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,5 the trials remain driven largely by market incentives, and evaluations of the measures in the United States1 and the European Union3 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

AUTHORS: Roderik F. Viergever, MDab and Carin M. A. Rademaker, PharmD, PhDc
aDepartment of Primary and Community Care, Radboud University Medical Center, Nijmegen, Netherlands; bFaculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, England; and cDepartment of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands

KEY WORDS
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.

www.pediatrics.org/cgi/doi/10.1542/peds.2013-1207
doi:10.1542/peds.2013-1207
Accepted for publication Oct 23, 2013
Address correspondence to Roderik F. Viergever, MD, Department of Primary and Community Care, Radboud University Medical Center, PO Box 9101, 6500HB Nijmegen, Netherlands. E-mail: rikviergever@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2014 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: Dr Viergever received payment to conduct this study from the World Health Organization. Dr Rademaker was personally salaried by her institution during the period of writing (although no specific salary was set aside or given for the writing of this article).

FUNDING: This work is a supplementary output of work funded by the World Health Organization.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.
determining how much research is needed for an age group, disease burden is just 1 factor. 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. When this percentage is taken as a measure of how many pediatric trials are needed, the proportion of all trials for neonates, this finding supports the conclusion that the age distribution of children participating in trials does not reflect the need for research. 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, but it is larger for pediatric trials, potentially reflecting that the lack of health R&D for population developments in 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). 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.

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-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: Age of Participants in Actively Recruiting Interventional Trials Registered on the WHO ICTRP in August 2012

<table>
<thead>
<tr>
<th>Age of Participants</th>
<th>No. of Trials in Sample That Recruited in Age Group</th>
<th>Burden of Disease (in million DALYs)</th>
<th>Estimated no. of Trials on the ICTRP per Million DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High-Income Region</td>
<td>Other Regions</td>
<td>Total</td>
</tr>
<tr>
<td>0–17 y</td>
<td>297</td>
<td>101</td>
<td>398</td>
</tr>
<tr>
<td>0–27 d</td>
<td>59</td>
<td>17</td>
<td>76</td>
</tr>
<tr>
<td>28–36 y</td>
<td>71</td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td>1–4 y</td>
<td>113</td>
<td>43</td>
<td>156</td>
</tr>
<tr>
<td>5–9 y</td>
<td>148</td>
<td>50</td>
<td>198</td>
</tr>
<tr>
<td>10–14 y</td>
<td>187</td>
<td>83</td>
<td>270</td>
</tr>
<tr>
<td>15–17 y</td>
<td>219</td>
<td>72</td>
<td>291</td>
</tr>
<tr>
<td>18–64 y</td>
<td>1794</td>
<td>357</td>
<td>2151</td>
</tr>
<tr>
<td>65+ y</td>
<td>1434</td>
<td>242</td>
<td>1676</td>
</tr>
</tbody>
</table>

Numbers are based on a 5% sample of all interventional and actively recruiting trials on the WHO ICTRP taken on August 10, 2012. 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 2012. 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. CI, confidence interval; DALY, disability-adjusted life-year.

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 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 210. 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.

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.
and middle-income countries and the overall trend toward noncommuni-
cable disease research must be inter-
preted with caution. Although clinical
trial registration is now broadly con-
sidered an ethical and scientific re-
ponsibility, compliance with trial
registration remains incomplete, par-
ticularly in low- and middle-income
countries. This is a broader prob-
lem; all sources of information that
are currently available to monitor
health research have substantial lim-
itations, especially with regard to
data from low- and middle-income
countries.4,5

Furthermore, there is a need for more
detailed information, to allow identi-
fication of specific causes of pediatric
disease burden that have remained negleceted in terms of research. More-
ever, 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 develop-
ing diagnostics.5

Although the need for increased moni-
toring of pediatric health research can
be addressed partly through research
studies such as ours, the comprehen-
sive nature of the information that is
needed requires a more systematic ap-
proach. 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 atten-
tion 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 func-
tions.4 This observatory will provide
a sustainable mechanism for regular,
global monitoring of health research to
improve the prioritization of re-
search, 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,
 improv ing 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 re-
search 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

ACKNOWLEDGMENTS
We gratefully acknowledge the contri-
butions of Robert Terry and Ghassan
Karam to this article.

REFERENCES
1. Boots I, Sukhai RN, Klein RH, et al. Stimula-
tion programs for pediatric drug research
2007;166(8):849–855
2. Bourgeois FT, Murthy S, Pinto C, Olson KI,
Ioannidis JPA, Mandl KD. Pediatric versus adult
drug trials for conditions with high pediatric
3. The European Medicines Agency with its
Paediatric Committee. 5-year Report to the
European Commission: General report on
the experience acquired as a result of the
application of the Paediatric Regulation
(EMA/428172/2012). London, United King-
dom: European Medicines Agency; 2012
available health R&D data: what’s there, what’s
missing and what role for a global observa-
5. Viergever RF, Terry RF, Karam G. Use of data
from registered clinical trials to identify
gaps in health research and development.
425C
6. Viergever RF. The mismatch between the
health research and development (R&D)
that is needed and the R&D that is un-
dertaken: an overview of the problem, the
causes, and solutions. Glob Health Action.
2013;6:22450
2010: design, definitions, and metrics. Lan-
cet. 2012;380(9859):2063–2066
# Finding Better Ways to Fill Gaps in Pediatric Health Research

Roderik F. Viergever and Carin M. A. Rademaker

*Pediatrics* 2014;133;e824; originally published online March 17, 2014; DOI: 10.1542/peds.2013-1207

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: /content/133/4/e824.full.html</th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 6 articles, 1 of which can be accessed free at: /content/133/4/e824.full.html#ref-list-1</td>
</tr>
<tr>
<td>Citations</td>
<td>This article has been cited by 1 HighWire-hosted articles: /content/133/4/e824.full.html#related-urls</td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): Medical Education /cgi/collection/medical_education_sub Research Methods &amp; Statistics /cgi/collection/research_methods_-_statistics_sub International Child Health /cgi/collection/international_child_health_sub</td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml</td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: /site/misc/reprints.xhtml</td>
</tr>
</tbody>
</table>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2014 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.
Finding Better Ways to Fill Gaps in Pediatric Health Research
Roderik F. Viergever and Carin M. A. Rademaker
Pediatrics 2014;133;e824; originally published online March 17, 2014;
DOI: 10.1542/peds.2013-1207

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/133/4/e824.full.html