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Public Health Emergencies: Research's Friend or Foe?

Stephanie Solomon

Saint Louis University

In Edwards' article, "Regulating Clinical Science in a Public Health Emergency: Drug Discovery at the Bedside," she points to a central challenge for medical research. How can one ethically evaluate whether a drug works in a context where neither employing the standard research procedures nor abandoning them entirely are ethically acceptable? This is not a new question, and it has been posed in varying contexts, including research on emergency procedures, research in developing countries and research on rare conditions. Edwards focuses on a further challenge to standard research procedures where evidence and access are often in direct tension with each other: public health emergencies. She attempts to provide a means by which this ethical dilemma can be dissolved, and regulators can both gain reliable evidence on the safety and efficacy of new therapies *and* desperate patients can be given access to novel therapies in a timely manner.

Edwards' first point is that the tightly controlled, rigorously staged, and cautiously distributed process by which therapies are normally evaluated are not appropriate in pandemic situations. She then argues that current approaches to adapting this process to ethical challenges, such as therapeutic privilege, parallel track, and compassionate/emergency use, are not successful in public health emergencies, so another solution is required. Finally, she suggests that the best means to study new therapies and provide the quickest access to them is through cluster randomized controlled trials (cRCTs) which simultaneously study a therapy's safety and efficacy and distribute it to those who most need it in a population.

The first important flaw in Edwards' argument is that she seems to believe that the current research strategy in which drugs are rigorously tested for both safety and efficacy before being accessed by the general public, or what she calls the "precautionary principle", is a strategy that sacrifices current patients for the benefit of future ones, or even the current health of patients for their future health. It is unclear whether she believes this is true merely in the case of pandemic emergencies, or in general. In either case, she disregards the primary intention of these precautions, which is to protect *current* patients from being harmed *in the present* by drugs with unknown safety profiles. In her chosen case of pandemics, these potential harms may be offset by the harms of the pandemic disease itself with no treatment, but it is important to note that this is a harm tradeoff within *current* patients, not a question of balancing present people and future ones. This misunderstanding is underlined by the author's frequent use of the term "new therapy" and "new treatment" for what is being

withheld by denying access to untested drugs before they have been through Phase III drug trials. The fact that it remains uncertain whether these drugs will be either therapeutic or actually treat the disease at issue (or treat it without causing more harmful effects), is why investigational drugs are not yet considered therapies or treatments. This confusion is further exemplified in her challenges that there is no equipoise in pandemic contexts, which importantly begs the question of whether there is deep uncertainty regarding whether an investigational drug will help, hurt, or do nothing at all.

The important implication of this mistake is that her argument for increasing access during a pandemic should not focus on the importance of current sufferers over future ones, but rather the dire circumstances that make current risks so great that even a drug with uncertain safety is preferable to no drug at all. She makes gestures in this direction by distinguishing the original intentions of the regulations in the context of the harms of elixir sulphanilamide and thalidomide and those which she is concerned, where the investigational drugs are intended to combat “deadly and communicable diseases.”

The second major issue with her discussion is that it does not adequately establish the failure of current attempts to resolve the issue of delayed access in desperate circumstances, namely: therapeutic privilege, parallel track and compassionate use. Each of these, in their own way, were developed to address the problem that she is pointing to, although she accurately points out that they are particularly focused on desperate individuals as opposed to populations. While they may all be insufficient individually to deal with the access issues of a pandemic, together they provide three venues for providing unproven drugs with promise to patients. Whether she is right that personalized medicine or short supply will make therapeutic privilege unhelpful, or that parallel track still requires an unsatisfactory delay in access are at least arguable.

Unfortunately, her criticisms of compassionate use, or emergency use, are at the best unclear, and at worst fatally flawed. The author appears to believe that there is an intrinsic connection between compassionate use and the “rule of rescue” which she defines as binding physicians to save their patients in any way they can. She finds it problematic to use the justification for compassionate use, as it is normally applied to individuals in desperate circumstances, and apply it to the population desperation faced in a public health emergency. There are two major problems with this claim.

First, according to the FDA, in order to qualify for access to investigational drugs outside of a clinical trial for emergency use, two criteria must be met. First, “the patient must have a serious or immediately life-threatening disease or condition and no comparable or satisfactory therapeutic alternatives.” Clearly, people in a pandemic have contracted an immediately life-threatening disease and most often no comparable alternatives exist, so this first condition holds. Second, “the drug manufacturer and the patient’s doctor must make special arrangements to obtain the drug for the patient¹.” It is perhaps this second requirement that suggests to Edwards that compassionate use intrinsically depends on the notion of the “rule of rescue” between a physician and an individual patient. But although

¹<http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.htm>

the doctor's judgment is invoked, this requirement is more for the protection of the patient, once again from the risks of being exposed to an investigational drug, than basing the obligation to provide it on the doctor's need to rescue. This implies that in a population context, someone's judgment (perhaps an FDA panel or other medical expert group) should decide whether the risks of providing access are outweighed by the risks of the threatening condition. Other than that, there seems to be no other aspect that doesn't translate directly to from the individual to the population level in the requirements for emergency use.

Second, compassionate use has already been used at the population level during a pandemic. During the 2009 H1N1 influenza pandemic, the FDA issued an emergency use authorization for peramivir, a drug that is *still* undergoing phase iii clinical testing today². It is puzzling that someone would argue that the compassionate use approach to providing access to investigational drugs in an emergency cannot be applied in a pandemic when it both *can* be used, and *has* been used in a pandemic situation.

These important criticisms being noted, Edwards recommendation still makes a novel contribution to the conversation. She is right that during public health emergencies, neither the time nor the control needed for phased trials exist. She is also right that when faced with a life-threatening communicable disease, the normal cautious approach to taking an investigative drug should be relaxed. In light of these two points, she suggests a unique approach that utilizes, instead of struggles against, the public health realities of a pandemic. She creatively suggests designing clinical trials in a way that map on to the social realities of pandemics, namely that drugs are developed gradually, disseminated piecemeal, people are often geographically contained and put in quarantine, and surveillance is increased (what she calls "non-pharmaceutical interventions"). Taking these qualities of the pandemic landscape into account, she suggests a cluster design of trials where those who can gain early access to investigational drugs serving as the intervention group, and those who, due to practical realities and not FDA fiat, do not have access serving temporarily as controls, or more accurately as delayed treatment comparison groups.

While this suggestion needs much more thought before being implemented, due to many of the challenges that Edwards herself brings up, the crucial point that she misses is the real relationship between her approach and the three current approaches of the FDA. She is wrong to argue that there is no way to provide people access to investigational drugs during a pandemic, the FDA has explicit measures to make it possible. But what her approach does is avoid the FDA's implicit either/or model. In other words, the FDA approach assumes that *either* investigational drugs can be studied in the proper scientific manner *or* exceptions must be made that sacrifice the science for the good of the people in emergency situations. What Edwards may not realize she does is explode this dichotomy and suggest that we get creative with our research designs so that good research can be done *and* the practical realities that people are facing, especially the dire realities of a pandemic, can be met. Instead of joining the tradition of science that sees the complexities of reality as a challenge to the purity of research design and the accuracy of data, she joins the growing movement of

²<http://us.bestpractice.bmj.com/best-practice/monograph/1178/treatment/emerging.html>

people who attest that research which incorporates the complexities of reality not only may be more ethical, but also may turn out to be better research.

REFERENCE

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