Introduction: COVID-19 Models and the Difficult Balance between Methods and Values

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The COVID-19 pandemic had an unprecedented impact not only on the socio-economic and political conditions worldwide but also on the practices of the scientific community and on the public image of science itself. The scientific community suddenly found itself in the spotlight and was pressured to rapidly produce evidence applicable to the management of the present health crisis. This in turn had some unexpected consequences, among which an increase of the publication speed and sometimes a decrease of the quality of peer review (see e.g., Chan 2020). At the same time, the public discussion of scientific issues related to COVID-19 among an audience often lacking the appropriate knowledge of the characteristics of modern science (e.g., critical reasoning, hypothetical nature of research, the role of uncertainty, …), was associated with the emergence of extreme stances in the population. These include distrust and refusal of the scientific authority, on the one side, and acritical scientism, on the other. It is plausible that such attitudes may have affected in a negative way the behaviors of people and their compliance to the preventive measures put in place to tackle the pandemic. In this respect, diffusion of knowledge about the way science really works and an increase of active participation in the critical-methodological discussion could be important for better managing the pandemic in the future. Who might start fostering a constructive and fruitful dialogue, and how to do so, is one of the crucial concerns from which this issue originates. Indeed, the pandemic has promoted an intense discussion between epidemiologists and philosophers of science (mainly, but not surprisingly, philosophers of medicine and epidemiology). This debate was mostly focused on methodological issues. The COVID-19 pandemic has obviously also prompted reflections by other types of scientists and philosophers. A notable example of plurality of perspectives is Boniolo and Onaga (2021). In this special issue we decided to focus on the epistemological and epidemiological views because we think they have proved of

Argumenta 7, 1 (2021): 9-17
© 2021 University of Sassari
ISSN 2465-2334
DOI 10.14275/2465-2334/202113.int

central importance in the last couple of years. Moreover, they can be of help—and often they cannot be ignored—also in evaluating contributions coming from other fields, such as bioethics, political philosophy, health policy assessment, and communication theory.

Since the very start of the pandemic, the lion's share of the debate was on the use and the utility of epidemiological models for the prediction of pandemic evolution and for supporting the decisions regarding the introduction of public health measures such as contact tracing, quarantine, and lockdowns. A thorough reflection on these models requires specifying what is the phenomenon to be modelled, the variables and the (causal) relations to consider, the optimal degree of realism/idealization, detail/abstraction of the model necessary to provide useful predictions and effective control strategies, the methods to evaluate the performance of models, the best way to communicate the results to inform policy decisions.

Epidemiologists use very different types of models to answer research questions typical of their field, but the most used ones are arguably the regression models. These methods are largely empiric, in the sense that they usually do not rely on strong a priori assumptions regarding the theoretical mechanisms behind the phenomenon being studied, but rather evaluate the association between independent variables (e.g., age, gender, smoking habit) and one or more dependent variables (e.g., risk of death) through a black-box, theory-free, approach. Some famous examples are the models for cardiovascular risk derived by the Framingham study (Mahmood 2014) and the plethora of models of cancer (Peto 2001), which are probably some of the hallmarks of modern epidemiology (Galea 2010). This tradition is rooted in what is sometimes defined as the "etiologic epidemiology of non-communicable diseases". During the Fifties, a new causal paradigm to explain the relationship between smoking and lung cancer was proposed and was then extended to most non-communicable diseases. This paradigm lies on the concept of risk factor to define a not necessary and not sufficient cause that increases the probability of an event to occur and found its consolidation in the so-called Austin Bradford Hill criteria, which base the evaluation of causality on observational data (Hill 1965). This second tradition of epidemiologic thinking evolved through the years, developing increasingly sophisticated methodological approaches (e.g., DAG, counterfactuals, etc.) to try to overcome the "original sin of non-randomization" and provide more robust causal inference from observational data (Vanderbroucke et al. 2016).

Interestingly, one of the effects of the COVID-19 pandemic in the scientific-philosophical debate has been to put in the spotlight a different type of models, which was substantially less common in epidemiology, namely the mathematical models of infectious disease. While the first examples of these models date back to the beginning of the 20th century, it was from the Seventies onward that these models gained a central role in infectious disease epidemiology (Koopman 2015). The main feature of these models is that they allow us to take into account the complex transmission dynamics of infective agents among the population, which is impossible using normal regression models.

Loosely speaking, models used for the prediction of COVID-19 trends can be divided into three broad groups (Adams 2020): compartmental models (e.g., SEIR models), individually-oriented models (e.g., Agent Based Models), and curve-fitting approaches. The first two groups include mathematical models that simulate the behavior of an epidemic based on a priori set of parameters' values.

The last group is more heterogeneous and includes models that estimate the values for the parameters directly from observed data. Differently from the models of the first two groups, curve fitting models are usually empiric (e.g., regression models based on the logistic function) or have a degree of theorization regarding the diffusion mechanisms of the agent substantially lower compared to compartmental models and agent-based models. This classification is obviously an oversimplification. In the real world, some models have features of both compartmental and individual models, and curve-fitting sometimes is carried out using compartmental models.

From the philosophical point of view, the debate on the use of models during the COVID-19 pandemic represents an interesting case study for at least three main reasons:

1) At the beginning of the pandemic, basic knowledge on SARS-Cov2 and COVID-19 (e.g., transmission rate, mortality rate, routes of transmissions, number of asymptomatic subjects in the population, and their role in the spread of the disease) was largely lacking (Bellan et al. 2020, Yanes-Lane et al. 2020, Caristia et al. 2020).
2) It was necessary to rapidly decide whether to implement public health interventions (i.e., lockdown) that would have substantially reduced personal freedom and possibly also had negative socio-economic consequences in the population.
3) The only quantitative results on which basing policy decisions were derived by complex mathematical models, lying on several assumptions, whose reliability was somewhat dubious even among the scientific community.

From this point of view, it is interesting to go back to a discussion on the reliability of mathematical models in COVID-19 started by the philosopher of medicine Jonathan Fuller during the first wave of the pandemic in May 2020. In a series of articles published in the *Boston Review*, Fuller (2020a, 2020b) suggests that two different traditions of epidemiological thinking, namely clinical epidemiology and public health epidemiology, have very different stances regarding what methodological approaches are to be considered acceptable to inform public health decisions during the pandemic. The former mainly refers to the principles of the movement known as Evidence-Based Medicine or EBM and the latter overlaps to what we previously defined as etiologic epidemiology. In particular, Fuller referred to John Ioannidis, professor of epidemiology at Stanford and well-known for his provocative meta-scientific contributions to the discipline, and Marc Lipsitch, professor of epidemiology at Harvard, as "champions" of the two traditions (Ioannidis 2020a, 2020b, Lipsitch 2020). The position of Ioannidis, which would be then largely stigmatized, was critical toward the use of models to support decisions on how to manage the pandemic, as they were felt by the author as based on low-quality data and based on types of studies not meeting the standards required by EBM. On the opposite, Lipsitch noted that in situations where uncertainty is high, time is scarce and stakes are high, it is necessary to consider any type of knowledge that could be useful to generate hypotheses and make predictions, including the theoretical knowledge coming from fields different from epidemiology and in general "weak" forms of evidence.

After almost two years from the beginning of this debate, the apparent contraposition from these two positions somewhat faded away (Fuller 2020b). It has become much clearer that it is useless to stick to dogmatic views about what constitutes evidence, and that, on the contrary, the peculiarity of the present situation requires exploring novel ways to better understand such a complex phenomenon and consequently to envision possible effective interventions. However, a general epistemic question remains somewhat unanswered: is there any way to thoroughly evaluate the knowledge coming from complex models, which are full of untestable (and often implicit) assumptions and approximations, and use it to inform public health decisions? This question, in turn, calls for further reflections regarding the values involved in such decisions ("is an intervention doing the best for whom?"). On this topic, see the conclusive remarks in Fuller (2020b, 2021) and the different communication strategies (e.g., is intelligibility for decision-makers a virtue of a model?). If anything, papers included in this special issue witness how the COVID-19 pandemic has discouraged a value-free vision of models and whole science in general.

The discussion launched by Fuller was not the only philosophical debate prompted by the pandemic. The journal *Nature* (June 2020) published a *Manifesto* for the correct use of models, written by a group of scientists and philosophers. The authors stressed that in many cases, the epistemic and social aspects of the use of modelling and of using models are not fully distinguishable. Model users should keep in mind that no one model can serve all purposes, as "results from the models will at least partly reflect the interests, disciplinary orientations, and biases of the developers" (Saltelli et al. 2020). Moreover, models can be inspired by different sets of values that should be explicitly declared by the modellers. In their conclusion, the authors made a plea for two things: (1) using models to question the world, rather than to provide definitive answers, and (2) allowing broad participation in the formulation and reflection on models. These two themes appear prominently in the contributions to this special issue, alongside "classical" themes in the philosophy of science. Consequently, the remarks on models that we present here can contribute to shedding light on how the pandemic has affected the way of doing science and philosophy of science.

The first of the aspects we have mentioned raises the question of the type of models adopted in the study of the spread of COVID-19. Olaf Damman's paper analyzes the explanatory function of a particular type of simulative model adopted in the pandemic, the ABM (Agent-Based Models). ABMs are non-deterministic models that simulate changes in populations over time based on the behavior of individual agents who interact according to rules defined in the program. Damman discusses three philosophical aspects of ABMs: their usefulness for causal inference as models of causal mechanisms, the question of whether they represent truly emergent phenomena, and their explanatory role. With regard to the third point, Damman argues that ABMs provide a particular kind of explanation, etio-prognostic explanation, of illness occurrence and outcome.

Till Grüne-Yanoff presents a reflection on what epistemic virtues should guide the choice of models, referring to a case study, the choice of a compartmental model by the Public Health Agency of Sweden (Folkhälsomyndigheten, or FoHM) in the first part of the pandemic. Grüne-Yanoff analyzes the considerations justifying the choice of a compartmental model, instead of an ABM model, by FoHM modellers. Although ABM can guarantee a higher degree of similarity to the target, compartmental models are simpler. The author argues in favor of the trade-off between similarity and simplicity discussing several epistemic virtues related to the latter. Interestingly, he includes ease of communication among epistemic virtues, which seems strange, since in general ease of communication does not seem to concern the creation of knowledge and therefore does not constitute an epistemic value. However, argues Grüne-Yanoff, ease of communication becomes an epistemic value when one considers the broad interdisciplinary nature of the teams of those called upon to build models to counter the pandemic.

As known, models can pursue various goals. Among them, representing causal relations is undoubtedly one of the main targets of models that are meant to drive decisions in the struggle against the pandemic: were we aware of the genuinely causal relations bringing about the disease, we would be able to intervene to either prevent or, at least, treat and cure it. However, looking for causes is not per se an easy task, nor does it rely on any univocal and universally shared understanding of what causes ultimately are and, even more so, where and how they are to be sought. Federico Boem draws some epistemologically relevant differences between proximate and ultimate causes, where the former can appear more clearly in front of us at present, whereas the latter are to be understood from an ecological, evolutionary, and socio-economic standpoint. His contribution advocates the idea that in such contexts as the COVID-19 pandemic modelling needs to combine different sorts of causes, including evolutionary and socio-economic factors, to reach an integrated understanding. Daniel Auker-Howlett and Jon Williamson, on their hand, focus their reflections on vaccination against COVID-19, stressing how local and social mechanisms can make a difference with respect to the assessment and refinement of vaccination intake interventions. Starting from recent epistemological reflections on causal evidence and what it can amount to in the context of Evidence Based Medicine—and, more specifically, stressing the advantages of the approach known as EMB+—Auker-Howlett and Williamson point out how the gathering of mechanistic knowledge and the elaboration of detailed mechanistic models can offer benefits for research on vaccination and lead to more effective interventions. Considerations on the relevance of genuinely mechanistic knowledge of how COVID-19 actually behaves are hence inserted in the wider debate on EBM, its pros and limits, and stress the importance of going beyond correlational knowledge.

Whereas Auker-Howlett and Williamson's paper highlight how, in the end, the applicability of results can be an extremely relevant guiding principle in the scientific enterprise, the contribution by Annibale Biggeri and Andrea Saltelli questions another epistemic virtue, precision, and in particular that expressed by the descriptions and predictions of the pandemic. However, the two authors point out that numbers are based on various assumptions, of which they do not guarantee the absence of bias. An emblematic example of how the precision of the numbers can mask controversial assumptions is given by the calculation of excess mortality during the first wave of the pandemic, defined as the difference between the total number of deaths and the expected number of deaths—i.e., the counterfactual number of deaths it would have been observed in absence of pandemic. As this indicator "depends strongly on the calculation of the expected death counts", it is strongly dependent on the assumptions on which the model is based. Here, the authors present a case study—a set of different estimates of the excess mortality during the first wave of the pandemic in Italy—to show how they varied under different methodological choices. In the conclusions, they suggest that the stimulus for a more careful analysis of the assumptions which underlie models could come from a new approach to the relationship between science and society.

These issues are also the focus of the contribution of Paolo Vineis et al. The authors highlight how in the description of epidemics idiographic, circumstantial aspects, such as chance, historical and geographical context, ..., count at least as much as nomothetic ones. Among the characteristic aspects of a pandemic there are factors belonging to heterogeneous categories but often linked by a relationship of mutual influence. The authors refer to Pierre Bourdieu's categories of different kinds of capitals: economic, social, and cultural capitals, to which should be added a "biological capital", including an "immunological capital". They point out that these categories should be considered in the construction of models, highlighting the ethical and political burden of models and measures aimed at countering the pandemic. How to make explicit and possibly formalize the consideration of values in model building is, the authors suggest, one of the new tasks that the pandemic seems to be assigning to us.

The contribution of Virginia Ghiara discusses even with more detail the particular aspects of the pandemic concerning vaccination policies. Ghiara emphasizes how the consideration of the 'mechanisms' defended by the authors who recognize themselves in the strand of research known as EBM+ is suitable for the assessment of effectiveness and efficiency of vaccines—both in the evaluation of potential pathways and future directions of research and in the analysis of vaccination behaviors, fundamental to design vaccination campaigns. A correct evaluation of these behaviors requires an analysis of the mechanisms of facilitation and impediment that influence vaccination behaviors in different social and geographical contexts. In this regard, Ghiara illustrates how the World Health Organization is promoting the collection of mechanistic evidence to understand the potential efficacy of particular vaccination interventions in different contexts.

Elena Rocca and Birgitta Grundmark devote their attention to pharmacovigilance, i.e., "the science of detecting and assessing possible adverse reactions from medical interventions". They discuss how the peculiar features of the COVID-19 pandemic—which, on the one hand, has provided us with unprecedented amounts of data and, on the other hand, has forced us to struggle with varied and uncertain evidence—call for a deeper reflection on the need of contributions from epistemology, ethics and philosophy of science in the understanding and managing of a crisis. Using critical thinking to tackle evidence and scientific success, one can better cope with uncertainty and deal with its challenges.

Given that, as recalled above, COVID-19 models have not only provided a theoretical understanding of the disease, but also guided political and economic decisions worldwide, and more or less successfully so, the very ideas of expertise and trust in science need to be brought into focus. Such ideas can constitute an essential terrain to discuss the interplay of epistemic and non-epistemic values in the construction and communication of scientific knowledge, bringing to light, on the one hand, the constraints under which science is pursued and the limits that can derive from them, and, on the other hand, why it keeps on being the most reliable form of knowledge. Why should society trust experts, and which experts should it trust? How is expertise achieved, how is it assessed, and what role does it play in the understanding of the pandemic and in the dissemination of scientific knowledge on the disease? Carlo Martini addresses questions along these lines, investigating possible ways of interaction between a model and expert options and different directions in which expert judgments can impact choices and uses of models themselves.

Cecilia Nardini and Fridolin Gross approach the topic of shared science from another perspective, that of bottom-up initiatives of independent citizens engaged in data production, data review, and, to some extent, model production. Such a perspective is typical of the so-called 'citizen science', to which current literature attributes two alternative modalities: the direct contribution of citizens to data collection under scientists' guidance, and the pressure on the scientific community to raise awareness on socio-political issues. Nardini and Gross analyze the activities of the community of non-professional users of COVID-related data on the software sharing platform GitHub and show that they cannot be framed in the two recognized strands of citizen science. Instead, they seem motivated by individual curiosity and the intent to improve the information received from the media.

Science belongs to society as a whole, and hence to citizens and groups, which have expectations with respect to science and its impact on their lives. Nicolò Gaj and Giuseppe Lodico's contribution deals with the dissemination and popularization of scientific outcomes regarding COVID-19, discussing scientism—as "a stance identifying science as the only reliable source of legitimate knowledge"—and its relations with naturalism and the debate on science's unity/disunity. A deeper analysis of such relations, with a stress on the plurality of methods and concepts adopted by science, can foster a better understanding of science's actual inner working and, hence, a more balanced public outlook on science, what it is and what it is not, its credibility in the social scenario, what we can and cannot expect from it. A subtle analysis of the whole range of methods and concepts put in place also in tackling the pandemic brings with it also a better understanding of what data and evidence amount to, how they can be gathered and amalgamated.

Alongside the issues of how data are produced and transmitted, we find the problem of how data are received. Years of research in the behavioral and cognitive sciences have made us aware that our perception of information and its use in decision-making deviate from the canons of classical rationality. Among the consequences of the COVID-19 pandemic, we can count a remarkable commitment of the social sciences in shaping the behavior of citizens towards the measures adopted by public health to ensure cognitive architectures capable of promoting bias-free behaviors. Not surprisingly, anti-vaccine behaviors have been a key component of this type of research. Stefano Calboli and Vincenzo Fano's contribution fits within this framework. After presenting what they believe to be the relevant psychological mechanisms in determining vaccine choice, the authors question the effectiveness of policy measures based on economic disincentives to vaccine refusal. The original explanation put forward by the two authors on the instances of the ineffectiveness of such measures is based on the tendency to keep as many options open as possible. The two authors outline an experiment to test their hypothesis, although they conclude with a call for epistemic caution in translating research findings.

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