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REGULAR ARTICLE

COVID-19, children, clinical trials and compassion: The ethical case for using innovative or compassionate treatments

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Abstract

Aim: Safe, effective SARS-CoV-2 treatment has not yet been determined, though some drugs have favourable mortality and morbidity benefits in specific situations. No treatments have been explicitly tested in children, who are, therefore, once again therapeutic orphans.

Method: We echo calls to enrol patients, including children, into trials but those children recruited to date have largely been additions to adult studies. Few were recruited during the initial pandemic despite the emergence of PIMS-TS/MIS-C, which surely demands paediatric-specific research.

Result: Must children be proscribed treatments effective in adults until child-specific data emerges, even in a pandemic? Will appropriately powered dedicated trials ever determine specific child-COVID-19 treatment pathways? Is the protracted time frame to assemble such data acceptable to children with severe COVID-19 today?

Such factors are relevant in considering whether children should have access to compassionate, innovative, pandemic-disease treatment.

Conclusion: We argue that children should be permitted, indeed have a right, to access innovative treatments early in any future pandemic, following an individual best interests consideration. This will remain the case until formal studies powered to determine children's optimal treatment commence, when the moral duty switches to ensuring children are enrolled, with any preceding innovative-use data made available to researchers.

KEYWORDS
children, compassionate use, COVID-19, ethics

1 | INTRODUCTION

The COVID-19 pandemic has rekindled the debate on whether or in what circumstances it is ethical to deliver experimental or innovative treatment to individuals on a compassionate basis. Such discussion is particularly relevant in a pandemic when there is a clear and urgent need to identify treatments that benefit populations. This includes children even if, as initially with COVID-19, relatively few develop serious illness. Experimental or innovative treatment has been defined as "any newly introduced treatment or a new modification to an existing therapy with unproven efficacy and side effect profile, which is being used in the best interests of a patient, often on an

Abbreviations: MEURI, monitored emergency use of unregistered and experimental interventions; RCT, randomised controlled trial.

experimental and/or compassionate basis."[1] As such, the focus is on the individual rather than populations.

There are currently no safe, effective curative treatments for SARS-CoV-2 infection, though some agents reduce mortality and morbidity.[2]Despite the call to enrol children into available trials,[3] no specific paediatric trials of COVID-19 treatment have commenced. Hence, the only paediatric trials are additions to adult studies, notwithstanding the emergence of post-COVID PIMS-TS/MIS-C as a distinct entity demanding specific paediatric research.

It seems that children are once again becoming therapeutic orphans.[4]To us, it seems counterintuitive and unfair if children are excluded from treatment known to be effective in adults. This applies not only to very rare conditions for which specific child-based evidence is lacking but also in pandemics where the focus may be on older people – as in COVID-19. It seems unlikely that there will ever be large enough trials to define dedicated evidence-based treatment pathways for children with severe COVID-19. The protracted time frame necessary to assemble such data is problematic to children, their parents and their peers at risk of suffering from the disease and whose needs are urgent. However, we accept that the dynamic approach to trials adopted during the pandemic is an innovation that can benefit both adults and children.

The purpose of this paper is to re-examine the ethical arguments concerning the use of experimental and innovative treatment, including to what extent the unprecedented circumstances of the pandemic may modify them. We have excluded vaccination of asymptomatic children who are at low risk from serious COVID-19 because the ethical issues raised differ from those posed by experimental or innovative therapies. We argue that the particular circumstances created by the pandemic do not trump an underlying ethical justification to accede to requests for novel paediatric treatments outside formal research studies. We commend the call for children to have fair, equitable access to specific trials but regard any interim embargo on children receiving innovative or experimental treatment on a compassionate basis, for example, the use of remdesivir, as ethically troubling.[3] This is particularly so if clinicians desist, on the basis of such strongly expressed views on the necessity of trial-verified therapy, from offering treatments that they consider potentially beneficial.

2 | ETHICAL PRINCIPLES AND THE STATUS OF CHILDREN DURING COVID-19

The stated overarching ethical principle that has defined the UK response to the COVID-19 pandemic is one of equal concern and respect. But socio-economic inequities and other disparities have been exacerbated rather than addressed by the pandemic and reactions to it. Children have not been well served: although they are less likely to have severe acute disease, their welfare and education have been adversely affected. They have suffered physical and social isolation, lack of recreational opportunities, increased risk of abuse and mental illness. The impact on those already socially and economically disadvantaged has been particularly severe.

Key Notes

- COVID-19 presented therapeutic dilemmas due to the lack of evidence-based treatments for novel SARS-CoV-2
- Rapidly constituted adult studies changed that situation, though the evidence base has emerged slowly and remains incomplete for children for whom no specific trial data exist
- We adapted innovative use protocols for early SARS-CoV-2 treatment in children and argue that any suggested prescription of "out of trial" drug breaches children's rights until appropriately powered paediatric studies commence

To address such inequalities, we should consider whether children merit any special moral consideration. Even in the context of the COVID pandemic, some have argued that children should have priority in the allocation of scarce resources, for example, access to intensive care,[5]and similar arguments can be made to support access to experimental treatments. The moral justification for granting children some priority is founded on a multi-principled approach, based on the ability to benefit, generativity (our special duty towards those who will succeed us),[6]and the complete lives/fair innings concept. The last considers harms caused if children fail to have the opportunities that older adults have enjoyed, with restriction of their right to an open future. Some account is taken of the child's lived experience, more meaningful in a teenager than a newborn.[7]These considerations apply in a wide range of child illness, but the particularly adverse circumstances of the pandemic have arguably invested them with greater moral weight.

Further support can be adduced from a rights-based approach (United Nations Convention on the Rights of the Child UNCRC) that makes children's best interests a primary consideration (Article 3). It affords them the right to enjoy *"the highest attainable standard of health and to facilities for treatment of illness and the rehabilitation of health."*(Article 24)[8]

A multi-principled approach also considers factors such as prognosis; the duty to maximise the number of lives saved; social equity; the future value of an individual's life; and also, the value of the life lived so far. These factors are relevant and have been used in considering whether children should have compassionate access to experimental and innovative treatment. They also have utility in addressing wider inequalities in healthcare provision in a pandemic.

3 | ACHIEVING EVIDENCE-BASED TREATMENTS

In a novel infectious agent pandemic, *all* therapies are initially experimental. Initial treatments are based on best guess therapeutic

options derived from related conditions. Clinicians also "learn by doing", for example, prone positioning in mechanical ventilation, abandoning hydroxychloroquine and the use of dexamethasone.

Ethical arguments for and against using novel treatments in children are summarised in Table 1.

In a pandemic, decisions to treat are necessarily based on incomplete/absent evidence. Time and other pressures may prevent prolonged deliberation, reflection or obtaining relevant second opinions. Clinicians may be predisposed to act and adopt new approaches in the face of clinical uncertainty or novel pathologies. The strong imperative to respond to pleas from relatives and others to "do something" or try anything that might help affects clinical judgment. The counterargument suggests a conservative approach in keeping with the ethical principle of minimising harm.

Nonetheless, there may be compelling arguments to support the idea that a novel treatment might be both scientifically valid and beneficial and that the potential harm produced is acceptable in the context of patients' critical conditions.

4 | THE PAUCITY OF RANDOMISED CONTROLLED TRIALS IN CHILDREN WITH COVID-19

Randomised Controlled Trials (RCTs) provide the most accepted, definitive way of determining safe and effective treatments. However, when RCTs are not used or delayed, as may be the case in pandemics, effective treatment is harder to define.[9]

Without RCTs, benefits cannot confidently be attributed to an intervention itself, and many initially promising interventions have subsequently failed. However, serendipitous observations of efficacy have been an impetus for later successful clinical trials, with "learning by doing" a good initial step if based on a scientifically valid approach.

Despite accelerated design techniques, regulatory approval and study implementation, enrolment may fail to keep pace with the pandemic's progress. Studies may occur in settings and systems, and with populations not envisaged by their designers. Even large-scale RCTs do not accommodate all minor variations in therapy and biological and social variability, which all can impact outcomes. Trials cannot take account of individual disease susceptibility, pharmacodynamics, pharmacogenetics and environmental exposures, so they generate generalisable information about populations rather than individuals. In contrast, innovative treatment aims to provide therapy in an individual's best interests rather than benefit future populations.

Although children have previously been enrolled in clinical trials during epidemics,[10] few registered trials have accepted children as research subjects in the current pandemic.[11]

In these circumstances, it is ethical to consider experimental or innovative treatments delivered on a compassionate basis.

TABLE 1 WHO criteria for the use of monitored emergency use of unregistered and experimental interventions MEURI

1) No proven effective treatment exists;
2) Not possible to initiate clinical studies immediately;
3) Data providing preliminary support of the intervention's efficacy and safety are available, at least from laboratory or animal studies; use of the intervention outside clinical trials has been suggested by an appropriately qualified scientific advisory committee based on a favourable risk-benefit analysis;
4) The relevant country authorities, as well as an appropriately qualified ethics committee, have approved such use;
5) Adequate resources are available to ensure the minimisation of risks;
6) Informed consent is obtained;
7) The emergency use of the intervention is monitored, and the results – successful or not – are both documented and promptly shared with the broader medical and scientific community.

5 | COMPASSIONATE AND INNOVATIVE TREATMENT IN CHILDREN WITH COVID-19

The ethical basis of innovative treatment is to provide available and reasonable opportunities to improve a patient's condition, including measures to mitigate suffering and enhance survival. The ability to benefit future patients cannot be known but is an appropriate aspiration. In adults, offering innovative treatment respects individual liberty rights to make informed choices. In children who lack the capacity to make informed choices, parents (or those legally authorised) can make decisions on their behalf, provided they act in the child's best interests.

Essential prerequisites that underpin the approach that we and others have adopted include the following: the proposed treatment is clinically necessary, there are no other relevant alternatives (including a pertinent RCT for which the child is eligible), a valid scientific basis (derived from laboratory/animal/adult studies providing some safety and likely efficacy data), satisfaction of best interests criteria, informed consent, evaluation of resource impact, a duty to record and report all outcomes and independent review, that is, IRB/ethics committee.1

One argument against the use of innovative treatments is potential harm, which is not always immediately apparent or predictable, for example, when treatments used in adults are used in children. Close data monitoring is vital in minimising harms. However, *all* treatments in these circumstances carry some risk of harm, and this is not in itself a valid reason to reject them. Instead, they should be viewed in the context of the child's clinical condition and anticipatable harms disclosed during consent.

Another argument against innovative treatment is that it produces potential harm to others by decreasing RCT enrolment and diverting scarce resources from such trials. However, there is little evidence of this effect in the current pandemic. Moreover, it is unlikely to apply to children, where the numbers of potential research subjects are fewer and RCT availability considerably less. Indeed, children may be considered doubly disadvantaged by the

non-availability of clinical trials and any reluctance to consider innovative treatments. It is therefore difficult to see whether in these particular circumstances the harms to others are sufficient and proportionate enough to trump the professional duty of rescue, or to act in the best interests of the child, and to respect children's rights.

6 | CHILDREN'S RIGHTS COVID-19 AND INNOVATIVE THERAPY

Public health measures to control the spread of COVID-19 have compromised the liberty rights of many. The ethical justification has been that it is necessary and proportionate to infringe individual liberty rights to minimise harms to others.

In contrast, the appropriate judicious use of innovative treatment is consistent with the obligation to make children's best interests a primary consideration and their right to the best available standard of health care and treatment. It is also consistent with article 37 of the Declaration of Helsinki.[12]

7 | INNOVATIVE AND UNPROVEN INTERVENTIONS IN A PANDEMIC: THE NEED FOR REGULATION

To safeguard patients' interests, experimental or innovative treatment proposals must be subject to independent ethical and scientific scrutiny and regulation. There may be circumstances when even the compassionate use of innovative therapy is not in the child's best interests, for example, when the burdens of disease or treatment outweigh the benefits. Criteria for the compassionate use of innovative therapies in children and the process of ethical evaluation have been identified and audited.[13]The WHO has identified regulatory criteria for "monitored emergency use of unregistered and experimental interventions" (MEURI) (see Table 1), to which our approach conforms.[14]Essentially, standards for ethical and scientific review should match those used to evaluate research protocols. However, the flexibility of the process we have outlined means that proposals for using an intervention can be reviewed in a timelier manner than even the accelerated review processes in large trials. Such rapidity of review is essential when the child's clinical state demands urgent intervention. All such interventions must be recorded accurately, with complete data collected, stored safely and shared in a meaningful and timely fashion. Wherever possible, clinicians and other responsible agents should then use their skills in advocating for children to ensure formal research studies occur designed to evaluate both safety and efficacy Table 2.

In support of this approach, we reported the use of our ethical framework to provide urgent access to compassionate treatment for children with life-threatening COVID-19 infection during the first wave.[15]Ethical discussions involving the relevant medical teams and parents took place within hours of referral and considered whether the prerequisites for innovative therapy had been fulfilled, taking account of mandatory external second opinions whilst acknowledging uncertainly. Examples included the antiviral drug remdesivir for a child with new leukaemia,[16]and another with COVID-induced acute respiratory distress syndrome and multiple organ failure.[17]

TABLE 2 Arguments for and against the use of innovative or experimental treatment in children

Arguments in favour
Fulfils the duty of rescue and the need to act in the best interests of individuals
Supports the right to make informed choices about treatment options
Supports the right to the best available, attainable standard of health care and the right to an open future
Encourages innovative solutions to complex problems and enables the development of future research projects
Delay in, or non-availability of, randomised controlled trials for children puts them at risk of harm
RCT development and regulatory approval may not keep up with the pace of change in pandemics
It helps address inequalities and inequity in vulnerable individuals
Arguments against
Children have been harmed by treatments introduced with best intentions before being thoroughly tested
Some promising innovative treatments have later proven of no benefit or even harmful
Use of experimental or innovative treatment without a control group cannot show claimed benefits
Use of experimental or innovative treatments may delay recruitment to, or progress of, RCTs so compromising identification of safe, effective therapies for others
May consume resources better utilised in large trials
Does not support a communitarian population-based approach to the threat of a pandemic
Fails to promote social cohesion, solidarity and equity

8 | CONCLUSIONS

The response to the COVID-19 pandemic has reactivated discussion over the compassionate use of experimental and innovative treatment. We argue that the conditions of the pandemic and its sequelae for children create the need to give special consideration to the moral claims of children and should not increase the harms/benefits threshold in best interests determinations. The lack of RCTs involving children establishes a justification for careful consideration of the use of experimental or innovative treatments. Such thinking is morally justifiable by an appeal to best interests and rights. However, the use of such therapies should be judicious and subject to independent ethical analysis and conform to defined criteria. We suggest such an approach is rational, relevant and realistic, even during a pandemic.

CONFLICT OF INTEREST

JB and VA declares no conflicts of interest. AC consults for Johnson & Johnson as chair of a panel of patient advocates, bioethicists, and physicians that advises the company on how to allocate investigational agents on a compassionate use basis.

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