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# Translating from egg- to antigen-based indicators for *Schistosoma mansoni* elimination targets: A Bayesian latent class analysis study.

Jessica Clark PhD<sup>1^</sup>, Arinaitwe Moses MSc<sup>2</sup>, Andrina Nankasi BSc<sup>2</sup>, Christina L. Faust PhD<sup>1</sup>, Moses Adriko MSc<sup>2</sup>, Diana Ajambo MSc<sup>2\*</sup>, Fred Besigye MSc<sup>2</sup>, Arron Atuhaire BSc<sup>2</sup>, Aidah Wamboko BSc<sup>2</sup>, Candia Rowell MSc<sup>2</sup>, Lauren V. Carruthers PhD<sup>1</sup>, Rachel Francoeur PhD<sup>1,3</sup>, Edridah M. Tukahebwa PhD<sup>2</sup>, Poppy H. L. Lambertson PhD<sup>1†</sup> & Joaquin M. Prada PhD<sup>4†</sup>

\*Deceased

† These authors have contributed equally and share last authorship.

1. Wellcome Centre for Integrative Parasitology, Institute of Biodiversity, Animal Health & Comparative Medicine, University of Glasgow, Glasgow, UK
2. Vector Control Division, Ministry of Health, Kampala, Uganda
3. Faculty of Science and Engineering, University of Chester, Chester, UK
4. Faculty of Health & Medical Sciences, University of Surrey, Guildford, UK

## ^Correspondence

Jessica Clark

[Jessica.clark@glasgow.ac.uk](mailto:Jessica.clark@glasgow.ac.uk)

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## Abstract

Schistosomiasis is a parasitic disease affecting over 240-million people. World Health Organization (WHO) targets for *Schistosoma mansoni* elimination are based on Kato-Katz egg counts, without translation to the widely used, urine-based, point-of-care circulating cathodic antigen diagnostic (POC-CCA). We aimed to standardize POC-CCA score interpretation and translate them to Kato-Katz-based standards, broadening diagnostic utility in progress towards elimination. A Bayesian latent-class model was fit to data from 210 school-aged-children over four timepoints pre- to six-months-post-treatment. We used 1) Kato-Katz and established POC-CCA scoring (Negative, Trace, +, ++ and +++), and 2) Kato-Katz and G-Scores (a new, alternative POC-CCA scoring (G1 to G10)). We established the functional relationship between Kato-Katz counts and POC-CCA scores, and the score-associated probability of true infection. This was combined with measures of sensitivity, specificity, and the area under the curve to determine the optimal POC-CCA scoring system and positivity threshold. A simulation parametrized with model estimates established antigen-based elimination targets. True infection was associated with POC-CCA scores of  $\geq +$  or  $\geq G3$ . POC-CCA scores cannot predict Kato-Katz counts because low infection intensities saturate the POC-CCA cassettes. Post-treatment POC-CCA sensitivity/specificity fluctuations indicate a changing relationship between egg excretion and antigen levels (living worms). Elimination targets can be identified by the POC-CCA score distribution in a population. A population with  $\leq 2\%$  ++/+++ , or  $\leq 0.5\%$  G7 and above, indicates achieving current WHO Kato-Katz-based elimination targets. Population-level POC-CCA scores can be used to access WHO elimination targets prior to treatment. Caution should be exercised on an individual level and following treatment, as POC-CCAs lack resolution to discern between WHO Kato-Katz-based moderate- and high-intensity-infection categories, with limited use in certain settings and evaluations.

## Contribution to the field

Schistosomiasis is caused by parasitic helminths that are inaccessible, so proxy diagnostics are relied upon to infer infection presence and intensity. The World Health Organization's 2021-2030 Neglected Tropical Disease Roadmap targets schistosomiasis for elimination as a public health problem. This is achieved when  $<1\%$  of all infections are heavy, where heavy is  $\geq 400$  eggs per gram of stool by the Kato-Katz method, which lacks sensitivity, is time-costly, and requires trained personnel. Alternatively, the point-of-care circulating cathodic antigen diagnostic (POC-CCA), recommended by the WHO, is faster, more sensitive, and requires no training but there are no available guidelines standardizing use or indicating elimination because it is unknown how egg counts relate to the discrete POC-CCA scoring. We developed a statistical model that established the functional form of the relationship between egg counts and POC-CCA scores. We show that the G-Score method improves upon the manufacturers scoring guidelines; that the distribution of POC-CCA scores in a population can be used to determine if a population has likely reached elimination; and that POC-CCA scores cannot be aligned with egg counts because the POC-CCA saturates at low infection intensities. These results expand the utility of the POC-CCA, enabling countries to make informed control decisions.

## 1 Introduction

2 Schistosomiasis, caused by a parasitic helminth, is endemic in 54 countries, infecting over 240 million people  
3 and has the second greatest socio-economic impact of any parasitic disease after malaria (Chitsulo et al., 2004)  
4 with several million people experiencing severe morbidity despite nearly two decades of interventions (Colley et  
5 al., 2014). Around 90% of cases are found on the African continent, caused by *Schistosoma mansoni* and  
6 *Schistosoma haematobium*, causing intestinal and urogenital schistosomiasis respectively.

7  
8 The World Health Organization (WHO) has targeted schistosomiasis for elimination as a public health problem  
9 (EPHP) by 2030 (World Health Organization, 2020a). This goal is achieved when there are <1% “heavy-  
10 intensity” infections in a target population. For *S. mansoni*, “heavy” is  $\geq 400$  eggs per gram of stool (epg), when  
11 measured by Kato-Katz from stool samples (World Health Organization). However, these thresholds are  
12 problematic because they assume that the egg count is linearly related to the unobservable infection intensity  
13 (adult worm density) and morbidity, and because Kato-Katz lack sensitivity and show significant within- and  
14 between-sample and -day variation (Engels et al., 1997; Lamberton et al., 2014). This categorization is therefore  
15 unlikely to be static in time, and underappreciates the contribution of light or moderate intensity infections to  
16 morbidity and transmission. These guidelines are also in contrast to community risk categories, which are given  
17 in terms of infection prevalence, not intensity (World Health Organization, 2020b).

18  
19 In 2017, the WHO endorsed the urine-based point-of-care circulating cathodic antigen diagnostic (POC-CCA)  
20 (World Health Organization, 2020b), which detects *S. mansoni* antigens (van Lieshout et al., 2000). The POC-  
21 CCA is more sensitive and can detect infections missed by the Kato-Katz (juveniles and non-reproducing  
22 worms), but may also lack specificity (Casacuberta Partal et al., 2021; Graeff-Teixeira et al., 2021). Current  
23 WHO guidance suggests a 10% difference between egg- and antigen-based prevalence estimates in high  
24 prevalence settings (World Health Organization, 2020b), but a 20% discrepancy in low- and moderate-  
25 prevalence settings. The evidence supporting this is unclear, with recent work in a high-risk community also  
26 suggesting a 20-30% difference (Clark et al., 2021). There is also no indication of how POC-CCA aligns with  
27 infection intensity-based targets, which is desperately needed to efficiently harness POC-CCA’s higher  
28 sensitivity (Utzing et al., 2015).

29  
30 The POC-CCA has traditionally been scored as Negative, Trace, +, ++ or +++ (referred to as POC-CCA+ from  
31 here on) as a semi-quantitative presumption of infection intensity, based on the colored response on the lateral  
32 flow assay. However, there is ongoing debate regarding the interpretation of Trace scores, as positive or  
33 negative, which leads to divergent epidemiological and drug-efficacy estimates (Danso-Appiah et al.,  
34 2016; Prada et al., 2018), and hinders analysis because strong interpretation assumptions must be made  
35 (Clements et al., 2017; Barenbold et al., 2018; Clements et al., 2018). To overcome this dilemma, the G-Score  
36 method was recently developed (Casacuberta-Partal et al., 2019). Diagnostic cassettes are compared to 10  
37 dummy cassettes, pre-labelled with reference scores from G1 (negative) to G10 (highest positive score), with  
38 the aim of reducing inter-reader differences and increasing resolution across the scores (Standley et al.,  
39 2010; Casacuberta-Partal et al., 2019). A score of G2 or G3 is supposedly equivalent to Trace, however, with no  
40 schistosomiasis diagnostic gold standard, it is still unclear whether Trace, and therefore G2 and G3, are negative  
41 or positive, and there is no indication of how the G-Scores relate to true infection intensities. It is also hard to  
42 ascertain how the G-Score performs in terms of sensitivity or specificity in comparison to the POC-CCA+.

43  
44 The overall aim of this study was to improve the interpretation and utility of the POC-CCA, to help guide  
45 policy, enabling countries to make informed decisions for *S. mansoni* control. We did this by 1) Determining  
46 how infection intensity relates to the POC-CCA scores; 2) Estimating the probability of infection, particularly  
47 those associated with Trace and G2 or G3 scores; 3) Quantifying and comparing the performance of G-Score  
48 and POC-CCA+ methods; and 4) Assessing the expected distribution of POC-CCA scores in EPHP settings,  
49 through a simulation study, to determine an analogous POC-CCA threshold to Kato-Katz egg counts.

## 51 Methods

### 52 Study design, enrolment and participants

53 The data used in this modelling study were collected pre-praziquantel treatment, and three-weeks, nine-weeks  
54 and six-months post-treatment, from September-March 2017/18. 220 randomly selected children of equal sex  
55 distribution aged 6-14 were enrolled into the study from Bugoto Lake View Primary School, Mayuge District,  
56 Uganda. Ten students provided no samples leaving a cohort of 210. A full description of the demographic  
57 breakdown of the cohort and estimated infection prevalence is provided elsewhere (Clark et al., 2021). Children  
58 present at each timepoint provided stool samples on three consecutive days with duplicate Kato-Katz smears  
59 made per stool, giving up to six Kato-Katz smears per timepoint. A single POC-CCA test was performed on one  
60 urine sample per timepoint, scored with the POC-CCA+ and G-Score methods. Observed treatment with  
61 praziquantel was administered at 40mg/kg alongside a carbohydrate-based meal (Castro et al., 2000).

### 62 Ethical clearance

64 Ethical Approval was granted from the Vector Control Division Research Ethics Committee (VCDREC/062),  
65 Uganda National Council of Science and Technology (UNCST-HS 2193) and University of Glasgow Medical,  
66 Veterinary and Life Sciences Research Ethics Committee (200160068). Informed consent was given by  
67 signature or thumb print, prior to data and sample collection, by the parent/legal guardian of all recruited  
68 children and informed assent from all children aged eight and older.

## 69 70 **Model structure**

71 We adapted an existing latent class model framework which considers the Kato-Katz and POC-CCA data for  
72 each individual as imperfect estimators of an individual's latent infection status (Clark et al., 2021). Specific  
73 details including the handling of missing data are in the supplementary material. Two models are presented: one  
74 with Kato-Katz and POC-CCA+ and one with Kato-Katz and G-Score. We used raw repeated Kato-Katz counts  
75 (eggs counted on each slide) and POC-CCA scores, transformed such that the POC-CCA+ and G-Scores were  
76 from 0-4 and 0-9 respectively. We assumed the POC-CCA results were related to infection intensity through a  
77 logistic function in the likelihood function for the POC-CCA data. The real number of the denominator was the  
78 true latent infection intensity as estimated by the model, and the numerator, the highest integer value of the  
79 POC-CCA scoring method. This meant that heavily infected individuals could have higher POC-CCA test  
80 results, but with no strong assumptions on the interpretation of Trace or G2/G3 scores as has previously been  
81 necessary (Barenbold et al., 2017; Clements et al., 2017; Clements et al., 2018; Lindholz et al., 2018). Analysis  
82 and visualizations were produced using R version 4.0.2 (R Core Team, 2018) and models fit with the *runjags*  
83 (Denwood, 2016) package.

## 84 85 *Relating POC-CCA scores to true infection intensity*

86 We reconstructed the form of the logistic function to visualize the relationship between true infection intensity  
87 and expected POC-CCA scores for POC-CCA+ and G-Score. This was performed by randomly sampling from  
88 model parameter posterior distributions for each POC-CCA scoring method.

## 89 90 *Interpretation of Trace and G2/G3*

91 Each iteration of the model runs, allocates an infection status to each individual. By averaging over the total  
92 number of iterations for each model, we determined for each individual the time-specific probability of being  
93 infected. Using the individuals with 0 egg when measured by Kato-Katz, we correlated each individual's  
94 estimated probability of true infection with their POC-CCA score.

## 95 96 *Assessing the performance of POC-CCA+ versus G-Score*

97 Calculated using the individual-level true infection status, as estimated by the model, we produced Receiver  
98 Operator Characteristic (ROC) curves (Sing et al., 2005) to compare the performance of the POC-CCA+ and G-  
99 Score methods at each timepoint. The overall performance of the two diagnostics were quantified with the Area  
100 Under the Curve (AUC) value, which, in this instance, is equal to the Wilcoxon-Mann-Whitney test statistic and  
101 describes the relationship between the true-positive (sensitivity) and false-positive (1-specificity) rates. We  
102 compared the ROC curves with the probability of infection to infer an optimal threshold for disease diagnosis.

## 103 104 *Estimating the EPHP target for antigen-based diagnostics*

105 We conducted a simulation study to determine a target for the POC-CCAs, analogous to the current Kato-Katz-  
106 based WHO EPHP target. Using 100 prevalence values ranging from 1-10% (in line with WHO low  
107 community-risk categorization (World Health Organization, 2020b) based on Kato-Katz counts, and where  
108 EPHP is most likely to be first reached), we simulated POC-CCA+ scores and G-scores for each prevalence  
109 level, simulating 50 target populations with 10,000 individuals each. Each individual was assigned an infection  
110 status (infected or not infected). The allocation of POC-CCA scores replicated the models. Details of the  
111 simulation can be found in the supplementary material file.

## 112 113 **Results**

114 Visualizing the raw data used to parametrize the models, it is evident that at all timepoints there is a positive  
115 association, as previously shown (Casacuberta-Partal et al., 2019), between the POC-CCA+ and G-Score  
116 scoring method (figure 1). However, whilst heavy intensity infections aggregate largely between G7-G10 or  
117 +++, zero egg by Kato-Katz and low intensity infections (1-99 epg) are distributed across all POC-CCA+ and  
118 G-Scores, at all timepoints, such that in the field there would be no indication of infection intensity from just the  
119 POC-CCA scores.

120  
121 This is because the POC-CCAs saturate at very low true infection intensities (figure 2). The logistic curve  
122 shows that for those who are definitely infected, true infection intensities (intensities not necessarily captured by  
123 Kato-Katz) as low as 1 epg, could illicit a score between Trace and +++ (figure 2A), and between G4 and G6  
124 (figure 2B). The G-Score reaches its maximum score of G10 by, on average, a true infection intensity of 25 epg.

125  
126 We show the probability of infection associated with each POC-CCA score (figure 3). For the POC-CCA+, the  
127 percentage probability of infection for a Trace score aggregates around 50%, whilst + and above is indicative of

128 almost certain infection. This aggregation around 50% for a Trace score indicates maximum uncertainty in the  
129 score allocation. For the G-Score method, a score of G2 has only a very low probability of infection associated  
130 with it, whilst G3 indicates a 62-75% probability of infection.

131  
132 As there were no Trace scores allocated pre-treatment and six-months post-treatment, there is no indication for  
133 whether this threshold would impact the AUC at these timepoints. However, at three- and nine-weeks post-  
134 treatment using Trace as the earliest positive diagnosis maintains sensitivity but with a false positive rate around  
135 50% (figure 4 A-D) reflecting the uncertainty in the probability of infection. The use of + as the threshold  
136 reduces sensitivity by around 20% but reduces this high false positive rate to almost 0 across all timepoints.  
137 Regarding G-scores, taking a G2 score to be positive would provide a highly variable false positive rate (30-  
138 80%) in relation to time since treatment. The severity of this false positive rate reduces with treatment but is  
139 seen again by six-months post-treatment. A score of G3 and above as the cut-off point provides a lower, more  
140 stable false positive rate, ~10-18%, whilst maintaining a high sensitivity (~90%), again depending on time since  
141 treatment (figure 4E-H).

142  
143 Though Kato-Katz epg and POC-CCA scores cannot be directly aligned, we can observe the distribution of  
144 WHO infection-intensity categories based on Kato-Katz egg counts across the POC-CCA scores (figure 5A and  
145 5C). Heavy intensity infections are found in the POC-CCA categories ++ and +++. These categories amount to  
146 2.3% of the total POC-CCA+ scores (figure 5A). We therefore propose this as a threshold, such that if a target  
147 population has  $\leq 2.3\%$  ++ or +++, it is likely EPHP has been achieved. Similarly for G-Score (figures 5C and  
148 5D), heavy intensity infections are found from G7 upwards, of which these categories make up 0.92% of the  
149 allocated scores. We therefore propose that if a target population has  $\leq 0.92\%$  G7 and above, it will likely have  
150 achieved EPHP.

## 151 152 Discussion

153 We present a quantitative analysis of *S. mansoni* diagnostic data to improve interpretations of the more  
154 sensitive, but not 100% specific, POC-CCA. We show, for the first time, that POC-CCA+ and G-Scores are not  
155 associated with a particular intensity of *S. mansoni* infection, because the POC-CCA test itself saturates at low  
156 infection intensities. We also show that in a high prevalence setting, the probability of infection cannot be  
157 estimated robustly for those with Trace scores. However, nearly three quarters of those with a G3 score are  
158 likely to be infected and that it is highly probable that a score of G2 reflects a true negative diagnosis. Using  
159 ROC curves, we show that considering Trace as positive will result in a high proportion of false positives,  
160 whilst G3 would produce far fewer false positives with little reduction in sensitivity. Most importantly, we show  
161 that if a population has  $\leq 2.3\%$  of POC-CCA+ scores of ++ and +++, or  $\leq 0.92\%$  of G7 and above then it is  
162 highly likely that the target population has achieved WHO's EPHP definition of <1% heavy infections.

163  
164 Our results provide quantitative evidence that at baseline (pre-treatment) the G2-G3 boundary provides a  
165 sensitive and specific cut off and we therefore recommend that G3 and above be considered positive. However,  
166 post-treatment this relationship changes. There is an alteration in clinical sensitivity and specificity that suggests  
167 a change in the biological relationship between the production and/or excretion of the eggs and antigens  
168 (captured in the model as a change in the shape of the logistic curve), rather than a change in the technological  
169 sensitivity and specificity. This is most likely due to the number of eggs being excreted per adult worm present,  
170 changing with treatment. This could also be due to juvenile worms surviving treatment and continuing to  
171 regurgitate antigens but not yet producing eggs, or previously egg-producing adult worms surviving treatment  
172 but becoming – at the very least, temporarily – sterilized (Lamberton et al., 2017) or otherwise unable to  
173 reproduce (McCusker et al., 2021).

174  
175 Having recognized this, we attempted to estimate by time, the *k* and *intercept* parameters that form the shape of  
176 the logistic function in the POC-CCA likelihoods. However, there were insufficient data to do this at individual  
177 timepoints. In future studies, larger sample sizes will be needed to sufficiently power the study to be able to  
178 estimate the shape of this relationship as a function of time post-treatment. Post-hoc investigative analyses  
179 showed that there were no significant differences between pre-treatment and at six months post-treatment,  
180 indicating that any biological perturbation in this relationship, caused by praziquantel treatment, has returned to  
181 that of pre-treatment by six-months post-treatment. This is supported by the observation that whilst true  
182 prevalence returns to pre-treatment levels within six-months of treatment, infection intensity measured by Kato-  
183 Katz does not (Prada et al., 2018).

184  
185 Both of our findings are novel, and due to their importance for diagnostic interpretation should be reflected in  
186 WHO guidelines: Pre-treatment, G3 and above should be considered positive. However, post-recent-treatment,  
187 POC-CCA scores cannot be compared against historical drug efficacy measures of egg reduction rates, not  
188 because the POC-CCA lacks accuracy post treatment, but because the POC-CCA scores do not correlate to egg  
189 excretion in the same biological way and therefore cannot be used as a proxy of infection intensity reduction in  
190 the same way. However, they may be better measures of drug efficacy, but not as it has been historically  
191 viewed. Additionally, this work may indicate that Kato-Katz cannot accurately measure drug efficacy on the

192 adult worms, and therefore are not the measures we should be guided by. The greater sensitivity gained by using  
193 POC-CCA tests may however enable a better understanding of who is infected and what proportion of people  
194 are contributing to transmission. However, it should be noted that it is the eggs that are excreted that contribute  
195 to transmission and therefore they will always still be of importance to accurately quantify. Conversely it is the  
196 eggs that are not excreted (i.e., those that cannot be detected by Kato-Katz) that contribute to morbidity, which  
197 is what the WHO aims to reduce, further highlighting the complexity of accurately diagnosing infections and  
198 morbidity without a gold standard for either.

199  
200 Recent evidence has shown that the WHO Kato-Katz-based infection-intensity categories do not correlate to  
201 morbidity, with low and moderate intensity infections also causing significant morbidity (Wiegand et al., 2021).  
202 This suggests that EPHP measured by Kato-Katz will not be enough to truly reduce the observed levels of  
203 morbidity. Low and moderate intensity infections are found in the ++ and +++ POC-CCA+ categories, and in  
204 G7 and above, in our simulated EPHP target populations. We therefore propose more conservative, and  
205 logistically easier, cut offs of  $\leq 2\%$  of ++ and +++ , or  $\leq 0.5\%$  of G7 and above, which means our proposed  
206 indicators of EPHP when using either POC-CCA scoring method, may reduce the prevalence and severity of  
207 morbidity further than the egg-based metric. However, more must be done to understand how morbidity  
208 manifests for those with low intensity infections, or those that have infections undetectable by Kato-Katz but  
209 with low POC-CCA scores. For example, it is common for adults to exhibit greater morbidity, but lower egg  
210 counts, than children, likely from long-lasting, untreated chronic infections (Mawa et al., 2021). Models have  
211 recently shown that in some settings, reaching these morbidity targets and reactively reducing treatment  
212 frequency could result in recrudescence (Ayabina et al., 2021). suggesting the morbidity targets are not an  
213 optimal stepping stone and that the reduction of prevalence as suggested elsewhere (Toor et al., 2019) will be  
214 more effective.

215  
216 To conclude, we present, for the first time, policy recommendations for the use of the antigen-based POC-CCA  
217 diagnostic to identify WHO 2030 EPHP targets. We advocate for the use of the newer G-scoring technique,  
218 using G3 as a *S. mansoni* positivity threshold. We suggest that if  $\leq 2\%$  of all POC-CCA+ infections are ++/+++  
219 or  $\leq 0.5\%$  G-Score are G7 and above, it is likely that EPHP has been reached.

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227 cassettes available for use.

## 228 229 **Figure Legends**

230  
231 *Figure 1. Raw data showing the correlation between G-Scores and POC-CCA+ colored by the WHO*  
232 *Schistosoma mansoni* *infection-intensity categories, as determined by Kato-Katz egg counts, and split by the*  
233 *timesteps used in the models: pre-treatment, and three-weeks, nine-weeks and six-months post-treatment.*

234  
235 *Figure 2. Figure 2. The functional form of the logistic curves showing the relationship between the Point of*  
236 *Care Circulating Cathodic Antigen scores and true Schistosoma mansoni* *infection intensity as eggs per gram of*  
237 *stool (epg). A. POC-CCA+, B. G-scores.*

238  
239 *Figure 3. The probability of Schistosoma mansoni* *infection associated with each Point of Care Circulating*  
240 *Cathodic Antigen score where the corresponding egg count was zero. A. POC-CCA+ B. G-Scores. Note that*  
241 *there were no scores of G10 given to those with zero egg counts.*

242  
243 *Figure 4. Receiver Operator Characteristic (ROC) curves showing the performance of each diagnostic scoring*  
244 *method at each timestep. A-D. POC-CCA+ E-H. G-Scores. Note that only at six-months post-treatment, was a*  
245 *score of G10 given.*

246  
247 *Figure 5. A. The distribution of given POC-CCA+ scores from a simulation of 100,000 people in 50 infected*  
248 *populations. B. the distribution of WHO infection-intensity categories across the given scores. Zero counts in*  
249 *light purple. Light/ Low infection intensities in dark purple. Moderate in fuchsia pink and heavy infection*  
250 *intensity in neon pink. C. The distribution of given G-scores scores. B. the distribution of WHO infection-*  
251 *intensity categories across the given scores. Zero counts in sea foam green. Light/ Low infection intensities in*  
252 *light green. Moderate in tree green and heavy infection intensity in dark green.*

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254  
255

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