Brief Communication

World Health Organization Essential *in vitro* Diagnostics 2020

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Introduction

In March 2017, the World Health Organization (WHO) Expert Committee on Selection and Use of Essential Medicines recommended that a list of Essential Diagnostics (EDL) be developed. WHO created an EDL Secretariat, which drafted the first edition of the EDL in consultation with colleagues in the various WHO disease programs. The EDL was then posted online for open consultation. WHO also created a Strategic Advisory Group of Experts on *In Vitro* Diagnostics (SAGE-IVD) to support the development of the EDL and to advise on other IVD policies and initiatives.

WHO published its first EDL[1] in 2018. This was a list of diagnostic tests that it considered essential for every healthcare system in the world. Apart from the standard haematology, biochemistry and urinalysis tests it focused on tests for diseases that WHO considered highest priority: human immune deficiency virus (HIV), hepatitis, tuberculosis, malaria, human papilloma virus (HPV) and Syphilis.

Many of these tests have been available for many years but their use has been inconsistent across countries. This edition examined the use of diagnostic tests in a range of settings from primary care through to a clinical diagnostic laboratory. The EDL is not intended to be prescriptive rather a guide to healthcare systems and laboratory managers.

One very important statement in the preface of this 1st edition is in keeping with the objectives of International Federation of Biomedical Laboratory Science (IFBLS): "While the EDL provides a list of important tests required at various levels of the health care system, it is important to note that the EDL itself cannot have an impact without an integrated, connected, tiered laboratory system, with adequate human resources, training, laboratory infrastructure, and regulatory/quality assurance systems."[1]

The EDL identifies diagnostic tests by category and is complementary to the "prequalified lists"(PQ) which include priority IVDs which have been assessed by WHO and are identified by brand. Within the disease specific categories where a WHO PQ or endorsed product exists it is cross referenced, along with WHO policies.

Open session with Stakeholders on the 2nd meeting of the WHO SAGE IVD, Geneva, Switzerland, March 18 2019. Photo: Marie Nora Roald

The second edition of the EDL was published in 2019.[2] New categories were added with general laboratory tests, anatomical pathology tests and therapeutic drug monitoring expanding the EDL from 62 to 122 categories. The disease specific tests were extended to include cancer tests. A new anatomical pathology section was added and consideration to blood safety was addressed by the addition of 7 test categories intended for screening of blood donations. Tests are further categorised to indicate if the test is used for screening, diagnosis, aid to diagnosis, monitoring, prognostic, surveillance or staging.

For countries where HIV is not endemic, the inclusion of flow cytometry as a test for primary care without laboratory may seem unusual, however the document is clear that every diagnostic repertoire depends on circumstances.

Selection and use of IVD

The 3rd edition, launched in January 2021[3], is a more substantial document compared to earlier versions. It includes a report of the third meeting of the WHO Strategic Advisory Group of Experts (SAGE-IVD) on *In Vitro* Diagnostics, 2020. The document acknowledges, by naming, the members of SAGE-IVD who provide WHO with technical advice on global policies and strategies related to priority, essential and neglected IVDs. The EDL is updated yearly, following a consensus process which includes face to face meetings, expert review and public consultation. It is remarkable that in the year of a pandemic that this document could be reviewed and expanded so thoroughly and that it has included considerations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) tests.

The members of SAGE are drawn from a range of academics, public health officials, pathologists and biomedical laboratory scientists. Members of SAGE are appointed for a period of 2 years and there are calls for membership each year.

The International Federation of Biomedical Laboratory Scientists (IFBLS) were consulted prior to the launch of the first edition and have provided input to numerous entries thereafter.

Innovations

Do Not Do

Perhaps as important as the recommendations on what tests are essential is the list of tests that are not useful in informing clinical management, performing surveillance or informing critical aspects of population health status: a list of "Do Not Do"

eEDL

It is intended that the EDL 3 be released in electronic format as well as in print. This will make it more accessible, searchable and facilitate updates. While it was intended that this be published in 2020 the beta version remains under review.

Harmonisation

Work is ongoing to align the EDL with the International Disease Classification system (ICD-11) and other global and regional nomenclature systems. It is intended that the EDL will also link into the Universal Health Coverage (UHC) compendium. This is a single interactive database which will facilitate searching for diagnostic tests, clinical interventions and essential medicines for any condition.

Health Technology Assessment (HTA)

It is recognized that all countries must undertake some level of assessment before introducing new services. Factors to be considered include clinical effectiveness, ethics, social issues and organizational frameworks. It is intended that the EDL will assist countries with this task.

As mentioned earlier one of the objectives of the EDL is to assist countries. SAGE considered options for achieving this by embedding the prioritisation into the EDL or developing a multi decision criteria and methodology. No decision on this was made and preferred method is to be researched prior to the 4th edition.

Applications for Addition to the EDL

The EDL is a living, evolving document and the 3rd edition is more substantial than the first two.

Table 1: Sectional Layout of the EDL

EDL Section	Description
Section 1a	General IVDs for community settings and health facilities without laboratories
Section 1b	Disease-specific IVDs for community settings and health facilities without laboratories
Section 11a	General IVDs for use in clinical laboratories
Section 11b	Disease-specific IVDs for use in clinical laboratories
Section 11c	Disease-specific IVDs for blood screening laboratories

Applications for additions, revisions and "do not do" recommendations to the EDL were submitted by academia, industry and WHO technical departments. Each is presented according to the section of EDL (Table 1).

Each proposal is organized and reviewed under the following headings:

- Proposal
- Applicant
- WHO Technical Department
- Background
    - Disease condition and impact on patients
    - Does the test meet a medical need?
    - How the test is used
- Public health relevance
- WHO or other clinical guidelines relevant to the test
- Basic test characteristics
- Evidence for diagnostic accuracy
- Evidence for clinical usefulness and impact
- Evidence for economic impact and/or cost–effectiveness
- Ethics, equity and human rights issues
- Summary of evidence evaluation
- Summary of SAGE IVD deliberations
- SAGE IVD recommendations
- References

The reviews are very thorough and informative. Decisions and the reasons for them are clear. Based on the current pandemic and the impact of testing for the Sars-CoV-2 virus on all biomedical laboratory scientists the specific applications relating to their inclusion are discussed below.

Sars-CoV-2

Given the global pandemic SAGE prioritized and fast-tracked consideration of testing under two sections. Section 1b Disease-specific IVDs for community settings and health facilities without laboratories where the introduction of SARS-CoV-2 antigen was considered and Section 11a.

Sars-CoV-2 antigen testing

The SARS-CoV-2 antigen testing was under consideration as an aid in the diagnosis of COVID-19 infection in symptomatic and asymptomatic individuals with known close contact with a confirmed case or to aid in the identification and investigation of outbreaks and community spread of COVID-19.

In considering medical need it was noted that; "WHO guidance on the use of rapid antigen tests recommends use in settings where "NAT is unavailable or where prolonged turnaround times preclude clinical utility". Given the generally lower sensitivity of these tests compared to reverse transcription polymerase chain reaction (RT-PCR), they should only be used to identify COVID-19 infection in patients who are within 5–7 days of the onset of symptoms."[3]

In considering the usefulness of the test, it is recommended that all negative tests do not rule out infection and should be confirmed by RT-PCR or repeat antigen test where the test is not available.

The caveats relating to negative tests are clearly described. However, it is evident that there is political pressure to use these tests in situations where the efficacy of the test is not confirmed.

Biomedical laboratory scientists should use their knowledge and competence to advise on the correct use of the test where possible.

SARS-CoV-2 nucleic acid test (NAT)

This application relates to the use of SARS-CoV-2 NAT to diagnose infection by SARS-CoV-2 in symptomatic and asymptomatic individuals suspected of exposure.

There can be no biomedical laboratory scientist who is unaware of the serious nature of this pandemic, its impact on patients and the role of the clinical diagnostic laboratory in the detection and monitoring of cases.

In considering the medical need for this test it is noted that; "The clinical utility of SARS-CoV-2 infection testing lies in early identification and isolation of cases, but also in choosing the right therapeutic approach in a clinical picture that can mimic several other entities."[3]

"Because SARS-CoV-2 is a global pandemic pathogen, in most areas the positive predictive value (PPV) of a SARS-CoV-2 diagnostic test based on PCR is high, especially for patients in high-risk groups."[3]

It is also noted the benefits of testing for case isolation and containment of infection spread and the proper use of personal protective equipment (PPE).

SAGE acknowledges the information is preliminary. However, it recommends that SARS-CoV-2 NAT be included in the third EDL using the NAT format. The test should be used on individuals suspected of being exposed to the virus, whether symptomatic or asymptomatic.

The specific evidence reviewed was for RT-PCR tests. Other nucleic acid tests require further evidence and review.

It might have been useful if some guidance was provided regarding the use of cycle threshold (CT) ratio, or other markers of viral load, in the interpretation of the results of analysis.

Applications for Modifications

Numerous requests were made to modify the entry in the EDL, some of these provided significant evidence and others did not. SAGE itself suggested some modifications such as the disaggregation of clinical chemistry metabolic panels, recognizing variations in practice in different countries.

While the indications for measuring D-dimers were modified their use in management of Covid-19 requires further consideration.

Conclusion

The development of the EDL through three editions demonstrates a commitment to the work by WHO and SAGE. The new edition is a very useful document which should be readily available, and consulted, in all clinical laboratories. It should be recommended reading for biomedical laboratory science students and indeed those planning services.

Biomedical laboratory scientists are advised to consult the EDL and audit their laboratory repertoire using the document. When areas are identified that need improvement, correction, addition or removal they should engage in the review process via a national process or via IFBLS.

The call for members of SAGE for the 4th Edition closed on 31st March 2021. The next of the EDL is already in gestation.

References

1. First WHO model list of in essential vitro diagnostics. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1017) (https://apps. who.int/iris/handle/10665/311567, accessed May 2019).

2. Second WHO model list of essential in vitro diagnostics, 2019 Website: https://www.who.int /publications /i/item/WHO-MVP-EMP-2019.0.

3. The selection and use of essential in vitro diagnostics: report of the third meeting of the WHO Strategic Advisory Group of Experts on In Vitro Diagnostics, 2020 (including the third WHO model list of essential in vitro diagnostics). Geneva: World Health Organization; 2021 (WHO Technical Report Series, No. 1031). Licence: CC BY-NC-SA 3.0 IGO.