

COVID-19: has EBM been replaced by hype-based medicine?

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When Donald Trump said that he had a 'good feeling' about hydroxychloroquine in the treatment of COVID-19, I had a bad feeling. In the midst of a pandemic, we are in a period of instability, which brings the potential of benefit—a loosening of bureaucratic restrictions—and risks—again, a loosening of bureaucratic restrictions. The situation is dramatic and understandably frightening. Emotions are high. No one is safe. Because we are in the middle of a pandemic, the argument goes, we cannot wait for trials. We feel compelled to do something.¹ We cannot allow people to die before randomised controlled trials are reported: we are urged to act. The inference is that the slow-footed are effectively killing family, colleagues, friends. It is usually easier and more popular to do something visibly and quickly than not. Of the influenza pandemic that followed the First World War, George Soper, a sanitation engineer wrote, in the journal *Science* in 1919: 'if doubt arises as to the probable efficacy of measures which seem so lacking in specificity it must be remembered that it is better for the public morale to be doing something than nothing and the general health will not suffer for the additional care which is given it'.²

Soper is right and wrong. The problem is that doing 'something' is often worse than doing nothing. To the external observer, this can look uncaring, unwilling, unbothered and negligent. Bed rest for back pain, routine counselling after traumatic events, vitamin supplements (A in particular) to prevent cancer, prone sleep positions for babies. All have been caring interventions which ended up harming people. The 'general health', as Soper has it, may in fact suffer. This means that we must know whether what we offer is useful and whether the benefits outweigh the harm. It is possible to improve morale through visible action—but kill people in the process. As Andre Kalil wrote in *JAMA* in March, 'The administration of any unproven drug as a 'last resort' wrongly assumes that benefit will be more likely than harm'.³ The 'certain uncertainty' over effective treatments in

this pandemic requires action, otherwise 'acquiescence in 'informed uncertainty' sometimes results in avoidable suffering and death on a wide scale'.⁴ In a pandemic, speed is crucial. The normal lead times for setting up trials must fall in order to be most useful. And indeed the planning that the WHO, and others, have done to ensure that quality research is done in the context of a pandemic is likely to have contributed to almost a thousand clinical trials being registered on the subject of COVID-19 as I write in May 2020.^{5,6}

But quantity is not quality. Out of the many interventions tested for Ebola, during the outbreak of 2014, only one (a triple monoclonal antibody cocktail) was investigated in a randomised controlled trial, leading to the conclusion that the 'tragedy of not discovering new therapies during an outbreak cannot be repeated'.^{3,7} Preprints may be widely shared and direct practice, but the speed of production may not be matched by critical analysis and the need for replication. Despite the lack of evidence for effective peer review it is not clear what happens when we do without it altogether.⁸ Yet, despite all the challenges of the Ebola outbreak, it was demonstrated that it is possible to conduct a randomised controlled trial in the context of a major public health emergency. Bravo, therefore, for the PRINCIPLE (Platform Randomised trial of Interventions against COVID-19 In older people), RECOVERY (Randomised Evaluation of COVID-19 Therapy) and REMAP-CAP (A Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia) trials (<https://www.recoverytrial.net/>), now underway, that are adaptive, agile and based on rigorous scientific principles.⁹

But we also need to know about non-drug interventions. An impassioned debate is currently taking place about whether the public should be compelled to wear cloth face masks. There are no trials of cloth mask use in the general population. A common argument is that trials would be too slow

and we cannot wait. The distress caused by a pandemic creates an urge to act before evidence is understandable. But corona will likely be with us a long time, and it is too important not to know what is, and is not, most effective against it. Knowledge about effective and ineffective interventions allows us to rely on useful measures and dismiss those which are not. A pragmatic, real-world randomised trial of delivering face masks and education on their use in one geographical population versus another 'usual care' group would be possible, especially with the use of smartphone technology monitoring for suspected or known cases. Research assessing and comparing behaviours of people choosing to use masks in public spaces such as transport systems is possible. All interventions in medicine have some sort of potential hazard. We do not know if people wearing masks will behave in ways which makes them accrue higher risks through a false sense of security, that changes society as a result. Reliance on a non-evidenced intervention may do harm to the population when it does not work yet is assumed to do so. We will only fully know the benefits and harms through high-quality research. It would be of grave concern if research into non-drug interventions was treated as second class. We must ensure that we continue to interrogate the uncertainties of COVID-19, review the totality of research to ensure we are not missing important data, register and report trials, and press for better, not necessarily more, research. Pandemics may feel frightening, but even more frightening is annexing the scientific method in dealing with it.

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