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A systematic review of drug allergy alert systems

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ABSTRACT

Background and objective: Drug allergy alert systems (DAAS), have been considered an effective strategy to reduce preventable adverse drug events (ADEs), improving patient's safety. To date, no review has been conducted analyzing characteristics of DAAS in the hospital setting. Therefore, the aim of this study is to identify, describe and summarize the DAAS used in hospitals. The secondary objectives are to analyse drug allergy alerts (DAA) characteristics, the override rate (OvR) and the clinical consequences of alert overrides.
Methods: Searches were conducted in Medline and Cochrane Library to identify studies describing DAAS. Systems characteristics, generated alerts, DAA, OvR, and its clinical consequences were extracted and analyzed.
Results: Twenty-eight articles were included in the review. Seventeen different electronic DAAS were identified, of which 53% were commercially available. Systems differed in drug allergy information and rules for generating alerts. DAA were generally interruptive, triggered by non-exact match at drug prescribing and when ignored, an override reason was mandatory. The OvR ranged from 43.7% to 97%. The main override reason given by providers was that 'patient had previously tolerated or had taken the drug without allergic reaction'. Clinical consequences of overriding DAA were only analyzed in four studies, with an ADE incidence between 0% and 6%.
Conclusions: Different DAAS are used in hospitals with some degree of heterogeneity. Accurate and updated drug allergy information is important to generate only high value alerts. A regular review of DAAS and a standardization of alert rules, alert information and override reasons are necessary to optimize systems. Future studies should evaluate the impact of the DAAS aspects on preventing ADEs.

1. Introduction

Approximately 10% of all patients in developed countries are harmed by adverse events during their hospitalization care [1]. Adverse drug events (ADEs), which are injuries resulting from pharmacological treatments, are the most frequent type of adverse events in hospitalized patients and have been associated with additional healthcare costs, and increased hospital length of stay and mortality [2–6].

Between 20 and 30% of all ADEs are considered to be preventable and a large percentage (56%) occurs at the time the drug is ordered; for example, when a drug is prescribed to a patient with a documented drug allergy to this particular drug [3,7,8]. In fact, Leape et al. identified that 8% of the errors were related to this issue, being therefore considered preventable [2].

The implementation of computerized physician order entry (CPOE) with clinical decision support (CDS) in health care systems have been identified as an effective way to prevent medical errors and to intercept and eliminate preventable ADEs, improving patient's safety and quality of care, which ultimately lead to reducing length of stay and costs [5,8–21].

The electronic drug allergy alert systems (DAAS) refer to a system that generates drug allergy alerts (DAA) in order to assist providers/users when ordering/signing/prescribing/administering a drug to a patient with a previously recorded theoretical allergy. They have been considered a basic component of CDS and one of the most valuable tools for patient safety [14,17]. A 56% reduction in medication errors secondary to known allergies has been reported after their implementation [5].

Abbreviations: ADE, adverse drug event; CDS, clinical decision support; CPOE, computerized physician order entry (CPOE); DAA, drug allergy alert; DAAS, drug allergy alert system; OvR, override rate.

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During the medication ordering or administration processes, drugs can be checked against the patient's allergy list, and alerts are generated to warn physicians of a possible allergy to the ordered drug. Providers can either accept the warning and not order the medication, or ignore (override) the warning and continue ordering. In some systems, an explanation for continuing the order, known as an 'override reason', must be entered to justify practitioner's actions [9,11,16,22].

However, while designed to be helpful, providers are exposed to a high number of irrelevant and unnecessary alerts [12,23–25]. This effect, commonly referred as 'alert fatigue', can cause clinicians to ignore both unimportant and important warnings, leading to patient harm, increasing risk of ADEs, or other unintended consequences [8,15,16,26].

Therefore, having an effective and well-designed order entry system that generates only important, accurate and high predictive value alerts is necessary to achieve a balance between appropriate alerting and over-alerting.

Different DAAS have been described in literature, and analyzing their designs, pros and cons, and their potential implications in healthcare professionals' performance and in quality of healthcare is of high interest. Analyzing these issues will help organizations to identify essential characteristics that a DAAS should have and/or aspects that need to be optimized in order to promote patient safety.

To our knowledge, to date no review has been done summarizing the information related to electronic DAAS in the hospital setting. The review by Van der Linden et al. identified systems that could prevent unwanted re-prescription of drugs that caused ADEs; however, it was focused both in electronic and non-electronic systems, but not in drug allergies [27]. Légat et al. carried out an overview of CDS for DAA. However, a detailed description of identified DAAS and alert overrides was not provided, and it was not focused on hospital setting [28]. Therefore, there is a need to complete the review by Légat et al. with updated evidence, and to analyze additional and relevant information about DAAS.

The main objective was to identify, describe and summarize the evidence regarding the different types of electronic DAAS in the hospital setting.

The secondary objectives consisted in analyzing characteristics of the generated DAA (accepted and ignored), DAA override rate (OvR) and its clinical consequences.

2. Material and methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [29].

2.1. Study inclusion criteria

Observational, quasi-experimental and experimental studies, as well as descriptive papers describing electronic DAAS were included.

In addition, the studies must analyze or describe at least one of the following aspects of DAAS in order to be considered for inclusion: allergy records, rule bases, alert information and/or actions after an alert.

Exclusion criteria were the following:

(a) Studies not describing electronic DAAS and/or describing only other type of alert systems. Studies analyzing electronic DAAS that consider both drug allergies and other aspects, such as drug interactions, dose adjustments, etc. were included only if the study provided a specific description on the electronic DAAS.
(b) Studies describing a DAAS that was not implemented in clinical practice.
(c) Studies not carried out in the hospital setting. Studies carried out both in the inpatient and outpatient setting were included only if they provided specific or separate information corresponding to inpatient setting. Only information related to the inpatient setting was considered.
(d) Studies not including the term 'allerg*' or 'hypersensitivit*' in their title or abstract.
(e) Animal studies or non-human studies.
(f) Study design: reviews, protocols, letters to editor, commentaries, answers, abstracts, news, and patients' case reports and case series that did not describe DAAS. Studies based on interviews or surveys, and studies analyzing pharmacovigilance databases were excluded.
(g) Studies published in a language other than Spanish, English or French.

References of the reviews were examined to identify additional studies that could potentially meet the inclusion criteria.

Additionally, articles referring to a previously identified DAAS and providing additional information regarding any of the predefined outcomes were also included.

2.2. Search methods

The search was conducted in two stages. In a first stage, the review by Légat et al. was taken as reference, as it analyzed evidence on drug allergy checking published up to February 2016 [28]. The articles included in this review were screened individually according to the inclusion and exclusion criteria defined in our protocol. The search strategy used by Légat et al. was completed with searches in Medline and Cochrane Library using the term 'hypersensitivity' and considering articles in Spanish and French (Appendix A).

In a second stage, Medline and Cochrane Library were searched to identify studies published from March 2016 to March 2020 using a combination of keywords and controlled vocabulary. The terms 'drug' and 'allerg*' or 'hypersensitivit*' were combined with 'Computerized Physician Order Entry' or 'Clinical Decision Support System' or 'alert', and other synonyms.

Additional identified references of interest that included information relevant to this review were included. The review was restricted to studies published in English, Spanish or French.

2.3. Study selection

Duplicated references were excluded. Two reviewers (ML and LL) independently screened titles and abstracts of all the identified references to assess for eligibility. References were classified as 'yes', 'no' or 'maybe'. The full texts of all the references classified as 'yes' or 'maybe' were reviewed in order to make a decision about their inclusion in the review. Any discrepancies between reviewers was resolved by discussion or if needed, by a third reviewer (AO).

2.4. Data extraction and analysis

One reviewer (ML) extracted data from included studies with a previously prepared data extraction form. Article appendixes were also reviewed. A second reviewer (LL) confirmed data extraction and any discrepancy was resolved by discussion.

Study general characteristics and specific information regarding DAAS, allergy information records, system rule bases, DAA characteristics and their management, and DAA overrides and their clinical consequences were extracted and analyzed. Regarding clinical implications of DAA, information on registered ADE was retrieved, assuming

the definition of ADE adopted by the authors of the identified primary studies (appendix B). Additionally, the type of ADEs was analyzed.

Due to heterogeneity in reporting information on DAAS, the proportion of systems with a specific characteristic among those reporting that issue was calculated.

When some data were missing but the study provided information to calculate them, these were calculated. Data were synthesized using narrative and tabular methods.

3. Results

3.1. Search results

A total of 979 references were identified in the initial search (Fig. 1). After removal of duplicates, 961 references remained for title and abstract review and screened. The full text of the remaining 54 references were reviewed, of which 20 were included and, additionally, 8 references identified through the review by Légat et al. and through reviewing the reference lists of selected articles were added. Therefore, the review finally included a total of 28 articles.

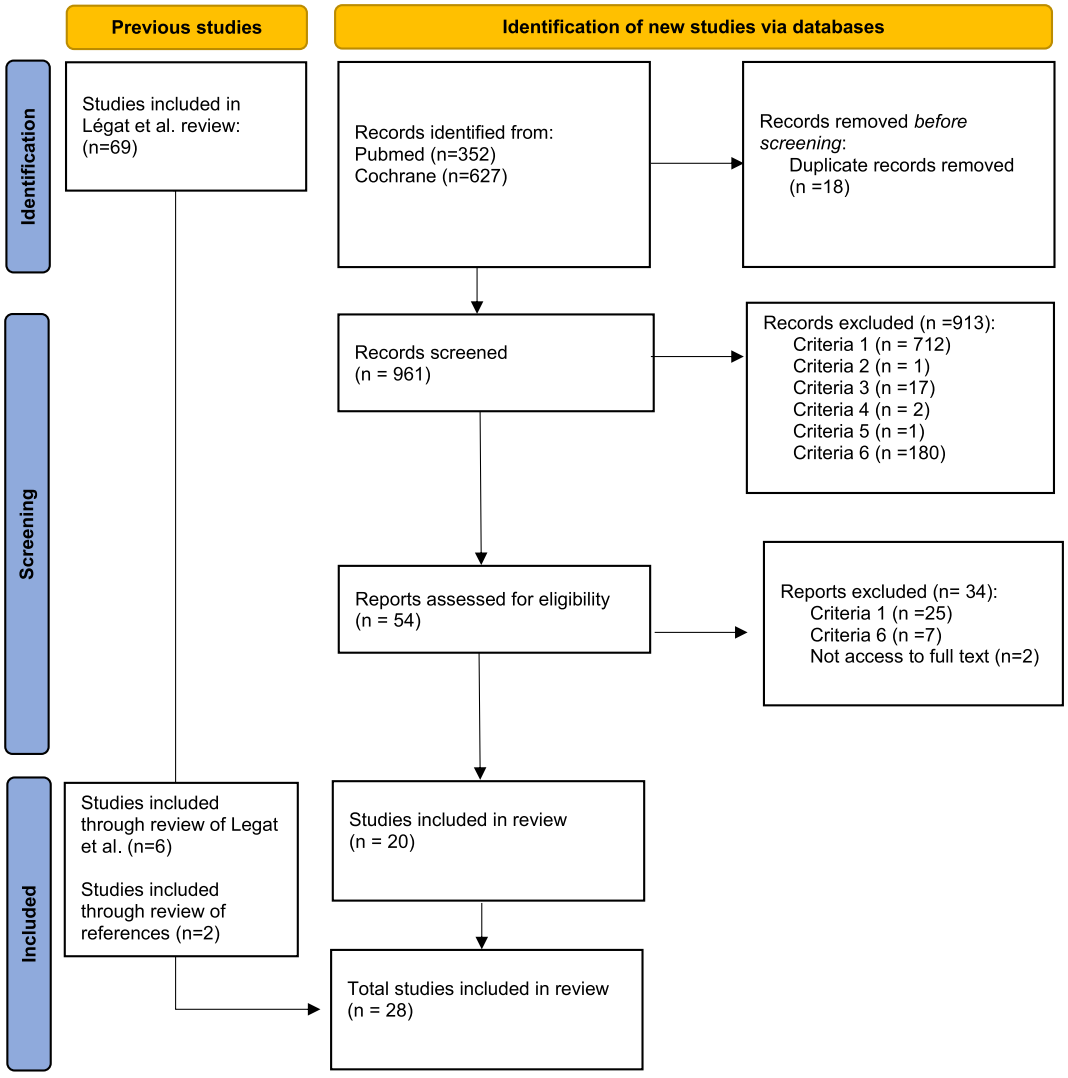
3.2. Study general characteristics

General characteristics of the studies are shown in Table 1. Most studies (82%) were published in 2005 or afterwards, were observational (57%), and were performed in the United States (US) (82%).

3.3. Drug allergy alert systems (DAAS)

The 28 included studies described a total of 17 different electronic DAAS. However, not all systems were described in full detail. Systems names and characteristics are shown in Table 1.

Nine (53%) of the 17 systems were commercially available. Three of the 17 DAAS referred to the Brigham Integrated Clinical Information System (BICS). It is a system shared between some hospitals and outpatient clinics in US, and although it has common aspects in both settings, each one has its own special feature and therefore were considered as different systems.



Exclusion criteria: (1) not describing electronic drug alert systems, (2) not implemented in clinical practice, (3) not in hospital setting, (4) not including 'allerg*' or 'hypersensitivit*' in title/abstract, (5) no human studies, (6) study design.

Fig. 1. Search results.

Table 1
Description of the included studies.

	Author, year	Country	Specific for DAA	Setting	Number of Hospitals	Hospital name	Hospital Type	Study design	Year	Duration of study	Study characteristics	System name	Type of system	Alert logic
1	Hulse (1976)[30]	USA	no	H	Single C	LDSHUUSM	Private Tertiary care Teaching Hosp	Descriptive		16 mo.		HELP	Custom design	FDB + Rev EC
2	Abookire (2000)[31]	USA	yes	H	Single C	BWH	Tertiary care Teaching Hosp	Trend analysis retrospective	1995–1999	5 y.		BICS - BWH	Custom design	FDB + Rev EC
3	Kuperman (2003) [32]	USA	yes	H/A	MultiC	BWH + MGH + out	Large Academic Medical Center	Descriptive				BICS – BWHBICS - MGH	Custom design	FDB + Rev EC
4	Hsieh (2004)[16]	USA	yes	H	Single C	BWH	Tertiary care Teaching Hosp	Observational retrospective	2002	3 mo.		BICS - BWH	Custom design	FDB + Rev EC
5	Topaz (2015)[18]	USA	yes	H	MultiC	BWH + MGH	Large Academic Medical Center	Observational retrospective	2004–2013	10 y.	Opioids	BICS – BWHBICS - MGH	Custom design	FDB + Rev EC
6	Topaz (2015)[11]	USA	yes	H	MultiC	BWH + MGH	Large Academic Medical Center	Cross-Sec observational	2004–2013	10 y.		BICS – BWHBICS - MGH	Custom design	FDB + Rev EC
7	Slight (2016)[9]	USA	yes	H/A	Single C	BWH + out	Tertiary care Teaching Hosp	Cross-Sec observational	2009–2011	3 y.		BICS - BWH	Custom design	FDB + Rev EC
8	Wong (2017)[33]	USA	no	H	Single C	BWH	Tertiary care Teaching Hosp	Observational retrospective	2009–11	3 y.	ICU	BICS - BWH	Custom design	FDB + Rev EC
9	Wong (2017)[34]	USA	yes	H/A	Single C	BWH + out	Large Academic Medical Center	Observational retrospective	2009–2011	3 y.	Exact match and anaphylaxis	BICS - BWH	Custom design	FDB + Rev EC
10	Nanji (2018)[35]	USA	no	H	Single C	BWH	Tertiary care Teaching Hosp	Cross-Sec observational	2009–2012	4 y.		BICS - BWH	Custom design	FDB + Rev EC
11	Wong (2018)[36]	USA	no	H	Single C	BWH	Tertiary care Teaching Hosp	Observationa prospective	2016–2017	9 mo.	ICU	BICS- NEW	Commercial	FDB
12	Wong (2017)[37]	USA	no	H	Single C	BWH	Tertiary care Teaching Hosp	Retrospective comparison	2011–2015	3 mo.	ICU	BICS- NEW VSBICS - BWH	Commercial VS Custom design	FDB + Rev EC
13	Zimmerman (2009)[38]	USA	yes	H/A	MultiC	UMHHC	Academic Medical Center	Descriptive				Eclipsys SCM-UMCL	Custom design + modified	Multum
14	Chafee (2010)[39]	USA	no	H/A	MultiC	UMHHC	Academic Medical Center	Descriptive				Eclipsys SCM-UMCL	Custom design + modified	Multum
15	Dekarske (2015)[12]	USA	no	H	Single C	UMH	Tertiary care Teaching Hosp	Prospective randomized crossover	Phase 1 2013 Phase 2 2014	3.5 mo.		Eclipsys SCM-UMCL	Custom design + modified	Multum
16	Payne (2002)[40]	USA	no	H/A	MultiC	VAPSHCS	Large Academic Medical Center	Obs Retrosp comparison		4 w.		VISTA - CPRS	Custom design	NDF + LDF
17	Lin (2008)[21]	USA	no	H/A	MultiC	VAPSHCS	Large Academic Medical Center	Obs Retrosp comparison	2006	9 d.		VISTA - CPRS	Custom design	NDF + LDF
18	Cuellar (2005)[41]	Spain	yes	H	Single C	La Fe Hospital	Tertiary care Teaching Hosp	Descriptive				PRISMA	Custom design	
19	Oliven (2005)[42]	Israel	no	H	Single C	B-Z MC	Acute care TH	Cross-Sec comparison		6 mo.	Internal Medicine	Unnamed OLIVEN	Custom design	
20	Swiderski (2007)[43]	USA	yes	H	Single C	OSUMC	Tertiary care Teaching Hosp	Retrospective analysis	2003–2005	20 w.		Siemens Inv CPOES	Commercial	FDB
21	Hunteman (2009)[44]	USA	yes	H	Single C	St. Luke's Hospital	Tertiary care Teaching Hosp	Observational retrospective	2017	1 mo.		Power-Chart	Commercial	
22	Jani (2011)[45]	UK	no	H	Single C	UCLH NHS	Tertiary care Pediatric Hosp	Observational retrospective	2005–2006	1 y.	Pediatrics	EP system	Commercial	
23		USA	no	H	MultiC				2013	4 d.			Commercial	

(*continued on next page*)

Table 1 (*continued*)

	Author, year	Country	Specific for DAA	Setting	Number of Hospitals	Hospital name	Hospital Type	Study design	Year	Duration of study	Study characteristics	System name	Type of system	Alert logic
	Bryant (2014)[15]					UWMC + HMC	2 primary Teaching Hosp	Observational retrospective				Cerner Millen-nium		Cerner's Multum
24	Knight (2015)[46]	USA	no	H	Single C	JHBMC	Academic Medical Center	Observational retrospective	2009–2010	7 mo.	All departments exc. UCI	MEDITECH	Commercial	
25	Brodowy (2016)[17]	USA	yes	H	Single C	UCSFMC	Teaching Hosp	Before and after interventional	Period 1 2013 Period 3 2015	7 mo.		Unnamed BRODOWY	Unknown	
26	Genco (2016)[8]	USA	no	H	Single C	UCSMD	Large Academic Medical Center	Observational retrospective	2012–2013	5 mo.	Opioids at Emergency Department	Epic ES	Commercial	FDB
27	Foreman (2020)[47]	Australia	yes	H	MultiC	NPH + RGH + PAHRGS	2 metropolitan and 1 regional Public Hosp	Cross-Sec observational retrospective	2003–2006	17 mo.		EPAS	Commercial	
28	Nakayama (2018)[48]	Japan	yes	H	MultiC	TUH	Teaching Hosp	Descriptive	2015–2017	2 y. & 2 mo.		Unnamed NAKAYAMA	Custom design	

Specific for DAA: DAA: drug allergy alerts. **Setting:** H: hospital, H/A: hospital and ambulatory, both. **Number of hospitals**: C: Center, MultiC: multicenter. **Hospital name**: BWH: Brigham and Women's Hospital, B-Z MC: Bnai-Zion Medical Center, JHBMC: Johns Hopkins Bayview Medical Center, LDSHUUSM: LDS Hospital and University of Utah School of Medicine, out: patient's clinics. MGH: Massachusetts General Hospital, NPH: Noarlunga Public Hospital, OSUMC: Ohio State University Medical Center, PAHRGS: Port Augusta Hospital and Regional Health Services, RGH: Repatriation General Hospital, TUH: Tohoku University Hospital, UCLH: University College London Hospital NHS Foundation Trust, UCSFMC: University of California San Francisco Medical Center, UCSMD: University of Colorado School of Medicine Denver, UMH: University of Michigan Hospital, UMHHC: University of Michigan Hospitals and Health care Centers, UWMC + HMC: University of Washington Health care system (UW Medical Center and Harborview Medical center), VAPSHCS: Veterans Affairs Puget Sound health care system. **Hospital type**: Hosp: hospital, **Study design**: Cross-Sec: cross-sectional, Obs Retrosp comparison: Observational retrospective comparison study. **Duration of study**: d: days, mo: month, w: week, y: year. **Study characteristics**: Exact match and anaphylaxis: Exact match and documented reaction of 'anaphylaxis' alerts, ICU: Intensive care unit. **System name**: BICS: Brigham Integrated Clinical Information System, Cerner Millennium: Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer), EPAS: Enterprise Patient Administration System, Epic ES: Epic Electronic system, Eclipsys SCM-UMCL: Eclipsys Sunrise Clinical Manager UM-CareLink, HELP: Health evaluation through logical processing, Siemens Inv CPOES: Siemens Invision CPOE system, VISTA- CPRS: Veterans information technology architecture computerized patient record system. **Type of system:** Custom design: hospital-custom design (in-house system), modified: hospital modifications. **Alert logic:** FDB: first databank, NDF + LDF: National drug file + local drug files, Rev EC: review by an expert committee.

3.4. Drug allergy documentation

Information regarding allergies registered by the different systems is shown in Table 2. There is no homogeneity between the different systems on what drug allergy information needs to be recorded or when, who and how should be recorded. Eight of the ten identified systems (80%) that provided the information limited the introduction of allergy information to physicians, pharmacists and/or nurses. Normally, the introduction of previous known allergies had to be completed at hospital admission (7 out of the 9 systems (78%) on which that information was reported).

Providers are required to enter allergy information or to indicate that the patient has no known allergies. In most systems (6 out of 9 systems, 67%) this action was obligatory and blocked the access to the electronic medication record until the allergy history was reported. The allergen (drug or group of drugs) had to be reported in all the systems, the reaction associated with the allergy history could be recorded in 10 systems (83%), and the severity of the reaction was only available in 5 of them (42%). Only 3 (18%) systems made possible to differentiate allergies from intolerances when recording the information.

Allergy information was recorded in a codified format in all systems. In some of them (5 of the 11 systems (45%) on which that information was reported) it was possible to use free text that did not generate alerts.

3.5. Alert rules

Drug-allergy interaction alerts are triggered when a prescribed medication matches recorded allergy information using a knowledge base.

The system rules that generated alerts varied between the different electronic DAAS (Table 2). The basis of systems was the exact match (when the ordered drug and the listed drug allergy are identical; e.g. codeine ordered and codeine documented allergy). The availability of other matches varied between systems. Group match (when the documented allergen matches the allergy group of one or more prescribed medications; e.g. ordering amoxicillin to a patient with a penicillin documented allergy) was available in 5 of the 9 systems on which that information was reported (55%). Cross-sensitivity/reaction match (when the drug prescribed has a cross-reaction with the reported allergy; e.g. cefuroxime order in a penicillin documented allergy) was present in 3 of 9 (33%) systems. Reverse allergy checking (when a new allergy is introduced in the allergy record, the system checks any interaction with prescribed drugs) worked in 3 (33%) systems. Two (22%) systems had an excipient or base active ingredient match (when an excipient or active ingredient of a prescribed medication matches the allergen). Only one system referred to have an additional chemical structures or functional match.

3.6. Drug allergy alert (DAA) information and characteristics

Alerts were triggered at prescription, when ordering the drug, except in one system (BICS-NEW [11]) that generated alerts at prescription signing. Some alerts were shown when drugs were scanned (1 of 16 systems (6%) on which that information was available), administrated (2 of 16 systems, 12%), or when allergy status was modified (3 of 16 systems, 19%) (Appendix C).

DAA were always interruptive, that refers to pop-up and workflow interrupt to prompt a change in therapy. The alert receiver was usually the physician (13 of 14 systems, 93%).

The information shown in the alert differed from one system to other. All systems displayed the ordered drug that generated the alert and the allergen or patient's allergy profile. Additional information such as the type of match, the reaction associated with the allergy event or the interaction severity, were available in some systems.

DAA rates varied between systems and ranged from 0.001 alerts per order (HELP system [30]) to 0.14 alerts per order (1st period of study at

Table 2
Drug allergy registers and system's rule bases.

SYSTEM NAME	Drug allergy registers/lists															Rule bases					
	Person registering				When			Registration		Allergy format		Information recorded				Differ. allergies from intoler.	Type of match				
	Physi-cian	Phar-macist	Nurse	Other	Admi-ssion	Before Prescri-	Admi- tting bingpharma.	Obliga-tory	Volun-tary	Codi-fied	Free Text	Aller- gen	Reac-tion	Seve-rity	Other		Exact Match	Group Match	Cross-Sens	Reverse-Allergy	Others
BICS - BWH	√				√			√		√	√	√ (Med, Med Group, Ingr)	*			No	√	√	√	√	
BICS - MGH	√				√			√		√		√ (Med, Med Group)	√				√	√		√	
BICS - NEW										√		√	√	√		Yes	√				unk
Eclipsys SCM-UMCL					√	√		√		√	√	√	√			No					
Cerner Millennium												√	√				√		√		
Epic ES																No	√	√			Base Ingr
PRISMA	√				√					√		√			Obs and Non-Drug All	No	√	√			Base Ingr, ChemM
PowerChart	√	√	√	√	√							√	√			No					
EP system								√		√						No				√	unk
MEDITECH				√ all users												No					
VISTA - CPRS	Aft: √	Bef: √Aft: √	Aft: √	Aft: √ (Diet)					√	Aft: √	Bef: √										
EPAS				√ all users					√	√	√	√	√	√	Food all, Contact all, Oth	Yes					
HELP		√	√				√		√			√ (Med, Med Group)									
Siemens Inv CPOES	√	√	√		√			√		√	√	√ (Med, Med Group)	√	√ **	Food all, oth	Yes	√	√	√		Group Match = Cross Sens
Unnamed BRODOWY	√	√	√							√		√	√	√		No					
Unnamed OLIVEN					√			√									√		√		
Unnamed NAKAYAMA										√	√	√	√	√	Cert, Lim						

System names: BICS: Brigham Integrated Clinical Information System, BWH: Brigham and Women's Hospital, Cerner Millennium: Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer), Eclipsys SCM-UMCL: Eclipsys Sunrise Clinical Manager UM-CareLink, EPAS: Enterprise Patient Administration System, HELP: Health evaluation through logical processing, Epic ES: Epic Electronic system, MGH: Massachusetts General Hospital, Siemens Inv CPOES: Siemens Invision CPOE system, VISTA- CPRS: Veterans information technology architecture computerized patient record system. **Person registering**: Aft: After, Bef: before, Diet: dieticians. **When the allergy is recorded**: Admitting-Pharma: admitting/trascribing orders at Pharmacy; **Allergy format**: Bef: before. **Information recorded:** All: allergy, Cert: certainty of the allergy (certain or uncertain ADE), Ingr: ingredient, Lim: limitations, Med: medication, Obs: observations, Oth: other allergies. **Differentiate allergies from intolerances** (differ. allergies from intoler.), **Type of match:** Base Ingr: base ingredient excipients check, Chem M: chemical structures/functional match, Cross- Sens: cross-sensibility, Group Match: group match or same class drug, M: match, Oth: others, Reverse Allergy: reverse allergy checking, Unk: unknown, = : no difference between them.
*not required **rate of allergy: (1) true allergy, (2) severe adverse drug reaction, or (3) mild ADE.

Table 3
Alerts generated in the different systems.

Author, year	System name	Number alerts triggered in study period (n) #	Number alerts triggered per day (n) #	Number alerts triggered per order (n) #	Type of Match (%)			Drug group (%)					Reaction type (%)					
					Exact Match	Group Match	Cross Sensibility Match	Opiates/ Narcotics	Sulfa-drugs	Antibiotics	Other Analgesic	Other Drugs	Skin	GIU	Itching	Immune mediatedreaction	Non-Immune Mediated reaction	Unk-nown
Hulse (1976)[30]	HELP	112	0.23	0.001														
Abookire (2000)[31]	BICS - BWH							7.6 Per 4.8 nar	12 Las				20.8*	17.5*	8.9*			
Hsieh (2004)[16]	BICS - BWH	7,761	86.23															
Topaz (2015)[18]	BICS - BWH and BICS - MGH	952,223	260.88		13.0	87.0		37.3					20.8*	17.5*	8.9*	40.6*	38.2*	
Topaz (2015)[11]	BICS - BWH and BICS - MGH	928,962	254.51		12.2	74.8	13.0	48.0		10.0	6.0		20.5	15.9				21.5
Slight (2017)[9]	BICS - BWH	131,615	120.20	0.025				50.9		13.7 cph& β-l		24.9	21.7	21	5.7			22.1
Wong (2017)[31]	BICS - BWH	1,851**	1.69**															
Wong (2017)[33]	BICS - BWH							11.3 cd 7.4 mph		18.3 pen			12.5	8.8				28.1
Nanji (2018)[35]	BICS - BWH	131,615	120.20															
Payne (2002)[40]	VISTA - CPRS	105	3.75	0.002														
Lin (2008)[20]	VISTA - CPRS	420	70.00	0.011														
Swiderski (2007)[43]	Siemens Inv CPOES	777	5.55															
Hunteman (2009)[44]	Power-Chart	643	21.43	0.013				69.0			9.0	10.0						
Jani (2011)[45]	EP system	71	0.19	0.003														
Bryant (2014)[15]	Cerner Millen	1,302	325.50	0.071	9.5		90.5											
Knight (2015)[46]	MEDITECH	2,371	11.29	0.009				31.5 hy 29 mph 26.8 oxy										
Brodowy (2016)[17]	unnamed Brodowy	F: 120,669	1st P: 1,340 2nd P: 900	1st P: 0.14 2nd P:0.09														

System names: BICS: Brigham Integrated Clinical Information System, BWH: Brigham and Women's Hospital, Cerner Millen: Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer), HELP: Health evaluation through logical processing, MGH: Massachusetts General Hospital, Siemens Inv CPOES: Siemens Invision CPOE system, VISTA-CPRS: Veterans information technology architecture computerized patient record system. **Number alerts triggered:** P: period; **Type match:** Group Match: group match or same class drug, **Drug or drug group ordered:** β-l: beta-lactams, Cd: codeine, Cph: cephalosporins, Hy: hydromorphine, Las: Lasix® (furosemide), Mph: morphine, Nar: Narcan® (naloxone), Oxy: oxycodone, Pen: penicillins, Sulf: sulfonamide drugs, Per: Percocet® (oxycodone/paracetamol). **Reaction recorded**: GIU: gastrointestinal upset.drug group (%: number of alerts/number of total alerts), *opioids drug allergy alerts, **anaphylaxis drug allergy alerts, # data calculated in this review if not given directly in the study.

Table 4
Override rate (OvR): overall OvR and OvR by group, type of match or recorded reaction.

Author, year	System name	Overall OvR	OvR by drug group					OvR by type of match			OvR by type of reaction									
			Opiates (%)	Anti-biotics (%)	Contrast media (%)	Other drugs high OvR (%)	Other drugs low OvR (%)	Exact match (%)	Group vatch (%)	Cross sens (%)	ImM (%)	non-ImM (%)	Life Threa (%)	non Life Threa (%)	Anphy (%)	Mya (%)	Itch (%)	GIU (%)	Unk (%)	Other (%)
Abookire (2000)[31]	BICS - BWH							P1: 49 P2: 73		P1: 54 P2: 80										
Topaz (2015)[18]	BICS - BWH & MGH	83.6	88.8					74.4**	90.9**		88.6	89	87.8	89						
Topaz (2015)[11]	BICS - BWH & MGH	83.9	88.7	74 Pen 79.1 Cph		88.3 Sta 85.3 NSAIDs	78.2 Sal	74.6	89.1	80.7	84.6	88	83.6	86.9					85.5	
Slight (2017)[9]	BICS - BWH	81.9	87.2	70.6 Pen 59.6 sulf	55.3	98.1 M−Ab 84.4 Non Atb-sulfa									70.9	86.2	85.2	85.3		75.1 Ang 81.2 Short Breath
Wong (2017)[34]	BICS - BWH							46*							68.7					
Lin (2008)[20]	VISTA - CPRS	81.2			66.7															
Bryant (2014)[15]	Cerner Millen	90.9	93	70		97 Diu 93 Analg	80 Phys	76		92										
Genco (2016)[8]	Epic ES	81.4	88.6			68.2 N-opi														
Hulse (1976)[30]	HELP	43.7																		
Hsieh (2004)[16]	BICS - BWH	80.0																		
Wong (2017)[37]	BICS - NEW vs BWH	BWH:90.7 NEW: 93.4																		
Nanji (2018)[35]	BICS - BWH	81.9																		
Wong (2018)[36]	BICS - NEW	83.6																		
Payne (2002)[40]	VISTA - CPRS	68.6																		
Swiderski (2007)[43]	Siemens Inv CPOES	56.0																		
Hunteman (2009)[44]	PowerChart	97.0																		
Jani (2011)[45]	EP system	63.4																		
Knight (2015)[46]	MEDITECH	89.7																		
Brodowy (2016)[17]	Unnamed Brodowy	1st P: 95 2nd P: 90 3rd P: 80																		

System names: Health evaluation through logical processing (HELP), Brigham Integrated Clinical Information System (BICS), Brigham and Women's Hospital (BWH), Massachusetts General Hospital (MGH), Veterans information technology architecture computerized patient record system (VISTA- CPRS), Siemens Invision CPOE system (Siemens Inv CPOES), Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer) (Cerner Millennium), Epic electronic system (Epic ES); **Global OvR**: P: period; **OvR by ordered drug or drug group:** Analg: other analgesics, N-opi: non-opioids, Cph: cephalosporins, Diu: diuretics, M−Ab: monoclonal antibodies, Non Atb Sulfa: non-antibiotics sulfonamides, NSAIDs: non– steroidal antiinflamatory drugs, Pen: penicillins, Sal: salicilates, Sta: statins, Sulf: sulfonamide antibiotics, Phys: phyquiatric drugs. **OvR by type match:** Cross-Sens: cross-sensitivity, Group Match: group match or same class drug, P: period; **OvR by reactions recorded**: ImM: immune mediated, N-ImM: non-immune mediated, Life Threa: life threatening, Non-Life Threa: non-life threatening, GIU**:** gastrointestinal upset, Anphy: anaphyaxisis, Mya: myalgia, Itch: itching, Ang: Angioedemae, Shor Breath: shortness of breath, Unk: unknown. *Exact Match + anaphylaxis alerts, **opioids alerts

Epic Electronic System [8]) (Table 3).

3.7. Management of the alert and override reasons

After an alert was triggered, in most systems (13 of 14 systems, 93%) users could cancel the order or keep it and override the alert (appendix C).

In case the alert was overridden, users were required to introduce an override reason on a mandatory (8 of 9 systems, 89%) or voluntary (1 of 9 systems, 11%) basis. Override reasons were codified in 6 of 9 systems (67%), but some systems still used free text format (5 of 9 systems, 55%). Two systems had both possibilities [44,48].

3.8. Drug allergy alert (DAA) overrides

3.8.1. Characteristics of overridden drug allergy alerts (DAA)

Overridden alerts were most frequently related to narcotics/opioids, acetaminophen, antibiotics (cephalosporins, penicillins), sulfur-containing drugs and non-steroidal anti-inflammatory drugs (NSAIDs) (appendix D).

Physicians were responsible for 71% of alerts overrides [43]. Most overridden alerts (between 96 and 90%) were triggered by non-exact match, except in an intensive care unit (ICU) study by Wong et al., in which most DDA overrides were due to an exact match (89.5%) [36]. This study also found that 10.4% (29/277) of overridden DAA had a potentially life-threatening documented reaction, being 45% (13/29) anaphylaxis.

3.8.2. Override rate (OvR)

One of the main problems of CDS is the high percentage of alert overrides. The OvR ranged from 43.7% to 97% [30,44] (Table 4). In articles published in the last 5 years, the OvR was higher, between 81.4% and 93.4% [8,37].

The OvR varied depending on the drug group that triggered the alert (Table 4). Opioids, monoclonal antibodies, non-antibiotic sulfonamides, statins and NSAIDs had higher OvR. OvR was lower with contrast media, salicylate analgesics and antibiotics.

One study showed that nurses led to a higher OvR (61%) than physicians and pharmacist (54% and 55%) [43]. The exact match had a lower OvR than the group match or the cross-sensitivity match.

When the allergy reaction was introduced in allergy registry, the OvR was higher when the referred reaction was myalgia, gastrointestinal upset or itching than when the reaction was anaphylaxis, angioedema or shortness of breath [9]. The OvR was higher in non-immune and non-life threatening reactions than immune and life threatening reactions [11,18].

3.8.3. Override reasons

The main override reasons (appendix E) were that the patient had previously tolerated the drug or that he/she had previously taken the drug without allergic reaction, that physician was aware or would monitor the patient or there was no reasonable alternative, that there was low-risk of cross-sensitivity reaction, that the patient reported no allergy, or that the allergy might not be true or was questionable and the benefit outweighed the risk.

3.9. Clinical consequences of drug allergy alert overrides

Few articles studied clinical consequences of DAA override, and all of them were done with the BICS system (Table 5).

Hsieh et al. referred an ADE incidence of 6% in 320 patients, most of them due to narcotics. A 63% of ADEs were gastrointestinal and a 16% were allergic events (cutaneous manifestations) [16]. ADEs were classified as significant in 53% of the cases and serious in the 47%. None of the events was life-threatening or fatal. The 95% of events resulted from a non-exact match alert override.

Table 5
Clinical consequences of drug allergy alerts overrides.

Author, year	System name	Study char	ADE Incidence		Reaction			Drug						Severity			Preventable	Type of match		Appropiateness of override	
			n	%	GIU n (%)	Allergic event n (%)	Red mn syndrome (%)	Others n (%)	Opiates n (%)	Sulfa-diuretics n (%)	Cepha-losporins n (%)	Insu-line n (%)	Vanco-mycin n (%)	Significant n (%)	Serious n (%)	Life Thr n (%)	yes/no	Exact match (%)	Non-Exact Match (%)	Inappropriate n (%)	Appropriate n (%)
Hsieh (2004)[16]	BICS - BWH		19 ADES/ 6 320 patients	6	12 (63%)	3 (16%)		1 (5%) hyTA, EC, JS, hyGI	16 (84%)	1 (5%)	1 (5%)	1 (5%)		10 (53%)	9 (47%)	0%	no	5%	95%		
Wong (2017)[34]	BICS - BWH	Anph + ExM	no harm	0																	
Wong (2017)[33]	BICS - BWH	ICU	1 ADE	unk			1 (100%)						1 (100%)	1 (100%)		0%	yes			1 (100%)	0
Wong (2018)[36]	BICS - NEW	ICU	4 ADES/ 207 DAAO	2	1 (25%)		1 (25%)	1 (25%) hal1% (25%) B, S & R	2 (50%) oxy/ace				2 (50%)	1 (25%)	3 (75%)	0%		75%	25%	3 (75%)	1 (25%)

System name: BICS: Brigham Integrated Clinical Information System, BWH: Brigham and Women's Hospital; **Study characteristics (cha):** anphy: anaphylaxis, ExM: exact match, ICU: intensive care unit; **Adverse drug events (ADEs) incidence:** DAAO: drug allergy alerts overrides, Unk: unknown; **Reaction:** GIU: gastrointestinal upset, HyTA: hypotension, EC: elevated creatinine, JS: jaw swelling, HyGl: hypoglycemia, Hal: hallucinations, B: blisters, S: sloughing, R: rash; **Drug:** Oxy/ace: oxycodone/acetaminophen, Sulfa-diuretics: sulfa containing diuretics; **Severity:** Life Thr: life threatening/fatal; **Preventable:** ADE preventable by clinical decision support

Wong et al. obtained an ADE incidence of 1.93% (4 ADEs on 207 overridden DAA) in the ICU [36]. Three ADEs were serious and one was significant. A significant increase in ADE rates was observed with inappropriate overrides (3/4) compared with appropriate overrides (1/4).

Wong et al., in other study, only referred one ADE due to DAA override, but the total number of overridden DAA was not provided [33]. The event occurred in the ICU, was due to vancomycin (red man syndrome) and was considered a significant and preventable ADE. The study reported that the ADE rate per 100 overridden DAA for the appropriately and inappropriately overridden alerts was 0 (95%CI 0–4.1) and 16.7 (95%CI 0.4–64.1), respectively.

In other sample of 93 inpatients DAA overrides that had an exact-match and a documented reaction of anaphylaxis, there were not found harms associated with DAA overrides [34].

4. Discussion

Different DAAS are described in literature. Systems are not homogeneous in allergy registries, rule bases, alerts or override reasons.

We identified 17 electronic systems that alert physicians, pharmacists or nurses about a recorded allergy. Nine systems were commercially available and 3 referred to the BICS system.

The introduction of allergy information is essential for an effective DAAS. In most systems, access to prescription was blocked until the allergy history was reported, encouraging the registry of information. Lists or records of allergies varied from one system to another, and to date, there is no consensus on the information to be registered or the format to be used. However, some authors propose to record essential information such as the allergen and the reactions suffered by patients in a codified format, avoiding free text [16,38]. It is also advised that drug allergy registers must be improved and regularly updated for an optimal functioning of systems and to decrease unnecessary alerts [9,11,15,16,22,34,43,44]. This, could lead to a reduction of the alert fatigue that can prevent achieving the system goals of harm prevention and reduction of ADEs [15,18]. To facilitate the deactivation and information update, it has been proposed to implement an automatic link to the allergy register after an alert override [9,16,43].

Discrimination between true allergies and intolerances is also essential, since this will diminish the amount of generated alerts, thereby contributing to an increase in the quality of the generated alerts [8,9,15,16,18,33,36,37]. In last terms, this approach will reduce alert fatigue and promote providers confidence in the DAAS. Nevertheless, only 4 of the identified DAAS (36.4%) carried out differentiation between allergies and intolerances. Some authors refer that this categorization (allergy vs intolerance) is complicated and of questionable usefulness due to the user's lack of experience and the limited understanding of ADEs mechanistic categorization [9,15,47]. However, we believe that implementing a committee to review and improve registries will help to overcome this difficulty.

Generally, systems rule bases were not described in detail, making it difficult to carry out an evaluation. Only the exact match was available in every system, being the basis of a DAAS. There is no consensus on which non-exact match (group, cross-sensitivity and reverse allergy match) generates important alerts. Regarding the override rate, some authors observed that exact matches had lower OvR than non-exact matches [15,18,30]. However, Bryant et al. considered that eliminating non-exact matches might not be a good option because cross-reactions represented a variable risk to each patient [15].

In most systems (93%) the triggered DAA were interruptive, but the presented information and the override reasons were not homogeneous. An analysis of what information is necessary to make a good alert evaluation is warranted.

Different strategies to reduce unnecessary alerts and improve generated alerts have been identified in the literature. Some examples include changing some interruptive DAA (such as intolerances, non-severe alerts, duplicated alerts, or previous tolerated medication) to non-interruptive, generating interruptive alerts only in the case of exact matches, and displaying the information in a non-interruptive manner in the case of non-exact matches [8,11,15,16,33,37,43]. Desensitization protocols could also be bypassed [34]. In addition, some authors have proposed to create a visual distinction between DAA and other type of alerts (e.g. drug-drug interaction alerts) or according to DAA severity to increase providers attention and compliance regarding most important alerts [15,32,49].

Another proposed strategy to reduce alert fatigue is prioritizing and presenting drug safety alerts depending on the 'context' or the patient's clinical situation [50,51]. A survey carried out to physicians in some European hospitals identified the 'severity of the effect' and 'clinical status of the patient' as the most useful contextual factors for prioritizing alerts [52]. However, no specific study for contextualizing DAA has been published.

In this review, it was not possible to identity which DAAS had better results in clinical practice or in patient's safety. The only article that compared two CDS systems (not specific of DAA) found that the DAA override rate was higher with a new commercial system than with the hospital-custom designed system [37]. It is a fact that every system has to be improved in order to generate only necessary alerts.

With regard to the clinical consequences of DAA overrides, different studies with the same DAAS obtained different conclusions. Hsieh et al. found that all alert overrides resulting in ADEs seemed clinically justifiable [16]. Wong et al. did not find harm incidents after anaphylaxis and definite alert overrides [34]. The same author obtained that inappropriately overridden alerts (not just allergy alerts) had a significantly higher incidence of ADEs than appropriately overridden alerts, but sample sizes were small [33,36]. These discrepancies in the impact of DAA overrides in the incidence of ADEs may be due to the use of different ADE definitions, type of patients or ADE registration. Studies carried out in the hospital setting comparing different DAAS and with sufficient power are needed to extract firm conclusions on this matter.

Apart from the OvR, other relevant factors need to be considered when evaluating system changes or making system improvements. It has been pointed out that to better evaluate order check systems, a regular qualitative and quantitative order check monitoring should be carried out [20]. Lin CP et al. said that if the system is not functioning properly, it would be necessary to redesign it increasing its "signal-to-noise" ratio in order to reduce the percentage of ADEs that could reach patients. The rules and logic that govern orders checks should be understandable, editable and maintainable by system operators and users [20]. System behavior should also be periodically evaluated, especially when there are significant changes in rules bases or in ordering policies or software feature changes [20]. We believe that machine learning and natural language processing will also improve health information systems and DAAS effectiveness.

This review has some limitations to underline. Literature search and screening was difficult due to the lack of standardization of the used terms, mixed information related to DAA with other type of alerts, and differences in studies objectives and settings. In addition, heterogeneity in data reporting and the low quality of the studies made the quantitative data extraction and synthesis difficult. Most studies were carried out in the United States, challenging the extrapolation of the obtained results to other settings. The review covers those systems on which published literature is available, being likely that additional systems exist on the market. Therefore, although the number of the different existing systems is unknown, review findings may have incurred an underestimation.

The review yielded an updated evidence and exhaustive analysis on electronic DAAS in the hospital setting. The findings can be of great value for healthcare providers and managers for improving the existing systems, which can ultimately improve patient safety in hospitals by reducing ADEs. Having an updated, codified, specific register for drug allergies can be considered a relevant aspect of the system. System rule bases should generate only necessary alerts to prevent fatigue, and alerts should be restricted to essential information for decision making. In addition, overridden alerts should be regularly analyzed to allow system improvements.

5. Conclusions

Several DAAS have been identified, which varied in recorded allergy information, rule bases, and provided alert information, among other issues. The high rate of reported alert overrides, between 43% and 97%, and the registered override reasons make systems improvement necessary. Drug allergy registers need to be accurate and updated, and data have to be codified. Additionally, a periodic review of rule bases has to be carried out to allow generating only transcendent alerts. And a regular review of every system must be conducted to identify problems and aspects that need to be optimized. Future studies aimed at determining the impact of the different characteristics of DAAS on preventing ADEs are needed, since this will allow identifying those aspects directly associated to an improvement in quality of healthcare.

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Authors' contributions

ML, LL, AO, GG, AI participated in the design of the study. ML conducted the main investigation. LL and ML made the search and selection of the included articles. LL, AO, GG and AI were responsible for critical evaluation of the search results and provided expert opinion on the topic. All authors critically evaluated the article and gave their final approval before submission.

Summary table

What was already known on the topic	What this study added to our knowledge
Drug allergy alert systems (DAAS) are an important tool used in hospitals to reduce preventable adverse drug events and improve patient's safety.	Different DAAS are used in hospitals but no homogeneity has been found in system's characteristics, recorded allergy information, rule bases or alert information, among others.
DAAS prevent prescribing medications to which the patient has a documented allergy.	The high override rates and the override reasons registered by providers identify different DAAS aspects to be improved.
Several problems have been associated with DAAS: alert fatigue, high override rates, low value alerts, etc.	A regular analysis of DAAS, standardization of allergy registers, alert information, rule bases and having an updated allergy information are necessary to optimize systems and improve them.

CRediT authorship contribution statement

Marta Luri: Methodology, Investigation, Data curation, Writing – original draft. **Leire Leache:** Methodology, Investigation, Data curation, Writing – review & editing. **Gabriel Gastaminza:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Antonio Idoate:** Conceptualization, Methodology, Supervision. **Ana Ortega:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Search strategy

1. Pubmed Search

1.1 Légat 2018 search

Step 1

Search CPOE:

- "computerized physician order entry"
- "computerized provider order entry"
- "computerized prescriber order entry"
- "computerized order entry"
- "computerised physician order entry"
- "computerised provider order entry"
- "computerised prescriber order entry"
- "computerised order entry"
- "electronic prescribing"
- "electronic prescription"
- "electronic physician order entry"

Step 2

Search CDSS:

– "clinical decision support"
– "clinical decision making"
– "decision support"

Step 3

Search Step 1 OR Step 2 CPOE OR CDSS

Step 4

Search Alert*:

- "alert"
- "alerting"

Step 5
Search Step 3 OR Step 4 (CPOE OR CDSS) OR Alert*
Step 6
Search Allerg*:

- "allergic"
- "allergy"

Step 7
Search (CPOE OR CDSS OR Alert*) AND Step 6 (Allerg*)
1.2 Completed Légat search
Step 8
Search drug:

- "Drug"
- "Drugs"
- "Medicin*"
- "Medication"
- "Medications"

Step 9
Search hypersensitivity:

- "Hypersensitivity"
- "Hypersensitivities"

Step 10
Search Step 8 (drug) AND Step 9 (hypersensitivity)
Step 11
Search drug hypersensitivity MESH

- "Drug Hypersensitivity"[Mesh]

Step 12
Search drug hypersensitivity (in general):
Search Step 10 (drug AND hypersensitivity) OR Step 11 (hypersensitivity MESH)
Step 13
Search Step 5 (CPOE OR CDSS OR Alert*) AND Step 12 (drug hypersensitivity general)
Step 14
Search Step 13 NOT Step 7
Limits: title/abstract and publication date: to 2016/02/31
1.3 Updated new search
General flow:
((DRUG AND ALLERGY) OR $MESH_1$) AND ((CPOE1 AND CPOE2) OR CDSS OR ALERT OR $MESH_2$)
Step 1
Search Drug:

- "Drug"
- "Drugs"
- "Medicin*"
- "Medication"
- "Medications"

Step 2
Search Allergy

- "Allergy"
- "Allergies"
- "Allergic"
- "Hypersensitivity"
- "Hypersensitivities"

Step 3
Search Drug AND Allergy:
Search Step 1 (Drug) AND Step 2 (allergy)
Step 4
Search Mesh 1:

- "Drug Hypersensitivity"

Step 5
Search (Drug AND Allergy) OR MESH 1
Search Step 3 (Drug AND allergy) OR Step 4 (mesh 1)
Step 6
Search CPOE1:

- "Computer"
- "Computerized"
- "Computerised"
- "Electronic"

Step 7
Search CPOE2:

- "Order entry"
- "Prescribing"
- "Prescription"
- "Order system"
- "Order systems"
- "Entry system"
- "Entry systems"
- "Medication system"
- "Medication systems"

Step 8
Search CPOE:
Search Step 6 (CPOE1) AND Step 7 (CPOE2)
Step 9
Search CDSS

- "Clinical decision support"
- "Clinical decision making"
- "Decision support"
- "Alert system"
- "Alert systems"
- "Reporting system"
- "Reporting systems"
- "Information system"
- "Information systems"
- "Surveillance system"
- "Surveillance systems"
- "Computer system"
- "Computer systems"

Step 10
Search Alert:

- "Alert"
- "Alerts"
- "Alerting"
- "Check"
- "Checks"
- "Cheking"

Step 11
Search MESH 2:

- "Hospital Information Systems"[Mesh]

- "Decision Support Systems, Clinical"[Mesh]
- "Drug Therapy, Computer-Assisted"[Mesh]
- "Medical Order Entry Systems"[Mesh]

Step 12
Search CPOE OR CDSS OR Alert OR MESH 2
Search Step 8 (CPOE) OR Step 9 (CDSS) OR Step 10 (Alert) OR Step 11 (MESH 2)
Step 13
Search ((Drug AND Allergy) OR MESH 1) AND (CPOE OR CDSS OR Alert OR MESH 2)
Search Step 5((Drug and Alllergy) OR MESH 1) AND Step 12 (CPOE OR CDSS OR Alert OR MESH 2)
Limits: Title/Abstract and publication date: 2016/02/01 till 2020/04/30.
2. Cochrane Database Search
2.1. Légat 2018 Search
Step 1
"computerized physician order entry" OR "computerized provider order entry" OR "computerized prescriber order entry" OR "computerized order entry" OR "computerised physician order entry" OR "computerised provider order entry" OR "computerised prescriber order entry" OR "computerised order entry" OR "electronic prescribing" OR "electronic prescription" OR "electronic physician order entry"
Step 2
"clinical decision support" OR "clinical decision making" OR "decision support"
Step 3
Step 1 OR Step 2
Step 4
"alert*"
Step 5
Step 3 OR Step 4
Step 6
"Allergic" OR "Allergy"
Step 7
Step 5 AND Step 6
2.2 Completed Légat search
Step 8
Search drug:

- "Drug"
- "Drugs"
- "Medicin*"
- "Medication"
- "Medications"

Step 9
Search hypersensitivity:

- "Hypersensitivity"
- "Hypersensitivities"

Step 10
Search Step 8 (drug) AND Step 9 (hypersensitivity)
Step 11
Search drug hypersensitivity MESH

- "Drug Hypersensitivity"[Mesh]

Step 12
Search drug hypersensitivity (in general):
Search Step 10 (drug AND hypersensitivity) OR Step 11 (hypersensitivity MESH)
Step 13
Search Step 5 (CPOE OR CDSS OR Alert*) AND Step 12 (drug hypersensitivity general)
Step 14
Search Step 13 NOT Step 7
2.4 Updated new search
General Flow
((DRUG AND ALLERGY) OR $MESH_1$) AND ((CPOE1 AND CPOE2) OR CDSS OR ALERT OR $MESH_2$)
Step 1
Search Drug:

- "Drug"

- "Drugs"
- "Medicin*"
- "Medication"
- "Medications"

Step 2
Search Allergy

- "Allergy"
- "Allergies"
- "Allergic"
- "Hypersensitivity"
- "Hypersensitivities"

Step 3
Search Drug AND Allergy:
Search Step 1 (Drug) AND Step 2 (allergy)
Step 4
Search MESH 1:

- "Drug Hypersensitivity"

Step 5
Search (Drug AND Allergy) OR MESH 1
Search Step 3 (Drug AND allergy) OR Step 4 (MESH 1)
Step 6
Search CPOE1:

- "Computer"
- "Computerized"
- "Computerised"
- "Electronic"

Step 7
Search CPOE2:

- "Order entry"
- "Prescribing"
- "Prescription"
- "Order system"
- "Order systems"
- "Entry system"
- "Entry systems"
- "Medication system"
- "Medication systems"

Step 8
Search CPOE:
Search Step 6 (CPOE1) AND Step 7 (CPOE2)
Step 9
Search CDSS

- "Clinical decision support"
- "Clinical decision making"
- "Decision support"
- "Alert system"
- "Alert systems"
- "Reporting system"
- "Reporting systems"
- "Information system"
- "Information systems"
- "Surveillance system"
- "Surveillance systems"
- "Computer system"
- "Computer systems"

Step 10
Search Alert:

- "Alert"
- "Alerts"
- "Alerting"
- "Check"
- "Checks"
- "Cheking"

Step 11
Search MESH 2:

- "Hospital Information Systems"[Mesh]
- "Decision Support Systems, Clinical"[Mesh]
- "Drug Therapy, Computer-Assisted"[Mesh]
- "Medical Order Entry Systems"[Mesh]

Step 12
Search CPOE OR CDSS OR Alert OR MESH 2
Search Step 8 (CPOE) OR Step 9 (CDSS) OR Step 10 (Alert) OR Step 11 (MESH 2)
Step 13
Search ((Drug AND Allergy) OR MESH 1) AND (CPOE OR CDSS OR Alert OR MESH 2)
Search Step 5((Drug and Alllergy) OR MESH 1) AND Step 12 (CPOE OR CDSS OR Alert OR MESH 2)
Limits: Title/Abstract and publication date: 2016/02/01 till 2020/04/30.

Appendix B. Adverse drug event definition according to the different studies

Author, year	ADE definition
Hsieh (2004)[16]	Injury resulting from medical intervention related to a drug
Wong (2017)[34]	No definition of the evaluated harm
Wong (2017)[33]	No ADE definition
Wong (2018)[36]	ADE: Injury occurring from use of a medication. A definite ADE was defined as harm that only could have occurred due to use of medication.

Appendix C. Drug allergy alerts

System name	Pop-up moment (when)					Pop-up type	Alert information						Receiver			Action after alert		Override reasons					
	Order entry	Order signing	Drug scanning	Drug administration	Allergy modification		Allergen	Prescribed drug	Type of match	Reaction	Interac type	Others	Phy	Pha	Nur	Accept override alert	Pr Pha warns Phy	Yes	No	Obligatory	Voluntary	Codifed format	Free Text
BICS - BWH	√				√	Int	√	√	√	√*		Previous override*	√			√		√	√				√
BICS - MGH	√				√	Int	√	√	√	√			√			√		√	√				√
BICS - NEW		√				Int							√			√		√					
Eclipsys SCM- UMCL	√					Int							√	√		√		√	Aft: √	Bef: √	Bef: √Aft: cus	√	Bef: √
Cerner Millennium	√					Int	√	√			√	Time, Hosp, user name, Cred, Practice Level	√	√	√	√		√	√		√		
Epic ES	√		√	√		Int							√	√	√	√							
PRISMA	√					Int	√	√					√		√	√		√					
Power-Chart													√	√	√	√		√	√		√		√
EP system	√				√	Int										√		√			√		
MEDITECH	√						√	√			√		√		√	√							
VISTA - CPRS	√					Int							√	√	√	√		√	√				√
EPAS	√																						
HELP	√					Int								√			√		√				
Siemens Inv CPOES	√						√	√	√			Severity	√			√		√	√			√	√
Unnamed BRODOWY	√												√	√				√	√			√	
Unnamed OLIVEN	√											Expl note	√										
Unnamed NAKAYAMA	√			√												√							

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System name	Pop-up moment (when)					Pop-up type	Alert information						Receiver			Action after alert		Override reasons				
	Order entry	Order signing	Drug scanning	Drug administration	Allergy modification		Allergen	Prescribed drug	Type of match	Reaction	Interac type	Others	Phy	Pha	Nur	Accept override alert	Pharmacist warns Phy	Yes	No	Obligatory	Voluntary	Codified format	Free Text

System names: BICS: Brigham Integrated Clinical Information System, BWH: Brigham and Women's Hospital, MGH: Massachusetts General Hospital, Eclipsys SCM-UMCL: Eclipsys Sunrise Clinical Manager: UM-CareLink, Cerner Millennium: Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer), Epic ES: Epic Electronic system, VISTA- CPRS: Veterans information technology architecture computerized patient record system, EPAS: Enterprise Patient Administration System, siemens Inv CPOES: Siemens Invision CPOE system, HELP: Health evaluation through logical processing. **Pop-up moment (when):** Allergy Modification: allergy status modifications. **Pop-up type:** Int: interruptive. **Alert information shown:** Interac type: Interaction type (drug-drug interaction alert, drug allergy alert, etc.), Hosp: hospital, Cred: credentials, Expl note: short explanatory note, **Receiver:** Phy: physician, Pha: pharmacist, Nur: nurse. **Action after alert:** Pha: pharmacist, Phy: physician. **Override reasons**: Aft: after, Bef: before, Cus: customized.*If known, if there are previous override reasons

Appendix D. Overridden drug allergy alerts characteristics

Author, year	System name	Drug or drug group that generated overridden alerts					Type of match			Reaction recorded in dug allergy lists				
		Opioids (%)	Antibiotics (%)	Sulfa drugs (%)	NSAIDs (%)	Other drugs (%)	Exact match (%)	Group match (%)	Cross-sensitivity (%)	GIU (%)	Rash (%)	Life threatening reactions (%)	Anaphylaxis (%)	Unknown (%)
Hsieh (2004)[16]	BICS - BWH	39	Cepha: 21	13	11	Other anti-biotics: 4	10	90 (non-exact match)						
Topaz (2015)[18]	BICS – BWH & MGH						10.9#	89.1# **						
Topaz (2015)[11]	BICS - BWH & MGH						10.6#	77.3#	12.1#					
Slight (2017)[9]	BICS - BWH	54.1#	Cepha & β-l: 13.5			Others: 22.7				25.8	17.1			26.0
Wong (2017)[33]	BICS - BWH	codeine: 11.3 morphine: 7.4	Penicillins: 18.3							8.8	12.5			28.1
Wong (2017)[37]	BICS - NEW vs BWH	Codeine: Prev: 19.3; New: 21.5 Oxy/ace: Prev:7.8; New: 6.6	Penicillins: Prev: 21.6 New: 11.5											
Wong (2018)[36]	BICS - NEW					Ace*: 39.9	89.5					10.4*	4.7*	
Swiderski (2007)[43]	Siemens Inv CPOES						6.0	94.0						
Bryant (2014)[15]	Cerner Millen						9.4 #		90.6#					
Genco (2016)[8]	Epic ES						14.5	85.5						

System names: BICS: Brigham Integrated Clinical Information System, BWH: Brigham and Women's Hospital, MGH: Massachusetts General Hospital, Siemens Inv CPOES: Siemens Invision CPOE system, Cerner Millen: Cerner Millennium (inpatients EMR) + Epic systems (admission, discharge, transfer), Epic ES: Epic Electronic system**; Drug or drug group that generated overridden alerts**: Oxy: oxycodone, Ace: acetaminophen, Prev: previous system, New: new system, Cepha: cephalosporins, β-l: beta-lactams; **Reaction recorded:** GIU: gastrointestinal upset. *Exact Match alerts, **opioids alerts, #data calculated in this review.

Appendix E. Override reasons given by providers

Author, year	Override reasons											
	Tolerated previously (%)	No allergy/ tolerated (%)	Aware/ will monitor (%)	Therapeuticallyappropriate (%)	Physician/ pharmacist approved (%)	Low risk Cross Sensitivity reaction (%)	Benefit outweighed risk (%)	Pre-medicated (%)	Desensi-tization (%)	Okey (%)	Other/ Free Text (%)	No override reason given (%)
Kupperman (2003)[32]	33	7	42								18	
Hsieh (2004)[16]	10	33	55								3	
Topaz (2015)[18]	29*	1.8*	7.1*								17.2*	44.9*
Topaz (2015)[11]	50.9	3.5	13.1					1.3			30.9	
Slight (2017)[9]	57.4		17.2			12.3				3.17	8.4	
Wong (2017)[33]	10.7**		7.6**						68.8**		12.9**	
Wong (2017)[34]	51.2		19.3			12.8						

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Author, year	Override reasons											
	Tolerated previously (%)	No allergy/ tolerated (%)	Aware/ will monitor (%)	Therapeuticallyappropriate (%)	Physician/ pharmacist approved (%)	Low risk Cross Sensitivity reaction (%)	Benefit outweighed risk (%)	Pre-medicated (%)	Desensi-tization (%)	Okey (%)	Other/ Free Text (%)	No override reason given (%)
Nanji (2018)[35]	57.4		17.2			12.3						
Wong (2018)[36]	37.9***		46.4***									
Swiderski (2007)[43]	70	9			6	9						
Hunteman (2009)[44]	49			24			29				8	
Jani (2011)[45]	14	18	68									
Bryant (2014)[15]					√							

Override reasons: Tolerated previously: Patient has tolerated the medication in the past with adequate tolerance, **No allergy/tolerated**: patient does not have the allergy or not true allergy or allergy questionable, **Aware/would monitor**: aware or will monitor or no reasonable alternative, **Therapeutically appropriate**: the medication was therapeutically appropriate, **Physician/pharmacist approved**: physicians or pharmacist approved drug administration, **Low risk Cross-sens:** low risk cross-sensitivity reaction, **Benefit > risk**: benefit outweighed risk, **Premedicated**: patient has sensitivity but will be pre-medicated prior to administration, **Desensitization**: administer per desensitization protocol, **Ok**: 'okey', **other/Free Text:** free text explanation or other reasons. *opioids alerts, **exact match and anaphylaxis reaction alerts, ***exact match and life threatening reactions

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