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Meta-analysis to explain unknown causes of the origins of SARS-COV-2

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ABSTRACT

New Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes the Coronavirus Disease 2019 (COVID-19), an infectious illness that has generated a pandemic crisis worldwide. One of the fundamental questions in science and society is how SARS-CoV-2 has been originated to design best practices directed to prevent and/or to cope with future hazardous pathogens. The study confronts this question here developing a meta-analysis, which endeavors to explain, whenever possible, unknown sources of the SARS-CoV-2. Findings suggest that the natural spillover of novel viral agents that generate more than 6.00 M deaths worldwide in about two years (such as, SARS-CoV-2 from February 2020 to March 2022) has a remote probability of occurrence (using an analogy with the probability of natural disasters generating a lot of fatalities), whereas science advances on hazardous viral agents and consequential lab accident have a (higher) probability of occurrence (about 13–20% like in manifold lab accidents). The findings of this meta-analysis suggest the vital role of improving the technical guidelines of biosafety at all levels in laboratories during the development of scientific research of experimental virology on hazardous pathogens to minimize risks of pandemic threats in environment and human society.

1. Introduction

New Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes the Coronavirus Disease 2019 (COVID-19), which is an infectious illness appeared for the first time in late 2019 at Wuhan (China) generating subsequently a pandemic crisis worldwide (Anand et al., 2021; Bontempi et al. (2021); Bontempi and Coccia (2021); Coccia (2020), 2021; Coccia (2022); Li et al. (2020). One of the critical questions in science and society is if the sources of SARS-CoV-2 are due to a natural event of spillover from wildlife or if it is associated with human activity of scientific research (Andersen et al., 2020; Boni et al., 2020; Frutos et al., 2021; Relman, 2020; Sachs et al., 2020; Segreto et al., 2021; Wolfe et al., 2007). Bloom et al. (2021) argue that information provided initially by Chinese scholars and institutions on SARS-CoV-2 does not clarify if this new viral agent is associated with a natural (zoonotic) spillover from bats (through an intermediate host) to humans or if it is due to a possible accident in laboratory. Frutos et al. (2022) discuss some factors of the natural origin of SARS-CoV-2, such as the accident at Mojiang mine (China) in 2012 when six miners died with an unknown viral pneumonia (cf., Rahalkar and Bahulikar, 2020). In this context, Sirotkin and 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 clearly identified, and the application of research techniques of gain-of-function may be one of the possible sources of this new viral agent (Latinne et al., 2020; Malaiyan et al., 2021; Riou and Althaus, 2020). In fact, the molecular analyses of specimens raise further questions that suggest additional investigations of the sources of SARS-CoV-2 (Sirotkin and Sirotkin, 2020). Relman (2020) maintains that it is important to unravel the origins of SARS-CoV-2 to avoid next pandemics like COVID-19. Sirotkin and Sirotkin (2020) also point out that the origin of SARS-CoV-2 has important scientific aspects to develop effective drugs and apply appropriate treatments to cope with new airborne infectious diseases. Overall, then, COVID-19 is still circulating in 2022 with mutations of the SARS-CoV-2 but its origin is still an unknown problem (Casadevall et al., 2021).

The present study confronts this problem here by developing a meta-analysis to clarify, whenever possible, likely sources of SARS-CoV-2 considering either the possibility of a natural spillover or of a lab accident consequential to the activity of scientific research. This study is part of a large research project directed to explain factors determining transmission dynamics of COVID-19 and design effective policy responses and best practices to cope with and/or to prevent pandemic threats in human society (Bontempi et al., 2021; Bontempi and Coccia,

Abbreviations: Origins of virus, Origins of SARS-CoV-2.

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2021; Coccia, 2020, 2020a, 2021, 2021a, 2021b, 2021c, 2021e, 2021f; 2022, 2022a, 2022c, 2022d, 2022e).

2. Materials and methods

COVID-19 is still circulating in 2022 with mutations of the initial coronavirus (SARS-CoV-2)[1] and is generating continuous infections and deaths in manifold countries (Johns Hopkins Center for System Science and Engineering, 2022). The method of inquiry here is based on multiple working hypotheses (MWHs) that might clarify the origin of SARS-CoV-2, which is likely to result from several causes, not just one (Chamberlin, 1897; Coccia and Benati, 2018; Coccia, 2018). The method of MWHs considers and compares several factors to clarify the scientific problem under study here, including the possibility that none of them are correct determinants and that new explanations may emerge (Johnson, 1990; Railsback, 2004).

Firstly, the method of inquiry, based on MWHs, analyzes the sources of SARS-CoV-2 comparing two events: A and B.

- *Event* A. Natural (zoonotic) spillover of new coronavirus
- *Event* B. Accident of laboratory consequential to the process of scientific research on coronaviruses

Secondly, the proposed events A and B are investigated by a meta-analysis for a comparative evaluation of their probability of occurrence in environment and human society. In particular:

- Assuming the analogy between COVID-19 pandemic and a big natural disaster, the first event A is assessed with estimates of the probability of occurrence used for big natural disasters that generate a lot of fatalities (USGS, 2022).
- The second event B is analyzed by detecting the research activity of virology on coronaviruses in scientific publications until the year 2018 with a structured process of Boolean search of "bats and SARS-CoV" in the on-line database of Scopus (2022). The approach detects documents published in international journals in these specific topics by research institutions to find out an accumulation of knowledge for possible science advances in new coronavirus. After that, meta-analysis and systematic review are based on studies concerning accidents in laboratories of biology and chemistry to assess, per analogy, the probability of an accident of laboratory in the activities of scientific research in virology for science advances on novel coronaviruses.

Finally, results of meta-analysis are used to compare the probability of events A and B and to assess if event A is more probable or not than event B.

3. Results

- *Event A*. Origin of the SARS-CoV-2 with natural (zoonotic) spillover

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has generated from late December 2019 to March 2022 more than 6.00 million of deaths worldwide (Johns Hopkins University, 2022). This new coronavirus driving COVID-19 pandemic is assumed to be here a natural event similar to a big natural disaster. U.S. Geological Survey (USGS) assesses natural disasters forecasting life loses. In fact, USGS (2022) 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.

Disasters	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 means of all disasters	2.0	4.0

Sources: USGS, Natural Disasters—Forecasting Economic and Life Losses, https://pubs.usgs.gov/fs/natural-disasters/figures/fig9.html (accessed January 2022).

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 in a period of 2 years more than 6.00 M deaths worldwide or more than 958,400 deaths in the USA, like COVID-19, is infinitely small (i.e., probability of occurrence is a rare event). This basic meta-analysis suggests that the natural event of zoonosis of new coronavirus, which generates millions of deaths in a short period, has a remote probability of occurrence.

- *Event B.* Lab accident for science advances on novel coronaviruses

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). Discoveries are driven by a process of scientific research, accumulation of knowledge and learning that is irreversible and that can never go back (Coccia, 2022b; Science, 1965). Principal laboratories can support the process of science advances and accumulation in virology by fundamental research in general virology, clinical aspects related virology and research on emerging diseases. Many labs and institutions, before the emergence of the novel coronavirus, have developed a lot of scientific research concerning the relationship between bats and SARS-CoV, as detected with an in-depth search in the on-line database of Scopus (2022). In fact, at global level, from 2005 (first year available in the database of Scopus, 2022) to 2018 (before the emergence of COVID in 2019), there are 133 document results in the specific topic concerning "Bat and SARS-CoV". These studies have been published in main international journals, such as Journal of virology, Mbio, Archives of biology, Journal of general virology, etc. (Fig. 1).

Leading countries in this specific field of research are in Fig. 2. Hence, this meta-analysis suggests a process of accumulation of scientific knowledge in virology of 13 years (2005–2018) with more than one hundred publications on relations between bats and coronaviruses before the emergence in 2019 of the SARS-CoV-2 (see Appendix A for further results).

Manifold studies describe several high-profile accidents in research laboratories of biology, chemistry and related disciplines (Ménard and Trant, 2020). In fact, Hellman et al. (1986), examining almost six hundred 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 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 accidents of laboratory represented 18.4% of the total incidents reported at the Iowa State University. Moreover, Kou et al. (2021) argue that major accidents of lab that involve personal injuries or main property damages have to be reported by law, but a lot

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

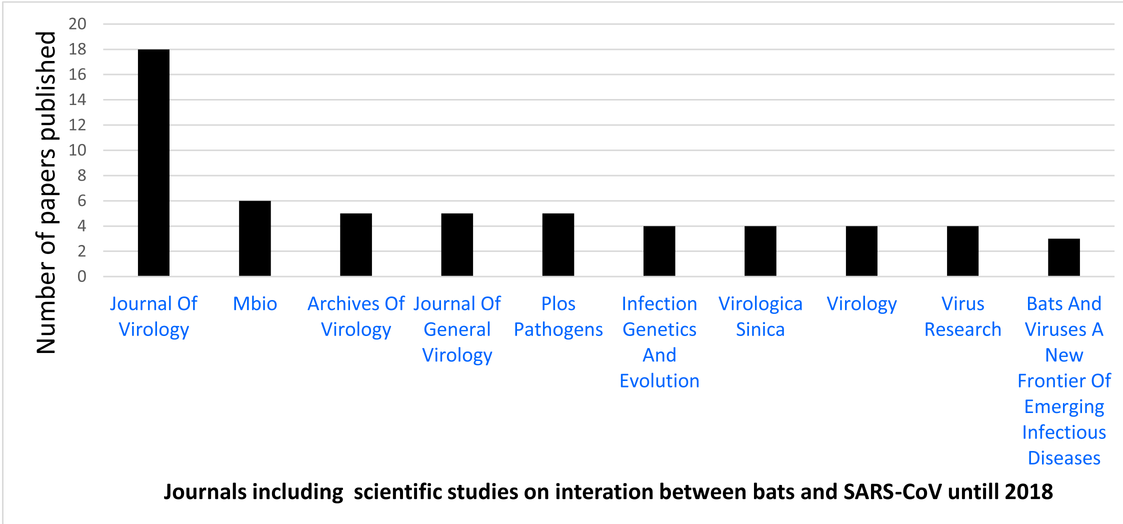

Fig. 1. Top 10 journals publishing scientific research on SARS-CoV from 2005 to 2018. *Source*: elaboration on data of Scopus (2022).

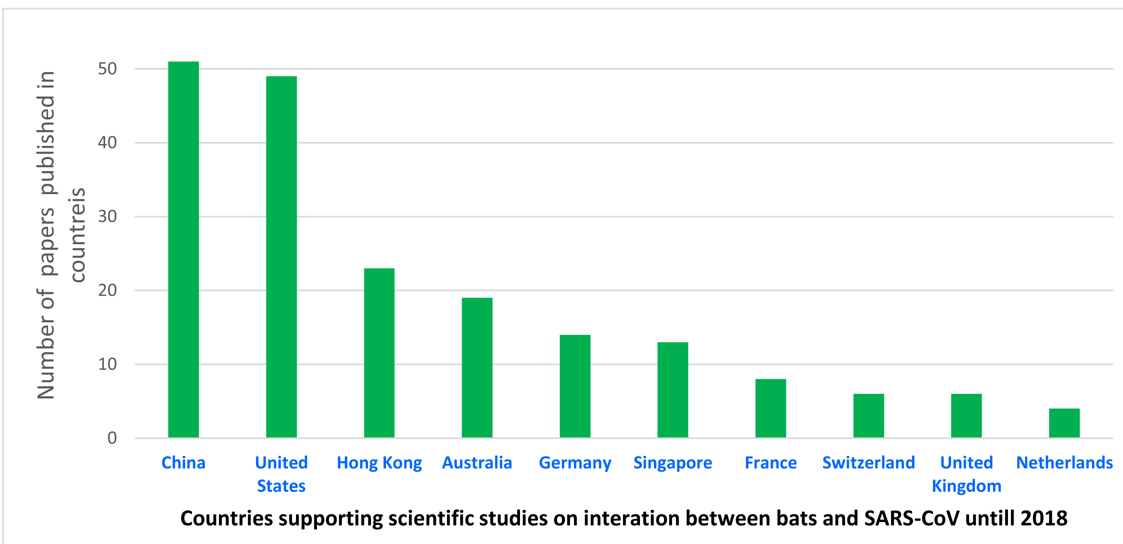

Fig. 2. Top 10 countries performing scientific research on SARS-CoV from 2005 to 2018. *Source*: elaboration on data of Scopus (2022).

of minor lab incidents or near misses concerning academic research tend to be not often reported. This study at Departments of Chemistry and Chemical Engineering & Materials Science in the University of Minnesota (USA) during 2014–2019 period (based on a platform of self-report safety stories occurring within the departments by researchers that were either directly involved with or witnessed a safety-related incident) reveals that the most frequently occurring hazards are: spill, fire, and equipment failures (Kou et al., 2021). Ménard and Trant (2020, p. 18) maintain that factors determining accidents of laboratory 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, these studies suggest that the sources of SARS-CoV-2 associated with a likely accident of lab and consequential diffusion in society seem to have a higher probability of occurrence.

Table 2 systematizes the results here showing a comparative analysis of the probability of occurrence of the events A and B under study here.

Table 2
Comparative probability of proposed events based on a meta-analysis.

Event A	Event B
Natural (zoonotic) spillover of new coronavirus	*Accident of lab in the process of research for science advances*
Average probability of occurrence of a big natural event generating more than 6.00 M deaths worldwide in two years	Average probability of an accident of laboratory in life sciences
≈0% (rare event, low risk)	**≈13–20% (medium risk)**

Source: personal elaboration by author (2022).

4. Discussions

The study here suggests that the natural spillover of new viral agents (e.g., SARS-CoV-2) that generate more than 6.00 M deaths worldwide in about two years (*event A*) is a rare event (using the analogy with the probability of occurrence of big natural disasters in environment that generate a lot of fatalities in human society; cf., USGS, 2022), whereas an accident of lab associated with scientific research on coronaviruses (*event B*) seems to have a higher probability of occurrence. In particular, zoonotic spillover of a new coronavirus from bats, through an intermediate host, to humans generating six millions of deaths over two years is a remote event because the nature is not an engineer that works with a conceived plan based on specific materials and equipment designed to achieve goals with its endeavors (Jacobs, 1977). Relman (2020) argues that the explanation of the origin of SARS-CoV-2 plays a vital role in forecasting future pandemics. If the natural spillover is based on convincing evidence of the casual event of SARS CoV-2 passing directly from bat to human, or through an intermediate host, then efforts of prevention have to be directed to improve the management of interactions between wildlife (and their ecosystems) and humans (cf., Latinne et al., 2020). In this context, Daszak et al. (2020) argue that to prevent next epidemics and/or a 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
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 source of new coronavirus is due to the process of 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. In fact, the event of likely accident of lab during the activity of research for science advances on coronaviruses leads to organizational aspects of the management of laboratories to improve the technical guidelines at all levels of biosafety in conducting scientific research and in performing tests on hazardous pathogens similar to SARS-CoV-2 for minimizing the risk of future pandemic crisis. Hence, international institutions, to prevent a pandemic threat of new viral agents, have to support R&D investments to reinforce the surveillance and biosafety procedures in public and private institutes of virology that study viruses and new viruses in order to avoid an accidently diffusion in surrounding environments with damages for population, vegetation and overall ecosystems (cf., Coccia, 2005; Mosleh et al., 2022; Roshani et al., 2021). In this specific field of research, international collaboration among scientists is a basic aspect to address these risks and support decisions of policymakers and R&D managers to prevent accidents of lab and therefore threats of future pandemics that create huge health and socioeconomic issues worldwide (National Health Commission of The People's Republic of China, 2020; Coccia and Wang, 2016). 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 various levels of organizations to better coordinate and allocate resources for targeted investigations and interventions to improve the biosafety of labs and facilitate a more comprehensive surveillance of risk for disease outbreak (cf. also, Jia and Yang, 2020). Moreover, the prevention and preparedness of pandemic threats have also to be directed to design and implement strategic actions of improvements of early warning systems in the international community using existing infrastructure to ensure a rapid detection of suspected cases of new virus in humans; moreover, international laboratories have to receive timely all data and clinical specimens needed for an accurate evaluation of emergence of pandemic risk. These best practices can be used at local and global level for reducing pandemic threats and consequential socioeconomic issues (Coccia, 2018, 2021d, 2022c, 2022d, 2021e).

5. Conclusions and prospects

The origins of new viral agents associated with future epidemics/pandemics pose, increasingly, fundamental questions for biosecurity and public health of nations and globally (Relman, 2020). A future pandemic similar to COVID-19 is not a question of whether will happen, but when it will happen. Impact of next pandemic will be determined by how well-prepared countries are when it occurs at any time with little warning, and how countries timely apply response policies (Coccia, 2021e, 2022d). Any delay in detecting and sharing new virus samples; and in developing, producing, distributing, or administering a therapeutic or new drug (e.g., vaccine or antiviral drug) could result in significant additional morbidity and mortality, and deterioration of socioeconomic systems (Coccia, 2021c, 2022a; Huang et al., 2021; Coccia, 2017). The findings of the study here suggest that natural spillover of new coronaviruses (e.g., SARS-CoV-2) that generate more than 6.00 M deaths worldwide in about two years has a remote probability of occurrence (using an analogy with the probability of big natural disasters generating a lot of fatalities), whereas the origin of an hazardous viral agent associated with an accident of lab during the process of science advances has a (higher) average probability of occurrence (about 13–20%, similarly to manifold lab accidents). For R&D managers of research institutions, hazard assessments in experiments of virology and incident reporting methods improve the research safety in the process of science advances (Coccia and Finardi, 2012; Coccia and Rolfo, 2000). In fact, academic and public awareness of lab accidents create valuable learning processes in organizations and institutions to prevent similar mishaps from happening in the future (Kou et al., 2021).

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 scientific activity of laboratory testing for hazardous pathogens, also because of classified information for national security. Second, not all possible confounding factors that affect the origins of this new coronavirus are taken into consideration and in future these factors (e.g., R&D investments and grants in these research fields, R&D performance, management of research institutes, international research collaborations, etc.) deserve to be analyzed for supporting results here (Coccia, 2003; Coccia and Rolfo, 2000; Coccia and Wang, 2016). Third, the lack of data to find parents additional genome sequences of coronaviruses and measurements of SARS-CoV-2 evolution under a variety of defined conditions (Deigin and Segreto, 2021; Segreto and Deigin, 2021; Kadam et al., 2021). Future research should consider new data and information when available, and to examine also other political and institutional factors associated with the process of science advances on new viral agents (Coccia, 2018a). Despite these limitations, results here show the critical aspect of production of scientific knowledge that is a main factor to support science advances in the field of virology but also the importance of best practices on biosecurity in laboratories to prevent accidents in dealing with hazardous pathogens (Wu et al., 2016; Zhang and Holmes, 2020). 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 and analyze relevant information and data directed to clarify unknown sources of new viral agents and to design appropriate best practices to prevent a pandemic crisis similar to COVID-19 (both if the SARS-CoV-2 is due to a natural spillover from wildlife and if it is due to the process of research for science advances and consequential accident of laboratory). In this context, science plays increasingly a significant role to explain sources of viral agents and cope with future pandemics with innovative drugs but it is also basic to invest in biosafety, in new technology, etc., to create the bedrock for possible crisis management. In particular, manifold factors of the origin of SARS-CoV-2 are not only related to medicine but also to other social, managerial, technological, political and economic sciences, and a comprehensive and interdisciplinary approach can explain causes, improve the biosecurity and support timely policy responses to prevent pandemics similar to COVID-19 and control negative effects of pandemic crises on public health, economy and society (cf., Ardito et al., 2021; Coccia, 2005a, 2015, 2017, 2019, 2019a, 2021g, 2022b; Coccia and Bellitto, 2018; Pagliaro and Coccia, 2021). Overall, then, the origins of the SARS-CoV-2 are still a question of hot discussion and debate between countries and scholars. Scientific investigation has powerful tools, but it is not enough to clarify the problem under study here because available data and information can provide only probable, not certain results about the sources of a new viral agent. To conclude, Relman (2020) provides farseeing words in this critical context for future science and society: “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".

Declaration of competing interest

The author declares that he has no known competing financial interests or personal relationships that could influence the work reported in this paper. This study has no funders.

Appendix A

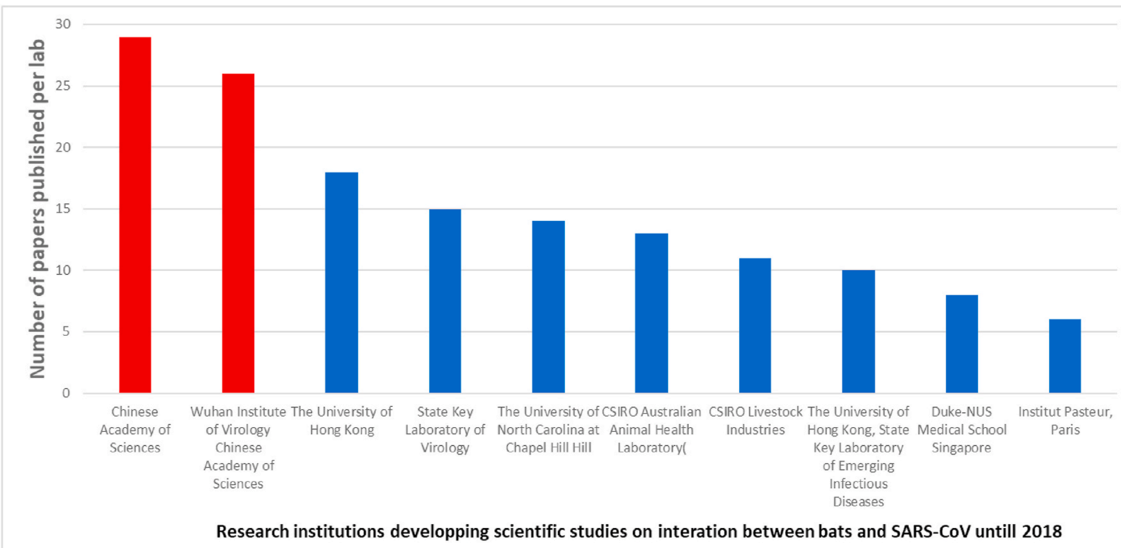

Fig. 1A. Leading top 10 laboratories in performing scientific research on SARS-CoV from 2005 to 2018. Source: Scopus (2022).

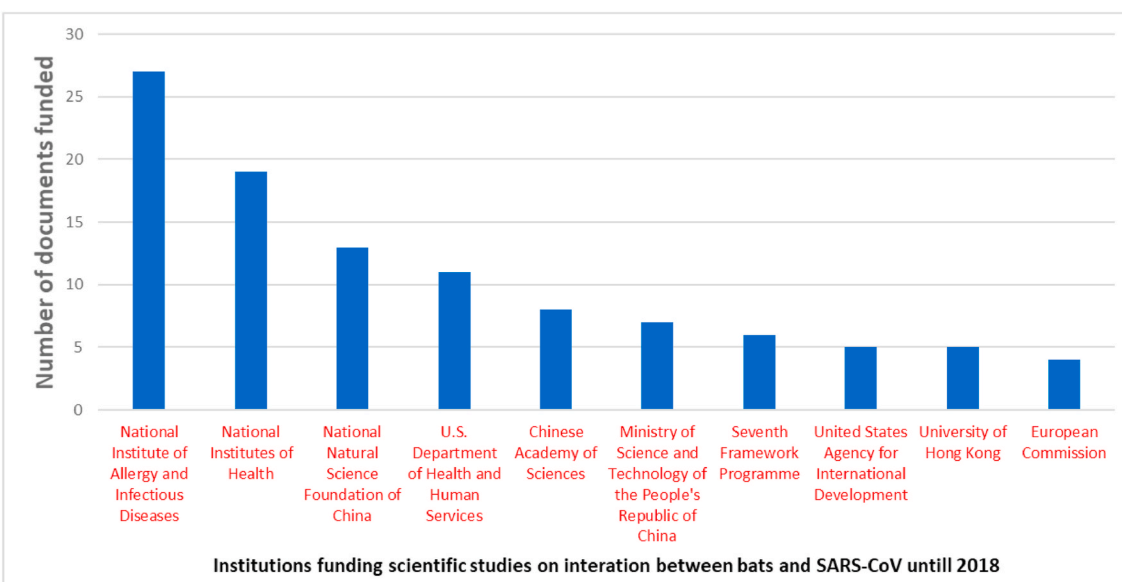

Fig. 2A. Top 10 funding sponsors of scientific research on SARS-CoV from 2005 to 2018. Source: Scopus (2022).

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