BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016546
Article Type:	Research
Date Submitted by the Author:	09-Mar-2017
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology
Keywords:	patient safety, Adverse events < THERAPEUTICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Comparison of two methods to estimate adverse events in the IBEAS STUDY (Iberoamerican study of adverse events): cross sectional versus retrospective design.

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ABSTRACT:

BACKGROUND

Adverse events epidemiology is the first step to improve practice in healthcare system. Usually, the preferred method used is the incidence study design, with retrospective reviews of the medical records. However this data collection involves a sophisticated sampling plan, and a process of intensive review of sometimes very heavy and complex medical records. Cross-sectional surveys or prevalence design is also a valid and feasible methodology to study adverse events.

OBJECTIVES: The aim of this study is to compare the adverse event detection using two different methodologies: cross sectional versus retrospective design.

SETTING: Secondary and tertiary hospitals in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru.

PARTICIPANTS: The IBEAS study is a cross sectional survey with a sample size above 11555 patients. The incidence retrospective study was obtained from a 10% random sample proportional to hospital size from the entire IBEAS study population.

METHODS: This study compares the one-day prevalence of the adverse events obtained in the IBEAS study with an incidence study one.

RESULTS: The prevalence of adverse events was 10,46% (95%CI: 9,91 to 11,04) (1206/11379), while the accumulated incidence in the retrospective incidence study was 28,9% (95%CI:25,9 to 31,2) (314/1088),). In both studies the highest risk of suffering adverse events was seen in ICU patients. Comorbid patients showed higher risk and also did patients with medical devices.

CONCLUSION: The incidence design, although requires more resources, allows to detect more adverse events than prevalence design.

ARTICLE SUMMARY

Strengths: The identification of adverse events is the first step to improve patient safety. We know prevalence studies are easier and less expensive to measure the adverse events.

This article adds the comparison between different study designs, and find the most efficient to find adverse events in the clinical practice.

We learn with this study that incidence design allows to detect more adverse events compared with prevalence ones. The ICU patients have more adverse events, and also patiens with comorbidities.

Limitations: All the results depend on the clinical history records quality. This could contribute to a low comparability between different countries and healthcare systems.

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INTRODUCTION

Valid and timely information about the frequency and impact of healthcare related adverse events (AE) and about the system's ability to detect, prevent and manage these AE is extremely important to understand the failures of healthcare, and to design and evaluate the effectiveness of risk reduction strategies. Increasingly, a large number of research studies have estimated such type of information in various health systems and organizational contexts[1], leading to a growing body of evidence about the burden and nature of adverse events caused by healthcare. One of the most important sources of information for such type of data are the patients' medical records, most frequently through the practice of retrospective reviews following agreed protocols and standard abstract forms. This methodology has consolidated itself as one of the most valid references in the field of patient safety research[2]. Nevertheless, despite the advantages of retrospective records reviews in identifying important and observable adverse events, there are also some concerns about the capacity to conduct such methodology in facilities with weaker data and research infrastructure, and moreover when certain periodicity is desirable for monitoring the effectiveness of risk reduction strategies.

Every research methodology and data collection system has their own caveats[3]. Routine information systems have limitations related to compliance and coding bias. Events reporting systems also show preference for the type of events that reporters consider more relevant and have difficulties tracing duplicates, in addition to still facing unresolved legal issues in many contexts, which penalize reporting and limit their effective use. Prospective studies tend to focus on the analysis of higher-risk patients in detriment of other patients. Medical records, electronic or not, are threatened as well by lack of completeness and recording bias, since clinicians tend to record the data that is more meaningful to them from a clinical point of view. In addition, medical retrospective records review involve a sophisticated sampling plan, and a resource intensive process of record retrieval, reviewing and abstracting of sometimes very heavy and complex medical records.

A data collection process that has been less frequently used in the field of patient safety research, despite its potential, consists of running periodic cross-sectional surveys aiming to assess the point prevalence of AE[4,5]. This design has been commonly used to monitor the frequency of healthcare associated infections in many hospitals across Europe and elsewhere[6], where it has proven to be a feasible and valid methodology, capable to be run with no excessive resources at large scale and across many institutions and organizational cultures. Among the advantages of this design are that instead of requiring a statistically savvy sampling plan, all patients admitted at a given time to the hospital can be surveyed at once, simplifying the sampling process as well as the search and retrieval of records from the archives, since these are usually located near the patients in the wards[7]. This design also gives researchers the opportunity to ask the attending clinicians for some clarifications in the records, including some missing data. The unit of observation in this design is typically one day of admission, which makes it much shorter and simpler for the reviewers, and gives an estimate of a one-day prevalence, as opposed to the period or incidence rate of a retrospective record review[8]. Because of its greater simplicity, the management of large and multi-centered research studies is also simplified.

The IBEAS study was a multi-country effort aiming to estimate for the first time the frequency of hospital related AE in a selection of hospitals from Argentina, Colombia, Costa Rica, Mexico and Peru[9]. The study was conducted in 2007, in 58 hospitals of the 5 countries, with the collaboration of Spain, and the Panamerican and World Health Organizations. It used a one-day prevalence design

due to the perceived simplicity, lesser demands, and the greater opportunities for strengthening local capacity and eventual replication of this approach. The researchers involved in designing IBEAS, aware of its innovative approach in the field of adverse event measurement, were mindful of determining the relationship between the estimates of the one day point prevalence design and the more traditional retrospective record review approach. In context Michel et al[10] evaluated the rates comparing tree different methods: cross sectional, prospective and retrospective. Therefore, we select a randomized sample of all IBEAS patients to fully examine retrospectively their medical records. The AE definitions used in both designs were those published by WHO in the International Classification for Patient Safety.[11]

METHODS

The IBEAS study had two parts[12], a cross-sectional (prevalence) study and a retrospective (incidence) study.

The cross-sectional or prevalence study involved determining how many patients admitted to the participating hospitals experienced harmful incidents attributable to health care on a given day (day 0). A prevalent AE is defined as one that originates during hospitalization and is clinically present on the day of the study, either as an after-effect or under treatment. This also includes those AE that were occasioned prior to hospitalization at any care level and which led to subsequent admission. AE that had occurred prior to the survey and whose effects had disappeared without prolonging the hospitalization on that particular day were not included.

The retrospective incidence study was conducted using a sample of patients with the aim of confirming whether the prevalence study could replace the conventional incidence study used to date. Specifically, the study involved reviewing the case notes of a random sample of 10% of patients (1.101 patients) hospitalized on day 0, proportional to hospital size, from the entire IBEAS study population. Case notes were scanned to ascertain whether, at some point during their hospitalization (or in a previous admission to the hospital), inpatients had experienced a harmful incident, regardless of whether the consequences of the incident were still present on day 0. Patients continued to be monitored until discharge. The sampling strategy and forms are available upon request. An incident AE is defined as one that occurs during any patient care process, as it may be detected at another level of care or in other hospital. In practical terms, as we carried out a retrospective study based on clinical hospital records, primary care AE were not included. Those that led to readmission in the same or another hospital were compensated by the AE which were detected during this hospitalization and which had been originated in a previous hospitalization.

The IBEAS study was made in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru. The number of hospitals included was 58, all of them secondary and tertiary level hospitals. We used a purposive sample of hospitals and the inclusion was voluntary.

The sample size was of above 11555 patients, with a minimum of 2000 patients per country.

In both studies (cross sectional and retrospective), researchers used two tools to detect harmful incidents, namely a Screening Guide and a Modular Questionnaire[13,14] to identify harmful incidents using the medical record review methodology[15,16].

First, the screening guide was applied to the patients in the study. This served as an alert and tracking system for possible incidents. All the patients admitted at hospital (except emergency room) were studied. The screening was made by well trained nurses.

If a patient screened positive for one or more of the 19 alert criteria in the screening guide, the case was studied using the case history. An in-depth study of case histories enabled researchers to conclude whether a patient did in fact present with the consequences of a harmful incident (true positive) and if so, to classify the type of event, its severity, any associated factors, and whether or not the incident could have been avoided, etc. This second confirmatory review was made (in both cross sectional and retrospective) by medical doctors with at least 5 years of clinical experience. A patient could have more than one AE in the same hospitalization, and in this case the study collects all of them.

The reviewers training took place in two stages. First, the trainer workshop addressed the national coordinating teams in Buenos Aires 2007. Second, the national coordinators trained in turn the national investigators. A concordance study was carried out in Bogotá in 2008 using clinical records from each country. The most complex cases were assessed and an agreement was reached.

The preventable AE and the gravity were assessed according to the recommendations in the Modular Questionnaire, and the reviewers were also trained in these criteria.

The cross sectional and the retrospective study were made by the same reviewers in each country.

The completed review forms of the retrospective study were entered in electronic files and submitted to a central repository managed exclusively by the principal investigators. Descriptive and multivariate analyses were conducted using SPSS 14. Logistic regression were used to estimate the prevalence and incidence of AE, once taking into account the effect of some covariates, such as patient's age and comorbidity (intrinsic factors), presence of catheter lines and medical devices (extrinsic factors), type of admission, and type of hospital. The IBEAS study maintained ethical conduct of research, and was approved by the PAHO Ethics Review Committee and by the national ethics review committees of each participating country.

RESULTS

The number of patients included in the cross sectional study was 11.379 patients. 3853 of them (33.9%) fulfilled at least one of the screening criteria. In the second phase of the cross-sectional study 1.191 patients had an AE, which means a prevalence of AE of 10,46% (CI 95%: 9,91 to 11,04).

For the retrospective study, a total of 1.101 patients (10%) were randomly selected from all the 11.379 patients included in the cross sectional study. The medical records of 13 of these patients (1,2%) could not be retrieved and were excluded from the study.

Table 1 presents the characteristics of the two study samples. Patients in the retrospective review study were of similar sex composition than the cross sectional study sample. Though they were slightly older, they did not show significant differences in their intrinsic factors (comorbidity). It seemed there were more patients in surgical wards and with slightly more procedures in the retrospective review sample than the patients in the one-day prevalence study. The composition of participating hospitals and type of admission was comparable in the two arms of the study.

Table 1. Characteristics of the study population.

		RETROSPECTIVE			CROSS SECTIONAL			p value
Patients studied		1088			11379			
Age	Median (IQR)*	41	42,0		39,0	44,00		0,03
	Mean (SD)*	42,1	26,0		40,2	26,99		0,02
		n	**%**	**CI 95%**	**n**	**%**	**CI 95%**	
Sex	Women	547	50,3	47,3-53,2	5975	52,5	51,6-53,4	n.s.
Age	Median (IQR)	41	42,0		39,0	44,0		0,03
	Mean (SD)	42,1	26,0		40,2	26,9		0,02
Department	Medical wards	371	34,1	31,3-36,9	4045	35,5	34,7-36,4	0,001
	Surgery/ gynaecology	435	40,0	37,1-42,9	3898	34,3	33,4-35,1	
	Obstetrics	109	10,0	8,2-11,8	1241	10,9	10,3-11,5	
	Paediatrics	128	11,8	9,9-13,7	1701	14,9	14,3-15,6	
	Intensive care	45	4,1	3-5,3	494	4,3	4-4,7	
Hospital Complexity	Tertiary	1011	92,9	91,4-94,4	10520	92,5	92-92,9	n.s.
	Secondary (with surgery and ICU wards)	77	7,1	5,6-8,6	859	7,5	7,1-8	
Admission type	Unplanned admission	726	79,3	63,9-69,5	8031	70,6	69,7-71,4	n.s.
	Planned admission	190	20,7	15,2-19,7	2099	20,7	17,7-19,2	
Intrinsic risk factors	Yes	615	56,5	53,6-59,5	6128	53,9	52,9-54,8	n.s.
	No	473	43,5	40,5-46,4	5251	46,1	45,2-47,1	
Extrinsic risk factors	Yes	844	77,6	75,1-80,1	8484	74,6	73,8-75,4	0,03
	No	244	22,4	19,9-24,9	2895	25,4	24,6-26,2	

*IQR: interquartilic range, SD: standard deviation
n.s.: no significant (p>0,05)

The screening phase of the retrospective review found about 44,5% of the medical records, corresponding to 484 patients, positive for at least one of the 19 triggers included in the forms. At the confirmatory phase, it was determined that 40 of those patients had experienced one or more incidents without harm or prolonged stay, and 288 patients had experienced at least one harmful patient safety incident. Of these, in 215 patients the incident was considered to be mostly related to the health care received rather than to the patient intrinsic vulnerability. Thus the proportion of patients suffering at least an adverse event related to the care received before or during their hospitalization was close to 19,8% (95% CI: 17,2 to 21,9). In total, there were 314 AE (because a patient could have more than one AE) related to healthcare corresponding to a retrospective incidence of AE 28,9% (95% CI: 25,9 to 31,2). Table 2 shows the results of the cross sectional study and the retrospective record review per country, showing the rate of positive screening and its positive predictive value and the corresponding final estimate in terms of one-day prevalence and the proportion of patients with at least one adverse event during their hospitalization. In the one-day prevalence study, the rate of positive screening review form (SRF) seemed to range more homogenously between 30 to 39% of all records, with Positive Predictive Values (PPV) between 25% and 37%. In the retrospective review, however, the range of positive screening was wider going from

about 17% to almost 64% of all records, and also reaching higher Positive Predictive Values from 24% to over 60%. In all countries, the percentage of patients suffering at least one adverse event during their hospitalization was significantly higher than the rate observed in the one-day study, with values going from 11% of patients to more than 36%.

Table 2. Adverse events frequency measures and screening form performance.

	Cross sectional study			Retrospective study		
	Positive Screening review form	Positive Predictive Values	Prevalence of adverse events	Positive Screening review form	Positive Predictive Values	Accumulated incidence of adverse events
Country 1	39,0	33,7	13,1	61,7	51,7	31,9
Country 2	30,6	25,3	7,7	38,9	32,1	12,5
Country 3	35,4	34,3	12,1	63,7	57,0	36,3
Country 4	34,5	24,7	8,5	46,9	24,4	11,4
Country 5	31,1	37,1	11,6	17,1	60,5	19,8

In both studies, the highest risk of suffering adverse events was seen in ICU patients. Surgical patients were associated with more risks than patients admitted in the medical wards. Whereas, in the cross sectional prevalence study, obstetrics and pediatric patients also showed higher risk than medical patients. Comorbid patients showed higher risk of suffering adverse events in both studies, as well as patients with catheter lines, and other procedures. Similarly, the length of stay before the day of study in the cross sectional study and the total length of stay in the retrospective one were associated with the higher risk of suffering adverse events. In the retrospective review, emergency hospitalizations seemed not to be associated to the risk of suffering adverse events as this seemed the case in the cross sectional prevalence study. Patient age was not retained as an independent variable or as a confounding factor in the final model in both studies (Table 3).

Table3. Correlates of adverse events in multiple logistic regression analyses.

	PREVALENCE				INCIDENCE			
Variables	p-value	OR	95% CI for OR		p-value	OR	95% CI for OR	
Department (1)	0,00				0,00			
Surgery and gynaecology	0,06	1,17	0,99	1,38	0,01	1,75	1,17	2,61
Obstetrics	0,02	1,37	1,06	1,78	0,05	0,38	0,15	0,99
Paediatrics	0,00	1,50	1,21	1,85	0,15	0,40	0,12	1,40
Intensive care	0,00	2,52	1,96	3,26	0,01	2,77	1,25	6,17
Complexity of the hospital (2) tertiary	0,02	1,45	1,07	1,97				
Type of admission (3) urgent	0,00	1,34	1,12	1,61	0,59	1,14	0,71	1,83
Length of stay until the day of study	0,03	1,00	1,00	1,00	0,01	1,00	1,00	1,01
Patient comorbidty (4) any	0,00	1,42	1,22	1,64	0,00	2,02	1,28	3,19
Use of medical devices (5) any	0,00	2,59	2,14	3,14	0,00	3,24	1,79	5,85
Country 1	0,00				0,00			
Country *2*	0,00	0,46	0,38	0,56	0,00	0,34	0,20	0,59
Country *3*	0,37	0,91	0,73	1,12	0,16	1,44	0,86	2,41

Country *4*	0,00	0,65	0,52	0,81	0,00	0,22	0,12	0,42
Country *5*	0,04	0,82	0,69	0,99	0,01	0,38	0,19	0,76
Constant	0,00	0,04			0,00	0,03		

Reference categories: (1) medical specialties; (2) secondary hospitals of intermediate complexity with at least surgical theatres, and postsurgical resuscitation wards; (3) planned admission; (4) and (5) absence of risk factors.

The types of AE identified in both the one-day prevalence study and the retrospective review showed similar distribution. The most frequent types of AE identified in any study were related to the occurrence of healthcare associated infections (more than 35% of all AE), followed by AE related to procedures (more than 26%). Medication related incidents represented less than 10% of all AE in each of the studies (Table 4).

Table 4. AE types and proportion of total AE.

Type of AE	Prevalence	Incidence
Care provided	13,27%	16,24%
Medication	8,23%	9,87%
Healthcare associated infections	37,14%	35,99%
Related to procedures	28,69%	26,75%
Diagnostic issues	6,15%	5,10%

Example of AE	Prevalence	Incidence
Nosocomial urinary tract infection	4,1%	5,1%
Nosocomial pneumonia	9,4%	6,4%
Post-surgical hematoma	2,9%	3,5%
Phlebitis	3,4%	5,7%
Neonatal complications	1,1%	0,3%

There were some differences in the impact caused by the adverse events identified in the prevalence study, versus the retrospective review. The adverse events identified through the prevalence study seemed to be associated more frequently with hospital readmissions and slightly more with prolonged stay, whereas the frequency of adverse events which did not caused prolonged stay or readmission was higher in the retrospective review (Table 5).

Table 5. Impact of Adverse events in hospitalization. n (%)

	Prevalence		Incidence	
Did not prolonged hospital stay	228	18,9%	87	29,9%
Prolonged hospital stay	759	62,9%	178	61,2%
Extra days same hospitalization	16,1	29,6	14,9	19,9
Causing admission	219	18,2%	26	8,9%
Extra days new hospitalization	21,4	69,7	19,0	22,3

The preventability of adverse events was very similar, with about 65% in the retrospective review and 60% for the one-day prevalence study.

DISCUSSION

The choice of the most appropriate epidemiological method in the study of magnitude of AE is not a trivial issue. The question has been analysed in different studies and the generalized consensus is that the choice of method should be based on the aims of the study and the need to combine the

minimization of bias and the validity of AE identification with the reproducibility of value judgements on their iatrogenic nature and/or preventability[17].

The retrospective design for the study of AE would be the method of choice once all national studies were carried out using this approach1, nevertheless it is a method which produces results which may be heavily influenced by the quality of clinical records.

A prospective study offers pedagogical and communicative advantages and facilitates a concomitant analysis of the root causes which provide the conditions for the occurrence of adverse events. However not only might it prove too costly, but it would also involve a high workload and excessive complexity.

On the other hand, the transversal design is more time and resource-efficient and easier to perform. Although it does not allow for a study of the total hospitalization episode, it has proved capable of sustaining over time a more stable system of observation. We also need to bear in mind that, as a result of a possible survival bias, those AE which lead to hospital admission will be over-represented, as will those related to nosocomial infection or those which are difficult to identify if the patient is not examined (such as bruising), due to the systemic approach itself of a prevalence study. As in the prospective approach, communication with the ward staff (the patient is hospitalized at this time) makes it easier to judge the causality of the adverse effect and its preventability.

The relationship between prevalence and incidence generally depends on the duration of the event under review and the period of observation[8]. In our case we calculated prevalence on a given day and not during the whole period. Consequently this relationship will not be well reflected. In figure 1 we see the possible AE which may occur and those that are detected on the basis of this approach.

When we compare the results of the prevalence study with those of the incidence study within the context of the IBEAS project, the differences are due exclusively to the design, as the methodology and sample are the same (assuming the representativeness of the incidence sub-cohort). In figures 1a and 1b, which represent the scheme followed in the methodology of this study, we see that the difference between the prevalence and incidence values on a given day are due to those AE which, having occurred during hospitalization, are not prevalent on the day of the study (represented by a yellow arrow in figure 1a). This also explains why the patients of the incidence study present more extrinsic risk factors (devices) than in the prevalence study.

The screening review form has been used in American[18,19] and Australian[20,21] cohort studies and in different European[22,23] countries. It is highly sensitive (84%) in the detection of AE and we therefore assume that the number of false negatives should be small. We also can detect with the revision of the modular questionnaire .

Appropriateness of the review forms to a point prevalence study was discussed during the training workshop. Modifications to adapt them to the context of Latin America were done not only bearing in mind vocabulary, but also adding common risk factors like malaria or prematurity.

The percentage of patients flagged in the SRF and the predictive value of this phase in the detection of AE are totally compatible with those found in those other AE studies of which we are aware. We can therefore state that the materials are sensitive enough and appropriate for the identification of both prevalence and incidence AE. However, in the retrospective study, the PPV (positive predictive value) of the SRF is higher. This may be due to the fact either that the guide was originally designed for an incidence study and proves more efficient in this type of study or that as the incidence study

was performed after the prevalence study, it is possible that the experience of the reviewers raised the performance level of the first questionnaire.

The Spanish version of the modular review form (MRF2) was adapted in Spain for the IDEA Project and modified after the ENEAS study[4]. The researcher must make value judgements through implicit criteria on most occasions. Characterization of AE caused by the care rather than the pathological process itself, is done by the reviewer scoring from 1 to 6 the probability that the AE is due to the care. A value of •4 is required to confirm this. The same criterion is used to evaluate the adverse event as preventable. Cross-sectional design allows researchers to consult the medical staff while they are collecting data in order to clarify any uncertainty or doubts associated with the adverse event. The reliability of the questionnaire in other studies has been assessed as moderate[23].

The frequency of AE in both the prevalence and incidence studies was greater than that found in previous studies, which may be due to the different characteristics of the patients, who had a higher average age and more risk factors. The nature of the sample selection and the peculiarities of the different search systems prevent statistical inferences and comparisons either within each country or between the countries which are part of the study.

In any case, higher prevalence means higher incidence. In some way the interdependence of these frequency measures remains when we use prevalence on a given day. The fact that prevalence is sensitive to the differences in the characteristics of the patients and that it reflects the differences found between countries, would make it a useful tool in the study and follow-up of the frequency of AE and in comparative studies. Furthermore, as the explanatory model for the occurrence of AE is the same, studying the factors which influence prevalence may provide the same clues when designing strategies for AE control and therefore provide a more efficient tool.

Moreover, the fact that the prevalence design detects proportionally more serious AE is not a drawback. On the contrary, these are precisely the AE which need to be prioritized when designing control strategies, and as we commented above, the detected AE were equally preventable in both designs. This reinforces the idea that preventability and seriousness of the EA are independent factors.

As the point prevalence design is more efficient in terms of time and resources, its validity is less dependent on the quality of the clinical records and allows simultaneous study through other observation and audit systems, regular prevalence on a given day studies might provide an efficient AE monitoring and control strategy.

CONTRIBUTORSHIP STATEMENT

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Principal publication's author. He has coordinated the IBEAS project and he is the team leader of this job.

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He has participated in the data collection, he has made the data analysis and the interpretation of the results, and he has participated in the composition of the manuscript.

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He has been coordinator of the IBEAS project, he has evaluated the manuscript and has contributed to improve the presentation.

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She has participated in the data collection, she has coordinated the project with Dr. Aranaz, she has made data analysis, and she has evaluated the results, and she has improved the manuscript.

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He has participated in the evaluation and improvement of the manuscript and data analysis

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She has participated in the evaluation of the manuscript and she has been the responsible of sending the manuscript to the reviewer and editorials.

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She has collaborated in the manuscript composition and she has contributed to the critical review.

Terol García E.

He has been coordinator of the IBEAS project. He has contributed to the critical review of this paper.

Sousa P. He has collaborated in the data analysis and critical review of this paper.

Larizgoitia Jauregui I. She has contributed to improve the paper composition and to the data analysis. She has been also IBEAS project coordinator.

Grupo de trabajo IBEAS: all the members have made the data collection.

COMPETING INTERESTS

None

DATA SHARING STATEMENT

Extra data is available by emailing: jesusmaria.aranaz@salud.madrid.org

ETHICS

The IBEAS project has the ethics approval for every institution in each country.

This study was founded by the Health Ministry of Spain and WHO, but for this article, we haven't had any financial support.

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Figure1a. Study of prevalent AE on a given day. PC: Primary Care, HCC: Healthcare Centre

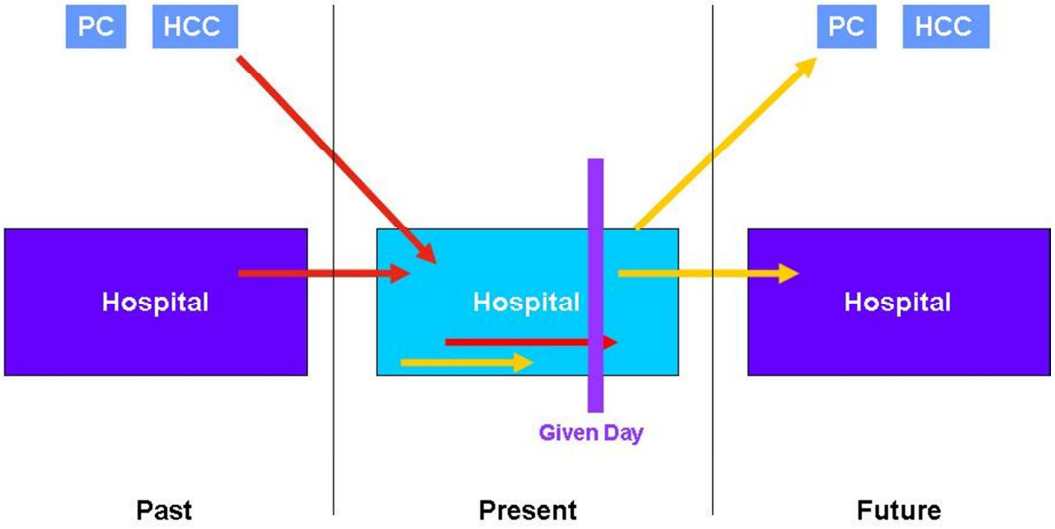

Figure note: For this study, a prevalent AE is defined as one that originates during hospitalization and is clinically present on the day of the study, either as an after-effect or under treatment. This also includes those AE that were occasioned prior to hospitalization at any care level and which led to subsequent admission.

Figure 1b. Scheme of incident AE study. PC: Primary Care, HCC: Healthcare Centre

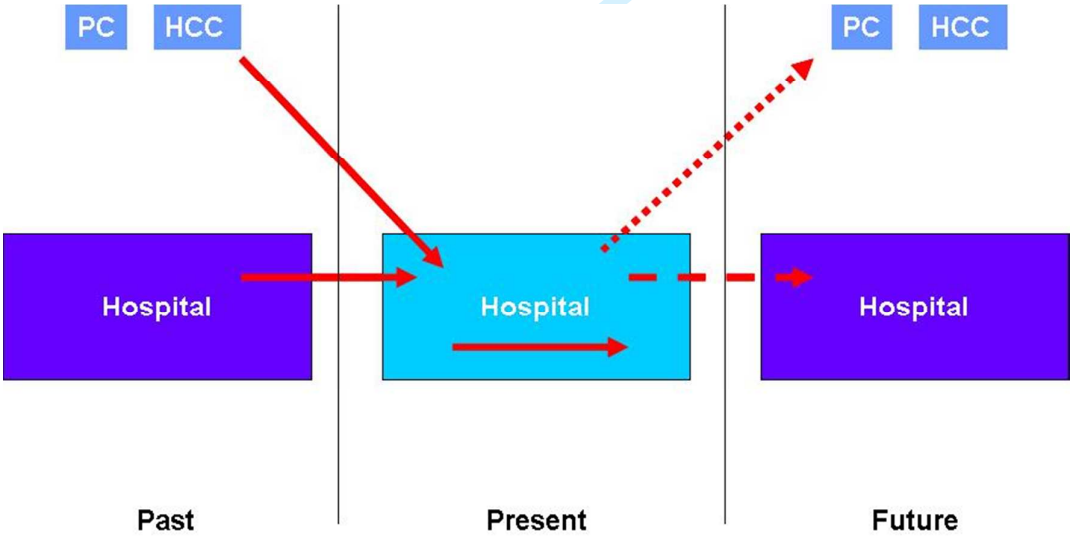

Figure note: An AE incident is defined as one that occurs during any patient care process, as it may be detected at another level of care or in other hospital. In practical terms, as we carried out a retrospective study based on clinical hospital records, primary care AE were not included. Those that led to readmission in the same or another hospital were compensated by the AE which were detected during this hospitalization and which had been originated in a previous hospitalization.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page 4**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4-5**
Bias	9	Describe any efforts to address potential sources of bias **Page 5**
Study size	10	Explain how the study size was arrived at **Page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 5, page 6**
		(b) Give reasons for non-participation at each stage **page 6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 5**
		(b) Indicate number of participants with missing data for each variable of interest **Page 5**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page 7**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Page 8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 10**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 11**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comparison of two methods to estimate adverse events in the IBEAS STUDY (Iberoamerican study of adverse events): cross-sectional versus retrospective cohort design.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016546.R1
Article Type:	Research
Date Submitted by the Author:	07-Jul-2017
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Patient-centred medicine, Health services research, Evidence based practice
Keywords:	patient safety, Adverse events < THERAPEUTICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Comparison of two methods to estimate adverse events in the IBEAS STUDY (Iberoamerican study of adverse events): cross-sectional versus retrospective cohort design.

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ABSTRACT:

BACKGROUND

Adverse events epidemiology is the first step to improve practice in healthcare system. Usually, the preferred method used to estimate the magnitude of the problem is the retrospective cohort study design, with retrospective reviews of the medical records. However this data collection involves a sophisticated sampling plan, and a process of intensive review of sometimes very heavy and complex medical records. Cross-sectional survey is also a valid and feasible methodology to study adverse events.

OBJECTIVES: The aim of this study is to compare the adverse event detection using two different methodologies: cross sectional versus retrospective cohort design.

SETTING: Secondary and tertiary hospitals in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru.

PARTICIPANTS: The IBEAS study is a cross sectional survey with a sample size of 11.379 patients. The retrospective cohort study was obtained from a 10% random sample proportional to hospital size from the entire IBEAS study population.

METHODS: This study compares the one-day prevalence of the adverse events obtained in the IBEAS study with the incidence obtained through the retrospective cohort study.

RESULTS: The prevalence of patients with adverse events was 10,47% (95%CI: 9,90 to 11,03) (1191/11379), while the cumulative incidence of the retrospective cohort study was 19,76% (95%CI: 217,35 to 22,17) (215/1088),). In both studies the highest risk of suffering adverse events was seen in ICU patients. Comorbid patients showed higher risk and also did patients with medical devices.

CONCLUSION: The retrospective cohort design, although requires more resources, allows to detect more adverse events than the cross-sectional design.

ARTICLE SUMMARY

Strengths: The identification of adverse events is the first step to improve patient safety. We know cross sectional studies are easier and less expensive to measure the adverse events.

This article adds the comparison between different study designs, and find the most efficient to find adverse events in the clinical practice.

We learn with this study that the retrospective cohort design allows to detect more adverse events compared with the cross-sectional one. The ICU patients have more adverse events, and also patiens with comorbidities.

Limitations: All the results depend on the clinical history records quality. This could contribute to a low comparability between different countries and healthcare systems.

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INTRODUCTION

Valid and timely information about the frequency and impact of healthcare related adverse events (AE) and about the system's ability to detect, prevent and manage these AE is extremely important to understand the failures of healthcare, and to design and evaluate the effectiveness of risk reduction strategies. Increasingly, a large number of research studies have estimated such type of information in various health systems and organizational contexts[1], leading to a growing body of evidence about the burden and nature of adverse events caused by healthcare. One of the most important sources of information for such type of data are the patients' medical records, most frequently through the practice of retrospective reviews following agreed protocols and standard abstract forms. This methodology has consolidated itself as one of the most valid references in the field of patient safety research[2]. Nevertheless, despite the advantages of retrospective records reviews in identifying important and observable adverse events, there are also some concerns about the capacity to conduct such methodology in facilities with weaker data and research infrastructure, and moreover when certain periodicity is desirable for monitoring the effectiveness of risk reduction strategies.

Every research methodology and data collection system has its strengths and drawbacks[3]. Routine information systems have limitations related to compliance and coding bias. Events reporting systems also show preference for the type of events that reporters consider more relevant and have difficulties tracing duplicates, in addition to still facing unresolved legal issues in many contexts, which penalize reporting and limit their effective use. Prospective studies tend to focus on the analysis of higher-risk patients in detriment of other patients. Medical records, electronic or not, are threatened as well by lack of completeness and recording bias, since clinicians tend to record the data that are more meaningful to them from a clinical point of view. In addition, medical retrospective records review involve a sophisticated sampling plan, and a resource intensive process of record retrieval, reviewing and abstracting of sometimes very heavy and complex medical records.

A data collection process that has been less frequently used in the field of patient safety research, despite its potential, consists of running periodic cross-sectional surveys aiming to assess the point prevalence of AE[4,5]. This design has been commonly used to monitor the frequency of healthcare associated infections in many hospitals across Europe and elsewhere[6], where it has proven to be a feasible and valid methodology, capable to be run with no excessive resources at large scale and across many institutions and organizational cultures. Among the advantages of this design are that instead of requiring a statistically savvy sampling plan, all patients admitted at a given time to the hospital can be surveyed at once, simplifying the sampling process as well as the search and retrieval of records from the archives, since these are usually located near the patients in the wards[7]. This design also gives researchers the opportunity to ask the attending clinicians for some clarifications in the records, including some missing data. The unit of observation in this design is typically one day of admission, which makes it much shorter and simpler for the reviewers, and gives an estimate of a one-day prevalence, as opposed to the cumulative incidence of a retrospective record review[8]. Because of its greater simplicity, the management of large and multi-centered research studies is also simplified.

The IBEAS study was a multi-country effort aiming to estimate for the first time the frequency of hospital related AE in a selection of hospitals from Argentina, Colombia, Costa Rica, Mexico and Peru[9]. The study was conducted in 2007, in 58 hospitals of the 5 countries, with the collaboration of Spain, and the Panamerican and World Health Organizations. It used a one-day cross-sectional design due to the perceived simplicity, lesser demands, and the greater opportunities for strengthening local capacity and eventual replication of this approach. The researchers involved in designing IBEAS, aware of its innovative approach in the field of adverse event measurement, were mindful of determining the relationship between the estimates of the one day point prevalence design and the more traditional retrospective cohort record review approach. In this same context Michel et al[10] evaluated the rates comparing three different methods: cross-sectional, prospective and retrospective. Therefore, we selected a randomized sample of all IBEAS patients to fully examine retrospectively their medical records.

METHODS

The AE definitions used in both designs were those published by WHO in the International Classification for Patient Safety.[11]

A patient safety incident is an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient.

An adverse event or harmful incident is an incident that results in harm to a patient.

Harm implies impairment of structure or function of the body and/or any deleterious effect arising there from, including disease, injury, suffering, disability and death, and may be physical, social or psychological.

In the IBEAS project the AD was defined as[9]: "Any event causing harm to the patient that is perceived to be more related to the healthcare management rather than to the patient`s underlying condition"

The IBEAS study had two parts[12], a cross-sectional study and a retrospective cohort study.

The cross-sectional study involved determining how many patients admitted to the participating hospitals experienced harmful incidents attributable to health care on a given day (day 0). A prevalent AE is defined as one that originates during hospitalization and is clinically present on the day of the study, either as an after-effect or under treatment. This also includes those AE that were occasioned prior to hospitalization at any care level and which led to subsequent admission. AE that had occurred prior to the survey and whose effects had disappeared without prolonging the hospitalization on that particular day were not included.

The retrospective cohort study was conducted using a sample of patients with the aim of confirming whether the cross-sectional study could replace the conventional retrospective cohort study used to date. Specifically, the study involved reviewing the case notes of a random sample of 10% of patients (1.101 patients) hospitalized on day 0, proportional to hospital size, from the entire IBEAS study population. Case notes were scanned to ascertain whether, at some point during their hospitalization (or in a previous admission to the hospital), inpatients had experienced a harmful incident, regardless of whether the consequences of the incident were still present on day 0. Patients continued to be monitored until discharge. The sampling strategy and forms are available upon request. An incident AE is defined as one that occurs during any patient care process, as it may be

detected at another level of care or in other hospital. In practical terms, as we carried out a retrospective study based on clinical hospital records, primary care AE were not included. Those that led to readmission in the same or another hospital were compensated by the AE which were detected during this hospitalization and which had been originated in a previous hospitalization.

The IBEAS study was carried out in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru. The number of hospitals included was 58, all of them secondary and tertiary level hospitals. We used a purposive sample of hospitals and the inclusion was voluntary.

The sample size was of 11379 patients, with a minimum of 2000 patients per country.

In both studies (cross sectional and retrospective cohort), researchers used two tools to detect harmful incidents, namely a Screening Guide and a Modular Questionnaire[13,14] using the medical record review[15,16].

First, the screening guide was applied to the patients in the study. This served as an alert and tracking system for possible incidents. All the patients admitted at hospital (except emergency room) were studied. The screening was made by well trained nurses.

If a patient screened positive for one or more of the 19 alert criteria in the screening guide, the case was studied using the case history. An in-depth study of case histories enabled researchers to conclude whether a patient did in fact present with the consequences of a harmful incident (true positive) and if so, to classify the type of event, its severity, any associated factors, and whether or not the incident could have been avoided, etc. This second confirmatory review was made (in both cross sectional and retrospective) by medical doctors with at least 5 years of clinical experience. A patient could have more than one AE in the same hospitalization, and in this case the study collects all of them.

The reviewers training took place in two stages. First, the trainer workshop addressed the national coordinating teams in Buenos Aires 2007. Second, the national coordinators trained in turn the national investigators. A concordance study was carried out in Bogotá in 2008 using clinical records from each country. The most complex cases were assessed and an agreement was reached.

The preventable AE and the gravity were assessed according to the recommendations in the Modular Questionnaire, and the reviewers were also trained in these criteria.

The cross sectional and the retrospective cohort study were made by the same reviewers in each country.

The completed review forms of the retrospective study were entered in electronic files and submitted to a central repository managed exclusively by the principal investigators. Descriptive and multivariate analyses were conducted using SPSS 14. Logistic regression were used to estimate the prevalence and incidence of AE, once taking into account the effect of some covariates, such as patient's age and comorbidity (intrinsic factors), presence of catheter lines and medical devices (extrinsic factors), type of admission, and type of hospital. The IBEAS study maintained ethical conduct of research, and was approved by the PAHO Ethics Review Committee and by the national ethics review committees of each participating country.

RESULTS

11.379 patients were included in the cross-sectional study (see Figure 1). 3853 of them (33.9%) fulfilled at least one of the screening criteria. In the second phase of the cross-sectional study 1.191 patients had an AE

For the retrospective cohort study (see Figure 2), a total of 1.101 patients (10%) were randomly selected from all the 11.379 patients included in the cross-sectional study. The medical records of 13 of these patients (1,2%) could not be retrieved and were excluded from the study.

The screening phase of the retrospective review found about 44,5% of the medical records, corresponding to 484 patients, positive for at least one of the 19 triggers included in the forms. At the confirmatory phase, it was determined that 40 of those patients had experienced one or more patient safety incidents without harm or prolonged stay, and 288 patients had experienced at least one AE (harmful patient safety incident). Of these, in 215 patients the AE was considered to be mostly related to the healthcare received rather than to the patient intrinsic vulnerability.

The characteristics of patients in the two types of study are presented in Table 1. Patients in the retrospective cohort study were of similar sex composition than the cross sectional study sample. Though they were slightly older, they did not show significant differences in their intrinsic factors (comorbidity). It seemed there were more patients in surgical wards and with slightly more procedures in the retrospective review sample than the patients in the one-day cross-sectional study. The composition of participating hospitals and type of admission was comparable in the two types of designs.

Table 1. Characteristics of the study population.

		CROSS SECTIONAL			RETROSPECTIVE COHORT			p value
		n	**%**	**CI 95%**	**n**	**%**	**CI 95%**	
Sex	Women	5975	52,5	51,6-53,4	547	50,3	47,3-53,2	n.s.
Age	Mean (SD*)	40,2	26,9		42,1	26	31,3-36,9	0,02
Department	Medical wards	4045	35,5	34,7-36,4	371	34,1	31,3-36,9	0,001
	Surgery/ gynaecology	3898	34,3	33,4-35,1	435	40,0	37,1-42,9	
	Obstetrics	1241	10,9	10,3-11,5	109	10,0	8,2-11,8	
	Paediatrics	1701	14,9	14,3-15,6	128	11,8	9,9-13,7	
	Intensive care	494	4,3	4-4,7	45	4,1	3-5,3	
Hospital Complexity	Tertiary	10520	92,5	92-92,9	1011	92,9	91,4-94,4	n.s.
	Secondary (with surgery and ICU wards)	859	7,5	7,1-8	77	7,1	5,6-8,6	
Admission type	Unplanned admission	8031	70,6	69,7-71,4	726	66,7	63,9-69,5	n.s.
	Planned admission	2099	18,4	17,7-19,2	190	17,4	15,2-19,7	
Intrinsic risk factors	Yes	6128	53,9	52,9-54,8	615	56,5	53,6-59,5	n.s.
	No	5251	46,1	45,2-47,1	473	43,5	40,5-46,4	

Extrinsic risk factors	Yes	8484	74,6	73,8-75,4	844	77,6	75,1-80,1	0,03
	No	2895	25,4	24,6-26,2	244	22,4	19,9-24,9	
Patients studied		11379			1088			

*SD: standard deviation
n.s.: no significant (p>0,05)

As Table 2 shows the prevalence of patients with AE was 10,47% (CI 95%: 9,90 to 11,03)
As a patient can have more than one AE, the total number of AE detected was 1349, so the global prevalence of AE was 11,85% (1349/11379) (CI 95% 11,26 to 12,46).

As Table 2 also shows the cumulative incidence of patients suffering at least one AE related to the care received before or during their hospitalization was 19,76% (95% CI: 17,35 to 22,17) (215/1088). In total, there were 314 AE (because a patient could have more than one AE) related to healthcare corresponding to a cumulative incidence of total AE of 28,86% (95% CI: 26,12 to 31,60) (317/1088).

Table 2. Differences in result measures in both study designs.

	Cross–sectional (prevalence)	Retrospective Cohort (cumulative incidence)
Patients with AE	1191/11379=10,47% (CI 95%: 9,90 to 11,03)	215/1088=19,76% (CI 95%: 17,35 to 22,17)
Total number of AE	1349/11379= 11,85% (CI 95%: 11,26 to 12,46)	314/1088= 28,86% (CI 95%: 26,12 to 31,6)

Table 3 shows the results of the cross-sectional study and the retrospective cohort record review per country, showing the rate of positive screening and its positive predictive value and the corresponding final estimate in terms of one-day prevalence and the proportion of patients with at least one AE during their hospitalization. In the one-day cross-sectional study, the rate of positive screening review form (SRF) seemed to range more homogenously between 30 to 39% of all records, with Positive Predictive Values (PPV) between 25% and 37%. In the retrospective cohort review, however, the range of positive screening was wider going from about 17% to almost 64% of all records, and also reaching higher Positive Predictive Values from 24% to over 60%. In all countries, the percentage of patients suffering at least one AE during their hospitalization was significantly higher than the rate observed in the one-day study, with values going from 11% of patients to more than 36%.

Table 3. Adverse events frequency measures and screening form performance.

	Cross sectional study			Retrospective study		
	Positive Screening review form	Positive Predictive Values	Prevalence of adverse events	Positive Screening review form	Positive Predictive Values	Cumulative incidence of adverse events
Country 1	39,0 % 926/2373 (CI 95%: 37,0 to 41,0)	33,7% 312/926 (CI 95%: 30,6 to 36,8)	13,1% 312/2373 (CI 95%: 11,8 to 14,5)	61,7% 145/235 (CI 95%:6,7 to 8,1)	51,7% 75/145 (CI95%:43,2 to 60,2)	31,9% 75/235 (CI95%:25,7 to 38,1)
Country 2	30,6 887/2897 (CI 95%: 28,9 to 32,3)	25,3% 224/887 (CI 95%: 22,3 to 28,2)	7,7% 224/2897 (CI 95%: 6,7 to 8,7)	38,9% 112/288 (CI95%:33,1 to 44,7)	32,1% 36/112 (CI95%:23,0 to 41,2)	12,5% 36/288 (CI95%:8,5 to 16,5)
Country 3	35,4 578/1632 CI 95%: 33,1 to 37,8)	34,3% 198/578 (CI 95%: 30,3 to 38,2)	12,1% 198/1632 (CI 95%: 6,7 to 8,7)	63,7% 107/168 (CI95%:56,1 to 71,3)	57,0% 61/107 (CI95%:47,2 to 66,9)	36,3% 61/168 (CI95%:28,7 to 43,9)

Country 4	34,5 692/2003 (CI 95%: 32,4 to 36,7)	24,7% 171/692 (CI 95%: 21,4 to 27,9)	8,5% 171/2003 (CI 95%: 7,3 to 9,8)	46,9% 82/175 (CI95%:39,2 to 54,5)	24,4% 20/82 (CI95%:14,5 to 34,3)	11,4% 20/175 (CI95%:6,4 to 16,4)
Country 5	31,1 770/2474 (CI 95%: 29,3 to 32,9)	37,1% 286/770 (CI 95%: 33,7 to 40,6)	11,6% 286/2474 (CI 95%: 10,3 to 12,8)	17,1% 38/222 (CI95%:11,9 to 22,3)	60,5% 23/38 (CI95%:43,7 to 77,4)	10,4% 23/222 (CI95%:6,1 to 14,6)
Total	33,9% 3853/11379 (CI 95%: 32,9 to 34,7)	30,9% 1191/3853 (CI 95%: 29,4 to 32,4)	10,5% 1191/11379 (CI 95%: 9,9 to 11,0)	44,5% 484/1088 (CI95%:41,5to 47,5)	44,4% 215/484 (CI95%:39,3 to 48,3)	19,8% 215/1088 (CI95%:17,3 to 22,2)

In both studies (Table 4), the highest risk of suffering AE was seen in ICU patients. Surgical patients were associated with more risk than patients admitted in the medical wards. Whereas, in the cross-sectional study, obstetrics and pediatric patients also showed higher risk than medical patients. Comorbid patients showed higher risk of suffering AE in both studies, as well as patients with catheter lines, and other procedures. Similarly, the length of stay before the day of study in the cross-sectional study and the total length of stay in the retrospective cohort one were associated with the higher risk of suffering AE. In the retrospective cohort review, emergency hospitalizations seemed not to be associated to the risk of suffering AE as this seemed the case in the cross-sectional study. Patient age was not retained as an independent variable or as a confounding factor in the final model in both studies.

Table 4. Correlates of adverse events in multiple logistic regression analyses.

	CROSS SECTIONAL				RETROSPECTIVE COHORT			
Variables	p-value	OR	95% CI for OR		p-value	OR	95% CI for OR	
Department (1)								
Surgery and gynaecology	0,06	1,17	0,99	1,38	0,01	1,75	1,17	2,61
Obstetrics	0,02	1,37	1,06	1,78	0,05	0,38	0,15	0,99
Paediatrics	0,00	1,50	1,21	1,85	0,15	0,40	0,12	1,40
Intensive care	0,00	2,52	1,96	3,26	0,01	2,77	1,25	6,17
Complexity of the hospital (2) tertiary	0,02	1,45	1,07	1,97				
Type of admission (3) urgent	0,00	1,34	1,12	1,61	0,59	1,14	0,71	1,83
Length of stay until the day of study	0,03	1,00	1,00	1,00	0,01	1,00	1,00	1,01
Patient comorbidty (4) any	0,00	1,42	1,22	1,64	0,00	2,02	1,28	3,19
Use of medical devices (5) any	0,00	2,59	2,14	3,14	0,00	3,24	1,79	5,85
Country 1								
Country *2*	0,00	0,46	0,38	0,56	0,00	0,34	0,20	0,59
Country *3*	0,37	0,91	0,73	1,12	0,16	1,44	0,86	2,41
Country *4*	0,00	0,65	0,52	0,81	0,00	0,22	0,12	0,42
Country *5*	0,04	0,82	0,69	0,99	0,01	0,38	0,19	0,76

Reference categories: (1) medical specialties; (2) secondary hospitals of intermediate complexity with at least surgical theatres, and postsurgical resuscitation wards; (3) planned admission; (4) and (5) absence of risk factors.

The types of AE identified in both the cross-sectional and the retrospective cohort studv showed similar distribution. The most frequent types of AE identified in any study were related to the occurrence of healthcare associated infections (more than 35% of all AE), followed by AE related to procedures (more than 26%). Medication related AE represented less than 10% of all AE in each of the studies (Table 5).

Table 5. AE types and proportion of total AE.

Type of AE	Prevalence	CI 95%	Cumulative incidence	CI 95%
Care provided	13,27%	11,46 to 15,08	12,16%	16,24 to 20,32
Medication	8,23%	6,76 to 9,69	6,57%	9,87 to 13,17
Healthcare associated infections	37,14%	34,56 to 39,72	30,68	35,99 to 41,30
Related to procedures	28,69%	26,27 to 31,10	21,86%	26,75 to 31,65
Diagnostic issues	6,15%	6,15 to 7,44	2,66%	5,10 to 7,53
Nosocomial urinary tract infection	4,08%	2,98 to 5,17	5,09%	2,50 to 7,69
Nosocomial pneumonia	9,41%	7,82 to 11,01	6,37%	3,51 to 9,23
Post-surgical hematoma	2,89%	1,96 to 3,82	3,50%	1,31 to 5,69
Phlebitis	3,4%	2,40 to 4,41	5,73%	3,00 to 8,46
Neonatal complications	1,1%	0,51 to 1,71	0,32%	0,01 to 1,76

There were some differences in the impact caused by the AE identified in the cross-sectional study, versus the retrospective cohort study. The AE identified through the cross-sectional study seemed to be associated more frequently with hospital readmissions and slightly more with prolonged stay, whereas the frequency of AE which did not cause prolonged stay or readmission was higher in the retrospective cohort study (Table 6).

Table 6. Impact of adverse events in hospitalization. n (%)

	Cross sectional		Retrospective cohort	
Did not prolonged hospital stay	228	18,91% (CI 95%: 16,65 to 21,16)	87	29,9%(CI 95%: 24,46 to 35,33)
Prolonged hospital stay	759	62,9% (CI 95%: 60,17 to 65,70)	178	61,2%(CI 95%: 51,88 to 63,58)
Extra days same hospitalization	Mean: 16,1 days SD (29,6)		Mean:14,9 daysSD (19,9)	
Causing admission	219	18,16% (CI 95%: 15,94 to 20,38)	26	8,9% (CI 95%: 5,48 to 12,38)
Extra days new hospitalization	Mean: 21,4 days SD (69,7)		Mean:19,0 daysSE (22,3)	

The preventability of AE (Appendix 1) was very similar, with about 65% in the retrospective cohort review and 60% for the cross-sectional study.

DISCUSSION

The choice of the most appropriate epidemiological design in the study of magnitude of AE is not a trivial issue. The question has been analysed in different studies and the generalized consensus is that the choice of method should be based on the aims of the study and the need to combine the minimization of bias and the validity of AE identification with the reproducibility of value judgements on their iatrogenic nature and/or preventability[17].

The retrospective design for the study of AE has been the method used in all all national studies[1], Nevertheless it is a method which produces results which may be heavily influenced by the quality of clinical records.

A prospective study offers pedagogical and communicative advantages and facilitates a concomitant analysis of the root causes which provide the conditions for the occurrence of AE. However not only might it prove too costly, but it would also involve a high workload and excessive complexity.

On the other hand, the cross-sectional design is more time and resource-efficient and easier to perform. Although it does not allow for a study of the total hospitalization episode, it has proved capable of sustaining over time a more stable system of observation. We also need to bear in mind that, as a result of a possible survival bias, those AE which lead to hospital admission will be over-represented, as will those related to nosocomial infection or those which are difficult to identify if the patient is not examined (such as bruising), due to the systemic approach itself of a prevalence study. As in the prospective approach, communication with the ward staff (the patient is hospitalized at this time) makes it easier to judge the causality of the AE and its preventability.

The relationship between prevalence and incidence generally depends on the duration of the event under review and the period of observation[8]. In our case we calculated prevalence on a given day and not during the whole period. Consequently this relationship will not be well reflected. In Figure 3 we see the possible AE which may occur and those that are detected on the basis of this approach.

When we compare the results of the cross-sectional study with those of the retrospective cohort study within the context of the IBEAS project, the differences are due exclusively to the design, as the methodology and sample are the same (assuming the representativeness of the incidence sub-cohort). In Figures 3 and 4, which represent the scheme followed in the methodology of this study, we see that the difference between the prevalence and incidence values on a given day are due to those AE which, having occurred during hospitalization, are not prevalent on the day of the study (represented by a yellow arrow in Figure 3). This also explains why the patients of the retrospective cohort study present more extrinsic risk factors (devices) than in the cross-sectional study.

The screening review form has been used in American[18,19] and Australian[20,21] cohort studies and in different European[22,23] countries. It is highly sensitive (84%) in the detection of AE and we therefore assume that the number of false negatives should be small. We also can detect with the revision of the modular questionnaire .

Appropriateness of the review forms to a point prevalence study was discussed during the training workshop. Modifications to adapt them to the context of Latin America were done not only bearing in mind vocabulary, but also adding common risk factors like malaria or prematurity.

The percentage of patients flagged in the SRF and the predictive value of this phase in the detection of AE are totally compatible with those found in those other AE studies of which we are aware. We can therefore state that the materials are sensitive enough and appropriate for the identification of both prevalence and cumulative incidence of AE. However, in the retrospective cohort study, the PPV (positive predictive value) of the SRF is higher. This may be due to the fact either that the guide was originally designed for an incidence study and proves more efficient in this type of study or that as the retrospective cohort study was performed after the cross-sectional study, it is possible that the experience of the reviewers raised the performance level of the first questionnaire.

The Spanish version of the modular review form (MRF2) was adapted in Spain for the IDEA Project and modified after the ENEAS study[4]. The researcher must make value judgements through implicit

criteria on most occasions. Characterization of AE caused by the care rather than the pathological process itself, is done by the reviewer scoring from 1 to 6 the probability that the AE is due to the care. A value of •4 is required to confirm this. The same criterion is used to evaluate the adverse event as preventable. Cross-sectional design allows researchers to consult the medical staff while they are collecting data in order to clarify any uncertainty or doubts associated with the adverse event. The reliability of the questionnaire in other studies has been assessed as moderate[23].

The frequency of AE in both the cross-sectional and retrospective cohort studies was greater than that found in previous studies, which may be due to the different characteristics of the patients, who had a higher average age and more risk factors. The nature of the sample selection and the peculiarities of the different search systems prevent statistical inferences and comparisons either within each country or between the countries which are part of the study.

In any case, higher prevalence means higher cumulative incidence. In some way the interdependence of these frequency measures remains when we use prevalence on a given day. The fact that prevalence is sensitive to the differences in the characteristics of the patients and that it reflects the differences found between countries, would make it a useful tool in the study and follow-up of the frequency of AE and in comparative studies. Furthermore, as the explanatory model for the occurrence of AE is the same, studying the factors which influence prevalence may provide the same clues when designing strategies for AE control and therefore provide a more efficient tool.

Moreover, the fact that the prevalence design detects proportionally more serious AE is not a drawback. On the contrary, these are precisely the AE which need to be prioritized when designing control strategies, and as we commented above, the detected AE were equally preventable in both designs. This reinforces the idea that preventability and seriousness of the EA are independent factors.

As the point prevalence design is more efficient in terms of time and resources, its validity is less dependent on the quality of the clinical records and allows simultaneous study through other observation and audit systems, regular prevalence on a given day studies might provide an efficient AE monitoring and control strategy.

CONTRIBUTORSHIP STATEMENT

Aranaz Andrés, Jesús María
Principal publication's author. He has coordinated the IBEAS project and he is the team leader of this job.

Limón-Ramírez R.
He has participated in the data collection, he has made the data analysis and the interpretation of the results, and he has participated in the composition of the manuscript.

Aibar-Remón C.
He has been coordinator of the IBEAS project, he has evaluated the manuscript and has contributed to improve the presentation.

Gea-Velázquez de Castro MT.
She has participated in the data collection, she has coordinated the project with Dr. Aranaz, she has made data analysis, and she has evaluated the results, and she has improved the manuscript.

Bolúmar F.
He has participated in the evaluation and improvement of the manuscript and data analysis.

Hernández Aguado I
He has participated in the evaluation and improvement of the manuscript and data analysis.

López Fresneña N.
She has participated in the evaluation of the manuscript and she has been the responsible of sending the manuscript to the reviewer and editorials.

Díaz Agero Pérez C.
She has collaborated in the manuscript composition and she has contributed to the critical review.

Terol García E.
He has been coordinator of the IBEAS project. He has contributed to the critical review of this paper.

Sousa P. He has collaborated in the data analysis and critical review of this paper.

Larizgoitia Jauregui I. She has contributed to improve the paper composition and to the data analysis. She has been also IBEAS project coordinator.

Grupo de trabajo IBEAS: all the members have made the data collection.

COMPETING INTERESTS
None

DATA SHARING STATEMENT
Extra data is available by emailing: jesusmaria.aranaz@salud.madrid.org

ETHICS
The IBEAS project has the ethics approval for every institution in each country.
This study was founded by the Health Ministry of Spain and WHO, but for this article, we haven't had any financial support.

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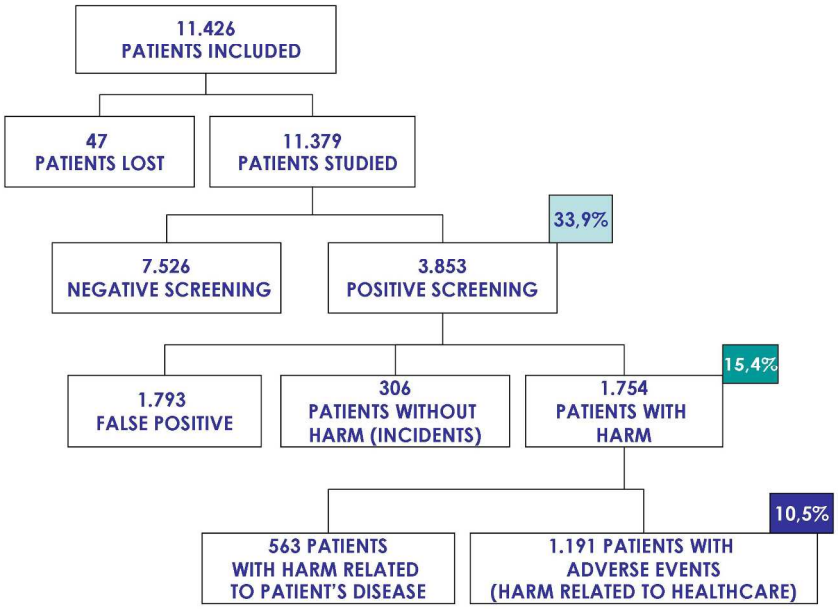
Figure legends:

Figure 1. Study patients in the cross sectional study

Figure 2. Study patients in the retrospective cohort study.

Figure 3. Study of prevalent AE on a given day. PC: Primary Care, HCC: Healthcare Centre

Figure 4. Scheme of incident AE study. PC: Primary Care, HCC: Healthcare Centre



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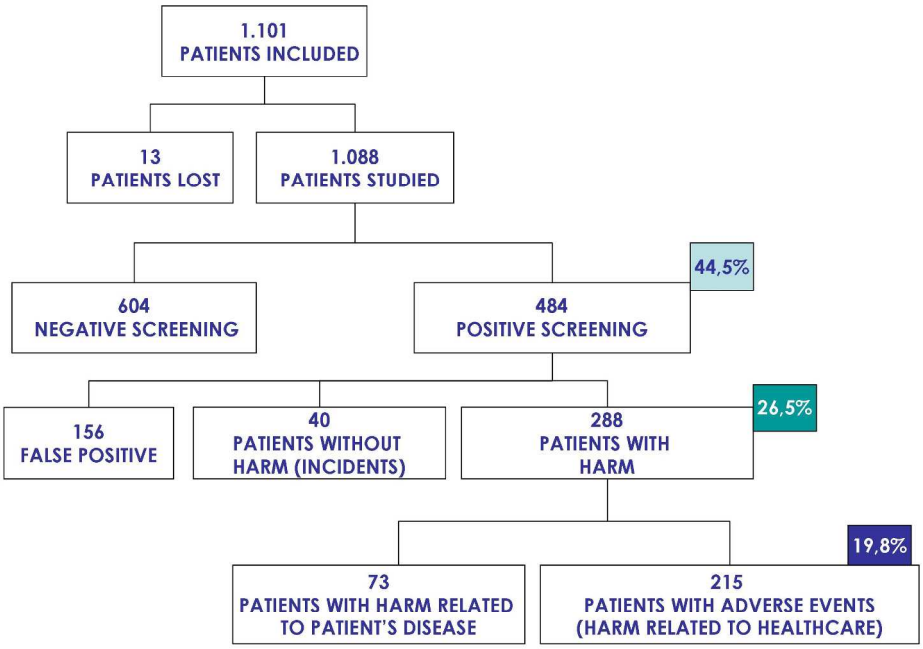

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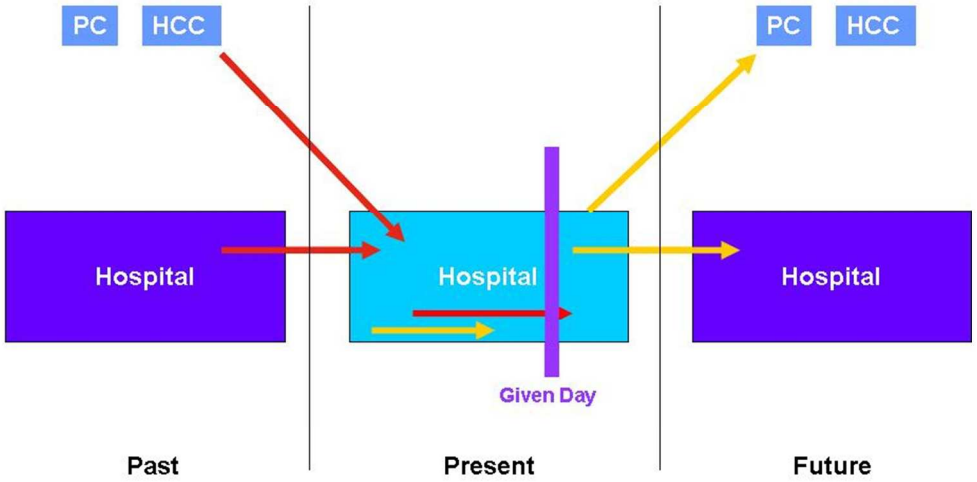

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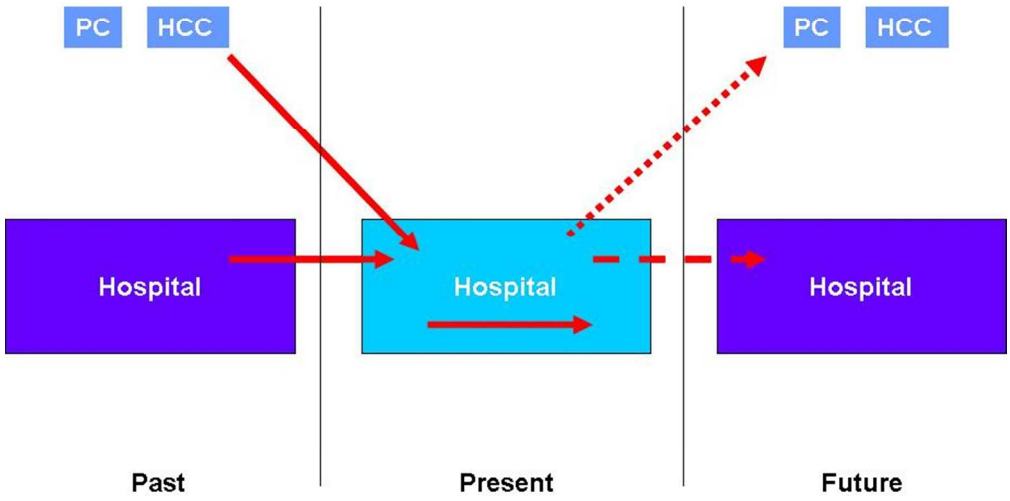

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APPENDIX 1: Preventability of Adverse Events

The Conceptual Framework for the International Classification for Patient Safety defines:

Preventable: is being accepted by the community as avoidable in the particular set of circumstances.

Preventability: To mine the preventability of the AE's, the possibility of their being prevented was scored on a 1-6 scale (1 = no evidence of preventability; 6= total evidence).

Those AE's score within the 1-3 range were considered unpreventable or hardly preventable, those scoring higher than 3 on this scale being considered preventable.

1. No evidence of preventable AE
2. Minimal probability of preventable AE
3. Slight probability of preventable AE
4. Moderate probability of preventable AE
5. Highly probable of preventable AE
6. Total evidence of preventable AE

This definition is proposed in Modular Questionnaire MRF2, in:

T.A. Brennan,L.L. Leape,N.M. Laird,L. Hebert,A.R. Localio,A.G. Lawthers. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med*, 324 (1991), pp. 370-376

APPENDIX 2. Study patients flow-chart

Figure 1: Study patients in the cross sectional study

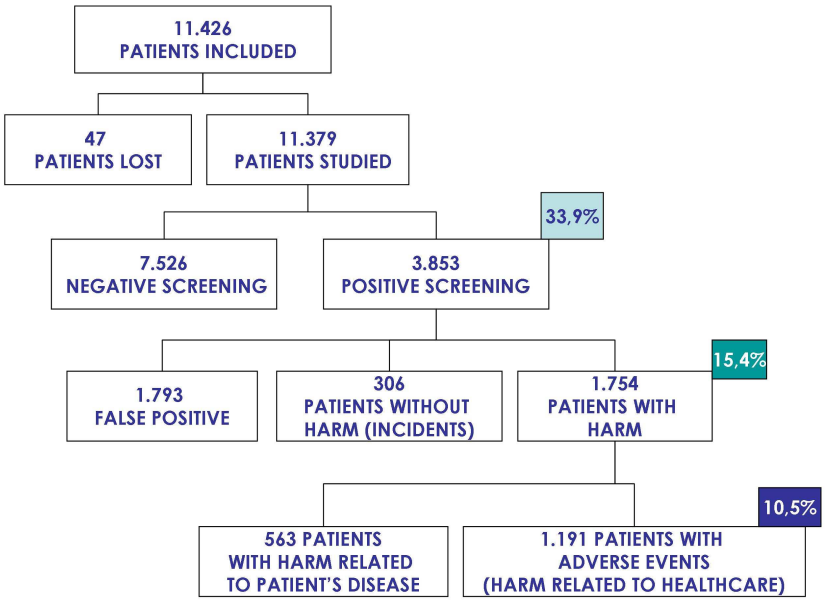
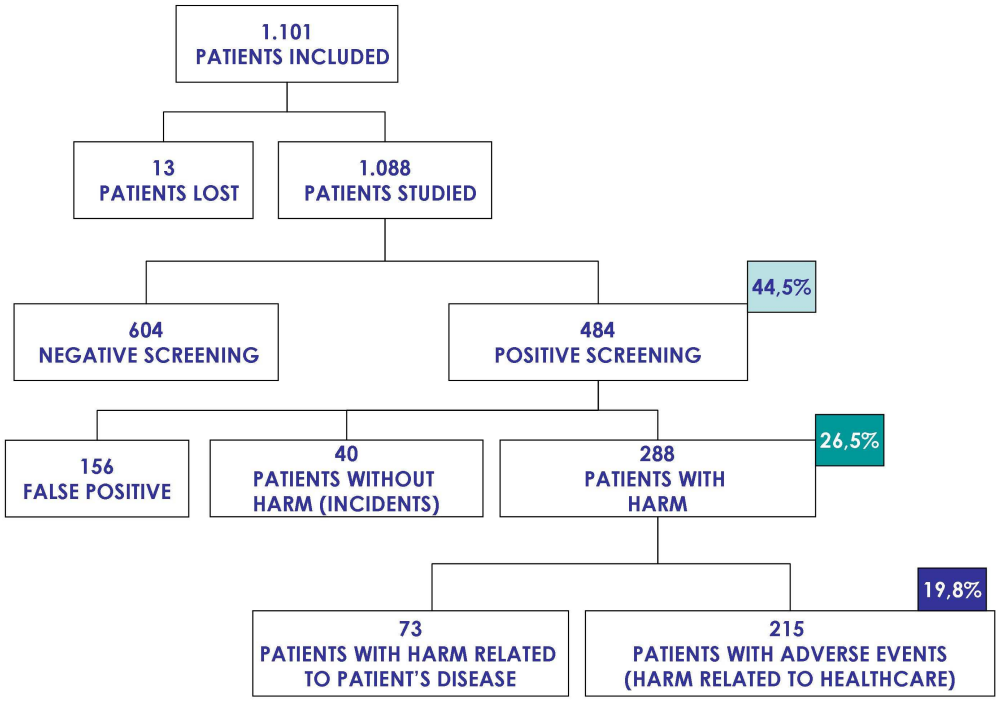


Figure 2: Study patients in the retrospective cohort study.



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page 4**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4-5**
Bias	9	Describe any efforts to address potential sources of bias **Page 5**
Study size	10	Explain how the study size was arrived at **Page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 5, page 6**
		(b) Give reasons for non-participation at each stage **page 6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 5**
		(b) Indicate number of participants with missing data for each variable of interest **Page 5**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page 7**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Page 8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 10**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 11**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comparison of two methods to estimate adverse events in the IBEAS STUDY (Iberoamerican study of adverse events): cross-sectional versus retrospective cohort design.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016546.R2
Article Type:	Research
Date Submitted by the Author:	14-Sep-2017
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Epidemiology, Patient-centred medicine, Health services research, Evidence based practice
Keywords:	patient safety, Adverse events < THERAPEUTICS, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Title:

Comparison of two methods to estimate adverse events in the IBEAS STUDY (Iberoamerican study of adverse events): cross-sectional versus retrospective cohort design.

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ABSTRACT:

BACKGROUND

Adverse events epidemiology is the first step to improve practice in healthcare system. Usually, the preferred method used to estimate the magnitude of the problem is the retrospective cohort study design, with retrospective reviews of the medical records. However this data collection involves a sophisticated sampling plan, and a process of intensive review of sometimes very heavy and complex medical records. Cross-sectional survey is also a valid and feasible methodology to study adverse events.

OBJECTIVES: The aim of this study is to compare the adverse event detection using two different methodologies: cross sectional versus retrospective cohort design.

SETTING: Secondary and tertiary hospitals in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru.

PARTICIPANTS: The IBEAS study is a cross sectional survey with a sample size of 11.379 patients. The retrospective cohort study was obtained from a 10% random sample proportional to hospital size from the entire IBEAS study population.

METHODS: This study compares the one-day prevalence of the adverse events obtained in the IBEAS study with the incidence obtained through the retrospective cohort study.

RESULTS: The prevalence of patients with adverse events was 10,47% (95% CI: 9,90 to 11,03) (1191/11379), while the cumulative incidence of the retrospective cohort study was 19,76% (95%CI: 17,35 to 22,17) (215/1088),). In both studies the highest risk of suffering adverse events was seen in ICU patients. Comorbid patients showed higher risk and also did patients with medical devices.

CONCLUSION: The retrospective cohort design, although requires more resources, allows to detect more adverse events than the cross-sectional design.

ARTICLE SUMMARY

Strengths: The identification of adverse events is the first step to improve patient safety. We know cross sectional studies are easier and less expensive to measure the adverse events.

This article adds the comparison between different study designs, and find the most efficient to find adverse events in the clinical practice. The study was made in five Latin American countries, so the data are strong for analysis.

We learn with this study that the retrospective cohort design allows to detect more adverse events compared with the cross-sectional one. The ICU patients have more adverse events, and also patients with comorbidities.

Limitations:

The sample used to evaluate the retrospective cohort was 10% of medical records used in the cross-sectional study, and proportional to hospital size, which could be not representative of all the population attended in the healthcare system. Tertiary hospitals have more complexity and it could be overestimated the number of adverse events, in comparison with the total number of patients attended in the country.

Another limitation is the quality of medical records. If the variability in the accomplishment between the different countries and healthcare systems were high the comparison between them could be weaker.

Competing interests: None declared

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INTRODUCTION

Valid and timely information about the frequency and impact of healthcare related adverse events (AE) and about the system's ability to detect, prevent and manage these AE is extremely important to understand the failures of healthcare, and to design and evaluate the effectiveness of risk reduction strategies. Increasingly, a large number of research studies have estimated such type of information in various health systems and organizational contexts[1], leading to a growing body of evidence about the burden and nature of adverse events caused by healthcare. One of the most important sources of information for such type of data are the patients' medical records, most frequently through the practice of retrospective reviews following agreed protocols and standard abstract forms. This methodology has consolidated itself as one of the most valid references in the field of patient safety research[2]. Nevertheless, despite the advantages of retrospective records reviews in identifying important and observable adverse events, there are also some concerns about the capacity to conduct such methodology in facilities with weaker data and research infrastructure, and moreover when certain periodicity is desirable for monitoring the effectiveness of risk reduction strategies.

Every research methodology and data collection system has its strengths and drawbacks[3]. Routine information systems have limitations related to compliance and coding bias. Events reporting systems also show preference for the type of events that reporters consider more relevant and have difficulties tracing duplicates, in addition to still facing unresolved legal issues in many contexts, which penalize reporting and limit their effective use. Prospective studies tend to focus on the analysis of higher-risk patients in detriment of other patients. Medical records, electronic or not, are threatened as well by lack of completeness and recording bias, since clinicians tend to record the data that are more meaningful to them from a clinical point of view. In addition, medical retrospective records review involve a sophisticated sampling plan, and a resource intensive process of record retrieval, reviewing and abstracting of sometimes very heavy and complex medical records.

A data collection process that has been less frequently used in the field of patient safety research, despite its potential, consists of running periodic cross-sectional surveys aiming to assess the point prevalence of AE[4,5]. This design has been commonly used to monitor the frequency of healthcare associated infections in many hospitals across Europe and elsewhere[6], where it has proven to be a feasible and valid methodology, capable to be run with no excessive resources at large scale and across many institutions and organizational cultures. Among the advantages of this design are that instead of requiring a statistically savvy sampling plan, all patients admitted at a given time to the hospital can be surveyed at once, simplifying the sampling process as well as the search and retrieval of records from the archives, since these are usually located near the patients in the wards[7]. This design also gives researchers the opportunity to ask the attending clinicians for some clarifications in the records, including some missing data. The unit of observation in this design is typically one day of admission, which makes it much shorter and simpler for the reviewers, and gives an estimate of a one-day prevalence, as opposed to the cumulative incidence of a retrospective record review[8]. Because of its greater simplicity, the management of large and multi-centered research studies is also simplified.

The IBEAS study was a multi-country effort aiming to estimate for the first time the frequency of hospital related AE in a selection of hospitals from Argentina, Colombia, Costa Rica, Mexico and Peru[9]. The study was conducted in 2007, in 58 hospitals of the 5 countries, with the collaboration of Spain, and the Panamerican and World Health Organizations. It used a one-day cross-sectional

design due to the perceived simplicity, lesser demands, and the greater opportunities for strengthening local capacity and eventual replication of this approach. The researchers involved in designing IBEAS, aware of its innovative approach in the field of adverse event measurement, were mindful of determining the relationship between the estimates of the one day point prevalence design and the more traditional retrospective cohort record review approach. In this same context Michel et al[10] evaluated the rates comparing three different methods: cross-sectional, prospective and retrospective. Therefore, we selected a randomized sample of all IBEAS patients to fully examine retrospectively their medical records.

METHODS

The AE definitions used in both designs were those published by WHO in the International Classification for Patient Safety.[11]

A patient safety incident is an event or circumstance that could have resulted, or did result, in unnecessary harm to a patient.

An adverse event or harmful incident is an incident that results in harm to a patient.

Harm implies impairment of structure or function of the body and/or any deleterious effect arising there from, including disease, injury, suffering, disability and death, and may be physical, social or psychological.

In the IBEAS project the AD was defined as[9]: "Any event causing harm to the patient that is perceived to be more related to the healthcare management rather than to the patient`s underlying condition"

The IBEAS study had two parts[12], a cross-sectional study and a retrospective cohort study.

The cross-sectional study involved determining how many patients admitted to the participating hospitals experienced harmful incidents attributable to health care on a given day (day 0). A prevalent AE is defined as one that originates during hospitalization and is clinically present on the day of the study, either as an after-effect or under treatment. This also includes those AE that were occasioned prior to hospitalization at any care level and which led to subsequent admission. AE that had occurred prior to the survey and whose effects had disappeared without prolonging the hospitalization on that particular day were not included.

The retrospective cohort study was conducted using a sample of patients with the aim of confirming whether the cross-sectional study could replace the conventional retrospective cohort study used to date. Specifically, the study involved reviewing the case notes of a random sample of 10% of patients (1.101 patients) hospitalized on day 0, proportional to hospital size, from the entire IBEAS study population. Case notes were scanned to ascertain whether, at some point during their hospitalization (or in a previous admission to the hospital), inpatients had experienced a harmful incident, regardless of whether the consequences of the incident were still present on day 0. Patients continued to be monitored until discharge. The sampling strategy and forms are available upon request. An incident AE is defined as one that occurs during any patient care process, as it may be detected at another level of care or in other hospital. In practical terms, as we carried out a retrospective study based on clinical hospital records, primary care AE were not included. Those that led to readmission in the same or another hospital were compensated by the AE which were detected during this hospitalization and which had been originated in a previous hospitalization.

The IBEAS study was carried out in five countries: Argentina, Colombia, Costa Rica, Mexico and Peru. The number of hospitals included was 58, all of them secondary and tertiary level hospitals. We used a purposive sample of hospitals and the inclusion was voluntary.

The sample size was of 11379 patients, with a minimum of 2000 patients per country.

In both studies (cross sectional and retrospective cohort), researchers used two tools to detect harmful incidents, namely a Screening Guide and a Modular Questionnaire[13,14] using the medical record review[15,16].

First, the screening guide was applied to the patients in the study. This served as an alert and tracking system for possible incidents. All the patients admitted at hospital (except emergency room) were studied. The screening was made by well trained nurses.

If a patient screened positive for one or more of the 19 alert criteria in the screening guide, the case was studied using the case history. An in-depth study of case histories enabled researchers to conclude whether a patient did in fact present with the consequences of a harmful incident (true positive) and if so, to classify the type of event, its severity, any associated factors, and whether or not the incident could have been avoided, etc. This second confirmatory review was made (in both cross sectional and retrospective) by medical doctors with at least 5 years of clinical experience. A patient could have more than one AE in the same hospitalization, and in this case the study collects all of them.

The reviewers training took place in two stages. First, the trainer workshop addressed the national coordinating teams in Buenos Aires 2007. Second, the national coordinators trained in turn the national investigators. A concordance study was carried out in Bogotá in 2008 using clinical records from each country. The most complex cases were assessed and an agreement was reached.

The preventable AE and the gravity were assessed according to the recommendations in the Modular Questionnaire, and the reviewers were also trained in these criteria.

The cross sectional and the retrospective cohort study were made by the same reviewers in each country.

The completed review forms of the retrospective study were entered in electronic files and submitted to a central repository managed exclusively by the principal investigators. Descriptive and multivariate analyses were conducted using SPSS 14. Logistic regression were used to estimate the prevalence and incidence of AE, once taking into account the effect of some covariates, such as patient's age and comorbidity (intrinsic factors), presence of catheter lines and medical devices (extrinsic factors), type of admission, and type of hospital. The IBEAS study maintained ethical conduct of research, and was approved by the PAHO Ethics Review Committee and by the national ethics review committees of each participating country.

RESULTS

11.379 patients were included in the cross-sectional study (see Appendix 1, Figure 1). 3853 of them (33.9%) fulfilled at least one of the screening criteria. In the second phase of the cross-sectional study 1.191 patients had an AE

For the retrospective cohort study (see Appendix 1, Figure 2), a total of 1.101 patients (10%) were randomly selected from all the 11.379 patients included in the cross-sectional study. The medical records of 13 of these patients (1,2%) could not be retrieved and were excluded from the study.

The screening phase of the retrospective review found about 44,5% of the medical records, corresponding to 484 patients, positive for at least one of the 19 triggers included in the forms. At the confirmatory phase, it was determined that 40 of those patients had experienced one or more patient safety incidents without harm or prolonged stay, and 288 patients had experienced at least one AE (harmful patient safety incident). Of these, in 215 patients the AE was considered to be mostly related to the healthcare received rather than to the patient intrinsic vulnerability.

The characteristics of patients in the two types of study are presented in Table 1. Patients in the retrospective cohort study were of similar sex composition than the cross sectional study sample. Though they were slightly older, they did not show significant differences in their intrinsic factors (comorbidity). It seemed there were more patients in surgical wards and with slightly more procedures in the retrospective review sample than the patients in the one-day cross-sectional study. The composition of participating hospitals and type of admission was comparable in the two types of designs.

Table 1. Characteristics of the study population.

		CROSS SECTIONAL			RETROSPECTIVE COHORT			p value
		n	**%**	**CI 95%**	**n**	**%**	**CI 95%**	
Sex	Women	5975	52,5	51,6-53,4	547	50,3	47,3-53,2	n.s.
Age	Mean (SD*)	40,2	26,9		42,1	26	31,3-36,9	0,02
Department	Medical wards	4045	35,5	34,7-36,4	371	34,1	31,3-36,9	0,001
	Surgery/ gynaecology	3898	34,3	33,4-35,1	435	40,0	37,1-42,9	
	Obstetrics	1241	10,9	10,3-11,5	109	10,0	8,2-11,8	
	Paediatrics	1701	14,9	14,3-15,6	128	11,8	9,9-13,7	
	Intensive care	494	4,3	4-4,7	45	4,1	3-5,3	
Hospital Complexity	Tertiary	10520	92,5	92-92,9	1011	92,9	91,4-94,4	n.s.
	Secondary (with surgery and ICU wards)	859	7,5	7,1-8	77	7,1	5,6-8,6	
Admission type	Unplanned admission	8031	70,6	69,7-71,4	726	66,7	63,9-69,5	n.s.
	Planned admission	2099	18,4	17,7-19,2	190	17,4	15,2-19,7	
Intrinsic risk factors	Yes	6128	53,9	52,9-54,8	615	56,5	53,6-59,5	n.s.
	No	5251	46,1	45,2-47,1	473	43,5	40,5-46,4	
Extrinsic risk factors	Yes	8484	74,6	73,8-75,4	844	77,6	75,1-80,1	0,03
	No	2895	25,4	24,6-26,2	244	22,4	19,9-24,9	
Patients studied		11379			1088			

*SD: standard deviation
n.s.: no significant (p>0,05)

As Table 2 shows the prevalence of patients with AE was 10,47% (CI 95%: 9,90 to 11,03). As a patient can have more than one AE, the total number of AE detected was 1349, so the global prevalence of AE was 11,85% (1349/11379) (CI 95% 11,26 to 12,46).

As Table 2 also shows the cumulative incidence of patients suffering at least one AE related to the care received before or during their hospitalization was 19,76% (95% CI: 17,35 to 22,17) (215/1088). In total, there were 314 AE (because a patient could have more than one AE) related to healthcare corresponding to a cumulative incidence of total AE of 28,86% (95% CI: 26,12 to 31,60) (317/1088).

Table 2. Differences in result measures in both study designs.

	Cross–sectional (prevalence)	Retrospective Cohort (cumulative incidence)
Patients with AE	1191/11379=10,47% (CI 95%: 9,90 to 11,03)	215/1088=19,76% (CI 95%: 17,35 to 22,17)
Total number of AE	1349/11379= 11,85% (CI 95%: 11,26 to 12,46)	314/1088= 28,86% (CI 95%: 26,12 to 31,6)

Table 3 shows the results of the cross-sectional study and the retrospective cohort record review per country, showing the rate of positive screening and its positive predictive value and the corresponding final estimate in terms of one-day prevalence and the proportion of patients with at least one AE during their hospitalization. In the one-day cross-sectional study, the rate of positive screening review form (SRF) seemed to range more homogenously between 30 to 39% of all records, with Positive Predictive Values (PPV) between 25% and 37%. In the retrospective cohort review, however, the range of positive screening was wider going from about 17% to almost 64% of all records, and also reaching higher Positive Predictive Values from 24% to over 60%. In all countries, the percentage of patients suffering at least one AE during their hospitalization was significantly higher than the rate observed in the one-day study, with values going from 11% of patients to more than 36%.

Table 3. Adverse events frequency measures and screening form performance.

	Cross sectional study			Retrospective study		
	Positive Screening review form	Positive Predictive Values	Prevalence of adverse events	Positive Screening review form	Positive Predictive Values	Cumulative incidence of adverse events
Country 1	39,0 % 926/2373 (CI 95%: 37,0 to 41,0)	33,7% 312/926 (CI 95%: 30,6 to 36,8)	13,1% 312/2373 (CI 95%: 11,8 to 14,5)	61,7% 145/235 (CI 95%:6,7 to 8,1)	51,7% 75/145 (CI95%:43,2 to 60,2)	31,9% 75/235 (CI95%:25,7 to 38,1)
Country 2	30,6 887/2897 (CI 95%: 28,9 to 32,3)	25,3% 224/887 (CI 95%: 22,3 to 28,2)	7,7% 224/2897 (CI 95%: 6,7 to 8,7)	38,9% 112/288 (CI95%:33,1 to 44,7)	32,1% 36/112 (CI95%:23,0 to 41,2)	12,5% 36/288 (CI95%:8,5 to 16,5)
Country 3	35,4 578/1632 CI 95%: 33,1 to 37,8)	34,3% 198/578 (CI 95%: 30,3 to 38,2)	12,1% 198/1632 (CI 95%: 6,7 to 8,7)	63,7% 107/168 (CI95%:56,1 to 71,3)	57,0% 61/107 (CI95%:47,2 to 66,9)	36,3% 61/168 (CI95%:28,7 to 43,9)
Country 4	34,5 692/2003 (CI 95%: 32,4 to 36,7)	24,7% 171/692 (CI 95%: 21,4 to 27,9)	8,5% 171/2003 (CI 95%: 7,3 to 9,8)	46,9% 82/175 (CI95%:39,2 to 54,5)	24,4% 20/82 (CI95%:14,5 to 34,3)	11,4% 20/175 (CI95%:6,4 to 16,4)
Country 5	31,1 770/2474 (CI 95%: 29,3 to 32,9)	37,1% 286/770 (CI 95%: 33,7 to 40,6)	11,6% 286/2474 (CI 95%: 10,3 to 12,8)	17,1% 38/222 (CI95%:11,9 to 22,3)	60,5% 23/38 (CI95%:43,7 to 77,4)	10,4% 23/222 (CI95%:6,1 to 14,6)
Total	33,9% 3853/11379 (CI 95%: 32,9 to 34,7)	30,9% 1191/3853 (CI 95%: 29,4 to 32,4)	10,5% 1191/11379 (CI 95%: 9,9 to 11,0)	44,5% 484/1088 (CI95%:41,5to 47,5)	44,4% 215/484 (CI95%:39,3 to 48,3)	19,8% 215/1088 (CI95%:17,3 to 22,2)

In both studies (Table 4), the highest risk of suffering AE was seen in ICU patients. Surgical patients were associated with more risk than patients admitted in the medical wards. Whereas, in the cross-sectional study, obstetrics and pediatric patients also showed higher risk than medical patients. Comorbid patients showed higher risk of suffering AE in both studies, as well as patients with catheter lines, and other procedures. Similarly, the length of stay before the day of study in the cross-sectional study and the total length of stay in the retrospective cohort one were associated with the higher risk of suffering AE. In the retrospective cohort review, emergency hospitalizations seemed not to be associated to the risk of suffering AE as this seemed the case in the cross-sectional study. Patient age was not retained as an independent variable or as a confounding factor in the final model in both studies.

Table 4. Correlates of adverse events in multiple logistic regression analyses.

	CROSS SECTIONAL				RETROSPECTIVE COHORT			
Variables	p-value	OR	95% CI for OR		p-value	OR	95% CI for OR	
Department (1)								
Surgery and gynaecology	0,06	1,17	0,99	1,38	0,01	1,75	1,17	2,61
Obstetrics	0,02	1,37	1,06	1,78	0,05	0,38	0,15	0,99
Paediatrics	0,00	1,50	1,21	1,85	0,15	0,40	0,12	1,40
Intensive care	0,00	2,52	1,96	3,26	0,01	2,77	1,25	6,17
Complexity of the hospital (2) tertiary	0,02	1,45	1,07	1,97				
Type of admission (3) urgent	0,00	1,34	1,12	1,61	0,59	1,14	0,71	1,83
Length of stay until the day of study	0,03	1,00	1,00	1,00	0,01	1,00	1,00	1,01
Patient comorbidty (4) any	0,00	1,42	1,22	1,64	0,00	2,02	1,28	3,19
Use of medical devices (5) any	0,00	2,59	2,14	3,14	0,00	3,24	1,79	5,85
Country 1								
Country *2*	0,00	0,46	0,38	0,56	0,00	0,34	0,20	0,59
Country *3*	0,37	0,91	0,73	1,12	0,16	1,44	0,86	2,41
Country *4*	0,00	0,65	0,52	0,81	0,00	0,22	0,12	0,42
Country *5*	0,04	0,82	0,69	0,99	0,01	0,38	0,19	0,76

Reference categories: (1) medical specialties; (2) secondary hospitals of intermediate complexity with at least surgical theatres, and postsurgical resuscitation wards; (3) planned admission; (4) and (5) absence of risk factors.

The types of AE identified in both the cross-sectional and the retrospective cohort studv showed similar distribution. The most frequent types of AE identified in any study were related to the occurrence of healthcare associated infections (more than 35% of all AE), followed by AE related to procedures (more than 26%). Medication related AE represented less than 10% of all AE in each of the studies (Table 5).

Table 5. AE types and proportion of total AE.

Type of AE	Prevalence	CI 95%	Cumulative incidence	CI 95%
Care provided	13,27%	11,46 to 15,08	12,16%	16,24 to 20,32
Medication	8,23%	6,76 to 9,69	6,57%	9,87 to 13,17
Healthcare associated infections	37,14%	34,56 to 39,72	30,68	35,99 to 41,30
Related to procedures	28,69%	26,27 to 31,10	21,86%	26,75 to 31,65
Diagnostic issues	6,15%	6,15 to 7,44	2,66%	5,10 to 7,53
Nosocomial urinary tract infection	4,08%	2,98 to 5,17	5,09%	2,50 to 7,69
Nosocomial pneumonia	9,41%	7,82 to 11,01	6,37%	3,51 to 9,23
Post-surgical hematoma	2,89%	1,96 to 3,82	3,50%	1,31 to 5,69
Phlebitis	3,4%	2,40 to 4,41	5,73%	3,00 to 8,46
Neonatal complications	1,1%	0,51 to 1,71	0,32%	0,01 to 1,76

There were some differences in the impact caused by the AE identified in the cross-sectional study, versus the retrospective cohort study. The AE identified through the cross-sectional study seemed to be associated more frequently with hospital readmissions and slightly more with prolonged stay, whereas the frequency of AE which did not cause prolonged stay or readmission was higher in the retrospective cohort study (Table 6).

Table 6. Impact of adverse events in hospitalization. n (%)

	Cross sectional		Retrospective cohort	
Did not prolonged hospital stay	228	18,91% (CI 95%: 16,65 to 21,16)	87	29,9%(CI 95%: 24,46 to 35,33)
Prolonged hospital stay	759	62,9% (CI 95%: 60,17 to 65,70)	178	61,2%(CI 95%: 51,88 to 63,58)
Extra days same hospitalization	Mean: 16,1 days SD (29,6)		Mean:14,9 daysSD (19,9)	
Causing admission	219	18,16% (CI 95%: 15,94 to 20,38)	26	8,9% (CI 95%: 5,48 to 12,38)
Extra days new hospitalization	Mean: 21,4 days SD (69,7)		Mean:19,0 daysSE (22,3)	

The preventability of AE (Appendix 2) was very similar, with about 65% in the retrospective cohort review and 60% for the cross-sectional study.

DISCUSSION

The choice of the most appropriate epidemiological design in the study of magnitude of AE is not a trivial issue. The question has been analysed in different studies and the generalized consensus is that the choice of method should be based on the aims of the study and the need to combine the minimization of bias and the validity of AE identification with the reproducibility of value judgements on their iatrogenic nature and/or preventability[17].

The retrospective design for the study of AE has been the method used in all national studies[1], Nevertheless it is a method which produces results which may be heavily influenced by the quality of clinical records.

A prospective study offers pedagogical and communicative advantages and facilitates a concomitant analysis of the root causes which provide the conditions for the occurrence of AE. However not only might it prove too costly, but it would also involve a high workload and excessive complexity.

On the other hand, the cross-sectional design is more time and resource-efficient and easier to perform. Although it does not allow for a study of the total hospitalization episode, it has proved capable of sustaining over time a more stable system of observation. We also need to bear in mind

that, as a result of a possible survival bias, those AE which lead to hospital admission will be over-represented, as will those related to nosocomial infection or those which are difficult to identify if the patient is not examined (such as bruising), due to the systemic approach itself of a prevalence study. As in the prospective approach, communication with the ward staff (the patient is hospitalized at this time) makes it easier to judge the causality of the AE and its preventability.

The relationship between prevalence and incidence generally depends on the duration of the event under review and the period of observation[8]. In our case we calculated prevalence on a given day and not during the whole period. Consequently this relationship will not be well reflected. In Figure 3 we see the possible AE which may occur and those that are detected on the basis of this approach.

When we compare the results of the cross-sectional study with those of the retrospective cohort study within the context of the IBEAS project, the differences are due exclusively to the design, as the methodology and sample are the same (assuming the representativeness of the incidence sub-cohort). In Appendix 2, Figures 3 and 4, which represent the scheme followed in the methodology of this study, we see that the difference between the prevalence and incidence values on a given day are due to those AE which, having occurred during hospitalization, are not prevalent on the day of the study (represented by a yellow arrow in Figure 3). This also explains why the patients of the retrospective cohort study present more extrinsic risk factors (devices) than in the cross-sectional study.

The screening review form has been used in American[18,19] and Australian[20,21] cohort studies and in different European[22,23] countries. It is highly sensitive (84%) in the detection of AE and we therefore assume that the number of false negatives should be small. We also can detect with the revision of the modular questionnaire .

Appropriateness of the review forms to a point prevalence study was discussed during the training workshop. Modifications to adapt them to the context of Latin America were done not only bearing in mind vocabulary, but also adding common risk factors like malaria or prematurity.

The percentage of patients flagged in the SRF and the predictive value of this phase in the detection of AE are totally compatible with those found in those other AE studies of which we are aware. We can therefore state that the materials are sensitive enough and appropriate for the identification of both prevalence and cumulative incidence of AE. However, in the retrospective cohort study, the PPV (positive predictive value) of the SRF is higher. This may be due to the fact either that the guide was originally designed for an incidence study and proves more efficient in this type of study or that as the retrospective cohort study was performed after the cross-sectional study, it is possible that the experience of the reviewers raised the performance level of the first questionnaire.

The Spanish version of the modular review form (MRF2) was adapted in Spain for the IDEA Project and modified after the ENEAS study[4]. The researcher must make value judgements through implicit criteria on most occasions. Characterization of AE caused by the care rather than the pathological process itself, is done by the reviewer scoring from 1 to 6 the probability that the AE is due to the care. A value of •4 is required to confirm this. The same criterion is used to evaluate the adverse event as preventable. Cross-sectional design allows researchers to consult the medical staff while they are collecting data in order to clarify any uncertainty or doubts associated with the adverse event. The reliability of the questionnaire in other studies has been assessed as moderate[23].

A limitation of this study could be the sample used to evaluate the retrospective cohort. It is a 10% of medical records used in the cross-sectional study and proportional to hospital size, which could be not representative of all the population attended in the health system. Tertiary hospitals have more complexity and it could be overestimated the number of adverse events, in comparison with the total number of patients attended in the country. Another limitation is the quality of medical records. If the variability in the accomplishment between the different countries were high the comparison between them could be weaker.

The frequency of AE in both the cross-sectional and retrospective cohort studies was greater than that found in previous studies, which may be due to the different characteristics of the patients, who

had a higher average age and more risk factors. The nature of the sample selection and the peculiarities of the different search systems prevent statistical inferences and comparisons either within each country or between the countries which are part of the study.

In any case, higher prevalence means higher cumulative incidence. In some way the interdependence of these frequency measures remains when we use prevalence on a given day. The fact that prevalence is sensitive to the differences in the characteristics of the patients and that it reflects the differences found between countries, would make it a useful tool in the study and follow-up of the frequency of AE and in comparative studies. Furthermore, as the explanatory model for the occurrence of AE is the same, studying the factors which influence prevalence may provide the same clues when designing strategies for AE control and therefore provide a more efficient tool.

Moreover, the fact that the prevalence design detects proportionally more serious AE is not a drawback. On the contrary, these are precisely the AE which need to be prioritized when designing control strategies, and as we commented above, the detected AE were equally preventable in both designs. This reinforces the idea that preventability and seriousness of the EA are independent factors.

As the point prevalence design is more efficient in terms of time and resources, its validity is less dependent on the quality of the clinical records and allows simultaneous study through other observation and audit systems, regular prevalence on a given day studies might provide an efficient AE monitoring and control strategy.

CONTRIBUTORSHIP STATEMENT

Aranaz Andrés, Jesús María
Principal publication's author. He has coordinated the IBEAS project and he is the team leader of this job.

Limón-Ramírez R.
He has participated in the data collection, he has made the data analysis and the interpretation of the results, and he has participated in the composition of the manuscript.

Aibar-Remón C.
He has been coordinator of the IBEAS project, he has evaluated the manuscript and has contributed to improve the presentation.

Gea-Velázquez de Castro MT.
She has participated in the data collection, she has coordinated the project with Dr. Aranaz, she has made data analysis, and she has evaluated the results, and she has improved the manuscript.

Bolúmar F.
He has participated in the evaluation and improvement of the manuscript and data analysis.

Hernández Aguado I
He has participated in the evaluation and improvement of the manuscript and data analysis.

López Fresneña N.
She has participated in the evaluation of the manuscript and she has been the responsible of sending the manuscript to the reviewer and editorials.

Díaz Agero Pérez C.
She has collaborated in the manuscript composition and she has contributed to the critical review.

Terol García E.
He has been coordinator of the IBEAS project. He has contributed to the critical review of this paper.

Sousa P. He has collaborated in the data analysis and critical review of this paper.

Larizgoitia Jauregui I. She has contributed to improve the paper composition and to the data analysis. She has been also IBEAS project coordinator.

Grupo de trabajo IBEAS: all the members have made the data collection.

COMPETING INTERESTS
None

DATA SHARING STATEMENT

Extra data is available by emailing: jesusmaria.aranaz@salud.madrid.org

ETHICS

The IBEAS project has the ethics approval for every institution in each country.

This study was founded by the Health Ministry of Spain and WHO, but for this article, we haven't had any financial support.

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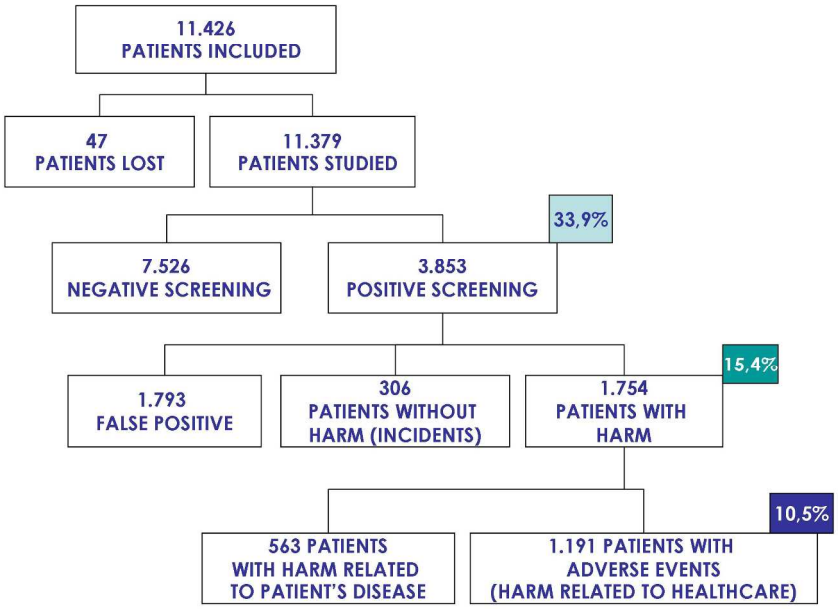
Figure legends:

Appendix 1. Figure 1. Study patients in the cross sectional study

Appendix 1. Figure 2. Study patients in the retrospective cohort study.

Appendix 2. Figure 3. Study of prevalent AE on a given day. PC: Primary Care, HCC: Healthcare Centre

Appendix 2. Figure 4. Scheme of incident AE study. PC: Primary Care, HCC: Healthcare Centre



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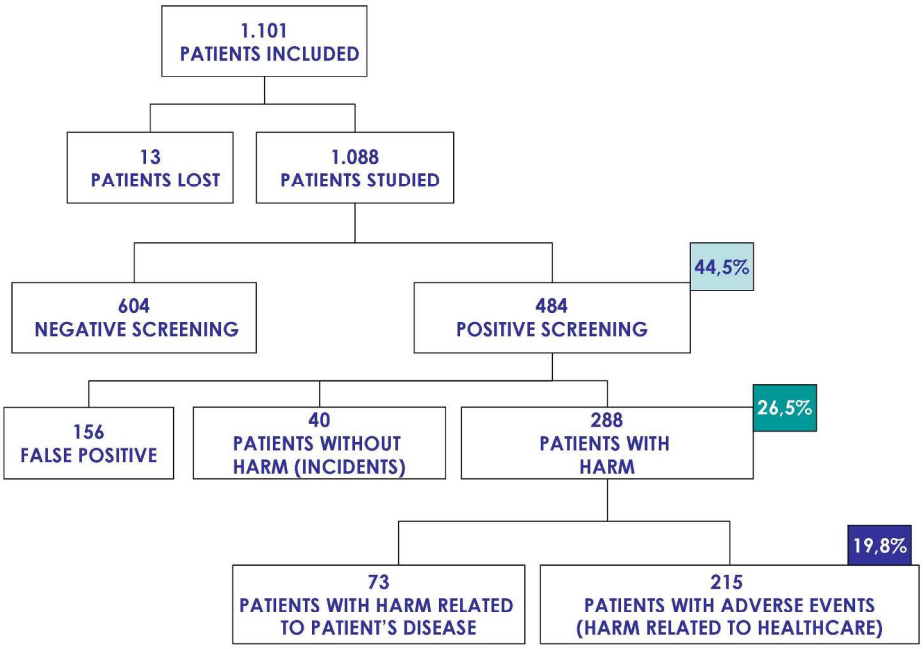

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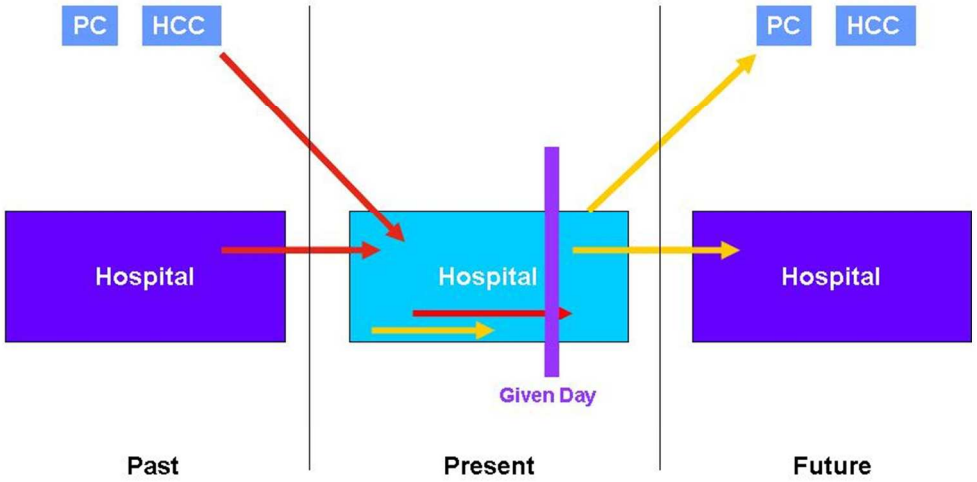

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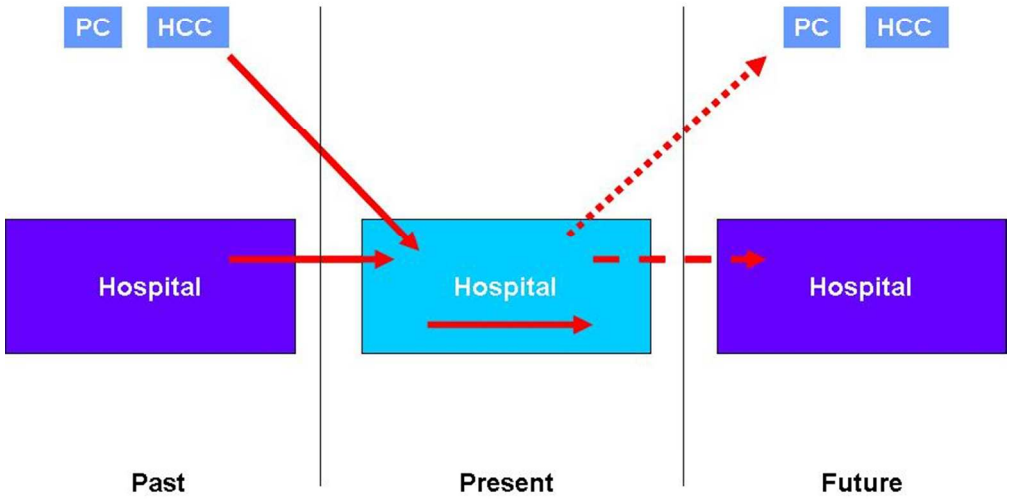

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APPENDIX 1. Study patients flow-chart

Figure 1: Study patients in the cross sectional study

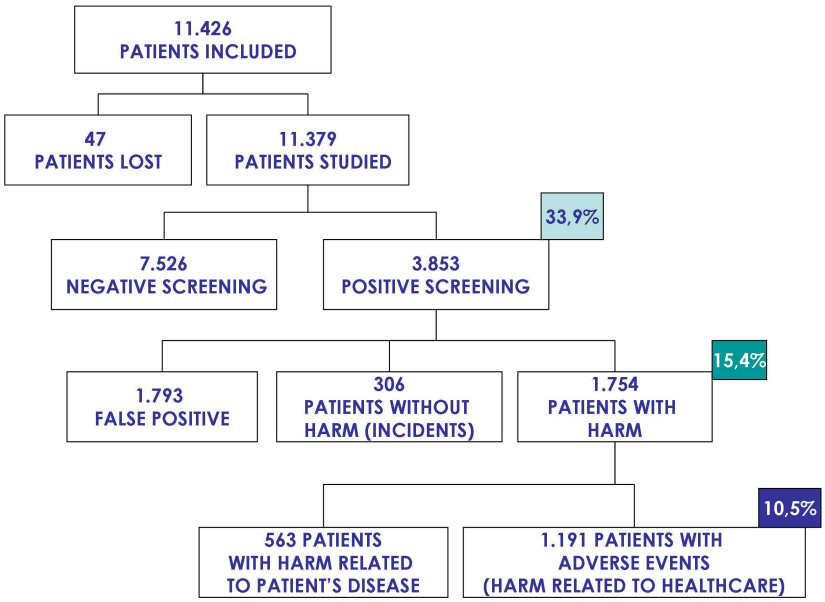
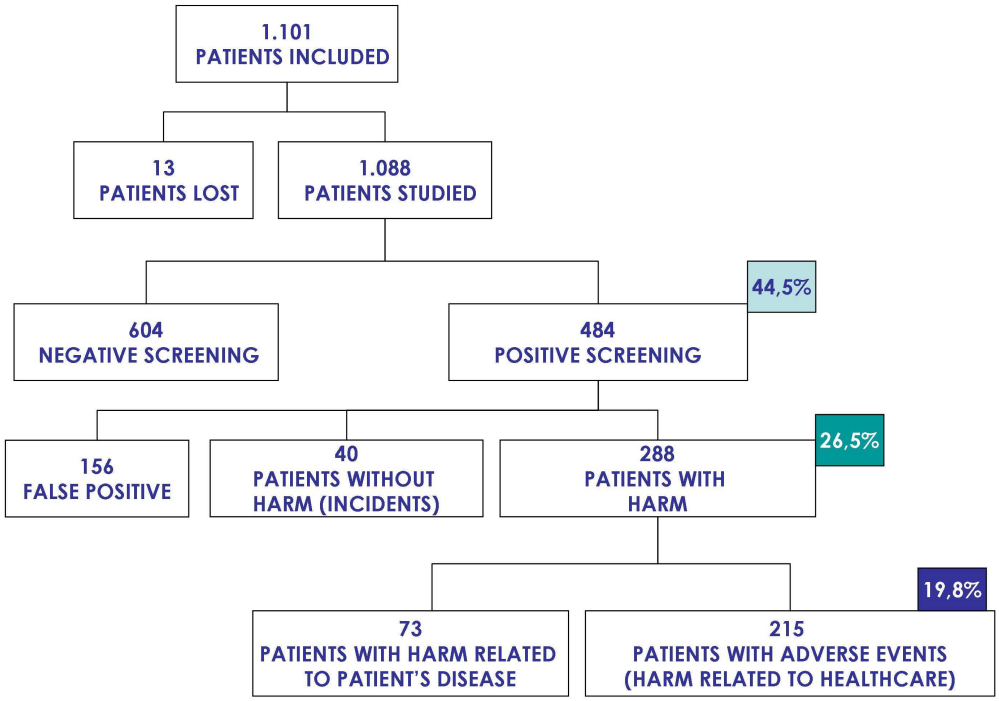


Figure 2: Study patients in the retrospective cohort study.



APPENDIX 2: Preventability of Adverse Events

The Conceptual Framework for the International Classification for Patient Safety defines:

Preventable: is being accepted by the community as avoidable in the particular set of circumstances.

Preventability: To mine the preventability of the AE's, the possibility of their being prevented was scored on a 1-6 scale (1 = no evidence of preventability; 6= total evidence).

Those AE's score within the 1-3 range were considered unpreventable or hardly preventable, those scoring higher than 3 on this scale being considered preventable.

1. No evidence of preventable AE
2. Minimal probability of preventable AE
3. Slight probability of preventable AE
4. Moderate probability of preventable AE
5. Highly probable of preventable AE
6. Total evidence of preventable AE

This definition is proposed in Modular Questionnaire MRF2, in:

T.A. Brennan,L.L. Leape,N.M. Laird,L. Hebert,A.R. Localio,A.G. Lawthers. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *N Engl J Med*, 324 (1991), pp. 370-376

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 1**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 3**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 4**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 4-5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Page 4** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants **Page 4**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 4**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Page 4-5**
Bias	9	Describe any efforts to address potential sources of bias **Page 5**
Study size	10	Explain how the study size was arrived at **Page 4**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **Page 5**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 5**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 5**
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **Page 5, page 6**
		(b) Give reasons for non-participation at each stage **page 6**
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Page 5**
		(b) Indicate number of participants with missing data for each variable of interest **Page 5**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Page 7**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures **Page 7**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Page 7**
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **Page 8**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 10**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Page 11**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.