CHAPAS-2

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Abstract # LB-08

Pharmacokinetics and acceptability of a new generic lopinavir/ritonavir sprinkle formulation compared with syrup/tablets in African, HIV-infected infants and children according to WHO weight-band dose recommendations (CHAPAS-2)

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Cipla Caring for life

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Introduction

- Protease Inhibitor based ART in children is used:
  - Second-line following NNRTI+2NRTI
  - First line in infants (particularly following perinatal exposure to nevirapine for PMTCT) [1]

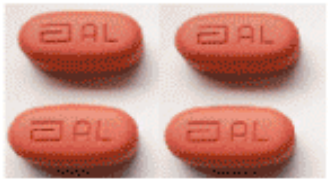
- Use of second-line ART remains low (<4%) [2] but is increasing in resource-limited settings:
  - Limited experience
  - Lack of appropriate formulations
  - Lopinavir/ritonavir (LPV/r) is only co-formulated PI:
    - Ritonavir liquid is very unpalatable and smallest solid formulation is 100mg

1. WHO Paediatric ART guidelines (2010)
2. UNAIDS/UNICEF (2010)

Lopinavir/ritonavir formulations

- Liquid formulation (80/20mg per ml)
  - Requires refrigeration
  - Has unpleasant taste
  - Expensive

- Tablet formulation
  - Adult (200/50mg) and paediatric (100/25mg) tablets are large
  - They must not be crushed/split (lose 45-47% bioavailability) [3]
    - Some children cannot swallow whole tablets



- Few PK data in infants or in African children

[3] Best BM et al. JAIDS 2011 Dec 1;58(4):385-91

Lopinavir/ritonavir sprinkles

- Using melt extrusion technology, Cipla Pharmaceuticals, India, developed LPV/r (40/10mg) as a sprinkle formulation
  - Appropriate for even the smallest children, as it allows the drug to be easily mixed in with food
  - Stored in capsules for easy administration; no need for refrigeration
  - Bioavailability proven in healthy adults (CROI 2012 poster 982)

Dosing table of LPV/r in tablet, syrup and sprinkle formulations (WHO 2010)

Drug	Formulation	Number of tablets/sprinkle capsules/ml by weight band (kg) twice daily								
		3-<4kg	4-<5kg	5-*<7kg	7-*<10kg	10-*<12kg	12-<14kg	14-<20kg	20-*<25kg	>25kg
LPV/r	**Sprinkle 40/10mg**	-	3	3	3	4	4	5	6	7
LPV/r	**Tablets 100/25mg**	-	-	-	-	2am 1pm	2am 1pm	2	3am 2pm	3
LPV/r	**Syrup 80/20 mg/ml**	1.5ml	1.5ml	1.5ml	1.5ml	2ml	2ml	2.5ml	3ml	3.5ml

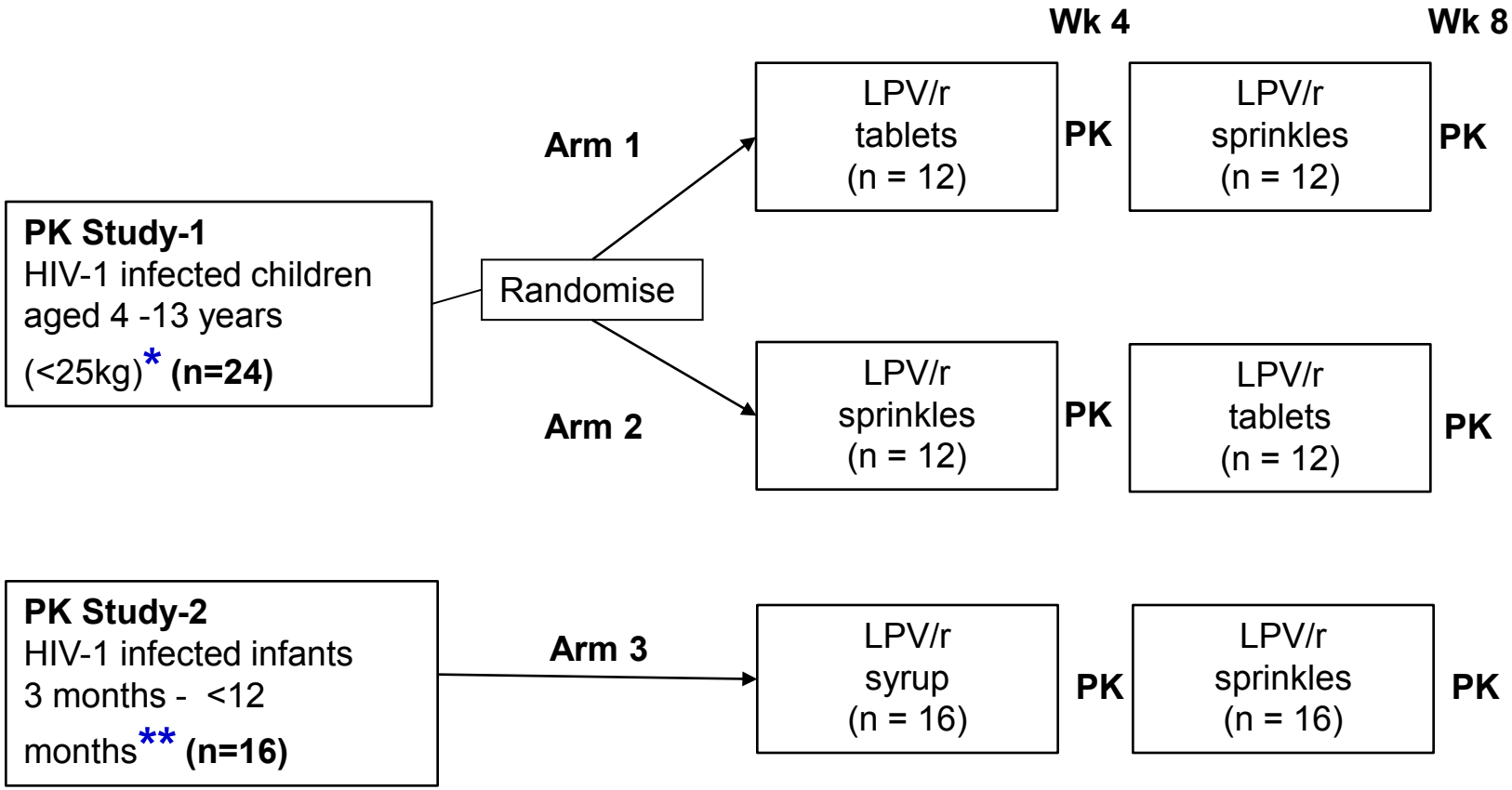
*tablets cannot be broken

The CHAPAS 2 trial: objectives

1. To determine and compare the PK of LPV/r in a twice daily paediatric co-formulated fixed dose **sprinkle** (Cipla) combination:
   - Versus twice daily paediatric co-formulated fixed dose **tablet** (Cipla) in 24 HIV-infected **children** aged 4-12 years
   - Versus twice daily paediatric co-formulated **syrup** (Abbott) in 16 HIV-infected **infants** under 1 year of age
     - All formulations given with food

2. To compare the formulation preferences of:
   - Sprinkle versus tablets among older children and carers
   - Sprinkle versus syrup among infants' carers

CHAPAS 2 trial design
PK Studies 1 and 2



** Children on or about to start Tablets and can definitely swallow them*

*** Infants on or about to start Syrups*

- PK day: time = 0, 1, 2, 4, 6, 8 & 12 hours after observed intake with food
- At week 8, children/carers chose which formulation to continue

Results
Baseline characteristics

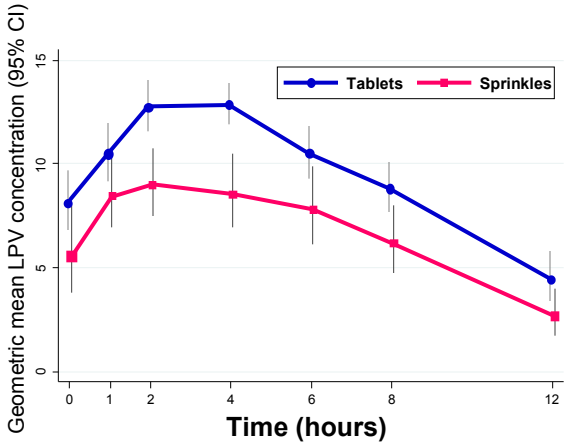
Child Demographics		
	PK study-1 (n=29)	PK study-2 (n=14)
Age, years	6.2 (5.8-8.0)	0.5 (0.4-0.6)
Male, n	13 (45%)	6 (43%)
Height, cm	113 (107-118)	62 (60-65)
Weight, kg	19.3 (17.9-20.9)	6.4 (6.1-6.7)
BMI, kg/m^2	15.2 (14.2-15.7)	17.1 (15.3-17.6)
CD4%	32 (26 to 38)	25 (17 to 29)
Height-for-age z-score	-1.24 (-2.06 to -0.33)	-1.86 (-2.57 to -0.78)
Weight-for-age z-score	-0.82 (-1.81 to -0.13)	-1.10 (-1.44 to -0.71)

Continuous values are median (interquartile range, IQR), categorical values are n (%)

Pharmacokinetic results Tablets vs Sprinkles (4-13 years)

	Tablets	Sprinkles	GMR (90% CI)	Historical data in children
PK parameter	GM (95% CI)	GM (95% CI)	Sprinkle:tablet	
$AUC_{0\text{-}12h}$(h.mg/L)	115.6 (103.3-129.8)	83.1 (66.7-103.5)	0.72 (0.60-0.86)	72.6 (41.5-103.7)
Cmax (mg/L)	13.9 (12.9-15.1)	10.3 (8.6-12.2)	0.74 (0.64-0.85)	8.2 (5.3-11.1)
C12h (mg/L)	4.4 (3.3-5.9)	2.6 (1.7-4.1)	0.59 (0.43-0.81)	3.4 (1.3-5.5)

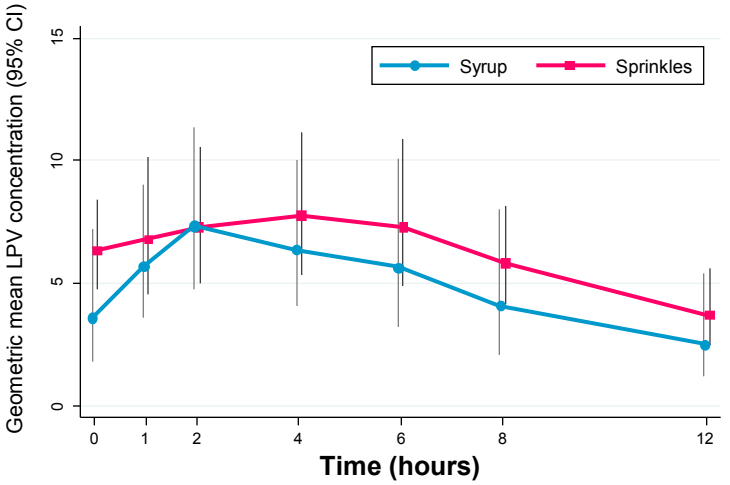
- LPV exposure in sprinkles comparable to historical data in children
- LPV exposure in tablets is higher than in sprinkles
- Variability all PK parameters is moderately high; CV%: 29 - 49%



Pharmacokinetic results Syrup vs Sprinkles (<1 year)

	Syrup	Sprinkles	GMR (90% CI)	Historical data in children
PK parameter	GM (95% CI)	GM (95% CI)	Sprinkle:tablet	
$AUC_{0\text{-}12h}$(h.mg/L)	62.5 (35.6-109.7)	70.9 (41.8-120.2)	1.13 (0.62-2.06)	72.6 (41.5-103.7)
Cmax (mg/L)	9.3 (6.2-13.9)	9.1 (6.1-13.7)	0.98 (0.65-1.49)	8.2 (5.3-11.1)
C12h (mg/L)	2.1 (0.9-5.1)	3.4 (2.1-5.7)	1.62 (0.67-3.96)	3.4 (1.3-5.5)

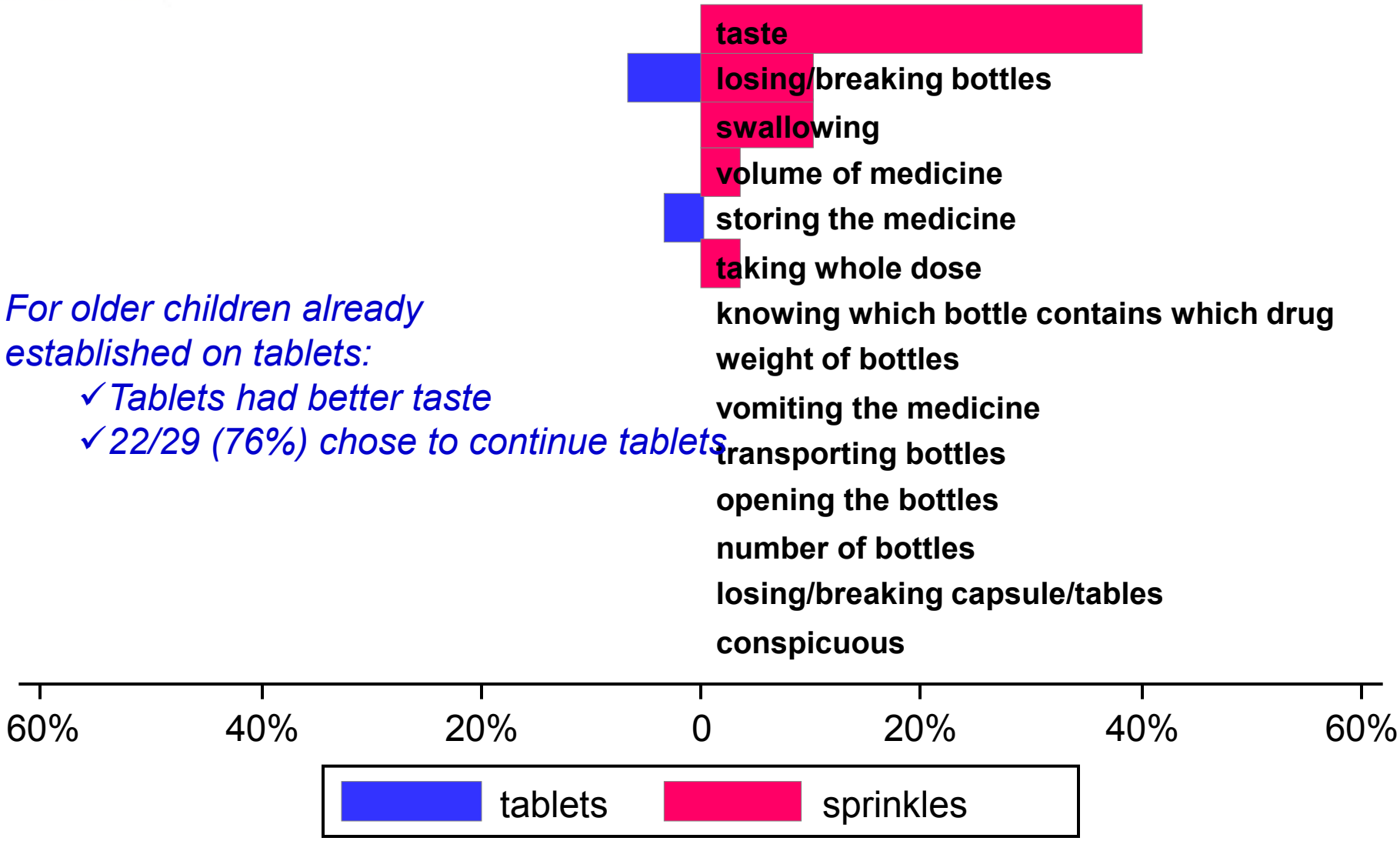
- Exposure LPV in sprinkles comparable to the Abbott oral solution and historical data
- Variability is high; CV%: 62-66%



Subtherapeutic PK values

- Sub-therapeutic trough levels in:
  - 4 (16%) sprinkles versus 1 (4%) tablets (p-value=0.35)
  - 0 (0%) sprinkles versus 3 (27%) syrup (p-value=0.21)

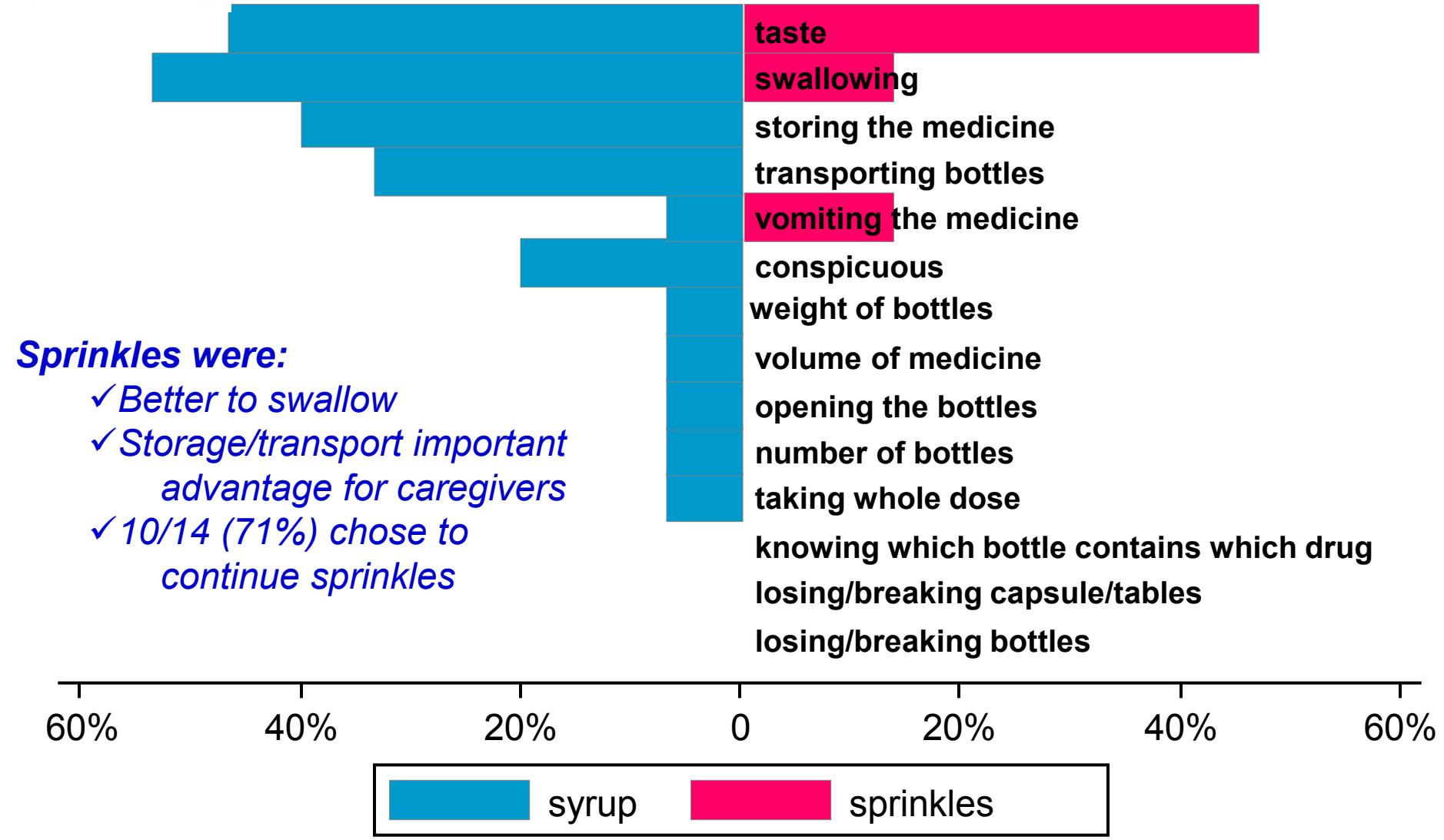
Acceptability
Percent reporting problems
(4-13 years n=28)



For older children already established on tablets:

- ✓*Tablets had better taste*
- ✓*22/29 (76%) chose to continue tablets*

Acceptability
Percent reporting problems
(<1 year n=14)



Sprinkles were:

- ✓*Better to swallow*
- ✓*Storage/transport important advantage for caregivers*
- ✓*10/14 (71%) chose to continue sprinkles*

Discussion and conclusions

- Exposure to LPV/r from sprinkles was comparable with syrup in infants and with historical data
- Exposure to LPV/r from tablets was higher than sprinkles in older children
- Variability in LPV/r PK parameters was high in all formulations
  - High prevalence of sub-therapeutic levels, but no sign of difference between formulation groups
  - Virological response data not available (awaited)
- For infants, sprinkles were more acceptable than syrups
- For older children ***already able to swallow tablets***, tablets were more acceptable than sprinkles
  - Taste of sprinkle was a concern

Next steps for CHAPAS 2

- Two further cohorts ongoing/planned in CHAPAS 2:
  - Young children aged 1-4 years on or starting syrups
  - Acceptability of improved granule formulation with better taste masking

Acknowledgements

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