A statistics-based approach of contextualization for Adverse Drug Events detection and prevention

Emmanuel CHAZARD [a,1], Stéphanie BERNONVILLE [a], Grégoire FICHEUR [a], Régis BEUSCART [a]

[a] *Public Health Department, CHU Lille; UDSL EA 2694; Univ Lille Nord de France; F-59000 Lille, France.*

Abstract. Several papers propose to take contexts into account for adverse drug events (ADE) detection and prevention, notably to decrease over-alerting of clinical decision support systems (CDSS). However, no statistical argument has been published till now. This works demonstrates, based on statistical analysis, that contextualization is necessary for ADE detection and prevention by 3 steps. A database of 115,447 inpatients stays from 6 hospitals, and 236 ADE detection rules are used. Step 1: the patients differ significantly between and within hospitals, regarding their medical background, their medication and several outcomes. Step 2: The estimated ADE rates vary between and within hospitals. Step 3: even when comparable conditions are present, the probability of ADE occurrence may differ between and within hospitals. Those 3 steps demonstrate that contextualization is necessary, and pave the way for a statistics-based method to contextualize ADE prevention (CDSS) and ADE detection tools.

Keywords. Adverse Drug Events, Clinical Decision Support System, Data Mining, Contextualization.

Introduction

Adverse Drug Events (ADEs) endanger the patients and instigate significant extra hospital costs [1]. They are an important subject of research, for both retrospective detection and prospective detection. For prospective detection, Clinical Decision Support Systems (CDSS) are widely used to improve patients' safety [2]. However, the over-alerting is an important issue in both fields and especially for the current CDSS. The too numerous and inappropriate alerts interrupt the clinicians' workflow. Consequently, events with potentially serious consequences can be disregarded [3].

A solution to improve those tools is to take into account the context [4]. The notion of context can be defined as "any information that can be used to characterize the situation of an entity" [5]. The context can be structured into three categories [6]: the user, the user's environment, and the user's task. Several approaches are proposed by researchers to design CDSS by considering contextualization, such as ontologies [7] or contextualized-CDSS [8]. However, even if many works deal with *how* to implement

[1] Corresponding Author: Emmanuel Chazard ; Clinique de Santé Publique, CHRU de Lille, 154 rue Yersin, 59037 Lille Cedex ; emmanuel.chazard@univ-lille2.fr

contextualization, it seems that no work has been published to demonstrate empirically *that* contextualization is necessary. The objective of this work is to demonstrate, based on statistical comparisons, that contextualization is necessary for ADE detection and ADE prevention. In this work, the contextualization will be studied in relation with the location (hospitals and medical departments).

1. Material and Methods

Anonymized data related to inpatients are extracted from six hospitals' electronic health records (EHRs) according to a common data model [9]. 115,447 records are extracted, allowing for a 4-year follow up (from 2007 to 2010). From those records, two sets of data are used as described in Table 1. The main dataset includes 54,803 inpatient stays from 6 hospitals having a length of stay equal or greater than 2 days, as this minimal duration is required for the retrospective ADE detection method. It will be used to study hospital-wise contextualization. A subset (one of the hospitals) is defined and includes 25,381 inpatient stays. It will be used to study department-wise contextualization. Those data have been routinely collected, and include administrative information (e.g. age, gender, etc.), diagnoses (ICD10 codes), medical procedures, drugs administered to the patient (ATC codes), and laboratory results.

Table 1. Description of the datasets.

Main dataset: 6 hospitals		
Hospital	**Activity**	**Nb stays**
Bu	Endocrinology	7,271
Dk1	General hospital	16,001
Dk2	General hospital	1,816
Fr1	General hospital	28,562
Fr2	Geriatrics	1,022
Fr3	Geriatrics & Cardiology	131
	Total	54,803

Subset: 6 departments from hospital Fr1	
Medical department	**Nb of stays**
Cardiology	6,186
Geriatrics	952
Gynecology Obstetrics	2,545
Internal medicine	4,663
Pneumology	4,014
Surgery	7,021
Total	25,381

A set of 236 ADE detection rules has been obtained in a previous work by data mining of EHRs and has been validated by a team of medical experts [10]. Those rules enable to automatically detect ADEs in past inpatient stays. Each rule is made up of a set of conditions that can lead to an outcome. The confidence of the rule is the probability that the outcome occurs once the conditions are met, while respecting temporal constraints. An example is provided in equations 1&2 (where NSAI stands for non steroidal anti-inflammatory drug, CRI for chronic renal insufficiency, and K^+ for potassium). The precision (positive predictive value) of the automated ADE detection method has been evaluated by an expert review and is available in Table 2 [10].

$$R_{182}: CRI \cap NSAI \cap no\ K^+\ sparing\ diuretic \rightarrow hyperkalemia \quad (1)$$

$$Confidence_{R182} = P(\ hyperkalemia\ /\ CRI \cap NSAI \cap no\ K^+\ sparing\ diuretic) \quad (2)$$

Table 2. Precision of the ADE detection rules for the two studied outcomes.

Outcome	Trigger	Comments	Precision
Hyperkalemia	Laboratory results: K^+>5.3mmol/l	Risk of lethal heart rhythm trouble	53.5%
High INR	Laboratory results: INR≥5	Risk of hemorrhage	55.6%
Other outcomes	*Laboratory results or drugs*	*Heterogeneous situations*	*38.3%*

Three steps are followed to demonstrate the need for contextualization in ADE detection and prevention.

The *step 1* consists in a statistical comparison of the inpatients stays. The patients are compared regarding general characteristics (age, gender and length of stay), the occurrence of two outcomes (high INR and hyperkalemia), the presence of chronic diseases (renal and hepatic insufficiency identified by ICD10 codes), and the administration of some drugs (vitamin K antagonists -VKA- and diuretics).

Then, the 236 detection rules are applied to those stays to automatically detect ADEs [10]. The detected cases have an outcome and compatible causes, but only some of those cases are real ADEs. The precision rates of the ADE detection provided in Table 2 are then applied to estimate the number and proportion of ADE cases. The *step 2* consists in comparing those proportions with respect to the location of the stays. We interest here on two outcomes: hyperkalemia and high INR.

Finally, as the outcomes are traceable in the data, it is possible to estimate the confidence of the rules in each location. In *step 3*, for each rule, a statistical test compares the proportion of outcome with respect to the location. The main result is the number of rules where the statistical test is significant, using a 5% threshold.

All the comparisons are performed between the six hospitals (hospital-wise contextualization) and then between the six departments within hospital Fr1, a French general hospital (department-wise contextualization). The statistical comparisons are performed using bilateral statistical tests. Proportions are compared using Chi² tests or Fisher's exact tests. Quantitative variables are compared using analysis of variance.

2. Results

2.1. Step 1: comparison of the stays

Table 3. Comparison of the inpatients stays between hospitals (***: $p<2.2E^{-16}$)

	Hospital :	**Bu**	**Dk1**	**Dk2**	**Fr1**	**Fr2**	**Fr3**	*p value*
General characteristics	**Age (years)**	49.8	64.5	58.9	60.2	75.1	79.4	***
	Length of stay (days)	7.01	6.81	8.57	8.01	13.98	53.92	***
	Men	26.8%	41.8%	43. 7%	40.8%	42.9%	20.6%	***
Abnormal lab results	**High INR**	0.03%	0.69%	0.28%	2.46%	3.33%	0.76%	***
	Hyperkalemia	7.89%	1.47%	1.93%	5.43%	18.1%	3.82%	***
Chronic diseases	**Renal insuf.**	4.74%	2.41%	1.21%	2.02%	11.2%	3.05%	***
	Hepatic insuf.	0.39%	0.99%	0.55%	4.90%	4.89%	1.53%	***
Administered drugs	**VKA**	1.88%	2.96%	2.15%	8.34%	1.86%	13.0%	***
	Diuretics	19.2%	26. 8%	11.4%	23.3%	38.5%	27.5%	***

Table 4. Comparison of the inpatients stays within the hospital Fr1 (***: $p<2.2E^{-16}$)

	Department:	**Cardio**	**Geriat.**	**Gyn. Obs.**	**Int. med.**	**Pneu.**	**Surg.**	*p value*
General characteristics	**Age (years)**	67.6	82.4	28.0	69.7	67.8	57.6	***
	Length of stay (days)	8.19	11.6	6.56	10.5	11.8	8.42	***
	Men	42.8%	28.8%	0.00%	39.4%	63.2%	37.8%	***
Abnormal lab results	**High INR**	4.04%	3.36%	0.00%	3.80%	4.36%	1.14%	***
	Hyperkalemia	8.55%	9.66%	0.04%	7.87%	6.75%	4.33%	***
Chronic diseases	**Renal insufficiency**	3.04%	4.83%	0.04%	4.20%	2.04%	0.60%	***
	Hepatic insufficiency	13.7%	2.42%	0.04%	6.26%	2.34%	1.47%	***
Administered drugs	**VKA**	15.5%	12.9%	0.00%	13.7%	14.8%	1.67%	***
	Diuretics	41.1%	30.1%	0.00%	31.6%	35.4%	12.9%	***

The results of the comparison of the inpatients stays between the hospitals are displayed in **Erreur ! Source du renvoi introuvable.**. Then, the results of the comparison of the stays between the medical departments of the hospital Fr1 are displayed in **Erreur ! Source du renvoi introuvable.**. In both tables, all the statistical tests are significant, showing that the patients differ between hospitals and between the medical departments of a hospital.

2.2. Step 2: comparison of the estimated ADE rates

The estimated ADE rates are presented in Table 5 with respect to the hospitals. Within hospital Fr1, the estimated ADE rates are presented in Table 6. The proportions vary significantly between hospitals, even between general hospitals (Dk1, Dk2, Fr1). The proportions also vary significantly between the medical departments of a hospital. In this sample, the estimated ADE rate is null in the Gynecology and Obstetrics department, whatever the outcome.

Table 5. Comparison of the estimated ADE rate between hospitals (***: $p<2.2\text{E}^{-16}$).

Hospital :	**Bu**	**Dk1**	**Dk2**	**Fr1**	**Fr2**	**Fr3**	*p value*
Hyperkalemia	0.03%	0.25%	0.47%	0.89%	5.65%	1.63%	***
High INR	0.00%	0.06%	0.00%	0.43%	0.00%	0.42%	***

Table 6. Comparison of the estimated ADE rate within the hospital Fr1 (***: $p<2.2\text{E}^{-16}$).

Department:	**Cardio.**	**Geriat.**	**Gyn. Obs.**	**Int. Med.**	**Pneu.**	**Surg.**	*p value*
Hyperkalemia	1.42%	1.82%	0.00%	1.43%	1.48%	0.48%	***
High INR	0.76%	0.00%	0.00%	0.90%	1.17%	0.08%	***

2.3. Step 3: comparison of the confidences of the ADE detection rules

For each of the 236 ADE detection rules, the confidence is computed. Equations 1 & 2 show the example of the rule R_{182} and its confidence. Its confidence is computed and compared between hospitals (Table 7) and between medical departments (Table 8). 171 of the 236 ADE detection rules are applicable, as at least 1 stay matches the conditions of the rule. Within those 171 rules, the confidences are significantly different between hospitals for 39 rules (23% of the rules, cf. Table 9). The confidences are significantly different within the hospital Fr1 for 32 rules (19% of the rules, cf. Table 10). Many ADE detection rules seem to be sensible to the context in relation with the hospital or the medical department, but it is not systematic.

Table 7. Example: comparison of the estimated confidence of the rule R_{182}, between hospitals.

Hospital :	**Bu**	**Dk1**	**Dk2**	**Fr1**	**Fr2**	**Fr3**	*p value*
Confidence_{R182}	0/56=0%	3/174=1.7%	3/34=8.8%	68/703=9.7%	5/43=11.6%	0/2=0%	*0.0061*

Table 8. Example: comparison of the estimated confidence of the rule R_{182} within the Fr1 Hospital.

Department:	**Cardio.**	**Geriat.**	**GynObs**	**Int. Med.**	**Pneu.**	**Surg.**	*p value*
Confidence_{R182}	27/255=10.6%	6/43=14%	0/0	23/253=9.1%	15/115=13%	3/47=6.4%	*0.818*

Table 9. Significance of the comparison of the confidences of 171 rules between the 6 hospitals.

Outcome	**# rules**	**# rules with p<5%**
Hyperkalemia	42	0 (0.0%)
High INR	47	18 (38.3%)
Other outcomes	82	21 (25.6%)

Table 10. Significance of the comparison of the confidences of 171 rules within the hospital Fr1.

Outcome	**# rules**	**# rules with p<5%**
Hyperkalemia	42	1 (2.4%)
High INR	47	4 (8.5%)
Other outcomes	82	27 (32.9%)

All rules	**171**	**39**	**(22.8%)**	**All rules**	**171**	**32**	**(18.7%)**

3. Discussion & conclusion

In this work we point up statistical evidences to support contextualization for ADE detection or prevention. We compare several hospitals and medical departments by 3 steps. Step 1 shows that the patients are different. Step 2 shows that the ADE occurrence rates are different. Step 3 shows that, even when comparable conditions are met, the probabilities of occurrence of some outcomes are different. According to those statistical evidences, it seems necessary to take into account location-related contexts while designing ADE detection or prevention tools.

This study only explores location-related contexts, and not user-related or task-related contexts, but similar approaches could also be used in those fields.

The advantage of this approach is that the contextualized statistics that are computed, especially the confidences of the rules (step 3), can be used in their turn to add “intelligent” behaviors in ADE detection or prevention tools. This statistics-based approach is already implemented in a Contextualized-CDSS [8] and in a tool for retrospective ADE detection called *ADE Scorecards* [11, 12]. In both applications, the statistical parameters for the current location are used to dynamically filter alerts and to decrease over-alerting based on environment context. Additional statistics are also used in both tools to provide healthcare professionals with contextualized information.

Acknowledgements: The research leading to these results has received funding from the European Community’s Seventh Framework Program (FP7/2007-2013) under Grant Agreement n°216130 – the PSIP project.

References

[1] Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. JAMIA. 2003; 10: 115-28.
[2] Garg AX, Adhikari NK, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA. 2005; 293: 1223-38.
[3] Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. JAMIA. 2006; 13: 138-47.
[4] Bricon-Souf N, Newman CR. Context-awareness in health care: A review. IJMI. 2007; 76: 2-12.
[5] Dey AK. Understanding and using context. PUCJ. 1999; 5(1):4-7.
[6] Schmidt A, Beigl M, Gellersen HW. There is more to Context than Location. Computers & Graphics Journal. 1999; 23: 893-902.
[7] Yao W, Kumar A. CONFlexFlow: Integrating Flexible Clinical Pathways into Clinical Decision Support Systems using Context and Rules. Decision Support Systems (DSS), Special Issue on Healthcare modeling. 2012, accepted for publication.
[8] Niès J, Koutkias V, Kilintzis V, Guillot B, Maglaveras N, Gliese Perdersen H, Berg A, Skjoet P. Information Contextualisation in Decision Support Modules for Adverse Drug Event Prevention. Stud Health Technol Inform. 2011; 166: 95-102.
[9] Chazard E, Merlin B, Ficheur G, Sarfati JC; PSIP Consortium, Beuscart R. Detection of adverse drug events: proposal of a data model. Stud Health Technol Inform. 2009;148:63-74.
[10] Chazard E, Ficheur G, Bernonville S, Luyckx M, Beuscart R. Data mining to generate adverse drug events detection rules. IEEE Trans Inf Technol Biomed. 2011 Nov;15(6):823-30.
[11] Chazard E, Baceanu A, Ferret L, Ficheur G. The ADE Scorecards: a tool for Adverse Drug Event detection in Electronic Health Records. Stud Health Technol Inform. 2011.

[12] Online demonstration: http://psip.univ-lille2.fr/prototypes/public/ (last accessed 17 April 2012)