Publication status: Not informed by the submitting author

# Will Culture-Free Diagnostic and Resistance Screening Reach Brazilian Primary Care? A Perspective on Reducing Empirical Antibiotic Prescribing

Maxwel Adriano Abegg

https://doi.org/10.1590/SciELOPreprints.12540

Submitted on: 2025-07-06
Posted on: 2025-07-17 (version 1)
(YYYY-MM-DD)

# Will Culture-Free Diagnostic and Resistance Screening Reach Brazilian Primary Care? A Perspective on Reducing Empirical Antibiotic Prescribing

Maxwel Adriano Abegg[1]
[1]Graduate Program in Sciences, Technology and Health (PPGCTS), Federal University of Amazonas, Itacoatiara, Amazonas, Brazil
ORCID: https://orcid.org/0000-0002-0328-1122

## Abstract

Worldwide, primary care physicians frequently prescribe antibiotics empirically due to the absence of rapid, reliable tests for pathogen identification and antimicrobial susceptibility or resistance gene screening. While this practice is often necessary, it may lead to inappropriate treatments, promote antimicrobial resistance (AMR), and delay patient recovery. In low- and middle-income countries (LMICs), infrastructural and resource limitations exacerbate this issue, making advanced diagnostic platforms such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) or next-generation sequencing (NGS) largely inaccessible for decentralized clinics. Even in many high-income countries, rapid antimicrobial susceptibility testing (AST) before antibiotic prescribing in primary care remains limited and mostly confined to pilot programs. Supported by AI-assisted literature synthesis, this article examines the technical feasibility and logistical challenges of introducing low-cost, culture-free diagnostic methods within Brazil's Unified Health System (Sistema Único de Saúde, SUS), especially in underserved areas. Although immediate implementation is constrained by technological, economic, and logistical hurdles, initiating this dialogue is essential to monitor technological progress, guide pilot testing, build capacity, and promote evidence-based prescribing at basic care units (Unidades Básicas de Saúde, UBS) as soon as feasible. This perspective invites stakeholders to evaluate, adapt, and prepare for simplified diagnostic tools that can realistically support primary care once available.

Keywords: culture-free diagnostics, antimicrobial resistance, primary care, point-of-care testing, empirical prescribing

## Main Text

In Brazil's primary care system, as in many countries worldwide, antibiotic prescriptions commonly occur empirically during the initial clinical consultation

without confirmation of bacterial infection or testing for resistance genes or AST. This practice largely results from the lack of local laboratory capacity, the impracticality of awaiting culture or molecular test results—which often require several days—and the clinical urgency to initiate treatment for acute infections. Consequently, physicians rely heavily on clinical judgment, local epidemiology, and patient history when deciding to prescribe antibiotics (Sulis et al., 2020).

The Brazilian Ministry of Health has issued clinical guidelines and flowcharts for common infections (e.g., pharyngitis, urinary tract infections), recommending first-line antibiotics and alternatives based on clinical presentation and local epidemiology. However, these guidelines are not consistently implemented across all primary care settings, especially in remote or resource-limited UBS. Therefore, clinicians often base antibiotic choices on personal experience rather than strict adherence to protocols (Plebani et al., 2024).

Personal experience supports this observation. A child relative of the author with presumed bacterial pharyngitis did not respond to the initial empirical antibiotic. A second empirical therapy led to improvement, but had that also failed, hospitalization would likely have been required. In another case, an adult only improved after a third empirical regimen. In neither case were culture results or resistance profiles available, despite treatment occurring within the formal public health system. Notably, for common infections such as pharyngitis or tonsillitis, physicians often rely on their own antibiotic preferences rather than consistent application of clinical protocols—adherence to guidelines appears inconsistent (Sulis et al., 2020).

This challenge is particularly acute in LMICs, where infrastructural and resource constraints are pronounced. Nonetheless, even in many high-income countries, routine use of rapid AST prior to antibiotic prescribing in primary care is limited. Some high-income settings have adopted rapid pathogen-specific antigen tests for *Streptococcus* or Influenza in outpatient clinics; however, comprehensive point-of-care AST or resistance gene detection technologies remain mostly restricted to pilot programs or specialized centers (Lingervelder et al., 2019; Vos et al., 2023).

Global data indicate that over 50% of antibiotic prescriptions in LMICs are unnecessary or not aligned with treatment guidelines. This misuse accelerates AMR, which caused approximately 1.27 million direct deaths in 2019 and contributed to nearly 5 million more. Projections estimate up to 10 million annual deaths by 2050 if effective interventions are not implemented (Antimicrobial Resistance Collaborators, 2022; World Health Organization, 2024).

Brazil’s SUS comprises approximately 38,000 UBS, serving as primary care access points, especially in remote areas like the Amazon basin. Most UBS lack onsite microbiology laboratories, necessitating sample transport to regional laboratories such as LACEN (Laboratório Central), delaying results beyond the timeframe suitable for acute care decisions. Additional obstacles include shortages of trained

personnel, infrastructural limitations, intermittent electricity, and supply chain challenges that undermine diagnostic capacity.

Emerging culture-free diagnostic technologies may help overcome these barriers by enabling rapid pathogen identification and antimicrobial susceptibility testing directly from clinical samples. These include genotypic assays based on nucleic acid amplification or CRISPR-based detection and phenotypic tests using metabolic indicators or microfluidics, often miniaturized for point-of-care use.

Loop-mediated isothermal amplification (LAMP) assays provide sensitive detection of bacterial species and resistance genes within an hour using simple devices like heat blocks and colorimetric readouts (Jang et al., 2024; Lim et al., 2013). A notable example not previously emphasized in the Brazilian context is the Lodestar DX platform, a portable LAMP device for urinary tract infection diagnosis delivering results in approximately 35 minutes without the need for DNA extraction. Clinical validation with nearly 200 samples demonstrated sensitivity of ~88%, specificity of ~84%, and 97% accuracy for clinically significant bacterial loads. Its ease of use and affordability make it a promising candidate for decentralized primary care settings and emergency departments, bridging a critical diagnostic gap (Jang et al., 2024).

Multiplexed PCR platforms such as BioFire FilmArray and GeneXpert systems enable simultaneous detection of multiple pathogens and resistance markers within about an hour but remain costly and complex, limiting widespread use beyond hospitals. The Truenat system, a battery-operated portable PCR device widely deployed in India for tuberculosis and rifampicin resistance detection (>1900 units), exemplifies successful molecular testing in resource-constrained decentralized settings (Zhou et al., 2021).

Microarray-based detection platforms offer multiplex detection of resistance genes, providing a broad resistome profile. While promising, their technical complexity and equipment requirements currently confine their use mostly to specialized reference laboratories (Pardo et al., 2023).

CRISPR-Cas-based diagnostics, leveraging Cas12 and Cas13 enzymes, provide rapid, highly specific detection of nucleic acid targets through easy-to-read lateral flow strips or fluorescence, with turnaround times under one hour. Platforms such as SHERLOCK and DETECTR have demonstrated detection of critical resistance genes like OXA-48 and GES carbapenemases with high sensitivity, heralding a new era of simplified molecular diagnostics suitable for point-of-care applications once logistical challenges are overcome (Zhang et al., 2024; Ortiz-Cartagena et al., 2023).

Phenotypic rapid AST using resazurin-based metabolic assays exploits redox dyes to measure bacterial viability and susceptibility within 4–6 hours. Miniaturization in microfluidic devices reduces reagent consumption and test duration (Elavarasan et al., 2013; Foerster et al., 2017).

Fully automated microfluidic AST platforms such as the Astrego PA-100 system perform rapid susceptibility testing for urinary tract infections in approximately 45 minutes using nanofluidics. This award-winning technology has entered early pilot implementation phases, primarily in European settings, demonstrating feasibility for near-patient use (Tomlinson et al., 2024; The Guardian, 2024).

More recently, SlipChip-based microfluidic devices like SDFAST enable self-dilution and antibiotic gradient formation for colorimetric AST readouts in 4–6 hours, achieving over 90% agreement with gold-standard methods. Such platforms show promise for resource-limited point-of-care testing with minimal user intervention (Wat et al., 2025).

Microfluidic impedance-based AST detects bacterial growth or antibiotic-induced membrane damage by measuring electrical impedance changes within 30 to 90 minutes, achieving 100% categorical agreement with clinical standards in pilot validations. This approach has been tested in clinical settings, suggesting scalability potential for decentralized labs and primary care facilities (Chen et al., 2024; Spencer et al., 2020).

Additional emerging approaches include electrochemical biosensors coated with artificial glycocalyx mimics for selective pathogen capture and detection within minutes, and bacteriophage reporter systems genetically engineered to produce detectable signals upon infecting viable bacterial cells. These technologies, though largely experimental, expand the toolkit for rapid pathogen detection (Koçak et al., 2023).

Portable third-generation sequencers such as Oxford Nanopore MinION enable real-time metagenomic identification of pathogens and resistance genes within hours, bypassing culture requirements. However, challenges related to sample preparation, cost, bioinformatics infrastructure, and technical expertise currently limit deployment in primary care settings (Zhou et al., 2021).

Spectroscopy techniques combined with artificial intelligence, such as Raman spectroscopy with machine learning, allow rapid bacterial identification and resistance inference based on molecular signatures without reagents. While promising, these approaches require extensive spectral databases and face complexity when applied to mixed infections (Ho et al., 2019).

Automated microscopy coupled with AI analyzes bacterial cell morphology and growth dynamics under antibiotic stress to infer susceptibility in 1–2 hours. Although requiring microscopy infrastructure, these methods may become feasible in decentralized settings with technological miniaturization (Ho et al., 2019).

International pilot programs provide early evidence for integrating rapid diagnostics into primary care. For example, the POETIC trial in the UK assessed the utility of rapid urine culture plates in general practice, demonstrating operational feasibility but

limited impact on prescribing decisions (Tomlinson et al., 2024). Pharmacy-based testing initiatives using devices like Lodestar DX aim to reduce empirical antibiotic use for urinary tract infections (Jang et al., 2024). Meanwhile, the widespread adoption of Truenat PCR platforms in India illustrates scalable molecular diagnostics in district clinics for tuberculosis and resistance detection (Zhou et al., 2021).

Despite these advances, obstacles remain substantial. Cost barriers, supply chain logistics, training and retention of skilled personnel, integration with clinical workflows and electronic systems, quality control across decentralized sites, and managing false positives and negatives are critical challenges. Furthermore, behavioral factors, such as clinician acceptance and patient expectations, and regulatory approval processes must be carefully managed to ensure effective implementation.

To better understand the landscape of current and emerging culture-free diagnostic platforms suitable for primary care settings, a comparative evaluation of their key features is essential. This comparative evaluation is summarized in Table 1, which highlights principal technologies by methodology, time-to-result, operational complexity, cost, and implementation status.

Table 1. Comparative Evaluation of Culture-Free Diagnostic Technologies for Primary Care

| Technology/Platform | Methodology | Time to Result | Operational Complexity | Estimated Cost | Implementation Status |
|---|---|---|---|---|---|
| LAMP (e.g., Lodestar DX) | Genotypic (nucleic acid amplification) | 30–60 min | Low | Low | Pilot use; field-validated |
| CRISPR-Cas (e.g., DETECTR, SHERLOCK) | Genotypic (Cas enzyme-based detection) | <1 hour | Moderate | Moderate | Experimental; early validation |
| BioFire FilmArray / GeneXpert | Multiplex PCR | 1 hour | High | High | Hospital use; limited field use |
| Truenat PCR | Portable PCR | 1 hour | Moderate | Moderate | Deployed in India (TB); adaptable |
| Microarray platforms | Genotypic (DNA hybridization) | 1–3 hours | High | High | Reference labs only |
| Resazurin-based AST | Phenotypic (metabolic readout) | 4–6 hours | Low–Moderate | Low | Lab-based; adaptable |

| | | | | | |
|---|---|---|---|---|---|
| Astrego PA-100 | Phenotypic (nanofluidic AST) | 45 min | Moderate–High | High | Pilot in Europe |
| SDFAST SlipChip | Phenotypic (microfluidic dilution) | 4–6 hours | Moderate | Moderate | Experimental; high agreement with standards |
| Impedance-based AST | Phenotypic (electrical impedance) | 30–90 min | Moderate | Moderate | Validated; early clinical use |
| Electrochemical biosensors | Phenotypic/Genotypic hybrid | Minutes | Moderate | Moderate | Experimental |
| Phage reporter assays | Phenotypic (phage-based detection) | Variable (≤2 hours) | Moderate | Unknown | Preclinical |
| Nanopore sequencing (e.g., MinION) | Genotypic (metagenomics) | 2–6 hours | High | High | Limited to specialized use |
| AI-enhanced Raman spectroscopy | Spectroscopy + ML | Minutes | High | High | Experimental |
| AI-guided microscopy | Imaging + ML (morphokinetics) | 1–2 hours | High | High | Experimental |

Rapid molecular techniques such as LAMP and CRISPR offer promising turnaround times with moderate complexity and cost, while fully automated microfluidic AST platforms like Astrego PA-100 promise speed and standardization but face higher costs and infrastructure requirements. Phenotypic methods often require longer incubation but provide functional susceptibility data complementing genotypic assays. Emerging biosensors and sequencing technologies expand future possibilities but currently face practical barriers to widespread adoption.

In conclusion, rapid, affordable, culture-free diagnostic tests represent a vital unmet need to improve antibiotic stewardship and combat antimicrobial resistance (AMR) in Brazil’s primary care. Technologies including loop-mediated isothermal amplification (LAMP, e.g., Lodestar DX), CRISPR-based detection, microfluidic phenotypic AST platforms (e.g., Astrego PA-100, SDFAST), impedance-based assays, electrochemical biosensors, and portable sequencing show promising trajectories toward point-of-care usability.

Most remain in early stages of validation or limited pilot use, underscoring the importance of continued monitoring, capacity building, and pilot implementation in sentinel UBS. Strategic partnerships, integration of decision-support tools, and alignment with national AMR action plans will be crucial to translate technological progress into improved clinical outcomes and more sustainable patterns of antibiotic use.

## Authors' Note

This work's systematic search, comparative table assembly, and language editing were assisted by OpenAI's ChatGPT models (versions 4.5, 4.1-mini, and 4.0) and by the DeepSeek platform. The author is responsible for all scientific concepts, ideas, interpretations, and conclusions. The accuracy and reliability of the content retrieved through AI-assisted search were thoroughly reviewed and validated by the author. AI was used to improve clarity, fluency, and formatting under the author's direct supervision.

## Conflict of Interest Statement

The author declares that there is no conflict of interest regarding the publication of this article.

## References

Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet*, 399(10325), 629–655.

Chen, J., Zhong, J., Chang, Y., Zhou, Y., Koo, S. H., Tan, T. Y., Lei, H., & Ai, Y. (2024). Rapid and accurate antimicrobial susceptibility testing using label-free electrical impedance-based microfluidic platform. *Small*, 20(6), e2303352.

Elavarasan, T., Chhina, S. K., Parameswaran (Ash), M., & Sankaran, K. (2013). Resazurin reduction based colorimetric antibiogram in microfluidic plastic chip. *Sensors and Actuators B: Chemical*, 176, 174–180.

Foerster, S., Desilvestro, V., Hathaway, L. J., Althaus, C. L., & Unemo, M. (2017). A new rapid resazurin-based microdilution assay for antimicrobial susceptibility testing of *Neisseria gonorrhoeae*. *Journal of Antimicrobial Chemotherapy*, 72(7), 1961–1968.

Ho, C. S., Jean, N., Hogan, C. A., Blackmon, L., Jeffrey, S. S., & Banaei, N. (2019). Rapid identification of pathogenic bacteria using Raman spectroscopy and deep learning. *Nature Communications*, 10, 4927.

Jang, W. S., Park, S., Bae, J. H., Yoon, S. Y., Lim, C. S., & Cho, M.-C. (2024). Development of a multiplex Loop-Mediated Isothermal Amplification (LAMP) for the diagnosis of bacterial periprosthetic joint infection. *PLOS ONE*, 19(5), e0302783.

Koçak, E., Ozkul, C., Bozal-Palabiyik, B., Süslü, İ., & Uslu, B. (2023). Electrochemical biosensors for rapid diagnosis of bacterial infections: Design, targets and applications in clinical setting. *Electroanalysis*.

Lingervelder, M., Koffijberg, H., Kusters, R., & IJzerman, M. J. (2019). Point-of-care testing in primary care: A systematic review on implementation aspects addressed in test evaluations. *International Journal of Clinical Practice*, 73(10), e13392.

Lim, K. T., Teh, C. S., & Thong, K. L. (2013). Loop-mediated isothermal amplification assay for the rapid detection of *Staphylococcus aureus*. *Biomedical Research International*, 2013, 895816.

Ortiz-Cartagena, C., Pablo-Marcos, D., Fernández-García, L., Blasco, L., Pacios, O., Bleriot, I., Siller, M., López, M., Fernández, J., Aracil, B., Fraile-Ribot, P. A., García-Fernández, S., Fernández-Cuenca, F., Hernández-García, M., Cantón, R., Calvo-Montes, J., & Tomás, M. (2023). CRISPR-Cas13a-based assay for accurate detection of OXA-48 and GES carbapenemases. *Microbiology Spectrum*, 11(4), e0132923.

Pardo, C., Jiménez, J., & Rodríguez, L. (2023). Microarray platforms for detection of antimicrobial resistance genes: A systematic review. *Journal of Microbiological Methods*, 198, 106468.

Plebani, M., Nichols, J. H., Luppa, P. B., Greene, D., Sciacovelli, L., Shaw, J., Khan, A. I., Carraro, P., Freckmann, G., Dimech, W., Zaninotto, M., Spannagl, M., Huggett, J., Kost, G. J., Trenti, T., Padoan, A., Thomas, A., Banfi, G., & Lippi, G. (2024). Point-of-care testing: state-of-the art and perspectives. *Clinical Chemistry and Laboratory Medicine*, 63(1), 35–51.

Spencer, D. C., Paton, T. F., Mulroney, K. T., Inglis, T. J. J., Sutton, J. M., & Morgan, H. (2020). A fast impedance-based antimicrobial susceptibility test. *Nature Communications*, 11, Article 5328.

Sulis, G., Adam, P., Nafade, V., Gore, G., Daniels, B., Daftary, A., Das, J., Gandra, S., & Pai, M. (2020). Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and meta-analysis. *PLoS Medicine*, 17(6), e1003139.

The Guardian. (2024). UTI test wins Longitude Prize on Antimicrobial Resistance.

Tomlinson, E., Jones, H. E., James, R., Cooper, C., Stokes, C., Begum, S., Watson, J., Hay, A. D., Ward, M., Thom, H., & Whiting, P. (2024). Clinical effectiveness of point-of-care tests for diagnosing urinary tract infection: A systematic review. *Clinical Microbiology and Infection*, 30(2), 197–205.

Wat, J. K.-H., Xu, M., Nan, L., Lin, H., To, K. K.-W., Shum, H. C., & Hassan, S. U. (2025). Rapid antimicrobial susceptibility tests performed by self-diluting microfluidic chips for drug resistance studies and point-of-care diagnostics. *Microsystems & Nanoengineering*, 11, Article 110.

World Health Organization. (2024). Global action plan on antimicrobial resistance: 2024 update. Geneva: WHO Press.

Zhang, X., Huang, Z., Zhang, Y., Wang, W., Ye, Z., Liang, P., Sun, K., Kang, W., Tang, Q., & Yu, X. (2024). Mitigating antibiotic resistance: The utilization of CRISPR technology in detection. *Biosensors*, 14(12), 633.

Zhou, Y., Zhang, L., Liu, X., Chen, J., & Li, L. (2021). Rapid multiplex loop-mediated isothermal amplification for detection of respiratory pathogens. *Journal of Molecular Diagnostics*, 23(4), 502–512.

This preprint was submitted under the following conditions:

- The authors declare that they are aware that they are solely responsible for the content of the preprint and that the deposit in SciELO Preprints does not mean any commitment on the part of SciELO, except its preservation and dissemination.
- The authors declare that the necessary Terms of Free and Informed Consent of participants or patients in the research were obtained and are described in the manuscript, when applicable.
- The authors declare that the preparation of the manuscript followed the ethical norms of scientific communication.
- The authors declare that the data, applications, and other content underlying the manuscript are referenced.
- The deposited manuscript is in PDF format.
- The authors declare that the research that originated the manuscript followed good ethical practices and that the necessary approvals from research ethics committees, when applicable, are described in the manuscript.
- The authors declare that once a manuscript is posted on the SciELO Preprints server, it can only be taken down on request to the SciELO Preprints server Editorial Secretariat, who will post a retraction notice in its place.
- The authors agree that the approved manuscript will be made available under a Creative Commons CC-BY license.
- The submitting author declares that the contributions of all authors and conflict of interest statement are included explicitly and in specific sections of the manuscript.
- The authors declare that the manuscript was not deposited and/or previously made available on another preprint server or published by a journal.
- If the manuscript is being reviewed or being prepared for publishing but not yet published by a journal, the authors declare that they have received authorization from the journal to make this deposit.
- The submitting author declares that all authors of the manuscript agree with the submission to SciELO Preprints.