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COVID-19 AND THE NEED FOR ROBUST RISK CONTROL STRATEGIES – CAN ICH-Q9 HELP?

ABSTRACT

The COVID-19 pandemic requires robust risk control strategies; these should be multi-layered, science-based and subjected to effectiveness checks and formal reviews, to identify any unintended consequences. They should be supported by communications informed by an understanding of biases and risk perception. While developing such strategies for COVID-19 is difficult, given the scale of the problem and the diversity of stakeholders, the approach to Quality Risk Management (QRM) used by the pharmaceutical industry provides governments and public health officials with a ready-made framework to arrive at such control strategies. This approach is set out in the ICH Guideline on Quality Risk Management (ICH Q9). This globally adopted guideline provides a structured QRM framework based on four key process elements - Risk Assessment, Risk Control, Risk Communication and Risk Review. This paper demonstrates how each of these elements can be used when developing robust and science-based risk control strategies for COVID-19.

INTRODUCTION

The COVID-19 pandemic has presented the world with very significant challenges from a risk-based decision making perspective - what is the best strategy to adopt, what are the key risk control measures, where and when should the various risk controls such as physical distancing, the wearing of masks, the shutting down of transportation systems, and the closing of schools be implemented, and in what order of priority? What data are needed to best track the pandemic, how much testing should be performed, and which groups in our societies should be prioritized for that testing, given the lack of testing kits and their related supplies in certain areas? When and how can regions reopen? These and a multitude of other COVID-19 questions require a science-based approach to tackle them.

But finding solutions is made complex due to the large and diverse number of stakeholders involved, such as national and local governments, public health experts, healthcare providers, business groups, not to mention patients, their families, and laypeople. Each has a vested interest in how those questions are answered.

Is there a common framework that might be adopted to assist with the risk-based decision making required for COVID-19? What characterizes an optimum process that will help arrive at scientifically sound risk-based decisions when dealing with a problem as complex as this one? Whatever process for risk-based and risk-informed decision making is utilized, it is important that it be science-based and preferably well recognized, as that can help achieve broad stakeholder agreement on its outputs.

In 2005, health authorities regulating pharmaceutical and biopharmaceutical firms and products, together with industry representatives, developed an approach for Quality Risk Management, as published in the ICH guideline ICH-Q9. Since then, the QRM approach to risk-based decision making in the pharmaceutical and biopharmaceutical industry has been adopted globally (1). ICH-Q9 presents guidance on the management of risks related to the quality of pharmaceutical products; it provides a structured QRM process so that decisions concerning such risks can be based on the principles of scientific knowledge and patient protection. It sets out four key process elements that underpin the management of such risks - risk assessment, risk control, risk communication, and risk review - and it provides an overview of the tools that can be used when performing risk assessments and other QRM activities (see Figure 1).

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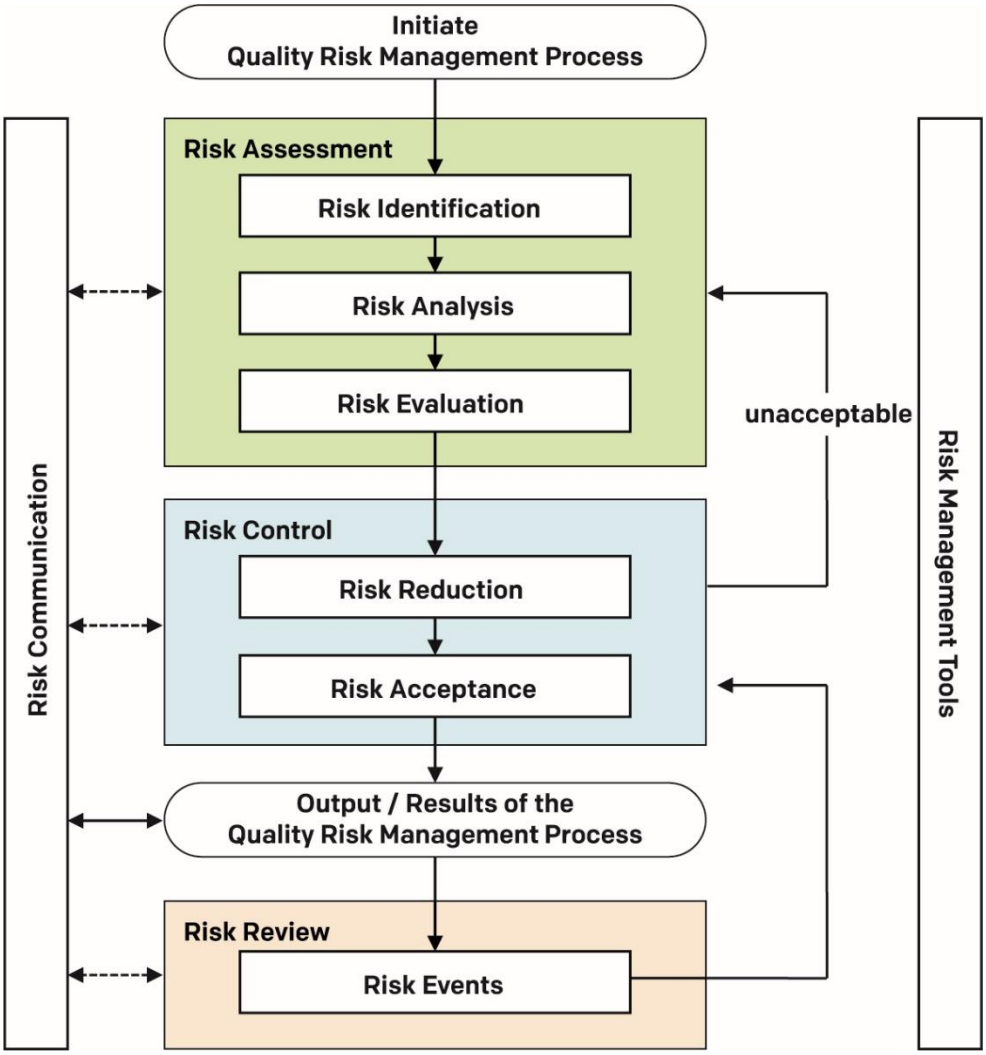

Figure 1. Overview of a typical quality risk management process (ICH, 2005)

The following sections discuss how the ICH-Q9 model for QRM can be useful for governments and public health policymakers when dealing with the multi-faceted risk-based decision making required for COVID-19 with a special focus on reopening. It emphasizes the need for a structured approach to Risk Control, it discusses the importance of understanding hazard and risk perception issues when developing Risk Communication strategies for COVID-19, and it explains the role of Risk Review in assuring the ongoing performance of the risk control strategy.

RISK ASSESSMENT AND COVID-19

In the Risk Assessment component of QRM, hazards are identified, and the risks associated with those hazards are analyzed and assessed. When answering the ICH-Q9 questions of "What might go wrong?", "What is the likelihood (probability) it will go wrong?" and "What are the consequences (severity)?", the risk assessment considers factors including the nature and magnitude

of hazards, any time-related factors that may exist, and their volatility. It will be influenced by the different perceptions of risk and the judgments of different stakeholders, and answering these questions needs to be done in a managed way because various stakeholders can have differences in how they perceive and make judgments on the risks.
Concerning consequences, recent experience has shown that the clinical consequences of acquiring the virus range from very minor to severe, from there being no discernible symptoms in some people, to death for others. But at the very early stages of the pandemic, with SARS-CoV-2 being a novel virus, there were many unknowns from a risk assessment perspective, such as the likely infection rate, the probability of harm occurring from virus transmission, and the general seriousness of the disease relative to other infections.

ICH-Q9 promotes the estimation of risk associated with identified hazards by combining the likelihood of occurrence and the severity of harms, to arrive at an estimate of the risk which is often expressed in terms of risk levels (high/medium/low) or numerical scores. The ability to detect the harm may also be taken into account in the estimation of risk. A key feature of the ICH-Q9 approach is the application of the science when arriving at risk estimates, and here, the strength of evidence that underpins all risk estimates is a key consideration, taking into account assumptions and reasonable sources of uncertainty.

Risk control and COVID-19 risk mitigation strategies

ICH-Q9 indicates that the purpose of risk control is to reduce risks to an acceptable level, where the amount of effort used should be proportional to the significance of the risk. It also indicates that one may accept risks, without any risk mitigation. It indicates that decision-makers might use different processes, including benefit-cost analysis, to understand the optimal level of risk control that is needed. The guideline suggests that the following questions should be asked during Risk Control activities:

- Is the risk above an acceptable level? What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

As described by the ISO 31000:2018 Risk Management standard, Table 1 summarizes the typical approaches to risk control include avoiding, reducing, optimizing, transferring, or retaining risk (2).

Risk treatment options as defined by ISO 31000:2018	**Applicability to controlling COVID-19**
Avoiding the risk by deciding not to start or continue with the activity that gives rise to the risk. *(This is often characterised as 'risk avoidance' and it can reduce the probability of occurrence to zero.)*	Not applicable – the virus leading to the COVID-19 pandemic had already entered the population.
Taking or increase the risk in order to pursue an opportunity.	Not appropriate
Removing the risk source *(This is often characterized as 'risk elimination' and it*	Not possible at a macro level, as the virus is so wide-spread and easily transmitted, but at a micro-level, removing the risk source is an option and is being used. For example, isolating

can reduce the probability of occurrence to zero)	individuals who have tested positive or who may have acquired the virus are manifestations of this control option.
Changing the likelihood	Reducing the possibility of virus transmission and acquisition through a set of measures, such as closing down borders, cancellation of travel, physical distancing, closing down certain businesses, schools, cancellation of public events, meetings, personal hygiene, use of personal protective equipment, etc. Isolation of confirmed cases and quarantining of contacts also reduces the likelihood of transmission.
Changing the consequences	Reducing the severity of the consequences of infection through a set of measures, such as increased availability of health professionals, hospital beds, intensive care units, respirators and ventilators, as well as via medication.
Sharing the risk (e.g. through contracts, buying insurance)	Not applicable
Retaining the risk by informed decision	Some countries adopted a herd-immunity approach, which is a form of retaining the risk. Unless the risk is fully avoided or eliminated, it will remain at certain levels despite all efforts to change the likelihood and consequences. Countries implementing plans to reopen businesses accept the retained risks.
Additional risk reducing actions	**Applicability to controlling COVID-19**
Communication: Informing people about hazards and risks leads to awareness raising and it can be a powerful type of risk control.	Communications about COVID-19 are at the forefront of the risk control measures that have been adopted, as they can lead to behavioural changes.
Building in new and improved detection mechanisms for hazards, their causes and effects.	Testing individuals for the virus is of course a control based on detection, but it is not the only one – temperature checks at airports and other ports is another detection control.
Taking measures to interrupt how the risk propagates from its initiating event or cause(s) to its consequences being experienced.	This is especially relevant to COVID-19, where widespread efforts are being taken to interrupt transmission of the virus (person-to-person, and person-to-surface-to-person)

Table 1. Risk treatment options and their applicability in controlling COVID-19

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The concepts of risk reduction and maintaining risks at or below acceptable levels are central to any risk control strategy. In this regard, it is useful to consider actions that mitigate the severity and probability of hazards and harm, as well as actions that improve their detectability.

But for such an approach to be successful, one must also consider the likely effectiveness of the various controls, and the timing of their implementation. Studies have shown higher impact when interventions (control measures) were introduced early (3-5).

The following selected risk mitigation actions have been implemented for COVID-19 to varying degrees in different countries:

1. Advising the public to use proper etiquette when sneezing and coughing (6)
2. Advising the public to not touch their mouths/nose/eyes (6)
3. Advising the public to wash their hands regularly (6-8)
4. Advising or mandating the wearing of face masks when outside the home (9)
5. Mandating various measures that lead to isolation – closing schools, closing certain types of workplaces, working from home, cancelling public events, curfews, general stay-at-home policies, staying off public transportation (3-5)
6. Screening arriving passengers at airports and other entry ports for signs of infection (10)
7. Requiring individuals to self-quarantine for 14 days after traveling from high-risk areas (11, 12)
8. Testing individuals for the virus after developing symptoms (13)
9. Performing contact tracing activities (14)
10. Proactively testing certain groups of people in society with no symptoms (e.g. doctors, nurses, and other health care workers) (15)
11. Wearing of personal protective equipment by healthcare workers in healthcare settings (16)
12. Medicating patients who develop symptoms of COVID-19 infection with antiviral medicines (17)

The first three controls have been almost universally adopted and can be considered to have a high impact against COVID-19, but they do require a high level of buy-in by individuals; wearing of masks has also had a high implementation level in many countries. The remaining controls are executed directly by the authorities, and/or responsible sectors in society (e.g. closing schools, curfews, testing, and contact tracing).

Analyzing the likely effectiveness of these risk controls is useful because it can inform public health officials and governments of where the gaps may be in their risk mitigation strategy. For example, the analysis may indicate an overreliance upon detection measures, at the expense of preventative controls to limit the acquisition/transmission of the virus and new infections. Such analyses can also help identify a lack of attention to reducing the severity of the effects of a SARS-CoV-2 infection (from minor to serious) when one has occurred.

Take, for example, prohibiting large sporting events, such as soccer matches in football stadiums. Some countries took this measure, but it proved problematic, due to unintended consequences - many people started congregating in friends' houses to watch the matches, leading to increased virus transmission risks. The issue was that the timing of the stadium restriction had not aligned well with the timing of other social distancing measures like restricting other social gatherings. Several other risk controls for COVID-19 had unintended consequences too – examples include quarantining and stay-at-home policies, which have been associated with increased rates of domestic violence and use of alcohol.

ICH-Q9 not only highlights the need to ask three key questions at the outset of the risk assessment process, it also indicates the importance of considering whether new risks are introduced as a result of the identified risks being controlled. It explains how

the implementation of risk reduction measures can introduce new risks or increase the significance of existing ones. It promotes reviewing risk assessments to identify and evaluate changes in risks after implementing a risk reduction process.

The aforementioned prohibition of attending large sporting events in football stadiums, and the resulting increases in soccer gatherings in homes, is an example of not taking a holistic and analytical approach to one's risk control strategy – the three ICH-Q9 questions were probably not given adequate attention. There may not also have been an in-depth analysis of each proposed control measure to identify any unintended problems it might give rise to.

For a long period, when and how to use masks had quite diverse recommendations, and this has been confusing for many in society. With infection rate increases, many countries introduced mask use in community settings, but the World Health Organization (WHO), in its interim guidance, underlined the following risks (9):

- The use of nonmedical masks in the community setting has not been well evaluated and there is no current evidence to make a recommendation for or against their use in community settings. (This also brings the issue of many countries having big quality variations in masks – where lower quality masks may create a false sense of security).
- Also, for any type of mask, appropriate use and disposal are essential to ensure that they are effective and to avoid any increase in transmission (touching the mask while wearing it, not replacing the masks as soon as they become damp, re-use of single-use masks and inappropriate discard).

Similarly, recommendations to stay at home and/or curfews introduced unintended consequences (i.e. new risks) concerning mental health issues, and in many countries, strategies still need to be put in place to cope with those – e.g. practical things to reduce stress, not only for adults but also for children (18, 19).

It seems that many countries introduced control measures in a piece-meal, reactive fashion, one after the other, without sufficient consideration being given to the overall risk control strategy that was needed and the possible inadequacies (or holes) in their approaches.

The Swiss Cheese Model approach to COVID-19 risk control strategies

A useful approach to holistically assessing the likely effectiveness of a control strategy is the Swiss Cheese model developed by James Reason (20). In this model, risk controls are represented as slices of Swiss cheese, lined up against each other. The holes in the slices (or, as cheese aficionados call them, "eyes") represent deficiencies or inadequacies in particular controls, but multiple layers of control, operating on different principles, can overcome those inadequacies, leading to a more robust risk control solution. These layers are sometimes called redundant controls – they aim to prevent an unwanted outcome. The system can produce failures when a hole in one slice momentarily aligns with one in the next, permitting "a trajectory of accident opportunity", so that a hazard passes through holes in all of the slices, leading to a failure (see Figure 2).

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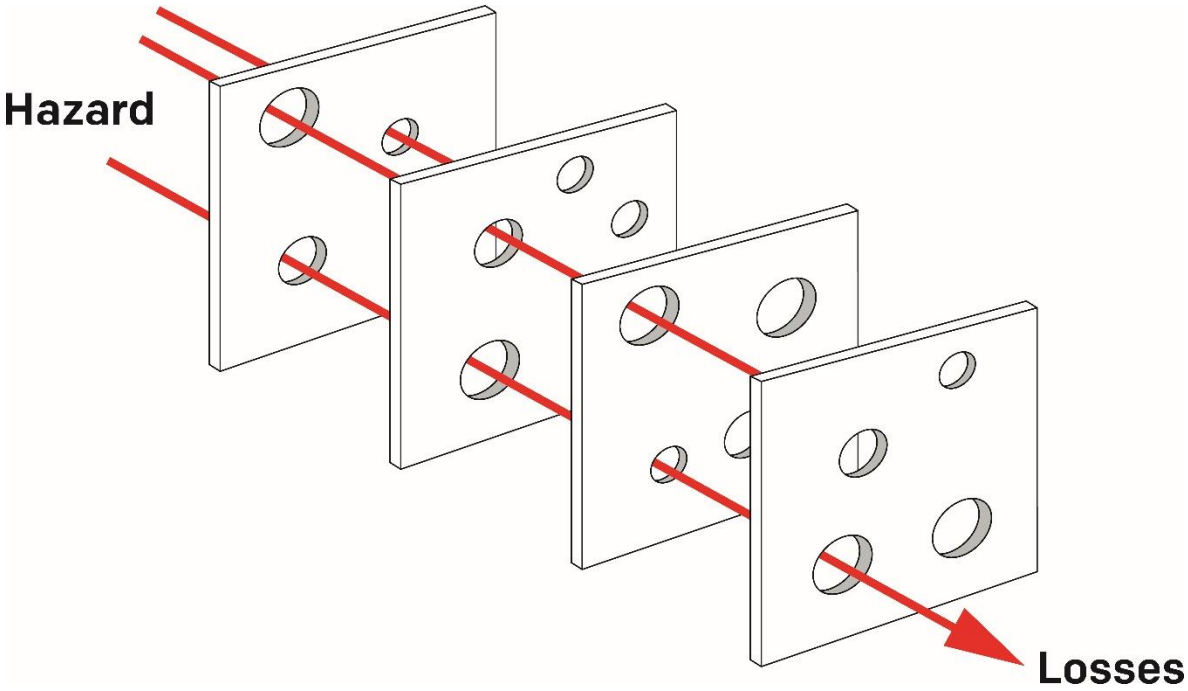

Figure 2. Swiss cheese model as described by James Reason

In the context of COVID-19, assessing control strategies using the Swiss Cheese model, as it prompts an assessment of what redundancy may be needed to prevent failures. When one applies the ICH-Q9 concept of asking "what might go wrong?" when putting new controls in place, a more robust control strategy can be the result.

Consider the mandatory wearing of masks when using public transport in some countries. For this control to be truly effective, only those passengers with masks might be allowed to board – others would be refused transit. The risk that this control measure address is virus transmission via droplets, due to the proximity of passengers to each other. But relying only on the wearing of masks and refusing entry to passengers without masks is likely to be an ineffective control, as it is heavily reliant on the correct use and handling of masks, and it is difficult to enforce. Applying the Swiss Cheese model can lead to additional (redundant) controls being identified, without having to refuse some passengers' entry. The additional measures might involve offering free masks to people before they board the bus, making hand sanitizers available at the entrance of busses, applying floor markings for appropriate physical distancing, displaying posters that remind passengers of good sneezing and coughing etiquette, regular sanitization of surfaces on public transport systems, and limiting how many passengers may board the bus. Using multiple layers of risk control allows for a more comprehensive control strategy that answers the "what might go wrong?" question including weaknesses that might be present in a single control.

For example, concerning the wearing of masks as risk control, it will be important that any problems of poor mask quality, unavailability, distribution delays, too few pick-up locations, etc., are identified and resolved. All of this can deliver a high level of assurance that the risk control strategy is robust, and studies have shown increased impact/effectiveness with the introduction of multi-layered control measures (21-27).

Event Tree Analysis is another method that can be used at different points in the QRM process including assessing the effectiveness of proposed control strategies. When planning a risk reduction strategy for COVID-19, event trees can help

determine the adequacy of the risk controls and the best- and worst-case outcomes, along with other possible outcomes. Figure 3 shows an event tree centred on the resumption of widespread air travel after the pandemic. It begins with an initiating event, shown on the left side of the diagram. Along the top, the different controls (analogous to slices of Swiss cheese, as described by Reason) that are intended to be put into place are listed, in the sequence in which they would be invoked. From the initiating event, each control is "tested" to determine what would happen if it works as intended (as indicated by an upward move of the line towards the top of the page, and green marking) or if it fails (indicated by a downward line, and red marking). If probabilities are known, these can be used to establish the likelihood of the different potential outcomes. When reviewing the results of the completed event tree, one can determine risk if the currently planned controls are adequate, or whether additional controls are needed.

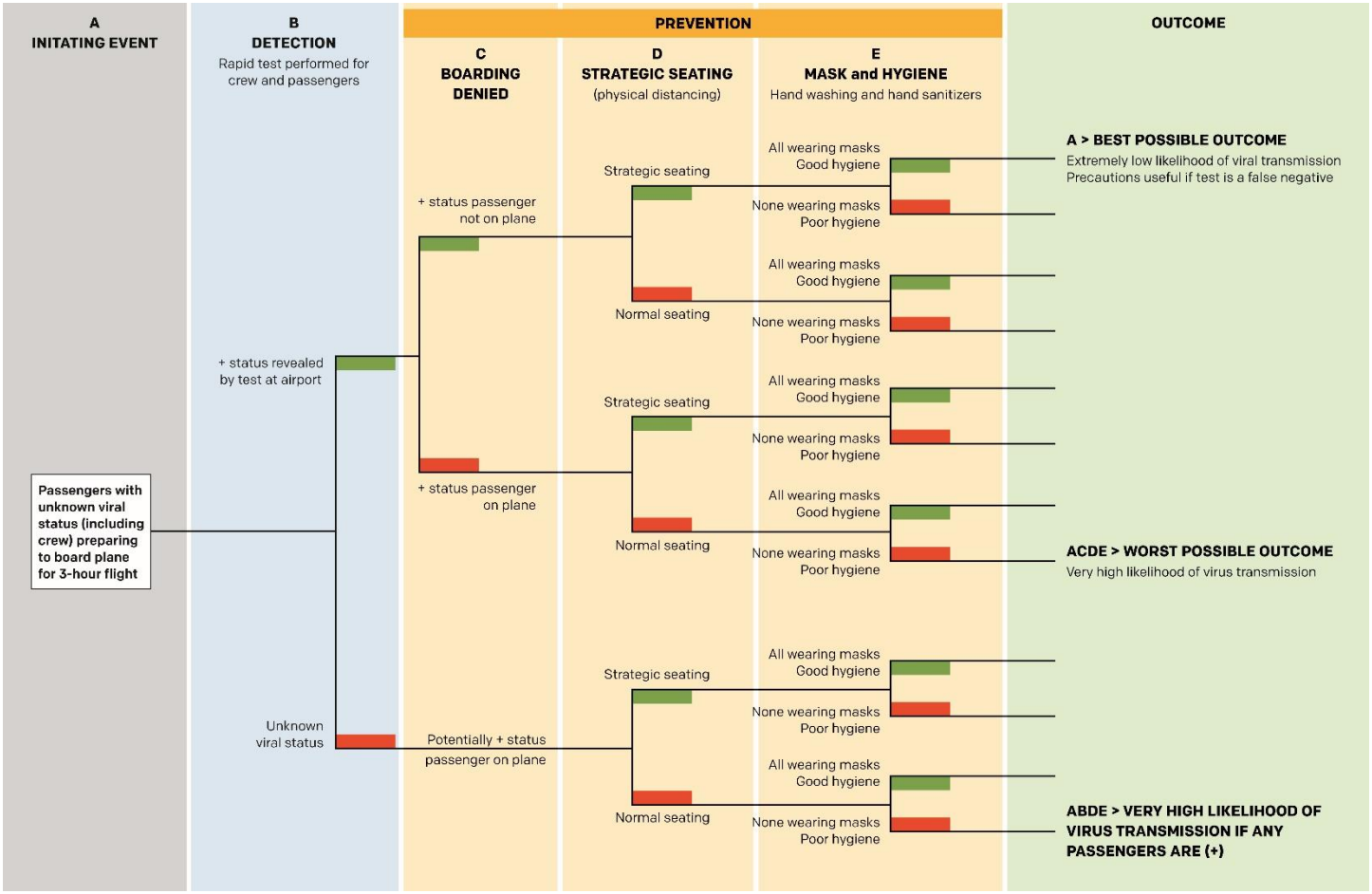

Figure 3. Event-tree analysis of the controls for resumption of air travel

Risk review and its importance for the success of COVID-19 risk control strategies

Risk Review not only lets us review the effectiveness of selected risk controls, but it also provides an opportunity to identify new hazards, and risks that may have arisen as a result of risk control strategies. Risk Review should be an ongoing process, where any important assumptions that were made earlier can be reassessed if they are no longer valid, and in this regard, the Risk Review process must take account of new information and experience.

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Risk Review processes have been utilized throughout the SARS-CoV-2 pandemic to date. Countries have created scientific committees to advise their governments, where new information can be considered to make any necessary adjustments in their control measures. For example, the Federal Office of Public Health (FOPH) in Switzerland banned meetings of over 1,000 participants at the very early stages of the pandemic; this was reduced to 500, then to 100, and finally to 5 as new cases continued to increase (28). There is evidence that this approach has helped avert deaths - via a study on the impact of non-pharmaceutical interventions in eleven European countries (5). Based on its findings, the researchers reported that "It is therefore critical that the current interventions remain in place and trends in cases and deaths are closely monitored in the coming days and weeks to provide reassurance that transmission of SARS-CoV-2 is slowing". The same study documented the impact of those interventions on the time-varying effective reproductive number (Rt) in various countries (Flaxman et al., 2020). This is a clear example of a Risk Review process in operation.

Another example of Risk Review in operation was an ongoing Swiss study which continuously provided emerging data on the pandemic to the FOPH in Switzerland. The basic reproduction number was found to be 2·78 (95% confidence interval, CI: 2·51–3·11), and it was found that the virus transmission rate decreased by 89% (95% CI: 83%-94%) with a subsequent strengthening of physical distancing measures. This resulted in an effective reproduction number (Re) of 0.32 (95% CI: 0·2 – 0·47), and this and other information was the main basis for the FOPH in Switzerland recommending the easing of control measures in three phases, starting on 27 April 2020 (25). Figure 4 illustrates the impact of such non-pharmaceutical interventions in Switzerland.

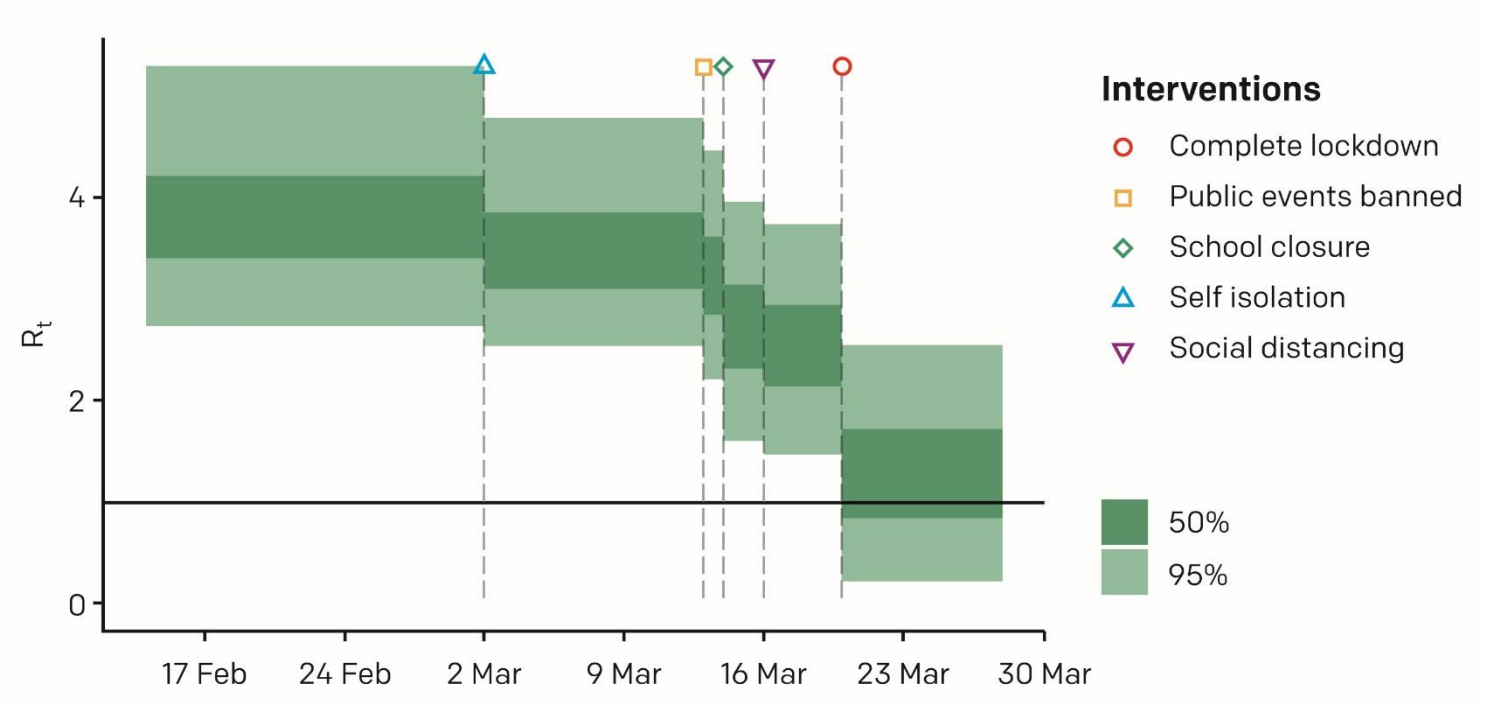

Figure 4. Impact of non-pharmaceutical interventions on the time-varying effective reproductive number Rt in Switzerland (Althaus, 2020)

A recent example of analysis of COVID-19 dynamics was a retrospective cohort study of COVID-19 cases in Shenzhen, China, and their close contacts (29). This provided new data about underlying infection patterns since the study looked for infections among contacts rather than just analyzing reported cases. Its findings generated useful learnings, such as how children were an important target for interventions aimed at reducing transmission, even if they do not get sick.

RISK COMMUNICATION AND THE COVID-19 PANDEMIC

Risk Communication is performed throughout the ICH-Q9 process. The guideline defines risk communication as the "sharing of information about risk and risk management between the decision-maker and other stakeholders" to provide "guidance … that can enable more effective and consistent risk-based decisions" (1). The desired outcomes of such communication are decisions, actions, and behaviors that are aligned with the level of risk present.

Risk communications can be significantly impacted by issues related to risk perception. There is a wealth of research that demonstrates that the perception of hazards and risks is strongly related to various cognitive biases that affect laypersons as well as subject matter experts (30, 31).
This research can shape robust risk communication strategies to achieve behaviors that are needed to control the SARS-CoV-2 pandemic.

Foundational research concerning the theory of communication, focused on telephonic communication identified three particular issues (32):

- **Technical problems** – the accuracy achieved in transmitting the signal between the transmitter and the receiver
- **Semantic problems** – issues in the interpretation of the information by the receiver compared against the sender's intended meaning
- **Effectiveness problems** – the success of the intended result of the information that has the desired outcome or result

While the research was centered on problems with one type of communication medium, it can be used as organizing principles for communication problems concerning COVID-19.

Regarding technology-related issues, we can see that the use of digital social network platforms such as Facebook and Twitter facilitate communication from sources that are not qualified to provide accurate, valid information (33). This has contributed to what the WHO's Director-General has identified as an infodemic – "an over-abundance of information, some accurate and some not, that makes it hard for people to find trustworthy sources and reliable guidance when they need it" (34, 35). Repeatedly providing people with links to credible, relevant sources of health information and resources reinforces messages that can contribute to risk-reducing behaviors.

Semantic problems when communicating risks can affect the meaning of the risk message, and its uptake. With COVID-19, they may impact the listener's ability to differentiate a low risk from high risk, and their understanding of how social distancing and wearing facemasks can lower the risk of transmitting/acquiring the virus. Contributing to this is the lack of health literacy – the ability to acquire, understand, and apply information – in the general population that can support community and individual preparedness (36). It is known that 'explaining the why' and providing in simple language the scientific rationales that underlie the risk control recommendations promotes compliance, for example with handwashing (37).

Another semantic problem in risk communication is the lack/inadequacy of the message for different audiences or specific groups within a society (38). While certain key messages concerning ways to reduce risks, ¬such as handwashing, physical distancing and wearing facemasks, are important for everyone, groups that are marginalized or have vulnerabilities and challenges (e.g. people with small children at home, limited economic resources, substance abuse, and unstable living conditions) need more targeted communications, and messages that are meaningful to them (39). The results of risk review activities – new risks that are observed or risk-reducing behaviors that may need to be enhanced – may also be points to communicate.

Communication effectiveness problems, however, are where the biggest challenges exist. This is because of the numerous factors that lead to decisions, actions, and behaviors that are inconsistent with the level of risk that is present. Research has shown that what influences individual and group behaviors is more related to how people perceive risk and not the actual danger that is present (40).

ICH-Q9 acknowledges that achieving a shared understanding risk management among stakeholders is difficult, because of how different stakeholders might perceive the potential harms, the probability of them occurring, and their severity.

One particular bias worth noting is confirmation bias – how people sometimes choose data or selectively interpret data to support a premise or position or ignore or explain away data that does not support the premise is ignored or explained away (41). This bias can be observed, in the tendency of people to get their news and information from sources they find compatible with their beliefs and ideology; opinion polls in the U.S. show that the polarization of news outlets significantly contributes to where people of different political viewpoints put their trust for news (42).

Two risk perceptions that can contribute to biases are the political worldview of the individual and the perceived trust that the listener has in the source of the information (43). Research has shown that those whose worldview is more rooted in conspiracy theories are much more likely to think that COVID-19 originated in a laboratory, or they associate the virus with 5G wireless technology (44-46).

Trust, which relates to the expertise and competence, motives, honesty, and empathy of the speaker, is one of the most important factors in whether people accept the communicated message (47, 48).

Overcoming biases and perceptions is probably the most complex problem in any risk communication strategy. It is interesting to note that a majority of US adults (66% to 84%) rated healthcare professionals as high or very high in terms of trustworthiness, with nurses being rated the highest (49). Since healthcare professionals may be among the most trustworthy source of health-related information, they should be among the risk communicators for COVID-19, their voices providing information and advice about risk and required risk controls while also countering the spread of misinformation (50). They need to present a fair and balanced perspective, including what is known and not known, in a language and with examples that can be understood by the audiences (51).

Such spokespersons should understand what can influence how risks are perceived by the listeners and the measures that can be taken to counteract the effects of those factors (52). On a practical level, knowing and practicing the 'dos and don'ts' of interviews, presentations, and press conferences will be an advantage to the communicator (53). It is also important that such a person model what is being asked of others, that is, that they "walk the talk."

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CONCLUSION

Integration Of ICH-Q9 Quality Risk Management Processes Into Pandemic Response Management Operations

Each of the four elements making up the ICH-Q9 QRM process - Risk Assessment, Risk Control, Risk Review, and Risk Communication - has direct applicability to COVID-19. The structured and science-based approach outlined in ICH-Q9 can provide governments and public health officials with a means to arrive at robust risk control strategies for COVID-19, which have been scientifically evaluated, subjected to formal reviews, and which are supported by reliable risk communications.

The actions that are taken to reduce the most important risks can be thought of as layers of control that, when considered together, form a robust risk treatment. Before implementing the control solutions, thought must be given to the level of residual risks that remain and what new unintended consequences might arise. For example, what are the impacts on health care providers and facilities if non-essential treatments and surgeries are discontinued? Or, if our hospital emergency departments are focused on COVID-19 patients, what could that mean to people experiencing other problems, such as heart disease or strokes? Or, with isolation measures, at least 13·5 million people may be missing out on their vaccinations due to postponements of campaigns and interruptions in routine immunization programs, and what are chances of a global resurgence of other killer diseases such as measles and polio?

As new information comes in about the virus and the preventive and treatment measures that are and are not effective, we need to step back, review what we are learning and determine how this affects our current trajectories – do they still make sense? Learning as we move forward, based on what we have experienced and the data we are amassing contributes to knowledge and understanding.

Throughout the QRM process, risk communication is essential. This is not pushing information into the media; it should involve listening and watching the effects that the message, and those providing it, is having. Problems presented by cognitive biases and risk perception when communicating about risk are important for governments and public health officials to consider, especially when communicating to the public about the risk control strategy that is required for the COVID-19 pandemic in their country.

With a problem as difficult, complex and high risk as COVID-19, it is necessary to have risk control strategies that are science-based, holistic and rigorous, supported by formal effectiveness checks, review activities and well devised risk communications. The approach we have presented in this paper reflects this. It draws not only upon the QRM process as presented by ICH-Q9, which is a useful framework to adopt, it also reflects the principles of QRM as set out in ICH-Q9, which are that the evaluation of risk should be based on scientific knowledge, where the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

DISCLAIMER

The views expressed in this article are those of the authors and are not necessarily those of Extensio et Progressio, the Health Products Regulatory Authority, or Valsource LLC.

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