Listériose materno-néonatale en 2024

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Listeria monocytogenes

Growth at 4°C, does not alter the taste of food

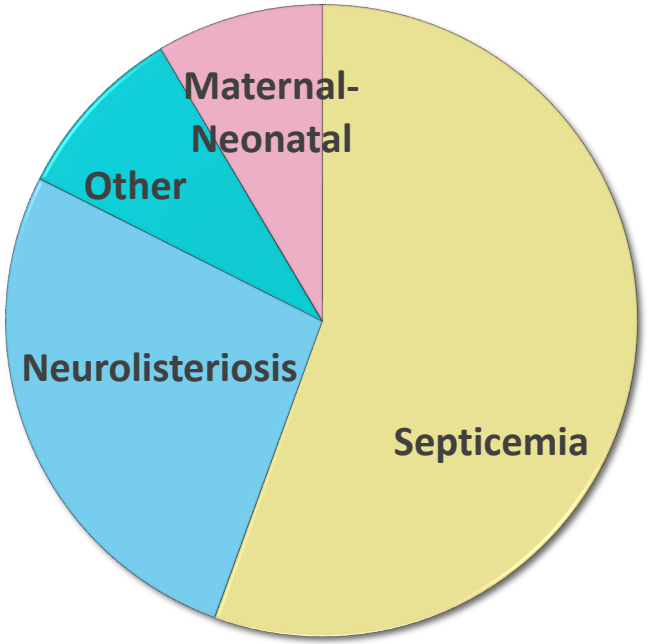
A strongly monitored infection

→ mandatory reporting

A rare infection

→ incidence $5/10^6$ in Europe

→ data largely lacking in emerging countries



Distribution of Listeriosis cases

%

NRCL data 2019

De Valk Isopol 2016

Maertens de Noordhout C LID 2014

A foodborne infection

Ubiquitous distribution, diversity of food sources

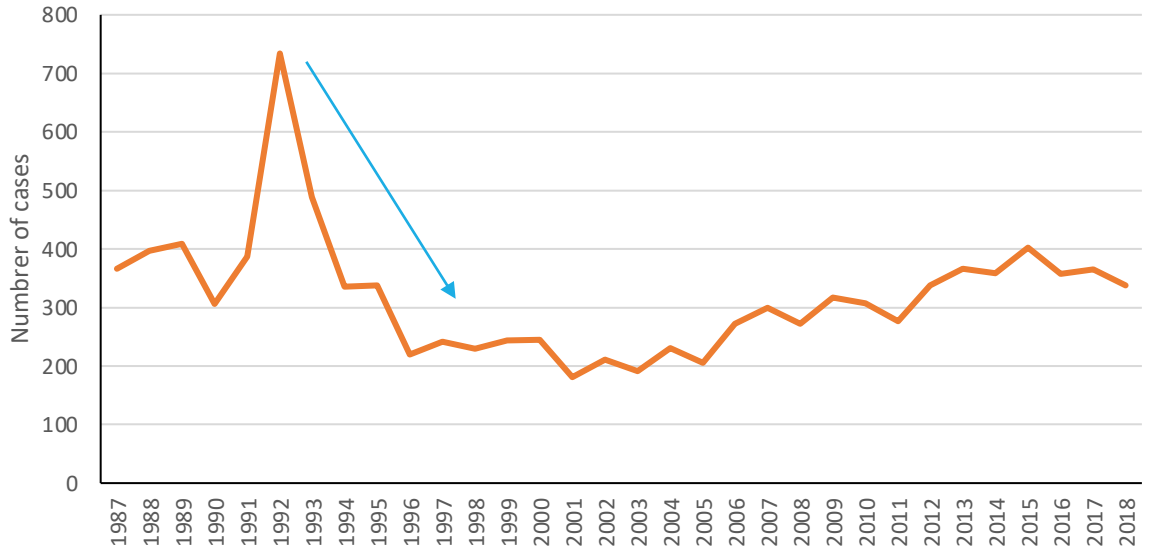
Dalton NEJM1997
Aureli NEJM 2000

Raw milk dairy products

Meat spreads patés

Ready to eat food

1980



A foodborne infection

Ubiquitous distribution, diversity of food sources

Dalton NEJM1997
Aureli NEJM 2000

Polony in South Africa (2016-7)

Raw milk dairy products

Meat spreads patés

Ready to eat food

Sprouts (USA 2009)

Cantaloupe (USA 2011)

Caramel apples (Canada 2014)

1980 → 2020



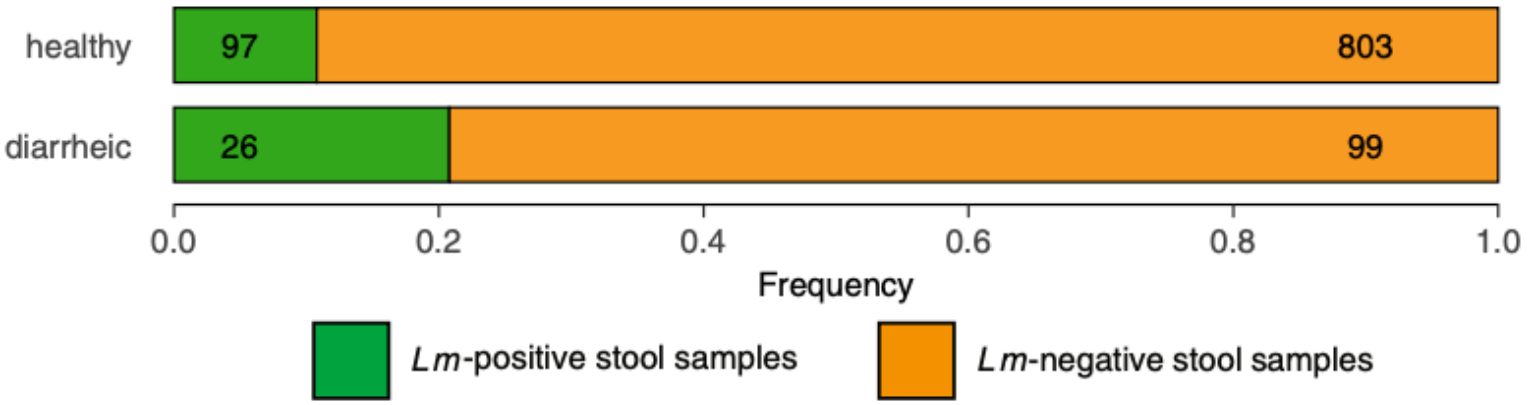




Listeria monocytogenes

Growth at 4°C, does not alter the taste of food

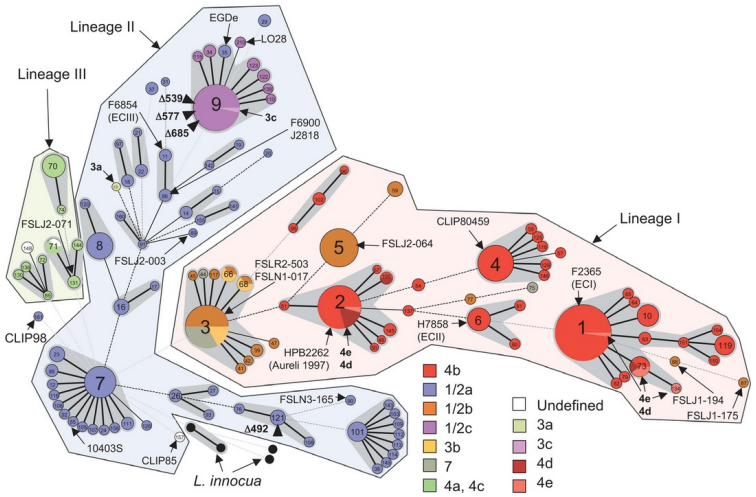
10% fecal colonization (20% in diarrheic stools)

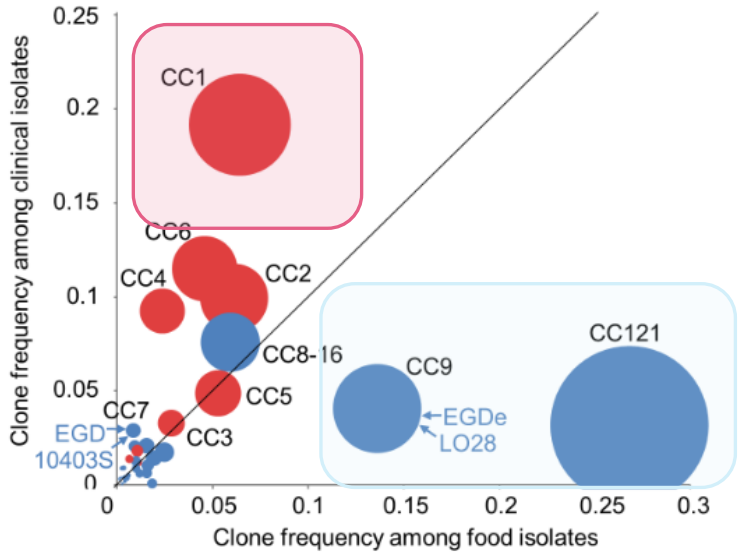


Hafner Nat Comm 2021

Listeria monocytogenes

A structured population





Hyper and

hypovirulent clones

CC1 : Dairy products

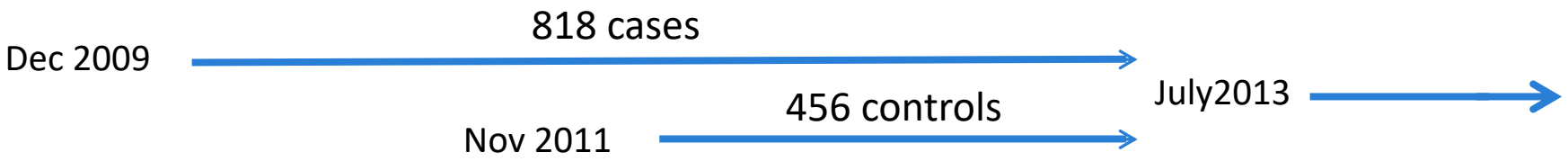
CC9-121 : Meat products

Ragon PLoS Pathogens 2008
Maury & Tsai Nature Genetics 2016
Moura EID 2017
Maury Nature Communic 2019

The MONALISA study

- Multicentric Observational National Analysis of LISteriosis and *ListeriA*
- Prospective case-control study

For each patient :
Clinical data > 500 items / patient D0 and >M3
Isolate et Biobank (PBMC, DNA, serum, plasma)



Charlier LID 2017

Maternal-neonatal listeriosis

Defined by the documentation of Lm in any sample of maternal, fetal or neonatal origin (< 4 weeks)

→ Distinctive definition from other maternal-fetal infections that reflect a distinctive pathophysiology, with hematogenous seeding

Maternal-neonatal listeriosis

Is there a specific patient profile?

Immunosuppression ?	**No** (92% of cases)
Food exposure ?	**Yes, but not discriminant :** 100% of cases and controls

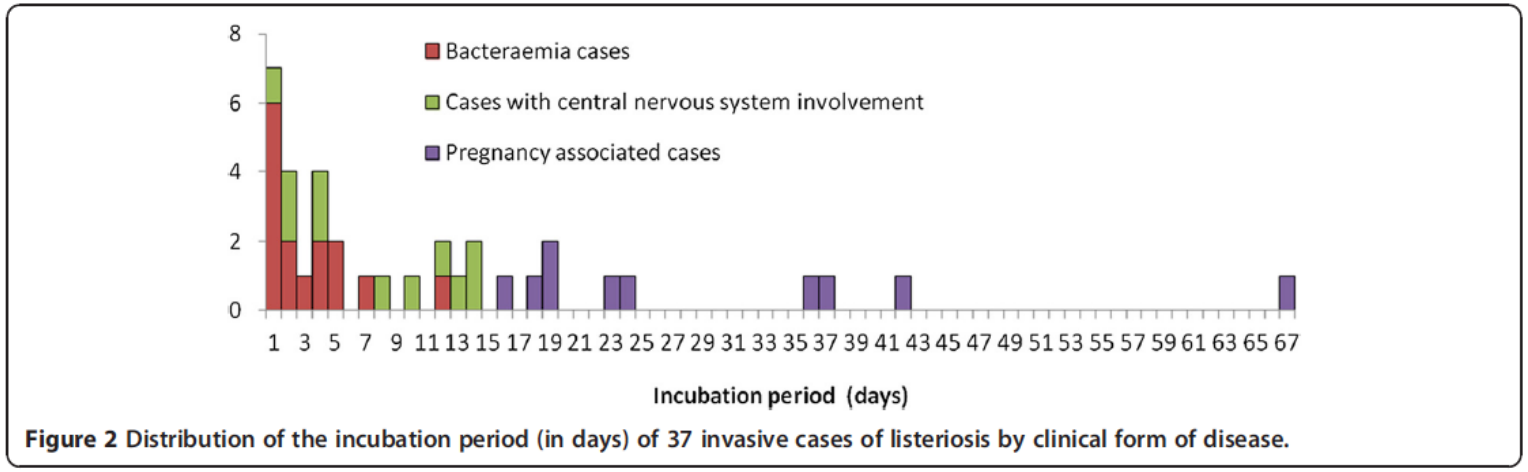


Figure 2 Distribution of the incubation period (in days) of 37 invasive cases of listeriosis by clinical form of disease.

	Med. incubation
Septicemia	**2d [1-12j]**
Neurolisteriosis	**9d [1-14d]**
Maternal listeriosis	**27.5d [17-67d]**

Goulet BMC Infect Dis 2012

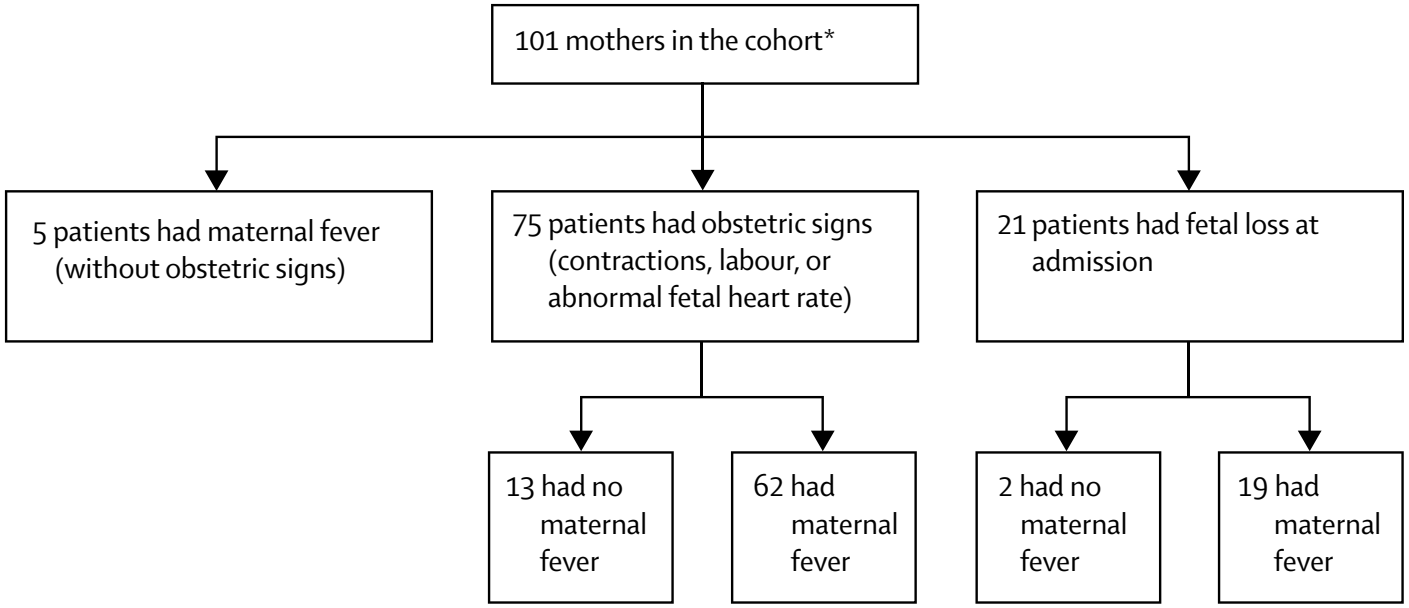
Maternal-neonatal listeriosis

Is there a specific patient profile?

Immunosuppression ?	**No** (92% of cases)
Food exposure ?	**Yes, but not discriminant :** 100% of cases and controls
Specific groups ?	**Yes, over-representation of mothers of African origin** → 35/107 (33%) (3x more than expected in the general population) → Cf. USA (Mexican minorities) GB (deprived background)
Specific term ?	**Yes and No, mostly 3rd trimester, but not always :** T1 =3, T2 =28, **T3 = 70**

Maternal-neonatal listeriosis

What is maternal presentation?



Maternal signs	
Time interval first symptom to diagnosis	3j
Fever	83%
Flu-like symptoms	35%
Diarrhea	8%
neurolisteriosis	0%

Adriani CMI 2012
Charlier LID 2017

- Almost no meningitis : 7 in the published literature

Maternal-neonatal listeriosis

How to diagnose it?

Serological testing is useless

- Poor specificity
- Delayed positivity

PCR (hly or 16s)

- Validated only in the CSF
- May be valuable in the placenta

Maternal samples	
Blood	47/85 (55%)
Cervical/vaginal swab	14/54 (26%)
Infant samples	
Placenta	50/64 (78%)
Blood	31/75 (41%)
CSF	10/56 (18%)
Amniotic fluid	8/15 (53%)
Peripheral samples	
Gastric aspirate	52/67 (78%)
Anus	18/26 (69%)
Ear	26/37 (70%)
Pharynx	10/20 (50%)
Other samples†	2/2 (100%)

Charlier LID 2017

Maternal-neonatal listeriosis

A gloomy outcome

Outcome	Total cases N=107	T1 [0-14 WG[N=3	T2 [14-28 WG[N=28	T3 [28-41 WG] N=70
Normal	5/107 (5%)	-	11%	3%
Fetal loss	26/107 (24%)	**100%**	**74%**	**3%**
Premature delivery	48/107 (45%)		14%	63%
Abnormal delivery	22/107 (21%)	-	-	31%
Late onset disease	6/107 (6%)	-	-	-

Benign maternal infection in Europe
No maternal death
No meningitis

Charlier LID 2017

Maternal-neonatal listeriosis

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Premature delivery	48/107 (45%)		14%	63%
Abnormal delivery	22/107 (21%)	-	-	31%
Late onset disease	6/107 (6%)	-	-	-

Severe obstetrical/infant prognosis

Only **10%** of pregnancies face uneventful outcome
> **80% major complications** (fetal loss, EOD, preterm < 32WG)
Term at the moment of infection is the main prognostic factor : No fetal loss beyond 32 WG
No fetal loss after 72 hours of adequate management

Neonatal listeriosis

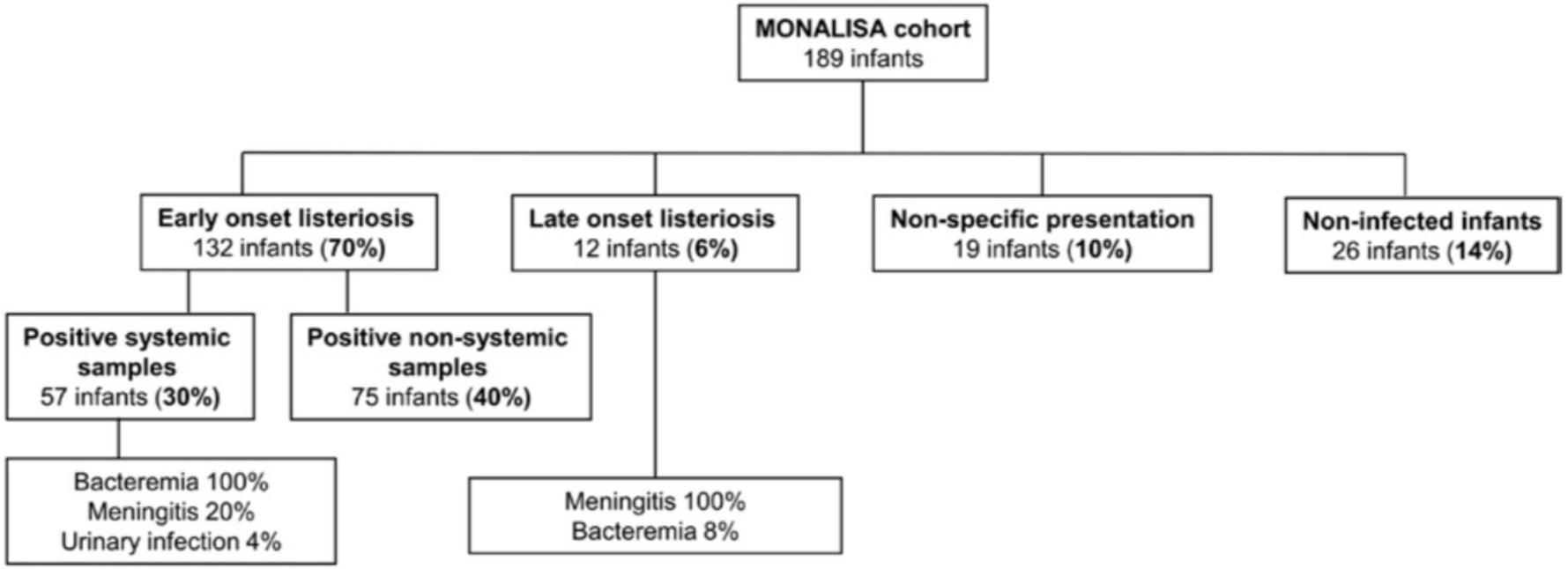

Figure 2. Distribution of the 189 infants of the cohort according to their clinical and biological presentation. Abbreviation: MONALISA, Multicentric Observational NAtional Study on LISteriosis and ListeriA.

Charlier CID 2022

Neonatal listeriosis

A gloomy outcome

57% premature deliveries
With 22% severe prematurity

Characteristic	Cohort, N = 189
Sex ratio	
Male	108/189 (57%)
Female	81/189 (43%)
Maternal origin[e]	
France	99/187 (53%)
Europe	13/187 (7%)
Africa	51/187 (27%)
Other	14/187 (3%)
Maternal immunosuppressive comorbidity[e,f]	17/187 (9%)
Median gestational age at birth (interquartile range, 25–75), WG	36 (33–39)
Premature delivery <37 WG	108/189 (57%)
Extremely preterm birth 24–27 WG	9/189 (5%)
Very preterm birth 28–31 WG	33/189 (17%)
Moderate preterm birth 32–33 WG	25/189 (13%)
Late preterm birth 34–36 WG	41/189 (22%)

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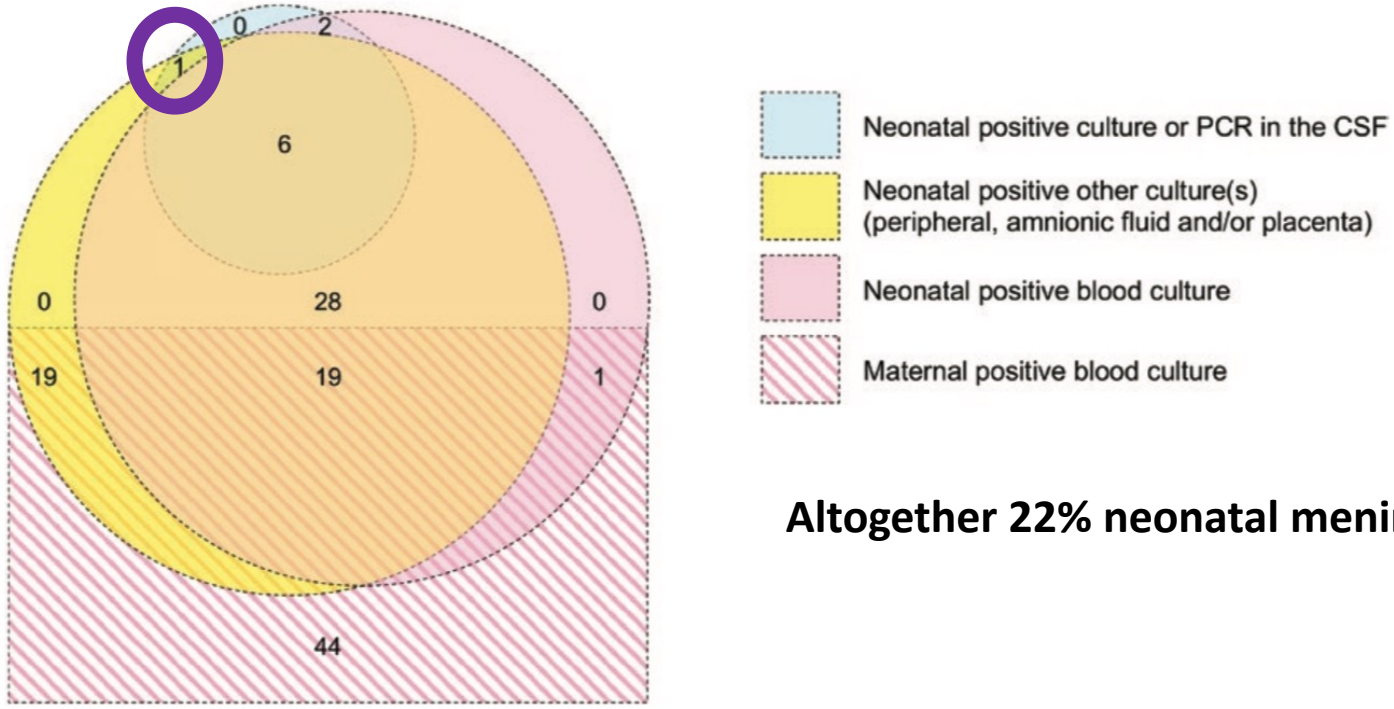
Neonatal listeriosis

Table 2. Clinical and Laboratory Features of the Study Population

	Cohort, N = 189	S Infants, N = 57	NS Infants, N = 75	M Infants, N = 45	Infants With Late-Onset Infection N = 12[a]	*P* Value S vs NS vs M[b]	*P* Value S vs NS[c]
Clinical features							
Any clinical sign	133/189 (70%)	56/57 (98%)	58/75 (77%)	7/45 (16%)	12/12 (100%)	<.0001	<.0001
Temperature >38°C	38/189 (20%)	15/57 (26%)	9/75 (12%)	3/45 (7%)	11/12 (92%)	.01	.03
Acute respiratory distress symptoms[d]	106/189 (56%)	52/57 (91%)	51/75 (68%)	3/45 (7%)	2/12 (17%)	<.0001	.001
Cardiocirculatory symptoms[e]	39/189 (21%)	26/57 (46%)	13/75 (17%)	0/45	0/12	<.0001	.0004
Neurological symptoms[f]	42/187 (22%)	24/56 (43%)	13/74 (18%)	2/45 (4%)	3/12 (25%)	<.0001	.002
Seizures	5/187 (3%)	3/56 (5%)	1/74 (1%)	0/45	1/12 (8%)	...	...
Median APGAR 1-minute score (IQR, 25–75)	7 (4–10)	5 (2–8)	5 (2–9)	10 (9–10)	10 (10–10)	...	...
Median APGAR 5-minute score (IQR, 25–75)	9 (8–10)	8 (7–9)	8 (6–10)	10 (10–10)	10 (10–10)	...	...
APGAR 5-minute score <7	36/189 (19%)	11/57 (19%)	23/75 (31%)	2/45 (4%)	0/12	.002	.14
Skin lesion[g]	19/186 (10%)	13/56 (23%)	6/73 (8%)	0/45	0/12	<.0001	.01
Macular and/or papular rash	9/186 (5%)	5/56 (9%)	4/73 (5%)	...	...	...	...
Purpura	5/186 (3%)	4/56 (7%)	1/73 (1%)	...	...	...	...
Vesicular and/or pustular	5/186 (3%)	4/56 (7%)	1/73 (1%)	...	...	...	...
Blood chemical tests							
Median C-reactive protein (IQR, 25–75), mg/L[h]	49 (11–96)	89 (53–127)	47.5 (23–97)	3 (1.75–6)	10 (4–24)	<.0001	<.001
C-reactive protein <10 mg/L	42/171 (25%)	2/57 (4%)	11/74 (15%)	23/28 (82%)	6/12 (50%)	<.0001	.0002
Median serum procalcitonin (IQR, 25–75), ng/mL	1 (.21–13)	23 (5–44)	4 (1–19)	.12 (.03–.17)	.27 (.18–.4)	<.0001	.11
Serum procalcitonin <.5 ng/mL[i]	16/39 (41%)	0/9	2/14 (14%)	6/6 (100%)	8/10 (80%)	<.0001	.50
Blood count							
Median leucocyte count (IQR, 25–75), cells per μL[j]	10 635 (6450–16 825)	7790 (482(-11 750)	11 000 (6800–15 400)	14 300 (9035–18 480)	21 980 (18 150–22 625)	<.0001	.04
Median polymorphonuclear cells (IQR, 25–75), cells per μL[k]	5490 (3168–10 038)	3900 (1470–6600)	5520 (3214–8725)	6670 (4290–18 480)	3655 (1750–5500)	.0001	.04
Monocytopenia[l]	11/110 (10%)	3/32 (9%)	7/53 (13%)	0/19	0/6	.40	.73

Neonatal listeriosis

A gloomy outcome



Altogether 22% neonatal meningitis

Figure 1. Distribution of culture-positive samples in the 177 infants without late-onset listeriosis (blue, infant CSF; pink, infant blood sample; yellow, other positive infant sample (gastric fluid, ear, skin, amnionic fluid, or placenta); hatched pink, maternal blood culture). Maternal data are missing for 4 mothers (for detailed maternal microbiological features, see Supplementary Table 1). Abbreviations: CSF, cerebrospinal fluid; PCR, polymerase chain reaction.

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Neonatal listeriosis

Long term outcome

Long-term neurological and neurodevelopmental outcome of neonatal listeriosis in France: a prospective, matched, observational cohort study

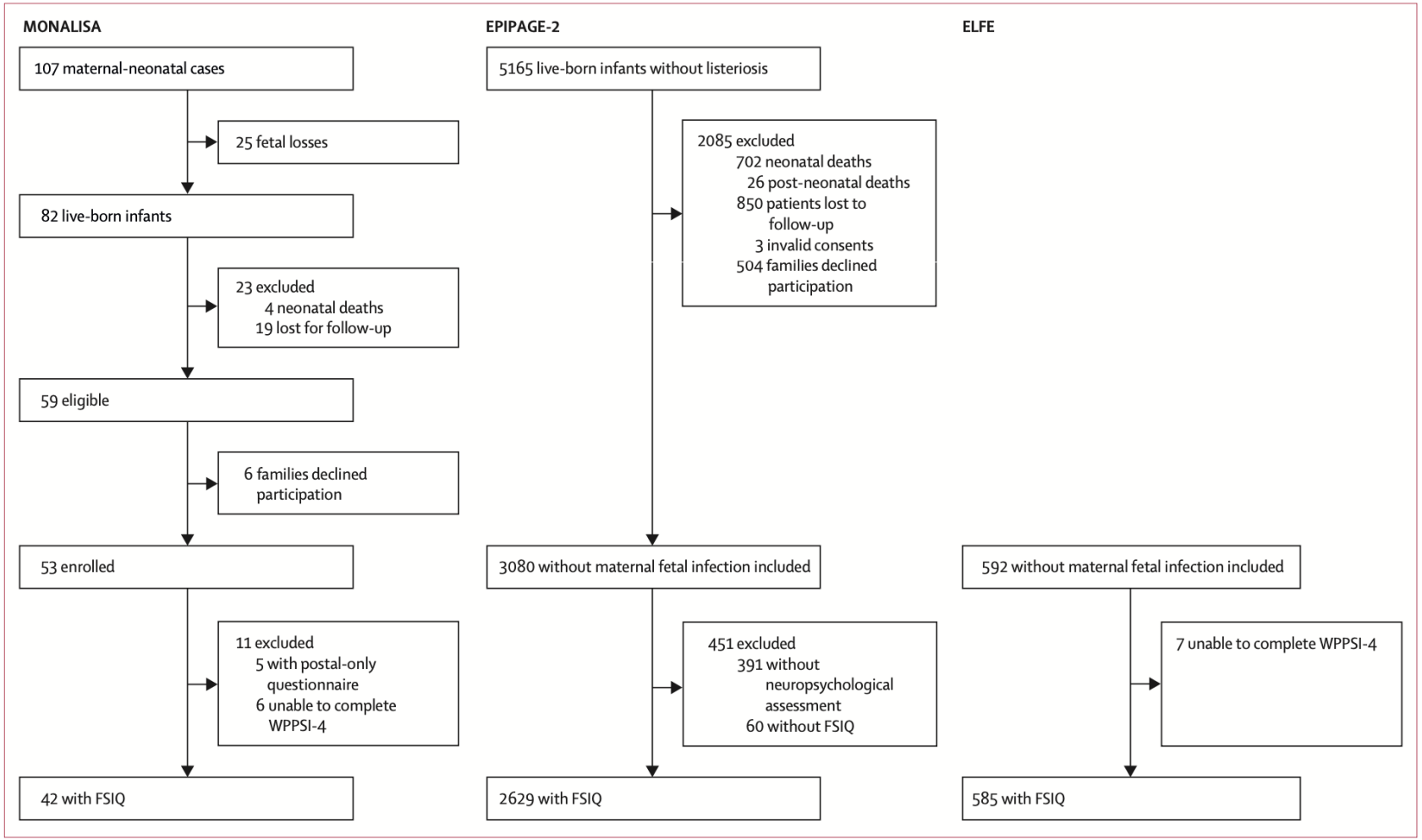

Figure: **Study profile**
FSIQ=Full Scale Intelligence Quotient. WPPSI-4=Wechsler Preschool and Primary Scale of Intelligence, fourth edition.

Charlier Lancet CAH 2024

Neonatal listeriosis

Long term outcome

Long-term neurological and neurodevelopmental outcome of neonatal listeriosis in France: a prospective, matched, observational cohort study

	n/N (%)	Unadjusted analysis		Adjusted for maternal SES and sex of the child		Further adjusted for mother's country at birth	
		RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
At least one neurodevelopmental disability							
With maternal–neonatal listeriosis (MONALISA BABY)	16/40 (40%)	1·12 (0·74 to 1·72)	0·59	0·99 (0·65 to 1·51)	0·98	0·99 (0·65 to 1·51)	0·97
Without maternal–neonatal listeriosis (EPIPAGE-2 and ELFE)	43/120 (36%)	1	..	1	..	1	..
FSIQ lower than –1 SD							
With maternal–neonatal listeriosis (MONALISA BABY)	12/38 (32%)	1·06 (0·60 to 1·85)	0·84	0·95 (0·56 to 1·63)	0·86	0·92 (0·54 to 1·54)	0·74
Without maternal–neonatal listeriosis (EPIPAGE-2 and ELFE)	35/114 (31%)	1	..	1	..	1	..
Mean FSIQ quantitative variable							
With maternal–neonatal listeriosis (MONALISA BABY)	98·13 (13·44)	–3·64 (–8·87 to 1·59)	0·17	–2·91 (–8·77 to 2·94)	0·33	–2·39 (–8·03 to 3·25)	0·41
Without maternal–neonatal listeriosis (EPIPAGE-2 and ELFE)	101·54 (16·07)	0	..	0	..	0	..

Denominators denote the number of infants for which the information is available. RR was computed with conditional Poisson regression for qualitative variables, and β (95% CI) was computed with generalised estimating equation for quantitative variable. Unexposed children were matched to exposed children (from the MONALISA cohort) on their gestational week at birth. Children with late-onset listeriosis were not retained for this analysis. FSIQ=Full Scale Intelligence Quotient. RR=relative risk. SES=socioeconomic status.

Table 4: **Neurological and neurodevelopmental outcomes of children with neonatal listeriosis (MONALISA) at 5 years and gestational age-matched children (EPIPAGE-2 and ELFE)**

Charlier Lancet CAH 2024

Neonatal listeriosis

Table 4. Antibiotic Treatment and Outcome of the Study Population

	Cohort, N = 189	S Infants, N = 57	NS Infants, N = 75	M Infants, N = 45	Infants With Late-Onset Infection, N = 12[a]	*P* Value S vs NS vs M[b]	*P* Value S vs NS[c]
Outcome							
In-hospital death	5/189 (3%)	2/57 (4%)	3/75 (4%)	0/45 (0)	0/45 (0)	.41	.88
Intensive care unit management	94/189 (50%)	39/57 (68%)	40/75 (53%)	8/45 (18%)	4/12 (33%)	<.0001	.11
Median hospital stay (n), days	16 (8–25) (171)	21 (12–28) (55)	16 (10–30) (71)	6 (4–10) (5)	21 (17–22) (12)	<.0001	.67

5% mortality is much lower than previously reported

- 30% in Europe 1960-1990
- 24% in Taiwan

MacLauchlin Epid Infect 1990
Tai J. Microb, Immunol and Infect 2019

Charlier CID 2022

Neonatal listeriosis

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Intensive care unit management	94/189 (50%)	39/57 (68%)	40/75 (53%)	8/45 (18%)	4/12 (33%)	<.0001	.11
Median hospital stay (n), days	16 (8–25) (171)	21 (12–28) (55)	16 (10–30) (71)	6 (4–10) (5)	21 (17–22) (12)	<.0001	.67
Intraventricular hemorrhage (n/prematurely born infants)	25/108 (23%)	12/39 (31%)	13/58 (22%)	0/11 (0)	…	.1	.35
Severe intraventricular hemorrhage[f]	12/25 (48%)[g]	8/39 (21%)[g]	4/58 (7%)	0/11 (0)	…	.003	.04
SBPD (n/prematurely born infants)[h]	3/189 (2%)	1/57 (2%)	1/75 (1%)	1/45 (2%)	…	.93	.84
Necrotizing enterocolitis (n/prematurely born infants)	0/189	…	…	…	…	…[1]	…[1]
Major adverse outcome (death and/or severe brain injury and/or SBDP)	17/189 (9%)	10/57 (18%)	6/75 (8%)	1/45 (2%)	…	.03	.11

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Neonatal listeriosis

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Outcome							
Maternal antibiotic treatment							
Prescription of anti-*Listeria* antibiotic before birth	38/189 (20%)	2/57 (4%)	17/75 (23%)	33/45 (73%)	0/12 (0%)	<.0001	.002
Median duration of anti-*Listeria* antibiotic before birth	0 (0–1)	8 (1–14)	1 (1–3)	56 (10–76)	…	<.0001	.57

Maternal antibiotic therapy ≥ 1 day before delivery

→ OR of 0.05 (95% CI .006–.21; *P* < .0001 of positive systemic infant sample

→ OR of 0.06 (95% CI, .02–.14; *P* < .0001) of any infant positive sample.

→ OR of 0.23 (95% CI, .09–.51; *P* < .0001) of neonatal initialseverity,

= requirement for inotropic drugs and/or fluid resuscitation and/or mechanical ventilation at birth

Charlier CID 2022

Maternal-neonatal listeriosis

Which maternal treatment?

No trial, low grade recommendations

Treatment must be preemptive

- Presentation is non specific
- Diagnosis is delayed and blood culture are not sensitive (45% negativity)
- **Early maternal treatment reduces infant's severity**

→ maternal fever without additional sign, +/- documented exposure

What preemptive treatment ?

- Failures with preemptive amoxicillin > 3g /d, > 5days
- Prefer amoxicillin 4-6g/d for 10 days

Charlier CMI 2012
Hof, FEMS Immun Med Microbiol 2003, Penn AAC 1982

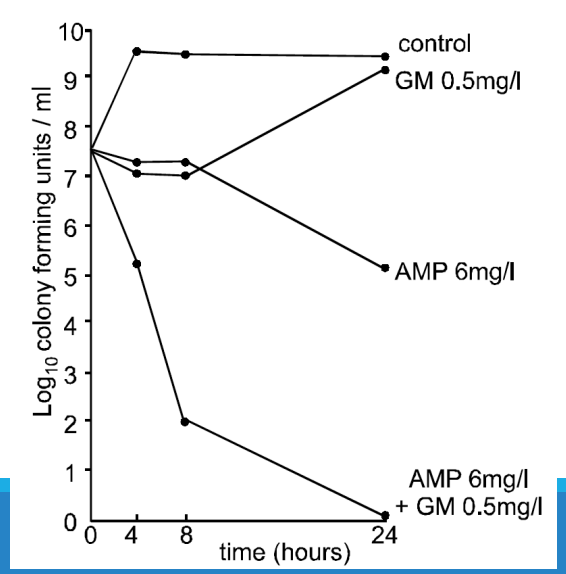
Prise en charge données *in vitro*

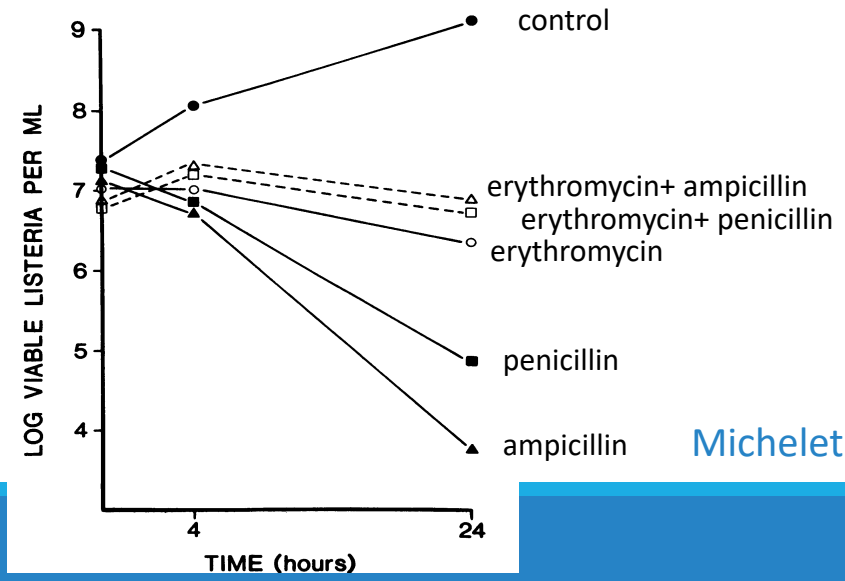
- ✓**Résistance naturelle**
- ✓Pas d'émergence de résistance antibiotique
- ✓Peu de molécules bactéricides *in vitro*

C3G,
Aztréonam,
Oxacilline,
Clindamycine,
Acide fusidique,
Acide nalidixique
Fosfomycine

Prise en charge données *in vitro*

- ✓**Résistance naturelle**
- ✓Pas d'émergence de résistance antibiotique
- ✓Peu de molécules bactéricides *in vitro*
- ✓Combinaisons antagonistes *in vitro*



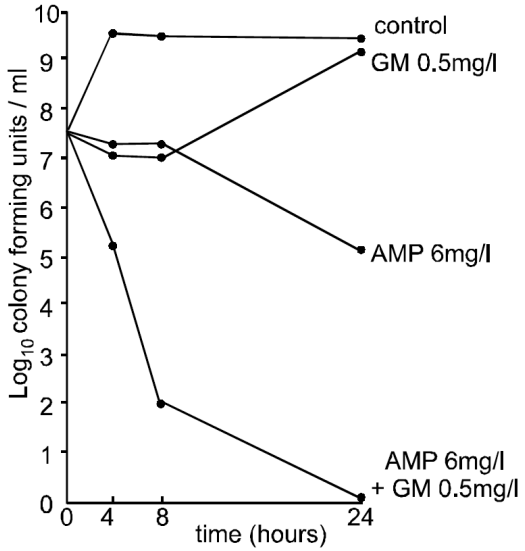


Penn AAC 1982
Hof CMR 1997
Naim 1995
Grayo AAC 2008
Tuazon AAC 1982
Winslow AAC1982
Scheld RID 1083
Michelet AAC 1994 and 1998

Maternal-neonatal listeriosis

Which maternal treatment?

For documented cases



- **Amoxicillin 100mg/kg/d 21 days**
- **Gentamicin 5mg/kg/d 3-5 d**
- **Cotrimoxazole** (avoid first trimester): 800/160 bid
- Avoid macrolides that are bacteriostatic and do not cross the placenta

Charlier CMI 2012
Hof, FEMS Immunology and Medical Microbiology, 2003, Penn AAC 1982

Maternal-neonatal listeriosis

Which maternal treatment?

1 rst line	2 nd line	3 rd line
Septicemic/ MN **Amoxicillin** 100mg/kg/d 14-21d + **Gentamicin** 5 mg/kg /d, 3-5 d **Neurolisteriosis** **Amoxicillin** 200mg/kg/d 21j + **Gentamicin** 5 mg/kg /d 3-5 d	**Cotrimoxazole** PO : (800/160) : 1 x 2 ou 3/d, 14-21d + **Gentamicin** 5 mg/kg /d 3-5 d	**Meropenem** IV 2g x 3/d or **Vancomycin** Loading dose 15mg/kg then 30mg/kg/d , 14-21d + **Gentamicin** 5 mg/kg /d 3-5 d

Documented failure of preemptive treatment in case of maternal fever For the amoxicillin 3g/d 5d regimen →amoxicillin > 3g/d > 5d

Listériose MN
Quelle prévention?

Lavage Mains

Aliments à vraiment éviter ?

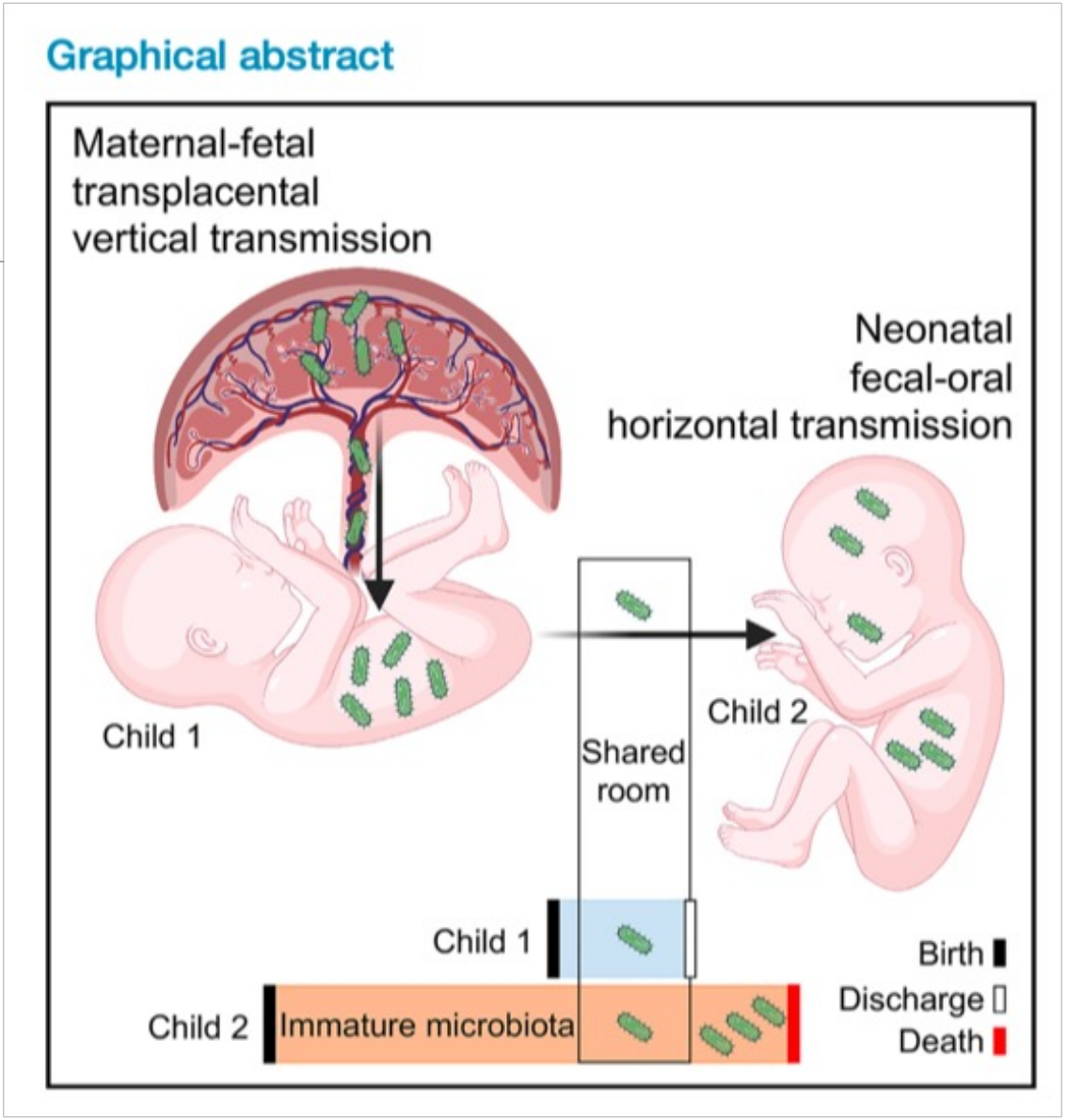
- Eviter le lait cru
- Eviter les charcuteries artisanales

Pour éviter tout risque avec le fromage : sans croûte, pâte cuite, pasteurisée

Listériose MN
Quelle prévention?

Transmission nosocomiale possible

Isolement contact recommandé



Charlier Cell Med Report 2023

Traitement post exposition

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RÉPUBLIQUE FRANÇAISE

AVIS DU CONSEIL SUPERIEUR D'HYGIENE PUBLIQUE DE FRANCE
(approuvé le 29 juin 1999)

SUR L'OPPORTUNITE D'UNE ANTIBIOPROPHYLAXIE POUR LES PERSONNES AYANT CONSOMME UN ALIMENT CONTAMINE PAR *LISTERIA MONOCYTOGENES*

Considérant :

- qu'il n'y a pas de données dans la littérature qui permettent d'apprécier réellement le risque lié à la consommation d'un aliment contaminé ;
- que les éléments recueillis par le CNR des *Listeria* et les données de l'InVS ont montré que le nombre de cas humains identifiés après différentes alertes alimentaires a toujours été extrêmement faible par rapport au nombre estimé de personnes ayant consommé l'aliment contaminé ;
- qu'il n'y a pas d'exemple, à sa connaissance, de pays recommandant une antibioprophylaxie à la suite de consommation d'aliment contaminé par *Listeria monocytogenes* ;
- qu'en revanche, la recommandation faite aux populations à risque est de consulter un médecin sans délai en cas de fièvre ou syndrome grippal durant les deux mois suivant la consommation d'un aliment contaminé ;

La section des maladies transmissibles du Conseil supérieur d'hygiène publique de France émet l'avis suivant :

En raison de la rareté des cas survenant après consommation d'un aliment qui s'avère *a posteriori* contaminé, de la relative faiblesse du risque tel qu'il apparaît dans l'état actuel des connaissances et de l'absence d'élément scientifique en faveur d'un traitement antibiotique en l'absence de signe clinique, **il n'y a pas lieu de recommander une antibioprophylaxie systématique en cas de consommation d'un aliment contaminé par *Listeria monocytogenes*.**

En revanche une information aux consommateurs est dans ce cas impérative, les invitant notamment à faire preuve de vigilance et à consulter sans délai devant l'apparition de fièvre, isolée ou accompagnée de maux de tête, survenant dans les deux mois qui suivent la consommation de l'aliment contaminé.

CET AVIS NE PEUT ETRE DIFFUSE QUE DANS SON INTEGRALITE SANS SUPPRESSION NI AJOUT

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