

The selection and use of essential in vitro diagnostics

Report of the fourth meeting of the WHO Strategic Advisory Group of
Experts on In Vitro Diagnostics, 2022
(including the fourth WHO model list of essential in vitro diagnostics)



World Health
Organization

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Abbreviations and acronyms

ACS	acute coronary syndrome
AKI	acute kidney injury
AMI	acute myocardial infarction
AMR	antimicrobial resistance
BG	blood glucose
BMD	bone mineral density
BUN	blood urea nitrogen
CAH	congenital adrenal hyperplasia
CDC	United States Centers for Disease Control and Prevention
CI	confidence interval
CKD	chronic kidney disease
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
cTn	cardiac troponin
CVD	cardiovascular disease
DALY	disability-adjusted life-year
DTA	diagnostic test accuracy
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
EDL	WHO model list of essential in vitro diagnostics
eEDL	electronic EDL
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
EML	WHO essential medicines list
ESC	European Society of Cardiology
EU	European Union

EV	enterovirus
FDA	U.S. Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
FMH	fetomaternal haemorrhage
G6PD	glucose-6-phosphate dehydrogenase
GBD	Global Burden of Disease Study
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GTB	WHO Global Tuberculosis Programme
HbA1c	glycated haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HEV	hepatitis E virus
HHV-6	human herpes virus-6
hs-cTnI	high-sensitivity troponin I
HSV	herpes simplex virus
ICER	incremental cost-effectiveness ratios
ICM	International Confederation of Midwives
ICU	intensive care unit
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assay
IQR	interquartile range
IVD	in vitro diagnostics
KB test	Kleihauer-Betke acid-elution test
LAMP	loop-mediated isothermal amplification
LF-LAM	lateral flow lipoarabinomannan
LMICs	low- and middle-income countries
LOS	length of stay
MD	mean difference

ME	meningitis and encephalitis
mPCR	multiplex polymerase chain reaction
NAAT	nucleic acid amplification test
NAT	nucleic acid test
NEDL	national essential in vitro diagnostics list
NGO	nongovernmental organization
NICE	National Institute for Health and Care Excellence, United Kingdom
NPV	negative predictive value
NSTEMI	non-ST-segment elevation myocardial infarction
PCR	polymerase chain reaction
PHPT	primary hyperparathyroidism
POC	point-of-care
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	parathyroid hormone
QALY	quality-adjusted life-year
qPCR	quantitative polymerase chain reaction
RDT	rapid diagnostic test
Rh	Rhesus factor
Rh(D)	Rhesus-D protein
RT-PCR	reverse transcriptase-polymerase chain reaction
SAGE IVD	Strategic Advisory Group of Experts on In Vitro Diagnostics
17-OHP	17-hydroxyprogesterone
SMBG	self-monitoring of blood glucose
SOC	standard of care
sPVS	selective parathyroid venous sampling
T1D	type 1 diabetes
TAT	turnaround time

Introduction

The 4th SAGE IVD meeting was held 14–18 November 2022 in a virtual format. On the first day of the meeting the WHO EDL Secretariat organized an open webinar session with the participation of worldwide laboratory medicine professionals and nongovernmental organizations (NGOs), and representatives of WHO regional offices, country offices and headquarters. In the subsequent days SAGE IVD members held closed discussions on the applications received for the fourth WHO model list of essential in vitro diagnostics (EDL 4) as well as on the way forward for the EDL and its role in increasing availability, access and proper use of IVDs. Dario Trapani (SAGE IVD member) chaired the closed sessions of the meeting.

This report includes the EDL 4 applications and provides a summary of SAGE IVD’s deliberations, decisions and recommendations. EDL 4 is provided in section 5 of this report.

1. The EDL structure and review process

The EDL is a health policy document, based on scientific evidence, consisting of a list of categories of IVD tests and recommendations for using those tests in relation to the assay format, test purpose, specimen type and health care setting.

EDL 4 lists IVD tests that are recommended by WHO for use in countries to improve access to IVD testing. The list is not intended to be prescriptive with respect to the specific tests nor the level of the health care system at which IVDs can or should be used. Rather, the list aims to serve as a reference to guide development of or to update a national EDL (NEDL) at the country level within the framework of universal health coverage. In all cases, countries are expected to decide for themselves which IVD tests to select and where to use them depending on their local context, needs and priorities.

1.1 Objective

The EDL was developed to provide evidence-based guidance to countries for creating or updating their NEDLs and to guide policy on access to clinical laboratory services and IVD testing (1). It can be used by countries to prioritize the IVDs that should be available at different levels of the health care system and to support them in allocating often scarce resources to essential IVDs for ensuring a healthier population.

The EDL can also be informative for United Nations agencies and NGOs that support the selection, procurement, supply, donation and provision of IVDs as well as for the private health technology and manufacturing sectors, so that they focus on the IVDs necessary to address global health issues (2).

1.2 Scope

The EDL includes general and disease-specific IVDs for noncommunicable diseases and infectious diseases. The EDL does not list branded products but rather categories of IVD tests.

1.3 Structure

EDL 4 is organized in two tiers based on levels of care within the health system:

- I. Community settings and health facilities without laboratories
- II. Health care facilities with clinical laboratories

Each tier includes a section for general IVD tests that can be used for routine patient care as well as for detection and diagnosis of various diseases and conditions, and a section for disease-specific IVDs. In addition, tier II includes

a section for disease-specific IVD tests recommended to screen blood for transfusion purposes.

EDL 4 also includes a special section titled Do Not Do recommendations, which lists IVD tests recommended for discontinuation based either on evidence of harm or lack of benefit.

1.4 Recommended use

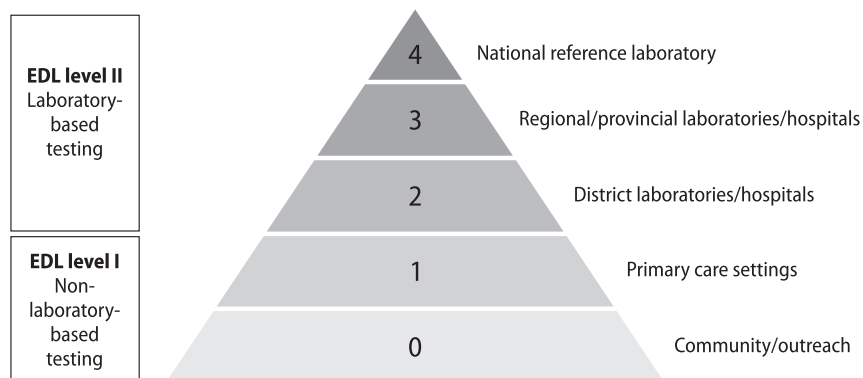
To use the EDL effectively and to adapt it for national requirements, Member States should consider factors such as local demographics, burden of disease, disease elimination priorities, availability of treatments (i.e. the NEDL should complement the national EML if available), training and experience of personnel, local unmet testing needs and gaps, supply chain, cost of IVDs, and of reagents and supplies, quality assurance capacity, financial resources, information technology capability and environmental factors.

EDL 4 should not be used in isolation but within the scope of integrated clinical laboratory testing services that meet the clinical needs and expectations of each country through its laboratory networks. Fig. 1 shows an example of a tiered health care delivery and laboratory network in a resource-limited country (1). The two first levels of the pyramid reflect testing at the community level and at primary care facilities, which serve most patients directly. Next, a smaller number of centralized facilities serve fewer patients directly. National reference laboratories and some provincial laboratories may not serve patients directly or may offer broad specialist consultation and serve as referral centres for quality assurance and training or for complex testing of samples sent either by facilities lower down the system and transported or from patients referred from other facilities. Other factors that determine use of IVDs are access to electricity, reagent-grade water and specialized human resources (3).

The two tiers of the EDL (I. Community settings and health facilities without laboratories and II. Health care facilities with clinical laboratories) are shown in levels 0 and 1 and levels 2, 3 and 4 in Fig. 1, respectively.

Fig. 1

Illustrative example of tiered testing services for use of IVDs



EDL: WHO model list of essential in vitro diagnostics; IVDs: in vitro diagnostics.

Source: adapted from (1).

1.5 Methods used to develop EDL 4

From a review of several WHO publications (4, 5, 6, 7), past SAGE IVD recommendations (8, 9), published work on IVDs for the medicines listed in the WHO EML (10) and requests from WHO technical experts, the WHO EDL Secretariat identified 71 candidate tests to inform the EDL 4 call for applications. Additional discussions took place, and SAGE IVD reached consensus on the following 23 tests, which were identified as high priority:

- therapeutic drug monitoring, amikacin
- therapeutic drug monitoring, gentamicin
- therapeutic drug monitoring, phenytoin
- therapeutic drug monitoring, lithium
- therapeutic drug monitoring, methotrexate
- nucleic acid testing, *Neisseria meningitidis*
- antigen test, *Entamoeba*
- total testosterone
- protein electrophoresis (in serum and urine)
- immunofixation electrophoresis
- free light-chain test (in serum)
- immunoglobulin M (IgM) antibodies against scrub typhus
- IgM antibodies against *Leptospira*

- serology, yellow fever
- nucleic acid testing, diphtheria
- IVDs for *Bordetella pertussis*
- IVDs for poliovirus
- IVDs for rotavirus
- lead
- hepatitis delta (rapid diagnostic tests (RDTs), enzyme immunoassays (EIA) and RNA polymerase chain reaction (PCR))
- hepatitis E (RDTs, EIA and RNA PCR)
- 17-hydroxyprogesterone
- parathyroid hormone.

The call for applications was opened from January to July 2022. Although the WHO EDL Secretariat especially invited applications for the 23 high-priority tests, the Secretariat also welcomed applications for tests not mentioned in the high-priority list.

Applications to the EDL can be submitted by any stakeholder, including Member States, academics, professional organizations, NGOs, companies in the IVD industry and WHO personnel from headquarters, and regional or country offices.

There are five types of applications:

- addition of new IVDs
- Do Not Do recommendations
- edits
- additional evidence in support of IVDs conditionally listed
- delisting.

For the addition of new IVD tests and for the Do Not Do recommendations, the application process proceeded in two phases. The first phase consisted of a presubmission in which applicants were required to submit information to allow the WHO EDL Secretariat, in collaboration with WHO technical experts, to determine the suitability of the application. Accepted presubmissions then moved towards the second phase, which consisted of submitting a full application form and the relevant supporting evidence, such as systematic reviews, peer-reviewed publications or clinical guidelines from expert bodies.

Other types of applications involved a single-phase submission process that also required applicants to provide relevant supporting evidence.

All the applications were reviewed by the WHO EDL Secretariat and WHO technical experts (when appropriate) for completeness of information before being shared with the 2021 SAGE IVD members and the methodologists. The review process by SAGE IVD started in August 2022 and was finalized in October 2022. Each application was reviewed by two experts from SAGE IVD and by one expert methodologist. All applications as well as the reviews carried out by SAGE IVD members and the methodologists were published online on 28 September 2022 for 3 weeks for public review and comment.

Due to some restrictions associated with the coronavirus disease 2019 (COVID-19) pandemic still in place in 2022 at WHO headquarters, the 4th SAGE IVD meeting was planned as a virtual meeting. The remote process developed for the 3rd SAGE IVD meeting in 2020 was updated and used to allow the experts to deliberate on EDL 4 applications before and during the 4th SAGE IVD meeting, which was held from 14 to 18 November 2022. Further details on the 2022 remote process for deliberations are provided in section 1.5.3.

To find out more about the EDL process, please consult *Selection of essential in vitro diagnostics at country level: using the WHO Model List of Essential In Vitro Diagnostics to develop and update a national list of essential in vitro diagnostics* (11).

1.5.1 SAGE IVD

SAGE IVD is the advisory body on matters of global policy and strategy related to IVDs, including advising WHO on the tests to be included in the EDL (1, 12). SAGE IVD members serve in their personal capacities and represent the broad range of disciplines required to advise on the many aspects of IVDs and other clinical laboratory-related activities. WHO organizes periodic calls for applications to become a SAGE IVD member and maintains a roster of experts on IVDs to support the selection of SAGE IVD members. The names and profiles of 2021–2023 SAGE IVD members involved in reviewing EDL 4 applications are available here: <https://www.who.int/groups/who-strategic-advisory-group-of-experts-on-in-vitro-diagnostics> (accessed 14 April 2023).

1.5.2 EDL 4 electronic application portal

Applications for EDL 4 were managed through a web-based application portal. Applicants received an individual access key and secret code to log in to the electronic portal to prepare and submit their applications. When technical issues prevented applicants from completing their applications in the electronic portal, the applications were submitted through the WHO EDL Secretariat email account using a word processor-based application form. The content of the electronic application form and the word processor-based application form was the same.

2.1.2 ABO blood groups and Rhesus factor typing point-of-care test

All content that is taken from the applications has been summarized and copy-edited for sense and clarity of language. The original application and the reviews are available in full at: https://www.dropbox.com/sh/dm1026anops6fe8/AACmVfzPz9Tpn_eT1KGJ1h0Ya?dl=0 (accessed 14 April 2023).

A. Proposal

The application proposed adding an ABO blood grouping and Rhesus (Rh) factor typing point-of-care (POC) dry format card test to the EDL as an IVD to determine ABO groups and Rh factor.

B. Applicant

ELDON Biologicals A/S

C. WHO technical department

None

D. Background (from application)

Disease condition and impact on patients

The proposed test intends to reduce the burden of Rh haemolytic disease of the fetus and newborn and complications of the disease, and expand access to blood products in settings with limited access to laboratory services.

Rh isoimmunization of fetus or newborn (also referred as Rh haemolytic disease or erythroblastosis fetalis) is caused by the passage of anti-Rh (anti-D) antibodies from an Rh-negative mother to her Rh-positive fetus, and results in stillbirths, neonatal deaths and brain damage due to severe hyperbilirubinaemia. At birth infants may have anaemia, hydrops fetalis, jaundice and hepatosplenomegaly.

Anti-Rh antibody development is caused by the entry of fetal Rh-positive red blood cells into the maternal circulation. It occurs in about 15% of pregnancies in which the fetus is Rh positive and the mother is Rh negative (1). Anti-Rh antibodies usually develop in the mother after birth, meaning that her first baby is typically not affected by Rh disease. However, in subsequent pregnancies, if the fetus is Rh-positive, the baby could be affected.

A series reported in the 1970s, when adequate prevention and management were not available, indicates that without treatment these pregnancies result in stillbirths (13%), neonatal deaths (25%) or severe hyperbilirubinaemia (25%), which can develop into irreversible brain damage (kernicterus) in 25% of cases but requires treatment in 33% of cases (2). Even

after therapy, which includes exchange transfusion, many surviving infants are at risk of permanent hearing loss.

Usually identified on antenatal screening tests, Rh disease is now uncommon in high-income countries (3). Administration of Rh immunoglobulin to the Rh-negative mother postpartum and during pregnancy is very effective in disease prevention (4).

When studying the gap between annual doses of anti-Rh(D) given and the annual doses required, it has been concluded that the highest priority is met only in high-income countries and countries such as Brazil, Czechia, Croatia, Greece, Hungary, the Islamic Republic of Iran, Lithuania, Malaysia, Saudi Arabia, Sri Lanka, the Republic of Korea, Thailand, Türkiye and Uruguay (4).

Treatment of a baby with Rh disease includes exchange blood transfusions, phototherapy and fetal transfusion. Prevention is preferable to avoid severe morbidity and mortality, as well as the cost and complications of therapy (3).

ABO haemolytic disease occurs when the mother's blood type is O and the infant's blood type is A or B. Maternal anti-A or anti-B immunoglobulins can cross the placenta and cause haemolysis in the infant. ABO is more frequent than Rh haemolytic disease; however, when promptly identified, ABO haemolytic disease is less likely to require exchange transfusion, or to cause brain damage or death than is Rh disease. Haemolysis with anaemia may progress during the first few weeks of life, and therefore careful monitoring of the newborn is necessary. There are no studies on the global burden of this condition.

Bilirubin-induced brain injury (kernicterus) is caused by severe jaundice and may result in death or long-term neurodevelopmental impairment. Jaundice within the first 24 hours of life is more likely to be haemolytic; total bilirubin levels may rise rapidly to very high levels. The main causes are Rh disease, ABO incompatibility, minor antigen incompatibility, glucose-6-phosphate dehydrogenase (G6PD) deficiency, hereditary spherocytosis and congenital infections. Extremely severe jaundice (bilirubin > 25 mg/dL) is estimated to affect 481 000 late-preterm and term newborns annually; 114 000 die and more than 63 000 survive with moderate or severe long-term neurological impairment (5).

Currently, standard practice in most countries during prenatal and antenatal care includes screening for ABO and Rh blood types in the mother. This test therefore identifies women with a blood group that is Rh-negative to administer postpartum anti-Rh immunoglobulin to avoid severe disease in future pregnancies. In the case of G6PD deficiency, neonatal screening using a blood spot has been shown to be effective and is cost-effective in regions with prevalence greater than 5%. Pre-discharge examination of women and their newborns will help identify early jaundice requiring more investigations, including blood typing and Coombs testing, and treatment.

Does the test meet a medical need?

The POC dry format card provides a reliable blood typing result that supports a final diagnosis of Rh incompatibility in pregnant women. The test is innovative and has the potential to address a need that is not met by current technologies. Existing strategies require venous blood samples, shipping the sample to specialized laboratory services and relocating Rh-negative women to deliver treatment. Compared with slide blood typing tests, the dry format card requires no electricity, no cold chain, no laboratory and no daily control of reagents, and therefore can be used as a POC test (6, 7).

The dry format card is currently being used in clinical practice in high-income countries and low- and middle-income countries (LMICs). In the United Kingdom the test is used to rule out Rh-negative women during pregnancy; and in LMICs the test has been used by Doctors Without Borders/Médecins Sans Frontières in emergency situations. Preliminary studies on feasibility and acceptability in LMICs show that the POC dry format card is accurate, user-friendly and acceptable for use by health professionals, lay workers and tested users (7, 8, 9).

While there are no studies on the cost-effectiveness of the POC test, prevention of Rh disease has been included among high-impact interventions to reduce stillbirths and neonatal deaths (10).

How the test is used

This POC test represents the first step in prevention of Rh disease by identifying Rh-negative women who can then receive preventive treatment with anti-D immunoglobulins (11). Additionally, the test will aid in the diagnosis of ABO incompatibility as the cause for haemolysis in newborns. Once a newborn is diagnosed, appropriate management of jaundice, anaemia and other complications can be initiated to prevent long-term disability and death.

E. Public health relevance (from application)

Prevalence

In LMICs access to laboratory facilities, prophylaxis and treatment for this condition is limited. Therefore, Rh disease continues to be a public health problem affecting more than 150 000 children annually (12). The prevalence of Rh negativity is not known in many LMICs. In Nigeria and India, it has been estimated at around 5% and in China at about 1%, whereas in Europe and North America prevalence is around 15% (3). Recent studies in Pakistan and Nigeria have found a prevalence comparable with that of industrialized countries (8, 9). However, due to the size of LMIC populations, millions of pregnant women are at risk. High fertility rates in some countries may also play a role as Rh disease becomes more severe with subsequent pregnancies. It is estimated that

50% of women around the world who require this type of immunoprophylaxis do not receive it (4). Globally, untreated Rh disease causes 52 000 stillbirths, 98 000 neonatal deaths, 67 000 cases of hyperbilirubinaemia and 17 000 cases of kernicterus each year (12).

Socioeconomic impact

Not provided.

F. WHO or other clinical guidelines relevant to the test (from application)

Guidelines for preventing Rh disease published by the International Federation of Gynecology and Obstetrics/International Confederation of Midwives (FIGO/ICM) in 2021 (11) provide recommendations to address the global burden of Rh disease, to be implemented according to a country's health system capacity (see box 1 on page 146 of the FIGO/ICM guideline).

Measures to prevent sensitization to Rh(D):

High priority

- Determine the maternal Rh factor, preferably in early pregnancy.
- For Rh(D)-negative women, determine the Rh factor of the newborn from umbilical cord blood.
- Administer anti-Rh(D) immunoglobulin within 72 hours of delivery to women with an Rh(D)-positive newborn, unless already sensitized.
- Use a dose of 500 IU (100 µg) of anti-Rh(D) immunoglobulin; if affordable and with sufficient supply, 1500 IU (300 µg) may be given, as is common in high-income countries. The intramuscular route is as effective as the intravenous route.

Middle priority

- Routine anti-Rh(D) prophylaxis during pregnancy: 1500 IU (300 µg) at 28–34 weeks.
- Anti-Rh(D) immunoglobulin prophylaxis (500 IU; 100 µg) after a surgical abortion or ectopic pregnancy (all gestational ages), or after spontaneous or medical abortion/miscarriage after 10 weeks.
- Anti-Rh(D) prophylaxis after bleeding, abdominal trauma in pregnancy and/or fetal death (500 or 1500 IU; 100 or 300 µg) during the second or third trimester. The Kleihauer-Betke test can be used to estimate the optimal dose.

Low priority

- Anti-Rh(D) prophylaxis after amniocentesis, chorionic villus sampling or external cephalic version (500 IU; 100 µg).

The FIGO/ICM guidelines specify that a prerequisite for prevention of Rh(D) sensitization is a priori knowledge of maternal Rh status and that the Rh(D) factor can be determined by collecting venous or capillary blood samples at local health care facilities and using classical or POC serologic methods. The guidelines also state that Rh(D) type should preferably be determined in the first trimester, because indications for anti-Rh(D) immunoprophylaxis may arise early in pregnancy, for example after miscarriage or ectopic pregnancy.

As reported in the FIGO/ICM guidelines, evidence shows that postpartum administration of anti-Rh(D) immunoglobulin reduces this risk to approximately 1.5% and is the most effective intervention in preventing Rh disease in subsequent pregnancies. Therefore, this approach should have the highest priority in countries and/or regions where no, or inadequate, prophylaxis is currently provided.

Prenatal administration seems to reduce sensitization further, from approximately 1.5% (achieved by administration of postpartum anti-Rh(D) immunoglobulin) to approximately 0.5%.

G. Basic test characteristics (from application)

Test formats available	POC test
Specimen types	Capillary whole blood
Equipment required	None required
Regulatory status	CE-marked, FDA-approved
Availability	Global
Price per test range	US\$ 0.75–3
Instrument price range	Not applicable

H. Evidence for diagnostic accuracy (from application)

No systematic reviews of the test's clinical accuracy yet exist. However, four studies have been published on the clinical accuracy, stability and reliability of the dry format POC test under different conditions in high- and middle-income countries.

The multicentre performance study published by Eldon Biologicals in 2004 evaluated the diagnostic accuracy of the dry format card test by comparing

results obtained blindly using EldonCards with results from conventional blood typing techniques in four blood testing centres in Denmark, Germany, Italy and the United Kingdom (13).

Of 2990 non-special samples regarding ABO blood types, 2988 concordant results were found at the initial testing (> 99.9% concordance). Of the eight weak A samples, three were detected by the dry card test, four were doubtfully positive and one was not detected. Of the 2988 samples, 2373 were found to be strong Rhesus D's by conventional testing. Of these, 2372 were detected by the experimental EldonCard at initial testing (> 99.9% concordance). Of the 39 weak Rh(D) samples, seven were detected by the anti-D formulation already in use on commercial EldonCards. The two new, experimental anti-D formulations on the cards were able to detect 15 and 19 of the weak D samples. The study concluded that the results of the ABO typing as well as the Rh(D) typing (including the results of the typing of weak D samples) show that an EldonCard is a reliable blood typing device which can be used for blood typing of patients and for primary screening of blood donors.

Bienek et al. assessed the accuracy of two dry card blood typing kits (the Eldon Home Kit 2511 and the ABO-Rh Combination Blood Typing Experiment Kit), tested under simulated military field conditions (6) and after long-term storage at various temperatures and humidities (14). Rates of positive tests among control groups, experimental groups and industry standards were measured and analysed using the chi-square and Fisher's exact tests to identify significant differences ($P \leq 0.05$). When the Eldon Home Kit 2511 was used under various operational conditions, the results were comparable to those obtained with the control group and with the industry standard. However, performance of the ABO-Rh Combination Blood Typing Experiment Kit was adversely affected by prolonged storage at temperatures above 37°C, indicating that performance of available kits varies with products and environmental conditions (6).

Ravichandran et al. evaluated the accuracy and reliability of the EldonCard test compared with the standard conventional slide and tube method in 808 volunteers selected randomly from Vinayaka Missions University, Salem, India. Compared with the standard laboratory method, both the sensitivity and specificity of the EldonCard method, as well as the positive and negative predictive value (PPV and NPV), were found to be 100%. The percentage of false positives and false negatives was 0% (7).

I. Evidence for clinical utility/impact (from application)

Primary studies on the POC dry format card test for blood group typing utility and impact have been conducted in Nigeria and Pakistan. Preliminary results have been presented at scientific meetings, and peer-reviewed papers are expected by the end of this year.

A study in Pakistan of the willingness of pregnant women to receive the POC test and the ability of health professionals to administer it and interpret the results showed 100% acceptance of the test and of treatment among Rh-positive women. Interpretation of the results had 100% concordance between health professionals and supervisors. These findings indicate that it will be feasible to implement a community-based programme for Rh haemolytic disease elimination in rural Pakistan (8).

Studies in Nigeria assessed feasibility and acceptability of the POC test in community settings targeting pregnant women and schoolchildren. The POC test was easy to perform and acceptable. In addition, it was easier for women to report their blood group through the card provided with the test result (9).

Implementation studies in Ghana, Kenya, Kyrgyzstan, Madagascar and Mexico are underway to develop community-based programmes to identify women who are Rh negative and to provide them with prophylaxis.

J. Evidence for economic impact and/or cost-effectiveness (from application)

Not provided.

K. Ethics, equity and human rights issues (from application)

The likelihood of an Rh-negative woman to have her baby affected by Rh disease is determined by where she lives. In high-income countries, stillbirth, neonatal mortality and disability due to this condition are uncommon. In contrast, in LMICs newborns affected by Rh disease often die either through lack of care at the lower level or inability to afford tertiary-level care. Inequities exist between and within countries, with women from the poorest communities facing the greatest barriers to access. In LMICs a large proportion of women do not have access to laboratory or preventive services.

The use of this ABO blood grouping and Rh factor typing POC dry format card will expand coverage of essential interventions for maternal and newborn health and reduce inequity. Women without access to laboratory facilities would know their Rh(D) antigen status and blood group and receive advice on accessing preventive care for Rh disease. Midwives could screen pregnant women in primary care facilities and at the home and immediately provide prophylactic treatment with anti-D immunoglobulin.

Diagnosis of haemolytic disease of the newborn will proceed more rapidly, and treatment could start to reduce the risk of kernicterus. Access to the screening test for Rh-negative and/or ABO status combined with access to the recommended treatment for preventing disease in pregnant women and for managing affected fetuses and newborns will lead to rapid elimination of the burden of Rh and ABO disease in less-developed countries (3, 4).

In addition, the POC dry format card could contribute to reducing maternal deaths due to obstetric haemorrhage by increasing access to blood

products in hard-to-reach settings through better access to blood typing for the pregnant women and in the general population.

No ethical issues were identified.

L. Summary of evidence evaluation

POC dry cards are a simple-to-use, cheap and easy-to-implement test. They aim to diagnose a severe condition which can have a significant impact on the lives of a large group of unborn children and their parents. Treatment for this condition appears to be effective.

The test requires limited infrastructure, facilities and training. The stability of samples is described in detail in technical documents (from the EldonCard producer). Documentation provided on diagnostic accuracy (e.g. sensitivity, specificity) in a real-world setting by untrained personnel is limited and of low quality. Nonetheless, given the clear effect (100% sensitivity and specificity) and the link with indirect evidence on concordance with laboratory tests (in a research setting), there is little reason to doubt the accuracy of this test. This is underpinned by the recommendation of several international guidelines.

Although the impact on clinical outcomes was not demonstrated using empirical studies (as is the case with the majority of diagnostic tests), the alternative of not providing this test would have severe consequences for a large group of unborn children and their parents. Given the anticipated costs of US\$ 1, minimal investment in supporting infrastructure and training, and the severity of the condition if left undetected and untreated, POC cards are expected to have a net positive cost-effectiveness. The availability of treatment, however, is a prerequisite for the IVD test to have any meaningful clinical impact. If availability is ensured, adopting the POC dry format card on the list would be recommended.

M. Summary of SAGE IVD deliberations

The ABO blood groups and Rh typing test is a straightforward, easy-to-use POC test for determining ABO groups and Rh. The test is very important in the context of maternal health care, in particular when laboratory-based tests are unavailable.

Several SAGE IVD members would have preferred a little more data on the impact of the test on clinical outcomes. The group noted that in the case of strong D antigen expression, concordance is reported to be 99.9%; performance in the case of weak D antigen expression is somewhat lower. One SAGE IVD member reported 100% concordance based on literature he consulted, although minor variants in ABO were not detected.

The experts proposed changing the title as submitted – “A, B and O blood groups and Rhesus (Rh) factor POC dry format card – to “ABO blood

groups and Rhesus factor typing point-of-care test” to be consistent with the way the test is reported in the literature. SAGE IVD made special note of the problem of weak D detection because it will have an impact on implementation.

Literature cited in the discussion:

Ravichandran S, Abraham P, Sugendran K, Hedegaard HO, Jones E. Trial and evaluation of dry format Eldon card for ABO & Rh blood grouping – “a new card concept”. *Natl J Basic Med Sci*. 2016;6(4):168–71.

N. SAGE IVD recommendations

SAGE IVD recommended including the ABO blood groups and Rh factor typing test category in EDL 4

- as a general IVD for use in community settings and health facilities without laboratories (EDL 4, Section I.a);
- using a POC test format;
- using capillary whole blood as specimen type;
- to determine ABO groups and Rh factor.

The group also noted that detection of the weak D antigen appears to be a limitation.

O. References (from application)

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