Vaccination Uptake Interventions: An EBM+ Approach

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Abstract

As the COVID-19 pandemic has demonstrated, barriers to vaccination uptake are heterogeneous and vary according to the local context. We argue that a more systematic consideration of local social and behavioural mechanisms could improve the development, assessment and refinement of vaccination uptake interventions. The EBM+ approach to evidence appraisal, which is a development of a recent line of work on the epistemology of causality, provides a means to evaluate mechanistic studies and their role in assessing the effectiveness of an intervention. We argue that an EBM+ methodology offers several potential benefits for research on vaccination uptake interventions. It also motivates the use of detailed mechanistic models, rather than the high-level logic models used by process evaluations, for example.

Keywords: Vaccination uptake interventions, Methodology, Evidence-based medicine, Mechanism, Mechanistic models; EBM+, Behavioural science.

1. Introduction

Immunisation is an integral part of global healthcare provision. It has helped to drive a massive reduction in worldwide annual child (under the age of 5) mortality, from 9.6 million in 2000 to 5.4 million in 2017 (WHO 2013; UNICEF 2018). It is estimated that annual deaths from just 5 vaccine-preventable diseases (diphtheria, measles, neonatal tetanus, pertussis and poliomyelitis) have dropped by 0.5 million a year since 2010. Vaccination coverage is one way of continuing to progress these achievements. There are licensed vaccines for 27 diseases, and to be licensed requires demonstration of efficacy. But effectiveness depends on much more than whether the vaccine elicits an appropriate immune response and protects the immunised from disease—vaccination coverage must also reach sufficient levels. The WHO's Global Vaccine Action Plan (GVAP) sets out a target of 90% coverage at the national level and 80% in every district by 2020. While coverage for most vaccines has substantially increased, many GVAP targets were not met. For example, global coverage for the 2nd dose of a measles vaccine has in-

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creased by approximately 2/3rds, but absolute levels are still below 70% (MacDonald et al. 2020). If not enough people are being vaccinated, then immunisation programmes will fail.

Coverage depends on two broad sets of requirements. A sufficient stock of vaccines and the capacity to administer the vaccine to the whole target population are examples of *supply* requirements. Problems of supply result from limitations of infrastructure and resourcing. Accordingly, they are dealt with by approaches that focus on efforts to obtain sufficient resources and improve political will, e.g., investment in manufacturing and international aid. Even with sufficient supply, vaccination coverage may still fail to ensure population immunity, which can be explained by a number of factors that are relevant to the *demand* for vaccines. Problems of demand result from a wide variety of factors, including beliefs about vaccine safety, efficacy and utility. Interventions to increase demand for vaccines tend to focus on changing individual—and sometimes societal—beliefs and values.

One way to increase demand is to apply behavioural science. The Behavioural Insights Team, for example, argue that using psychological, sociological and related research to change vaccination behaviours is an avenue with much potential to increase demand for vaccination (Merriam and Behrendt, 2020). The World Health Organisation (WHO) have endorsed this strategy. Behavioural insights also play a major role in the response to COVID-19—see WHO 2020 and Betsch et al. 2020. Having obtained a sufficient supply of an efficacious vaccine, the focus shifts to interventions on behaviour to ensure there is sufficient uptake for the vaccine to be effective.

For the many infectious diseases that are the target of vaccination programmes worldwide, the methodology used to guide the development and assessment of interventions is crucial. In recent decades, the focus of efforts to increase vaccination coverage has been on low to middle income countries (LMICs) on whom the burden of infectious disease falls most heavily. COVID-19 has exposed how the consequences of getting vaccination programmes right can affect countries across the economic spectrum. In LMICs it is particularly important not to devote limited resources to vaccination programmes unless they are likely to have enough uptake to be effective. On the other hand, while high income countries (HICs) may be able to devote resources to vaccination programmes, lack of uptake threatens to hinder any progress made against an infectious disease that for the first time in half a century poses a real and present danger to the health and economy of HICs. This paper argues that the development and assessment of interventions to increase vaccination uptake would benefit from changes to methodology motivated by the EBM+ programme. As explained in §3, EBM+ emphasises the importance of mechanistic evidence when assessing causal claims. Here, the causal claims of interest are claims about the effectiveness of vaccine uptake interventions.

EBM+ is a development of the recent mechanistic turn in the philosophy of science. Russo and Williamson 2007 argued that in order to establish a causal claim in medicine one needs to establish that the putative cause and effect are correlated and that they are linked by some mechanism that can account for this correlation. If correct, this suggests that present-day evidence-based medicine (EBM), which focusses on clinical studies to the exclusion of mechanistic studies, may be overlooking important evidence (Williamson 2019). EBM+ augments EBM with methods for properly assessing mechanistic studies and integrating

these assessments with those of clinical studies in order to assess causation (Parkkinen et al. 2018).[1]

EBM+ therefore also has important consequences for the use of models in establishing causal claims. In particular, well-confirmed mechanistic models can help to establish the existence of a linking mechanism, thereby confirming a causal claim of interest. Thus mechanistic models can be useful when establishing the effectiveness of vaccine uptake interventions. This suggests a greater role for mechanistic models than, say, the logic models of process evaluations, which are currently used to assess vaccine uptake interventions.

In §2 we describe the current methodology for assessing effectiveness and argue that it has certain limitations. We present the alternative EBM+ approach in §3. We then develop two case studies of the use of EBM+. In §4 we consider an example in which EBM+ would deem evidence of effectiveness to be weak and in §5 an example in which evidence of effectiveness is strong. We argue that each case would benefit from an EBM+ approach. We conclude in §6 that an EBM+ approach has much to offer vaccination uptake research.

2. The Status Quo

The dominant methodology for the assessment of interventions to increase vaccination uptake is that of the standard approach to assessment in the health sciences, namely evidence-based medicine (EBM). This methodology prioritises evidence obtained by association studies—particularly randomised controlled trials (RCTs)—when assessing the effectiveness of interventions, and downplays the evidential role of mechanistic studies. An association study of a vaccination uptake intervention tests whether the intervention is associated with uptake, and usually also ascertains the extent of any observed correlation between the two. On the other hand, a mechanistic study aims to shed light on features of the complex of mechanisms by which the intervention might influence uptake, including the variables that are intermediate between cause and effect and the entities and activities involved in the mechanisms and their organisation. According to EBM, mechanistic evidence may help to suggest a new intervention, but it provides at best very weak evidence of effectiveness. Thus mechanistic evidence is rarely considered by EBM-based systematic reviews of effectiveness (Williamson 2019: §1.3).

Vaccination uptake interventions, in particular, follow present-day EBM, which deems mechanistic evidence relevant to the context of discovery (i.e., hypothesising the intervention) but not the context of justification (i.e., assessing effectiveness). For example, behavioural science is used to suggest interventions. These interventions may exploit particular cognitive biases that have been identified by theoretical psychology. For instance, omission bias is the tendency for people to judge harmful actions more harshly than inaction, even where both cause equivalent harm (Merriam and Behrendt 2020: 13). There is some evidence that omission bias plays a part in a mechanism that influences vaccination attitudes in the US. An intervention may thus be proposed to target omission bias. This process is analogous to the way in which pharmaceutical interventions are suggested by 'basic science' research. Methods of the biomedical sciences are used

[1] EBM+ is not without its critics. See Williamson 2019: §1 and references therein for further discussion.

to identify features of mechanisms of action of potential pharmaceuticals. Those that show promise are then tested in clinical trials.

That the current assessment of the effectiveness of vaccination uptake interventions favours association studies over mechanistic studies is witnessed by the fact that systematic reviews of vaccination uptake interventions typically only include evidence obtained in RCTs (Manakongtreecheep 2017; Jacobson Vann et al. 2018; Merriam and Behrendt 2020). Moreover, standard EBM evaluative frameworks are adapted and used to evaluate the quality of the evidence for these interventions. For example, Merriam and Behrendt 2020 use the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework to evaluate the quality of the studies included in their review. GRADE focusses on association studies.

It is clear that current methodology downplays or outright excludes mechanistic evidence from the assessment of vaccination uptake interventions. There are however some exceptions. First, the WHO 'tailoring vaccination programmes' guidance instructs designers of programmes to refine interventions to take account of barriers to, and facilitators of, vaccination (WHO Europe 2013). Second, a recent move to emphasise 'theory' in the design and evaluation of behavioural change interventions, where theory is defined as a "set of analytical principles or statements designed to structure our observation, understanding and explanation of the world" (Moore et al. 2019: 3). This brings the importance of mechanisms to light, but is unlikely to account for all the mechanisms at work for an intervention in a specific context (Moore and Evans, 2017). Third, *process evaluations* seek to elucidate the causal assumptions of an intervention, and attempt to identify how an intervention works (Craig et al. 2019). Alongside the testing of factors important to the implementation of association studies, process evaluations look for the mechanisms relevant to an intervention's effectiveness. We will revisit process evaluation in §5.

While these efforts cannot be discounted, the failure of the wider field to systematically consider mechanistic evidence is a problem for several reasons. Firstly, extrapolating the results of research from one population to another benefits from a careful scrutiny of mechanisms. In particular the social and behavioural mechanisms that the mechanism of action of the intervention interacts with will differ between contexts. For example, educational barriers to vaccination in HICs primarily concern beliefs about safety or importance, whereas in LMICs access to information about the benefits of vaccines is the main educational barrier (Gardner et al. 2010; Sadaf et al. 2013). Developing an intervention in a LMIC that addresses safety without improving access to information about benefits would be misguided (Aronson et al. 2021: §5). Second, association studies can play only a limited role in identifying why an intervention succeeds or fails. Articulating and evaluating the mechanisms that impinge on whether an intervention brings about an effect can help here. For example, one intervention to increase Human Papillomavirus (HPV) vaccination coverage in teenage girls involves administering vaccines in schools. In an evaluation of such a programme in the USA, parental approval was required for vaccination, so their beliefs about the importance of vaccination may have accounted for low participation rates (Stubbs et al., 2014). Taking account of the features of this parent-mediated mechanism is one way to improve the effectiveness of school-based HPV vaccination programmes (Stubbs et al. 2014). Last but not least, association studies alone are typically not enough to warrant a causal conclusion. Only several concordant

studies with the best designs and implementation can do this. When an evidence base fails to meet this standard—and it often does—high-quality evidence of mechanisms helps to establish a causal connection, as we discuss in the next section. Indeed, RCTs, often cited as the gold-standard kind of association study, may be viewed as undesirable on epistemic grounds (Worrall 2007) or because they are often costly and ethically questionable, and can lead to research biases (Ravallion 2020). Thus the use of mechanistic evidence promises to improve the development and assessment of vaccination uptake interventions. A new methodology for causal evaluation, EBM+, systematises the evaluation of mechanistic evidence. Next, we introduce this methodology, before moving on to showing how it can improve upon the methods employed in two very different examples of public health interventions.

3. EBM+

EBM+ adds to standard EBM the explicit evaluation of evidence obtained by mechanistic studies (Parkkinen et al. 2018).

Figure 1 portrays the role of evidence in establishing a causal claim, according to EBM+. Association studies can be used to directly test whether the putative cause and effect are correlated (evidential channel C_1 in Figure 1). However, correlation is insufficient for causation: while some observed correlations are causal, others are attributable to various kinds of study bias, to confounding, to various kinds of non-causal relationship, or even to mere coincidence. What is distinctive about a correlation that is attributable to causation is that there is some mechanism complex by which instances of the cause are responsible for instances of the effect and which can account for the extent of the observed correlation. Some association studies—notably large, well-conducted RCTs—can provide indirect evidence of the existence of such a mechanism (channel C_2), by reducing the probability that any observed correlation is due to confounding. But there is a more direct way to ascertain whether there is an underlying mechanism that can account for the correlation: posit key features of the mechanism and assess whether mechanistic studies show those features to be present (channels M_1 and M_2). If these mechanism features are well confirmed then this in turn can make the causal claim more plausible. (In certain circumstances, it can even make it more plausible that there is a genuine correlation—channel M_3.) This account of the epistemology of causation is sometimes called 'Evidential Pluralism', to distinguish it from a monistic account that focuses exclusively on association studies, as is the case with standard EBM.

Mechanistic studies investigate features of the complex of mechanisms linking cause to effect. This mechanism complex includes the mechanism of action, by which the cause directly contributes to the production (or prevention) of the effect, together with any mechanisms that counteract or enhance the influence on the effect attributable to the mechanism of action: together, these mechanisms can explain the net correlation between cause and effect. Where the causal claim is a claim about the effectiveness of a medical intervention, this mechanism complex might involve mechanisms responsible for the functioning of systems in the human body; the progression of disease; the metabolism of pharmaceuticals; the functioning of medical devices; the distribution of and access to the intervention; and compliance with the intervention. Thus, the relevant mechanisms can be biological, physiological, chemical, physical, infrastructural, social, behavioural

and psychological.[2] Accordingly, the methodologies employed by mechanistic studies are very heterogeneous. The key point such studies have in common is that they provide evidence for specific mechanism hypotheses, which hypothesise key features of the mechanism complex linking the intervention to the outcome.

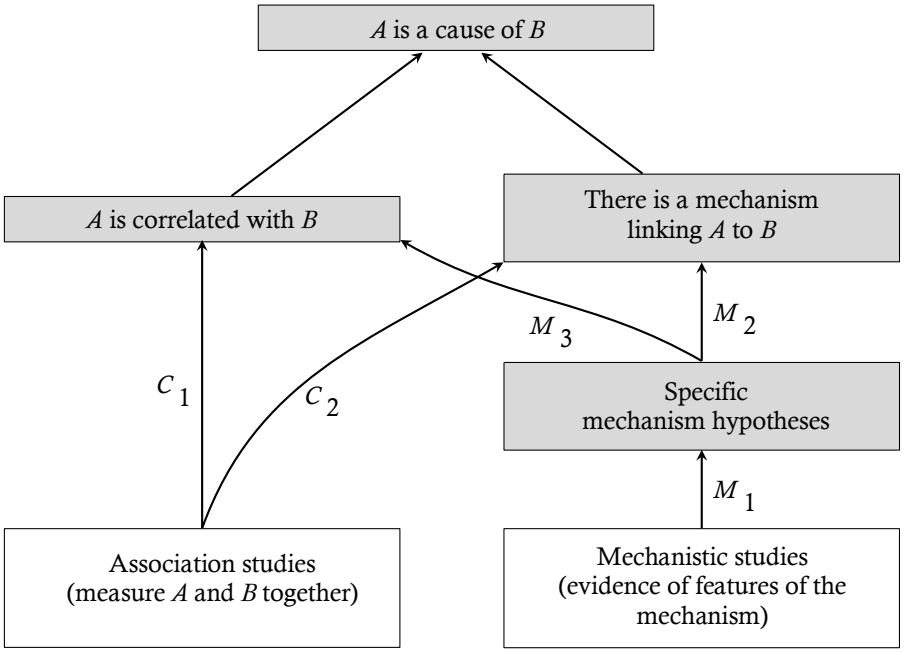

Figure 1: Evidential relationships for assessing a causal claim (Williamson 2021).

In the present context, the outcome of interest is increased uptake of vaccination in a target population, so infrastructural, social, behavioural and psychological mechanisms are particularly important. For example, vaccination appointment reminders offer the potential to increase vaccination uptake (see §4). The mechanism of action is straightforward: a reminder prompts individuals to get their children or themselves vaccinated, which they then remember to do. This intervention intervenes on the 'pathology' of forgetting to have a vaccination, or of forgetting the correct vaccination date and time, and is supported by psychological mechanisms. Prospective memory is a type of memory that involves remembering to perform a specific action at a future time: in this case, remembering the date and time of vaccination. Many factors can decrease the reliability of prospective memory, including the emotional and motivational state of an individual (Jeong and Cranney 2009; Rendell et al. 2011; Schnitzspahn et al. 2014). This evidence supports the existence of the mechanism of action, whereby reminders intervene on an individual's memory of the vaccination appointment, which might have been diminished by external stressors affecting their emotional state and/or their motivation to procure vaccination. However, the mechanism of action interacts with a number of other mechanisms. For example, parents might be aware that the risk of death or serious illness from COVID-19 in children is

[2] See Kelly et al. 2014; Kelly and Russo 2018 for discussions of how many of these mechanisms can interact.

minimal (Viner et al. 2020). This information may make them believe that it is not worth their while to get their children vaccinated against COVID-19. This belief figures in a separate psychological mechanism operating concurrently with the mechanism of action and counteracting its effect. Evidence that this counteracting mechanism also operates in the target population will undermine confidence that the mechanism complex will lead to overall effectiveness. This is why it is important to consider various potential pathways in the mechanism complex, rather than solely the mechanism of action of the intervention.

Crucially, it is not enough to simply have a *story* of a mechanism—for EBM+, decisions must be based on evidence. According to EBM+, one needs to systematically evaluate the mechanistic studies relevant to those key features of the mechanism complex that are not already established by prior evidence. Thus, mechanistic studies are treated in the same way that association studies are treated by standard EBM. EBM+ provides methods for the systematic review of mechanistic studies, and guidance for combining this evidence with evidence from association studies to make a judgement about the plausibility of causality. See Parkkinen et al. 2018 for a detailed guide to these methods, and Auker-Howlett 2020: Ch.3 for an example of EBM+ applied to an evaluation of a pharmaceutical intervention on Middle East respiratory syndrome (MERS). Here, we shall just note some general features of the EBM+ evaluation process.

The first task for an EBM+ evaluation is to assess the association studies to determine whether they establish the existence of an appropriate correlation and an appropriate mechanism (evidential channels C_1 and C_2 in Figure 1). See Williamson 2019 for a discussion of what counts as 'appropriate' here. Existing evaluation techniques (e.g., 'GRADE') can be applied. If correlation and mechanism are both established then causation is established.

If a correlation has been found but it is not clear that this correlation is causal—i.e., attributable to an underlying mechanism—then the next step is assessing the quality of the individual mechanistic studies. To be rated as high quality, the methods used in the studies must be well understood, the experimental system must be similar to the target system, and the methods must be implemented properly.

Then one needs to consider whether the mechanistic studies establish the key features of the mechanism complex (M_1).[3] This is done on different grounds: do we have multiple studies showing consistent results across similar and different kinds of methods? In effect, we are checking here for a kind of robustness of results to changes in background conditions.

If evidence is missing for key features of the posited mechanism, or the mechanism could not plausibly account for the size of the observed correlation, then one's confidence in the mechanism is undermined (M_2). On the other hand, one's confidence may be raised if all the key features of a mechanism are confirmed in sufficient detail and if the mechanism can account for the correlation and its size. Only those mechanistic evidence bases that are high quality and support high confidence in a mechanism claim can establish the existence of a suitable mechanism complex. The status of a mechanism complex is then a function of both the quality of evidence and one's confidence in the mechanism complex. For example, the status is *established* when high quality evidence warrants high confidence

[3] See Parkkinen et al. 2018: 83-84, and Steel 2008 on what constitute 'key features' of a mechanism.

in the claim but only *provisionally established* when moderate quality evidence warrants high confidence. Lower status levels include *arguable*, *speculative*, *arguably false*, *provisionally ruled out* and *ruled out* (Parkkinen et al. 2018: 27).

The challenge for research on vaccination uptake is to articulate, evaluate and integrate mechanistic evidence, in order to design and assess interventions. EBM+ offers a method for systematising this process. In the next two sections we analyse two case studies to show how the EBM+ methodology can be employed to improve current practice.

4. SMS Reminders and Cash Incentives for Increased Vaccination Coverage

Our first case study is one in which the evidence base has significant deficiencies.

4.1 The Evidence Base and its Limitations

As noted above, one kind of intervention to boost vaccination demand involves *reminders*: these take the form of phone, text or email reminders sent to the individuals to be vaccinated or to parents of children to be vaccinated. Vaccine reminders have been extensively investigated as an intervention in HICs. A Cochrane review including a meta-analysis of 55 studies found that reminders increased vaccination rates by 8% (Jacobson Vann et al. 2018). What evidence there is arising from association studies in LMICs has been reviewed by Merriam and Behrendt 2020, who conclude that reminders are 'generally effective'. However, both evidence bases are beset by numerous problems with the quality of evidence: there are a number of defects of the evidence base.

In the LMIC evidence base, variability of intervention is a problem. Indeed, some studies implement a combination of interventions. For example, a large RCT in Kenya supposedly demonstrates the effectiveness of SMS reminders, but in fact it is SMS reminders plus cash incentives that are associated with increased vaccination uptake (Gibson et al. 2017). A trial arm testing only SMS reminders displayed no increase in uptake relative to controls. There is another form of variability of intervention: different kinds of reminders. For example, another RCT, this time in Nigeria, found that phone call reminders were effective compared with a training programme for health care workers (Brown et al. 2016). This result was corroborated by Ekhaguere et al. 2019. Thus the evidence can be interpreted as supporting the effectiveness of phone call reminders, but not SMS reminders. The small size of the LMIC evidence base exacerbates this problem, while the larger HIC evidence base for each kind of reminder may ameliorate the issue.

A second defect of the LMIC evidence base concerns specificity of outcome. The conclusion of Gibson et al. 2017 was that SMS messages together with cash incentives were effective at increasing vaccination coverage. However, the results of the study do not support this general conclusion. Vaccination coverage here refers to 'full immunisation' of 8 vaccines, yet only for the measles vaccine was there a significant increase in coverage. Baseline coverage—measured for the control group—was near 100% for the other 7 vaccines. An increase from 87% to 90% in the measles group boosted the average. This pattern of results is replicated by Ekhaguere et al. 2019. A more precise claim is that reminders are effective for increasing measles vaccine uptake. This is no mean feat of course, but in these

cases the claim should have been made specific to the vaccine, rather than to vaccination in general. Compounding this problem is the high baseline coverage in the studies of Gibson et al. 2017 and Ekhaguere et al. 2019. Interventions on vaccination uptake are motivated by the fact that baseline coverage is generally below levels sufficient to ensure population immunity. Recall from §1 that the WHO GVAP sets a target of 90% coverage for all vaccines (WHO 2013). In the study of Gibson et al. 2017, even the measles vaccine baseline was 87%, and the remaining 7 vaccines ranged from 96% to 98%. The authors hypothesised that this was due to the high rate of study dropouts, consisting of the poorest, most mobile and youngest mothers. Plausibly, such people are those who are the primary targets of uptake interventions. Thus the sample tested in this study appears to be highly unrepresentative of the target population. The results of Ekhaguere et al. 2019 are less worrisome. Although only coverage for measles and the third of three doses of pentavalent vaccine (a combination vaccine for diphtheria, tetanus, whooping cough, polio, and Haemophilus influenzae type b disease) is lower than the 90% target, the dropout rate was only 8%. So in the context of those specific vaccinations the reminders may still be effective. Thus, a third defect of the evidence base concerns the representativeness of the sample.

A fourth defect that affects both evidence bases arises from a lack of blinding of participants or researchers to trial arm allocation. For example, Haji et al. 2016 reported that researchers checked up on one trial arm whose participants were given stickers to remind them of vaccination dates. This would have involved researchers knowing which trial arm the participant was in and opens the possibility that these interactions influenced outcomes—a form of bias. Performance bias and detection bias both result from lack of blinding of trial personnel to study group allocations. Jacobson Vann et al. 2018 rates 28% of studies conducted in HICs to be at low risk of performance bias, 66.7% at unclear risk, and 5% at high risk. For detection bias, figures are 29.3% low, 68% unclear, 2.7% high. One example of a study at low risk of both kinds of bias is an RCT on the effect of reminder/recalls (Szilagyi et al. 2013). While trial personnel were indeed blinded to study group allocations, trial participants were not. The review does not consider the kinds of biases resultant from lack of blinding of trial participants. The problem is that it is plausible that the participants' knowledge of being in an experiment may be what influences vaccination uptake, rather than the intervention itself. Worse still, there may be a general inability to blind participants in studies in the social sciences (Cartwright and Deaton 2016). So this defect may be unavoidable for vaccination uptake research.

4.2 An EBM+ Perspective

A closer scrutiny of the LMIC evidence base reveals that the evidence base only slightly supports the effectiveness of reminders, and that this is only for phone call reminders and only for the measles vaccine. A review of specific kinds of reminders, or studies that test single vaccines, might be more informative. This recommendation accounts for defects 1-3 and is in line with the EBM perspective: the standard response to defects in the evidence base is to demand more and better trials to be carried out. Large scale trials are costly and time consuming, but funders may see the worth of carrying out trials if vaccination coverage can be boosted. However, even if resources can be committed to more trials, it is not clear that the EBM perspective can resolve the issues presented here. The fourth

defect is something quite general that might limit all trials performed in this context—it is very difficult to come up with "placebo" reminders.

From the perspective of EBM+, it seems plausible that the studies establish that a correlation exists between reminders and vaccine uptake. The errors that thwart a causal conclusion could be explained away if one could establish that an appropriate mechanism complex exists linking reminders and vaccination uptake. The basic logic of an EBM+ causal evaluation would then lead us to attribute the correlation to a causal relationship. Let us first apply this logic to the reminder case, and then advance some reasons why this improves on the EBM perspective. Take for example Haji et al. 2016, where researchers might have known who was in each group. One plausible explanation of the observed correlation is that researchers knowingly or unknowingly influenced participants in the SMS reminder group to get vaccinated. Were we however to establish that there is a mechanism of action linking SMS reminders to vaccination uptake, and that other mechanisms in the target population could not fully counteract the mechanism of action (see §3), then this would warrant greater confidence in the effectiveness of the intervention in the target population.

Note that, on both the EBM and EBM+ perspectives, low-quality clinical trials fail to establish *causation*, but on the EBM+ perspective such trials may still provide high-quality evidence of *correlation*. Similarly, mechanistic evidence does not normally suffice to establish causation on either perspective, but EBM+ treats this kind of evidence seriously, and can evaluate it as high-quality evidence of *mechanism*. Taken together, such evidence can be high-quality evidence for causation. Thus, one reason why the EBM+ perspective improves on standard EBM is that it appeals to different kinds of studies, which can reinforce one another. The standard problems that make it hard to infer causation just from mechanistic studies (the complexity of mechanisms, and the presence of counteracting mechanisms, both of which makes it hard to establish a net correlation) are different to those that make it hard to infer causation just from association studies (bias, confounding, statistical blips, non-causal connections). Establishing a correlation is just what is required to overcome the limitations of mechanistic studies, and establishing the existence of a mechanism is just what is required to overcome the limitations of association studies. Thus, by considering both sorts of study together, EBM+ can avoid the pitfalls of each.

The EBM+ approach can also enable quicker decisions, which may be vital in resource- and time-limited contexts such as vaccination uptake research. Repeating trials takes time and money. We have recently seen the need for timeliness in COVID19 vaccination research, and, as Aronson et al. 2021 show, a consideration of the mechanisms at play can lead to a more conclusive evidence base, obviating the need for further association studies. Mechanistic studies can be carried out concurrently with, or very often before, association studies. A causal evaluation including both trial and mechanistic evidence can then be carried out at the close of the trials.

It is important to note that the problem with the current research on reminders is a lack of evidence of mechanisms—not evidence that there is no mechanism. This means that the effectiveness claim is still open, and that more research into relevant mechanisms may well help. An EBM+ approach therefore helps to identify the gaps in the evidence base which need to be filled by commissioning further research. Another advance that EBM+ offers in this area is in the *evaluation* of

mechanistic evidence. It is not enough to just *conduct* mechanistic studies. A systematic approach to evaluating evidence is also needed—this is something that both EBM and EBM+ agree on.

In the next section we identify some methods currently used in public health interventions to evaluate mechanisms, and how EBM+ may improve on these methods.

5. The Welsh National Exercise Referral Scheme

Our second case study is an example of a public health intervention for which there is stronger mechanistic evidence. Although this case is not related to vaccination, it is instructive because it helps to show what constitutes a strong evidence base, as well as the usefulness of EBM+ in framing the assessment of the evidence base.

5.1 The Evidence Base

Increased physical activity is an important means to reduce chronic disease. The Welsh national exercise referral scheme (NERS) implements an intervention to increase physical activity, namely *exercise referral*. Exercise referral schemes (ERS) "typically [...] involve health professional referral to a leisure facility, agreement of an exercise programme with an instructor, and discounted access to leisure facilities for 10–12 weeks" (Littlecott et al. 2014: 2). The study that assessed NERS was a pragmatic RCT (Murphy et al. 2012) which found that "the intervention was associated with significant improvements in physical activity for patients referred with coronary heart disease risk factors (though not for patients referred for mental health reasons)" (Littlecott et al. 2014: 2).

However, ERS have in general seen little long-term impact on physical activity. This may be explained by a number of factors: ERS are heterogeneous in design; they differ in their mechanisms of action (e.g., one intervention may increase social support by forming new social groups in class-based exercise, while another directly targets an individual's motivation); and demographic factors and health conditions can each affect physical activity. Evaluating the mechanisms at work in particular schemes is a way to explain whether, why and how the intervention worked.

It is now recommended that process evaluations be used to evaluate complex interventions (Craig et al. 2008; Moore and Evans 2017; Craig et al. 2019). The primary goal of this kind of evaluation is to refine the implementation of the intervention, by taking account of the social and behavioural mechanisms that the mechanism of action interacts with. For NERS, to understand the theoretical assumptions being made by the design of the intervention, and the mechanisms by which the intervention brings about the effect, a mixed methods process evaluation was undertaken (Moore et al. 2013; Littlecott et al. 2014). This evaluation used quantitative and qualitative studies to identify key psychosocial mediators as well as factors that influenced whether the intervention was effective or not.

A qualitative study used interviews to "explor[e] patients' motivations for attending NERS, their opinions of the scheme, perceived impacts, mechanisms of change, barriers and facilitators of attendance and future exercise intentions" (Moore et al. 2013: 483). This study found that important factors for success were: effective professional supervision and guidance; having the social support of other

patients; and the range of classes, times and locations. Such factors are key components of mechanisms crucial to how NERS brought about its effect. For instance, having adequate social support was found to be crucial to adherence in NERS. But social support was often dependent on having a referral from a physician. This was because the participant's family were more willing to support their efforts when referral came from a health authority, as the scheme was perceived as important for improving more than just general fitness. So the social support mechanism also includes referral from a physician. Psychological theory also suggests a number of mechanisms by which NERS brings about its effects. Change in activity is hypothesised to occur when individuals have high levels of autonomous motivation, e.g., when they find an activity enjoyable. Indeed, autonomous motivation is associated with increased physical activity. When individuals see some behaviour change as an effective means of achieving desired outcomes, and as within their capabilities, they are more likely to enact that change. This 'self-efficacy' mechanism has again been associated with increased levels of physical activity.

A quantitative study tested whether referral to NERS was associated with effects on these mechanisms at 6 months, and whether impacts on physical activity were mediated by change in the mechanisms at 12 months. To test for effects on these hypothesised mediators at 6 months, participants were interviewed and effects were assessed by regression tests. Assessing whether a variable mediates change in physical activity involved statistical tests that looked for: (i) whether the proposed mediator is associated with the outcome (by separately calculating estimates for the effects of the intervention and mediator on physical activity while adjusting for the other variable), and (ii) what proportion of the total effect is explained by indirect effects (Littlecott et al. 2014: 4-5). This assessment found significant effects for autonomous motivation and social support for exercise, but none for self-efficacy. The authors conclude that the intervention's effect on exercise activity is mediated by autonomous motivation, and that the findings of this analysis support the use of self-determination theory as a framework for development and implementation of the exercise referral scheme.

5.2 An EBM+ Perspective

In some ways, process evaluations align with EBM+ methodology. 'Theory' is being used to suggest specific mechanism hypotheses: psychosocial mediators are features of the mechanisms. The studies then provide evidence for the existence of these features, and for the existence of a mechanism complex that accounts for the correlation—in EBM+ parlance they are mechanistic studies. Additionally, the combination of the results of the association studies and the process evaluation is viewed as more informative than the results of the association studies alone. Thus, the use of the process evaluation demonstrates that it is feasible to consider mechanistic evidence when assessing complex public health interventions. However, a full EBM+ approach improves upon current methodology on two fronts.

Firstly, a process evaluation goes as far as testing features of mechanism hypotheses in mechanistic studies, but EBM+ goes further in requiring a systematic evaluation of evidence generated by these studies. Systematic reviews of the evidence obtained in association studies are commonplace in vaccination and public health research. EBM+ does not differ from EBM in this respect and provides its

own methods for the evaluation of mechanistic evidence (Parkkinen et al. 2018). This improves upon current methodology, because it is not enough merely to have some mechanistic evidence—that evidence must also be high quality. As described in §3, Parkkinen et al. 2018 provide guidance for evaluating the quality of mechanistic evidence and for integrating such evaluations with association study evidence to assess causal claims.

On its own, a process evaluation is less able to establish causality. The main difficulty is in establishing the existence of an appropriate mechanism. This is unsurprising, as the core goal of a process evaluation is to identify whether the intervention has been implemented correctly. The elucidation of relevant mechanisms is important for achieving this task, but the central goal of a process evaluation is not to articulate the mechanism of action in order to confirm causation. However, the studies conducted in the process evaluation for NERS would come out as providing strong mechanistic evidence according to an EBM+ evaluation: the experimental and target systems are almost identical; the methods are well established in public health research; and, both qualitative and quantitative methods identified autonomous motivation as a feature of the mechanism complex, thus demonstrating robustness of results. While the evidence is strong, it is not clear that any mechanism is definitively established—there are too many un-evidenced gaps in the mechanism complex. However, studies conducted outside of the process evaluation could also provide evidence for the relevant mechanisms at work in NERS. For example, Littlecott et al. (2014: 7) note that "improvements in autonomous motivation after attendance at an exercise referral scheme have been described by a number of previous studies" and provide one example: Markland and Tobin 2010. But only a full systematic evaluation of all the relevant evidence would allow those extraneous studies to bear on the status of the relevant mechanisms. This is something that EBM+ but not a process evaluation offers. The detail provided by an EBM+ evaluation evidently goes beyond the detail provided by the process evaluation.

Additionally, EBM+ benefits from its appeal to the *concept* of mechanism. Process evaluations talk of 'theory' and 'mediators', but it is not made clear that what is elucidated is a mechanism complex. Talk of 'facilitators' and 'barriers' in vaccination research is also rather impoverished, although perhaps more suggestive. On the other hand, EBM+ draws on a rich seam of work in the philosophy of science on how best to characterise mechanisms, e.g., Machamer et al. 2000; Illari and Williamson 2012; Craver and Darden 2013. Mechanisms decompose into component entities, activities and organisational features and are connected by processes. This richer characterisation helps because it is clearer where each feature acts in a causal pathway. In the NERS example, individuals have varying degrees of *autonomous motivation*, which is credited with playing a mediating role on the effectiveness of the programme. This psychosocial mediator is thus a feature of a mechanism, but it is clear that it is a component of a mechanism consisting of a much richer structure. Thinking about how this component acts on other components, and how that sequence is organised, facilitates a description of a testable mechanism hypothesis. One way in which this method is better than thinking in terms of 'mediators' of a causal pathway is that it includes organisational information.

Organisation is key to understanding the mechanism, and it is baked into the characterisation of mechanisms used by EBM+. Another benefit of a richer characterisation is that it helps to identify other features that are crucial to whether the

mechanism operates. For example, identification of two linked entities in a mechanism and no activity between them implies that an activity is missing from the mechanism description. Thus, the appeal to the concept of mechanism helps to identify gaps in the evidence base. This kind of reasoning is used widely in mechanism discovery (see, e.g., Darden and Craver 2002; Craver and Darden 2013), but it is also useful when evaluating the plausibility of mechanisms in intervention assessment—an evaluation of an incorrect characterisation of a mechanism hypothesis is evidently impoverished.

6. Conclusion

Aronson et al. 2021 suggested that an EBM+ approach might benefit several areas of COVID-19 research, including COVID-19 vaccination research. In this paper we have developed the case for an EBM+ approach to vaccination uptake research. The COVID-19 pandemic has demonstrated the problems that a mixture of vaccine hesitancy and logistical difficulties pose for vaccine roll-out. The EBM+ approach to intervention assessment is readily applicable to vaccine uptake interventions, because the barriers and facilitators to vaccination depend on local social and behavioural mechanisms. A mechanistic perspective leads to systematic scrutiny of mechanistic studies—and mechanistic models—in addition to association studies, and this broader evidence base can lead to better judgements of effectiveness. The mechanistic perspective can also aid the development and refinement of vaccination uptake interventions, and their extrapolation to new populations.

The foregoing analysis presents a positive picture of EBM+ compared with current public health intervention research: it provides a systematically evaluated evidence base supporting more accurate effectiveness judgements, and all grounded in a richer conceptual framework. The benefits of more accurate effectiveness judgements were discussed in §4, but the fuller picture presented here has further implications for vaccination research. Consider the 'increasing vaccination model' in Figure 2. The authors of the model constructed it to represent the multiple strategies for increasing vaccination uptake, and Merriam and Behrendt 2020 use it as a basis for conceptually organising different kinds of vaccination uptake research. However, this model would benefit from the kind of EBM+ treatment the analysis in §5 applied to process evaluations. In one respect, the model is a representation of a very high-level mechanism, e.g., "what people think and feel" is a feature of a mechanism hypothesis that affects a "motivation" feature. However, this mechanism will in reality be much richer, and the mechanistic models employed by EBM+ can capture this. Moving to an EBM+ approach would thus improve the 'increasing vaccination model' by increasing its accuracy. For example, 'reminder' interventions are categorised by Merriam and Behrendt 2020 as a set of interventions that deal with passive under-vaccination, which arises from ambivalence, uncertainty, or logistical issues. Factors that contribute to passive under-vaccination fall into the 'what people think and feel' element of the model. So reminders intervene on thoughts and feelings and bring about effects on 'motivation'. Brewer et al. 2017 suggest that successful vaccination uptake will often require employing multiple strategies, and the model makes sense of how they all fit together. One can categorise various interventions according to the model and work out which strategies they will be similar to, or which they will be causally downstream from. Yet without knowing the key details of the various mechanisms that reminders are intervening on, this model tells us little

about how they may integrate with other strategies, e.g., cash transfers. In fact, without more detail, and as independent mechanisms often counteract one another, it is plausible that the mechanisms of action of the various vaccination uptake interventions counteract one another as well. If such models are to inform reasoning about vaccination uptake interventions, the detailed mechanistic models employed by EBM+ are a better option.

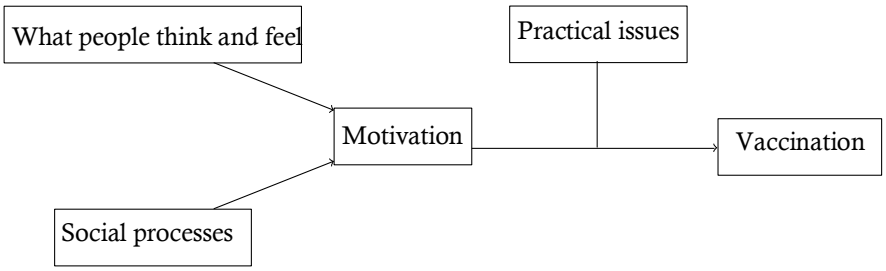

Figure 2: Increasing vaccination model, derived from Brewer et al. 2017.

With all that said, one might think that establishing mechanisms in complex public health interventions—such as COVID-19 vaccination uptake interventions—will simply be too difficult. Research into mechanisms in the biomedical sciences can isolate and manipulate systems in laboratory studies. Research on the behaviour of humans is more limited in this respect. So asking for mechanisms in order to establish effectiveness might seem to be setting the bar too high. However, as we noted above, behavioural mechanisms can be and have been established. Moreover, even where causation cannot be conclusively established, EBM+ nevertheless facilitates judgements about the relative plausibility of the effectiveness of several interventions. Relative plausibility is important, as recommendations on the widespread implementation of interventions need not be restricted to interventions for which effectiveness is established. Indeed, the GRADE system separates judgements of effectiveness from judgements of the adequacy for recommendation. Judging adequacy involves assessing benefits and costs of both intervening and failing to intervene (Andrews et al. 2013). If the evidence for the effectiveness of an intervention is less than conclusive, but there are few costs, then a recommendation for widespread implementation may yet be reasonable.[4]

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