Why clinical research in the paediatric population should be a priority

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Vaccination Special Interest Group

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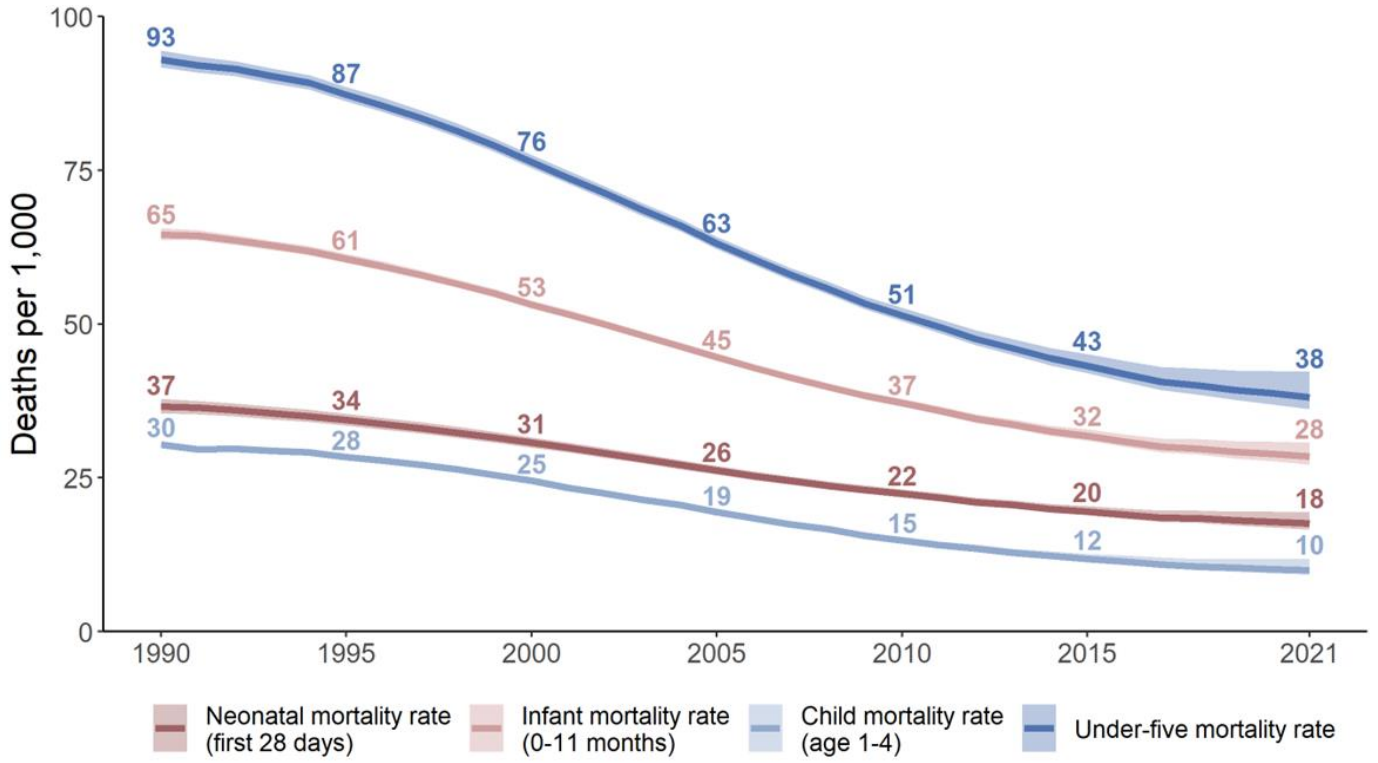
Infectious Diseases
International Scientific Committee

Outline

- The need
- Pandemic
  - Vaccines
  - Therapeutics
  - Non-pharmaceutical measures
- Barriers & potential solutions

The need for paediatric research

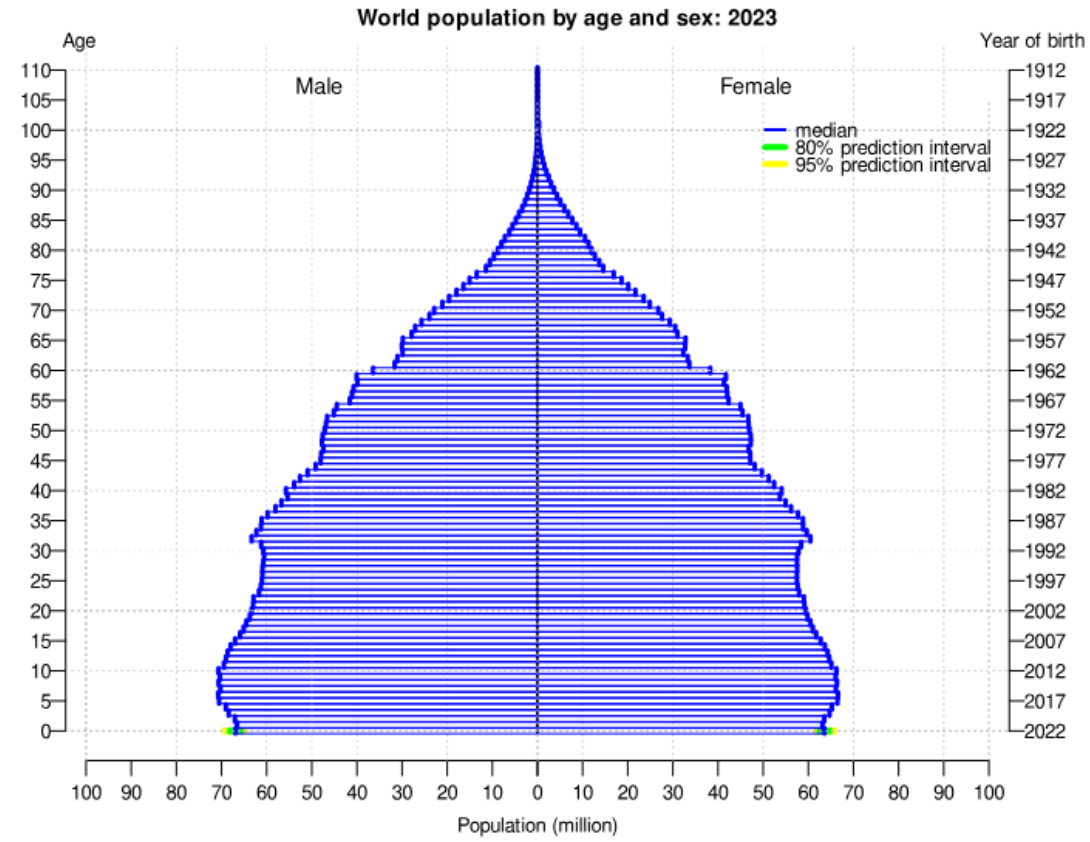
- Rates of decline in infant & child mortality have been levelling off since 2015 despite high or increasing coverage of proven interventions



UNIGME report https://childmortality.org/wp-content/uploads/2023/01/UN-IGME-Child-Mortality-Report-2022.pdf

The need for paediatric research

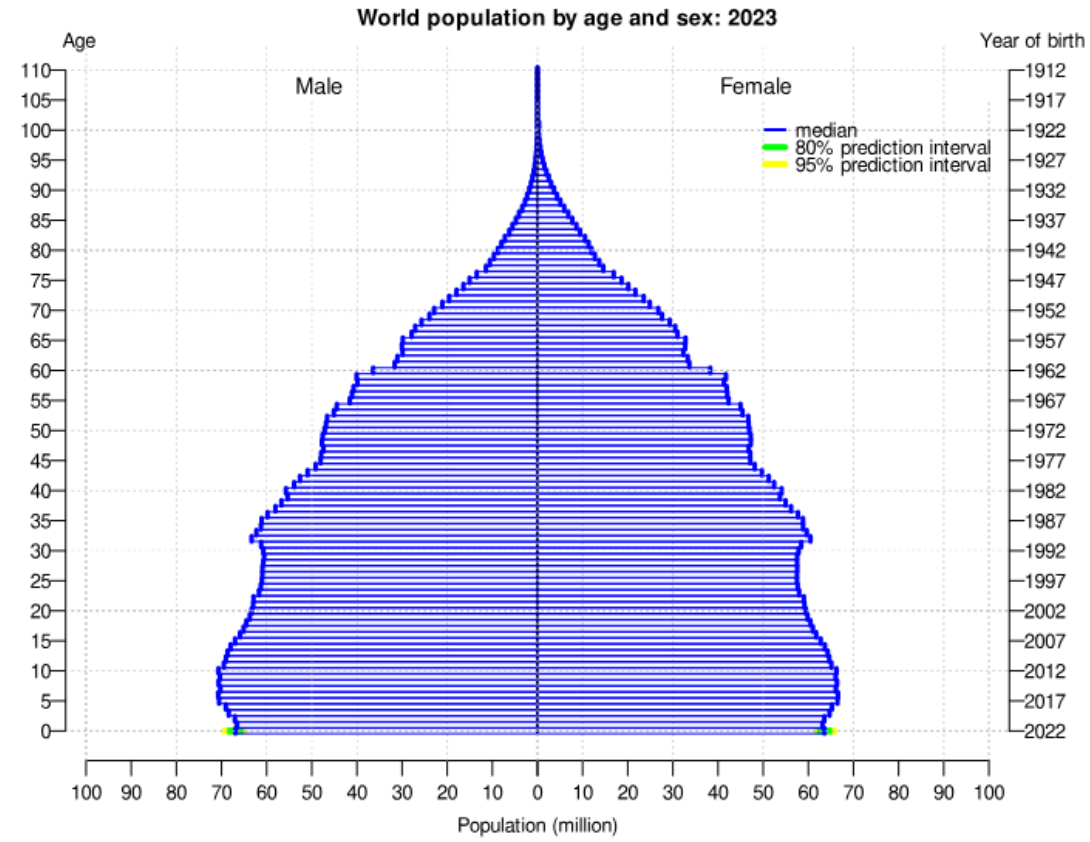
- Rates of decline of infant and child mortality have been levelling off since 2015



United Nations, DESA, Population Division. *World Population Prospects 2022*. http://population.un.org/wpp/

The need for paediatric research

- Rates of decline of infant and child mortality have been levelling off since 2015
- Growing child populations in LMICs
  - By 2100, 8 in 10 people will live in Africa or Asia



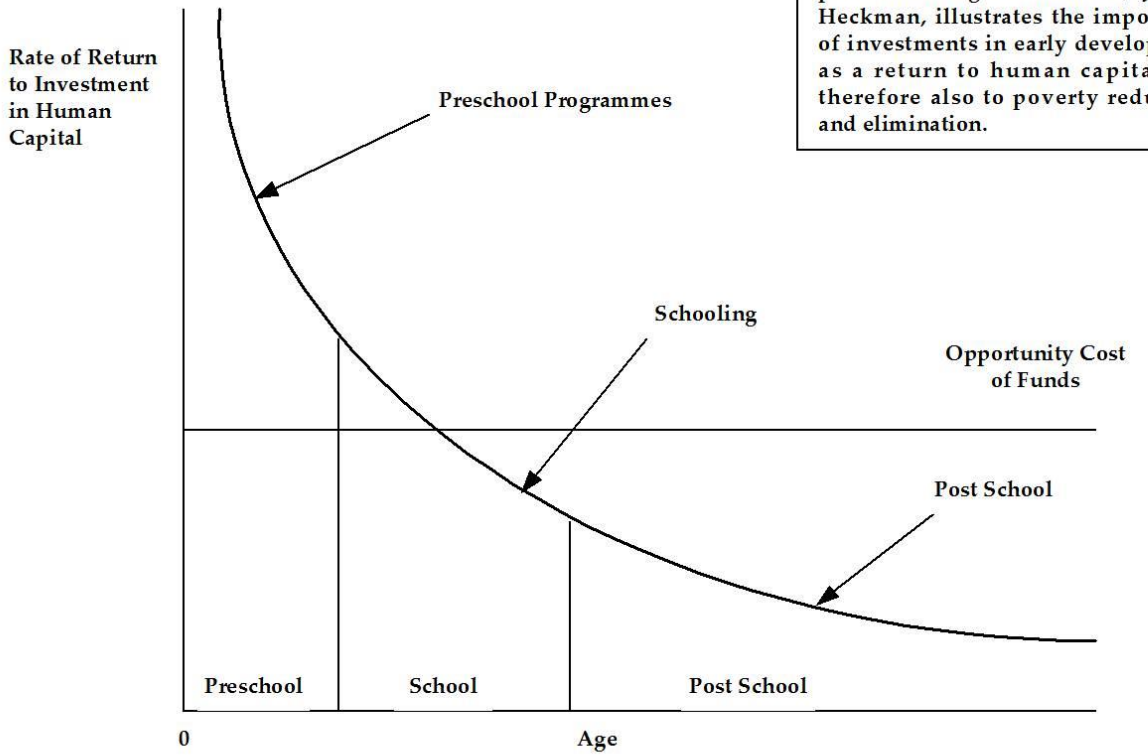
United Nations, DESA, Population Division. *World Population Prospects 2022*. http://population.un.org/wpp/

The need for paediatric research

- Rates of decline of infant and child mortality have been levelling off since 2015
- Growing child populations in LMICs
- The investment return for interventions in young children greatly outweigh the return in any adult population
(Heckman, Nobel Laureate, Economics)

Figure 1: Rates of Return to Human Capital Investment Initially Setting Investments to be Equal Across all Ages

The schematic on the left, from Nobel prize-wining economist, James Heckman, illustrates the importance of investments in early development as a return to human capital and therefore also to poverty reduction and elimination.



Rates of Return to Human Capital Investment Initially Setting Investments to be Equal Across all Ages

The need for paediatric research

- Rates of decline of infant and child mortality have been levelling off since 2015
- Growing child populations in LMICs
- The investment return for interventions in young children greatly outweigh the return in any adult population
- **Prenatal & postnatal health sets a lifelong trajectory of health & disease**

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HEALTH POLICY | VOLUME 390, ISSUE 10104, P1792-1806, OCTOBER 14, 2017 Download Full Issue

Building the foundations for sustainable development: a case for global investment in the capabilities of adolescents

Peter Sheehan, DPhil • Kim Sweeny, PhD • Bruce Rasmussen, PhD • Annababette Wils, PhD • Howard S Friedman, PhD • Jacqueline Mahon, MPH • et al. Show all authors

Published: April 19, 2017 • DOI: https://doi.org/10.1016/S0140-6736(17)30872-3 • Check for updates

Summary
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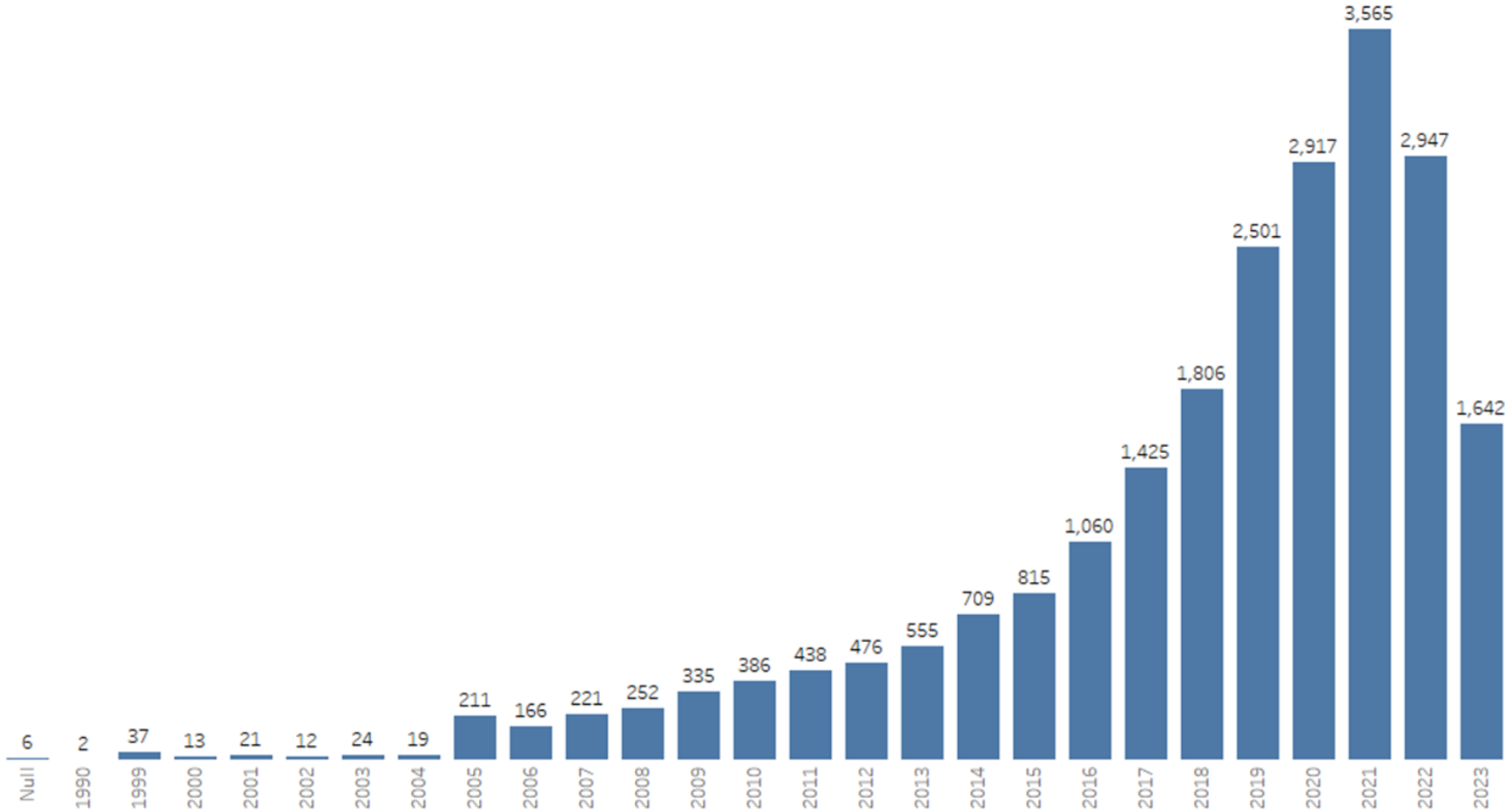
Related Commission

Summary

Investment in the capabilities of the world's 1·2 billion adolescents is vital to the UN's Sustainable Development Agenda. We examined investments in countries of low income, lower-middle income, and upper-middle income covering the majority of these adolescents globally to derive estimates of investment returns given existing knowledge. The costs and effects of the interventions were estimated by adapting existing models and by extending methods to create new modelling tools. Benefits were valued in terms of increased gross domestic product and averted social costs. The initial analysis showed high returns for the modelled interventions, with substantial variation between countries and with returns generally higher in low-income countries than in countries of lower-middle and upper-middle income. For interventions targeting physical, mental, and sexual health (including a human papilloma virus programme), an investment of US$4·6 per capita each year from 2015 to 2030 had an unweighted mean benefit to cost ratio (BCR) of more than 10·0, whereas, for interventions targeting road traffic injuries, a BCR of 5·9 (95% CI 5·8–6·0) was achieved on investment of $0·6 per capita each year. Interventions to reduce child marriage ($3·8 per capita each year) had a mean BCR of 5·7 (95% CI 5·3–6·1), with the effect high in low-income countries. Investment to increase the extent and quality of secondary schooling is vital but will be more expensive than other interventions—investment of $22·6 per capita each year from 2015 to 2030 generated a mean BCR of 11·8 (95% CI 11·6–12·0). Investments in health and education will not only transform the lives of adolescents in resource-poor settings, but will also generate high economic and social returns. These returns were robust to substantial variation in assumptions. Although the knowledge base on the impacts of interventions is limited in many areas, and a major research effort is needed to build a more complete investment framework, these analyses suggest that comprehensive investments in adolescent health and wellbeing should be given high priority in national and international policy.

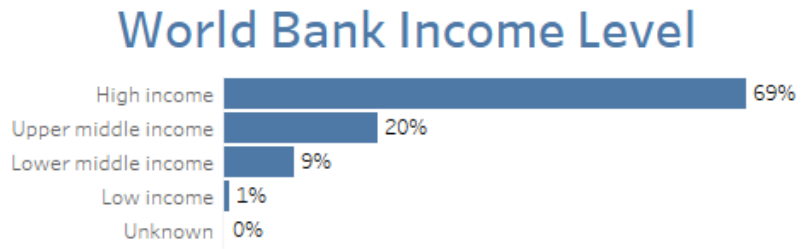
*"If we **change** the **beginning of the story**, we **change the whole story**"*

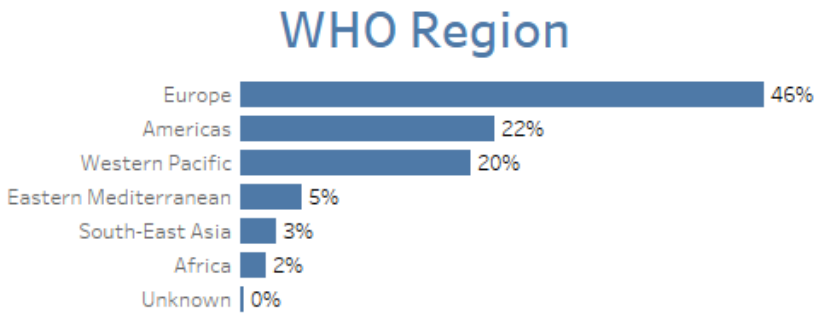
Only 10% of ongoing registered clinical trials include children



International Clinical Trials Registry Platform (ICTRP), October 2023

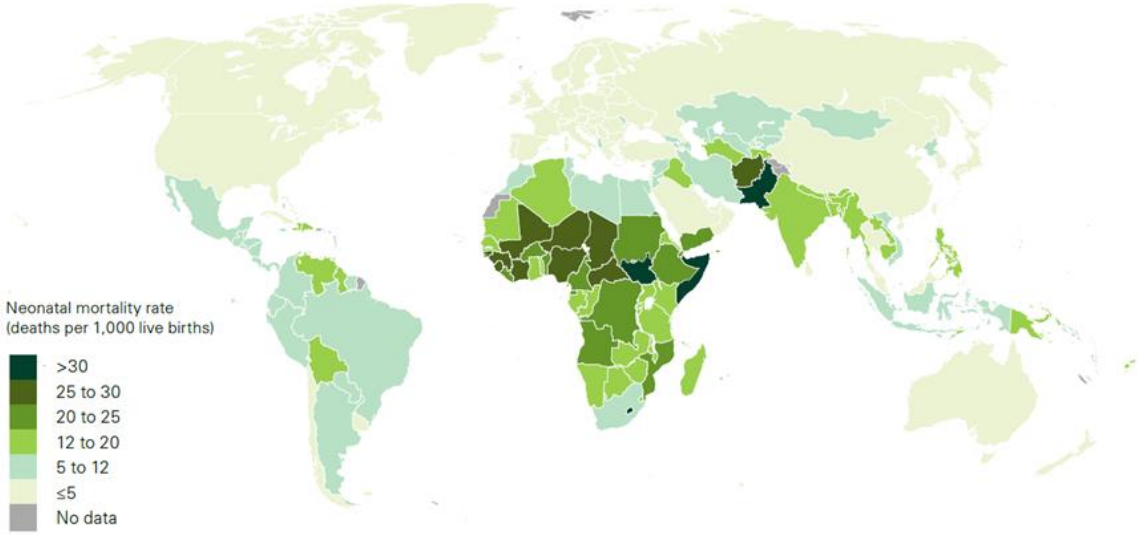
70% of these are conducted in high income settings
Only 10% in LMICs





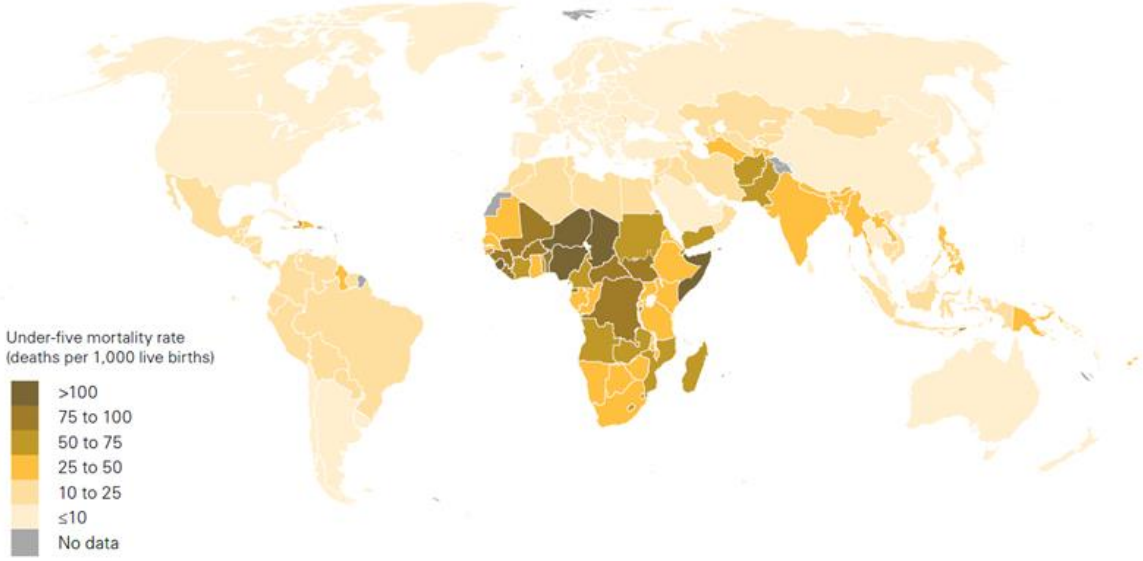
International Clinical Trials Registry Platform (ICTRP), October 2023

…where 70% of the under 5 mortality is occurring



Note: Categories are based on unrounded numbers; value ranges are greater than the lower bound number and less than or equal to the upper bound number. This map does not reflect a position by UN IGME agencies on the legal status of any country or territory or the delimitation of any frontiers.

Neonatal mortality



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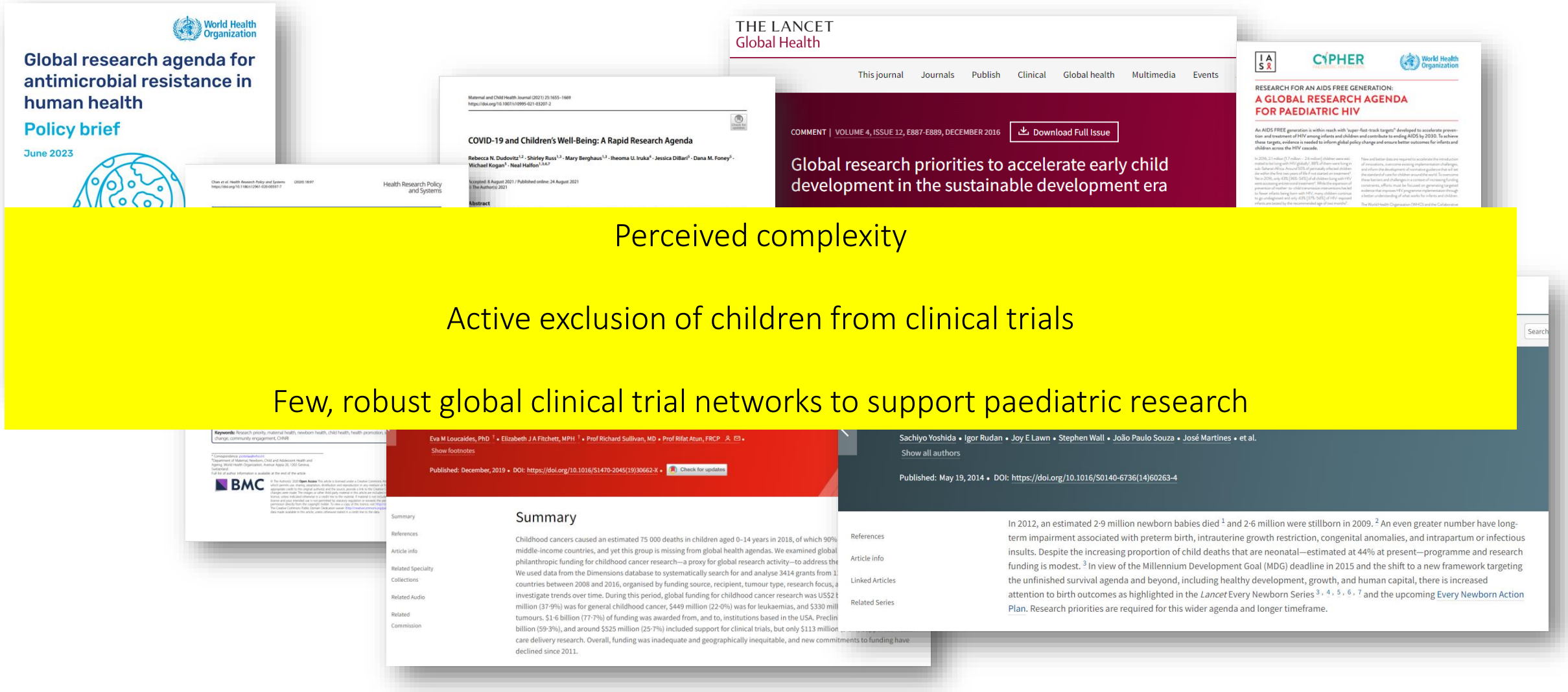
Child mortality

UNIGME report https://childmortality.org/wp-content/uploads/2023/01/UN-IGME-Child-Mortality-Report-2022.pdf

Only a fraction of global research priorities are being addressed across the child health domain



Perceived complexity

Active exclusion of children from clinical trials

Few, robust global clinical trial networks to support paediatric research

Pandemic preparedness must include the needs of children

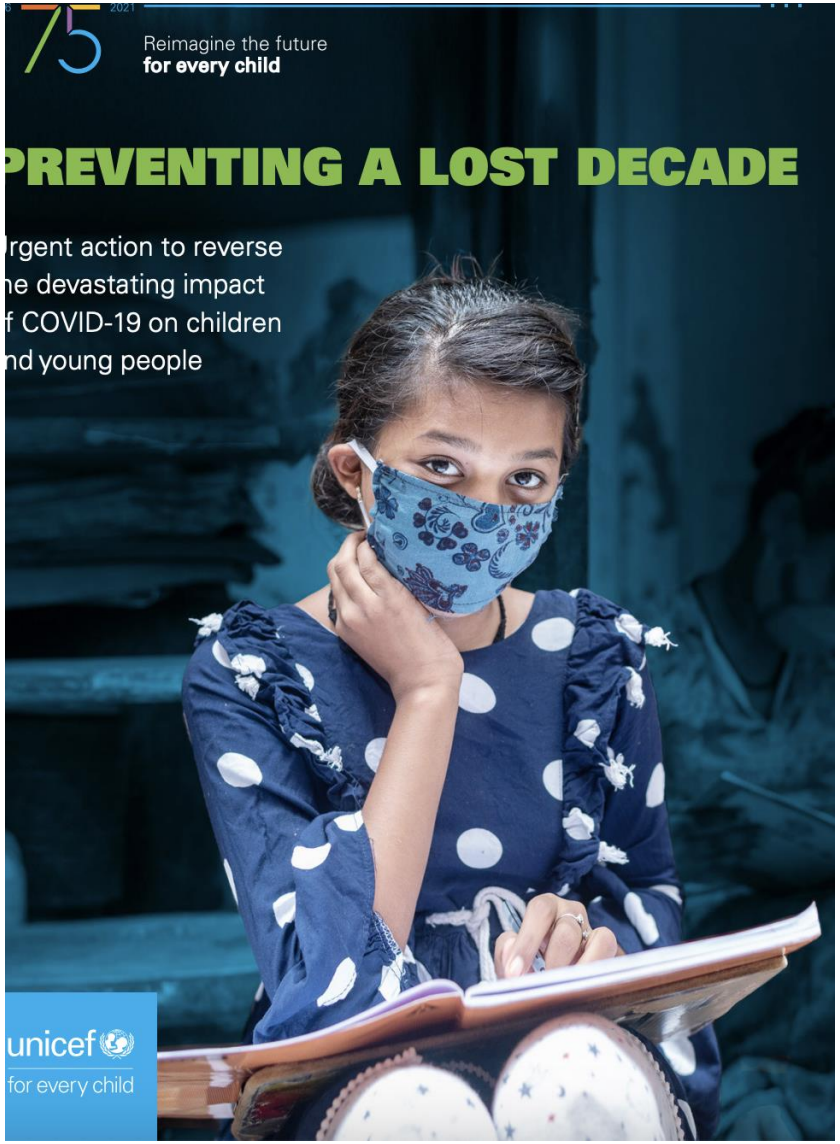
Pandemic caused devastating indirect effects- societal costs unknown, but substantial

Requires “whole person, whole of society” approach

- Must include the developmental needs of children
- School plan

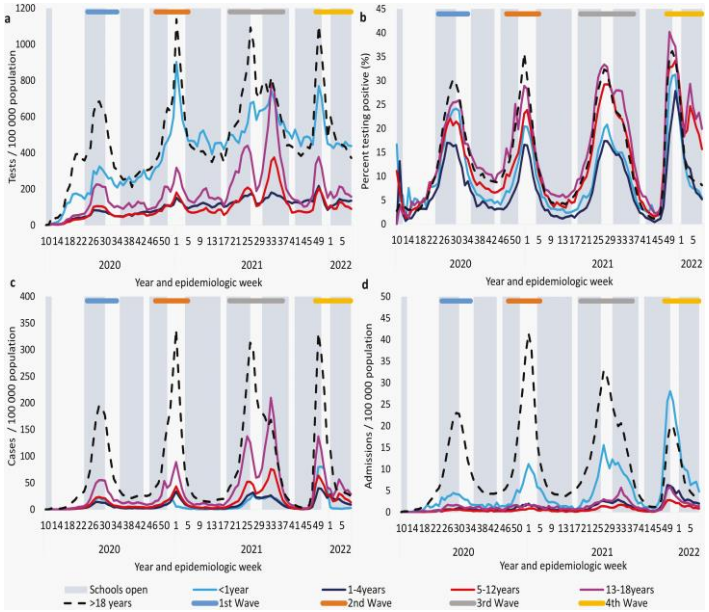
Next pandemic- direct effect on child morbidity & mortality may be substantial

- Need to be ready with therapeutic, vaccine, NPI trial platforms



Pandemic- direct effects

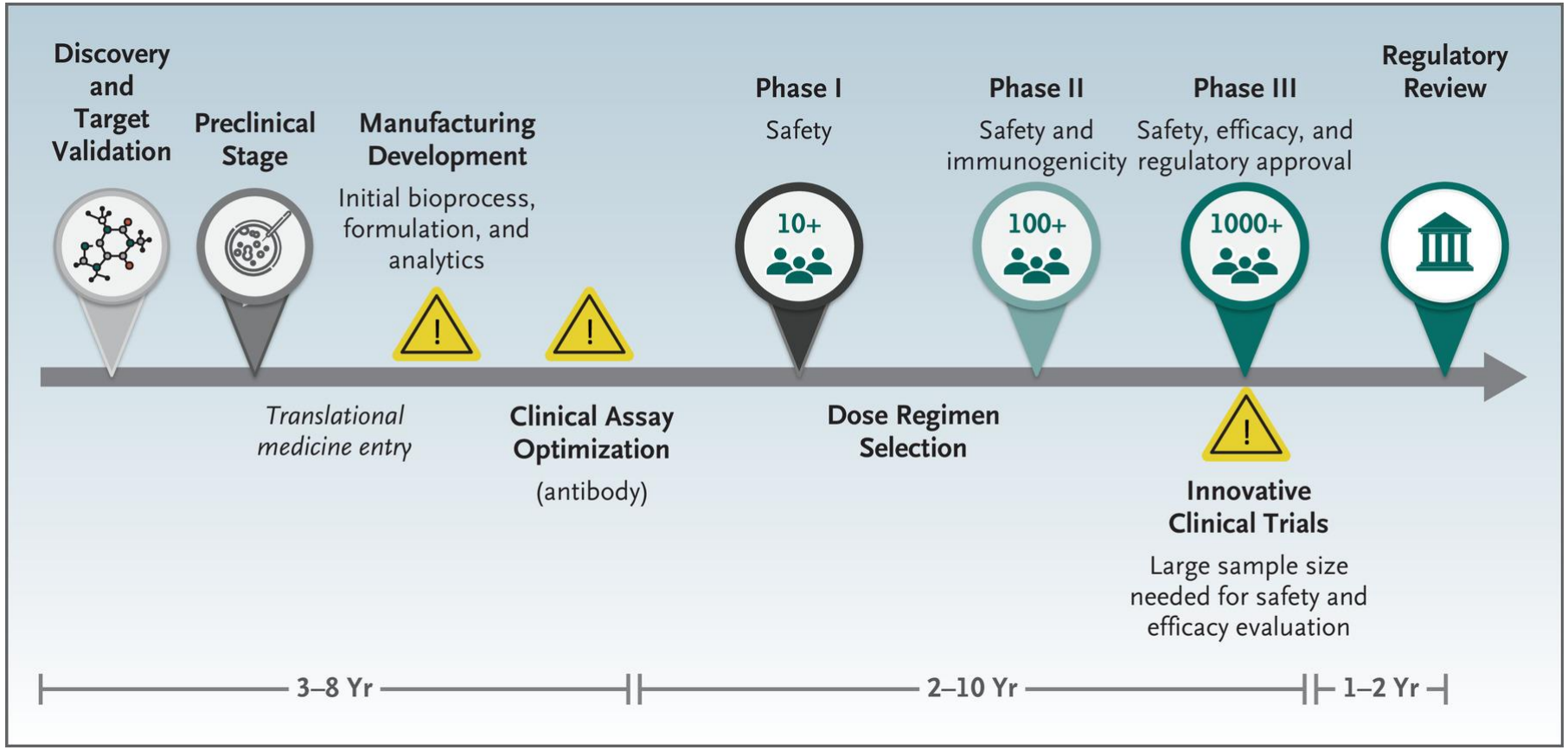
- Children mostly spared from direct effects of COVID
- But still a burden esp LMICs
- Brazil
  - Disparities in health care, poverty & comorbidities can contribute to magnifying the burden of COVID-19 in more vulnerable & socioeconomically disadvantaged children & adolescents
- South Africa
  - Admission rate for children <5y higher in 4th wave vs previous
  - Overall outcome less severe
  - Children with 1+ comorbidity had increased odds of severe disease, warranting consideration for vaccination



Chiwandire et al. PIDJ 2023

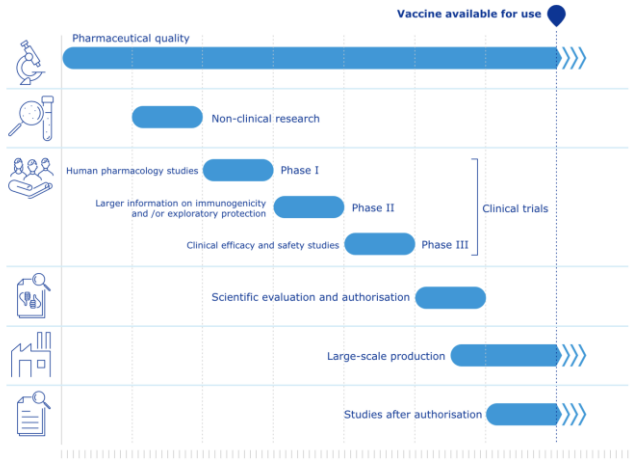
Oliveria EA et al, Lancet Child Adol Health, 2021

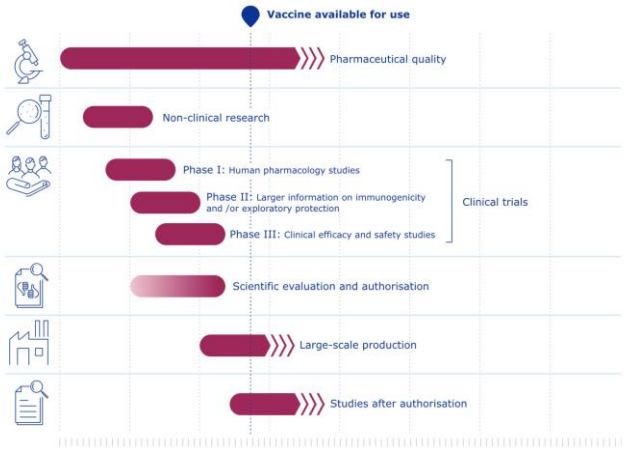
Traditional vaccine development



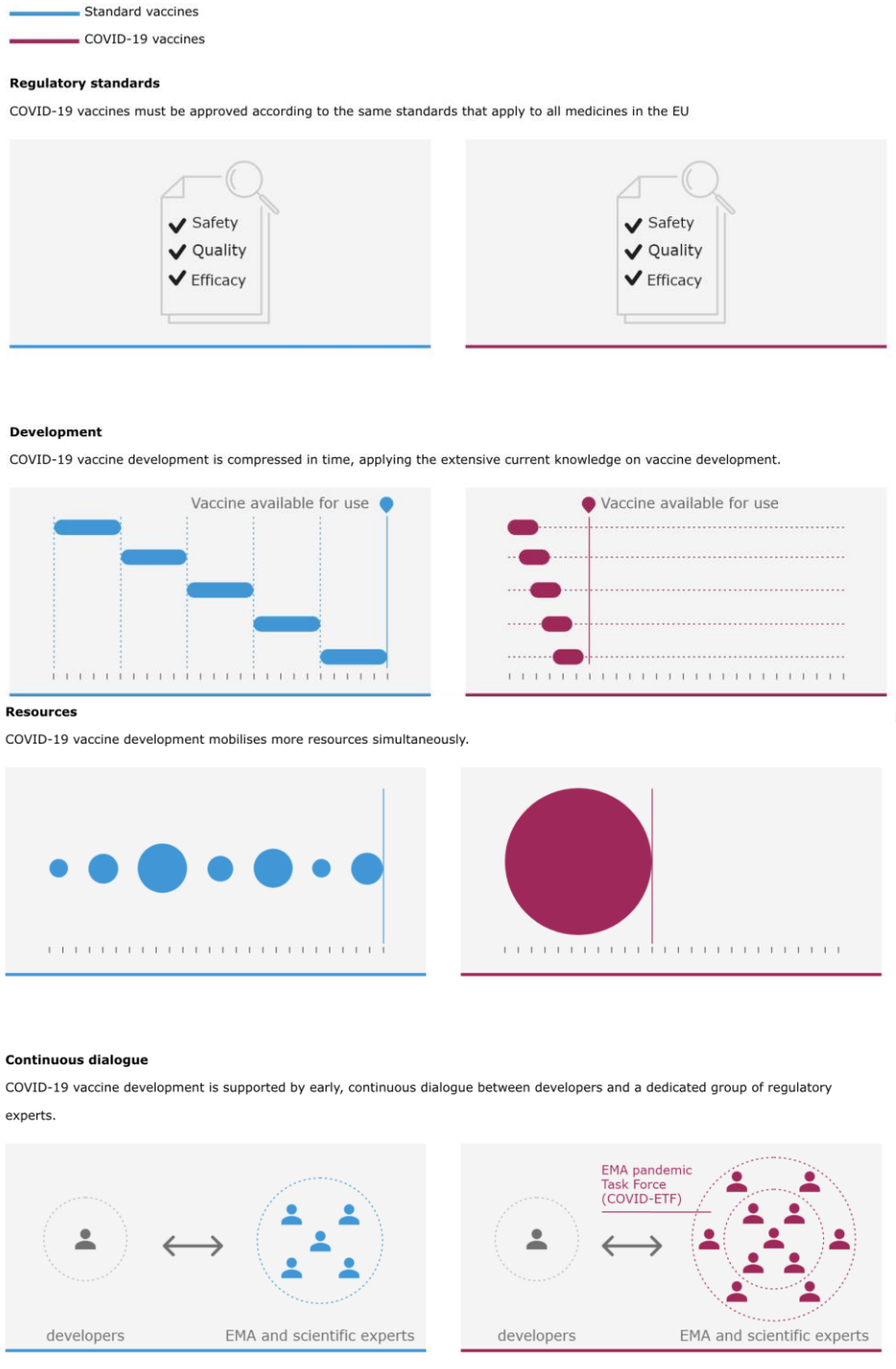
Heaton P, NEJM 2020

Timeline for COVID-19 vaccines versus standard vaccines





Need to ensure there is a mechanism to get to the target population quickly



COVID-19 vaccines: development, evaluation, approval and monitoring; EMA

BMJ Paediatrics Open

Considerations for vaccinating children against COVID-19

John D Hart ,[1,2] Darren Suryawijaya Ong,[1,2] Kulkanya Chokephaibulkit,[3,4] Anna T Ong-Lim,[5] Ilisapeci Vereti,[6] Nigel W Crawford,[2,7] Fiona Russell[1,2]

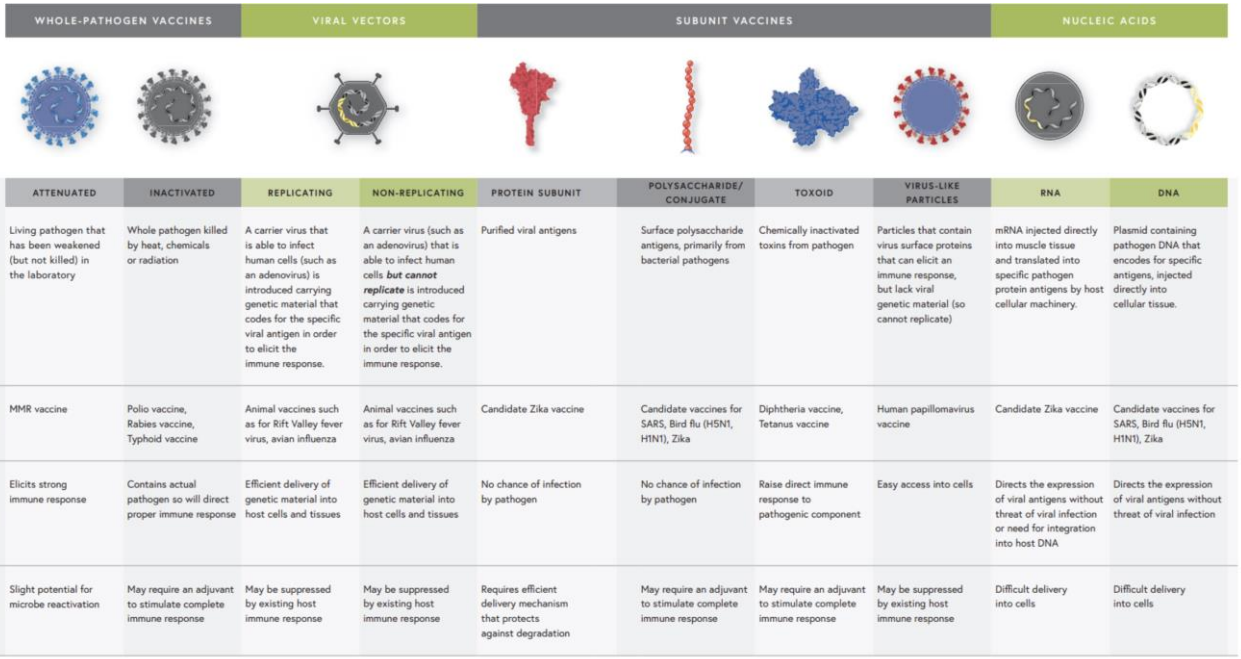
- By the time vaccines were available for children, infection-derived immunity provided similar protection to vaccine-derived immunity
- Countries who have not vaccinated children now need to consider whether to vaccinate based on their own context
- Ongoing research priorities for COVID-19 vaccination in children & adolescents- needs to be part of development plan
- COVID-19 continues to have an impact on children until all high-risk children are offered vaccination

Box 3 Research priorities for COVID-19 vaccination in children and adolescents

⇒ Immunogenicity and duration of protection in high-risk populations
⇒ Understanding the burden of disease and severity with each variant of concern, including in LMICs
⇒ The role of hybrid immunity with new variants and response to vaccination and reinfections
⇒ Clinical trials of the safety and immunogenicity of co-administration of other childhood vaccines with COVID-19 vaccines
⇒ Vaccination dosage requirements in the context of lower disease burden and high levels of infection-derived immunity
⇒ Vaccine hesitancy and barriers to uptake

LMIC, low-income and middle-income countries

Pandemic paediatric vaccine trial risk mitigation



	WHOLE-PATHOGEN VACCINES		VIRAL VECTORS		SUBUNIT VACCINES				NUCLEIC ACIDS	
	ATTENUATED	INACTIVATED	REPLICATING	NON-REPLICATING	PROTEIN SUBUNIT	POLYSACCHARIDE/ CONJUGATE	TOXOID	VIRUS-LIKE PARTICLES	RNA	DNA
DESCRIPTION	Living pathogen that has been weakened (but not killed) in the laboratory	Whole pathogen killed by heat, chemicals or radiation	A carrier virus that is able to infect human cells (such as an adenovirus) is introduced carrying genetic material that codes for the specific viral antigen in order to elicit the immune response.	A carrier virus (such as an adenovirus) that is able to infect human cells ***but cannot replicate*** is introduced carrying genetic material that codes for the specific viral antigen in order to elicit the immune response.	Purified viral antigens	Surface polysaccharide antigens, primarily from bacterial pathogens	Chemically inactivated toxins from pathogen	Particles that contain virus surface proteins that can elicit an immune response, but lack viral genetic material (so cannot replicate)	mRNA injected directly into muscle tissue and translated into specific pathogen protein antigens by host cellular machinery.	Plasmid containing pathogen DNA that encodes for specific antigens, injected directly into cellular tissue.
EXAMPLES	MMR vaccine	Polio vaccine, Rabies vaccine, Typhoid vaccine	Animal vaccines such as for Rift Valley fever virus, avian influenza	Animal vaccines such as for Rift Valley fever virus, avian influenza	Candidate Zika vaccine	Candidate vaccines for SARS, Bird flu (H5N1, H1N1), Zika	Diphtheria vaccine, Tetanus vaccine	Human papillomavirus vaccine	Candidate Zika vaccine	Candidate vaccines for SARS, Bird flu (H5N1, H1N1), Zika
PROS	Elicits strong immune response	Contains actual pathogen so will direct proper immune response	Efficient delivery of genetic material into host cells and tissues	Efficient delivery of genetic material into host cells and tissues	No chance of infection by pathogen	No chance of infection by pathogen	Raise direct immune response to pathogenic component	Easy access into cells	Directs the expression of viral antigens without threat of viral infection or need for integration into host DNA	Directs the expression of viral antigens without threat of viral infection
CONS	Slight potential for microbe reactivation	May require an adjuvant to stimulate complete immune response	May be suppressed by existing host immune response	May be suppressed by existing host immune response	Requires efficient delivery mechanism that protects against degradation	May require an adjuvant to stimulate complete immune response	May require an adjuvant to stimulate complete immune response	May be suppressed by existing host immune response	Difficult delivery into cells	Difficult delivery into cells

Comparison of Vaccine Platforms
Source: ASM Microcosm 2020

- Accelerated development plan that includes children & adolescents
- First evaluate vaccine platforms with good safety profile in children (eg. subunit vaccine)
- Adolescents could be included in adult phase II/III RCTs
- Importance of informed consent
- Undertake stringent RCTs with experienced, trusted personal
- Phase IV safety studies
- High risk children in the development plan

Therapeutics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

6 February 2023
EMA/635567/2022
Paediatric Medicines Office

Boosting the development of medicines for children

The actions were grouped according to the five topic areas highlighted by the Commission in the 10-year report on the implementation of the Regulation:

Topic areas
1. Identifying paediatric medical needs
2. Strengthening of cooperation of decision makers
3. Ensuring timely completion of paediatric investigation plans (PIPs)
4. Improving the handling of PIP applications
5. Increasing transparency around paediatric medicines

PostScript

Letter

Paediatric treatment trials for COVID-19 are an ethical imperative

Our proposal to perform a randomised trial of antiviral treatments for children with moderate to severe COVID-19 has frequently been met with the view that it is not ethical. Central concerns have been that children frequently have no symptoms (when in fact symptoms occur in 21% of children), that severe presentations are rare (2%)[1] and that treatments should only be evaluated in children once the results of adult trials are available.

Certainly, medical research involving children raises distinctive ethical issues. Children are more vulnerable than most adults, and many lack capacity to provide informed consent to potentially harmful research.[2] As with all human research, the risks of a trial in children must be carefully weighed against the possible benefits to both research participants and to other children.

Nevertheless, we challenge the notion that therapeutic trials in children with COVID-19 must await completion of adult trials. Of more than 6 million people infected in these last 6 months of the pandemic, up to 10% were children.[3] At the time of writing, there were 416 children in the USA with COVID-19 admitted to intensive care.[4] Furthermore, the spectrum of disease in children is evolving with reports of paediatric inflammatory multisystem syndrome temporally associated with severe acute respiratory syndrome coronavirus 2, a condition for which studies of therapeutic approaches are urgently needed and unlikely to be informed by trials in adults.[5] Notably, a recent report found that up to 61% of children admitted to intensive care in Canada and the USA are already receiving therapeutic agents.[6]

Risks associated with therapeutic trials in children for COVID-19 can be mitigated by first evaluating medications already licenced in children for other indications (eg, hydroxychloroquine and ascorbic acid) or medications that have a reassuring safety record when used off-label (eg, anakinra). These agents have established dosing recommendations and safety profiles. While risk cannot be eliminated entirely, the stringent oversight of a clinical trial will mitigate the risk of potential harms posed by these agents—certainly compared with experimental use outside of the context of a trial. If no suitable trial opportunities are available, approval from a hospital drug and therapeutics committee and clinical ethics committee should be obtained prior to use.[7]

A crucial ethical consideration in this evolving pandemic is the urgency of the need for effective paediatric treatments and the number of children who stand to benefit. The potential benefits lie in minimising morbidity and mortality associated with severe disease if treatment is effective and also in preventing unnecessary, costly and potentially harmful treatment if ineffective.

In the race to find treatments for COVID-19, children are being left behind. There is a compelling ethical case to include children in rigorously designed and regulated clinical trials to determine the safety and efficacy of potential treatments for COVID-19 as soon as possible.

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Competing interests AG attended the MSD Asia Pacific forum in 2019.

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"we challenge the notion that therapeutic trials in children with COVID-19 must await completion of adult trials"

Risk mitigation

- First evaluate medications already licenced in children for other conditions
- Use medications that have a reassuring safety record when used off- label
- Undertake stringent quality safety oversight in RCTs

An Approach to the Treatment of Children With COVID-19

Alison Boast, BBiomedSci, MD,†‡ Nigel Curtis, FRCPCH, PhD,*†‡ Johanna Holschier, BPharm,§*
Rachael Purcell, MBBS, MPH,† Samantha Bannister, MBBS, MPH,*†‡ Christine Plover, BPharm, MClinPharm,§*
Maidhili Chinnapan, MBBS, David Burgner, FRACP, PhD,*†‡ Suzanne L. Boyce, MBBS, FRACP,*‡*
Sarah McNab, MBBS, PhD,†‡ and Amanda Gwee, FRACP, PhD,*†‡ on behalf of the RCH COVID-19 Treatment Working Group*

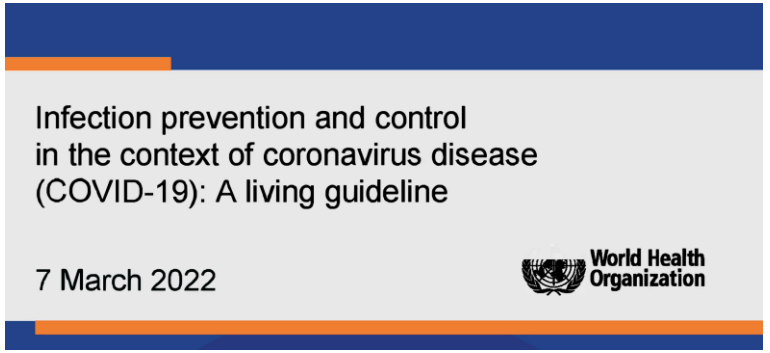
PRECAUTIONARY NOTE

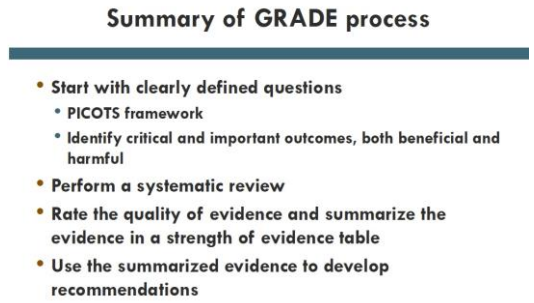
The major limitation of the described approach to treating COVID-19 is the extrapolation of evidence from trials in adult to children in the absence of dedicated pediatric studies. Some of the drugs described, including tocilizumab, budesonide and dexamethasone, have established pharmacokinetic and safety data in children. However, newer medications, including remdesivir, baricitinib, casirivimab-imdevimab, ritonavir-boosted nirmatrelvir, tixagevimab and cilgavimab and sotrovimab, do not. Although case series and cohort studies report the widespread use of these drugs in younger age groups, there have been no RCTs to demonstrate safety and efficacy. This is particularly problematic in younger children in whom drug pharmacokinetics often differ (<2 years). In addition, a major limitation of all guidelines is the rapidity in which they can become outdated in light of new evidence, particularly as new strains emerge. Finally, the applicability of this algorithm will vary according to accessibility to therapeutics across different national jurisdictions within a timely manner.

lack of pediatric safety data for many of the therapeutic options for the treatment of COVID-19, pharmacovigilance and adverse event reporting, data collection to contribute to the existing literature, and parent/guardian informed consent is required.

Non-pharmaceutical interventions

WHO/UNICEF Guideline Development Group for mask guidelines in children





Certainty of evidence low to very low

Research Needs

There are significant limitations in the available evidence on benefits and harms of mask use in children including a lack of evidence on important developmental and long-term outcomes. Future studies should consider evaluation of the effectiveness of mask use by children of different age groups in reducing transmission of SARS-CoV-2, impacts on learning and development, psychological health and quality of life. While RCTs would be ideal, well conducted observational studies that control for other infection control measures, exposures and other confounders would also be informative.

World Health Organization

SEVENTY-FIFTH WORLD HEALTH ASSEMBLY
Agenda item 16.2

WHA75.8
27 May 2022

Strengthening clinical trials[1] to provide high-quality evidence on health interventions and to improve research quality and coordination

The Seventy-fifth World Health Assembly,

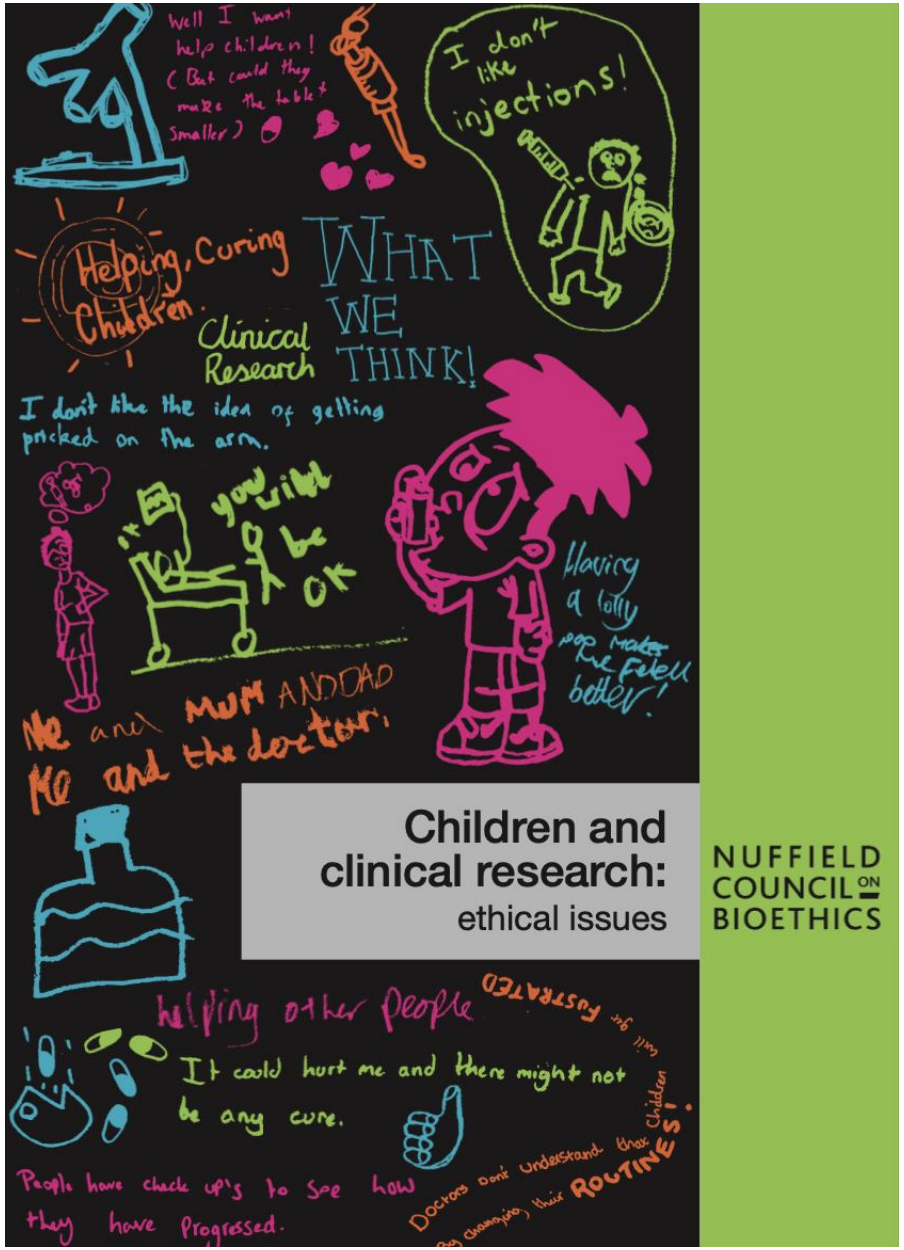
First WHO Global Clinical Trials Forum- Nov 2023

- **Objectives**
  - Develop a joint vision on strengthening clinical research capabilities aligned with the World Health Assembly resolution 75.8 (*Strengthening clinical trials to provide high-quality evidence on health interventions and to improve research quality and coordination*)
  - Discuss how to help build, enhance & sustain functional clinical trial capacity that is used all the time
  - Identify key clinical research networks

- **Expected outcomes**
  - Metrics to enable capacity development of researchers, research institutions, of research ethics committees, & of national regulatory authorities
  - Possible solutions to barriers

Barriers

- Failure of the global research community to efficiently coordinate and align, including processes between national government, communities, researchers, regulators, industry and funders to address the most pressing evidence gaps for infants and children



Risks & benefits

43. Most jurisdictions require that research procedures should pose no more than minimal risk or burden to children and young people participating in the research, unless those risks and burdens are judged to be outweighed by the prospect of direct (health) benefits. Such an approach, however, stands in contrast to the risks that children and young people of a similar age are permitted, or even encouraged, to run in other areas of their daily life that may far exceed any definition of 'minimal', such as those involved in contact sports, or in learning to drive. While in some cases these risks may be recognised and explicitly justified by the (direct or indirect) benefits they are perceived to bring, this cannot always be assumed, particularly where participation is compulsory as in some school-based activities. How are members of RECs to respond to these conflicting societal messages as to what degree of risk is acceptable for what degree of (potential) gain? Rather than attempting to reproduce or revise any such lists of acceptable procedures, or comparator activities in daily life, we suggest that it is more appropriate to focus on the *expertise* that RECs, those tasked on a regular basis with making these judgments, are able to draw upon when approaching these questions.

44. **We conclude that, in order for RECs to be well placed to make these (sometimes very finely balanced) decisions as to whether, in a particular case, the burdens and risks presented by a study protocol can ethically be justified, it is essential for them to have access to appropriate expertise. We highlight two forms of such expertise: that of professionals with specialist knowledge of children's healthcare; and that of children and families** (paragraph 5.23).

Solutions
WHO Paediatric Working Group- clinical trials

A coordinated, transparent process with an accountability mechanism to complete high quality research that provide policy makers with evidence to inform interventions that reduce mortality & improve health & development

- Over the next 5 years have research collaborations to address agreed research priorities
  - High quality evidence to inform policy
  - Builds sustainable research infrastructure
  - Supported by enabling ethical & regulatory environment
  - With accountability mechanism

Summary

- Impact of the current pandemic on children has been devastating
  - Societal impact unknown, but likely to be substantial- can’t happen again

- Can’t afford not to be pandemic ready for paediatric trials

- Ensure high quality paediatric RCT platforms are established in multiple settings & all regions (including LMICs), with the ability to rapidly pivot in a pandemic

- WHO developing pre-approved generic pandemic protocols (vaccines & therapeutics)

Thank you