Addressing diagnostic limitations in enteric fever in resource-limited settings

Sabina Dongol

Medical Microbiologist

OUCRU Nepal

Current enteric fever diagnostics and its limitations

Major Limitations:

- Low sensitivity (depends on blood volume, timing, prior antibiotics)
- Expensive and slow → delays treatment
- Requires trained personnel & lab facilities

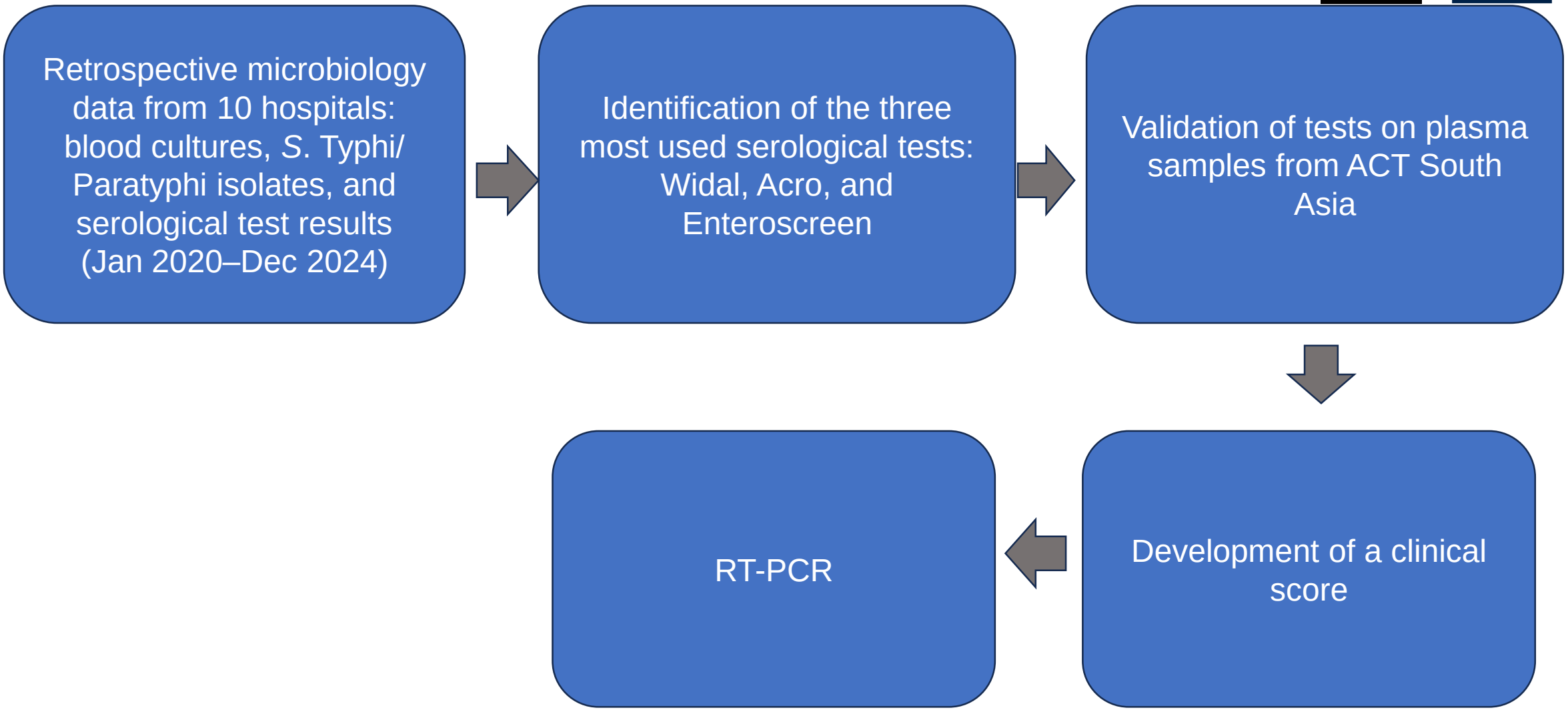
Major Limitations:

- Cross-reactivity → **false positives**
- May be negative **early in infection**
- Diagnostic accuracy in LMICs **poorly validated on local samples**

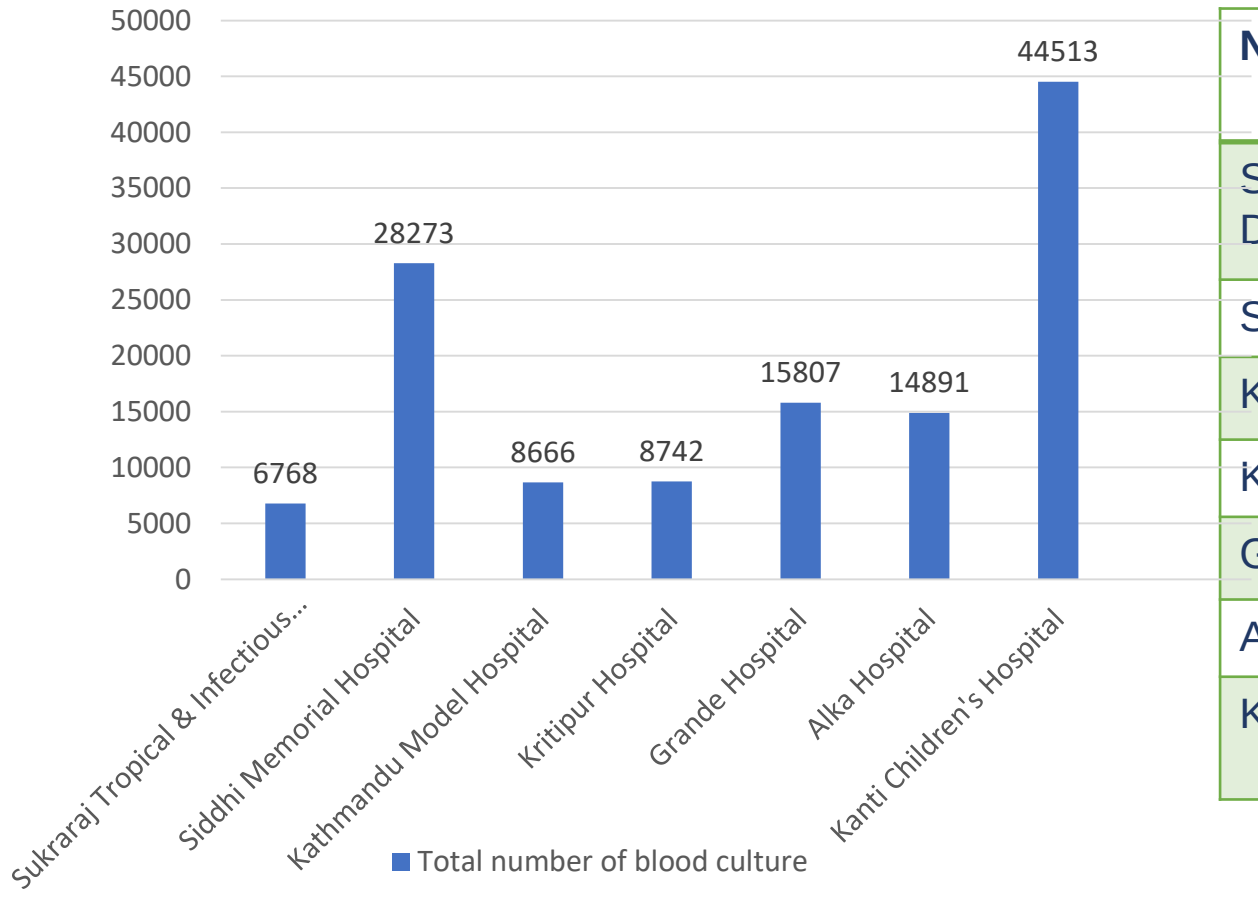
Current practice in enteric fever diagnosis

- Diagnosis and treatment are primarily guided by clinical judgment
- Patients with fever lasting more than 3 days and suggestive symptoms are often started on empirical oral antimicrobials
- Widal and RDTs widely used — ***Widal most preferred***
- Blood culture performed in some cases but not routine
- Publications on the use of PCR with variable results. Not used in practice

Overview of study methods



Blood culture data from 7 hospitals



Name of Hospitals	Total *Salmonella* isolates (%)
Sukraraj Tropical & Infectious Disease Hospital	159 (2.3%)
Siddhi Memorial Hospital	12 (0.04%)
Kathmandu Model Hospital	125 (1.4%)
Kirtipur Hospital	73 (0.84%)
Grande International Hospital	28 (0.18%)
Alka Hospital	194 (1.3%)
Kanti Children's Hospital	34 (0.08%)

Comparison of RDTs (IgM) & WIDAL results with blood culture validation of RDT tests

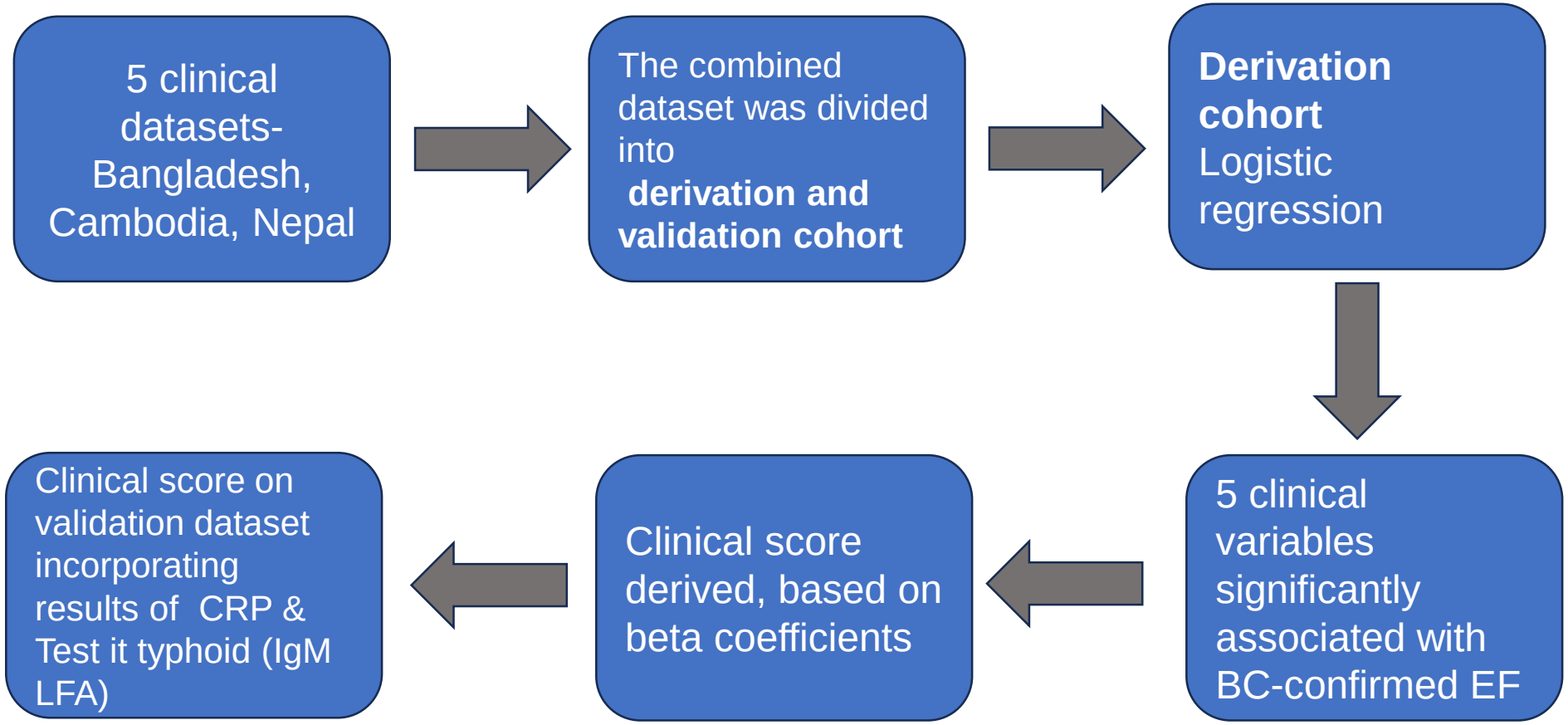
Total sample tested	Culture positive for *Salmonella* Typhi	Culture negative
426	58	368

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ACRO_IgM	41.4	96.2	63.2	91.2
Enteroscreen_IgM	13.8	98.6	61.5	87.9
WIDAL (TYDAL)	8.6	100.0	100.0	87.3

Inter- and intra-assay agreement of RDTs

Test (IgM)		Kappa	Agreement
ACRO	ACRO_IgM_**inter**	0.7	good agreement
Enteroscreen	Tulip_IgM_**inter**	0.6	moderate agreement
ACRO	ACRO_IgM_**intra**	0.8	good agreement
Enteroscreen	Tulip_IgM_**intra**	0.7	good agreement

Developing a clinical score



Comparison of common symptoms -Logistic regression

Symptom	Odds ratio (95% CI)	β-coefficient	p-value
Headache	6.75 (3.51-12.96)	1.909	<0.001
Vomiting	0.73 (0.45-1.20)	-0.310	0.214
Abdominal pain	1.66 (1.03-2.70)	0.509	0.039
Diarrhoea	2.42 (1.44-4.07)	0.884	0.001
Constipation	1.47 (0.77-2.78)	0.383	0.241
Absence of cough	1.66 (1.21-3.23)	0.508	0.040
Temperature ≥ 39°C	1.98 (1.21-3.23)	0.682	0.007
Pulse of <100 bpm	1.38 (0.84-2.26)	0.322	0.200

Clinical features	Point value score
If history of fever < 3 days and aged under 1 year and over 55 years	0
If history of fever ≥ 3 days and aged ≥ 1 year and < 55 years score symptoms as below:	
Headache	2
Abdominal pain	1
Diarrhoea	1
Absence of cough	1
Temperature ≥ 39^{o}C	1
Total	6

Performance of the Clinical Scoring System

Score group	Culture positive	Total	% positive
< 5 points	22	293	7.5%
≥ 5 points	82	292	28.1%

Performance summary

Parameter	Value
Threshold	≥ 5 points
Sensitivity	**78.8%**
Specificity	**56.3%**
Culture-positive detected	**82/104 (78.8%)**

Improved Predictive Value of Test-it Typhoid IgM Using Clinical Score

Group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All participants (any fever duration)	67.3	74.4	36.2	91.3
Sub-group with positive clinical score	67.3	74.4	**51.9**	91.3

RT PCR

- Two Primers sets

S. Typhi:
STY201 (virulence region)
*tvi*B (capsule gene)

- **S. Paratyphi A:**

SPA2308 (specific marker)
*sse*J (negative marker)

		Blood culture		
		Positive	Negative	Total
PCR	Positive	11	7	18
	Negative	62	220	282
Total		72	228	300

	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
PCR	15.28%	96.49%	61.11%	78.01%

Summary

- WIDAL test is widely used but performs poorly
- Locally available RDTs had poor diagnostic accuracies & results were not very reproducible
- We are looking at HlyE antigen as a better sero-diagnostic antigen
- Our results with PCR also showed poor sensitivity as others have found
- Finally, we derived a **simple clinical score** which could be used to enhance the PPV of a typhoid RDT
- Major limitation of this study is the imperfect sensitivity of blood culture for typhoid which makes evaluation of new diagnostics for the disease very challenging

Acknowledgements

Christopher Parry, Buddha Basnyat, Abhilasha Karkey
Nhukesh Maharjan, Typhoid Study Group of Nepal, Bangladesh, Cambodia

Dr. Sabina Dongol is the Head of Laboratories at OUCRU Nepal and a medical microbiologist with a DPhil from the University of Oxford. Her work focuses on enteric fever, antimicrobial resistance, and improving diagnostic strategies in resource-limited settings, alongside strengthening laboratory capacity and supporting clinical research.

Thank You