Making Best Use of the Available Evidence: Mechanistic Evidence and the Management of the Covid-19 Pandemic

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Abstract

In this paper, I argue that evidence of biological and socio-behavioural mechanisms can contribute to the management of Covid-19. I discuss two examples that show how scientists are using different forms of evidence, among which mechanistic evidence, to answer questions about the efficacy of vaccines against Covid-19 and the effectiveness of vaccination interventions in different contexts. In the first example I claim that, due to the fast pace of the pandemic, mechanistic reasoning and evidence of biological mechanisms play an important role in the study of vaccines' efficacy and the development of new adaptations based on possible future virus mutations. In the second example, I explore the use of evidence of the socio-behavioural mechanisms influencing vaccination behaviours and I show that the World Health Organisation is promoting the collection of this type of evidence to understand whether particular vaccination interventions can fit in local contexts. Overall, this discussion supports the claim that the dominant evidence-based medicine (EBM) approach, which relies heavily on difference-making studies to assess the effectiveness of clinical and public health intervention, is inadequate and should be replaced by a new approach, EBM+, that systematically considers mechanistic studies alongside association studies.

Keywords: Causation, Evidential pluralism, Mechanistic evidence, Mechanistic reasoning.

1. Introduction

In 2007 Federica Russo and Jon Williamson introduced a version of evidential pluralism according to which:

> To establish causal claims, scientists need the mutual support of mechanisms and dependencies. […] The idea is that probabilistic evidence needs to be accounted for by an underlying mechanism before the causal claim can be established (Russo and Williamson 2007: 159).

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The account put forward by Russo and Williamson, known by the name of the Russo-Williamson thesis, challenged the dominant evidence-based medicine (EBM) approach, which relies heavily on difference-making studies to assess the effectiveness of clinical and public health interventions. According to the EBM approach, causation can be established if it is possible to establish a probabilistic relationship between the cause and the effect (the intervention A causes B only if A raises the probability of the occurrence of B), or a counterfactual relationship between them (A and B are actual events, and if A had not occurred, then B would not have occurred).

Among difference-making studies, randomised controlled trials (RCTs) have been often described as 'the gold standard', whereas other types of studies are often not considered as useful when establishing if a clinical or public health intervention is effective. In particular, mechanistic studies that examine the mechanism through which an intervention exerts its impact on the effect, are often disregarded as less useful (Guyatt et al. 1992). In several versions of EBM, in fact, mechanistic knowledge is partly taken into account, and probabilistic correlations are based on some forms of causal models (see for instance Howick 2011, and Spirtes et al 2000). This form of knowledge, however, is not given the same relevance that is given to difference-making studies.

The thesis suggested by Russo and Williamson paved the way for the EBM+ approach, a development of EBM that treats mechanistic studies on a par with association difference-making studies. Based on the more nuanced picture of causal assessment proposed by the Russo-Williamson thesis, since in real-world studies it is often impossible to completely rule out the possibility that a difference-making relationship is due to bias, confounders, or relationships other than causation, it is important to include an explicit scrutiny of mechanistic studies when assessing causal claims. What distinguishes causal from spurious correlations is the presence of a mechanism between A and B, therefore causation can be established only if it is possible to establish the existence of a mechanism of action as well as the existence of a correlation.[1]

The EBM+ approach carefully distinguishes between types of evidence and types of evidence-gathering methods: difference-making studies mostly generate direct evidence that the putative cause A and the putative effect B are correlated, but they can also provide evidence that indirectly supports the existence of a mechanism (see for instance Illari 2011). Mechanistic studies, on the other hand, can provide not only mechanistic evidence, but also evidence of a correlation between A and B. In most cases, however, establishing the presence of a mechanism requires direct evidence from mechanistic studies, which helps to confirm or disconfirm mechanistic hypotheses.

In a recent paper, Aronson et al. (2020) reviewed the role of mechanistic reasoning in four major areas that are relevant to the management of Covid-19: treatments, pharmacological surveillance, preventative public health interventions and vaccination programmes. Aronson et al. published their article when vaccines against Covid-19 were still under development. Over the last 6 months, however,

[1] The Russo-Williamson thesis has generated interest both in the health and in the social sciences. The thesis has not been immune to critiques, and some authors have discussed counter-examples to the Russo-Williamson (see for instance Claveau 2012, Klement and Bandyopadhyay 2019, Reiss 2009). Some of these criticisms have been examined in Ghiara 2019.

the debate on Covid-19 has been dominated by discussions about the real efficacy of the current vaccines against variants, and current vaccination behaviours. Due to the coronavirus pandemic's pace, the opportunities to conduct RCTs to explore such issues are still limited, and there are situations when scientists and policy-makers have combined different sources and types of evidence to understand how to best manage Covid-19. In July 2021, a systematic review of randomized controlled trials assessing the effect and safety of COVID-19 vaccines identified only 14 trials assessing 10 types of COVID-19 vaccines, the majority of which on phase I or II (Chen et al. 2021). Emani et al. (2020), moreover, analysed RCTs that assessed possible treatment options and concluded that that literature was very limited and most studies were characterised by significant methodological limitations.

In this paper, I will review the role that mechanistic evidence is playing in addressing such challenges.

2. Causal Mechanisms and Mechanistic Evidence

The term mechanism can be understood broadly in three ways: i) as a complex system consisting of entities and activities organised in such a way that, together, they are responsible for the phenomenon under study (as described by Machamer et al. 2000); ii) as a mechanistic process through time and space; this process can be understood as a process propagating a signal (Dowe 2007; Reichenbach 1958; Salmon 1997) or as a chain of events that leads to specific effects (as described in the social sciences by Maxwell 2004), and iii) as a combination of a complex system and a process.

Although there are differences between biological and social mechanisms, this categorisation can be applied to different types of mechanisms. The complex molecular system of long-term memory, organised in entities (neurons, proteins and genes) and activities (such as protein movements and gene expressions), and Schelling's well-known social segregation mechanism (1978), organised in individuals and their discriminatory preferences are two examples of complex systems consisting of organised entities and activities. The propagation of an electrical signal from an artificial peacemaker to the appropriate part of the heart, and the political causal chains leading to revolutions identified by Skocpol (1979), moreover, are examples of causal processes (for more on this point, see Ghiara 2019).

Mechanistic evidence, in turn, is evidence that supports the existence of a mechanism.

3. Efficacy and Effectiveness

When examining the use of mechanistic reasoning, it is important to distinguish between efficacy and effectiveness. The term 'efficacy' refers to the effect of some intervention in ideal conditions. Establishing efficacy is typically the first step to evaluate whether an intervention works. For instance, in the case of Covid-19 vaccines, establishing efficacy would require evidence that the vaccine can reduce Covid-19 incidence under optimal conditions within a study population.

Study populations, however, often differ from the target population in significant ways. For example, a study population for evaluating Covid-19 vaccines might exclude those with multiple morbidities or young people; or a study population for evaluating vaccination campaigns might exclude minority groups. For

this reason, establishing whether an intervention actually works requires investigating its 'effectiveness', which means the effect of the intervention 'in the real world', in the target population. Evidence of mechanisms plays a crucial role in establishing both efficacy and effectiveness (Parkkinen et al. 2018). The sections below discuss two examples of how mechanistic evidence is being used to establish vaccines' efficacy and vaccination programmes' effectiveness.

4. Assessing the Efficacy of Vaccines Against Current and Future Covid-19 Variants

It is well known that mutations are a normal part of viruses' life cycles, and that through such mutations new variants are likely to arise. Multiple Covid-19 variants have been documented in the last 6 months, and their discovery has been followed by long debates on whether such variants will persist, and what impact these can have on the efficacy of the current Covid-19 vaccines.

Randomised controlled trials appear to support the claim that most of the existing variants will not completely undercut the efficacy of this first generation of vaccines (Madhi et al. 2021; Abdool Karim and de Oliveira 2021),[2] however concerns have emerged over variant 501Y.V2 found in South Africa and Brazil, also known as variant B.1.351, as new evidence showed that it was able to evade virus-blocking antibodies produced by most people previously infected with first-wave strains, and that some of the existing vaccines have a reduced efficacy against it (Callaway and Ledford 2021).

The questions scientists need to answer are not only whether current vaccines are able to protect against current variants, but also whether they will be able to protect against future variants of the virus. Answering these questions is, undoubtedly, very challenging. As mentioned by Mascola et al. (2021), this situation is like tackling a moving target. On the one hand, there is limited time to evaluate vaccines' efficacy against current variants, on the other hand answering the second question requires making predictions about the key features of future variants. In this situation, mechanistic evidence can help both to address the first question and to develop new hypotheses about what adaptations or other types of vaccines might work against future variants.

A case in point showing how mechanistic evidence can contribute to the response against the virus' variants is the recent study published by Clark et al. (2021). In their study, the authors reported results from experiments conducted on lab-made, non-infectious reproductions of eight Covid-19 mutations found in a patient receiving immune-suppressive treatments for an autoimmune disorder. Over 5 months, Clark et al. reported, these mutations had clustered on a section of the spike called the receptor-binding domain. This finding attracted the researchers' attention, as the spike is what current antibody treatments and vaccines target to prevent Covid-19 from entering human cells. Through a series of experiments the authors showed that, of the eight mutations reproduced in their laboratory, two evaded both antibodies naturally occurred in people who survived the infection, and lab-made antibodies now used for the clinical treatment of Covid-19.

[2] My argument refers to the first generation of vaccines, which include vaccines based on different technologies including mRNA vaccines, inactivated vaccines, viral vector vaccines and subunit vaccines (Chen et al. 2021).

Interestingly, the mutations analysed by Clark and colleagues have not yet been identified in the mutations already detected. However, the authors highlighted the importance of this mechanistic evidence since "How the spike responded to persistent immune pressure in one person over a five-month period can teach us how the virus will mutate if it continues to spread across the globe" (Pesheva 2021). Thinking about the mechanisms of mutation, in turn, can help to determine whether the existing vaccines would work against such mutations, and what adaptations would be successful against them.

In particular, this evidence has advanced some mechanistic hypotheses on how a next generation of vaccines should target less mutable segments of the virus to work against mutations. Scientists have started examining T cells, immune cells that can target and destroy virus infected cells, to look for evidence suggesting that such cells could help to preserve lasting immunity. The hypothesis that T cells could play a role in providing immunity partly relies on mechanistic reasoning and background knowledge: as reported by Daina Graybosch, a biotechnology analyst at investment bank SVB Leerink in New York City, although data is still not sufficient to draw conclusion, "it makes sense biologically" (Pesheva 2021). Researchers have focused their attention on two groups of T cells. The first group is that of killer T cells (or CD8 T cells), which identify and destroy cells that are infected with the virus. Another group of T cells, called helper T cells (or CD4 T cells), support the production of antibodies and killer T cells. Based on these cells' functions, researchers hope that T cells could destroy the virus-infected cells before they spread from the upper respiratory tract, and could reduce transmission by reducing the amount of virus circulating in an infected person. Additional evidence on T cells, furthermore, suggests that they could be less vulnerable to Covid-19 mutations: Sette et. al (2021), examined that infected people generally produce T cells targeting at least 15-20 different portions of coronavirus proteins.

Mechanistic hypotheses, of course, can offer only partial support to understand vaccinations' efficacy against current and future variants, and what adaptations might be required. In such uncertain times, however, this evidence helps to identify potential pathways and future research directions.

5. Examining Barriers and Enablers and the Effectiveness of Vaccination Programmes

As claimed in the "Tailoring Immunization Programmes" guide published by the WHO's Regional Office for Europe (2019), it is crucial to understand the psychological, contextual, and social mechanisms that influence vaccination behaviours in order to design an effective campaign. In October 2020, the WHO advisory group reviewed some of the mechanistic evidence concerning possible barriers to vaccination and published the report "Behavioural considerations for acceptance and uptake of COVID-19 vaccines". Through a review of the literature, the authors identified three categories of barriers and enablers in relation to vaccine uptake: environment, social influences, and motivation.

Social influence was recognised as a main factor when promoting vaccination against Covid-19, and the authors recommended several supporting strategies based on mechanistic studies. For instance, it was observed that the general beliefs of a community and the corresponding behaviours are likely to influence the individual attitude towards vaccination, and that if vaccine uptake is made

"visible" to others (e.g. through social signalling such as badges or via social media), members of community will more easily perceive vaccine uptake as consistent with their community's social norm (Karing 2018; WHO 2020). It was also considered that the behaviours of respected members of the community, who share similar values and characteristics with the targeted group (for instance, with the same religious or ethnic identity), are likely to influence vaccination uptake within their community (CASS 2020).

Motivation to get vaccinated is also linked, according to the report, to the perceived risk of contracting Covid-19, or to the perceived health consequences of the infection. Behavioural studies showed that most people use shortcuts to assess risks in complex circumstances, and their perception might be based on personal experiences and rumours (Kahneman 1973; Tversky et al. 1974). It follows that clear communication is crucial in order to help people judge risks accurately. A behavioural mechanism that appears to influence perceived risks and motivation is known by the name of "anticipated regret": when people anticipate that a negative outcome in the future would lead them to wish they had behaved differently (Brewer et al. 2016; Brown et al. 2010). This mechanism can be used in favour of vaccination, suggested the authors, through the description of the consequences of not getting vaccinated (for instance health practitioners might discuss with patients how they would feel if they do not get vaccinated and get infected or transmit the virus to their family).

As predictable, most of the studies used to develop such recommendations had been published before the current pandemic, and were focused on specific geographical areas, or specific communities. For instance, the social signalling recommendation was mainly based on a study conducted in Sierra Leone, while the role played by members of the community was explored through studies of Sub-Saharan African communities. Moreover, most of the studies were focused on other health concerns (such as seasonal flu or Ebola), and some targeted only child vaccination and parents' behaviours. It follows that it is questionable whether health policies based on such recommendations would be effective to promote vaccinations against Covid-19 in different contexts.[3]

To answer this question, policymakers need to use their knowledge that something had a particular impact somewhere to extrapolate that the same thing will exert a similar impact in a different context. Going from evidence of efficacy ('this has a given effect in an experimental population in context X') to evidence of effectiveness in a different context ('this will have the same effect in a target population in context Y') can be challenging. For instance, Nancy Cartwright (2010) showed that untested assumptions about the possibility of extrapolating evidence from a nutrition program conducted in Southern India to Bangladesh led to a big failure due to substantial differences in the social contexts.

The risk of falling into the same trap when developing Covid-19 vaccination strategies has not been discussed in detail in the report published by WHO in October 2020, but it is certainly one of the challenges policymakers face when using general recommendations regarding Covid-19 vaccinations. Although

[3] An additional caveat needs to be added in the case of behavioural studies: internal validity and the replicability of the experiments can be questioned too. The problem of replicability has been discussed in relation to several experiments on cognitive biases (see for instance Romero 2019, and Schimmack, Heene and Kesavan 2017). It follows that the use of evidence from behavioral studies in health policies needs to be carefully examined.

evidence shows that the virus impacts in very similar ways all populations, this does not mean that the same barriers and enablers, and the corresponding vaccination strategies, will work in the same way in different contexts.

Understanding the behavioural and social mechanisms operating in different contexts, hence, is an important step to ensure vaccination behaviours are promoted in an effective way. This consideration is one of the reasons why WHO published, in February 2021, a new guide entitled "Data for action: achieving high uptake of COVID-19 vaccines" (WHO 2021). In this guide, which was then updated in April 2021, the authors adapted the Brewer's general mechanistic model to Covid 19. The assumption is that, regardless of the context, all the included factors can play a role, however their influence might vary in different contexts, and the effectiveness of targeted strategies might change when applied to different populations.

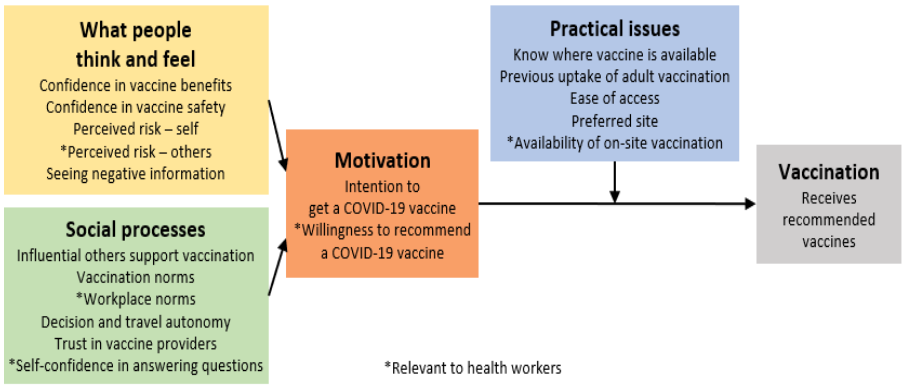

Figure 1: The adaptation of Brewer's model that explores personal, social, motivational and practical barriers to Covid-19 vaccinations (WHO 2021: 16).

Using the adapted Brewer's model, a global group of experts have developed survey questions and qualitative interview topic guides to help national policymakers collect mechanistic evidence and identify how such factors impact vaccination in a given context. Why is this process important? Understanding the local mechanisms of actions is a critical aspect to test whether the barriers and enabling mechanisms in the target population are sufficiently similar to those in the study population where the study or experiment was conducted. This, in other words, helps to investigate the external validity of particular causal links between environment, social influences, and motivation, and vaccination behaviours.

Understanding such similarities between the study and the target populations, in turn, can help policymaker to understand whether an "intervention is feasible in specific contexts" (WHO 2021: 16) or, put differently, whether it is possible to expect that an intervention (such as on-site vaccination or an educational campaign) will work equally well in the study and target population.

A case in point that illustrates how the same campaign might have different (or even opposite) effects is the example of a herd immunity campaign: knowledge of the importance of herd immunity might lead people to get vaccinated to protect others, but could also lead to free-riding behaviours, where people avoid individual costs of vaccination because they know they will benefit from others' immunisation. Some studies have identified differences between contexts: Betsch et al.

(2017), for instance, observed that emphasising social benefit appears to work better in Western cultures, that tend to be more individualistic, than in more collectivist Eastern cultures. Making the individual benefits of a herd immunity too obvious, on the other hand, might have a stronger impact on Western culture, where more people might decide to free-ride (Betsch et al. 2013).

As the example above shows, a detailed understanding of the similarities and differences between the relevant mechanisms in the study and the target populations is crucial to ensure vaccination interventions will be effective, and can complement difference-making evidence collected in the study and targeted populations.

6. Conclusion

In this paper, I illustrated how evidence of biological and socio-behavioural mechanisms can contribute to the management of Covid-19. The two cases described above are illustrative and not exhaustive, as other studies on Covid-19 are likely to use different forms of evidence to answer different questions.

The first case I discussed shows that, since the fast pace of the pandemic limits the possibility of running randomised controlled trials and requires scientists to design adaptations based on possible future virus mutations, mechanistic reasoning and evidence of biological mechanisms can play an important role to determine the current and future efficacy of vaccines against Covid-19. In the second case I explored the use of evidence of the socio-behavioural mechanisms influencing vaccination behaviours. I showed that the World Health Organisation is promoting the collection of this type of evidence to understand whether particular vaccination interventions can fit in local contexts, and I claimed that mechanistic evidence can play a crucial role to establish external validity and extrapolate interventions.

This paper does not want to argue that evidence of mechanisms is sufficient to answer causal questions concerning Covid-19. To assess the efficacy of vaccines and to establish if a vaccination intervention works in a local context, difference-making evidence is essential. The fast pace of the pandemic, however, requires scientists and policymakers to make fast decisions, and trials often require time to ensure the collection of robust difference-making evidence. As a consequence, this uncertain time casts a new light on the benefits of using mechanistic evidence and on the limitations of the traditional evidence-based medicine (EBM) approach.

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