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Balancing benefits and potential risks of vaccination: the precautionary principle and the law of unintended consequences

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Abstract

Vaccination is a life-saving endeavour, yet risk and uncertainty are unavoidable in science and medicine. Vaccination remains contentious in the public mind, and vaccine hesitancy is a serious public health issue. This has recently been reignited in the discussion over potential side effects of COVID-19 vaccines, and the decision by several countries to suspend measures such as the AstraZeneca vaccine. In these instances, the precautionary principle has often been invoked as a rationale, yet such heuristics do not adequately weigh potential harms against real benefits. How we analyse, communicate and react to potential harms is absolutely paramount to ensure the best decisions and outcomes for societal health, and maintaining public confidence. While balancing benefits and risks is an essential undertaking, it cannot be achieved without due consideration of several other pertinent factors, especially in the context of vaccination, where misguided or exaggerated fears have in the past imperilled public health. While well meaning, over reactions to potential hazards of vaccination and other health interventions can have unintended consequences, and cause lingering damage to public trust. In this analysis, we explore the challenges of assessing risk and benefit, and the limitations of the precautionary principle in these endeavours. When risk is unclear, cautious vigilance might be a more pragmatic and useful policy than reactionary suspensions.

The advent of several effective vaccines against the scourge of COVID-19, created in record time, is a towering medical and scientific triumph. These interventions have the collective ability to stem the deadly tide of COVID-19, and ultimately to banish the sheer misery the pandemic has wrought. Yet optimism has been somewhat marred by reports of an unusual type of blood clot associated with both the AstraZeneca vaccine (Vaxzevria) and the Johnson & Johnson's Janssen vaccine.

This phenomenon, currently dubbed vaccine-induced thrombosis and thrombocytopaenia (VITT),[1] has dominated discourse on vaccine safety worldwide. This has been especially pronounced in Europe, with several European nations opting to temporality suspend the AstraZeneca vaccine in March 2021. Following the European Medicine's Agency clarification that 'benefits of Vaxzevria outweigh its risks in adults of all age groups',[2] suspensions were reversed in many countries, but a sense of scepticism remains. In several states, reintroduction came with additional restrictions, including France, Spain, Finland, Sweden and Germany, limited to only older groups. It remains suspended in Denmark and Norway.

In the USA, Johnson & Johnson's similar offering was also temporarily suspended by the FDA, based on similar rare reports, and born of what the FDA described as an 'abundance of caution', with use of the vaccine since been resumed. In both the USA and Europe, however, opinion on the wisdom of these suspensions has been polarised, with many regulatory bodies quite reasonably insisting that investigatory pauses are vital to maintain safety standards and public confidence. The opposite, equally reasonable position, argues that suspensions based on such limited data were damaging over-reactions to events which occur at most a handful of times per million.

Vaccine safety itself is a topic long contentious in the public mind. It is also impossible to consider the issue divorced from the deadly reality of COVID-19. This ongoing debate is a microcosm of how we deal with risk and uncertainty - and one from which it is vital we draw some important lessons.

Emergent risks and uncertain data

A total of 252 cases of thrombotic events with low platelet counts following Vaxzevria vaccination were reported by 28 April 2021 in the UK,[3] of which 93 were cerebral venous sinus thrombosis (CVST). With 22.6 million doses given by the same date, this suggests an incidence of approximately 11.15 cases per million people vaccinated (4.12 cases CVST per million vaccinated). Estimated background incidence of CVST ranges from 5 to 15 cases per million people per year,[4] this in isolation might seem to imply no obvious elevation due to the vaccine. But emergent cases of postvaccination CVST coincide with low platelet count, an unusual combination potentially hinting at a deeper association. Interpretation, however, is complicated by the fact that there is only limited data on the incidence of CVSTs occurring with thrombocytopaenia.[3]

The ongoing situation is a perfect exemplar of the difficulties of making decisions when data is limited and in rapid flux; both typical CVST and VITT are vanishingly rare, and even a handful of recorded events can skew interpretations. This renders estimates of true incidence intrinsically

uncertain, compounded by the fact that CVST incidence itself varies with age, sex and other risk factors—the conceptive pill, for instance, is associated with a sevenfold increase in CVST risk for women aged 15–50.[5] And while COVID-19 infection itself is associated with both substantially increased risk of CVST[6] and reduced platelet count,[7] the available evidence to date suggests that the specific combination of thrombotic events and concurrent thrombocytopaenia is not a common feature of COVID-19 infection.[3]

Available data on VITT too are transient and subject to change: initially, it was hypothesised that condition might only affect females, but this position has evolved with growing evidence. Risk, however, does appear elevated in younger cohorts—UK data to date suggests that the incidence in those aged 18–39, the risk of these side effects could be as high as 1 in 50 000—roughly double that of other age cohorts.[3] Yet making a causal connection is a fraught affair, and it remains unclear whether the association is due to the vaccine platform, some unknown immunological mechanism or even whether the relationship is spurious.

The precautionary principle

It would of course be completely remiss if national health bodies failed to react to evidence of harm, regardless of how rare or evanescent this signal might be. For regulators across Europe, the decision to suspend AstraZeneca's offering was justified by invocation of the precautionary principle. This concept itself originated in 1970s German law as the Vorsorgeprinzip, or the principle of foresight, with the laudable aim of regulating potential hazards from air pollution. What exactly it entails, however, is not always clear, as there is no universally accepted definition of the precautionary principle,[8] rendering interpretations of the principle somewhat nebulous. Broadly speaking, variants of the principle can be categorised as either 'weak' or 'Strong', with some common variants given in box 1.

Weak formulations of the precautionary principle are rarely controversial, and widely practised: very few of us would object to wearing a seat belt to mitigate against the low but plausible risk of being in a car accident, for instance. In this respect, the weak formulation has even been described by some authors as a truism.[9] Strong variations illicit far more criticism; one recurring criticism has been that these formulations are inherently one sided, making no attempt to balance risk and benefit. Other authors have argued the principle is entirely logically inconsistent.[10] Sunstein points out that the principle in this formulation is self-defeating, noting that there are 'risks of one kind or another are on all sides of regulatory choices, and it is therefore impossible, in most real-world cases, to avoid running afoul of the principle'[9] in its strong formulation.

It is important to note that the principle itself is designed solely when considering plausible threats in an environment of uncertainty. The European commission suggest that '…recourse to the precautionary principle presupposes that potentially dangerous effects deriving from a phenomenon, product or process have been identified, and that scientific evaluation does not allow the risk to be determined with sufficient certainty.'[11] Crucially, the precautionary principle only applies to uncertainty, for situations when an activity poses a plausible risk of harm and when the extent of that harm is unknown. It explicitly does not apply in situations where the risk of harm can be accurately quantified, and a desired level of protection defined. It is mistaken to conflate risk and uncertainty in applications of the principle, as it only applies reasonably to the latter scenario.

Box 1 Weak and strong formulations of the precautionary principle

Weak (or minimal) interpretations of the principle maintain that scientific uncertainty does not justify inaction, and legislation or safety measures may be warranted despite an absence of complete scientific or medical evidence concerning specific hazards. Variations include:

- 'Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation'—Rio Declaration (1992)
- 'When human activities may lead to morally unacceptable harm that is scientifically plausible but uncertain, actions shall be taken to avoid or diminish that harm'—UNESCO (2005)

Strong (or maximal) interpretations, by contrast, reverse the burden of proof for harm, and insist that scientific uncertainty necessitates legislation or suspension until the absence of hazard has been proven. Formulations include

- 'When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not established scientifically. In this context the proponent of the activity, rather than the public, should bear the burden of proof.'—Wingspan declaration (1998)
- '[When] potential adverse effects are not fully understood, the activities should not proceed'—United Nations World Charter for Nature (1992)

Balancing risk and benefit

The precautionary principle is well intentioned, but it is no substitute for evidence-based decision making. Risk itself is rarely a monolithic entity and must be considered in context—ascertaining whether an intervention is ultimately beneficial or detrimental requires an investigator to be cognisant of other factors. With regard to vaccination, this means that rare or hypothetical harms must be contrasted with the very real and substantial harms of the disease itself. Consider the case of younger cohorts; while they are less at risk of death from COVID-19 than older groups, the infection fatality rate in this group is not zero, with recent estimates putting it at approximately 1 in 2500. From UK data, the incidence of VITT in this cohort is $p_v = \frac{1}{50000}$, with an overall fatality rate of $f_r = 0.2$, or 20%.[3] To a first approximation, benefits of vaccination in this group outweigh potential harms when

$$(I_{FR})\, E > p_v f_c$$

where E is the exposure to COVID-19 in a particular grouping, presuming that VITT is a direct consequence of vaccination. This calculation however is not trivial, because one's exposure risk to COVID-19 is highly dynamic and dependent on several factors, chiefly population incidence and the rate eligible people are vaccinated in that population. In the extreme situation where everyone in the younger cohort was instantaneously vaccinated, this would imply four deaths per million from VITT, if no risk mitigation for thrombotic events was undertaken. At the opposite extreme, if an entire young population were infected at once with

no vaccination, one would expect about 400 deaths per million from COVID-19, a figure two orders of magnitude greater. Neither situation is of course realistic, because the dynamics of those infected and vaccinated vary with time. Additionally, VITT risk, when pre-empted, can be mitigated against. Even in populations at potentially elevated risk of adverse effect, high rate of vaccination remains the optimum scenario for the well-being of the entire cohort until incidence of COVID-19 in the population is extremely low.

Public perception and the law of unintended consequences

Faced with a non-zero risk of harm, it was understandable that some regulators moved to suspend the AstraZeneca vaccine. But while understandable and well meaning, this was not a zero-risk strategy. The first reason is pragmatic; suspensions of an effective vaccine inevitably leave vulnerable people unprotected from the virus, prolonging the pandemic. Nor do suspensions mitigate the spread of COVID-19, or stem the tide of hospital admissions and needless deaths the vaccine prevents. This harm becomes even more severe when we consider ramifications beyond the calculus of risk and benefit. Public confidence and perception of risk are not mere functions of the data, but reflect broader media, psychological and communication influences.

The controversy over this vaccine highlights a glaring problem in modern science: the disconnect between scientific and public understanding of adverse effects. In our hyperconnected world, misleading narratives can quickly take hold, to our detriment. Reporting of the hypothetical risks of the vaccine tended towards hyperbole, and frequently did not give sufficient context for a reader to infer that benefits outweighed potential risks . This feeds into a spiral of mistrust where harms are perceived as amplified while benefits are side lined in discourse over interventions like vaccination. This is not unexpected—public perception is inherently affected by regulatory action and skewed reporting examples of which are given in box 2.

Vaccine hesitancy is a spectrum,[12] and while vaccine suspensions are carried out by regulators in good faith, it takes very little effort for bad-faith actors to present this as unassailable evidence of harm to an unsuspecting audience, nudging people away from vaccination. This effectively means that laudable attempts to be transparent with potential risk with the aim of reassuring can be weaponised into achieve the precise opposite—a grim example of the law of unintended consequences. Even before the pandemic began, antivaccine propaganda was a serious threat to public health.[13] Exposure to antivaccine conspiracy theories had a marked negative impact on parental intention to vaccinate,[14] and a dark renaissance of once virtually conquered diseases across the world led the WHO to declare vaccine hesitancy a top 10 threat to public health in 2019. Antivaccine myths have undergone an alarming resurgence online, with a staggering rise in targeted disinformation and conspiracy theories propagated about the vaccine.[15] It is thus crucial that decisions and communication on vaccine safety are taken with full cognisance of how they could be perceived by vested interests, and effects this might have on wider public perception. As Heidi Larson noted, vaccine confidence is not down solely to trust in the medical and scientific professions, but '…trust in government and the policies they create is essential, along with the government's own trust in science to inform their policy decisions.'[16]

Responding to future risk and uncertainty

While it is crucial to accurately convey risk and uncertainty in all health endeavours, Voltaire's famous dictum about 'the perfect being the enemy of the good' is sometimes unfortunately realised in health settings, to our collective detriment. it is imperative that risks and benefits are carefully weighed up and contrasted, adjusted as the data becomes more robust. Moreover, it is critical to be cognisant of how public health actions might be perceived. When confronted with uncertainty, reacting before ample reflection is ill advised for two reasons. First, it increases the likelihood of making a poor

Box 2 Vaccination confidence crises and unintended consequences

- Measles-mumps-rubella (MMR) (UK, Samoa): In 1998, physician Andrew Wakefield asserted a fraudulent and now debunked link between MMR vaccination and autism. These claims were prominent in UK media in the early 2000s, and led to increased vaccine hesitancy, with MMR vaccine uptake declining from 92% in 1996 to 84% in 2006, and as low as 61% in parts of London in 2003, and numerous continuing avoidable outbreaks worldwide.[18] In 2018, the accidental death of two children in Samoa led to mass rejection of the MMR vaccine, stoked by antivaccine campaigners, driving vaccination rates to lows of 31%. A single case of measles that August ultimately led to over 5700 cases and 83 deaths by early 2020 in a country of just over 200 000 people.[19]
- Human papilloma virus (HPV) (Japan, Denmark, Ireland): Japan's Ministry of Health, Labor and Welfare temporarily suspend government recommendations for the HPV vaccination in 2013, following sensational media reports of women harmed by the vaccine. Even though these ostensible adverse effects were shown to have no causal relationship with the vaccine, uptake plummeted from 70% to less than 1% in a year.[13 20] Despite efforts to rebuild public confidence, uptake of the genital cancer-preventing HPV vaccine in Japan remains abysmal, estimated to cost over 11 000 lives in future.[21] Similar fears (perpetuated by antivaccine activists and eventually echoed by politicians and broadcasters) in Denmark in 2014 saw uptake collapse from 79% to 17%.[22] The following year, Ireland was hit by similar disinformation which saw uptake fall from highs of 87%–51% within a year. Ireland was able to reverse this trend thanks to sustained efforts from the government, health service, physicians, scientists and patient advocates.[23 24]
- Pertussis (UK): Press coverage of a 1974 report ascribing 36 reactions to the pertussis vaccine and suggestions by physician Gordon Stewart that the vaccine risks outweighed benefits initiated a scare, driving vaccine uptake down from 81% to 31%. A spate of pertussis epidemics and deaths ensued, despite mainstream medical opinion at the time being clear on the benefits of vaccination. Public confidence was only restored after the publication of a national reassessment of vaccine efficacy, which eventually saw uptake increase above 90%.[25]

judgement. Second, actions taken without full consideration of context and related issues can fall victim to unintended consequences and subpar outcomes. In the case of vaccination, this can manifest not only as temporarily diminished public health responses, but lingering damage to public confidence and increased vaccine hesitancy; as the adage reminds us, the road to hell is paved with good intentions, and an oversensitivity to ostensible side effects can lead to long-term confidence problems.

With regard to COVID-19 vaccination specifically, it is likely that potential harms were somewhat ameliorated by the existence of alternative mRNA vaccines. But future situations will arise when an inoculation or health measure does not have a ready alternate, as has happened historically (box 2). How we best navigate these scenarios in future is something with urgent relevance. The precautionary principle, while commonly invoked as a rationale for action, is only truly appropriate when risk cannot be quantified. Despite its frequent invocation, it is not an ideal heuristic to assess or respond to potential vaccination risks; weak formulations are unobjectionable but do not lead to any clear course of action. Strong formulations, by contrast, would insist that vaccination be suspended indefinitely, without consideration of the risks and harms of suspending a life-saving programme. More subtly, the precautionary principle is inappropriate when risk can be accurately quantified and should be applied only to uncertainty itself. When risk can be broadly quantified, then Risk-Benefit analysis[17] is more informative than more vague approaches.

So how might we proceed in future? Suspensions might be an over-reaction to small signals of harm, but conversely it would be irresponsible to ignore simply because it is small. But it is a false dichotomy to suppose the only choices are to continue haphazardly or outright suspend; perhaps a more pragmatic approach is the fusion of both schools; a cautious vigilance where vaccinated individuals are monitored for warning signs of rare side effects so that ill effects can be circumvented without impeding vaccine drives. Aided by mathematical modelling and constant monitoring, approaches should be flexible, and the risk–benefit balance constantly updated so that maximum benefit can be derived. How this is communicated too is of paramount importance—full transparency must be maintained in how decisions are made, lest adjustments in the light of new data are misinterpreted as the censoring of vaccine risks, which could inadvertently play in the narrative of antivaccine activists. This invokes the deeper question of how the reporting of adverse effects impacts public understanding, a complex question beyond the scope of this analysis. Even so, a cognisance of this dimension is vital on the part of policy-makers.

The inescapable reality is that while risks can be reduced, they can never be eliminated. Measures that mitigate one risk must be balanced with competing hazards, and the net benefit or harms considered; your car seat belt may decapitate you in an accident, but it is far more likely to save your life. Abstract and nebulous as risk can be, it is vital that perspective is maintained, and that positions evolve with emerging evidence. While true of all medical interventions, this is especially resonant with vaccination, which, despite incredible life-saving efficacy, remains contentious in the public mind. While striving to ensure safety, we should not overlook the fact that over-reactions to phantom safety signals in the past have inflicted lingering damage on public trust and health. To circumvent this, we must ensure decisions are evidence-based, can strike a considered balance between risk and benefit.

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Contributors DRG has international expertise in the spread of health disinformation and public trust in science. He also advises internationally on science and health policy, chiefly on vaccination and public understanding. DRG is the guarantor of this article.

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