The Promise of Clinical Decision Support Systems Targetting Low-Resource Settings

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(Methodological Review)

***Abstract*—Low-resource clinical settings are plagued by low physician-to-patient ratios and a shortage of high-quality medical expertise and infrastructure. Together, these phenomena lead to over-burdened healthcare systems that under-serve the needs of the community. Alleviating this burden can be undertaken by the introduction of clinical decision support systems (CDSSs); systems that support stakeholders (ranging from physicians to patients) within the clinical setting in their day-to-day activities. Such systems, which have proven to be effective in the developed world, remain to be under-explored in low-resource settings. This review attempts to summarize the research focused on clinical decision support systems that either target stakeholders within low-resource clinical settings or diseases commonly found in such environments. When categorizing our findings according to disease applications, we find that CDSSs are predominantly focused on dealing with bacterial infections and maternal care, do not leverage deep learning, and have not been evaluated prospectively. Together, these highlight the need for increased research in this domain in order to impact a diverse set of medical conditions and ultimately improve patient outcomes.**

***Index Terms*—Clinical decision support, low-resource.**

I. Introduction

LOW-RESOURCE clinical settings are commonly characterized by two phenomena. The first is low physician-to-patient ratios which average around 0.3 physicians per 1000 patients, ten-fold less than that found in developed nations [1], [2]. Fig. 1 illustrates this ratio for various countries since 1960. Secondly, such physicians, when accessible, operate in an environment that lacks high-quality expertise and medical infrastructure [3]. Combined, these phenomena lead to an over-burdened healthcare system that under-serves the needs of the community. This can manifest itself in the form of patients left untreated or even worse, poorly treated. Over-burdened healthcare systems, however, are not limited to low-resource clinical settings. Increasingly, health systems in developed nations such as the National Health Service (NHS) in the United Kingdom are coming to terms with such a realization [4].

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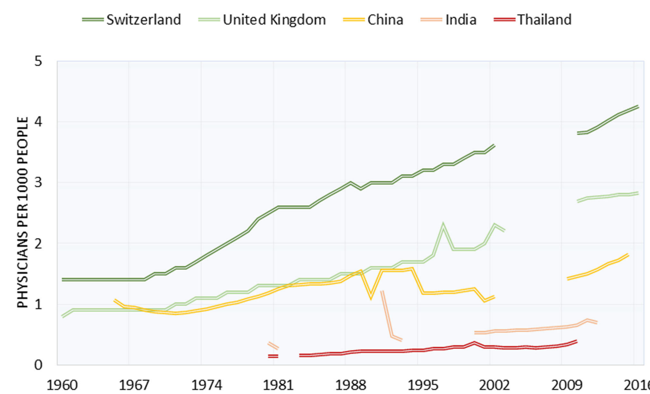

Fig. 1. Ratio of physicians per 1000 people in various countries since 1960. Note the significantly lower values exhibited by low and middle income countries (China, India, and Thailand) compared to those found in high-resource countries (Switzerland, United Kingdom) [1].

To alleviate the exigent burden, many researchers and healthcare professionals are increasingly turning their attention towards systems that support healthcare professionals in their day-to-day activities. For instance, the NHS Long Term Plan, introduced at the beginning of 2019, underscored the importance of digital systems and artificial intelligence in transforming their existing service [5]. Such systems can be broadly grouped under the term Clinical Decision Support Systems (CDSS).

One of the earliest CDSS, then known as Medical Diagnostic Decision Support Systems was introduced in 1954 by Nash [6] and consisted of a table that associated symptoms and diseases together in order to aid medical students in classifying diseases. A thorough review of such systems between the years 1954 and 1993 was performed by Miller just before the turn of the 20th century [7]. That review was shortly followed and complemented by that of Greenes [8] and Musen *et al.* [9]. In an effort to study the utility of CDSS, Kawamoto *et al.* [10] discovered that they improved clinical practice in 68% of studied randomized-control trials that incorporated them. Recently, CDSS have experienced renewed interest partly due to the burgeoning rise of medical data and artificial intelligence. Prominent examples include algorithms capable of diagnosing breast lesions based on mammograms [11], identifying patients with low ejection-fraction based purely on electrocardiogram

(ECG) recordings [12], and predicting the onset of acute kidney injury among hospitalized patients [13].

Although the work revolving around CDSS and their implementation in high-resource clinical settings is abundant and impressive, translating that success into low-resource settings is not so straightforward. The difficulty in doing this was emphasized by Wheeler *et al.* [14] who showed the inability of early warning scores developed in high-resource settings to generalize to patients in Malawi. Nonetheless, there have been several successes in India [15]. Artificial intelligence has recently been discussed in the context of rural health applications [16] and global health [17]. However, no-one, to the best of our knowledge, has explored the role of CDSS and outlined existing implementations within low-resource *clinical* settings. Consequently, this review aims to shed light on clinical decision support systems that target stakeholders within low-resource clinical settings or diseases commonly found in such environments.

II. Clinical Decision Support Systems Overview

Clinical decision support systems are commonly considered to be tools that assist clinicians in their decision-making. According to Musen *et al.* [9], they can be split into three types based on their purpose; tools for managing information, focusing attention, and providing recommendations. In this review, we expand the definition of clinical decision support systems to encompass tools that target and assist stakeholders within a clinical setting including physicians, nurses, patients, and potentially hospital administrators. Although such systems can take on many forms [18], we group them primarily based on whether they are manual or electronic. Within these two categories, the studies are further clustered according to their medical application. The motivation behind this categorization can be found in Section III.

A. Manual vs. Electronic Systems

In the context of this paper, manual decision support systems are those that require manual chart review, data entry, and calculations to arrive at a particular output such as an early warning score. Electronic systems, on the other hand, can range from simple digitized versions of paper-based systems to more complex models that capture non-linearities in the data.

B. Rule-Based Algorithms

Before the adoption of electronic health records (EHR), manual CDSS manifested themselves in various forms. One form was through the guidance of medical diagnosis and treatment which remains, to this day, heavily dependent on logic-based algorithms. For instance, decision tree algorithms were implemented to properly manage Parkinson's disease [19], discern between patients with and wihout prostate cancer [20], and determine which patients might be at risk of serotonin toxicity [21].

This dependence is even greater in low-resource settings as evident by a report published by the World Health Organization in 2013. It predominantly contained rule-based algorithms and decision trees deemed appropriate as medical interventions for non-communicable diseases specifically in low-resource settings [22].

C. Scoring Systems

Another form of CDSS still implemented within healthcare systems is early warning scores (EWS); scores used to categorize patients according to the severity of the condition based on the values of certain physiological parameters. One of the earliest of such scoring systems is the Modified Early Warning Score (MEWS) which exhibited a high correlation with intensive care unit (ICU) admission, death at 60 days, and other primary endpoints [23]. Since then, a plethora of early warning scores have been introduced including, but not limited to the VitalPAC Early Warning Score [24] for adult patient deterioration, National Early Warning Score [25] for operation at a national scale within the UK, and most recently, Targeted Real-Time Early Warning Score [26] for septic shock.

D. Machine-Learning Based Systems

As times progressed, certain hospitals made the transition towards electronic clinical decision support systems. Till this day, however, their adoption rate remains low. Such low adoption rates have not dissuaded academics, researchers, or even private companies from developing more sophisticated algorithms that rely on machine or deep learning. Deep learning, a domain that depends on the use of neural networks to approximate functions between inputs and their corresponding outputs, has experienced recent successes in particular due to the rise in available medical data and improvements in hardware capabilities. A high-level review of deep-learning algorithms as they pertain to healthcare can be found in [27].

III. Methods

A. Search Strategy

A search was conducted up until June 30th 2020 using the online databases (Google Scholar, PubMed). An expression with the following keywords was used [(low resource OR resource constrained OR developing country OR low and middle income country (LMIC)) AND (decision support system OR algorithm OR decision tree OR machine learning) AND (clinical OR hospital)].

Given the paucity of data in this field, the search was not limited to a particular range of dates. The search produced 520 results in total, 385 of which were excluded based on the irrelevance of the title. After fully reading the remaining 135 articles, only 75 were included in this review.

The inclusion criteria for an article are the following:

1) It must describe, implement, or evaluate a system that targets a stakeholder within a clinical setting as described by Higginson *et al.* [28].
2) It must target individuals or medical conditions found in low and middle-income countries as determined by the Organization for Economic Co-operation and Development [29].

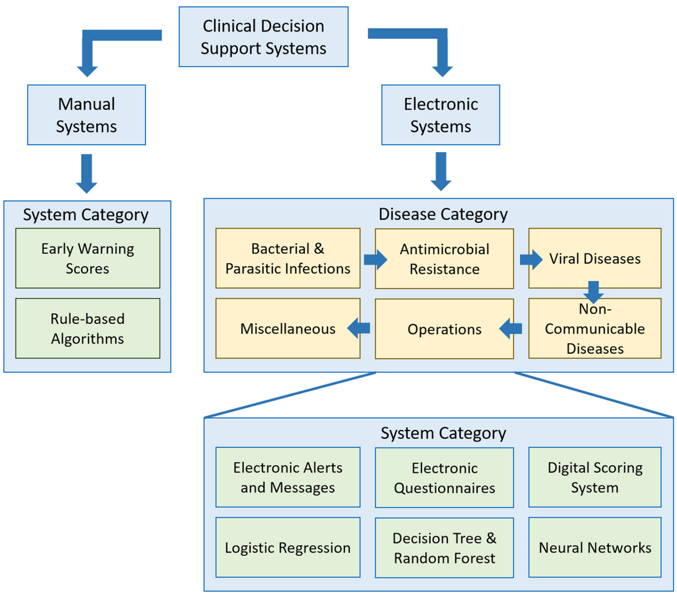

Fig. 2. Chart that illustrates how the current review delineates clinical decision support systems (CDSSs) and how it presents the findings. CDSSs are split according to whether they are manual or electronic. Within the electronic system category, the findings are presented in terms of their clinical application and in the order indicated by the arrows. Throughout this stage, the diverse set of electronic systems are outlined.

Articles that involved mobile decision support systems or those targetting *rural* non-clinical settings are beyond the scope of this review. For such work, interested readers are directed towards a recent review by Karageorgos *et al.* [30].

B. CDSS Application Categories

The publications are presented according to Fig. 2. After being split according to whether they refer to manual or electronic systems, they are further categorized according to the following application areas:

1) Bacterial/Parasitic Infections
2) Antimicrobial Resistance
3) Viral Diseases
4) Non-Communicable Diseases
5) Operations
6) Miscellaneous

We decide to present the results categorized according to application areas in order to make it more convenient for subject matter experts to identify the state of the research in their domain. This then allows them to either leverage existing technology or identify gaps that they can fill. Moreover, it allows machine learning and medical researchers alike to identify clinical domains that may not be well addressed by current decision support systems. Consequently, such domains will stand to benefit from further research.

When discussing each study, we generally follow this multi-step approach. 1) We outline the purpose of the study and the location in which it was performed. 2) We then move on to discuss the clinical parameters involved in the design of the decision support system, examples of which include but are not limited to heart rate, drug dosage, and nurse compliance. 3) We identify the clinical decision support system itself and evaluate its performance (if applicable). 4) Lastly, we critically appraise any of the aforementioned points, 1–3, for their feasibility and appropriateness before suggesting an action that may benefit the study, e.g., conducting a prospective analysis, using different evaluation metrics, and obtaining a larger cohort. We believe that such an approach holistically summarizes the studies and allows for easy comparison amongst them.

IV. Results

Unlike in the developed world, low-resource settings exhibit a paucity of decision support systems. The most recent review of information technology in primary care settings in developing countries was performed in 2004 by Tomasi *et al.* [31]. In one section, they discuss clinical decision support systems implemented between 1992 and 2002. Although the review is meant to encompass developing countries, only 2 of the 20 CDSS articles were based in such a country. Therefore, their review actually summarized CDSS in the developed world and simply acknowledged the difficulty of retrieving academic papers discussing the developing world and which are not registered in international databases. This paucity in findings is juxtaposed by the increasing interest in work at the intersection of decision support, health, and low-resource settings. Recently, Wahl *et al.* [32] evaluated the potential impact of artificial intelligence on healthcare within low-resource settings.

A. Manual Systems

When medical infrastructure ranging from hospital monitors to CT scanners is lacking in low-resource settings, the ability of clinicians to accurately diagnose conditions is impaired. Therefore, many attempt to adapt rules developed among patients in the developed world to those in low-resouce settings. A summary of such adapted scoring systems can be found in Table I.

Berkowitz *et al.* [33] acknowledge the absence of suitable scoring systems and in the context of discerning between ischemic and hemorrhagic strokes simply recommend to overperscribe aspirin. Although their recommendation is based on the likehlihood that a patient experiences a hemorrhagic stroke, such a broad one-size-fits-all approach is reckless and dangerous.

Others attempted to adapt the UK MEWS to surgical settings in the developing world, more specifically in Cape Town, South Africa [34]. This included changes to the thresholding values for each physiological parameter and the addition of qualitative components such as a binary response to the question "looks unwell?" While promising, this Cape Town Ward MEWS may not translate well to clinical settings in other developing nations, let alone different clinical settings within the same hospital. Such an early-warning score was then evaluated by a randomized control trial [35]. Unfortunately, it was found that when patients triggered the MEWS algorithm, the nurses response was not different to that of those not dealing with the MEWS system. More recently, the Practical Approach to Care Kit (PACK) was introduced in [36] as a decision support system

TABLE I
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON MANUAL SCORING SYSTEMS

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
Kyriacos *et al.*, 2014 [34]	Cape Town, South Africa	General ward, public hospital	Adaptation of UK MEWS to form ward-specific EWS	Cape Town Ward EWS that is similar to MEWS and scores a patient based on certain parameter thresholds	12 medical professionals	No evaluation performed
Riviello *et al.*, 2015 [38]	Kigali, Rwanda	Wards and ICU	Implementation of Kigali ARDS scoring system on 1046 patients	Adapted ARDS scoring system	126 hypoxic patients	Berlin ARDS (original) scoring system would have missed all ARDS patients
Kyriacos *et al.*, 2015 [35]	Cape Town, South Africa	General ward, public hospital	Randomized Control Trial of Cape Town Ward EWS	Cape Town Ward EWS	114 cases reviewed	Nurses with EWS did not respond differently to control group without EWS
Merriel *et al.*, 2017 [39]	Bulawayo, Zimbabwe	Mpilo Central Hospital	Evaluation of a Modified Obstetric Early Warning Score (MOEWS)	MOEWS with adaptations to Zimbabwean population	207 patients	Statistically significant increase in stablization of patients preoperativelly (23% to 44% of all patients).
Rudd *et al.*, 2018 [40]	10 LMIC	General Wards, ICUs	Comparison of qSOFA and SIRS in predicting in-hospital mortality for patients with infections	qSOFA and SIRS scoring systems	6569 adult patients	High qSOFA scores correlated well and better than SIRS (AUC of 0.69 and 0.59, respectively).
Ramos *et al.*, 2019 [41]	Sao Paulo, Brazil	Tertiary Hospital	Decision tool to reduce inappropriate ICU admissions	Decision Tree	2201 patients	No significant effect on number of inappropriate admissions. Increase in ICU bed availability
Richard-Greenblatt *et al.*, 2019 [42]	Dar Es Salaam, Tanzania	Outpatient Clinics	Predicting 28-day mortality of adult febrile patients using sTREM-1 biomarker	Addition of biomarker value to qSOFA and GCS scores	507 febrile adults	Improvement in AUC of qSOFA and GCS scores from 0.80 to 0.91 and 0.72 to 0.94, respectively.

for primary care clinicians in low and middle income countries (LMIC). It is a 120-page book that succinctly summarizes one symptom per page. Stemming from South Africa, PACK has been implemented in Nigeria, Botswana, Ethiopia, and Brazil. Most recently, however, PACK was translated into an electronic decision support tool for use within South Africa [37].

Within the realm of respiratory conditions, several CDSS in low-resource settings have existed such as the Silverman Anderson Respiratory Severity Score (RSS) [43] and the Downes Respiratory Distress Syndrome (RDS) Score. The first score was recently evaluated in a prospective study on 140 neonates and found to correlate well with partial pressure of carbon dioxide and increased respiratory support [44]. Despite these promising findings, these scores are limited in that they solely depend on respiratory effort. Consequently, the TRY algorithm was introduced as a rule-based system that determines which infants should be placed on a Continuous Positive Airway Pressure (CPAP) device. Decision support in this domain is essential as it allows for efficient resource allocation of limited CPAP devices in low-resource clinical settings. The TRY-CPAP algorithm was evaluated by Crehan *et al.* [45] in a Malawian district hospital achieving a high level of consistency between nurses' and physicians' diagnoses. It also fared well (92% sensitivity) relative to the reference diagnosis made by paediatricians not using the TRY algorithm.

Olusanya *et al.* [46] propose a tool to assist clinicians in deciding which patients afflicted with hyperbilirubinemia should receive a treatment known as exchange transfusion. Their work clearly illustrates the benefit of decision tools as its relates to triaging patients in the absence of sufficient resources. To assist with this triage, the tool categorizes infants at least 48 hours old into three risk categories. Such classification is grounded in thresholds placed on various clinical and biochemical parameters such as the total serum to plasma bilirubin ratio. Their proposed framework, however, is not evaluated to determine the impact on patient outcomes. Only then can one see if these rules are applicable and generalizable to a clinical population.

Sepsis, which has garnered increased interest in the past couple of years, disproportionately afflicts those in low-resource settings (approximately 90% of all cases). Rudd *et al.* [40] find that a higher quick Sequential Organ Failure Assessment (qSOFA) score correlates well and better than the Systemic Inflammatory Response Syndrome (SIRS) score in predicting in-hospital mortality for patients in low-resource settings that have sepsis. The value of this study lies in the generalizability of its results given that it was performed across 17 hospitals in 10 different low-resource countries. Their finding of a high correlation implies that qSOFA can act as a tool to determine the severity of a patient's infection. As mentioned in [47], the utility of such a score in low-resource settings is even higher than scores that preceded it due to its simplicity; it only requires the measurement of respiratory rate, systolic blood pressure, and altered mental status via the Glasgow Coma Score (GSC).

Most recently, in 2019, Ramos *et al.* [41] reported on a manual decision-aid tool designed to minimize the number of inappropriate ICU admissions. This study was conducted in a tertiary academic hospital in Sao Paulo, Brazil and compared outcomes before and after the decision tool was introduced. In this case, their system consisted of a simple decision tree that depended on information and questions typically found in an ICU admission form (usually completed by an ICU physician). They divided their population into several priority levels based on two sets of international guidelines regarding inappropriate admissions. As a result, they were able to determine whether improvements were made at certain priority levels. It was found that their tool led to improvements among high priority patients, however had a net negative effect when viewed in the aggregate. In other words, it appeared to increase inappropriate admissions among certain populations. This was not statistically significant, however. On the other hand, the implementation of the tool coincided with an increase in the availability of ICU beds at referral time.

Richard-Greenblatt *et al.* [42] suggest and evaluate the use of a biomarker known as sTREM-1 to improve the identification of febrile patients in Tanzanian clinics who are at risk of death within 28 days. When incorporating sTREM-1 into the traditional qSOFA and GSC, the AUC for predicting 28-day mortality increased from 0.80 to 0.91 and 0.72 to 0.94 for the respective scoring systems. Such an improvement is drastic and can assist with the triage and treatment process of individual patients. Given that this implementation is catered specifically to low-resource settings, one must question the ease and cost with which sTREM-1 can be obtained. If it requires a high degree of expertise, then it may be difficult to incorporate into such settings.

B. Electronic Systems

In addition to manual CDSSs in low-resource settings, there has been an increasing number of electronic CDSSs. Before discussing such systems in depth, it is worthwhile to mention the work of Vuong *et al.* [65] who discuss the feasibility of implementing AI systems in low-resource medical settings, more specifically in Vietnam. They emphasize the importance of financial and data infrastructure in facilitating research and adoption of new technology. Although they mention several of the studies included in this review, their list lacks technical detail and is by no means exhaustive. Their paper does, however, illustrate the demand for the implementation of technology within Vietnam's clinical settings. Based on the studies identified, we found it best to cluster them according to the medical condition or disease which they address.

1) Bacterial Infections: Bacterial and parasitic infections disproportionately affect those in low-resource settings [66]. Most publications in this space have focused on pulmonary tuberculosis (PTB) and are summarized in Table II.

In the context of diagnosing PTB, the work in [48] spurred a long line of research. One example is in [56] where Aguiar *et al.* use two neural networks to classify PTB and patient risk, respectively. This is performed using the data of 315 patients in a hospital in Rio de Janeiro, Brazil. Their motive is that a more accurate diagnosis can allow for better intervention and thus reduce the rate at which the disease spreads. In 2018, Filho *et al.* [62] perform the same dual task as above. Diagnosis is performed using a fully-connected network with 2 layers fed with binary variables such as age, gender, etc. Here, they achieve an area under the receiver operating characteristic curve (AUC) of 0.74. On the other hand, risk assessment is done with an adaptive resonance model known as iART. The appropriateness of the clustering is supported by the observation that patient feature values were consistent with the assigned cluster. For instance, fever and weight loss happened to be most common in the high risk group. A more recent multi-layer perceptron algorithm [61] manages to achieve high sensitivity (97%) for a binary prediction of the disease despite a small cohort of 105 patients. This is promising given the low amount of electronic health data that exists for patients in low-resource settings. A similarly small cohort of 155 patients suspected of having tuberculosis meningitis was analysed by Solari *et al.* [53] in Peru. They used a logistic regression model based on enzyme concentration and presence of a cough to classify patients into three different risk groups. Such an output would assist physicians when unsure of the disease status of their patient. The PK-PD Compass [58], [67], although not explicitly designed for low-resource clinical settings, is a mobile application aimed at clinicians to guide the antimicrobial dosing regimens they assign their patients. Extensive studies have been performed with this application which takes as input patient variables, their infection, and suspected pathogen. By exploiting updated databases that contain patient responses to various drugs, the application recommends various antibiotics and lists their corresponding uptake for that individual patient. While promising, these studies do not emphasize how they are different from the three extant tools on the market. Moreover, they claim to use Bayesian methodologies to 'personalize' the suggestions. The extent to which such suggestions are population-based and are accurate is debatable as of yet.

Inspired by the use of crackle sounds to diagnose various pathologies, Kosasih *et al.* [54] propose a wavelet-based approach to diagnose pneumonia among patients in low-resource settings. In addition to traditional feature extraction, the wavelet transform of auditory crackle sounds recorded via microphones is obtained. Once the features are fused, they are input into a logistic regression model using a leave-one-out cross validation methodology. Given the dependence of a wavelet transform on the particular wavelet function, the authors investigate six different types and identify the Morlet as the ideal wavelet function. When features were combined, the algorithm resulted in a sensitivity and specificity of 0.9412 and 0.8750, respectively. The simplicity of this work in that it solely depends on two microphones paired with the high performing algorithms is astonishing. Due to the rise and success of deep learning, and in particular convolutional neural networks, many have attempted to apply such techniques to diagnosing tuberculosis. Santiago *et al.* [63] fine-tune a VGG16 convolutional network [68] using grayscale images from a test known as Microscopic Observed Drug Susceptibility. After minimal preprocessing and a 5-fold cross-validation evaluation method, the authors achieved an average sensitivity and specificity of 94.74% and 97.83%, respectively. While impressive, such an outcome only barely outperforms a simple logistic regression model (96.9% and 96.3% sensitivity and specificity, respectively) they implemented. Therefore, the need for a more complex neural network in this context is doubtful. Moreover, the authors claim that the network has learned useful features that mimic those deemed important by medical professionals; a claim that is not-convincing based on the blurry images shown in the paper. On the flip side, the most promising component of this study was the apparent robustness of the model to images of various quality levels, a challenge all too common in low-resource countries.

Quinn *et al.* [57] propose a convolutional neural network to diagnose malaria, tuberculosis and intestinal parasites based on microscope images. They motivate the need for such a system by the insufficient number of trained experts capable of

TABLE II
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON BACTERIAL/PARASITIC INFECTIONS

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
El-Sohl *et al.*, 1999 [48]	Buffalo, New York	Erie County Medical Center	Diagnosis of Pulmonary Tuberculosis (PTB) based on estimate of likelihood of active PTB	3-Layer General Regression Neural Network (GRNN)	$N = 682$	c-index (similar to AUC) of 0.923 relative to 0.716 of physicians
Steinhoff *et al.*, 2005 [49]	Cairo, Egypt	Abu Reesh Hospital	Analysis of manual decision rule to diagnose pharyngitis in patients between 2 and 13 years old	Multivariate logistic regression of clinical variables	410 children	Sensitivity and specificity of 93% and 38%, respectively.
Smeesters *et al.*, 2006 [50]	Brasilia, Brazil	3 Emergency Departments of Public Hospitals	Prospective study of manual decision rule to identify group-A Streptococcus pharyngitis and reduce unnecessary antibiotic prescription	Thresholding based on clinical parameters	220 children	Reduction of unnecessary antibiotic prescription by 18% and an increase in untreated patients by 7%. ROC not reported.
Joachim *et al.*, 2010 [51]	Brasilia, Brazil	2 Emergency Departments and 1 Medical Unit	Prospective study of manual decision rule to identify group-A Streptococcus pharyngitis and reduce unnecessary antibiotic prescription	Thresholding based on clinical parameters	576 children	Reduction of unnecessary antibiotic prescription by 46% and an increase in untreated patients by 14%. ROC is 0.66.
Soto *et al.*, 2013 [52]	Lima, Peru	Emergency room and internal medicine ward	Clinical prediction rule to categorize smear-negative TB patients into one of three severity classes	Decision tree based on sputum cultures and other clinical variables	670 patients	Sensitivity and specificity of 88% and 96%, respectively.
Solari *et al.*, 2013 [53]	Lima, Peru	2 hospitals	Development of a Clinical Prediction Rule that scores patients suspected of having TB	Logistic regression	155 patients	AUC of 0.87
Kosasih *et al.*, 2014 [54]	Indonesia	Respiratory Medicine Unit, Sardjito Hospital	Algorithm to diagnose pneumonia based on auditory crackle sounds	Logistic regression	91 patients	Binary classification of pneumonia with sensitivity and specificity of 0.9412 and 0.8750, respectively.
Catalani *et al.*, 2014 [55]	Kenya	Clinics	Determine appropriate administration of isoniazid preventive therapy to HIV patients at risk of developing TB	Computer-based rules	Not mentioned	Qualitative interviews with users claim CDSS is not accurate
Aguiar *et al.*, 2016 [56]	Rio de Janeiro, Brazil	High complexity hospital	Development of algorithm for classifying patients with PTB and assigning them with risk score	2 MLPs, one for classification of PTB, the other for classification of risk	315 patients	Sensitivity of 96% and specificity of 89%
Quinn *et al.*, 2016 [57]	Uganda	Pathology laboratory	Development of algorithm for classifying malaria, tuberculosis, and hookworm based on microscopy images	Convolutional Neural Network (CNN)	≈250K patches	AUPRC = 0.97, 0.93, and 0.93 on three tasks, respectively.
Bulik *et al.*, 2017 [58], [59]	N/A	N/A	PK-PD Compass – a mobile application that guides antibiotic dosing regimens	Pharmacokinetic-Pharmacodynamic models and Monte Carlo simulations	Not mentioned	Clinical improvement in patient outcomes 48h after choice of antibiotic.
Alcantara *et al.*, 2017 [60]	Lima, Peru	Not mentioned	Binary classification of presence of TB and multi-class classification of TB categories based on X-Ray images	GoogleNet	4701 X-ray images	Accuracy of 89.6% and 63% on binary and multi-class classification, respectively
Orjuela *et al.*, 2018 [61]	Santa Clara, Bogota, Colombia	Hospital Santa Clara (HSC)	Development and evaluation of a supervised and unsupervised algorithm for diagnosis of PTB with feature importance performed	3-Layer MLP for supervised learning and Self-Organizing Maps (SOM) for unsupervised learning	105 patients	MLP – Accuracy 77.5%, Sensitivity 97%, Specificity 71.4% SOM – Accuracy 85.7%, Sensitivity 89.3%, Specificity 71.4%
Filho *et al.*, 2018 [62]	Rio de Janeiro, Brazil	Second level health unit	Predict probability of TB diagnosis and patient risk level	Multi-layer perceptron and adaptive resonance model (iART)	1114 patients	Binary TB diagnosis had an AUC of 0.74. Clustering technique finds interpretable medical findings.
Santiago *et al.*, 2019 [63]	Callao, Trujillo, Lima, in Peru	3 molecular biology laboratories	Binary diagnosis of TB based on Microscopic Observed Drug Susceptibility images	Fine-tuning VGG16 CNN	$N =$ 12510	Binary TB diagnosis had an average sensitivity and specificity of 0.9747 and 0.9783, respectively. Mild improvement over Logistic Regression
Gorriz *et al.*, 2019 [64]	Catalunya, Spain	Laboratory	Detection of three classes of Leshmaniasis disease based on microscope images	Unsupervised U-Net model	45 images	Mean Jacard Index of 0.41, 0.47, and 0.68 for the Promastigote, Adhered, and Amastigote classes respectively

reading these images. During the classification pipeline, they experience class imbalance, a scenario in which the number of negative cases significantly outnumber the positive cases. This is alleviated by under-sampling the negative cases, during training, to maintain a 1:100 ratio. When performing inference, the model achieves an AUROC=1.00, 0.99, and 0.99 on the malaria, tuberculosis, and hookworm classification tasks, respectively. In the presence of severe class imbalance, AUROC is not the preferred metric. Instead, the area under the precision recall curve (AUPRC) should provide a better estimate of the generalization performance. Their reported AUPRC results are 0.97, 0.93, and 0.93, respectively. This is impressive in light of the class imbalance.

2) Antimicrobial Resistance: The high burden of bacterial infections coupled with the poor diagnostic capabilities of frontline healthcare workers usually leads to the over and mis-prescription of antibiotics in low-resource settings [69]. Such behaviour contributes to the high rates of antimicrobial

TABLE III
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON ANTIMICROBIAL RESISTANCE

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
Rambaud *et al.*, 2015 [70]	Tazania	N/A	Development of ALMANACH (Algorithm for Management of Acute Childhood Illnesses) to tackle antibiotic prescription	Rules adapted from original IMCI guidelines	N/A	No evaluation of the algorithm is performed yet.
Shao *et al.*, 2015 [71]	Dar es Salaam and Ifakara, Tanzania	6 primary health facilities	Evaluation of ALMANACH among healthcare workers	Decision tree	40 clinicians	Qualitative interviews implied that tool assisted the workflow and diagnosis of patients.
Shao *et al.*, 2015 [72]	Tazania	2 pairs of primary health facilities	Evaluation of ALMANACH on antibiotic prescription	Decision tree	1465 patients	Anitibiotic over-prescription rate is 0% with ALMANACH. Standard arm prescriptions given to 84.3% of patients (only 38.7% needed them).
Rambaud *et al.*, 2017 [73]	Dar es Salaam, Tanzania	3 health centres and 6 dispensaries	Evaluation of ALMANACH on antibiotic prescription	Decision tree	504 consultations	Higher checks of danger signs relative to paper algorithm (41% to 71&). No significant difference in antibiotic prescription rates.
Keitel *et al.*, 2018 [74]	Varied	Primary care settings	Review of electronic CDSS for children afflicted with febrile illnesses in low-resource settings	Examples include ALMANACH, Bangladesh digital IMCI	Varied	Some studies lacked evaluation from a patient impact and cost perspective
Bernasconi *et al.*, 2018 [75]	Kabul, Afghanistan and Tanzania	Basic health centres	Determine whether children should receive a rapid diagnostic test and what form of intervention is required	ALMANACH	599 consultations	Reduction in antibiotic prescription from 63% to 21.8%
Bernasconi *et al.*, 2018 [76]	Kabul, Afghanistan	Basic health centres	Evaluation of digital algorithm (ALMANACH) introduced into basic health centres	Blood pressure of pregnant women	599 consultations	Rate of appropriate examination (23.8% vs. 84%) and correct treatment (34.5% vs. 85%). Received at least one antibiotic (86.1% vs. 30%)
Bessat *et al.*, 2019 [77]	Burkina Faso	272 centres for primary healthcare	Electronic tool for management of childhood illnesses based on IMCI	Electronic IMCI	21 health workers	Tool lacked treatment options, and is overly cautious, yet helped justify antibiotic prescription.

resistance, leaving healthcare systems with fewer effective tools to deal with bacterial infections, and thus exacerbating the exigent burden. A summary of solutions for tackling this issue can be found in Table III.

In the past couple of years, antimicrobial resistance has become the focus of the World Health Organization. This is exacerbated by the over-prescription of antibiotics to infants with febrile illnesses, especially in low-resource settings. In attempt to reduce these over-prescriptions, electronic CDSSs that accurately diagnose febrile illnesses have a played a vital role. In this context, Keitel *et al.* [74] review 6 different systems that have been implemented within low-resource primary-care settings. The most recent example is ALMANACH (Algorithm for Management of Acute Childhood Illnesses) [71] which is developed by the Swiss Tropical and Public Health Institute. It uses a decision tree based on data from rapid diagnostic tests to detect certain conditions and has been evaluated in basic health centres in Afghanistan and Tanzania [76]. Preliminary results indicate that the introduction of the CDSS significantly improved the percentage of correct examinations and treatments administered to patients. This occurred with a simultaneous reduction in antibiotic prescription (63% to 21.8%) [75]. It must be noted, however, that the cost-effectiveness of such an implementation and whether suggestions made by the system are taken into consideration have not been evaluated. An electronic tool that emulates the Integrated Management of Childhood Illness (IMCI) guidelines put forth by the WHO was introduced in 2008 by Derenzi *et al.* [78]. Although the tool, piloted in primary care settings in Tanzania, was found to improve adherence to various essential medical tasks, it appeared to increase the amount of time spent by the healthcare professional with each patient. Bessat *et al.* [77] build on the extensive amount of work in the space of electronic IMCI decision support. They attempt to evaluate the impact of the tool on the behaviour of primary health workers in Burkina Faso. Results were primarily based on interview responses and contained several takeaway messages; the tool lacked certain treatment recommendations, helped justify their prescription of antibiotics, and seemed to be overly cautious when diagnosing infants. Although the authors claim to quantify the impact on antibiotic prescription, this evaluation is weak and not patient-centred. Nonetheless, this work can be viewed as a proof-of-principle that requires significant improvement.

3) Viral Diseases: Although there exists a spectrum of viral diseases such as Hepatitis, Human-Papilloma Virus, and Human Immunodeficiency Virus (HIV) that afflict populations in low-resource settings [86], the latter continues to demand the greatest attention. A summary of studies focusing on such infectious diseases can be found in Table IV.

Within sub-Saharan Africa, tackling HIV is still ongoing. To determine whether healthcare professionals should alter an AIDS patient's treatment, Mitchell *et al.* [79] introduce and trial an electronic CDSS that takes as input the answers to various medical questions. Based on these responses, the decision to refer the patient to a consultant is made. The gold-standard binary decision of referral is made by physicians who respond to a questionnaire at the end of their daily clinical shift. Unfortunately, the results of this study are not published. To better deal with HIV patients, the Academic Model Providing Access to Healthcare (AMPATH) was introduced with its most prominent activity occurring within Kenya. Patient data manually recorded on paper are input into a medical record system created by AMPATH, known as the AMPATH Medical Record System (AMRS) [87]. This system, which is built on the Open Medical Record Systems [88] then generates patient-specific summaries

TABLE IV
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON VIRAL DISEASES

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
Mitchell *et al.*, 2009 [79]	South Africa	Primary care physicians in two clinics	Electronic tool to determine continuation of treatment protocol of AIDS patients	Questionnaire	N/A	Binary outcome of continue treatment or refer patient to consultant is not evaluated.
Allison *et al.*, 2011 [80]	Papua New Guinea	Port Moresby General Hospital	Decision rule to identify HIV-positive patients in the absence of HIV testing equipment	Logistic regression models of clinical variables	487 children	Sensitivity and specificity of 96% and 25%, respectively.
Anokwa *et al.*, 2012 [81]	Kenya	Kenyan hospitals and health centres	Development of tool that provides clinicians with patient summaries and generates alerts and reminders	Open Data Kit (ODK) Clinic – a mobile application with alerts and recommendations	6 clinicians	Positive qualitative feedback on system. No quantitative evaluation.
Oluoch *et al.*, 2012 [82]	Sub-Saharan Africa and Carribean	Not Mentioned	Systematic review of decision support systems implemented for HIV care	Basic alerts and reminders for drug dosage, communication, etc.	Varied	Reduction in data input errors, missing laboratory results, etc.
Balcha *et al.*, 2014 [83]	Ethiopia	5 health centres	Tool to quantify risk of HIV-infected patients in developing TB	Multivariate Logistic Regression coupled with WHO tool	812 patients	AUC improved from 0.70 to 0.75 when tested on entire population
Wang *et al.*, 2019 [84]	Guangxi, China	Not mentioned	Comparison of models for forecasting HIV incidence	ARIMA and LSTM models	Not mentioned	LSTM performed best with an MSE of 0.0308 and 0.0026 for the years 2015 and 2016, respectively.
Tadesse *et al.*, 2020 [85]	Ho Chi Minh City, Vietnam	ICU	Diagnosis of tetanus and hand foot and mouth disease	Inception neural network model	74 patients	Multi-modal transfer learning with Inception outperforms single-modality SVM achieving an F_1=0.967 and 0.860, respectively.

which are presented to the clinicians. Such summaries are vital in clinical settings that are burdened by large patient populations. Several limitations of AMRS, however, are mentioned in [81]. Most notable of these critiques is the potential lag and inaccuracies that arise from inputting the data into the electronic system. Consequently, Anokwa *et al.* have devised Open Data Kit (ODK) Clinic, a mobile-phone based application that works in conjunction with AMRS to overcome its existing challenges. Similar to AMRS, the system provides patient summaries and generates alerts and reminders as necessary. While they do limit the number of alerts shown, their accuracy is not evaluated. Furthermore, what drives these reminders is not explicitly stated, but is assumed to be thresholds on clinical data stored within the application. It also allows clinicians to edit and input extra patient data through the application, therefore mitigating the previously mentioned lag and inaccuracies. Although it augments AMRS, ODK Clinic does not completely solve the issue of missing or inaccurate patient data. It also expects clinicians to be comfortable using the device and be capable of altering erroneous information after it has already been input. Finally, the decision support is quite primitive and manifests itself in the form of reminders to order certain medication tests. Most recently, Tadesse *et al.* [85] proposed a multi-modal approach to diagnose tetanus and hand foot and mouth disease (HFMD). They first convert electrocardiogram and photoplethysmogram time-series data to their spectrogram counterparts. These spectrograms are then fed into a pre-trained Inception neural network for feature extraction and classification of disease severity. They illustrate the superiority of transfer learning with multi-modal inputs as compared to an SVM with a single modality (e.g. ECG), achieving an F_1=0.957 and 0.860, respectively. Such strong performance in addition to the use of widely-available wearable sensors suggests that this approach has the potential to benefit resource allocation and patient outcomes within low-resource settings. To quantify this benefit, further evaluation on a larger and more diverse patient cohort would be required.

4) Non-Communicable Diseases: Non-communicable diseases such as hypertension, diabetes, and cardiovascular diseases are becoming increasingly important in low-resorce countries. More specifically, as high as 80% of all deaths caused by such diseases occur in low and middle-income countries [89]. Although there appears to be a significant amount of work focusing on mobile-health solutions for such diseases, research on clinical-decision support systems is less common. A summary of the latter can be found in Table V.

Electronic CDSSs can come in the form of mobile devices such as tablets. This is increasingly true in low-resource settings where high costs are a barrier and infrastructure is little to non-existent. In the domain of non-communicable diseases, Jindal *et al.* [94] introduce and assess 'mWellcare', a mobile-health post-diagnosis CDSS, in low-resource primary care settings in India. This was a holistic approach that involved devices such as blood-pressure apparatus and the training of physicians. The recommendations provided by the system agreed with those of the physicians' 61% and 70% of the time for hypertension and diabetes, respectively. While still nascent, mWellcare with higher agreement rates has the potential to alleviate the burden on currently overwhelmed physicians. Adepoju *et al.* [106] discuss several relevant CDSS implementations. For instance, Decision Support and Integrating Record Keeping is a 3-part system that stores data, contains a rule-based algorithm focused on diagnosing hypertension, and allows for historical patient data viewing. Deployed to target patients in Kenya, the system is offered through a tablet and is distributed to nurses in rural clinical settings. Unfortunately, this work does not go beyond a feasibility study, and thus its impact is not evaluated quantitatively [92].

A clinical decision support system focused on diagnosing and treating various components of hypertension is introduced by Anchala *et al.* [91]. Given the implementation of the algorithm in India, the authors' algorithm was a rule-based one grounded in the India Hypertension II guidelines. The algorithm performed

TABLE V
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON NON-COMMUNICABLE DISEASES

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
			Cardiovascular Disease			
Mendis *et al.*, 2010 [90]	China and Nigeria	10 clinical facilities in each country	Cluster-randomized trial to assess WHO's cardiovascular disease risk package	WHO-specific decision tree	$N =$ 2397	Patients in intervention arm experienced statistically-significant reduced systolic pressure by 2 mmHg compared to those in control arm
Anchala *et al.*, 2013 [91]	Andhra Pradesh, India	Primary care setting	DSS-HTN – a rule-based decision tool for diabetes manegement	Rule and logic-based	60 patients	Blood pressure-staging and drug management agreement between results of tool and experts of 90% and 85%, respectively.
Anchala *et al.*, 2013 [91]	Andhra Pradesh State India	Primary health care clinical	Algorithm to diagnose and treat patients with hypertension	Logic-based algorithm grounded in India Hypertension II Guidelines	60 patients	AUC of 0.848 for drug management.
Vedanthan *et al.*, 2015 [92]	Kenya	Rural Kenyan clinical settings	Feasibility study of CDSS focused on hypertension	Decision Support and Integrated Record-Keeping	57 incidents	Human factors play significant role in implementation. No quantitative evaluation.
El-Sappagh *et al.*, 2015 [93]	Mansoura, Egypt	Mansoura University-affilied hospitals	Algorithm to diagnose type 2 diabetes based on laboratory and clinical variables	Ontology model leveraging case-based reasoning	60 cases	Diabetes diagnosis with an accuracy of 97.67%.
Jindal *et al.*, 2018 [94]	Haryana, and Karnataka, India	Community Health Centres (CHCs)	Pilot test of a mobile-health post-diagnosis CDSS to recommend treatment for hypertension and diabetes	mWellcare software outsourced to Dimagi, comes with blood pressure apparatus, and training of physicians	631 patients	Agreement in recommendations between algorithm and physicians is 61% and 70% of the time for hypertension and diabetes
			Maternal and Fetal Care			
Derenzi *et al.*, 2008 [78]	Mtwara, Tanzania	Dispensary	Electronic Integrated Management of Childhood Ilness (E-IMCI) based on WHO guidelines	Rules based on WHO guidelines	2 clinicians	Improved adherence to various medical tasks
Blank *et al.*, 2013 [95]	Burkina Faso, Ghana, Tanzania	Primary health centres	Description of system focused on improving maternal and perinatal monitoring	QUALMAT; rules based on WHO guidelines 'Pregnancy, Childbirth, Postpartum and Newborn Care'	57 incidents	No evaluation performed
Homer *et al.*, 2013 [96]	Winterveldt, South Africa	Kgabo Community Health Centre	The Basic Antenatal Care Information System (BACIS) system for improving adherence to 18 antenatal care tasks	Checklist based on guidelines from South African department of Health	125 patients	Compliance to 18 tasks improved from 85.1% to 89.3%.
Mensah *et al.*, 2015 [97]	Ghana and Tanzania	24 healthcare facilities	Assessment of effect of QUALMAT algorithm on healthcare workflow	QUALMAT algorithm based on WHO guidelines	362 observations	Statistically significant increase in women who returned for subsequent examinations ($p<0.001$) in Ghana
Olusanya *et al.*, 2016 [46]	LMIC	N/A	Tool to categorize hyperbilirubinemia infants into one of three risk scores for triage purposes	Thresholding of clinical and biochemical parametrs	N/A	Evaluation not performed. Framework for tool is proposed.
Khan *et al.*, 2016 [98]	Norweigan University of Science and Technology	St. Olavs University Hospital	Derivation of fetal mean abdominal diameter using ultrasound images	First-order Sobel derivative and Kalman filters	61 Images	R^2-value of 0.96. Error range is -26.74 to 26.26 mm.
Balaji *et al.*, 2017 [99]	Belgaum, India	NICU and PICU	Discussion of implementation of Artemis within low-resource setting	Artemis systems implementation	N/A	No evaluation performed.
Duffy *et al.*, 2017 [100]	Uganda	Maternal Theatre, Kitovu Hospital	MedNav – an application that guides midwives on neonatal rescuscitation	Decision tree	46 midwives	Average percent completion of necessary activities was 46% and 94% in the control and experimental groups, respectively.
Vessel *et al.*, 2019 [101]	Nairobi, Kenya	Maternity hospital (Jacaranda Heath)	Feasibility of INTERGROWTH-21st guidelines to improve fetal observation	Questionnaire	29 clinicians	Significant increase in number of ultrasounds performed. Non-significant increase in identification of high-risk pregnancies.
Heuvel *et al.*, 2019 [102]	Wolisso, Ethiopia	St. Lukes Catholic Hospital	Detection of fetal head and estimation of its circumference based on ultrasound images	Reduced VGG and U-Net networks trained from scratch	183 pregnant women	Head detection accuracy (95% to 98%). Mean absolute difference in head circumference estimation (12 to 30mm).
Amoakoh *et al.*, 2019 [103]	Ghana	250 health facilities	Evaluate impact of mobile CDSS on neonatal mortality	Communication with patients via text-messages and phone-calls	$N =$ 65831	Intervention arm experienced significantly higher number of neonatal deaths (p=0.051)
Kwizera *et al.*, 2019 [104]	Rwanda	1 hospital	In-hospital mortality prediction	Random Forest	949 children	Evaluation on 5-fold cross-validation with AUROC $= 0.79$
Rittenhouse *et al.*, 2019 [105]	Lusaka, Zambia	1 hospital	Binary classification of preterm births	SuperLearner algorithm	1450 pregnant women	Evaluation on 10-fold cross-validation with AUROC $= 0.98$

the following tasks for 60 hypertensive patients: determining the staging of blood pressure and the patient's risk category, drug management, and lifestyle advice, in addition to other events. This is an ambitious goal that exceeds those expressed by other studies. The ground-truth values for all these categories were determined by two independent physicians not directly involved with the primary healthcare centres used in the study. When the algorithm outputs were compared to this reference value, the agreement percentage ranged from 83.33% to 91.67%, suggesting strong results. Moreover, the former achieves an AUC of 0.848 when evaluated based on drug management. Unfortunately, the aforementioned results can be interpreted as optimistic since only hypertensive patients were enrolled in this study. Consequently, expecting strong performance by such an algorithm on a more general audience is debatable.

In addition to the importance of cardiovascular diseases, the significance of maternal health was emphasized by the recent WHO publication that aims to reduce, by 2030, the global maternal mortality rate (MMR) to below 70 deaths per 100,000 births [107]. Placing this number into context, currently some low-resource countries face an MMR value of around 600 [108].

Agarwal *et al.* [109] discuss the impact of their introduction of ThalCare, an ICT-based tool that, among other things, assists nurses and doctors in dealing with and treating thalassemia patients. It is capable of storing patient information and allows for the monitoring of patient status in a periodic manner through weekly and monthly reports. Moreover, the application coordinates with blood banks in order to speed up deliveries and ensure faster treatment. Lastly, patients can access this information if they wish in order to remain updated on their health status. They release their tool to 5 different clinical centres in India and attempt to evaluate its effect in various ways. For instance, patient visits increased from "a mean of 0.7 visits per month to 1.1". Barring the limitation that the significance of this change was not commented on, such a result can be interpreted as positive since it may indicate increased patient commitment to their health. More noteworthy was the management of iron by patients, where 53% of drug dose changes were a result of the system's alerts. Although this indicates that the alerts were guiding clinicians, it does not illustrate whether such guidance led to improved patient outcomes. This appears to be a promising tool that can streamline the treatment of thalassemia in a scalable manner among patients in LMIC.

Khan *et al.* [98] design a portable ultrasound machine and an algorithm that attempts to derive the mean abdominal diameter (MAD) of a fetus. In this case, the ground truth values were obtained via manual annotations of the ultrasound images. Using such images, the authors performed two main tasks; fetal abdomen detection and diameter derivation. The former was done in a somewhat traditional manner using image gradient methods such as the first-order Sobel derivative. Once the fetal abdomen was detected, a Kalman-based algorithm was used to determine the actual MAD. In this regression task, the authors managed to achieve an impressive R^2 value of 0.96 when comparing the predictions to the ground truth. The errors, however, ranged from -26.74 to 26.26 mm. Since the acceptable error range from a clinical perspective is not mentioned, the aformentioned error values cannot be evaluated properly.

Balaji *et al.* [99] discuss the prospects of implementing Artemis, an established decision support system used in the 'West', in a low-resource setting. More specifically, they plan to implement this software in neonatal and pediatric intensive care units (NICUs and PICUs) in Belgaum Children's Hospital in India. Even though they only suggest a study outline, their work reiterates the scarcity of resources in such regions and the importance of low-cost, durable, and sustainable solutions.

Dealing with the issue of neonatal rescuscitation, Duffy *et al.* [100] design and trial an application catered to midwives in hospital settings in order to improve their ability to perform such rescuscitation. The application guides the users through a decision tree, asking them to perform necessary procedures on the neonate, such as checking their heartbeat, recording the Apgar score, and so forth. A 6-month implementation of the program at Kitovu Hospital in Uganda indicated a substantial increase in the percentage of necessary procedures performed. Although the 'necessary' procedures were selectively chosen, they do seem based on clinical reasoning. Nonetheless, it would have been interesting to observe how consistently other activities were performed. Moreover, their focus on the percent completion of activities detracts from two important points; the quality with which those procedures were performed and the impact of the device on neonatal outcomes. More recently, Huevel *et al.* [102] attempt to detect fetal heads and estimate their circumference and thus gestational age by using state-of-the-art neural network architectures such as VGG [68] and U-Net [114] architecture reduced in the number of parameters. The obstetric sweep protocol was performed to obtain high quality ultrasound images. To emulate conditions in low-resource settings where equipment quality and expertise is low, the authors investigate the impact of poor-quality images on the network's accuracy. Promisingly, their fetal head detection network seems robust to images downsampled even by a factor of 20. Accuracy for this task ranges between 95% and 98% depending on the downsampling factor. Unfortunately, the more challenging task of circumference estimation was less robust to image quality and, at its worst, produced a mean absolute difference of 30mm. Such mis-estimation could lead to under or over-estimating the gestational age of the fetus by up to 2 weeks. Furthermore, the study is weakened by the significant amount of filtering performed on the data before inputting it into the model. Although pre-processing is an important step in machine learning, the eradication of datapoints that would most probably represent the norm in settings with poorly-trained professionals is not realistic.

Kwizera *et al.* [104] retrospectively perform mortality prediction on 949 children admitted to a hospital in Rwanda. To do so, they input six different parameters including age, respiratory rate, altered mentation, capillary refill time, temperature, and heart rate into a Random Forest classifier. By exploiting all six of these parameters and evluating their model via 5-fold cross validation, the authors achieved an AUROC of 0.79. The advantage of this approach over existing comparable methods is

TABLE VI
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON OPERATIONAL ACTIVITIES

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
Ahmed *et al.*, 2009 [110]	Kuwait	Government hospital	Algorithm to maximize the number of patients seen in an emergency department given budgetary and resource constraints	Simulation optimization model involving a non-homogenous Poisson process	145 patients	Algorithm indicates that actual throughput of patients can be increased by 28% and patient waiting time can be reduced by up to 40%.
Bradley *et al.*, 2014 [111]	The Gambia	Not mentioned	Discrete event simulation (DES) model to simulate the temporal demand for medical oxygen for children with pneumonia	Simulation based on seasonality, treatment duration, etc.	N/A	Simulated demand exceeds annual average 68% of the time.
Maharlou *et al.* 2018 [112]	Shiraz, Iran	Intensive care units of 3 hospitals	Predicting the length of stay of patients in the ICU after cardiac surgery	Multi-layer perceptron and adaptive neuro-fuzzy inference system (ANFIS)	311 patients	When predicting length of stay, MLP and ANFIS algorithm achieved a mean squared error of 21 and 7 days, respectively.
Yousefi *et al.* 2018 [113]	Belo Horizonte, Brazi	Emergency department of Risoleta Tolentino Neves Hospital	Algorithm to minimize the average length of stay (ALOS) of patients in emergency departments	Ensemble of simulation optimization algorithm, RNN, ANFIS, and FFNN	24,000 samples	Simulation optimization algorithm reduces ALOS by 26.6% compared to baseline.

its dependence on simple parameters that can be easily measured within a low-resource clinical setting. Moreover, the authors remind us that their model's achieved performance is similar to that achieved by qSOFA when implemented amongst adults in high-income countries. Despite such a finding, the generalizability of such an algorithm is called into question by the small cohort size. Rittenhouse *et al.* [105] propose to exploit maternal and fetal parameters in order to determine whether neonates can be classified as pre-term births. They performed the analysis on 1450 pregnant women from a hospital in Lusaka, Zambia. After implementing the SuperLearner algorithm [115] using 10-fold cross-validation, the authors were able to achieve an AUROC of 0.98 on the binary classification task. Such strong performance causes one to believe that such a task might have been too trivial and thus not clinically-useful. On the other hand, in settings where expertise is lacking, such an algorithm may allow for a reduction in the number of misclassifications. This can be identified via a prospective trial, something that would be relatively feasible in this scenario given the minimal harm imposed on the patient by the decision of the algorithm. Most recently, Evans *et al.* [116] convened 22 neonatal experts in order to gauge their agreement on algorithms used for the diagnosis of various neonatal conditions in low-resource settings. These conditions included neonatal sepsis, hypoxic ischaemic encephalopathy, respiratory distress, and hypothermia. Conducting such a process is vital given the lack of transferability of algorithms designed in high-resource settings to low-resource settings. By arriving at diagnostic criteria that the majority of participating experts agree to, one can begin to design more reliable diagnostic algorithms. In fact, the research team is planning to incorporate these findings into a neonatal digital platform entitled NeoTree.

5) Operations: Operations research revolves around optimizing a multi-variate system subject to various constraints such as transportation routes, stock management, and resource allocation. A summary of studies working on operations research within a low-resource clinical context can be found in Table VI.

Improving resource allocation is tackled by Ahmed *et al.* [110] who focus on doing so in a government hospital in Kuwait. They design a simulation optimization problem to increase the number of patients seen per unit time subject to constraints on financial budgets and patient waiting times. Experimentation is performed with processes, modelled as Poisson distributions with a time-varying rate parameter, in order to obain an optimal set of parameters for the hospital at hand. In achieving a turnover rate of approximately five patients per hour, the authors claim that the algorithm reduces patient waiting time by 40%. Although significant, these results are quite specific to the studied emergency department and may not generalize to other emergency departments or even to the same one at some point in the future. Nonetheless, this work acted as a springboard for others in low-resource settings. Most recently, Yousefi *et al.* [113] implement a constrained-optimization problem in order to reduce the average length of stay (ALOS) of patients in an emergency department in Brazil. Their base model is a recurrent neural network which is optimized using a genetic algorithm where inividual 'chromosomes' are deemed 'unfit' based on whether they violate the pre-defined constraints. Interestingly, the authors illustrate the graded effect of the availability of doctors and nurses on the ALOS. More specifically, a threefold increase in the number of doctors and nurses will, on average, reduce the ALOS by 50%. Such outcomes can help guide specific workforce allocation within hospital settings in order to improve efficiency.

6) Miscellaneous: In addition to the publications that were categorized based on application, a number of studies that were diverse in application and did not fall under the pre-defined categories are mentioned here. A summary of such studies can be found in Table VII.

In 2017, Elsevier, the publisher of scientific journals, announced that it would make ClinicalKey [118], a search-engine catered to clinicians at the point-of-care, available to healthcare professionals in low-resource settings [124]. Although it appears similar to MD consult and UpToDate, its creators are confident of its superiority. At the end of the day, it is simply a database that can provide clinicians with information in a convenient and quick way. The efficacy of such a system within low-resource settings, however, has yet to be evaluated.

Others have used machine learning to predict patient mortality post-discharge in both resource-rich and low-resource settings [125]. The SuperLearner algorithm uses patient demographic

TABLE VII
SUMMARY OF CDSS IN LOW-RESOURCE SETTINGS FOCUSED ON MISCELLANEOUS ACTIVITIES

Study/Year	Location	Clinical Setting	Purpose	Decision Support System	Pop. Size	Outcome
Tomasi *et al.*, 2004 [31]	Varied	Varied	Review of IT use in primary-care settings and how LMICs can benefit from this	Several mentioned e.g. diagnosis screening for skin cancer, examination recommendation, etc.	Varied	Only 2 of the 20 CDSSs are actually in a LMIC
Cowling *et al.*, 2006 [117]	Hong Kong and Toronto, Canada	Not mentioned	Prognosis of patients afflicted with Severe Acute Respiratory Syndrome (SARS) in high resource settings based on data from low-resource settings	2 logistic regression models of clinical variables	2046 patients	Basic and extended regression models achieved an AUC of 0.860 and 0.882, respectively.
Vardell *et al.*, 2013 [118]	Varied	High resource settings and LMIC hospitals	Report on medical search database	Search database similar to UptoDate providing clinicians with medical information	N/A	No evaluation performed
Puttkammer *et al.*, 2014 [119]	Haiti	Hopital St. Michel, Hopital St. Antoine	Predicting patients at risk of not adhering to anti-retroviral therapy medication	Logistic regression	923 patients	Pharmacy-related data predicted non-adherence the best with an AUC of 0.61.
Adepoju *et al.*, 2017 [106]	Varied	Urban and rural clinical settings	Review of mobile CDSS	Varied	Varied	Varied
Haque *et al.*, 2017 [120]	Dhaka, Bangladesh	District and sub-district hospitals	Evaluation of tool for diarrhea management	WHO algorithm for dehydration assessment	841 patients	Adherence to recommendations increased in a statistically significant manner
Cornick *et al.*, 2018 [36]	South Africa, Nigeria, Botswana, Ethiopia, and Brazil	Varied	Development of 120-page clinical symptoms book aimed at clinicians (found to be used during consultations)	Practical Approach to Care Kit (PACK)	N/A	Location-specific recommendations are essential for book success. No quantitative evaluation.
Vissoci *et al.*, 2018 [121], [122]	Tanzania	Kilimanjaro Christian Medical Centre Hospital	Algorithm-based prognosis of patients with traumatic brain injury to guide triage	Bayesian Generalized Linear Model	3138 patients	Binary prognosis of good recovery vs. bad recovery achieved a sensitivity and specificity rate of 0.890 and 0.713, respectively.
Agarwal *et al.*, 2019 [109]	India	5 clinical centres in India	ThalCare – an ICT-based system for streamlining thalassemia treatment	Software not mentioned	1110 patients	Increase in patient visits (significance not mentioned). System alerts guided 53% of iron dose changes.
Hunt *et al.*, 2019 [123]	Sao Paulo, Brazi	Barretos Cancer Hospital	Binary classification of microscope image as neoplastic	Segmentation of nuclei and calculation of abnormal nuclei density	200 women	Algorithm sensitivity and specificity of 96% and 65%, respectively.

data, medical history, vital sign measurements, and treatment in order to derive its output. After being evaluated on trauma patients from the United States, South Africa, and the Cameroon, the algorithm achieves an area under the curve of 96% relative to standard scoring systems currently in use such as the Trauma Injury Severity Score (~92%) and Global Alignment and Proportion (~87%). The interesting outcome of this paper is the generalizability of the results to trauma cohorts from other countries. Such a finding lends support to the notion of transfer learning. On the other hand, it is important to note that this is a high-level retrospective study and although mortality prediction has the potential to guide clinical decisions, the effectiveness of the algorithm at the individual patient level is not evaluated.

Machine learning was used by Vissoci *et al.* [121] to generate a binary prognosis of patients who experienced traumatic brain injury (TBI). Data over a three year period corresponding to patients entering an emergency centre with TBI was collected and used for analysis. After inputting demographic information, the Glasgow coma score, and other factors such as whether ICU beds were available into a Bayesian generalized linear model, a prognosis was arrived at. A sensitivity and specificity of 0.890 and 0.713, respectively was achieved. The utility of such a prognostic model lies in its ability to help clinicians allocate resources efficiently to the patients that need them most. Some of the same authors build on this work in [122] and explicitly elucidate the benefit of such an algorithm to triaging patients. As it pertains to the prognosis labels, they are very crude and their clinical utility is not evaluated. One would assume that more specific prognoses with temporal information would further increase the efficiency of a TBI triage system.

The National Institutes of Health recently set up the Affordable Health Technologies program in effort to reduce the burden of cancer in low and middle income countries. The work by Pearlman *et al.* [126] sheds light on promising cancer detection and diagnosis work already taking place globally. Hunt *et al.* [123] conducted a prospective randomized trial evaluating the performance of al algorithm designed to identify neoplastic processes from microscopic pathology images. Impact of the algorithm on diagnostic follow-ups was evaluated relative to the standard of care procedure; colposcopy. For all cases, the ground-truth diagnosis was confirmed via a biopsy, an invasive procedure that excises a piece of tissue for further analysis. When comparing the microscopic images approach to colposcopy, the former achieves a sensitivity and specificity of 96% and 65%, respectively. The latter approach performs similarly with a sensitivity and specificity of 94% and 60%, respectively. It can be seen that both methods are overly cautious and result in a high degree of false-positives. Hu *et al.* [127] use a region-based convolutional neural network to classify cervical images as cancerous. This network first locates the cervix in cervigram images before outputting the probability of a positive case. Although the authors report superior AUROC performance (0.91) relative to the standard of care (0.69), a better evaluation metric would be the AUPRC. This is because the AUROC is less sensitive to changes in the number of false positives due to the presence of a large number of negative cases. Moreover, the authors acknowledge the limitations associated with depending on cervicography, as it is an obsolete method. Nonetheless, their overall approach is promising for pushing forward cervical cancer diagnosis. Most recently, Pelle *et al.* [128] convened 39 experts across a variety of domains in order to draft what is known as a target product profile (TPP). This TPP outlines the recommended minimum and optimal requirements surrounding the implementation of clinical decision support algorithms in low-resource settings. As it pertains to these algorithms specifically, their findings emphasized the importance of evidence-based algorithms and those that are human interpretable. Although the experts agreed upon the significance of abiding by data privacy regulations, such as the European Union's General Data Protection Regulation, they fail to mention potential solutions that are specific to low-resource settings. This suggests that greater focus on data privacy and regulation is necessitated. As it stands, this TPP simply acts as broad guidance for the community and does not delve into the technical requirements of a clinical decision support system.

V. Future Research Directions

A. Deep Learning

Under 10% of the studies we identified involved deep learning methodologies yet globally researchers have been successful in applying such techniques to tackle complex healthcare issues. These include the diagnosis of breast lesions [129], the classification of dermatological conditions [130], and the identification of optimal medication doses for hospitalized sepsis patients [131]. Although promising, most of this work has exclusively been performed in the developed world where medical expertise and infrastructure are in abundance relative to that found in low-resource settings. Consequently, the latter regions arguably stand to benefit the most from the potential of deep learning. To leverage the full potential of deep learning in low-resource clinical settings, advancements need to be made on both a social and technical level. We first outline some social factors then transition to deep learning research avenues.

1) Social Factors:

- **Medical Infrastructure** - the availability of hospital monitors and physiological sensing devices such as wearable sensors are critical to monitoring and recording the physiological condition of patients within a hospital setting. This generates significant amounts of data that can be fed to notoriously data-hungry algorithms.
- **Transition to Digital Platforms** - there needs to be a way to store and manage the troves of data generated by the healthcare industry in order to streamline the downstream decision support pipeline.
- **Trust and Confidence** - engendering trust in CDSS is a global challenge [132] that is more prominent in low-resource settings. This is due to the decreased exposure of medical professionals to such systems during their medical training and in their direct environment.

2) Technical Factors:

- **Transfer Learning** - involves training a neural network on a task that consists of large amounts of labelled training data then transferring those parameters to a downstream task with minimal data. Since low-resource clinical settings are characterized by a paucity of data, this approach can improve the generalization performance of algorithms trained on rare medical conditions. Transfer learning has arguably been the cornerstone of modern computer vision applications, allowing models in the medical imaging domain to achieve stong performance [133]–[135]. Recently, however, doubt has been cast on the utility of transfer learning for medical imaging [136].
- **Active Learning** - involves the acquisition and labelling of unlabelled datapoints during training in order to improve performance while being sample-efficient [137]. Such an approach is useful when large sets of unlabelled data are present. This can be common in low-resource clinical settings as labelling is an expensive and time-consuming process that requires a certain level of expertise. The generic role of active learning in biomedical data classification was explored in [138].
- **Self-supervised Learning** - is a branch of unsupervised learning that creates auxiliary tasks based solely on the input data. For instance, tasks can be set up to predict the rotation of images [139] and the arrow of time in videos [140]. Such an approach is an alternative method for exploiting large sets of unlabelled data and can allow networks to learn useful representations. These representations have the potential to improve the classification of downstream tasks that lack suffcient data [141].

B. Applications

The diversity of medical conditions covered in this review is limited compared to the scope of diseases that afflict low-resource settings. Over 50% of the studies we identified were either related to bacterial/viral infections or maternal and fetal health. Therefore, we identified an increased need for decision support systems that target the plethora of under-treated diseases that continue to significantly burden low-resource settings. Some of these conditions are outlined below.

1) Sepsis: Sepsis, a serious infection that affects more than 30 million people worldwide, is estimated to disproportionately affect those in low-resource settings [142]. Its potentially fatal nature is exacerbated by the high rates of antimicrobial resistance found in such regions. Despite this issue, the burden of sepsis remains to be understudied [143] and not fully understood given the high variability of the condition itself and of the regions that experience it. Although algorithms focusing on tackling sepsis exist [144], their implementation within a clinical setting and among diverse patient populations has not been evaluated.

2) Diabetes: Despite the large impact of non-communicable diseases on low-resource settings, the number of algorithms and clinical decision support systems focused on this issue are lacking. For instance, 70% of diabetes patients are found in low and middle income countries [145]. While the generalizability of algorithms designed in the developed world to global regions has been discussed [146], most of the research either discusses remote interventions (outside of the clinical setting) or are manual in nature. The introduction of electronic predictive algorithms can help alleviate the burden placed on healthcare systems by non-communicable diseases and thus reduce costs and improve patient outcomes.

3) Cardiovascular Disease: Non-communicable diseases, and in particular cardiovascular disease (CVD), disproportionately afflict those living in low-resource settings [147], [148]. It is estimated that approximately 80% of global CVD cases can be found in low and middle-income countries [149]. Cardiovascular disease consists of various disorders such as coronary heart disease, peripheral arterial disease, and the presence of pulmonary emboli. Although existing mobile-based algorithms have filled a gap, they are not a sustainable solution for healthcare settings. To achieve this long-term impact within a clinical setting, more research is needed on CDSS that directly tackle CVD. These can take on the form of patient monitoring, diagnosis of cardiac conditions, and personalized prediction of adverse events. For instance, prediction scores for pulmonary emboli are in the process of being validated in Cameroon [150]. Moreover, the extension of the American Heart Association hypertension guidelines to low-resource settings is also being explored [151]. The focus on CVD as a whole, however, is vital for two reasons. Firstly, we would like to emphasize the equal importance of disorders that fall within the CVD umbrella. Secondly, the design of setting-specific CVD risk scores will allow for an easier comparison to existing scores such as the Joint British Societies 2 and QRisk2 scores [152].

C. Clinical Implementation

Few clinical algorithms and support systems have been translated into clinical practice. To increase this translation rate, algorithms need to be assessed for their reliability on various patient populations and evaluated in a prospective manner.

1) Reliability: Algorithms identified in this review were predominantly evaluated on a specific subset of patients from a certain division within the clinical setting e.g. intensive care unit. Consequently, we identified the need for increased evaluation of such models in their ability to generalize. Reliable models can be thought of as those that perform equally well (generalize) on diverse patient populations from different clinical settings but also those that remain robust over time. In other words, they also perform equally well among the same patient population at different timepoints in the future. From this perspective, there is a scarcity of algorithms in the literature, both in the developed and developing world, that are evaluated according to the aforementioned notions of generalizability. For instance, Wiens *et al.* [153] attempt to leverage data from multiple hospitals to make hospital-specific predictions, whereas Oh *et al.* [154] attempt to predict infection rates at two large hospitals. The importance of generalizability was recently emphasized by the Food and Drug Administration's white paper on regulating machine learning based systems [155].

2) Prospective Evaluation: Our findings illustrated that decision support systems were predominantly evaluated retrospectively. To determine the utility of such systems, they would need to be evaluated prospectively. Globally, few initiatives are attempting to do so. For instance, Wong *et al.* [156] prospectively evaluate the impact of a medication decision support system within an ICU setting by measuring the rate of patient adverse drug reactions due to recommendation over-rides by physicians. Another example is GP at Hand, a system that has partnered with the NHS to help connect patients with physicians through a mobile-application and provides them with a medical history to make informed decisions [157]. In tackling acute-kidney injury, Connell *et al.* [158] evaluated Streams, a mobile-application focused on streamlining the treatment process within a hospital setting, citing reduced time to recognize the injury. Several of the aforementioned examples are mobile-applications, potentially lessening the need for expensive medical infrastructure within a clinical setting. This would be ideal for implementation in low-resource settings.

VI. Conclusion

This review has summarized the publications focused on clinical decision support systems targetting stakeholders and medical conditions within low-resource clinical settings. Despite the significant burden of a wide array of diseases on such regions, the majority of the publications discuss systems aimed at dealing with bacterial infections and maternal/fetal care. This implies that greater emphasis needs to be placed on under-treated diseases such as sepsis and non-communicable diseases. Furthermore, very few of the support systems reviewed were evaluated prospectively and in randomized-control trials, the gold-standard for determining clinical utlity. By elucidating these shortcomings, this review hopes to encourage the future development and evaluation of algorithms in low-resource clinical settings with the overall aim of improving patient outcomes.

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