

VITEK® REVEAL™

Stewardship and Access Plan (SAP)



GRAM-NEGATIVE (GN01-AST) PANEL FOR BLOODSTREAM INFECTIONS





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Abbreviations

Abbreviation	Definition
AMR	Antimicrobial resistance
ASP	Antimicrobial stewardship program
AST	Antimicrobial susceptibility testing
BSI	Bloodstream infection
BARDA	Biomedical Advanced Research and Development Authority
BMD	Broth microdilution
CLIA	Clinical Laboratory Improvement Act
CSR	Corporate Social Responsibility
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance and Use Surveillance
GPPS	Global Point Prevalence Survey
IVD	<i>in vitro</i> diagnostics
MIC	Minimum Inhibitory Concentration
PBC	Positive blood culture
VOC	Volatile organic compound

1. Product Definition

1.1 The VITEK® REVEAL™ AST System

The VITEK® REVEAL™ AST System is an automated *in vitro* diagnostic (IVD) system for quantitative and qualitative phenotypic antimicrobial susceptibility testing of organisms directly from positive blood culture. The system consists of two devices (the VITEK® REVEAL™ Instrument and the VITEK® REVEAL™ Sealer) which process the consumables (i.e., the VITEK® REVEAL™ AST Panel GN01 and the VITEK® REVEAL™ Sensor panel). The VITEK® REVEAL™ system software controls the two devices and generates the VITEK® REVEAL™ AST Panel GN01 panel test report.

The VITEK® REVEAL™ AST System utilizes broth microdilution principles to rapidly establish Minimum Inhibitory Concentrations (MICs) for a wide range of antibiotic drugs. In combination with species identification (obtained from a separate test method or platform), the Reveal Rapid AST system software creates antibiograms by automatic determination of Susceptible / Intermediate / Resistant (S/I/R)-calls based on EUCAST 2021 breakpoints and EUCAST Expert guidelines (v3.2) for the species tested.

The system and the VITEK® REVEAL™ AST panel 'AST Panel GN01' received a CE-IVD mark under the In Vitro Diagnostic Medical Devices Directive in October 2020. The system has been submitted to the Food and Drug Administration for 510(k) clearance in April 2023¹. A CLIA complexity level has not been assigned to the VITEK® REVEAL™ system yet, but it is expected that it will be classed as a 'highly complex' assay, like other antimicrobial susceptibility assays on the market². Moreover, the VITEK® REVEAL™ Rapid AST System has received Breakthrough Device Designation from the U.S. Food and Drug Administration in August 2022.

VITEK® REVEAL™ AST assays are indicated for antimicrobial susceptibility testing (AST) of specific pathogenic bacteria commonly associated with or causing bacteremia. The VITEK® REVEAL™ System delivers phenotypic results in an average of 5.5 hours³ directly from positive blood cultures. A separation of red blood cells in the positive blood culture sample is not required, and the sample preparation for VITEK® REVEAL™ AST assays takes less than 3 minutes⁴.

The VITEK® REVEAL™ System is an *in-vitro* diagnostic (IVD) automated system for antimicrobial susceptibility testing of organisms direct from positive blood cultures. The VITEK® REVEAL™ AST Panel GN01 Assays is indicated for susceptibility testing of specific pathogenic bacteria commonly associated with or causing bacteremia. Results are intended to be used in conjunction with Gram stain, organism identification and other clinical laboratory findings⁵. Given that the vast majority of patients with positive blood cultures are inpatients, and given the complexity of the test interpretation, VITEK® REVEAL™ is designed for hospital use.

While standard AST methods require at least 16-24 hours to provide a phenotypic antibiogram, the VITEK® REVEAL™ GN01 panel provides both MICs and susceptibility categories (S/I/R) for 176 [drug-pathogen] combinations within 5.5h on average ([Figure 2](#)). This faster antimicrobial susceptibility testing reduces the time needed to adjust broad-spectrum empiric antibiotic therapy in patients with proven bloodstream infections, e.g., by early antibiotic escalation, or by early de-escalation of unnecessary antibiotic compounds that were part of the initial empiric therapy.

1.1.1 The VITEK® REVEAL™ Instrument

The **VITEK® REVEAL™ Instrument** is a benchtop incubator and optical scanner that processes up to four AST test panels (cf. [Figure 1](#)) per module. Every 10 minutes the VITEK® REVEAL™ instrument monitors sensor color changes caused by bacterial growth in the AST panels. During cell division, bacteria release volatile organic compounds (VOCs) which are captured by color-active chemical sensors spotted on the VITEK® REVEAL™ sensor panels. Depending on the quantity of volatile organic compounds, sensor colors will change and the system software will translate color changes into minimal inhibitory concentrations for all antibiotics present on an AST panel (cf. [1.4.1](#)).

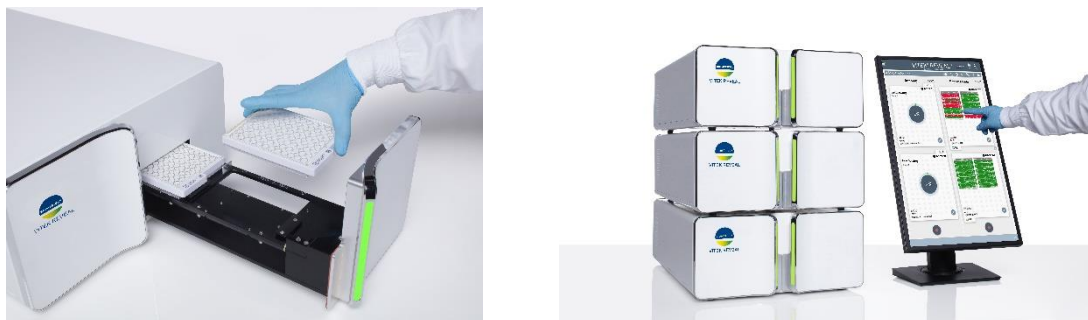


Figure 1 Left image: Loading of 2 sealed AST Panels to the right drawer of a VITEK® REVEAL™ instrument module. Each module has two drawers and can process up to 4 AST panels simultaneously.

Right image: shows 3 VITEK® REVEAL™ instrument modules connected to a workstation that is controlled by the VITEK® REVEAL™ system software on a touchscreen. Up to 8 instrument modules can be connected to one workstation.

VITEK® REVEAL™ is a fully automated, modular platform. In order to save laboratory bench space, up to 3 units of the VITEK REVEAL Instrument can be stacked, and up to 8 modules can be connected to the same PC in order to meet laboratory needs. Each instrument module can process up to 4 rapid AST assays during a typical 8-hour shift in the laboratory.

The REVEAL Instrument is controlled via a large touchscreen through the REVEAL Rapid AST system software which automatically collects, stores, and analyses the generated raw data and combines both MIC values and antimicrobial susceptibility categories (S/I/R) in a comprehensive AST test report.

1.1.2 The VITEK® REVEAL™ AST Panel GN01 and the VITEK® REVEAL™ Sealer

The VITEK® REVEAL™ AST Panel GN01 is the first commercially available rapid phenotypic antimicrobial susceptibility testing (AST) assay for the VITEK® REVEAL™ instrument. The panel consists of: **(1)** the VITEK® REVEAL™ AST panel, and **(2)** the VITEK® REVEAL™ Sensor panel which will be sealed together during sample preparation (cf. [1.2.2](#)) by means of the VITEK® REVEAL™ Sealer **(3)**.

1. The **VITEK REVEAL AST panels** are 96-well microtiter plates that are pre-filled with various concentrations of antibiotic drugs that are incubated with aliquots of a positive blood culture broth. [Figure 2](#) below shows the list of antibiotic agents and the range of two-fold dilutions tested on the VITEK® REVEAL™ AST GN01 panel. Up to 23 antibiotic agents are tested against the

10 Gram-negative pathogens that have been validated for the use of VITEK® REVEAL™ panel. Given that some pathogens are known to be naturally resistant against specific antibiotic molecules, only clinically relevant [drug-pathogen] combinations will be eventually reported by VITEK® REVEAL™. Depending on the pathogen incubated on the VITEK® REVEAL™ AST Panel GN01, between 8 (*A. baumannii*) and 23 (*E. coli*) antibiotics will be tested in a single analysis. Overall, the AST Panel GN01 can determine MIC values for 176 different [drug-pathogen] combinations.

ANTIMICROBIAL DRUG	MIC CALLING RANGE (µg/ml)	<i>A. baumannii</i>	<i>C. freundii</i>	<i>C. koseri</i>	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. aerogenes</i>	<i>K. oxytoca</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>P. aeruginosa</i>	
Amikacin	4 - 16	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Amoxicillin / Clavulanate	4/2 - 16/2			✓		✓		✓	✓	✓		5
Ampicillin	4 - 8				✓					✓		2
Aztreonam	1 - 16		✓	✓	✓	✓	✓	✓			✓	8
Cefepime	0.125 - 64		✓	✓	✓	✓		✓	✓	✓	✓	8
Cefotaxime	0.125 - 4		✓	✓	✓	✓	✓	✓	✓			8
Cefoxitin	8 - 16			✓	✓		✓	✓	✓			5
Ceftazidime	0.125 - 64		✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Ceftazidime / Avibactam	0.25/4, 1/4 - 16/4		✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Ceftazidime / Clavulanate	0.25/4 - 8/4				✓		✓	✓				3
Ceftolozane / Tazobactam	1/4 - 4/4				✓	✓	✓	✓			✓	6
Ciprofloxacin	0.06, 0.25 - 1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Ertapenem	0.125 - 1		✓	✓	✓	✓	✓	✓	✓			8
Gentamicin	2 - 4	✓	✓	✓	✓	✓	✓	✓	✓			9
Imipenem	1 - 8	✓	✓	✓	✓	✓	✓	✓			✓	9
Levofloxacin	0.25 - 1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Meropenem	0.125 - 8	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Meropenem / Vaborbactam	2/8 - 8/8		✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Piperacillin	8 - 16		✓		✓	✓	✓	✓	✓	✓	✓	8
Piperacillin / Tazobactam	4/4 - 16/4		✓	✓	✓	✓	✓	✓	✓	✓	✓	9
Tigecycline	0.5 - 1			✓	✓							2
Tobramycin	2 - 4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Trimethoprim / Sulfamethoxazole	2/38 - 4/76	✓	✓	✓	✓	✓	✓	✓	✓			9
TOTAL		8	17	19	18	23	17	21	21	18	14	176

Figure 2 [Antibiotic – Pathogen] combinations for which the VITEK® REVEAL™ AST GN01 panel determines MIC values. The range of antibiotic concentrations tested are indicated in the column ‘MIC Calling Range’ (cf. 1.5.1 for more details).

- The VITEK® REVEAL™ Sensor panel detects volatile organic compounds like aldehyds or ketones that are emitted by microorganisms as they grow. Sensor panels are made of printed color-active chemical sensors that are placed on top of the each well of the inoculated antibiotics plate, and a change in color indicates that the incubated microorganisms are growing despite the presence of antibiotic drugs. The Sensor panel is sealed onto the VITEK® REVEAL™ AST Panel (cf. Figure 3) by means of the VITEK® REVEAL™ Sealer (cf. Figure 4).

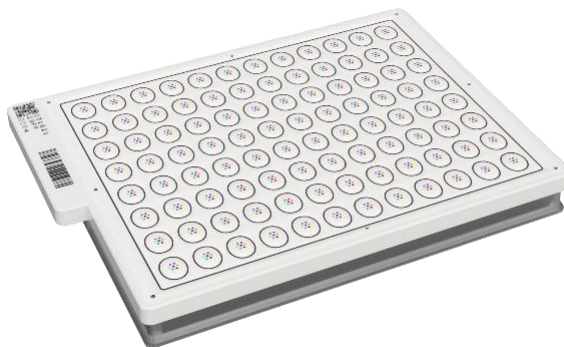


Figure 3 VITEK® REVEAL™ sensor panel (white) positioned on a VITEK® REVEAL™ AST GN01 panel (gray). Prior to incubation in a VITEK® REVEAL™ instrument module, the sensor panel and the AST GN01 panel need to be sealed together by means of the VITEK® REVEAL™ Sealer.

3. The **VITEK® REVEAL™ Sealer** is a benchtop device that is used to assemble the VITEK® REVEAL™ Sensor array and the VITEK® REVEAL™ AST panel GN01 in a process that takes less than 25 seconds. The Sensor array sealed onto the antibiotic drug plate form the AST test panels which are incubated in the VITEK® REVEAL™ Instrument.



Figure 4 VITEK® REVEAL™ Sealer device. The Sealer hermetically assembles the VITEK® REVEAL™ Sensor plate onto the VITEK® REVEAL™ AST panel GN01 in a process that takes less than 25 seconds.

1.2 VITEK® REVEAL™ sample preparation and instrument workflow

1.2.1 Prerequisites for VITEK® REVEAL™ testing

The VITEK® REVEAL™ system provides ‘**direct AST**’, i.e., the systems directly use aliquots of a clinical sample (for now, only applications on positive blood culture broth are available, cf. 1.3), rather than using *isolated bacterial colonies cultured overnight*. Given that overnight culture is no longer necessary in these systems, direct antimicrobial susceptibility testing has the advantage of providing AST results about one day earlier compared to standard AST methods. On the other hand, conducting AST on isolated colonies has the benefit of avoiding testing on polymicrobial infections – indeed, most antibiotic susceptibility testing techniques *fail in the presence of polymicrobial samples* as it will be unclear which of the two or more pathogens in a test well / agar / cassette / card were resistant or susceptible to a given antibiotic⁶.

In order to avoid an incubation of polymicrobial specimens with the VITEK® REVEAL™ system, a Gram stain should be conducted. The Gram stain result will also inform if the VITEK® REVEAL™ AST Panel GN01 is appropriate for the analysis of a clinical sample, as this panel only covers *Gram-negative* organisms.

Finally, the VITEK® REVEAL™ expert software can only assign MIC categories (=S/I/R) to a clinical sample when the pathogen inoculated on a VITEK® REVEAL™ AST GN01 panel had been identified with a CE-IVD marked or FDA-cleared technology. While the VITEK® REVEAL™ can be started *before* the pathogen identity is known, the system will not provide a results report *until* the pathogen ID has been entered to the system.

1.2.2 VITEK® REVEAL™ sample preparation

Positive blood culture broth is loaded onto the VITEK® REVEAL™ AST GN01 array according to the steps shown in [Figure 5](#) and [Figure 6](#) below. The AST GN01 panel must be used within 16 hours following blood culture positivity. The hands-on time needed to load a positive blood culture sample into the VITEK® REVEAL™ Instrument is less than three (3) minutes, and it requires no more skill than e.g. inoculation of the disposables of other widely available AST systems⁴.

To perform the VITEK® REVEAL™ AST GN01 array, 3-5 ml of blood culture broth are aspirated from a Positive Blood Culture (PBC) using a 5 ml syringe and dispensed into a 15 ml conical tube. The sample is then vortexed to ensure even cell distribution, and a 1:1000 dilution (25 µl of blood culture broth diluted in 25 ml of pluronic water) is made and transferred to the VITEK® REVEAL™ AST GN01 panel ([Figure 5](#)). The dilution is gently inverted in the tube 8-10 times to ensure the suspension is homogenous and poured into a rehydrator /inoculator loading tray (cf. Step #4 below). Using a transfer pipette, each of the 96 wells of the VITEK® REVEAL™ AST GN01 panel is filled with 115 µL of the sample. Any signs of droplets on the surface of the AST panel are wiped away to ensure there is no liquid on the surface of the panel, as any moisture on the surface will affect the quality of the sensor panel seal.

Once the AST panel had been inoculated, the sample must be sealed and loaded on the Reveal AST System (cf. below) within 20 minutes.

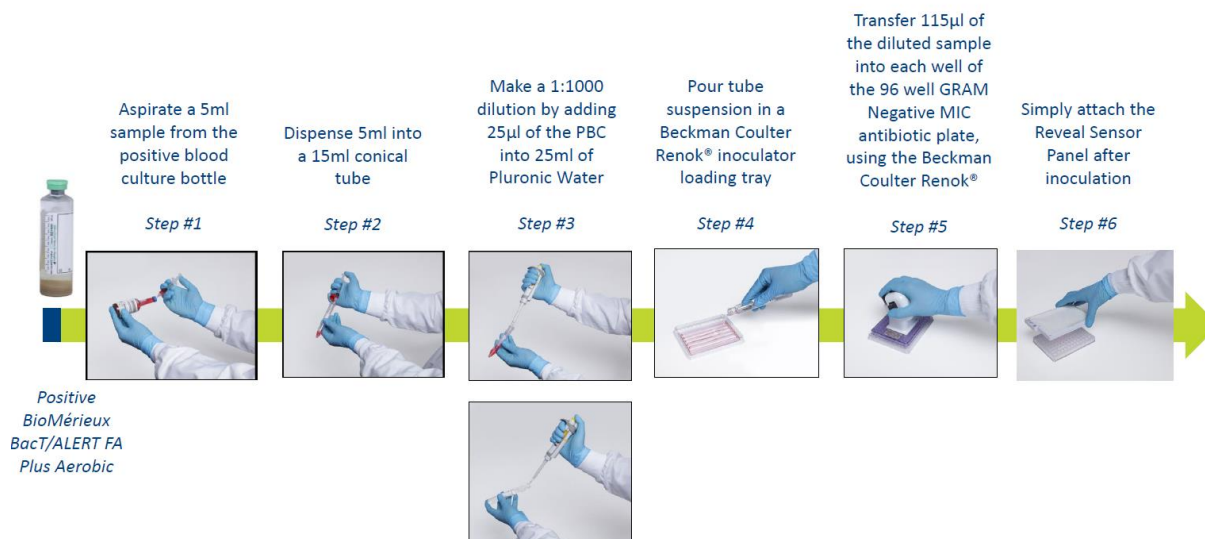


Figure 5 First part of the sample preparation for the VITEK® REVEAL™ AST GN01 panel. The second part of the procedure is described in Fig. 6.

The VITEK® REVEAL™ AST GN01 antibiotic plate is then covered with the VITEK® REVEAL™ Sensor panel, with the sample ID barcode being placed adjacent to the A1 well, i.e., in the upper left corner of the 96-well plate. The Sensor panel should always be handled by the edge of the frame and never touched on its surface, nor on the bottom side of the sensor. The assembly is then placed into the drawer of the VITEK® REVEAL™ Sealer and fixed by gently pressing down on the edges of the AST GN01 panel (cf. Step #7, [Figure 6](#)). The sealer will automatically seal the panel once the drawer is closed and eject the drawer open once the seal is complete, i.e., after about 25 seconds.



Figure 6 Second part of the sample preparation for the VITEK® REVEAL™ AST GN01 panel. The first part of the procedure is depicted in Fig. 5.

The sealed assembly is then transferred to the VITEK® REVEAL™ instrument, the Sensor Panel barcode is scanned, and the AST analysis is started by means of the VITEK® REVEAL™ User Interface.



The GN01 test plate is then incubated at 37°C and rocked at 100 rpm. In the situation where bacteria grow despite the presence of increasing concentrations of antibiotics in each well, the 7 color sensors placed on top of each well will capture volatile organic compounds that are emitted from the growing bacterial population (cf. [1.4.1](#)). The resulting change in sensor color will be imaged every 10 min to monitor the color intensity over time. In addition, one well with growth media but no antibiotic and another well with no growth media act as a positive growth control and negative no-growth control, respectively.

1.3 VITEK® REVEAL™ sample types

The performance of the VITEK® REVEAL™ AST Panel GN01 has been evaluated on the most frequently used type of blood culture bottles:

- o BD BACTEC Plus Aerobic/F Medium
- o BD BACTEC Plus Anaerobic
- o BD BACTEC Standard Aerobic
- o BD BACTEC Standard Anaerobic
- o BD BACTEC Lytic Anaerobic
- o BD BACTEC Peds Plus
- o bioMérieux BACT/ALERT FA Plus Aerobic
- o bioMérieux BACT/ALERT FN Plus Anaerobic
- o bioMérieux BACT/ALERT PF Plus
- o bioMérieux BACT/ALERT SA Standard Aerobic
- o bioMérieux BACT/ALERT SN Standard Anaerobic

However, the AST GN01 panel should not be used to test blood culture media that contain charcoal. Finally, given that the GN01 panel only tests for susceptibility to antibiotics active against Gram-negative pathogens, blood culture samples containing yeast or Gram-positive bacteria or that include *more than one organism* (i.e., polymicrobial samples) are NOT indicated to be tested with the AST GN01 panel.

In March 2023 bioMérieux announced that its affiliate BioFire Defense, LLC, has received a contract from the BARDA (Biomedical Advanced Research and Development Authority) to accelerate development of the VITEK® REVEAL™ Rapid AST System. The BARDA contract supports expansion of the VITEK® REVEAL™ Rapid AST System test menu to include other sample types starting with Gram-negative isolates. The contract also includes options to expand the menu to include Gram-positive blood culture and Gram-positive isolates⁷.

1.4 VITEK® REVEAL™ mechanism of action

1.4.1 Volatile organic compound sensors

The VITEK® REVEAL™ AST system uses a novel sensor technology to detect the growth of bacterial populations via their emission of volatile organic compounds (VOCs). Such compounds (including families of small molecules like amines, aldehydes or esters) are naturally emitted from growing bacteria prior to cell division. Each of the compounds is detected by a different sensor, and a hexagonal array of 7 sensors is the basic detection unit of the VITEK® REVEAL™ technology ([Figure 3](#))¹. The sensors are made of color-active chemical indicators that are embedded in a nanoporous matrix that enhances the surface area of the sensor, thereby increasing the analytical sensitivity of the test. The more volatile organic compounds are captured in the matrix, the more intense will be the color-change of the chemical indicators embedded in the matrix respond. The VITEK® REVEAL™ system scans the quantitative color change of the sensors every 10 minutes to monitor the change in color intensity over time, and the VITEK® REVEAL™ system software will transform the scanned raw data into bacterial growth curves (cf. [1.4.2](#))^{4,8}.

Ninety-six (96) sensor arrays are arranged on the VITEK® REVEAL™ sensor panel in a way that they cover the headspace of all wells of 96-well antibiotic plates. When the VITEK® REVEAL™ sensor panel is sealed to an inoculated VITEK® REVEAL™ AST panel, an array of seven colorimetric sensors sits over each well and detects the volatiles emitted by microorganisms during bacterial growth in the presence and absence of antimicrobials, thereby enabling the determination of antimicrobial susceptibility profiles.

The detection of VOCs outside the liquid [pathogen-drug] inoculum in the 96 wells entails two analytical benefits. On the one hand, the sensor array's broad spectrum of sensitive chemical interactions and its high degree of sensitivity allows the sensor array to rapidly respond to microbial VOCs, thereby reducing the time needed to determine minimum inhibitory concentrations. Second, because the sensors respond to volatiles in the headspace above each well, optical access to the fluid (as with turbidity, laser scattering or microscopy-based methods) is not required. This means that optically active compounds like red blood cells do not need to be removed from positive blood culture samples during sample preparation for VITEK® REVEAL™.

1.4.2 Definition of Minimal Inhibitory Concentrations (MICs) by VITEK® REVEAL™

As mentioned in [1.4.1](#), bacterial growth in the absence or presence of antibiotic compounds is measured through sensor color changes induced by volatile organic compounds released during bacterial growth in the wells of the VITEK® REVEAL™ AST GN01 panel. Changes in sensor color are monitored every 10 minutes by line scan in the VITEK® REVEAL™ Instrument, and these color changes are recorded over a time period of several hours. Sensor color changes provide a phenotypic identification of bacterial growth, and the associated MICs can be determined by comparing color changes obtained from pathogen growth in the presence of increasing amounts of antibiotics to the color changes obtained from positive (i.e. pathogens inoculated in growth media without any antibiotic) and negative (i.e. no growth media) controls ([Figure 7](#)).

¹ cf. also short video at <https://www.youtube.com/watch?v=Y0GWCgzik-k>

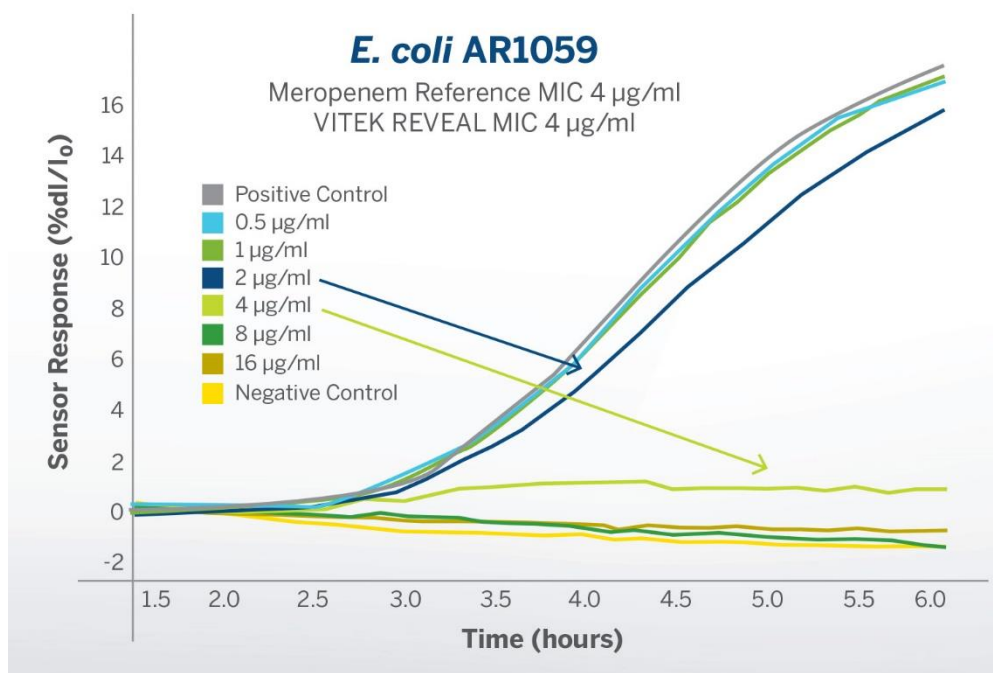


Figure 7 Illustration of MIC determinations by the VITEK® REVEAL™ system. For more details, cf. Section 3.2.5.2.

[Figure 7](#) illustrates how VITEK® REVEAL™ determines MIC values for [drug-pathogen] combinations. In this example, the MIC of the antibiotic agent Meropenem against the bacterial strain *E. coli* AR1095 is determined. The VITEK® REVEAL™ AST GN01 panel includes 6 wells with increasing, two-fold dilutions of Meropenem in the concentration range from 0.5 – 16 µg/ml. Each well was inoculated with 115 µl of bacterial suspension (cf. [1.2.2](#)). Bacterial growth will lead to a color change in the sensor arrays placed above the wells, and this color change is monitored every 10 minutes by the VITEK® REVEAL™ instrument. As expected, no color change is detected over the entire assay run time in the negative control well, which lacks growth media (cf. yellow trace in [Figure 7](#)). On the other hand, the signals from the positive-control well (black trace) and meropenem wells at concentrations of 2 µg/mL and *below* indicate growth, while the signals from the negative-control well (yellow trace) and wells with meropenem concentrations *above* 2 µg/mL are flat, indicating no bacterial growth. The divergence of sensor response in growth wells from the negative control allows the determination of MIC, which is 4 µg/mL in this example⁴. The different bacterial growth curves shown in [Figure 7](#) illustrate how the VITEK® REVEAL™ software generates both MIC values and antibiotic susceptibility categorizations by integration of color sensor changes in 8 wells over several hours. However, the intermediate data shown in [Figure 7](#) is not provided by the VITEK® REVEAL™ system, which will directly indicate the MIC values ([1.5.1](#)).

1.5 Interpretation of VITEK® REVEAL™ test results

The VITEK® REVEAL™ system software automatically processes the sensor color change raw data into minimum inhibitory concentrations (MICs) and susceptibility categories (S/I/R). The lab personnel need then to approve the VITEK® REVEAL™ test reports before they will be sent to the laboratory information system (LIS). Microbiologists can also revise or manually curate the reports, e.g., in cases where some of the antibiotics that are part of the VITEK® REVEAL™ AST GN01 panel *should not be reported* to the prescribing physician in order to avoid confusion. Indeed, it is standard care in many microbiology labs to communicate MICs only for such antibiotics that are part of the local reference list (or formulary) of antibiotics.

1.5.1 [Antibiotics – Pathogen] combinations tested by the VITEK® REVEAL™ AST Panel GN01

[Figure 2](#) above lists all [antibiotic drug – pathogen] combinations that the VITEK® REVEAL™ AST GN01 panel tests for. The panel includes 23 antimicrobial drugs at various concentrations, and 10 pathogen species had been validated for use on the panel, which theoretically gives rise to 230 possible [antibiotic drug – pathogen] combinations. However, some pathogens are known to be either naturally resistant to certain types of pathogens, like *Klebsiella spp* against ampicillin⁹, or antibiotic concentrations needed to kill a bacterial strain are so high that these concentrations cannot be achieved under standard treatment conditions. In these cases, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) or the Antibiogram Committee of the French Microbiology Society (CA-SFM) reference standards did not issue official breakpoints for a [antibiotic drug – pathogen] combination, and the VITEK® REVEAL™ system software will not be able to assign an MIC. This explains why the system provides antimicrobial susceptibility information for 176 out of the 230 possible combinations (cf. [Figure 2](#)).

The number of antibiotic concentrations tested against each pathogen varies between antibiotic agents and can be inferred from the column ‘MIC Calling Range’ shown in [Figure 2](#). The VITEK® REVEAL™ AST GN01 panel follows the principles of broth microdilution (BMD) antibiotic susceptibility testing, which uses twofold dilution series for each antibiotic agent. The MIC calling range of 4-16 µg/ml for Amikacin (cf. [Figure 2](#)) for instance means that the VITEK® REVEAL™ AST GN01 panel includes three wells pre-filled with concentrations of 4, 8 and 16µg/ml of Amikacin, and that these 3 combinations will be used to determine the pathogens MIC against Amikacin.

Likewise, the MIC calling range ‘4/2 – 16/2’ for the compound antibiotic Augmentin, which includes the beta-lactam antibiotic Amoxicillin and the beta-lactamase inhibitor Clavulanic acid, is tested in three different combinations, i.e. (a) 4µg/ml Amoxicillin + 2µg/ml Clavulanic acid, (b) 8µg/ml Amoxicillin + 2µg/ml Clavulanic acid and (c) 16µg/ml Amoxicillin + 2µg/ml Clavulanic acid. The lower part of the VITEK® REVEAL™ user interface schematized a VITEK® REVEAL™ AST GN01 panel, and it indicates which well of the panel contains which antibiotic(s) at which concentration ([Figure 8](#)).

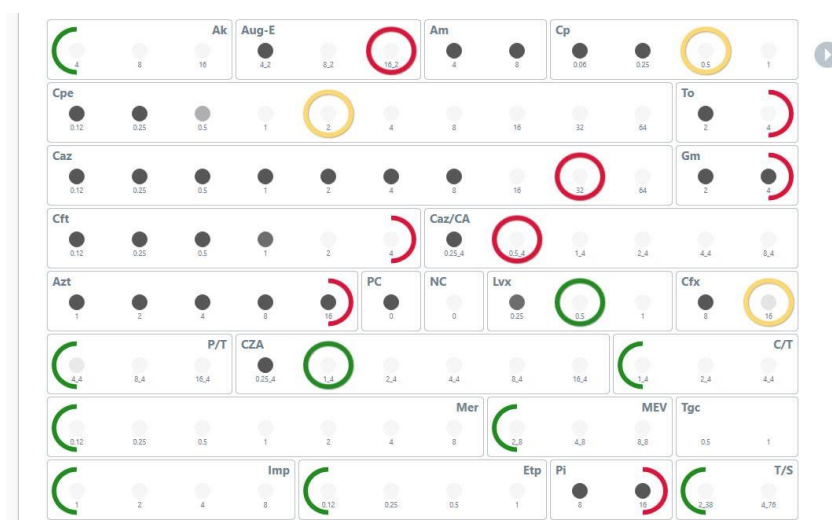


Figure 8 The lower part of the VITEK® REVEAL™ user interface schematizes the VITEK® REVEAL™ AST GN01 panel and gives a quick visual overview of analysis results. Dark dots indicate actual pathogen growth, and light gray dots indicate growth inhibition. Green indicates that a pathogen is susceptible to an antibiotic ('S'), red indicates that the pathogen is resistant ('R'), and yellow stands for 'susceptible at increased exposure'('I'). In this example, the tested pathogen is susceptible to Amikacin (Ak), with an MIC below 4µg/ml (cf. first row on the left).

1.5.2 VITEK® REVEAL™ AST Panel GN01 test report

The test report from the VITEK® REVEAL™ AST GN01 panel (Figure 9) is automatically displayed upon completion of a test run. The bacterial species for which antimicrobial susceptibility is tested is notified in the heading of the Results table. The VITEK® REVEAL™ system does not provide pathogen identification, which needs to be obtained using a CE IVD-marked or FDA-cleared identification system and entered to the system prior to, during or after a VITEK® REVEAL™ test run. Given that both minimal inhibitory concentrations (MICs) and categorical susceptibility interpretations (S/I/R) are *specific* to each bacterial species, the system can only provide a test report once the pathogen identity has been entered to the system.

Species: ***K. pneumoniae***

Abx	MIC (µg/ml)	SIR	TTR	Abx	MIC (µg/ml)	SIR	TTR
Am	-	IR ^{§§}		Mer	≤ 0.12	S	6:30
Pi	> 16	R [*]	3:50	Imp	≤ 1	S	6:30
Aug-E	16	R	6:30	MEV	≤ 2	S	6:30
P/T	≤ 4	S	6:30	Cp	0.5	I ^{##}	4:30
Cft	> 4	R	6:30	Lvx	0.5	S	4:10
Caz	32	R	6:00	Ak	≤ 4	S	5:00
Cpe	2	I	6:10	Gm	> 4	R	4:50
Cfx	16	I [#]	6:30	To	> 4	R	4:50
C/T	≤ 1	S	6:30	T/S	≤ 2	S	4:50
CZA	0.5-1	S	6:30	ESBL		Pos	
Azt	> 16	R	6:00	Caz/CA	0.5	Pos	4:30
Etp	≤ 0.12	S	6:30				

§§ The species is intrinsically resistant to the antibiotic.

* Modified by EUCAST Expert rule v3.2

No EUCAST breakpoints, CA-SFM 2019 v2 breakpoints applied here.

Warning: MIC falls in the Area of Technical Uncertainty

Figure 9 Test report of VITEK® REVEAL™ AST GN01 panel as shown on the user interface. For more details, cf. [1.5.1](#)).

The Results table comprises four columns:

- (1) **Column [ABX]** indicates the **antibiotic compound(s) tested**
- (2) **Column [MIC]** lists the **MIC** (minimal inhibitory concentration, in [µg/ml]) that has been determined for the tested clinical specimen. The MIC represents the lowest concentration of an antibiotic that prevents visible growth of a microorganism
- (3) **Column [SIR]** assigns an antibiotic susceptibility *category* to the bacterial species in the tested specimen, based on the **minimal inhibitory concentration** that has been observed. EUCAST 2021 breakpoints and EUCAST Expert rules (v3.2) are used by the VITEK® REVEAL™ system to determine these categories. This column can contain various codes:
 - *R* = resistant
 - *S* = susceptible
 - *I* = susceptible, increased exposure (Intermediate)
 - *E* = insufficient evidence
 - *R/I* = resistant or Intermediate (R breakpoint not covered by the panel)
 - *IR* = intrinsic resistance
 - *Pos* = extended spectrum beta-lactamases (ESBL)-test positive
 - *Neg* = extended spectrum beta-lactamases (ESBL)-test positive
 - *Ind*: Indetermined

Of note: in case that EUCAST does not provide clinical breakpoints for a specific [antibiotic-pathogen] combination, the VITEK® REVEAL™ analysis software uses breakpoints defined by the French Microbiology Society (CA-SFM)

(4) **Column [TTR] ('time to result')** indicates the **time the assay needed to determine a test interpretation.**

The VITEK® REVEAL™ AST GN01 panel provides both minimum inhibitory concentrations and antibiotic resistance categories. However, and like for all AST-results, VITEK® REVEAL™ results have to be validated by a qualified microbiologist before they can be sent to the lab information system (LIS) or a laboratory middleware. The VITEK® REVEAL™ system can also create PDF-reports which could be curated if needed. It is for instance standard practice that microbiology labs do not communicate MIC-values for all antibiotics tested, e.g., in order to be in line with local antimicrobial stewardship guidelines or to avoid confusion by providing a long list of antibiotics an isolated pathogen would be susceptible to. The final antibiotic choice should be made by trained healthcare professionals in conjunction with a patient's signs and symptoms and other available diagnostic information.

1.6 Patients who are expected to benefit most from VITEK® REVEAL™ AST GN01

The VITEK® REVEAL™ AST Panel GN01 is an *in vitro* diagnostic (IVD) test for antimicrobial susceptibility testing of a selection of Gram-negative organisms direct from positive blood culture. Bloodstream infections due to Gram-negative organisms are a significant cause of morbidity and mortality which require urgent treatment with antibiotics to minimize excess clinical, treatment, and economic burden. Early adequate antimicrobial therapy is one of most important interventions for patients with BSI worldwide¹⁰. However, many recent studies reported an incidence of inappropriate empiric antibiotic therapy of 30-40% in Europe, the United States and Asia¹¹. With the rise of antimicrobial resistance among several species of Gram-negative organisms and the concern for inappropriate empiric antibiotic therapy, the prescription of broad-spectrum antibiotics has become widespread practice for the empiric treatment of BSIs caused by Gram-negative organisms in many parts of the world.

Rapid antimicrobial susceptibility tests reduce the time to optimal antibiotic therapy¹²⁻¹⁴. The use of rapid phenotypic antimicrobial susceptibility testing (AST) with VITEK® REVEAL™ supports both fast antimicrobial therapy *escalation* when necessary (to avoid further clinical deterioration) AND timely *de-escalation* in cases with unnecessarily broad-spectrum antimicrobial administration (in order to limit overtreatment and antimicrobial resistance).

However, given that the VITEK® REVEAL™ AST Panel GN01 cannot test for *all* possible [antibiotic – pathogen] combinations, clinical experts mentioned that the test will be an add-on diagnostic test that will complement other established automated AST methods. The experts further agreed that for budget reasons, add-on testing in the microbiology lab could only be done on selected patients for whom rapid AST results would be of particular medical and/or economic value. After in-depth discussions, an expert panel identified the following patients who are expected to benefit most from VITEK® REVEAL™:

- Patients with a risk of BSI due to resistant Gram-negative bacteria

- BSI patients with sepsis or septic shock, as they have a higher risk for poor clinical outcomes in case of inappropriate empiric antibiotic therapy
- Patients with confirmed Gram-negative bloodstream infections who are at higher risk of developing sepsis (e.g., immunocompromised patients such as hemato-oncological or transplant patients, patients in extreme age groups, etc.)
- Sepsis patients not responding to first-line empiric antibiotics

2. Obstacles and Constraints to Stewardship & Access

2.1 General constraints to Stewardship and Access

As mentioned in [1.6](#), it is anticipated that the VITEK® REVEAL™ AST Panel GN01 will be used to complement other traditional automated AST methods for a selection of patients with severe bloodstream infections. It is therefore anticipated that only laboratories who already have access to an effective workflow for the work-up of bloodstream infections (including a systematic incubation of blood cultures, routine Gram stain capabilities and routine methods for the identification and the antimicrobial susceptibility testing of pathogens from positive blood cultures, cf. [Figure 10](#)) will

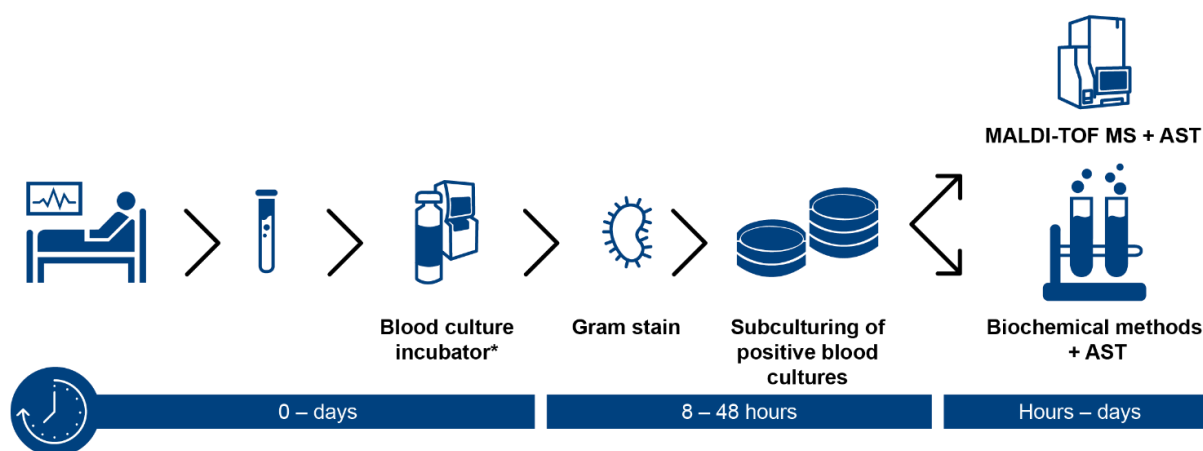


Figure 10 Traditional diagnostic pathway of patients with suspected bloodstream infection.

*Blood cultures are performed with continuous monitoring blood culture systems which detect the growth of microorganisms based on the emission of carbon dioxide during microbial metabolism. Blood cultures are incubated for up to 5 days, with microorganisms typically detected within 24–48 hours¹³³.

AST: antimicrobial susceptibility testing; MALDI-TOF MS: matrix-assisted laser desorption/ionization time of flight mass spectrometry.

leverage the full benefit of VITEK® REVEAL™. Access to sufficient financial and human resources are therefore crucial to leverage the full potential of VITEK® REVEAL™, especially when taking into consideration that in many low to middle income countries (LMIC) up to 90% of microbiology testing is conducted in the public health care sector.

However, bioMérieux supports various initiatives that aim at **supporting the use of effective microbiology tests to fight antimicrobial resistance worldwide:**

- bioMérieux is present in **45 countries across all continents and serves more than 160 countries** with the support of a large network of distributors². This presence facilitates the delivery of product and medical training in all countries that have access to bioMérieux products. bioMérieux is also developing a range of open access educational manuals on topics related to antimicrobial resistance and antimicrobial stewardship. These practical handbooks are available in English on a dedicated educational website³. Furthermore, bioMérieux supports continuing education sessions leading to accreditations for healthcare professionals¹⁵.
- In order to support local in person medical education, **bioMérieux opened a training center in Abidjan dedicated to healthcare professionals**. More than 150 laboratory technicians have received special training in blood culture, identification and antimicrobial susceptibility testing (AST) to combat microbial resistance in 2019. In 2022, bioMérieux also supported awareness-raising and educational activities regarding antimicrobial stewardship in several countries including Ivory Coast, Burkina Faso, Kenya, Benin, Mauritania, Nigeria and Algeria. Scholarships are also awarded to scientific societies for medical education activities (ESCMID, ISID, ESICM, Africa CDC, ASEAN, the Latin American ALADDIV)¹⁵.
- In addition to the investments in medical education, bioMérieux also supports global AMR surveillance studies. Indeed, at the community level, diagnostics is the only tool capable of providing surveillance data (human, veterinary and environmental) to monitor the status and progression of antimicrobial resistance and thus to construct and update antimicrobial stewardship recommendations. bioMérieux therefore decided to continue to be the sole private sponsor of the **Global Point Prevalence Survey (GPPS)**, in collaboration with the University of Antwerp. GPPS is a study of antibiotic use and antimicrobial resistance (AMR) in hospitals around the world. Between 2015 and 2019 alone, GPPS has been conducted in nearly 800 hospital centers, in 80 countries and has collected data from over 200,000 hospitalized patients¹⁶. In 2021, over 90 countries participated, involving over 1,000 hospitals and more than 450,000 patients. Moreover, bioMérieux entered a six-year partnership with JMI Laboratories in April 2023 to undertake collaborative projects to evaluate the performance of innovative microbiology diagnostics as important tools in the battle against AMR¹⁷. Through the partnership with JMI, bioMérieux will be able to continually assess AST results and validate against evolving global antimicrobial susceptibility data collected through the JMI-led SENTRY program.
- Finally, one pillar of bioMérieux's corporate strategy is to expand access to its AMR products globally and to augment the value of individual test results by leveraging data and IT solutions (cf. p. 13 of ¹⁵). As an example, bioMérieux was chosen by the **Fleming Fund** as a partner in a UK investment program endowed with £265 million to combat antimicrobial resistance in 21 resource-limited countries. bioMérieux, chosen for the performance of its diagnostics solutions, its organizational capacity in the targeted countries and its expertise in training healthcare professionals in microbiology and antimicrobial resistance, became responsible for deploying its solutions in 15 LMIC¹⁸. In each of these countries, a clinical

² [bioMérieux Worldwide | Pioneering Diagnostics \(biomerieux.com\)](https://www.biomerieux.com)

³ [Educational Booklets | Pioneering Diagnostics \(biomerieux.com\)](https://www.biomerieux.com)



laboratory and a veterinary reference laboratory have been equipped with the VITEK® MS, VITEK® 2 and MAESTRIA™ systems. Since 2021, bioMérieux has equipped laboratories in Laos, Malawi, Nepal, Tanzania, Senegal, Swaziland, Zambia, Zimbabwe, Bhutan, Bangladesh, India, Indonesia, Nigeria and Vietnam. The facilities in Sierra Leone and Senegal have completed this first phase of the program. Two main objectives of bioMérieux's Public Health Mission are to increase in the number of patient results that support a rational use of antibiotics by 30% by 2025, and to ensure that its AST solutions (including VITEK 2 and VITEK® REVEAL™) include at least 80% of listed human antibiotics (cf.¹⁵, section 3.4.2).

- It is also of note that bioMérieux collaborates with other diagnostics and Pharma companies to fight antimicrobial resistance worldwide. bioMérieux has been involved in launching the AMR Industry Alliance⁴, a consortium aimed at making and measuring progress in combating antimicrobial resistance in industry. bioMérieux participated in the survey that formed the basis of the 2021 Progress Report on the life science industry's commitment to combating antimicrobial resistance¹⁵.

2.2 Product-specific constraints to Stewardship and Access

As mentioned previously ([1.1](#) and [2.1](#)), a main product-specific constraint to Stewardship and Access is that the medical value of the VITEK® REVEAL™ AST Panel GN01 can only be leveraged in laboratories that have **robust microbiology test capabilities** in place. The ability to rapidly identify pathogens from positive blood culture broth is crucial given that VITEK® REVEAL™ AST results, which are available in an average of 5.5 hours after blood culture positivity^{3,19}, can only be interpreted if the lab can provide pathogen identification in the same time frame. This technical prerequisite reduces the number of laboratories that could make full benefit of the VITEK® REVEAL™ solution.

Another technical constraint is that positive blood culture samples must be run on the VITEK® REVEAL™ AST System **within 16 hours of blood culture positivity**. This condition might exclude the use of the assay in certain hub and spoke models, where blood cultures are incubated at distal hospitals sites, and shipped to a central lab in case of culture positivity. Due to the 16-hour rule, the test might not be appropriate for a hospital network with large geographical distances between the hub and the central laboratory.

Moreover, the VITEK® REVEAL™ panels and devices are exclusively manufactured in and shipped out of the United States. If applicable, existing commercial regulations that limit the shipment to certain areas in the world (e.g., trade embargoes) do apply.

Finally, the VITEK® REVEAL™ AST GN01 panel has been validated for the use **with ten bloodstream infection-causing pathogens** ([Figure 2](#)) While these pathogens indeed are the most common causes of BSI, there might be cases of bloodstream infections with a Gram-negative germ that are not covered by the test. Established automated ID/AST methods with a broader spectrum on tested pathogens, like the VITEK 2 device (which has the ability to detect more than 150 Gram-negative pathogens²⁰), might be more appropriate for microbiology labs suffering from limited financial and human resources.

There are a few additional technical limitations that might prevent the use of VITEK® REVEAL™. The VITEK® REVEAL™ Rapid AST System is built per industry standard for *in-vitro* diagnostics (IVD) testing. VITEK® REVEAL™ technology doesn't require any special considerations to be used in low-to-middle

⁴ [Home - AMR Industry Alliance](#)

income countries; however, the below listed technical specifications need to be fulfilled in order to guarantee a reliable long-term use of VITEK® REVEAL™:

- Temperature – The system contains temperature sensors and notifies the end user when the system temperature falls outside the acceptable range
- Humidity – The system has an adjustable fan inside the instrument to mitigate against ambient environment. The VITEK® REVEAL™ Instrument and the Sealer are compatible with 10-90% relative humidity (non-condensing)
- Dust – The system provides preventative maintenance guidelines to ensure adequate system performance
- Stability – The system power input is universal. The system meets EMC (Electromagnetic Compatibility) regulations for a medical device
- Power supply – An Uninterruptible Power Supply (UPS) is made available to the end user, should an incoming power be interrupted. The VITEK® REVEAL™ system can operate at 85-264 VAC / 50-60 Hz
- Cold-storage – The system reagent labels provide storage guidelines. The VITEK® REVEAL™ Sensor panel must be stored at 5-25°C, and the VITEK® REVEAL™ AST Panel GN01 at 2-25°C. If needed, the reagents can be stored in any regular refrigerator or cold-storage.

As mentioned in [2.1](#), bioMérieux is present in 45 countries across all continents and serves more than 160 countries with the support of a large network of distributors⁵. This implies that VITEK® REVEAL™ system would be technically accessible to all countries that are served by bioMérieux, thanks to a solid, established supply chain process and reliable distribution partners. bioMérieux's broad global presence also provides sufficient training and support capabilities that would ensure an appropriate level of service and product training in laboratories that have access to prerequisite (rapid) pathogen identification technology worldwide. Given the very precise indication for use of VITEK® REVEAL™ (i.e. the use in patients with bloodstream infections caused by a single Gram-negative bacterial species, cf. [1.1](#)), the volume of tests required to serve bioMérieux customers worldwide is not expected to cause particular precautionary measures in terms of assay manufacturing. In 2023, there are no plans to redesign the VITEK® REVEAL™ AST GN01 panel in order to facilitate stewardship and access.

⁵ [bioMérieux Worldwide | Pioneering Diagnostics \(biomerieux.com\)](https://www.biomerieux.com)

2.3 Constraints to Stewardship and Access due to local health system capabilities

The VITEK® REVEAL™ AST Panel GN01 is designed to accelerate antimicrobial susceptibility testing in patients with severe bloodstream infections. In order to leverage the full medical value of the test, hospitals need to have a significant routine use of blood cultures and have access to rapid pathogen identification methods from positive blood culture broth. Moreover, hospitals need to have access to a broad selection of antibiotics in order to make full use of VITEK® REVEAL™. However, this is not the case in low resource settings, and bioMérieux is not able to act on these prerequisites for an efficient use of VITEK® REVEAL™.

The interpretation of VITEK® REVEAL™ AST GN01 panel results requires highly trained microbiology experts, even if minimal inhibitory concentrations (MICs) for all tested antibiotics are directly indicated in the test report (cf. [Figure 9](#)). A main difficulty resides in the selection of the most appropriate antibiotic in case that the BSI-causing pathogen is susceptible against several antibiotics tested. The classification of alternative methods to conduct antimicrobial susceptibility testing (including VITEK 2 cards²) as ‘complex assays’ by Clinical Laboratory Improvement Act (CLIA) regulations testifies this. Moreover, given the severe disease state of the BSI patients, it is imperative to determine the most appropriate treatment option. bioMérieux therefore provides microbiology training at all levels to improve the appropriate interpretation and use of its tests worldwide^{15,18}.

The VITEK® REVEAL™ system will significantly support an effective antimicrobial stewardship of severely sick patients with Gram-negative bloodstream infections. However, alternative, BMD-based technologies like VITEK2 seem more appropriate for the development of local antibiograms, mainly (a) because of VITEK® REVEAL™’s use in a rather small number of patients, and (b) because bloodstream infections can be both hospital *and* community-acquired, while local antibiograms should be specific for either setting. Rather than using VITEK® REVEAL™, local antibiograms can be developed using high-throughput systems like VITEK 2 and VITEK MS (for pathogen identification). bioMérieux established partnerships with specialized organizations in order to improve the current understanding of the epidemiology of resistance mechanisms worldwide through active antimicrobial surveillance, and such project are based on the use of VITEK 2 and VITEK MS^{16,17}.

Finally, the cost of VITEK® REVEAL™ can be an issue in LMICs. But even if ample funding would be available, the above-mentioned organizational requirements would lead to a suboptimal use of the VITEK® REVEAL™ system.

3. Strategies to achieve timely Market Approvals in Target Territories

The VITEK® REVEAL™ AST System is an *in-vitro* diagnostic (IVD) automated system for antimicrobial susceptibility testing (AST) of organisms direct from positive blood culture. The VITEK® REVEAL™ system and the VITEK® REVEAL™ AST panel GN01 received a CE-IVD mark under the In Vitro Diagnostic Medical Devices Directive (IVD-D) in October 2020. A 510(k) premarket notification has been submitted to the Food and Drug Administration in April 2023¹. Moreover, the VITEK® REVEAL™ Rapid AST System has received Breakthrough Device Designation from the U.S. Food and Drug Administration in August 2022. Given that VITEK® REVEAL™ goes through a standard process of Market Approvals, bioMérieux is not considering using alternative or accelerated registration mechanisms (e.g., FDA Emergency Use Authorization or WHO Emergency Use Listing) for VITEK® REVEAL™.

bioMérieux has subsidiaries in 45 countries and serves more than 160 countries through a large distribution network (cf. [Figure 11](#)). All subsidiaries have access to Regulatory Affairs experts who manage local and regional marketing approvals, and bioMérieux does not anticipate using external consultancy to accelerate Market Approval.

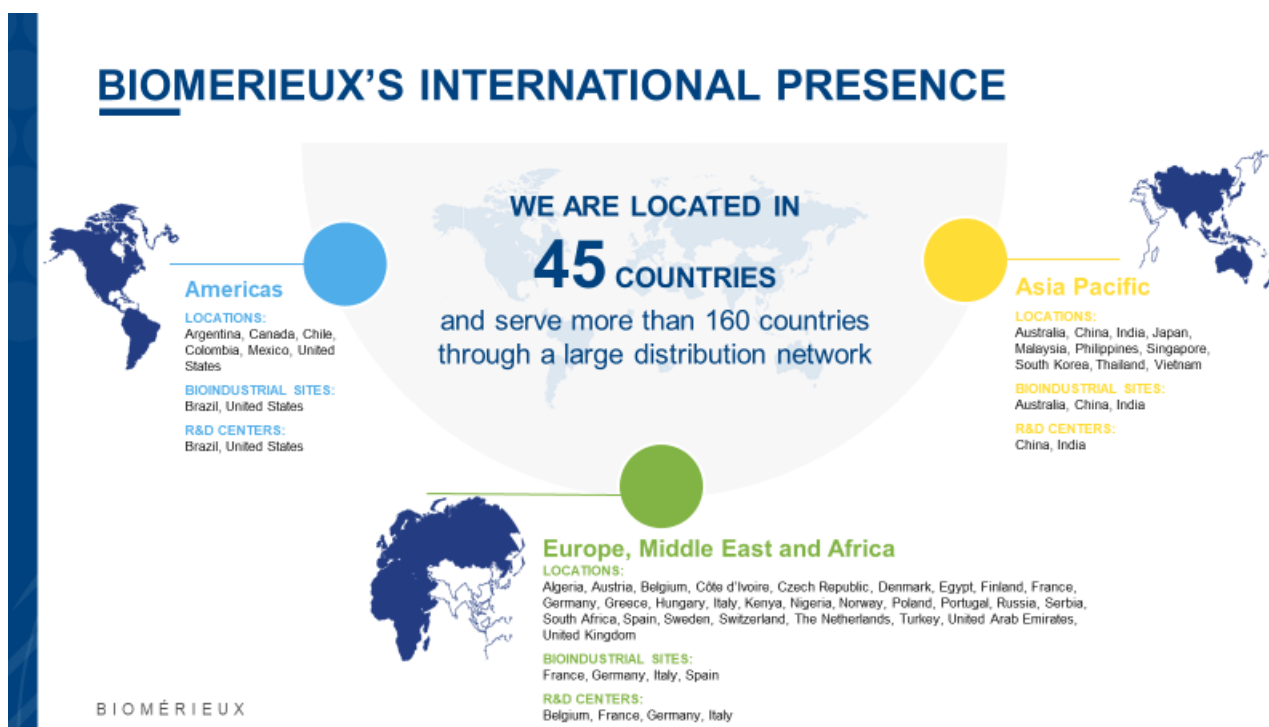


Figure 11 Overview of countries that host bioMérieux subsidiaries, production sites and R&D centers across the world (source: bioMérieux Corporate Presentation 2023)

The VITEK® REVEAL™ AST Panel GN01 determines the susceptibility of 10 Gram-negative bacterial species against 23 antibiotic agents (cf. [Figure 2](#)). Based on broth microdilution (BMD) principles, the test establishes both quantitative Minimum Inhibitory Concentrations (MICs) and qualitative antibiotic susceptibility categories [i.e. ('Susceptible' (S) / 'Susceptible at increased exposure' (I) / 'Resistant' (R)], based on EUCAST 2021 breakpoints and EUCAST Expert guidelines (v3.2) for the species tested.

A major question related to Market approval is whether the product would help to solve an unmet medical need in a region or country. Given that VITEK® REVEAL™ allows to establish antimicrobial susceptibility patterns for the 10 bacterial species ([Figure 2](#)), it needs to be assessed

- a. if bloodstream infections are indeed caused **by the bacterial species** for which VITEK® REVEAL™ has been clinically validated and
- b. if the **antibiotic agents** tested by the VITEK® REVEAL™ AST GN01 panel are **part of the local formularies**

The SENTRY surveillance study gives insights into the identity of pathogens that cause bloodstream infections. The SENTRY study collected over 260,000 BSI episodes from more than 200 medical centers in 45 nations between 1997 and 2016, and it provided both species identification and antimicrobial susceptibility testing results²¹. The study results, which are partially summarized in [Table 1](#), show that *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, *A. baumannii* and *S. marcescens* were the most frequent Gram-negative pathogens that caused BSI in all 4 geographical regions (i.e. North America, Latin America, Europe and Asia-Pacific) in the most recent study period from 2013-2016. VITEK® REVEAL™ has been validated for all but one (= *S. marcescens*) of these pathogens-

Frequency of BSI-causing species in the period 2013-2016								
Rank	North America	% of BSI	Latin America	% of BSI	Europe	% of BSI	Asia-Pacific	% of BSI
1	<i>S.aureus</i>	24.3	<i>E.coli</i>	18.3	<i>E.coli</i>	27.0	<i>E.coli</i>	33.7
2	<i>E.coli</i>	19.8	<i>S.aureus</i>	16.4	<i>S.aureus</i>	16.9	<i>S.aureus</i>	13.9
3	<i>K.pneumoniae</i>	8.6	<i>K.pneumoniae</i>	13.6	<i>K.pneumoniae</i>	10.1	<i>K.pneumoniae</i>	13.5
4	<i>E.faecalis</i>	5.4	<i>P.aeruginosa</i>	7.1	<i>P.aeruginosa</i>	5.8	<i>P.aeruginosa</i>	5.7
5	<i>P.aeruginosa</i>	4.8	<i>E.cloacae</i>	5.9	<i>E.faecalis</i>	5.4	<i>E.cloacae</i>	3.0
6	<i>S.epidermidis</i>	4.6	<i>A.baumannii</i>	5.5	<i>S.epidermidis</i>	4.1	<i>E.faecalis</i>	2.9
7	<i>E.faecium</i>	3.4	<i>S.epidermidis</i>	5.4	<i>E.faecium</i>	4.0	<i>A.baumannii</i>	2.7
8	<i>E.cloacae</i>	3.1	<i>E.faecalis</i>	5.0	<i>E.cloacae</i>	2.6	<i>E.faecium</i>	2.6
9	<i>S.pneumoniae</i>	2.4	<i>S.marcescens</i>	3.3	<i>A.baumannii</i>	2.4	<i>S.epidermidis</i>	2.5
10	<i>S.agalactiae</i>	2.2	<i>E.faecium</i>	2.4	<i>P.mirabilis</i>	2.3	<i>S.agalactiae</i>	1.9

Table 1 Frequency of bloodstream infection causing pathogens in different regions of the world, from 2013-2016 [adapted from Diekema *et al.* 2019]⁴

Unfortunately, there is very little published evidence on the types of pathogens causing bloodstream infections in **Africa**. The SENTRY study did not include laboratories from this continent, and there are only a few large studies available^{22,23}. The meta-analyses published by both Reddy *et al.*²² and Droz *et al.*²³ reported that overall, Gram-negative BSI was more frequent (>58%) compared to Gram-positive infections across African countries, mainly due to a large number bloodstream infections caused by *Salmonella spp* (typhoidal and non-typhoidal serotypes). Lochan *et al.*²⁴ also found that pediatric BSI patients in a tertiary care hospital in South Africa were predominantly infected by Gram-negative pathogens. It therefore seems that a use of VITEK® REVEAL™ would partially cover the spectrum of

bacteria that cause BSI in Africa (*Salmonella spp* is not covered by VITEK® REVEAL™), but that more epidemiology data is warranted in order to understand which percentage of the bloodstream infections in this continent could benefit from VITEK® REVEAL™. It is also important to note that both Malaria and tuberculosis also frequently cause bloodstream infections in some parts of the world²². However, these diseases are caused by protozoa and mycobacteria, which are beyond the scope of VITEK® REVEAL™.

The second major aspect is the **access of patients across the world to the antibiotic agents tested by the VITEK® REVEAL™ GN01 AST assay**. The access to antibiotic drugs varies from country to country, and even from hospital to hospital. It is therefore impossible to give a clear assessment of where in the world ALL antibiotic agents tested by the VITEK® REVEAL™ GN01 AST assay are available. It is assumed that high-income OECD countries will have access to (almost) all antimicrobial agents, while hospitals in low-to-middle income countries (as defined by the World Bank⁶) will only have a small selection of well-established and less costly antibiotic agents at their disposal. Gebretekle *et al.*²⁵ reported in a study from a 800-bed tertiary hospital in Ethiopia with 20,000 inpatients (average lengths of stay: 9.3 days) that the annual budget for antibiotic was 448,000 USD (i.e. 2.4 USD per inpatient day), and that 66% of the antibiotic cost was spent on only 4 antibiotics (i.e. vancomycin, meropenem, ceftriaxone and ceftazidime). Given that hospitals in many countries will have no access to a significant part of the antibiotics tested on the VITEK® REVEAL™ GN01 AST panel, a use of the panel seems inappropriate at this time.

Besides the representativeness of the bacterial pathogens and antibiotic agents assessed on VITEK® REVEAL™, there are a few other prerequisites that need to be fulfilled in order to make an optimal use of the VITEK® REVEAL™ GN01 AST panel. One consideration is that the VITEK® REVEAL™ system only provides *antimicrobial susceptibility testing*, but *not pathogen identification*. VITEK® REVEAL™ will only report MICs and categorical interpretations when the identity of a pathogen detected in a blood culture was entered into the Reveal AST System. Leveraging the full benefits of the VITEK® REVEAL™ system requires laboratories to have access to technologies that allow for **broad and rapid pathogen identification** from positive blood cultures. The clinical and economic value of the VITEK® REVEAL™ system indeed resides in its ability to determine minimum inhibitory concentrations for 23 antibiotic agents in an average of 5.5 hours after blood culture positivity^{3,19}. However, these 5.5 hours to full AST results can only be achieved if the lab can provide pathogen identification in the same time frame. This prerequisite might be a true obstacle in many countries. Gebretekle and colleagues for instance reported that prior to a research program on the Cost–utility of an antimicrobial stewardship program at a tertiary teaching hospital in Ethiopia, a 800-bed hospital only prepared 2 blood cultures per day²⁵ – which means that patients with BSI will receive an empiric antibiotic therapy without any microbiology testing involved.

Apisarnthanarak²⁶ also reported that the use of rapid diagnostic tests for antimicrobial stewardship has high clinically utility in the Asia Pacific region, but that a selective approach is required, depending on the resources available. In areas with limited financial and human resources, *rapid diagnostic tests* should be mainly used to decide on the *initiation* of an antibiotic treatment, while standard diagnostics could be used to determine the need to continue or to stop an antibiotic treatment.

bioMérieux plans to conduct Early Evaluation Programs (EEPs) in different countries in Africa, Latin America and Asia. The objective of these local studies will be to determine if and how VITEK® REVEAL™ can be integrated seamlessly into the local standards of care, and if the full clinical and economic value of the use of VITEK® REVEAL™ can be reached in these environments.

⁶ [World Bank Country and Lending Groups – World Bank Data Help Desk](#)

4. Strategies to Support Stewardship and Access in Other Territories

4.1 Strategies related to product pricing

The commercialization of the VITEK® REVEAL™ AST Panel GN01 follows bioMérieux's standard pricing strategy, which is based on test volume and other parameters.

Based on market accessibility, the presence of other bioMérieux products in the market (e.g., BIOFIRE® BCID2 panel) and on existing relationships with funding partners, bioMérieux will explore opportunities to bring VITEK® REVEAL™ AST Panel GN01 to the market and support long term stewardship initiatives.

4.2 Strategies related to product licensing

There are currently no plans to license the product to a third-party organisation.

4.3 Strategies related to product supply chains and manufacturing

Product supply chain

bioMérieux has access to 160 countries worldwide through a high-quality distribution network, and the supply of the VITEK® REVEAL™ system will rely on this distribution network when needed.

Quality standards are upheld before products are released into finished good inventory and components / spare parts. There are dedicated teams for quality review at each manufacturing site. Across bioMérieux's network of international distribution centers the product is stored and shipped according to the relevant SOPs (e.g., shipping conditions and temperature monitoring).

Manufacturing and waste management

bioMérieux is committed to reducing its environmental impact, from manufacturing through waste management. The company applies an eco-design approach to the product development process in order to ensure to use fewer, locally sourced, recycled and recyclable resources and to work towards extending the lifespan of manufactured devices⁷.

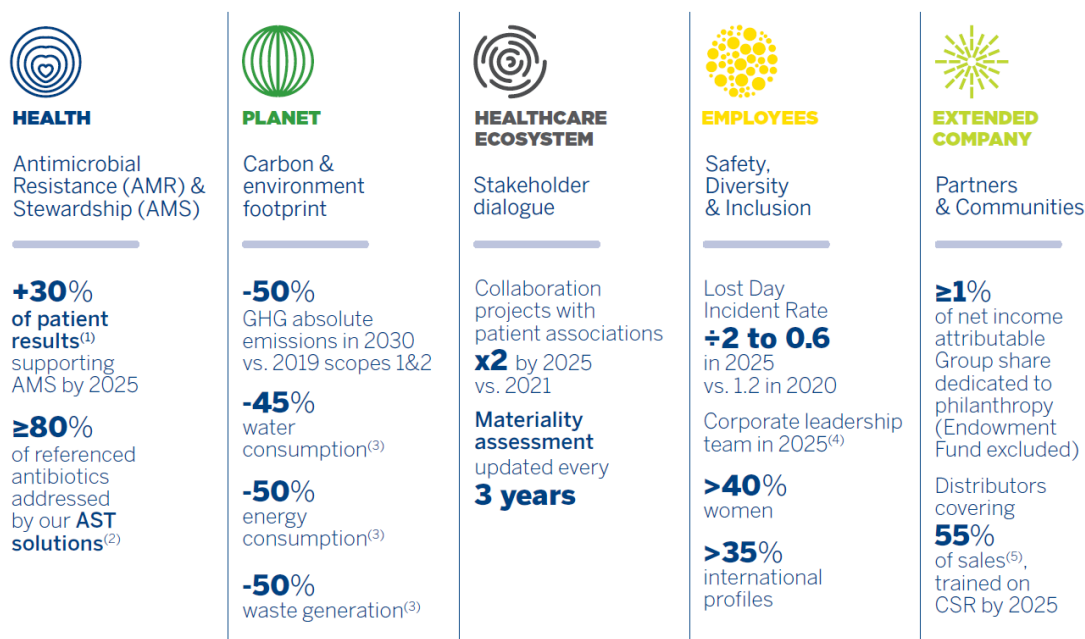
As defined in the Corporate Social Responsibility (CSR) plan, bioMérieux is committed to reduce its absolute greenhouse gas (GHG) emissions by 50% (2030 vs 2019, scopes 1&2), and reduce its water – (-45%) and energy (-50%) consumption, as well as its waste generation (all: per M€ in revenue, in 2025 vs 2015)¹⁵ (Figure 12) bioMérieux is currently conducting pilot projects to the reduce total waste, with an objective to achieve 'Zero Landfill' over the next years. The manufacturing sites for

⁷ [Eco-design | Pioneering Diagnostics \(biomerieux.com\)](#)

the VITEK® REVEAL™ devices and reagents are part of these projects.

Regarding manufacturing, several projects are ongoing in order to increase capacity and lower manufacturing costs, and to optimize manufacturing processes.

OUR MAIN CSR COMMITMENTS



(1) 2019 estimation: 183 million results.

(2) At least 80% based on EUCAST list and 90% based on CLSI cat A,B,U list.

(3) Per million € of revenue, in 2025 vs. 2015.

(4) Direct reports to the Executive Committee with a Global Corporate mission (international profiles are defined as non-French).

(5) Sales realized through the distributors network.

Figure 12 bioMérieux's main Corporate Social Responsibility (CSR) objectives

(source: bioMérieux Universal Registration Document 2022, p. 11)

4.4 Strategies related to Product support

The VITEK® REVEAL™ system will benefit from bioMérieux high quality product support, including for example:

- Pre-installation visits, installation and connection to lab information systems
- Protocols and material for in-lab product quality controls are available
- On-site training for routine use and remote support, including a remote video service
- Access to expert hotline and field support
- Various options for product warranty

Given its large international presence (bioMérieux serves more than 160 countries with the support of a large network of distributors), it is expected that bioMérieux has sufficient experience and

capacities to support the use of the VITEK® REVEAL™ instruments and assays worldwide. bioMérieux does not envisage product design changes to further improve or facilitate product support in the future.

4.5 Strategies related to responsible promotion and Sales Strategies

The VITEK® REVEAL™ AST Panel GN01 is an *in vitro* diagnostic (IVD) test for antimicrobial susceptibility testing of a selection of Gram-negative organisms direct from positive blood culture. Bloodstream infections due to Gram-negative organisms are a significant cause of morbidity and mortality which require urgent treatment with antibiotics to minimize excess clinical, treatment, and economic burden. However, given that the VITEK® REVEAL™ AST GN01 panel cannot test for all possible [antibiotic – pathogen] combinations, clinical experts expect that the test will **be an add-on diagnostic test that will complement other established automated AST methods**. Moreover, laboratories must have access to rapid pathogen identification methods from positive blood culture broth in order to leverage the full medical value of VITEK® REVEAL™. The experts further agreed that for budget reasons, add-on testing in the microbiology lab could only be done on **selected patients** for whom rapid AST results would be of particular medical and/or economic value (cf. [1.6](#)).

In view of these **technical and clinical prerequisites** for the optimal use of VITEK® REVEAL™, it is anticipated that no exceptional measures **beyond the standard compliance processes** are required to do a responsible promotion of VITEK® REVEAL™. As VITEK® REVEAL™ will be exclusively used in hospitals, it will be the local healthcare professionals who will make sure that VITEK® REVEAL™ as a high medical value test that supports the appropriate use of antibiotics in very sick patients will be used in an appropriate manner.

4.6 AMR Surveillance

bioMérieux participates in several AMR surveillance studies today. bioMérieux is for example the sole private sponsor of the GLOBAL-Point Prevalence Survey (GPPS), in collaboration with the Laboratory of Medical Microbiology of the Antwerp University. GPPS is a study of antibiotic use and antimicrobial resistance (AMR) in hospitals around the world¹⁶ (cf. [6.3](#)). Moreover, bioMérieux **and JMI Laboratories (JMI) entered a six-year partnership** in 2023 to continuously evaluate antimicrobial susceptibility (AST) data in order to detect new and emerging strains of pathogens from across the globe¹⁷ (cf. [6.5](#)).

bioMérieux's most significant effort to support global AMR surveillance, however, is its partnership with the Fleming Fund. In 2022, bioMérieux was indeed chosen by the Fleming Fund as a partner due to the outstanding performance of its diagnostic solutions, its organizational capacity in the targeted countries and its extensive expertise in training healthcare professionals in microbiology and AMR²⁷.

The Fleming Fund clearly identified some major barriers to the implementation of effective AMR surveillance network, including:

- a lack of microbiology labs with a solid infrastructure
- reluctant support from public health authorities to support AMR surveillance networks

- missing or undersized quality assurance standards, including lacking standards for sample shipment and lab equipment maintenance
- little perceived use of surveillance data and low interest from policy makers

The Fleming Fund seeks to address these challenges to AMR surveillance by investing in microbiology laboratory infrastructure, a qualified lab workforce and local surveillance systems and by promoting the rational use of antibiotics in general¹⁸.

bioMérieux has been chosen to deploy its microbiology testing solutions in 15 countries of the Fleming Fund's program. In each of these countries, a clinical laboratory and a veterinary reference laboratory have been equipped with the VITEK® MS, VITEK® 2 and MAESTRIA™ systems ([Figure 13](#)).

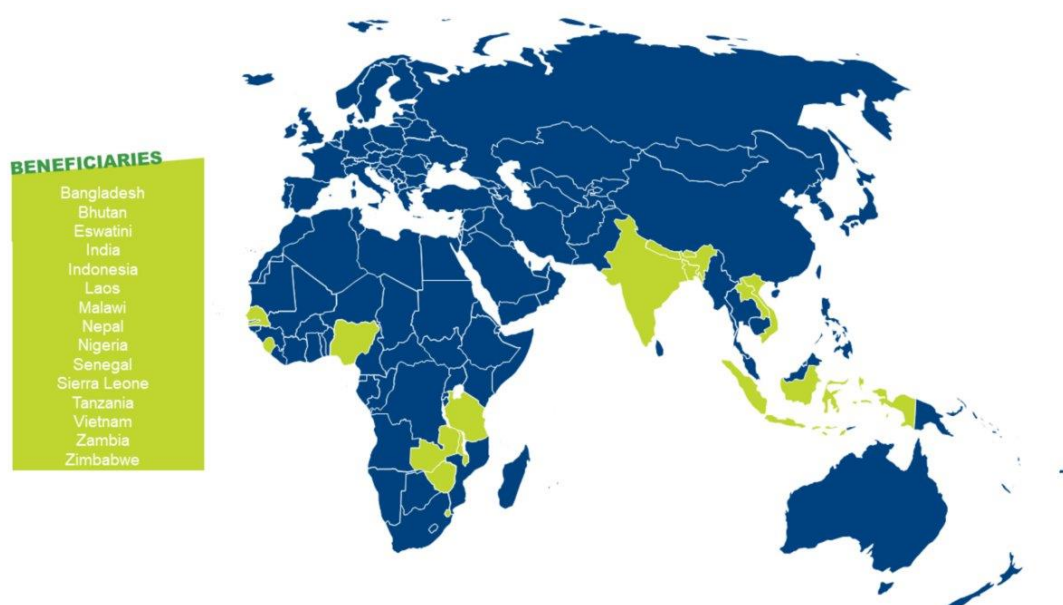


Figure 13 The Fleming Fund mandated bioMérieux to staff one clinical microbiology and one veterinary laboratory with VITEK® MS, VITEK® 2 and MAESTRIA™ systems in order to support the Fleming Fund's local AMR networks in these countries.

These devices will generate and analyze AMR data with integrated, advanced analytics. The results can then be used in the development of national antibiotic guidelines to guide antibiotic treatment for patients based on the local epidemiology and known AMR rates. In addition, the AMR data from these monitoring systems will become part of the WHO's Global Antimicrobial Resistance and Use Surveillance (GLASS) database to help inform stewardship strategies at a global level¹⁸. AMR surveillance data from all the sentinel surveillance sites will be reported to central reference laboratories to be merged, analyzed, cleared and submitted to GLASS⁸.

In 2023, bioMérieux does not plan to participate in additional global surveillance studies.

⁸ Health data transfers are subject to national regulation. Countries might not allow to share national antimicrobial resistance data.

4.7 Educational activities

bioMérieux develops continuing medical education programs in collaboration with leading experts. It also supports independent programs created by learned societies through educational grants with, for example but not limited to, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the Global Health Impact Group (GHIG), the Center for Infectious Disease Research and Policy (CIDRAP) or the International Society of Infectious Diseases (ISID)¹⁵. The vast majority of the documents, white papers and presentations created in collaboration with external organizations and medical societies address general issues about antimicrobial resistance, and the deliverables are usually unbranded and without any mention of bioMérieux products and services. bioMérieux also tries to link congress symposia to Continuing Medical Education (CME) credits where possible, which implies the accreditation of the deliverable by an independent body.

bioMérieux's educational hub⁹ also hosts numerous webinars and tutorials, online courses and educational booklets developed in collaboration with renowned medical and scientific experts. These support documents don't include any bioMérieux product information, even if the bioMérieux visual corporate identity is used.

4.8 Therapeutics stewardship

It is not expected that VITEK® REVEAL™ will accelerate or improve the deployment of an antimicrobial agent, mainly because well-established conventional AST methods already exist to conduct antimicrobial susceptibility testing for all antibiotic agents present on the VITEK® REVEAL™ AST Panel GN01. Alternative antimicrobial susceptibility testing for recently commercialized antibiotic combinations like Ceftolozane / Tazobactam or Ceftazidime / Avibactam (cf. [Figure 2](#)) for instance also exist on VITEK 2 or as an E-test.

The main benefit of the VITEK® REVEAL™ AST GN01 Panel resides in its capacity to rapidly determine minimum inhibitory concentrations for a numerous antibiotic agents. The availability of phenotypic AST results within 5.5 hours on average³ will support the reduction of inappropriate antimicrobial therapy in patients with bloodstream infections caused by Gram-negative pathogens.

5. Strategies for Supporting Project IP Rights in Other Territories

There are no opportunities to outsource aspects of product licensing or manufacturing today.






⁹ [Educational support | Pioneering Diagnostics \(biomerieux.com\)](#)



6. Strategies for Monitoring Effectiveness of Stewardship and Access Activities

6.1 bioMérieux’s Corporate Social Responsibility (CSR) objectives

As a pioneer in the diagnosis of infectious diseases, bioMérieux develops tests that can identify pathogens, detect their potential antimicrobial resistance, and analyze their antimicrobial sensitivity in order to help physicians precisely determine the appropriate treatment. bioMérieux assesses its impact on healthcare by monitoring the number of results provided to clinicians with an effect on the prescription of antibiotics. The aim is to help reduce the inappropriate use of these treatments and preserve their efficacy both now and for future generations. For this reason, bioMérieux has committed to increase the number of results provided in the fight against AMR by 30% between 2019 and 2025. In addition, bioMérieux’s AST solutions provide clinicians with crucial information enabling them to adjust antibiotic therapy based on the resistance of bacteria and their sensitivity to these treatments. bioMérieux has therefore committed to ensuring that its AST solutions include at least 80% of listed human antibiotics¹⁵. **These two metrics are part of bioMérieux’s Corporate Social Responsibility (CSR) objectives for 2025 and are therefore tracked annually (Figure 14).**

 HEALTH Antimicrobial Resistance and Stewardship (AMS)	 PLANET Carbon & environment footprint	 HEALTHCARE ECOSYSTEM Stakeholder dialogue	 EMPLOYEES Safety, Diversity & Inclusion	 EXTENDED COMPANY Partners & Communities
<p>+30% of patient results⁽¹⁾ supporting AMS by 2025</p> <p>≥80% of referenced antibiotics addressed by our AST solutions⁽²⁾</p>	<p>-50% GHG absolute emissions in 2030 vs. 2019 Scopes 1&2</p> <p>-45% water consumption⁽³⁾</p> <p>-50% energy consumption⁽³⁾</p> <p>-50% waste generation⁽³⁾</p>	<p>Collaboration projects with patient associations x2 by 2025 vs. 2021</p> <p>Materiality assessment updated every 3 years</p>	<p>Lost Day Incident Rate ÷2 to 0.6 in 2025 vs. 1.2 in 2020</p> <p>Corporate leadership team in 2025⁽⁴⁾</p> <p>>40% women</p> <p>>35% international profiles</p>	<p>≥1% of net income attributable to the parent company dedicated to Philanthropy (Endowment Fund excluded)</p> <p>Distributors covering 55% of sales⁽⁵⁾ trained on CSR by 2025</p>

(1) 2019 estimate: 183 million results.

(2) At least 80% based on EUCAST list and 90% based on CLSI cat A, B, U list.

(3) In 2025 vs 2015, per € million of revenue.

(4) Direct reports to the Executive Committee with a Global Corporate mission (international profiles are defined as non-French).

(5) Sales realized through the distributors network.

Figure 14 bioMérieux’s global contribution to Antimicrobial Stewardship is part of the company’s Corporate Social Responsibility plan and tracked annually.

6.2 bioMérieux’s Antimicrobial Stewardship Centers of Excellence

bioMérieux also engages **on a regional level** to promote antimicrobial stewardship in general. In 2021, bioMérieux established the Antimicrobial Stewardship Centers of Excellence program to bring attention to the threat of antimicrobial resistance and to accelerate the impact that infectious diseases diagnostics have in facilitating antimicrobial stewardship and better patient care. bioMérieux has formalized partnerships with 12 hospitals globally, including sites in the United

States, India, China, Malaysia, Morocco, France, Italy, Colombia, Chile, Mexico and Kenya (Figure 15). These sites are leaders in their countries and regions in regards to integrating diagnostics into antimicrobial stewardship. The partnerships will focus on generating and showcasing real-world medical and economic data and best practices about the value of combining diagnostics, medical education, lab consultancy services, and information technology solutions²⁸



Figure 15 bioMérieux's global network of Antimicrobial Stewardship Centers of Excellence

6.3 The Global Point Prevalence Survey (GPPS) of antibiotic use

bioMérieux is the sole private sponsor of the Global-Point Prevalence Survey (GPPS), in collaboration with the Laboratory of Medical Microbiology of the Antwerp University. GPPS is a study of antibiotic use and antimicrobial resistance (AMR) in hospitals around the world. Between 2015 and 2019 alone, GPPS has been conducted in nearly 800 hospital centers, in 80 countries and has collected data from over 200,000 hospitalized patients¹⁶. In 2021, over 90 countries participated, involving over 1,000 hospitals and more than 450,000 patients¹⁵. By regularly participating in this survey, each hospital can assess its performance and compare its practices with those of other sites in order to improve them. In some cases, the survey has resulted in national improvement programs. Global-PPS has been written about in major publications, including *Lancet Global Health*, and is now recognized by international organizations such as the WHO, Médecins Sans Frontières, the Center for Disease Dynamics, Economics & Policy (CDDEP), the Infectious Diseases Society of America (IDSA) and the British Society for Antimicrobial Chemotherapy (BSAC)¹⁵.

6.4 bioMérieux as a partner of the Fleming Fund

As a global leader in diagnosis of infectious diseases, bioMérieux has made responsible antimicrobial management one of its priorities. On the strength of this expertise, bioMérieux was chosen by the **Fleming Fund** as a partner in a UK investment program endowed with £265 million to combat



antimicrobial resistance in 21 resource-limited countries. bioMérieux, chosen for the performance of its diagnostics solutions, its organizational capacity in the targeted countries and its expertise in training healthcare professionals in microbiology and antimicrobial resistance, thus has become responsible for deploying its solutions in 15 countries of this program. In each of these countries, a clinical laboratory and a veterinary reference laboratory have been equipped with the VITEK® MS, VITEK® 2 and MAESTRIA™ systems. Since 2021, bioMérieux has equipped laboratories in Laos, Malawi, Nepal, Tanzania, Senegal, Swaziland, Zambia, Zimbabwe, Bhutan, Bangladesh, India, Indonesia, Nigeria and Vietnam. The facilities in Sierra Leone and Senegal have completed this first phase of the program. This program contributes to the third United Nations Sustainable Development Goal, which is that of health and well-being, in which antimicrobial resistance (AMR) has been recently officially added.

6.5 Collaboration with JMI to support the SENTRY surveillance program

In April 2023, **bioMérieux and JMI Laboratories (JMI) entered a six-year partnership** to undertake collaborative projects evaluating the performance and increasing potential of rapid and innovative microbiology diagnostics as important tools in the battle against AMR¹⁷. Through the partnership with JMI, bioMérieux will be able to continually assess AST results and validate against evolving global antimicrobial susceptibility data collected through the JMI-led SENTRY program. While Antimicrobial Stewardship Programs (ASPs) are critically dependent on rapid, reliable testing, there is an essential need for AST results to be continuously evaluated against new and emerging strains of pathogens from across the globe that may have developed new resistance mechanisms or additional levels of resistance to current treatments.

6.6 Collaboration to support the Nigerian CDC in the fight against AMR

In 2021, bioMérieux signed a collaboration agreement with the German Agency for International Cooperation (GIZ) in order to support the Nigerian Center for Disease Control (NCDC) in the fight against AMR. The goal is to promote and implement antimicrobial stewardship programs. This is the first time that bioMérieux has carried out a partnership of this type in Africa¹⁵.

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