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Socially optimal pandemic drug dosing

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Randomised controlled trials are essential to show a drug's efficacy, but they ignore the possibility that the drug under study might become too scarce to treat a population. Scarcity of life-saving drugs harms patients who lack access to them and exacerbates inequities. Generally, scarce resources should be rationed to maximise benefits and mitigate health inequities.[1] Optimal dosing thus becomes a crucial clinical, ethical, and global public health equity question. Dose-ranging clinical trials—especially in pandemics—are a moral imperative.

Dose-ranging trials help prevent drug waste due to over-dosing and clarify dosing ambiguities that otherwise lead to harm.[2] Moreover, a dose-ranging trial on a drug with known efficacy requires less time and money and fewer patient volunteers than are needed for conventional research (in which the dose is not questioned) to increase benefits by the same magnitude. To this end, the lack of urgency towards SARS-CoV-2 vaccine dose-optimisation has had grave global public health consequences. Half-doses (50 µg) of the Moderna vaccine (mRNA-1273) generate nearly equivalent quantities of viral-neutralising antibodies as the full (100 µg) dose.[3] Despite the potential for doubling of the supply of one of the world's mRNA vaccines, no large randomised controlled trials evaluating half-dose mRNA vaccines are underway. Similarly, the best available evidence for extending the interval between doses of mRNA vaccines comes from (overwhelmingly successful) calculated risk-taking in the UK.[4,5] Early attention to dose and timing strategies would have facilitated population vaccination strategies and benefited those tasked with crafting policy.

The disconnect between individually and socially optimal doses is best shown through thought experiment: assume 100 µg and 50 µg doses of a given vaccine are 95% and 75% effective, respectively, in preventing death in the same at-risk population. Halving a scarce vaccine's dose enables a doubling of people vaccinated. In this scenario, 50 µg provides comparatively less individual protection but prevents about 60% more deaths. In a hypothetical population of 200 individuals who would otherwise die, administering the 100 µg dose to the first 100 individuals prevents 95 deaths but leaves the remaining 100 unprotected. Administering the 50 µg dose to the entire at-risk population prevents 150 deaths, 75 in the first 100 individuals receiving a half-dose vaccine and another 75 in the second 100 individuals. 55 more deaths are prevented by administering the less individually efficacious dose to all individuals than administering the more individually efficacious dose to only half, reflecting an approximately 60% (55/95) improvement—before accounting for the social benefits that might be gained by achieving herd immunity faster. In this thought experiment, as a social strategy, 50 µg is better than 100 µg because it raises the marginal efficacy of the scarce resource—the number of deaths prevented per µg of drug. Policy makers may be tasked with maximising the population benefits of a scarce vaccine resource. Doing this with confidence requires an understanding of the dose–response relationship.

Once a given drug's efficacy is established, the core public health problems become maximising the drug's social benefits at the margins and rapidly and equitably scaling its availability. Future ethical pandemic research should build upon the successes of UK-based clinical trial platforms and simultaneously investigate multiple candidate drugs for efficacy signals.[6] On discovery of efficacy, however, focus must be paid to assessing the drug's dose–response relationship and identifying its socially optimal dose through integrated, randomised dose-finding expansion cohorts.

Potential criticisms to a two-stage, socially focused pandemic drug development model are at least four-fold. The first criticism is whether negative dose-ranging studies enhance social welfare. We reply in the affirmative: regardless of the end result, dose-ranging studies help avoid physically injurious (to patients) and morally injurious (to prescribers) rationing decisions.[7] The second is whether dose-optimisation studies are necessary. Clearly, we believe they are: cost–utility analyses represent an excellent starting point for dosing,[8] but rethinking the dose from a social welfare perspective is justified. The third is whether dose-optimisation lengthens development timelines. In response, we promote two-staged results reporting in parallel—efficacy followed by dose-optimisation—guided by input from regulators, health system leadership, and consensus guideline committees.

Finally, sceptics contend that vaccine dose reduction in particular risks creating resistant viral variants. Although insufficient selective pressure due to a lower dose theoretically increases the likelihood that a resistant viral strain emerges, so too does actively choosing not to maximise vaccine availability.[9] Real-world data support an activist approach to vaccine dosing[4,5] and, to our knowledge, no vaccine-resistant strains have emerged in the UK. We all must acknowledge that even in the best of pandemic circumstances—infinite vaccine supply allowing for strict adherence to dosing guidance from randomised controlled trials—the emergence of a vaccine-resistant viral strain is a known unknown.

In conclusion, research during the COVID-19 pandemic has been marked by a number of innovations, among them the rise of clinical trial platforms. But we must acknowledge that we have failed to identify the socially optimal dose of nearly every major therapeutic or vaccine, constraining our ability to maximise benefits and mitigate inequities. Incorporating dose-ranging studies into clinical trial platforms will be a key step towards building a global, supply-minded, integrated, and resilient system of pandemic clinical trials research for the future.

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