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REVIEWER'S REPORT

Manuscript No.: IJAR-56425
Title: Integrated approach for the detection of bacterial resistance in Mali using chromogenic media

Recommendation:
Accept as it is .....
Accept after minor revision.....
Accept after major revision .....YES.....
Do not accept (*Reasons below*) .....

Rating	Excel.	Good	Fair	Poor
Originality		√		
Techn. Quality			√	
Clarity		√		
Significance		√		

Reviewer Name: Prof. Dr. Dillip Kumar Mohapatra

Detailed Reviewer's Report

Overall Evaluation

This manuscript presents a large, multi-year study (2020–2024) assessing a decentralized, two-step diagnostic strategy for antimicrobial resistance (AMR) detection in rural Mali. The approach combines manually prepared CHROMagar screening media with confirmatory testing using **MALDI-TOF MS**, **VITEK 2**, and PCR at the **University of Liege** reference laboratory.

The study addresses a critical global health issue—antimicrobial resistance—in a resource-limited African setting and proposes a pragmatic surveillance solution.

Overall impression: **Scientifically relevant, operationally innovative, but requires major revision before publication.**

Strengths

1. High Public Health Relevance

Focuses on AMR in sub-Saharan Africa, where surveillance data remain limited

Aligns with the **World Health Organization** Global AMR priorities and the GLASS framework.

Addresses bloodstream infections, which carry high mortality in LMICs.

2. Large Sample Size and Long Study Period

508 blood cultures over 4 years.

6,638 culture plates monitored for contamination.

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Provides 95% confidence intervals consistently.

3. Innovative Two-Step Diagnostic Model

On-site chromogenic screening followed by centralized confirmation.

Demonstrates feasibility of decentralized AMR surveillance.

Performance metrics (Sensitivity 80%, Specificity 85%) are acceptable for screening in low-resource settings.

4. Comprehensive Laboratory Methodology

Phenotypic testing (disk diffusion, VITEK 2)

Molecular confirmation (PCR detection of CTX-M, TEM/SHV, carbapenemases, mecA, vanA/vanB)

Cost analysis included (€14.41 per test)

5. Strong Data on Resistance Patterns

High ESBL rates (CTX-M 39%)

Detection of carbapenemase genes (15%)

MRSA and VRE documented

Correlation between prescription patterns and resistance profiles

Weaknesses

1. Overly Long and Redundant Results Section

Numerous antibiotic resistance figures (Figures 1–11) could be summarized into fewer tables.

Repetition of resistance percentages in text and figures reduces readability.

2. Statistical Analysis is Basic

Only descriptive statistics used.

No multivariate analysis or risk factor assessment.

No agreement analysis (e.g., kappa coefficient) between CHROMagar and VITEK 2.

3. Inconsistencies in Sample Numbers

148 positive cultures vs 112 isolates vs 86 resistant strains.

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The flow of samples should be clarified in a consolidated diagram.

4. Poor Performance for Pseudomonas spp.

Sensitivity 25% and specificity 20%.

This significantly weakens the universal applicability of the screening approach.

5. Cost Analysis Needs Strengthening

No comparison with standard automated systems.

No cost-effectiveness or cost-benefit modeling.

6. Language and Formatting Issues

Typographical inconsistencies (e.g., β-lactamase formatting).

Occasional grammatical errors.

Some figures are overcrowded and need redesign.

Scientific and Clinical Significance

Regional Significance: HIGH

Provides rare AMR surveillance data from rural Mali.

Demonstrates feasibility of decentralized microbiology capacity.

Global Significance: MODERATE–HIGH

Offers scalable model for other LMICs.

Shows that chromogenic media can support early detection of:

ESBL

Carbapenemase producers

MRSA

VRE

Operational Significance: VERY HIGH

Cost per analysis (€14.41) is remarkably low.

Low contamination rate (1.64%) supports feasibility of manual preparation.

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Key Points of the Manuscript

A simplified two-step model can strengthen AMR surveillance in rural Africa.

ESBL-producing Enterobacteriaceae are highly prevalent.

Carbapenem resistance genes (KPC, NDM, OXA-48, VIM) are already circulating.

High empirical prescription of cephalosporins correlates with high resistance.

CHROMagar performs well for Enterobacteriaceae but poorly for Pseudomonas spp.

Decentralized screening + centralized confirmation is operationally viable.

Major Concerns Requiring Revision

Clarify Study Flow

Provide a simplified flowchart:

508 cultures → 148 positive → 112 isolates → 86 resistant → confirmed strains.

Improve Statistical Analysis

Add:

Cohen's kappa agreement between CHROMagar and VITEK 2.

Comparative cost analysis.

Possibly resistance trend over time (2020–2024).

Strengthen Discussion

Compare findings with other West African AMR data.

Discuss implications for Mali's national AMR strategy.

Address poor detection of Pseudomonas spp.

Reduce Redundancy

Condense multiple resistance figures into summary tables.

Minor Concerns

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Ensure uniform EUCAST version reporting.

Clarify transport conditions to Belgium (temperature monitoring?).

Improve figure quality and English editing.

Ensure consistent use of bacterial nomenclature (italicization).

Ethical and Operational Considerations

Ethical approval statement should be clearly presented.

Informed consent process should be clarified.

Biosafety measures for transport of resistant strains should be detailed.

Recommendation

Final Decision: MAJOR REVISION

WHY MAJOR REVISION? JUSTIFICATION

TITLE (Lines 1–2)

"Integrated approach for the detection of bacterial resistance in Mali using chromogenic media"

Concern:

The term **"Integrated approach"** is vague.

Does not specify:

Study design (prospective? diagnostic accuracy?)

Population (bloodstream infections)

Setting (rural)

Comparator (reference laboratory confirmation)

Required Revision:

Clarify design and context:

"Prospective evaluation of a decentralized chromogenic screening strategy for bloodstream antimicrobial resistance detection in rural Mali."

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ABSTRACT (Lines 3–27)

Lines 4–9 (Objective & Methods)

 Issue 1: Study Design Missing

The abstract does not specify:

Prospective or retrospective?

Diagnostic accuracy study?

Cross-sectional?

Time frame?

This violates STARD guidelines for reporting diagnostic studies.

Issue 2: Reference Standard Not Clearly Defined

The abstract says:

"phenotypic and genotypic confirmation"

But:

Is VITEK® 2 the gold standard?

Is PCR the gold standard?

Was discordance resolved?

This is critical for interpreting sensitivity/specificity.

Lines 10–15 (Prevalence Reporting)

Issue 3: Denominator Confusion

508 cultures

148 positive

86 resistant strains

But:

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Table later shows 112 isolates.

PCR denominators differ (126, 123, 127).

This inconsistency creates major interpretability problems.

A diagnostic accuracy paper must include a clear flow diagram (STARD requirement).

Lines 16–21 (Genetic Data)

Issue 4: Different Denominators for Each Gene

Examples:

CTX-M: 49/126

TEM/SHV: 32/123

Carbapenemases: 19/127

Why are denominators different?
Were all isolates tested for all genes?
Were some PCR failures excluded?

Without explanation, this appears statistically weak.

Lines 22–24 (Diagnostic Performance)

Issue 5: PPV and NPV Calculation Problem

You report:

Sensitivity 80%

Specificity 85%

PPV 90%

NPV 72%

But PPV and NPV depend on prevalence.

You did not:

State resistance prevalence used in calculation.

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Provide 2×2 table in abstract.

This weakens scientific transparency.

Lines 25–27 (Conclusion)

Issue 6: Overstatement

You conclude:

"confirm the potential of this simplified approach"

But:

Pseudomonas sensitivity = 25%

Specificity = 20%

This directly contradicts a broad "confirmation."

Conclusion must be species-specific.

INTRODUCTION (Lines 33–125)

Lines 40–46 (AMR Mortality Data)

Issue 7: Potentially Outdated / Conflicting Numbers

You cite:

1.27 million global deaths

250,000 deaths in WHO Africa 2024

1.05 million African deaths in 2019

These figures appear inconsistent.

Data from **World Health Organization** and **The Lancet Global Health** must be harmonized and updated.

Major revision required to verify accuracy.

Lines 100–109 (GLASS Description)

You reference:

WHO

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FAO

WOAH

But you do not cite:

GLASS enrollment status of Mali

Current AMR national data

Context remains descriptive, not analytical.

Lines 111–125 (Objective)

Issue 8: Objective Not Statistically Framed

You state:

"validate the use of simplified method"

But:

No predefined hypothesis

No non-inferiority margin

No expected sensitivity threshold

Diagnostic validation requires pre-specified performance targets.

MATERIALS AND METHODS

2.1 Study Design (Line 127)

Issue 9: Design Not Clearly Declared

Is this:

Prospective?

Cross-sectional?

Diagnostic accuracy study?

This is a major reporting deficiency.

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2.4 Blood Culture Systems (Lines 156–165)

You changed from:

Signal™ to BacT/Alert

Issue 10: Methodological Heterogeneity

Changing blood culture systems mid-study introduces:

Detection bias

Variability in positivity rates

No statistical adjustment reported.

Major methodological concern.

2.4.2 Transport to Belgium (Lines 192–195)

Samples transported under:

"ambient conditions within 48 h"

Issue 11: No Temperature Monitoring Reported

Without temperature logging:

Risk of bacterial viability loss

Risk of resistance profile alteration

This affects validity of reference confirmation.

2.6 Antimicrobial Testing

Issue 12: EUCAST Version Inconsistency

You use:

EUCAST 10.0 (2020)

EUCAST 11.0 (2021)

Study period: 2020–2024.

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Breakpoints change over time.

Were historical isolates reinterpreted?

This requires clarification.

2.7 Statistical Analysis

Issue 13: Only Descriptive Statistics Used

For a 4-year diagnostic study, missing:

Cohen's kappa (agreement)

McNemar test (paired diagnostic comparison)

Multivariate risk factor analysis

Trend analysis over time

Statistical depth is insufficient for publication in strong journals.

2.8 Cost Analysis

Issue 14: No Comparator

You estimate €14.41 per test.

But:

No comparison with automated system cost.

No cost-effectiveness ratio.

No sensitivity analysis.

Cost evaluation is incomplete.

RESULTS

Table 4 (Demographics)

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Issue 15: Missing Data (27.8% sex not recorded)

High missing data not addressed.
No sensitivity analysis performed.

Table 5 (112 isolates vs 86 resistant strains)

Issue 16: Flow Inconsistency

508 cultures
→ 148 positive
→ 112 isolates
→ 86 resistant

But explanation of exclusions is missing.

Major STARD violation.

Pseudomonas Performance (Lines 520–523)

Sensitivity: 25%
Specificity: 20%

Issue 17: Extremely Poor Performance

This dramatically reduces generalizability.

Yet manuscript concludes overall approach is validated.

Conclusion and results are misaligned.

DISCUSSION

Blood Culture Positivity (Line 546)

You claim:

> Higher than African average

But:

> No statistical comparison test.

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No adjustment for case mix.

This is descriptive, not analytical.

General Discussion Weakness

Missing:

Limitation of transport bias

Effect of blood culture system change

Small sample sizes (e.g., Salmonella n=2)

No external validation

OVERALL SCIENTIFIC REASONS FOR MAJOR REVISION

Domain	Problem	Severity
Study design reporting	Not clearly defined	Major
Sample flow clarity	Inconsistent denominators	Major
Statistical depth	Descriptive only	Major
Diagnostic validation	No agreement statistics	Major
Method heterogeneity	Blood culture system change	Major
Performance inconsistency	Pseudomonas failure	Major
Cost analysis	No comparator	Moderate
Data harmonization	EUCAST version differences	Major
Missing data handling	Not addressed	Moderate

FINAL JUSTIFICATION

This manuscript addresses an important AMR surveillance issue aligned with priorities of the **World Health Organization**.

However, it requires **MAJOR REVISION** because:

Diagnostic study reporting standards (STARD) are not fully met.

Statistical analysis is insufficient for validation claims.

Internal data inconsistencies weaken reliability.

Methodological heterogeneity is not controlled.

Conclusions overstate findings relative to species-level performance.

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