health if undiagnosed or untreated. There is a need to integrate HIV and STI prevention interventions.

The implementation of oral PrEP within a combination approach for HIV and STI prevention that includes behavioural, social, and biomedical approaches specific to adolescents is greatly needed. Ensuring access to combination youth-friendly prevention services that include PrEP, support for more consistent condom use, and other interventions from the prevention toolbox is crucial. Future studies should look at effective implementation strategies to improve adherence, for example strategies that provide additional support and look at novel medication delivery systems, including long-acting injectable PrEP, intravaginal rings for women, and long-acting implants.

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Access to paediatric formulations for the treatment of childhood tuberculosis

Treatments for tuberculosis infection and disease can be difficult to complete by children who cannot swallow pills. In the absence of commercially-available, child-friendly formulations, adult tablets must be crushed and mixed with food or liquid to mask the taste, a practice termed compounding. Despite the risks and challenges of compounding,[1,2] it remains a common (and, in some cases, recommended) method of tuberculosis treatment administration for children.[3,4] Paediatric formulations, in the form of dispersible tablets, have many advantages over compounded medicines: quality assurance, ease of administration and storage, improved palatability, and the ability to achieve accurate, weight-appropriate doses.[5]

There are 13 commercially available paediatric tuberculosis formulations (appendix). However, in many communities, paediatric tuberculosis formulations remain inaccessible to children for a variety of reasons. These reasons include large gaps in diagnosis, the resulting small and fragmented market, and the failure of existing regulatory incentives and pathways to persuade manufacturers to register paediatric tuberculosis formulations with Stringent Regulatory Authorities (SRAs).

With the exception of bedaquiline, none of the paediatric formulations listed in the appendix are approved for use in the EU, USA, Canada, or Australia. The manufacturers of these paediatric formulations have filed with the WHO Prequalification of Medicines Programme (PQP), unlocking access to the Collaborative Registration Procedure. PQP allows manufacturers to

See **Online** for appendix

access the global market while circumventing the costs and challenges associated with registering products with SRAs.[6] The SRAs in the EU, USA, Canada, and Australia do not mutually recognise WHO PQP, and existing regulatory pathways and incentives have failed to attract manufacturers to register paediatric tuberculosis formulations in these countries.

In the EU, bedaquiline, delamanid, and pretomanid benefit from orphan status, qualifying the corresponding paediatric formulations for European Medicines Agency (EMA) approval upon completion of a Paediatric Investigation Plan. No clear regulatory pathway exists for manufacturers interested in registering paediatric formulations of medicines that do not already have an EU marketing authorisation for tuberculosis in adults (eg, clofazimine, cycloserine). Although the EMA's Paediatric Use Marketing Authorisation pathway could be applied for off-patent, non-tuberculosis-indicated paediatric formulations, it is untenable given that paediatric studies are focused primarily on dosing and safety with efficacy extrapolated from data collected in adults.[7] The effort required to obtain an indication for paediatric tuberculosis in the absence of an existing indication for tuberculosis in adults outsizes manufacturer interest and potential return.

In the USA, paediatric exemptions intended to incentivise the development of orphan drugs allow companies to register new compounds for orphan diseases without doing any investigations to support use and labelling for children. As a result, sponsors of new medicines for orphan diseases, like tuberculosis, decide whether or not to do paediatric investigations and to register paediatric formulations with the US Food and Drug Administration (FDA). There is a modest incentive for sponsors to do paediatric studies in the form of an additional 6 months of marketing exclusivity. Paediatric formulations of off-patent products indicated for tuberculosis in adults or with an FDA-approved paediatric reference product can be submitted as a new drug application under section 505(b)(2) or as an abbreviated new drug application under section 505(j) of the Federal Food, Drug, and Cosmetic Act. Similar to the situation in the EU, the regulatory pathway remains less straight forward in the USA for registering paediatric formulations of medicines that do not have a tuberculosis indication or a reference paediatric product in the USA.

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Health Canada and the Australian Therapeutic Goods Administration do not offer any separate or substantially incentivised regulatory pathways for paediatric medicines nor do they require that manufacturers supply paediatric-specific data unless a paediatric indication is being pursued. In Australia, sponsors can apply for orphan determination, or priority or provisional designations, which might confer benefits to the sponsor. Both countries have special programmes designed to facilitate access to unregistered medicines; however, these programmes have many limitations and are not fit for the purpose of ensuring timely, sustainable access to essential paediatric formulations.[8]

Existing regulatory pathways or other workarounds for accessing globally-available, child-friendly products in the EU, USA, Canada, and Australia are resource-intensive, complicated, and unsustainable. WHO PQP dossier assessments and site inspections are based on the standards of, and largely done by staff from, the world's leading regulatory authorities. To promote equitable access to paediatric formulations, WHO should explore establishing new types of reliance mechanisms for paediatric medicines as per principles described in the WHO good reliance practices in regulatory decision making document[9] or special waivers for paediatric formulations that meet the following criteria: (1) the product has demonstrable public health value through WHO recommendation; (2) there is no equivalent formulation available on the local market; (3) available incentives have failed to attract manufacturers to register locally because of the small market, the low burden of the disease, or the challenge to identify a local legal representative; and (4) the product has been prequalified by the WHO PQP.

The regulatory rules we describe present a major challenge to ensuring that children everywhere can

benefit from child-friendly treatments for tuberculosis. The absence of mutual recognition of WHO PQP assessments on the part of the regulatory authorities we have highlighted promotes a double standard for children affected by tuberculosis in high versus low-income and middle-income countries, especially considering that the EU, USA, Canadian, and Australian governments support WHO PQP and helped fund the development, evaluation, and introduction of the paediatric tuberculosis formulations in over 90 countries.[10]

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Successful youth participation in health research depends on the attitudes of adults

The rights of young people to hold views, have a voice, and be heard by adults are enshrined in the UN Convention on the Rights of the Child,[1] and recognised by various international institutions.[2] Participatory research has become the subject of considerable scholarship and policy development, as adults seek to operationalise youth participation in health research and translation. This process refers to a collaborative approach that carries out research with young people, rather than on them. The drive to involve young people in research is underpinned by a commitment to respect their rights and to achieve better services and professional practices that improve outcomes in health and wellbeing.

Genuine youth participation in health-care research and service provision is scarce. Contemporary health care is constructed around an adult's perspective—from the expert-driven culture of health research to adult-centred policy and the adult-led nature of health-care services. We propose that many of the challenges associated with inclusive youth health research are rooted in the implicit and explicit attitudes of adult stakeholders involved in the research and translation process (including parents, health-care workers, academics, teachers, ethics committees, and policy makers). Therefore, adults' attitudes towards youth participation is useful to explore, and how these attitudes impede innovative work that could improve adolescent health is useful to understand.


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Much to be learned about adults' attitudes towards participatory youth research can be found within the social sciences, in which inclusive research has a rich tradition. Although social scientists argue that participatory research is beneficial for young people and their communities, one substantial barrier is that "adult filters are always at work".[3] From a pragmatic perspective, clinicians often view participatory research as too resource-intensive and costly, and view the data as poor quality.[4] For many researchers, it might simply be hard to