Simplifying Medicine Dosing for Children by Harmonizing Weight Bands Across Therapeutic Areas

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**An overview of the consulted expert panelists can be found in the Supplementary Material, pages 2 - 4.

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Summary

Generally, dose recommendations for children are expressed as fixed dosing increments related to body weight known as weight bands. The weight bands recommended by WHO vary between therapeutic areas, leading to complexity and potential dosing errors when treating children for multiple diseases simultaneously. The introduction of a harmonized weight banding approach for drugs administered orally across therapeutic areas may streamline dosing for young children, but implementing such an approach would require some changes in current dosing recommendations. In this work, we describe the process we undertook to (i) identify therapeutic areas for harmonization, (ii) propose a harmonized weight-banding system to align with current use of weight bands in antibiotics, and (iii) simulate the expected impact of dose-adjustments due to harmonization. Each step of this process, along with the impact and feasibility of weight band harmonization was discussed with clinical and pharmacology experts representing four therapeutic areas: tuberculosis, HIV, malaria and hepatitis. Updated dosing recommendations in harmonized weight bands could simplify treatment for children across disease areas and are being considered for therapeutic areas that currently are not dosing based on weight bands.

Key messages

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1. WHO guideline documents providing treatment recommendations for children currently do not use the same dosing principles which creates potential confusion and dosing errors when used together.

2. In this work, we investigate the feasibility of a harmonized weight banding system for pediatric TB, HIV, HCV, and malaria, that requires minimal changes from the current guidelines which would clarify and simplify dosing for children
3. Six WHO policy documents support dosing in weight bands were investigated. Simulations for 102 medicines were performed and discussed with a panel of clinical and pharmacology experts.
4. These discussions indicate that harmonized weight bands can be implemented, that use 5 kg increments above 10 kg and narrower bands for lower weights to accommodate non-linear scaling of body size. Investigating dosing based on weight and age is recommended or weights below 10 kg.
5. Positive feedback from expert panels and simulations suggests harmonized weight bands simplify treatment protocols, improving clarity and efficiency, particularly in LMICs where multiple medications may be combined to treat complex diseases, ultimately contributing to better health outcomes for children.
6. Support from WHO, pharmaceutical companies, and regulators is crucial for implementation, particularly for future medicines.

Background

Administering the appropriate dose to achieve optimal drug concentrations is critical to ensure safe and efficacious medicine-based treatment and prevention. This is particularly relevant in children, where body weight and age have a major impact on a drug's pharmacokinetics (the relationship between dose and achieved concentrations) and need to be carefully considered to ensure optimal drug exposures. The effect of age on pharmacokinetics is generally limited to the first 2 years of life, during which drug clearing organs and metabolic pathways mature, while after 2 years of age, drug exposure is primarily

93 determined by body size.[1] Thus, weight-based dosing has become the norm in the treatment of most
94 pediatric diseases, often with separate age dependent dosing for neonates and young infants.
95 Although no randomized study is available, evidence from several smaller explorative studies suggests
96 that dosing tables with predefined weight- or age-groups effectively reduce dosing errors and simplify
97 the dosing process compared to strategies that require calculations such as mg/kg body weight, or
98 dosing based on mg/m^2 body surface area.[2–8] In one study among 450 medication orders written by
99 doctors in a pediatric accident and emergency department in the United Kingdom, the prescription
100 dose-error rate for medications prescribed according to dosing tables by weight or age (n = 194) were all
101 prescribed correctly while the dose error rate was 9.4% (n = 256) for medicines prescribed without
102 dosing tables.[8] Moreover, dosing flexibility is often limited by the available formulations, usually tablets,
103 so even doses calculated based on mg/kg ultimately result in dose bands due to the necessary rounding.
104 The World Health Organization (WHO) guidance documents for dosing in children, which are used to
105 shape national treatment practices, especially in low- and middle-income countries,[9] often follow fixed
106 cut-off points that divide dosing into weight intervals called weight bands. WHO provides dosing
107 recommendations for many therapeutic areas (i.e. distinct fields of medical treatment focused on
108 specific diseases or conditions) including human immunodeficiency virus (HIV) tuberculosis (TB), malaria,
109 and hepatitis-C (HCV). Each of these employs different weight banding strategies for pediatric dosing
110 (i.e., different cut-offs between weight bands), leading to complexity and potential confusion when
111 treating multiple diseases (Figure 1). For example, when a child receives treatment for both HIV and
112 tuberculosis TB, which often occur together, dose changes happen at nine different weight intervals
113 between 3 to 25 kg.[10,11] This is because the WHO guidelines for TB and HIV use different weight bands,
114 so dose changes are required at different weights (Figure 1). Similarly, TB-preventive treatment is
115 recommended for children with HIV, and the same children are also at risk of acquiring malaria, bacterial
116 infections, or HCV.[12–14] These additional treatments follow, yet again, different weight banding strategies

and when combined, subsequent dose changes are introduced, further complicating the dosing process. Given that dosing errors can and do occur,[15,16] it is reasonable to expect that harmonization of weight bands would result in improved and more practical care for children.

The weight bands that are used for the different therapeutic areas mostly have their origin from mg/kg or mg/m^2 (body surface area) dosing adapted to pragmatic doses achievable with the available formulations. This raises a crucial question: Are the differences in cut-off points and the related dose changes strictly necessary to deliver optimal dosing of children, or would it be possible to harmonize the weight band cut-off points across therapeutic areas and still achieve similarly safe and efficacious treatment in all children?

To answer this question and with the aim to assess the feasibility of implementing a harmonized weight banding approach, the WHO Global Accelerator for Pediatric Formulations (GAP-f, https://www.who.int/initiatives/gap-f) convened a core team and engaged several stakeholders, including clinical and pharmacology experts and multiple WHO technical departments representing different therapeutic areas. In this contribution, we summarize and report the outcome of this process.

Description of the weight band harmonization project

Project Overview and Phases

This project was structured in two phases. In the first phase, the project team mapped out the current use of weight bands in WHO-recommended drug dosing across key therapeutic areas, i.e. bacterial infections, HIV, TB, malaria, hepatitis. Based on this overview, we propose a harmonized weight band framework for possible implementation. In the second phase, the team convened panels of clinical and pharmacokinetic experts from each therapeutic area to consult them on the feasibility of weight band harmonization. To facilitate the discussion, the core project team summarized the necessary information around pediatric drug dosing for each drug considered for harmonization. Whenever no

direct clinical experience was available for the proposed dosing of a drug, modeling and simulation was used to examine the expected impact on exposure that switching to harmonized weight bands would have. The results of the simulations were reviewed, discussed, and refined with the expert panels who evaluated any concerns regarding drug safety and efficacy arising from the expected changes in exposure.

Mapping Current use of Weight Bands in Pediatric WHO Guidance Documents

We identified and reviewed three documents that guide global drug-based treatment for children: the Essential medicines list for children,[17] the pocketbook for hospital care in children (hereafter referred to as 'the pocket book'),[18] and the handbook for integrated management of childhood illness (IMCI).[19] This review led to the identification of six priority areas, or policy documents, that recommend dosing in weight bands for drugs mostly taken orally and in an outpatient setting. These policy documents are: the weight banding tables of the pocket book, the WHO AWaRe (Access, Watch, Reserve) Antibiotic Book, (hereafter referred to as 'the antibiotic book'), and WHO policy documents on HIV, TB, malaria, and hepatitis C (HCV).[10,11,20–24] Combined, these documents recommend dosing for children in weight bands for 102 drugs, while other therapeutic areas currently do not use weight bands in their dosing recommendations.

An overview of the current recommendations using weight bands is provided in Figure 1. The pocket book, the antibiotic book, and the guidelines for pediatric HIV each use their own distinct weight banding system, which is consistently applied to all recommended drugs within the area. The guidance documents for Drug-susceptible tuberculosis (DS-TB) and rifampicin-/multidrug-resistant tuberculosis (RR-/MDR-TB) recommend weight bands that are uniform within each document but differ between the two indications. Separate weight bands are also applied specifically to levofloxacin monotherapy and

weekly isoniazid with rifapentine, both used as preventive treatment. On the other hand, dosing guidance for malaria and HCV have drug-specific weight bands.[10,11,20–24]

Besides weight, additional age-based rules for infants are included in most of the reviewed therapeutic areas, with separate dosing for children below 2 months of age in the pocket book for hospital care in children, below 4 weeks of age for infants with HIV, and below 3 to 6 months of age for specific medicines used for the treatment of MDR/RR- TB. The WHO treatment guideline for HCV does not recommend HCV treatment for children younger than 3 years.[21]

Proposed Harmonized Framework

Based on the review of the current guidelines, we proposed a harmonized weight band strategy that would be easy to adopt, because it aligns with the antibiotic book and the pocket book, and it is very similar to the weight bands used in malaria, HIV, and HCV. The weight bands are 3 to <6 kg, 6 to <10 kg, and subsequent weight band cut-off points every 5 kg thereafter (15, 20, 25 kg, and so on), with an upper weight limit of <45 kg, after which the adults' guidelines can be used. Within the framework, additional age-based dosing advice is recommended for young children in accordance with existing guidance in the therapeutic areas. The proposed harmonized weight bands start from 3 kg, which is the lowest weight used in the WHO policy documents, and it is also a weight cut-off at children (mostly neonates) will require specialized care, for which a harmonized approach may not be appropriate.

Feasibility of the harmonization - Methods

We examined the impact of dosing harmonization on the dosing recommendations from the 6 policy documents that were reviewed. We prioritized for inclusion in the harmonized framework medicines taken orally and given in an outpatient setting, where simplifying dosing may be more useful. This is

because harmonizing dosing of medicines with formulations that enable precise dosing (such as injectable medications administered by trained personnel in specialized settings), is expected to yield less benefit because dosing for these formulations can be titrated to an optimized dose for weight.[27]

To assess the impact of harmonization on drug dosing and evaluate the methods used for this analysis, unbiased expert panels were convened, including pharmacology and clinical experts for each therapeutic area. The experts were identified based on recommendations from the WHO technical departments and by reviewing recent literature for additional experts (the project team and expert panels are defined in the Supplementary Material, pages 2 - 4). Following the panel discussions, the WHO technical departments reviewed and provided feedback on the findings.

For all the drugs for prospective inclusion in the harmonized weight bands, we collected or generated information to support the discussion with the expert panels. As a first step, we identified medicines for which the dosing in the proposed harmonized weight bands is already in line with current dosing recommendations (by WHO or the United States Food and Drug Administration [FDA] drug labels) or has been previously investigated in a clinical trial.

For the other medicines where no alternative guidelines or direct clinical experience available, we employed population PK modeling and simulation to assess the changes in drug exposure related to the dose harmonization and allow the expert panel to consider safety and efficacy. For each medicine under investigation, we followed the assessment process as described in Figure 2. 1) We examined essential information to assess the feasibility of harmonization: identification of pharmacokinetic parameters (e.g. C_{max}, AUC) associated with drug efficacy and toxicity and population pharmacokinetic models capable of accurately predicting these parameters.[25–49] 2) We implemented the identified models (R software version 4.2.2 and the package Mrgsolve version 1.0.6) and used a representative virtual pediatric population[50] to simulate the drug exposures in 1-kg intervals using both the current dosing recommendations and alternative approaches using the harmonized weight bands. 3a) The doses for

the harmonized weight bands were defined assuming the use of current preferred-use formulations, aiming to match the drug concentration levels reached with current dosing recommendations. 3b) We also compared the simulated exposures with predefined reference values for safety and efficacy when these were clearly defined in the literature.[51] 4) We then consulted the expert panels for potential safety and efficacy concerns of the predicted drug exposures. More details about the process and simulated exposures for each drug, can be found in the report added in the Supplementary Material, pages 5 - 115.

Feasibility of the harmonization - Results

For 68 of the 102 investigated medicines, current dosing recommendations are already aligned with the proposed harmonized weight bands. For 5 medicines used for the treatment of HIV, the chosen harmonized weight band approach is in line with the FDA drug label, e.g. abacavir,[52] or has been previously investigated in a clinical trial, e.g., efavirenz,[53] so no additional simulations were required. (Figure 3). For the remaining 29 medicines, we simulated the changes in exposures and discussed with expert panels whether efficacy or safety could be affected. Table 1 shows an overview of the evidence supporting harmonization for the 34 medicines for which weight band harmonization would require dose changes. Some of these 29 drugs (e.g. isoniazid) required dosing simulations for multiple indications. The expert panels observed that for all but 2 of these medicines (piperaquine and dihydroartemisinin) the dose changes gave no cause for concern when dosed in proposed harmonized weight bands in combination with age-based dosing for young children. The expert panels agreed that harmonization towards the proposed weight banding system was feasible for the majority of the investigated medicines. The only exceptions were two medicines used in malaria treatment, for the malaria expert panel recommended that additional safety and efficacy data should be obtained, due to concerns regarding decreased exposure to dihydroartemisinin in the context of emerging drug

resistance, and increased exposure to piperaquine due to concerns about toxicity. A summary of panel discussions is available in the Supplementary Material, pages 7 -115.

Discussion

In this work, we have reviewed the use of pediatric weight band-based dosing in WHO guidance documents and mapped the differences between the recommendations for pediatric treatment with antibiotics, and for HIV, TB, HCV, and malaria. Based on this analysis, we proposed a harmonized weight banding system, simulated the impact of dose changes resulting from harmonization, and discussed its implications with expert panels representing each therapeutic area. The feasibility of harmonization was subsequently presented to WHO technical departments from each therapeutic area.

The proposed weight bands are 3 to <6 kg, 6 to <10 kg, and subsequent weight band cut-off points in 5-kg increments thereafter (e.g. 15, 20, 25 kg), with an upper weight limit of <45 kg. This weight banding system aligns with weight bands already used in the pocket book and the antibiotic book, which are widely implemented in healthcare facilities worldwide,[54] particularly for the most commonly prescribed drugs, such as antibiotics.[55] Minimal adjustments would be required for weight bands used in pediatric HIV, HCV, and malaria, while exposure simulations suggest that adequate drug exposures can be achieved for the changes needed in TB. The weight bands are narrower for the lower weight ranges to allow for more precise dosing, and from 10 kg of body weight it uses 5-kg increments which are easy to remember and may facilitate its implementation in clinical practice.

Our simulations showed that above 10 kg, dosing can easily be adapted to harmonized weight bands and is expected to cause only minimal changes in drug exposure. This result is consistent with

developmental pharmacokinetics.[56] Pediatric dosing needs to consider the relationship between an individual's characteristics such as body size and age, and the pharmacokinetic parameters which determine the exposure.[57] Most children weighing more than 10 kg have reached an age where drug elimination pathways have mostly matured, so the main effect that needs to be adjusted for is that of body size, which affects most drugs in a consistent and predictable manner.[56]

On the contrary, harmonizing dosing in younger children is more challenging, because unique drug elimination processes mature at varying rates in early infancy. In addition, at the lowest weights, relative weight differences within a weight band are larger, inevitably making differences in drug exposure within a weight band greater. For instance, a child weighing 6 kg might get the same dose as a child half its size with a weight of 3 kg. The proposed weight banding system uses two weight bands below 10 kg: 3 to <6 kg and 6 to <10 kg. Alternative weight banding systems were explored that have more weight bands below 10 kg, for instance, the 3 to <5 kg, 5 to <7 kg, and 7 to <10 kg weight bands as are used in MDR/RR-TB.[23] However, this would unnecessarily add complexity by adding a weight band and changing all doses of therapeutic areas that have so far only employed only two weight bands below 10 kg. In contrast, the currently suggested harmonized weight bands align with weight banding systems of the investigated therapeutic areas, requiring minimal adjustments for adaptation.

In any case, because of the high variability in young children weighing below 10 kg, using weight bands alone may not provide enough granularity for medicines with a narrow therapeutic range that require precise dosing. A solution that is already in use in some guidelines to guarantee accurate dosing for these youngest children is to dose based on both weight and age. Given that drug elimination in young infants is mostly affected by age rather than weight because of immature drug elimination pathways such as liver enzymes, the current guidance documents provide additional dosing instructions for children below a certain age, for example below 4 weeks old in HIV guideline documents,[11] or below 3 or 6 months for dosing of specific MDR-TB medicines.[10] Harmonizing the weight bands and retaining or

even extending dosing recommendations based on age for the youngest children aligns with pharmacological principles and provides sufficient flexibility to dose children safely and effectively. [251110]Neonates and even pre-term children are beyond the scope of this project, however, we recommend further standardization of general dosing principles should be explored for newborns.

Limitations and considerations

In our study we did not generate any clinical evidence on the adequacy of the dosing guidelines based on the new harmonized weight bands, but we rather relied on clinical evidence obtained from previous studies and used modelling and simulation to fill any gaps and support the expert panels with their recommendations.

It is important to note that simulations are inherently predictions and not direct clinical observations. However, population PK modelling is a well-established and US FDA-recommended method to inform drug dosing strategies, with a history of effectively predicting drug effects, and founded on knowledge of physiology, pharmacology, and evidence-based assumptions.[58] The accuracy of the predictions is determined by the reliability of the models used for simulation, so selecting the right models is pivotal in this process. For our project, we chose pooled analyses of robust clinical data including children with weights and ages spanning the whole weight range of the dosing tables, thereby minimizing extrapolations. For some medicines with only limited data available on the pharmacokinetics in young children, we used models with the same assumptions about the maturation profile of the drug that were used to establish the current doses in young children.[29,36,45] The fact that our goal was to compare exposures between the harmonized and current weight bands using the same model (as opposed to comparing exposures to therapeutic targets), puts less importance on the specific model selected, and

made the results of the comparison more robust. This is because, in a within-model comparison, the focus shifts on how the effects of body size and age (i.e. allometry and maturation) are accounted for within the model, which is an aspect that has extensively been studied and for which there is ample consensus.[56,59] For instance, if a model were to overestimate the exposure in a specific age/weight range of children, it would do so consistently on both sides of the comparison (original vs harmonized weight bands). In any case, the assumptions underlying the predictions were extensively discussed with each expert panel.

A possible approach would have been to compare the simulated exposures in each weight band to therapeutic targets for efficacy and toxicity, thus investigating if any values in any of the weight bands were of concern. However, such targets are often poorly defined, with no clear consensus available for most of the drugs in the investigation. The uncertainty regarding the therapeutic targets for each drug would have made the interpretation of the simulation results challenging, even more so because some of the current dosing recommendations are not necessarily consistent with these targets. Redefining optimal doses was beyond the scope of the current investigation, so we pragmatically chose to rather use the simulations to evaluate whether the drug exposures with the harmonized weight bands are comparable to those with the current recommendations.

One possible critique of using harmonized weight bands is that this might restrict the flexibility in dosing for future medications, as guidelines for new drugs will be constrained to fir into the harmonized weight bands. However, this has already been the case for pediatric HIV, TB, and HCV, where the dosing guidelines of any new agent has had to conform to existing weight banding systems of each therapeutic area, which are largely a legacy of those originally created for earlier treatments. For these therapeutic

areas, adopting the harmonized weight banding system is not expected to complicate future dosing more than adhering to currently used weight bands. On the other hand, for novel medicines that may have a narrow therapeutic window and for which the maturation pathways are still unknown, we acknowledge that it may be challenging to directly fit the pediatric dosing within the harmonized weight bands. Careful exploration of maturation pathways might be necessary in clinical trials before recommending dosing.

Any dosing system, including the use of weight bands, is a trade-off between achieving precise dosing, and what is practically feasible in the field. The ultimate objective of harmonization is to improve treatment and care for children. On a public health level, harmonization may provide benefits through greater clarity and simplification especially when multiple medicines need to be combined to treat a disease, such as is the case within each of the investigated therapeutic areas. On the other hand, there are situations where precision dosing is required and feasible, such as neonates, premature babies, and other scenarios where intensive or in-hospital care is delivered (e.g. children with TB meningitis). In these situations, precision dosing might be preferred over a harmonized dosing strategy. For this reason, dosing below 3 kg is not included in the harmonized weight bands. Similarly, dosing based on pharmacogenetic factors, malnutrition, or other specific circumstances should remain in the dosing recommendations, if it is required for effective treatment. The reviewed guideline documents and harmonized weight banding system that we propose are meant to provide a framework for situations that may benefit from it, they are not intended to prevent precise dosing where this is deemed necessary.

The positive feedback from the expert panels suggests a significant opportunity to streamline drug dosing practices by adopting harmonized weight bands for currently used medicines, and when

exploring new doses. In addition, harmonized weight bands are an opportunity for those areas that do not currently provide dosing in weight bands for children to explore dosing based the harmonized framework we propose. Even with our simulations restricted to current preferred-use formulations and doses, the simulations and discussions with expert panels revealed that, for all but two medicines, these changes are not expected to decrease safety or efficacy. Going forward, the implementation is expected to become even easier, if formulations and dosing strategies are designed directly to fit the proposed harmonized weight bands.

In addition, even though weight bands are used in international policies and in clinical practice, pediatric registration trials rarely implement weight bands when developing pediatric dosing.[60,61] Harmonized weight bands used across therapeutic areas and endorsed by regulatory agencies could encourage the pharmaceutical industry to adopt weight bands in drug development.

Conclusions

Our work demonstrates that a harmonized pediatric weight banding strategy across therapeutic areas is possible and provides sufficient flexibility for safe and effective pediatric dosing for treatment and prevention across therapeutic areas. The results have been shared with WHO and their technical advisory bodies for consideration. Further harmonization in the context of future therapeutic options in the pipeline will require a shift in the clinical development programs. Endorsement and support by pharmaceutical companies and regulators would allow the global community to implement the proposed harmonized weight bands and simplify pediatric care on the ground. This work represents a step towards a more integrated approach in pediatric clinical management in LMIC contributing to our shared global goal of better health outcomes for children in need.

Contributors

HW, RW, and PD developed the initial outline of the manuscript. HW coordinated coauthors inputs and developed the final version of the manuscript based on coauthor feedback. MP and WW initiated the project. All authors critically reviewed, revised, and approved the final draft of the manuscript. HW finalized the draft and coordinated the submission process.

Role of the funding source

The project was funded by the WHO's Global Accelerator for Pediatric Formulations (GAP-f). Study design, project management and the final report were all prepared in collaboration with GAP-f members and separate WHO technical departments.

Declaration of Interests

We declare no competing interests.

Tables and figures

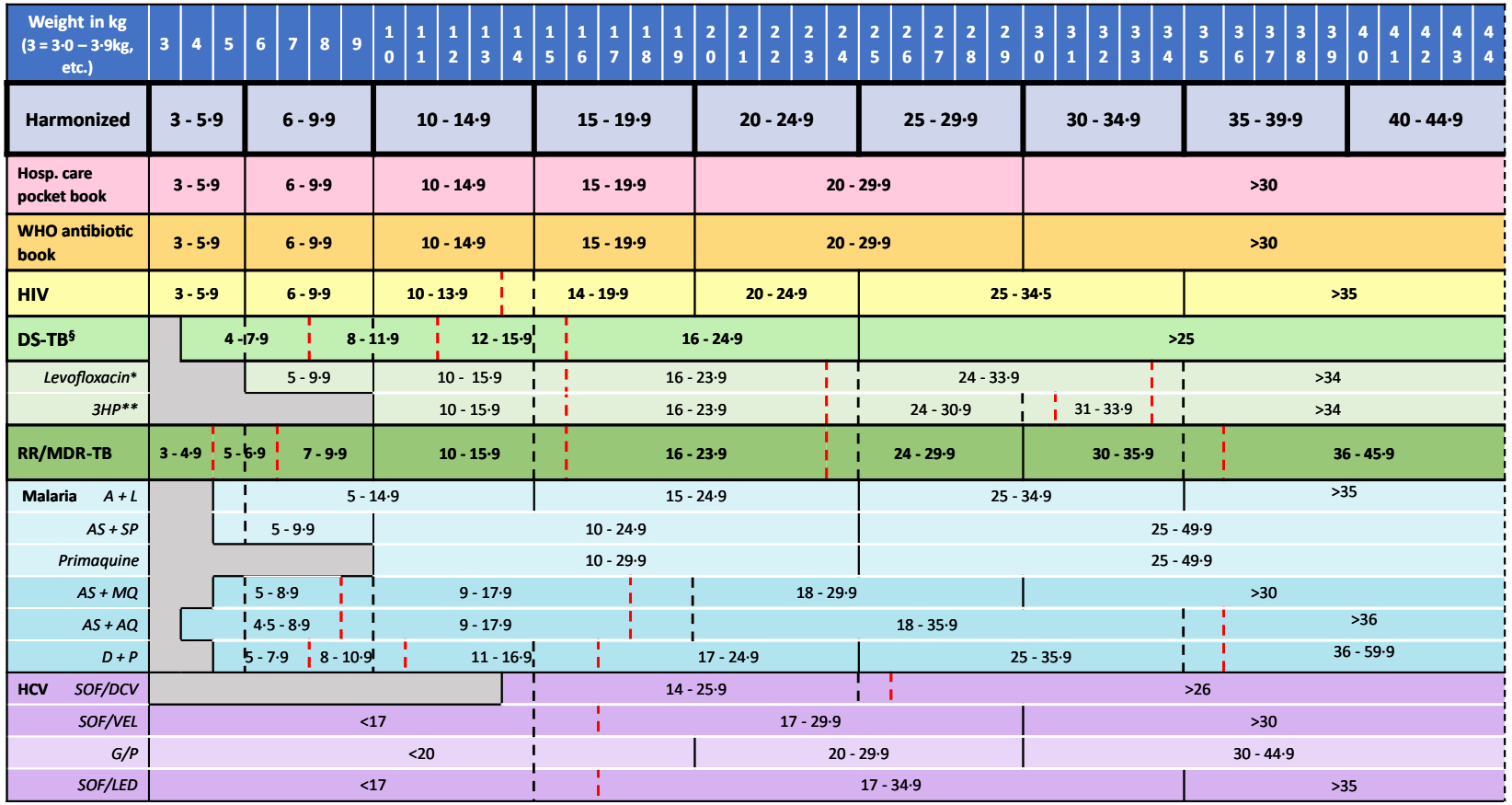

Figure 1. ***Differences between the proposed harmonized weight bands and weight bands within the Pocket Book for Hospital Care in Children, the WHO antibiotic book, and WHO dosing guidance for HIV, tuberculosis (TB), malaria, and hepatitis C (HCV).*** *Red dashed vertical lines represent weight bands that would be affected by harmonization and blue dashed vertical lines show where the weight band cut-off points would go to. If the dose over two weight bands is the same, no cut-off point is shown. §treatment and*

*prevention of drug susceptible tuberculosis (DS-TB);*levofloxacin for prevention of multidrug resistant tuberculosis (MDR-TB); **: three months of weekly rifapentine and isoniazid treatment for prevention of drug-susceptible tuberculosis (DS-TB). RR-TB: rifampicin resistant tuberculosis; A + L: artemeter + lumefantrine; AS + SP: artesunate + sulfadoxine/pyrimethamine; AS + MQ: artesunate + mefloquine; AS + AQ: artesunate + amodiaquine; D + P: dihydroartemisinin + piperaquine; SOF/DCV: sofosbuvir/daclatasvir; SOF/VEL: sofosbuvir/velpatasvir; G/P: glecaprevir/piprentasvir; SOF/LED: sofosbuvir/ledipasvir.*

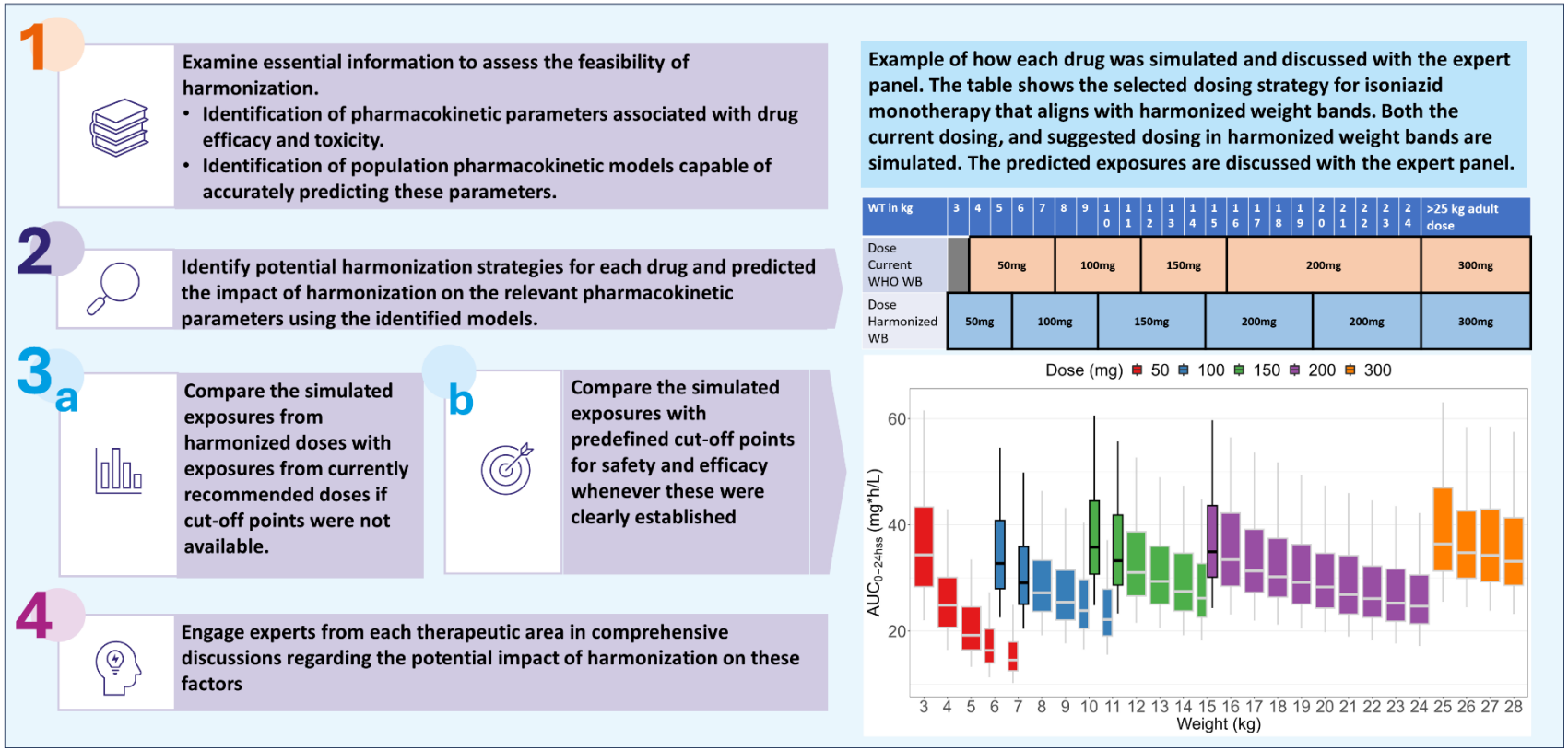

Figure 2. Overview of the drug assessment process. Drug exposures were simulated and discussed with expert panels for each drug that required additional evidence to support the discussion on the feasibility of dosing harmonization. The image and table used here are for illustrative purposes only, details on the methods and results can be found in the project report (Supplementary Material, pages 22 - 24).

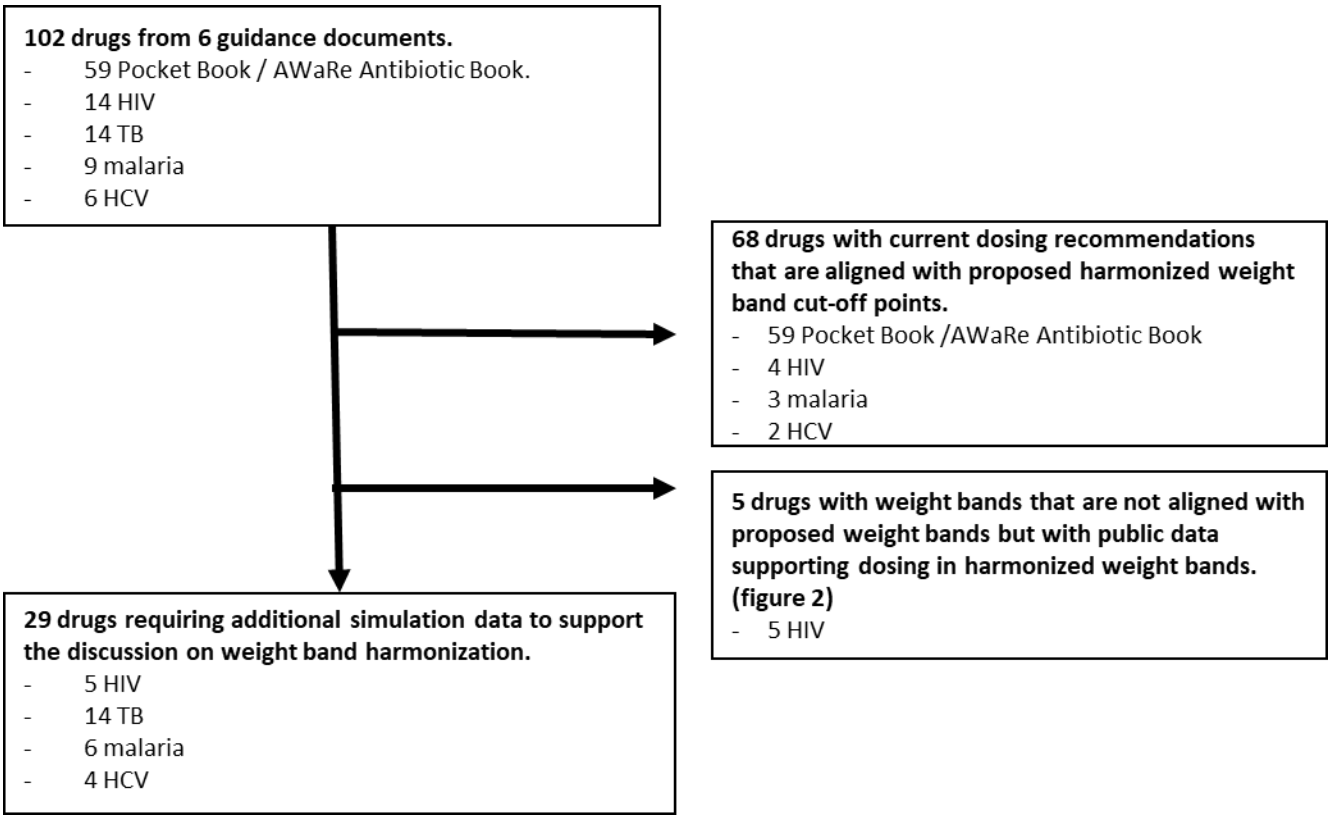

Figure 3. Flowchart showing different levels of evidence required for harmonization.

Table 1. Evidence required to support dosing in harmonized weight bands for medicines with current dosing in weight bands that are not aligned with proposed harmonized weight bands.

Therapeutic Area	Stage of Disease	Medicine	Assessment Method	Exposure Target	Reference(s)	Feedback Category
HCV	No difference between disease stages	Sofosbuvir/velpatasvir, Ledipasvir, Daclatasvir	Exposure simulations comparing current and harmonized doses	AUC, Cmax	[33–35]	No concerns for loss of efficacy or toxicity
	No difference between disease stages	Glecaprevir/pibrentasvir	Proposed harmonization does not change dosing recommendations	-	-	No dose change required
HIV	No difference between disease stages	Tenofovir alafenamide fumarate/tenofovir	Exposure simulations with minimum/maximum AUC targets	AUC	[62,63]	No concerns for loss of efficacy or toxicity
	No difference between disease stages	Tenofovir disoproxil fumarate, Atazanavir/ritonavir, Darunavir/ritonavir, Bictegravir	Proposed harmonization does not change dosing recommendations	-	-	No dose change required
	No difference between disease stages	Abacavir, Lamivudine, Emtricitabine, Zidovudine	Harmonized dose aligns with FDA recommendations	-	-	No concerns for loss of efficacy or toxicity
	No difference between disease stages	Efavirenz, Nevirapine	Published trial data or exposure target	AUC, Ctrough	[42,64]	No concerns for loss of efficacy or toxicity
	No difference between disease stages	Lopinavir/ritonavir, Dolutegravir, Raltegravir	Based on Ctrough target	Ctrough	[43,44,65,66]	No concerns for loss of efficacy or toxicity
Malaria	Malaria treatment	Amodiaquine, desethylamodiaquine, Artesunate, Mefloquine	Exposure simulations comparing current and harmonized doses	AUC, Cmax, Cday7	[25,67]	No concerns for loss of efficacy or toxicity
	Malaria treatment	Dihydroartemisinin	Exposure simulations comparing current and harmonized doses	AUC	Unpublished model, [67]	**Additional safety data recommended especially for children below 10 kg**
	Malaria treatment	Piperaquine	Exposure simulations with QT-prolongation parameter	AUC, Cmax, Cday7, QT	[26,27,68]	**Additional safety data recommended especially for children below 10 kg**
	Malaria treatment	Artemether, Lumefantrine, Primaquine, Sulfadoxine/pyrimethamine	Proposed harmonization does not change dosing recommendations	-	-	No dose change required
	SMC	Amodiaquine,	Exposure simulations comparing current and harmonized doses	AUC	[25]	No concerns for loss of efficacy or toxicity
	SMC	Sulfadoxine/pyrimethamine	Proposed harmonization does not change current dosing recommendations	-	-	No dose change required
Tuberculosis	DS-TB	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	Exposure simulations comparing current and harmonized doses	AUC	[49,69,70]	No concerns for loss of efficacy or toxicity
	TB-prevention	Rifapentine, Levofloxacin	Exposure simulations comparing current and harmonized doses	AUC	[40,71]	No concerns for loss of efficacy or toxicity
	MDR-TB/RR-TB	Clofazimine, Delamanid, Bedaquiline, Cycloserine, Ethionamide, Moxifloxacin, PAS	Exposure simulations comparing current and harmonized doses	AUC	[28–30,36,40,41,45,49,69–72]	No concerns for loss of efficacy or toxicity **when combined with age-based dosing for children below 10 kg**

Feedback Categories: No concerns for loss of efficacy or toxicity: Harmonized dosing achieves similar safety and efficacy as current dosing; No dose change required: Harmonization does not require changes to current recommendations; Additional safety data recommended: Further data is needed to confirm safety or efficacy in children.
Abbreviations: HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; SMC: Seasonal Malaria Chemoprevention; DS-TB: Drug-Sensitive Tuberculosis; MDR-TB: Multidrug-Resistant Tuberculosis; RR-TB: Rifampicin-Resistant Tuberculosis; AUC: Area Under the Curve (pharmacokinetic parameter); Cmax: Maximum Concentration of the drug in plasma; Cday7: Drug Concentration on Day 7; Ctrough: Trough Concentration (lowest concentration of drug before the next dose); QT: QT interval on an electrocardiogram (used to assess heart rhythm); FDA: Food and Drug Administration (United States)

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