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Subnational analysis of pediatric sepsis incidence and mortality from official records in Chile and Mexico: a longitudinal study from 2014 to 2024

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TITLE: Subnational analysis of pediatric sepsis incidence and mortality from official records in Chile and Mexico: a longitudinal study from 2014 to 2024

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ABSTRACT

Background: Pediatric sepsis is a leading cause of global morbidity and mortality, yet high-resolution, granular subnational assessments remain scarce. Chile and Mexico are the only countries in Latin America that possess robust vital registration systems and open access databases with marginal levels of missing cases. This offers a unique opportunity to quantify the subnational burden of pediatric sepsis, identify healthcare system constrictions, and guide targeted public health interventions.

Methods: This retrospective longitudinal study analyzed official hospital discharge and non-fetal death records of pediatrics (<10 years old) from Chile and Mexico between 2014 and 2024. Age-standardized incidence (ASIR) and mortality (ASMR) rates, standardized ratios, and the mortality-to-incidence ratio (MIR), were calculated to assess mortality relative to subnational hospital output. A novel dynamic risk stratification matrix was developed to classify ICD-10 sepsis-related causes into four risk/severity quadrants based on year-specific ASIR and MIR indicators.

Results: A total of 656,234 discharges and 2,035 deaths in Chile, and 964,452 discharges and 77,252 deaths in Mexico were analyzed. Subnational trends were highly heterogeneous. Chile exhibited a predominantly low pediatric MIR (median <1%) with isolated hotspots with significant structural deviations to the North. High-severity sepsis causes in Chile were relatively rare. Conversely, Mexico displayed an alarmingly high MIR (median 7.2%), with systemic persistency in States such as Chiapas and Nuevo León. Strikingly, high-severity causes in Mexico (*e.g.*, unspecified septicaemia, bacterial meningitis) were highly frequent, accounting for 88–97% of pediatric sepsis deaths. Furthermore, systemic instances of code-specific MIR > 1.0 in Mexico suggest significant health system fragmentation and decoupling of hospital discharge from vital statistic registries.

Conclusions: Pediatric sepsis in Latin America encompasses distinct realities, ranging from localized critical care gaps to high-lethality persistency. One-size-fits-all national policies may be inadequate. These findings advocate for precision public health, urging the deployment of decentralized, data-driven interventions and specialized resource allocation based on high-risk subnational hotspot identification.

INTRODUCTION

Sepsis is a life-threatening organ dysfunction induced by an infection [1] and is a public health emergency that requires a concerted public and political focus [2]. A recent global report estimated 166 million cases of sepsis and 21.4 million deaths worldwide for the year 2021 [3]. In another global report, sepsis incidence and mortality were shown high in early childhood, with around 20 million cases and 3 million deaths occurring in children under 5 years old, highlighting the relevance and urgency to develop and implement health policies for this age group [2]. Despite efforts to understand the global burden of sepsis, there is still a lack of country-specific analyses. In fact, despite official records being available on an open-access fashion, we have no account of any report integrating incidence and mortality for pediatric sepsis.

In an exploratory analysis by our group (data not shown), among member countries of the Organisation for Economic Co-operation and Development (OECD), only Chile and Mexico were found to have official open access data of hospital discharge and death records with a level of completeness close to 100%. Although belonging to a region with limited and unequal economic resources [4, 5], Chile and Mexico have also been acknowledged for the reliability of their vital registration [6–8]. Thus, an immeasurable opportunity to use official records to quantify the burden of sepsis, identify critical points in the health system, and suggest new public health policies presents itself.

Accurately assessing the burden of sepsis is crucial for allocating resources and implementing a targeted prevention. Previous studies have analyzed official records in the context of other health issues [9, 10] with results and observations that are easily translatable into recommendations for health policies, resource allocation, and targeted prevention. To respond to the 2025-2029 Pan American Health Organization's Strategy and Plan of Action to Decrease the Burden of Sepsis [11], the 2025 European Sepsis Alliance (ESA) call to action [12], the Global Sepsis Alliance (GSA) 2030 agenda for sepsis [13], the Sustainable Health

Agenda for the Americas [14], and the 2017 World Health Organization's sepsis resolution [15], we present trends of pediatric sepsis incidence and mortality, assessing subnational hotspots, and appraising individual cause contribution from 2014 to 2024 in Chile and Mexico.

METHODS

Data sources and processing

This retrospective longitudinal study followed the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) checklist [16]. Due to the study design, written informed consent was waived for all subjects. Hospital discharges were retrieved from the Chilean Department of Health Statistics and Information (*Departamento de Estadísticas e Información de Salud*, DEIS) [17] and the Mexican General Directorate of Health Information (*Dirección General de Información en Salud*, DGIS) [18]. Non-fetal death records were also retrieved from Chilean DEIS and from the Mexican National Institute of Statistic and Geography (*Instituto Nacional de Estadística y Geografía*, INEGI) [19]. Population figures were retrieved from the Chilean National Institute of Statistics (Instituto Nacional de Estadísticas, INE) [20] and the Mexican National Population Council (*Consejo Nacional de Población*, CONAPO) [21]. Records of neonatal subjects were not excluded. Data was handled and analyzed using R version 4.3.2. A complete detail about data processing is presented in Supplementary Material and Supplementary Figures 1-4.

Data integrity and harmonization

Randomness bias in missing data was assessed using a chi-square goodness-of-fit test in dataframes with variable completeness <99.5%. Within root dataframes of death, discharge, and population, age was found to be expressed both as a continuous and categorical variable (Supplementary Table 1). Therefore, to enable comparability across dataframes and to preserve interpretability, age was harmonized and recoded as a categorical variable of levels under 1 year old (infants) and 1–9 years old (children). Immediate cause of death and primary admission diagnosis, coded as International Classification of Diseases (ICD)-10 codes, were queried for structure integrity (*e.g.*, cases including illegal or lowercase characters, missing the first letter component, ending in a letter, etc.) and length (*i.e.*, 3- or 4-character code). To identify sepsis-related codes, a 3-pass harmonization algorithm was applied (Supplementary Material, Supplementary Figure 5) based on ICD-10 codes listed in report by Rudd *et al.* [2] (Supplementary Table 2). A detailed account of placeholder "X"-bearing ICD-10 codes contribution to sepsis-related causes after the 3-pass harmonization algorithm is presented in Supplementary Figure 6.

Statistical analysis

Crude incidence and mortality rates for sepsis-related causes were calculated as a rate between the sum of corresponding deaths or discharges (numerator) and corresponding population figures (denominator). Crude rates were further adjusted by age proportion of the 2026 population to calculate figures of age-standardized incidence rate (ASIR) and age-standardized mortality rate

(ASMR), expressed as per 100,000 population. Standardized incidence (SIR) and mortality (SMR) ratios were calculated as the ratio of Region-specific ASIR or ASMR (numerator) to the national ASIR or ASMR (denominator) for each year. Assuming a Poisson distribution for observed case counts, 95% confidence intervals (CIs) were calculated using Garwood's exact method. Output was considered significant when such CI excluded the null value (1.0). The mortality-to-incidence ratio (MIR) was calculated as the quotient between the number of deaths (numerator) and the number of hospital discharges (denominator) to assess the burden of mortality relative to hospital system output. Calculations were conditional on non-zero discharge counts to prevent artifacts in low-population regions. Region-specific excess MIR compared to the national baseline were analyzed yearly using a one-sided binomial test. Output was considered significant when p-value < 0.05. Statistical differences between yearly MIR magnitudes of Chilean Regions or Mexican States were calculated with a Kruskal-Wallis nonparametric test, followed by Dunn's *post hoc* test with Bonferroni adjustment. Differences were considered significant with a p-value <0.05.

Risk stratification

Crude rates, adjusted rates, and standardized ratios were also calculated for each sepsis-related cause on an ICD-10 code and Region basis. Code-specific MIR was calculated as the ratio of ASMR (numerator) to ASIR (denominator). Mortality-to-incidence ratio values exceeding 1.0 were retained as indicators of surveillance discrepancies where registered mortality exceeded hospital capture capacity. Year-specific ASIR and MIR medians were used as cut-offs to construct a dynamic risk stratification matrix to classify each sepsis-related cause into four quadrants ($risk^{hi/low}$/$severity^{hi/low}$, Supplementary Figure 7).

RESULTS

The total number of cases of each end-dataframe was 2,035 deaths (Supplementary Figure 1) and 656,234 hospital discharges (Supplementary Figure 2) for Chile, and 77,252 deaths (Supplementary Figure 3) and 964,452 hospital discharges (Supplementary Figure 4) for Mexico.

Trends of incidence and mortality

Pediatric sepsis-related incidence and mortality showed an overall (national) displacement with a negative trend between 2014 and 2024 in both Chile (Figure 1A) and Mexico (Figure 1B). A temporal deviation consistent with the COVID-19 pandemic could be observed. Subnational decomposition of overall trends showed that pediatric sepsis-related ASIR and ASMR displayed heterogeneous patterns (Figures 2-3, Supplementary Tables 3-4). In general, 2 out of the 16 Chilean Regions (Figure 2A) and 7 out of the 32 Mexican States (Figure 3A) showed a trend of increased pediatric ASIR, and 4 out of the 16 Chilean Regions (Figure 2B), and 4 out of the 32 Mexican States (Figure 3B) showed a trend of increased pediatric ASMR between 2014 and 2024. In yearly analyses, SIR was predominantly higher in 5 out of the 16 Chilean Regions and 15 out of the 32 Mexican States, and SMR was predominantly higher in 7 out of the 32 Mexican States, with few Chilean Regions showing significant differences (Figures 2-3). A deviation in the ASIR trend was visible in both countries during the COVID-19 pandemic (Figures 2A and 3A).

Among Chilean Regions, ASIR was highest in Los Ríos, Aysén, and Biobío, and lowest in Arica y Parinacota (Figure 2A), while ASMR was highest in Antofagasta and lowest in Los Ríos. Among Mexican States, ASIR was highest in Ciudad de México and Tlaxcala, and lowest in Nuevo León (Figure 3A), while ASMR was highest in Chiapas and lowest in Colima (Figure 3B).

Spatiotemporal evolution of the mortality-to-incidence ratio

Pediatric sepsis MIR progression in Chile was found predominantly low (median 0.004, interquartile range [IQR] 0.004). However, extreme outliers were observed in Arica y Parinacota, reaching a maximum ratio of 0.75 in 2014 and 0.15 in 2022 (Figure 4). Even excluding these anomalies, Arica y Parinacota displayed MIR magnitudes > 0.01 in 5 out of the 11 years under analysis. Binomial analyses revealed significant increases for over 5 years in Antofagasta and Arica y Parinacota (Figure 4). In contrast, MIR in Los Ríos was found the lowest across all years analyzed (median 0.0016, IQR 0.0016). Cumulative MIR was found highest in Arica y Parinacota (mean 0.018, SE 0.004, excluding outliers) and lowest in Los Ríos (mean 0.0017, SE 0.0003, Supplementary Figure 8A). Consistently, the highest number of pairwise differences of mean MIR between Regions was observed in Arica y Parinacota (Supplementary Figure 8B).

Pediatric sepsis MIR progression in Mexico was found predominantly under 0.10 (median 0.072, IQR 0.040, Figure 5). Alarmingly, five States displayed MIR magnitudes consistently exceeding the national median in all years under analysis (Chiapas, Coahuila, Nuevo León, Puebla, and Veracruz), with differences significantly higher than the national baseline (Figure 5). States with significant increases for over 5 years include Chihuahua, Jalisco, Michoacán, Nuevo León, and Tabasco. States with the lowest MIR were Guanajuato (median 0.041, IQR 0.007) and Tlaxcala (median 0.042, IQR 0.012). Cumulative MIR was found highest in Chiapas (mean 0.15, SE 0.008) and lowest in Guanajuato (mean 0.042, SE 0.003, Supplementary Figure 9A). Consistently, the highest number of pairwise differences of mean MIR between States was observed in Chiapas (Supplementary Figure 9B).

Dynamic risk stratification

Dynamic risk stratification matrix classified sepsis-related causes into four quadrants. Most of these causes were found in the low severity ($risk^{hi/low}/severity^{low}$) quadrants in both countries analyzed (Figure 6). No pattern of persistency could be observed for sepsis-related causes classified in the high severity ($risk^{hi/low}/severity^{hi}$) quadrants among Chilean pediatrics from 2014 to 2024 (Figure 6A).

During this period, sepsis-related causes in the high severity ($risk^{hi/low}/severity^{hi}$) quadrants accounted for 67 infant deaths in Chile, of which, causes in the $risk^{hi}/severity^{hi}$ quadrant accounted for 36 infant deaths. Also, sepsis-related causes in the high severity ($risk^{hi/low}/severity^{hi}$) quadrants accounted for 28 child deaths, of which, causes in the $risk^{hi}/severity^{hi}$ quadrant accounted for 11 child deaths (Supplementary Table 5). Thus, the gap between high severity causes that presented more and less frequently in the health system was approximately 8% among infants and 22% among children.

In sharp contrast, sepsis-related causes A41.9 (Septicaemia), E87.2 (Acidosis), G00.9 (Bacterial meningitis), G03.9 (Meningitis), G04.9 (Encephalitis, myelitis and encephalomyelitis), K63.1 (Perforation of intestine), K65.9 (Peritonitis), N17.9 (Acute renal failure), P22.0 (Respiratory distress syndrome of newborn), P23.9 (Congenital pneumonia), and P29.1 (Neonatal cardiac dysrhythmia), were persistent and systematically classified in the high severity ($risk^{hi/low}$/$severity^{hi}$) quadrants among Mexican infants from 2014 to 2024. During this period, sepsis-related causes in the high severity ($risk^{hi/low}$/$severity^{hi}$) quadrants accounted for 46,207 infant deaths, of which, causes in the $risk^{hi}$/$severity^{hi}$ quadrant accounted for 45,487 infant deaths (Supplementary Table 6). Thus, the gap between high severity causes that presented more and less frequently in the health system was approximately 88% among infants.

Additionally, sepsis-related causes A41.9 (Septicaemia), D65.5 (Disseminated intravascular coagulation), G04.9 (Encephalitis, myelitis and encephalomyelitis), K72.0 (Acute and subacute hepatic failure), and K72.9 (Hepatic failure), were also persistent and systematically classified in the high severity ($risk^{hi/low}$/$severity^{hi}$) quadrants among Mexican children from 2014 to 2024. During this period, sepsis-related causes in the high severity ($risk^{hi/low}$/$severity^{hi}$) quadrants accounted for 4,254 child deaths, of which, causes in the $risk^{hi}$/$severity^{hi}$ quadrant accounted for 3,995 child deaths (Supplementary Table 6). Thus, the gap between high severity causes that presented more and less frequently in the health system was approximately 97% among children.

Data quality and bias assessment

Assessment of ICD-10 code string completeness and integrity (Supplementary Material) revealed a 100% completeness in all SCOD dataframes handled and use of illegal characters (".", "-", " ", or lowercase in the first position) only in the Mexican SCODi dataframe. Use of placeholder "X" was more recurrent in the Chilean SCODe dataframe (present in 17.85% of all cases, Supplementary Figure 6A). Variables unrelated to SCOD were found >99.5% complete except for the Chilean hospital discharge dataframe (Supplementary Figures 1-4).

Randomness bias was assessed only in the Chilean hospital discharge dataframe (for which completeness was found <99.5%, Supplementary Figure 2). Not available content in this dataframe was observed perfectly matched between variables related to the year of the discharge and the group of age. Chi-square goodness-of-fit test revealed that differences between counts of year of discharge were not random ($p < 0.001$), favoring the year 2024, differences between counts of age groups were not random ($p < 0.001$), favoring the group 1-4 years old, and differences between counts in Region were not random ($p < 0.001$), favoring use of code "99" (Ignored) (Supplementary Table 7).

DISCUSSION

To our knowledge, this is the first study to analyze pediatric sepsis at the population level subnationally. Our results reveal two separate realities: one with a low-MIR landscape, dotted with persistent regional exceptions, and another with a high-MIR landscape, characterized by a systemic persistence of severe sepsis-related causes. While progress from 2014 to 2024 in the national reduction of pediatric ASIR and ASMR independently cannot be overlooked neither in Chile nor in Mexico, sharp differences in MIR are evident between these two nations (Figures 2-3 and Supplementary Figures 8-9). The average 8-fold difference in cumulative MIR suggests profound disparities in healthcare access, early recognition, resource availability, and infrastructure for pediatric critical care [3], unmasking the false sense of security conveyed by national trends of ASIR or ASMR. In Chile, despite a national median MIR being below 1%, Arica y Parinacota exhibited a 3-fold increase. Located to the north of the country, this increase may reflect the country's inability to decentralize and properly deploy ICU specialist —a concern raised not by a branch of the government, but by academics in an independent and isolated report [22]. In Mexico, high MIR has aggregated to the North and to the South for over a decade with no effective reaction from the authorities. We call for an urgent implementation of public health policies aimed at reducing national MIR, starting with Nuevo León and Coahuila to the North, and Puebla, Chiapas, and Veracruz to the South. Exploratory analyses (*i.e.*, univariate correlations, cross sectional multivariate regressions, and pooled OLS analyses) performed by our group (data not shown) suggest that standard socio-economic variables (*e.g.*, human development index, poverty, unemployment) may be poor predictors of MIR and that causality in these priority States may be a complex goal to achieve. Further research is encouraged to pinpoint tangible points of action.

A hallmark contribution of this study is the use of the dynamic risk stratification matrix. In Chile, sepsis-related causes classified as high-severity were relatively rare. The small gap (8% among infants and 22% among children) between high-severity causes that presented frequently versus those that presented rarely suggests an efficient health system capable of containing outbreaks and managing common infections before they progress to fatal sepsis. In sharp contrast, Mexican pediatrics face a scenario where high-severity causes are also the most frequent. The large gap (97% among infants and 88% among children) highly suggests that lethal sepsis etiologies in Mexico are not sporadic outliers but endemic features of the hospital ecosystem. The systematic classification of septicaemia (A41.9) and bacterial meningitis (G00.9) in the risk^{hi}/severity^{hi} quadrant indicates a failure in early recognition and management. Furthermore, the prominence of code A41.9 (Unspecified septicaemia) as a persistent high-severity cause points to a dual burden: high mortality coupled with low diagnostic precision, hindering targeted antimicrobial stewardship. The systematic persistence of respiratory distress syndrome (P22.0) and congenital pneumonia (P23.9) in the risk^{hi}/severity^{hi} quadrant for infants suggests gaps in neonatal care quality, ventilation strategies, or early antibiotic administration in neonatal intensive care units. The systematic persistence of encephalitis (G04.9) and hepatic failure (K72) suggests that sepsis mortality is often driven by complex, organ dysfunction-related clinical courses that may be inadequately managed settings of limited resources. Our results support the hypothesis that MIR in Mexico is driven by known causes and by the inability of the health system to contain such known conditions.

While MIR > 1.0 is generally considered epidemiologically impossible in linked datasets, this longitudinal study of unlinked data was sensitive enough to find one event of MIR > 1.0 in Chile (*i.e.*, code I40.9, acute myocarditis, 2021) and several others in

Mexico (Figure 6). This likely suggests that Chilean hospital discharge coding system maintains a high degree of coherence with vital statistics, with only rare decoupling. In contrast, Mexico exhibited a systemic pattern of MIR > 1.0, with 48 instances involving over 3,700 deaths and 17 codes (A04.7, A41.5, A41.9, A77.0, A79.9, A91, B34.0, D65, E87.2, K65.0, K65.9, K72.0, K72.9, N00.9, N17.9, P29.1, P37.5). This divergence suggests that these risk$^{hi/low}$/severity^{hi} causes are visible in the vital statistics system (INEGI) but «invisible» in hospital discharge records (DGIS), likely revealing a significant proportion of sepsis mortality occurring in facilities not reporting to the central discharge database, or a tacit asymmetry to code sepsis as underlying/primary cause. Further research is required to explore the use of MIR > 1.0 as a red flag for health system fragmentation.

During the COVID-19 pandemic, deviations in ASIR and ASMR in both countries (Figure 1) likely represent a combination of reduced healthcare-seeking behavior for non-COVID illnesses, the repurposing of pediatric beds for adult COVID care, and potential under-diagnosis of bacterial sepsis masked by SARS-CoV-2 coinfection, returning to baseline levels in the following years.

Although non randomness of undetermined content, favoring the year 2024, the age group 1-4 years old, and code “99” (Ignored) (Supplementary Table 7) found in the Chilean hospital discharge dataframe may constitute a limitation to our interpretations, the extent of such non randomness bias is reasonably below 5%, representing 2.86% of the sepsis dataframe.

In countries where data of high quality is already at disposal, the challenge of tackling pediatric sepsis is one step closer than countries where data is unreliable or lacks a digital framework. The next logical step for Chile and Mexico would be to assemble and deploy de-centralized mobile units of health data science personnel capable of interpreting and flagging local risk matrices in real-time (rather than waiting for retrospective national reports). Thus, practical challenges for Chile would be concentrated around data decentralization and human resources. While for Mexico, given the systemic MIR > 1.0 signal, we hypothesize that the current digital infrastructure fails to link vital statistics (INEGI) with Hospital Discharges (DGIS). An interoperability upscale between recordkeepers may have to be implemented before deploying health data science units. Nonetheless, it is without a doubt that both countries are in a formidable position to counterattack, especially if MCOD data is available internally.

STRENGTHS AND LIMITATIONS

Previous studies have reported the burden of sepsis using indirect estimations [3], systematic reviews of the literature [23], or skewed data from critically ill children in intensive care units or secondary level care units [24]. In contrast, our study reports figures of incidence and mortality based on official government records enabling us to carry out an analysis at the subnational level in two countries often neglected in major studies [25]. This inextricably binds the precision of our recommendations to the capacity of each country to keep vital registration with a high standard of quality. While the latter may not the case for all countries in Latin America, it is for Chile and Mexico [6–8].

Sepsis is a multifaceted condition that may be identified not only as a direct cause of death but also as an intermediate or underlying cause of death [26]. Both the Chilean DEIS and Mexican INEGI explicitly state that the cause of death made available in open-access datasets is not the direct cause or any intermediate cause, but the underlying cause of death. This kind of data is classified as single cause of death (SCODe), in contrast to multiple cause of death (MCODe) —in which all codes contributing to the deadly outcome are made available. Additionally, single cause of discharge (SCODi) and multiple cause of discharge (MCODi) data follow a similar logic but with primary and secondary causes of hospitalization. As a previous discussion from our group pointed out [27], Brazil's is the only open-access MCODe/MCODi (MCOD) database available in the world, but it is only 99.5/59% complete. Therefore, in-depth analyses of the burden of sepsis must inextricably resort to SCODe/SCODi (SCOD) data, a dual input that is crucial for our algorithm that few countries of the OECD make available with open access. In fact, within Latin America, only Chile and Mexico fit such condition, limiting the scope of the present article to those countries. Bias from the use of SCOD instead of MCOD data has been comprehensively tested recently [27]. In summary, use of SCODe determines an average underestimation of 24.1% for ASMR. Because the coupled use of ASMR and ASIR is *sine qua non* for our approach, and assuming an underestimation for SCODi in the range of 24.1%, use of MIR surfaces as a clever alternative to turn this limitation into a strength.

Verisimilitude of ICD classification will ultimately depend on the attending physician or the medical examiner. In line with PAHO's CVRS [28, 29], Chile offers continuous training to physicians through different courses, updated standards, recommendations, and guidelines, through the National Reference Center for the Family of International Classifications (*Centro Nacional de Referencia de la Familia de las Clasificaciones Internacionales*), based in the Undersecretariat of Public Health (*Subsecretaría de Salud Pública*) and implemented by the DEIS. Similarly, Mexico complies with the Terms of Reference agreed between the Ministry of Health and PAHO/WHO, is involved in various Reference Groups (*e.g.*, morbidity, mortality, functioning and disability, and verbal autopsy), and offers continuous training for physicians [30]. Although availability and use of country-specific morbidity data and/or a validation set would be ideal, confidence in Chilean and Mexican vital statistics is determined by their compliance with PAHO/WHO standards, its use as reference for global reports [2, 3], and its use in a recent peer-reviewed publication [27]. Nevertheless, we acknowledge reliance on hospital records as a source of inaccuracy in our ecological study.

Endorsed by PAHO since the 1990s [31], a significant challenge was posed by the use of character "X" in the fourth place of the 4-character ICD code string to preserve code length [32, 33] in both SCODe and SCODi data from both countries. Our pragmatic harmonization approach, described in detail in Supplementary Figure 5, classified sepsis-related codes into 3 groups. We acknowledge that only in the sepsis (trimmed) group certainty might be disputed. By trimming 4-character codes from the definition of sepsis, specificity brought by the use of the fourth character might have been compromised to a degree yet to be uncovered by case-wise analyses warranting further collaborative investigation with the Global Burden of Disease [2]. However, a comprehensive account of the potential extent of this bias showed the proportion of the sepsis (trimmed) group to range between 0.29%-0.46% of SCODe datasets (2.79%-4.87% of all sepsis cases identified) and 1.03%-1.44% of SCODi datasets (9.09%-10.34% of all sepsis cases identified) (Supplementary Figure 6).

CONCLUSION

Pediatric sepsis remains a major public health challenge in Latin America. The "one-size-fits-all" approach to national sepsis guidelines appears insufficient for regions like Chiapas or Arica y Parinacota, which face distinct MIR landscapes. Our findings support a shift toward precision public health: prioritizing resource allocation, diagnostic strengthening, and specialized training in the specific territories identified as high-persistecy hotspots. Reducing the burden of sepsis requires not just national protocols, but targeted sub-national action.

HUMAN ETHICS AND CONSENT TO PARTICIPATE

This study was based exclusively on the analysis of publicly available, fully anonymized, and aggregated administrative health datasets provided by the Department of Health Statistics and Information (DEIS) of the Ministry of Health in Chile, the General Directorate of Health Information (DGIS) of the Secretariat of Health in Mexico, and the National Institute of Statistics and Geography (INEGI) in Mexico. Because the research did not involve human subjects, primary data collection, or identifiable patient information, the requirement for ethical approval and informed consent was waived in accordance with national legislation and institutional guidelines.

CONFLICTS OF INTEREST / COMPETING INTERESTS

The authors declare that they have no competing interests.

AVAILABILITY OF DATA AND MATERIALS

The datasets analyzed in this study were found and may be accessible in the official websites of the *Departamento de Estadísticas e Información de Salud*, (DEIS), available at: https://deis.minsal.cl, the *Instituto Nacional de Estadísticas* (INE), available at: https://www.ine.gob.cl/estadisticas/sociales/demografia-y-vitales/proyecciones-de-poblacion, the *Dirección General de Información en Salud,* (DGIS), available at: http://www.dgis.salud.gob.mx/contenidos/basesdedatos/da_egresoshosp_gobmx.html, the Instituto Nacional de Estadística y Geografía (INEGI), available at: https://www.inegi.org.mx/programas/mortalidad/#Microdatos, and the Consejo Nacional de Población (CONAPO), available at: http://www.conapo.gob.mx/work/models/CONAPO/Datos_Abiertos/Proyecciones2018/pob_mit_proyecciones.csv. Processed datasets are included as supplementary material. Further inquiries may be directed to the corresponding author.

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CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AUTHORS' CONTRIBUTIONS

SG conceived the idea for this research. PC, FD, RJ, NK, and FS provided overall guidance. SG and FS verified the data, and all authors had full data access. All authors participated in the preparation of all drafts of the manuscript and finalized it based on comments from each other. SG, FS, and NK were responsible for the decision to submit the manuscript.

FIGURE LEGENDS

Figure 1. National trends of pediatric sepsis incidence and mortality. Evolution of national age-standardized incidence rates (ASIR) and age-standardized mortality rates (ASMR) from 2014 to 2024 in **A**) Chile and **B**) Mexico.

Figure 2. Spatiotemporal trends of pediatric sepsis burden in Chile (2014–2024). A) Age-standardized incidence rate (ASIR) of pediatric sepsis per 100,000 population across 16 Chilean Regions. Trends highlight significantly higher or lower ASIR with respect to year-matched standardized incidence ratios (SIR). **B**) Age-standardized mortality rate (ASMR) of pediatric sepsis per 100,000 population across 16 Chilean Regions. Trends highlight significantly higher or lower ASMR with respect to year-matched standardized mortality ratios (SMR). Shaded areas highlight the COVID-19 pandemic period.

Figure 3. Spatiotemporal trends of pediatric sepsis burden in Mexico (2014–2024). A) Age-standardized incidence rate (ASIR) of pediatric sepsis per 100,000 population across 32 Mexican States. Trends highlight significantly higher or lower ASIR with respect to year-matched standardized incidence ratios (SIR). **B**) Age-standardized mortality rate (ASMR) of pediatric sepsis per 100,000 population across 16 Mexican States. Trends highlight significantly higher or lower ASMR with respect to year-matched standardized mortality ratios (SMR). Shaded areas highlight the COVID-19 pandemic period.

Figure 4. Heatmap of mortality-to-incidence ratio (MIR) evolution in Chile (2014-2024). Grid displays the yearly MIR magnitude for each Chilean Region from 2014 to 2024. Magnitudes in a black square are significantly different from year-matched national baseline. Presence of 2 outliers is highlighted in blue.

Figure 5. Heatmap of mortality-to-incidence ratio (MIR) evolution in Mexico (2014-2024). Grid displays the yearly MIR magnitude for each Mexican State from 2014 to 2024. Magnitudes in a black square are significantly different from year-matched national baseline

Figure 6. Dynamic risk stratification matrix of sepsis-related causes. Categorical dot plot classification of ICD-10 sepsis-related codes based on their age-standardized incidence rate (ASIR, X-axis) and mortality-to-incidence ratio (MIR, Y-axis). Dashed lines represent the cut-offs for each metric, dividing the plot into four risk quadrants illustrated in Supplementary Figure 7.

Supplementary Figure 1. Algorithm of inclusion/exclusion for Chilean death datasets used in this study.

Supplementary Figure 2. Algorithm of inclusion/exclusion for Chilean hospital discharge datasets used in this study.

Supplementary Figure 3. Algorithm of inclusion/exclusion for Mexican death datasets used in this study.

Supplementary Figure 4. Algorithm of inclusion/exclusion for Mexican hospital discharge datasets used in this study.

Supplementary Figure 5. Three-pass harmonization algorithm for sepsis-related ICD-10 codes. A series of examples illustrate this layered approach: **A**) ICD-10 codes without a match in the operational list (ICD-10 codes listed in report by Rudd *et al.* [2] [Supplementary Table 2]) were not classified as sepsis; **B**) Four-character ICD-10 codes with a match in the operational list were flagged as «Sepsis (4-char)»; **C**) Four-character ICD-10 codes without a match in the operational list were trimmed to 3-character, matched with the operational list, and flagged as «Sepsis (3-char)»; **D**) If after trimming matching is unsuccessful, then codes in the operational list are trimmed to 3-characters, and matches are flagged as «Sepsis (trimmed)».

Supplementary Figure 6. Detailed account of placeholder "X"-bearing ICD-10 code contribution to sepsis-related causes. Proportional distribution, global, and internal share of ICD-10 codes used to define sepsis across 4 input databases: Chile's death (**A**) and hospital discharge (**B**), and Mexico's death (**C**) and hospital discharge (**D**). Placeholder "X"-bearing codes represented a fraction (of approximately less than 10%) of sepsis-related ICD-10 codes. See Supplementary Figure 5 for nomenclature reference.

Supplementary Figure 7. Conceptual framework of the dynamic risk stratification matrix. Sepsis-related causes were classified into four quadrants (risk$^{hi/low}$ and severity$^{hi/low}$) based on their year-specific median age-standardized incidence rate (ASIR, defining the risk axis) and their code-specific mortality-to-incidence ratio (MIR, defining the severity axis).

Supplementary Figure 8. Cumulative Region mortality-to-incidence ratio (MIR) for pediatric sepsis in Chile. **A**) Bar chart displaying the cumulative mean MIR by Chilean Region (2014–2024), highlighting outliers and consistency over time. **B**) Matrix of significant pairwise differences of mean MIR among Chilean Regiones calculated using a Kruskal-Wallis nonparametric test followed by Dunn's post hoc test with Bonferroni adjustment.

Supplementary Figure 9. Cumulative State mortality-to-incidence ratio (MIR) for pediatric sepsis in Mexico. **A**) Bar chart displaying the cumulative mean MIR by Mexican State (2014–2024), highlighting outliers and consistency over time. **B**) Matrix of significant pairwise differences of mean MIR among Mexican States calculated using a Kruskal-Wallis nonparametric test followed by Dunn's post hoc test with Bonferroni adjustment.

Supplementary Table 1. Type of encoding for age and age group in the dataframes of death, discharge, and population, for Chile and Mexico.

Supplementary Table 2. ICD-10 codes for the identification of sepsis considered in this study.

Supplementary Table 3. Processed dataframe of Chilean rates and ratios by Region.

Supplementary Table 4. Processed dataframe of Mexican rates and ratios by State.

Supplementary Table 5. Processed dataframe of Chilean rates, mortality-to-incidence ratio (MIR), risk, and severity, by Region and individual ICD-10 code.

Supplementary Table 6. Processed dataframe of Mexican rates and mortality-to-incidence ratio (MIR), risk, and severity, by State and individual ICD-10 code.

Supplementary Table 7. Output of chi-square goodness-of-fit tests performed on undetermined cases in the variables year, age group and Region before exclusion from the Chilean hospital discharge dataframe (Supplementary Figure 2).

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