Informatics Tools To Monitor Progress And Outcomes Of Patients With Drug Resistant Tuberculosis In Peru

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ABSTRACT

Multi-drug resistant tuberculosis (MDR-TB) is an important and growing problem in many developing countries. New strategies have been developed to combat the disease but require complex treatment regimens and close monitoring of patients' bacteriology results. We describe a web-based medical record system deployed in Peru to support the management of MDR-TB. Web-based analyses have been developed to track drug sensitivity test results, patterns of sputum smear and culture results and time to conversion from positive to negative cultures. Individual and aggregate drug requirements can also be monitored in real time. Multiple analyses can be linked together and data can be graphed or downloaded to spreadsheets. Over 1200 patients are currently in the system. We argue that such a web-based clinical and epidemiological management system is an important component for successful implementation of complex health interventions in resource poor areas.

INTRODUCTION

While the death toll from tuberculosis (TB) has remained high among poor populations for centuries, interest in the disease has risen dramatically in recent years and TB has now been identified as one of the so-called "emerging" or "re-emerging" infectious diseases.[1] Indeed, TB case rates have been rising (often in association with HIV infection) and TB is still one of the leading infectious causes of adult mortality in the world each year. The World Health Organization (WHO) recommends that all TB patients receive 6 months of directly observed, standardized short course chemotherapy (DOTS). However, significant numbers of patients in certain areas are infected with strains of *Mycobacterium tuberculosis* resistant to the two most important antituberculous chemotherapeutic agents, isoniazid and rifampicin. While the DOTS strategy has proven to be one of the most important public health interventions in recent decades, it has been shown to be inadequate for patients with multi-drug resistant tuberculosis (MDR-TB)[2]. For those patients, it is clear that regimens containing second-line anti-tuberculous drugs are required. Treatment of MDR-TB can be complex, requiring close attention to the drug sensitivity patterns of the mycobacterium, the previous and current drug regimens and any clinical and radiological signs of disease progression.

WHO and its partners are currently studying the use of second-line drugs for the treatment of MDR-TB in developing countries through a series of pilot studies, the largest of which is the subject of this paper. In this strategy, which has been called "DOTS-Plus"[3], patients receive at least five antituberculous agents and often require additional medication to control side-effects of the second-line drugs. Treatment typically takes at least 18 months. It has been argued that complex treatment regimens of this sort are too difficult to implement in developing countries. However, MDR-TB treatment programs in several countries have shown that it is possible to treat such patients successfully even in impoverished areas such as Peru[4]. A project run by Socios En Salud in Lima, the Peruvian National TB Program (NTP) and the Program in Infectious Disease and Social Change (PIDSC) at Harvard Medical School is the first directly observed, community-based, individualized treatment program for MDR-TB in a resource-poor setting. Patients were referred to the program after failing repeated courses of standardized therapy. To support this project, we have developed a web-based electronic medical record system (EMR). This allows close monitoring of patients' status, detection of early indications of problems and accurate resource planning. We describe here the software tools that have been developed to display and analyze patterns of patient data in the EMR including bacteriology (smears, cultures and drug sensitivity test results), drug regimens and overall patient status.

Requirements

Managing medical interventions in developing countries can be challenging due to lack of infrastructure and transport links, poor communications and shortage of trained staff. These limitations can have detrimental impacts even on relatively straightforward interventions such as vaccination programs, but represent a particular challenge for the more complex management of chronic diseases such as MDR-TB. In addition to case finding and diagnosis, patients require the creation of complex regimens sometimes with more than 7 drugs. These regimens are either based on knowledge of the patients' individual drug resistance patterns (individualized regimens), or are created for groups of patients based on the drug resistance patterns for the population (standardized or empiric regimens). Patients in treatment must be monitored for bacteriological status (whether sputum smears and culture are positive) and side effects.

To ensure high quality care, supplies of special second-line anti-tuberculous drugs must be ordered well in advance and carefully maintained to prevent stock-outs, while minimizing the expenditure on these drugs. Also, samples for laboratory tests must be tracked and managed. The *Drug Sensitivity Tests* (DST) samples frequently have to be tested out of the country. Peruvian samples are often sent to the Massachusetts State Laboratory Institute (MSLI) in Boston which constitutes the reference lab for DST in Peru. The results are then sent to Peru for review by the physicians and incorporation in the patient's chart.

Technical Infrastructure

While few institutions (let alone individuals) have high speed internet access in the developing world, dialup connections to local ISPs are fairly widely available in many countries, especially in Latin America. All the current Socios En Salud/PIDSC MDR-TB treatment sites are in the greater Lima area with generally good quality dialup Internet access available at the office sites in Carabayllo and San Borja though the cost of local phone calls is high. Fast internet access is available in certain areas of down-town Lima but costs over $5000 per year for a 128Kbs dedicated line. Therefore a web based EMR must function well by dialup connection.

METHODS

Figure 1 shows the basic infrastructure for the project with a web/database server in Boston, USA and web access to the system in Peru. This approach was chosen due to the lack of suitable hosting sites in Peru at the start of the project, and the ease of setup and administration of the server. Depending on the nature of the facilities in a developing country it can also improve the security of the server and data. The disadvantages are the potential for slow connections over international Internet links, and possibly a sense of loss of control in the distant sites. A well-designed Web-based system should require fairly limited bandwidth unless large digital images are transmitted. Another advantage is that it is not necessary to install and support special software on users' computers in remote sites. Sensitive clinical data must clearly be managed in a highly secure fashion, and the Web provides effective tools for this purpose such as the Secure Socket Layer Protocol[5]. However, servers must be carefully administered to reduce the chance of security breaches, and users must be properly authenticated.

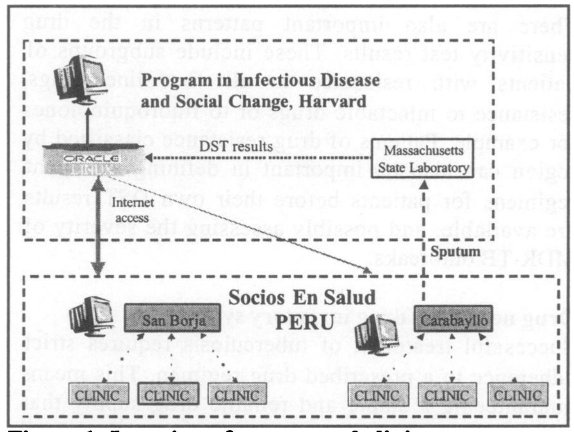

Figure 1: Location of servers and clinics

Information management requirements

Good management of clinical data is essential in creating effective treatment strategies and monitoring the patient's condition. There are several key pieces of information required for this process:

- The patient's clinical status (history and physical).
- Bacteriology results (monthly sputum smear and cultures).
- Drug sensitivity testing results.
- The current drug regimen.
- A list of drugs the patient has previously been exposed to.
- Chemical pathology and hematology results
- Drug complications and adverse events.
- Chest x-ray (CXR) reports, preferably including digital images.
- Background information on the patient including their occupation, living circumstances and possible contacts.

Monitoring of patients' outcomes relies heavily on bacteriological smear and culture results. In the project in Peru, these are normally ordered once per month. Patients receiving a standard 2 year course of MDR-TB treatment will therefore have 50 or more bacteriology results. Patterns in this data have important significance for patient management. For a patient starting with a positive culture, two negative cultures at least 30 days apart constitutes "culture conversion", an important indicator of effective initial therapy. Reconversion is characterized by a subsequent positive result in a patient with documented conversion. Cure is defined as a sequence of unbroken negative culture results, varying from 6 to 12 months depending on the program. Finally treatment failure is defined as persistent positive cultures for greater than 6 months (again the exact definition varies by program). There are also important patterns in the drug sensitivity test results. These include subgroups of patients with resistance to all first line drugs, resistance to injectable drugs or to fluoroquinolones for example. Patterns of drug resistance classified by region can also be important in defining treatment regimens for patients before their own DST results are available, and possibly assessing the severity of MDR-TB outbreaks.

Drug needs and drug inventory systems

Successful treatment of tuberculosis requires strict adherence to a prescribed drug regimen. This means guaranteeing a stable and reliable drug supply that meets the individual and aggregate needs of all patients. Given the issues of availability and logistics in the developing world for many of these second-line pharmaceuticals, a highly accurate model of both drug needs and supply is essential. Typically this is based on analysis of drug inventory and monthly use from the warehouse. However, where the drug regimens of most or all patients are known, a drug needs estimation system can be implemented to provide estimates of expected drug use to complement warehouse estimates.

RESULTS

The core system is a database-backed Web site which provides reliable, secure, real-time access to individual patient records from anywhere with Internet access. This was built using free software: Linux, Apache Web server and Tomcat Java servlet engine. An Oracle™ database was used, though other databases may be substituted. Web pages are written using Java server pages. As of July 2002 we have over 1200 patients in the system with almost 700 in active treatment, more than 2300 DST results and almost 20,000 bacteriology results. Recruitment is running at approximately 50 patients per month. While DSTs performed at the MSLI are entered in Boston, all other data are entered via the Web in Peru. Clinicians and clinical researchers are able to access the site and review patients chart or perform real-time analyses from any Web browser. Pages are available in both English and Spanish, though free text remains in the language in which it was entered, usually Spanish.

Clinical data on the patients' past medical history, TB history, previous treatment and surgery, TB contacts and physical examination are collected on forms at patient registration. These data, along with lab tests are entered in Web forms in Peru. Digital images of chest x-rays are acquired with a digital camera, processed with custom software[6] and uploaded to the system. Drug regimens are recorded in detail including the starting date of the drug, the expected treatment duration and the daily and weekly dosages (TB drugs are usually given 6 days per week in this program).

Analysis pages

Analysis types currently available on the Web are described below. The analyses chosen are intended to allow the patients' progress and outcomes to be monitored on a monthly basis or more frequently, and allow rapid testing of research hypotheses. Each analysis allows the user to filter the patient group by cohort dates and the district of Lima in which treatment is delivered. In addition, analyses can be chained together to apply several selections to the data, for example filtering by gender, then searching for a particular drug resistance pattern, and finally graphing culture conversion rates of the resulting patient set. Other selection criteria include age range, district, and treatment status (active, cured, died etc.). Sets of patients generated by the selection criteria can be downloaded for further analysis in a spreadsheet or statistical package.

Types of analysis

Drug sensitivity testing analyses allow the user to:

- Create graphs of resistance to each of the antituberculous drugs (figure 2)
- Search for patients with resistance to particular drugs or combinations, such as all first line TB drugs
- Compare DSTs prior to the start of treatment with those collected once treatment has commenced

Sputum smear and culture analyses allow the user to:

- Create graphs of the number of patients smear and culture positive by month
- Search for groups of patients with particular patterns of smear or culture results that may indicate failing treatment or probable cure (diagram 3 & 4)
- Create graphs of numbers of patients that have culture (or smear) converted by a

certain time (90, 120, 180 days for example).

- Create graphs of numbers of patients that have reconverted back to positive culture at selected times as above

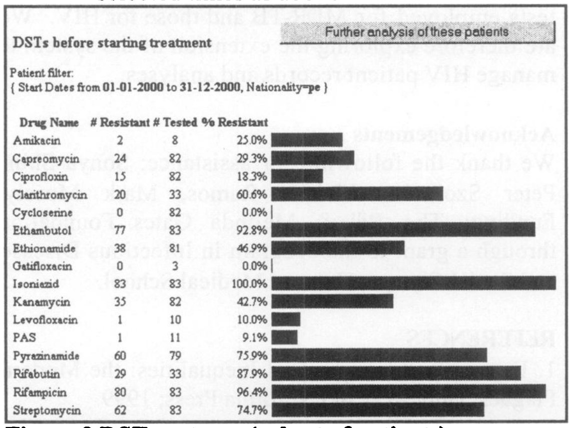

Figure 2 DST patterns (subset of patients)

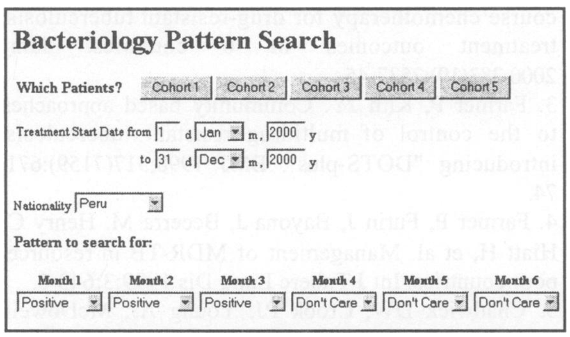

Figure 3 Selecting bacteriology patterns by month

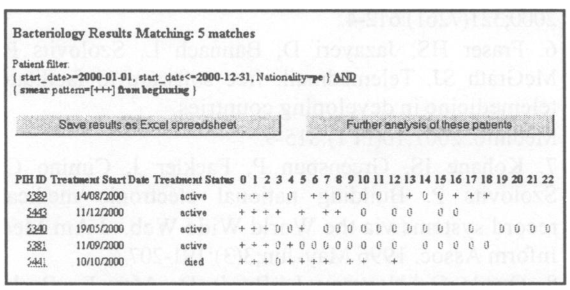

Figure 4 showing subset of patients selected in figure 3 and a summary of smear status by month

Drug regimen analyses allow the user to:

- Create reports of the number of doses of each drug expected to be required within a given time period (such as the next 100 days or for the month of July 2002).
- Create reports of the quantities of drugs required for a particular patient for 1 month
- Create graphs of percentage of patients on each drug
- Search for groups of patients receiving specific drugs or combinations of drugs

These analyses complement a commercial drug inventory system that has been implemented to manage the drug supply for the project in Lima.

DISCUSSION

There is a pressing need to codify the complex management of MDR-TB so as to simplify its application to sites with limited facilities and staff. Good communication systems should assist in sharing expertise between different sites, and ensure high standards of patient care. A badly run MDR-TB management program may increase drug resistance and create pan-resistant organisms, as well as harming individual patients. A key priority in improving management of MDR-TB is performing epidemiological studies and clinical research. This includes

- Early recognition of sub-groups who may be failing, for closer monitoring and intervention.
- Detection of changes in DST patterns that may indicate amplification of resistance in a group of patients
- Recognition of drug regimens that may be associated with particularly good or particularly poor outcomes

This work has similarities with previous web based medical record systems[5,7] and the ARGONAUTA telemedicine system[8]. Programs to analyze clinical data in EMRs have been available since Clinquery[9] or before. A project at Childrens Hospital in Boston created a Java applet that allows clinicians and researchers to analyze clinical data from the hospital's SQL database[10]. Our approach is similar in applying an easy to use set of web-based selection criteria to sets of patients in an EMR, but analyses here are more complex and more specific to TB management. The purely server-side approach used here also minimizes bandwidth requirements.

Limitations

Clearly the implementation of relatively high technology systems in a developing country context is not straightforward. Several concerns arise, some common to informatics projects in the US and some specific to resource-poor settings.

Cost. With severely limited health care resources in developing countries can we justify spending money on IT systems? The first requirement is that projects are driven by specific needs identified by healthcare workers in the country(s) involved. Our project started with paper-based information management supplemented by limited IT (mainly spreadsheets). However the rapid scaling up from 100 to over 500 patients required more powerful tools. It becomes increasingly difficult to track lab results and clinical status over large, spread out groups of patients. The need to perform research studies and report outcomes and best practices also requires good access to organized data which inevitably requires data collection and entry into a database of some sort. In addition, a large part of the cost of this project is for drug acquisition and distribution. It is essential that this is carried out in an efficient and fully accountable fashion to ensure good clinical outcomes and minimize urgent purchases or stock loss.

Data security, confidentiality and authorization. While the use of an SSL web server provides good data security, the issue of who should have access to the site can be problematic. Access to different parts of the site is dependent on the role of the user such as clinical or data entry or epidemology.

Reusability. A well designed system should be usable by other programs for the cost of a new server, and training and support (the software will be free). This should ease the process of setting up other MDR-TB management programs. However this requires a robust and flexible design and also support for data exchange standards.

Data entry. Ensuring complete and accurate data entry remains the biggest challenge as with most projects of this sort. Supervision can be difficult, so careful instruction and training are essential, augmented by validation rules in the data entry forms (in the correct local language!) and regular checks of entered data. Chart review and cross checking of original sources is also required in many cases. To reduce transcription errors, electronic transfer of DST data diect from the laboratory is now being set up.

CONCLUSIONS

We are currently working with the WHO, the US Centers for Disease Control, and the Peruvian, Latvian and South African National TB programs, to finalize common criteria and standards for monitoring the management of MDR-TB. Once these are finalized we will be able to test and apply the criteria with the analysis systems described here.

There is concern that projects seeking to manage complex diseases in the developing world will be unable to ensure high quality care due to a lack of infrastructure and expertise. In some cases this issue has been cited as a reason not to develop and fund such projects. We believe that providing tools to aid the process of clinical management and ensure that problems are detected early can make treatment programs more effective and accountable, and therefore more sustainable. This approach should be important in the management of other diseases in developing countries. There are many similarities in the complex and expensive drug regimens and lab tests employed for MDR-TB and those for HIV. We are therefore exploring the extension of the system to manage HIV patient records and analyses.

Acknowledgements

We thank the following for assistance: Sonya Shin, Peter Szolovits, Malena Ramos, Mark Mosely. Funding: The Bill & Melinda Gates Foundation through a grant to the Program in Infectious Disease and Social Change, Harvard Medical School.

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