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Pharmacokinetic research in children: an analysis of registered records of clinical trials

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ABSTRACT

Background

Reported off-label/unlicensed prescribing rates in children range from 11% to 80%. Research into pharmacokinetic profiles of children's medicines is essential in the creation of more knowledge on the safety and efficacy of medicines in children. This study investigated how often pharmacokinetic data are collected in clinical trials of medicines in children by analysing registered records of clinical trials.

Methods

The registered records of all clinical trials in children that were recruiting on 22 May 2009 were identified on the International Clinical Trials Registry Platform (ICTRP) using a Clinical Trials in Children search filter. The records of trials in children below 12 years of age, in which the intervention was one or more medicines, were assessed for evidence that pharmacokinetic data would be collected.

Results

Of 1081 eligible trial records, 257 (24%) declared that pharmacokinetic data would be collected. Of these trials, 199 (77%) recruited in Northern America; recruitment in all other regions was below 20%. Trials recruited most often in children over 2 years of age (74%), and least often in newborn infants (32%). Most trials researched medicines in the field of cancer (29%). Trials investigated one third of the medicines that were indicated as a priority for pharmacokinetic research by the European Medicines Agency.

Conclusions

There is a need for increased knowledge of the pharmacokinetic profiles of children's medicines. The amount of currently ongoing pharmacokinetic research does not seem to adequately address the lack of knowledge in this area. This study sets a baseline for monitoring of future progress on the amount of ongoing pharmacokinetic research in children.

ARTICLE SUMMARY

Article focus

- The main aim of this study was to assess how many registered records of clinical trials of medicines that were recruiting children and were identifiable on the ICTRP Search Portal contained evidence that pharmacokinetic data would be collected.
- Secondary aims were to assess which pharmacokinetic data were collected and what types of trials were reporting pharmacokinetic data.

Key messages

- This study quantifies, for the first time, the amount of currently ongoing research into pharmacokinetic profiles of medicines in children.
- It shows how much and what kind of pharmacokinetic research is being carried out worldwide as registered at clinical trial registries and analyses the types of trials that perform this research.
- It sets a baseline for future studies, to monitor progress in the amount of pharmacokinetic research that is performed in children.

Strengths and limitations of this study

Strengths:

Our study is one of the first studies of its kind, in that it has created a comprehensive oversight of the amount of ongoing research in one particular research area, by analysing information in registered records of clinical trials. Using information in clinical trial databases as such offers a unique, and currently underused, method for informing future research prioritisation efforts at a policy level (in our case of paediatric off-patent medicines by the European Medicines Agency).

Limitations:

This study is limited by the quality of information in the included registered records. Studying registered records of clinical trials is not the same as studying how clinical trials were in fact conducted. However, in the absence of open access to complete trial protocols we have no other choice than to use the information entered into a trial registry for this type of analysis.

INTRODUCTION

Knowledge on the efficacy and safety of medicines for children is still very limited. Off-label (outside the product license) and unlicensed (without a license for children) prescription rates in children range from 11% to 80%.[1] Only 20-30% of drugs that have been approved by the U.S. Food and Drug Administration (FDA) in the past, were also labelled for use in children.[2] Adult dosing cannot be logically extrapolated to paediatric dosing according to weight or age because of different pharmacokinetic and pharmacodynamic profiles in children as compared to adults.[3-5] Differences in drug metabolism between children and adults also lead to differences in susceptibility to adverse drug reactions.[6] Worryingly, adverse drug reactions have been shown to occur more frequently with off-label prescribed drugs.[7] The magnitude of this problem is exemplified by one source which estimates that almost one quarter of all children in the US used at least one prescription drug in the last month and that the total number of drugs used per 100 children in the US over 2004 and 2005 was 338.4.[8] To accelerate progress towards improved availability and access to safe child-specific medicines for all children below 12 years of age, the 'Make medicines child size' campaign was launched by the World Health Organization (WHO) in 2007.[9]

It has been a requirement of the International Committee of Medical Journal Editors (ICMJE) since 2004 that all clinical trials be prospectively registered in a publicly available clinical trials registry in order to be considered for publication of trial results.[10] As of April 2011 the WHO International Clinical Trials Registry Platform (ICTRP) offers a single point of access (the ICTRP Search Portal) to data from over 130,000 clinical trials made available by clinical trial registries around the world.[11] The importance of high quality information on clinical trials recruiting children is increasingly being recognised. The Pan African Clinical Trials Registry (PACTR) (a WHO Primary Registry to the ICTRP) has, for example, recently created a child strategy,[12] and the European Union has implemented legislation mandating that the EudraCT database of clinical trials "should include a European register of clinical trials of medicinal products for paediatric use".[13] To improve access to information on clinical trials in children for health care workers, researchers, and patients and their parents, the ICTRP has developed a filter (referred to as the Clinical Trials in Children or CTC filter) on the ICTRP Search Portal which makes it possible to search the portal for clinical trials in children with reasonable accuracy.[14]

Collecting pharmacokinetic data in paediatric drug trials is fundamental in the development of a larger body of evidence on the safety and efficacy of children's medicines. The aim of this study was to assess how many registered records of clinical trials of medicines that were recruiting children and were identifiable on the ICTRP Search Portal contained evidence that pharmacokinetic data would be collected.

METHODS

Data sources

The ICTRP Search Portal imports the WHO Trial Registration Data Set (the minimum amount of trial information that must appear in a register in order for a given trial to be considered fully registered) from registries that meet WHO criteria, including ClinicalTrials.gov.[15] As the format of each data item differs across registries, data are currently imported into the portal as text. The ICTRP publishes a hyperlink to the record in the source registry (i.e. the registry that provided the data) so users can view additional information, if required. At the time of this study, nine registries provided data to the ICTRP: The Australian New Zealand Clinical Trials Registry (ANZCTR), the Chinese Clinical Trial Register (ChiCTR), the Clinical Trials Registry - India (CTRI), ClinicalTrials.gov, the German Clinical Trials Register (DRKS), the Iranian Registry of Clinical Trials (IRCT), the International Standard Randomized Controlled Trial Number Register (ISRCTN), the Netherlands National Trial Register (NTR), and the Sri Lanka Clinical Trials Registry (SLCTR).

During this study, the CTC filter operated through a search paradigm of over 4000 keywords that were compiled by consulting child health experts who identified key terms relevant to children and adolescents.[14]

Study selection

The ICTRP database was searched for all recruiting, interventional clinical trials in children using the CTC filter. The resulting records were scanned manually for eligibility. To be eligible, trial records needed to describe trials that included children below 12 years of age. For trials where inclusion of participants below 12 years was unclear from the record, the record was considered eligible only when an explicit statement was present that the trial was recruiting children, or when the investigated

disease was listed as child-specific in the CTC search filter keyword database. When a trial researched an intervention in pregnant mothers, records were only included when outcomes were defined for the child.

Eligible trials also needed to have at least one arm that involved the evaluation of one or more medicines. Interventions were coded to be medicines or not by using the coding system for intervention types on ClinicalTrials.gov.[16] Interventions that were drugs, biologicals or dietary supplements were considered to be medicines. Excluded were records of trials that researched general dietary interventions (as opposed to dietary supplements), vaccines, IV fluids (without mentioning of specific substance names), oxygen and nitric or nitrous oxide treatments, transplantations or transfusions, sucrose and glucose water for treatment of pain in newborns, alcohol cleansing of intravenous materials, somatic cell transplants and transfusions, pro- and prebiotics, and surfactant treatments.

Data extraction

The following information was collected manually for all eligible registered records: the age of included participants, country / countries of recruitment, study phase, and nature of sponsorship. Geographical regions of the United Nations Statistics Division were used to group countries.[17] Age of participants was categorised according to the International Conference on Harmonisation topic E11 age classification of paediatric patients.[18]

Eligible registered records were searched for the presence or absence of collection of pharmacokinetic data. Pharmacokinetic data were defined as parameters that describe the fate of externally administered substances to humans after administration. Both parameters of the drug and its metabolites were denoted to be pharmacokinetic data (e.g. 25(OH)D or $1,25(OH)_2D$ levels were recorded as pharmacokinetic outcomes of vitamin D treatment). Collection of pharmacokinetic data could be mentioned in the outcome entry fields or elsewhere in the record.

It was determined whether pharmacokinetics were recorded as a primary or a secondary outcome measure (if collection of pharmacokinetic data was mentioned outside the outcome fields, it was denoted a secondary outcome measure). Furthermore, it was documented which of the following pharmacokinetic data were studied: absorption, area under the curve (AUC) of plasma or tissue

concentration, autoinduction response, balance, bioavailability, breakdown, clearance, distribution, elimination, excretion, faecal clearance, faecal excretion, lowest concentration, metabolism, peak concentration, plasma half-life ($t_{1/2}$), plasma or tissue concentration, renal clearance, time to lowest concentration, time to peak concentration, urinary excretion, volume of distribution, or general mentioning of pharmacokinetic data collection or a pharmacokinetic study design. Use of a population pharmacokinetic design and additional general mentioning of pharmacodynamic data collection or the use of a pharmacodynamic study design were denoted.

The primary health condition or problem studied and the drug, biological or dietary supplement that was under investigation were denoted for trials that reported collection of pharmacokinetic data. The primary health condition or problem studied was categorised according to WHO ICD-10 chapters.[19] For drugs, biologicals and dietary supplements, we adhered to the names for the interventions as denoted in the registered record, except when proprietary names were used, which we converted to nonproprietary names. When there were multiple medicines described, but there was one main intervention, and the record lacked specification for which medicines pharmacokinetics would be determined, it was assumed that pharmacokinetics would be determined for the main intervention. The drugs, biologicals and dietary supplements that were found were compared with the medicines for which there was a priority need for pharmacokinetic data, according to the European Medicines Agency (EMA) revised priority list for studies into off-patent paediatric medicinal products from 2008, which was the most recent version at the time of this study.[20] Furthermore, we analysed the EMA 2009 and 2010 priority lists to see whether medicines from the 2008 list endured to be priorities for pharmacokinetic investigation. Lastly, to investigate whether there were trials that studied EMA priority medicines without collecting pharmacokinetic data, we searched the scientific and public titles of all studies in our sample for mentioning of the EMA priority medicines.

All records were scanned for eligibility by RFV who then, in case of inclusion, extracted and coded the data. During eligibility assessment and data extraction trial records for which data were ambiguous were further assessed by DG. Conflicts were resolved by mutual agreement.

Microsoft SPSS version 16.0.1 was used for descriptive analyses of the data.

RESULTS

The ICTRP Search Portal was searched using the CTC filter on 22 May 2009 resulting in the identification of 3051 records of interventional clinical trials in children, of which 1081 were investigating one or more medicines (i.e. the intervention was a drug, biological or dietary supplement) and mentioned inclusion of children below 12 years of age. 257 (24%) of these records reported that pharmacokinetic data would be collected. The medicines that were investigated by the corresponding trials were drugs or biologicals in 209 records (81%) and dietary supplements in 48 records (19%).

The 1081 records of children's trials reported recruitment of participants in 92 countries; the records that reported collection of pharmacokinetic data recruited in 48 countries. Of the 257 records that reported collection of pharmacokinetic data, 199 records (77%) reported recruitment in Northern America; recruitment in all other regions was below 20% (Table 1). Among the 824 records of trials without pharmacokinetic data collection, Northern America was also the most frequent geographical region of recruitment, but less so (57%).

Looking more closely at the age of participants being recruited in trials that reported collection of pharmacokinetic data, 81 records (32%) involved preterm or term newborn infants (0 to 27 days), 126 records (49%) infants and toddlers (28 days to 23 months), and 190 records (74%) children between the ages of 2 and 11 years.

Mention of pharmacokinetic data collection was most frequent in records of trials that were Phase 1 (62%) or Phase 1 and 2 (57%). 39% of all trials that reported pharmacokinetic data collection were Phase 1 or Phase 1 and 2, 43% were Phase 2 to 4 (in 19% of records study phase was not provided).

Almost half of the trials that were reported to collect pharmacokinetic data were sponsored by a university or a hospital. Though there were fewer federal (15%) and industry (26%) sponsored trials performing research into medicines in children under 12 years, these trials were more likely to collect pharmacokinetic data (32% and 37% respectively) than university or hospital sponsored studies (19%).

	Records from trials that reported collection of PK data (N=257)		Records from trials that did not report collection of PK data (N=824)		Total	Percentage of total reporting collection of PK data per age group, region, Phase, or sponsor
	Number of records	Percentage of N=257	Number of records	Percentage of N=824		
Age[1]						
Newborn infants (0 to 27 days)	81	32%	226	27%	307	26%
Infants and toddlers (28 days to 23 months)	126	49%	371	45%	497	25%
children between the ages of 2 and 11 years	190	74%	680	83%	870	22%
Not indicated	3	1%	19	2%	22	-
Geographical region[1]						
Africa	16	6%	44	5%	60	27%
Asia	26	10%	94	11%	120	22%
Europe	50	19%	217	26%	267	19%
Latin America and the Caribbean	25	10%	61	7%	86	29%
Northern America	199	77%	469	57%	668	30%
Oceania	13	5%	83	10%	96	14%
Not specified	12	5%	35	4%	47	-
Phase						
0	0	0%	3	0%	3	0%
1	69	27%	43	5%	112	62%
1&2	31	12%	23	3%	54	57%
2	45	18%	149	18%	194	23%
2&3	11	4%	32	4%	43	26%
3	38	15%	215	26%	253	15%
3&4	0	0%	4	0%	4	0%
4	15	6%	146	18%	161	9%
Not indicated	48	19%	209	25%	257	-
Sponsorship						
Collaborative research groups	25	10%	80	10%	105	24%
Federal	39	15%	84	10%	123	32%
Industry	67	26%	114	14%	181	37%
University or hospital	121	47%	502	61%	623	19%
Other[2]	5	2%	43	5%	48	10%
Not indicated	0	0%	1	0%	1	-
Total	**257**		**824**		**1081**	

Table 1 – Age groups of study participants, geographical regions of recruitment, study phase, and sponsorship of trial records included in the study

[1] Percentages for geographical regions and age groups do not add up to 100% because records regularly pertain to trials recruiting in multiple regions, or recruiting in multiple age groups.

[2] Other sponsorship included foundations, contract research organizations, research centres, and individuals.

Of the 257 records that reported collection of pharmacokinetic data, 56 records (22%) mentioned only the measuring of serum or tissue concentrations, and did not mention a pharmacokinetic study design, or any of the other pharmacokinetic parameters (34 of these 56 records (61%) were of trials that investigated dietary supplements). Which pharmacokinetic data were reported to be collected in records is shown in more detail in Figure 1. 124 records (48%) reported pharmacokinetic data as a primary outcome and 163 (63%) reported pharmacokinetic data as a secondary outcome (overlap is due to mentioning of pharmacokinetic data as both a primary and a secondary outcome measure in 30 records). 11 records (4%) mentioned use of a population pharmacokinetic design. 52 records (20%) mentioned pharmacodynamic data collection or the use of a pharmacodynamic study design in addition to pharmacokinetic data collection (out of the 824 records that did not report pharmacokinetic data collection, 12 records mentioned collection of pharmacodynamic data).

The primary health condition or problem studied in trials that collected pharmacokinetic data was most often cancer (29%) (Figure 2). The distribution of health conditions or problems studied differed per age group, with less of a propensity for cancer research among the group of newborn infants (Figure 3).

A detailed oversight of the medicines that were investigated by trials that reported collection of pharmacokinetic data can be found in Web Only File 1. Of the 28 medicines on the EMA revised priority list for studies into off-patent paediatric medicinal products from 2008 for which collection of pharmacokinetic data was indicated to be a priority, we found 9 medicines (32%) to be investigated in trials identified in our search (Table 2).

Of the 28 medicines that were EMA priorities in 2008, 14 (50%) were still a priority in 2009 and 12 still in 2010 (43%). Of the 9 medicines for which we found pharmacokinetic data collection, 2 were still a priority in 2010 (22%). Of the 19 medicines for which we did not find pharmacokinetic data collection, 10 were still a priority in 2010 (53%).

Academic and public titles of the 1081 records in the sample were searched for the names of the 19 medicines that we did not find pharmacokinetic data collection for in any record. 8 (42%) of these medicines were identified in 29 trial records as an intervention.

Name of medicine	notes	Investigated in trial records identified on the ICTRP search portal?	Still in 2009 EMA priorities?	Still in 2010 EMA priorities?	Medicine investigated in trials without collection of PK data?	In how many trial records?
6-mercaptopurine	in infants	yes	yes	no		
Actinomycin	below the age of 6 years	yes	no	no		
Asparaginase	in infants	yes	no	no		
Baclofen		yes	no	no		
Bumetanide		no	no	no	no	
Carboplatin	below the age of 3 years	no	no	no	yes	10
Cladribine		no	no	no	no	
Clindamycin		no	yes	yes	no	
Clonidine		no	yes	yes	yes	6
Cyclophosphamide	data on PK of metabolites	yes, including metabolites	no	no		
Cytarabine	in infants	yes	yes	no		
Daunorubicin	in infants	yes	yes	yes		
Ethosuximide		no	yes	yes	no	
Foscarnet		no	no	no	no	
Glibenclamide	above 6 years and adolescent	no	yes	yes	no	
Hydrochlorothiazide		no	no	no	no	
Ibuprofen	parenteral formulation	no[1]	yes	yes	yes	1
Itraconazole		no	yes	yes	no	
Levamisole		no	no	no	no	
Meropenem	below 3 months of age	no	no	no	no	
Metformin	See [2]	no	yes	yes	yes	2
Midazolam		no	no	no	yes	4
Milrinone		no	yes	yes	yes	2
Oxybutynin		no	no	no	no	
Propranolol		no	yes	yes	yes	2
Temozolomide	in children particularly below the age of 3 years	yes	no	no		
Topotecan		yes	yes	yes		
Unfractionated heparin		no	yes	yes	yes	2
Percentage "yes"		9/28=32%	14/28=50%	12/28=43%	8/19=42%	

Table 2 - EMA 2008 priorities for PK analysis

Legend Table 2: This table shows which of the medicines that were identified as a priority for pharmacokinetic (PK) evaluation by the EMA in 2008 were found to collect PK data in our study sample. We also assessed whether these medicines were still

present in the EMA 2009 and 2010 priority lists. Lastly, we searched titles of all 1081 trial records in our sample to assess for which EMA priority medicines trials were conducted without PK data collection (or it was not denoted in the record).

[1] One trial investigated ibuprofen pharmacokinetics, but in oral formulation.

[2] Data on PK and efficacy in DM II in children above the age of 6 years. Data on PK, efficacy and safety in small-for-gestational-age children with precocious/early/rapidly progressing puberty.

DISCUSSION

To our knowledge, this is the first study to report on the global activity of collection of pharmacokinetic data in clinical trials in children. It assessed all paediatric trials that were recruiting on 22 May 2009, as registered at clinical trial registries that are a part of the ICTRP registry network. Of 1081 records of trials researching medicines in children, one quarter reported that they would be collecting pharmacokinetic data. So is this a lot, or a little? In view of the current paucity of knowledge on safety and efficacy of children's medicines, the degree to which this knowledge is in arrears as compared to our understanding of adult medication, and the widespread prescribing of medicines to children, we would argue that it is not enough.

The fact that only one fifth of the records that mentioned collection of pharmacokinetic data also mentioned to be studying pharmacodynamics adds to this conclusion. Additionally, our analysis of the types of trials researching pharmacokinetics show that there might be significant pharmacokinetic research gaps in terms of geographical area, studied diseases and age categories. Over 75% of all studies recruited participants in Northern America, while recruitment in all other geographical regions was below 20%. This unequal distribution appears to exist for all paediatric drug trials, but especially for studies collecting pharmacokinetic data. Given the existence of interethnic differences in pharmacological effects on the body [21] and that many diseases are not prevalent in Northern America, this gap is a reason for concern. Similarly, the distribution of pharmacokinetic research across different ICD-10 disease categories suggests that the lacking knowledge of pharmacokinetics in children is only marginally addressed in some areas. Previous studies have shown that paediatric research in general often does not address priority research areas.[22, 23] Finally, although knowledge on pharmacokinetic profiles in children is at an inadequate level for all age groups, the least is known about pharmacokinetics in the youngest age group of neonates.[24, 25] This study shows that this age group, worryingly so, is also the least likely to be studied.

In addition, trials in our study sample were found to collect pharmacokinetic data only for one third of the medicines on the EMA priority list for studies into off-patent paediatric medicinal products.[20] Although our study investigated a cross-sectional sample of recruiting paediatric trials at one moment in time, one third seems like a low percentage to us. Taking also into consideration that a considerable amount of medicines endured to be priorities for research over several years, and that there were ongoing clinical trials in which pharmacokinetic properties of these medicines could potentially have been studied, this might suggest that more research on pharmacokinetic profiles in children is not only necessary, but also achievable.

The paediatric research community has much to gain from the inclusive database of clinical trials in children that the ICTRP search portal provides through its Clinical Trials in Children search filter.[26] Clinical trials registration allows for doctors and patients and their parents to inform themselves more adequately about trials open to recruitment.[27] It is likely to promote collaboration among researchers, by facilitating knowledge transfer on currently ongoing research, thus also preventing duplication of research.[28] Furthermore, it has the potential to contribute to establishing more reliable research evidence by aiding in the prevention of selective reporting and publication bias.[27, 29] Although the ethical and legal pressure to adequately report the results of clinical trials is increasing,[30] selective reporting and publication bias are still important problems.[31, 32] If all trials (and their outcomes) are registered before start of the trial, researchers that withhold publication of trial results or the original outcomes because of negative results can be held accountable.[30, 33, 34] Finally, clinical trials registration facilitates priority setting in paediatric research, identifying gaps between burden of disease and research efforts in different therapeutic areas.[35] This study confirms that analysis of clinical trials identified on the ICTRP database can be a powerful tool to comprehensively assess the amount of currently ongoing research in a particular research area.

The need for improved availability of and access to safe child-size medicines has received growing attention in recent years.[1, 36] WHO addresses this issue through its 'make medicines child size' campaign.[9] Other initiatives that promote trials on medicines in children include US and EU legislation.[13, 37] While these legislative measures are a positive development and have resulted in an increased number of trials being conducted in the paediatric population,[37, 38] they have not been

free from critique.[23, 39] Given how crucial pharmacokinetic research is in the creation of more knowledge on the safety and efficacy of medicines in children and the concerns that the present study raises on the amount of such research currently being conducted, it is of great importance that the collection of pharmacokinetic data in clinical trials in children continues to be monitored in the future. The Clinical Trials in Children search filter of the ICTRP offers a platform to do so.

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CONFLICTS OF INTEREST

DG is Coordinator of the International Clinical Trial Registry Platform (ICTRP) of the World Health Organization. CMAR and RFV have no conflict of interest to report.

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AUTHORS' CONTRIBUTIONS

RFV and DG designed the study, RFV collected the data, RFV, DG and CMAR analysed and interpreted the data, RFV wrote the first draft of the paper, CMAR and DG contributed to the writing of the paper, all agree with the manuscript's results and conclusions.

DATA SHARING STATEMENT

Dataset available from the corresponding author at roderik.viergever@lshtm.ac.uk .

WEB ONLY FILES

File name: Web Only file 1

Format: Excel (.xls)

Title of data: Medicines that were researched in trials that collected pharmacokinetic data

Description of data: This file describes the names of the medicines (drugs, biologicals or dietary supplements) as mentioned in the 257 trial records that reported collection of pharmacokinetic data.

FIGURE LEGENDS

Figure 1 – Collected pharmacokinetic (PK) data in paediatric drug trials

Legend Figure 1: Every first bar represents which pharmacokinetic data were reported as a primary outcome, every second bar those that were reported as a secondary outcome.

Figure 2 – Investigated health conditions or problems in trials that collected pharmacokinetic data

Legend Figure 2: -

Figure 3 – Investigated health conditions or problems per age group

Legend Figure 3: The graph on the top left displays the distribution of health conditions or problems studied in trials that recruited only newborn infants; the top right graph displays this information for trials that recruited only infants/toddlers; the middle left graph for trials that recruited only children > 2 years of age; the middle right graph for trials that recruited newborn infants and infants/toddlers; the lower left graph for trials that recruited infants/toddlers and children > 2 years of age; and the lower right graph for trials that recruited newborn infants, infants/toddlers, and children > 2years of age.

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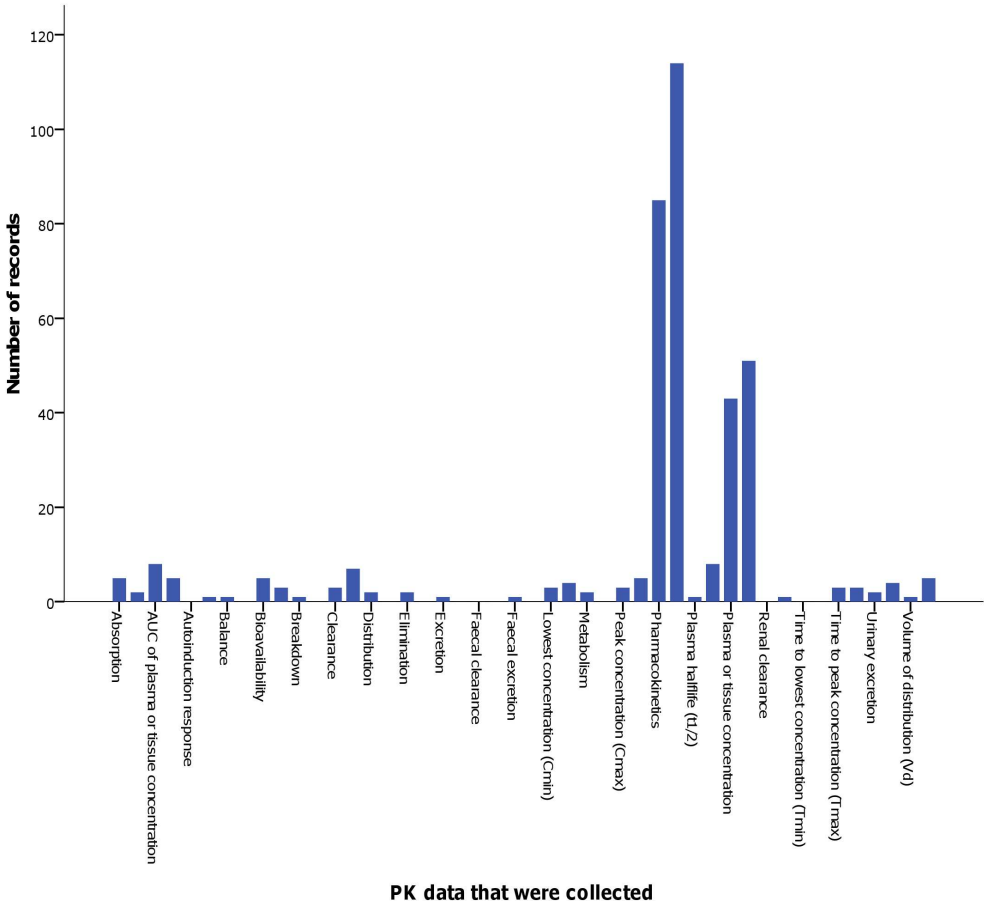

Figure 1 - Every first bar represents which pharmacokinetic data were reported as a primary outcome, every second bar those that were reported as a secondary outcome.

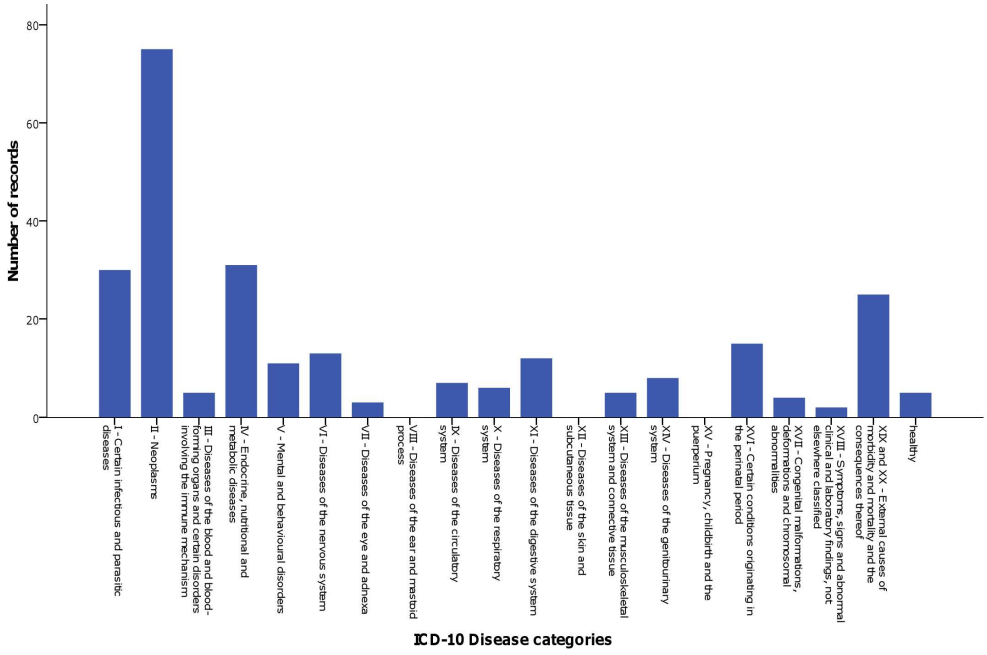

Figure 2

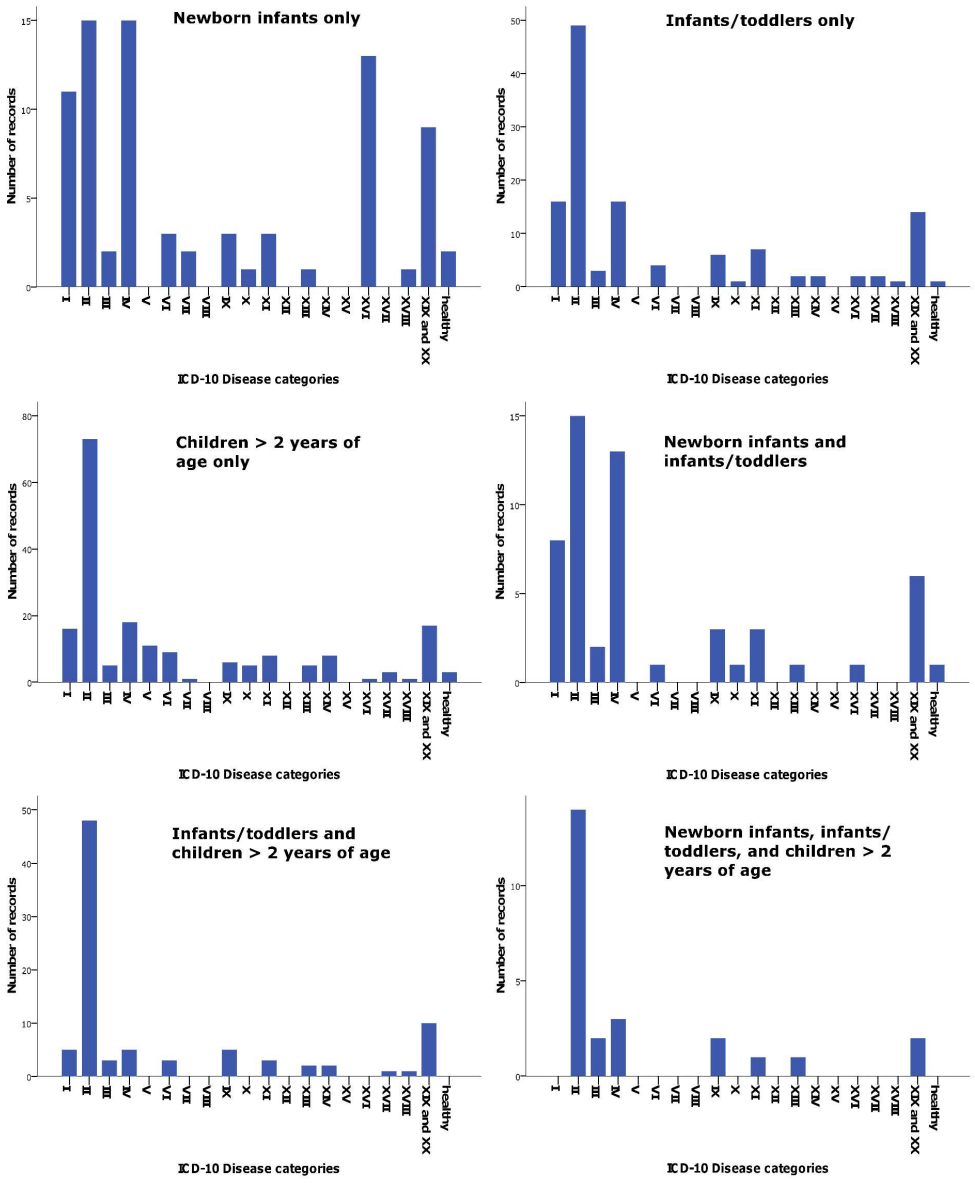

Figure 3 - The graph on the top left displays the distribution of health conditions or problems studied in trials that recruited only newborn infants; the top right graph displays this information for trials that recruited only infants/toddlers; the middle left graph for trials that recruited only children > 2 years of age; the middle right graph for trials that recruited newborn infants and infants/toddlers; the lower left graph for trials that recruited infants/toddlers and children > 2 years of age; and the lower right graph for trials that recruited newborn infants, infants/toddlers, and children > 2years of age.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of ~~participants~~ eligible records
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of ~~individuals~~ trial records at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram → deleted upon suggestion of peer-reviewer
Descriptive data	14*	(a) Give characteristics of ~~study participants~~ included trial records (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of ~~participants~~ trial records with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.