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Deaths from sepsis: underlying causes of death after investigation in 60 Brazilian municipalities in 2017

Mortes por sepse: causas básicas do óbito após investigação em 60 municípios do Brasil em 2017

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ABSTRACT: ***Introduction*:** Sepsis represents the occurrence of systemic inflammatory response syndrome triggered by the initial infection of an organ or system. When sepsis is certified as the cause of death, the first diagnosis is lost, leading to inaccurate information as to its origin. ***Objective:*** To analyze the underlying causes of death from sepsis after investigation in 60 Brazilian municipalities in 2017. ***Methodology*:** All deaths recorded in the Mortality Information System (SIM) as sepsis in 2017 were selected, and the proportions of reclassified deaths were calculated based on the results of research conducted in hospitals and other health services. ***Results*:** Of the 6,486 deaths from sepsis that occurred in the 60 municipalities, 1,584 (24.4%) were investigated, and of these, 1,308 (82.6%) were reclassified with other underlying causes. Individuals aged from 70 to 89 years old showed the highest concentration in the records, with 49.3% of cases. More than 60% of the deaths from sepsis reclassified after the investigation had chronic non-communicable diseases as underlying causes (65.6%), with diabetes being the most common specific cause in this group. Communicable diseases (9.6%) and external causes (5.6%) such as falls were also detected as underlying causes. ***Conclusion*:** The investigation of deaths from sepsis made it possible to identify the true causes of death and the proportions of reclassification. This information will improve the quality of mortality data and support the planning of public health actions in Brazil.

***Keywords*:** Mortality. Cause of death. Sepsis. Health information systems.

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RESUMO: ***Introdução*:** A sepse representa a ocorrência de síndrome de resposta inflamatória sistêmica desencadeada por infecção inicial de um órgão ou sistema. Quando a sepse é atestada como causa do óbito, perde-se o primo diagnóstico, condicionando perda de informação quanto à sua origem. ***Objetivo*:** Analisar as causas básicas após investigação de óbitos por sepse em 60 municípios do Brasil em 2017. ***Metodologia*:** Foram selecionados todos os óbitos registrados em 2017 no Sistema de Informação sobre Mortalidade como sepse, e analisadas as proporções dos óbitos reclassificados após investigação em hospitais e outros serviços de saúde. ***Resultados*:** Entre os 6.486 óbitos por sepse ocorridos nos 60 municípios foram investigados 1.584 (24,4%) e, destes, 1.308 (82,6%) foram reclassificados com outras causas básicas. A faixa etária de 70 a 89 anos obteve a maior concentração de registros, com 49,3% dos casos. Mais de 60% dos óbitos por sepse reclassificados após investigação tiveram doenças crônicas não transmissíveis como causa básica (65,6%), sendo a diabetes a causa específica mais comum neste grupamento. Doenças transmissíveis (9,6%) e causas externas (5,6%) como quedas foram também detectadas como causas básicas. ***Conclusão*:** A partir das investigações dos óbitos por sepses foi possível conhecer a verdadeira causa de morte e as proporções de reclassificação. Essas informações contribuirão para melhorar a qualidade dos dados de mortalidade e para subsidiar o planejamento de ações em saúde pública no Brasil.

***Palavras-chave*:** Mortalidade. Causas de morte. Sepse. Sistemas de informação em saúde.

INTRODUCTION

Sepsis, the current name for the term septicemia, may be characterized by the occurrence of a systemic inflammatory response syndrome with organic dysfunction, triggered by an improper reaction to the infection[1-3]. The infectious diagnosis is usually related to an organ or system that initiates the inflammatory process throughout the body. Identifying the origin of the infection is fundamental in establishing the etiology in a case of sepsis and is an important step in choosing the most appropriate treatment[3].

The underlying cause (UC) of death refers to the injury or disease responsible for triggering the factors that culminated in death, and is of importance to public health in the prevention of the original cause and consequently of death[4]. When sepsis is certified as the UC of death, the first diagnosis and its specificity are lost, leading to loss of information on its origin. The UC registered as sepsis are considered to be of no use to public health and classified as garbage codes (GC). These codes should not be used to codify the UC of death, as they refer to intermediate or final causes, which do not provide relevant information about the circumstances that triggered death and thus cannot contribute to the planning of healthcare actions[5,6].

In the Global Burden of Disease Study 2017 (GBD 2017)[5], GCs are classified on a scale from 1 to 4, levels 1 and 2 being the most serious as they have the greatest impact on the quality of information regarding causes of death. Sepsis is considered a level 1 GC of greater impact, as the triggering cause may belong to any of the broader groups of GBD causes,

and it is not possible to determine if the first diagnosis was a communicable or noncommunicable disease, or the result of an external cause.

One of the main reasons for the large number of nonspecific causes of death is the incorrect registering of the event chain in the death certificate (DC). Actions taken to reduce these causes include investigating the circumstances related to death in health institutions and training doctors on how to correctly fill out the DC[7-11].

Since 2005, the Ministry of Health (MS) has been conducting investigations on ill-defined causes (IDC) of death related to the GCs listed in chapter 18 of the International Statistical Classification of Diseases and Related Health Problems – 10th revision (ICD-10)[4]. The investigations include the collection of information from health records and households regarding death process , using standardized forms to define the UC[12]. In 2017, the causes to be investigated were focused on a priority GC list according to the protocol proposed by the Data for Health (D4H) project, coordinated by the Ministry of Health in partnership with Universidade Federal de Minas Gerais, with support from the Bloomberg Foundation through Vital Strategies and the University of Melbourne. Sixty municipalities located in over 5 regions of the country were part of this project.

This article aims to identify the specific causes detected after the investigation of deaths from sepsis in 60 municipalities of the country in 2017, and evaluate whether these municipalities correctly registered the information.

METHOD

Initially, deaths that occurred in 2017 in 60 Brazilian cities participating in the D4H project, with original UC registered as sepsis (A40-A41 codes of CID-10[4]), such as streptococcal septicemia and other septicemia, were selected from the database of the Mortality Information System (SIM). The deaths investigated by the municipalities were selected based on the information of the DC inserted in the SIM, following the guidelines of a protocol for investigation of deaths with causes classified as garbage, according to the classification list of the GBD study 2015[13]. Deaths from sepsis were considered as priority garbage causes.

The investigation of the deaths was performed with the data collection instruments provided for this purpose. The Investigation of Deaths from Ill-Defined Causes – Hospital (IOCMD-H) form, which included sections for the indication of diagnostic certainty, was used to qualify hospital deaths. These evidence criteria, based on the proposal of Serina et al.[14], were used by a certifying physician, responsible for analyzing the investigations and filling out a new epidemiological DC with the causes of death, and to justify the change.

In the IOCMD-H form, it was possible to identify 3 categories of diagnostic certainty: definitive, possible and probable. These categories were singled out based on clinical evidence and/or laboratory tests used to justify the change in the cause of death.

The "definitive" category was used to justify the change in the cause of death based on exclusive tests and diagnosis with high level of evidence. The "possible" category was used in the absence of specific tests and in the presence of clinical history and signs and symptoms pertinent to the diagnosis. The "probable" category had the least diagnostic certainty, with the change in the cause of death being based on family history only, in the absence of supporting documents.

All investigations performed, with or without reclassification of the cause of death, were initially registered in the SIM, and the complementary data from the IOCMD-H form were registered in an online system developed by the MS, called Collect2, used for monitoring and analyzing the investigations of the 60 municipalities. The source data of the system are imported from SIM, and with Collect2 it is possible to qualify the death by inserting the information verified after the investigation, based on the IOCMD-H form and the respective degrees of diagnostic certainty attributed after reclassification of the cause.

In this study, in addition to SIM, complementary information launched in the Collect2 system regarding the death records selected from SIM were used. The municipalities' performance was evaluated based on the proportion of deaths from sepsis investigated and reclassified in the SIM, and also the respective proportions registered in Collect2. The reclassification of death consists in the modification after the investigation of the UC that was initially inserted in SIM. The cause of death included in the system with the initial insertion of the DC is compiled in the database using the variable "CAUSABAS_O", called the original underlying cause. If the original underlying cause is changed after the investigation, the new code will be registered in the database in the variable "CAUSABAS", which corresponds to the last included cause.

Due to operational problems, not all investigated cases were registered in Collect2 by the municipalities. As a result, the causes registered in SIM that were reclassified after the investigation were analyzed instead. In order to evaluate the accuracy of this reclassification, the causes of death included in Collect2 that were reclassified with definitive and probable diagnostic certainty were also analyzed.

The UCs detected after the investigation were coded into 4-character subcategories of ICD-10[4] and classified into groups of causes according to the list of the GBD study 2015, with causes classified considering their relevance for the development of public policies and healthcare actions[13]. This list is organized hierarchically according to the causes' specificity level. For this study, level 3 causes were analyzed. Tabwin (version 4.15) and Microsoft Office Excel 2010 were used for data selection and tabulation.

This study was approved by the Research Ethics Committee of Universidade Federal de Minas Gerais (CAEE: 75555317.0.0000.5149) and developed in accordance with the ethical precepts established in Ordinance No. 466/2012 of the National Health Council.

RESULTS

In Brazil, 21,745 deaths with sepsis as UC were reported in SIM in 2017. Of this total, 19,680 deaths (90.5%) occurred in hospitals, 1,331 (6.1%) in other health facilities, such as emergency units, basic health units or clinics, and 591 (2.7%) at home (Table 1).

A total of 6,486 deaths from sepsis occurred in the 60 selected municipalities, corresponding to 29.8% of the country's total. The data on the proportional distributions by sex, age, ethnicity and place of occurrence of the 60 municipalities were similar to those in Brazil. In the 60 cities, about 55% of the deaths from sepsis were female and white individuals, the majority being 70 to 89 years old (49.3% of cases). Regarding the distribution by region, it was noted that the proportion of deaths in both the 60 cities and in the country was higher in the Southeast (52.1% and 65.8%, respectively) and lower in the Midwest (4.3% and 2%, respectively) (Table 1).

Table 1. Proportional distribution of deaths from sepsis as original underlying cause according to selected variables. Brazil and 60 cities, 2017.

Variable*	Brazil		60 cities			
			Total		Investigated	
	n	%	n	%	n	%
Sex						
Female	11,161	51.3	3,475	53.6	853	53.9
Male	10,582	48.7	3,010	46.4	731	46.1
Age group						
0 to 9 years old	925	4.3	247	3.8	121	7.6
10 to 29 years old	595	2.7	151	2.3	72	4.5
30 to 69 years old	7,123	32.8	1,958	30.2	586	37.0
70 to 89 years old	10,592	48.7	3,197	49.3	671	42.4
90 and older	2,493	11.5	923	14.2	133	8.4
Ethnicity/Color						
White	11,718	53.9	3,543	54.6	734	46.3
Mixed	7,456	34.3	2,189	33.7	671	42.4
Black	1,636	7.5	533	8.2	100	6.3
Yellow	98	0.5	39	0.6	8	0.5
Indigenous	57	0.3	4	0.1	2	0.1

Continue...

Table 1. Continuation.

Variable*	Brazil		60 cities			
			Total		Investigated	
	n	%	n	%	n	%
Place of occurrence						
Hospital	19,680	90.5	5,861	90.4	1,442	91.0
Another health facility	1,331	6.1	495	7.6	120	7.6
Home	591	2.7	103	1.6	16	1.0
Public highway	33	0.2	4	0.1	2	0.1
Other	106	0.5	21	0.3	4	0.3
Region						
Southeast	11,339	52.1	4,265	65.8	641	40.5
Northeast	5,330	24.5	1,345	20.7	530	33.5
South	3,051	14.0	215	3.3	142	9.0
North	1,097	5.0	529	8.2	183	11.6
Midwest	928	4.3	132	2.0	88	5.6

* Deaths with unreported or ignored records were excluded.

Source: Mortality Information System.

Table 2 presents deaths from sepsis in municipalities with 10 or more cases, the proportion of cases investigated and reclassified in the SIM, and the reclassified cases included in Collect2 with definitive or probable diagnostic criteria. It was noted that 24.4% (n = 1,584) of deaths from sepsis were recorded in the SIM as investigated, and of these, 82.6% (n = 1,308) were reclassified to other underlying causes, corresponding to 20.2% of all deaths from sepsis.

The cities with the highest proportion of reclassification were Joinville, Florianópolis, Blumenau, Cuiabá and Várzea Grande, all over 70%. Despite the lower proportion of reclassified cases, Rio de Janeiro, São Paulo and Belo Horizonte, the 3 municipalities with the highest concentration of deaths from sepsis, accounted for more than 30% of the total reclassifications in the country (Table 2).

Of the 60 cities, only 32 registered the investigations in the Collect2 system. Therefore, out of the 1,308 cases reclassified in the SIM, 901 (68.8%) were not included in the system, i.e., only 407 investigations of the deaths from sepsis were included. Of the cases included in Collect2, 42.5% (n = 173) were reclassified as having a definitive degree of certainty, and 39.3% (n = 160) as having a probable degree of certainty. The municipalities of Sobral, Blumenau, Joinville and Florianópolis included all of the investigations in Collect2, while Belo Horizonte, Aracaju e Porto Velho included more than 50% of them (Table 2).

Table 2. Number and percentage of cases reclassified in SIM and Collect2 according to certainty of diagnosis in 60 cities. Brazil, 2017.

60 cities	SIM					Collect2	
	Total deaths from sepsis	Investigated		Reclassified		Reclassified and registered*	
	n	n	%	n	%	n	%
North							
Manaus	135	22	16.3	1	0.7	–	–
Belém	84	27	32.1	23	27.4	14	16.7
Porto Velho	67	42	62.7	39	58.2	38	56.7
Ananindeua	56	13	23.2	8	14.3	1	1.8
Santarém	47	19	40.4	16	34.0	–	–
Macapá	46	3	6.5	2	4.3	1	2.2
Northeast							
Salvador	237	23	9.7	21	8.9	11	4.6
Fortaleza	201	78	38.8	66	32.8	–	–
Recife	142	92	64.8	70	49.3	–	–
Maceió	131	65	49.6	50	38.2	–	–
Natal	102	39	38.2	37	36.3	11	10.8
Aracaju	88	74	84.1	52	59.1	47	53.4
João Pessoa	88	19	21.6	13	14.8	1	1.14
Itabuna	64	25	39.1	13	20.3	–	–
Feira de Santana	59	2	3.4	–	–	–	–
Jaboatão dos Guararapes	41	12	29.3	10	24.4	–	–
Maracanaú	30	21	70.0	10	33.3	–	–
Sobral	28	15	53.6	14	50.0	14	50.0
Vitória da Conquista	27	7	25.9	5	18.5	–	–
Caucaia	26	8	30.8	5	19.2	–	–
Arapiraca	25	19	76.0	9	36.0	–	–
Caruaru	25	4	16.0	4	16.0	–	–
Lagarto	23	22	95.7	12	52.2	10	43.5

Continue...

Table 2. Continuation.

60 cities	SIM					Collect2	
	Total deaths from sepsis	Investigated		Reclassified		Reclassified and registered*	
	n	n	%	n	%	n	%
Southeast							
Rio de Janeiro	2,100	195	9.3	167	8.0	–	–
São Paulo	853	148	17.4	135	15.8	–	–
Belo Horizonte	311	154	49.5	148	47.6	84	27.0
São Gonçalo	247	34	13.8	31	12.6	3	1.2
Niterói	231	9	3.9	7	3.0	–	–
Nova Iguaçu	189	15	7.9	13	6.9	–	–
Duque de Caxias	113	21	18.6	18	15.9	–	–
Ribeirão Preto	83	40	48.2	31	37.3	–	–
Sorocaba	79	8	10.1	1	1.3	–	–
São José do Rio Preto	36	6	16.7	5	13.9	–	–
Itu	23	11	47.8	11	47.8	–	–
South							
Curitiba	71	23	32.4	15	21.1	1	1.4
Joinville	38	32	84.2	31	81.6	31	81.6
Florianópolis	32	30	93.8	26	81.3	26	81.3
Blumenau	30	22	73.3	22	73.3	22	73.3
Midwest							
Goiânia	70	34	48.6	32	45.7	10	14.3
Cuiabá	30	23	76.7	21	70.0	5	16.7
Várzea Grande	23	22	95.7	20	87.0	14	60.9
Other municipalities†	155	106	68.4	94	60.6	63	40,6
Total	6,486	1,584	24.4	1,308	20.2	407	6.3

*Reclassified cases registered in Collect2 with definite, probable and possible degree of certainty; † Fourteen municipalities with less than 10 total cases in SIM were excluded.

Source: Mortality Information System and Collect2.

Table 3 presents data on the reclassification of deaths originally attributed to sepsis, according to the inclusion of the final cause obtained after the investigation in SIM (n = 1,308), and the inclusion of the cases reclassified with definite and probable degrees of certainty in Collect2 (n = 333). Of deaths from sepsis that were reclassified after the investigation, 858 (65.5%) had noncommunicable chronic diseases (NCDs) as UC. Diabetes was the main specific cause of death after the investigation, accounting for 7.6% of the total deaths reclassified in SIM. In Collect2, digestive disorders accounted for 11.4% (n = 38) of the reclassified deaths, and diabetes accounted for 6.3% (n = 21) of them.

Diarrheal diseases were the predominant causes in the group of communicable, maternal, neonatal and nutritional diseases, in both databases analyzed. In the group of accidents and violence, falls represented the main specific cause among the reclassified deaths. Table 3 also shows that some reclassified causes migrated to other GC, corresponding to 11.4% of the total deaths in the Collect2 system and 19.2% of those in SIM.

Table 3. Reclassified causes registered in SIM and Collect2 after the investigation of deaths originally attributed to sepsis. Brazil, 60 cities, 2017.

GBD Causes – 2015	SIM		Collect2*	
	n	%	n	%
Group I – Communicable, maternal, neonatal and nutritional	126	9.6	29	8.7
Diarrheal diseases	24	1.8	8	2.4
Lower respiratory tract infections	16	1.2	7	2.1
HIV/aids	13	1.0	3	0.9
Tuberculosis	12	0.9	1	0.3
Other group 1 diseases	61	4.8	10	3.3
Group II – Noncommunicable and chronicle	858	65.6	244	73.3
Diabetes mellitus	100	7.6	21	6.3
Digestive disorders	100	7.6	38	11.4
Neoplastic diseases	90	6.9	29	8.7
Chronic kidney disease	89	6.8	26	7.8
Urinary diseases	62	4.7	18	5.4
Other cardiovascular diseases	61	4.7	22	6.6
Chronic obstructive pulmonary disease	58	4.4	17	5.1
Stroke	48	3.7	18	5.4
Alzheimer's and other dementias	42	3.2	7	2.1
Cirrhosis	42	3.2	7	2.1
Other group II diseases	166	12.6	41	12.3

Continue...

Table 3. Continuation.

GBD Causes – 2015	SIM		Collect2*	
	n	%	n	%
Grupo III – Accidents and violence	73	5.6	22	6.6
Falls	45	3.4	16	4.8
Adverse effects of medical treatment	8	0.6	0.0	0.0
Other accidents and violence	20	1.6	6	1.8
Garbage codes	251	19.2	38	11.4
Total reclassified deaths from sepsis	1,308	100.0	333	100.0

* Records with "definitive" and "probable" degree of diagnostic certainty.

Source: Mortality Information System and Collect2.

DISCUSSION

The assessment of the investigation of deaths from sepsis carried out in the 60 municipalities showed that over 80% of them were reclassified as belonging to one of the 3 major groups of causes in the GBD study 2015[13], especially NCDs. In this group, diabetes mellitus stands out as the main specific cause of death after the investigation, corresponding to 7.6% of cases. Deaths with diagnostic certainty registered in the Collect2 system after the investigation were also considered, 42.5% with a definitive degree of certainty and 39.3% with a probable degree of certainty, of which 6.3% were reclassified as diabetes. This analysis, based on cases with a high level of clinical evidence employed in reclassifications after referring to hospital records, highlights the importance of considering information obtained after the investigations.

Sepsis is a condition commonly treated in hospitals that requires intensive care, given the severity of the symptoms manifested by the syndrome and the care complexity required for treatment[15,16]. The results of this study showed that the highest concentration of sepsis-related deaths in Brazil in 2017 occurred in hospitals. This finding reinforces the need to strengthen the investigation of deaths from sepsis to clarify the true cause of death. Moreover, the fact that 42.5% of the investigations in the 60 cities were registered in the Collect2 system with definite degree of certainty indicates that the information on the causes of death could be obtained from hospital records. Hobson and Meara[7] also found, in an analysis of death records from UK hospital cohort, that 47% of death certificates had no reports of Parkinson's disease in any field of causal sequence of death in patients previously diagnosed with the disease. Therefore, physicians should be trained on the importance of correctly filling out the DC.

One of the main reasons for the large number of non-specific causes of death in death certificates is the incorrect registering of the death event chain[7,17,18], and a large

portion of these errors stems from the insertion of a terminal event as the underlying cause. The study by Maharjan et al.[18] identified a significant association between the severity of the diagnosis of sepsis and the presence of errors in death certificates, as sepsis correlates with multiple organ failure, opening up several possibilities for intermediate or multiple causes, which may confuse the certifying physician.

In addition to the severity of the diagnosis, factors such as sex, age and associated diseases can make it difficult to establish the UC of death. High mortality rates for septic patients have been observed in people over 60 years old, as well as a higher proportion of GC attributed to older women, probably because of the complexity in establishing a single cause due to the many associated comorbidities[17-23]. Similar results were found in this study, in which the highest rate of deaths from sepsis was attributed to individuals aged from 70 to 89 years old, and the predominant gender being female. Several other studies show that most patients diagnosed with sepsis have some type of comorbidity[15], the main ones being diabetes, lung disease, kidney disease and cancer[16,17,19,20]. In the analysis by Barros et al.[20], performed in an intensive care unit in Brazil, Acquired Immunodeficiency Syndrome (AIDS), hypertension and heart failure were also described as preponderant comorbidities in patients with sepsis.

Regarding the reclassification of deaths from sepsis, Melo Jorge et al.[24], in a study published in 2002, found different results from those of our study, when they analysed changes in death rates following an investigation in which most of the detected specific causes corresponded to infectious diseases. Regarding diabetes, which was the main specific cause identified in this study after the reclassification, the literature shows that the disease has pathophysiological mechanisms that aggravate the prognosis of infection, thus contributing to the increase in the rate of deaths from sepsis[25,26].

In the GBD study 2010[27], almost 49% of the deaths from sepsis were reclassified as belonging to the chronic disease group after using algorithms for redistribution of garbage causes, with 10% of deaths allocated to the group "Diabetes, urogenital, blood and endocrine diseases". However, less than 1% of the deaths were attributed to diabetes alone, a much lower proportion than that found in this study. On the other hand, our results corroborate the findings of the GBD study 2010[27] for digestive disorders, wherein 13.6% of the deaths from sepsis were attributed to this group, which corresponded to 11.4% of the deaths reclassified in Collect2 and was the second leading group of the causes reclassified in SIM.

The distribution of sepsis cases in the SIM according to the variables gender, age group, ethnicity/color and place of occurrence is similar to the distribution of these variables for the total number of deaths in the country, indicating good representativeness of the selected municipalities. However, a limitation of this study relates to the fact that, of the 1,584 deaths from sepsis investigated in the 60 municipalities, 68.8% were not included in the Collect2 system, possibly due to limited availability of municipal resources for processing data from the investigations. The small proportion of reclassified deaths from sepsis recorded in Collect2 (n = 407) implied a low number

of reclassified cases with definitive and probable diagnostic certainty (n = 333). There was a discrepancy between the SIM and Collect2 regarding the percentage of some causes reclassified after the investigation, indicating the lack of representativeness of Collect2, probably due to the different proportions of registration in the 60 municipalities. This fact points to the need to establish mechanisms that guarantee the registration in Collect2, in order to allow the proper monitoring of the investigations.

In general, the investigation of deaths from GC in the 60 municipalities showed the feasibility of such interventions, since the death investigation routines allowed clarifying the diagnoses that triggered death. The adoption of these procedures should be encouraged in all municipalities to improve the quality of mortality data reported in the SIM. However, further studies on this subject are needed to ensure the validity and feasibility of this practice. Investments to promote the investigation, which demonstrated the several possibilities of diagnoses associated with sepsis, in addition to improving the quality of death certification by physicians, would contribute to a better understanding of the UC of these deaths.

CONCLUSION

The results presented by the municipalities that are part of the D4H initiative, in view of the reclassification of the deaths from sepsis, show the importance of the investigation of GC to refine and increase the quality of mortality data. These results may offer a more adequate methodology to studies using indirect methods for the redistribution of deaths from sepsis. Death investigation practices and investment in the training of physicians on how to correctly fill out the DC should be incorporated in health services to ensure better quality of mortality information in the country.

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