TARGET PRODUCT PROFILES FOR ANTIBACTERIAL RESISTANCE DIAGNOSTICS

17 January 2020

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ISBN 978-92-4-000040-7

Acknowledgements

We are grateful to the individuals and institutions who provided feedback, including the ABR diagnostic TPP development group members, the individuals who attended the technical consultation held on 27–28 March 2019 and the other external stakeholders who provided comments.

WHO Secretariat

Francis Moussy and Maurine Murtagh (consultant).

Funding

This work was supported by the Wellcome Trust.

Table of Contents

Abbreviations and acronyms

ABR	antibacterial resistance
AC	alternating current
AMR	antimicrobial resistance
AST	antimicrobial susceptibility testing
CAI	community-acquired infection
CE-IVD	European Commission certification mark for in vitro diagnostic medical devices
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
CSF	cerebrospinal fluid
CSV	comma-separated values file
DHCP	dynamic host configuration protocol
DNS	domain name system
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	US Food and Drug Administration
GI	gastrointestinal infection
GMP	good manufacturing practices
GPS	global positioning system
GSM	global system for mobile communications
HAI	hospital-acquired infection
HTTPs	hypertext transfer protocol secure
IC	internal control
ID	identification
IP	Internet protocol
ISO	International Organization for Standardization
LAN	local area network
LMICs	low- and middle-income countries
MALDI-TOF-MS	matrix-assisted laser desorption/ ionization time-of-flight mass spectroscopy
MIC	minimum inhibitory concentration
NG	*Neisseria gonorrhoeae*
OEM	original equipment manufacturer
R&D	research and development
RFID	radio-frequency identification
SFTP	SSH file transfer protocol
SIR	susceptible, intermediate, resistance
SMS	short message service
TPP	target product profile
UPS	uninterruptable power supply
USB	universal serial bus
UTI	urinary tract infection
WHO	World Health Organization

Introduction

The increasing prevalence of antimicrobial resistance (AMR), which the World Health Organization (WHO) defines as the "ability of a microorganism – like bacteria, viruses and some parasites – to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it" (*1*) is a serious threat to global public health and disproportionately burdens low-resource countries (*2*, *3*). The growing resistance to antibiotics of bacterial pathogens is recognized as the largest of these threats (*4*). The importance of diagnostics in efforts to combat AMR has also been recognized (*5*). In particular, there is a need to stimulate the development of, and access to, appropriate rapid diagnostic tools for bacterial pathogen identification (ID) as well as antimicrobial susceptibility testing (AST) at all levels of the healthcare system in low- and middle-income countries (LMICs).

In order to address these needs, WHO undertook an initiative to map available and pipeline diagnostics against antibacterial resistance (ABR), identify gaps in the availability of such diagnostics in LMICs, and establish a research and development (R&D) priority list of diagnostics against ABR for the next 3–5 years. This mapping and list of gaps and priorities provided the basis for developing consensus target product profiles (TPPs) for the highest-priority diagnostics on the R&D priority list. Details on the process used are provided in the next section.

A TPP is a planning tool for the development of health products, including diagnostics. Industry uses in-house TPPs as planning tools to strategically guide development towards desired product characteristics. In particular, TPPs specify the product's intended use, target populations and desired attributes, and guide product development programmes.

WHO develops TPPs that are intended to support the development of products needed for public health for which gaps have been identified. As a result, WHO TPPs are needs-based and focused on public health priorities. WHO TPPS also emphasize that access, equity and affordability are integral parts of the innovation process and need to be considered at all stages, not just after a product is developed.

The WHO TPP document informs product developers, regulatory agencies, procurement agencies and funders on R&D and public health priorities. It is intended to facilitate the most expeditious development of products addressing the greatest and most urgent public health needs.

The development of WHO TPPs follows a standardized procedure and includes a number of steps. These include (i) doing a needs assessment; (ii) constituting a scientific TPP development group (with standard WHO Declaration of Interest procedures); (iii) drafting and sharing an initial draft of the TPP with the development group; (iv) revising, posting and disseminating a new version of the TPP for public consultation for 28 days (with comment form); (v) revising and finalizing the TPP (an additional consultation step may be needed in case of significant disagreement); and (vi) posting and disseminating the final version of the TPP.

All WHO TPPs should be considered to be living documents that may require modification if the status of science or the pipeline in the area changes.

Process used for the development of TPPs for antibacterial resistance diagnostics

Needs assessment

- A mapping of commercially and available diagnostics against ABR was conducted from July 2018 to March 2019. The following key parameters were prioritized: (i) diagnostics to improve clinical/syndromic management of patients to reduce over prescription of antibiotics; (ii) antibiotics exhibiting the highest proportion of resistance; (iii) diagnostics that can be performed at primary and secondary care facilities in LMICs; (iv) diagnostics targeted at pathogens primarily related to community-acquired infections (CAIs) and secondarily at bacterial infections that are most frequently acquired in hospitals (HAIs); and (v) diagnostics to help distinguish bacterial from nonbacterial infections.
- This step resulted in a draft document mapping the diagnostics landscape against ABR with lists of gaps and R&D priorities. The draft document was sent to more than 40 external experts for comment during fall 2018 and was also posted on the WHO website for public consultation for 1 month in February 2019.
- The map, gaps and TPPs to be developed were discussed and agreed on during a technical consultation held on 27–28 March 2019 in Geneva. The standard WHO Declaration of Interest procedures were followed for the participants. The meeting report can be found at: https://apps.who.int/iris/bitstream/handle/10665/326481/WHO-MVP-EMP-IAU-2019.08-eng.pdf?ua=1&ua=1. The diagnostics landscape is available at: https://apps.who.int/iris/bitstream/handle/10665/326480/9789241516280-eng.pdf.
- From the landscape document and the discussion during the technical consultation, it was determined that although many diagnostic methods and platforms are available for identifying bacterial pathogens and determining their resistance/susceptibility to antibiotic agents, for the most part these methods are not available at primary (level 1) or secondary (level 2) healthcare facilities in LMICs. There is an acute need for faster, easier and less expensive testing methods at those levels of the health system to assure accessibility to appropriate testing, including detection of pathogens in syndromic diagnoses; for patient management, including prescription of appropriate antibiotics; and for surveillance. Six specific gaps in priority diagnostics to combat ABR in LMICs were identified:
  - improved near-patient testing for tuberculosis;
  - simplified phenotypic ID and AST;
  - host response tests;
  - improved diagnosis and AST for *Neisseria gonorrhoeae* (NG);
  - a multiplex diagnostic platform suitable for level 2 healthcare facilities to identify WHO prioritized bacterial pathogens associated with clinical syndromes and to ascertain genetic determinants of antibiotic resistance/susceptibility or phenotypic AST with respect to the pathogens identified; and
  - a simple, easy-to-use reflex test suitable for level 2 or level 1 healthcare facilities to detect AST of prioritized bacterial pathogens performed in parallel with, or following, confirmation or ID of bacterial pathogens on a separate test or test platform.
- For the first four gaps, TPPs have already been developed (and did not need to be revised at this time). The last two gaps did not have TPPs and thus are the focus of this document.

TPP development

- Following the 27–28 March 2019 technical consultation, initial TPPs for (i) the multiplex diagnostic platform suitable for level 2 healthcare facilities and (ii) the simple, easy-to-use reflex test suitable for level 2 or level 1 healthcare facilities to detect AST as mentioned above were drafted by Maurine Murtagh (WHO consultant) and Francis Moussy (WHO).
- The draft TPPs were shared with a TPP development group: Cassandra Kelly (FIND, Geneva, Switzerland), Francis Ndowa (Skin and GU Medicine Clinic, Harare, Zimbabwe), Nada Malou (Médecins Sans Frontières, Paris, France), Trevor Peter (Clinton Health Access Initiative, Botswana) and Flavia Rossi (Hospital das Clínicas

da Faculdade de Medicina da Universidade de São Paulo, Brazil). The standard WHO Declaration of Interest procedures was followed.

- The TPPs were revised and sent to more than 40 external stakeholders as well as to other WHO staff members for comments.
- The TPPs were further refined based on the comments received and posted on the WHO website for public consultation for 28 days during September 2019. The posting was advertised to the relevant stakeholders.
- After final revisions, the TPPs were finalized. Each TPP includes key optimal and minimal characteristics and performance specifications. Ideally, the platforms would be designed and developed to achieve as many of the optimal specifications as feasible, while still meeting the minimal criteria for all enumerated features, recognizing that not all optimal specifications can be met using currently available technologies. The TPPs are intended as guidance to developers and are not meant to inhibit the development of diagnostics of alternative design that can achieve the intended use of the TPP – e.g. a non-instrument-based reflex test that can perform phenotypic AST.

The TPPs for the proposed multiplex diagnostic platform and for the proposed AST platform are attached hereto as Annex I and Annex II, respectively.

References

1. Growing antibiotic resistance forces updates to recommended treatment for sexually-transmitted infections [news release]. Geneva: World Health Organization; 2016 (https://www.who.int/en/news-room/detail/30-08-2016-growing-antibiotic-resistance-forces-updates-to-recommended-treatment-for-sexually-transmitted-infections, accessed 27 December 2019).
2. Antimicrobial resistance [fact sheet]. Geneva: World Health Organization; 2018 (http://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance, accessed 27 December 2019).
3. Bebell LM, Muiru AN. Antibiotic use and emerging resistance – how can resource-limited countries turn the tide? Glob Heart. 2014;9(3):347–58.
4. High-level meeting on antimicrobial resistance [press release]. New York: United Nations; 2016 (http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-on-antimicrobial-resistance/, 27 December 2019).
5. O'Neill J. Review on antimicrobial resistance. Tackling drug-resistant infections globally: final report and recommendations. 2016 (https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf, accessed 27 December 2019).

Annex I: TPP for a multiplex platform for ID and resistance testing/AST of prioritized bacterial pathogens

	Characteristic	Minimal requirement	Optimal requirement
		Scope of the platform	
1	**Intended use**	For purposes of patient management and antibiotic stewardship,[1] ID of (i) multiple WHO prioritized bacterial pathogens[2] associated with clinical syndromes such as bloodstream infections, respiratory infections, urinary tract infections (UTIs) and gastrointestinal infections (GIs), and (ii) either genetic determinants of antibiotic susceptibility/resistance or phenotypic antimicrobial susceptibility[3] with respect to select antibiotics for the pathogens identified.	For purposes of patient management and antibiotic stewardship, ID of (i) multiple prioritized bacterial pathogens associated with clinical syndromes such as bloodstream infections, respiratory infections, UTIs and GIs, and (ii) either genetic determinants of antibiotic susceptibility/ resistance or phenotypic antimicrobial susceptibility with respect to the full range of antibiotics for the pathogens identified.
2	**Description of system**	The system will consist of an instrument[4] designed for use in combination with a self-contained, disposable assay cartridge(s)[5] containing all reagents required to execute a test from sample to result.	
3	**Target use setting**	Level 2[6] healthcare facility (district hospital or above) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust and medical staff on-site; The target use setting does not include mobile testing facilities.	
4	**Target user**	Trained laboratory personnel (e.g. 1–2-year certificates)	
5	**Target population**	Adults to children > 6 months of age, including immunocompromised individuals.[7]	Same, plus neonates (including premature infants) up to 6 months of age.
		Instrument	
6	**Instrument design**	Single integrated instrument with port(s) capable of interfacing with one or more cartridge designs for (i) identifying multiple pathogens and genetic determinants of antibiotic resistance **or** (ii) identifying multiple pathogens followed by phenotypic AST to achieve the intended use.	
7	**Size**	Small, table-top instrument (50 x 75 x 50 cm or smaller)	
8	**Weight**	≤ 25 kg	

[1] WHO defines diagnostic stewardship as "coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions": Diagnostic stewardship: a guide to implementation in antimicrobial resistance surveillance sites. WHO Global AMR Surveillance System (GLASS). Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/handle/10665/251553/WHO-DGO-AMR-2016.3-eng.pdf?sequence=1&isAllowed=y, accessed 27 December 2019). This includes determining targeted therapy with antibiotics to preserve the use of second- and third-line antibiotics.

[2] WHO prioritized bacterial pathogens and resistance targets are set out in Appendix 1.

[3] Genetic markers of antibiotic susceptibility/resistance refer to genetic resistance mutations or genes, the absence of which is consistent with wild-type genotype and antibiotic susceptibility. Detecting the presence or absence of resistance mutations does not provide confirmation of susceptibility. Rather, it predicts the likelihood of resistance, since mechanisms of resistance other than those detected by specific genetic marker(s) may exist.

[4] "Instrument" is used throughout the document; however, any innovative design/embodiment that meets the described characteristics is acceptable.

[5] "Assay cartridge" is used throughout the document; however, any innovative design/mechanism that meets the described characteristics is acceptable.

[6] See Appendix 2 for healthcare-level definitions.

[7] In order to detect certain bacterial pathogens, including Salmonella, blood volume up to 5 mL is required. Because this volume of blood is difficult to obtain from infants under 6 months of age, the minimal target population specification is limited to persons over that age.

(Annex I, continued)

	Characteristic	Minimal requirement	Optimal requirement
9	**Power requirements**	Local 110–220 AC mains power, plus uninterruptable power supply (UPS) to complete current cycle; UPS and circuit protector must be integrated within the system.	Same, with rechargeable battery backup (8-hour operation).
10	**Sample capacity**	Option of doing one cartridge at a time; Multiple cartridge bays preferred such that one sample does not occupy the instrument – i.e. random access/parallel analysis.[8]	Multiple samples and multiple bays at a time (without batching required); Random access/parallel analysis required.
11	**Environmental stability – operating range of platform**	Operation at 10–35°C and up to 90% non-condensing humidity at altitude up to 2500 metres; Able to function in direct sunlight and low light; Able to withstand dusty conditions.	Operation at 5–45°C and up to 90% non-condensing humidity at altitude up to 3000 metres; Able to function in direct sunlight and low light; Able to withstand dusty conditions.
12	**Biosafety**	Closed, self-contained system; easy decontamination of instrument surfaces; alarms for organisms that pose a biosafety risk for laboratory-acquired infections preferred.	
13	**Training**	≤ 2 days of training for skilled laboratory staff	
14	**Service, maintenance and calibration**	Daily preventive maintenance can be performed by laboratory staff in < 30 minutes (with hands-on time < 10 minutes); Mean time between failures of at least 24 months; Self-check alerts operator to instrument errors or warnings; Need for instrument calibration on-site on a yearly basis by minimally trained technician.	Routine preventive maintenance no more than 30 minutes 1x per week (with hands-on time < 10 minutes); Mean time between failures of at least 36 months; Self-check alerts operator to instrument errors or warnings; Ability to be calibrated remotely, or no calibration needed.
15	**Patient ID capability**	Manual entry of alphanumeric patient identifier keypad or touchscreen compatible with protective gloves.	Same, plus bar code, RFID or other reader.
16	**Result readout**	Qualitative ID of bacterial pathogens and either (i) genotypic resistance markers or (ii) quantitative AST results (minimum inhibitory concentrations [MICs]) or interpretive results (susceptible, intermediate, resistance [SIR] based on CLSI or EUCAST standards of interpretation) reported for select targeted antibacterial agents associated with pathogens identified.	Qualitative ID of bacterial pathogens and either (i) genotypic resistance markers or (ii) MICs and interpretive results (SIR) based on CLSI or EUCAST standards of interpretation reported for the full range of targeted antibacterial agents associated with pathogens identified; Ability to select which test results are reported to the user based on the intended use in the regional epidemiological context in which the test is applied.
17	**Data display**	On-instrument visual readout with ability to function in various lighting conditions ranging from direct sunlight to low ambient light conditions; ability to add information (patient ID, operator ID, date, location, etc.).	
18	**Connectivity**	Integrated local area network (LAN) port; Integrated Wi-Fi 802.11b/g/n; USB 3.0; Internally designatable static IP address; Support for DHCP-issued IP addresses; Support for HTTPs and SFTP protocols; Integrated global positioning system (GPS); Ability to update connectivity software stack via USB or LAN.	Same as minimal, plus: Multiband global system for mobile communications (GSM) chipset 2G, 3G, 4G, 5G, LTE; Integrated Bluetooth 5.0; Integrated Wi-Fi 802.11ac; Bidirectional communication – ability to update connectivity software stack.

[8] "Random access" refers to the capability of the device to perform any test in any sequence at any time, with no interdependence on other test runs.

(Annex I, continued)

	Characteristic	Minimal requirement	Optimal requirement
19	**Data export**	Export of all instrument and test data over integrated hardware; Secure data export end-to-end encryption; Data export in CSV and Excel file formats; Configurable destination IP and DNS addresses; User-initiated data export; Connectivity to external printer.	Same as minimal, plus: Scheduled/automatic data export using interoperable standards via the GSM SMS.
20	**Manufacturing and regulatory**	Good manufacturing practices (GMP) compliant; ISO 13485:2016 certified and authorized for use by a stringent regulatory authority (e.g. FDA or CE-IVD marking).	
21	**List price[9] of instrument**	≤ US$ 15,000	≤ US$ 10,000
		Assay cartridge	
22	**Description of assay cartridge**	Self-contained, disposable cartridge(s) compatible with the instrument's cartridge port(s), containing all reagents required to execute a test from sample input to result.[10]	
23	**Pathogen targets**	In order to achieve the intended use, the ability to detect multiple target bacterial pathogens and either (i) to detect genetic determinants of antibiotic resistance to select antibiotics for identified pathogens at the same time from a single specimen in one or more assay cartridges or (ii) to perform phenotypic AST with respect to targeted antibacterial agent(s) associated with pathogens causing syndromes previously identified without the need of isolates.	In order to achieve the intended use, the ability to detect multiple target bacterial pathogens and either (i) to detect genetic determinants of antibiotic resistance to the full range of antibiotics for identified pathogens at the same time from a single specimen in one or more assay cartridges or (ii) to perform phenotypic AST with respect to targeted antibacterial agent(s) associated with pathogens causing syndromes previously identified without the need of isolates.
24	**Clinical sensitivity for pathogen ID**[11]	≥ 90% (95% CI) per pathogen based on optimal sample volume input.	≥ 95% (95% CI) per pathogen based on optimal sample volume.
25	**Clinical specificity for pathogen ID**	≥ 95% (95% CI) per pathogen based on optimal sample volume input.	≥ 98% (95% CI) per pathogen based on optimal sample volume input.
26	**Clinical sensitivity to predict genotypic resistance**	≥ 95% (95% CI) sensitivity per pathogen for detecting genetic determinants of AMR.	≥ 98% (95% CI) sensitivity per pathogen for detecting genetic determinants of AMR.
27	**Clinical specificity to predict genotypic resistance**	≥ 95% (95% CI) specificity per pathogen for detecting genetic determinants of AMR.	≥ 98% (95% CI) specificity per pathogen for detecting genetic determinants of AMR.
28	**AST – essential agreement**[12]	≥ 90% essential agreement	≥ 95% essential agreement
29	**AST – category agreement**[13]	≥ 90% category agreement	≥ 95% category agreement
30	**Very major errors**[14]	≤ 5%	≤ 3%

[9] "List price" is the price the manufacturer has arrived at for the product, taking into account the cost of goods and other factors (e.g. margin); the list price does not include any volume or other discounts or potential markup for distribution or other costs, such as freight, taxes, etc.

[10] An assay cartridge that meets "semi-open" design specifications made available by the manufacturer of the multiplex diagnostic platform to selected assay developers worldwide for use on such platform is preferred. A semi-open system would likely consist of three basic components or variants thereof:

1. Instrument manufacturer: designs, develops and manufactures the multiplex diagnostic instrument and designs an open cartridge for use on it.
2. OEM cartridge manufacturer: manufactures open cartridges to predesigned specifications on behalf of the instrument manufacturer.
3. OEM assay manufacturers (multiple): develop assays for the cartridge based on an assay developer's toolkit provided by the instrument manufacturer.

[11] In each case, clinical sensitivity and clinical specificity should be measured against an appropriate reference standard. For pathogen ID, this will likely be manual or automated culture methods, but could include MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectroscopy); for genotypic resistance, this will include gene sequencing.

[12] Essential agreement: Agreement, expressed as a percentage, of MIC determination within +/– 1 doubling dilution between the device under evaluation and the reference method. For detailed information on essential agreement, category agreement and discrepancies/errors, see Class II special controls guidance document: antimicrobial susceptibility test (AST) system. FDA guidance document 2009. Silver Spring, MD: US Food and Drug Administration; 2009 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/class-ii-special-controls-guidance-document-antimicrobial-susceptibility-test-ast-systems, accessed 27 December 2019).

[13] Category agreement: Agreement, expressed as a percentage, of interpretive results (SIR) between the device under evaluation and a standard reference method.

(Annex I, continued)

	Characteristic	Minimal requirement	Optimal requirement
31	**Multiplexing capabilities**	Ability to detect and identify a minimum of six pathogens to genus/species level at the same time and either (i) identify relevant genetic determinants of resistance or (ii) perform AST with respect to select antibiotics for detected pathogens.	Ability to detect and identify a minimum of 15 pathogens at genus/species level at the same time and either (i) identify relevant genetic determinants of resistance or (ii) perform AST with respect to the full range of antibiotics for detected pathogens, in either case from the same sample.
32	**Test kit**	All materials required for the test, including the assay cartridge, reagents, buffers, internal control (IC) or other consumables to test one patient, included in an individually packaged, self-contained kit. Sampling materials should be provided and packaged separately.	
33	**Additional third-party consumables**	None, except for sample collection and sample prep (e.g. volumetric pipettes).	None; cartridges contain all required reagents.
34	**Specimen type**	For pathogen ID and genotypic resistance testing, ability to accept multiple specimens (e.g. whole blood, serum, plasma, urine, stool, cerebrospinal fluid [CSF] and nasopharyngeal swabs), as appropriate, in order to achieve the intended use. For AST, no isolates required.	Same, as well as the ability to accept additional sample types (e.g. sputum, saliva, and various specimen swabs [rectal, vaginal, oral]) as appropriate in order to achieve the intended use; ability to use inactivated specimens, as required. For AST, no isolates required.
35	**Sample volume – pathogen ID**	For purposes of pathogen ID, the minimum sample volume required to reach clinically relevant sensitivities.[15]	
36	**Sample preparation**	Minimal sample processing; no more than three steps (requiring operator intervention); no more than one precision step (e.g. volumetric pipetting); centrifugation or other off-cartridge sample processing steps acceptable.	All sample processing steps are self-contained and performed within the assay cartridge; no precisions steps required to be performed by the user.
37	**Cross-reactivity – pathogen ID**	No relevant cross-reactivity with microorganisms outside the scope of the pathogens of interest; i.e. targets should be designed to not cross-react with other species within a genus or species that could be considered contaminants within the laboratory environment (e.g. *Staphylococcus aureus* vs *Staphylococcus epidermidis*).	
38	**Interfering substances – pathogen ID**	No interference for an individual or mixtures of analytes due to interfering substances.	
39	**Test result**	Qualitative ID of bacterial pathogens and either (i) genotypic resistance markers or (ii) MICs or interpretive categories (SIR) based on CLSI or EUCAST standards of interpretation reported for select targeted antibacterial agents associated with identified pathogens.	Qualitative ID of bacterial pathogens and either (i) genotypic resistance markers or (ii) MICs and interpretive categories (SIR) based on CLSI or EUCAST standards of interpretation) reported for the full range of targeted antibacterial agents associated with identified pathogens.
40	**Time to result – ID and genotypic resistance testing**	≤ 90 minutes	≤ 60 minutes
41	**Time to result – ID and AST**	Same day	2–3 hours
42	**Controls – internal process**	An internal process control must be integrated into the assay cartridge and the instrument.	
43	**Controls – positive/negative**	External positive and negative controls are not required for each test, but are performed daily.	External positive and negative controls are not required for each test and do not need to be run daily.

[14] Very major error: A discrepancy between the device under evaluation and the reference method, whereby the new device MIC is greater than +/– 1 doubling dilution and/or the SIR category is different (e.g. reference category result is R and new device result is S).

[15] Volume requirements could be circumvented by off-cartridge processing steps as defined in the sample preparation characteristic (line 36).

(Annex I, continued)

	Characteristic	Minimal requirement	Optimal requirement
44	**Environmental stability – transportation**	No cold chain requirements; Stable at 2–45°C for up to 7 days; Ability to tolerate short-term temperature fluctuations from 0 to 50°C; Up to 90% non-condensing humidity for up to 7 days.	No cold chain requirements; Stable at 2–45°C for up to 15 days; Ability to tolerate short-term temperature fluctuations from 0 to 50°C; Up to 90% non-condensing humidity for up to 15 days.
45	**Environmental stability – operating range**	10–35°C	5–45°C
46	**Waste/disposal requirements**	Direct disposal or incineration of consumables; Conform to WHO guidance and any country regulations.	Same, and no use of cyanide-containing reagents or chlorine gas.
47	**Shelf life and storage conditions**	12 months, 70% humidity from date of manufacture (based on real-time/accelerated stability studies) at up to 30°C.	18 months, 95% humidity from date of manufacture (based on real-time/accelerated stability studies) at 40°C.
48	**Regulatory**	WHO prequalification or stringent regulatory body (e.g. FDA or CE-IVD marking).	
49	**List price of assay cartridge**	≤ US$ 15 at volume production.	≤ US$ 10 at volume production.

Annex II: TPP for a platform to detect phenotypic antimicrobial susceptibility of prioritized bacterial pathogens to facilitate antibiotic stewardship

	Characteristic	Minimal requirement	Optimal requirement
		Scope of the platform	
1	**Intended use**	A reflex test to detect phenotypic AST of prioritized bacterial pathogens[16] associated with clinical syndromes such as bloodstream infections, respiratory infections, UTIs and GIs in parallel with or following confirmation or positive ID of such pathogens on a separate test or test platform in order to facilitate antibiotic stewardship.[17]	
2	**Description of system**	The system will consist of an instrument[18] designed for use in combination with a self-contained, disposable assay cartridge(s)[19] containing all reagents required to execute a test from sample to result.	
3	**Target use setting**	Level 2[20] healthcare facility (district hospital or above) defined as having a functioning laboratory with trained personnel, water, electricity with intermittent surges and/or outages, limited climate control, dust and medical staff on-site.	Level 1[19] healthcare facility defined as having a basic laboratory with minimally trained laboratory personnel, unreliably available water, electricity with surges and/or outages, no climate control, dust and limited medical staff on-site.
4	**Target user**	Trained laboratory personnel (e.g. 1–2-year certificates).	Minimally trained laboratory personnel.
5	**Target population**	Adults to children > 6 months of age, including immunocompromised individuals.	Same, plus neonates (including premature infants) up to 6 months of age.
		Instrument	
6	**Instrument design**	Single integrated instrument with port(s) capable of interfacing with one or more cartridge designs for detecting AST of prioritized bacterial pathogens to achieve the intended use.	
7	**Size**	Small, table-top instrument (50 x 75 x 50 cm, or smaller)	
8	**Weight**	≤ 25 kg	≤ 10 kg
9	**Power requirements**	Local 110–220 AC mains power, plus UPS to complete current cycle; UPS and circuit protector must be integrated within the system.	Same, with rechargeable battery backup (8-hour operation); possibility to use solar or other power sources.
10	**Sample capacity**	Option of doing one cartridge at a time; multiple cartridge bays preferred such that one sample does not occupy the instrument – i.e. random access/parallel analysis.[21]	Multiple samples and multiple bays at a time (without batching required); random access/ parallel analysis.

[16] WHO prioritized bacterial pathogens and resistance targets are set out in Appendix 1.

[17] WHO defines diagnostic stewardship as "coordinated guidance and interventions to improve appropriate use of microbiological diagnostics to guide therapeutic decisions": Diagnostic stewardship: a guide to implementation in antimicrobial resistance surveillance sites. Global AMR Surveillance System (GLASS). Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/handle/10665/251553/WHO-DGO-AMR-2016.3-eng.pdf?sequence=1&isAllowed=y, accessed 27 December 2019). This includes determining targeted therapy with antibiotics to preserve the use of second- and third-line antibiotics.

[18] "Instrument" is used throughout the document; however, any innovative design/embodiment that meets the described characteristics is acceptable.

[19] "Assay cartridge" is used throughout the document; however, any innovative design/mechanism that meets the described characteristics is acceptable.

[20] See Appendix 2 below for healthcare-level definitions.

[21] "Random access" refers to the capability of the device to perform any test in any sequence at any time, with no interdependence on other test runs.

(Annex II, continued)

	Characteristic	Minimal requirement	Optimal requirement
11	**Environmental stability – operating range of platform**	Operation at 10–35°C and up to 90% non-condensing humidity at altitude up to 2500 metres; Able to function in direct sunlight and low light; Able to withstand dusty conditions.	Operation at 5–45°C and up to 90% non-condensing humidity at altitude up to 3000 metres; Able to function in direct sunlight and low light; Able to withstand dusty conditions.
12	**Biosafety**	Closed, self-contained system; easy decontamination of instrument surfaces; alarms for organisms that pose a biosafety risk for laboratory-acquired infections preferred.	
13	**Training**	≤ 2 days training for skilled laboratory staff.	< 2 days for minimally trained laboratory staff.
14	**Service, maintenance and calibration**	Daily preventive maintenance can be performed by suitably trained staff in < 30 minutes (with hands on time < 10 minutes); Mean time between failures of at least 24 months; Self-check alerts operator to instrument errors or warnings; Need for instrument calibration on-site on a yearly basis by minimally trained technician.	Routine preventive maintenance no more than 30 minutes 1x per week (with hands-on time < 10 minutes); Mean time between failures of at least 36 months; Self-check alerts operator to instrument errors or warnings; Ability to be calibrated remotely, or no calibration needed.
15	**Patient ID capability**	Manual entry of alphanumeric patient identifier keypad or touchscreen compatible with protective gloves.	Same, plus bar code, RFID or other reader.
16	**Result readout**	Quantitative AST results (MICs) or interpretive results (SIR) based on CLSI *or* EUCAST standards of interpretation) reported for each targeted antibacterial agent associated with identified pathogens.	Quantitative AST results (MICs) *and* interpretive results (SIR) based on CLSI or EUCAST standards of interpretation reported for each targeted antibacterial agent associated with identified pathogens.
17	**Data display**	On-instrument visual readout with ability to function in various lighting conditions ranging from direct sunlight to low ambient light conditions; ability to add information (patient ID, operator ID, date, location, etc.).	
18	**Connectivity**	Integrated LAN port; Integrated Wi-Fi 802.11b/g/n; USB 3.0; Internally designatable static IP address; Support for DHCP-issued IP addresses; Support for HTTPs and SFTP protocols; Integrated GPS; Ability to update connectivity software stack via USB or LAN.	Same as minimal plus: Multiband GSM chipset 2G, 3G, 4G, 5G, LTE; Integrated Bluetooth 5.0; Integrated Wi-Fi 802.11ac; Bidirectional communication – ability to update connectivity software stack.
19	**Data export**	Export of all instrument and test data over integrated hardware; Secure data export end-to-end encryption; Data export in CSV file format; Configurable destination IP and DNS addresses; User-initiated data export; Connectivity to external printer.	Same as minimal plus: Scheduled/automatic data export using interoperable standards via the GMS SMS; Offline data export/transfer that can be retrieved by the system promptly if connectivity is lost.
20	**Manufacturing**	GMP compliant; ISO 13485:2016 certified and authorized for use by a stringent regulatory authority (e.g. FDA or CE-IVD marking).	
21	**List price[22] of instrument**	≤ US$ 15,000	≤ US$ 10,000

[22] "List price" is the price the manufacturer has arrived at for the product, taking into account the cost of goods and other factors (e.g. margin); the list price does not include any volume or other discounts or potential markup for distribution or other costs, such as freight, taxes, etc.

(Annex II, continued)

	Characteristic	Minimal requirement	Optimal requirement
22	**Description of assay cartridge**	Self-contained, disposable cartridge(s) compatible with the cartridge port(s) of the instrument, containing all reagents required to execute a test from sample input to result.[23]	
23	**Antibacterial targets**	In order to achieve the intended use, the ability to perform AST with respect to targeted antibacterial agent(s) associated with pathogens causing syndromes previously identified from a single specimen in one or more assay cartridges without the need of isolates.	
24	**Essential agreement**[24]	≥ 90% essential agreement	≥ 95% essential agreement
25	**Category agreement**[25]	≥ 90% category agreement	≥ 95% category agreement
26	**Very major errors**[26]	< 5%	< 3%
27	**Multiplexing capabilities**	Ability to perform AST with respect to the minimal number of antibacterial agents that would identify 75–80% of organisms causing the targeted syndrome.	Ability to perform AST with respect to the minimal number of antibacterial agents that would identify 90–95% of organisms causing the targeted syndrome.
28	**Test kit**	All materials required for the test, including the assay cartridge, reagents, buffers, IC or other consumables to test one patient, included in an individually packaged, self-contained kit. Sampling materials should be provided and packaged separately.	
29	**Additional third-party consumables**	None, except for sample collection and sample prep.	None; cartridges contain all required reagents.
30	**Specimen type**	Any sample that achieves the intended use and other requirements of the TPP for which no isolates are required.	
31	**Sample preparation**	Minimal sample processing; no more than three steps (requiring operator intervention); no more than one precision step (e.g. volumetric pipetting); centrifugation or other off-cartridge sample processing steps acceptable.	All sample processing steps are self-contained and performed within the assay cartridge; no precision steps required to be performed by the user.
32	**Test result**	Quantitative AST results (MICs) *or* interpretive results (SIR) based on CLSI or EUCAST standards of interpretation reported for each targeted antibacterial agent associated with identified pathogens.	Quantitative AST results (MICs) *and* interpretive results (SIR) based on CLSI or EUCAST standards of interpretation reported for each targeted antibacterial agent associated with identified pathogens.
33	**Time to result**	Same day	2–3 hours
34	**Quality control**	Internal quality control must be integrated into the assay cartridge and the instrument.	
35	**Controls – positive/negative**	External positive and negative controls are not required for each test, but are performed daily.	External positive and negative controls are not required for each test and do not need to be run daily.

[23] An assay cartridge that meets "semi-open" design specifications made available by the manufacturer of the diagnostic platform to selected assay developers worldwide for use on such platforms is preferred. A semi-open system is likely to consist of three basic components or variants thereof:

1. Instrument manufacturer: designs, develops and manufactures the multiplex diagnostic instrument and designs an open cartridge for use on it.
2. OEM cartridge manufacturer: manufactures open cartridges to predesigned specifications on behalf of the instrument manufacturer.
3. OEM assay manufacturers (multiple): develop assays for the cartridge based on an assay developer's toolkit provided by the instrument manufacturer.

[24] Essential agreement: agreement, expressed as a percentage, of MIC determination within +/– 1 doubling dilution between the device under evaluation and the reference method. For detailed information on essential agreement, category agreement and discrepancies/errors, see Class II special controls guidance document: Antimicrobial susceptibility test (AST) system. FDA guidance document 2009. Silver Spring, MD: US Food and Drug Administration; 2009 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/class-ii-special-controls-guidance-document-antimicrobial-susceptibility-test-ast-systems, accessed 27 December 2019). See also Humphries RM, Ambler J, Mitchell SL, Castanheira M, Dingle T, Hindler JA et al. CLSI methods development and standardization working group best practices for evaluation of antimicrobial susceptibility tests. J Clin Microbiol. 2018;56e01934-17 (https://jcm.asm.org/content/jcm/56/4/e01934-17.full.pdf, accessed 27 December 2019).

[25] Category agreement: agreement, expressed as a percentage, of interpretive results (SIR) between the device under evaluation and a standard reference method. See references in note 24.

[26] Very major error: a discrepancy between the device under evaluation and the reference method, whereby the new device MIC is greater than +/– 1 doubling dilution and/or the SIR category is different (e.g. reference category result is R and new device result is S). See references in note 24.

(Annex II, continued)

	Characteristic	Minimal requirement	Optimal requirement
36	**Environmental stability – transportation**	No cold chain requirements; Stable at 2–45°C for up to 7 days; Able to tolerate short-term temperature fluctuations from 0 to 50°C; Up to 90% non-condensing humidity for up to 10 days.	No cold chain requirements; Stable at 2–45°C for up to 15 days; Able to tolerate short-term temperature fluctuations from 0 to 50°C; Up to 90% non-condensing humidity for up to 15 days.
37	**Environmental stability – operating range**	10–35°C	5–45°C
38	**Waste/disposal requirements**	Direct disposal or incineration of consumables; conforms to WHO guidance and any country regulations.	
39	**Shelf life and storage conditions**	12 months, 70% humidity from date of manufacture (based on real-time/accelerated stability studies) at up to 30°C.	18 months, 95% humidity from date of manufacture (based on real-time/accelerated stability studies) at 40°C.
40	**Regulatory**	WHO PQ or stringent regulatory body (e.g. FDA or CE-IVD marking).	
41	**List price of assay cartridge**	≤ US$ 15 at volume production.	≤ US$ 10 at volume production.

Appendix 1: List of priority pathogens (WHO)[27]

Pathogen	Resistance	Sample type	Gold standard
Mycobacterium tuberculosis[28]	Drug resistance, in order of decreasing importance: (i) rifampicin; (ii) fluoroquinolones, including moxifloxacin; (iii) isoniazid and pyrazinamide; and (iv) aminoglycoside and capreomycin.	Sputum	Culture
Acinetobacter baumannii	Carbapenem-resistant	Whole blood	Blood culture
Pseudomonas aeruginosa	Carbapenem-resistant	Whole blood	Blood culture
Enterobacteriaceae: Escherichia coli and Klebsiella pneumoniae	Carbapenem-resistant/ESBL-producing	Whole blood	Blood culture
Clostridioides difficile	Multidrug-resistant, including: cephalosporin-resistant, fluoroquinolone-resistant	Stool	Toxigenic stool culture
Neisseria gonorrhoeae[29]	Cephalosporin-resistant, fluoroquinolone-resistant	Endocervical swab (women); urethral swab (men)	Culture
Enterococcus faecium	Vancomycin-resistant	Whole blood	Blood culture
Staphylococcus aureus	Methicillin-resistant/vancomycin-intermediate and -resistant	Whole blood	Blood culture
Helicobacter pylori	Clarithromycin-resistant	Blood, stool	Urea breath test
***Campylobacter* spp.**	Fluoroquinolone-resistant	Stool	Culture (Fitzgerald)
***Salmonella* (typhoidal and non-typhoidal)**	Fluoroquinolone-resistant	Whole blood	Blood culture
Streptococcus pneumoniae	Penicillin-non-susceptible	Whole blood, CSF	Blood culture and serotyping
Haemophilus influenzae	Ampicillin-resistant	Whole blood, CSF	Blood culture and serotyping
***Shigella* spp.**	Fluoroquinolone-resistant	Stool	Culture

[27] Global priority list of antibiotic-resistant bacteria to guide research, discovery and development of new antibiotics. Geneva: World Health Organization; 2017 (https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1, accessed 27 December 2019).

[28] Extensive work has been done on TPPs for testing (ID and resistance/susceptibility). TPPs are available at: https://www.who.int/tb/publications/tpp_report/en/, accessed 27 December 2019.

[29] Extensive work is being done on TPPs with respect to *Neisseria gonorrhoeae* (ID and resistance/susceptibility). A link to these TPPs will be added once they are available.

Appendix 2: Definition of health system infrastructure levels according to Ghani et al.[30] and the Maputo Declaration[31]

Characteristics	Level 0	Level 1	Level 2	Levels 3 and 4
Description	In the community or home	Lowest level of healthcare system with a laboratory	First level of referral healthcare and laboratories	Second and higher levels of referral healthcare and laboratories
Examples of locations	In homes, health fairs, health posts, clinics with no lab, pharmacies	Health centres (Africa), rural health centres (Asia and Latin America)	Hospitals (Africa), urban health clinics (Asia and Latin America), clinical labs in the developed world	Hospitals (Latin America and Asia), national clinical/reference laboratories (Africa), surveillance laboratories, research laboratories
Electricity	Not reliably available	Not reliably available	Available, expected to have refrigeration	Available
Clean water	Not reliably available	Not reliably available	Available	Available
Physical lab infrastructure and lab equipment	No laboratory	Not all facilities have labs. If present, minimal lab (e.g. microscope, centrifuge) or moderate lab (see level 2 description)	Moderately equipped lab (e.g. additional equipment for basic chemistry and manual immunoassays)	Well-equipped laboratories (e.g. automated and advanced equipment)
Personnel	Community healthcare worker, nurse, family member, pharmacist, traditional medicine practitioner	Nurses, sometimes physicians, laboratorians with a range of training	Nurses, physicians, moderate and well-trained laboratorians	Nurses, physicians, well-trained laboratorians

[30] Ghani AC, Burgess DH, Reynolds A, Rousseau C. Expanding the role of diagnostic and prognostic tools for infectious diseases in resource-poor settings. Nature. 2015;528:S50–52.

[31] The Maputo Declaration on strengthening of laboratory systems. Geneva: World Health Organization; 2008 (http://www.who.int/diagnostics_laboratory/Maputo-Declaration_2008.pdf, accessed 27 December 2019).

WORLD HEALTH ORGANIZATION
Avenue Appia 20
CH-1211 Geneva 27
Switzerland
T +41 22 791 55 03
F +41 22 791 48 90
www.who.int

ISBN 978 92 4 000040 7