Master of Public Health

Master de Santé Publique

Acquisition of Extended-Spectrum Beta-Lactamase Producing Enterobacterales (ESBL-PE) in Infants from Madagascar and Cambodia

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M2 – Epidemiology and Biostatistics
Master of Public Health – 2023-2025

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ACKNOWLEDGMENTS

This thesis is the result of two very fruitful years of constant learning, that, when hard times would come, I would focus on this very day, when I would be able to write what I have acknowledged as the end approaches. Although this is the conclusion of my master's degree and of the work I have conducted during my internship, the feeling is of a fresh start.

First, I would like to thank for the opportunity of working so closely to inspiring women, my professional supervisors Anne-Lise Beaumont and Bich-Tram Huynh at Institut Pasteur. Your guidance has pushed me to excellence, and my admiration for your work grows every day. Thank you for trusting me to conduct such an important study. I would also like to thank my academic supervisor, Judith Mueller, who has always been supportive not only of this thesis, but also of my professional aspirations.

Second, I thank my dear friends, who have supported and encouraged me, making themselves home when I am away from mine. You became the missing pieces I found along the way. May life always be made full of moments I get to share with you.

Lastly, I would like to thank my family, especially my mother Cristiane and my sister Sanny. Your love gives me all the tools I need for me to be. Thank you for your endless support and care. As this is part of an academic work, citations are necessary to support arguments, and Luís de Camões very wisely summarized my love for you when he wrote "*para tão longo amor tão curta a vida*". Muito obrigada por me apoiarem incansavelmente a cada passo que eu dou. Toda e qualquer palavra que eu diga não carrega consigo a grandeza do amor que por vocês sinto.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

ESBL-PE	Extended-spectrum beta-lactamase-producing Enterobacteriaceae
LMICs	Low- and middle-income countries
CI	Confidence Interval
aHR	adjusted Hazard Ratio
BIRDY	Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries
BIRDY2	Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries 2
PEEC NIC	Producing Extended Spectrum Beta Lactamase Enterobacteria Carriage in Newborns and Infants in Cambodia
MSANP/CE	Ministère de la Santé Publique/Comité d'Ethique (Madagascar)
NECHR	National Ethics Committee for Health Research
IRB	Institutional Review Board
IP	Institut Pasteur
CHROMagar	Chromogenic agar
MALDI–ToF	Matrix-Assisted Laser Desorption Ionization – Time of Flight
µg	Microgram
CA-SFM	Comité de l'antibiogramme de la Société Française de Microbiologie
Pibnet	Pasteur International Bioresources Network
DNA	Deoxyribonucleic acid
rRNA	Ribosomal ribonucleic acid
API	Analytical Profile Index
BLASTn	Nucleotide Basic Local Alignment Search Tool
ANI	Average Nucleotide Identity
MCAR	Missing Completely At Random
SD	Standard Deviation
IQR	Interquartile Range
COVID-19	Coronavirus Disease 2019
g	grams
ST	Sequence type
FU	Follow-up

NA	Not available / Missing data
3GCR-E	Third-Generation Cephalosporin-Resistant Enterobacterales
FT-IR	Fourier transform infrared spectroscopy

ABSTRACT

Background: Extended Spectrum Beta-Lactamase-Producing Enterobacteriaceae (ESBL-PE) are a major public health concern, particularly in low- and middle-income countries (LMICs), contributing to antimicrobial resistance, especially in neonates and infants.

Objectives: To estimate the prevalence of ESBL-PE colonization among infants in Cambodia and Madagascar, to investigate ESBL-PE genomic characteristics and to identify associated risk factors for first ESBL-PE acquisition in Madagascar infants.

Methods: The study was conducted in urban and semi-rural areas in Cambodia and Madagascar. Mothers were enrolled during the third semester of pregnancy and newborns were included at birth and followed during their first year of life. Maternal stools at delivery and newborn stools at Months 1, 3, 6, and 12 were collected to determine prevalence rates. ESBL-PE underwent whole-genome sequencing. The incidence of first ESBL-PE acquisition for Madagascar infants was assessed. A Cox proportional hazards model was conducted for the first three months of life.

Results: In Cambodia, the prevalence rates ranged from 46.5% [95%CI: 38.4–54.6%] to 54.6% [46.3–62.6]. In Madagascar, the highest prevalence was 35.6% [30.5–40.9], while the lowest was 20.8% [16.4 –26.0]. Prevalence among mothers in Cambodia was significantly higher (79.4% [71.6–85.4]), compared to Madagascar (42.2% [37.2–47.2]) (p>0.001). The most prevalent species in Cambodia was *Escherichia coli* (72.4%, n=275/380), whereas in Madagascar, *Klebsiella spp.* and *Enterobacter spp.* had the highest first acquisition rates (36.6% each, n=86/233). The incidence of first acquisition in Madagascar was 26.6 per 1000 newborn-days [23.2–30.3]. Factors independently associated with higher risk of first acquisition were maternal ESBL-carriage (aHR 1.66, [1.21-2.28]), cesarean delivery (2.85 [1.95-4.17]), resuscitation (1.74 [1.18-2.56]) and antibiotics use (1.54 [1.05-2.26]).

Conclusion: This study highlights significant regional differences in species distribution and complexity of early-colonization dynamics for ESBL-PE in the community, underscoring continued surveillance to better address transmission for further targeted strategies to prevent antibiotic-resistant infections.

Key words: ESBL-PE, Acquisition, Colonization, Antimicrobial resistance, Risk Factors, Infants, Low- and middle-income countries

1. INTRODUCTION

Under-five mortality continues to be a great public health challenge, with 4.8 million deaths in 2023, many of which were preventable.[1] Approximately 84% of all under-five deaths worldwide occurred in just two regions: Sub-Saharan Africa accounted for 58%, while South Asia for 26%.[1] Infections are a major contributor to these deaths, and bacterial sepsis is one of the leading causes.[2] The neonatal period, defined as the first 28 days of life, is particularly susceptible to infections due to immune immaturity, accounting for 49.2% of deaths during this age.[3] Neonates have a higher incidence of bacterial infections compared to any other pediatric age group,[4] making them highly vulnerable to severe conditions.

In low and middle-income countries (LMICs), among the most important causes of serious bacterial diseases is the Enterobacteriaceae family, which includes species such as *Escherichia coli* and *Klebsiella pneumoniae.* Extended-Spectrum β-lactamase-producing Enterobacterales (ESBL-PE) are commonly isolated in neonatal sepsis, and their resistance to antibiotics pose an increasing concern.[5] This group of bacteria produce enzymes, known as ESBLs, that confer resistance to a broad range of β-lactam antibiotics, including both first- and second-line antibiotics.[5] The treatment of choice for ESBL-PE infections is carbapenems, often unavailable or unaffordable in low- and middle-income countries (LMICs).[6]

Since colonization often precedes infection, understanding ESBL-PE carriage is crucial. However, literature focusing on ESBL-PE carriage in infants within community settings, especially in LMICs, remains limited. A recent systematic review on the topic identified mostly hospital-based studies, primarily in neonatal intensive care units, and highlighted the urgent need for more data on community-dwelling infants.[7]

In addition to estimating prevalence, understanding when colonization occurs and identifying the risk factors associated with ESBL-PE acquisition in early life are crucial for designing effective public health interventions. This knowledge can help guide targeted strategies to limit transmission within households and communities, particularly in high-risk settings. Moreover, there is a notable lack of literature assessing the genomic characteristics of ESBL-PE in community settings. Such analyses are majorly important to understand the genetic mechanisms underlying antibiotic resistance, to further elucidate the mechanisms of spread.

The primary objective of this study is to estimate the prevalence of ESBL-PE in newborns, infants, as well as to characterize the genomic features of these ESBL-PE strains in two LMICs, Madagascar and Cambodia. The secondary objective is to estimate the first acquisition of ESBL-PE during the first three months of life and to identify the risk factors associated with this acquisition in infants in Madagascar.

2. METHODS

2.1 Study Design

This study was nested within the “Bacterial Infections and antibiotic Resistant Diseases among Young children in low-Income countries” (BIRDY) project, an international and multicentric cohort, which aimed to estimate the incidence and risk factors of resistant bacterial infections in infants from birth until their first birthday within the community. Within the BIRDY project framework, we specifically analyzed data from two studies: the BIRDY2 study in Madagascar and the “Producing Extended Spectrum Beta Lactamase Enterobacteria Carriage in Newborns and Infants in Cambodia” (PEEC NIC) study in Cambodia (Figure 1).

Both studies share common features. Participants were recruited from two distinct regions: one urban (Antananarivo in Madagascar, Phnom Penh in Cambodia) and one rural/semi-rural (Moramanga and Kampong Speu, respectively). Pregnant women were enrolled during their third trimester of pregnancy and monitored to ensure the enrollment of their neonates at birth. For each mother, sociodemographic, medical and obstetric characteristics, along with delivery information were collected. Maternal fresh stools were sampled at the time of delivery. Newborns were enrolled at birth and followed for 12 months. Active follow-up for the infants consisted of home visits. At each visit, stools samples or endorectal swabs were collected to detect the presence of ESBL-PE. Potential factors associated with ESBL-PE acquisition were queried at each visit, including diet pattern, characteristics of the household environment, animal contacts, hospitalization and antibiotic intake in the previous days. In Madagascar, home visits were arranged for days 3, 14, 21 and 28 of life, for 45, 60, 75 and 90 days of life, and 6, 9 and 12 months of age, resulting in 13 follow-up visits, including the initial assessment at birth. In Cambodia, the follow-up of infants consisted of five home visits: at birth, and at 1, 3, 6 and 12 months of age (Figure 2).

BIRDY study was approved by the ethics committees of Madagascar (N° 068-MSANP/CE), Cambodia (N° 108-NECHR and N° 275-NECHR, relative to PEEC NIC), and the Institutional Review Board of Institut Pasteur (N° IRB/2016/08/03), France.

Figure 1. Geographical locations of the studies conducted in Madagascar and Cambodia.

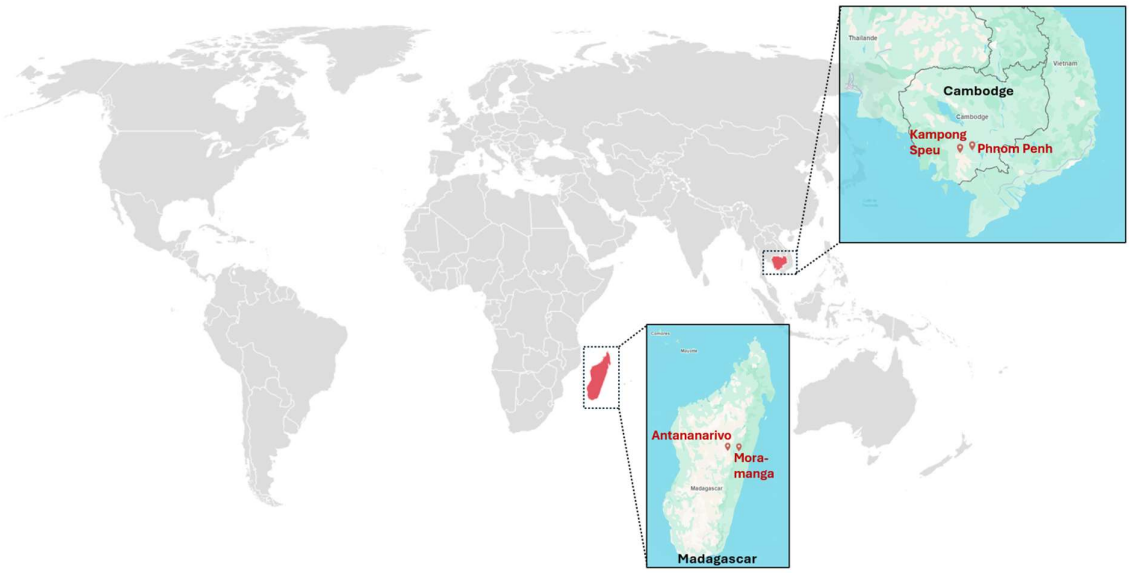
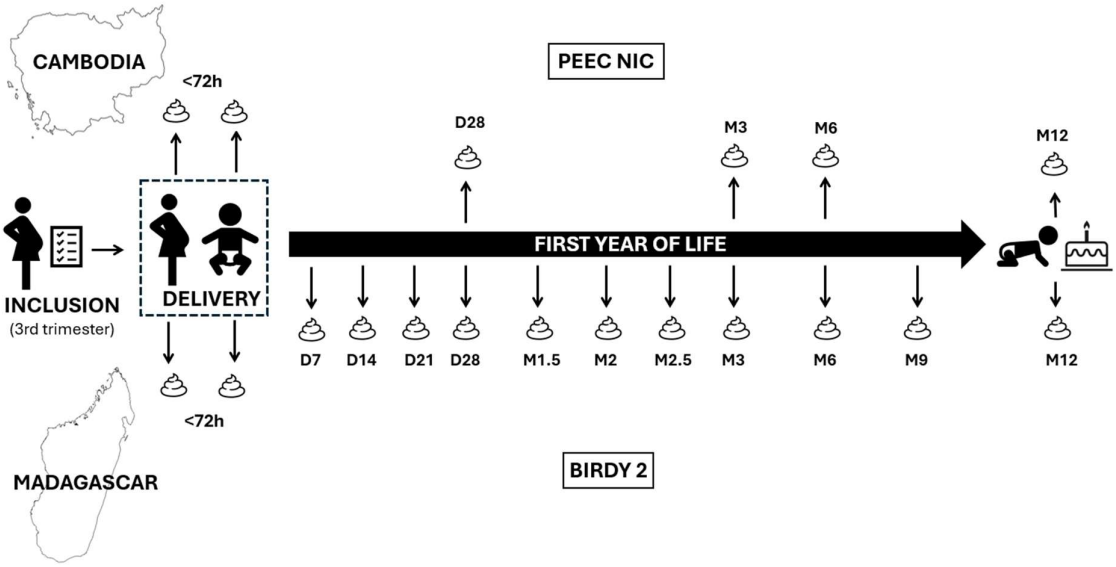


Figure 2. Study design for BIRDY 2 in Madagascar and PEEC NIC in Cambodia.



Note. D: day; M: month.

2.2 Microbiological Analysis

After collection, samples were transported on the same day to the Institut Pasteur (IP) of the study site (IP Cambodia or IP Madagascar) for immediate analysis. Particularly in Madagascar, samples were stored frozen at −80°C until further analyses.

For culture, all samples were pre-enriched following the method described by Jazmati et al.[8] Subsequently, they were inoculated onto antibiotic-supplemented media and incubated

overnight in an aerobic atmosphere at 36.5 ± 2°C. In Cambodia, Drigalski plates supplemented with 2 mg/L cefotaxime (Bio-Rad, Marnes-La-Coquette, France) were used, while in Madagascar, CHROMagar ESBL (CHROMagar, Paris, France) media were employed. Up to three colonies per plate were selected based on their color and morphological characteristics. Single bacterial colonies were cultured further, until pure isolates were obtained. Species identification was performed using MALDI–ToF (Madagascar) or API 20E system (Cambodia). ESBL production was detected by the double-disc synergy test by placing the disk of cefotaxime (30 µg), ceftazidime (30 µg) and combination of amoxicillin/clavulanic acid (20 µg/10 µg) on a lawn culture of bacteria on Muller-Hinton agar plate, with a 20 mm distance between each disk from center to center. The microbiological analyses were conducted according to the CA-SFM guidelines (Antibiogram Committee of the French Society of Microbiology).[9]

2.3 Whole-genome sequencing and genomic analysis

Whole-genome sequencing was performed on ESBL-PE isolates from both Cambodia and Madagascar. In Cambodia, all isolates were sequenced. In Madagascar, due to financial constraints, we focused on sequencing the isolate identified at the time of first acquisition. The sequencing process utilized Illumina NextSeq 500 instruments and Nextera XT libraries with a 2x150 bp paired-end protocol. Small subunit gene segments coding for 16S rRNA were assembled using ASSU v1.1,[10] and genome sequences were assembled using fq2dna v24.02.[11] Quality controls were performed using various metrics (e.g. coverage depth distribution, N50).

Taxonomic assignment of each isolate was performed in two steps: (i) the assembled 16S rRNA segment was used as a query to perform a BLASTn search against the RefSeq Targeted Loci Project sequences[12] to assess the genus (i.e. the one associated to the best BLASTn hit); (ii) the Average Nucleotide Identity (ANI) between the assembled genome and every type strain genome from its genus was computed using FastANI61 v1.33 to assess the species (i.e. the one of the closest type strain genome with ANI > 96%). Sequence types (ST) were determined using mlst v2.23.0.[13] ESBL-encoding genes were searched using AMRfinder v3.12.8.[14]

2.4 Biostatistical Analysis

2.4.1 Descriptive analysis

For descriptive analysis, to compare differences in proportions for categorical variables, we conducted Chi-square (X^2) or Fisher's Exact tests, if criteria for the Chi-square test application were not met, across urban and rural sites within each study, as well as between

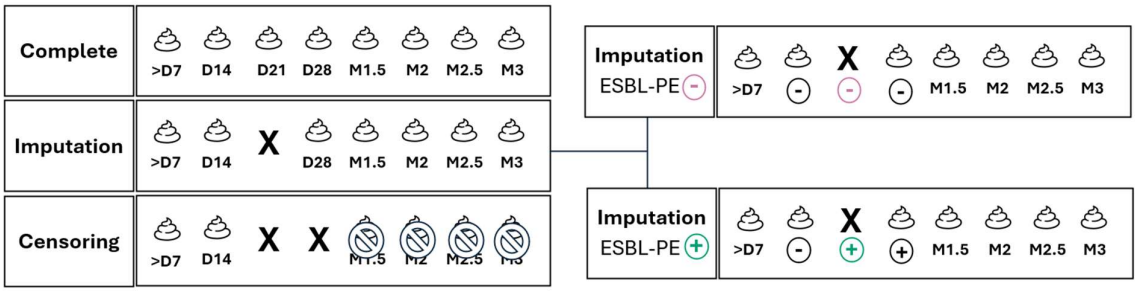
the two countries. Means and medians were compared using Student's t-test for normally distributed continuous variables and Wilcoxon rank-sum for those not normally distributed, respectively. Low birth weight was defined as birth weight under 2500 g. Household density was calculated as the ratio of persons inhabiting the residence per number of rooms. Prevalence was calculated as the proportion of infants or mothers positive for ESBL-PE out of the total number of participants screened at the different timepoints, expressed as percentage. It was estimated for each common timepoint across the two study designs to allow comparability.

2.4.2 Time-to-event analysis

To analyze the first acquisition of ESBL-PE in Madagascar during the first three months of life, we included infants with complete follow-up data on samples within this timeframe, specifically those with samples collected in the first week of life and who had at most one missing data point between any two consecutive visits. The rule applies until the first positive result. Missing data were mainly attributable to logistical impairments during the COVID-19 pandemic, that imposed barriers for conducting home visits for follow-up assessments. For infants with no positive results during the follow-up, missing values were assumed to indicate absence of colonization. Missing values that preceded positive results were imputed as positive. Similarly, missing values preceding a negative result were imputed as negative (Figure 3). These imputations were performed to provide a cautious and plausible estimate of the timing of first ESBL-PE acquisition, without overestimating colonization events.

Follow-up was censored after the first three months of life, or earlier if two consecutive data points were missing. Incidence rates of the first acquisition of ESBL-PE were calculated per 1000 infant-days. ESBL-PE acquisition curves were obtained by the Kaplan-Meier analysis and compared through the Log-Rank statistic.

Figure 3. Rules for handling missing data and censoring first ESBL-PE acquisition analysis.



To identify factors associated with ESBL-PE first acquisition, we employed a Cox Proportional Hazards model. Potentially associated variables were included, such as maternal ESBL-PE colonization, hygiene, sociodemographic and hospital-related. Infants'

hospitalization and use of antibiotics over the course of the first three months of life were examined as time-dependent variables, with one-month effect after date of report. This approach ensures that the impact of these factors begins on the actual date they occurred and is not restricted to the day of occurrence, as it is known they have prolonged effect on colonization. All factors associated with first acquisition with a p-value < 0.2 in the univariable analysis were included in the multivariable model. A backward selection strategy was applied to identify the factors that were independently and significantly associated with the outcome. For all factors included in the Cox model, the proportional hazards assumption was validated using a test on Schoenfeld residuals. The threshold for statistical significance was 0.05 and all analyses were performed using R software v4.5.0.[15] Data manipulation and visualization were performed using the *tidyverse* package (Wickham et al., 2019).[16] Time-to-event analysis was conducted using the *survival* and *survminer* packages (Therneau, 2023; Kassambara et al., 2019).[17] Figures were generated with *ggplot2* (Wickham, 2016).[18]

3. RESULTS

3.1 Characteristics of the study population

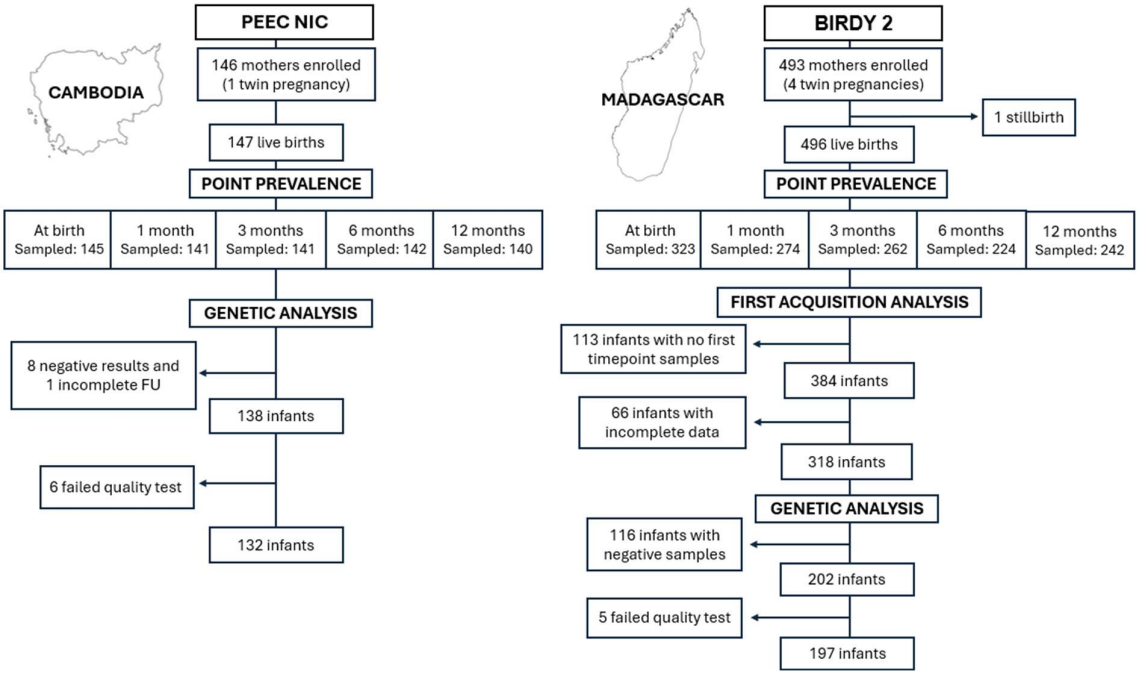
A total of 493 pregnant women were included in the study in Madagascar, with 4 of them having twin pregnancies, resulting in 496 live births (Figure 4). Throughout the study, the mean number of visits per infant was 6.1 (Standard Deviation (SD): 3.2). In Cambodia, 146 pregnant women were enrolled, with 1 twin pregnancy, leading to 147 live births (Figure 2). The mean number of visits per infant in Cambodia was 3.2 (SD: 1.5).

Table 1 presents the general sociodemographic characteristics of mothers and newborns within and between countries. The median age of the mothers in Madagascar was 24 years (Interquartile Range (IQR): 20-30), while mothers in Cambodia were slightly older, with a median age of 27 years (IQR: 24-30), ($p < 0.001$). Both countries had similar proportions of primiparous mothers, with approximately 35% in Madagascar and 36.7% in Cambodia. For marital status, 96% of Madagascar mothers were either married or in a common-law partnership, while in Cambodia approximately 98% were married ($p < 0.001$). Education attainment was lower in Cambodia, with 62.3% having no education or only primary education, compared to 56.5% in Madagascar with partial secondary education ($p < 0.001$). The proportion of unemployment was higher in Madagascar (56.3%) compared to Cambodia (31.5%) ($p < 0.001$), where 62.3% of mothers were employed in manual jobs. Regarding household conditions, the median household density was 2.5 persons per room (IQR: 1.7, 3.3) in Madagascar, slightly higher in Cambodia, with 3 persons per room (IQR: 2-4) ($p < 0.001$). More than 80% of households in Madagascar had toilets outside without flushing system, compared to 49.3% in Cambodia ($p < 0.001$). Access to electricity was not available to 22.6%

of households in Madagascar, whereas nearly all households in Cambodia reported having electricity ($p < 0.001$).

For the newborns, the distribution of sex was balanced in Madagascar (50.7% males and 49.3% females), whereas in Cambodia, 56.5% were female. The mean birth weight of newborns in Madagascar was 3018 grams (g) (SD: 462 g), compared to 3110 g (SD: 526 g) in Cambodia. Low birth weight occurred in similar proportions in both countries, with 7.5% of newborns in Madagascar and 5.4% in Cambodia (NS, $p=0.3$). A significant majority of births in Cambodia took place in healthcare facilities (98%), contrasting with 48.8% in Madagascar ($p < 0.001$). Both countries presented similar rates of cesarean deliveries, with 13.5% in Madagascar and 13.6% in Cambodia. Post-birth resuscitation was required for 12.7% of newborns in Madagascar and 8.2% in Cambodia. During the first three months of life, 36.1% of the Malagasy newborns received antibiotics, whereas in Cambodia it was lower, with 15% receiving antibiotics ($p < 0.001$). In Madagascar, 9.3% of infants were hospitalized during the first three months of life, compared to 11.6% in Cambodia.

Figure 4. Flowchart showing inclusion of participants in Cambodia and Madagascar studies.



Note. The high number of missing data in Madagascar was mainly attributable to logistical impairments during the COVID-19 pandemic, that imposed barriers for conducting home visits for follow-up assessments. FU: follow-up.

Table 1. Characteristics of mothers and infants from Madagascar and Cambodia.

CHARACTERISTICS MOTHERS	MADAGASCAR				CAMBODIA				Comparison Countries
	Total N = 492	**Urban Area** n = 242	**Semi-Rural Area** n = 250	***p***	**Total** N = 146	**Urban Area** n = 65	**Rural Area** n = 81	***p***	***p***
Age	24 [20, 29]	24 [19, 29]	25 [21, 30]	0.1	27.97 [±5.03]	26.9 [±5.37]	28.8 [±4.59]	**0.02**	**<0.001**
Household density	2.5 [1.7, 3.3]	3 [2, 4]	2 [1.5, 3]	**<0.001**	3 [2, 4]	3 [2, 4]	3 [2, 4]	0.2	**<0.001**
Parity				>0.9				0.4	0.6
Primiparous	171 (34.8%)	84 (34.7%)	87 (34.8%)		54 (36.7%)	27 (41.5%)	27 (33.3%)		
Multiparous	321 (65.2%)	158 (65.3%)	163 (65.2%)		92 (63.3%)	38 (58.5%)	55 (66.7%)		
Education				0.7				**0.001**	**<0.001**
No education or Primary	89 (18.1%)	43 (17.7%)	46 (18.4%)		91 (62.3%)	35 (53.8%)	56 (69.1%)		
Partial Secondary	278 (56.5%)	141 (58.2%)	137 (54.8%)		28 (19.2%)	21 (32.3%)	7 (8.6%)		
Complete Secondary or University	125 (25.4%)	58 (23.9%)	67 (26.8%)		27 (18.5)	9 (13.8%)	18 (22.2%)		
Marital Status				0.6				0.8	**<0.001**
Single	20 (4.1%)	12 (4.9%)	8 (3.2%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		
Common-law partnership	231 (47.0%)	112 (46.2%)	119 (47.6%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		
Married	241 (49.0%)	118 (48.8%)	123 (49.2%)		143 (97.9%)	63 (96.9%)	80 (98.8%)		
Divorced	0 (0.0%)	0 (0.0%)	0 (0.0%)		3 (2.1%)	2 (3.1%)	1 (1.2%)		
Employment				**<0.001**				**0.01**	**<0.001**
Unemployed	277 (56.3%)	126 (52.1%)	151 (60.4%)		46 (31.5%)	27 (41.5%)	19 (23.5%)		
Manual Employment	191 (38.8%)	112 (46.2%)	79 (31.6%)		91 (62.3%)	37 (56.9%)	54 (66.7%)		
Office jobs	24 (4.9%)	4 (1.6%)	20 (8.0%)		9 (6.2%)	1 (1.5%)	8 (9.9%)		
Toilet				0.09				**<0.001**	**<0.001**
Outside without flush	402 (81.7%)	191 (78.9%)	211 (84.7%)		72 (49.3%)	22 (33.8%)	50 (61.7%)		
Outside with flush	32 (6.5%)	18 (7.4%)	14 (5.6%)		0 (0.0%)	0 (0.0%)	0 (0.0%)		
Inside without flush	16 (3.3%)	3 (1.2%)	13 (5.2%)		68 (46.6%)	37 (56.9%)	31 (38.3%)		
Inside with flush	22 (4.5%)	11 (4.5%)	11 (4.4%)		6 (4.1%)	6 (9.2%)	0 (0.0%)		
Electricity				**<0.001**				>0.9	**<0.001**
No	111 (22.6%)	211 (87.2%)	170 (68.0%)		1 (0.7%)	0 (0.0%)	1 (1.2%)		
Yes	381 (77.1%)	31 (12.8%)	80 (32.0%)		145 (99.3%)	65 (100.0%)	80 (98.8%)		
Animal ownership				**<0.001**					-
No	339 (68.9%)	198 (81.8%)	141 (56.4%)		-	-	-		
Yes	153 (31.1%)	44 (18.2%)	109 (43.6%)		-	-	-		

Table 1. Characteristics of the mothers and newborns from Madagascar and Cambodia (Continued).

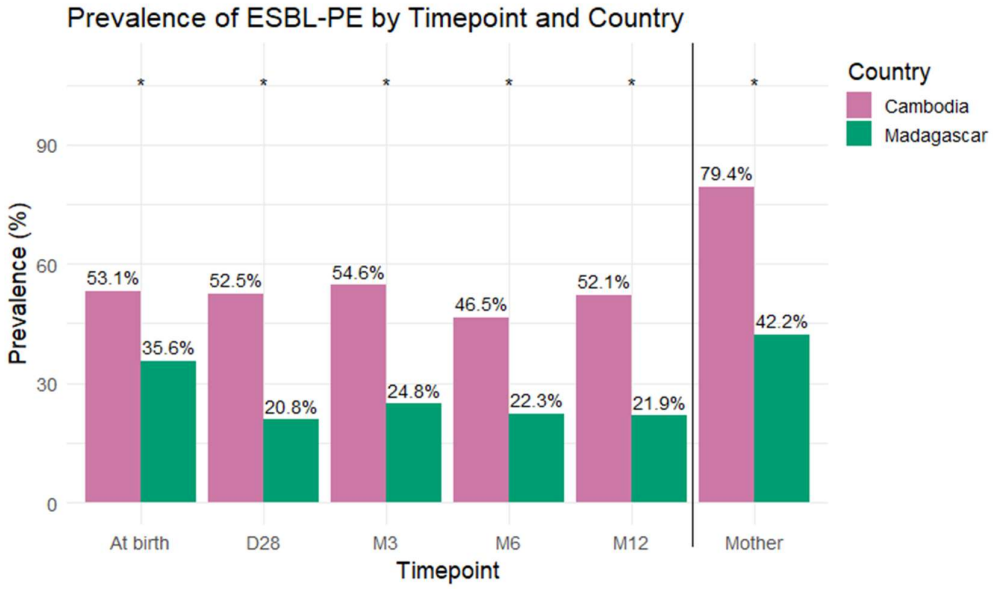
CHARACTERISTICS NEWBORNS	MADAGASCAR				CAMBODIA				Comparison Countries
	Total N = 496	Urban Area n = 246	Semi-Rural Area n = 250	p- value	Total N = 147	Urban Area n = 65	Rural Area n = 82	p- value	p- value
Sex				0.1				0.6	0.1
Male	252 (50.7%)	116 (47.2%)	135 (54.0%)		64 (43.5%)	30 (46.2%)	34 (41.5%)		
Female	245 (49.3%)	130 (52.8%)	115 (46.0%)		83 (56.5%)	35 (53.8%)	48 (58.5%)		
Low birth weight				0.3				>0.9	0.4
< 2500 g	37 (7.5%)	21 (8.5%)	16 (6.4%)		8 (5.4%)	4 (6.2%)	4 (4.9%)		
≥ 2500 g	443 (89.3%)	212 (86.1%)	231 (92.4%)		139 (94.6%)	61 (93.8%)	78 (95.1%)		
Place of delivery				0.3				>0.9	**<0.001**
Home birth	241 (48.6%)	122 (49.5%)	119 (47.8%)		3 (2.0%)	1 (1.5%)	2 (2.4%)		
Healthcare facility	242 (48.8%)	112 (45.5%)	130 (52.2%)		144 (98.0%)	64 (98.5%)	80 (97.6%)		
Cesarean delivery				0.05				>0.9	>0.9
No	429 (86.5%)	205 (83.3%)	224 (89.6%)		127 (86.4%)	56 (86.2%)	71 (86.6%)		
Yes	67 (13.5%)	41 (16.7%)	26 (10.4%)		20 (13.6%)	9 (13.8%)	11 (13.4%)		
Resuscitation at birth				**0.2**				0.6	0.1
No	432 (87.1%)	219 (89.0%)	213 (85.2%)		135 (91.8%)	61 (93.8%)	74 (90.2%)		
Yes	63 (12.7%)	26 (10.5%)	37 (14.8%)		12 (8.2 %)	4 (6.2%)	8 (9.8%)		
Hospitalization (0–3 months)				0.1				0.03	0.5
No	450 (90.7%)	218 (88.6%)	232 (92.8%)		130 (88.4%)	226 (91.5%)	213 (94.0%)		
Yes	46 (9.3%)	28 (11.4%)	18 (7.2%)		17 (11.6%)	21 (8.5%)	15 (6.0%)		
Antibiotics (0–3 months)				**<0.001**				0.07	**<0.001**
No	317 (63.9%)	197 (80.1%)	120 (48.0%)		125 (85.0%)	207 (83.8%)	171 (68.4%)		
Yes	179 (36.1%)	49 (19.9%)	130 (52.0%)		22 (15.0%)	40 (16.2%)	79 (31.6%)		

Note. The high number of missing data in Madagascar was mainly attributable to logistical impairments during the COVID-19 pandemic, that imposed barriers for conducting home visits for follow-up assessments. Not available data were considered.

3.2 Prevalence of ESBL-PE

The prevalence of ESBL-PE colonization in the Cambodian and Madagascar study populations by timepoint is displayed in Figure 5 and in Table A1 (Appendix). At birth, Cambodian newborns showed a significantly higher prevalence of ESBL-PE colonization, of 53.1% [95% CI: 45.0% – 61.4%], in comparison to Madagascar with a prevalence of 35.6% [95% CI: 30.5% – 40.9%] ($p < 0.001$). Subsequent samples collected at the end of the neonatal period – 28 days – show a decrease in the prevalence in Madagascar, that remains stable throughout the follow-up, with a prevalence rate of 25.6% [95% CI: 23.3% – 28.0%], ranging from 20.8% and 24.8%. In Cambodia, the prevalence rate remained stable over the follow-up period at 51.7% [95% CI: 48.0% – 55.4%], with a range of 46.5% to 54.6%. Regarding maternal ESBL-PE colonization at birth, Cambodian mothers had a high prevalence of 79.4% [95% CI: 71.6% – 85.4%], compared to Madagascar mothers ($p < 0.001$), with also an important prevalence of 42.2% [95% CI: 37.3% – 47.2%].

Figure 5. Distribution of prevalence of ESBL colonization by timepoint and country.

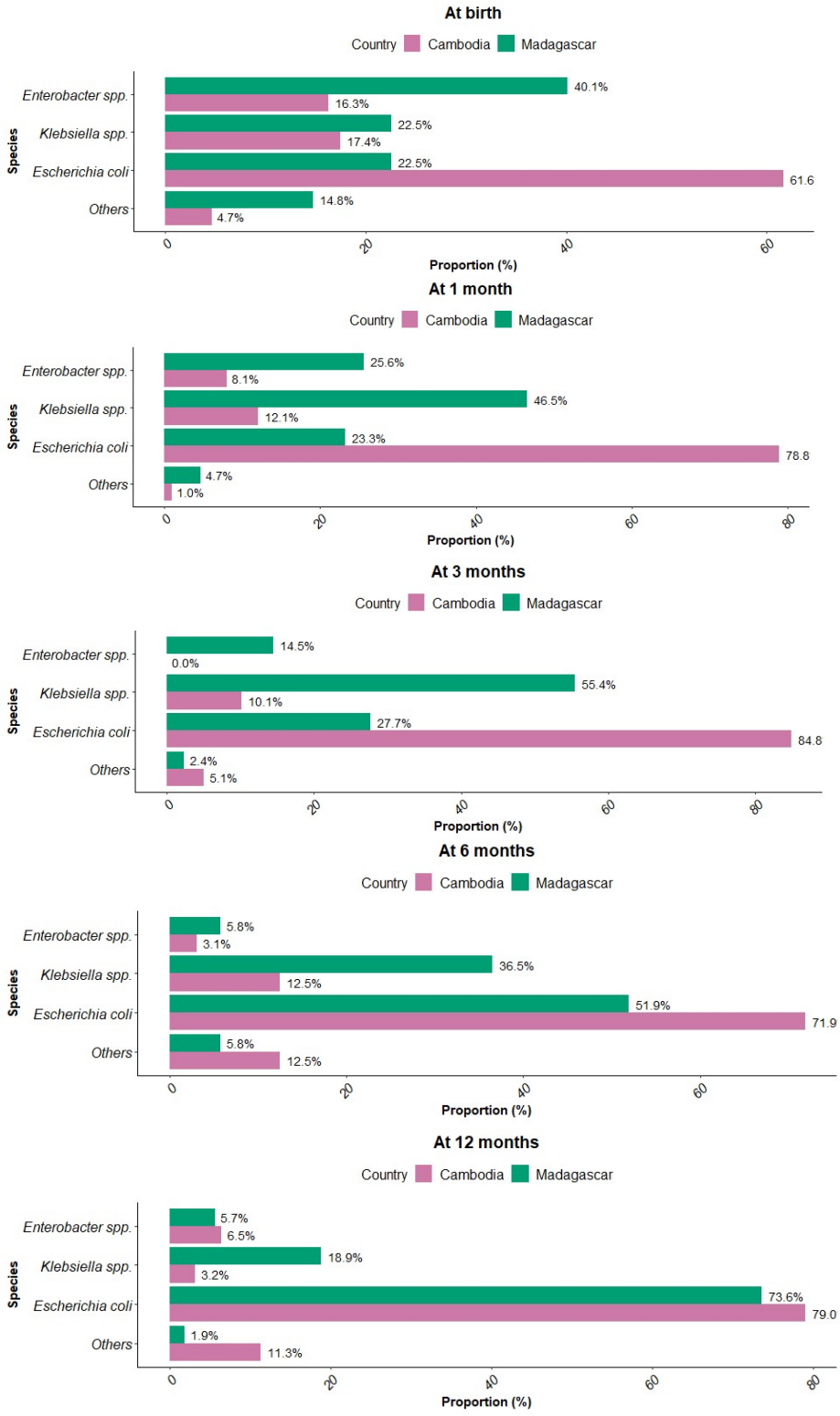


3.3 ESBL-PE Most Common Species

The ESBL-PE species identified in the Cambodian and Madagascar study populations show significant differences at birth, 1, 3, 6 and 12 months of age, as illustrated in Figure 6. In both countries, *Enterobacter spp.*, *Klebsiella spp.* and *Escherichia coli* were the most prevalent species across different time points. In Cambodia, *E. coli* was consistently the most prevalent species at all timepoints, comprising 72.4% (n = 275/380) of all isolates. In Madagascar, of 459 identified isolates, the prevalence patterns varied more over time: *Enterobacter spp.* was the most prevalent at birth (40.1%, n = 57/142), followed by *Klebsiella spp.* at 1 month (46.5%, n

= 60/129) and 3 months of age (55.4%, n = 46/83). *E. coli* became the most prevalent species at 6 months (51.9%, n = 27/52) and 12 months of age (73.6%, n = 39/53).

Figure 6. Distribution of ESBL-PE Species by Country at different timepoints.

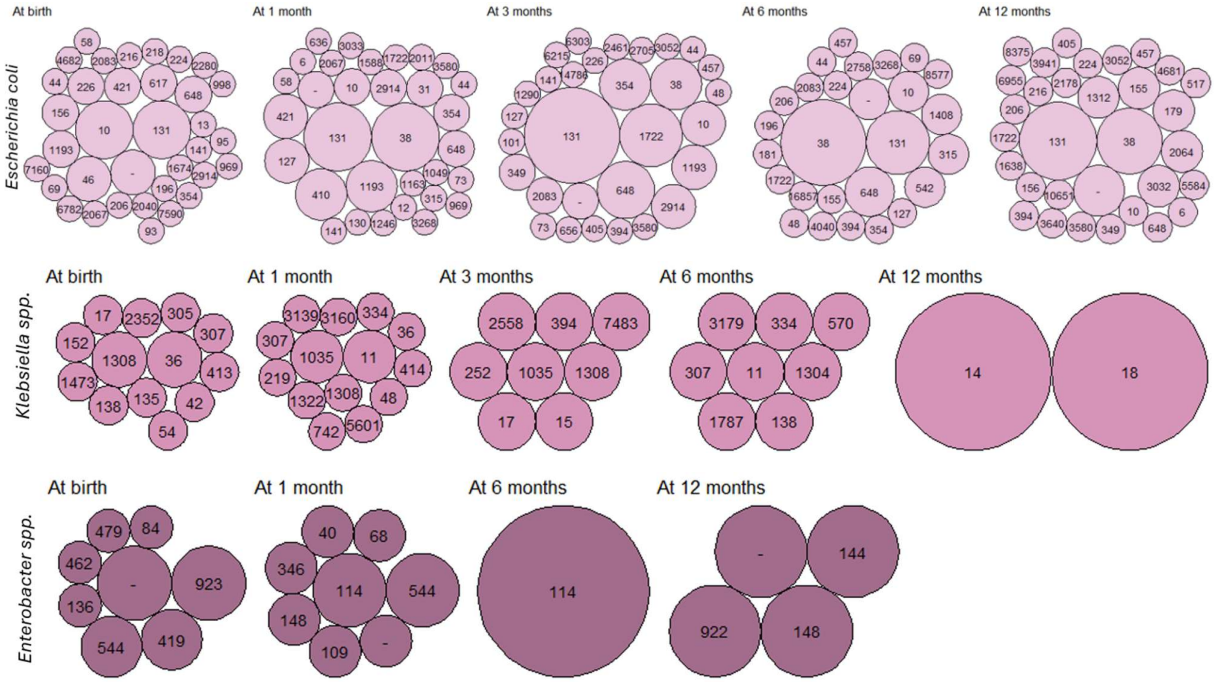


3.4 ESBL-PE Most Common Sequence Types by Species

3.4.1 Distribution of ESBL-PE Sequence Types by Species in Cambodia

Sequence types (STs) were analyzed by species across all five timepoints in Cambodia (Figure 7). A complete list of STs can be found in Table A2 (Appendix). *Escherichia coli* exhibited the greatest variability of STs within timepoints. Of the 89 different STs identified (n = 275/380), the most prevalent one were ST131 (n = 38/275, 13.8%), ST38 (n = 25/275, 9.1%), and ST648 (n = 13/275, 4.7%). For *Klebsiella spp.*, ST1308 was the most prevalent (n = 4/49, 8.2%), followed by ST1035, ST11, ST307, and ST36 (each n = 3/49, 6.1%) among the 35 different STs identified (n = 49/380). In *Enterobacter spp.*, out of the 15 STs detected (n = 30/380, the most common were ST114 and ST544, both representing 13.3% (n = 4/30 each).

Figure 7. Distribution of sequence types per timepoint in Cambodia *for Escherichia coli*, *Klebsiella spp.* and *Enterobacter spp.*



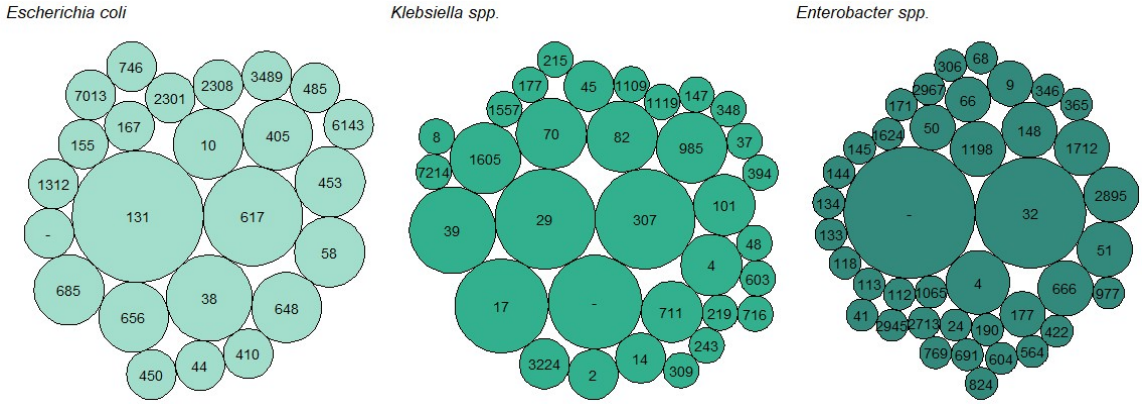
Note. The diameters are scaled consistently across timepoints, which prevents direct comparison of the number of isolated STs. Symbol "-" indicates cases where no ST could be assigned, either because one or more alleles have not been described, or because the combination of alleles has not yet been reported.

3.4.2 Distribution of ESBL-PE Sequence Types by Species in First Acquisition in Madagascar

Of the 197 newborns included in the first acquisition analysis, and whose samples were sequenced, the frequence by isolated species was the same for *Enterobacter spp.* and *Klebsiella spp.* (n = 86/233, 36.6%) each. The complete list shows all STs is shown in Table A3 (Appendix). The distribution for *Escherichia coli* was lower (n = 42/233, 17.9%). The most frequent species identified were *Enterobacter hormaechei* (n = 58/86, 67.3%) among *Enterobacter spp.*, *Klebsiella pneumoniae* (n = 70/86, 81.4%) for *Klebsiella spp.*, and *Escherichia coli* (n = 41/42, 97.6%) among *Escherichia spp*.

For *Enterobacter spp.*, there was high diversity of identified STs (n=40), most frequent being ST32 (n = 12/86, 14.0%). For *Klebsiella spp.*, with 33 different STs analyzed, the most prevalent ones were ST29 and ST307, accounting for 9.3% (n = 8/86) each, followed by ST17 (n = 7/86, 8.1%). Among *Escherichia coli*, with 24 STs detected, the most frequently identified STs were ST131 and ST617, found in 16.7% (n = 7/42) and 9.5% (n = 4/42) of the isolates, respectively (Figure 8).

Figure 8. Distribution of sequence types in *Escherichia coli*, *Klebsiella spp.*, and *Enterobacter spp.* isolates from first acquisition in Madagascar.



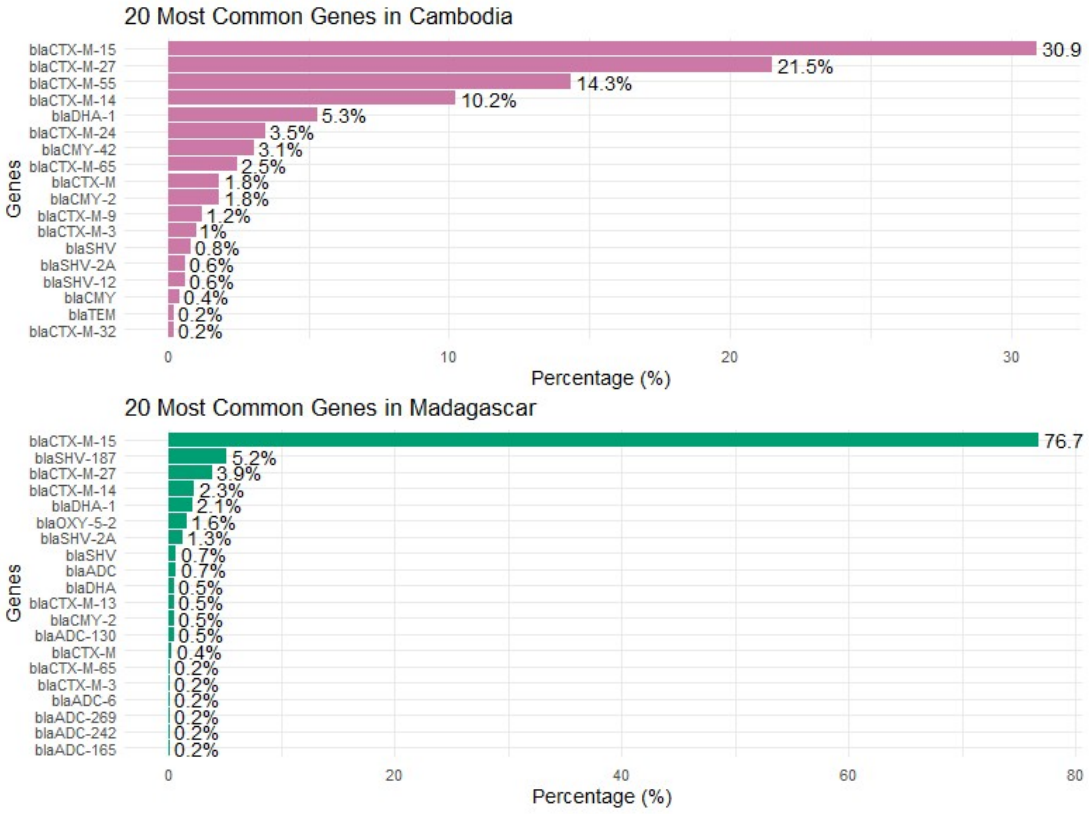
Note. The diameters between timepoints are not comparable in number of isolated STs. Symbol "**-**" indicates cases where no ST could be assigned, either because one or more alleles have not been described, or because the combination of alleles has not yet been reported.

3.5 ESBL-PE Genes in Madagascar and Cambodia

The distribution analysis of genes was performed at five timepoints in Cambodia, while in Madagascar, the analysis focused on infants followed up during the first three months of life (Figure 9, Table A.4). In Cambodia, among 489 isolates, the most prevalent genes were *bla*$_{\text{CTX-M-15}}$ (n = 151/489, 30.9%), *bla*$_{\text{CTX-M-27}}$ (n = 105/489, 21.5%), *bla*$_{\text{CTX-M-55}}$ (n = 70/489, 14.3%), and *bla*$_{\text{CTX-M-14}}$ (n = 50/489, 10.2%). In Madagascar, within the first three months of life, the most

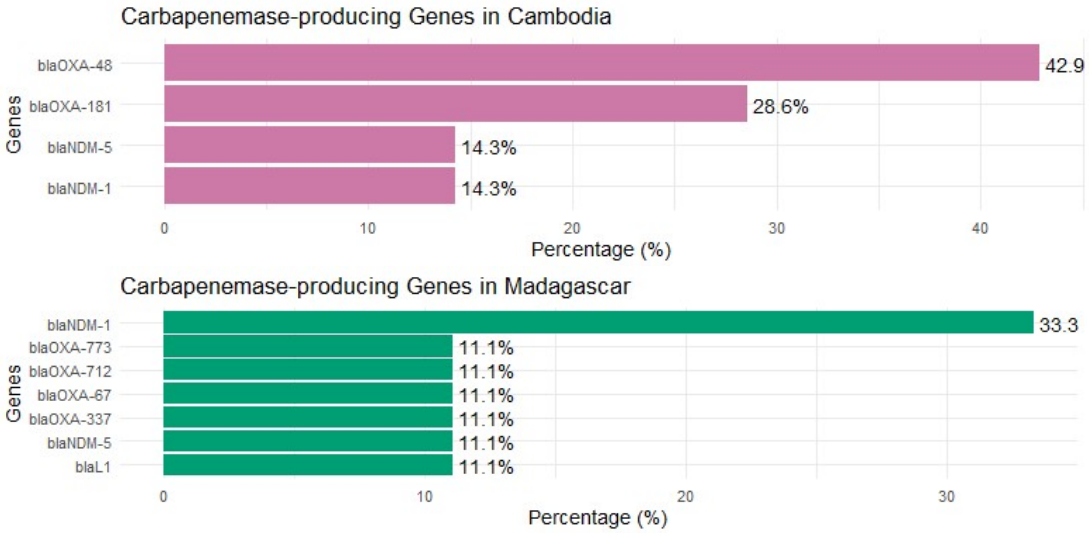
common gene among 559 isolates was *bla*$_{\text{CTX-M-15}}$ (n = 429/559, 76.7%), followed by *bla*$_{\text{SHV-187}}$ (n = 29/559, 5.2%) and *bla*$_{\text{CTX-M-27}}$ (n = 22/559, 3.9%). Notably, *bla*$_{\text{CTX-M-15}}$ was the most common gene identified in both countries.

Figure 9. Distribution of the most common bacterial genes in Cambodia and Madagascar.



For carbapenemase-producing genes, both countries showed different distributions (Figure 10). In Cambodia, the most prevalent carbapenemase-producing gene was *bla*$_{\text{OXA-48}}$ (n = 3/7, 42.9%), followed by *bla*$_{\text{OXA-181}}$ (n = 2/7, 28.6%). In Madagascar, the most prevalent carbapenemase-producing gene was *bla*$_{\text{NDM-1}}$ (n = 3/9, 33.3%). The complete list of carbapenemase-producing genes is shown by Table A.5 (Appendix).

Figure 10. Distribution of most common Carbapenemase-producing genes for Cambodia and Madagascar.

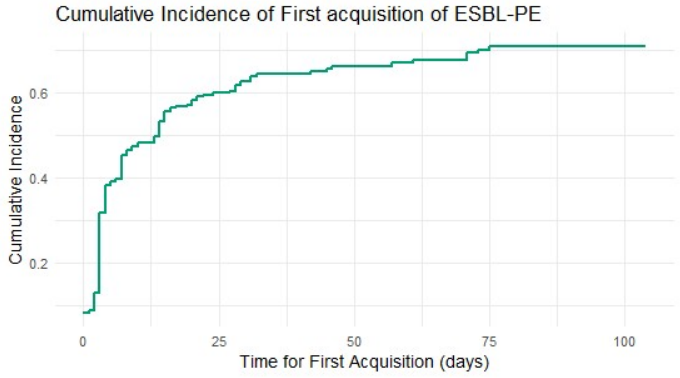


3.6 ESBL First Acquisition Analysis in Madagascar

3.6.1 Time to First ESBL-PE Acquisition Curves – Stratified Kaplan-Meier Curves

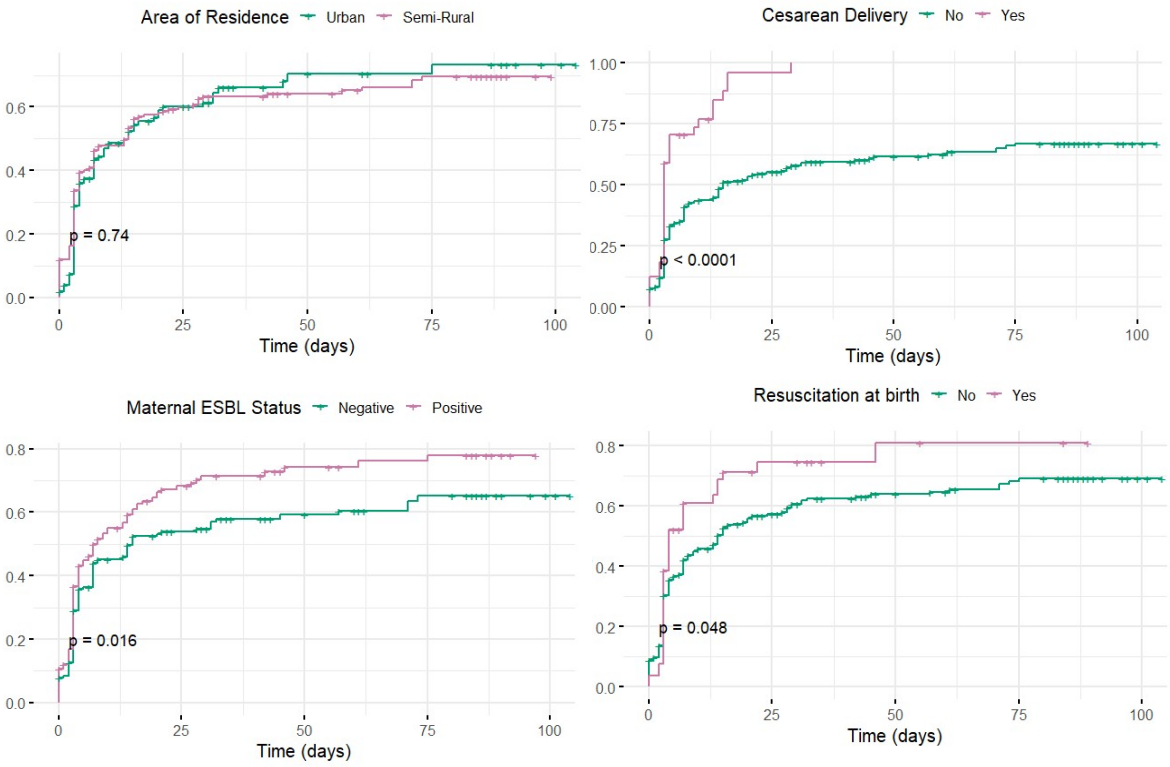
Out of 496 newborns, a total of 112 were excluded from the survival analysis due to the absence of samples during the first two visits, resulting in a final population of 384 newborns. We compared included and excluded infants to assess representativeness. Maternal age and education showed no significant differences. However, the area of residence differed significantly ($p < 0.001$). The overall incidence of ESBL-PE first acquisition was 26.6 per 1000 newborn-days [95% CI: 23.2 – 30.3]. Time to first ESBL-PE acquisition curve considered the newborns with samples in the first three months of life. 384 newborns were included in the analysis. Figure 11 shows the Kaplan-Meier time-to-event curve. The median time for the first ESBL-PE acquisition was 14 days [95% CI: 7 - 16].

Figure 11. Kaplan-Meier curve for time to First ESBL-PE acquisition in Madagascar infants.



ESBL-PE acquisition curves according to area of residence, cesarean delivery, maternal ESBL colonization status, and resuscitation at birth are displayed in Figure 12. Cesarean delivery, maternal ESBL colonization and resuscitation at birth show statistically significant difference in ESBL acquisition (Log Rank test, $p < 0.05$). In contrast, there was no statistically significant difference of acquisition between urban and semi-rural areas (Log Rank test, p=0.74).

Figure 12. Cumulative Incidence according to Madagascar's study areas, cesarean delivery, maternal ESBL colonization status and resuscitation at birth.



3.6.2 Multivariable Cox Proportional Hazards Model: Risk factors for ESBL-PE First Acquisition

Of the 384 infants included, 66 were excluded due to incomplete data, resulting in 318 infants. The univariable and multivariable analyses for first colonization by ESBL-PE in newborns are shown in Table 2. All variables included on multivariable analyses met the Proportional Hazards assumption. The factors independently associated with a higher risk of ESBL-PE first acquisition were maternal ESBL-carriage [aHR = 1.66, 95% CI: 1.21 - 2.28], cesarean delivery [aHR = 2.85, 95% CI: 1.95 - 4.17], resuscitation at birth [aHR = 1.74, 95% CI: 1.18 - 2.56], and the use of antibiotics with one month effect [aHR = 1.54, 95% CI: 1.05 - 2.26].

Table 2. Cox proportional hazard analysis of risk factors for first ESBL-PE acquisition and newborns in the first three months of age in Madagascar.

CHARACTERISTICS	Person days	Univariable Analysis		Multivariable Analysis	
		Crude HR [95% CI]	*p*	Adjusted HR [95% CI]	*p*
Maternal ESBL-carriage			**0.001**		**0.002**
No	5749	Ref.		Ref.	
Yes	3139	1.74 [1.25, 2.42]		1.66 [1.21, 2.28]	
Cesarean delivery			**<0.001**		**<0.001**
No	8730	Ref.		Ref.	
Yes	158	3.38 [2.39, 4.76]		2.85 [1.95, 4.17]	
Resuscitation at birth			**<0.001**		**0.005**
No	8304	Ref.		Ref.	
Yes	584	2.18 [1.52, 3.14]		1.74 [1.18, 2.56]	
Use of Antibiotics			**0.001**		**0.027**
No	8089	Ref.		Ref.	
Yes	799	1.81 [1.26, 2.60]		1.54 [1.05, 2.26]	
Area of Residence			0.1		
Urban	2067	Ref.			
Semi-Rural	6821	0.77 [0.56, 1.07]			
Place of birth			**0.001**		
Home birth	5411	Ref.			
Healthcare facility	3477	1.59 [1.12, 2.24]			
Toilet			0.06		
Outside without flush	7610	Ref.			
Outside with flush	273	1.35 [0.75, 2.44]			
Inside without flush	595	0.76 [0.29, 1.96]			
Inside with flush	410	0.27 [0.07, 0.97]			
Maternal use of Antibiotics during labor			0.1		
No	7823	Ref.			
Yes	1065	1.37 [0.93, 2.02]			
Sex			0.9		
Male	5382	Ref.			
Female	3506	0.98 [0.70, 1.37]			
Low birth weight			0.06		
No	264	Ref.			
Yes	8624	0.58 [0.33, 1.02]			
Hospitalization			<0.001		
No	8772	Ref.			
Yes	116	2.96 [1.87, 4.71]			

HR = Hazard Ratio, CI = Confidence Interval

4. DISCUSSION

4.1 Interpretation of Findings

This study investigated the prevalence of ESBL-PE colonization in infants from Cambodia and Madagascar over their first year of life. The findings reveal high prevalence rates of ESBL-PE in both countries, especially in Cambodia. Maternal colonization at delivery, a known risk factor for neonatal colonization, also showed high prevalences. *E. coli, Enterobacter spp.* and *Klebsiella* spp. were the most prevalent species. With *E. coli* as the most prevalent species in Cambodia across timepoints, a shift was observed in Madagascar throughout the follow-up period. Both countries demonstrated high genetic diversity among the species identified. Compared to the BIRDY study conducted in 2015-2016, there was a significant increase in the incidence of first ESBL-PE acquisition, from 10.4 to 26.6 per 1000 newborn-days.[19] The major risk factors associated with ESBL-PE acquisition in infancy included maternal ESBL-carriage, cesarean delivery, post-birth resuscitation and use of antibiotics during the first three months of life.

Within community settings, a high prevalence of ESBL-PE was observed in infants during their first year of life and their mothers at delivery, with particularly elevated rates in Cambodia. A recent meta-analysis estimated a pooled prevalence of 30.2% of third-generation cephalosporin-resistant Enterobacterales (3GCR-E) - which encompasses all ESBL-PE - among newborns and infants in LMICs.[7] This prevalence aligns with observations in Madagascar but is notably lower than the estimates for Cambodia, where it ranged from 46.5% to 54.6% along the follow-up. Although both countries are classified as LMICs, they differ in terms of geography, market dynamics, and population movement, factors that can contribute to ESBL-PE dissemination and may explain the higher prevalences reported for Cambodia, approximately two times higher than that identified in Madagascar. Notably, Madagascar is an island nation, a geographic feature that may reduce cross-border bacterial transmission and partially explain the lower prevalence observed compared to Cambodia. In contrast, Cambodia's location in mainland Southeast Asia, with higher regional connectivity and trade, may facilitate greater microbial exchange and resistance spread.

These findings are consistent with regional trends: The Western Pacific region has been identified as having one of the highest prevalence rates of ESBL-PE in the general healthy population, with a pooled prevalence of 46%, compared to 22% in Africa. These contrast with other regions where ESBL-PE pooled prevalence rates are much lower: Europe with 4% and the Americas with 2%.[20]

A notable difference in the prevalence of ESBL-PE species was observed between Cambodia and Madagascar. In Cambodia, *E. coli* was consistently prevalent across all timepoints. A study showed that within Cambodians, the prevalence of community-acquired

ESBL-producing *E. coli* increased from 28.9% in 2012 to 48.2% in 2015,[21] consistent to our findings in infants.

In contrast, the findings in Madagascar showed a dynamic shift in species prevalence over the infants' follow-up. *Enterobacter spp.* was the most prevalent species at birth, changing to *Klebsiella spp.* at 1 and 3 months of age, and revealing *E. coli* as the most prevalent at 6 and 12 months of age. This shift in prevalence at the species-level highlights a more complex ESBL-PE scenario in Madagascar. While regional differences influencing species prevalence are expected, observing such significant changes over a short period in infants is uncommon. Additionally, for first ESBL-PE acquisition, the most commonly isolated species were Enterobacter *spp.* and *Klebsiella spp*. This is in opposition to previous data from the first BIRDY study, where *E. coli* was identified as the predominant species during the first neonatal acquisition in 2015-2016.[19] To our knowledge, this is the first study to report *Enterobacter spp.* distribution rate at 36.6% in infants from a community-based setting. Most studies assessing ESBL-PE colonization have focused on specific species, such as *E. coli* and *Klebsiella* spp, however, with the observed high prevalence of other species, we underscore the necessity of broadening the scope of future research to encompass a more diverse range of bacterial species. These findings suggest that early-life colonization dynamics in Madagascar may be influenced by distinct environmental exposures, maternal reservoirs, or horizontal transmission pathways that differ from other LMIC contexts. Further research is warranted to understand the determinants driving these species-specific trends.

In Cambodia, there was great diversity of STs among *E. coli* isolates, being ST131 the most found among isolates, among the 89 different STs identified. This pattern aligns with findings from other studies,[22] underscoring dynamics complexity. In Madagascar, the diversity of STs for first ESBL-PE acquisition was also high, particularly for *Enterobacter spp*. with 40 different STs detected.

Despite this genetic diversity, a commonality across both countries was the predominance of the gene $bla_{\text{CTX-M-15}}$. This finding is consistent with global trends, where $bla_{\text{CTX-M-15}}$ is reported to be the most prevalent ESBL gene,[22] showing its role in the potential dissemination of antibiotic resistance in both countries.

Maternal ESBL-PE carriage was associated with a 2-fold increased hazard of infants being colonized with ESBL-PE in Madagascar. This is consistent with existing literature that emphasizes vertical transmission as one of the most common risk factors for newborn and infant ESBL-PE colonization, and potential infection.[23] Regarding evidence for this transmission route, the incidence of ESBL-PE colonization was found significantly earlier in infants born to colonized mothers at birth,[24] while *Denkel et al.* showed that the ESBL-PE incidence was six times higher among infants born to colonized mothers. [23] Moreover, studies assessing mother-to-child transmission show that most colonized infants born to colonized

mothers at birth were identified with the same bacterial strain,[24,25] reinforcing the likelihood of direct maternal transmission. Additionally, one study conducted in Israel showed that ESBL-PE isolates were more common in neonates of mothers with positive cultures,[26] supporting vertical transmission as one of the main routes of acquisition. All together, these findings suggest that reducing maternal colonization could be a potential strategy to limit neonatal carriage.

Cesarean delivery was associated with nearly a 3-fold increased hazard for first ESBL-PE acquisition. Cesarean section can affect the patterns of early colonization, as it impedes the exposure to maternal vaginal and gut flora and consequently their microbiome development, switching from beneficial communities to potentially pathogenic communities.[27,28]

Consistent with our findings, previous research from the BIRDY study in Madagascar, also identified cesarean delivery as a risk factor for first acquisition.[19] A community-based study in Lebanon also found cesarean delivery to be associated with an increased risk of ESBL-PE carriage among infants during their first year of life.[29] Similarly, newborn colonization was associated with cesarean section in Bangladesh.[30]

While cesarean sections are essential and lifesaving when medically indicated, these findings underscore the importance of considering their potential downstream effects, including altered microbial colonization and increased susceptibility to colonization by antibiotic-resistant bacteria. Supporting healthy microbiome development, through practices such as exclusive breastfeeding and cautious antibiotic use, may help mitigate these effects, particularly in settings where the risk of ESBL-PE acquisition is high.

Antibiotics use has also been identified as a risk factor for the first ESBL-PE acquisition, with a 1.5 higher hazard compared to those not exposed to therapy. This is consistent with a meta-analysis that showed that early antibiotics administration was associated with higher likelihood of 3GCRE colonization, with pooled OR of 2.96.[7] Infants may be particularly vulnerable to the effects of antibiotics, due to rapid shifts in their microbiota and increased bacterial selection pressure compared to older children or adults.[7] Antibiotic use potentially disrupts the normal gut microbiota, reducing abundance of protective commensal bacteria, which facilitates colonization by resistant organisms, such as Enterobacteriaceae.[31] A hospital-based study in Madagascar also found that ESBL-PE carriage increased 35.9% during hospitalization, having antibiotic therapy as its only independent risk factor.[32] Additionally, one study assessing multidrug-resistant bacteria in Ghana reported association of antibiotic administration with 3GCR-E carriage in neonates admitted to neonatal units.[33]

Infants who underwent resuscitation at birth had a 1.74 higher hazard of first ESBL-PE compared to those who did not require intervention. This finding may reflect a broader association between perinatal complications and increased risk of colonization, possibly due

to early and intensive medical interventions, including antibiotic exposure and invasive procedures. Birth in hospital settings has also been associated with higher ESBL-PE colonization rates, likely linked to increased contact with healthcare environments where resistant organisms are more prevalent.[7] A recent study examining the presence of antibiotic resistance genes in mothers and their offspring in LMICs reported that difficult births - such as those involving emergency cesarean sections or preterm premature rupture of membranes (PPROM) - were associated with a higher likelihood of carrying β-lactamase genes.[34] These observations suggest that complicated deliveries and early neonatal interventions may serve as important risk factors for the acquisition of resistant bacteria, emphasizing the need for enhanced infection control practices and careful monitoring of antibiotic use in perinatal and neonatal care.

4.2 Strengths of the study

The prospective design of both cohorts, conducted in two distinct epidemiological settings, represents a major strength of this study. By including mothers at delivery and following their infants longitudinally for twelve months, the study provides valuable insights into the prevalence and acquisition dynamics of ESBL-PE within these diverse communities.

Furthermore, the comprehensive genomic analysis of ESBL-PE strains isolated from infants in community settings offers an in-depth understanding of the species, strain diversity, and resistance genes involved in colonization.

Together, these elements contribute to a nuanced and robust picture of ESBL-PE epidemiology, informing future prevention and control strategies tailored to different LMIC contexts.

4.3 Limitations of the study

The present study has some limitations. First, the two studies included in this analysis, BIRDY2 and PEEC NIC, do not share the same design, which hindered further comparisons between countries. In the BIRDY2 study, the high number of missing values that necessitated imputation may not fully capture the complexity and thoroughness of the data. Additionally, limited financial resources in Madagascar restricted the capacity to perform whole-genome sequencing on all isolates, potentially affecting the comprehensiveness of the genomic characterization in this setting.

Another limitation is the potential selection bias introduced by the difference between included and excluded infants for first acquisition analysis. Although there were no significant differences for maternal age and education, we found the area of residence with a significant difference between both groups. This may affect the generalizability of our findings, as the infants included may not fully represent the original population.

5. CONCLUSION / RECOMMENDATIONS / IMPLICATIONS

This study provides valuable insights into the prevalence, acquisition, and genomic diversity of ESBL-producing Enterobacterales in infants across two distinct low- and middle-income country settings. The findings highlight significant regional differences in species distribution. It also identifies key risk factors such as maternal colonization, cesarean delivery, antibiotic exposure, and perinatal complications. These results underscore the complex dynamics of early-life colonization by resistant bacteria and the critical role of both community and healthcare environments in shaping these patterns.

Moving forward, there is a clear need for continued longitudinal surveillance combining epidemiological, clinical, and genomic data to better understand transmission pathways and inform targeted interventions. Strengthening antimicrobial stewardship, infection prevention measures, and maternal health programs - especially around the time of delivery - will be crucial to curb the spread of ESBL-PE. Moreover, expanding research to include diverse LMIC settings will enhance the generalizability of findings and support the development of context-specific strategies to protect vulnerable newborns and infants from antibiotic-resistant infections.

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APPENDIX

Table A1. Prevalence of ESBL-PE at common timepoints in Madagascar and Cambodia.

Timepoints	Madagascar		Cambodia		Comparison Countries
	Positive/Total	Prevalence (95% CI)	Positive/Total	Prevalence (95% CI)	
At birth	115/323	35.6 [30.5 – 40.9]	77/145	53.1 [45.0 – 61.4]	**<0.001**
D28	57/274	20.8 [16.4 – 26.0]	74/141	52.4 [44.8 – 60.5]	**<0.001**
M3	65/262	24.8 [19.9 – 30.3]	77/141	54.6 [46.3 – 62.6]	**<0.001**
M6	50/224	22.3 [17.3 – 28.2]	66/142	46.4 [38.4 – 54.6]	**<0.001**
M12	53/242	21.9 [17.1 – 27.5]	73/140	52.1 [43.9 – 60.2]	**<0.001**
Mother	159/377	42.1 [37.2 – 47.2]	104/131	79.3 [71.6 – 85.4]	**<0.001**

Table A2. Species and Sequence Types in Cambodia at all timepoints.

Species	n (380)
Escherichia coli	275 (72.4%)
Klebsiella spp.	49 (12.9%)
Enterobacter spp.	30 (7.9%)
Others	26 (6.8%)

Species	n (380)
Escherichia coli	275 (72.4%)
Escherichia coli	274 (99.7%)
Escherichia fergusonii	1 (0.4%)
Enterobacter spp.	30 (7.9%)
Enterobacter cloacae	5 (16.7%)
Enterobacter hormaechei	23 (76.7%)
Enterobacter quasiroggenkampii	1 (3.3%)
Enterobacter roggenkampii	1 (3.3%)
Klebsiella spp.	49 (12.9%)
Klebsiella aerogenes	1 (2.0%)
Klebsiella pneumoniae	33 (67.3%)
Klebsiella quasipneumoniae	15 (30.6%)
Others	26 (6.8%)
Atlantibacter sp. ?	1 (3.8%)
Citrobacter amalonaticus	1 (3.8%)
Citrobacter cronae	1 (3.8%)
Citrobacter farmeri	2 (7.7%)
Citrobacter freundii	1 (3.8%)
Citrobacter portucalensis	1 (3.8%)
Citrobacter sedlakii	2 (7.7%)
Enterococcus faecalis	1 (3.8%)
Morganella morganii	1 (3.8%)
Phytobacter spp.	2 (7.7%)
Proteus mirabilis	13 (50.0%)

Escherichia coli	n (275)
Scheme ecoli_achtman_4	
131	38 (13.8%)
38	25 (9.1%)
10	13 (4.7%)
648	13 (4.7%)
1193	9 (3.3%)
1722	9 (3.3%)
354	8 (2.9%)
2914	6 (2.2%)
127	5 (1.8%)
421	5 (1.8%)
410	4 (1.5%)
44	4 (1.5%)
2083	4 (1.5%)
141	3 (1.1%)
155	3 (1.1%)
156	3 (1.1%)
206	3 (1.1%)
224	3 (1.1%)
226	3 (1.1%)
315	3 (1.1%)
349	3 (1.1%)
3580	3 (1.1%)
394	3 (1.1%)
457	3 (1.1%)
46	3 (1.1%)
1312	2 (0.7%)
1408	2 (0.7%)
179	2 (0.7%)
196	2 (0.7%)
2064	2 (0.7%)
216	2 (0.7%)
3032	2 (0.7%)
3052	2 (0.7%)
31	2 (0.7%)
3268	2 (0.7%)
405	2 (0.7%)
48	2 (0.7%)
542	2 (0.7%)
58	2 (0.7%)
6	2 (0.7%)
617	2 (0.7%)
69	2 (0.7%)
73	2 (0.7%)
969	2 (0.7%)
101	1 (0.4%)
1049	1 (0.4%)
10651	1 (0.4%)
1163	1 (0.4%)
12	1 (0.4%)
1246	1 (0.4%)
1290	1 (0.4%)
13	1 (0.4%)
130	1 (0.4%)
14786	1 (0.4%)
1588	1 (0.4%)
1638	1 (0.4%)
1674	1 (0.4%)
16857	1 (0.4%)
181	1 (0.4%)
2011	1 (0.4%)
2040	1 (0.4%)
2178	1 (0.4%)
218	1 (0.4%)
2280	1 (0.4%)
2461	1 (0.4%)
2705	1 (0.4%)
2758	1 (0.4%)
3033	1 (0.4%)
3640	1 (0.4%)
3941	1 (0.4%)
4040	1 (0.4%)
4681	1 (0.4%)
4682	1 (0.4%)
517	1 (0.4%)
5584	1 (0.4%)
6215	1 (0.4%)
6303	1 (0.4%)
636	1 (0.4%)
656	1 (0.4%)
6782	1 (0.4%)
6955	1 (0.4%)
7160	1 (0.4%)
7590	1 (0.4%)
8375	1 (0.4%)
8577	1 (0.4%)
93	1 (0.4%)
95	1 (0.4%)
998	1 (0.4%)
-	12 (4.4%)

Enterobacter spp.	n (30)
Scheme ecloacae	
114	4 (13.3%)
544	4 (13.3%)
923	3 (10.0%)
148	2 (6.7%)
109	1 (3.3%)
136	1 (3.3%)
144	1 (3.3%)
346	1 (3.3%)
40	1 (3.3%)
462	1 (3.3%)
479	1 (3.3%)
68	1 (3.3%)
84	1 (3.3%)
922	1 (3.3%)
-	5 (16.7%)
Scheme cronobacter	
419	2 (6.7%)

Klebsiella spp.	n (49)
Scheme klebsiella	
1308	4 (8.2%)
1035	3 (6.1%)
11	3 (6.1%)
307	3 (6.1%)
36	3 (6.1%)
138	2 (4.1%)
17	2 (4.1%)
334	2 (4.1%)
1304	1 (2.0%)
1322	1 (2.0%)
14	1 (2.0%)
1473	1 (2.0%)
15	1 (2.0%)
152	1 (2.0%)
1787	1 (2.0%)
18	1 (2.0%)
219	1 (2.0%)
2352	1 (2.0%)
252	1 (2.0%)
2558	1 (2.0%)
305	1 (2.0%)
3139	1 (2.0%)
3160	1 (2.0%)
3179	1 (2.0%)
394	1 (2.0%)
413	1 (2.0%)
414	1 (2.0%)
42	1 (2.0%)
48	1 (2.0%)
54	1 (2.0%)
5601	1 (2.0%)
570	1 (2.0%)
742	1 (2.0%)
7483	1 (2.0%)
-	3 (3.5%)
Scheme kaerogenes	
135	1 (2.0%)

Others	n (26)
Scheme cfreundii	
C. freundii	
1007	2 (7.7%)
124	9 (34.6%)
135	3 (11.5%)
230	1 (3.8%)
404	1 (3.8%)
674	1 (3.8%)
696	2 (7.7%)
714	1 (3.8%)
776	1 (3.8%)
948	1 (3.8%)
No scheme	
-	4 (15.4%)

Table A3. Species and Sequence Types in Madagascar for First ESBL-PE Acquisition.

Species	n (235)
Enterobacter spp.	86 (36.6%)
Klebsiella spp.	86 (36.6%)
Escherichia coli	42 (17.9%)
Others	21 (8.9%)

Species	n (235)
Escherichia coli	42 (17.9%)
Escherichia coli	41 (97.6%)
Shigella boydii	1 (2.4%)
Enterobacter spp.	86 (36.6%)
Enterobacter hormaechei	58 (67.5%)
Enterobacter kobei	14 (16.3%)
Enterobacter rongchengensis	5 (5.8%)
Enterobacter roggenkampii	4 (4.7%)
Enterobacter spp.	2 (2.3%)
Enterobacter quasiroggenkampii	1 (1.2%)
Enterobacter vonholyi	1 (1.2%)
Enterobacter asburiae	1 (1.2%)
Klebsiella spp.	86 (36.6%)
Klebsiella pneumoniae	70 (81.4%)
Klebsiella michiganensis	9 (10.5%)
Klebsiella quasipneumoniae	4 (4.7%)
Klebsiella variicola	2 (2.3%)
Klebsiella pasteurii	1 (1.2%)
Others	21 (8.9%)
?	3 (14.3%)
Atlantibacter hermannii	1 (4.8%)
Citrobacter bitternis	1 (4.8%)
Citrobacter cronae	1 (4.8%)
Citrobacter freundii	9 (42.9%)
Citrobacter sedlakii	1 (4.8%)
Citrobacter youngae	1 (4.8%)
Morganella morganii	2 (9.5%)
Leclercia adecarboxylata	2 (9.5%)

Escherichia coli	n (42)
Scheme ecoli_achtman_4	
131	7 (16.7%)
617	4 (9.5%)
38	3 (7.1%)
10	2 (4.8%)
405	2 (4.8%)
453	2 (4.8%)
58	2 (4.8%)
648	2 (4.8%)
656	2 (4.8%)
685	2 (4.8%)
1312	1 (2.4%)
155	1 (2.4%)
167	1 (2.4%)
2301	1 (2.4%)
2308	1 (2.4%)
3489	1 (2.4%)
410	1 (2.4%)
44	1 (2.4%)
450	1 (2.4%)
485	1 (2.4%)
6143	1 (2.4%)
7013	1 (2.4%)
746	1 (2.4%)
-	1 (2.4%)

Enterobacter spp.	n (86)
Scheme ecloacae	
32	12 (14.0%)
4	4 (4.8%)
1198	3 (3.5%)
148	3 (3.5%)
1712	3 (3.5%)
2895	3 (3.5%)
51	3 (3.5%)
666	3 (3.5%)
177	2 (2.3%)
50	2 (2.3%)
66	2 (2.3%)
9	2 (2.3%)
1065	1 (1.2%)
112	1 (1.2%)
113	1 (1.2%)
118	1 (1.2%)
133	1 (1.2%)
134	1 (1.2%)
144	1 (1.2%)
145	1 (1.2%)
1624	1 (1.2%)
171	1 (1.2%)
190	1 (1.2%)
24	1 (1.2%)
2713	1 (1.2%)
2945	1 (1.2%)
2967	1 (1.2%)
306	1 (1.2%)
346	1 (1.2%)
365	1 (1.2%)
41	1 (1.2%)
422	1 (1.2%)
564	1 (1.2%)
68	1 (1.2%)
691	1 (1.2%)
769	1 (1.2%)
824	1 (1.2%)
977	1 (1.2%)
-	17 (19.8%)
Scheme cronobacter	
604	1 (1.2%)

Klebsiella spp.	n (86)
Scheme klebsiella	
29	8 (9.3%)
307	8 (9.3%)
17	7 (8.1%)
39	6 (7.0%)
1605	4 (4.7%)
70	4 (4.7%)
985	4 (4.7%)
101	3 (3.5%)
4	3 (3.5%)
711	3 (3.5%)
14	2 (2.3%)
2	2 (2.3%)
3224	2 (2.3%)
45	2 (2.3%)
1109	1 (1.2%)
1119	1 (1.2%)
147	1 (1.2%)
1557	1 (1.2%)
215	1 (1.2%)
219	1 (1.2%)
243	1 (1.2%)
309	1 (1.2%)
348	1 (1.2%)
37	1 (1.2%)
394	1 (1.2%)
48	1 (1.2%)
716	1 (1.2%)
7214	1 (1.2%)
8	1 (1.2%)
-	3 (3.5%)
Scheme koxytoca	
82	4 (4.7%)
177	1 (1.2%)
603	1 (1.2%)
-	4 (4.7%)

Others	n (21)
Scheme cfreundii	
C. freundii	
95	7 (33.3%)
116	1 (4.8%)
62	1 (4.8%)
1182	1 (4.8%)
242	1 (4.8%)
-	1 (4.8%)
No scheme	
-	9 (42.8%)

Table A4. Genes for Cambodia across follow-up and Madagascar for First Acquisition.

Genes Cambodia	n (489)
blaCTX-M-15	151 (30.9%)
blaCTX-M-27	105 (21.5%)
blaCTX-M-55	70 (14.3%)
blaCTX-M-14	50 (10.2%)
blaDHA-1	26 (5.3%)
blaCTX-M-24	17 (3.5%)
blaCMY-42	15 (3.1%)
blaCTX-M-65	12 (2.5%)
blaCTX-M	9 (1.8%)
blaCMY-2	9 (1.8%)
blaCTX-M-9	6 (1.2%)
blaCTX-M-3	5 (1.0%)
blaSHV	4 (0.8%)
blaSHV-12	3 (0.6%)
blaSHV-2A	3 (0.6%)
blaCMY	2 (0.4%)
blaCTX-M-32	1 (0.2%)
blaTEM	1 (0.2%)

Genes Madagascar	n (559)
blaCTX-M-15	429 (76.7%)
blaSHV-187	29 (5.2%)
blaCTX-M-27	22 (3.9%)
blaCTX-M-14	13 (2.3%)
blaDHA-1	12 (2.1%)
blaOXY-5-2	9 (1.6%)
blaSHV-2A	7 (1.3%)
blaADC	4 (0.7%)
blaSHV	4 (0.7%)
blaADC-130	3 (0.5%)
blaCTX-M-13	3 (0.5%)
blaDHA	3 (0.5%)
blaCMY-2	3 (0.5%)
blaCTX-M	2 (0.4%)
blaCTX-M-3	1 (0.2%)
blaCTX-M-65	1 (0.2%)
blaCTX-M-9	1 (0.2%)
blaL2	1 (0.2%)
blaOXY	1 (0.2%)
blaOXY-1-18	1 (0.2%)
blaOXY-1-2	1 (0.2%)
blaOXY-1-7	1 (0.2%)
blaOXY-2-7	1 (0.2%)
blaOXY-4-1	1 (0.2%)
blaOXY-5-1	1 (0.2%)
blaOXY-5-5	1 (0.2%)
blaADC-165	1 (0.2%)
blaADC-242	1 (0.2%)
blaADC-269	1 (0.2%)
blaADC-6	1 (0.2%)

Table A5. Carbapenemase-producing genes for Cambodia across follow-up and Madagascar for First Acquisition.

Genes Cambodia	n (7)
blaOXA-48	3 (42.9%)
blaOXA-181	2 (28.6%)
blaNDM-1	1 (14.3%)
blaNDM-5	1 (14.3%)

Genes Madagascar	n (9)
blaNDM-1	3 (33.3%)
blaL1	1 (11.1%)
blaNDM-5	1 (11.1%)
blaOXA-337	1 (11.1%)
blaOXA-67	1 (11.1%)
blaOXA-712	1 (11.1%)
blaOXA-773	1 (11.1%)

ABSTRACT IN FRENCH

Contexte: Les Entérobactéries productrices de bêta-lactamases à spectre étendu Entérobactéries productrices (E-BLSE) représentent un enjeu majeur de santé publique, particulièrement dans les pays à faible et moyen revenu, en contribuant à la résistance antimicrobienne chez les nouveau-nés et nourrissons.

Objectifs: Estimer la prévalence de la colonisation par les E-BLSE chez les nourrissons au Cambodge et à Madagascar, investiguer les caractéristiques génomiques et identifier les facteurs de risque associés à la première acquisition chez les nourrissons malgaches.

Méthodes: L'étude a été menée dans des zones urbaines et semi-rurales au Cambodge et à Madagascar. Les mères ont été enrôlées au cours du troisième trimestre de grossesse et les nouveau-nés inclus à la naissance et suivis jusqu'à un an. Les selles maternelles à l'accouchement et les selles des nouveau-nés à 1, 3, 6 et 12 mois ont été collectées pour déterminer les taux de prévalence. Les E-BLSE ont subi un séquençage complet du génome. L'incidence de la première acquisition de E-BLSE chez les nourrissons malgaches a été évaluée. Un modèle de Cox à risques proportionnels a été réalisé pour les trois premiers mois de vie.

Résultats: Au Cambodge, les taux de prévalence variaient de 46,5% [IC95%:38,4–54,6%] à 54,6%[46,3–62,6]. À Madagascar, la prévalence la plus élevée était de 35,6%[30,5–40,9], tandis que la plus faible était de 20,8% [16,4–26,0]. La prévalence chez les mères cambodgiennes était significativement plus élevée (79,4%[71,6–85,4]) par rapport à Madagascar (42,2%[37,2–47,2]) (p>0,001). L'espèce la plus prévalente au Cambodge était *Escherichia coli* (72,4%,n=275/380), tandis qu'à Madagascar, *Klebsiella spp.* et *Enterobacter spp.* avaient les taux de première acquisition les plus élevés (36,6% chacun, n=86/233). L'incidence de la première acquisition à Madagascar était de 26,6 pour 1000 jours-nourrisson [23,2–30,3]. Les facteurs de risque indépendants pour la première acquisition incluaient le portage maternel d'E-BLSE (HRa1,66[1,21–2,28]), l'accouchement par césarienne (2,85[1,95–4,17]), la réanimation (1,74[1,18–2,56]) et l'utilisation d'antibiotiques (1,54[1,05–2,26]).

Conclusion: Cette étude révèle des différences régionales significatives dans la distribution des espèces et la complexité de la dynamique de colonisation précoce par les E-BLSE dans la communauté, soulignant la nécessité d'une surveillance continue pour mieux cibler les interventions visant à prévenir les infections résistantes aux antibiotiques.

Mots-clés: E-BLSE, Acquisition, Colonisation, Résistance antimicrobienne, Facteurs de risque, Nourrissons, Pays à faible et moyen revenu