# Appendix S3 – Additional meta-analysis results

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# Sensitivity and Specificity Forest Plots and SROC Curves

# **Crystal VC on Direct Samples**

#### Figure 1. Forest plot results for Crystal VC - direct samples sensitivity and specificity meta-analysis

Study	Events Total	Proportio	on 95%-Cl	Study	Events Total	Pro	portion 95%-CI
Group = Culture George 2014 Mukherjee 2010 Islam 2019 Sayeed 2018 Matias 2017 Random effects mode Heterogeneity: I <sup>2</sup> = 96%, 1	$\begin{array}{ccccccc} 42 & 64 & & \\ 66 & 72 & \\ 117 & 162 & & \\ 19 & 19 & \\ 283 & 286 & \\ 803 & \\ t^2 = 2.6916,  p < 0.01 \end{array}$	• 0.61 • 0.97 • 0.77 • 1.00 • 0.97 • 0.97	56         [0.527; 0.771]           17         [0.827; 0.969]           22         [0.647; 0.790]           00         [0.824; 1.000]           90         [0.970; 0.998]           26         [0.719; 0.984]	Group = Culture George 2014 Mukherjee 2010 Islam 2019 Sayeed 2018 Matias 2017 Random effects mode Heterogeneity: J <sup>2</sup> = 93%, 1	$56  61 \\ 102  140 \\ 4395  5703 \\ 46  57 \\ 135  225 \\ 6186 \\ c^2 = 0.2935, p < 0.01$		0.918 [0.819; 0.973] 0.729 [0.647; 0.800] 0.771 [0.760; 0.782] 0.807 [0.681; 0.900] 0.600 [0.533; 0.665] 0.771 [0.665; 0.851]
Group = Culture or PC Page 2012 (clinicans) Random effects mode Heterogeneity: not applica	CR 171 186 el 186 uble	0.9 0.9	19 [0.870; 0.954] 19 [0.871; 0.951]	Group = Culture or PC Page 2012 (clinicans) Random effects mode Heterogeneity: not applica	R 57 69 I 69 ble		0.826 [0.716; 0.907] 0.826 [0.718; 0.898]
Group = PCR Ontweka 2016 Harris 2009 Random effects mode Heterogeneity: $I^2 = 0\%$ , $\tau^2$	$\begin{array}{ccc} 34 & 36 \\ 65 & 67 \\ 103 \\ 2 = 0, p = 0.53 \end{array}$	0.94 0.97 0.90	44 [0.813; 0.993] 70 [0.896; 0.996] 61 [0.901; 0.985]	Group = PCR Ontweka 2016 Harris 2009 Random effects mode Heterogeneity: / <sup>2</sup> = 0%, τ <sup>2</sup>	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		0.797 [0.678; 0.887] 0.750 [0.566; 0.885] 0.781 [0.688; 0.853]
Random effects mode Heterogeneity: $I^2 = 93\%$ , $\tau$ Residual heterogeneity: $I^2$	<b>a 892</b> $\tau^2 = 1.6839, p < 0.01$	0.9 0.7 0.8 0.9 1 Sensitivity	33 [0.837; 0.975]	<b>Random effects mode</b> Heterogeneity: $I^2 = 86\%$ , Residual heterogeneity: $I^2$	<b>6351</b> $t^2 = 0.1903, p < 0.01$ $t^2 = 88\%, p < 0.01$ 0.6	0.7 0.8 0.9 Specificity	0.777 [0.707; 0.833]

Figure 2. SROC Curve: Crystal VC - Direct Samples



SROC curve (bivariate model) for Diagnostic Test Accuracy

### **Crystal VC on Enriched Samples**

Figure 3. Forest plot results for Crystal VC - enriched samples, sensitivity and specificity meta-analysis



#### Figure 4. SROC Curve: Crystal VC – Enriched Samples



#### SROC curve (bivariate model) for Diagnostic Test Accuracy

### **Cholera Screen**



Figure 5. Forest plot results for Cholera Screen, sensitivity and specificity meta-analysis



#### Figure 6. SROC Curve: CholeraScreen



SROC curve (bivariate model) for Diagnostic Test Accuracy

False Positive Rate

# **IP Dipstick**







Figure 8. SROC Curve: IP Dipstick - Direct Samples



#### SROC curve (bivariate model) for Diagnostic Test Accuracy

False Positive Rate

### **DOR Analysis**

#### **Methods**

To allow comparison of tests using one measure of diagnostic accuracy, an additional analysis was undertaken on diagnostic odds ratio (DOR) according to the methods outlined in Shim et al, 2019<sup>1</sup>. Diagnostic odds ratio is the ratio of the odds of the index test being positive when an individual has a disease (i.e., positive result from a reference test), compared to the odds of the index test being positive when an individual does not have the disease (i.e. negative result from a reference test). A DOR of 1 therefore indicates an index test is uninformative. The DOR is calculated as follows:

$$DOR = \frac{TP \times TN}{FP \times FN}$$

Where: TP = True Positive; TN = True Negative; FP = False Positive; FN = False Negative

A random effects model was used to account for variation across studies. Only one DOR estimate per study was included in each meta-analysis to ensure no duplication of samples. Where studies had more than one estimate (e.g., due to lab technicians and field technicians both undertaking the test), priority was given to results obtained from settings most similar to that intended by the test. Multiple results from the same study group were included only if estimates were based on samples from distinct geographical locations.

<sup>&</sup>lt;sup>1</sup> Shim SR, Kim S-J, Lee J. Diagnostic test accuracy: application and practice using R software. Epidemiol Health. 2019;41. doi:10.4178/epih.e2019007

## **Results and Discussion**

Test	No. Studies Included [reference number]	Total Sample Size (Range)	Diagnostic Odds Ratio meta- estimate (95% CI)
Crystal VC – Direct Samples	8 [10,32,34,40,45,47,50,56]	7243 (76-5865)	42.90 (17.51-105.10)
Crystal VC – Enriched Samples	5 [10,24,30,32,40]	1614 (100-673)	238.61 (32.56-1748.70)
Cholera-Screen – Direct Samples	3 <sup>1</sup> [25,29,39]	250 (17-99)	70.05 (14.39-340.99)
IP Dipstick – Direct Samples	2² [49,59]	414 (102-172)	136.31 (25.44-730.38)

#### Table 1. Summary of results of meta-analyses

<sup>1</sup>One study undertaken in 2 separate locations so 4 results included <sup>2</sup>One study undertaken in 2 separate locations so 3 results included

The high Diagnostic Odds Ratio meta-estimates shown in Table 1 indicate that all four tests show good diagnostic accuracy: patients with a positive test have much greater odds of having cholera (as diagnosed by the reference tests) than patients with a negative test. The variability between studies within each meta-analysis is shown visually in the forest plots below.

However, these results must all be interpreted with caution. Diagnostic Odds Ratios are sensitive to studies where sensitivity or specificity are close to or at 100%, resulting in small or zero cell values during odds ratio calculation<sup>2</sup>. Therefore, while all four tests showed high diagnostic odds ratios, we cannot conclusively determine which test is most accurate on this basis

<sup>&</sup>lt;sup>2</sup> Huang Y, Yin J, Samawi H. Methods improving the estimate of diagnostic odds ratio. Commun Stat - Simul Comput. 2018;47: 353–366. doi:10.1080/03610918.2016.1157183

#### **DOR Forest Plots**

Figure 9. Forest plot results for Crystal VC - Direct Samples, DOR meta-analysis

044.	Experin	nental	C	ontrol		0.0	05% 01
Study	Events	Iotai	Events	Iotal	Odds Ratio	OR	95%-01
Group = Culture George 2014 Mukherjee 2010 Islam 2019 Sayeed 2018 Matias 2017 Random effects model Heterogeneity: $l^2 = 86\%$ , $\tau^2$	42 66 117 19 283 = 1.2725	47 104 1425 30 373 <b>1979</b> 5, <i>p</i> < 0	22 6 45 0 3	78 108 4440 46 138 4810		21.382   29.526 [* 8.736   157.696 [8 141.500 [4 32.759 [10	[7.481; 61.115] 11.826; 73.720] [6.161; 12.389] 3.849; 2810.291] 3.986; 455.191] 0.534; 101.872]
Group = Culture or PCF Page 2012 (clinicans) Random effects model Heterogeneity: not applicab	<b>171</b> Ie	183 183	15	72 72	*	54.150 [2 54.150 [2	3.942; <mark>1</mark> 22.473] 3.942; 122.473]
Group = PCR Ontweka 2016 Harris 2009 Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2 = 0\%$	<b>34</b> 65 = 0, p = 0	47 73 120 0.74	2 2	53 26 79	*	66.692 [1 97.500 [1 79.984 [2	4.146; 314.425] 9.321; 492.018] 6.104; 245.078]
Random effects model Heterogeneity: $l^2 = 85\%$ , $\tau^2$ Residual heterogeneity: $l^2$	= 1.2493 = 82%, p	<b>2282</b> 8, p < 0 < 0.01	.01	4961 (	0.001 0.1 1 10 1000 Diagnostic Odds Ratio	42.896 [1]	7.508; 105.100]

\*Experimental: Events = True Positives; Total = True Positives + False Positives. Control: Events = False Negatives; Total = True Negatives + False Negatives

Figure 10. Forest plot results for Crystal VC - Enriched Samples, DOR meta-analysis

Study	Experin Events	nental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI
Group = Culture George 2014 Bwire 2017 Islam 2019 Random effects model Heterogeneity: $l^2 = 78\%$ , $\tau^2$	48 91 28 <sup>2</sup> = 2.8653	49 92 81 222 8, p = 0.	16 1 13	76 10 533 619		180.000 - 819.000 21.132 106.775	[23.042; 1406.113] [47.130; 14231.995] [10.328; 43.238] [11.707; 973.815]
Group = PCR Ontweka 2016 Debes 2016 Random effects model Heterogeneity: $l^2 = 0\%$ , $\tau^2$	31 25 = 0, p = 0	31 28 59	5 7	69 645 714		- 738.818 759.524 755.577	[ 39.599; 13784.370] [185.377; 3111.908] [212.094; 2691.709]
Random effects model Heterogeneity: $l^2 = 86\%, \tau^2$ Residual heterogeneity: $l^2$	² = 4.0766 = 67%, p	<b>281</b> 5, p < 0. = 0.03	.01	1333	0.001 0.1 1 10 1000 Diagnostic Odds Ratio	238.606	[ 32.557; 1748.702]

\*Experimental: Events = True Positives; Total = True Positives + False Positives. Control: Events = False Negatives; Total = True Negatives + False Negatives

#### Figure 11. Forest plot results for Cholera Screen, DOR meta-analysis

	Experin	nental	C	ontrol			
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI
Colwell 1992 (Guatemala)	10	14	0	3	+ = -	16.333	[0.691; 385.864]
Colwell 1992 (Bangladesh)	49	55	1	22	· · · · · · · · · · · · · · · · · · ·	171.500	[19.428; 1513.881]
Carillo 1994	80	94	1	5		22.857	[2.376; 219.849]
Islam 1994	4	4	0	53		- 963.000	[17.010; 54518.815]
Random effects model		167		83	÷	70.051	[14.391; 340.985]
Heterogeneity: $I^2 = 25\%$ , $\tau^2 =$	0.6692, p	= 0.26	6				
					0.001 0.1 1 10 1000 Diagnostic Odds Ratio		

\*Experimental: Events = True Positives; Total = True Positives + False Positives. Control: Events = False Negatives; Total = True Negatives + False Negatives

Figure 12. Forest plot results for IP Dipstick - Direct Samples, DOR meta-analysis

	Experin	nental	C	ontrol			
Study	Events	Total	Events	Total	Odds Ratio	OR	95%-CI
Wang 2006	67	90	5	82		44.861	[16.160; 124.538]
Nato 2003 (Madagascar)	65	68	1	72		1538.333	[156.086; 15161.275]
Nato 2003 (Bangladesh)	49	57	3	45		85.750	[21.370; 344.079]
Random effects model		215		199		136.306	[25.438; 730.380]
Heterogeneity: $I^2 = 74\%$ , $\tau^2$	= 1.5752	p = 0.	02				
					0.001 0.1 1 10 1000 Diagnostic Odds Ratio		

\*Experimental: Events = True Positives; Total = True Positives + False Positives. Control: Events = False Negatives; Total = True Negatives + False Negatives