Master of Public Health

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Impact of changes in early-onset neonatal bacterial infection management in France between 2014 and 2022: a segmented time series analysis

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List of acronyms

ABX	Antibiotic treatment
ANAES	Agence nationale d'accréditation et d'évaluation de santé
ATIH	Agence technique de l'information sur l'hospitalisation
EONI	Early-onset neonatal infection
GBS	Group B *Streptococcus*
ICD-10	International Classification of Diseases, 10th Revision
ICU	Intensive care unit
INBP	Infections néonatales bactérienne précoces
MSO	Medicine, surgery or obstetrics units
PD	Primary diagnosis
PMSI	Programme de Médicalisation des Systèmes d'Information
RD	Related diagnosis
SAD	Significant associated diagnosis
SFN	Société Française de Néonatologie
SFP	Société Française de Pédiatrie

Abstract

Introduction: In 2017, the French public health authorities revised guidelines for managing early-onset neonatal infections (EONI) to reduce unnecessary antibiotic use and improve diagnostic accuracy. These guidelines emphasized clinical monitoring and risk-based assessments over routine bacteriological sampling.

Objectives: To assess the impact of the revised 2017 guidelines on infection diagnoses in newborns.

Method: This study analyzed data from the French National Hospital Discharge Database (PMSI) for neonates ≥34 weeks' gestation from January 2014 to December 2022 diagnosed with an EONI. Four series of monthly incidence rates per 1,000 live births were constructed: overall EONI, non-severe infections, severe infections (including sepsis and meningitis), and severe infections with bacterial confirmation. A segmented time series regression with autocorrelated errors was used to compare expected incidence rates if the implementation had no effect with estimated rates after the implementation of the revised guidelines.

Results: The analysis included 64,993 hospitalizations for EONI. Following the guideline revision, the incidence of non-severe infections decreased from 12.61 to 3.08 per 1,000 live births, with a significant relative decrease of -0.31 (-0.38 to -0.24) at the end of the implementation period. Severe infection rates remained stable, with a slight decrease from 3.41 to 1.92 per 1,000 live births, and a nonsignificant relative difference of -0.01 (-0.13 to 0.12).

Conclusion: Using a nationwide database, we showed that the implementation of the 2017 guidelines for managing EONI in France effectively reduced excessive EONI diagnoses without increasing severe infections. These findings support the effectiveness of clinical monitoring and risk-based approaches in managing neonatal infections, ensuring timely and accurate treatment.

Introduction

Neonatal infections are defined as infections occurring during the first month of life. Among these, a distinction is typically made between early-onset infections (EONI), which occur within the first 72 hours of life, and late-onset infections, which occur 3 to 28 days after birth. Although incidence rates of proven infection in developed countries are relatively low, ranging from 0.7 to 1.1 per 1,000 live births for early-onset neonatal sepsis (1), neonatal infections remain a major cause of neonatal morbidity and mortality, and are a largely preventable cause of neonatal death (2,3). Sepsis and meningitis are the most serious and potentially fatal forms of neonatal infections, often leading to severe neurodevelopmental sequelae. The term sepsis is commonly used when the infection is life-threatening as a result of dysregulated inflammatory response in the host, but there is no consensus definition of neonatal sepsis, unlike in pediatric or adult sepsis (4). Clinical symptoms initially present as mild and nonspecific but can quickly progress to more severe manifestations, including multisystem organ failure, sometimes within only a few hours. Recognizing signs of infection is challenging, as many early symptoms are subtle, vary widely, and can mimic other disorders of the postnatal transition to the extra-uterine environment, such as tachypnea, respiratory distress, or temperature dysregulation (3,5).

EONI typically result from vertical transmission from the mother, either antenatally, usually *via* ascending bacteria entering the uterus from the vagina following membrane rupture, or during delivery when an infant passes through the birth canal, leading to bacterial colonization of the mucous membranes, lungs, or intestines. The most common microbial cause of infection is Group B *Streptococcus* (GBS), followed by *Escherichia coli*. Other causative bacteria include *Streptococcus* species*, Enterococcus* species*, Haemophilus* species, *Listeria* monocytogenes, and *Staphylococcus aureus* (3,5). Risk factors for infants include maternal colonization with GBS, EONI in a previous pregnancy, prolonged rupture of membranes, unexplained spontaneous preterm birth, and maternal fever (6,7). Given the serious consequences and the non-specific nature of the symptoms, a broad screening approach allows for the identification of potential issues early on, which is crucial in preventing further complications. This extensive screening process ensures that even subtle signs are not overlooked, enabling timely intervention and management.

In France, the guidelines regarding the screening and management on EONI have changed dramatically over the last decades. Previously, the 2002 national guidelines from the Agence nationale d'accréditation et d'évaluation de santé (ANAES) for managing newborns ≥34 weeks' gestation at risk of developing EONI stated that newborns with risk factors should undergo both central and peripheral microbiological sampling (8). However, subsequent studies showed that, at birth, more than half of newborns born at ≥34 weeks gestation underwent bacteriological sampling (gastric fluid and/or peripheral samples), and about a quarter underwent blood sampling. These recommendations

also resulted in antibiotic overuse due to the inadequate sensitivity and specificity of peripheral samples, with 4% of neonates receiving antibiotics for suspected infections, even when the infant was asymptomatic (9).

While recent research has highlighted the negative impacts of excessive antibiotic therapy in newborns, including the development of antibiotic resistance (10), disruption of the newborn's intestinal flora, and increased rates of allergies, autoimmune diseases, and obesity later in life (11), the Société Française de Néonatologie (SFN) and the Société Française de Pédiatrie (SFP) jointly published a revision of the 2002 guidelines in September, 2017. The updated recommendations (*Management of newborns ≥34 weeks' gestation at risk of early bacterial neonatal infection*) advocate discontinuing peripheral sampling, relying on close clinical monitoring, and initiating antibiotic treatment only in symptomatic newborns (7). The aim of the recommendation change was to reduce suspected cases, leading to an overall decrease in antibiotic treatments by adopting a more targeted approach, rather than blanket treatment of suspected or at-risk individuals.

The impact of the 2017 SFN/SFP recommendations for the management of newborns at risk of EONI has received limited attention in France. Our objectives are to determine whether the implementation of these new guidelines results in more precise diagnoses, thereby reducing unnecessary examinations, antibiotic administration, and hospitalizations in neonates who do not require them. Additionally, we aim to assess if the new guidelines ensure that neonates with actual infections are accurately identified and receive the appropriate treatment in a timely manner, despite the reduction in clinical monitoring due to focusing on high-risk individuals. To achieve this, we analyzed national data on EONI trends in France from 2014 to 2022 using segmented time-series analyses.

This work was conducted at the Institut Pasteur under the direction of Bich-Tram Huynh, Laurence Watier, and Elsa Kermorvant. All data management, analysis, and writing were done by Bérénice Varga with guidance from the professional advisors. Bich-Tram Huynh is a medical epidemiologist who specializes in infectious diseases and maternal and child health in low-income countries, with a focus on neonatal infections and antibiotic resistance in Asia and Africa (12). Laurence Watier is a researcher at Inserm who specializes in biostatistics, and epidemiology, and the use of medico-administrative databases (13). Elsa Kermorvant works as a clinician in the Department of Neonatology and neonatal intensive care at the Hôpital Necker-Enfants Malades and brought clinical expertise to the team (14).

Methods

Data source

Data was extracted retrospectively from the French National Hospital Discharge Database (PMSI: Programme de Médicalisation des Systèmes d'Information), a system that defines healthcare facility

activities, utilizing regulated coding for budget allocation. For acute-care facilities, PMSI data includes all discharge summaries of hospitalization and covers all hospital stays in publicly funded and private institutions including acute-care facilities (medicine, surgery or obstetrics units: MSO). For each stay, the diagnoses are coded with International Classification of Diseases, 10th Revision (ICD-10) codes as primary diagnosis (PD: condition requiring hospitalization), related diagnosis (RD: adds information to the PD) and significant associated diagnosis (SAD: complications and co-morbidities potentially affecting the course or cost of hospitalization). While PD and RD are unique for each stay, several SAD can be attributed per stay. Additional information is available about the patients, such as sex or age and about the hospital stays such admission source, length of stay, intensive care unit (ICU) admission, hospital discharge (including death) or medical procedures (15). Since only discharge month and year were available before 2019 in the PMSI, admission dates were estimated using the length of stay and the 15th day of the discharge month.

Study population and selection of hospital stays with neonatal infection

The study population included infants with a gestational age ≥ 34 weeks who were hospitalized within the first 3 days of life for a neonatal infection in Metropolitan France between January 1, 2014, and December 31, 2022. Hospital stays less than 24 hours that did not end in death were excluded to eliminate transient and emergency room stays.

EONI, including non-septic infections, sepsis, and meningitis, were identified using ICD-10 codes in the PD, RD, or SAD fields (**Appendix A**). Codes specified the bacterial cause, with a separate code for unspecified bacteria. We included non-septic infections with a specified bacterium and all cases of sepsis and meningitis, regardless of bacterial identification, assuming a strong clinical indication of infection. We excluded non-septic infections without bacterial identification due to the high risk of false positives.

Severe infections were defined as sepsis and meningitis, while non-severe infections were categorized as non-septic infections. When multiple relevant ICD-10 codes were found for a given stay, the most severe code was selected, regardless of whether it was in the PD, RD, or SAD. If multiple severe codes were identified, the PD was retained.

Live births selection

The number of live births during the study period in Metropolitan France was also estimated using the PMSI database and ICD-10 codes as described in **Appendix B**. If multiple relevant birth codes were found for a single stay with conflicting information on the number of births, the more conservative code was retained. For mothers with multiple births in the same year, those occurring less than six months apart were removed (16). Month and year of births were retained to obtain the number of monthly live births.

Description of newborns and hospital stays

For each year, newborn characteristics such as sex, age at diagnosis, and gestational age were recorded. Hospitalization details included hospital location, length of stay, ICU admission, and in-hospital mortality. ICU admission was determined by stays containing a neonatal intensive care unit code, as per the Agence technique de l'information sur l'hospitalisation (ATIH) guidelines (codes: 02A, 03A, 05, 06, 13A, 14A, 14B, 16) (17), while in-hospital mortality was identified through stays with a discharge status of deceased (18).

Qualitative variables were presented as frequencies and percentages. Due to low variability, age was categorized as ≤24 hrs old or older. The quantitative variable, length of stay, was described using the median and interquartile range and categorized as a qualitative variable. Length of stay categories were based on recommended antibiotic treatment (ABX) use: stays of 3 days or less assumed negative culture results with appropriate discontinuation of ABX; stays of 4 to 6 days assumed negative culture results or newborn improvement with continued ABX; and stays of 7 days or more assumed positive culture results with correct ABX administration (7).

Trend was assessed using a Cochrane-Armitage test for all variables except hospital location.

Incidence rates

The annual overall incidence rate and 95% CI were calculated from 2014 to 2022 and expressed as the number of cases per 1,000 live births at ≥ 34 weeks gestation. Rates were stratified by infection severity: non-severe infection and severe infection as detailed above and in **Appendix A** (19,20). Additionally, incidence rates were further stratified by identified bacteria: GBS, and other pathogens. Incidence rate trends were also assessed using a Cochrane-Armitage test.

Time series analysis

Time series are generally constructed and analyzed from data collected over time, usually at regular intervals. Since time series often exhibit autocorrelation, specific methodologies should be used to account for the dependence between observations. In linear models, the series can be split into two additive parts: a deterministic part (including trend and seasonality) and a stochastic part corresponding to the autocorrelation structure. To study the impact of an "intervention," several models are available, ranging from the simplest (segmented regressions) to the most complex (ARIMA with transfer functions) (21–23). We chose segmented regression with autocorrelated errors for this analysis because it allows for clear identification and estimation of changes in trend and level at specific intervention points, which is essential for evaluating the impact of the 2017 SFN/SFP recommendations. Segmented regression is also more straightforward to interpret and implement compared to more complex models like ARMA or ARIMA with transfer functions. Additionally,

segmented regression can effectively handle multiple intervention points and provide immediate insights into the effect of the recommendations on EONI trends over time (23,24).

From our dataset, monthly time series indicators were constructed from 2014 to 2022 and segmented regression models with autocorrelated errors were used to study the impact of new management measures. Since we are interested in determining the effect of a change in care on a healthcare indicator, it is important to consider that changes in the health field are often debated before implementation and usually take several months to be fully applied. Therefore, our model excludes observations recorded 6 months before and after the implementation of the new measures to account for the gradual implementation during this period.

Rates of hospitalizations for EONI per 1,000 live births at ≥ 34 weeks gestation were calculated per month, accounting for the evolving referent population. Monthly incidence rates were then calculated as the number of cases per 1,000 live births.

Four series were created: total EONI, non-severe infections, severe infections, and severe infections with an identified pathogen, combining both GBS and other pathogens. The study period, January 1, 2014, to December 31, 2022, was divided into three segments: the pre-implementation phase (January 2014 to February 2017), the implementation phase (March 2017 to February 2018, spanning six months before and after the publication of the new recommendations), and the post-implementation phase (March 2018 to December 2022). When annual seasonality was observed, regression lines with trigonometric functions were estimated. If parameters were found to be non-significant, they were removed from the model and not included in the result table.

The general formulation of the model can be written as follows:

$$Y_t = \sum_{i=0}^{1} (\beta_{0i} + \beta_{1i} t)\, I_i + \sum_{i=0}^{1} \left(\gamma_i cos \frac{2\pi_t}{12} + \delta_i sin \frac{2\pi_t}{12} \right) I_i + \nu_t$$

Notation:

t = time index, from 1 to 108,

i = period index, from 0 to 1, i=0 for the pre-recommendation change period (January 2014 to February 2017) and i=1 for the post-recommendation change period (March 2018 to December 2022)

Y_t = number of neonatal infections of interest at time t (month) per 1,000 live births,

I_i = dummy variable for period i,

β_{0i}= intercept parameter for period i,

β_{1i} = slope parameter for period i,

γ_i and δ_i = cosinus and sinus parameters of period i,

ν_t is modelled as an AR(p) process, with residual variance σ^2.

To assess the validity of the model, Ljung-Box test was used to test if residuals were independently distributed and Shapiro-Wilk normality test for the Gaussian distribution of the residuals.

Absolute and relative differences in incidence rates between the two periods were assessed at the end of the implementation period using a multivariate delta method (25). For the post-implementation period (period 1) starting in March 2018 (t*), the estimated level is defined as $\hat{Y}_{t^*} = \beta_{01} + \beta_{11}t^*$. The predicted level, assuming no change in the evolution, is $\overline{Y}_{t^*} = \beta_{00} + \beta_{10}t^*$.

For each period, the absolute difference was defined by: $AD = \hat{Y}_{t^*} - \overline{Y}_{t^*}$; and the percentage change was calculated by: $PC = \frac{\hat{Y}_{t^*} - \overline{Y}_{t^*}}{\hat{Y}_{t^*}} \times 100$.

If the variance of AD can be obtained using different scripts (e.g., by estimating an intercept over the entire study period), a delta method approach, as described by Zhang *et al.* (26), was used to approximate the variance of PC.

The variance of $100 \times PC$ was defined as follows, the subscripts $t^*$are suppressed in order not to overburden the notation:

$$Var\left(\frac{\hat{Y} - \overline{Y}}{\overline{Y}}\right) = \left(\frac{\hat{Y}}{\overline{Y}}\right)^2 \left[\frac{Var(\hat{Y})}{\hat{Y}^2} + \frac{Var(\overline{Y})}{\overline{Y}^2} - 2\frac{Cov(\hat{Y}, \overline{Y})}{\hat{Y}\overline{Y}}\right]$$

Then 95% confidence interval can be calculated.

Statistical analyses were computed using SAS® Enterprise Guide (Version 9.4; SAS Institute Inc., Cary NC, USA).

Ethical statement

Since this study was a retrospective, longitudinal, non-interventional study based on an anonymous database, patient consent and ethics committee approval were not required, as per French Law. Data was accessed *via* the ATIH portal using the Institut National de la Santé et de la Recherche Médicale (Inserm) permanent access to the PMSI.

Results

Population description and trends in hospitalization

From 2014 to 2022, there were a total of 64,993 hospitalizations for EONI. These cases occurred more frequently in male infants (n=35,602, 54.8%) and in those born in Ile-de-France (n=18,898,

29.1%). Additionally, 90.1% (n= 58,570) of the infants had a gestational age of at least 37 weeks. Diagnoses typically occurred within the first 24 hours of life (n=61,939, 95.3%). Newborns were hospitalized for a median of 5 days (IQR 4–7 days), with 20.3% (n=13,201) admitted to an ICU and 0.6% (n=376) succumbing during their hospitalization (**Table 1**). Between 2014 and 2022, the number of hospitalizations with a diagnosis of EONI decreased substantially from 12,038 to 3,306.

Despite this decrease, the demographic characteristics of age, sex, and hospital location remained relatively stable. The gestational age of newborns diagnosed with EONI showed a slight change, with term newborns accounting for 90.6% (n=10,902) of cases in 2014 and 85.9% (n=2,840) in 2022. The percentage of hospitalizations with a length of stay lasting 3 days or less increased by 4.9% from 2014 to 2022, while the percentage of stays lasting at least 7 days saw a more significant rise, with an increase of 11.9% over the same period. Conversely, stays lasting 4 to 6 days decreased from 53.5% in 2014 to 36.8% in 2022. The percentage of newborns admitted to an ICU during their stay remained relatively constant around 17% until 2017, after which it continuously increased to 33.2% (n=1,098) in 2022. While the crude number of deaths remained stable, the percentage rose from 0.4% (n=43) in 2014 to 1.42% (n=47) in 2022.

Incidence rates

The number of births per year stayed relatively stable with a slight decrease from 2014 to 2022 (751,419 and 660,331 respectively).

The overall incidence rate of EONI more than halved from 16.02 (95% CI 15.73-16.31) cases per 1,000 live births in 2014 to 5.01 (95% CI 4.84-5.18) in 2022. However, different trends emerge when stratifying the data by infection severity, as shown in **Figure 1**. The incidence rate of hospitalizations for severe infections remained relatively constant, decreasing slightly from 3.41 (95% CI 3.28-3.54) cases per 1,000 live births in 2014 to 1.92 (95% CI 1.82-2.03) in 2022. In contrast, the incidence rate of non-severe infections decreased substantially from 12.61 (95% CI 12.35-12.86) cases per 1,000 live births in 2014 to 3.08 (95% CI 2.95-3.22) in 2022. All incidence rates are detailed in **Appendix C**.

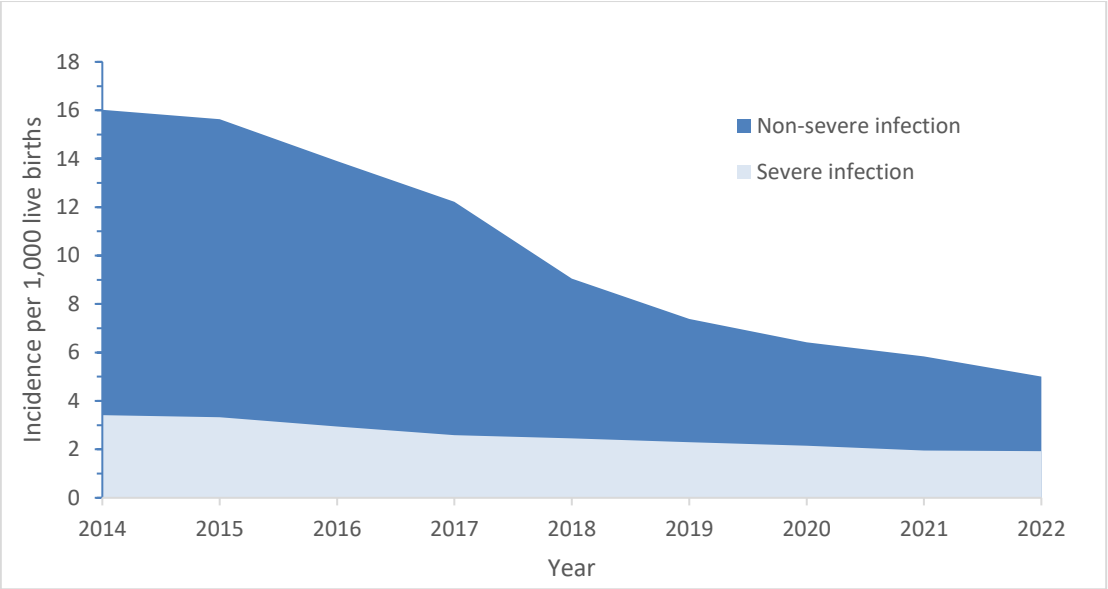
Table 1. *Characteristics of Newborns and Hospitalizations with Early-Onset Neonatal Infection per Year – PMSI, France, 2014 – 2022*

	2014 N=12,038 **n (%)**	**2015** N=11,458 **n (%)**	**2016** N=9,994 **n (%)**	**2017** N=8,589 **n (%)**	**2018** N=6,280 **n (%)**	**2019** N=5,075 **n (%)**	**2020** N=4,310 **n (%)**	**2021** N=3,943 **n (%)**	**2022** N=3,306 **n (%)**	**P-value[a]**
Newborn characteristics										
Male	6,615 (54.95)	6,256 (54.60)	5,550 (55.53)	4,685 (54.55)	3,397 (54.09)	2,722 (53.64)	2,331 (54.08)	2,187 (55.47)	1,859 (56.23)	0.01 (.496)
Age at diagnosis < 24hrs	11,548 (95.93)	10,946 (95.53)	9,540 (95.46)	8,221 (95.72)	5,991 (95.40)	4,799 (94.56)	4,075 (94.55)	3,733 (94.67)	3,086 (93.35)	-6.83 (<.001)
Gestational age										
Late preterm (34-36 WG)	1,136 (9.44)	1,007 (8.79)	957 (9.58)	774 (9.01)	655 (10.43)	479 (9.44)	506 (11.74)	443 (11.24)	466 (14.10)	8.66 (<.001)
Term (≥ 37 WG)	10,902 (90.56)	10,451 (91.21)	9,037 (90.42)	7,815 (90.99)	5,625 (89.57)	4,596 (90.56)	3,804 (88.26)	3,500 (88.76)	2,840 (85.90)	
Hospital stay characteristics										
Length of first stay (in days)										
≤ 3	1,865 (15.49)	2,164 (18.89)	1,940 (19.41)	1,859 (21.64)	1,318 (20.99)	1,008 (19.86)	1,008 (23.39)	1,023 (25.94)	673 (20.36)	13.98 (<.001)[b]
4-6	6,444 (53.53)	5,902 (51.51)	5,052 (50.55)	4,182 (48.69)	2,893 (46.07)	2,241 (44.16)	1,710 (39.68)	1,492 (37.84)	1,216 (36.78)	-26.53 (<.001)[b]
≥ 7	3,729 (30.98)	3,392 (29.60)	3,002 (30.04)	2,548 (29.67)	2,069 (32.95)	1,826 (35.98)	1,592 (36.94)	1,428 (36.22)	1,417 (42.86)	16.42 (<.001)[b]
Median (Q1 - Q3)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-7)	5 (4-8)	5 (4-8)	5 (3-8)	6 (4-9)	
Intensive care unit admission	2,002 (16.63)	1,897 (16.56)	1,736 (17.37)	1,523 (17.73)	1,328 (21.15)	1,323 (26.07)	1,181 (27.40)	1,113 (28.23)	1,098 (33.21)	30.13 (<.001)
Hospital location										
Ile-de-France	3,602 (29.92)	3,486 (30.42)	2,885 (28.87)	2,449 (28.51)	1,673 (26.64)	1,399 (27.57)	1,240 (28.77)	1,094 (27.75)	1,070 (32.37)	
Hauts-de-France	1,517 (12.60)	1,306 (11.40)	1,080 (10.81)	900 (10.48)	770 (12.26)	702 (13.83)	528 (12.25)	388 (9.84)	340 (10.28)	
Auvergne-Rhône-Alpes	1,111 (9.23)	1,003 (8.75)	979 (9.80)	795 (9.26)	450 (7.17)	334 (6.58)	230 (5.34)	173 (4.39)	154 (4.66)	
Occitanie	1,070 (8.89)	1,024 (8.94)	727 (7.27)	535 (6.23)	500 (7.96)	498 (9.81)	568 (13.18)	509 (12.91)	307 (9.29)	
Provence-Alpes-Côte d'Azur	1,008 (8.37)	1,026 (8.95)	1,182 (11.83)	1,075 (12.52)	718 (11.43)	699 (13.77)	523 (12.13)	712 (18.06)	528 (15.97)	
Grand Est	873 (7.25)	808 (7.05)	674 (6.74)	600 (6.99)	452 (7.20)	305 (6.01)	241 (5.59)	195 (4.95)	167 (5.05)	
Nouvelle-Aquitaine	627 (5.21)	613 (5.35)	613 (6.13)	674 (7.85)	507 (8.07)	235 (4.63)	185 (4.29)	177 (4.49)	164 (4.96)	
Bourgogne-Franche-Comté	556 (4.62)	597 (5.21)	447 (4.47)	302 (3.52)	207 (3.30)	163 (3.21)	135 (3.13)	122 (3.09)	135 (4.08)	
Pays de la Loire	541 (4.49)	523 (4.56)	526 (5.26)	491 (5.72)	354 (5.64)	177 (3.49)	172 (3.99)	194 (4.92)	148 (4.48)	
Bretagne	401 (3.33)	386 (3.37)	306 (3.06)	239 (2.78)	194 (3.09)	160 (3.15)	140 (3.25)	129 (3.27)	104 (3.15)	
Normandie	368 (3.06)	314 (2.74)	312 (3.12)	297 (3.46)	254 (4.04)	269 (5.30)	239 (5.55)	157 (3.98)	123 (3.72)	
Centre-Val de Loire	345 (2.87)	339 (2.96)	244 (2.44)	215 (2.50)	178 (2.83)	109 (2.15)	94 (2.18)	79 (2.00)	45 (1.36)	
Corse	19 (0.16)	33 (0.29)	19 (0.19)	17 (0.20)	23 (0.37)	25 (0.49)	15 (0.35)	14 (0.36)	21 (0.64)	
Gestational age at death										
Late preterm (34-36 WG)	9	15	21	9	7	10	13	10	14	3.21 (<.001)[c]
Term (≥ 37 WG)	34	28	33	30	41	32	16	21	33	6.38 (<.001)[c]

[a] P-value of Cochrane-Armitage test for trend; [b] Probability of stays lasting this length or not; [c] Probability of death within this gestational age category.

WG, weeks' gestation; PMSI, Programme de Médicalisation des Systèmes d'Information.

Figure 1. *Incidence Rates of Newborns ≥ 34-Weeks' Gestation Hospitalized in France for an Early-Onset Neonatal Infection*



Time series analysis

A segmented time series regression with autocorrelated error was fitted to each series: all EONI, non-severe, severe, and severe with an identified pathogen, combining both GBS and other pathogens. All series met the goodness-of-fit criteria (**Appendix D**).

The overall EONI and non-severe EONI series exhibited slight seasonality prior to the recommendation change (p-values of 0.007 and 0.012, respectively), whereas the severe EONI series did not. No seasonality was observed after the recommendations. In the severe EONI series where a pathogen was identified, no significant autoregressive parameters were found, but all other series showed significant autoregressive parameters (p-value < 0.05). Overall, the incidence rate of EONI decreased even before the recommendation change. No differences in the slope were observed before and after the recommendation, regardless of the series considered (**Appendix E**).

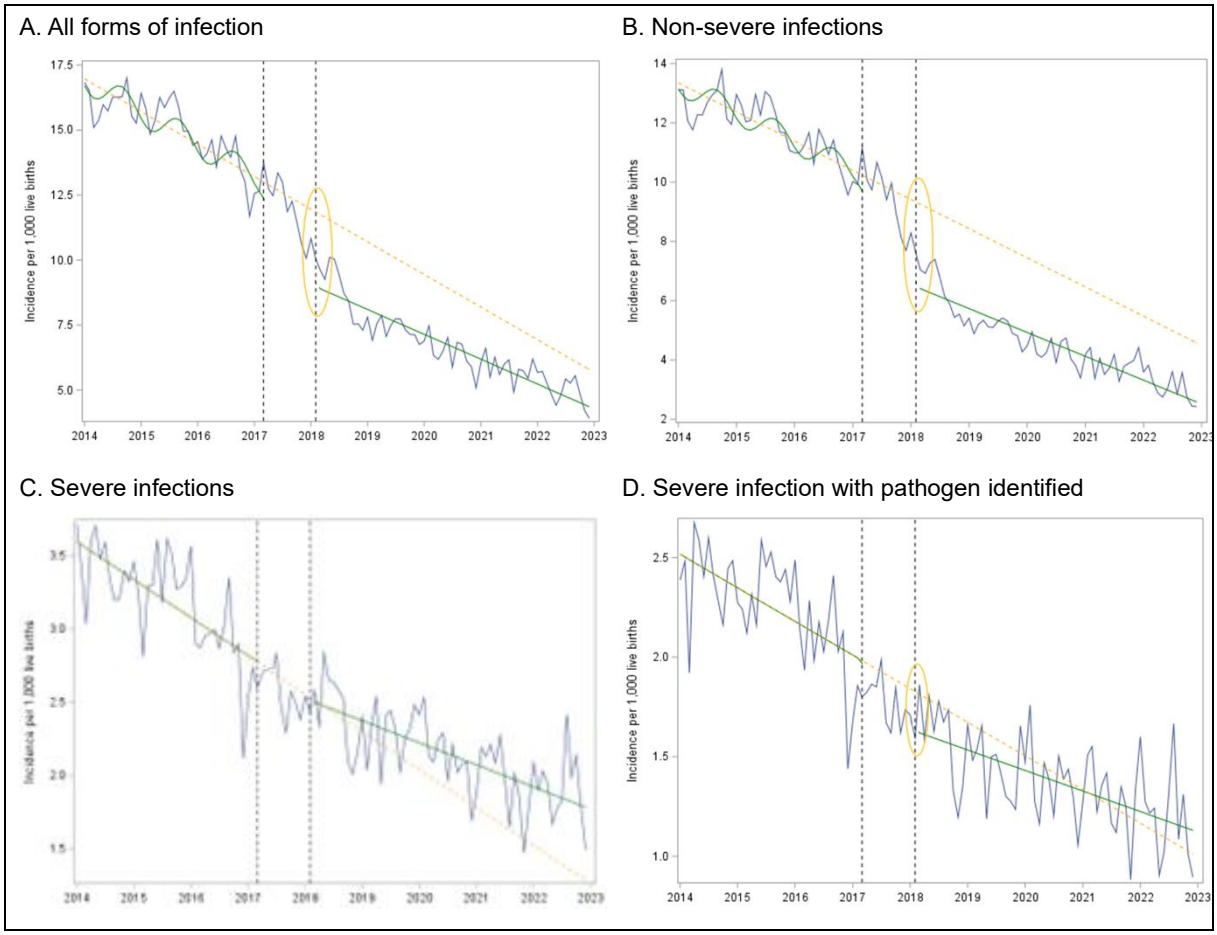
The estimated differences in monthly incidence rates of EONI per 1,000 live births for all series following the recommendation change are reported in **Table 2**. Significant decreases were observed in the overall incidence rate of EONI and in non-severe cases, with relative differences of -0.24 (95% CI -0.31 to -0.18) and -0.31 (95% CI -0.38 to -0.24) cases per 1,000 live births, respectively. However, the decrease in severe EONI cases was not significant, with a relative difference of -0.01 cases per 1,000 live births (95% CI -0.13 to 0.12). When specifically considering severe cases where a pathogen was identified, the relative difference becomes more pronounced at -0.11 (95% CI -0.22 to 0.00), though the significance of this

result is debatable. Visual representations of the models and the significant differences observed can be seen in **Figure 2**.

Table 2. *Estimated Variation in Incidence per 1,000 Live Births of Newborns ≥34-Weeks' Gestation Hospitalized in France for an Early-Onset Neonatal Infection due to Changes in Recommendations*

Series	Expected incidence (95% CI)	Absolute difference (95% CI)	Relative difference (95% CI)
All neonatal early-onset infections	11.75 (10.86 to 12.63)	-2.85 (-3.81 to -1.88)	-0.24 (-0.31 to -0.18)
Non-severe	9.25 (8.49 to 10.01)	-2.85 (-3.67 to -2.02)	-0.31 (-0.38 to -0.24)
All severe	2.52 (2.23 to 2.80)	-0.02 (-0.33 to 0.30)	-0.01 (-0.13 to 0.12)
Severe with pathogen	1.81 (1.62 to 2.01)	-0.19 (-0.41 to 0.02)	-0.11 (-0.22 to 0.00)

Figure 2. *Time Series Analysis of Incidence Rates of Newborns Hospitalized with Early-Onset Neonatal Infections in France, 2014-2022*



Black dotted lines mark the implementation period; blue line is the observed incidence rate; green line is the model; dotted yellow line is the prediction if the pre-implementation trend continued; and yellow circle shows if a significant difference was observed at the beginning of the post-implementation period. The scale of the y-axis was adjusted for each series to enhance the visibility of the relative changes in the data.

Discussion

We observed a significant decrease of 2.85 (-3.67 to -2.02) in the absolute incidence rate of non-severe diagnoses of EONI following the change in recommendations, which was not observed in severe diagnoses (**Table 2**). We believe that this decline may be attributed to improved management of at-risk newborns in-line with the 2017 SFN/SFP recommendations, and the hospitalization of solely true cases of infection. Our results do not support the concern that reducing biological sampling would increase severe cases.

Two other localized French studies also demonstrated that the new recommendations are optimal and do not lead to more severe outcomes. In one study, Schmitt et al. conducted a study in the level III Maternity Hospital of the CHRU in Nancy, France. Level III maternity wards receive the highest risk pregnancies, including preterm births ≤33-weeks' gestation, as they offer obstetric, neonatology, and resuscitative services on site and have an ICU. This study compared asymptomatic newborns ≥36 weeks' gestation with risk factors in 2017 before and in 2018 after the recommendation changes. They performed statistical comparisons between the two groups and found no difference in mortality before and after implementing the new recommendations (27).

Similarly, Dalut et al. conducted a similar study in the level III Maternity Hospital of the CHU in Clermont-Ferrand, France. However, in this study, the pre-implementation group was from 2020 and the post-implementation group was from 2021, and they excluded neonates admitted directly. Their comparative statistical analysis revealed no difference in rehospitalizations between the classified low- and high-risk groups. This suggests that newborns classified as low-risk, who did not receive clinical monitoring and were possibly discharged within 48 hours, were not more likely to develop an infection post-discharge (28).

Caution is warranted when comparing to our results to these studies as we included late preterm infants between 34- and 36-weeks' gestation. As late preterm infants are slightly more at risk for severe disease and complications (29), this may explain some of the difference in results. Our findings indicate an increase in the percentage of ICU admissions and mortality. As crude numbers did not vary, specifically regarding the mortality, we can hypothesize that the increase observed may be due to an increase in the relative proportion of severe cases as these cases more often need intensive care and have a higher likelihood of mortality (**Figure 1**). In 2014, severe cases made up 21.3% (n=2,564) of all EONI compared to 38.4% (n=1,270) in 2022. Further analysis is needed to determine if the increase in the percentage of ICU admissions and mortality observed in our study is truly due to the increase in the relative proportion of severe cases.

The decrease observed in the non-severe cases may be linked to a reduction in aggressive treatments and procedures. While the study conducted by Schmitt et al. in Nancy, France found a decrease in laboratory testing following implementation of the new recommendations (27), this is a point of speculation in our study since we did not directly analyze testing data. Similarly, a study in Tarbes, France by Cabaret and Latry also reported a significant decrease in laboratory testing post-implementation. This study was conducted in a level II-B maternity hospital, comparing asymptomatic newborns ≥35-weeks' gestation at risk of EONI before the recommendation changes in 2017 to after the changes in 2018. Level II-B maternity wards receive moderate-risk pregnancies ≥33-weeks' gestation and are similar in services to level III wards, except they do not have resuscitation services. As in the other studies, they excluded newborns admitted directly (30). Laboratory testing, particularly invasive procedures such as blood draws and gastric fluid sampling, can be traumatic for newborns and may offer limited added value in detecting cases of EONI. Duvoisin et al. evaluated a similar change in recommendations in Switzerland from 2006 to 2011 and found that clinical monitoring led to a significant decrease in laboratory testing without delaying the timely initiation of ABX (31). Additionally, Cantoni et al. found that physical examination alone was sufficient to detect cases of EONI, and that laboratory testing did not improve detection rates (32).

Similarly, the decrease observed in our study may also be linked to a reduction in antibiotic use, as demonstrated by Dalut et al. They observed a decrease in the duration of hospital stays following implementation of the new recommendations (28), which aligns with our findings that the proportion of hospitalizations with stays shorter than 72-hrs increased. Per the new recommendations, ABX should be discontinued after 48-hrs if the diagnosis of EONI is not confirmed. Therefore, we can suppose that if the percentage of shorter stays increased, clinicians were correctly discontinuing treatment for non-confirmed diagnoses. A case of EONI is considered non-confirmed if bacterial cultures are negative, C-reactive protein levels remain negative, and symptoms improve (7). This supposition is based on the broader context of antibiotic stewardship and the findings of other studies, as we did not specifically analyze antibiotic use.

Reducing antibiotic use and discontinuing treatments when cultures are negative and the infant improves can decrease antibiotic selective pressure (10,33). Though our study did not directly evaluate antibiotic prescription practices, both Dalut et al. and Schmitt et al. found an overprescription of initial antibiotics likely due to suspicion of infection, but they also reported shorter treatment durations, likely due to better adherence to guidelines recommending discontinuation if cultures are negative and the infant remains asymptomatic (27,28). Duvoisin et al. also found a decrease in duration of antibiotic use in Switzerland following recommendation changes (31). Therefore, the 2017 SFN/SFP recommendations may

contribute to improving antimicrobial stewardship in a population where antibiotic use is an important concern.

The overprescription of antibiotics leads to bacterial resistance, making infections harder to treat and disrupting the gut microbiome, causing side effects at the individual level. At the population level, it contributes to the emergence and spread of resistant strains and increased healthcare costs due to more complex treatments. This creates a public health challenge with limited treatment options for future infections. Antibiotic resistance is a growing concern globally and has been identified as a top public health threat by the World Health Organization (34). These findings emphasize the importance of administering antibiotics only when absolutely necessary (35).

Another notable study investigating the impact of the recommendations was conducted by Sikias et al. in Paris. They found an incidence rate of 0.32 per 1,000 live births ≥34 weeks' gestation from 2019 to 2021, which is much lower than the incidence rate found in our study. However, their study used different inclusion criteria and diagnostic protocols, such as requiring a positive culture, which limits the direct comparability of incidence rates and outcomes between the two studies (1). Utilizing positive bacterial cultures is considered the gold standard for diagnosing infections in adults. However, this approach poses challenges in newborns due to their low bacteremia. Some studies indicate that 60% of infants under 2 months with clinical signs and symptoms of sepsis had blood counts below 10 colony-forming units per milliliter, necessitating at least 1 mL of blood to accurately detect the infection (36). Yet, more than half of pediatric blood cultures have insufficient volume, and this issue is even more pronounced in neonates (37,38).

Previous French studies, including those by Dalut et al. and Schmitt et al., did not have any culture-confirmed cases despite obvious clinical symptoms (27,28). This underscores the difficulty in relying solely on culture confirmation in neonates. Our study, which investigates rates of EONI based on clinical diagnosis rather than culture confirmation alone, aims to provide a more comprehensive estimate of the true burden of this disease. It's important to note that while culture-confirmed infections offer a "hard" definition with high specificity, they likely underestimate the incidence due to the challenges in obtaining sufficient samples from newborns. On the other hand, a broader clinical definition may overestimate the incidence due to the non-specific nature of early symptoms. Therefore, the true incidence likely lies between these two approaches.

To validate our results regarding the incidence rates, we can compare them with several studies that have used similar clinical definitions. However, the results of these studies vary significantly, with most focusing solely on neonatal sepsis rather than all forms of infection (39).

Caution should be exercised due to the lack of an international consensus definition of neonatal sepsis. For instance, Born et al. reported an overall incidence rate of 10.06 cases of neonatal sepsis per 1,000 live births in Germany from 2010 to 2016, including all infants under 28 days of age and all gestational ages (40). In contrast, a study from the United States reported a lower incidence rate of 4.5 to 9.7 cases per 1,000 births from 1995 to 2005 (41). These rates are still higher than those observed in our study. One possible explanation is the timing of these studies, as both were conducted before our study period, during which the incidence rate may have already been decreasing.

When compared to national estimates for group B Streptococcus (GBS) sepsis, our incidence rates (**Appendix C**) fall close to the expected rate of 0.3 cases per 1,000 live births (42). These national benchmarks provide a useful context for interpreting our results and affirm the reliability of our data collection and analysis methods. Furthermore, the characteristics of the EONI cases observed in this study align closely with existing literature, with over 95% of cases occurring within the first 24 hours of life (3). The birth estimates also align closely with published ATIH data with a percent error less than 1% (43).

A significant strength of this study is the use of a national database, which encompasses all hospitalizations across the country. This comprehensive dataset allows for a robust analysis of incidence rates and trends on a national scale, providing a more accurate and generalizable understanding of neonatal infections. Another key strength is that we include all infants diagnosed with EONI. This approach differs from previous studies that focused only on at-risk populations (27,30). By including all diagnosed cases, we can investigate the overall impact of the new recommendations on all newborns, not just those at risk. Further studies may be needed to assess the impact on outcomes for infected infants to determine if there is an improvement due to increased clinical monitoring included in the new recommendations.

While the use of clinical diagnoses is a strength, it is also a limitation since these diagnoses were not bacteriologically confirmed. This reliance on clinical judgment may result in an overestimation of the true infection rates. However, several other limitations could lead to a slight underestimation. One such limitation is the possibility of coding errors within the national database due to different coding practices. Coding is normally done by doctors who, though trained, may make errors and may not be trained in the same manner. These errors can lead to misclassification of cases, potentially underestimating the true incidence rate if our selection of codes was not inclusive enough. Also, due to some particularities of the PMSI database, for same-sex multiple births, it was not possible to differentiate between siblings due to the use of anonymous coding. This limitation may have led to inaccuracies in tracking individual cases.

Lastly, there are limitations inherent to the nature of the database and the analysis methods used. Due to the constraints of the PMSI database, we were unable to access additional clinical details such as complications, medications administered, or specific risk factors, which limits our ability to fully understand the context and severity of each case. While our time series analysis enables us to observe temporal trends, it does not allow us to infer causality. Isolating the impact of the new recommendations from other factors, such as general antibiotic use, medical advancements, and improved perinatal care, is challenging, and these confounding factors may have influenced the observed trends. Additionally, the study spans an eight-year period during which subtle changes in clinical practices and healthcare policies may have occurred, potentially affecting our findings.

Furthermore, some studies suggest that the French recommendations took time to be implemented in various healthcare establishments, with implementation delays ranging from a few months to several years (27,28,30,44). The varying delay in implementation of the new recommendations could attenuate the impact observed in our study. Moreover, many other countries such as the United States (45), Switzerland (46), and New Zealand (47) had revised their guidelines prior to 2017, adopting a risk-based evaluation and clinical surveillance of at-risk newborns similar to the 2017 SFN/SFP recommendations. This allowed for supporting evidence to the utility and safety of this approach (48). Cabaret and Latry suggest that clinicians may already have modified their protocols to limit aggressive treatments of asymptomatic newborns (30), further attenuating the impact observed in our study.

Conclusion

The results of this study have significant implications for public health. Firstly, the findings provide insight into the success of the recommendation changes, as evidenced by the decrease in EONI diagnoses and the shift toward more specific diagnoses of severe cases. This suggests that the reduction in non-severe infections may be associated with a decrease in unnecessary invasive exams and antibiotic use, potentially avoiding unnecessary hospitalizations. This decrease in antibiotic use further supports efforts to reduce overall antibiotic consumption, combating antibiotic resistance and the spread of nosocomial infections by avoiding unnecessary prolonged hospital stays. Additionally, the reduction in exams, treatments, and shorter hospitalizations is likely to lower healthcare costs.

To further enhance public health outcomes and address remaining research gaps, additional studies are needed to investigate the associated complications of neonatal infections and the evolving patterns of antibiotic resistance. Understanding the long-term outcomes for infected newborns is crucial, as is examining any shifts from early-onset to late-onset infections. Future research should also focus on the impact of these infections on mortality rates and the

economic burden they impose on healthcare systems. Addressing these areas will provide a more comprehensive understanding of neonatal infections and inform more effective prevention and treatment strategies.

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Appendix

Appendix A. *ICD-10 Codes Used to Identify Infections with or without Sepsis and with Meningitis*

Type of infection	**ICD-10 code**
Non-severe infection	
Infection without sepsis	P36.09, P36.19, P36.29, P36.39, P36.49, P36.59, P36.89, P37.2
Severe infection[a]	
Infection with sepsis	P36.00, P36.10, P36.20, P36.30, P36.40, P36.50, P36.80, P36.90
Infection with meningitis[b]	A32.1, A39.0, G00, G00.0, G00.1, G00.2, G00.3, G00.8, G00.9, G01, G04.2, G05.0

[a] with specified or unspecified bacteria; [b] ICD-10 codes to identify bacterial meningitis in the perinatal period do not exist, so the codes used are those that identify bacterial meningitis in any population.

Appendix B. *ICD-10 Codes Used to Identify Births*

Label	**ICD-10 code**
Singleton birth, live child[a]	Z37.0
Twin birth, twins born alive	Z37.2
Twin birth, one of the twins born alive, the other stillborn[a]	Z37.3
Twin birth, one of the twins born alive, the other stillborn, excluding termination of pregnancy for medical reasons[a]	Z37.30
Twin birth, one of the twins born alive, the other stillborn, following a termination of pregnancy for medical reasons[a]	Z37.31
Other multiple births, all born alive[b]	Z37.5
Other multiple births, some live births	Z37.6
Other multiple births, some children born alive, excluding termination of pregnancy for medical reasons	Z37.60
Other multiple births, some children born alive, following medical termination of pregnancy	Z37.61

[a] These codes count as 1 live birth; [b] These codes count as 3 live births; All other codes not specified count as 2 live births.

Appendix C. *Incidence Rates (per 1,000 live births) of Newborns ≥ 34 Weeks' Gestation Hospitalized for an Early-Onset Neonatal Infection, by Severity and Pathogen Identification per Year – France, 2014-2022*

	2014	2015	2016	2017	2018	2019	2020	2021	2022	P-value[b]
Live births[a]	751,419	732,940	719,105	702,516	693,936	687,352	671,594	674,843	660,331	
All early onset neonatal infection										
	16.02 (15.73, 16.31)	15.63 (15.35, 15.92)	13.90 (13.63, 14.17)	12.23 (11.97, 12.48)	9.05 (8.83, 9.27)	7.38 (7.18, 7.59)	6.42 (6.23, 6.61)	5.84 (5.66, 6.03)	5.01 (4.84, 5.18)	<.001
Non-severe infection										
Total	12.61 (12.35, 12.86)	12.31 (12.05, 12.56)	10.95 (10.71, 11.19)	9.64 (9.41, 9.87)	6.60 (6.41, 6.79)	5.09 (4.92, 5.26)	4.27 (4.11, 4.43)	3.89 (3.74, 4.04)	3.08 (2.95, 3.22)	<.001
GBS[c]	3.45 (3.32, 3.58)	3.01 (2.88, 3.13)	2.60 (2.48, 2.72)	2.27 (2.15, 2.38)	1.47 (1.38, 1.56)	1.17 (1.09, 1.26)	1.10 (1.02, 1.18)	1.04 (0.96, 1.12)	0.82 (0.75, 0.89)	<.001
Other[d]	9.16 (8.94, 9.37)	9.30 (9.08, 9.52)	8.35 (8.14, 8.56)	7.37 (7.17, 7.58)	5.13 (4.96, 5.29)	3.92 (3.77, 4.06)	3.17 (3.04, 3.31)	2.85 (2.73, 2.98)	2.26 (2.15, 2.38)	<.001
Severe infection										
Total	3.41 (3.28, 3.54)	3.33 (3.20, 3.46)	2.95 (2.82, 3.07)	2.58 (2.47, 2.70)	2.45 (2.33, 2.57)	2.29 (2.18, 2.41)	2.15 (2.04, 2.26)	1.95 (1.85, 2.06)	1.92 (1.82, 2.03)	<.001
GBS[c]	0.74 (0.68, 0.80)	0.64 (0.58, 0.70)	0.54 (0.48, 0.59)	0.49 (0.44, 0.54)	0.35 (0.30, 0.39)	0.29 (0.25, 0.33)	0.26 (0.22, 0.30)	0.22 (0.19, 0.26)	0.17 (0.14, 0.20)	<.001
Other[d]	1.66 (1.57, 1.75)	1.71 (1.61, 1.80)	1.57 (1.47, 1.66)	1.29 (1.21, 1.37)	1.26 (1.17, 1.34)	1.16 (1.08, 1.24)	1.11 (1.03, 1.19)	1.06 (0.98, 1.14)	1.04 (0.97, 1.12)	<.001

[a] ≥ 34 weeks gestation; [b] Cochrane-Armitage test for trend; [c] Group B *Streptoccocus*; [d] Includes E. coli, Listeria, Staphylococcus, other Streptococci, and unidentified anaerobic, gram-negative and gram-positive bacteria.

Appendix D. *Estimations (Standard Errors) and P-values of the Parameters Included in the Model for each Series*

Parameters	All neonatal early-onset infections		Non-severe		All severe		Severe with pathogen	
Regression parameters								
β_{00}	17.075 (0.312)	p<.001	13.431 (0.269)	p<.001	3.617 (0.097)	p<.001	2.531 (0.066)	p<.001
β_{10}	-0.105 (0.014)	p<.001	-0.082 (0.012)	p<.001	-0.022 (0.004)	p<.001	-0.014 (0.003)	p<.001
β_{01}	12.961 (0.600)	p<.001	9.825 (0.518)	p<.001	3.140 (0.187)	p<.001	2.057 (0.127)	p<.001
β_{11}	-0.080 (0.007)	p<.001	-0.067 (0.006)	p<.001	-0.013 (0.002)	p<.001	-0.009 (0.002)	p<.001
Seasonal parameters								
δ_0	-0.533 (0.191)	p=.007	-0.417 (0.163)	p=.012	-	-	-	-
Autoregressive parameters								
ϕ_1	-0.440 (0.096)	p<.001	-0.460 (0.094)	p<.001	-0.239 (0.103)	p=.022	-	-
Residual variance								
σ^2	0.31		0.21		0.05		0.04	
Diagnostic tests (p-value)								
Independence	0.65		0.52		0.51		0.25	
Normality	0.91		0.27		0.2		0.57	

[a]Ljung-Box non correlation test up to lag 24; [b]Shapiro-Wilk normality test.

Appendix E. *Estimated Variations in Incidence per 1,000 Live Births of Newborns ≥34 Weeks' Gestation Hospitalized in France for an Early-Onset Neonatal Infection Due to New Recommendations*

Parameter	All neonatal early-onset infections (95% CI)		Non-severe (95% CI)		All severe (95% CI)		Severe with pathogen (95% CI)	
Level change	-2.848 (-1.884 to -3.811)	p<.001	-2.845 (-2.020 to -3.671)	p<.001	-0.017 (-0.331 to 0.297)	p=.916	-0.194 (-0.412 to 0.024)	p=.072
Slope change	0.025 (-0.007 to 0.056)	p=.123	0.015 (-0.012 to 0.042)	p=.282	0.009 (-0.001 to 0.019)	p=.070	0.005 (-0.001 to 0.012)	p=.105

Abstract in French

Introduction : En 2017, les autorités sanitaires françaises ont révisé les recommandations pour la gestion des infections néonatales bactérienne précoces (INBP) afin de réduire l'utilisation inutile des antibiotiques et d'améliorer la précision diagnostique. Ces recommandations mettent l'accent sur la surveillance clinique et les évaluations basées sur les risques plutôt que sur les prélèvements bactériologiques systématiques.

Objectifs : Évaluer l'impact des nouvelles recommandations de 2017 sur les diagnostics d'infection chez les nouveau-nés.

Méthode : Cette étude a analysé les données de la Programme de Médicalisation des Systèmes d'Information (PMSI) pour les nouveau-nés de ≥34 semaines d'aménorrhée de janvier 2014 à décembre 2022 diagnostiqués avec une INBP. Quatre séries de taux d'incidence mensuels pour 1 000 naissances vivantes ont été construites : INBP globale, infections non-sévères, infections sévères (y compris la septicémie et la méningite) et infections sévères avec confirmation bactérienne. Une série temporelle segmentée avec erreurs auto-corrélées a été utilisée pour comparer les taux d'incidence attendus si l'application des recommandations n'avait aucun effet avec les taux estimés après la mise en œuvre des nouvelles recommandations.

Résultats : L'analyse a inclus 64 993 hospitalisations pour EONI. Suite à la révision des recommandations, l'incidence des infections non sévères a diminué de 12,61 à 3,08 pour 1 000 naissances vivantes, avec une diminution relative significative de -0,31 (-0,38 à -0,24) à la fin de la période de mise en œuvre. Les taux d'infections sévères sont restés stables, avec une légère diminution de 3,41 à 1,92 pour 1 000 naissances vivantes, et une différence relative non-significative de -0,01 (-0,13 à 0,12).

Conclusion : En utilisant une base de données nationale, nous avons démontré que la mise en œuvre des recommandations de 2017 pour la gestion des INBP en France a effectivement réduit les diagnostics excessifs d'INBP sans augmenter les infections sévères. Ces résultats soutiennent l'efficacité de la surveillance clinique et des approches basées sur les risques dans la gestion des infections néonatales, assurant un traitement opportun et précis.