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Exploring new directions in disease surveillance for people with diabetes: Lessons learned and future plans

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Abstract

The main objective of this paper is to report our achievements in investigating new directions in the disease surveillance field. Targeting the vulnerable group of people with diabetes, we explored the possibility of early detection of infections using an electronic disease surveillance system (eDSS); this system could collect data for certain physiology indicators, e.g. blood glucose and white blood cell count, by incorporating specific point-of-care (POC) devices. We performed an analysis using the data of two large-scale clinical studies that involved people with type-1 and type-2 diabetes correspondingly; also, we conducted a feasibility study to examine the available POC technology. Even though the analyses provided us with some evidence for further investigation, the available technological solutions appeared to have significant limitations, mainly in terms of usability. Based on our first-hand findings we defined the next steps of our research, i.e. the data collection in a controlled study and the subsequent development of the eDSS. Furthermore, the lessons learned in our project could facilitate the related research for other vulnerable population groups.

Keywords:

Infection, Surveillance, Diabetes, Point-of-care systems

Introduction

The utilization of reliable and accurate means for the timely detection of infections may prevent contagious disease outbreaks or even pandemics. Biological threats still exist, such as the avian influenza that, according to World Health Organization (WHO) reports, has caused almost 60% deaths among the total number of cases reported from 2003 to September 2009 [1]. The recent influenza virus threat (H1N1 – swine flu), has alerted the health authorities and governments over the globe, and increased the pandemic fear. Such pathogens can spread over and affect the general population but, primarily, the most vulnerable individuals.

The 2005 International Health Regulations articulated surveillance as 'the systematic ongoing collection and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary' [2]. The existing disease surveillance systems collect data after the onset of the first symptoms and eliminate the incubation period[1] from their processes; thus, a significant delay from the actual onset of the infection threat occurs. Beyond that, they mainly target the general population and work less on vulnerable groups, such as people suffering from chronic diseases (diabetes, chronic heart failure etc.) and elderly; these groups are likely to be at heightened risk even in non-outbreak settings, such as in the case of cryptosporidiosis and other waterborne diseases [3]. Indicatively, the National Center for Chronic Disease Prevention and Health Promotion (Atlanta, GA, U.S.A.) has recently announced special guidelines for H1N1 flu and diabetes [4].

To address these needs we explored some new directions in the field of disease surveillance under the umbrella of an ongoing project, which investigates the automatic detection of infections; this project is supported by the Tromsø Telemedicine Laboratory (TTL). The core of our approach is the identification of an infection before people even know, through the onset of the symptoms, that they have been infected; specific physiology indicators and other personal health data could be used for that. Also, we are particularly interested in investigating this idea in people with diabetes and, furthermore, in exploring the possibility of building a dedicated electronic Disease Surveillance System (eDSS) for them.

The starting point for our study was based on the hypothesis that blood glucose (BG) and white blood cell (WBC) count could be the potential indicators for the early detection of infections in people with diabetes: BG may increase at a very early stage of infestation, immediately after the infection manifestation [5]; also, WBCs play a key role in the body's defense against infections and in most of the cases their count is increased at the early stages of incubation period [6]. Hypothetically, an eDSS could collect the appropriate data for these parameters incorporating monitoring devices and, subsequently, process this input in combination with other personal data; early indications for infection threats, i.e. quite before the onset of the symptoms, could be the system output.

[1] The subjects have no symptoms during the incubation period but have already been infected and become contagious.

In order to investigate these assumptions we defined the specific study objectives and attempted to meet them following a certain plan, which is presented below. This plan has been implemented over a period of 3 years (March 2007 – March 2010) and most of our findings have been already published (references are provided accordingly). The current paper attempts to give an overview of our efforts to explore novel approaches in the disease surveillance of people with diabetes, the main tasks that we have accomplished and the lessons that we have learned. Based on our experience we further discuss the potential future directions in the field.

Materials and Methods

In the beginning of our study the potential use of the suggested physiology indicators for disease surveillance purposes was investigated. This was highly prioritized considering that there are no solid findings for the BG elevation during the incubation period as well as for the exact timing of this alteration. The technological aspects had to be examined as well; for example, even though there are various BG monitors available that could be used as part of the eDSS, it is questionable whether similar devices for WBC count can be found in the market.

External Data Sources

In order to study the physiology response to infections for people with diabetes, we should either run a clinical study to collect the appropriate data for thorough analysis and model development or use external data sources to further investigate our ideas. The latter option was explored considering that diabetes is a condition that has been studied extensively in randomized controlled trials (RCTs); thus, we assumed that the huge data collection in a RCT might contain information both for infection incidents and continuous blood glucose monitoring. Subsequently, we gained access to the data collection of two RCTs:

- *Diabetes Control and Complications Trial (DCCT)*. DCCT was a full-scale multi-centre clinical trial, which recruited 1441 people with type-1 diabetes and was conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [7]. The participants were randomized into two arms (conventional vs. intensive therapy arm) and data was collected every three months, i.e. during the follow-up visit. Among the numerous parameters of this study, glycosylated haemoglobin (HBA_{1c}) and disease-related parameters were further assessed. Adult males and females were studied separately. The null hypothesis that the diseased HBA_{1c} values were equal to the non-diseased values was tested for both sexes and arms [8].
- *Informatics for Diabetes Education and Telemedicine (IDEATel)*. The population of IDEATel study consisted of 1665 people with type-2 diabetes who were enrolled through the primary care practices in the New York City [9]. With the enrolment hub at the NewYork-Presbyterian Hospital/Columbia University Medical Centre (NYP/CUMC), the study participants either received a set of telemedicine services (intervention group) or remained under the usual care of their primary care providers (control group). The intervention group measured and uploaded their BG values into the NYP/CUMC Clinical Information System Repository and used the inpatient and outpatient health services in the same hospital as well. Consequently, it was possible to access and analyze inpatient and outpatient healthcare data (related to infection incidents) as well as glycemic control data (BG and time of measurement) for a certain number of people with diabetes.

Electronic Disease Surveillance System – Feasibility study

In order to incorporate a set of physiology indicators into a disease surveillance system and support patients' monitoring, it should be primarily checked whether the existing technology could support the development of this system. For example, our approach to use WBC count required the existence of a point-of-care (POC) device that could accurately measure this parameter at the user's location and not at the healthcare facility; even though such a device existed, it had to be examined whether it fitted our purposes. Furthermore, the cost-effect relationship could not be otherwise evaluated but in the context of a feasibility study. This study was performed in the city of Tromsø, using four POC devices that could monitor temperature, blood pressure, blood glucose level and certain hematological variables. It should be also mentioned that we selected validated and approved devices, which were shown to produce results equivalent to laboratory equipment [10].

Results

Table 1 shows the results of the DCCT data processing. Paired comparisons of diseased HBA_{1c} values (during the infection incident) vs. average HBA_{1c} values (before or after the infection incident) were performed using t-test statistics; the values for the intensively treated females were normalized to correct the skew and normalize the distribution. In almost all cases (excluding the intensively treated females case) HBA_{1c} values rose after infection despite the tight BG control held in the DCCT study, and returned to the non-diseased levels when the initial infection cause ceased; the complete analysis and results have already been published and presented at MIE 2008 conference (Göteborg, Sweden) [8].

Regarding the processing of IDEATel data we could briefly mention that glycemic control (blood glucose values and time of measurement) was shown to be altered when a person with type-2 diabetes was exposed to a pathogen. The complete analysis and results are fully presented in another paper, which is still under review; thus, it is not possible to discuss the findings of this work here.

Table 1- The results of testing the null hypothesis using the DCCT data; the mean paired difference (Mean), the standard deviation of the difference (SDev), the 95% confidence interval of the difference (95% CI) and the p-values of the t-test statistics [8].

		HBA_{1c}	Mean	SDev	95% CI		P
Conventional Arm	Female	Diseased – Average Before	0.288	0.719	0.163	0.412	<0.001
		Diseased – Average After	0.273	0.851	0.126	0.421	<0.001
	Male	Diseased – Average Before	0.267	0.722	0.151	0.384	<0.001
		Diseased – Average After	0.225	0.681	0.115	0.335	<0.001
Intensive Arm	Female *	Diseased – Average Before	0.007	0.081	-0.009	0.023	0.342
		Diseased – Average After	0.016	0.076	0.001	0.031	0.021
	Male	Diseased – Average Before	0.169	0.450	0.077	0.261	<0.001
		Diseased – Average After	0.115	0.563	0.001	0.230	0.049

* normalized values

The findings of the feasibility study suggested that it is not possible to use the available devices for our purposes, even if they are really promising. Particularly, the POC device measuring certain hematological variables appeared to be the most problematic due to the repeated failures during the feasibility study; moreover, the thermometer accuracy was questioned as well as the blood pressure measurements. The blood glucose monitor operation was quite acceptable; however, it caused dissatisfaction among the users because it required manual quality control. An overall limitation factor was the excessive time needed for the measurements (prepare consumables, perform tests, wait for results), with the average time for performing all measurements being 20 minutes. It should be also mentioned that the total cost of the four devices per subject was approximately $5,200, while the appropriate consumable costs were approximately $350 per subject for performing daily measurements in a one month period. These costs were further split per subject, device and daily measurement (Table 2).

Table 2- Equipment costs; all prices are calculated in USD (no taxes included) [10]

Devices	Price	Consumables*	Accessories**
Haematologic Analyzer	4,000.00	8.00	500.00
Blood Glucose Monitor	400.00	3.50	40.00
Blood pressure Monitor	167.00	N/A	25.00
Thermometer	55.00	0.40	N/A

*N/A: Not Applicable, * Cost per measurement, ** Cables, software, printer*

Specific details for the devices (vendors, trade names etc.) as well as the complete results of the feasibility study can be found in the manuscript that has been already published [10].

Discussion

The main scope of this project was to work on new directions in the disease surveillance field targeting the early detection of infections. Particularly, in the context of the existing disease surveillance systems that have been studying mainly the general population [11-13], our disease surveillance approach for vulnerable population groups with special physical needs is novel. For completeness, we should refer to Mohtashemi et al. [14] who described a system for the early (still after the onset of the symptoms) detection of tuberculosis outbreaks among the San Francisco homeless population; however, homeless individuals should be considered vulnerable mainly due to social and not physiology reasons. As a first approach to our idea we considered that diabetes could be the ideal research area since:

- People with diabetes are highly motivated to monitor their infection status;
- Diabetes is a condition that has been extensively studied before and, thus, we expected to:
  - get access to external data sources with numerous variables and complete data,
  - attract the interest of other researchers in the field, and
  - disseminate our ideas rapidly;
- The diabetes monitoring technology has advanced more than the technology in other chronic conditions;
- Our team has years of experience in the field [15-16].

One of our primary mid-term goals was to build the theoretical background of our approach. Thus, it was necessary to investigate our claims regarding the early detection of infections and, mainly, the possibility of using certain physiology indicators for accomplishing this task. Normally, a dedicated clinical study is required to fulfill this demanding task. However, it is often risky to allocate a considerable amount of resources before examining the solidity of a novel idea. In this context, the solution of getting access to external data sources was the most appropriate.

Subsequently, we have managed to access the archives of two large-scale RCTs, the DCCT and the IDEATel studies that involved people with type-1 and type-2 diabetes correspondingly [7, 9]. This allowed not only the processing of two large data sets but also the investigation of our approach in both types of diabetes condition. The idea of blood glucose elevation and the alteration of glycemic control during the incubation period were supported by the results of the analyses in both cases [8]. It was not possible though to investigate either the contribution of other parameters (e.g. WBC count, insulin intake) or the detailed physiology mechanisms.

Unambiguously, the methodology that was followed in the first phase of our project had some limitations. First of all, both studies were not specific for our purposes and, thus, it could be argued that the results are inadequate to base any further research. Nevertheless, it should be mentioned that our main intention was to seek for evidence and reserve our resources for a dedicated clinical study. The same strategy was followed in the feasibility study where approved devices were tested in a low-budget schema.

Additionally, the study of devices that measure symptomatic (i.e. temperature) and non-infection-related (i.e. blood pressure) parameters could be considered as irrelevant to our purposes. However, our disease surveillance approach should be viewed as an effort towards personalized medicine; otherwise users might not see the potential benefits and be skeptical on such systems. Subsequently, the examination of other 'pieces of the puzzle' is important; this is further discussed below.

Considering that the end point of our project was the development of an eDSS that would incorporate specific devices for the continuous monitoring of physiology parameters, it was important to test the available technology. As aforementioned this was the reason for conducting the feasibility study, which showed that technology is still immature both in terms of accuracy and usability [10]. On the other hand, a successful eDSS requires the collection of accurate data in order to fulfill its purposes. Consequently, the idea of performing continuous monitoring for multiple physiology indicators should be abandoned, especially in the case of diabetes where only blood glucose can be measured in a reliable manner.

Based on our up to date progress, we are able to define our next step that is the conduction of a dedicated clinical study to collect the appropriate data. Taking into account the results of the feasibility study and, particularly, the high cost of the POC equipment, the main characteristics of the proposed study should mainly include:

- A cohort of 100 people with diabetes, either type-1 or type-2;
- Continuous data collection (BG values, insulin, physical activity, food intake, infection-related data, temperature, diagnosis of infections);
- A study period of one year to be able to accurately define the participants' profile and maximize the possibility of observing infection incidents.

The tools that should be used in this study are also important; the selection should be based both on the conclusions drawn from the feasibility study and on the characteristics of the existing equipment solutions. Keeping in mind that users' involvement is critical for the success of any system (before, during and after system development), the following criteria should be considered:

- A simple device for continuous BG monitoring is definitely more usable and should be part of the clinical study; however, more accurate devices should be used as part of the final eDSS. The BG monitor that was used in the feasibility study was comparable to laboratory equipment in terms of accuracy and should be examined prior to building the final product [17];
- A mobile device carrying a dedicated software for data input should be used, like the one that has been developed by Arsand et al [16];
- The secure communication infrastructure should support the data collection in a central repository for further processing;
- An important component of the eDSS is the mathematical model that will process the incoming data, send feedback to people with diabetes/physicians and trigger alarms if necessary. The potential modeling approach should be examined before the initiation of the clinical study and then adjust its parameters at predefined time points.

Our approach could also empower the development of personalized health care systems that involve portable devices, sensors and wireless networks [18]. In this context a personalized eDSS could adjust its parameters to support each subject, e.g. by alerting them for an infection threat in a region. Systems of the kind could also interoperate with Electronic Health Record (EHR) systems and provide health care professionals with adequate information to take the necessary actions and support the information sharing between vulnerable individuals. For example, a threat raised by monitoring one person with diabetes could be used in evaluating the relevant threats for the community of people with diabetes living in the same area. This would also consist an excellent opportunity to build a social network with special interest and a huge impact on the infection control.

The project objectives were decided upon but not limited to the initial selection of people with diabetes; our approach is broader and we aim to study other vulnerable populations, too. Among our intentions was to form the basis for a further exploitation of our findings in the general population or otherwise healthy groups that are very interested in getting early

alerts for their condition, such high-competition athletes. The related research might initially target individual surveillance and then move up to the population level (bottom-up approach). Beyond the study that is required to determine the exact physiology alterations after infection, the role of medical informatics regarding the eDSS conceptual, organizational, architectural and technological aspects is crucial.

Conclusion

The development of strategies for the detection of infections before the onset of the symptoms is critical, especially given the limitations of the current disease surveillance systems that are based only on people's awareness of their health status. This is particularly important for vulnerable population groups, such as people with diabetes, that their health status is altered significantly when they are infected. Here, we highlighted the lessons learned in our project, the difficulties of this approach as well as our future plans. We hope that this work will provoke the thoughts for new directions within the disease surveillance field.

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