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Coronavirus Pandemic

Routine laboratory tests: Potential practical parameters to detect coronavirus disease-2019 in resource-limited settings

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Abstract

Introduction: The diagnosis of Coronavirus Disease-2019 (COVID-19), an ongoing global pandemic with more than 3 million cases worldwide both in developed and developing countries, requires molecular or serological tests that are not available in some settings. This systematic review provides further evidence to assess the diagnostic accuracy of routine laboratory tests to detect COVID-19 in suspected COVID-19 patients in resource-limited point of care and mobile laboratory.

Methodology: Comprehensive and systematic literature search in electronic databases (PubMed, Cochrane, and Online Wiley Library) was conducted to retrieve studies published between December 2019 and April 2020 reporting the diagnostic value of routine laboratory tests in the diagnosis of COVID-19. The quality of each study was assessed using QUADAS2. Literature search and study selection were depicted in PRISMA 2009 Flow Diagram.

Results: Three studies were included in this review. Two studies reported poor accuracy (AUC 0.075 and 0.624) of lymphopenia to detect COVID-19. One study reports good accuracy (AUC 0.858) of neutrophilia to detect COVID-19 amongst suspected cases. One multi-gated cross-sectional study reports poor discriminatory ability (AUC 0.65) of neutrophilia to discriminate between COVID-19 and CAP. Because of its big variability between patients and poor diagnostic accuracy (AUC 0.112 and 0.624), leukocyte count should not be a single parameter to determine COVID-19 patient status.

Conclusions: Neutrophil percentage might be helpful to determine COVID-19 status for suspected patients at the primary point of care or even in a mobile laboratory for countries with limited resources, but further study is needed to support this statement.

Key words: Coronavirus disease-19; COVID-19; diagnosis; routine laboratory test; resource-limited.

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Introduction

In December 2019, an outbreak of a newly discovered infectious disease emerged in Wuhan city, China. Five months later, the disease, namely Coronavirus Disease 2019 (COVID-19), spreads with more than 3 million cases worldwide [1]. Unfortunately, the diagnosis of the ongoing global pandemic requires molecular or serological tests which are not available in some settings [2]. In most cases, the early manifestation of COVID-19 is rather unspecific. Patients suspected of COVID-19 show fever and upper respiratory symptoms i.e. cough or shortness of breath with one of the following: (1) travel history to community transmission area 14 days prior, (2) contact history with confirmed/probable case 14 days prior, or (3) no other causes and in need for hospitalization. Some people infected with SARS-CoV-2 can also be relatively asymptomatic. That is why physical examinations, as well as laboratory and radiological tests, have to be done to rule out the differential diagnosis [2,3].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a relatively large encapsulated, single-stranded, positive-sense, ribonucleic acid (RNA) virus that is classified in nidovirales order and coronaviridae family. The S protein of the virus binds to the angiotensin-converting enzyme-2 (ACE2) receptor in the human respiratory tract [2]. The diagnosis of COVID-19 is established based on clinical findings and adjuvant tests. The gold standard of the diagnosis is by identifying the antigen (i.e., viral RNA) by quantitative reverse transcription-polymerase chain reaction (qRT-PCR) analysis of specimens from the upper and lower respiratory tract. It takes approximately 24-48 hours to get the result. If the qRT-PCR is unavailable, an antibody test i.e. IgM enzyme-

linked immunosorbent assay (ELISA) can be done 5 days after the onset of clinical manifestation. Both tests are done in central laboratories in urban health centers [2,4,5].

Point-of-care testings (POCTs) of both antigen and antibody are available as rapid tests with less accuracy. POCTs or commonly called Rapid Diagnostic Tests (RDTs) are portable. They do not require laboratory facilities or technology platforms. The result is available within a few minutes or hours of the tests are relatively expensive, especially in developing countries. Limited testing capability causes the lack of reliable data and underestimation of the prevalence of the disease in their population [5,6]. This can also lead to delayed diagnosis and treatment causing further progression of the disease and a lower rate of survival [7]. Therefore, a practical parameter is needed.

In Indonesia, limited testing capability using RT-PCR and RDT is clearly evident. As of the 7th of May 2020, with total confirmed cases of 12,776, only 95,717 people are tested for COVID-19 out of more than 273 million Indonesian citizens [8]. The number most likely does not represent the actual present condition of COVID-19 in Indonesia [9]. Limited RT-PCR testing, especially in rural areas, is mainly because it can only be done at central laboratories in urban health centers. On the other hand, RDTs are relatively expensive (US$50 to more than US$100) and hard to obtain [8]. Because of its possible high false positive and negative rate, these tests are not recommended to be used to make clinical decisions [10]. The shortages of health workers in rural or remote areas with a lack of basic testing skills especially to collect nasopharyngeal swabs may also be the reason for the unreadiness of both RDTs and RT-PCR testing. Health workers that are not properly trained in performing such tests could lead to false-negative results. This simple blood test might potentially become a cost-effective and rapid test to support the mass screening of COVID-19 in the primary point of care or even in a mobile laboratory for countries with limited resource [11].

Routine laboratory tests include complete blood count, blood biochemical tests, and coagulation profile. Amongst the three, the complete blood count is without a doubt the most preferable choice for it doesn't cost as much and doesn't require expensive equipment, certified central laboratory, or highly-trained labor forces [12]. Recent studies showed significant alteration of hematologic parameters in COVID-19 patients [13,14]. Routine laboratory parameters for infection and inflammation are easily accessed in standard laboratories of many healthcare facilities might help the triage of suspected COVID-19 patients. Laboratory tests might not be able to completely replace molecular or serology tests to determine COVID-19 status but might help reduce the uncertainty of the suspected patient's status in resource-limited settings. This could potentially prompt clinical actions, i.e. further diagnostic testing, early isolation, and treatment initiation or modification, and improve survival as well as disease control. This systematic review provides further evidence to assess the diagnostic accuracy of routine laboratory tests to detect COVID-19 in suspected COVID-19 patients in the resource-limited primary point of care and mobile laboratory.

Methodology

Inclusion criteria

Diagnostic test accuracy studies of all designs, single-gate or multi-gate, were included in this review. Studies conducted on human adults and written in English are included. Due to the scarcity of published studies in this area at present and to diminish potential publication bias, eligible grey literature (i.e., preprints indexed in BioRxiv and MedRxiv databases) were included in this systematic review [12]. The target condition was laboratory-confirmed COVID-19. Studies using routine laboratory parameters as index tests were also included. Studies using qRT-PCR as the reference standard for diagnosis were also considered eligible.

Exclusion criteria

Editorial articles and irrelevant studies were excluded.

Search methods

A comprehensive and systematic literature search in electronic databases (PubMed, Cochrane, and Online Wiley Library) was conducted on the 5th and 6th May 2020 based on clinical queries to retrieve studies published between December 2019 and April 2020 reporting the diagnostic value of routine laboratory tests in the diagnosis of COVID-19. The keywords were (COVID-19 OR SARS-CoV-2 OR 2019 Novel Coronavirus) AND (routine laboratory tests OR routine laboratory parameters). The search was designed to be highly sensitive to prevent relevant studies from being omitted. The reference lists of included studies were screened to get additional relevant studies [15].

Data collection

Three reviewers (MF, IAL, and BS) independently performed data collection. A consensus was reached in

case of any differences in opinions or views for eligibility assessments. After screening the title and abstract, duplicates and inaccessible studies were removed. Full texts of the shortlisted studies were read to assess eligibility based on pre-specified inclusion and exclusion criteria.

Data extraction and analysis

Data extraction and analysis were done by one reviewer (BS) and verified by other reviewers. Data extraction was done using piloted forms, including study characteristics, population, target condition, reference standard, and outcomes of each index test. The principal diagnostic accuracy measure reported was the area under the curve (AUC). The data was summarized and presented in a table.

Assessment of the methodological quality

Data extracted from selected studies were assessed for their methodological quality using the quality assessment of diagnostic accuracy studies-2 (QUADAS-2) checklist [16] for the assessments of risk of bias and applicability concerns. Poor-quality studies with a high risk of bias and/or high applicability concerns were excluded.

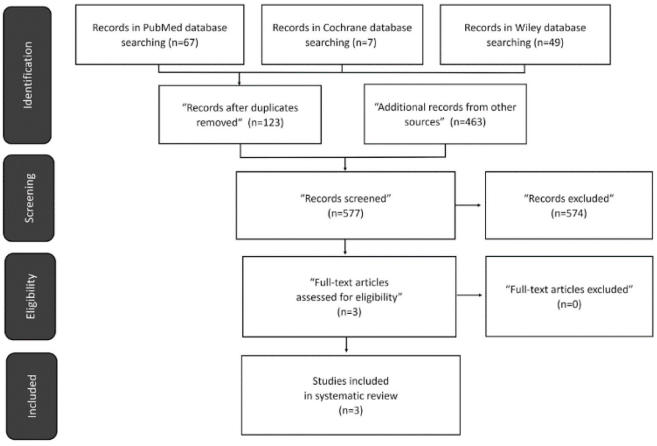
Eligible studies reporting the diagnostic value of routine laboratory tests to aid the diagnosis of COVID-19 were finally chosen to be reviewed. The process of literature search and study selection was depicted in PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) 2009 Flow Diagram [17].

Results

A total of 586 studies were screened from electronic databases (PubMed, Cochrane, Online Wiley Library, Biorxiv, and Medrxiv) including 463 additional studies from other sources. Search strategies used in this study are depicted in Table 1.

After removing duplicates and inaccessible studies, full texts of 577 studies were obtained, 3 of which were assessed for risk of bias and applicability concerns. Finally, three studies were selected for the review. The search and selection methodology used in this study is shown in Figure 1.

Figure 1. PRISMA 2009 flow diagram of study search and selection.



This flow diagram depicted the study search and selection. Three eligible studies were included in this systematic review.

Data extracted from selected studies were summarized and presented in Table 2. Assessment of methodological quality using the QUADAS-2 checklist (Table 3) showed that all three of the diagnostic test accuracy studies have good quality with low risk of bias and low applicability concerns.

Discussion

Laboratory parameters mainly discussed in this systematic review are lymphocyte, neutrophil, and WBC. A systematic review from 12 studies (7 case-control and 5 cross-sectional) shows insignificant laboratory findings in the early stage, but significant alterations of the parameters as the disease progresses: increased WBC (10 studies), increased neutrophil (7 studies), and decreased lymphocyte (10 studies) [14].

In accordance with Mardani *et al.* [18] and Pan *et al.* [19], many studies report the decrease in lymphocyte count (lymphopenia), more specifically CD8+ T cell

Table 1. Search strategies used in electronic databases and other sources.

Database	Terminology	Filters	Hits	Selected
PubMed	(Covid-19 OR SARS-CoV-2 OR 2019 Novel Coronavirus) AND (routine laboratory tests OR laboratory parameters)	Text availability: full text; Publication dates: December 2019 – April 2020	67	1
Cochrane		Cochrane Library publication date from December 2019 to April 2020; Word variations have been searched	7	0
Online Wiley Library		Publication Type: Journals; Publication Date: Last 6 Months	49	1
BioRxiv		Date Posted: December 2019 – April 2020	75	0
MedRxiv		Date Posted: December 2019 – April 2020	388	2

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2.

Table 2. Characteristics of diagnostic test accuracy studies included in this systematic review.

Author (Publication year)	Design	Sample size and participant characteristics	Clinical settings	Target condition definition	Reference standard	Index tests	Threshold value	AUC (95% CI)
Mardani *et al.* [18] (2020)	Single-gate cross sectional	200 suspected Covid-19 patients (70 Covid-19 RT-PCR positive and 130 Covid-19 RT-PCR negative)	Behpooyan Clinic Medical center, Tehran Province, Iran	Suspected Covid-19 (outpatients with initial respiratory signs, fever, myalgia, and cephalgia) with positive RT-PCR result.	RT-PCR	WBC	$< 0.6 \times 10^9$ cells/mm^3	Poor 0.075 (0.03-0.11)
						Lymphocyte percentage	< 0.6 %	Poor 0.112 (0.05-0.16)
						Neutrophil Percentage	> 0.70 %	Good 0.858 (0.79-0.92) Sufficient
Pan *et al.* [19] (2020)	Multi-gate cross sectional	425 patients (84 Covid-19 patients, 120 healthy control, 221 CAP patients)	Zhongnan Hospital of Wuhan University, Wuhan Shi, Hubei Sheng, China	Suspected patients with positive real time RT-PCR result.	RT-PCR	WBC	not mentioned	Poor 0.68 (0.62-0.75)
						Neutrophil count	not mentioned	Poor 0.65 (0.59-0.72)
Ai *et al.* [21] (unpublished, patent)	Single-gate cross sectional	315 suspected hospitalized patients (108 Covid-19, 207 non-Covid-19)	Xiangyang No. 1 People's Hospital, Xianyang Shi, Shaanxi Sheng, China	Suspected patients with positive repeated RT-PCR result.	Repeated RT-PCR	Lymphocyte count	$< 1.53 \times 10^9$/L	0.624 (0.558-0.69)

COVID-19: Coronavirus disease 2019; RT-PCR: reverse transcriptase polymerase chain reaction; WBC: White Blood Cell; AUC: Area Under the Curve; CI: Confidence Interval.

absolute count, in COVID-19 patients. The absolute count of both B cells and NK cells is not altered [20]. However, Mardani *et al.* [18] and Ai *et al.* [21] reported poor accuracy (AUC 0.075 and 0.624) of lymphopenia to detect COVID-19. This might be because the alteration of lymphocyte count depends on the disease severity and progression. It is more common and more severe in severe cases [22]. T cells are the lowest during the first week (4 to 6 days after onset) together with cytokine concentration peak, and slowly recover during the second and third week [20].

T lymphocytes, especially CD8+ cytotoxic T cells (CTLs), play an essential role in viral clearance. During the incubation period, approximately 1 to 14 days before onset, as well as in the early asymptomatic phase of COVID-19, lymphocyte counts are normal or slightly reduced [23]. Following viremia (indicated by the appearance of symptoms), SARS-CoV-2 enters alveolar epithelial cells by binding to the ACE2 receptor, which is also expressed on the lymphocyte surface. Thus, the virus can directly infect lymphocytes leading to its lysis [12]. Furthermore, antigenic stimulation causes the migration of lymphocytes from blood to the lung, resulting in a notable lymphopenia [20].

Table 3. Quality assessment using QUADAS-2 checklist.

Quality Assessment of Diagnostic Accuracy Studies			Mardani (2020)	Ai (unpublished)	Pan (2020)
	"Description"	"Describe methods of patient selection"; "Describe included patients (prior testing, presentation, intended use of index test and setting)"	The study included suspected Covid-19 patients presented to Behpooyan Clinic Medical from February 22nd to March 14th, 2020.	Suspected Covid-19 patients hospitalized in Xiangyang No. 1 People's Hospital until Feb 9th, 2020 were included.	Medical Records of laboratory confirmed Covid-19 patients based on World Health Organization interim guidance for Covid-19 presented to Zhongnan Hospital of Wuhan University from Dec 26th 2019 to Jan 30th 2020 were included.
Patient Selection	"Signalling questions (yes/no/unclear)"	"Was a consecutive or random sample of patients enrolled?"	YES	YES	UNCLEAR
		"Was a case-control design avoided?"	YES	YES	YES
		"Did the study avoid inappropriate exclusions?"	YES	YES	YES
	"Risk of bias: High/low/unclear"	"Could the selection of patients have introduced bias?"	LOW	LOW	UNCLEAR
	"Concerns regarding applicability: High/low/unclear"	"Are there concerns that the included patients do not match the review question?"	LOW	LOW	LOW

Table 3 (continued). Quality assessment using QUADAS-2 checklist.

Quality Assessment of Diagnostic Accuracy Studies			Mardani (2020)	Ai (unpublished)	Pan (2020)
Index Test	"Description"	"Describe the index test and how it was conducted and interpreted"	WBC, NEU, LYMP	Lymphocyte count (hypolymphemia)	WBC and differential count
	"Signaling questions (yes/no/unclear)"	"Were the index test results interpreted without knowledge of the results of the reference standard?"	YES	YES	YES
		"If a threshold was used, was it pre-specified?"	YES	YES	YES
	"Risk of bias: High/low/unclear"	"Could the conduct or interpretation of the index test have introduced bias?"	LOW	LOW	LOW
	"Concerns regarding applicability: High/low/unclear"	"Are there concerns that the index test, its conduct, or interpretation differ from the review question?"	LOW	LOW	LOW
Reference Standard	"Description"	"Describe the reference standard and how it was conducted and interpreted"	RT-PCR	Repeated RT-PCR with 24-hour time interval	RT-PCR
	"Signaling questions (yes/no/unclear)"	"Is the reference standard likely to correctly classify the target condition?"	YES	YES	YES
		"Were the reference standard results interpreted without knowledge of the results of the index test?"	YES	YES	YES
	"Risk of bias: High/low/unclear"	"Could the reference standard, its conduct, or its interpretation have introduced bias?"	LOW	LOW	LOW
	"Concerns regarding applicability: High/low/unclear"	"Are there concerns that the target condition as defined by the reference standard does not match the review question?"	LOW	LOW	LOW
Flow and timing		"Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram)"	All patients were included in analysis.	All patients were included in analysis.	All patients were included in analysis.
	"Description"	"Describe the time interval and any interventions between index test(s) and reference standard"	Pharyngeal swab and blood samples were collected from each participant. After that, a routine blood test and RT-PCR were performed.	Hospitalized suspected patients that were tested for routine laboratory tests and repeated RT-PCR tests with time interval of 24 hours at least.	Laboratory confirmed SARS-CoV-2 infected patients were tested for routine laboratory parameters. The blood and swab sample is taken at the same time with no interventions given in between.
		"Was there an appropriate interval between index test(s) and reference standard?"	YES	YES	YES
	"Signaling questions (yes/no/unclear)"	"Did all patients receive a reference standard?"	YES	YES	YES
		"Did all patients receive the same reference standard?"	YES	YES	YES
		"Were all patients included in the analysis?"	YES	YES	YES
	"Risk of bias: High/low/unclear"	"Could the patient flow have introduced bias?"	LOW	LOW	LOW

COVID-19: Coronavirus disease 2019; RT-PCR: reverse transcriptase polymerase chain reaction; CAP: community acquired pneumonia; WBC: White Blood Cell; NEU: neutrophil; LYMP: lymphocyte.

Roughly 7 to 14 days after the onset, a surge of clinical symptoms arises along with a pronounced and rapid increase of inflammatory cytokines called a cytokine storm, causing marked lymphopenia in severe patients [23,24] Inflammatory cytokines such as TNF-α, IL-6 and IL-10 might be responsible for T cell decrease in COVID-19. TNF-α interacted with TNF-Receptor-1 to promote apoptosis, especially in aged T cells [25]. Dysregulated IL-6 synthesis might also cause T cells to decrease [26]. IL-10 causes T cell proliferation inhibition and T cell exhaustion. To make it worse, regulatory T cells which are important for diminishing overactive immune responses during viral infection are also decreased [27]. This phenomenon also occurs in other respiratory viral infections like SARS in 2002 and is assessed as the cause of acute respiratory distress syndrome and multiple organ dysfunction syndrome [28]. This is the hyperinflammatory state with hyperactivation of lymphocytes (proven by reactive lymphocyte population such as lymphoplasmacytoid subset). Hyperactivation of CD4+ T cells also occurs which is indicated by an increased level of IL-2R and IFN-γ [20].

The hyperactivation state is followed by the rapid exhaustion of CD8+ T cells. This inhibitory state of lymphocytes in the final stage of COVID-19 (which is marked by increased PD-1 and Tim-3) leads to loss of cytokine production capability, reduced function, and lymphocyte anergy [20,29]. With the impaired immune function, the disease further progresses and the condition of the patient deteriorates.

Other hypotheses about the cause of lymphopenia in COVID-19 are direct lymphatic organs (thymus, spleen) disruption by the virus and inhibition of lymphocytes by lactic acidosis which is found in severe COVID-19 patients [20,24].

Mardani *et al.* [18] and Pan *et al.* [19] in concurrence with many studies report increased neutrophil count (neutrophilia) in COVID-19 [14,20]. Increased neutrophil in peripheral blood as well as extensive infiltration of neutrophils in the lung is the host acute inflammatory response to eradicate virus [22,24]. Marked neutrophilia with cytoplasmic and morphological anomalies are the consequence of a hyperinflammatory state of cytokine storm in severe cases [30].

Mardani *et al.* [18] report good accuracy (AUC 0.858) of neutrophilia to detect COVID-19 amongst suspected cases but Pan *et al.* [19] report poor discriminatory ability (AUC 0.65) of neutrophilia to discriminate COVID-19 and CAP. Clinical findings of both COVID-19 and CAP are indeed similar including fever and respiratory symptoms, but the contact/travel history evidently differs. Pan *et al.* [19] fail to grasp this difference because the study design is multi-gate cross-sectional and the study is retrospective using secondary data (medical records). The starting point of a single-gate study is suspected COVID-19 patients with apparent contact/travel history or other etiology ruled out, whereas Pan *et al.* reviewed medical records of already diagnosed CAP patients and included them regardless of contact/travel history. History taking is of foremost importance as a diagnosis can not be established by blindly looking at laboratory results.

A meta-analysis of 1994 COVID-19 cases reports a decrease of WBC (leukopenia) in 29% of the cases [13]. Leukopenia is also reported in several studies [31, 32]. However, a lot of studies report leukocytosis instead [14,33–35]. Data from a single study on the clinical characteristics of 1099 cases shows that on admission, a majority of COVID-19 patients presented with lymphocytopenia (83.2%), whereas only 33.7% showed leukopenia [36]. Mardani *et al.* [18] and Pan *et al.* [19] also report poor accuracy (AUC 0.112) of leukocytes to detect COVID-19 and poor ability (AUC 0.624) to discriminate between COVID-19 and CAP. Because of its big variability between patients and poor diagnostic accuracy, leukocyte count should not be a single parameter to determine COVID-19 patient status. However, leukocytosis combined with other laboratory parameters might help to detect COVID-19 in suspected COVID-19 patients in resource-limited settings with better diagnostic accuracy.

Lymphopenia and neutrophilia are oftentimes reported in COVID-19 patients. The magnitude of lymphopenia suggests the impairment of the immune system and the level of neutrophilia suggests the intensity of inflammatory response in COVID-19 patients [22]. Although current evidence fails to prove its accuracy, lymphopenia is consistently reported in most COVID-19 patients. To increase diagnostic accuracy, a combination of these parameters that is an increased neutrophil-to-lymphocyte ratio (NLR) might give more satisfactory diagnostic accuracy. Several studies already prove NLR as the most significant and useful parameter to early predict severe COVID-19 [36,37]. We encourage future diagnostic test accuracy studies with NLR as a potentially better parameter to detect COVID-19.

This simple blood test might potentially become the cost-effective and rapid test to support the mass screening of COVID-19 in primary points of care or even in a mobile laboratory for countries with limited resources. WHO encourages further study to determine

the diagnostic value and its mechanism to detect COVID-19 [10]. To comply with WHO recommendations, multiple single-gate cross-sectional studies with larger sample sizes are indeed needed to generalize the findings.

The major limitation of this systematic review is the scarcity of eligible diagnostic test accuracy studies to be reviewed. Although it is understandable because it has only been five months since the disease emerged. For future studies, since the magnitude of lymphopenia and possibly other laboratory parameters depend on the disease progression, we recommend measuring diagnostic accuracy at a specific time interval after the onset. We also suggest adding consumption of drugs or antivirals before admission as exclusion criteria because it could interfere with all results of routine blood tests [33].

Conclusions

This systematic review provides further evidence to assess the diagnostic accuracy of routine laboratory tests to detect COVID-19 in suspected COVID-19 patients in resource-limited primary point of care and mobile laboratory. Neutrophil percentage might be helpful to help reduce the uncertainty of COVID-19 status in resource-limited settings for suspected patients, showing fever and upper respiratory symptoms with travel/contact history or with no other causes and in need of hospitalization. However, further study is needed to support this statement. We also encourage future diagnostic test accuracy studies with NLR as a potentially better parameter to detect COVID-19. This simple blood test might potentially become the cost-effective and rapid test to support the mass screening of COVID-19 at the primary point of care or even in a mobile laboratory for countries with limited resources. This could potentially prompt clinical actions, i.e. further diagnostic testing, early isolation, and treatment initiation or modification, and improve survival as well as disease control.

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