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The Application and Relevance of Typhoid IgG and IgM Serological Assays in the Management of Enteric Fever

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Abstract

Enteric fever, primarily caused by Salmonella enterica serovar Typhi, remains a major global public health challenge. Accurate and rapid diagnosis is critical for effective patient management and the prevention of complications. While blood culture is the diagnostic gold standard, its utility is limited by low sensitivity, long turnaround times, and resource constraints in endemic areas. Serological assays detecting Typhoid IgG and IgM antibodies offer a rapid, accessible alternative. IgM antibodies appear early in the acute phase of infection, serving as a primary marker for active or recent disease. Conversely, IgG antibodies rise later, persisting for months to provide insights into past exposure, chronic carriage, or secondary immune responses. This article reviews the clinical application, diagnostic relevance, limitations, and operational utility of Typhoid IgG/IgM testing in contemporary enteric fever management.

Keywords: Enteric Fever, Typhoid Igg/Igm Assay, Blood Culture, Typhoid Conjugate Vaccine, Multidrug Resistance, Resource-Poor Settings

Introduction

Enteric fever is a systemic infection encompassing typhoid and paratyphoid fevers. It continues to cause substantial morbidity and mortality worldwide, particularly in developing nations with inadequate sanitation and unsafe water supplies[1]. Early diagnosis is paramount to initiate appropriate antimicrobial therapy, reduce transmission, and prevent life-threatening complications like intestinal perforation[2].

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For decades, clinicians have relied on the Widal test, which detects agglutinating antibodies against Salmonella O and H antigens[3]. However, the Widal test is notorious for cross-reactivity, poor specificity, and the requirement of paired acute and convalescent sera for definitive interpretation[3,4]. Modern serological assays that specifically target Typhoid-specific Immunoglobulin G (IgG) and Immunoglobulin M (IgM) antibodies have emerged as vital diagnostic tools[5]. These assays aim to bridge the gap between slow culture-based methods and inaccurate traditional serology[6].

Literature Review

Dynamics of IgM and IgG Production

The human immune response to *Salmonella* Typhi involves the sequential production of specific immunoglobulins[1]. IgM is the first antibody isotype secreted by B cells following exposure to typhoid antigens, typically becoming detectable within 4 to 7 days after the onset of fever[7]. Because IgM degrades relatively quickly, its presence strongly indicates an acute, current, or very recent infection[8].

IgG antibodies develop later in the course of the disease, usually peaking during the second or third week of infection[7]. Unlike IgM, IgG antibodies persist in the circulation for months or even years[9]. This temporal separation allows clinicians to differentiate between an active primary infection (IgM positive, IgG negative or low) and a past exposure or reinfection (IgM negative, IgG positive)[10].

Clinical Application and Interpretation

In clinical settings, lateral flow immunochromatographic assays (rapid diagnostic tests) and Enzyme-Linked Immunosorbent Assays (ELISA) are widely used to detect these antibodies[11]. Interpretation of the results requires careful clinical correlation:

- **IgM Positive / IgG Negative:** Indicates early acute typhoid fever. Immediate treatment is usually warranted if clinical symptoms align[10,11].
- **IgM Positive / IgG Positive:** Indicates an active infection in a patient who has been symptomatic for over a week, or a secondary immune response due to reinfection[11].
- **IgM Negative / IgG Positive:** Suggests past infection, successful vaccination, or chronic carrier status[9,10]. It generally rules out acute primary typhoid fever unless evaluated as a rising titer in paired sera.
- **IgM Negative / IgG Negative:** Reduces the likelihood of typhoid fever, though false negatives can occur if the blood sample is drawn too early in the disease course[11].

Sensitivity and Specificity Percentages

The diagnostic accuracy of Typhoid IgG/IgM assays varies heavily depending on the study population, geographical region, and test format[12]. Systematic reviews and large-scale diagnostic accuracy evaluations show wide performance ranges across commercial kits:

- **Typhidot/Typhidot-M Assays:** The pooled sensitivity ranges from 78% to 94%, while the specificity ranges from 65% to 89%[12,13].
- **Other Combo Rapid Diagnostic Tests (RDTs):** Individual test performances exhibit substantial variance. For example, evaluations of standard commercial immunochromatographic cassettes report an IgM sensitivity of 46.2% to 72.7% and a specificity of 86.5% to 95.1%[6,13].
- **IgG Components:** The IgG portion of commercial rapid cassettes often displays significantly lower diagnostic sensitivity for acute cases (ranging from 9.1% to 49.6%), though it maintains high specificities up to 98.9% in non-endemic controls[10,11].

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- **ELISA Formats:** High-throughput IgG and IgM ELISAs offer superior precision compared to lateral flow formats, yielding optimized sensitivities of 95% to 96% and specificities of 94% to 95%[7,8].

Diagnostic Accuracy: IgG/IgM Tests vs. Blood Culture Gold Standard

Blood culture remains the traditional diagnostic gold standard due to its near 100% specificity; isolation of *Salmonella* Typhi provides definitive proof of infection[3]. However, its true sensitivity in real-world clinical practice is highly imperfect, often dropping to between 40% and 60%[1,3]. This low sensitivity stems from pre-analytical factors such as low bacterial loads in peripheral blood, inadequate sample volumes, and widespread, unprescribed antibiotic usage prior to sample collection[13,14].

When evaluated directly against blood culture, rapid IgG/IgM assays often show poor baseline concordance, sometimes yielding a sensitivity as low as 34.5% and a specificity of 45.0% in specific prospective cohorts[10]. This gap exists because a culture confirms the presence of viable bacteria in the bloodstream, whereas IgG/IgM tests detect the host's immunological footprint[6,11]. Consequently, an IgM test may return a positive result in a culture-negative patient who has already started antibiotic therapy, capturing an additional cohort of true enteric fever cases that culture missed[13]. Conversely, immunodiagnostic assays are prone to false-positive results where culture is negative, because they cannot differentiate active *S.* Typhi from lingering antibodies or cross-reactive immune responses triggered by non-typhoidal *Salmonella* or other febrile illnesses[10,12].

Extended Discussion

The Temporal Relationship in Typhoid Diagnosis

The clinical utility of blood culture versus antibody testing is inherently governed by a shifting temporal window from the onset of fever[3]:

- **Week 1 (Days 1–7):** This is the optimal window for blood cultures, yielding a peak sensitivity of 70% to 75% as bacteremia is at its highest before intracellular sequestration occurs[1,3]. Conversely, rapid antibody tests are highly unreliable during these first 5 days, frequently resulting in false negatives because the host's adaptive immune response has not yet produced detectable titers of IgM or IgG[11].
- **Week 2 and Beyond (Day 8+):** As the intracellular phase takes hold and circulating bacteria decrease, blood culture sensitivity drops sharply, frequently falling below 30–40%[14]. However, this phase marks the peak efficacy for serological diagnostics[9]. By day 5 to 7, anti-typhoid IgM titers rise above detection thresholds, establishing rapid antibody tests as the superior tool for late-presenting patients[11,13].

Vaccination-Induced Diagnostic Interference

The global rollout of modern typhoid vaccination strategies—particularly the World Health Organization-prequalified Typhoid Conjugate Vaccines (TCVs)—has introduced a complex confounding factor into serological diagnostics[14]. TCVs induce a robust and highly durable humoral immune response characterized by elevated systemic anti-Vi IgG titers that persist for years after a single dose[1,15].

Because many commercial lateral flow and ELISA kits measure total or broad-spectrum Typhoid IgG to gauge exposure history or carriage, vaccination systematically compromises test specificity[11,12]. In communities with high TCV coverage, a healthy vaccinated child will naturally possess an abundance of anti-Vi IgG[15]. If that child later presents with an unrelated febrile illness (such as malaria or dengue), a rapid typhoid combo test will trigger a strong false-positive IgG line[10,13]. This artifact makes it impossible

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to distinguish between vaccine-mediated protection and an active, secondary enteric infection based on IgG alone[12]. Consequently, in TCV-implemented regions, clinical triage must rely strictly on acute-phase IgM lines, or alternative non-Vi antigen targets (such as anti-LPS or anti-H-d flagellin), to prevent widespread over-diagnosis and inappropriate antibiotic usage[8,11].

Impact of Prior Antibiotic Usage on Diagnostics

In many typhoid-endemic, resource-poor nations, over-the-counter access to antimicrobials leads to extensive self-medication before a patient seeks formal medical care[14,15]. This pre-admission antibiotic use exerts diametrically opposed pressures on blood cultures and serological assays[3]:

- **Suppression of Blood Culture:** Even a single dose of an effective oral antibiotic (such as ciprofloxacin or azithromycin) rapidly sterilizes peripheral blood or reduces the circulating bacterial load below detectable thresholds[1,14]. This drives blood culture sensitivity down drastically, often yielding false-negative results despite an ongoing intracellular infection[3,13].
- **Blunting vs. Persistence of Antibody Responses:** In contrast, serological assays are not directly hindered by the presence of circulating antibiotics[11]. If a patient self-medicates late in the first week or during the second week of illness, the immune cascade has already been initiated[7]. The rapid test will successfully detect the circulating IgM or IgG footprint, allowing for an accurate diagnosis where culture fails[13]. However, if highly effective antibiotics are administered very early in the disease course (Days 1–3), bacterial replication is arrested prematurely[1]. This minimizes antigen exposure to host lymphocytes, which can blunt the subsequent antibody surge and cause false-negative IgM results later in the illness[7,11].

Specific Molecular Mechanisms of MDR and XDR *S.* Typhi Strains

The evolution of *Salmonella* Typhi has been marked by sequential acquisitions of antimicrobial resistance (AMR), significantly complicating clinical management and raising the stakes for rapid diagnostic triage[1,14]. Multidrug-resistant (MDR) *S.* Typhi is classically defined as resistance to the historic first-line core therapies: ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole[1,12].

The molecular foundation of the MDR phenotype is predominantly mediated by the acquisition of large, self-transmissible **IncHI1 plasmids** (such as pHCM1) or stable chromosomal integrations via composite transposons[1,14]. These mobile genetic elements carry a conserved resistance cassette containing specific genes: *blaTEM-1* encoding beta-lactamases (ampicillin resistance), *catA1* encoding chloramphenicol acetyltransferase (chloramphenicol resistance), and the *sul1/sul2* paired with *dfrA1* or *dfrA7* genes conferring resistance to antifolates[14].

The rapid horizontal dissemination of these IncHI1 vectors in the late 20th century forced a global clinical pivot toward fluoroquinolones (e.g., ciprofloxacin)[1,3]. However, chromosomal mutations rapidly emerged within the quinolone resistance-determining regions (QRDR) of the essential bacterial topoisomerase genes—specifically **gyrA** (mutations at codons Ser83 and Asp87) and **parC**[1,14]. These alterations reduce drug-binding affinity, causing fluoroquinolone treatment failures.

More critically, the emergence of Extensively Drug-Resistant (XDR) *S.* Typhi strains—particularly the dominant **H58 haplotype** clone originating in South Asia—exhibits the baseline MDR plasmid structure combined with the acquisition of an **IncY plasmid** carrying the **blaCTX-M-15 gene**[14,15]. This gene encodes an extended-spectrum beta-lactamase (ESBL) that renders the bacteria completely resistant to third-generation cephalosporins (e.g., ceftriaxone), leaving toxic or highly expensive options like azithromycin or carbapenems as the sole remaining therapeutic solutions[14].

Relevance and Operational Utility in Resource-Poor Countries

In resource-limited settings, the operational realities of healthcare delivery redefine the utility of diagnostic tests[13]. While blood culture is highly specific, it requires 3 to 5 days of incubation, specialized laboratory infrastructure, continuous electrical power, and highly trained personnel[3,14]. These resources are severely scarce in rural clinics and district hospitals across Sub-Saharan Africa and South Asia, where enteric fever is heavily endemic[1,15].

In these decentralized nodes of care, rapid Typhoid IgG/IgM lateral flow tests provide significant clinical value despite their diagnostic imperfections[11,13]. They function as true point-of-care tools: they cost less than US$1.00 per test, require no cold-chain logistics, use simple whole-blood fingerpricks, and deliver visual results within 15 minutes[11]. In the absence of diagnostic testing, clinicians in resource-poor countries frequently resort to presumptive, empirical treatment for any prolonged febrile illness[12,13]. This practice fuels global antimicrobial resistance and risks misdiagnosing concurrent deadly pathogens like malaria or dengue[10,13]. Strategically deploying IgG/IgM tests—prioritizing early acute IgM detection—gives healthcare workers a rapid triage mechanism to guide rational antibiotic prescription where cultures are completely unavailable[11,12].

Diagnostic Interpretation Matrix

The following clinical summary table outlines diagnostic interpretations based on serological combinations, pre-admission antibiotic exposure, and TCV vaccination status:

Serological Profile	**Patient Clinical History / Timeline**	**Blood Culture Yield Probability**	**Primary Clinical Interpretation**	**Recommended Clinical Action Plan**
IgM (+) **IgG (-)**	Fever ≥ 5 days; No prior antibiotics; Unvaccinated	**High** (If within Week 1)	Early acute primary *S.* Typhi infection.	Collect blood culture if available; immediately initiate appropriate target antibiotic therapy (e.g., Azithromycin).
IgM (+) **IgG (-)**	Fever 1–4 days; Prior early antibiotic use (Days 1–2)	**Very Low** (Antibiotic suppression)	Acute typhoid fever; culture yields sterilized but immune response initiated.	Do not rely on culture. Treat fully based on clinical presentation and IgM positivity. Monitor for clinical complications.
IgM (+) **IgG (+)**	Fever ≥ 10 days; No prior antibiotics;	**Moderate to Low** (Bacteremia declining)	Active acute typhoid fever (mid-to-late phase) OR secondary acute reinfection.	Initiate empirical treatment immediately. Evaluate for localized secondary complications (e.g., intestinal perforation risk).

	Unvaccinated			
IgM (-) IgG (+)	Presenting with fever; Prior TCV vaccination within past 3 years	**Low** (Unless non-typhoid)	Vaccine-induced IgG persistence. Current fever is likely a non-typhoid febrile illness (e.g., malaria, dengue).	Investigate for alternative febrile etiologies. Avoid empirical anti-typhoid prescriptions based on isolated IgG line.
IgM (-) IgG (+)	Afebrile or chronic abdominal symptoms; Unvaccinated; Endemic region	**Near Zero**	Potential chronic carrier state (*S.* Typhi reservoir in gallbladder) OR historical exposure.	Perform serial stool cultures to rule out active chronic shedding. Counsel on food hygiene handling.
IgM (-) IgG (-)	Fever ≥ 8 days; No prior antibiotics; Unvaccinated	**Low**	Enteric fever is highly unlikely. The host would have been seroconverted by this timeline.	Investigate alternative differential diagnoses (e.g., rickettsial infections, brucellosis, malaria).
IgM (-) IgG (-)	Fever 1–3 days; Prior heavy antibiotic use (Days 1–2)	**Extremely Low**	Indeterminate. Early antibiotics may have sterilized blood and blunted subsequent seroconversion.	Maintain high clinical suspicion. Treat empirically if clinical manifestations match enteric fever criteria; re-test IgM in 48–72 hours.

Conclusion

Typhoid IgG and IgM antibody testing represents a practical, rapid, and cost-effective advancement in the diagnostic toolkit for enteric fever. The diagnostic timeline dictates that while blood cultures excel during early bacteremia in week one, antibody assays become dominant as bacterial loads drop and immunoglobulins emerge in week two. Furthermore, prior antibiotic consumption heavily suppresses culture yields, whereas serological assays remain capable of detecting the host's immune footprint. Though their baseline sensitivity and specificity fall short of replacing microbiological gold standards, their rapid 15-minute deployment fills a critical diagnostic vacuum in resource-poor countries. As high-endemic regions increasingly adopt Typhoid Conjugate Vaccines and face mounting pressures from molecularly complex MDR and XDR H58 strains, clinicians must adapt to vaccine-induced IgG diagnostic interference by looking past IgG markers and focusing on acute IgM indicators to maintain diagnostic accuracy and preserve antibiotic stewardship.

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