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Dose Optimization and Scarce Resource Allocation: Two Sides of the Same Coin

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Key Messages

- Drug scarcity reflects gross mismatch between supply and demand; societies strive to allocate scarce resources allocated in a manner that reflects their values
- A deep understanding of the relationship between a scarce drug's dose and clinical response is necessary to appropriately distribute a supply-constrained drug
- Future pandemic clinical trials should obtain dose optimization data in order to enable appropriate distribution

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Contributors and sources

GWS is a clinical trialist and health services researcher whose work centers on dose-optimization to combat drug scarcity and financial toxicity. He is a contributor to the World Health Organization's Rapid Evidence Appraisal for COVID-19 Therapies. GP is a bioethicist and health law researcher. He has participated in a rapid expert consultation for the National Academies of Sciences, Engineering, and Medicine (USA) on COVID-19 therapeutic allocation. WFP is an intensivist and bioethicist whose work centers on scarce resource allocation. He chairs his institution's COVID-19 Ethics Resource group. SM is an intensivist and infectious disease physician. He is a co-investigator of REMAP-CAP and is the co-chair of the WHO Clinical Characterization and Management research committee for COVID-19.

Patient involvement

No patients were involved in the planning or conduct of this work.

Dose Optimization and Scarce Resource Allocation

Abstract

Drug scarcity reflects gross mismatch between supply and demand. Under conditions of scarcity, societies strive to allocate scarce resources in a manner that best reflects their values, whatever they may be. Maximizing benefits and reducing inequities are two major values that guide allocation decisions. A deep understanding of the relationship between a scarce drug's dose and clinical response is necessary to appropriately distribute a supply-constrained drug along these lines. The vast majority of drug development and repurposing during the COVID-19 pandemic – an event that has made clear the ever-present scarcity in healthcare systems – has been ignorant of scarcity and dose optimization's ability to help address it. Future pandemic clinical trials systems should obtain dose optimization data, as these appear necessary to enable appropriate scarce resource allocation according to societal values.

Keywords: global health, public health, medical ethics, clinical trials

Background

Absolute scarcity – when demand for a resource vastly exceeds a limited supply – has been a recurring theme of the COVID-19 pandemic.[1] Under absolute scarcity, resource allocation is inevitably zero sum. Increasing supply of an absolutely scarce resource through increased production is one approach, but this may not be feasible (scientifically or politically) over the timescale required to nimbly and effectively respond to scarcity for certain resources.[2] Societies must then confront these tragic situations imposed by allocating absolutely scarce resources in a manner that reflects their values, whatever those values may be.[2 3] In a strained health environment, many countries will seek to allocate scarce medical interventions in a manner that balances benefit maximization with inequity minimization. Doing so requires first knowing how much of the absolutely scarce resource is available, and second, knowing how much benefit recipients can expect to gain from each additional unit of the resource received. This second, key piece of information requires an understanding of the relationship between the scarce resource's dose and clinical efficacy.[4]

A resource's ability to benefit individuals and populations depends on its abundance or scarcity. For resources that are *not* abundant, tradeoffs between the relative welfares of individuals and populations become inevitable.[2] These tradeoffs become especially acute when considering the absolute scarcity of medical resources during a pandemic.

The conventional drug development paradigm is oriented toward the individual, assuming abundance with neither limitation on access nor tradeoffs between recipients. Critically, to the individual who is eligible to receive a given candidate therapy in the context of a clinical trial, that therapy is itself abundant. The resulting dosing regimen, then, does not impact other potential recipients' access. Dose-finding and efficacy studies strive to maximize the net benefit for each individual recipient of the candidate therapy. In the context of an early phase clinical trial (of an abundant drug), administering more than the minimum amount needed to achieve maximum benefit presents no issue, so long as the additional amount does not increase harms.

The abundance assumption implied by conventional drug development falters under scarcity. Drug resources, including those that appear abundant before a disaster hits,[5 6] can quickly become absolutely scarce. When absolute scarcity emerges – with its attendant tradeoffs – administration of excessive amounts of drug reduces total benefits by excluding potential recipients, and exacerbates inequities between those with access and those without.[7] In truth, an infinite number of dose levels are theoretically possible for a given drug. For physicians and policymakers navigating scarcity dosing of an

absolutely scarce resource is an optimizable choice – but it requires re-approaching dosing with a scarcity mindset.

Main Text

Selected Dose Levels in COVID-19

On the basis of demonstrated clinical benefit, 13 drugs (including vaccines) have been approved or authorized by high-income governments for the treatment or prevention of COVID-19 as of October 1, 2021, with still more in development.[8] Dosing uncertainty persists for each (**Table 1**), in turn reducing health system capacity, efficiency of supply utilization, and population health. To better understand the specific dose level that we ought to target in pandemic drug development, however, it is useful to review the dose levels that have been chosen thus far.

Labeled Dose for Prior Indication

The dosages of drugs repurposed for treatment of COVID-19 have almost uniformly duplicated those in the drug's original, pre-COVID-19 indication (**Table 1**). Prior clinical information provides investigators with the pharmacokinetic and safety information needed to rapidly incorporate a candidate drug into a clinical trial, bypassing traditional front-end dose-finding.[9] In such a trial, if the dose used for the original indication *exceeds* the minimum dose needed to demonstrate efficacy in COVID-19, then investigators are able to determine whether the drug is efficacious in COVID-19. The speed conferred by bypassing front-end dose-finding benefits patients through earlier identification of efficacious drugs. But this strategy, by not attempting to identify an optimal dose for the drug in COVID-19 introduces two major risks: First, that, because of relative *underdosing*, a clinical trial may reach a false negative conclusion about the drug's efficacy and second, that the appropriate dose for one indication is in truth excessive for COVID-19, exacerbating scarcity and potentially resulting in excess harms (neither of which are knowable at trial initiation).

Model-Informed Drug Repurposing

Model-informed drug repurposing (MIDR) uses *in vitro* estimates of a repurposed drug's activity against a novel pathogen, such as COVID-19, to guide initial anti-infective dosing. As a pathogen is better characterized during the course of a pandemic, investigators can connect pharmacokinetics to epidemiologic modeling, enabling clinical trials to administer the (presumed) right dose of therapy at the right time, enhancing the odds of demonstrating efficacy if it truly exists.[10] Importantly, however, the

small molecule antiviral drugs for which MIDR has been employed have not been shown to reduce COVID-19-related mortality.[11] In the COVID-19 pandemic, the pathogen-directed approaches that reduce mortality have uniformly been new chemical entities.[12 13] Coupled with MIDR's requirement for *in vitro* assay development and validation to guide dosing decisions, the benefits of host-targeted therapies,[14] and the speeds with which novel antibody-based antiviral and mRNA vaccine development can occur, MIDR may be ill-suited to both rapid and accurate action in future viral pandemics.

Dosing Informed by Randomized, Dose-Ranging Trials

Randomized, placebo-controlled dose-ranging studies directly compare multiple dose levels (including placebo) to one another to identify signs of clinical activity and the extent to which a dose-response relationship exists. These trials are often conducted in phase 2, *before* confirmatory efficacy trials. Timing is critical: Randomized, placebo-controlled dose-ranging studies evaluating key clinical endpoints can enable dosing that responds to emergency conditions. For example, the BLAZE-1 trial evaluated whether any of three different doses (700mg, 2800mg, 7000mg) of bamlanivimab reduced SARS-CoV-2 viral load.[15] Despite only the 2800mg arm reducing SARS-CoV-2 viral load, the 700mg dose was granted Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration due to its comparable reduction in emergency care utilization and hospitalization – instantaneously providing a many-fold increase in the number of patients who could benefit from a limited supply.

More disappointing for global health advocates, however, has been an absence of urgency in pursuing SARS-CoV-2 vaccine dose optimization. For example, half-dose (50µg) mRNA-1273 generates SARS-CoV-2-neutralizing antibodies and seroconversion at rates nearly equivalent to full dose, with all half-dose recipients in the trial seroconverting by six weeks after the first dose.[16] Similar findings have been suggested for the BNT162b2 mRNA vaccine.[17] Similarly, quarter-dose (25µg) mRNA-1273 is sufficient to generate durable cellular immunity against SARS-CoV-2.[18] As it relates to boosters, dose-finding studies might even allow for a massive reduction in vaccine supply utilization while minimizing risk of adverse events.[19] Yet this concept has not been pursued in follow-up trials, despite the potential to instantaneously increase access at least 2-4 fold while simultaneously reducing the likelihood of adverse events, especially in the adolescent and young adult subpopulations at risk for vaccine-related mycoarditis.

Potential Dose Levels for Future Pandemic Drug Development

The extent to which a pandemic drug's dose is ideal depends on the lens through which one views the allocation problem. Optimizing dose to population health versus that of the individual can lead to very different dosing decisions. Two approaches to dosing are described below.

Minimum Dose with Satisfactory Efficacy

The minimum dose with satisfactory efficacy (MDSE) approach pre-defines a satisfactory level of efficacy and then identifies the minimum amount of drug needed to achieve that level, based on the dose-response information provided by dose-ranging studies.[20] The MDSE approach is best suited for a clinical context in which a drug is *known* to have efficacy when administered at a given dose, frequency, route of administration, and duration. Downsides to the MDSE-focused approach include the time needed to optimize the drug's dose and the suboptimal efficacy likely to be experienced by at least one dose cohort in a clinical trial in order to identify the MDSE. Low-dose tocilizumab[21] and pre-clinical attempts toward mRNA vaccine dose minimization are examples of attempted MDSE identification during the COVID-19 pandemic.[16 18] MDSE-based drug development operates from a socially-minded yet individual-dominant perspective, wherein the arrived upon MDSE depends upon one's definition of *"satisfactory"*.

Socially Optimal Dose

The socially optimal dose (SOD) is still more socially-minded. SOD is the theoretical dose at which individual efficacy-per-unit is maximized (**Figure 1**). Utilization of the SOD sacrifices maximal efficacy for each recipient in order to increase population-level benefit by increasing the number of recipients.[4] The SOD, derived from estimates of the population-level dose-response relationship, attempts to maximize the quantity of benefit the drug produces without regard to distribution, and may facilitate allocation strategies that focus solely on maximizing population-level efficacy. One real-world example of (more) socially optimal dosing – outside the bounds of a clinical trial – was the use of extended-interval dosing of mRNA vaccines, in which the potential risk of worsened individual-level outcomes due to the extended dose interval was accepted in exchange for the potential benefit of protecting more people, acknowledging recipients may receive sub-optimal protection by straying from the evidence base.[22 23] In retrospect, although this was a successful calculated risk, testing the strategy prospectively would have been preferred.[24-26]

Strategic Pandemic Clinical Trial Systems for the Future

Under the relative abundance present outside a pandemic, once an efficacious therapy is identified, clinical trialists most commonly turn their attention to the *next* candidate drug – for example, by asking *"Can addition of a new therapy improve a given individual's outcome?"* However, from a population health perspective, the key question often is *"How do we, as a health system, maximize the benefits generated by this therapy's finite supply?"*

During a pandemic, however, conscientious policymakers will often adopt strategies that allocate scarce resources according to societal values, including toward maximization of benefit and reduction of inequities.[3] Simulations of vaccine allocation in which lives saved is the primary outcome,[17] as well as real-world evidence,[24 25] demonstrate the necessity of knowing in real-time the dose-efficacy relationship and an approach that aligns with allocation of scarce resource based on SOD. Either MDSE- or SOD-based allocation schemas would be well-suited to navigating pandemic-fueled drug scarcity in order to improve population health, but their derivation may require dose-ranging clinical trials. How, then, to incorporate dose-optimization studies and enable welfare maximization more efficiently in the future?

Incorporation of dose-optimization studies into platform trials is a next step toward maximizing population health, and the answer likely resides in blended trials that combine efficacy assessment with dose-optimization. Employed at scale, platform trials have allowed for rapid identification of efficacious repurposed therapies through simultaneous evaluation of multiple candidate drugs.[9] Therefore, a two-step approach in which efficacy is first determined in a platform trial, followed immediately by randomized, dose-ranging studies aimed at dose optimization (perhaps guided by surrogate endpoints derived from the earlier, larger definitive RCTs) can provide physicians and policymakers with the information needed to best allocate scarce resources toward population health aims. Seamless clinical trial designs proceeding from dose-finding to efficacy assessment have previously been conducted.[27 28] Given the need to rapidly begin generating benefits, a future pandemic research paradigm should begin first with an assessment of a drug's potential to generate benefits for an individual patient, followed by a thorough exploration of the dose-efficacy relationship to inform optimal allocation.

Considerations for Trialists, Health Systems, and Policymakers

Incorporation of dose optimization of scarce medical resources is not without its challenges or criticisms. First, clinicians, researchers, and participants must be convinced that the risk to an individual involved in a dose-optimization trial is reasonable, when viewed in relation to the social value that the trial

provides. Individuals enrolled in dose-optimization studies ultimately bear the risks of these trials. Chief among these is the risk that the lower dose has lower efficacy than the previously tested dose, a risk that can be mitigated by allowing for crossover. Counterintuitive *benefits* may emerge: Lower doses may have improved safety profiles and individuals enrolling in dose-optimization trials may receive access to therapies earlier than those who do not. Individuals enrolled in dose-optimization trials may therefore, on balance, *benefit* from the lower dose – while also contributing to potentially substantial population benefit. While the populations to which MDSE and SOD will apply are more heterogeneous than the population in which a dose-ranging clinical trial is conducted, a dose-ranging study would be a potentially high-reward incremental step.

Second, critics may worry that dose optimization will lengthen development, repurposing, and authorization or approval timelines, or unnecessarily *increase* the rate at which stockpiles of absolutely scarce drugs are used. Dose optimization indeed requires time, but simulation and real-world studies suggest it can enable implementation strategies that save more lives.[4 17 24-26] Two-staged result reporting – efficacy trial result first, followed by dose optimization – may allow patients to benefit from a therapy with demonstrated efficacy while dose optimization efforts are ongoing. Unpredictable supply chains and increased demand leave clinicians and patients to grapple with a fundamental question "Is it worth the risk *to this patient*, who has access to the scarce medicine, to potentially provision a lower dose?" Within the individual doctor-patient relationship, public health arguments lack an advocate, resulting in an answer of "No." Health authorities and regulators must make efforts to ensure adequate drug supply for dose optimization clinical trials, and hospital authorities should cordon off supplies for dose optimization trials that may serve the greater good.

Third, the successes of corticosteroids in COVID-19 might suggest avoiding the need for dose optimization by limiting our efforts to abundant therapies. This line of thinking represents supply-consciousness but has strategic flaws: It limits the universe of potential therapies that can be tested, no matter how well-reasoned mechanistically; fails to anticipate that a therapy being studied could become scarce in the future; and neglects geographic heterogeneity in abundance/scarcity. Extending the supplies of relatively abundant drugs *in the event of higher than anticipated demand* is consistent with a benefit-maximizing, inequity-minimizing strategy. Moreover, failing to reconsider the dose of abundant drugs risks *under-dosing* and failure to capture population benefits that otherwise could have been achieved.

Some may contend that lower doses should not be used until clinical efficacy is established in a confirmatory clinical trial comparing low-dose to standard-dose, implying that development timelines

will be lengthened. While of course a reasonable concern, risk calculus is contextual. Whether to adopt a lower dose of an absolutely scarce therapy based on suboptimal evidence must be decided in awareness of the dangers resulting from ongoing absolute scarcity. Expanding population access to a therapy by lowering the dose – even if doing so sacrifices some degree of individual-level efficacy – may be socially optimal, ethical, and in line with the goals of a given society.[4 29] Generation of this information alone does not compel policymakers to action.

Last, some may worry that dosing strategies that aim to promote population health treat *individual* recipients inequitably, by providing a dose that is less beneficial than the dose that would be provided under abundance. But, under scarcity, maintaining the dosing strategies used under abundance may exclude many who can benefit. Maximizing benefits for a few recipients while leaving many unprotected for want of access is likely to neither maximize population welfare nor serve a society's equity goals. Indeed, a dose-optimized approach to scarce medicines may facilitate fulfillment of rational pharmacotherapy's goal of ensuring therapeutically sound and cost-effective use of medicines in a post-COVID-19 world.

Conclusions

Maximizing the benefits generated by limited drug supplies due to a scarcity of information. Clinical care under scarcity and clinical care under abundance are different. Research questions and the clinical trials used to answer them must acknowledge this reality in order to serve population health goals. Policymakers must make strategic decisions, and medicine's role is to provide the information that guides these decisions. Dosing remains a major inefficiency to be improved upon during the COVID-19 pandemic. In a post-COVID-19 future, these issues are likely to persist *after* the COVID-19 pandemic for high-cost cancer and rheumatology drugs in low- and middle-income countries.[29 30] Clinical trial systems, supported by policy-makers, must acknowledge scarcity and take appropriate steps to optimize dosing. Though methodologic questions remain, a two-step model of innovation that recognizes the inherent tension between population health and individual health under scarcity is one potential approach moving forward.

List of Abbreviations

COVID-19: Novel coronavirus disease 2019

EUA: Emergency Use Authorization

MDSE: Minimum dose with satisfactory efficacy

MIDR: Model-informed drug repurposing

MRNA: Messenger ribonucleic acid

RCT: Randomized, controlled trial

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SOD: Socially optimal dose

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Table and Figure Legends

Table 1. Dose optimization of repurposed and new molecular entities for SARS-CoV-2 and COVID-19 as of Summer 2021. Drugs that have received regulatory approval or authorization, as well as U.S. guideline-recommended drugs, for the prevention or treatment of COVID-19 are summarized in the table. From left to right, columns demonstrate minimal pre-RCT dose-finding in COVID-19, a limited number of welfare-maximizing dose optimization trials, and the absence of any MDSE identification in COVID-19 therapeutics. **Abbreviations:** RCT, randomized, controlled trial; MDSE, minimum dose with satisfactory efficacy; IL-6, interleukin-6; CAR-T CRS, chimeric antigen T-cell receptor-related cytokine release syndrome; EMA, European Medicines Agency; JAK, Janus kinase; STAT, signal transducer and activator of transcription proteins; ARDS, acute respiratory distress syndrome.

Figure 1. Distinctions between individually and socially optimal dosing approaches for a hypothetical vaccine. (A) A randomized dose-finding study reveals the dose-response curve shown, where a vaccine is found to have maximal efficacy at a 100mcg dose and approximately 75% relative efficacy at quarter-dose. (B) By evaluating the drug's efficacy relative to the amount of drug administered, we derive the socially optimal dose, maximizing the efficacy gained per microgram administered. Abbreviations: MDSE, minimum dose with satisfactory efficacy; RCT, randomized, controlled trial.

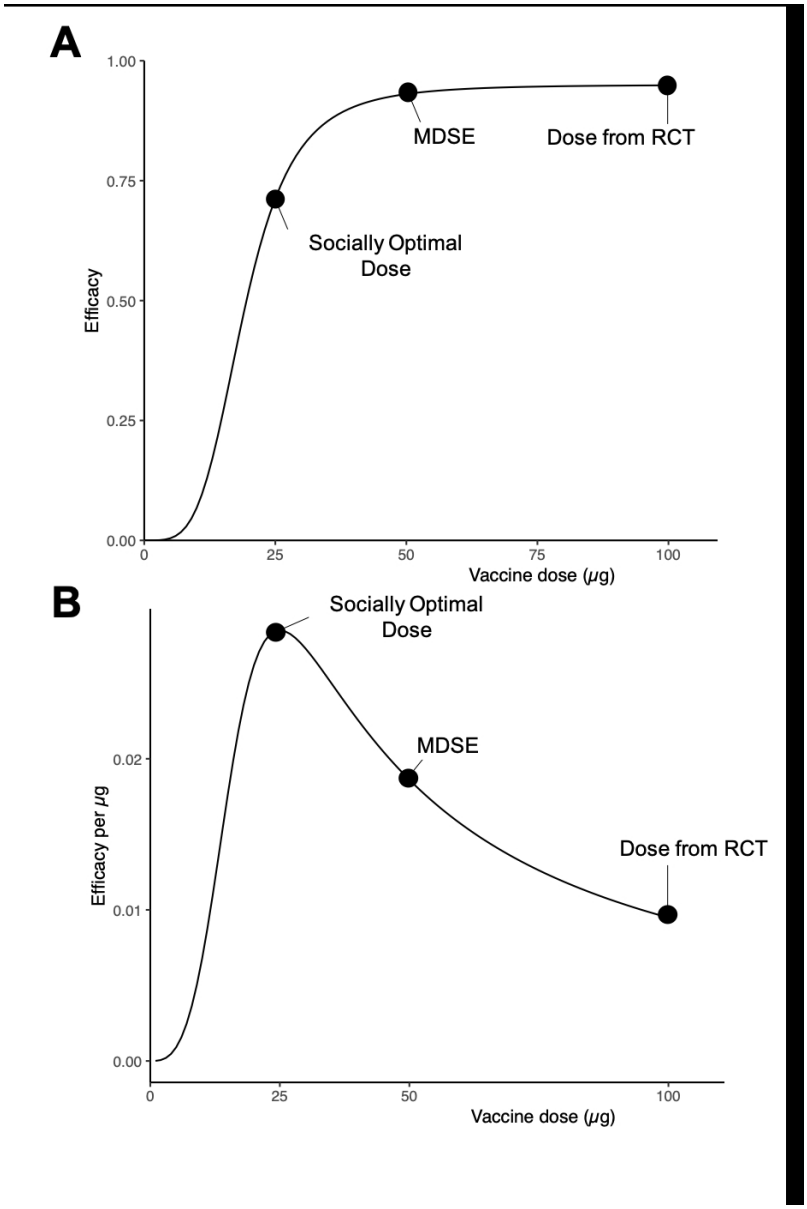

Figure 1

158x237mm (150 x 150 DPI)

Drug (Manufacturer)	*Dedicated COVID-19 Dose-Finding Study*	*Post-RCT Dose Optimization or Supply Expansion Clinical Trial*	*Defined Dose-Response Relationship or MDSE*
Repurposed Molecular Entities			
Anto-SARS-CoV-2 Drugs			
Remdesivir (Gilead)	None (Ebola dose)[1]	5 vs 10 days duration[2]	No
Immunomodulators			
Anti-IL6			
Sarilumab (Sanofi)	None, two dosing arms in randomized phase 3 trial[3]	N/A	No
Tocilizumab (Genentech/Roche)	None (CAR-T CRS dose)[4]	Adaptive dose-ranging phase 2, 4 dose levels[5] Confirmatory RCT ongoing[6]	No
Anti-JAK/STAT			
Baricitinib (+ remdesivir) (Eli Lilly)	None (EMA dose)[7]	Phase 1/2, including 4mg and 2mg[8]	No
Corticosteroids			
Dexamethasone (Various)	None (Sepsis/ARDS dose)[9]	10mg daily (experimental) vs 6mg daily (authorized dose) ongoing[10]	No
Hydrocortisone (Various)	None (Sepsis/ARDS dose)[11]	None	No
New Molecular Entities			
Vaccine			
mRNA-1273 (Moderna)	Non-human primate (2 dose levels)[12]	Surrogate endpoint-based, 50ug vs 100ug[13]	No
BNT162b2 (Pfizer/BioNTech)	Randomized, phase 1/2, 5 dose levels[14,15]	Simulation-based study of lower doses[16] Heterologous combo (BNT162b2, ChAdOx1 nCov-19)	No
Ad26.COV2.S (Janssen)	Randomized phase 1/2, 2 dose levels[17]	No	No
ChAdOx1 nCov-19 (AstraZeneca-Oxford)	Randomized phase 1/2, 2 dose cohorts (single vs two doses, all same dose)[18]	Heterologous combination (BNT162b2 & ChAdOx1 nCov-19)	No
Anti-SARS-CoV-2 Drugs			
Bamlanivimab Etesevimab (Eli Lilly)	Randomized phase 1/2/3, 3 dose levels (bamlanivimab)[19] Randomized phase 1/2/3, 2 dose levels (etesevimab)[19]	No	No
Casirivimab Imdevimab (Regeneron)	Randomized phase 1/2/3, 2 dose levels (combination)[20]	No	No
Sotrovimab (GlaxoSmithKline)	Industry-sponsored randomized Phase 1/2/3 (no dose range)[21]	No	No

Table 1.

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Dose Optimization and Scarce Resource Allocation: Two Sides of the Same Coin

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Key Messages

- Resource scarcity reflects gross mismatch between supply and demand; societies strive to allocate scarce resources allocated in a manner that reflects their values
- With regard to drugs and vaccines, a deep understanding of the relationship between a scarce drug's dose and clinical response is necessary to appropriately distribute a supply-constrained drug
- Future pandemic clinical trials should obtain dose optimization data in order to enable appropriate distribution

Declarations

Ethics approval and consent to participate: Not applicable

Consent to publish: Not applicable

Availability of data and materials: Not applicable

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GWS is a clinical trialist and health services researcher whose work centers on dose-optimization to combat drug scarcity and financial toxicity. He is a contributor to the World Health Organization's Rapid Evidence Appraisal for COVID-19 Therapies. GP is a bioethicist and health law researcher. He has participated in a rapid expert consultation for the National Academies of Sciences, Engineering, and Medicine (USA) on COVID-19 therapeutic allocation. WFP is an intensivist and bioethicist whose work centers on scarce resource allocation. He chairs his institution's COVID-19 Ethics Resource group. SM is an intensivist and infectious disease physician. He is a co-investigator of REMAP-CAP and is the co-chair of the WHO Clinical Characterization and Management research committee for COVID-19.

Contributorship Statement

GWS designed and conceptualized the work, interpreted findings, and drafted and revised the manuscript for intellectual content. GP, WFP, and SM interpreted findings, revised the manuscript, and provided intellectual content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GWS is the guarantor.

Patient involvement

No patients were involved in the planning or conduct of this work.

Abstract

Drug scarcity reflects gross mismatch between supply and demand. Under conditions of scarcity, societies strive to allocate scarce resources in a manner that best reflects their values, whatever they may be. Maximizing benefits and reducing inequities are two major values that guide allocation decisions. A deep understanding of the relationship between a scarce drug's dose and clinical response is necessary to appropriately distribute a supply-constrained drug along these lines. The vast majority of drug development and repurposing during the COVID-19 pandemic – an event that has made clear the ever-present scarcity in healthcare systems – has been ignorant of scarcity and dose optimization's ability to help address it. Future pandemic clinical trials systems should obtain dose optimization data, as these appear necessary to enable appropriate scarce resource allocation according to societal values.

Keywords: global health, public health, medical ethics, clinical trials

Background

Absolute scarcity – when demand for a resource vastly exceeds a limited supply – has been a recurring theme of the COVID-19 pandemic.[1] Under absolute scarcity, resource allocation is inevitably zero sum. Increasing supply of an absolutely scarce resource through increased production is one approach, but for certain resources, this may not be feasible (scientifically or politically) over the timescale required to nimbly and effectively respond to scarcity.[2] Societies must then confront the tragic dilemmas scarcity imposes by allocating absolutely scarce resources in a manner that reflects their values, whatever those values may be.[2 3] In a strained health environment, many countries will seek to allocate scarce medical interventions to balance benefit maximization with inequity minimization. Doing so requires first knowing how much of the absolutely scarce resource is available, and second, knowing how much benefit recipients of the resource can expect to gain from each additional unit they receive. This second, key piece of information requires an understanding of the relationship between the scarce resource's dose and clinical efficacy.[4]

A resource's ability to benefit individuals and populations depends on its abundance or scarcity. For resources that are *not* abundant, tradeoffs between the relative welfares of individuals and populations become inevitable.[2] These tradeoffs become especially acute when considering the absolute scarcity of medical resources during a pandemic.

The conventional drug development paradigm is oriented toward the individual. It assumes that the drug is abundant with respect to the potential recipient, with neither limits on access nor tradeoffs between different recipients. Critically, for the individual who is eligible to receive a given candidate therapy in the context of a clinical trial, that therapy is itself abundant because the dosing regimen does not impact other potential recipients' access. Drug development thus occurs under a critical assumption: Maximizing the benefit that each individual recipient gleans from a drug will necessarily maximize total population benefits. Dose-finding and efficacy studies therefore strive to maximize the net benefit for each individual recipient of the candidate therapy. In the context of an early phase clinical trial of an abundant drug, administering more than the minimum amount needed to achieve maximum benefit presents no issue, so long as the additional amount does not increase harms.

The abundance assumption implied by conventional drug development falters under scarcity. Drug resources, including those that appear abundant before a disaster strikes,[5 6] can quickly become absolutely scarce. When absolute scarcity and its attendant tradeoffs emerge, administration of excessive amounts of drug to some individuals, by excluding other potential recipients from *any* benefit, *reduces* the total population benefits that could have been gleaned. Further, this form of overdosing

exacerbates inequities between those with access and those without.[7] In truth, an infinite number of dose levels are theoretically possible for a given drug. For physicians and policymakers navigating scarcity dosing of an absolutely scarce resource is an optimizable choice – but it requires re-approaching dosing with consideration of both scarcity and public health.

Main Text

Selected Dose Levels in COVID-19

On the basis of demonstrated clinical benefit, 13 drugs (including vaccines) have been approved or authorized by high-income governments for the treatment or prevention of COVID-19 as of October 1, 2021, with many more in development or subsequently approved.[8] Dosing uncertainty persists for each of these drugs (**Table 1**), in turn reducing health system capacity, efficiency of supply utilization, and population health. To better understand the specific dose level that we ought to target in pandemic drug development, however, it is useful to review the dose levels that have been chosen thus far.

Labeled Dose for Prior Indication

The dosages of drugs repurposed for treatment of COVID-19 have almost uniformly duplicated those in the drug's original, pre-COVID-19 indication (**Table 1**). Prior clinical information provides investigators with the pharmacokinetic and safety information needed to rapidly incorporate a candidate drug into a clinical trial evaluating efficacy, bypassing traditional early-phase dose-finding research.[9] If the dose used for the original indication *exceeds* the minimum dose needed to demonstrate efficacy in COVID-19, then investigators are able to determine whether the drug is in fact an efficacious therapy for COVID-19. The speed conferred by bypassing front-end dose-finding benefits patients through earlier identification of efficacious drugs. But this strategy, by not attempting to identify an optimal dose for the drug specific for COVID-19 introduces two major risks: First, that, because of relative *underdosing*, a clinical trial may reach a false negative conclusion about the drug's efficacy and second, that the appropriate dose for the original indication is in truth excessive for COVID-19, exacerbating scarcity and potentially resulting in excess harms (neither of which are knowable at trial initiation). While there are clear efficiencies to be gained by building on prior knowledge of the drug's performance for its original indication, the absences of both individual- and population-level dose optimization may exhaust drug supplies or harm individual recipients at rates far higher than necessary.

Drug (Manufacturer)	*Dedicated COVID-19 Dose-Finding Study*	*Post-RCT Dose Optimization or Supply Expansion Clinical Trial*	*Defined Dose-Response Relationship or MDSE*
Repurposed Molecular Entities			
Anto-SARS-CoV-2 Drugs			
Remdesivir (Gilead)	None (Ebola dose)[10]	5 vs 10 days duration[11]	No
Immunomodulators			
Anti-IL6			
Sarilumab (Sanofi)	None, two dosing arms in randomized phase 3 trial[12]	N/A	No
Tocilizumab (Genentech/Roche)	None (CAR-T CRS dose)[13]	Adaptive dose-ranging phase 2, 4 dose levels[14] Confirmatory RCT ongoing[15]	No
Anti-JAK/STAT			
Baricitinib (+ remdesivir]) (Eli Lilly)	None (EMA dose)[16]	Phase 1/2, including 4mg and 2mg[17]	No
Corticosteroids			
Dexamethasone (Various)	None (Sepsis/ARDS dose)[18]	10mg daily (experimental) vs 6mg daily (authorized dose) ongoing[19]	No
Hydrocortisone (Various)	None (Sepsis/ARDS dose)[20]	None	No
New Molecular Entities			
Vaccine			
mRNA-1273 (Elasomeran [INN]) (Moderna)	Non-human primate (2 dose levels)[21]	Surrogate endpoint-based, 50ug vs 100ug[22]	No
BNT162b2 (Tozinameran [INN]) (Pfizer/BioNTech)	Randomized, phase 1/2, 5 dose levels[23] [24]	Simulation-based study of lower doses[25] Heterologous combo (BNT162b2, ChAdOx1 nCov-19)	No
Ad26.COV2.S (Janssen)	Randomized phase 1/2, 2 dose levels[26]	No	No
ChAdOx1 nCov-19 (AstraZeneca-Oxford)	Randomized phase 1/2, 2 dose cohorts (single vs two doses, all same dose)[27]	Heterologous combination (BNT162b2 & ChAdOx1 nCov-19)	No
Anti-SARS-CoV-2 Drugs			
Bamlanivimab Etesevimab (Eli Lilly)	Randomized phase 1/2/3, 3 dose levels (bamlanivimab)[28] Randomized phase 1/2/3, 2 dose levels (etesevimab)[28]	No	No
Casirivimab Imdevimab (Regeneron)	Randomized phase 1/2/3, 2 dose levels (combination)[29]	No	No
Sotrovimab (GlaxoSmithKline)	Industry-sponsored randomized Phase 1/2/3 (no dose range)[30]	No	No

Table 1. Dose optimization of repurposed and new molecular entities for SARS-CoV-2 and COVID-19 as of Summer 2021. Drugs that have received regulatory approval or authorization, as well as U.S. guideline-recommended drugs, for the prevention or treatment of COVID-19 are summarized in the table. From left to right, columns demonstrate minimal pre-RCT dose-finding in COVID-19, a limited number of welfare-maximizing dose optimization trials, and the absence of any MDSE identification in COVID-19 therapeutics. **Abbreviations:** RCT, randomized, controlled trial; MDSE, minimum dose with satisfactory efficacy; IL-6, interleukin-6; CAR-T CRS, chimeric antigen T-cell receptor-related cytokine release syndrome; EMA, European Medicines Agency; JAK, Janus kinase; STAT, signal transducer and activator of transcription proteins; ARDS, acute respiratory distress syndrome.

Model-Informed Drug Repurposing

Model-informed drug repurposing (MIDR) uses *in vitro* estimates of a repurposed drug's activity against a novel pathogen, such as COVID-19, to guide initial anti-infective dosing. As a pathogen becomes better characterized during the course of a pandemic, investigators can connect pharmacokinetics to epidemiologic modeling, enabling clinical trials to administer the (presumed) right dose of therapy at the right time, enhancing the odds of demonstrating efficacy if it truly exists.[31] Importantly, however, the small molecule antiviral drugs for which MIDR has been employed have not been shown to reduce COVID-19-related mortality.[32] Instead, in the COVID-19 pandemic, the pathogen-directed approaches demonstrated to reduce mortality have uniformly been new chemical entities.[33 34] Coupled with MIDR's requirement for an *in vitro* assay to be developed and validated to guide dosing decisions, the benefits of host-targeted therapies,[35] and the speeds with which novel antibody-based antiviral and mRNA vaccine development can occur, MIDR may be ill-suited to both rapid and accurate action in future viral pandemics.

Dosing Informed by Randomized, Dose-Ranging Trials

Randomized, placebo-controlled dose-ranging studies directly compare multiple dose levels (including placebo) to one another to identify signs of clinical activity and the extent to which a dose-response relationship exists. These trials are often conducted in phase 2, *before* confirmatory efficacy trials that use gold-standard clinical endpoints. Timing is critical: Randomized, placebo-controlled dose-ranging studies evaluating key surrogate clinical endpoints can enable dosing that responds to emergency conditions. For example, the BLAZE-1 trial evaluated whether any of three different doses (700mg, 2800mg, 7000mg) of bamlanivimab reduced SARS-CoV-2 viral load.[36] Despite only the 2800mg arm reducing SARS-CoV-2 viral load, the 700mg dose was granted Emergency Use Authorization (EUA) by the U.S. Food and Drug Administration due to its comparable reduction in emergency care utilization and hospitalization – instantaneously providing a many-fold increase in the number of patients who could benefit from what would be a very limited initial supply of drug. BLAZE-1 was not powered to make a determination of small differences in these important outcomes between different dose levels. Despite this limitation, though, a decision that prioritized population health over individual health was made.

More disappointing for global health advocates, however, has been an absence of urgency in pursuing SARS-CoV-2 vaccine dose optimization. For example, half-dose (50µg) mRNA-1273 generates SARS-CoV-2-neutralizing antibodies and seroconversion at rates nearly equivalent to full dose, with all half-dose recipients in the trial seroconverting by six weeks after the first dose.[22] Similar findings have been suggested for the BNT162b2 mRNA vaccine.[25] Similarly, quarter-dose (25µg) mRNA-1273 is

sufficient to generate durable cellular immunity against SARS-CoV-2.[37] As it relates to boosters, dose-finding studies might even allow for a massive reduction in vaccine supply utilization while minimizing risk of adverse events.[38] Yet this concept has not been pursued in follow-up trials, despite the potential to instantaneously increase access at least 2-4 fold while simultaneously reducing the likelihood of adverse events, especially in the adolescent and young adult subpopulations at risk for vaccine-related myocarditis.

Administering drug at a lower dose, known as fractional dosing, rations divisible scarce resources to increase the number of recipients who have the potential to benefit from a relatively fixed supply of scarce resource. The approach acknowledges that individuals who receive a lower dose could be "worse off" than if they had access to and received the full dose. However, the social value gained by multiplying the number of recipients by two-fold (or more) more than compensates for the potentially reduced efficacy each recipient experiences. In the COVID-19 pandemic, for example, meaningful reductions in both infections and deaths would likely have occurred had a half-dose mRNA vaccine achieved an efficacy 70% that of the full-dose mRNA vaccine.[39] In light of the evidence cited above showing the near-equivalence of low-dose mRNA vaccines[22 25 37] as well as the possibility that the emergence of SARS-CoV-2 variants would have been *reduced* by using a fractional dosing strategy focused on vaccinating as many individuals as possible, as quickly as possible,[40] it is plausible that the failure to optimize doses and enact fractional dosing led not only to unnecessary morbidity and mortality but also a lengthening of the COVID-19 pandemic.

Potential Dose Levels for Future Pandemic Drug Development

The extent to which a pandemic drug's dose is ideal depends on the lens through which one views the allocation problem. Optimizing dose to population health instead of individual health often leads to very different dosing decisions. Two approaches to dosing are described below.

Minimum Dose with Satisfactory Efficacy

The minimum dose with satisfactory efficacy (MDSE) approach pre-defines a satisfactory level of efficacy and then identifies the minimum amount of drug needed to achieve that level, based on the dose-response information provided by dose-ranging studies.[41] The MDSE approach is best suited for a clinical context in which a drug is *known* to have efficacy when administered at a given dose, frequency, route of administration, and duration. Ideally, the MDSE would be identified in clinical trials; the presence of at least one cohort of patients that receives a dose level(s) that is less than the MDSE provides a measure of confidence that MDSE is, in fact, MDSE. Downsides to the MDSE-focused approach include the time needed to optimize the drug's dose after confirming its efficacy at the higher, non-MDSE dose and the suboptimal efficacy that would be experienced by any study arms that receive a dose lower than MDSE in a clinical trial. Low-dose tocilizumab[14] and pre-clinical attempts toward mRNA vaccine dose minimization are examples of attempted MDSE identification during the COVID-19 pandemic.[22 37] MDSE-based drug development operates from a socially-minded yet individual-dominant perspective, wherein the arrived upon MDSE depends upon a society's definition of "satisfactory".

Socially Optimal Dose

The socially optimal dose (SOD) is still more socially-minded. SOD is the theoretical dose at which individual efficacy-per-unit is maximized (**Figure 1**). Utilization of the SOD sacrifices maximal efficacy for each recipient in order to increase population-level benefit by increasing the number of recipients.[4] The SOD, derived from estimates of the population-level dose-response relationship, attempts to maximize the quantity of benefit the drug produces without regard to distribution, and may facilitate allocation strategies that focus solely on maximizing population-level efficacy. One real-world example of (more) socially optimal dosing – outside the bounds of a clinical trial – was the use of extended-interval dosing of mRNA vaccines, in which the potential risk of worsened individual-level outcomes due to the extended dose interval was accepted in exchange for the potential benefit of protecting more people, acknowledging recipients may receive sub-optimal protection by straying from the evidence base.[39 42] In

retrospect, although this was a successful calculated risk, testing the strategy prospectively through clinical trials would have been preferred.[43-45]

Mathematical Models' Guidance

Epidemiologic models of viral pandemics, in combination with economic models describing implementation of mitigation and vaccination, enable side-by-side comparison of resource allocation strategies against a range of counterfactuals and under a range of assumptions.[39 40 46-48] Conditioned on a given drug or vaccine having been shown to be efficacious, the most relevant question for public health becomes how to, in an efficient and accurate manner, maximize the population benefits that can be derived from a scarce supply of that resource. Determining what "socially optimal" may be in the rapidly evolving evidence space of a global pandemic is inherently challenging and depends upon multiple, imperfectly known factors, including: vaccine effectiveness, *relative* effectiveness of lower doses, the maximum rate with which vaccination efforts proceed, and characteristics of the pandemic itself (e.g., incubation period, rates of spread and replication, and mortality). Prior outbreaks, including influenza,[49] cholera,[50] and yellow fever, demonstrate the value of taking a rational approach to scarce vaccine allocation guided by mathematical models. Such efforts came about, however, once scarcity had arrived, rather than pre-emptively, *during* drug and vaccine development.

Strategic Pandemic Clinical Trial Systems for the Future

Under the relative abundance present outside a pandemic, once an efficacious therapy is identified, clinical trialists most commonly turn their attention to the *next* candidate drug – for example, by asking *"Can addition of a new therapy improve a given individual's outcome?"* However, from a population health perspective, the key question often is *"How do we, as a health system, maximize the benefits generated by this therapy's finite supply?"*

During a pandemic, conscientious policymakers will often adopt strategies that allocate scarce resources according to societal values, including toward maximization of benefit and reduction of inequities.[3] Simulations of vaccine allocation in which lives saved is the primary outcome,[25] as well as real-world evidence,[43 44] demonstrate the necessity of knowing in real-time the dose-efficacy relationship and an approach that aligns with allocation of scarce resource based on SOD. Either MDSE- or SOD-based allocation schemas would be well-suited to navigating pandemic-fueled drug scarcity in order to improve population health, but their derivation may require dose-ranging clinical trials. How,

then, to incorporate dose-optimization studies and enable welfare maximization more efficiently in the future?

Incorporation of dose-optimization studies into platform trials is a next step toward maximizing population health, and the answer likely resides in blended trials that combine efficacy assessment with dose-optimization. Employed at scale, platform trials have allowed for rapid identification of efficacious repurposed therapies through simultaneous evaluation of multiple candidate drugs.[9] Therefore, a two-step approach in which efficacy is first determined in a platform trial, followed immediately by randomized, dose-ranging studies aimed at dose optimization (perhaps guided by surrogate endpoints derived from the earlier, larger definitive RCTs, such as correlates of protection[51 52]) can provide physicians and policymakers with the information needed to best allocate scarce resources toward population health aims. Seamless clinical trial designs proceeding from dose-finding to efficacy assessment have previously been conducted.[53 54] Given the need to rapidly begin generating benefits, a future pandemic research paradigm should begin first with an assessment of a drug's potential to generate benefits for an individual patient, followed by a thorough exploration of the dose-efficacy relationship to inform optimal allocation.

Optimizable Components of Dose

Once a given drug's efficacy has been established, optimization research is needed to understand the patient- and drug-related factors most responsible for the drug's success. A drug's efficacy depends upon the extent to which its target is exposed to the drug (i.e., the exposure). Exposure itself is a function of dose, which can be framed as the discrete quantum of drug administered (whether it be a flat dose for all subjects or a personalized, weight-based dose), the frequency with which that quantum is administered (e.g., once vs recurring), the time duration over which a patient is exposed to the drug, and the route of administration. Lowering the quantum administered, reducing the frequency and duration of administration, and altering the route of administration can all help reduce the total amount of drug used while, simultaneously, achieving sufficient exposure.

As discussed in preceding sections, this question is orthogonal to, but no less important than, the original efficacy question more commonly examined in conventional studies. Clinical trial methods that efficiently accomplish the task of dose optimization while 1) adhering to core ethical constraints (namely the absence of a placebo arm once a given drug's efficacy has been established) and 2) recruiting efficiently are at this time being elucidated. Dose optimization *after* confirmation of a drug's efficacy is, essentially, a one-way sensitivity analyses: That is, they would evaluate the impact of lower

quanta, less frequent administration, shorter duration, and/or different routes on efficacy. These designs may come to resemble DURATIONS designs previously developed to efficiently examine antibiotic regimen durations.[55 56] Clever use of Bayesian prospective clinical trials in sequence may unlock new efficiencies.

Considerations for Trialists, Health Systems, and Policymakers

Incorporation of dose optimization of scarce medical resources is not without its challenges or criticisms. First, clinicians, researchers, and participants must be convinced that the risk to an individual involved in a dose-optimization trial is reasonable, when viewed in relation to the social value that the trial provides. Individuals enrolled in dose-optimization studies ultimately bear the risks of these trials. Chief among these is the risk that the lower dose has lower efficacy than the previously tested dose, a risk that can be mitigated by allowing for crossover. Counterintuitive *benefits* may emerge: Lower doses may have improved safety profiles and individuals enrolling in dose-optimization trials may receive access to therapies earlier than those who do not. Individuals enrolled in dose-optimization trials may therefore, on balance, *benefit* from the lower dose – while also contributing to potentially substantial population benefit. While the populations to which MDSE and SOD will apply are more heterogeneous than the population in which a dose-ranging clinical trial is conducted, a dose-ranging study would be a potentially high-reward incremental step.

Second, critics may worry that dose optimization will lengthen development, repurposing, and authorization or approval timelines, or unnecessarily *increase* the rate at which stockpiles of absolutely scarce drugs are used. Dose optimization indeed requires time, but simulation and real-world studies suggest it can enable implementation strategies that save more lives.[4 25 43-45] Two-staged result reporting – efficacy trial result first, followed by dose optimization – may allow patients to benefit from a therapy with demonstrated efficacy while dose optimization efforts are ongoing. Unpredictable supply chains and increased demand leave clinicians and patients to grapple with a fundamental question “Is it worth the risk *to this patient*, who has access to the scarce medicine, to potentially provision a lower dose?” Within the individual doctor-patient relationship, public health arguments lack an advocate, resulting in an answer of “No.” Health authorities and regulators must make efforts to ensure adequate drug supply for dose optimization clinical trials, and hospital authorities should cordon off supplies for dose optimization trials that may serve the greater good.

Third, the successes of corticosteroids for hospitalized patients with COVID-19 who require supplemental oxygen might suggest avoiding the need for dose optimization by limiting our efforts to

abundant therapies. This line of thinking represents supply-consciousness but has strategic flaws: It limits the universe of potential therapies that can be tested, no matter how well-reasoned mechanistically; fails to anticipate that a therapy being studied could become scarce in the future; and neglects geographic heterogeneity in abundance/scarcity. Extending the supplies of relatively abundant drugs *in the event of higher than anticipated demand* is consistent with a benefit-maximizing, inequity-minimizing strategy. Moreover, failing to reconsider the dose of abundant drugs risks *under-dosing* and failure to capture population benefits that otherwise could have been achieved.

Some may contend that lower doses should not be used until clinical efficacy is established in a confirmatory clinical trial comparing low-dose to standard-dose, implying that development timelines will be lengthened. While of course a reasonable concern, risk calculus is contextual. Whether to adopt a lower dose of an absolutely scarce therapy based on suboptimal evidence must be decided in awareness of the dangers resulting from ongoing absolute scarcity. Expanding population access to a therapy by lowering the dose – even if doing so sacrifices some degree of individual-level efficacy – may be socially optimal, ethical, and in line with the goals of a given society.[4 57] Generation of this information alone does not compel policymakers to action.

Last, some may worry that dosing strategies that aim to promote population health treat *individual* recipients inequitably, by providing a dose that is less beneficial than the dose that would be provided under abundance. But, under scarcity, maintaining the dosing strategies used under abundance may exclude many who can benefit. Maximizing benefits for a few recipients while leaving many unprotected for want of access is likely to neither maximize population welfare nor serve a society's equity goals. Indeed, a dose-optimized approach to scarce medicines may facilitate fulfillment of rational pharmacotherapy's goal of ensuring therapeutically sound and cost-effective use of medicines in a post-COVID-19 world.

Applying Scarcity-Oriented Development to the *Next* Pandemic

Many of these same themes and debates have re-emerged in the past 6 months. Since this manuscript was initially submitted, monkeypox has been declared a public health emergency of international concern.[58] Authorities in the U.S. appear keen to avoid the accessibility issues that plagued the COVID-19 vaccine rollout. In addition to adopting a "first doses first" strategy in some localities,[59] federal-level policymakers will allow federal drug regulators to provide EUA for fractional dosing of monkeypox vaccine (modified vaccinia Ankara [MVA]),[60] drawing on a previously conducted randomized, controlled trial comparing full-dose subcutaneous injection of two different forms of MVA with one-fifth dose

intradermally.[61] Notably in the trial, recipients received *two* doses of MVA.[61] Alongside this extrapolation and concern that intradermal injection will be suboptimal when implemented in the real world, adoption of fractional dosing has been criticized.[62]

Recognizing the evidentiary ambiguity, clinical trialists are starting to ask the right, public health-oriented questions. The U.S.-based National Institute of Allergy and Infectious Diseases is sponsoring a prospective, randomized, controlled phase 2 trial evaluating two doses of one-fifth dose MVA (intradermal), two doses of one-tenth dose MVA (intradermal) against two doses of a full-dose standard of care (delivered subcutaneously).[63 64] There is, however, cause for great concern in the execution of this research vision. The proposed trial,[64] which is not yet recruiting, employs a non-inferiority hypothesis structure in evaluating peak antibody in patients 18 to 50 years of age. Of note, the initial trial plan does not include a *clinical* efficacy endpoint. Together, these factors raise the worrying possibility that this much-needed dose optimization trial could, despite not having defined the minimal antibody response needed to confer protection, reject the fractional dosing strategy on the basis of inferior peak antibody responses alone and, simultaneously, fail to identify *clinical* near-equivalence between the three tested dose levels if it does exist. The BLAZE-1 trial may be informative: Even underpowered clinical outcomes can influence decision-making. Moreover, the COVID-19 experience suggests that even a positive trial that demonstrates the non-inferiority of fractional dosing's antibody response would fail to convince skeptical public health authorities or regulators, due to the failures to provide either a clinical endpoint or meaningful data for patients over 50 years of age. The extent to which the science of fractional dosing will be furthered is limited by the trial's inability to independently correlate threshold antibody titers with clinical protection as well as its likely inability to identify both the MDSE and SOD. Finally, by virtue of the study's three-arm design, the potential vaccine supply expansion is inherently capped at a 10-fold increase, which may not be sufficient to protect all individuals in some locales.

Conclusions

Clinical care provided under conditions of scarcity and clinical care provided under conditions of abundance are profoundly different. Society's ability to maximize the benefits that could be generated from its scarce drug supplies was hampered by a lack of information and an inability or unwillingness to ask key questions. Research questions and the clinical trials used to answer them must acknowledge the stark differences between care under scarcity and care under abundance in order to serve population

health goals. Policymakers must make strategic decisions to navigate scarcity, and medicine's role is to provide policymakers with information that guides decision-making. Dosing remains a major inefficiency to be improved upon in pandemic preparedness. Indeed, in a post-COVID-19 future, these issues are likely to persist for high-cost cancer and rheumatology drugs in low- and middle-income countries, where the drugs may be available but the means to acquire them are scarce.[57 65] Clinical trial systems, supported by policy-makers, must acknowledge scarcity and take appropriate steps to optimize dosing. Though methodologic questions remain, a two-step model of innovation that recognizes and then balances the inherent tension between population health and individual health under scarcity is one potential approach moving forward.

List of Abbreviations

COVID-19: Novel coronavirus disease 2019

EUA: Emergency Use Authorization

MDSE: Minimum dose with satisfactory efficacy

MIDR: Model-informed drug repurposing

MRNA: Messenger ribonucleic acid

RCT: Randomized, controlled trial

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

SOD: Socially optimal dose

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Table and Figure Legends

Table 1. Dose optimization of repurposed and new molecular entities for SARS-CoV-2 and COVID-19 as of Summer 2021. Drugs that have received regulatory approval or authorization, as well as U.S. guideline-recommended drugs, for the prevention or treatment of COVID-19 are summarized in the table. From left to right, columns demonstrate minimal pre-RCT dose-finding in COVID-19, a limited number of welfare-maximizing dose optimization trials, and the absence of any MDSE identification in COVID-19 therapeutics. **Abbreviations:** RCT, randomized, controlled trial; MDSE, minimum dose with satisfactory efficacy; IL-6, interleukin-6; CAR-T CRS, chimeric antigen T-cell receptor-related cytokine release syndrome; EMA, European Medicines Agency; JAK, Janus kinase; STAT, signal transducer and activator of transcription proteins; ARDS, acute respiratory distress syndrome.

Figure 1. Distinctions between individually and socially optimal dosing approaches for a hypothetical vaccine. (A) A randomized dose-finding study reveals the dose-response curve shown, where a vaccine is found to have maximal efficacy at a 100mcg dose and approximately 75% relative efficacy at quarter-dose. (B) By evaluating the drug's efficacy relative to the amount of drug administered, we derive the socially optimal dose, maximizing the efficacy gained per microgram administered. Abbreviations: MDSE, minimum dose with satisfactory efficacy; RCT, randomized, controlled trial.

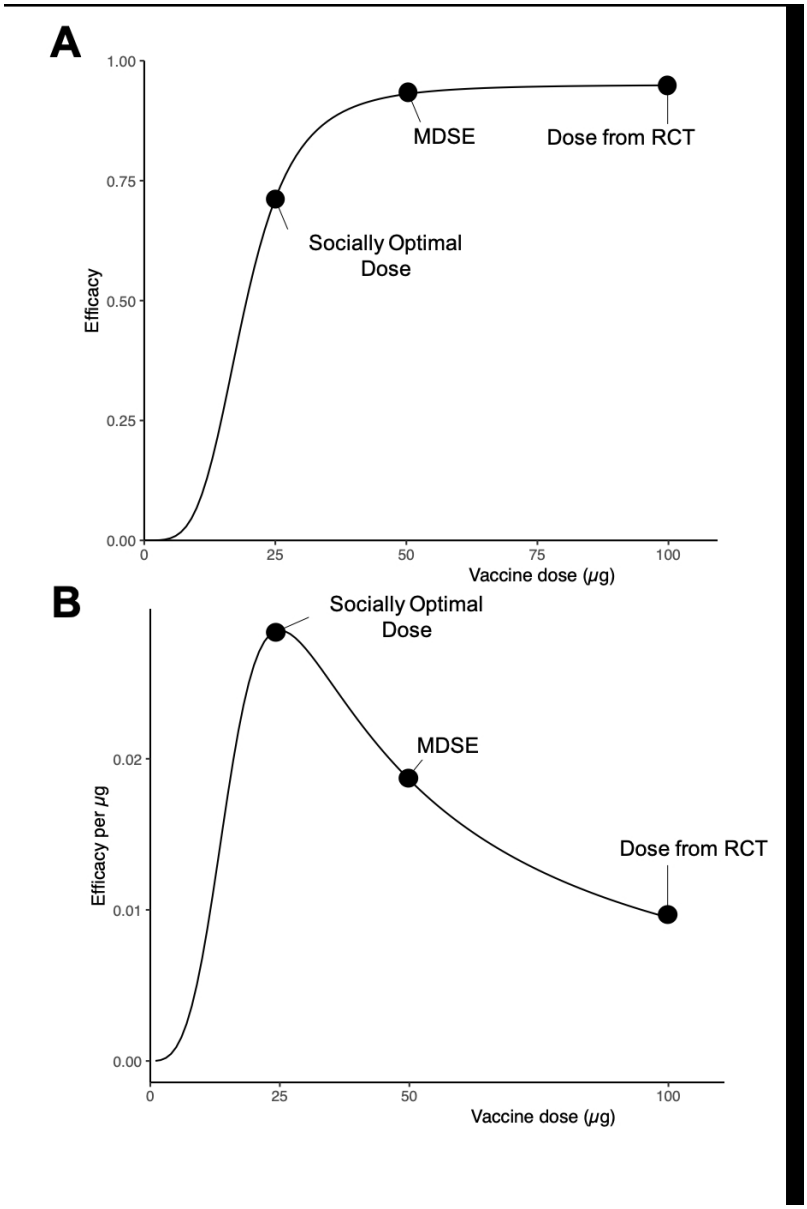

Figure 1

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