Teleclinical Microbiology

An Innovative Approach to Providing Web-Enabled Diagnostic Laboratory Services in Syria

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KEY POINTS

- Teleclinical microbiology (TCM) is an alternative that provides remote diagnostic services in hard-to-reach, war-affected, and low-resourced areas.
- TCM can use local surveillance capacities to monitor and inform actions to contain the spread of antimicrobial resistance during protracted humanitarian crises.
- Static image-capture techniques are still the most widely used and probably the most suitable modality for TCM in settings of limited resources.

KEY WORDS

Telemedicine; Telepathology; Conflict medicine; Antimicrobial resistance; Urinalysis

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ABSTRACT

Objectives: Telemedicine can compensate for the lack of health care specialists in response to protracted humanitarian crises. We sought to assess the usability of a teleclinical microbiology (TCM) program to provide diagnostic services in a hard-to-reach region of Syria.

Methods: A semimobile station was equipped with conventional micrograph and macrograph digital imaging systems. An electronic platform (Telemicrobiology in Humanitarian Crises, TmHC) was created to facilitate sharing, interpreting, and storing the results. A pilot study was conducted to identify the bacterial species and antimicrobial susceptibility pattern of 74 urinary clinical isolates. An experience survey was conducted to capture the feedback of 8 participants in the program.

Results: The TmHC platform (https://sdh.ngo/tmhc/) enabled systematic transmission of the laboratory records and co-interpretation of the results. The isolates were identified as *Escherichia coli* (n = 61), *Klebsiella pneumoniae* (n = 12), and *Proteus mirabilis* (n = 1). All the isolates were multidrug resistant. The performance of our TCM module was rated 4 (satisfying) and 5 (very satisfying) by 6 and 2 users, respectively. Data security of and cost-effectiveness were the main perceived concerns.

Conclusions: Although we encountered several context-related obstacles, our TCM program managed to reach a highly vulnerable population of 4 million people confined in the northwest region of Syria.

INTRODUCTION

Telemedicine has the potential to overcome geographical barriers and increase access to medical care worldwide, especially during the current COVID-19 pandemic.[1] It involves remote clinical diagnosis, treatment, and prevention of diseases in addition to distance medical research and education.[2] Teleclinical microbiology (TCM) is the use of information and communication technologies to enable the delivery of routine clinical microbiology services by specialists who are located some distance from the medical laboratory.[3] TCM is a relatively novel telemedicine module for the fields of infectious diseases and laboratory medicine.[4,5]

The workflow of a standard TCM module includes (1) the preparation and examination of clinical specimens by local staff, (2) digitization of specimen assets (eg, culture plates, glass slides) and generating an electronic file for each clinical case, (3) transmission of or providing remote access to the digitalized results and electronic files, (4) review and analysis of the clinical data and results by remote teleconsultants, (5) sending electronic feedback on each clinical case, and (6) delivering diagnostic reports for the patients. In addition to rendering clinical diagnoses, TCM promotes the application of quality assurance programs, enhances the performance of surveillance and early warning systems, endorses initiatives to tackle antimicrobial resistance, and provides a tool to transfer skills and knowledge.[6-10] Yet, only a few pilot TCM projects have so far been established.[3]

The protracted conflict in Syria has created one of the worst humanitarian crises in modern history. According to the United Nations Office for the Coordination of Humanitarian Affairs, as of December 2020, more than 11 million people in Syria required humanitarian assistance, including 4.7 million children (https://www.unocha.org/fr/syria). One of the major challenges the Syrian health sector faces is the immense outflow of professionals and skilled workers. It is estimated that thousands of health care workers have left the country,[11] including many laboratory diagnostic specialists and technicians. Communicable diseases were reported to be the largest contributor to morbidity among children younger than 5 years of age in northern Syria between 2013 and 2016.[12] This study examined the usability of a newly established TCM program in the context of the ongoing humanitarian crisis in Syria.

MATERIAL AND METHODS

Establishment and Implementation

A purpose-specific TCM station, housed in a mobile caravan 3 × 10 m[2] in size FIGURE 1, was established in the city of Idleb in northwest Syria in December 2019. The station was equipped with standard laboratory devices, including a class 2 laminar airflow cabin, light microscope, autoclave, incubator, centrifuges, turbidity meter, refrigerator, and freezer. The light microscope (Olympus CX23) had a mounted eyepiece digital camera (AmScope MD500) to allow for the capture of static digital micrographs. BIOMIC V3, a digital imaging device with accompanying software from Giles Scientific, was used to automate reading antimicrobial susceptibility tests.[13] The BIOMIC V3 system was also used to generate images of bacterial colonies cultured on agar plates. Macrographs of the biochemical identification tubes and dipsticks were taken using a generic smart mobile device with camera (eg, cell phone).

A supply chain was established to procure consumables for Gram staining, bacterial culture media, biochemical identification tests, and antimicrobial susceptibility tests. The local staff included 2 part-time diagnostic laboratory specialists, 1 technician, and 1 data entry officer. All scientific aspects were supervised by a committee of volunteer pathology, infectious diseases, and telemedicine specialists based abroad in Lebanon, Sweden, Norway, the United Kingdom, Canada, and the United States. An Arabic-speaking medical coordinator was appointed to manage the workflow of services, offer rapid response in uncomplicated cases, and mediate smooth communication between the local staff and teleconsultants. In addition to the medical coordinator, 4 teleconsultants with bachelor of medicine degrees and postgraduate clinical microbiology specialization, contributed to reviewing the cases and approving the results.

A web-based platform (Telemicrobiology in Humanitarian Crises [TmHC]) was custom made to facilitate entering, sharing, and storing the clinical data of our TCM station. The platform was built using the open-source content management system WordPress (https://wordpress.org/) and hosted on a commercial web-hosting server. A booklet of instructions was developed to demonstrate how to use the platform (Supplemental File S1; all supplemental materials can be found at *American Journal of Clinical Pathology* online). Protocols and videos on relevant clinical microbiology tests were created, translated into Arabic, and uploaded to the platform (https://sdh.ngo/tmhc/home-page/our-laboratory/protocols-and-training-videos/). Continuous on-the-job, 1-to-1 communication was maintained between the lab technician and the medical coordinator throughout the period of implementation of the TCM program. When needed, Skype freeware was used for ad hoc video conferences, allowing screen sharing and interactive group discussions.

Data Entry and Management

Access to the electronic laboratory record (ELR) system was password protected, and the platform traffic was encrypted using the Transport-Layer Security protocol. A new entry was created for each new case using the New Medical Sample form, tailored for urinalysis in low-resource settings (Supplemental File S2). In addition to the patient's demographic and clinical data, the ELR included images of all the laboratory results. Each ELR had a unique identifier to minimize the probability of multiple registrations, facilitate follow-up, and conceal personal data, when needed. The submission of a new case generated an email to the medical coordinator with a link to the case. Henceforth, the entry appeared with deidentified personal data, to which the medical coordinator could respond by clicking the "Add comment" or "Approve" button. Clicking either of these buttons initiated an electronic notification to the local staff. Some cases were further discussed using WhatsApp voice or text messages. The entry was accordingly edited by the medical coordinator or the local staff. Once approved, a PDF print version of the ELR was archived (Supplemental File S3). The PDF prints, representing a backup copy of the data, were locally stored. In parallel, local staff kept their own hard-copy files. The clinical data were collected and entered by the middle of each working day. The medical coordinator was in charge of reviewing, providing comments and feedback, approving the results, and forwarding them to other

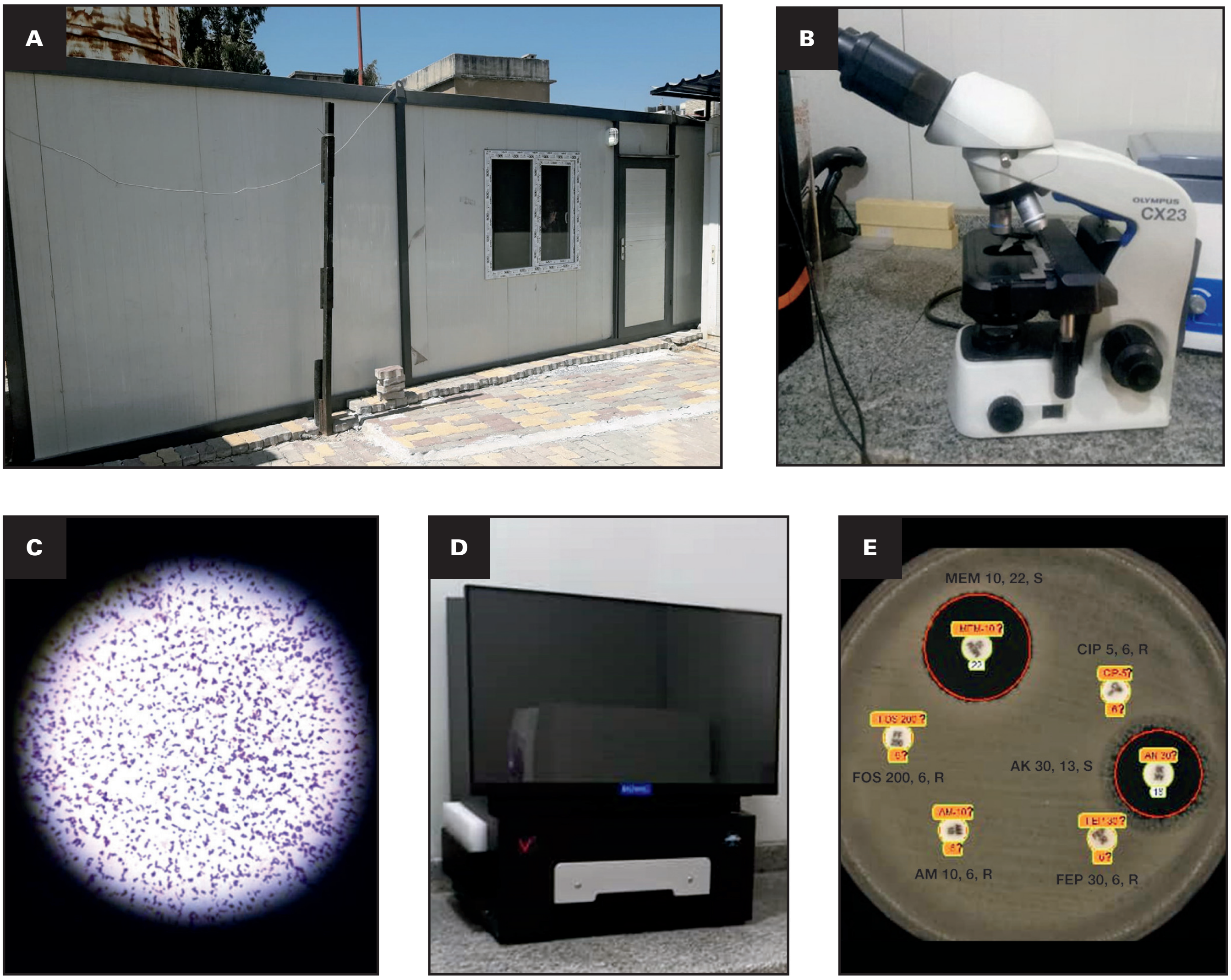

FIGURE 1 Photos of the movable caravan used in our teleclinical microbiology project (**A**); the light microscope mounted with an eyepiece digital camera (**B**); the microscopic field of a Gram-stained smear (**C**); the BIOMIC V3 device (Giles Scientific) (**D**); and the antimicrobial susceptibility agar plate of 1 of the clinical isolates included in the pilot study (**E**).

teleconsultants, typically on the same day an email of "new entry" was received. To avoid delay in conveying results to patients, all the reports were delivered 2 days after receiving the sample regardless of whether the medical coordinator or teleconsultants approved them.

Pilot Study: Biochemical Identification and Antimicrobial Susceptibility Testing of Urinary Clinical Isolates

The study included 74 nonduplicate bacterial isolates collected from clean-catch urine samples on a consecutive basis between September 2020 and April 2021 (Supplemental Table S1). The samples were self-obtained at the laboratory or the patients' home following an in-house–made booklet of instructions (Supplemental File S4). The transport time varied between a few minutes and 1 hour. All the samples were analyzed within 30 minutes of arrival. None of the samples were catheter associated or hospital acquired. All samples were subjected to urine dipstick testing (Combur 10, Roche Diagnostic) and microscopic examination of the urinary sediment. Results of the dipstick nitrite test were compiled as either negative or positive. Pyuria was defined by the presence of more than 10 WBCs per high-power field of the urinary sediment or any positive result for the urine dipstick leukocyte esterase test.[14]

Urine culture and biochemical identification of the isolates were performed as described in a recently published guideline.[15] In brief, urine was inoculated using a sterile 1-µL inoculating loop on Oxoid Nutrient Agar (Thermo Scientific), Oxoid MacConkey Agar (Thermo Scientific), and glucose-topped MacConkey Agar plates. Commercially available sterile 5% glucose intravenous infusion solution was used to prepare the glucose-topped MacConkey Agar. All the plates were incubated aerobically at 37°C for 18 hours. Because all the isolates were glucose-fermenting Gram-negative rods, a panel of 11 biochemical identification tests was used for bacterial identification—namely, lactose fermentation, oxidase, indole, citrate utilization, Voges-Proskauer, urease, motility, hydrogen sulfide (H_2S) production, and lysine decarboxylation. The differential capacity of these tests was verified on 4 reference strains (*Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 13883, *Enterobacter cloacae* ATCC 23355, and *Proteus mirabilis* ATCC 25933).

Susceptibility of the isolates to 15 antimicrobial agents was investigated using the agar diffusion method following the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://www.eucast.org/antimicrobial_susceptibility_testing/). Disks (Bioanalyse) of ampicillin (10 µg), piperacillin/tazobactam (30/6 µg), cefepime (30 µg), ceftazidime (30 µg), ceftriaxone (30 µg), imipenem (10 µg), meropenem (10 µg), aztreonam (30 µg), ciprofloxacin (5 µg), amikacin (30 µg), tobramycin (10 µg), tigecycline (15 µg), fosfomycin (200 µg), nitrofurantoin (100 µg), and trimethoprim/sulfamethoxazole (1.25/23.75 µg) were used in line with previous studies.[9,16] *E coli* ATCC 25922 was used as a control strain. Susceptibility patterns were interpreted according to the clinical breakpoints defined by EUCAST (https://eucast.org/antimicrobial_susceptibility_testing/). The WHONET desktop application was used for the management and surveillance of antimicrobial resistance data (http://whonet.org/software.html). The urinalysis, urine culture, and antimicrobial susceptibility results were conveyed to the patients in the form of a printed report (Supplemental File S5) 2 days after receiving the sample.

Experience Survey

At the end of the pilot study, an experience survey was conducted to capture the feedback of all 8 users of the TmHC platform (Supplemental File S6). First, we created and disseminated a questionnaire using Google Forms (https://docs.google.com/forms/). This questionnaire was followed by bilateral WhatsApp conversations between the medical coordinator and users to review and discuss the results. The survey included 3 opening questions about the user's position title and his or her years of experience in clinical microbiology and digital pathology applications. Next, we included 8 questions to rate the performance of the TmHC platform using a 5-point Likert summative scale (1 = very poor, 2 = poor, 3 = average, 4 = good, and 5 = very good), similar to earlier studies.[17] The survey ended with 2 nominal questions about the obstacles and potentials of the TCM module, including 5 to 6 preselected answers and a supplementary open-ended component to collect further responses.

Patient and Public Involvement

The local communities, including patients and public health care staff, were not involved in the design, analysis, or reporting of this study.

RESULTS

The TCM Module: Operational Observations

The TCM module enabled a systematic and efficient exchange of the ELR with the scientific committee. Static color images (micrographs or macrographs) of Gram-stained smears, bacterial cultures, biochemical identification tube and dipstick tests, and antimicrobial inhibition zones were easily uploaded online, although this upload was occasionally hindered by the low speed of the internet. The quality of images the microscope-mounted camera took was modest. Nonetheless, the resolution was sufficient to retrieve a result from these images. The TCM module allowed remote management of the diagnostic process, even when only 1 microbiology technician was on site.

Seventy-two cases (97%) showed definitive results FIGURE 2, each taking about 15 minutes to be confirmed by an expert. Remote reading of these cases was in agreement with the initial reading made by the local staff. The remaining 2 cases (3%) warranted a second round of review because they had atypical colony morphology and false-positive or imprecise results from their motility test using the semisolid motility-indole-lysine agar method. Each of the latter 2 cases took approximately 30 to 60 minutes to agree on the identification of the pathogen. In addition to the platform-facilitated commentary service, there was a need to use WhatsApp to discuss the identification of 4 cases (5%). WhatsApp was also used to discuss the antimicrobial susceptibility results in 10 cases (13%). In only 1 case (reference No. 3039 in Supplemental Table S1) did the local staff made direct contact with the referring physician to advise on an optimal treatment plan.

Biochemical Identification of Urinary Clinical Isolates

All the isolates grew well on the MacConkey Agar media, appeared as Gram-negative rods, were oxidase negative, yielded a positive glucose fermentation result, and were accordingly assigned into the *Enterobacterales* order.[18] Sixty-one isolates (82.4%) were identified as *E coli* based on their positive result for lactose fermentation, indole, motility, and lysine decarboxylase, along with a negative result for the H_2S production, citrate utilization, Voges-Proskauer, and urease tests (Supplemental Table S2). Twelve isolates (16.2%) were classified as *K pneumoniae* for yielding a positive result for the lactose fermentation, citrate utilization, Voges-Proskauer, urease, and lysine decarboxylase tests, while the oxidase, indole, motility, and H_2S production tests were negative. One isolate (1.4%) was identified as *P mirabilis* because it was negative for lactose fermentation, indole, lysine decarboxylase, and Voges-Proskauer tests but positive for H_2S production, citrate utilization, urease, and motility.

Antimicrobial Susceptibility Patterns

The isolates showed nonsusceptibility rates of 100% to ampicillin (74/74), ceftazidime (73/73, 1 result not available), and fosfomycin (73/73, 1 result not available); 89% to cefepime (66/74); 86% to ceftriaxone (64/74); 76% to aztreonam (56/74); 72% to trimethoprim/sulfamethoxazole (53/74); 70% to ciprofloxacin (52/74); 63% to piperacillin/tazobactam (47/74); 57% to tobramycin (42/74); 49% to gentamicin (34/69, 5 results not available); 26% to tigecycline (19/72, 2 results not available); 25% to amikacin (18/72, 2 results not available); 16% to nitrofurantoin (12/74); 4% to meropenem (3/74); and 3% to imipenem (2/74), as shown in FIGURE 2 and Supplemental Table S1. All the isolates were nonsusceptible to at least 1 agent in 3 or more antimicrobial categories and accordingly defined as multidrug resistant.[19]

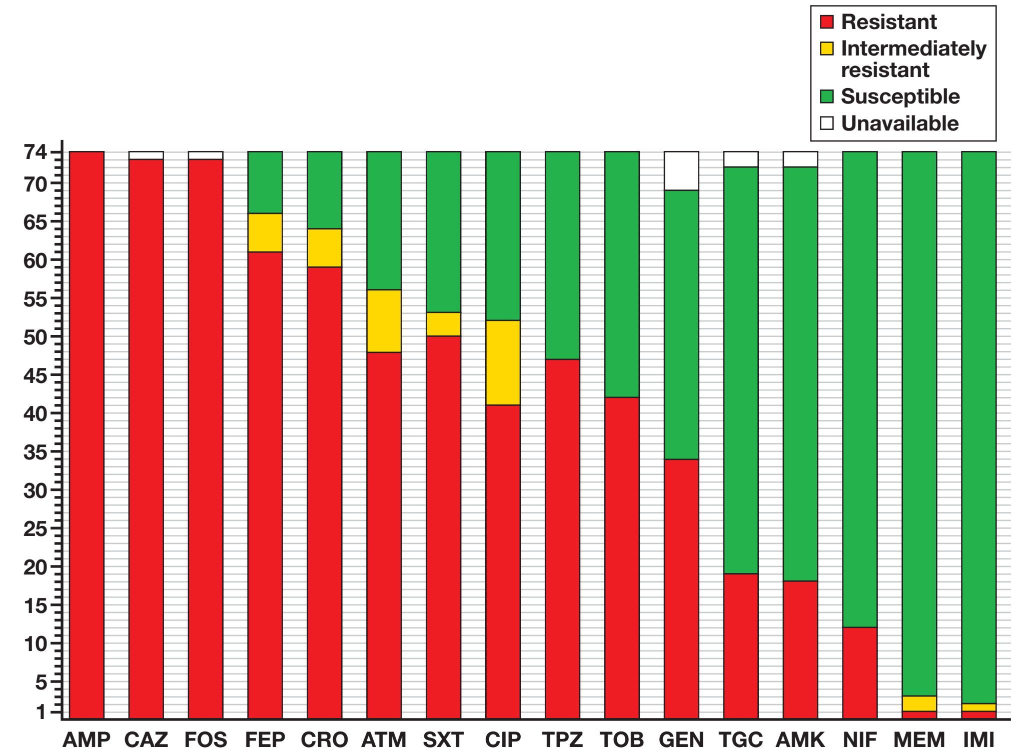

FIGURE 2 Antimicrobial susceptibility rates for 74 urinary clinical isolates included in the pilot study. AMK, amikacin (30 µg); AMP, ampicillin (10 µg); ATM, aztreonam (30 µg); CAZ, ceftazidime (30 µg); CIP, ciprofloxacin (5 µg); CRO, ceftriaxone (30 µg); FEP, cefepime (30 µg); FOS, fosfomycin (200 µg); GEN, gentamicin (10 µg); IMI, imipenem (10 µg); MEM, meropenem (10 µg); NIF, nitrofurantoin (100 µg); SXT, trimethoprim/sulfamethoxazole (1.25/23.75 µg); TGC, tigecycline (15 µg); TOB, tobramycin (10 µg); TPZ, piperacillin/tazobactam (30/6 µg).

Extracts From the Users' Experience

The users, 3 on-site staff and 5 teleconsultants, reported practicing laboratory diagnostics or medical microbiology for a median of 9.5 years (Supplemental Table S3). Only 1 user had previous experience of 8 years in telemedicine. Satisfaction with the overall performance of our TCM module was rated 4 or higher (ie, satisfied [n = 6] and very satisfied [n = 2]). Satisfaction with the flow of notifications, ELR, and quality of digital pictures had median rates of 4. One user was dissatisfied with the quality of digital pictures. The median rate for "how comfortable and confident the user would feel applying the TmHC platform to reach a diagnostic result" was also 4, ranging between average (n = 1), comfortable (n = 4), and very comfortable (n = 3). Satisfaction with the TmHC website with regard to having a user-friendly interface, being easy to navigate, and allowing easy data management and file uploading had median rates of 3, 4, and 4, respectively.

The users perceived concerns related to data security (n = 5), cost-effectiveness (n = 4), timeliness of reporting (n = 3), usability (n = 3), accuracy of results (n = 2), legal issues (n = 1), and the availability of high-speed internet (n = 1). All users expressed the need for improvement, including the addition of a built-in communication tool (n = 6), advanced statistical analytics (n = 4), machine learning (n = 4), advanced informatics (n = 3), and further focus on education (n = 2). Some users also mentioned the need to integrate a digital ruler, upgrade the level of testing and molecular assays, perform systematic measurements of the efficiency of remote consultation, and explore the potential of using rapid diagnostic tests. Importantly, a gradual decrease in enthusiasm was noted among the local staff. Demonstrating improvement in the accuracy of results, treatment success rates, and patient satisfaction was proposed to remotivate the staff. All users identified access to funding as a key factor in scaling up the project.

DISCUSSION

The ongoing instability and insecurity in Syria were a major challenge throughout the period of implementation of the TCM module. Hostilities continued, including airstrikes, bombardments, shelling, and explosion of vehicle-borne improvised explosive devices.[20] The living hardship, apprehensive work conditions, and exposure to human rights violations continued to be a daily concern for the locals, with a common feeling that there was no solution in the near future. The setting was further hampered by a swift increase in the number of confirmed cases of COVID-19.[21] Such observations highlighted the complexity of initiating nontraditional health care projects in countries affected by protracted conflict.

The lab technician, with 2 years of education in a state-run vocational health college and several years of experience in clinical laboratory work, was a key member of the local team. Having such an experienced staff member with good hands-on skills was a major help to implement the project. The study did not involve systematic measurements of behavioral changes among the referring physicians nor of their treatment decisions to indicate and assess the outcome of our TCM program. Nonetheless, we received informal feedback from a few referring physicians, pointing out that their treatment plans became routinely guided by the laboratory results.

The results of our pilot study were consistent with previous studies describing *E coli* and other coliform bacteria as the most commonly detected urinary pathogens.[22] The absence of *Staphylococcus saprophyticus* and other Gram-positive cocci among our isolates, however, was not in line with the typical etiology of community-acquired urinary tract infection (UTI).[22,23] This finding could be related to practice-related or actual differences between high-income and low-income countries with regard to the frequency of less common uropathogens.[24] The identification of 2 isolates as *K pneumoniae* and *P mirabilis* (Supplemental File S7) was confirmed using the analytical profile index strips for *Enterobacteriaceae* (API 20 E; BioMerieux). Notably, several of the frozen-preserved cultures did not grow upon reculturing. These isolates were not viable, most likely because of frequent freeze-thaw repeats caused by electrical power failures.

Although the size of our collection was small and insufficient to draw definite statistical analyses, we noted that the sensitivity of the urine dipstick nitrite test to detect UTI was 62% (Supplemental Table S1). In contrast, the dipstick esterase test and microscopic detection of pyuria had sensitivity rates of 96% and 100%, respectively. Urine culture was used as a reference standard for calculating the sensitivity and specificity of these tests. The nitrite test's modest sensitivity was in the range reported by other studies, while the sensitivity of pyuria was comparatively higher,[25] probably influenced by asking the referring physicians to send difficult cases (selection bias).

The high rates of antimicrobial resistance were in accordance with a recent consensus paper describing the prevalence of multidrug-resistant strains of *E coli* in Syria and the Middle East.[26] Carbapenems were the only option for treatment in 1 case (reference No. 738 in Supplemental Table S1). The scientific committee recommended optimizing the selected panel of antimicrobial agents—for instance, by including amoxicillin with clavulanic acid, cefuroxime, and ertapenem. Conversely, tigecycline could be excluded because it is not sufficiently excreted in urine and data on its efficacy for treatment of UTI are limited.[27] The committee perceived the need to conduct further studies to investigate the prevalence of extended-spectrum β-lactamase, AmpC, or carbapenemase-producing isolates. The necessity of applying a robust antimicrobial stewardship program to improve the use of antibiotics in Syria was also noted.

Several points captured by our users' survey concurred with previous findings in the literature. Wilkowska and Ziefle[28] demonstrated that privacy and data security in e-health were commonly perceived to be of high importance among the beneficiaries. The authors concluded that elaboration of effective solutions to these issues would mediate successful adoption of medical technology. A scoping review on the impact and implementation challenges of telepathology reported that small telepathology networks, such as our TCM module, expressed low concern regarding organizational and legal issues.[29] Suren et al[30] described an integrated information technology platform for coordination of diagnosis, treatment, and aftercare of prosthetic joint infection. Improving the ability of their platform to facilitate real-time communications affected efficient collaboration and minimized the loss of information.

Effective application of advanced informatics tools, including expert laboratory information systems, decision support algorithms, databases of biochemical reactions and software for profile matching, and automated image analysis tools, has been endorsed by expert studies as a key step in optimizing and scaling up the capacity of TCM modules.[31] Likewise, digital imaging and machine learning have been used successfully to detect malaria parasites and predict antimicrobial resistance patterns.[32,33] Experts have also underlined the potential of integrating machine learning and artificial intelligence systems into real-world settings.[34,35] Many members of the UK pathology community highlighted the importance of securing funds for initial hardware and software and to cover staff remuneration to promote increased uptake of digital pathology modules.[36]

CONCLUSIONS

Lack of clinical microbiologists and infectious diseases specialists hinders correct diagnosis and appropriate management of infectious diseases in countries affected by protracted conflict. Our TCM module, along with the TmHC platform, offers a tool to the few laboratory staff remaining on the ground in Syria to share diagnostic results with remote international experts, facilitating the provision of laboratory-guided infection treatments. In addition to empowering the local staff, the TCM module can reduce the need to dispatch specimens or patients to other locations. As such, it opens the door to a durable, scalable solution for the staffing challenge the health system in Syria or other crisis-affected countries face. In parallel and to promote value-based continuation and dissemination of the telehealth component of our TCM program, there is a need to ensure interoperability and to apply procedures for the measurement of clinical outcomes, patient satisfaction, and expenditure.

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