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Delivering Antibiotic Resistance Information Specifically Tailored to Location and Time

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Abstract

Antibiotic resistance poses a significant threat to humanity. Hundred years since the beginning of the era of antibacterial drugs, we are facing increasing numbers of infections with multi-resistant pathogens. The current approach of distributing information on antibiotic resistance in printed form in the clinics has disadvantages with respect to the actuality of the data and the regional heterogeneity of resistance patterns. We developed an application named qRe using representational state transfer as a communication standard to deliver antibiotic resistance percentage information to the end user. The data is selected specifically for his/her geographic location. The user can display the information using either the application for Android smart phones or the web application. With the presented software we show the technical feasibility of delivering antibiotic resistance information specifically tailored to location and time. A short evaluation of the software showed an overall positive response from physicians. Based on recommendations of previous investigations, we expect a measurable clinical impact.

Keywords:

Microbial Drug Resistance, Mobile Health, Geographic Information Systems, Clinical Decision Support Systems.

Introduction

The impact of bacterial infections on human health and healthcare is tremendous. More than 25,000 deaths are attributed each year to multi-resistant infections in the EU [1], and "the incidence of sepsis exceeds that of colon cancer, breast cancer, and AIDS" [2]. The estimations of its economic threat range between € 1.5 billion in the EU [3] and US$ 20 billion in the USA [4].

The history of antibacterial drugs is quite short. The first chemical agent for systemic usage against a bacterial infection – salvarsan – has been developed in the laboratories of Paul Ehrlich in 1910 [5]. Followed by the famous discovery of penicillin by Sir Alexander Fleming [6] and the discovery of sulfonamides by Gerhard Domagk [7], many life threatening infections could now be treated.

Nearly as old as the development of antimicrobial drugs is antibiotic resistance. Importantly, scientists of the old days informed the scientific community about the risk of inappropriate usage of these new drugs. Sir Alexander Fleming stated in his Nobel lecture 1945: "Exposing [...] microbes to non-lethal quantities of the drug make them resistant" and "If you use penicillin, use enough" [8]. In that period, the first reports on clinical antibiotic resistance to penicillin were also published [9]. The first report on methicillin-resistant Staphylococcus aureus (MRSA) – a multi-resistant pathogen with sustained impact on human health nowadays – dates back to 1961 [10]. In the 28 member states of the European Antimicrobial Resistance Surveillance Network (EARS-Net), the mean MRSA resistance rate was 17.4% in 2010, ranging between 0.5% (Norway) and 52.2% (Portugal) [1].

Today the percentage of resistant pathogens is still increasing. More and more bacteria develop mechanisms against our drugs. In the past few years, more and more abbreviations for antibiotic resistance – like CA-MRSA, VRE, ESBL, KPC, and OXA-48[1] – enter the common vocabulary in the clinics. Tracing the latest threat – the New Delhi metallo-beta-lactamase (NDM-1) – we have an excellent marker for the rapid dissemination of new resistance genes. Originating around 2008 on the border region between Pakistan and India, now more than 22 countries on four continents are affected [11].

The patterns of antibiotic resistance are regionally heterogeneous. Not only do the resistance rates between countries differ, also within a country this phenomenon can be observed. In Figure 1 the percentage of *Escherichia coli* resistant to 3[rd] generation cephalosporins within Austria can be found. Notably, this is not the maximum level of granularity of antibiotic resistance patterns. Even between wards of the same hospital, differing percentages can be observed [12].

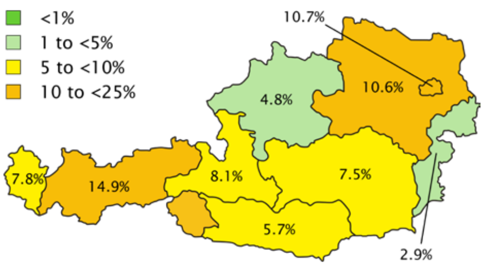

Figure 1 - Resistance patterns of Escherichia coli to 3rd generation cephalosporins. Data from the AURES 2011 [13]

[1]CA-MRSA: community-acquired methicillin-resistant *Staphylococcus aureus*; VRE: vancomycin resistant *Enterococcus spp.*; ESBL: extended-spectrum beta-lactamase; KPC: *Klebsiella pneumoniae* carbapenemase; OXA-48: oxacillinase variant 48

Experts around the globe agree that many different steps need to be undertaken to regain control over antibiotic resistance. The main focus areas are medical research, public hygiene and education, professional education, infection prevention, and the development of new antibiotics or alternative treatments. One part of professional education with prime importance will be the distribution of antibiotic susceptibility information close to real-time to physicians [14].

In a clinical setting, when prescribing an anti-infectious drug, healthcare providers are encouraged to take many different patient conditions into account, including the pathogens involved and its antibiotic susceptibility. Antibiotics susceptibility testing takes time – between hours and days – but antibiotic therapy needs to be started immediately. The clinician has to choose the appropriate drug for the infection empirically, without the possibility to rely on exact data. To support the healthcare providers in these situations, antibiotic susceptibility information is available as reports or printed on hard paper as antibiotic susceptibility cards for easy carry-on. One big disadvantage comes with this method of data delivery: the actuality of the data.

To provide a solution for the timely delivery of antibiotic resistance information, we developed an application called "qRe" – short for "query Resistances" and pronounced "cure". It delivers antibiotic resistance information of the geographic area of the user directly to his/her hands.

The data is processed and managed on a server, and is visible to the clients through a web service interface. We developed a client for Android smart phones as well as a web application for all other devices. For demonstration purposes, the application's range is currently limited to Austria.

Materials and Methods

For the implementation of our application, we used a service-oriented client-server design pattern. The resulting system architecture is graphically depicted in Figure 2. The server application is written in JavaEE version 6. The SQL database on the server is MySQL version 5.2. The Android client is programmed with Dalvik/Android with a minimum API level of 9 (minimum Android version: 2.3/Gingerbread). The web client uses PHP5, HTML4, HTML5, CSS2, CSS3, and JavaScript. Communication between the server and the clients is handled using representational state transfer (REST). Data is encapsulated using the JavaScript Object Notation (JSON). Some functionality has been imported using external libraries. These are the libraries "achartengine" [15] for the display of charts on the Android client, and "nategood/httpful" [16] for the REST capabilities of the web client.

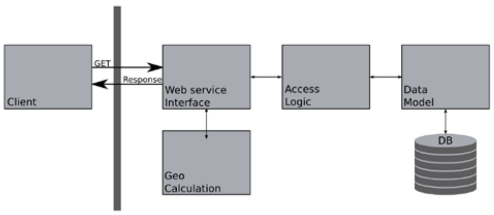

Figure 2 - The service-oriented architecture for the qRe application, including subcomponents

In a typical usage scenario, the client sends a request to the web service interface, thereby providing the user's current geographic location. The server then calculates the area surrounding the user, selects all data that belongs to it and returns it to the user.

Data sources and database

The only data source of the application currently in use is the Austrian Antibiotic Resistance Surveillance Report (AURES), which is published annually and describes the antibiotic resistance situation of the past year [13]. In this report, only few bacteria and antibiotics are reported. We used this data source as it is available instantly and sufficient to build a client to demonstrate our intentions.

The granularity of the data is acceptable for our approach. It is published for each state separately. Data introduced into the database are the number of resistant, intermediary resistant, and susceptible isolates for the antibiotic–bacterium pair; the corresponding state as the geographic area; and the first day of the year as the date of the event. The records have been introduced for each state separately.

Selected data from the aforementioned report are gathered and transferred manually to a single SQL database, containing four separate tables; two tables contain all types of bacteria and antibiotics, one table contains definitions of all geographic areas, and the last table contains antimicrobial resistance data comprising the number of susceptible, resistant, and intermediary resistant isolates, the date of the susceptibility testing, and the latitude and longitude of the location of the result. The amount of antibiotic resistance data for 2006 until 2011 is 1670 tuples.

Geographic calculation

The software presents the antibiotic resistance information of the surrounding area of the user. We defined this area as the square surrounding the current location of the user, with a diameter of 185 km, or a side-length of 130 km (Figure 3). These values are based upon the mean diameter of all Austrian states that is 185 km.

Figure 3 - Demonstration of the square surrounding the user

Calculating the surrounding square is done by first calculating the longitude and latitude offset using formula (1) and (2).

$$\Delta_{longitude} = \frac{180 \cdot r_{square}}{\cos\left(\frac{latitude \cdot \pi}{180}\right) \cdot r_{earth} \cdot \pi} \tag{1}$$

$$\Delta_{latitude} = \frac{r_{square} \cdot 180}{r_{earth} \cdot \pi} \qquad (2)$$

The corner points of the surrounding square are obtained by adding (resp. subtracting) the calculated latitude and longitude offsets.

Additionally, the Austrian states are represented in the single database as rectangles, defined by the two points with the minimum, or maximum, latitude and longitude. Each state, whose rectangle representation intersecting the square surrounding the current position of the user, is taken into account for the calculation of the resistance situation.

Access logic

The dataset retrieved from the database with these algorithms is then aggregated to a maximum of one record per antibiotic–bacterium pair, after which the final dataset is returned to the client. Calculation of the percentage of resistance is performed as described in formula (3). P corresponds to the percentage of resistance, R is the absolute amount of resistant isolates, same applies to S for susceptible, and I for intermediary resistant events.

$$P = \frac{R+I}{R+S+I} \cdot 100 \qquad (3)$$

Web service interface

The web service interface offers four different access methods via REST. Two of these methods deliver the names, abbreviations, and family structure of the bacteria, or antibiotics, respectively. The third method delivers the antibiotic resistance data for the surrounding area of the latitude and longitude passed over as a parameter. Finally, the last method is used by the clients to retrieve the data to display the flow of resistance in the past for the desired antibiotic–bacterium pair.

Client

Currently, two client applications were implemented to demonstrate the feasibility of communication with the web service interface, an Android-based client and a web-based client. Both versions are essentially the same, but for differences in the underlying implementation of location services.

In the Android-based client, the location of the user is determined using the spatial location services available through the Android API. Both coarse-grain and fine-grain location services can be used by the software. By default, the coarse location service is used to save on battery consumption.

In the web-based client, location retrieval is handled using two different mechanisms. For HTML5 capable web browsers, the location is retrieved using the JavaScript function navigator.geolocation.getCurrentPosition(). In case the release of the user's exact location is not allowed, or if a non-HTML5-capable web browser is used, the user is prompted to select the nearest ZIP code.

The Android client also supports data caching to improve performance and decrease bandwidth usage. Data retrieved via REST is being cached locally in a single SQLite database to ensure functionality of the client even without internet access. The six last full datasets retrieved from the web service interface are cached in the database. Additionally, by using Android's built-in preferences system, the time and location of the corresponding updates are stored.

Updates are triggered every time the local database is accessed. Additionally, an update trigger can be initiated by the user manually. Once the process started, the current location is retrieved first. The software then checks if the latitude and longitude of the new location is closer than 5 km to one of the stored last locations, and if the time since one of the last updates is not older than one week. If records are found that fulfill both criteria, they are used immediately without updating the database. In all other cases, the service initiates an update call to the web service, after which data and the user interface are updated.

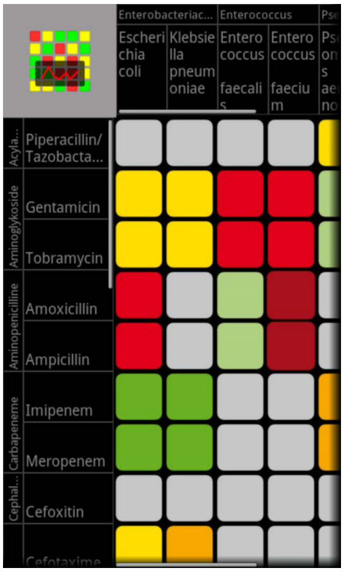

Figure 4 - Screenshot of the Android client

The graphical user interface consists mainly of two views. The first view, which is a tabular view as depicted in Figure 4, shows resistance data with the percentage of resistance represented by different colors. The colors are derived from the EARS-Net reports [1], and the corresponding ranges are explained in Figure 5.

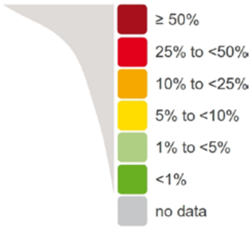

Figure 5 - The colors used in the GUI, with its corresponding percentage ranges

A second view, which is only available in Android clients, displays the flow of antibiotic resistance for the current location. To note, for the proper functioning of the second view, an active internet connection is necessary.

Results

We reported earlier on the prototype of this application [17]. The Android client, the web application, and the server application have now been implemented, tested, and released to the public on the European Antibiotic Awareness Day, November 18, 2012. The Android application can be found in the Google Play Store[2], and the web application is accessible at http://qre.q-re.org.

Evaluation

The usability of the software has been evaluated by a sample of twelve doctors – five pediatricians, four internists and three surgeons. In this evaluation, the users were first introduced to the software. Subsequently, three tasks had to be solved by the evaluators, while time needed to perform the tasks was recorded. In detail, the doctors had to use the Android application and respond to the study person the percentage of resistance for the asked antibiotic−germ combination. Lastly, a short questionnaire had to be filled out, asking for individual opinions about the software. The semi-quantitative polar questions were: "The graphical interface is clear," "The operation of the software is intuitive," "The software can be smoothly operated," "The size of the symbols is." Possible answers for questions 1-3 were "yes," "rather yes," "indifferent," "rather no," "no," and for question 4 "too big," "just perfect," "too small." Additionally, two open questions have been asked to the users: "What has been negative, what has been positive, while using the software?," and "Do you have any suggestions for improvement."

The measured time (min.: 2,98s, max.: 30s) was decreasing from the first to the last task in ten of the twelve test cases. This conforms with the observation that the users got more habituated to the software. Due to the small sample, no statistical analysis of the measured time was performed. The overall response of the evaluators was positive. The majority confirmed that the interface was intuitive and easy to understand. A major stumbling block of the software was the unusual sorting of the antibiotics and bacteria in the tabular view. However, all users commented that the impact on usability would be minor, as the sorting order is something they would get used to very quickly.

Data quality of the software was evaluated as well using a manual approach. No errors were found, and we assume that both the algorithms and the introduced data are correct and reliable.

Discussion

We developed a system to provide reliable antibiotic resistance information to healthcare providers – both timely and geographically selected. With qRe we demonstrated that with new technologies the current situation of the information distribution concerning antibiotic resistance can be improved. The current state of the software offers basic functionality, but more features need to be implemented in the future. The actuality of the data is of prime importance for the software to help to reduce morbidity, mortality, and prolonged hospital stays, and to minimize the economic burden. We are currently working on a software tool for the automatic processing of antibiotics susceptibility tests (antibiograms) to generate data usable by qRe closer to real-time. With the current approach to use the Austrian resistance report, the data is always at least one year old. With automatic processing of data, we aim to generate updated data weekly.

Within the usability walkthrough performed, the evaluators agreed that the software fits into the current clinical workflow of prescribing antibiotics and is a useful complementation. Importantly to note, at no time point is the expertise of the healthcare providers replaced – the software only supports the decisions of the doctors by providing crucial information.

According to Burke [18], the usage of systems that follow a clinician-centered approach for data-delivery offer several advantages, compared to the traditional approach with published national treatment guidelines or administrative policies. Our system does not only focus on the clinician, but also ensures that the data is always cutting-edge. Our software at the current point of development already offers all of these criteria enumerated by Burke.

Additionally, our system offers a cost-effective solution for resistance surveillance. According to Carlet et al. [19], due to the current financial crisis in Europe, expenses in the healthcare sector and for medical research are prone to decrease. They postulate that this upcoming monetary cut leads to a more rapid spreading of multi-resistant bacteria. With the information provided by qRe, the available resources could be utilized more aimed and cost for the healthcare system could be reduced.

To be sure on the exact clinical impact of the software with hard facts and hard numbers, a thorough clinical evaluation is necessary. Recent research in Pubmed (query: "antibiotic resistance" AND ("mobile health" OR "ehealth" OR "e-health" OR "m-health" OR "mHealth")) revealed no software projects with the same or a similar approach. A systematic review of the literature on systems intended for usage directly by the doctors that aim for reduction of antibiotic resistance would be a good idea for ongoing research.

The diameter of the area surrounding the user – 185 km – is a value based upon mathematical considerations. It needs to be investigated, if this value is too rough. The value can be changed programmatically easily, when evidence for need of modification arises. Importantly, the granularity of the data has to be improved to be able to reduce the diameter.

With the current size of the diameter, the preferred usage of the coarse location provider in Android, or the ZIP-code mechanism in the web client, is sufficient. This location sensing mechanism uses GSM/WCDMA triangulation or the location available from the WiFi network. The mean distance of a cell phone to the next cellular tower ranges between four kilometers in rural, and few hundred meters in urban areas, which corresponds to a maximum imprecision of roughly 2.2 percent inside the square for resistance calculation.

Within the presented application, at no time is patient data visible to the public nor accessible by the clients. In the future, when patient data will be used to calculate the aggregated resistance percentage for a location, security mechanisms will be implemented, partly physically, and partly by modifying the data transfer methods.

Various considerations have been made for the choices to use REST and JSON for the design of the web service interface. For one, both are communication standards and broadly used. Additionally, REST and JSON are very lightweight in means of bandwidth consumption. By implementation of an Android client and a web application, we demonstrate that the chosen

[2] https://play.google.com/store/apps/details?id=org.pmeng.qre

approach does not depend on special programming languages, specific external libraries, or client architecture. It is noteworthy that development on other target platforms is easily possible. It is also feasible to integrate the functionality of qRe into other software – such as hospital information systems.

Two main areas are of prime importance for the software: improving the granularity of the data, and evaluation of the software. Data import from clinical laboratories and hospitals is already in work. An important step done was the incorporation of a standardized nomenclature of pathogens and antibiotics using SNOMED-CT to map to the future data sources. In a side project, we are currently also developing a specialized version of qRe for usage in hospitals only, offering the most granular data possible – specifically calculated for every single ward. Evaluation of the software is planned, but it needs more preparation time, as well as human resources.

Although currently only available for Austria, the usage of qRe is not necessarily limited to this country. If we receive data from other countries with similar granularity, the software can instantly be used there. Unfortunately, the data presented in the European resistance surveillance report of the countries participating in the EARS-Net is only recorded per-country and therefore too rough for rational usage in qRe.

Conclusion

With qRe, we provide a tool that can be used to improve the clinical outcomes and antibiotic resistance rates by offering data on the current situation of antibiotic resistance to the treating doctors to improve empiric antibiotic therapy while microbiological test results are not yet available. We demonstrate that through the usage of modern technologies, data can be delivered to the hands of the users in an attractive and intuitive way.

References

[1] European Centre for Disease Prevention and Control (ECDC). Antimicrobial Resistance Surveillance in Europe 2010. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-NET), 2011. http://www.ecdc.europa.eu/en/publications/Publications/1111_SUR_AMR_data.pdf

[2] Lipman J, Boots R. A new paradigm for treating infections: "go hard and go home". Crit Care Resusc. 2009;11: 276-81.

[3] Norrby R, Powell M, Aronsson B, Monnet DL, Lutsar I, Bocsan IS, et al. The Bacterial Challenge: Time to React. ECDC/EMEA Joint Technical Report, Stockholm: European Centre for Disease Prevention and Control, 2009. http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.

[4] Roberts RR, Hota B, Ahmad I, Scott RD 2nd, Foster SD, Abbasi F, et al. Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: Implications for antibiotic stewardship. Clin Infect Dis. 2009; 49(8):1175-84.

[5] Thorburn AL. Paul Ehrlich: pioneer of chemotherapy and cure by arsenic (1854-1915). Brit J Ven Dis. 1983;59(6): 404–5.

[6] Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. Br J Exp Pathol. 1929;10(3):226-36.

[7] Domagk G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen. Dtsch Med Wochenschr. 1935;61(7):250-3.

[8] Fleming A. Penicillin. Nobel Lecture, December 11, 1945. http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.pdf.

[9] Spink WW and Ferris V. Quantitative action of penicillin inhibitor from penicillin-resistant strains of staphylococci. Science. 1945;102(2644):221-3.

[10] Barber M. Methicillin-resistant staphylococci. J Clin Pathol. 1961;14:385-93.

[11] Rogers BA, Aminzadeh Z, Hayashi Y, and Paterson DL. Country-to-country transfer of patients and the risk of multi-resistant bacterial infection. Clin Infect Dis. 2011;53(1):49-56.

[12] Niederman MS. Can guidelines for the treatment of respiratory infections lead to reduced rates of antibiotic resistance? Semin Respir Infect. 2001;16(3):203-9.

[13] Resistenzbericht Österreich AURES 2011. Wien: Bundesministerium für Gesundheit, 2012. http://bmg.gv.at/cms/home/attachments/7/4/0/CH1086/CMS1321350847355/aures2011_druckversion_20121114.pdf

[14] Bush K, Courvalin P, Dantas G, Davies J, Eisenstein B, Huovinen P, et al. Tackling antibiotic resistance. Nat Rev Microbiol. 2011; 9(12):894-6.

[15] AChartEngineGroup. Available from: https://code.google.com/p/achartengine/, accessed 10 December 2012.

[16] Github. Available from: https://github.com/nategood/httpful, accessed 10 December 2012.

[17] Meng P, Fehre K, Blacky A, De Bruin JS, and Adlassnig KP. QRe – A prototype for localized up-to-date antibiotic resistance information. In: Schreier G, Hayn D, Hörbst A, and Ammenwerth E, eds. Tagungsband der eHealth2012 – Health Informatics meets eHealth – von der Wissenschaft zur Anwendung und zurück, Mobile Health & Care – Gesundheitsvorsorge immer und überall, 10.–11. Mai 2012, Wien. Wien: Österreichische Computer Gesellschaft, 2012; p. 145-50.

[18] Burke JP. Rational approaches to combating resistance. Int J Clin Pract Suppl. 2002;(125):29-36; Discussion 37-9.

[19] Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D, and the Participants of the 3rd World Healthcare-Associated Infections Forum. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action. Antimicrob Resist Infect Control. 2012;1(1):11.

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