

Assay

Randomised Controlled Trials during epidemic

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In epidemics there is an urgent need for new knowledge on drug efficacy to help policymakers fight the crisis. Yet the best research methodology to do this is a matter of debate, write Philippe Brouqui, Pierre Verger and Didier Raoult.

The outbreak of an emerging infectious agent needs the rapid involvement of research to bring new knowledge. Past experience with Ebola virus outbreaks and, more recently SARS-CoV 2, have raised a question over the place of randomised controlled trials (RCTs) as the methodology of choice to answer clinical questions in a novel epidemic situation.

Drug safety and effectiveness is a long process which can take years. For antimicrobials, just 25% of drugs submitted to phase 1 succeed to Phase 3 and further licensing (1). This is why, in an epidemic, drug repurposing is often looked at, because drug toxicity has already been evaluated (2).

An RCT is designed to attempt to reduce bias, particularly in trials evaluating new drugs. The principle is to random assign volunteers into two or more treatment options and then compare them against a measured outcome. As RCTs reduce causality and spurious bias, they are considered to be the most reliable form of scientific evidence. For these reasons, they are required for market authorisation of a new pharmaceutical drug and cited by healthcare policies as a mandatory means for decision-making about treatments.

When gold standard becomes unethical

In emerging disease outbreaks, there is an urgent lack of treatments for the new pathogen. When a particular therapeutic option is supported by scientifically demonstrated efficacy *in vitro* and or *in animal model*, and supported further by clinical case reports and/or pilot series in humans, it is ethically difficult to argue that the data still needs to be confirmed in an RCT before it can be made available to patients. Especially if it seems "obvious" that control (untreated) subjects will have poorer outcomes than those receiving treatment. As one study mocked, there would be few volunteers for the placebo group in an RCT on the parachute's effectiveness in avoiding death by jumping out of an airplane, unless the jump had an average height of 0.6 m (3).

When even imperfect scientific data show a particularly obvious effect, it is no longer ethical to perform an RCT since it forces patients to accept either not to be treated (in the control arm), or to be treated with a molecule known to be effective. Consider the advent of penicillin. It took five patients before Sir Edward Abraham could definitively demonstrate that penicillin saved 100% of patients with staphylococcus or streptococcus infections. Nobody today would dare to test the efficacy of penicillin on pneumococcal pneumonia compared to placebo.

The Ebola epidemic of 2013-2016 has given rise to much controversy on this subject between proponents of RCTs and those of observational therapeutic studies. The former say that the results would not be definitive if the trial was not randomised and controlled. The latter stress the unethical and "out of care" side of proposing a placebo in a disease with a severe prognosis (4).

In establishing the efficacy of favipiravir on the Ebola virus, the authors of a 2016 paper wrote of the unethicalness of randomising patients from the same village to receive or not to receive treatment when the outcome of the disease and the absence of other treatment were known. They preferred to compare the patients treated with favipiravir in their study versus historical data of patients who could not be treated (4).

Although the conclusion of the trial is debatable and leaves the door open for a possible new trial, neither viral load reduction nor mortality were significantly different in the two groups (99 single-armed patients treated versus historical data). Some might argue that the trial lacked the power to demonstrate this difference and that the number of patients should have been increased. But drugs with low expected efficacy, for which studies with thousand hundred patients are needed to show an effect, arguably do not merit such efforts during an outbreak.

Are RCTs useful for decision making during the outbreak?

RCTs are based upon an assumption of drug efficacy (a demonstrable difference compared to standard treatment). But we usually only have this assumption from initial positive evidence from anecdotal reports, case series or uncontrolled trials. Such information is not available at the beginning of an outbreak.

As such, the design of an RCT for an outbreak scenario must enroll sufficiently large numbers of patients for efficacy, if it exists, to show. And the larger the number of patients, the longer the time it takes to recruit to the trial. It's no surprise then that RCTs evaluating new drugs in an epidemic have usually had no prior studies indicating efficacy and usually stand little chance of success in an RCT. Examples include lopinavir/ritonavir or remdesivir for covid-19 treatment.

It takes several months to conduct an RCT before it is published, and the data before publication are generally limited to the medical community. Circumstances are different in an epidemic, when medical data must be obtained in a limited time frame and made widely accessible to help inform decision-makers on crisis management (see table).

The fact is, publication takes time. With the time it takes to set up and conduct the trial, then process and peer review the manuscript, the paper is usually only available at the end of the epidemic (5). Because of the administrative burden, an RCT rarely starts before the peak of the epidemic and the results are rarely available during the epidemic (6).

Of 11 trials registered on the European registry of clinical trials (EudraCT) with the keyword "Ebola", eight were registered during the first epidemic in Guinea in 2013-16. All but one of which were vaccine RCTs, and the only therapeutic trial - of Brincidofovir - was abandoned. (7) On ClinicalTrials.gov, a search for the keyword "Ebola" between 2014-2019 shows 75 randomized, controlled clinical trials listed, four of which have been withdrawn, seven not yet recruiting, five still recruiting, and 52 completed but with no results available for 41 of them. The only completed and published therapeutic trial is the PALM trial, whose interim analysis showed no effect on the

mortality of ZMapp and remdesivir (8). The 2014 Ebola epidemic is considered to have passed (although not ended) in March 2016.

For covid-19, of the 22 controlled therapeutic trials of chloroquine for covid-19 treatment listed in the Chinese registry of clinical trials: 10 are stopped, 10 are still recruiting and one is completed.

Conflicts of interest

Because RCTs involve large numbers of patients and many clinical recruiting centres, often in several countries, the cost is high, sometimes up to US\$12 million per trial (9). Moreover, the funding relationship can lack transparency.

The pharmaceutical industry funds most RCTs (drug or vaccine evaluations) either fully or partially. This is the case for most of the trials currently being promoted for Ebola and Covid-19 infections, as no rapid means are currently available for state funding.

As reported by Roseman et al, out of 509 RCTs investigated, only 318 cited their sources of funding. Of them, 219 (69%) were funded fully or in part by the pharmaceutical industry. Similarly, of the 509 RCTs studied, only 132 declared author conflicts of interest, of which 91 reported industry financial links with one or more authors (10).

It has been reported that RCTs sponsored by the industry are more likely to be associated with significant pro-industry outcomes (11). RCTs in which investigators have a conflict of interest are also more likely to be of lower methodological quality than RCTs without a financial conflict of interest (12). A recent example is a report on the use of remdesivir in patients with covid-19 published in the New England Journal of Medicine and funded by Gilead Sciences that reports a 68% improvement in the health of patients treated with the drug. This success was not confirmed by a recently published RCT involving 236 patient that was not supported by the industry (2)

Industry, as sponsor, data owner and data holder under the terms of the original trial contract can ask investigators not to publish negative results.

Investigators should not have financial conflicts of interest in the RCTs they set up. And if they do, methods should be critically evaluated, the results be interpreted with caution, and conclusions with scepticism.

Bias is everywhere

Researchers in fields such as medicine, psychology and economics often argue that the RCT is the only reliable way to properly inform medical, social and political decisions. Proponents argue that RCTs are the ultimate benchmark against which other methods can be evaluated. And that they are free (or as exempt as possible) from the strong theoretical assumptions, methodological biases and researcher influence that non-randomized methods are subject to.

However, RCTs are not free of all biases and are often as methodologically questionable as observational studies. In contrast to case reports, RCTs generally inspect few variables, rarely reflecting the full picture of a complex clinical situation (e.g., patient history, physical examination, diagnosis, psychosocial aspects, follow-up). In drug intervention, many of them, for ethical reasons, add the experimental drug to the standard treatment regimen, which in many situations includes

other drugs which may affect the outcome. This has been seen in the recent trial evaluating remdesivir, with some patients also being shown to have also received azithromycin and anti-IL6 treatments (2).

In a recent review, the top 10 most cited RCTs were analysed for their potential bias and ultimately the quality of scientific service provided. These RCTs, which have influenced policy, contained biased results such as participants switching between trial groups, variation in dosage along the trail, missing data, unequal length of follow up between arms. The background traits of participants that influence outcomes such as patient medical history and co-morbidity, physical signs and symptoms, psychosocial aspects, follow-up, were often poorly distributed among trial groups. And among many other issues, only two were double blinded (13).

Other options

Most of the scientific knowledge obtained during outbreaks has been obtained through single case reports or series, observational studies with or without comparison, and only occasionally through RCTs. So alternatives or adaptations of RCTs are available.

Adaptive RCTs, for instance, have recently been designed to shorten trial duration. This is based on the use of data accumulated during the study to modify study elements in a pre-specified manner. These include sample size, end point, eligible population, randomization ratio and intervention, with the plan for change specified in advance. This design has been reported to shorten the time needed to progress from phase 1 to phase 2 trials. But in phase 2 and 3 clinical trials this design did not reduce the number of patients needed to be enrolled, which is often the main factor determining trial duration.

Smaller but multi-centre studies, which have the advantage of shorter patient recruitment time, are another option although they must take into account the heterogeneity of standard treatments between investigating centres. Some investigators, however, prefer large single-center studies, which tend to be easier and quicker to set up.

Uncontrolled case series have the disadvantage of often being unreplicable, the outcome being at the mercy of chance or dependent on the quality of care provided. However, they have the advantage of quickly suggesting a clinically relevant effect of the drug on the outcome. They are adapted to the peculiar epidemic situation especially because they bring quickly new information allowing more controlled trials which may or not confirm usable information in time for policy use.

Although not perfect, it has been suggested that single-arm observational studies with external comparators would be the quickest design to set up and meet the above criteria. All things being equal, the best external ethically acceptable comparators are historical arms - literally comparing to past data - as suggested by Sissoko et al. (1) .

In summary, during an outbreak we must not put the cart before the horse. Because time is limited, the aim should be to clearly and quickly identify efficient drug candidates to policymakers. Repurposing of drugs already in use, and deploying small series, uncontrolled trials, and comparative observational studies are therefore more suitable options. It is not appropriate for RCTs to be the main step in the evaluation of drugs in such times of crisis.

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Competing Interest

Authors have nothing to declare”

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Biography: Didier Raoult is the Director of IHU Méditerranée infection and is particularly involved in clinical trials during COVID pandemic with Philippe Brouqui, Medical director of IHU, and Pierre Verger director of regional health observatory. The challenge with clinical trial during this coronavirus outbreak leads them to write this essay to open debate on the relevance of RCT and possible other better adapted option.

Reference List

- (1) Wong CH, Siah KW, Lo AW. Estimation of clinical trial success rates and related parameters. *Biostatistics* 2019 Apr 1;20(2):273-86.
- (2) Wang Y, Zhang D, Du G, Du R, Ahao J, Jin Y, et al. Remdesivir in Adults With Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial. *Lancet* 2020 Apr 29;395:1569-78.
- (3) Yeh RW, Valsdottir LR, Yeh MW, Shen C, Kramer DB, Strom JB, et al. Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial. *BMJ* 2018 Dec 13;363:k5094.
- (4) Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. *PLoS Med* 2016 Mar;13(3):e1001967.
- (5) Davey RT, Jr., Dodd L, Proschan MA, Neaton J, Neuhaus NJ, Koopmeiners JS, et al. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. *N Engl J Med* 2016 Oct 13;375(15):1448-56.
- (6) Rojek AM, Dunning J, Leliogdowicz A, Castle L, Van LM, Carson G, et al. Regulatory and Operational Complexities of Conducting a Clinical Treatment Trial During an Ebola Virus Disease Epidemic. *Clin Infect Dis* 2018 Apr 17;66(9):1454-7.
- (7) EudraCT Number: 2014-004458-33 status: abandoned. European registry of clinical trials (EudraCT). <https://www.clinicaltrialsregister.eu/ctr-search/search?query=ebola> . 2020.
- (8) Mulangu S, Dodd LE, Davey RT, Jr., Tshiani MO, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med* 2019 Dec 12;381(24):2293-303.
- (9) Johnston SC, Rootenberg JD, Katrak S, Smith WS, Elkins JS. Effect of a US National Institutes of Health programme of clinical trials on public health and costs. *Lancet* 2006 Apr 22;367(9519):1319-27.
- (10) Roseman M, Milette K, Bero LA, Coyne JC, Lexchin J, Turner EH, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA* 2011 Mar 9;305(10):1008-17.
- (11) Bhandari M, Busse JW, Jackowski D, Montori VM, Schunemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004 Feb 17;170(4):477-80.
- (12) Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003 Jan 22;289(4):454-65.
- (13) Krauss A. Why all randomised controlled trials produce biased results. *Ann Med* 2018 Jun;50(4):312-22.