Pandemic treatments on trial: the bigger picture.

N of many thinking in an N of one scenario

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The tension between immediately using any potentially useful novel therapy in COVID-19 and trialling all novel therapies as rigorously as possible is addressed from a bigger picture perspective. https://bit.ly/3fZVuxg

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Confusion of goals and perfection of means seems to characterize our age — Albert Einstein

Wisdum don't consist in knowing more that iz new, but in knowing less that is false — Josh Billings

Introduction

That the above two quotes are arguably truer now than at the time they were written is perhaps surprising. That this truth resonates equally for the authors who have experienced the two most recent respiratory infection pandemics (H1N1/09 influenza and coronavirus disease 2019 (COVID-19)) and the ongoing bias towards relatively small, uncontrolled treatment trials from very different perspectives, across, between and within hemispheres, countries, healthcare systems, socio-economic-political cultures, populations and individuals [1–6], is even more so.

Why? How so? What next?

We would humbly submit that the bigger picture, as always, is both in the framing and the detail.

Although it has always been accepted that evidence-based medicine is the best guide to clinical decision making at a population level, there has always been a debate regarding what constitutes "all the evidence" for an individual patient and how this should be weighed up against specific risk and value system scenarios. This ever-present fundamental tension and all its associated nuances in clinical practice have been expressed and amplified many times over during the current "pressure cooker" environment that is the COVID-19 pandemic.

At one extreme, all patient-centred care revolves around the *n of 1* clinical trial that embraces the unique bio-psycho-social profile of each individual and frames all therapeutic risk/benefit assessments within this setting. This is where the irreducible richness of clinical ethics sits. There is no particular right or wrong

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"truth" and the validity of a proposition can only be tested against the process that generated it. It is wholly dependent on open dialogue with the patient, participatory informed consent and all sense of justice is scenario specific. At the other end of the spectrum, ever-improving scientific models provide us with useful "statistical" conceptions of truth/falsity and validity that help guide the management of specific groups of patients. This is where the "capturing" power of epistemology, the scientific method and the randomised controlled trial (RCT) sits. Here, the size of one's world view is critically important, but truth and falsehood are mutually exclusive and, by definition, there is no excluded middle. Where there is clear "equipoise" between "doing good" and "doing harm" for any particular agent, an RCT helps clarify the risk/benefit ratio for specific patient cohorts on top of the best standard of care available – but it can never be completely prescriptive for any one patient. Additionally, the relevance of this clarification for a specific patient is dependent on both the external and internal validity of the RCT in question. Hence, at the very least, the type of patients included in any RCT is defining (specific inclusion/exclusion criteria). Further framing relevances are: study stratification protocols for major confounder variables (especially illness severity as well as other treatments, comorbidities and demographics); the randomisation process itself to control for "unaccounted for variables"; the selection and measurement of key outcome variables; the broader study design parameters surrounding both the magnitude and level of uncertainty being sought for any clinically significant effect; and the total number of patients to be recruited.

Given the stated extremes above, there is a clear trade-off between "doing all that one can for individual patients with currently available information in a timely manner and despite significant uncertainty" and "group treatment of individuals to be enrolled in properly conducted but costly (effort, time and money) clinical trials for specific therapeutic approaches that will help inform the evidence-base for future patients". In many ways this is a false dichotomy as both are necessary frameworks with clearly defined validity and purpose, which should ideally sit comfortably next to each other. The lack of a clear transition zone between these two frames of reference necessitates ambidextrous frame-shifts. Ideally, frame-shifting would be sensitive and responsive to the prevailing environment when healthcare provision is at its best for any level of resource constraint. Although this may be difficult to define in positive terms of agility, dynamic range and contextual fit across and within multiple frames, it is most easily identifiable by its absence. This absence is even more obvious when the "in-between" situation is excessively encroached upon as some sort of compensatory way forward. Here, therapies are prescribed to patients for varying reasons that can only be partly rationalised on the basis of either individual or group interests. The resultant case series and uncontrolled observational studies therefore quickly transition from a reasonable, adaptive initial response to explore large efficacy and safety signals in poor clinical outcome settings to efforts that are maladaptive when excessive. At best, these efforts minimally progress either individual patient care decisions or the broader evidence-base necessary to inform integrating guidelines. At worst, unchecked biases may lead to false-positive results whilst simultaneously diverting resources from potentially more useful strategies. That there has been an excess of small and uncontrolled trials in the setting of a COVID-19 pandemic which itself is very much an *"n of 1"* situation is therefore worthy of further reflection and exploration.

Whose needs are being met?

How do we best explore and exploit our overall clinical management and scientific research approach during the COVID-19 pandemic? There is little argument with upholding the public health principles and standards of supportive care in relatively mild community cases that are likely to recover without ill effect. But how do we minimise the risks of progression in more severe hospitalised cases, particularly older patients with risk factor comorbidities? How do we maximise compassionate use of available, potentially useful but unproven therapies when no other alternatives exist? How do we minimise the risks of these very same therapies for individual patients? And how do we quickly establish and conduct difficult and costly randomised, controlled clinical trials for the most promising old and new therapies where there is a clear equipoise between possible benefits and potential risks? All these questions so far turn on what is hopefully an impartial assessment of what is in the best interests of the patient. However, there are also other potential factors at play, albeit very difficult to quantify. These include (in no specific order):

1) The difficult research environment that would necessarily follow from healthcare systems that are overwhelmed in a pandemic setting;
2) Specific resource and funding constraints in such systems;
3) Widespread fear and anxiety at all levels of the community, including healthcare providers;
4) Clinician–researcher and other interested party belief systems and potential "saviour" mentalities;
5) Potential pharmaceutical industry interests regarding expanding re-purposed drug possibilities;
6) Potential biotech start-up/pharma interests regarding new agent fast-tracking opportunities;
7) Potential political and economic interests; and
8) Potential media and socio-cultural factors.

Although it is impossible to quantify in any meaningful way the magnitude of these factors and how they may all interact with each other, an enlightened awareness of all these possibilities is an essential first step to both prevention and any countering response. It is also the quintessential function that underpins all drug evaluating regulatory agencies/processes that we discard or bypass at our peril.

What does not far enough and too far look like?

In the midst of a pandemic that has overwhelmed many healthcare systems globally it is indeed very impressive that several large, collaborative clinical trials have already been established to meaningfully assess potential COVID-19 therapies, including the World Health Organization's "Solidarity" trial (see below). Ideally this list should be extended to all other therapies where there may be a potential benefit seemingly counterbalanced by potential risk. However, at all points decisions will need to be weighed and taken. Which drugs to trial? Which patients? What disease severity? What dose? What to measure?, and how?, and why? Which endpoints? How to adjust for confounder variables? How many patients? Additionally, analytical integrity is all. Not enough design control and internal validity is threatened, too much and there will be a problem with external validity. Even with well-controlled RCTs for specific agents, uncertainty can never be completely eliminated. The best we can hope for is to optimally quantify key uncertainties, thereby elevating our certainty base for future decision-making. The more iterative this process can be, the better. Notwithstanding this, however, there will always be a tension between the ideal of increasingly covering all testing possibilities for completeness and the practicalities of getting on with the real-time demands of work to be done. Paradoxically, the almost immediate establishment of a well-designed RCT to test the combination anti-viral treatment lopinavir–ritonavir in Wuhan, China during the beginning of the pandemic exemplified this tension in a most unusual way when trial recruitment ceased early due to falling COVID-19 case numbers [7].

It is clearly not possible to immediately perform a well-controlled RCT on all potentially useful therapies. Hence, in trying to do everything one can for individual patients with severe disease who are likely to die it is compassionate and reasonable to empirically trial available products off-label where the existing information base suggests potential benefit outweighing any potential harm. This of course all turns on our shared understanding of "likely to die", "likely to benefit" and "potential for harm" at the very least. The more we use these therapies, however, in patients with less severe illness, where the uncontrolled benefit signal may be significantly "overcalled" by a positive natural history and the risks of harm may become increasingly unacceptable, the more it behoves us to go down the path of a properly controlled and conducted RCT. Excellence here is not the enemy of "*good enough*", as may be argued in the exceptional circumstances of a pandemic or indeed any uniquely uncertain area of clinical medicine, but the standard that should always be aspired to. Indeed, an enlightened view of excellence would expand its horizon to embrace "*good enough*" in the most excellent way possible for any specific situation. Anything less than this is professionally and personally diminishing as it quickly contracts down to no-risk comfort zones and sets us down the murky path of "*good enough for who*" questions and excusable actions that are answerable to no-one.

Under pandemic conditions of overwhelming healthcare system stress and understandable urgencies to try untested therapies, the introduction of novel therapeutic practices may therefore take on a life of its own and become disproportionately uncoupled from any primary purpose. Hence, randomly collected case series and uncontrolled smaller trials may proliferate without necessarily being in the best interests of either individual patients or specific patient cohorts.

The example of hydroxychloroquine/chloroquine is a case in point where some early *in vitro* evidence of efficacy against SARS-CoV-2 has been taken both "too far" and "not far enough". Hence, it has been used empirically in a large number of small and uncontrolled "trials" around the world despite its potential for cardiac toxicity, and in one larger, poorly controlled observational study no significant benefit and potential for significant harm signal was inconclusive [8], thereby paving the way for rationalising any position one may wish to take. More recently, the controversial results of a multinational registry study examining the risk/benefit ratio of hydroxychloroquine/chloroquine with or without macrolide for treatment of COVID-19 also weighed into the evidence debate only to now be retracted by the authors [9]. Add to this a heady mixture of high profile, celebrity supporters and trial by media and you have a recipe for compounding one crisis with another.

Also very illuminating is the story of the antiviral remdisivir: from early, uncontrolled results that reported a clinical improvement in 68% of 53 "analysable" patients [10], through to a negative RCT study result involving 236 patients, which was stopped early due to reduced case numbers in China resulting in a trial with reduced power to detect any smaller clinically significant benefit with any certainty [11], to further preliminary reports of potentially positive results in larger trials sponsored by the remdisivir patent holder [12].

Similar stories abound for many other therapies being used to manage hospitalised patients with more severe COVID-19-related illness, including various respiratory support strategies and their combinations, a range of anticoagulation protocols, novel immunotherapeutic agents including the anti-IL-6 receptor monoclonal antibody tocilizumab, and various combination strategies and therapies [13–21].

At the other end of the spectrum are the much more inclusive, simplified and highly "capturing" RCT approaches, such as the World Health Organization Solidarity international clinical trial across multiple countries [22] and the Oxford University led RECOVERY trial in the UK [23], both designed to compare different treatment options against usual of care for as many hospitalised COVID-19 patients as possible within their jurisdictions. With large number of enrolments helping to counter the large degree of individual case heterogeneity that comes with a simplified approach, the Solidarity Trial's international steering committee discontinued the trial's hydroxychloroquine and lopinavir/ritonavir arms in early July 2020 as interim trial results for both these treatment arms showed little or no reduction in the mortality of hospitalised COVID-19 patients [22]. The large RECOVERY trial in the UK (n>11 800 as of 29 June, 2020) almost simultaneously confirmed these findings for both hydroxychloroquine and lopinavir/ritonavir, and by contrast, revealed that low dose dexamethasone (6 mg given once daily for up to 10 days) reduces the risk of death by about one-third among patients receiving ventilation and by one-fifth in those requiring oxygen alone (with no benefit among those not requiring ventilatory support) [23, 24]. Other treatment arms in the RECOVERY trial include azithromycin, tocilizumab and convalescent plasma [23].

Who checks the checkers?

A closer look at what transpired during the 2009 influenza A H1N1/09 pandemic, our most recent pandemic prior to COVID-19, is very salient. Patients were frequently treated for pandemic influenza viral pneumonia with drugs not specifically registered for this indication and rarely under circumstances of high-quality data capture. This resulted in experimental drugs being used largely on compassionate grounds with no real improvement in our understanding of the potential benefits and harms of specific treatments. However, further reflections on the above outcomes led some clinician–researchers to a unifying multicentre embrace of master protocols, adaptive trial platforms and overarching statistical plans. These are designed to build operational "checks and balances" into a modular study framework that remains congruent across time and space and promotes a culture of learning as you go. Hence, although REMAP-CAP was originally designed to study severe pneumonia requiring ICU management in over 160 sites across many countries, it was quickly adapted after the H1N1/09 pandemic be pandemic influenza-ready, making it relatively easy to switch its focus to the current COVID-19 pandemic. A key feature of adaptive trial design is that researchers are required to add and remove treatment groups as the trial is running in order to minimise the diluting effects of futile treatments and maximise the signal to noise ratio of more promising treatments according to certain trigger thresholds. And so, no algorithmic approach can completely substitute for imaginatively insightful, thoughtfully rational and well-equilibrated ethical thinking.

Additionally, there is the increasing appreciation that although adaptive trial designs for treatments is a great start, they may not go far enough. Given the extensive variation in clinical outcomes with COVID-19 infection in the population at large, we may well need to also integrate some well-chosen deeper phenotype and genotype factors into our adaptive trial designs and analyses. The benefits of any such extended approach will of course need to be weighed up against the potential for greatly increasing the logistical complexity of adaptive trials beyond what is practically manageable and of course the inexorable law of diminishing returns, even with the potential help of enhanced machine learning protocols.

Conclusion

As always, appropriately managing individual patient case priorities is a central pillar of ethical clinical practice. This is true both within an exploratory *n of 1* framework and in exploiting *n of many* RCTs. Hence, although the uncontrolled, compassionate use of specific off-label therapies may be acceptable in one framework, a completely different framework is required to generate a quality evidence base for improved pandemic management practices now and in the future. Additionally, discussions within frameworks matching rights and responsibilities is generally much more comfortable than between frameworks. And yet, individuals and the society they belong to are irrevocably intertwined and interdependent. Negotiating the deep chasm between frameworks is a key challenge for treating clinicians so that we don't get lost in a multitude of poorly controlled studies but leap towards a hierarchy of larger clinical trials arranged according to likelihood of success based on early but uncertain signals in smaller numbers of patients. Ethical leadership therefore requires us to be agile, proportionate and adaptive in aligning, balancing and contextualising patient needs across many dimensions both simultaneously and separately. During a pandemic these fundamentals are unchanged, although our responses now have to be both speedier and as complete as possible with a varying emphasis on each, depending on the guiding

framework and associated driving purpose. With this in mind, *doing the most right thing, at the most right time, in the most right way* for the one and the many is the ethicist's embrace of epistemological excellence and the flourishing of all.

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