RESEARCH ARTICLE

Vaccination with vector type vaccines – is it worth the risk?

"To jab, or not to jab, is that the question?"

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Abstract

COVID-19 has the potential to re-frame the whole debate about individual and societal risk, risk balancing, benefit-cost analysis, individual rights, societal responsibilities of individuals and responsibilities of Governments within the overall context that there are limits to what can be achieved in particular instances, and in totality across society.

There has been considerable discussion and debate globally about the real and perceived risks of having a vaccination against COVID-19. This might be interpreted as having contributed to the uncertainty in the vaccine debate and contributed to doubt and even erosion of trust in some of the population. Some of this has been due to an understandable demand for immediate answers, before the necessary and detailed data were available and verified. The recent publication of unexpected negative side effects from the Astra Zeneca version of the vector-type vaccine, "vaccine induced prothrombotic immune thrombocytopenia" (VIPIT), has been the latest complicating development, which has caused further concerns, uncertainties and confusion.

The risk figures that Governments use are derived from whole population data and processed to give a smeared out average "societal" risk. But to the individuals having to make the choice, these figures may, or may not, be relevant.

The corresponding societal estimate of an individual's chance of being stuck by lightning is the well-known 1 in a million. But individuals know intuitively that for someone who never goes out in bad weather, this is way too high. Conversely someone who goes out to fly a kite in a thunderstorm has an almost certain chance of being fried.

In this paper we discuss the current arguments put forward, which accept the 1 in a 100,000 as acceptable collateral damage for societal exposure. It then contrasts them against the numbers that could be derived, if it is approached from the point of view of a particular individual's risk benefit calculations. Subsequently we discuss how communication and information by policy makers and media may influence the decisions of individuals to have or not have themselves vaccinated. While the current debate about vaccinations provides data and the central focus of this paper, the issue is a general matter, it is symptomatic of a much wider risk question which the vaccine debate has brought into focus; and not just for other vaccines and medical interventions.

1 Introduction

There has been considerable discussion and debate globally about the real and perceived risks of having a vaccination against COVID-19. A number of distinguished Professors, Government ministers and officials have produced reams of data and statistics, which as they have been increasingly modified in light of experience, might be interpreted as having contributed to the uncertainty in the vaccine debate and contributed to doubt and even erosion of trust in some of the population. Some of this has been due to an understandable demand for immediate answers, before the necessary and detailed data were available and verified. This has been further exacerbated by the differing views that different regulatory and official bodies took on the significance of the various trials that were undertaken and the supporting contextual information qualifying them. These ranged from the early estimates of effectiveness (60 – 95%) to the importance of dose timings and quantities. This compares with an efficacy of 40-60% for the regular "flu shot".[1]

The changing and differing views of different Governments on the appropriate age groups that should receive the different vaccine options, also did not help particularly, as political and even nationalistic overtones became apparent. The recent publication of unexpected negative side effects from the Astra Zeneca version of the vector-type vaccine, "vaccine induced prothrombotic immune thrombocytopenia" (VIPIT), has been the latest complicating development, which has caused further concerns, uncertainties and confusion. In severe cases, thrombocytopenia can be fatal. There have been deaths from VIPIT associated with the AstraZeneca vaccine, including 19 in the United Kingdom at the time of writing.[2] According to data collated by the Thrombosis and Haemostasis Society of Australia and New Zealand, VIPIT occurred at 1 in 500,000 people vaccinated. But the society notes the data are incomplete. In the Netherlands the incidence rate was reported to be 1 in 100,000 and the associated deathrate 2 in a million.[3] Norway reported 1 in 25,000 vaccinated adults under the age of 65[2]. As naturally occurring thrombocytopenia affects about one in 30,000 adults a year in the United States, it seems to be more common in the general population than among those who have been vaccinated.[2] Soon after, the use of the Johnson and Johnson version of the viral vector was paused in the USA owing to the detection of a different type of blood clot, cerebral venous sinus thrombosis (CVST)[4] in a very small number of cases (6 cases in 6.8 million doses or approximately 1:1,000,000).

The official reaction in the United Kingdom (UK) has been that at an estimated chance of 0.000095% or approximately 1 in a million, was negligible, and the risk benefit analysis was overwhelmingly in favour of having the vaccination. The numerical value of what constitutes a negligible risk to an individual used by Government in the UK has been 1:1,000,000 for over 30 years.[5, 6]

The same numbers led other countries to ban the AstraZeneca vaccine altogether or restrict its use to the over 55s or over 60s. The argument used in those countries seems to be that although on average the benefits of the AstraZeneca vaccine still outweigh the disadvantages, this may not be the case for age groups under 60.

In this paper we discuss the current arguments put forward, which accept the 1 in a 100,000 as acceptable collateral damage for societal exposure. It then contrasts them against the numbers that could be derived, if it is approached from the point of view of a particular individual's risk benefit calculations. Subsequently we discuss how communication and information by policy makers and media may influence the decisions of individuals to have or not have themselves vaccinated. While the current debate about vaccinations provides data and the central focus of this paper, the issue is a general matter, it is symptomatic of a much wider risk question which the vaccine debate has brought into focus; and not just for other vaccines and medical interventions. For instance, in the case of flood protection s in

the Netherlands, if the flood defences comply with the new standards, the probability of 10,000 casualties is approximately equal to 1/100,000 per year.[7] In the United States, the US Army Corps of Engineers (USACE) has adopted an interim position where "The goal is to keep the risks associated with USACE program dam and levees from increasing the probability of death for an individual above annual mortality rates". The selection of USACE has chosen to use 1 in 10,000 per year (1E-04) for the probability of life loss for an individual or group of individuals most at risk as guidance.[8]. The 1:100,000 value of interest is thus within a range from what is often termed as being "just tolerable 1:10,000", to "essentially negligible, 1:1,000,000[5, 6]", 2001), a range that typifies risks to people from a broad spectrum of societal activities involving risk.

For the purpose of demonstrating the points made in the paper, the data used in this paper is readily available and pertains largely to the risk issues concerning the Astra Zeneca version of the viral vector type vaccine as set in the context of the mortality data amassed during the first year of the COVID-19 pandemic. It is expected that the approach is similarly effective means of examining the issues in other contexts and with other similar interventions.

2 The Science of Risk Analysis

For this paper, the most important issues when considering the risks of vaccination, are;

- the purpose of activity under consideration,
- the benefits,
- the costs in terms of side effects and
- the context in which the risk is assessed.

The purpose of vaccination is twofold. A vaccine protects the vaccinated individual against an illness, or at least against being seriously harmed by an illness. It also protects society against a rapid and wide spread of an endemic illness. Limiting the rate of spread of an endemic illness reduces the pressure on the health care system. It also reduces the probability that a virus mutates naturally towards a more dangerous variant, which better helps it to resist countermeasures and hence facilitates its preferential survival as a more lethal pathogen.

The lethality of COVID-19 depends on age and general condition such as pre-existing heart conditions and overweight. For most people the symptoms of COVID-19 are mild (Figure 1). For some patients, death is almost unavoidable, and treatment is restricted to palliative care. There is a strong dependency between age and lethality given infection. In most countries patients over 80 are not admitted to Intensive Care Units (ICU) because the probability of surviving that level of intensive treatment, is low for that age group. Below 30 most people infected show only mild symptoms. For the over 80's the policy is aimed and restricted to preventing infection as much as possible. For the age bracket between 30-80 treatment in hospital which saves lives. Therefore, if the health care system is overwhelmed and patients can no longer be admitted to hospitals, these patients are likely to die. This would at least double the number of deaths.

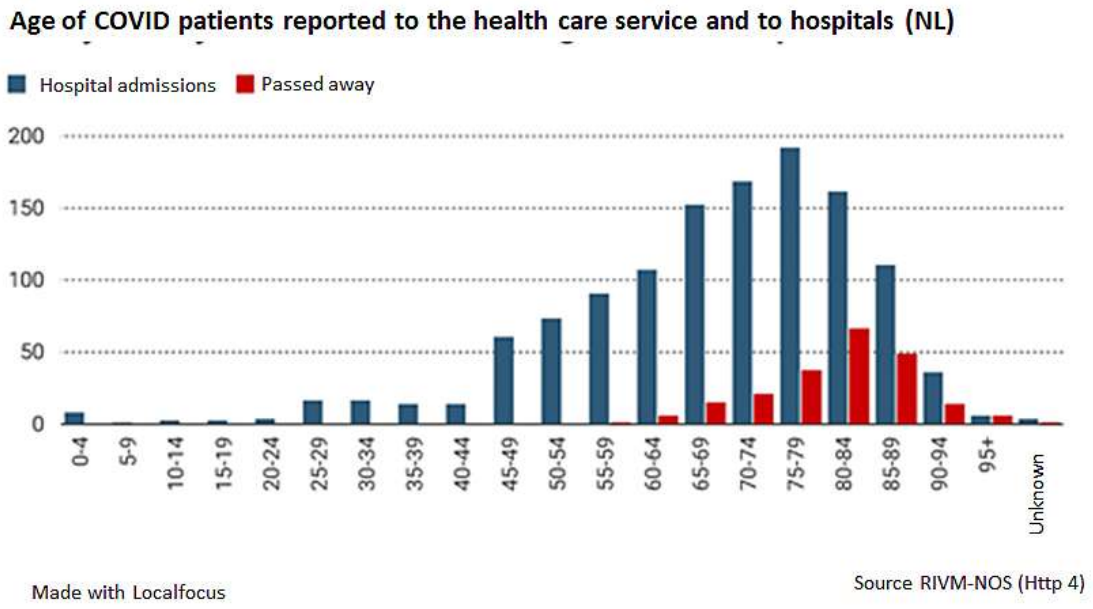

Figure 1: Age distribution of patients (adapted from Van Klundert (2021))

Therefore, most countries chose a policy to "flatten the curve". An additional benefit of these policies emerged when the vaccines became available. People that were not infected yet, could be protected against infection, serious illness and death, if they could be vaccinated before the infection reached them. In Europe, the race between the rate of vaccination and the rate of infection, was made more difficult, because of the emergence of the so-called UK variant (B 1.1.7), which is more infectious than the original virus; and which has emerged independently in several countries, but which first emerged in the UK during the Christmas holiday period, when the measures against spread of the virus where temporarily relaxed.

Infection rates can also be lowered by "herd immunity", although what constitutes "herd immunity" is debatable.[1, 9] For lethal and highly contagious diseases such as measles and poliomyelitis, vaccination programs are set up to create individual immunity at a young age and maintain herd immunity in the population. In this way the whole population is protected including the small percentage of the population that is not vaccinated, e.g. for allergic contra-indications. Herd immunity also results when enough people have been exposed and have gone through the illness. This is the case with the winter flu. Although it is deemed necessary to vaccinate the elderly, because for those, the effects of a flu can be lethal, or at least very serious, while the rest of the population has acquired enough resistance against the flu, due to previous exposures in previous winters; even although the flu virus, like all these viruses, mutates over time.

At the onset of the COVID-19 pandemic several countries contemplated letting the illness sweep through the population to create this herd immunity, but, in most countries, it became apparent that such a policy would lead to such a large number of deaths, in such a short period of time, that such a policy would not be accepted by the population. As we have described elsewhere,[10] in most countries there has been a counter movement from the onset claiming among other that the collateral damage of the anti-COVID-19 measures outweighed the benefits, often using Sweden as an example.[11] However even in Sweden, people were advised to

protect themselves and as a result, even there, the spread of the disease was too slow to achieve herd immunity before the arrival of vaccines started to support immunity. As it turned out later in the development of the pandemic, the level of individual immunity depends on the seriousness of the symptoms, which has the result that people with no symptoms do not necessarily become immune and keep spreading the virus – even without knowing themselves. This further complicates the debate especially if "herd immunity" is a policy factor.[12]

In summary, the policies of most countries were aimed at not overwhelming the health services. The measures taken, were mostly the minimum required given the available capacity of the health service and the rate of spread, to avoid excessive collateral – economic - damage. This is probably also the explanation as to why there appears to be not much difference in the effects of various stringencies of lock-downs, leading some authors to the erroneous conclusion that these measures did not make any difference at all.[13]

These measures though did have a societal effect of lowering overall numbers of death and lower overall death rates. It also affected the risk to the individual, by lowering the instantaneous number of infected people, which in turn lowered the probability of encountering an infected person: and it improved the probability of successful treatment in hospital, should the symptoms become serious.

With these considerations in mind, a conventional assessment of the risk can be made. The steps are:

- first determine what consequences are considered,
- second to determine what probabilities can be assigned to either the events that produce these consequences, or directly to the consequences and then
- to decide as to what metric to be used to express the risk.

2.1 *Consequences to be considered*

There is a range of consequences to be considered, both for a government as well as for each individual.

For governments, as we have noted, the expressed primary concern is of overwhelming the health service. Although there still is some discussion about the Infection Fatality Rate (IFR) and the Case Fatality Rate (CFR),[14] the estimates have not really changed since the onset of the pandemic. As an example, according to Vo[15,] the CFR was 2.3% and on 13/04/2021 according to CNN there were in the US 562,533 death in 31,268,400 cases amounting to a CRF of 1.8%.

However, without a vaccine, these fatalities are unavoidable. Any policy therefore is not aimed at fatalities, but at the number of patients that are to be admitted to hospital. The maximum number is determined by the number of "normal" and "ICU" beds available. This number is not easily expanded as this number is not so much determined by the number of physical beds, but the number of qualified staff, the training of which takes some four years.

The other major concern is the economic damage caused by any measure taken. In addition, there is the concern of public acceptance of measures, the psychological and sociological damage e.g. by confining vulnerable elderly to their quarters without contact with family and friends and long-term societal damage such as caused by prolonged closure of schools.

For individuals, the main concern is contracting the disease, being hospitalized, or dying. The other concerns are loss of income and not having a normal life. Because COVID-19 has had a much more negative effect on the elderly, and protection of society involves measures to be taken by all, the policy conflict between the young and the elderly was, and still is, inherent in the way COVID-19 affects people.

Vaccination influences all these consequences. In the first place the number of unavoidable deaths can be considerably reduced. Those who have not

died before they are vaccinated will most probably survive. For the Netherlands the number of deaths per percent of the population infected turned out to be about 2000, twice the official number at the end of 2020.[16] At the beginning of the vaccination campaign some 10% of the population was infected, meaning that still 90% of the population was not infected. Getting the vaccine to the people in time therefore potentially saves 90000 lives; if additionally, sufficient measures are taken not to overwhelm the health service during the time that the vaccination program is executed.

Once sufficient immunity is generated in the population, the economy can safely be opened again. It should be remarked though that such opening of the economy is not unrestricted. As long as the virus circulates in parts of the world, the interconnectivity between nations brings the risk of transporting mutations from one part of the world to another. But the remaining restrictions probably will only affect minor parts of the economy, such as the leisure travel business.

For society as a whole vaccination therefore is beneficial. And since the probability of being infected is reduced dramatically if a society enters in the state of "herd immunity", vaccination is beneficial for individuals as well: as long as a vaccine does not have serious side effects. In that case probabilities start to play a role in the decision making and the cost benefit ratio may be different for society and for individuals.

2.2 *Probability*

The probability of death for an individual depends on the probability of being infected, the probability of becoming a "case" after infection and the probability of death given that a person becomes a case, the CRF. As an example, we use the following data:

- the age distribution for the CFR[14] (table 1 column 2),
- the regular age dependent probability of surviving the next year for the Netherlands (table 1, column 3).
- The population of the Netherlands is 17,282,163.

Table 1: probability of surviving next year depending on age (Netherlands)

Age group	CFR	probability of surviving next year without corona
0	0.000000	0.996567
10	0.002000	0.999928
20	0.002000	0.999732
30	0.002000	0.999568
40	0.004000	0.999058
50	0.013000	0.997382
60	0.036000	0.992590
70	0.080000	0.981187
80	0.148000	0.939698

The probability of getting ill given infection, is taken to be equal for all age groups and to be 15%.[17] If it is assumed that 60% of the population is infected in a single year the resulting probability of surviving the next year can be evaluated.

As can be seen from figure 2, from the age of 50, the probability of survival is significantly influenced by COVID-19. At that age, the

probability of not surviving is increased by 0.1%. At the age of 80 the probability of non-survival is increased by 1.4%.

This additional probability of death can be compared with the additional probability of death from vaccination. According to the data available to date, probability of getting thrombocytopenia from the AstraZeneca viral vector-type vaccine is 10^{-5} and the probability of death is $2*10^{-6}$. For a 60-year-old this is 1.7% of the probability of dying from COVID-19, so it looks as if the choice is obvious: vaccination is beneficial also from the point of view of an individual.

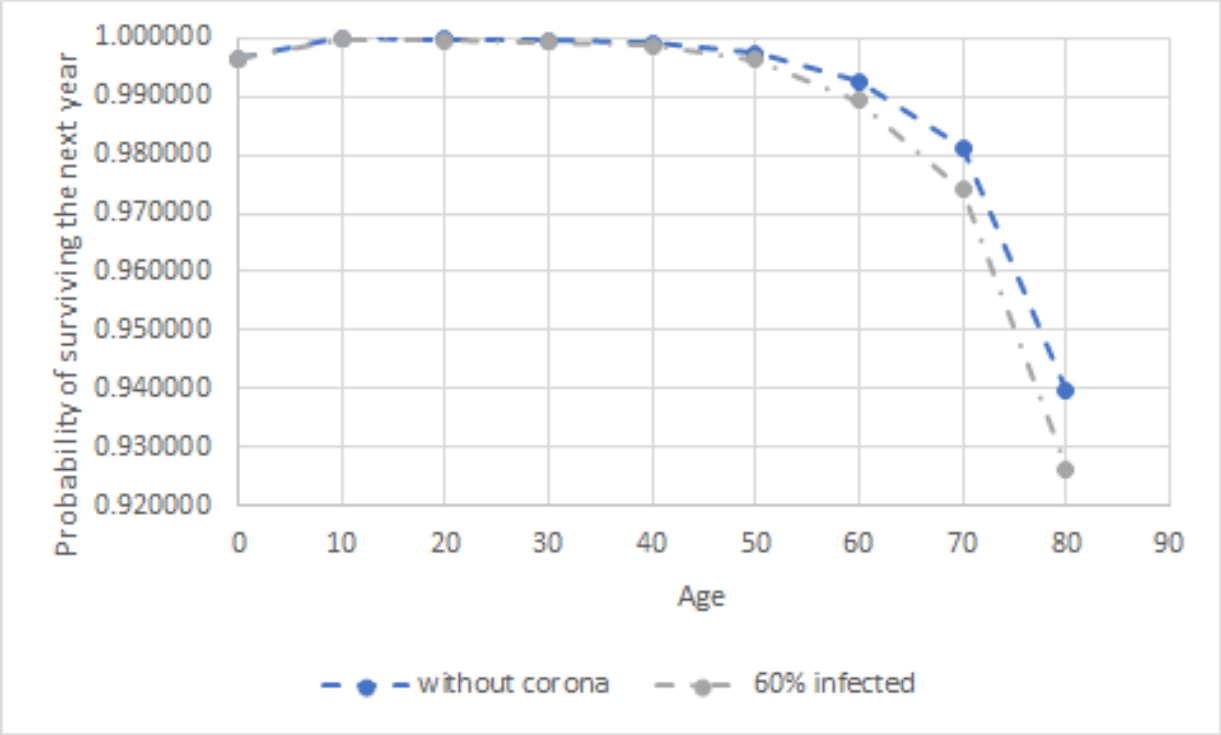

Figure 1: probability of surviving the next year depending on age

3 Costs and Benefits

However, it is not that simple. The reason being that, if herd immunity is reached, the probability of death for a non-vaccinated individual reduces to almost zero. In the Netherlands almost all children are vaccinated against Poliomyelitis. After 1993 no cases have been reported not even among the children who – for various reasons - have not been vaccinated. Therefore, it might be assumed that COVID-19 will be eradicated if herd immunity is reached – at least the known variants against which the vaccine is effective. From this point onwards the benefits of vaccination no longer necessarily outweigh the costs even at a lethality level of 10^{-6}.

Take as an example a working woman of between 30 and 40 years old, with one or two children and an elderly mother. If she has compassion for the world at large, she would contribute to the build-up of herd immunity, by taking the vaccine. Her individual risk although nonzero, would be much lower than the UK Health and Safety Executive (HSE) would deem acceptable for individual risk around chemical installations[6]. However, she could also consider that, should she be the unfortunate victim of the side effect and become

seriously long term ill, or die, there would be nobody to take care of her children and mother. It would not be unnatural to have more compassion for her direct family, than for society as a whole, and herd immunity would also be attained anyway, without her single vaccination. Given that after a successful vaccination program in the wider population, her risk of COVID-19 would be effectively zero, there would be no point in taking the vaccination risk.

In other cases, where the interests of an individual are in conflict with the interests of society, the balance is struck by democratic (or dictatorial) procedures. Although there are not many people who voluntarily pay taxes, the collective realization that the costs for collective provisions such as roads or health care should be paid for collectively, leads to the collective decision that taxation of all is reasonable. And even a non-willing individual is required by law to pay tax. But paying tax does not kill you.

The above puts a government in a difficult spot. Should vaccination as quickly as possible using all available vaccines be mandated, even if it means that about 2 in every million women under 60 who receive a particular type of vaccine might be expected to die?

For males the probability of death by vaccine is smaller. For the Netherlands some 14 deaths could be expected as a result directly related to compulsory vaccination with a viral-vector type vaccine. On the other hand, if viral vector-based vaccination is not mandated, and most women in the age group between 20 and 60 would choose not to be vaccinated, herd immunity would not be reached and more people in the elderly would die as a result. However, if all the elderly are vaccinated, they will not die anyway. Therefore, perhaps one can accept a situation in which the virus would still circulate, but the vulnerable portion of the population would be protected. Such a situation is not that different from other infectious diseases such as the winter flu. The vulnerable are protected by vaccination, the remaining population gets the illness without serious consequences and there is enough capacity to care for the exceptions: those who develop serious symptoms anyway. For the more exotic contagious diseases which circulate in some parts of the world, there is advice, or regulation regarding travel, vaccination and quarantine. If all countries would have the same policy objective – not overwhelming the local health service with a single type of patients - it could also make it acceptable for countries to let people cross their borders.

4 Trust

It already takes some effort to explain to the public, that it is not a scientific failure that very rare complications were not detected in the trials, because of the small scale of these trials when compared with the large numbers being vaccinated. A further complication is created by the way the information on the side effects of the viral vector-based vaccines became public. Although in the UK a significant number of people had been vaccinated, the existence of a serious and potentially lethal effect was first reported by Austria, where the number of vaccinations was much smaller. After an initial hesitancy by the World Health Organisation,[18] and the European Medicine Agency,[19] and apparent silence from the industry. Even when it was finally recognized that the problem could be caused by the vaccine, it was maintained by Governments, that vaccination was beneficial and less risky than COVID-19 itself. But when it became apparent that the complication merely affected that part of the population for which the COVID-19 risk was small to begin with, and which had problems with adhering to restrictive measures to protect the vulnerable from the start of the pandemic,[10] people started to make their own risk-benefit balancing decisions, rather than going along with that of the government. The intervention by the UK government telling other countries that is was a grave mistake to – temporarily – halt vaccination but later to restrict its use to older age groups may have given the impression outside the UK that the health of

people was subordinate to the political status of the 'UK – vaccine',

In the Netherlands, just as in many other countries, people under 60 started to not show up at their vaccination appointment; in some cases, even if they had been offered to be vaccinated with another vaccine. The uncertainty about the safety of vaccines and the uncertainty about the supply, started to undermine the whole vaccination program, which was not only detrimental for the health services, but also for the economy. In the US and in the Netherlands, this balancing act was dealt with in terms of the argument, that less risky vaccines were already available.

It is not uncommon that the costs of a risk fall on one particular group of the population and the benefits on another. Neighbours of hazardous installation bear the risk, while the benefits are for the company. The nuisance of airfields, nuclear power stations, or wind turbines, fall on their neighbours and the benefits to society as a whole. In these cases, a policy is developed and implemented that in essence, gives the population affected a say in the decision, but no choice once the decision in made. In the case of vaccination, however, it is neither ethical, nor allowed, to leave people no choice. As the universal declaration of human rights says: Everyone has the right to life, liberty and security of person. Vaccination cannot be made compulsory without violating basic human rights. This holds even firmer if a vaccination could invoke a lethal side effect.

When the interests of society as a whole and the interests of a group of individuals no longer coincide and there is no way for an authority to force the issue and make the individual interest subordinate to the interests of society, the only way left to secure societal interest is by persuasion, which in turn can only be successful when authority is trusted.

Towards mid-April 2021, some countries had had enough, and terminated the use of the AstraZeneca vaccine altogether,[20] for a particular reason, among others, which was to prevent the loss of trust in vaccination as a whole.

5 Wider Implications

COVID-19 has the potential to re-frame the whole debate about individual and societal risk, risk balancing, benefit-cost analysis, individual rights, societal responsibilities of individuals and responsibilities of Governments within the overall context that there are limits to what can be achieved in particular instances, and in totality across society. To be comprehensive, the re-framing must be considered in the context of wider political considerations which in the case of COVID-19 has resulted in numerous disruptions to supply chains, prior agreements and contracts, interventions by governments in "the market", which in the case of COVID-19 are of global proportions.

That the position of individuals concerning risks that affect them is context dependent is not new, "…public expectations about the levels of protection required, or the level of risk which can be tolerated, may well differ according to the nature of the hazard in question and people's knowledge or feelings about it[5]". In this respect, while the need to consider the limitations of rational choice theory has been recognised for several decades, [21] and the need to recognise the context within which any risk is considered, as well as what people know about the risk and how they feel about these risks in isolation and in combination with other risks that are affecting them or that they know about. While it has been recognised that these considerations are not readily accommodated within Rational Choice theory, a great many decisions of societal importance concerning risk to life are still made largely on the basis of economic rationality.[22]

For many years, research in judgment and decision-making has examined behavioural violations of rational choice theory with the underlying notion that those who violate the theory are not behaving rationally. However,

non-conformance with an economic theory does not constitute a wrong or even an error, rather there is a broader view of what constitutes rational.

Individuals are faced with numerous "risky choices", with many of the choices are accepted as being safe in the sense of free of risk to life and health, including safe water supply, safe food products and safe medical products. In reality there is always a risk that these life-supporting and life-saving or life enhancing products and services are not safe in the absolute sense. Food chains and water supply systems can be contaminated but in general risks are perceived as being so low as to be considered negligible even if the risks if quantified (or are quantifiable) are actually higher than the risks associated with viral vector-based vaccines. The net result is that individuals and governments make choices about risks without the benefit of the whole risk picture that can be interpreted in a uniform way by all.

This means that individuals and Governments are faced with the difficult task of putting a specific risk into some type of relevant perspective, where the complexity of risk perception, and differences between any individual's perceptions of risks are compounded by genuinely held fears.[23, 24]. The vaccine risk "landscape" is much more dynamic than many other risk situations, and it is quite possible that the hands of Governments and some individuals will be forced by the extent to which the COVID-19 virus is "winning" the race between the spread of the disease and the suppressing effects of vaccines regardless of the vaccine risk. Affordability of vaccines in any national context can also be expected to weigh in any decision concerning the availability of vaccines.

6 Conclusions and Recommendations

From the above a few conclusions can be drawn.

Even if the trials of a vaccine have been successful, it would be wise to realise that particularly very rare complications will probably not have been found yet.

It is unwise to dismiss weak signals such as a potential lethal side effect, as not influencing the balance between costs and benefits

It is unwise to make vaccination a matter of nationalist or populist policy

It is unwise to dismiss private concerns of individual citizens as unimportant, in deference to the common good.

It is unwise to assume that a private person will not make their own cost benefit analysis, and that the absence of trust, or even the suspicion that information is withheld, will weigh significantly on the cost side of their deliberation.

It is unwise to assume that the people will necessarily, be convinced, or persuaded, if they have a choice.

It would be wise to treat people and their concerns with respect; and address / consult them properly, especially when people have to accept a burden for the larger good.

7 Postscript

The corona situation changes rapidly. It may well be that the status quo will have changed considerably by the time this paper reaches publication. However, this paper reflects on what has passed and sets out lessons to be learned from the first phase of this pandemic for the future, and as such can be expected to be more resilient.

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