Modeling Pandemic: Proximate and Ultimate Causes

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Abstract

In the understanding and prediction of a pandemic phenomenon, epidemiology is obviously the dedicated discipline. However, epidemiological models look at what we might call the proximate causes of the pandemic. On the other hand, the ultimate causes, those of an ecological, evolutionary, and socio-economic nature, are often too simplified or reduced to "minor" variables in epidemiological models. In this article, in dealing with a pandemic, we want to support the need to extend the study and design of responses to the ultimate causes and the disciplines that investigate them, with the hope of building an integrated approach for the future.

Keywords: Scientific modelling, Pandemic, Philosophy of medicine, Epidemiology, Ecology, Causation.

1. Introduction

The main goal of this article is to offer a different perspective on what are the possible *causes* of the COVID-19 pandemic. Generally (and in the first instance) the pandemic phenomenon has been approached as a medical/epidemiological problem. This is obviously understandable and also reasonable. In fact, this type of approach allows the scientific community and, in turn, policymakers to understand some salient aspects of the pandemic phenomenon that not only offer an epistemic advantage but are also essential to be able to think of strategies that aim to face and contain it.

From this point of view, it is therefore obvious that essential aspects are both the biological characteristics of the virus (such as its sequence) and the mechanisms and modalities of diffusion and infection. Specifically concerning phenomena of this type, scientific knowledge often focuses on the construction of *models*, both to explain and to predict such phenomena.

However this perspective, despite being visibly central and necessary, does not take into account those causal aspects of the pandemic that are more "distant" but must be seen as the context conditions that made the phenomenon possible in its actual realization. In this sense, specialists from fields other than medicine

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and epidemiology, such as theoretical ecologists, economists, and social scientists, have proposed to model the pandemic in the sense of trying to offer analysis for those factors that, even if of greater granularity, they are no less important or negligible.

The article is structured as follows. First, I will briefly present some established (to the scientific community) evidence about the nature of the SARS-CoV-2 virus and the pandemic. Secondly, I will describe what is generally meant by the activity of *modeling the pandemic*, especially from an epidemiological point of view. Next, I will introduce the distinction (originally developed by the naturalist Ernst Mayr) between "proximate causes" and "ultimate causes", and I will try to show how such a theoretical distinction can be useful in reference to the pandemic phenomenon. Fourth, I will present what I call the ultimate causes of the pandemic and what are the attempts at modeling them. Finally, I will try to show how these different aspects can contribute, not as alternatives but in a complementary way, in view of a broader, more complete, and adequate understanding of the pandemic.

2. Covid-19 Pandemic and SARS-CoV-2

On 11 March 2020, the World Health Organization (WHO) officially declared the Covid-19 pandemic. A pandemic is in fact a way of characterizing an epidemic that has specific characteristics. In general, the term, already etymologically, implies the tendency to spread everywhere and in a relatively short time. Therefore a pandemic occurs when some specific conditions are met. These are the presence of a highly virulent pathogen, the possibility of intra-specific transmission within the human species, and the lack of specific immunization towards the pathogen in the human population. Nevertheless, some experts point out that the term "pandemic" itself, although it may be still useful for communications in emergency situations, does not have a precise definition in quantitative and measurable terms (Singer et al. 2021). In this context, therefore, I will use the term "pandemic" in its broadest meaning (also according to the deployment of the WHO) of a global epidemic.

Faced with an emergency of this magnitude, alongside the studies that observe and try to describe the phenomenon, the other main activity of scientific research is to aim to figure it out. In other words, to understand its *causes*.

This, in turn, implies providing an explanation for the phenomenon but also building reliable predictions on its behavior. The two concepts, *explanation* and *prediction*, are obviously linked (intuitively, a well-founded explanatory model should also have good predictive power) but they must not be confused (Diéguez 2009, Douglas 2013, Findl and Suárez, 2021, Frigg and Hartmann 2020, Potochnik 2017, Shmueli 2010).

There are in fact, especially in disciplines such as computational biology, empirically predictive models but with little explanatory power. Conversely, explanatory models can be constructed that are not strictly predictive. Roughly speaking, within scientific practice, while explanatory models are those designed

to test causal hypotheses about abstract constructs[1], predictive models just aim to forecast the behavior of a phenomenon (Potochnik 2017, Shmueli 2010). I will come back to these aspects further.

As a matter of fact, when investigating the causes of the pandemic, it is clear that epidemiology (among other disciplines) must be addressed.

Epidemiology is a discipline (which arises from the encounter of different areas of research) that studies the frequency with which certain pathologies occur in different groups of people and concerns the reasons for such scenarios. Based on these analyzes, epidemiology then builds models to plan and evaluate interventions in order to counter the spread of a certain disease or to prevent or treat it in those subjects in which it had developed[2].

Epidemiology obviously interfaces with other research areas, especially in the biological and medical sectors. In the case of an infectious disease such as Covid-19, one of the first steps is to understand the nature of the pathogen, its mechanisms of spread and infection, and its evolutionary origin.

During its development, it was learned how the Covid-19 was *caused* by a specific pathogen, which was then identified and classified as SARS-CoV-2. The SARS-CoV-2 coronavirus is a viral strain belonging to the subgenus *Sarbecovirus*, of the coronavirus subfamily (*Orthocoronavirinae*). Such a group is quite well known among researchers. In fact, several members of this set of viruses are responsible for various diseases (such as the common cold), including also quite serious diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (Zhu et al. 2020, Sironi et al. 2020). In a short time, it was possible to determine the viral sequence of SARS-CoV-2, the main routes of diffusion, while there are still open hypotheses on its origin and on the steps regarding the transition to the human species (Sironi et al. 2020).

The surprise of Covid-19 must not suggest that pandemics are new phenomena. Pathologies of this type have accompanied the history of the human species since the Neolithic period. This period of human history is normally associated with the transition from a nomadic culture to forms of aggregation of a permanent nature. This is also the period in which the anthropogenic footprint on the environment has grown and the first forms of animal domestication are established. This step is essential given the zoonotic nature of Covid-19. Indeed, Covid-19 is a *zoonosis*, that is, an infection that originates in animals other than humans and is then transmitted to our species. This type of transmission can occur either directly (from species x to species Homo sapiens) or indirectly (through another intermediate species between the two). When this happens, we are in the presence of the phenomenon known as *spillover*. When a population of a given species, with its associated pathogens, comes into contact with a population of a different species, some pathogens of the starting species can adapt to a new species, generating a new form of the disease. Spillover is a fairly common occurrence in human history. In fact, over 60% of human viruses (including HIV and measles) are of zoonotic nature (Gibb et al. 2020).

[1] In saying this, I do not mean that the "causal view on scientific explanation" is the correct one. In making this distinction here I limit myself to describing a vision that is well represented within the scientific community (from the point of view of scientific practice) and thus not to take a position in the philosophical debate on this issue.

[2] See for instance https://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated/1-what-epidemiology (accessed April 27, 2021).

3. Modeling a Pandemic

As already stated, in order to *understand* a phenomenon (in the sense of being able to comprehend a part of its behavior in order to develop responses to it) such as a pandemic, alongside the biological characteristics of the pathogen and the knowledge on the functioning of certain biological mechanisms, scientists build *models*.

Without going into too much detail, a scientific model can be seen as some form of *representation* (for a more detailed discussion see Frigg and Hartmann 2020). In other words, models can be understood as forms of scientific representation that stand for a "portion of the phenomenic world", which is what one wants to represent [3]. Some scientific models are physical objects (enlarged or reduced) that represent the phenomenon under scientific investigation on a different scale. Other models instead try to capture properties of the object of scientific interest and to use analogous (even abstract ones) structures, often more manageable and manipulable, in order to act on the model and infer properties of the phenomenon or predict its behavior under certain conditions.

Accordingly, models must represent phenomena, but what does it mean that a representation is scientifically adequate? In fact, a good model does not always materialize by providing a faithful representation. Some models do not mimic the phenomenon to be represented but rather try to highlight certain properties (both to explain it and to provide predictions on its behavior). This is because, generally speaking, scientific modeling tends to display some kind of *idealization* (on this aspect see, among the others, Potochnik 2017). Philosophers have proposed and analyzed several types of idealization. As a matter of fact, for most of the philosophical debate, it is possible to refer to two main types of idealization: so-called the Galilean one and the Aristotelian one. Simplifying, the Galilean idealization implies a form of distortion in the analysis and the representation of the phenomenon (e.g. considering the spread of the virus in a uniform way over the entire population concerned). The Aristotelian idealization, on the other hand, involves building a model in which some relevant properties of the phenomenon are privileged, leaving out other real properties but considered not involved with its explanation or prediction (for example, understanding the rate of spread of the virus does not require detailed knowledge of its molecular structure).

Nevertheless, it is not necessary here to go into such details. Thus, by simplifying it, idealization in this context means that the model selectively represents certain properties of the object excluding others, or it operates distortions/simplifications.

Indeed, mathematical models, a kind of model largely used in epidemiology, are usually idealized models. Simplifying a bit, a mathematical model is a representation of a certain object, process, or phenomenon through a formal (and often quantitative) structure. There are obviously many ways to use mathematics to build a model, but in general, we can say that the construction of a mathematical model will start with the choice of some elements, considered fundamental, of the reference system and with the determination of the possible relationships between them.

[3] There is a debate whether all models should be seen as representations. For the scope of this paper there is no need to further develop this distinction. However, for a discussion of this aspect see Grüne-Yanoff 2013.

Thus, roughly speaking, in epidemiology a model is a mathematical construction trying to represent some parameters (considered relevant) involved in the genesis and subsequent development/behavior of the phenomenon studied, such as infectious diseases.

There are many different epidemiological models. One of the most used (also used to offer Western governments the first estimates on the behavior of the pandemic), is the so-called *compartment model*. Simplifying, this kind of model describes the progress of an epidemic on the basis of specific *assumptions* about the infection. Such assumptions, such as the mode of transmission or the infectious capacity of the virus, do depend on the *empirical data* collected. Thus, the stronger and more reliable the data, the more robust the assumptions will be. Subsequently, based on these assumptions, the population is divided into epidemiological groups or *compartments*. For an infection such as SARS-CoV-2, a standard model divides the population into 3 distinct groups: there are the *susceptible* (those who run the risk of becoming infected), the *infectious* (those who have already been infected and who can spread the virus), and *recovered* (which includes those who no longer transmit the virus, either because they recovered or because deceased). This standard epidemiological model is also called "SIR" (from susceptible, infectious, recovered)[4]. Normally, diffusion analysis is based on the first consideration that the risk of infection is an internal characteristic of the system. This means that the number of those who are infectious and those who can transmit the virus are the two initial factors to consider in determining the risk of infection. As a matter of fact, a model is a dynamic tool. Since the number of infected varies over time, it also affects the value given to the risk of infection. Obviously, this situation represents a simplified and idealized scenario. And it should be because it is a model. Indeed, in the real phenomenon, there are several other factors that influence the risk of infection. For example, specific health policy interventions, such as lockdowns, curfews, physical distancing, the obligation to wear masks, the prohibition of gatherings, etc., all have an impact on the progress of the epidemic. Surely, when building a model, not all the relevant factors could be known. Therefore, depending on the aim, a good model might need to be updated, to include some of these factors. However, the fewer parameters a model has, the more manageable and applicable it becomes. The choice of a model, therefore, depends on various factors and on trade-offs between different epistemic needs (e.g. applicability vs adequacy). Indeed, an effective model is obviously based on the collection of certain data. However, data alone do not say anything, since it is crucial to know where they come from and how to use them. Thus, it is also extremely important to find out where and how data have been originated, i.e. information on the collection strategy adopted for data is required. Next, data management usually implies certain formal tools (such as statistics). But statistical analysis cannot be simply applied out of the blue. Rather, it needs the choice of a model. In order to decide which model to use (a decision that might involve, as in this case, the need of a higher predictive capacity) it is fundamental to recall that every model is based on specific assumptions, degree of accuracy, and applicability. Assumptions are aspects given for granted that should serve as the empirical background. However, there will always be a tension, between those who are experts in the phenomenon (such as virologists and public

[4] https://nautil.us/issue/84/outbreak/whats-missing-in-pandemic-models (accessed May 2, 2021).

health scholars) and the modelers (such as theoretical epidemiologists, statisticians, etc.), on what aspects should be considered in the model and what elements can be neglected/reduced. Next, modelers themselves could disagree on the granularity and precision of their tools: i.e. the different values given to approximation. Finally, another source of the debate can come from discussions taking place when model outcomes become available, by considering the degree of applicability of the model (e.g. how much is similar to the target phenomenon or its manipulability in relation to its empirical adequacy) (on these aspects see, among the others, Frigg and Hartmann 2020, Potochnik 2017).

For example, a model with many parameters will need a massive amount of data and therefore will be more empirically supported, but perhaps it will be more difficult to build and less useful. Conversely, a model with few parameters will need fewer data to function and provide predictions, but its degree of distortive power will be higher and therefore it will be more difficult for it to provide robust indications. In this case (but it is not the only one) the difficulty of building effective (in terms of prediction) and accurate (in terms of empirical adequacy) models is given by the need (undoubtedly not easy), to harmonize constraints, methods, needs, and objectives of different disciplines (such as mathematics, virology, immunology, epidemiology, pharmacology, and medicine).

To understand how much a model is dependent on its assumptions, consider this case. In March 2020, the famous Imperial College model (the first to try to understand the Covid-19 epidemic) was produced by Neil Ferguson and his group (Adam 2020, Ferguson et al. 2020). According to this study, the Covid-19 epidemic, in the absence of specific containment measures, would have produced (in the following months)[5] around 510,000 deaths in the UK and more than 2 million in the US. This data also did not include the possible deaths resulting from the impact of the epidemic itself on the health system. Concerning the Italian situation, the model predicted more than 250,000 deaths (in total), if a strict lockdown had not been applied. The same model estimated, in the presence of quarantine, up to 30,000 deaths in a peak week with as many hospitalizations in intensive care (Ferguson et al. 2020).

Fortunately, this model turned out to be quite wrong in the predictions. However, this is not because the scientists worked improperly (or at least it is not just that), but because of the types of *assumptions* made. For instance, concerning the Italian case, the model assumed that children transmitted the infection exactly like adults. A fact that has proved false, but which was not known at the time of modeling and which was not so foolish to suppose. Furthermore, the model considered the Italian territory too homogeneously, treating high-density regions in the same way as the less populous ones. Finally, given the health fragmentation of the country (for which health policies and their organization are organized on a regional basis), the model did not consider the differences in response possibilities and resources between the different regions.

Indeed, a few months later Ferguson commented that the first model was being adapted from an earlier model used to simulate a flu pandemic. Given the need to generate a model in a short time, but being in the absence of specific data (such as the characteristics of the virus, etc.), it was necessary to build it starting from some *previous assumptions*, considered reliable and of a similar nature (e.g. a pathology which has many characteristics similar to Covid-19) (Chawla 2020).

[5] Roughly, from April 2020 to August 2020.

As a matter of fact, the problems concerning the construction and the application of the model show very well how real the potential risk of *scientific induction* is (but also how difficult it is sometimes not to take it).[6]

4. Epistemic Issues with Models: Causality

Regarding epidemiological models, the physician and philosopher Jonathan Fuller highlighted how the difficulty of modeling something like a pandemic also lies in some crucial *epistemic choices*. For example, the spread of SARS-CoV-2 obviously depends on the mechanisms of infection of the virus (and therefore on the interaction between these and human biology) but also on human behavior. Indeed, according to Fuller,

> Yet more sophisticated disease-behavior models can represent the behavioral dynamics of an outbreak by modeling the spread of opinions or the choices individuals make. Individual behaviors are influenced by the trajectory of the epidemic, which is in turn influenced by individual behaviors (Fuller 2020).[7]

This also means not only thinking deeply about the assumptions that are made and why they are made, but also trying to use different models to capture diverse aspects of the phenomenon. As Fuller recalls, alongside the compartment models, *multi-agent models* were also used during the pandemic, which tries to capture and represent the behavior of individual citizens (also in response to the different contexts in which they operate), and *curve-fitting models*, which on the basis of the trend of infections, considered similar in certain aspects, build possible scenarios on the current one.

Leaving aside other problems, the question I want to address here is whether these models offer any representation of *causal* links. In other words, whether these epidemiological models are *causal models*. Before doing this, certain theoretical premises should be discussed.

The concept of *cause* is as central as it is ancient in philosophical reflection. Simplifying, by "cause" it is generally meant something or a process that determines a certain effect. In other words, the cause would represent the origin or the condition of possibility of the occurrence of another fact. However, this conception (in the simple sense of elements, being either processes or objects, such as "A causes B"), although it captures aspects common to all causal accounts, remains too vague to be applied operationally. Therefore, looking at the differences between the various ways of understanding the notion of cause, it is quite evident that the literature on the topic is boundless. Leaving aside David Hume's famous (and still relevant) foundational critique of the notion of causality (linked to the assumptions on the regularity of nature and therefore connected to the problem of induction, see footnote 6), in the contemporary debate it is possible to distin-

[6] The problem of induction, briefly the question concerning the degree of certainty to be ascribed to the results obtained by inductive reasoning, is one of the central problems of the philosophy of science and scientific methodology. Obviously, this is not the place to examine this issue in general. For a more in-depth discussion see Henderson 2020, Henschen 2021.

[7] https://nautil.us/issue/84/outbreak/whats-missing-in-pandemic-models (accessed May 20, 2021).

guish at least five lines of research on causality: the *probabilistic* account, the *manipulative* one, the *mechanistic* one, the *counterfactual* one and finally that the *causal networks* (for a more detailed discussion on these aspects see Campaner 2011, 2012). From the point of view of scientific practice, as regards the construction of models, the employed idea of causality is not always made explicit.

Moreover, as far as diseases (and therefore epidemiology) are concerned, the concept of cause is not static, but also reflects a historical development. Thus, it is possible to briefly outline both the evolution of the idea of *causality* and how it is represented. By looking at the development of medicine as a modern discipline and especially considering epidemiology, the type of account generally adopted, more focused on the description of health determinants and risk factors rather than their underlying mechanistic understanding, has been progressively accused to display, concerning causation, a lack of adequacy (Campaner 2011). This is also due to the fact that, in the past, scientists and physicians were prone to reduce causal factors to simple, monadic, proximate, and detectable ones (such as the presence of a specific pathogen as in the Koch's postulates). Moreover, the single individual as such has been, traditionally, the main focus (both in terms of investigation and explanatory target) of epidemiology, this resulting in a diminished consideration of other determinants of health and disease. On the contrary, disciplinary advancements have instead promoted a more dedicated interest in groups and populations (especially in relation to infectious diseases) making epidemiology a central discipline for hygiene and public health policies (Campaner 2011).

Indeed diseases seem not to be entirely explainable assuming they are mainly determined by a single *factor.* Indeed, there are cases in which the cause of a condition, such as smallpox, is somehow simple since no smallpox can take place without the peculiar virus presence. However*,* advancements in clinical research have shown how the *causes* of a disease (in the plural) should be rather seen as a set of *sufficient conditions*, which generate favorable scenarios for the development of the disease.

Following this perspective, in 2005, Rothman and Greenland argued that the attribution of causality, in epidemiology, should not be conceived as the top-down formulation of criteria aimed at determining the presence of a certain effect, but as the "measurement of an effect" (Rothman and Greenland 2005). Roughly speaking, Rothman and Greenland claim that the origin of a disease can be traced back to a "sufficient causal complex" (pictured as a "pie"), which is represented by the composition of several constituent causal factors. Accordingly, if all those factors occur together, then the disease process initiates. This complex is then a necessary requirement for the disease.

Despite its success and adoption by many epidemiologists, this perspective on causality has been criticized by Vineis and Kriebel (2006), suggesting that the situation depicted by Rothman and Greenland is certainly a possible scenario but it is also too reductive. Indeed, it is usually the case that the association of several factors is more complex than "a single pie", meaning that there might be several different sets of causes capable of forming a "sufficient causal complex" for the same disease.

Furthermore, the situation is even more complex when attempting to distinguish between the causal dimension of the disease as a single occurrence in a given individual and the disease in its occurrence at the population level. Concerning this point, Vineis and Kriebel (2006) in fact argue that there is no doubt that, on a population level, certain phenomena, such as tobacco consumption,

constitute a causal factor of certain forms of tumors (particularly lung cancer). However, it cannot be always stated that a particular case of this type of disease is necessarily attributable to smoking.

This is, for instance, the case of the famous "hallmarks" of cancer (Hanahan and Weinberg 2011). These hallmarks should be conceived as those factors which, both individually and in combination, can determine the onset of neoplastic pathologies. Indeed, these hallmarks are elements that raise the chance to develop such a condition at a population level, but it may certainly be the case that a single patient does not present most of them. This is also because, when dealing with the causes of a disease, it is extremely difficult to discriminate between variables that can serve as determinants or confounders of the causal pathway leading to the onset of a clinical condition (Vineis and Krieber 2006).

Similarly, Hill's famous criteria can be read in this light (Hill 1965). In summary, these criteria are *temporality* (the cause must precede the effect); *consistency* (the association between risk factor and disease must be confirmed in different contexts); the *strength of an association* (ie an association between a presumed determinant of disease and the disease itself can be more or less "strong"); *specificity* (the constancy with which a specific exposure produces a given disease, obviously, the more the biological response to the presumed cause is constant, the more likely it is that the latter is an actual cause); *biological plausibility* (i.e. the fact that the alleged cause is likely to be framed in the context of biological knowledge on the subject and on the pathogenesis). According to a recent study (Shimonovich, Pearce, Thomson et al. 2020) rather than conceiving these criteria as conditions of causality, it would be more appropriate to think of them as *aspects* that must be taken into consideration when talking about causes.

Simplifying, we could say that, from a methodological point of view, epidemiologists would consider an empirical relationship (between a disease determinant and a parameter of occurrence) as causal, when it persists even after verifying (in principle) all possible confounding effects. Discriminating real causal effects from confounding factors may not be an easy task. Among others, a particularly interesting modeling approach in dissecting causal aspects from confounding effects is the one based on *direct acyclic graphs* (DAGs). In those statistics models based on DAGs, the graph nodes are the possible elements in play, while the arrows represent causal effects. Those models can be useful in offering a better representation of the causal paths, on which to build a quantitative estimation/strength of the association.

Philosophically, the question here concerns the confrontation of different and alternative causal accounts. On the one hand, in fact, it is certainly possible to try to derive knowledge of a causal nature starting from statistical models. This can be done, for instance, by assuming some form of a theory of causality based on regularity and therefore probabilistically tractable (see, among the others, Hájek and Hitchcock 2016)

However, it is also important to point out that *biologically significant* phenomena do not always mean *statistically significant* phenomena. This means that it is not always possible to capture relevant biological relationships, of a causal nature, through purely statistical methods. In other words, it is very difficult to derive all relevant causal connections concerning a biological phenomenon, deriving them simply from models of a purely statistical nature. This is because statistical models, based on the analysis of variance, have no direct way of discriminating (even

qualitatively) the nature of the diversity of biological interactions. Indeed, considering the complex relationship between biological objects and their interaction with the surrounding environment (a bio-ecological relationship for which organisms shape the environment and are in turn modified by it), Vineis and Kriebel directly report:

> [A]nalysis of variance will correctly correspond to an "analysis of causes" (i.e., quantifying the relative importance of the main effects of genes, environment and their interactions) only when: (a) environmental exposure-response relationships are linear for individuals with each of the different genetic polymorphisms, and (b) the study includes a sufficiently broad range of exposures to provide statistical power to detect an interaction (Vineis and Kriebel 2006: 5).

The study of biological and ecological interactions, as determining factors in the onset and development of a disease, is therefore crucial for a causal investigation in epidemiology. On the one hand, the development of models capable of capturing the diversity of possible interactions is certainly central (probably different models will be more suitable for certain interactions than others). However, as Vineis and Kriebel (2006) recall, it is good to remember that interactions cannot be totally captured and consequently modeled by an approach that reduces them to elements that can be manipulated with statistics. Even the theoretical modeling in epidemiology, although it must be idealized and abstract for the explanatory and predictive purpose, cannot ignore a deeper knowledge of what are the biological and ecological notions of causality, concerning the phenomena in progress.

Finally, as Fuller recalls (2021), in the case of compartment models, such as those adopted to model Covid-19, there is also *epistemic friction* involving a clash between diverse accounts of causation. According to Fuller, this friction occurs because, on the one hand, those models are conceived as *causal* (by virtue of their formally representing the mechanism of infection and spread of the virus), and on the other hand not all scholars would admit that simple manipulation of the parameters of such models allows making *causal inferences* (with which to discover or determine new "causes" (previously unknown) regarding the pandemic). This is because compartment models can provide causal explanations when the underlying mechanism (which they are based upon) embeds a form of interventionist/manipulative causal account. Thus, playing with the "gears of the mechanism", such as the adoption of a particular policy as physical distancing or the use of masks, it is possible to evaluate their causal role in terms of produced effects. However, as Fuller recalls:

> [T]hese estimations simply involve manipulating model parameters and comparing what falls out of the model under different values, and 'causal inference' is typically thought to combine causal information with non-causal information to infer a novel causal conclusion. Thus, the idea that compartment models are causal models may be in tension with the idea that on their own they can do causal inference. If they are purely causal models, then we may intuitively think that we cannot infer new causal knowledge simply by manipulating them; any causal conclusions we derive must in a sense already be contained within the model. While we can hang on to the commitment that compartment models are causal models by accepting that manipulating parameters generates causal predictions and retrodictions rather than so-called causal inferences, it may be difficult to shake

> the intuition that we learn about novel causal relationships (including their quantitative strength) by tweaking model parameters (Fuller 2021: 47).

In researching the causes of the pandemic, therefore, one requires, as Fuller also suggests,[8] the need to think philosophically. This definitely means to adopt a general, critical attitude towards data and methods, but it may also mean taking a step back, and asking what kind of question is that which concerns the causes of a biological phenomenon (and thus also reflecting on possible different accounts of causation). Such a "mode of thinking" also entails (probably) going beyond the confines of epidemiology as such. However, it is to be hoped that these aspects can then be adequately included in epidemiological analysis.

5. Ernst Mayr's Revisited: Ultimate and Proximate Causes of a Pandemic

In 1961, the famous naturalist Ernst Mayr published an article (which later became a classic) on the concept of cause in the life sciences. Mayr proposes the idea that there are essentially *two types of cause* in biology. To better put it, he argues that there are two epistemic accounts of causal investigation in biology, irreducible to each other, both fundamental and, in a sense, complementary.

Following Mayr's terminology, a cause can be "proximate" or "ultimate". The proximate causes answer the question about *how* a particular phenomenon occurs. Mayr seemed to have in mind that proximate causes capture a sort of mechanistic causal link[9] precisely because they deal with mechanistic representations that allow scientists to unravel how certain phenomena take place) (Mayr 1961). For example, a proximate cause of SARS-CoV-2 infection is to be found in the "spike" protein that allows the virus to "enter" a certain type of cell. Another proximate cause might concern the mechanisms of diffusion through small particles of liquid contained in breathing or in a sneeze.

On the other hand, we have ultimate causes. It answers the question about the *why* of a given phenomenon. In this perspective, the ultimate causes, therefore, aim to explain the pandemic not in its etiological-epidemiological mechanisms but rather in the reasons/conditions that allowed such a global epidemic to take hold. According to Mayr, the ultimate causes are often the evolutionary causes of a certain biological phenomenon.

The exquisitely epistemological dimension of Mayr's account is evident. Indeed, the naturalist does not place the understanding of a biological phenomenon as a choice between these two alternatives. Rather, he argues that if the causes of a certain biological phenomenon are to be understood, it is essential to recognize that different causal links answer different questions, distinct but complementary, and that also answer different research methodologies. The composition of these perspectives would allow us to offer an understanding of the phenomenon in its complexity.

The distinction made by Mayr has greatly shaped the epistemic attitude of biologists from the second half of the twentieth century onwards. For example,

[8] https://nautil.us/issue/84/outbreak/whats-missing-in-pandemic-models (accessed May 2, 2021).

[9] In the sense of the physiological mechanisms that "govern the responses of the individual (and his organs)" (Mayr 1961: 1503).

even today, many scholars see molecular biology as a discipline that investigates proximate causes while evolutionary biology investigates the latter. The distinction is both extensive and much debated. While some recognize that it still captures a fundamental insight into causal aspects in biology, others argue that too rigid a reception may even hinder the development of research (Laland et al. 2011). It is also worth remembering that some of Mayr's concerns and observations also depend on the state of research in the 1960s. For example, as we saw in the previous section, more refined models (such as DAGs) allow us to easily represent situations with numerous causal factors. Particularly in epidemiology (which Mayr was not an expert of), as we have seen, the diversity of approaches and methods made possible a refined modeling, able to grasp and manipulate otherwise intractable relationships.

However, it is a fact that the epidemiological models adopted, although they have tried to include more and more variables of a socio-behavioral nature, have not, in Mayr's terminology, properly investigated *why* Covid-19 has become a global threat. In other words, the evolutionary and ecological aspects of the pandemic, although not neglected, did not constitute precise variables in the modeling.

6. Why Covid-19?

The ecological and evolutionary perspective on the pandemic seems to somehow confirm Mayr's proposal. If it is obvious that to act against the spread of the virus it is appropriate to work on the proximate causes of Covid-19, the possibility of preventing such a threat from happening again, and with this magnitude, lies in understanding the root causes. In other words, acting on proximate causes means on the one hand building models that allow the development of specific interventions, represented by specific variables, which can change the course of the infection, and on the other hand, working on the production of drugs and vaccines that defeat the virus itself in infected people and reduce the possibility of new infections. However, these approaches necessarily neglect the ultimate causes of the pandemic. In other words, to prevent a new pathogen from having such a great impact, it is necessary to pay attention to both the evolutionary dimension of viruses and their ecological dimension. Furthermore, this also involves trespassing into other disciplines. The economic production system, especially in Western countries (with the associated lifestyles) has been severely tested, as well as the organization of health systems and the very idea of public health policies.

In fact, according to a report by the United Nations Environment Program (UNEP) and the International Livestock Research Institute (ILRI), addressing just the proximate causes means, in fact, treating the health and economic *symptoms* of the pandemic but not its *causes* (UNEP and IRLI report 2020).[10] Instead, the causes are to be found in the disruption of ecosystems and the impact of human species on the environment. Limiting ourselves to containing the virus, mitigating its effects, or even eliminating it without having to deal with the organization of economic framework, public health policies, and without heavy interventions on the environmental contexts that create the conditions for *spillover*, we will soon find ourselves faced with other pandemics. The report states that the number

[10] https://www.unep.org/resources/report/preventing-future-zoonotic-disease-outbreaks-protecting-environment-animals-and (accessed April 28, 2021).

of "zoonotic" epidemics is generally increasing worldwide. Several new pathogens cause 2 million victims every year, mainly in the poorest countries. However, precisely for not having investigated the ultimate causes of the pandemic (and of other pandemics), the (Western) world found itself unprepared for the latest pandemic. Accordingly, Covid-19 has been treated as a purely medical problem, with repercussions on the economy and on people's lives but not as an ecological issue. According to ecologists, however, its origins are in the environment, in global food systems, and in the interactions between non-human and human-animal species (Gibb 2020). In particular, ecologists argue that the global expansion of agricultural and urban land (a phenomenon still growing and predominant in low-income countries) is one of the main reasons for the creation of zoonotic pandemic reservoirs, in which wild and domesticated species they are in close contact with each other and with human beings (Gibb 2020). Thus, a number of diverse, interconnected, factors form a causal web that is not easy to treat in a single way. As a matter of fact, overpopulation, deforestation, land consumption, the increase in urbanized areas and human intrusion into natural habitats, deforestation in favor of agriculture and intensive farming and mining are leading to the impoverishment of ecosystems and, in turn, fostering the conditions for the spread of pathogens.

Various researches in the field of ecology also show that the progressive alteration of global ecosystems is the main risk factor for the development of pandemics. In fact, the destruction of ecosystems very often involves the reduction (even the extinction) of some species, especially the more specialized ones. On the other hand, this involves the proliferation of more adaptable species which are more frequently the natural reservoirs of pathogens. According to this perspective, the conservation of biodiversity (with specific interventions, such as policies that limit or prevent deforestation and indiscriminate soil consumption), becomes a measure that acts directly on *ultimate causal factors*, significantly reducing the risk of future pandemics (Gibb 2020, Murányi and Varga 2021, Finlay et al. 2021).

According to a world program of the WHO, called "One Health", the future of research also in the medical field (especially with repercussions on public health) concerns the ecological aspect of diseases.[11] According to this perspective, the very concept of *human health* must be updated and integrated with *animal health*, and more generally with an ecological perspective that includes the "health of the ecosystem". It follows that pandemics must be tackled with a multidisciplinary strategy, keeping together epidemiology, climate sciences, species protection, and risk communication (Fronteira et al. 2021). This is particularly crucial considering that of the emerging pathogens, about 75% are of zoonotic origin. Furthermore, zoonotic pathogens are twice as likely to generate emerging diseases compared to non-zoonotic pathogens (Taylor et al. 2001).

Another aspect, distinct but obviously connected, concerns the more properly evolutionary dimension. Biological entities such as viruses are in fact almost ubiquitous in nature and interact with every known form of life. Furthermore, it is now established that viruses play a crucial role in the dynamics concerning the genesis and development of all living forms (Harris and Hill 2021), and some scholars have even suggested that they constitute one of the determining factors of the evolutionary process (Koonin and Dolja 2013). This allows us to make some considerations on the character of epidemics and pandemics. As

[11] https://www.who.int/news-room/q-a-detail/one-health (accessed May 10, 2021).

already mentioned, they are nothing new in the history of the human species. Furthermore, infectious diseases have contributed to determining the development of the human species (operating as a selective filter) but have also conditioned human nature itself by virtue of the biological possibilities of interaction between the human species with other living forms (Gilbert et al. 2012, Harris and Hill 2021, Brett et al. 2021).

Furthermore, according to many experts, relationships between human urbanization, public health, and biodiversity need also to be investigated. Aspects of an ecological nature are therefore intertwined with issues of a social and cultural nature, making it even more difficult to deal with this level of causality treatable by a single discipline. First of all, the social and technological modality with which the human species has configured itself (especially the following industrialization) establishes a situation that is particularly suitable for the spread of pandemics. Contemporary human societies are made up of millions (sometimes billions) of individuals concentrated above all in certain areas where they live in close contact and according to dynamics that provide for strong social and physical interaction (Brett et al. 2021).

No less important is the aspect concerning the organization of health systems. The pandemic has clearly shown how the model (especially Western) built more and more around poles of excellence, but not very attentive to the medicine and health of the territory and creator of situations of health inequality and inequality, was one of the causes of the global disaster. From this perspective, Covid-19 was more of a crisis in the organization of health systems than a medical crisis (El Bcheraoui et al. 2020, Pescaroli et al. 2021).

Furthermore, this issue affects not only the practical dimension but also involves some of the very foundations of public health (again, especially in the Western world), such as the concept of "hygiene" (Brett et al. 2021). If it is definitely true, in fact, that the development of public health (and the very promotion of the concept of "hygiene" have eradicated many infectious diseases and significantly increased people's life expectancy, it is equally true that this model, typical of a society progressively urbanized, consisting of increasingly mediated interactions, has also produced a significant decrease in the microbial ecosystem with which the human species has evolved, including a reduction in the biodiversity of the human microbiota (a phenomenon often associated with the onset of various diseases, above all autoimmune in nature, but also susceptibility to some infectious diseases). This theoretical framework proposes that the changes, over time, that different human populations have undergone, have led to a consistent loss of biodiversity of microorganisms. These changes concern some characteristic elements of contemporary life (especially in Western countries): urbanization, the indiscriminate use of antibiotics, the hygiene of living and working environments, the homologation of food (towards a greater presence of food industrially produced), and excessive consumption of alcohol and tobacco (Brett et al. 2021).

Finally, part of the ultimate causes of the pandemic is to be found in the purely social, political, and economic dimensions. Regarding this point, it is decisive to make some specifications in order to avoid simplifications or striking statements that could be supported by little evidence. To argue that aspects far from biological and epidemiological mechanisms (such as the ecological dimension) play an ultimate causal role on pandemic means (following the spirit of Mayr's theoretical distinction) to investigate those causal factors that have determined the possibility of a certain state of affairs rather than another. In other words, if it is obvious that the

pandemic has its necessary and proximate cause in the Sars-CoV-2 virus, that pathogen has nevertheless been able to be as such and to generate a phenomenon such as a global pandemic due to a set of causes at a systemic level.

Therefore, this is why many experts claim that it is undeniable that the pandemic was, in addition to a health emergency, also a political and social emergency (Morens and Fauci 2020, Brett et al. 2021, Leach et al. 2021). According to some economists and human development scholars, this also entails the need to think differently about the growth modalities of human societies and what interventions are fundamental for a rethinking that acts precisely on the ultimate causes of the pandemic (Leach et al. 2021). In other words, to identify the causes of the pandemic, to develop tools to manipulate its effects and stem its origins, it is essential to act on some key nodes of the organization of society itself (especially in the West).

For some experts, this means above all recognizing the limits and inconsistencies of the current economic growth model (also due to the aforementioned repercussions on the environment and biodiversity). This also means promoting forms of greater awareness (citizen empowerment) and participation by citizens in public policies, especially health. As some scholars write:

> Where traditional approaches to development have been top-down, rigid and geared towards narrow economic goals, post-COVID-19 development must be centered on a radically transformative, egalitarian and inclusive knowledge and policy (Leach et al. 2021: 1).

Indeed, as numerous specialists have noted in recent months, the impact of the pandemic has not been the same for all individuals, nor for all affected countries. The disparities and inequalities (both social and economic) of the different contexts have created a scenario that is anything but homogeneous. Therefore, many have argued that Covid-19 should not be considered a pandemic but rather a *syndemic* (Bambra et al. 2021, Fronteira et al. 2021, Griffith 2021, Horton 2021, Islam et al. 2021, McMahon 2021).

The notion of syndemic was originally developed by the medical anthropologist Merrill Singer in the 1990s. More recently, he and colleagues have proposed a model of approach to syndemic diseases (Singer et al. 2017). This means scientifically examining the *biosocial complex*, formed by the interaction of pathologies with social and environmental factors (either parallel to the onset of the disease or resulting from it). According to this perspective, this implies a new and different conception of the disease itself, not as a process sharply distinct from others, but rather a frame that puts it in relation to the other pathologies and the social, political, and economic contexts in which the disease occurs. The term "syndemics" therefore wants to emphasize the synergistic effects with which these different factors combine and their consequences. This translates into the study of why some pathologies focus on particular individuals or groups, and the ways in which contexts in which social inequality and economic disparity are determining factors in estimating the incidence of the disease.

This perspective obviously proposes to manage health emergencies in a different way (also from a causal point of view). As Singer and colleagues write:

> A syndemic approach provides a very different orientation to clinical medicine and public health by showing how an integrated approach to understanding and

treating diseases can be far more successful than simply controlling epidemic disease or treating individual patients (Singer et al. 2017: 947).

7. Other Models and Possible Integrations

The factors that refer to what we have defined as the *ultimate cause*s of the pandemic appear crucial not only to understanding the pandemic itself but also to its management and to averting possible new future pandemics. In fact, as some scholars suggest (Leach et al. 2021), the understanding of the pandemic as a complex and global phenomenon (not only in its epidemiological meaning), requires a more in-depth study on the structural dynamics that concern various aspects (connected to each other) such as internal human interactions (e.g. social and economic relations) and those towards the biological world in an ecosystemic perspective (i.e. looking at human activity both as the cause of certain phenomena and as shaped by those phenomena themselves). Taking into consideration not only Covid-19 but also previous experiences (such as Sars and Zika), this also means recognizing that the elements of ecological disturbance (such as the reduction or destruction of ecosystems) are closely linked to material constraints, choices concerning policies, and economic, political and social conditions (Zabaniotou 2020, Leach et al. 2021). In fact, a response to the pandemic that deals only with its proximate causes, without questioning the global model that generated it, unequivocally linked to the kind of factors already mentioned, is not only incomplete but is limited to dealing only with the visible and symptomatic aspects, thus completely neglecting the triggering elements of the phenomenon.

From the point of view of scientific understanding, this also means that the modeling of a single level of description of the phenomenon, such as the epidemiological one, does not appear sufficient. As some researchers have pointed out (Engen et al. 2021), the compartment models used in epidemiology do not seem suitable to adequately represent the phenomenon. This is not to be understood in a simplistic way, as if it were a theoretical oversight or methodological neglect. On the contrary, this feature reflects the fact that the variables, parameters, and conditions are too many to be included in the model in a consistent way, also considering the necessary distortions of the model and the scarcity of more in-depth information (and not always available) on aspects necessary for the operation of the model itself. As a matter of fact, theoretical ecology, which daily works with the challenge of dealing with complexity without making excessive reductions, has over time developed models and approaches to contemplate the so-called "noise", which is one of the main characteristics of complex systems and in particular of biological ones. This implies to switch from more fixed and deterministic approaches to stochastic, noise-inclusive modelling strategies. Thus, according to some scholars in this field, applying this type of modeling to epidemiology can provide valuable tools both for measuring how an epidemic can take hold and for providing predictions about its development and possible responses to it (Engen et al. 2021).

On the other hand, there is no need to load a disciplinary perspective with miraculous or salvific properties. Indeed, there is also a debate within theoretical ecology on the explanatory and predictive scope of models (Schuwirth et al. 2019). As with epidemiological models, ecological models also make assumptions and approximations and cannot be considered comprehensive solutions, especially if not discussed with other experts coming from field studies and from

experimental research. Moreover, not all ecological models are the same. For instance, recently there has been a quite intense debate concerning the feasibility and the pertinence of *species distribution models* (SDMs) for unravelling crucial features of Covid-19 (Araújo et al. 2020, Carlson et al. 2020a, 2020b). SDMs are tools to model complex "objects" such as habitats that have been progressively adopted in biomedical geography, linking ecological determinants to cases of epidemiological interest. Despite their success, some scholars have recommended attention to their adoption in the case of covid, given the scarcity of information still available to be able to model more substantially some crucial aspects of transmission (Carlson et al. 2020a). On the other hand, other researchers (Araújo et al. 2020), while recognizing the limitations and dangers of generalizations coming from ecological models (often less able to provide a mechanistic understanding of certain phenomena, as is the case with epidemiological models), have argued for the need to recognize the specific epistemic virtues of these tools and to consider the results of both approaches in a more open and interdisciplinary way. In this sense, in defending a pluralistic approach, which contemplates the use of different types of models (also from different disciplinary sectors) these authors write:

> While correlative models can provide insight concerning the environmental persistence of the pathogen (thus affecting spread of the disease), mechanistic approaches allow projecting numbers of infections and fatalities as a function of management policies. Rather than building walls across scientific disciplines, building bridges will be more effective to understand the spread of SARS-CoV-2 and its effects on human health (Araújo et al. 2020: 1153).

Accordingly, the adoption of ecological models (also in their diversity) should therefore not be conceived in contrast with the epidemiological description as much as in an integrative sense. For example, some ecological models (Coro 2020) can provide additional information (for instance on certain environmental aspects and biogeographical conditions that could favor or limit the spread of the virus) that is not traditionally contemplated in epidemiological modeling.

However, the ecological perspective (strictly speaking) is not the only relevant dimension for future modeling. Indeed, in order to build pandemic management policies (both at an emergency level and of a more structural layer), ecosystemic factors are intertwined with social and economic ones.

Regarding this point, it seems obvious that a single modeling that integrates all these variables in a complete way is almost impossible (and even where it was feasible, it would be difficult to use.). Therefore, public health specialists are starting to develop overarching operational schemes that can serve as a meta-theoretical framework capable of considering heterogeneous data together with a view to their consistent and coordinated use (Raboisson and Lhermie 2020).

In conclusion, as Campaner (2011) also recalls, the objective of integrating epidemiological and ecological accounts is to provide an integrated perspective of the scientific explanation that contemplates different levels of description without imposing forms of reductionism.

The complexity of a phenomenon such as a pandemic in fact implies that its explanation (in the sense of exhibiting a causal structure) cannot only concern those obvious and *proximate* causal aspects, but also those that make a difference in the way the pandemic itself manifests and develops (i.e. the *ultimate* causes).

This aspect also helps to bring out the first and foremost epistemological (rather than ontological) perspective of modeling and the need for integration at this level (rather, here too, than at the ontological one). In fact, as Campaner (2011) always reminds us, if it is certainly true that the entire causal dynamic of the pandemic is entirely given and objectively traceable (as a theoretical possibility), the explanation of its aspects will also be dictated by the context, interests and disciplinary approaches, with their differences.

8. Conclusion

The Covid-19 pandemic has proved to be an unprecedented global threat. Both in health terms and in terms of impact on human life and its organization, on a global scale.

The scientific community has tried to understand this partly totally new phenomenon by designing experiments to dissect its properties (such as the virus sequences or its mechanism of infection) and building models to understand its general behavior. These efforts, taken together, have tried both to *explain* the pandemic and to *predict* its progress, with the idea that these two concepts are the key for addressing a phenomenon, and for developing the capacities to control it.

Faced with an infectious threat of this magnitude, epidemiology has obviously been one of the essential resources to manage the emergency. Through the construction of various types of models it has been possible to try to evaluate the effectiveness of certain measures, the ineffectiveness of others and to plan not only health policies but all the activities that govern modern societies.

In their attempt to capture the causes of the pandemic, epidemiological models, although indispensable, work on those that explain the "how" of the occurrence of Covid-19, but neglect the study of the reasons behind Covid-19.

In this article, I have tried to outline how the fact of the pandemic also requires an attempt to answer the "why" of its being. In other words, an attempt to incorporate, within the scientific explanation, also the ultimate causes of the phenomenon: namely the ecological, evolutionary, and socio-economic factors related to the pandemic. This effort entails an ecosystemic perspective in at least two meanings. On the one hand, this perspective is purely disciplinary, that is, it concerns the methods and approaches used by the sciences of complex phenomena, such as ecology and by the social sciences. On the other hand, the reference to the systemic character refers to the epistemological level, that is to conceive the scientific explanation as organized on several levels, both in terms of granularity and of shape according to specific interests (also in relation to their ability to offer manipulations of the phenomenon in question).

This is not just a theoretical wish or a declaration of intent. It must be translated into effective practices. Thus, such an effort will require not only interdisciplinarity as such but also new integration strategies, concerning both differences in data production methods and diversities in methodological approaches.

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