

# Design, Evaluation, and Dissemination of a Plastic Syringe Clip to Improve Dosing Accuracy of Liquid Medications

GARRETT J. SPIEGEL,<sup>1</sup> CINDY DINH,<sup>1</sup> AMANDA GUTIERREZ,<sup>1</sup> JULIA LUKOMNIK,<sup>1</sup> BENJAMIN LU,<sup>1</sup> KAMAL SHAH,<sup>1</sup> TARA SLOUGH,<sup>1</sup> PING TERESA YEH,<sup>1</sup> YVETTE MIRABAL,<sup>1</sup> LAUREN VESTEWIG GRAY,<sup>1</sup> STEPHANIE MARTON,<sup>2</sup> MICHELLE ADLER,<sup>2</sup> GORDON E. SCHUTZE,<sup>2</sup> HADLEY WICKHAM,<sup>3</sup> MARIA ODEN,<sup>1</sup> and REBECCA RICHARDS-KORTUM<sup>1</sup>

<sup>1</sup>Rice 360°: Institute for Global Health Technologies, Rice University, 6100 Main St., Houston, TX 77005, USA; <sup>2</sup>Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; and <sup>3</sup>Department of Statistics, Rice University, 6100 Main St., Houston, TX 77005, USA

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**Abstract**—Pediatricians in Africa requested a tool to improve caregiver dosing of liquid antiretroviral medication. We developed, evaluated and disseminated a clip to control the amount of medication drawn into an oral syringe. In a laboratory, a user tested clips of different lengths, corresponding to different volumes, by drawing water into a syringe with a clip. In Texas and Malawi, 149 adults attempted to measure Pepto-Bismol™ using a syringe with a clip, a syringe without a clip, and a dosing cup, in a randomly assigned order. In the laboratory, the volume of liquid, ranging from 1 to 4.5 mL, drawn into the syringe was always within at least 5  $\mu$ L of the intended dose. In Texas, 84% of doses were accurate within  $\pm 10\%$ , vs. 63% using the syringe alone, and 21% with the dosing cup. In Malawi, 98% of doses were accurate to within  $\pm 10\%$ , vs. 90% using the syringe alone, and 27% with the dosing cup. For target accuracy values within  $\pm 45\%$  ( $\pm 21\%$ ), a significantly higher fraction of Houston (Kamangira) participants delivered an accurate dose using the syringe with the clip than with the syringe alone ( $p < 0.05$ ). The clip enables a greater proportion of users to accurately measure liquid medication.

**Keywords**—Dosing error, Measuring devices, Medication administration, Medication errors, Global health, Low-resource settings.

## INTRODUCTION

The Beyond Traditional Borders (BTB) initiative at Rice University is an undergraduate education

program in which students from all disciplines work collaboratively to use the engineering design process to develop technological solutions to challenges of health and healthcare delivery in the developing world.<sup>19</sup> These challenges are identified by healthcare providers working in low-resource settings.<sup>19</sup> In this paper, we describe the design, evaluation, and implementation of a syringe clip, a student-designed technology developed through this process to help improve the accuracy of dosing liquid medication. The syringe clip fits into the barrel of an oral dosing syringe to regulate the amount of liquid drawn into the syringe according to dosage. The syringe clip was tested in community settings in Houston, Texas, and Kamangira, Malawi. The syringe clip, which has dual application in the developed and developing worlds, has been licensed to private industry and implemented countrywide in Swaziland's National Prevention of Mother to Child Transmission (PMTCT) of HIV/AIDS program.

Studies in the developed world show that inaccurate dosing of liquid medication, particularly in the home-setting, is a common occurrence. Liquid medications are commonly used in the pediatric population; one study reported that more than 80% of children have received liquid acetaminophen by 6 months of age.<sup>8</sup> Most medications for children are administered by their parents or guardians, and a number of studies show that 40–60% of parents make errors when giving medications to their children.<sup>4,5,10,20,24</sup>

Dosing devices for oral medications include oral syringes, oral droppers, dosing spoons, and plastic medicine cups.<sup>11</sup> Even when such calibrated delivery

Address correspondence to Rebecca Richards-Kortum, Rice 360°: Institute for Global Health Technologies, Rice University, 6100 Main St., Houston, TX 77005, USA. Electronic mail: rkortum@rice.edu

devices are used, they do not eliminate inaccurate dosing. Recent studies in the developed world show that more than half of parents made errors in dosing with plastic dosing cups, primarily overdosing.<sup>21,26</sup> While several comparisons of dosage delivery devices have demonstrated that oral syringes are superior to other devices,<sup>13,21,26</sup> one study found that a large proportion of caregivers could not measure the proper amount of medication using either an oral dosing syringe or a dosing cup.<sup>21</sup> In addition, small markings on oral syringes can be difficult to read by users with limited visual acuity and can wash off after multiple uses. Studies in the developed world have shown that caregivers with low health literacy are at greatest risk for inaccurate dosing.<sup>25,26</sup>

Little is reported about caregiver dosing accuracy in the developing world. However, there are many studies that focus on adherence to antiretroviral medication for HIV-positive patients in the developing world. Young HIV-positive children receiving treatment and infants receiving treatment prophylaxis for the PMTCT of HIV/AIDS are often prescribed liquid antiretroviral medication, which is administered using an oral dosing syringe.<sup>15</sup> Dosing regimens, especially for HIV treatment, can be complex, requiring different volumes for each drug and the continual increase of the volume of the dose as the child grows.<sup>15</sup> For caregivers who are unfamiliar with liquid measurements or who are elderly with poor visual acuity, correct dosing can be a challenge.<sup>2,7,15</sup> Bagenda *et al.*<sup>2</sup> found that users of syrup formulations, particularly elderly or illiterate caregivers, had difficulty measuring precise dosing measurements using a calibrated syringe and/or cup, and that adherence to syrups is lower than adherence to tablets. Some studies find that caregivers in the developing world overestimate their children's adherence to antiretroviral medication.<sup>3,22</sup> Some physicians in the developing world have noted that if oral syringes are not available, patients use bottle tops, spoons, medicine caps, and other improvised tools for dosing,<sup>17</sup> which may exacerbate inaccurate dosing.

To address these concerns, in 2007, pediatricians prescribing liquid antiretroviral medication to HIV-positive children in Swaziland identified a need for a low-cost dosage delivery device for liquid drugs that could be preset by a health care professional and given to a caregiver to administer to a patient, regardless of the caregiver's visual acuity, manual dexterity, literacy, or numeracy skills. To address this need, students first designed a mechanical, metered dosing pump for liquid medications.<sup>16</sup> After receiving feedback on the design from physicians in the United States, Botswana, Malawi, and Rwanda,<sup>16</sup> a second team of students designed a simple syringe clip that can be inserted into a standard oral dosing syringe to limit the distance that

the plunger can be pulled back, dictating the amount of medication that can be drawn into the syringe. Different lengths of the clip correspond to different dosages of medication. The dosing clips are color-coded by dosage; when prescribing liquid medication to be delivered with an oral syringe, a physician can prescribe the color of clip that corresponds with the correct dosage. A pharmacist then includes this color of clip with the syringe when dispensing medication to the patient. In this paper, we describe an assessment of the accuracy of the dosing clip in a laboratory and community setting. We discuss efforts to disseminate the technology in low-resource settings.

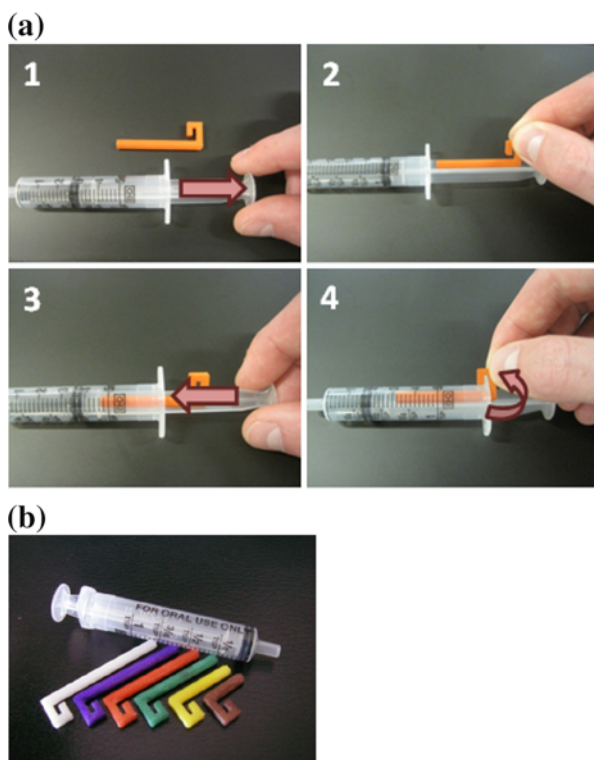
## MATERIALS AND METHODS

Standard oral dosing syringes are designed to deliver variable doses of liquid medication. In order to deliver the proper dose, the user must identify markings corresponding to the intended dose on the outside of the syringe barrel and pull the plunger back until the liquid level in the barrel matches the correct marking. We designed a plastic clip that can be inserted into a standard oral dosing syringe to simplify the process of delivering an accurate dose of medication. Clips used for this study were made from ABS plastic using a 3D-printer (SST 768, Dimension/Stratasys). Using this low-volume method of manufacture, clips can be produced for a materials cost of approximately \$0.23 per clip. At current production levels, the clips cost approximately \$0.10 per clip. By comparison, when the clips are mass produced, we anticipate that the price of the clips will change to \$0.02–\$0.05 per clip. Syringes can be purchased at a distributor discount of approximately \$0.35 per syringe; thus, the clips cost about one-third the price of the syringe. Because treatment regimens for antiretroviral medication often call for decreases in dosage over time, a combination of different syringe sizes would be required. Including syringes of all necessary sizes, rather than simply including clips at different lengths for a single syringe, would increase costs. Additionally, the tooling expenses required to make alternate lengths of clips is significantly lower than that required to build syringes of different volumes, and in some cases, the dosages are unusual volumes. It is therefore more economical to make many different lengths of clips than to make many different syringes.

Figure 1a shows a photo of the clip, which consists of two segments: a distal straight segment which is inserted into the barrel of the syringe, and a proximal C-shaped segment which clips over the neck of the syringe and holds the clip in place. To use the clip, a physician, pharmacist, nurse, health educator, or

caretaker inserts it into the barrel of the syringe and rotates the clip in order to secure it to the lip of the barrel. The distal tip of the clip limits the extent to which the plunger can be pulled back. Therefore, the length of the distal segment of the clip determines the dosage; clips can be color coded to indicate dose (Fig. 1b).

The accuracy of the dosage of medication that could be delivered using the clips was tested first in a laboratory setting. Eight lengths of clips, representing eight intended doses ranging from 1.0 to 4.5 mL in 0.5 mL increments, were tested by a single user. For each intended dose, four clips were tested. In the test, the same clip was inserted into three different oral syringes, and water was drawn into each syringe three times, for a total of nine trials per clip, or 36 trials per dose. The weight of water drawn into the syringe for each trial was measured using a balance. The volume of the delivered dose was then calculated using the known density of water.



**FIGURE 1.** (a) The process of inserting the dosing clip into a standard oral dosing syringe. (1) The plunger is pulled back; (2) the clip is placed alongside the plunger; (3) the plunger and clip are pushed into the syringe barrel until the C-shaped upper segment of the clip reaches the lip of the barrel; (4) the clip is rotated to lock the clip into place. With the clip in place, the syringe plunger can only be pulled back until it reaches the distal tip of the clip. (b) The length of the distal segment of the clip determines the dose which can be delivered; clips are color coded and labeled according to dose.

The performance of the clips was then compared to standard oral dosing syringes and cups in community settings in Houston, Texas, and Kamangira, Malawi. The study was reviewed and approved by the Institutional Review Board at Rice University. In Houston, 89 adults attending a health fair at a YMCA were recruited to participate in the study; all participants gave written informed consent. Participants completed an anonymous questionnaire to collect demographic information, including age and highest level of completed education. In Malawi, village elders recruited 60 interested adults to participate; 49 had never measured liquid medication before. Due to comparatively low literacy levels, all participants gave informed consent and answered selected survey questions verbally in the local language of Chichewa. For each participant, an investigator or translator read identical instructions and demonstrated proper measurement of a 2.5 mL dose of liquid using each of the three dosing methods: a standard 5 mL oral dosing syringe with a clip, a standard 5 mL oral dosing syringe without a clip, and a standard oral dosing cup. In Houston, a standard 15 mL commercially available liquid medication dosing cup was used, and in Malawi, a standard 10 mL dosing cup was used, reflecting the current stock of the local hospital. The 2.5 mL dose was selected because it is a mid-range dose for the 5 mL oral dosing syringe and within range for pediatric dosing. After watching the demonstration, participants were then asked to measure a 2.5 mL dose of Pepto-Bismol™ using the three dosing methods; the order in which participants completed the three tasks was randomly assigned. Pepto-Bismol™ was used due to its higher viscosity to simulate medications such as Kaletra, a standard antiretroviral medication for children in developing countries. The amount of liquid was weighed and recorded for all dosing methods; the volume of the delivered dose was calculated using the density of the liquid.

## RESULTS

Table 1 compares the intended dose and the dose delivered using the clips in a laboratory setting. Using the dosing clips, the volume of water drawn into the syringe was within 5  $\mu$ L of the intended dose for all doses tested. This finding held across all combinations of clips and syringes.

Eighty-nine participants from Houston and 60 participants from Kamangira were recruited to participate in the study in the community setting; participants ranged in age from 18 years old to >70 years old (Fig. 2). Table 2 shows the average, SD, range of the dose of Pepto-Bismol™ for each dosing method in each participant group. On average, the dose delivered using the oral dosing syringe, either with or without a

dosing clip, was closest to the intended dose. The use of the dosing clip was associated with least variation in delivered dose, as assessed both by the SD and the range of the delivered dose. When using the syringe with a dosing clip, no participants delivered a dose greater than 2.55 mL. In contrast, when using the syringe alone, some participants delivered a dose of almost double the intended dose (4.66 mL). For both study populations, the average dose delivered using the dosing cup was furthest from the intended dose. The dosing cup was associated with the greatest variation in delivered dose for both groups, with some participants delivering more than five times the intended dose (14.16 mL).

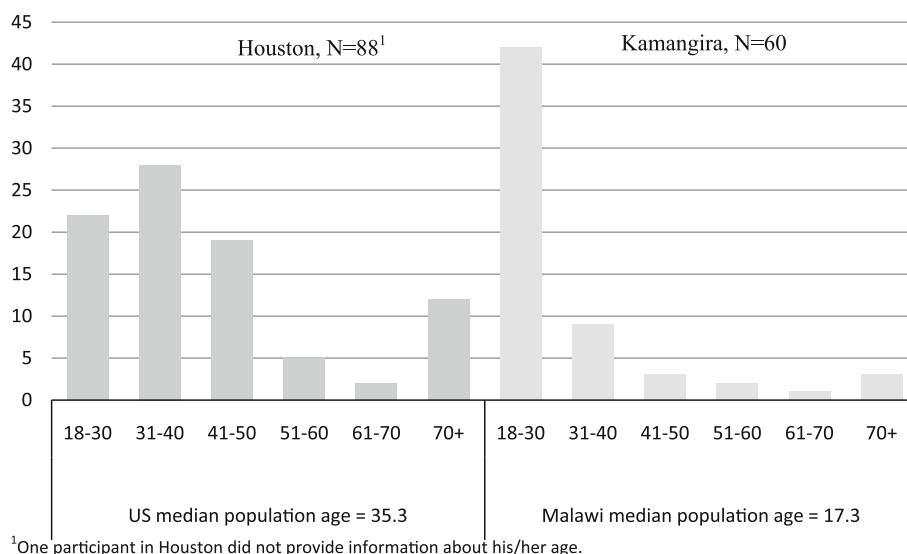
Figure 3a shows a cumulative frequency plot indicating the fraction of Houston participants who delivered a volume of Pepto-Bismol™ less than or equal to the dose indicated. The dotted line shows the expected step-function result if all participants had delivered the correct dose of 2.50 mL. Figure 3b shows a similar cumulative frequency plot for the Kamangira population. Results for both groups indicate that doses delivered with the dosing clip are most similar to the ideal result.

**TABLE 1. The average dose ( $\pm 1$  SD) delivered using dosing clips vs. intended dose measured in a laboratory setting.**

Intended dose (mL)	Measured dose (mL)
1.0	1.001 $\pm$ 0.004
1.5	1.501 $\pm$ 0.004
2.0	2.002 $\pm$ 0.004
2.5	2.500 $\pm$ 0.003
3.0	3.001 $\pm$ 0.003
3.5	3.500 $\pm$ 0.003
4.0	3.999 $\pm$ 0.004
4.5	4.504 $\pm$ 0.003

A  $\chi^2$  test with correction for cells with fewer than five entries was used to assess whether differences in the fraction of participants achieving the target accuracy (in terms of % error) were statistically significant<sup>9</sup>; results are shown in Figs. 4a and 4b. Differences in accuracy associated with the dosing cup were statistically significant at all accuracy thresholds. For target accuracy values less than or equal to  $\pm 45\%$ , a significantly higher fraction of Houston participants could deliver an accurate dose using the syringe with the clip than using the syringe alone ( $p < 0.05$ ); for target accuracy values of less than or equal to  $\pm 21\%$  a significantly higher fraction of the Kamangira participants delivered an accurate dose using the syringe with the clip compared to the syringe alone ( $p < 0.05$ ).

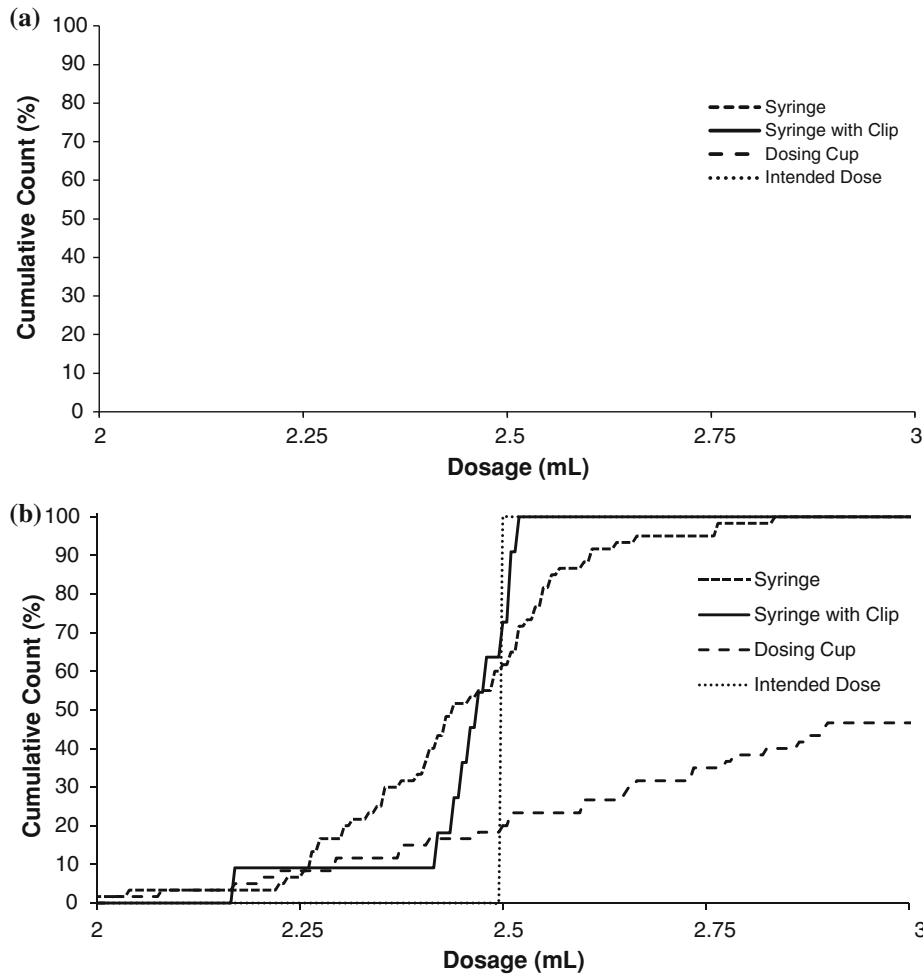
The target accuracy for our clip is the set dose of  $\pm 10\%$ , consistent with other studies of dosing accuracy, which ranged from  $\pm 4$  to  $20\%$ .<sup>13,21,24,26</sup> We evaluated the percentage of participants who prepared a dose within these limits (Fig. 5). Using the dosing clip resulted in 84% of doses in the target range of  $2.5 \text{ mL} \pm 10\%$  for the Houston participant group. Within this same group, only 63% drew the target dose with the oral syringe alone and 21% met this target with the dosing cup. In addition, with the dosing clip in place, the maximum volume of Pepto-Bismol™ that any participant measured was 2.50 mL, indicating that the dosing clip did not allow more than the intended liquid to be drawn into the syringe. In contrast, using the dosing syringe alone, more than 10% of participants drew more than 2.5 mL into the syringe, with a maximum of 4.66 mL. In the Kamangira study group, using the dosing clip resulted in 98% of doses in the target range of  $2.5 \text{ mL} \pm 10\%$ . Within this same group, 90% drew the target dosage of Pepto-Bismol™ using the oral syringe alone; only 27% met this target with the dosing cup



**FIGURE 2. The number of participants by age range (in years).**

**TABLE 2. Average ( $\pm 1$  SD) and range of doses of Pepto-Bismol™ for each dosing method measured in a community setting.**

Pepto-Bismol™ 2.5 mL target dose	Houston		Kamangira	
	Average dose (mL)	Range (mL)	Average dose (mL)	Range (mL)
Syringe	2.37 $\pm$ 0.47	1.08–4.66	2.43 $\pm$ 0.16	1.90–2.82
Syringe with clip	2.39 $\pm$ 0.11	1.92–2.50	2.47 $\pm$ 0.05	2.15–2.55
Dosing cup	4.44 $\pm$ 3.63	0.96–14.16	3.19 $\pm$ 0.80	2.01–5.87



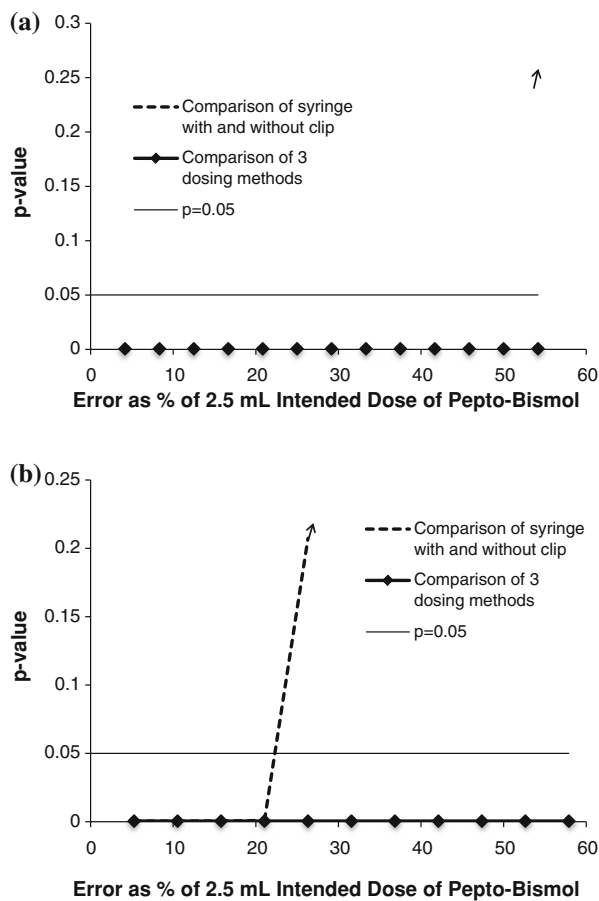
**FIGURE 3. The cumulative count (as a percentage of the total) of the (a) Houston and (b) Kamangira participants' measured doses of Pepto-Bismol™. For each delivery method, the graph shows the percentage of participants delivering a volume less than or equal to the dose indicated. The dotted curve labeled 'Intended Dose' represents an ideal population response where the entire population delivers a dose of 2.5 mL.**

(Fig. 5). With the dosing clip in place, the maximum volume of Pepto-Bismol™ that any participant in this subgroup measured was 2.55 mL. However, when using the dosing syringe alone, 35% of participants drew more than 2.5 mL into the syringe, with a maximum dose of 2.82 mL.

### DISCUSSION

Misdosing liquid medications has potentially serious consequences. For prescription medications, such as

antiretroviral medication, the ramifications of inaccurate dosing of liquid medications could be even more serious. For HIV-positive and exposed patients, consistently excellent adherence to drug regimens is required for viral suppression, the prevention of resistance, disease progression, and death,<sup>14</sup> and effective prophylaxis. This is a special concern in the PMTCT of HIV/AIDS, as children are provided semi-daily doses of liquid antiretrovirals for an extended period of time. In 2010, the World Health Organization presented new guidelines for PMTCT which state



**FIGURE 4.** *p* value for comparison of dosing accuracy (in terms of % error) of all three methods (solid line) and syringe without clip vs. syringe alone (dashed line) with Pepto-Bismol™ for (a) Houston and (b) Kamangira. At all target accuracy values, the dosing cup was significantly less accurate than the syringe with or without the clip. For target accuracy values less than or equal to  $\pm 45\%$ , a significantly higher fraction of Houston participants could deliver an accurate dose using the syringe with the clip than using the syringe alone; for target accuracy values less than or equal to  $\pm 21\%$  a significantly higher fraction of the Kamangira participants delivered an accurate dose using the syringe with the clip compared to the syringe alone.

that all infants born to HIV-positive women should receive nevirapine (NVP) or zidovudine (AZT) for 4–6 weeks. If the mother is not on antiretroviral therapy and is breastfeeding, exposed infants should receive NVP until 1 week after exposure to breastfeeding ceases. Non-breastfeeding exposed infants should receive NVP or sd-NVP and AZT for 4–6 weeks.<sup>1</sup>

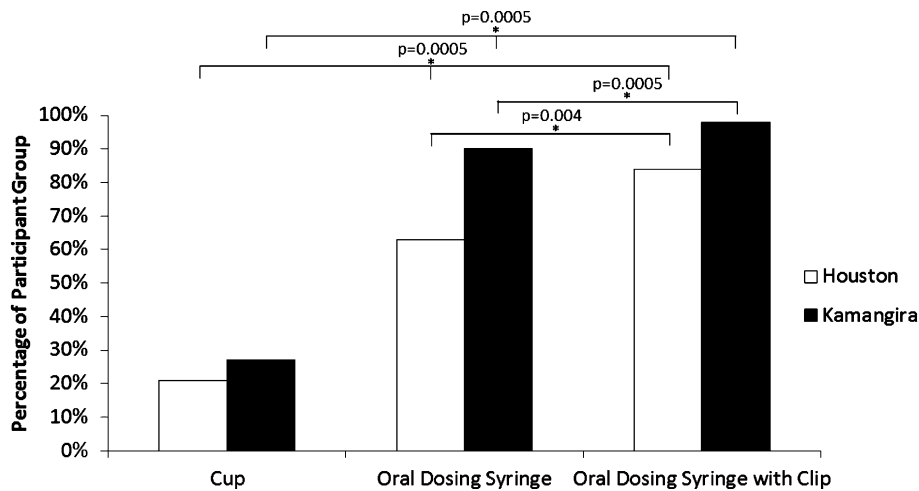
Most studies of inaccurate caregiver dosing have been performed in developed world settings. These studies have found that inaccurate dosing occurs for a number of reasons. Caregivers who have low health literacy are at greatest risk for inaccurate dosing.<sup>25,26</sup> One study in India that examined the dosing accuracy of parents using an etched dosing cup, 1 mL medicine dropper, and

a 5 mL syringe found that lower educational attainment was associated with dosing errors for these devices.<sup>18</sup> In addition, studies focused on antiretroviral adherence for children in the developing world have identified as barriers to adherence poor socio-economic circumstances and low literacy.<sup>3,22</sup> Mills *et al.*<sup>14</sup> reported that two barriers to antiretroviral adherence reported by adult patients in the developing world are difficulty understanding the treatment instructions and complicated regimens. Malawi<sup>12</sup> has a relatively low literacy rate (74% of adults can read). 98% of middle school students in Malawi fail to demonstrate skills beyond basic numeracy.<sup>23</sup> These conditions may impose additional limitations upon health literacy and decrease caregivers' ability to adhere to accurate dosing.

Additionally, accidental overdoses in the developed world have been attributed, in part, to markings on dosage devices that are misleading or incompatible with labeled dosing directions.<sup>6</sup> A recent study showed that 74% of 200 top-selling pediatric oral liquid over-the-counter medications were packaged with measuring devices<sup>27</sup>; 98.6% of these products had inconsistencies between the medication's dosing directions and markings on the dosage delivery device.<sup>27</sup> To address the lack of standardized measuring devices and labeling directions, the US Food and Drug Administration issued voluntary industry guidelines regarding dosage delivery devices for over-the-counter liquid drug products in late 2009.<sup>6</sup> FDA recommendations state that over-the-counter drugs should include a dosage delivery device, dosage delivery devices should be clearly calibrated and consistent with the product's directions, and dosage devices should include only necessary markings and not be substantially bigger than the largest intended dose. In addition, the FDA recommends that usability studies be performed to confirm accurate use by consumers.<sup>6</sup>

There is surprisingly little information available about effective strategies to reduce dosing errors. Yin *et al.*<sup>24</sup> demonstrates that pictogram-based instruction sheets could reduce medication dosing errors. In 83 families randomized to receive standard counseling or a pictogram-based intervention, the fraction observed to draw up more than 20% above or below the prescribed dose dropped from 47.8% with standard counseling to 5.4% with pictogram-based intervention. McMahon *et al.*<sup>13</sup> showed that marking an oral dosing syringe with a line at the correct dose and demonstrating its proper use increased the number of patients receiving the correct dose. In this study, 90 families were randomized to one of three groups: the first received a prescription for liquid medication and verbal dosing directions; the second received the prescription, an oral dosing syringe, and a demonstration; and the third received the prescription, an oral dosing

## Plastic Syringe Clip to Improve Dosing Accuracy



**FIGURE 5.** The percentage of participants who delivered a Pepto-Bismol™ dose of 2.5 mL  $\pm$  10% with each dosing method ( $*p < 0.05$ ).

syringe marked at the correct dose, and a demonstration. Only 11% of caregivers in the first group were observed to draw up the correct dose ( $\pm 4\%$ ) at a follow up visit, while 83 and 100% of caregivers drew up the correct dose in the second and third groups, respectively. Moreover, Frush *et al.*<sup>4</sup> showed that color-coding regions of the dosing syringe to match directions for dosing improved accuracy. Here 101 caregivers visiting a pediatric emergency room were randomized to two groups, and asked to demonstrate dosing oral over-the-counter medication using either conventional dosing instructions or the color-coded method. The average deviation from the recommended dosage was 25.8% in the group receiving conventional dosing directions, compared to 1.7% for the group receiving color-coded directions.

The purpose of this study was to evaluate a new dosing clip to improve dosing accuracy with an oral dosing syringe. We found that the simple addition of a dosing clip to a standard oral dosing syringe increases substantially the fraction of participants who can deliver the correct dose of liquid medication; however, the clip appears to underdose patients on average. The use of the dosing clips increased both the accuracy and the precision of dosing liquid medications in both the Houston and the Kamangira populations. Surprisingly, the Malawian population measured liquid medication more accurately than the Houston study group despite comparatively lower levels of literacy and numeracy. This may be attributed to different cultural norms; the Malawian participants were noticeably eager to impress researchers who were guests in their village. Participants followed the verbal instructions as closely as possible. The impact of the dosing clip in this study is consistent with other

interventions to improve dosing accuracy. Using a similar definition of correct dose as McMahon *et al.*,<sup>13</sup> we found that 21% more participants in Houston and 8% more in Malawi could deliver the correct dose of Pepto-Bismol™ using a dosing syringe with a dosing clip compared to using an oral dosing syringe alone.

There are limitations to our study. We did not test the dosing clips in settings where a caregiver is dosing medication for a child or with repeated use. While we have not undertaken an exhaustive study of how the clip responds to washing, removal, or reinstallation, we have removed and reinstalled the clips hundreds of times in the laboratory. The clips have not broken, nor is accuracy affected. Breakage with removal and reinstallation has also not been noted as a problem in Swaziland, where more than 200,000 clips have been distributed over the course of 18 months.

Our sample size was not large enough to permit subanalysis based on age in each population. Further, the populations in each location are not especially well matched, largely due to the demographic differences between the Americans and the Malawians; the median age of the participants in the United States is 35.3 years old, while in Malawi the median age of participants is 17.3 years old. The clips were designed to fit 5.0 mL oral dosing syringes manufactured by Becton–Dickinson and were thus tested with these syringes only; however, the clips could be adjusted to fit oral dosing syringes with larger or smaller maximum volumes, or from other manufacturers. The clips are incompatible with syringes that have solid plunger rods. The clips are labeled to indicate the syringes they are intended to be used with.

In summer 2010, undergraduates in the BTB initiative traveled to Swaziland as international interns.

They were given the task of demonstrating the syringe clips to clinicians to gather feedback on the design. While they were there, they demonstrated the syringe clips to physicians, pharmacists, non-governmental organizations, and the Ministry of Health in Swaziland. As a result of the students' presentation, the Ministry of Health, in collaboration with the Clinton Health Access Initiative, ordered approximately 213,000 clips for use in the country's PMTCT program, which had recently been revised to include a more efficacious prophylaxis regimen. Compatible syringes were also provided as part of the program. The clips were delivered in spring 2011 and are now being used by more than 11,000 mothers to accurately dose liquid antiretroviral medication for their infants to prevent the transmission of the disease. The clips have been licensed to 3rd Stone Design, a private industry partner in San Francisco, California. 3rd Stone Design is selling the clips with preferred pricing for developing countries. Initially, partnerships with NGOs providing care in low-resource settings provide an entry point for clip dissemination. Moreover, the clips may be useful in high-resource settings, and proceeds from sales in these settings could further support dissemination of the clips in low-resource settings. Initial reports on the use of the clips in Swaziland have been positive, and in fall 2012, another order was placed for the clips for use in the PMTCT program in Swaziland.

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### CONFLICT OF INTEREST

Drs. Richards-Kortum, Oden, Ms. Dinh, Ms. Gutierrez, and Ms. Lukomnik submitted a patent application for the dosing clip described in this paper. Drs. Richards-Kortum and Oden have waived their financial interest in this patent.

### REFERENCES

<sup>1</sup>Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants: Recommendations for a Public Health Approach. World Health Organization. 2010. [http://whqlibdoc.who.int/publications/2010/9789241599818\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf). Accessed November 4, 2012.

- <sup>2</sup>Bagenda, A., L. Barlow-Mosha, D. Bagenda, R. Sakwa, M. G. Fowler, and P. M. Musoke. Adherence to tablet and liquid formulations of antiretroviral medication for paediatric HIV treatment at an urban clinic in Uganda. *Ann. Trop. Paediatr.* 31:235–245, 2011.
- <sup>3</sup>Davies, M. A., A. Boule, T. Fakir, J. Nuttall, and B. Eley. Adherence to antiretroviral therapy in young children in Cape Town, South Africa, measured by medication return and caregiver self-report: a prospective cohort study. *BMC Pediatr.* 8:34, 2008.
- <sup>4</sup>Frush, K. S., X. Luo, P. Hutchinson, and J. N. Higgins. Evaluation of a method to reduce over-the-counter medication dosing error. *Arch. Pediatr. Adolesc. Med.* 158(7):620–624, 2004.
- <sup>5</sup>Gribetz, B., and S. A. Cronley. Underdosing of acetaminophen by parents. *Pediatrics* 80(5):630–633, 1987.
- <sup>6</sup>Guidance for industry: dosage delivery devices for OTC liquid drug products. US Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM188992.pdf>. Accessed on November 15, 2010.
- <sup>7</sup>Haberer, J., and C. Mellins. Pediatric adherence to HIV antiretroviral therapy. *Curr. HIV/AIDS Rep.* 6:194–200, 2009.
- <sup>8</sup>Hawkins, N., and J. Golding. A survey of the administration of drugs to young infants. The Alspac Survey Team. Avon Longitudinal Study of Pregnancy and Childhood. *Br. J. Clin. Pharmacol.* 40:79–82, 1995.
- <sup>9</sup>Hope, A. C. A. A simplified Monte Carlo significance test procedure. *J. R. Stat. Soc. B* 30:582–598, 1968.
- <sup>10</sup>Li, S. F., B. Lacher, and E. F. Crain. Acetaminophen and ibuprofen dosing by parents. *Pediatr. Emerg. Care* 16(6):394–397, 2000.
- <sup>11</sup>Madlon-Kay, D. J., and F. S. Mosch. Liquid medication dosing errors. *J. Fam. Pract.* 49:741–744, 2000.
- <sup>12</sup>Malawi—Statistics. The United Nations Children's Fund. [http://www.unicef.org/infobycountry/malawi\\_statistics.html](http://www.unicef.org/infobycountry/malawi_statistics.html). Accessed on November 4, 2012.
- <sup>13</sup>McMahon, S. R., M. E. Rimsza, and R. C. Bay. Parents can dose liquid medication accurately. *Pediatrics* 100(3 pt 1):330–333, 1997.
- <sup>14</sup>Mills, E. J., J. B. Nachega, D. R. Bangsberg, S. Singh, B. Rachlis, *et al.* Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. *PLoS Med.* 3(11):2039–2064, 2006.
- <sup>15</sup>Nahiryra-Ntege, P., A. Cook, T. Vhembo, W. Opilo, R. Namuddu, *et al.* Young HIV-infected children and their adult caregivers prefer tablets to syrup antiretroviral medications in Africa. *PLoS ONE* 7(5):1–8, 2012.
- <sup>16</sup>Oden, M., Y. Mirabal, M. Epstein, and R. Richards-Kortum. Engaging undergraduates to solve global health challenges: a new approach based on bioengineering design. *Ann. Biomed. Eng.* 38(9):3031–3041, 2010.
- <sup>17</sup>Phelps, B. R., and N. Rakhmanina. Antiretroviral drugs in pediatric HIV-infected patients: pharmacokinetic and practical challenges. *Pediatr. Drugs* 13(3):175–192, 2011.
- <sup>18</sup>Ravikiran, S. R., and Y. M. Shivarajashankara. Dosing ability of Indian parents for liquid medication. *Indian Pediatr.* 48:153–154, 2011.
- <sup>19</sup>Richards-Kortum, R., L. V. Gray, and M. Oden. Engaging undergraduates in global health technology innovation. *Science* 336:430–431, 2012.
- <sup>20</sup>Simon, H. K., and D. A. Weinkle. Over-the-counter medications: do parents give what they intend to give? *Arch. Pediatr. Adolesc. Med.* 151(7):654–656, 1997.



- <sup>21</sup>Sobhani, P., J. Christopherson, P. J. Ambrose, and R. L. Corelli. Accuracy of oral liquid measuring devices: comparison of dosing cup and oral dosing syringe. *Ann. Pharmacother.* 42(1):46–52, 2008.
- <sup>22</sup>Vreeman, R. C., S. E. Wiehe, E. C. Pearce, and W. M. Nyandiko. A systematic review of pediatric adherence to antiretroviral therapy in low- and middle-income countries. *Pediatr. Infect. Dis. J.* 27(8):686–691, 2008.
- <sup>23</sup>World Data on Education. United Nations Educational, Scientific and Cultural Organization. International Bureau of Education. [http://www.ibe.unesco.org/fileadmin/user\\_upload/Publications/WDE/2010/pdf-versions/Malawi.pdf](http://www.ibe.unesco.org/fileadmin/user_upload/Publications/WDE/2010/pdf-versions/Malawi.pdf). Accessed on November 4, 2012.
- <sup>24</sup>Yin, H. S., B. P. Dreyer, L. Van Schaick, G. L. Foltin, C. Dinglas, and A. L. Mendelsohn. Randomized controlled trial of a pictogram-based intervention to reduce liquid medication dosing errors and improve adherence among caregivers of young children. *Arch. Pediatr. Adolesc. Med.* 162(9):814–822, 2008.
- <sup>25</sup>Yin, H. S., M. Johnson, A. L. Mendelsohn, M. A. Abrams, L. M. Sanders, and B. P. Dreyer. The health literacy of parents in the United States: a nationally representative study. *Pediatrics* 124(suppl 3):S289–S298, 2009.
- <sup>26</sup>Yin, H. S., A. L. Mendelsohn, M. S. Wolf, *et al.* Parents' medication administration errors: role of dosing instruments and health literacy. *Arch. Pediatr. Adolesc. Med.* 164(2):181–186, 2010.
- <sup>27</sup>Yin, H. S., M. S. Wolf, B. P. Dreyer, L. M. Sanders, and R. M. Parker. Evaluation of consistency in dosing directions and measuring devices for pediatric nonprescription liquid medications. *JAMA* 304(23):2595–2602, 2010.