Evidence–time dilemma in a pandemic with high mortality: Can outcome-driven decision making on vaccines prevent deaths?

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INTRODUCTION

When the first vaccines were authorized for coronavirus disease 2019 (COVID-19) in December 2020, its death toll exceeded 2,500,000 deaths globally. Basic science showed an unprecedented pace in its response to the virus with the synthesis of mRNA-1273 (Spikevax), the active substance of a COVID-19 vaccine, on January 13, 3 weeks prior to the first confirmed death in the United States. Can regulatory science accelerate access to vaccinations, prevent deaths, and overcome the evidence–time dilemma in future pandemics?

The death toll of the COVID-19 pandemic has only been exceeded by the Spanish Flu in 1918. Early in the first wave of the pandemic, a highly disproportionate distribution of COVID-19 infections and deaths was observed between the age groups with a disproportionately high case fatality rate in the elderly subpopulation (<1% in <64-year-old, 8.0% in 70–79-year-old, and 14.8% in >80-year-old subjects).1 Already at the start of the pandemic, it was obvious that effective vaccines will be the ultimate tool to control the COVID-19 pandemic and bring societies back to normality. So, science excelled with the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) virus genome being sequenced on January 11, the active substance, mRNA-1273, synthesized on January 13, 2020.2 By December 2020, with an unprecedented speed of less than a year, the mRNA-1273 and the BNT162 (Comirnaty) vaccine were developed and granted an Emergency Use Authorization (EUA) in the United States.2,3 In April 2020, the International Coalition of Medicines Regulatory Authorities (ICMRA) discussed aspects for COVID-19 therapeutic developments, including clinical trials, real-world evidence (RWE), and compassionate use. They expressed the need for robust evidence to establish safety and efficacy for the proposed medicines, leading to timely regulatory decisions and thus guiding clinicians in defining the best treatment options for COVID-19 to serve the patients’ needs in the fastest fashion possible.4 In support of the EUA, the pivotal clinical evidence was generated in large randomized controlled trials (RCTs) in an ideal-world setting, in the broad adult population, with prevention as the primary end point (starting in July 2020).2 Due to the limited availability of the first two authorized COVID-19 vaccines, the United States and almost all other countries prioritized the elderly in the vaccination process. This decision was based on modeling approaches revealing that mortality is minimized in scenarios where the subpopulation with the highest risk of COVID-19-related deaths is vaccinated first, already established for influenza vaccinations.

Unfortunately, in a pandemic with such high mortality, there is an evidence–time dilemma; during the clinical evidence generation, the death toll continues to rise in the real world. Knowing that the second wave is often bigger than the first and was expected to start in autumn 2020 and last until spring 2021 further emphasizes the limited time. Indeed, emergencies and crises often act as
a magnifying glass for known shortcomings in the drug development and regulatory decision making related to the evidence–time dilemma. First, the ideal-world (efficacy and prevention) versus real-world (effectiveness and mortality) dilemma. Second, the evidence versus access dilemma. Third, the population versus subpopulation dilemma.

**EARLY ACCESS TO VACCINES IN THE HIGH-RISK SUBPOPULATION**

Before the first COVID-19 vaccines were granted an EUA, there was a very high unmet medical need, especially in the subpopulation with the highest burden, risk of hospitalization, and COVID-19-related deaths, namely the elderly. I, therefore, propose the consideration of early access to the most advanced vaccines at the time of enrollment of the pivotal RCTs via managed access programs (MAPs) for the target population, here, the elderly. Especially as the majority of subjects in pivotal RCTs, mainly young adults, are not the ones with the highest benefit. The implications of early access are discussed regarding evidence generation, benefit-risk assessment, regulatory decision making, and, finally, prevention of deaths.

**SIMULTANEOUS OUTCOME-FOCUSED EVIDENCE GENERATION**

Regulatory science permanently evolves and provides multiple solutions to overcome the evidence–time dilemma in general, including the abovementioned shortcomings.

First, it offers new approaches to generate high-quality, broader evidence in simultaneous efficacy and effectiveness trials. That way, additional RWE on effectiveness can be generated with mortality as an outcome measure in cluster-randomized pragmatic vaccination trials in the elderly in long-term care facilities. It thereby complements the evidence on efficacy that the classical vaccine development paradigm (CVDP) generates in the ideal-world setting with prevention as the primary end point. Simultaneous efficacy and effectiveness trials before authorization can address the ideal-world versus real-world dilemma intrinsic to the classical regulatory framework.

Second, studying the effectiveness of vaccines on mortality in its most affected subpopulation in long-term care facilities, where, in this pandemic, 45% of the total COVID-19-related deaths were observed, offers the opportunity of high-quality evidence on clinically relevant outcomes in a short time. Thus, it addresses the subpopulation versus general population and the access versus evidence dilemma.

Interestingly, one innovative approach to overcome the evidence–time dilemma was implemented in the RCTs for COVID-19 vaccines within the CVDP: the adaptive clinical trial design with preplanned interim analyses. However, in October 2020, additionally required safety information, for the benefit-risk assessment (BRA) and the issuance of the EUA in the United States, prevented all but the last one of the preplanned interim analyses and reflect an asymmetric focus on risks compared with benefits. Positive results of earlier interim analyses regarding efficacy could enable early and rapid access to vaccines for the elderly via MAPs and could thus prevent deaths.

**DIFFERENTIATED BENEFIT-RISK ASSESSMENT OF VACCINES FOR THE GENERAL POPULATION AND THE HIGH-RISK SUBPOPULATION**

A pandemic with such high mortality and dynamic time course, occurring in waves and evolving virus variants, likewise requires highly dynamic, transparent, and consistent decision making from all relevant stakeholders, ideally in real-time based on the dynamically changing totality of evidence (ToE).

At the time of authorization of COVID-19 vaccines, clinical evidence was only available on a single short-term benefit, prevention, and on the risks of acute and short-term side effects. Mid- and long-term benefits and risks (e.g., the vaccine’s effect on mortality or long COVID-19), remained unknown. Assessing the benefits and risks of vaccines only on the broad population level does not consider the substantial difference in the mortality rate between elderly and young adults. The classical pivotal RCTs do not generate evidence regarding this effectiveness outcome. Thus, the BRA so far disregards the probable epidemiological and clinical dependency between preventing disease and reducing disease-related deaths. It misses the opportunity to grant high-risk subgroups the potential benefits of vaccines when no effective treatment alternatives are available. The ToE, showing clear dose-effect relationships in early exploratory dose-ranging studies resulting in immune responses for both mRNA vaccines, might justify early access for future pandemics. When the pivotal RCTs for the broad adult population, including the elderly, are authorized, regulatory agencies could authorize early access restricted to the elderly within a MAP, too. Restriction to the elderly, vaccine administration by
physicians, and real-time monitoring of acute safety issues in a similar way, as in pivotal RCTs, minimize the risks associated with early access. Consequently, these risks can be considered low for the elderly subpopulation as additional high-level RWE is parallelly generated in pragmatic RCTs. Above all, considering the known high benefit-risk ratio of vaccines in general, the most relevant benefit, the prevention of deaths, can be expected to outweigh the risks.

The implementation of the proposed new approach during the COVID-19 would have been associated with a degree of uncertainty regarding potential safety and quality issues considering the new mRNA technology and the already very short development time of the first mRNA COVID-19 vaccines. On the one hand, those safety or quality issues, if occurring in the managed access program, could result in negative downstream consequences on the willingness of patients/caregivers to be vaccinated with the vaccines once they are authorized. On the other hand, earlier, ensuring evidence on additional effectiveness outcomes, such as hospitalization and mortality, generated in the MAP could even facilitate and accelerate vaccination campaigns.

Finally, transparent and consistent communication by regulators and policymakers of key benefits and risks (known, unknown, and expected) and respective uncertainties of vaccines at key milestones during the clinical development, ideally supported by valid quantitative BRA methods, will be critical to enable appropriate and responsible informed consent procedures and shared decision making between patients and physicians, and an informed public.

**EMERGING EVIDENCE SUPPORTS AN EARLY ACCESS APPROACH - SAVING LIVES IN THE HIGH-RISK SUBPOPULATION**

Currently, evidence emerges in support of the proposed early access to the high-risk subpopulation. An observational study within a nationwide vaccination setting in Israel demonstrates effectiveness when preventing COVID-19-related deaths in 72% of the subjects aged greater than or equal to 70 years. In the largest pandemic of the last 100 years, the first pandemic in the 21st century, early access to effective vaccines with the potential to prevent infection, burden, and death, could have been considered. Regulatory decision making based on the ToE, accepting moderate levels of uncertainty where the risks can be managed and giving high-risk patients access to the potential benefits, can save lives in a pandemic.

**FUTURE PANDEMICS - PLAN FOR OUTCOME-DRIVEN EVIDENCE GENERATION IN SUPPORT OF REGULATORY DECISIONS BASED ON TRANSPARENT, CONTINUOUS, AND DIFFERENTIATED BRA**

To maximize the future impact of regulatory science regarding the development of new treatments and their regulatory review, it is imperative to take appropriate actions on two levels. First, solutions adapted successfully during the COVID-19 crisis should continue to be applied thereafter. Second, lessons learned, and insights gained during the crisis need to be transformed into future solutions. The unprecedented speed of the development and approval of the first COVID-19 vaccines can mainly be attributed to four factors: rapid development of active substances for efficacious vaccines, operationally fast RCTs required by regulators combined with streamlined/reduced nonclinical requirements prior to first-in-human trials, the rolling review by regulatory agencies, and the spending of governments and nongovernmental organizations on manufacturing of COVID-19 vaccines at risk. However, options from the current regulatory science toolbox (e.g., early/managed access programs, simultaneous efficacy, and effectiveness trials), and quantitative methods for differentiated BRA and model-informed regulatory decision making, carry additional potential. Further, adaptive designs with interim analyses without additional safety requirements allow for compassionate use of early access to vaccines and their potential benefits. The proposed early access to vaccines for the high-risk subpopulation based on the ToE contributes to a faster translation of basic science into life-saving vaccines. It demonstrates how well-known dilemmas in the classical clinical drug development and regulatory decision making framework can be addressed in the future, in the interest of public health, and, in particular, high-risk subpopulations. The ToE approach is consistent with Eichler et al., explaining that the future is not about RCTs versus RWE but RCTs and RWE—not just assessing efficacy and safety but also effectiveness. Approving vaccines using a platform approach based on the available prior evidence on the mRNA vaccine technology should be able to permit even earlier access to effective and safe vaccines. This carries the potential to prevent future pandemics at the stage of local outbreaks with new viruses.

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**AUTHOR CONTRIBUTION**
KE developed the design and collected, analysed, and interpreted the data for this article. KE also drafted, wrote, critically revised, and approved the article and agrees to be accountable for all aspects of his work.

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