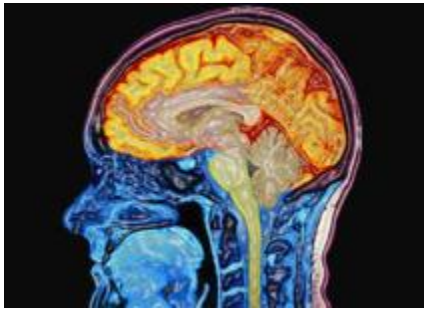
JNI 20es Journées Nationales d'Infectiologie
Lyon
et la région Auvergne-Rhône-Alpes
du mercredi 5 juin 2019
au vendredi 7 juin 2019

Best of 'Neuro-Infectieux'

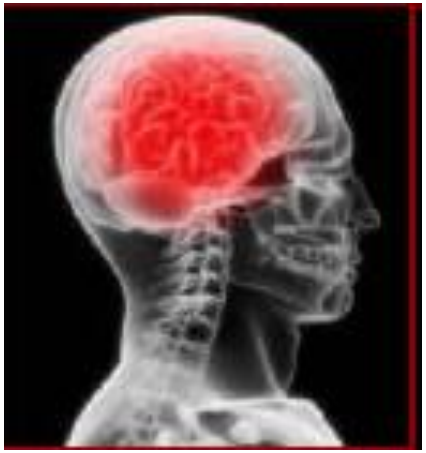
Prof. Pierre Tattevin
Maladies Infectieuses et Réanimation Médicale
Hôpital Pontchaillou, CHU Rennes



Liens d'intérêt

- **Conseil scientifique / financement recherche ou congrès**
  - Gilead
  - Astellas
  - Correvio
  - Mylan
  - Pfizer
  - Shionogi

1. Méningites



Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study

Fiona McGill, Michael J Griffiths, Laura J Bonnett, Anna Maria Geretti, Benedict D Michael, Nicholas J Beeching, David McKee, Paula Scarlett, Ian J Hart, Kenneth J Mutton, Agam Jung, Guleed Adan, Alison Gummery, Wan Aliaa Wan Sulaiman, Katherine Ennis, Antony P Martin, Alan Haycox, Alastair Miller, Tom Solomon, on behalf of the UK Meningitis Study Investigators*

- **Contexte**
  - Baisse d'incidence des méningites bactériennes
  - Boom diagnostique des méningites virales
    (x7 de 2004 à 2013)

- **Cohorte prospective observationnelle**
  - Angleterre, 42 Hôpitaux, 2011-2014
  - **PCR systématiques**: HSV, VZV, EV, PCQ, méningo
  - **Suivi à 1 an**

638 patients had meningitis

231 viral meningitis
- 127 enteroviruses
- 55 herpes simplex virus
- 43 varicella zoster virus
- 6 other virus§

99 bacterial meningitis
- 53 *Streptococcus pneumoniae*
- 29 *Neisseria meningitidis*
- 17 other bacteria§

267 unknown cause

55% documentation (40% virus & 15% bactéries)

- **virus:** 55% Entérovirus, 25% HSV, 20% VZV
- **bactéries:** 50% PCQ, 30% Méningo

McGill F et al. Lancet 2018

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	Estimated annual corrected incidence per 100 000 population (95% CI)	Estimated number of cases a year in the UK (95% CI)
Enteroviral meningitis	1·57 (1·11–2·14)	802 (567–1091)
Herpes simplex virus meningitis	0·78 (0·48–1·27)	399 (242–647)
Varicella zoster virus meningitis	0·36 (0·19–0·59)	182 (94–303)
Total confirmed viral meningitis	2·73 (2·13–3·44)	1389 (1084–1750)
Streptococcus pneumoniae meningitis	1·04 (0·53–1·73)	529 (268–884)
Neisseria meningitidis meningitis	0·12 (0·04–0·25)	63 (23–125)
Total confirmed bacterial meningitis	1·24 (0·76–1·87)	631 (390–951)
Meningitis of unknown cause	10·58 (8·4–13·14)	5390 (4277–6695)

McGill F et al. Lancet 2018

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130 neutrophilic meningitis (≥50% neutrophils)	433 lymphocytic meningitis (>50%)
14 enteroviruses 1 herpes simplex virus 1 other virus§	105 enteroviruses 54 herpes simplex virus 43 varicella zoster virus 4 other virus§
38 *Streptococcus pneumoniae* 24 *Neisseria meningitidis* 10 other bacteria§	8 *Streptococcus pneumoniae* 4 *Neisseria meningitidis* 6 other bacteria§
41 unknown cause	200 unknown cause

- **Méningites à neutrophiles**
  - 60% bactéries
  - 10% virus
  - 30% 'indéterminées'
- **Méningites lymphocytaires**
  - 50% virus
  - 5% bactéries
  - 45% 'indéterminées'

McGill F et al. Lancet 2018

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Etude des pratiques en Angleterre

- **Imagerie**
  - 81% imageries cérébrales
  - Dont 70% avant PL
  - **Justifiée dans 12% des cas…**

- **Délais médians post-admission**
  - **ATB: 2 h** (IQR, 0-10) => 3 h si imagerie
  - **PL: 8 h** (3-22) => 18 h si imagerie

- **Durée moyenne séjour méningite virale = 4 j (3-7)**

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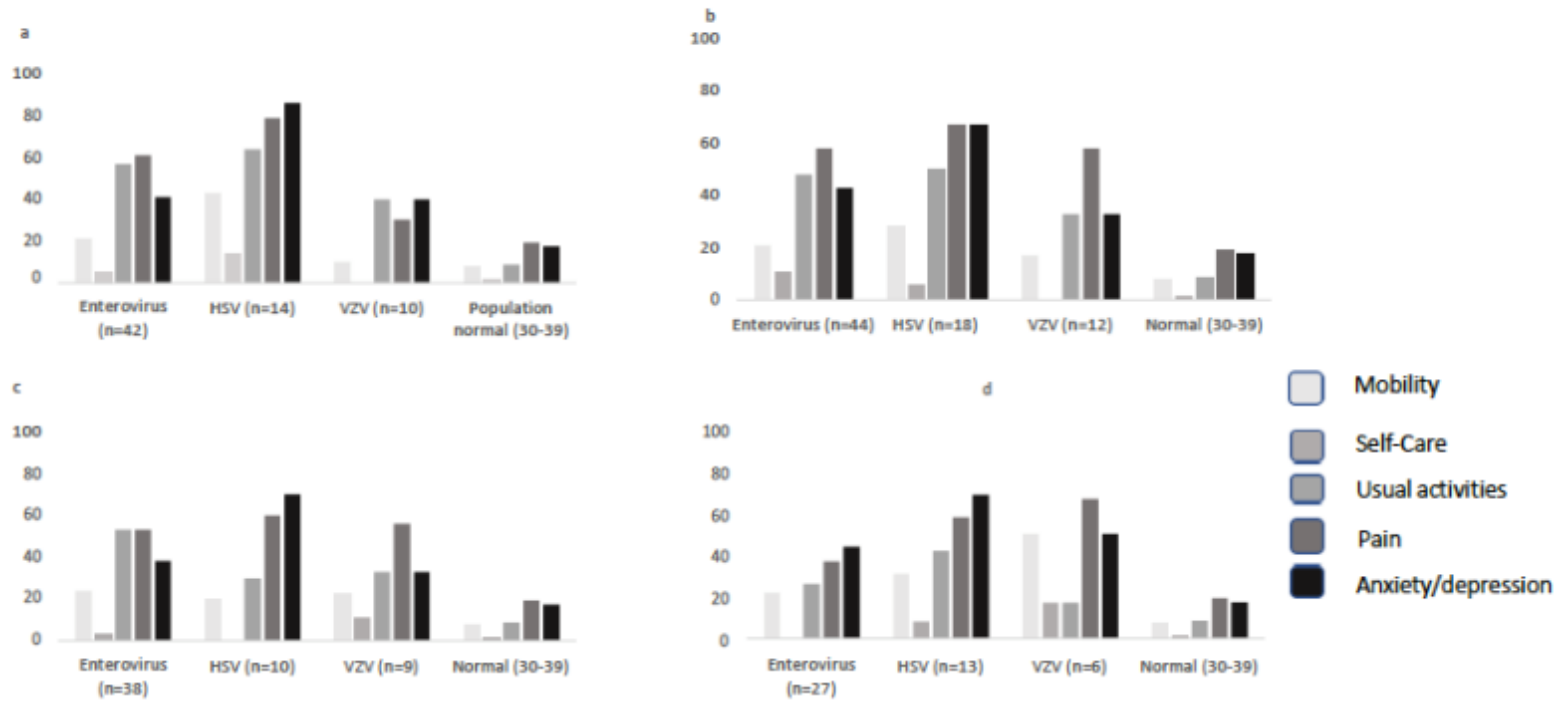
- **Séquelles:**

Figure S3. Percentage of respondents with problems in each of the domains of the EQ5D over time. A) – 6 weeks, b) -12 weeks, c) 24 weeks and d) 48 weeks .



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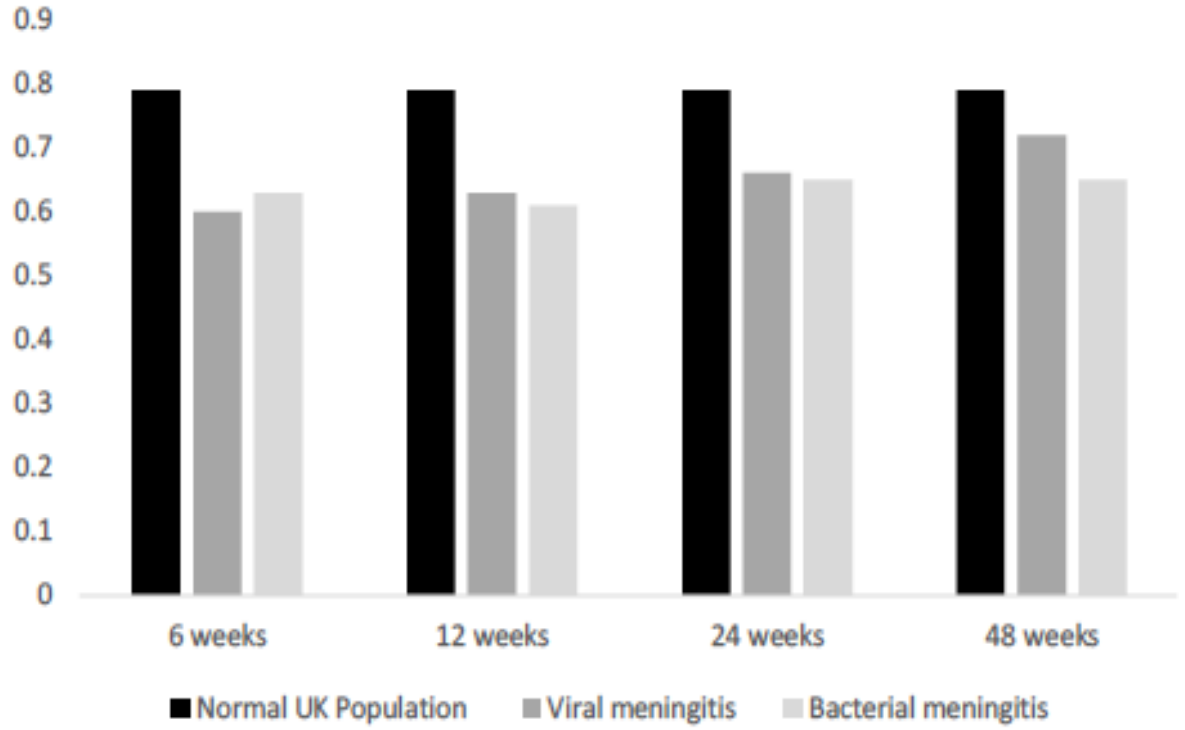
- **Séquelles: les méningites virales ne sont pas 'bénignes' !**

Figure S4. SF-6D utility scores over time in patients with viral or bacterial meningitis compared with the UK normal population.

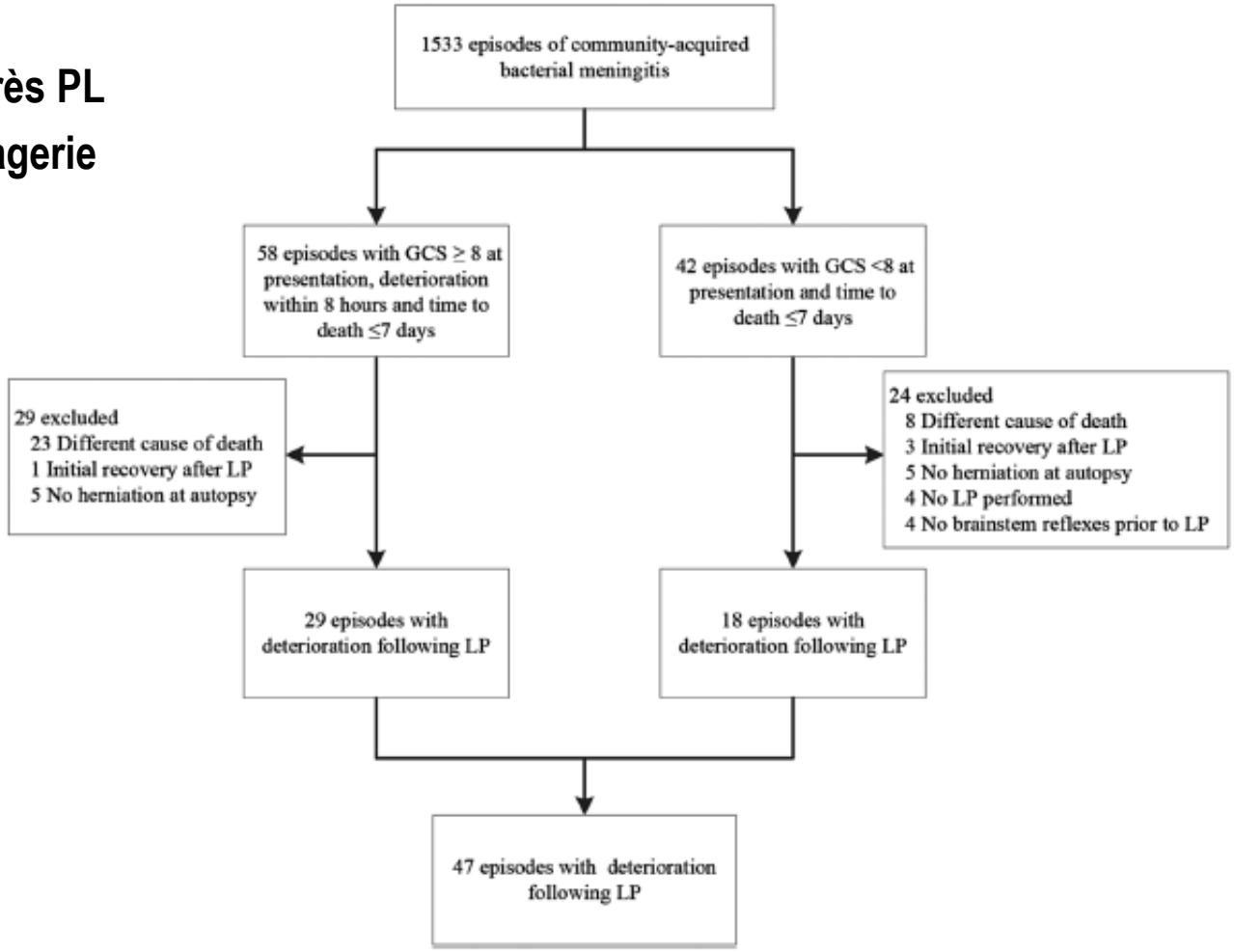


McGill F et al. Lancet 2018

Cranial Computed Tomography, Lumbar Puncture, and Clinical Deterioration in Bacterial Meningitis: A Nationwide Cohort Study

Joost M. Costerus,[1] Matthijs C. Brouwer,[1] Marieke E. S. Sprengers,[2] Stefan D. Roosendaal,[2] Arie van der Ende,[3,4] and Diederik van de Beek[1]

- **Questions**
  - **Risque engagement après PL**
  - Valeur prédictive de **l'imagerie**
- **Cohorte Pays-Bas**
  - Méningites bactériennes
  - 2006-2014
- **Analyse rétrospective**
  - 2 neurologues
  - 2 neuroradiologues



Costerus JM et al. Clin Infect Dis 2018

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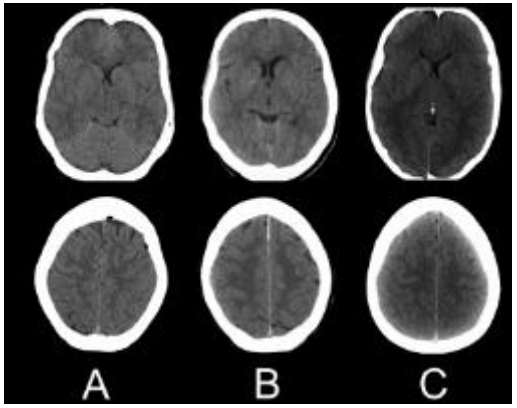
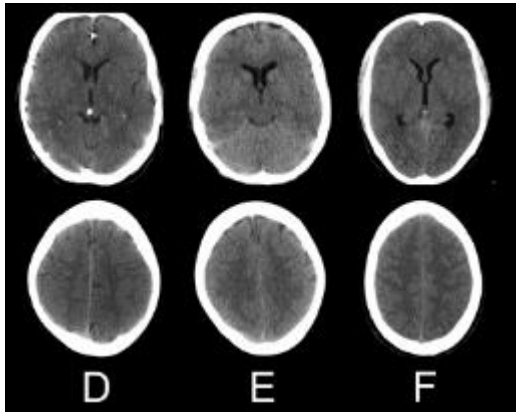
- **Résultats**
  - Incidence **engagement post-PL 0,1%-3%**
  - Imagerie avant PL: 43/47
    - 92% avec une bonne indication (guideline)
    - Dont **79% = troubles vigilance (GCS<10)**



- **PL contre-indiquée par imagerie**
  - 20-40% des cas selon experts (reproductibilité 'modérée')
  - **2/2 (100%)** pour les engagements certains (détérioration <1h)
    - TDM interprété comme normal par le radiologue
    - **Relecture experte = œdème cérébral généralisé**



- **Conclusions**
  - Engagement post-PL **rare et prédictible par imagerie**
  - **Troubles vigilance isolés** = critère à ne pas négliger ?

Costerus JM et al. Clin Infect Dis 2018

Early versus late diagnosis in community-acquired bacterial meningitis: a retrospective cohort study

J. Bodilsen [1,*], C.T. Brandt [2], A. Sharew [3], M. Dalager-Pedersen [1], T. Benfield [4], H.C. Schønheyder [5,6], H. Nielsen [1,6]

- **Méthodes**
  - Cohortes rétrospectives méningites bactériennes Danemark
  - 3 CHU, 1998-2014

- **Méningites de diagnostic tardif = 3 critères**
  1. Aucune mention de la suspicion dans le mot d'accueil
  2. PL non envisagée initialement
  3. Pas de prescription d'ATB à visée 'méningite'

- **Résultats**
  - 113/358 (32%) méningites bactériennes avec diagnostic tardif
  - Indépendamment de la période, de l'heure d'admission
  - **Diagnostic initial**
    - 54/113 (48%) = autre maladie SNC
    - 32/113 (28%) = infection hors SNC

Bodilsen J et al. Clin Microbiol Infect 2018

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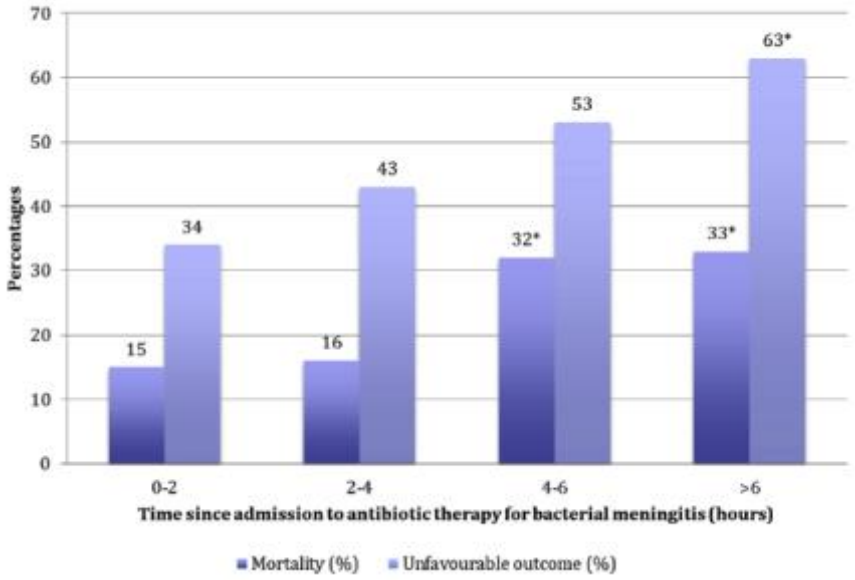
	Early diagnosis $n = 245$	Late diagnosis $n = 113$
Time to antibiotic therapy	1.3 (0.8–3.0)	13.0 (4.8–26.2)*
Dexamethasone treatment	140/245 (57)	41/113 (36)*
In-hospital mortality	43/245 (18)	41/113 (36)*
Unfavourable outcome at discharge	91/245 (37)	75/113 (66)*



Bodilsen J et al. Clin Microbiol Infect 2018

Improving the microbiological diagnosis of tuberculous meningitis: A prospective, international, multicentre comparison of conventional and modified Ziehl–Neelsen stain, GeneXpert, and culture of cerebrospinal fluid

A. Dorothee Heemskerk[a,b,1,2], Joseph Donovan[a,b,1,*], Do Dang Anh Thu[a], Suzaan Marais[c,d], Lidya Chaidir[e], Vu Thi Mong Dung[a], Chad M. Centner[f], Vu Thi Ngoc Ha[a], Jessi Annisa[e], Sofiati Dian[e,g], Louise Bovijn[c], Nguyen Thi Hoang Mai[a,h], Nguyen Hoan Phu[a,h], Nguyen Van Vinh Chau[a,h], Ahmad Rizal Ganiem[e], Cao Thao Van[a], Ronald B. Geskus[a,b], Nguyen Thuy Thuong Thuong[a,b], Rovina Ruslami[e], Graeme Meintjes[c], Reinout van Crevel[b,g], Robert J. Wilkinson[c,i,j], Guy E. Thwaites[a,b]

- **Méthodes**
  - Etude prospective (Vietnam, Indonésie, Afrique du Sud)
  - 618 adultes suspects de TB méningée (2015-2016)
    - ✓ **Rentabilité tests diagnostiques** vs. diagnostic clinique & vs. culture
    - ✓ Facteurs prédictifs de TB documentée

	CZN ($N = 612$)	MZN with cytospin ($N = 605$)	MZN without cytospin ($N = 604$)	culture ($N = 602$)	Xpert ($N = 610$)
Positive tests in TBM	129/380	129/374	116/375	119/374	95/379
Sensitivity (%)	33.9	34.5	30.9	31.8	25.1
(95% CI)	(29.4–38.8%)	(29.9–39.4%)	(26.5–35.8%)	(27.3–36.7%)	(21.0–29.7%)
Specificity (%)	100	100	99.6	100	100

Heemskerk AD et al. J Infect 2018

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  - 618 adultes suspects de TB méningée (2015-2016)
    - ✓ Rentabilité tests diagnostiques vs. diagnostic clinique & vs. culture
    - ✓ **Facteurs prédictifs de TB documentée**
    1. **Volume LCS (+30% par mL supplémentaire)**
    2. **Hypoglycorachie**
    3. **Lactatorachie**

Heemskerk AD et al. J Infect 2018

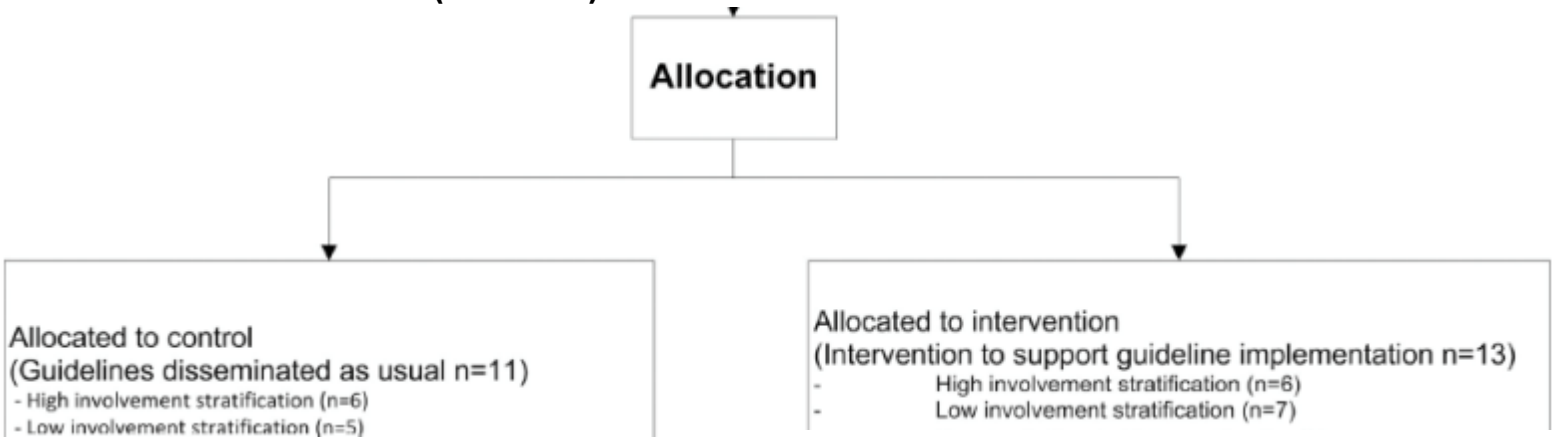
2. Encéphalites

A pragmatic cluster randomised controlled trial of a tailored intervention to improve the initial management of suspected encephalitis

Ruth Backman[1,2], Robbie Foy[3], Peter J. Diggle[4,5], Rachel Kneen[1,6], Ava Easton[1,7], Sylviane Defres[1,8,9], Fiona McGill[1,8,9], Benedict Daniel Michael[1,10], Tom Solomon[1,9,10]*, on behalf of the ENCEPH UK Programme Steering Committee¶

- **Objectifs**
  - Evaluer une stratégie d'amélioration du respect des guidelines

- **Méthodes**
  - **Analyse des 'barrières'**
  - Choix d'une stratégie (éducation & training, pack PL, feedback)
  - **Randomisation en cluster (24 sites)**



Backman R et al. PLoS ONE 2018

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		Intervention			Control		
		Number eligible	Number meeting outcome	Percentage	Number eligible	Number meeting outcome	Percentage
Primary outcome Lumbar puncture performed within 12 hours and IV aciclovir administered within 6 hour	Total	266	36	13.53	223	33	14.80
	Adults	206	25	12.14	190	29	15.26
	Paediatrics	60	11	18.33	33	4	12.12
Lumbar puncture with CSF/serum glucose ratio calculated	Total	266	86	32.33	223	78	35.00
	Adults	206	65	31.55	190	65	34.21
	Paediatrics	60	21	35.00	33	13	39.39
Lumbar puncture and a sample taken for HSV PCR	Total	266	182	68.42	223	175	78.48
	Adults	206	141	68.45	190	147	77.37
	Paediatrics	60	41	68.33	33	28	84.85

Backman R et al. PLoS ONE 2018

The shift in rabies epidemiology in France: time to adjust rabies post-exposure risk assessment

Perrine Parize[1], Laurent Dacheux[1], Florence Larrous[1], Hervé Bourhy[1], the French network of antirabies clinics[2]

- **Contexte**
  - France indemne de rage chez les mammifères terrestres non-volants depuis 2001
  - Dernier cas humain autochtone France métropolitaine = 1924

=> **Données CNR rage: cas humains** 1995-2016, et prophylaxies post-exposition (**PEP**)

Human laboratory-confirmed rabies cases, France, 1995–2016 (n=7)

Year	Age group (years)	Country of exposure	Animal	Incubation period	Duration of clinical symptoms	Diagnosis intra-vitam	Diagnosis post-mortem	PEP
1996	0-4	Madagascar	Dog	2 months	6 days	NA	FAT and RTCIT on brain sample	No
1996	60-64	Algeria	Dog	2 months	5 days	NA	FAT and RTCIT on brain sample	No
1996	70-74	Algeria	Dog	1.5 months	3 days	RT-PCR on saliva and CSF	NA	No
1997	50-54	India	Dog	12 days	14 days	RT-hnPCR on CSF and saliva	NA	Yes, but no RIG
2003	0-4	Gabon	Dog	2 months	7 days	RT-hnPCR on skin biopsy and saliva	NA	No
2008	40-44	France (French Guiana)	NK	NK	7 days	RT-hnPCR on skin biopsy and saliva	NA	No
2014	55-59	Mali	NK	NK	19 days	RT-hnPCR on skin biopsy and saliva	NA	No

Parize P et al. Eurosurveillance 2018

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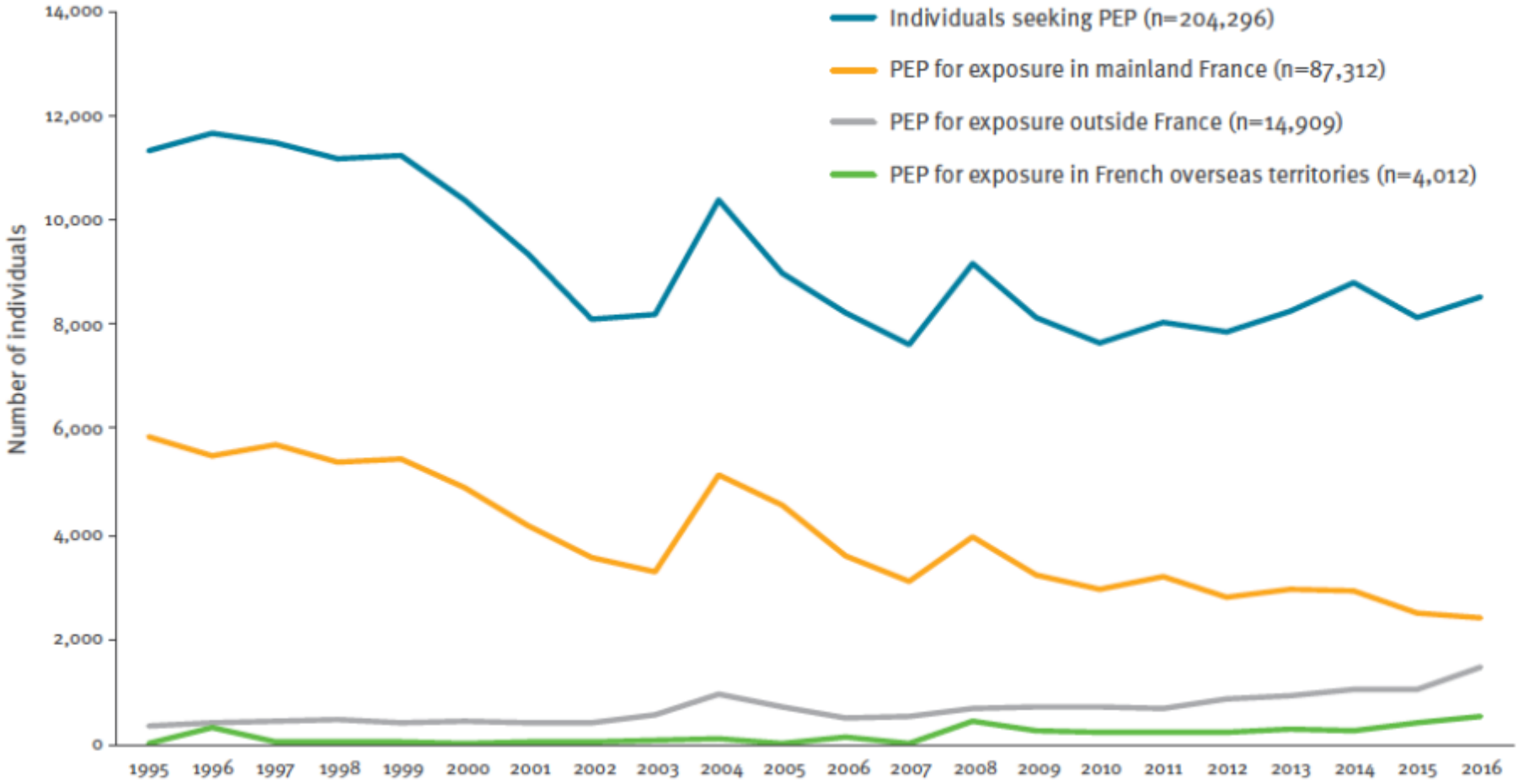
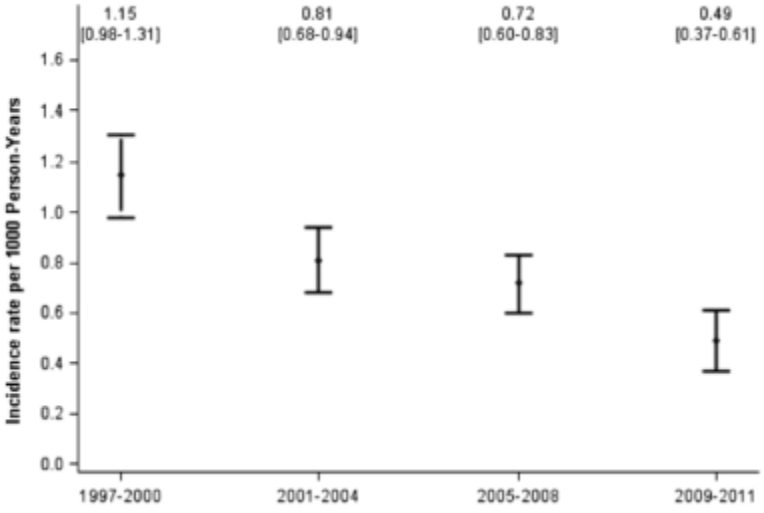


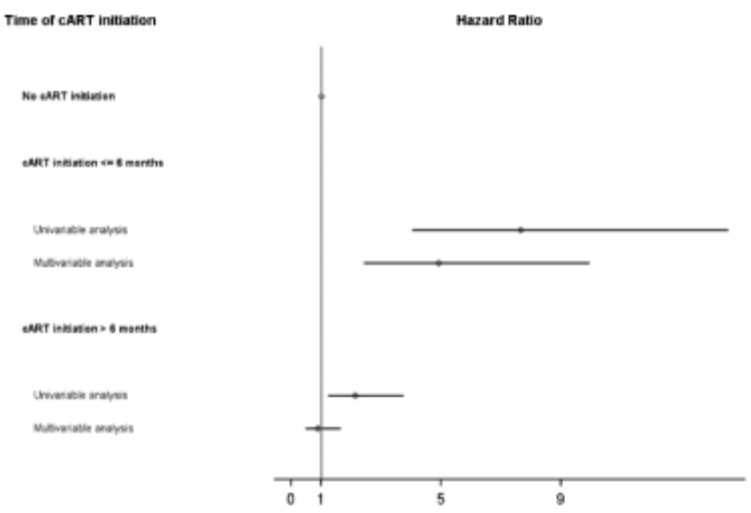
Parize P et al. Eurosurveillance 2018

Risk of Progressive Multifocal Leukoencephalopathy in the Combination Antiretroviral Therapy Era in the French Hospital Database on Human Immunodeficiency Virus (ANRS-C4)

Hugues Melliez,[1,2] Murielle Mary-Krause,[1] Laurence Bocket,[3] Marguerite Guiguet,[1] Sophie Abgrall,[1,4] Pierre De Truchis,[5] Christine Katlama,[1,6] Guillaume Martin-Blondel,[7,8] Aurelia Henn,[9] Matthieu Revest,[10] Olivier Robineau,[2] Marie-Aude Khuong-Josses,[11] Anna Canestri,[12] Nathalie De Castro,[13] Véronique Joly,[14] Saadia Mokhtari,[15] Karine Risso,[16] Jacques Gasnault,[17,a] and Dominique Costagliola[1,a]; for the French Hospital Database on HIV

- **Méthodes**
  - 97 905 PVVIH suivis en France (70 sites), 1997-2011
  - **Cas incidents de LEMP** (n=555)





Melliez H et al. Clin Infect Dis 2018

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- **FDR de LEMP (analyse multivariée)**

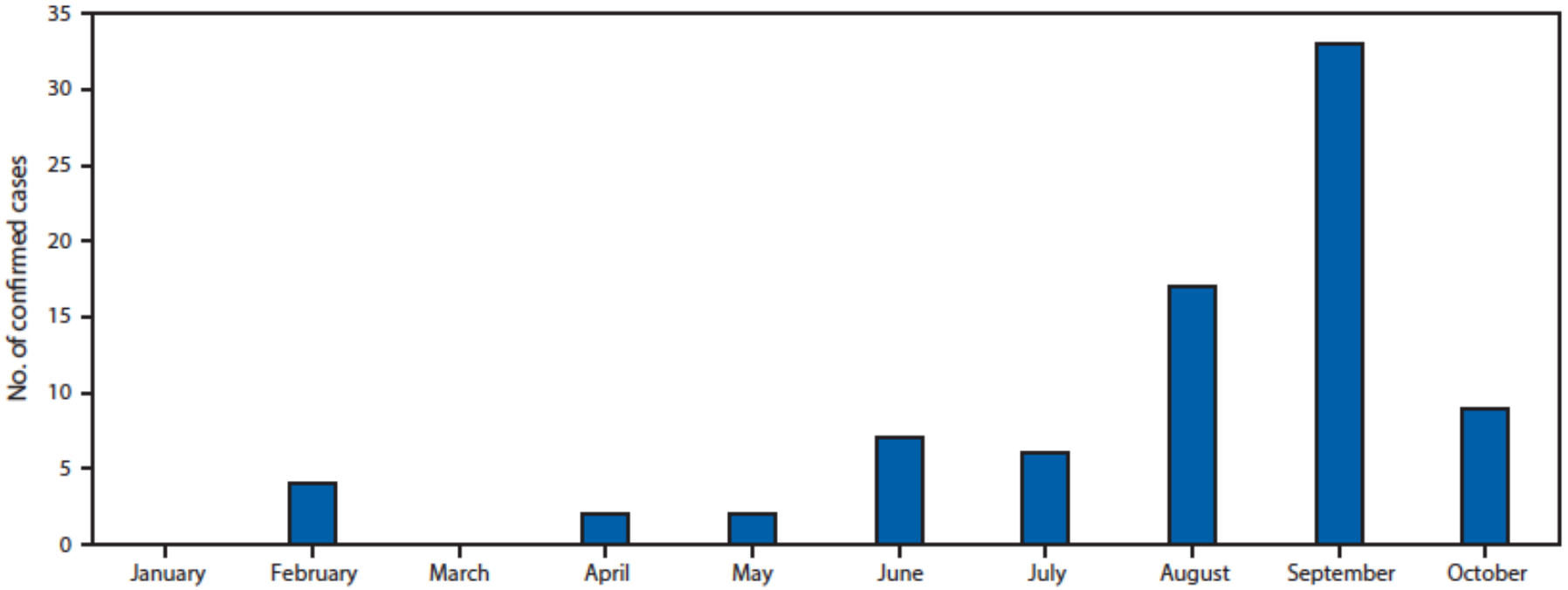
Sex and transmission group	
MSM	1
Male IDUs	1.80 (1.32–2.45)
Other men	1.05 (.82–1.35)
Female IDUs	1.68 (1.13–2.48)
Time-dependent covariables	
AIDS stage	
No	1
Yes	1.86 (1.55–2.23)
$CD4^+$ cell count, cells/μL	
≤50	1
>50 to ≤100	0.46 (.35–.60)
>100 to ≤200	0.19 (.15–.25)
>200 to ≤350	0.09 (.07–.11)
>350	0.03 (.02–.04)
VL, copies/mL	
≤500	1
>500	1.87 (1.53–2.29)

3.

Increase in Acute Flaccid Myelitis — United States, 2018

Susannah L. McKay, PhD[1,2]; Adria D. Lee, MSPH[2]; Adriana S. Lopez, MHS[2]; W. Allan Nix, PhD[2]; Kathleen L. Dooling, MD[2]; Amelia A. Keaton, MD[3]; Emily Spence-Davizon, MPH[4]; Rachel Herlihy, MD[4]; Thomas A. Clark, MD[5]; Sarah E. Hopkins, MD[6]; Daniel M. Pastula, MD[2,7]; James Sejvar, MD[8]; M. Steven Oberste, PhD[2]; Mark A. Pallansch, PhD[2]; Manisha Patel, MD[2]; Janell A. Routh, MD[2]

FIGURE. Number of confirmed cases of acute flaccid myelitis (AFM) reported to CDC, by month of onset — United States, January–October, 2018*



- **Alerte CDC**
  - Signalement **myélite aiguë flasque x 3 vs. 2017**
  - Pas de zone particulière

McKay SL et al. MMWR 2018

Increase in Acute Flaccid Myelitis — United States, 2018

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- **Caractéristiques (n=125)**
  - **Âge médian, 4 ans** (**IQR 2,4-7,6**), max = 32 ans
  - Prodromes **'virose' dans les 4 semaines = 99%** (**respiratoire 80%,** gastro 40%)
  - **Paralysies**: membre(s) sup = 50%, inf = 10%, les 2 = 40%
  - **Méningite, 98%** (médiane, 103 éléments/mm^3; IQR 56-194)
  - Pas de décès, mais **60% admissions en réa**

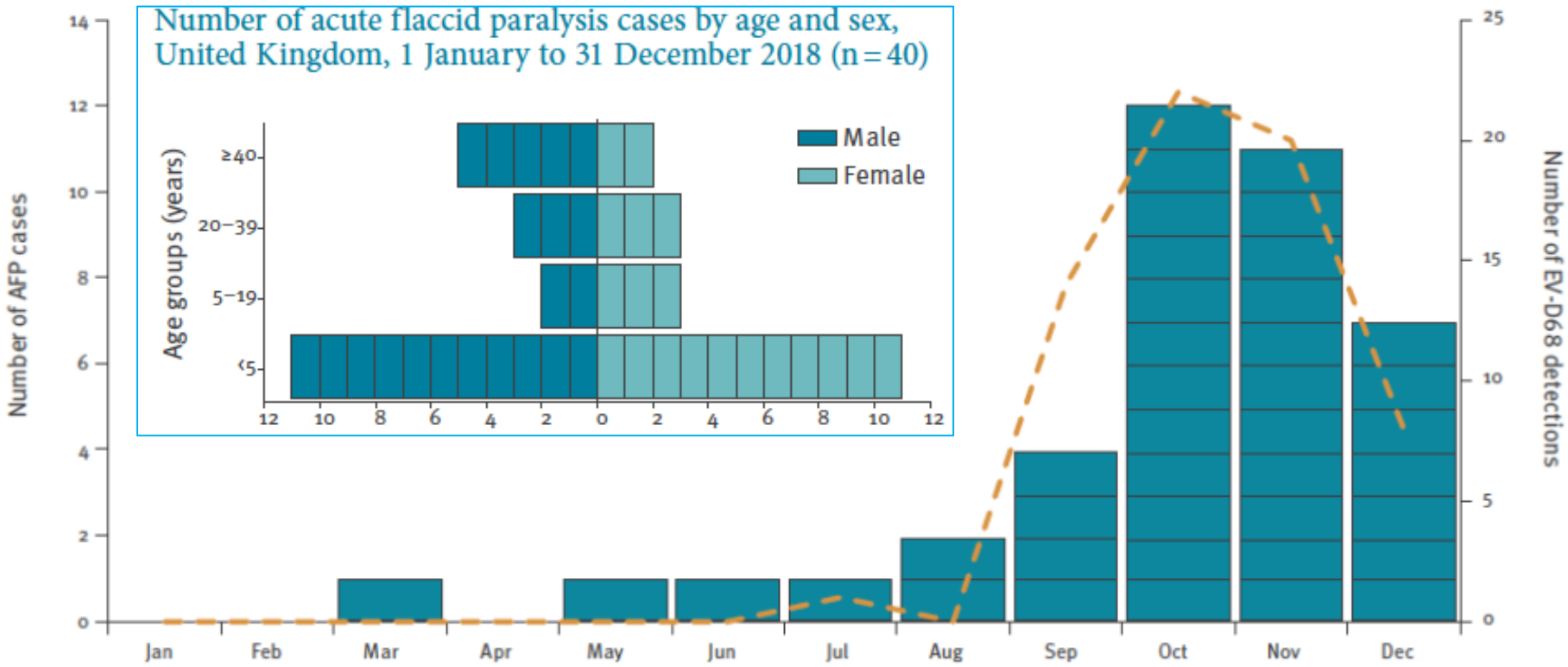
Enterovirus and rhinovirus testing, by type	CSF specimens (n = 21)	Respiratory specimens (n = 59)	Stool/Rectal swab specimens (n = 45)	Total (N = 125)
EV- or RV-positive no. (%)	**2 (10)**	**31 (53)**	**17 (38)**	**50**
Subtype, no. (%) positive[†]				
EV-A71	1 (50)	10 (32)	10 (59)	21 (42)
EV-D68	1 (50)	13 (42)	1 (6)	15 (30)

McKay SL et al. MMWR 2018

An increase in reports of acute flaccid paralysis (AFP) in the United Kingdom, 1 January 2018–21 January 2019: early findings

The United Kingdom Acute Flaccid Paralysis (AFP) Task Force[1]

Number of acute flaccid paralysis cases (n = 40) and enterovirus D68 detections (n = 65) by month, United Kingdom, 1 January–31 December 2018

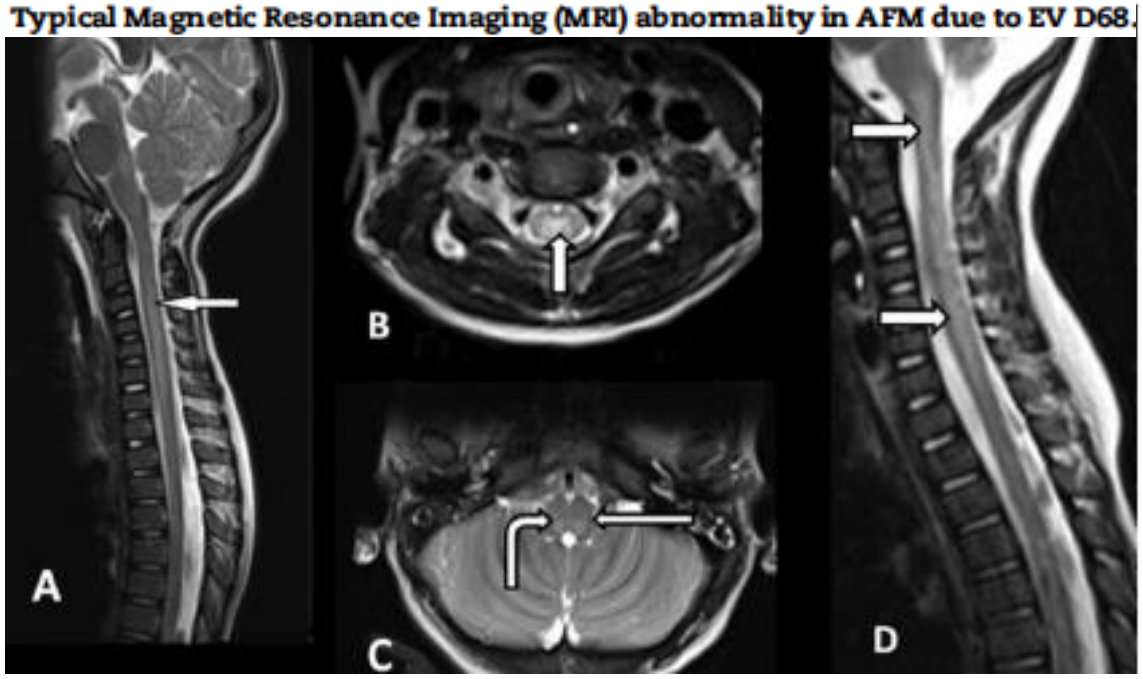


UK AFP Task Force. Eurosurveillance 2019

Acute flaccid myelitis caused by enterovirus D68: Case definitions for use in clinical practice

Rolf Kramer [a,b,*], Bruno Lina [b,c], Jay Shetty [d,e]

- **Myélite aiguë flasque**
  - **Faiblesse de(s) membre(s) d'installation aiguë**
  - **IRM** = lésions moelle, prédominant en substance grise, plusieurs niveaux
  - **Méningite** (≥5 éléments/mm^3)



Kramer R et al. Eur J Ped Neurol 2019

Acute flaccid myelitis caused by enterovirus D68: Case definitions for use in clinical practice

Rolf Kramer [a,b,*], *Bruno Lina* [b,c], *Jay Shetty* [d,e]

Table 1 – Case classifications of acute flaccid myelitis caused by enterovirus D68.

Suspected	A possible case is defined as a person presenting with symptoms of either acute myelitis/paralysis or Guillain-Barré Syndrome, particularly during periods of EV-D68 circulation indicated by epidemiological alerts or systematic surveillance.
Probable	A probable case is defined as a person presenting with symptoms of either acute myelitis/paralysis or Guillain-Barré Syndrome and at least one of the following criteria: - MRI abnormality representing with T2 hyperintensity in spinal cord grey matter with or without hyperintensity at dorsal brain stem - investigations showing an axonal neuropathy including reduced compound motor action potentials with normal conduction velocities and absence of conduction blocks compatible with anterior horn cell disease - detection of enteroviruses in a respiratory specimen obtained from the lower respiratory tract during periods of EV-D68 circulation.
Confirmed	A confirmed case is defined as a person presenting with the following criteria: - acute flaccid myelitis/paralysis - MRI abnormality representing with T2 hyperintensity in spinal cord grey matter with or without hyperintensity at dorsal brain stem - detection of enterovirus-D68-specific nucleic acids in a respiratory specimen using a validated PCR assay targeting the VP1 gene with subsequent sequencing and typing

Kramer R et al. Eur J Ped Neurol 2019

Long term survival, health, social functioning, and education in patients with European Lyme neuroborreliosis: nationwide population based cohort study

Niels Obel,[1] Ram B Dessau,[2] Karen A Krogfelt,[3] Jacob Bodilsen,[4] Nanna S Andersen,[5] Jens K Møller,[6] Casper Roed,[1] Lars H Omland,[1] Claus B Christiansen,[7] Svend Ellermann-Eriksen,[8] Jette M Bangsborg,[9] Klaus Hansen,[10] Thomas L Benfield,[11] Kenneth J Rothman,[12,13] Henrik T Sørensen,[12] Christian Ø Andersen,[14] Anne-Mette Lebech[1]

- **Contexte**
  - Le devenir à long terme des neuroborrélioses traitées est mal connu

- **Méthodes**
  - Registres nationaux Danemark
    - **Neuroborrélioses prouvées (synthèse intra-thécale), 1986-2016 => n=2067**
    - **Contrôles appariés sur âge & sexe => n=20670**

Obel N et al. BMJ 2018

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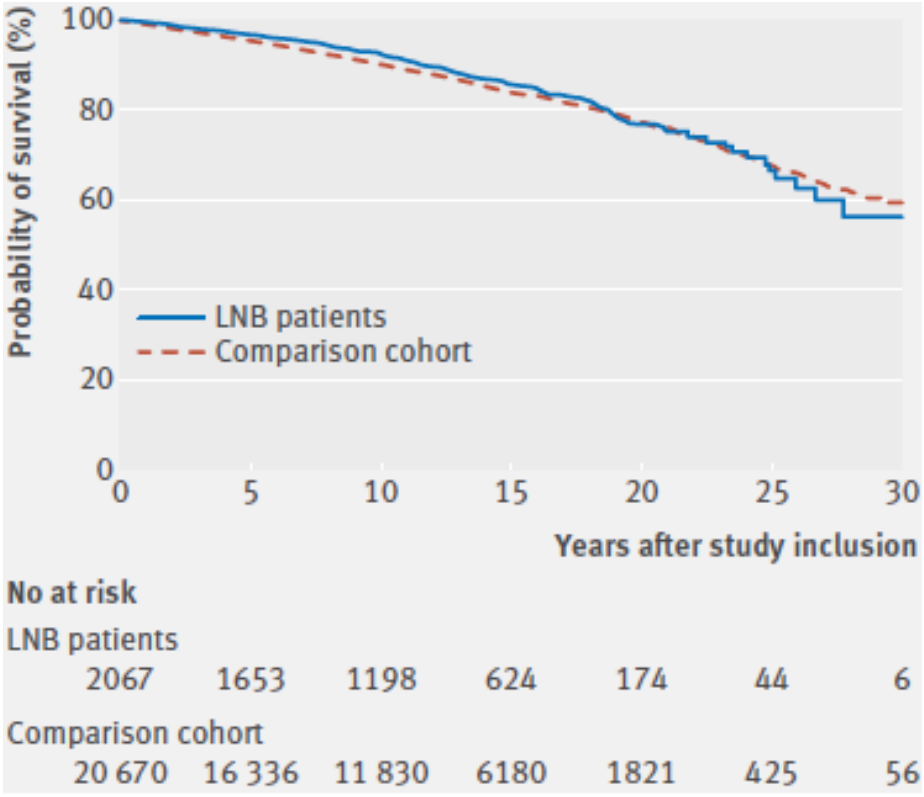

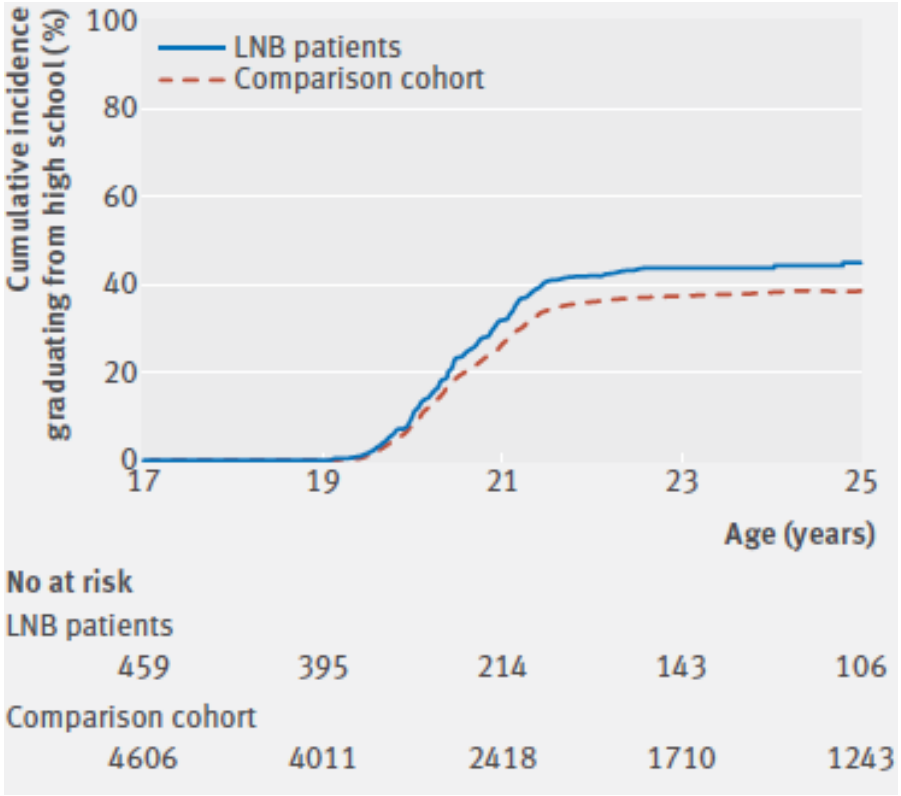

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	LNB patients v population comparison cohort members
Mortality	0.90 (0.79 to 1.03)
Cancer	1.32 (1.15 to 1.52)
Non-haematological cancer	1.19 (1.00 to 1.14)
Haematological cancer	3.07 (2.03 to 4.66)
Lymphoma	4.10 (2.20 to 7.64)
Myelomatosis	2.62 (0.98 to 7.019)
Leukaemia (not chronic lymphatic leukaemia)	1.36 (0.41 to 4.54)
Chronic lymphatic leukaemia	3.67 (1.54 to 8.72)
Non-melanoma skin cancer	1.49 (1.18 to 1.88)
Multiple sclerosis	1.24 (0.37 to 4.12)
Arthritis <1 year after study inclusion*	9.04 (3.67 to 22.24)
Arthritis ≥1 year after study inclusion	1.58 (0.88 to 2.84)
Skin diseases	0.88 (0.41 to 1.91)
Cerebral infarction <1 year after study inclusion*	4.85 (2.92 to 8.05)
Cerebral infarction ≥1 year after study inclusion	1.18 (0.93 to 1.50)
Heart block or cardiac arrest	1.00 (0.54 to 1.87)

Obel N et al. BMJ 2018

Best of Neuro-Infectiologie 2019: Conclusions

- **Méningites virales: pas si bénignes ?** (cf. suivi à 1 an étude UK)
- **Engagement post-PL: 0,1%,** évitable par imagerie bien lue
- **1/3 des méningites bactériennes non repérées à l'admission**
- **Diagnostic TB méningée:** seul le volume de LCS compte
- **Echec de l'essai randomisé en cluster pour une meilleure prise en charge des suspicions d'encéphalite**
- **Evolution du risque rabique en France => nouvelles recos**
- **LEMP diminue avec les cART, sur-risque chez UDI**
- **Myélites aiguës post-infections respiratoires à EV-D68**
- **Bon pronostic à long terme des neuroborrélioses de Lyme**

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Actualités diagnostiques et thérapeutiques en pathologie neuro-infectieuse

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10 & 11 OCT. 2019
ICM, PARIS

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