e, Haskins, 1965) . 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 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.

3. 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*

	1,000 fatalities per event	
	Exposure time	
	1 year	2 years
Disaster	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

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 and 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 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.

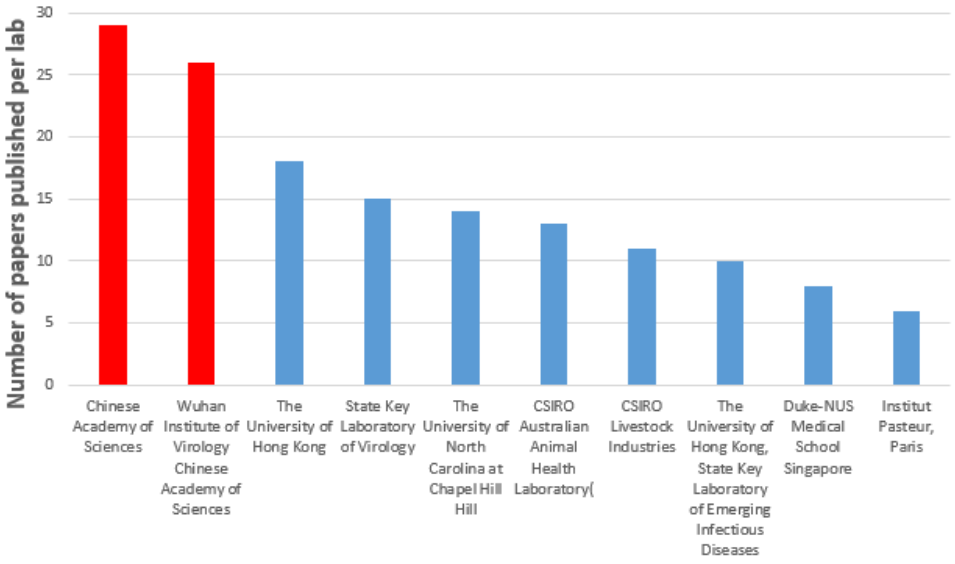

Figure 2. *Leading top 10 laboratories in performing scientific research on SARS-CoV from 2005 to 2018.*

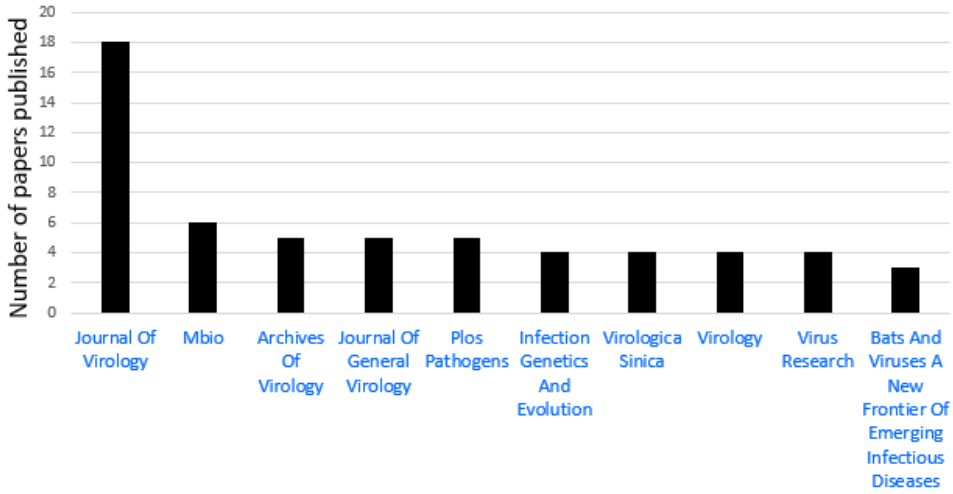

Figure 3. *Top 10 journals publishing scientific research on SARS-CoV from 2005 to 2018.*

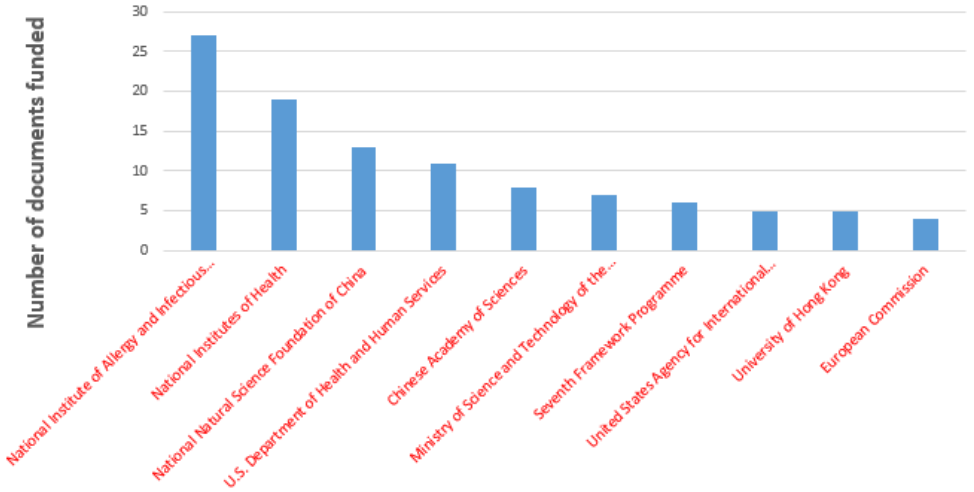

Figure 4. *Top 10 funding sponsor of scientific research on SARS-CoV from 2005 to 2018.*

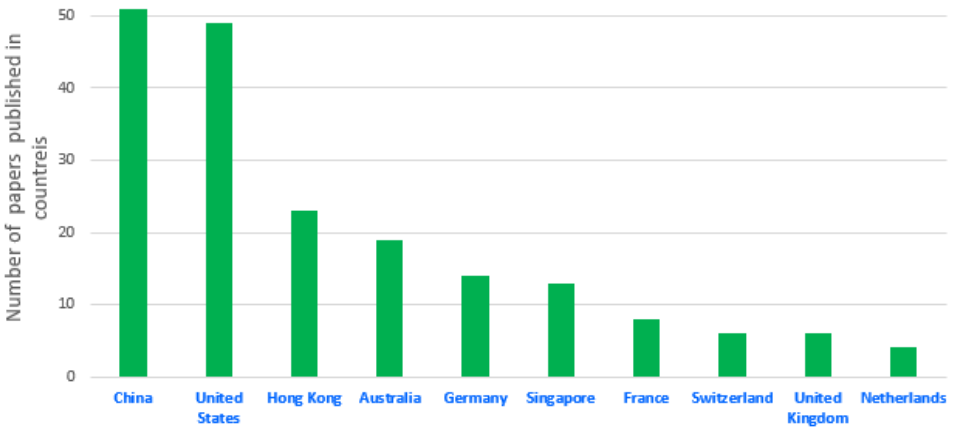

Figure 5. *Top 10 countries performing scientific research on SARS-CoV from 2005 to 2018.*

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).

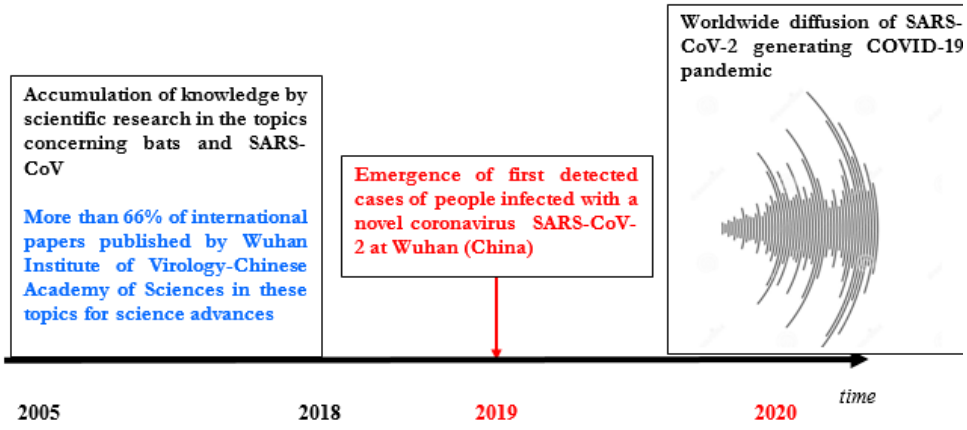

Figure 6. *Chronology of events associated with COVID-19 pandemic shock*

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.

4. Discussions

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 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 nations 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 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 and 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 and 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).

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

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

Ménard and 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 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). 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 and 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).

5. Conclusions

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 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, 2021l; 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 and 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.

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

Ge, X. Y., Wang, N., Zhang, W., Hu, B., Li, B., Zhang, Y. Z., Zhou, J. H., Luo, C. M., Yang, X. L., Wu, L. J., Wang, B., Zhang, Y., Li, Z. X., & Shi, Z. L. (2016). Coexistence of multiple coronaviruses in several bat colonies in an abandoned mineshaft. Virologica Sinica, 31(1), 31–40. https://doi.org/10.1007/s12250-016-3713-9

Ge, X. Y., Yang, W. H., Zhou, J. H., Li, B., Zhang, W., Shi, Z. L., & Zhang, Y. Z. (2017). Detection of alpha- and betacoronaviruses in rodents from Yunnan, China. Virology journal, 14(1), 98. https://doi.org/10.1186/s12985-017-0766-9

Hu, B., Zeng, L. P., Yang, X. L., Ge, X. Y., Zhang, W., Li, B., Xie, J. Z., Shen, X. R., Zhang, Y. Z., Wang, N., Luo, D. S., Zheng, X. S., Wang, M. N., Daszak, P., Wang, L. F., Cui, J., & Shi, Z. L. (2017). Discovery of a rich gene pool of bat SARS-related coronaviruses provides new insights into the origin of SARS coronavirus. PLoS pathogens, 13(11), e1006698. https://doi.org/10.1371/journal.ppat.1006698

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Zhou, P., Fan, H., Lan, T., Yang, X. L., Shi, W. F., Zhang, W., Zhu, Y., Zhang, Y. W., Xie, Q. M., Mani, S., Zheng, X. S., Li, B., Li, J. M., Guo, H., Pei, G. Q., An, X. P., Chen, J. W., Zhou, L., Mai, K. J., Wu, Z. X., … Ma, J. Y. (2018). Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature, 556(7700), 255–258. https://doi.org/10.1038/s41586-018-0010-9

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