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Finding Better Ways to Fill Gaps in Pediatric Health Research

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PEDIATRICS PERSPECTIVES

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Pediatric health research and development (R&D) has long lagged behind health R&D for adults. Methodological and ethical challenges associated with pediatric research increase the costs of running pediatric trials, and the market for pediatric products is relatively small.[1,2] The subsequent knowledge gaps and lack of child-specific product development have resulted in high off-label and unlicensed medication prescription rates in children.[2] The past decade has seen increased recognition of this problem, and both the United States and the European Union have implemented legislative measures to stimulate pediatric health research by providing incentives and funding for pediatric studies and by requiring pediatric studies for new drug applications when appropriate.[1–3] Although these measures have led to an increase in the number of pediatric trials being conducted and to several knowledge gaps being addressed,[3] the trials remain driven largely by market incentives, and evaluations of the measures in the United States[1] and the European Union[3] show that other areas remain neglected. Moreover, the majority of the global pediatric disease burden lies with populations in low- and middle-income countries, for whom the lack of health R&D remains a significant problem.[4]

To better understand the gaps in the current pediatric health R&D landscape, with respect to medicine development but also to other pediatric R&D areas such as the development of nonmedicinal interventions or health systems research, it is necessary to have information on what research is needed and what research is already being undertaken. Unfortunately, such information is not always available. Particularly, our knowledge of what health research is being conducted globally, where it is being conducted, by whom, and how is limited.[4,5]

Mapping the health R&D landscape requires a triangulation of different sources of information on R&D inputs (eg, investments), R&D processes (eg, clinical trials), and R&D outputs (eg, publications or products).[4,5] Recently, we conducted an evaluation of registered clinical trials on the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).[5] Previous analyses have shown a discrepancy between the pediatric disease burden and the amount of clinical trial research devoted to pediatric populations.[2] Our analysis confirms this finding for low- and middle-income countries but not for high-income countries (Table 1). However, in

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clinical trials, priority setting, pediatric medicines, children, research gaps, R&D

ABBREVIATIONS
ICTRP—International Clinical Trials Registry Platform
R&D—research and development
WHO—World Health Organization

Dr Viergever designed the study methods, conducted all data collection and analysis, and wrote the first draft of the manuscript; Dr Rademaker aided in the interpretation of the study results and contributed to the writing of the manuscript; and both authors approved the final manuscript as submitted.

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TABLE 1 Age of Participants in Actively Recruiting Interventional Trials Registered on the WHO ICTRP in August 2012

Age of Participants	No. of Trials in Sample That Recruited in Age Group			Burden of Disease (in million DALYs)			Estimated no. of Trials on the ICTRP per Million DALYs		
	High-Income Region	Other Regions	Total	High-Income Region	Other Regions	Total	High-Income Region (95% CI)	Other Regions (95% CI)	Total (95% CI)
0–17 y[a]	297	101	372	19	802	821	314.4 (282.9–348.8)	2.5 (2.1–3.0)	9.1 (8.3–9.9)
0–27 d[b]	59	17	72	3	241	245	351.0 (272.9–450.5)	1.4 (0.9–2.2)	5.9 (4.7–7.4)
28–364 d	71	25	88	2	181	183	685.9 (545.7–860.5)	2.8 (1.9–4.0)	9.6 (7.8–11.8)
1–4 y	113	43	141	2	194	196	1010.3 (844.2–1206.7)	4.4 (3.3–5.9)	14.4 (12.3–16.9)
5–9 y	148	50	182	3	66	69	1063.7 (910.3–1240.4)	15.2 (11.7–19.6)	53.0 (46.1–60.8)
10–14 y	187	63	229	4	65	69	877.0 (764.6–1003.9)	19.3 (15.3–24.1)	65.9 (58.3–74.5)
15–17 y	219	72	273	4	55	59	1049.2 (925.3–1187.3)	26.1 (21.1–32.1)	92.1 (82.4–102.8)
18–64 y	1794	357	2034	141	1089	1230	254.0 (250.3–257.2)	6.6 (6.3–6.8)	33.1 (32.6–33.5)
65+ y	1434	242	1574	109	333	441	264.1 (256.9–271.0)	14.6 (13.4–15.7)	71.4 (69.4–73.3)

Numbers are based on a 5% sample of all interventional and actively recruiting trials on the WHO ICTRP taken on August 10, 2012.[5] The total number of trials in the sample was 2381. For 2254 trials, age information was available. Numbers are disaggregated to trials recruiting in the high-income region versus 1 of 6 other regions, as defined by the Global Burden of Disease study in 2010.[7] Estimated numbers of trials on the WHO ICTRP were calculated by multiplying numbers from the sample by 20. The 95% CIs reflect the confidence with which the numbers, measured in our sample of records, predict true numbers for all trials on the WHO ICTRP. When summed, the numbers in the table exceed 100% because trials regularly recruited participants from multiple age groups and multiple regions. Burden of disease for the age group 15–17 y was calculated using the method of Bourgeois et al.[2] CI, confidence interval; DALY, disability-adjusted life-year.

[a] It matters how one defines a pediatric trial. We defined pediatric trials as all trials that recruited in age groups <18 y. When pediatric trials are defined as by Bourgeois et al[2] as "trials with maximum age criteria of 17 y as well as trials with a maximum age criteria of ≥18 y but where the midpoint of the age range is <18 y," numbers of pediatric trials in our sample almost halved to 213. Of the 191 trials in our sample that recruited both adults and children, 159 (83%) were adult trials according to this categorization and only 32 (17%) were pediatric trials.

[b] Numbers for newborns are likely inflated. Our study investigated in which age groups clinical trials on the WHO ICTRP recruited according to the trials' age inclusion criteria, but for several studies where newborns fell within the inclusion criteria, inclusion of newborns was likely only marginal given the health problem under study.

determining how much research is needed for an age group, disease burden is just 1 factor.[6] A more nuanced picture can be obtained by also including other factors. In Europe, for example, pediatric investigation plans were required for 70% of all recent medicine applications for adults.[3] When this percentage is taken as a measure of how many pediatric trials are needed, the proportion of all trials that are pediatric, <20% (Table 1), appears low.

Our analysis also provides insight into gaps in the pediatric health R&D landscape. Both in high-income countries and in low- and middle-income countries, fewer clinical trials are registered for younger age groups, both in absolute numbers and as compared with the burden of disease (Table 1). Because the percentage of children using a prescription drug is relatively high in the first year of life, and off-label and unlicensed prescribing rates are particularly high for neonates, this finding supports the conclusion that the age distribution of children participating in trials does not reflect the need for research.[1] In addition, we found fewer registered trials for communicable, maternal, perinatal, and nutritional conditions (22% of trials; 71% of the global burden) than for noncommunicable diseases (74% of trials; 21% of the global burden). This disparity is also present in adult trials,[5] but it is larger for pediatric trials, potentially reflecting that the lack of health R&D for populations in developing countries disproportionately affects children.

Knowledge of imbalances in the global distribution of pediatric clinical trial research is essential to be able to address gaps in the pediatric health R&D landscape. However, clinical trials constitute only 1 part of all health research. More information is needed to obtain a complete picture of what pediatric health research is being conducted. For instance, another important approach is to analyze funding flows toward health research. This is not an easy task; many funders do not publicly report their health research spending (such data are available for only 37% of all countries[4]). The funders that do report spending data use different classification schemes to categorize their spending to health areas and research types, making aggregate analysis of what funders fund exceedingly problematic. Analyzing funding flows toward health research for children is even more challenging, because spending data are generally not disaggregated to pediatric or adult research. Nonetheless, analyses from other health areas make clear that such challenges can be overcome. The Global Funding of Innovation for Neglected Diseases (G-FINDER) survey has been collecting information about global funding flows toward neglected disease R&D for years, building a much better knowledge base of what the largest gaps are in that area.[6]

In addition to the need for information from a greater variety of sources, there is a need for more accurate information. In our own study, the numbers of trials recruiting in low-

and middle-income countries and the overall trend toward noncommunicable disease research must be interpreted with caution. Although clinical trial registration is now broadly considered an ethical and scientific responsibility, compliance with trial registration remains incomplete, particularly in low- and middle-income countries.[4,5] This is a broader problem; all sources of information that are currently available to monitor health research have substantial limitations, especially with regard to data from low- and middle-income countries.[4,5]

Furthermore, there is a need for more detailed information, to allow identification of specific causes of pediatric disease burden that have remained neglected in terms of research. Moreover, there is a need to go beyond looking at diseases and identify which interventions are being studied, or neglected, for each disease.[6] In our study of the ICTRP, 63% of all pediatric trials, across all health problems, investigated drugs, biologicals, or vaccines, whereas only 5% studied diagnostics (other large categories of interventions were surgery and other procedures, at 15%, and behavioral interventions, at 11%). Health R&D is often more focused on developing drugs and vaccines than on developing diagnostics.[6]

Although the need for increased monitoring of pediatric health research can be addressed partly through research studies such as ours, the comprehensive nature of the information that is needed requires a more systematic approach. Additionally, there is a need for periodic monitoring, as opposed to singular studies, allowing a continuous process of identifying the largest gaps, evaluating whether they have been addressed, providing renewed attention for those that have not been, and identifying newly emerging gaps. A global observatory on health R&D, recently approved by the World Health Assembly, could fulfill these functions.[4] This observatory will provide a sustainable mechanism for regular, global monitoring of health research to improve the prioritization of research, with a special focus on the needs of low- and middle-income countries.[4,6] Because the observatory will increase our understanding of what the largest gaps are in pediatric health research, it is an important first step in redressing the lack of health research for children. However, improving pediatric health research monitoring alone will not be enough. The pediatric health research that is prioritized at this global level will subsequently need to be funded and conducted. A discussion of how this might be achieved for pediatric research gaps in various geographic contexts is needed, to determine what measures could address the gaps left by existing measures in the United States and European Union.[1–3]

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