VALUE-Dx Summary

October 2019

VALUE-Dx

University of Antwerp

BIOMÉRIEUX

wellcome

UNIVERSITY OF OXFORD

UMC Utrecht

Penta
Child Health Research

UNIVERSITÀ di VERONA

THE UNIVERSITY of EDINBURGH

University Medical Center Groningen

RAMBAM
Health Care Campus

UNIVERSIDAD DE LA RIOJA

BOSTON UNIVERSITY

BIOASTER
MICROBIOLOGY TECHNOLOGY INSTITUTE

FIND

NICE National Institute for Health and Care Excellence

Gesundheit Österreich GmbH

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

Berry Consultants
Statistical Innovation

IBBL
INTEGRATED BIOBANK OF LUXEMBOURG
FOR NEXT GENERATION HEALTHCARE

ZonMw
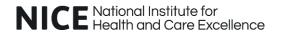
Janssen

ACCELERATE DIAGNOSTICS

Abbott

BIO·RAD

BD

VALUE-Dx project summary

VALUE-Dx (Value of diagnostics to combat antimicrobial resistance by optimizing antibiotic use) is the first Innovative Medicines Initiative (IMI) project initiated by **six in vitro diagnostic companies:**
- bioMérieux;
- Janssen Pharmaceutica;
- Bio-Rad;
- Abbott;
- Becton-Dickinson;
- Accelerate Diagnostics;

who joined forces with **twenty non-industry partners:**
- University of Antwerp, Belgium;
- University Medical Center Utrecht, Netherlands;
- PENTA Fondation, Italy;
- University of Verona, Italy;
- University of Edingburgh, UK;
- University Medical Center Groningen, Netherlands;
- The Health Corporation RAMBAM, Israel;
- Universidad De La Rioja, Spain;
- Boston University, USA;
- BIOASTER, France;
- National Institute for Health and Care Excellence, UK;
- Foundation for Innovative New Diagnostics, Geneva;
- Gesundheit Österreich, Austria;
- European Society of Clinical Microbiology and Infectious Diseases, Switzerland;
- European Respiratory Society, Switzerland;
- Berry Consultants, USA;
- Luxembourg Institute of Health, Integrated Biobank of Luxemburg;
- ZorgOnderzoek Nederland, Netherlands)

to combat antimicrobial resistance (AMR) and improve patient outcomes. VALUE-Dx is a unique multidisciplinary consortium, with participation of **clinicians, microbiologists, health economists, social scientists, and industry,** that should help to build the medical and economic case for rapid diagnostics as a public good in the fight against antibiotic resistance. The project is coordinated by the **University of Antwerp**, and co-funded by the **European Commission (IMI)**, **The Wellcome Trust** and **private companies**, with a total budget of around 14 million euros over 4 years (1 April 2019 – 31 March 2023).

VALUE-Dx will focus its research on **community care**, which is defined as the first point of contact with health services. This includes medical clinics (including general practice, urgent care centres, accident and emergency and other acute services in hospitals, paediatric care centres, and rehabilitation and long-term care facilities), both in and out of office hours care. Innovative diagnostics could transform clinical care, especially in community care settings where the majority of antibiotics are prescribed, by reducing uncertainty about potential benefit antibiotics may offer to individuals. More specifically, VALUE-Dx will **focus** on diagnostic strategies relevant to reducing AMR **in Community-Acquired Acute Respiratory Tract Infections (CA-ARTI)**. The **purpose** of VALUE-Dx is to transform medical practice to achieve more personalised, evidence-based antibiotic prescription and use in community care settings through the widespread use of clinical and cost-effective innovative diagnostic strategies.

Objectives

The objectives of VALUE-Dx are:
- To design a health-economic framework to assess and demonstrate the value of diagnostics both for individual patients and for public health impact by reducing antibiotic use and subsequent antibiotic resistance among patients;
- To establish a sustainable European Standardised Care Network adequately trained and resourced to conduct clinical trials evaluating the value of diagnostics;
- To design and implement clinical studies to demonstrate the value of diagnostics in the optimal management of CA-ARTIs;
- To explore, define and attempt to resolve the psychological, ethical and social barriers which prevent the more widespread adoption of diagnostics delivering healthcare to the population.

During the **first winter season of 2019-2020** we will conduct a web-based point prevalence audit survey **(PPAS)** of the presentation and management of CA-ARTI. This study aims to record information about patients who seek healthcare for CA-ARTI (e.g. acute cough, sore throat). This will help researchers benchmark patterns of testing and antibiotic prescribing in contrasting European settings simply by observing what happens now in routine care. The study will run during the first winter season over a 2 to 8-week period from January to March 2020 in approximately **20 European countries** (most likely: Armenia, Belgium, Croatia, France, Georgia, Germany, Greece, Hungary, Ireland, Italy, Moldova, Netherlands, Norway, Poland, Romania, Spain, UK, Ukraine).

Researchers will collect information from a range of health care settings where antibiotics are prescribed for patients who have respiratory infections, including general practice, urgent care centres, accident and emergency and other acute services in hospitals, paediatric care centres, and long-term care facilities, both in and out of office-hours care. Children and adults with symptoms of lower RTI where acute cough is the main symptom, or, where patients have symptoms of acute sore throat will be registered. Patients with only nasal, ear, rhinosinusitis symptoms will not be registered. This will be an anonymous cross sectional audit study, and because this study is purely descriptive, there is no intervention (study drug, test or interview) and no personally identifiable information will be collected, patients will not be asked to provide written informed consent.

During the **second (2020-2021) and third (2021-2022) winter season**, we will conduct a Platform randomised controlled trial of point of care diagnostics for enhancing the quality of antibiotic prescribing for CA-ARTI in community care in Europe **(PRUDENCE)**. The PRUCENCE trial will evaluate clinical algorithms that incorporate a point of care test (POCT) for CA-RTI. The clinical and cost effectiveness of algorithms that incorporate a point of care test will be compared to outcomes from management that does not include point of care testing. The goal of the overall program is to better target antibiotic prescribing in order to combat antibiotic resistance. The design of the trial will be complex: we aim for the trial to be flexible, in that once pre-specified criteria are met and a decision made about the success or otherwise of a CA-RTI-POCT algorithm in meeting those requirements, CA-RTI POCT may be dropped from the trial after the first winter and new CA-RTI POCTs may be included subsequently. However, it will nevertheless

be possible to include only a limited number of POCTs in this evaluation. Because of the huge variation of the algorithms combined with the POCT in different settings, direct comparison between CA-RTI POCTs in terms of effect on clinical decision making and patient outcomes will therefore not be appropriate.

The trial will preferentially include the POCTs of the industry consortium partners, as well as a few other POCTs, preferably developed by SMEs, that will be selected by specially constituted committee that will consider practical, feasibility, and scientific information. CA-RTI POCTs included in the trial need to be supported by existing, sufficiently convincing data about its accuracy for the purposes of care of people eligible for inclusion in the trial. Other performance and feasibility aspects will need to be taken into account, as any test will need to be compatible with existing clinical care routines. Some of the information relevant to these considerations will come from **systematic review and meta-analysis** work being undertaken in VALUE-Dx during the first year and from a **landscaping exercise** where a database is being constructed in a systematic approach to collect information that will guide assessments about suitability for inclusion in the trial. This landscaping exercise is done in conjunction with another project, ND4ID (New Diagnostics for Infectious Diseases), a Marie-Curie Innovative Training Networks project funded from March 2016 to February 2020.

Currently, in this **landscaping exercise**, we are collecting information on close to 300 diagnostic tests for RTI. Information collected includes: intended use, setting, performance, patient type, method, target, analysis, detection, detected pathogens, detected AMR, storage conditions, shelf life, kit components, volume/amount required, test preparation, sample processing, controls, calibration, maintenance, hands on time, results readout, time to result, instrumentation, instrument specifications, connectivity, waste disposal, samples per run, patient population, sensitivity, specificity, PPV, NPV, reproducibility, limit of detection, cross-reactivity, interference, training, required, on-site training, cost of kit (€), instrument availability in Europe, cost of instrument (€)/leasing possibility, calibration, maintenance/support, stage of development, market region, regulatory approval, and CLIA complexity.

The **systematic review and meta-analysis** will provide evidence for the use of diagnostics for CA-ARTI to develop clinical algorithms in different settings (primary care, long-term care facility, emergency department) and in various subgroups of patients by age, setting, comorbidities, and severity of disease. The systematic review will identify and evaluate evidence derived from the sensitivity, specificity, and predictive values of patients' signs and symptoms; radiologic and biomarker assessments; and pathogen-based diagnostic tests to determine the optimal components of an algorithm for optimizing decisions to recommend antibiotic treatment. Synthesis for quantitative variables will be performed with meta-analysis where possible and appropriate. The protocol will be based on the PRISMA-DTA (Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy studies) statement and the standard guideline for systematic reviews of diagnostic tests by the Cochrane Collaboration.

The systematic review will address three areas of the diagnosis of CA-ARTI:

- to assess the diagnostic accuracy of clinical signs/symptoms and testing for the diagnosis of CA-ARTI;
- to assess the diagnostic accuracy of clinical signs/symptoms and testing for identifying the aetiology of CA-ARTI;
- to assess the diagnostic accuracy for detecting antibiotic resistance in bacteria causing CA-ARTI.

The protocol for this first systematic review has been finalised in July and the work will start in August. Data extraction should be completed by mid-October 2019. There will be a second systematic review, after completing this first one, assessing the impact of testing on clinical outcomes in patients with CA-ARTI. The protocol for this second systematic review will start in December 2019, and should be completed by August 2020.

One of the main objectives of VALUE-Dx is **to ensure continuation** of operational infrastructures of VALUE-Dx and processes beyond the VALUE-Dx funding and beyond the scope of CA-ARTI. Therefore, **a business plan** will be developed in close collaboration with the VALUE-Dx partners, and the VALUE-Dx External Advisory Panel, consisting of representatives of the key stakeholder organisations of VALUE-Dx. The VALUE-Dx business plan will serve as the central strategic guidance for the post-project continuation of three core components of the VALUE-Dx research infrastructure and supporting processes and policies:

1| A pan-European Standardised Care Network, including clinical trial networks in primary care, hospital care, paediatric care and long-term care, linked with a laboratory network.
2| Central biobank of clinical samples, pathogens and DNA isolated from CA-ARTI patients
3| An integrated database and data management system.

The integrated VALUE-Dx Business Plan should be fully compatible with the ECRAID Business Plan. ECRAID is the working acronym to establish a sustainable European clinical research network on ID capable of conducting high quality clinical studies to combat EID and AMR. This clinical research organisation should be capable to conduct clinical trials on new antivirals, antifungals, vaccines and diagnostics. ECRAID-Plan has received funding from the European Commission's H2020 programme under grant number 825715 to develop the business plan for ECRAID, starting 1 January 2019 and to be completed by 31 December 2020. After tendering, Deloitte was selected to help writing the business plan for ECRAID and VALUE-Dx and the activities of Deloitte to write the business plan of VALUE-Dx have started in June 2019. Both ECRAID and VALUE-Dx business plans will be presented at an international conference on 10 December 2020 in Antwerp, Belgium.

Other activities that started during the first year of VALUE-Dx:

1| Building a technical roadmap, that incorporates recommendations for short- and long-term goals to help companies and research institutions prioritize investment decisions in the field of CA-ARTI diagnostics (first meeting in April 2019).
2| A two-step survey on resources (collections of biological material and databases) that are relevant for AMR research, and, in parallel, collection of information about services that are provided by research infrastructures and some biobanks (survey started in July 2019). This is a joint activity of the JPI-AMR and VALUE-Dx. The aim of the first survey is to get an

overview of existing resources and services that are relevant for AMR research. The second survey will then aim to gather more detailed information about these resources and services, while also addressing issues regarding fundability and sustainability. The first questionnaire was sent in July 2019 and the second questionnaire will be sent end of 2019.

3| Building a pilot interoperability network to allow connections between laboratory information systems. Our aim is to show how modern connectivity (e.g. usage of HL7 as constrained by IHE laboratory profile) and interoperability solutions (e.g. usage of LOINC to describe test and SNOMED CT to describe test results values) can be used to collect relevant AMR data (e.g. bacterial identification and susceptibility data and bacterial phenotypes) from diverse sources and systems in a timely, accurate and efficient manor, and shared with concerned stakeholders (first meeting in June 2019).

4| Writing the protocols for establishing health-economic models to determine the long-term clinical, public health and economic impact of diagnostics in terms of AMR prevention, and develop a new framework to accelerate market entry and accessibility to cost-effective diagnostics able to reduce AMR.

5| Establishing the External Advisory Panels for the different work packages (should be completed in October 2019).

6| Building a website (will be launched in October 2019).

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