

Why the nephrotic hotspots ?

A look at the epidemiology and demographics
of nephrotic syndrome.

EMEESY– 12th oct 2018

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Hôpital Robert-Debré - Paris



Idiopathic nephrotic syndrome



- Universal disease
- Immune disorder
- 2 – 10 years
- Infectious trigger
 - URTI at onset or relapse
- Genetic susceptibility
 - Ethnicities
 - HLA DQA, DQB
- Host/Environment interaction disease

Yap, Ped Nephrol 2001

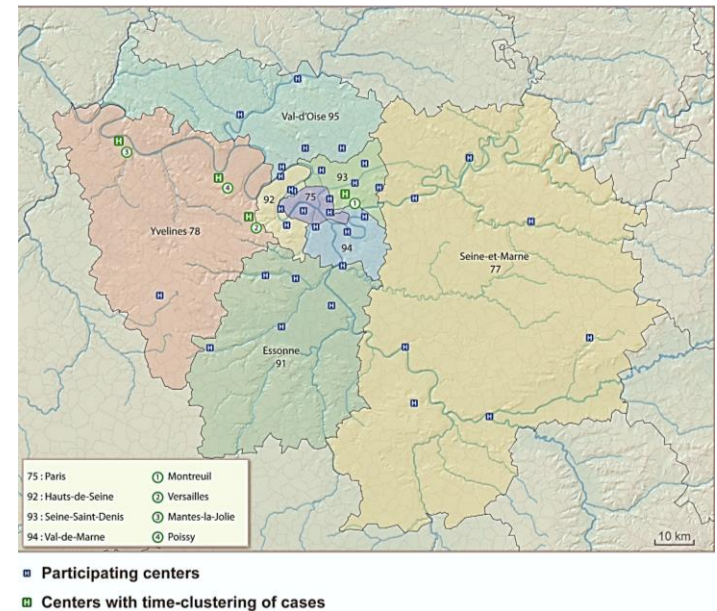
Sharples 1985, Banh CJASN 2016

Mid-West Consortium, JASN 2015, Debiec JASN 2018

The NEPHROVIR Cohort



- NEPHROVIR-1 study
- Prospective
- Multicentric (N=39)
- Case-control study
- 30 months (2007-2010)
- All children aged 6m-16y at onset of INS
- **Link between viral infection and INS onset**

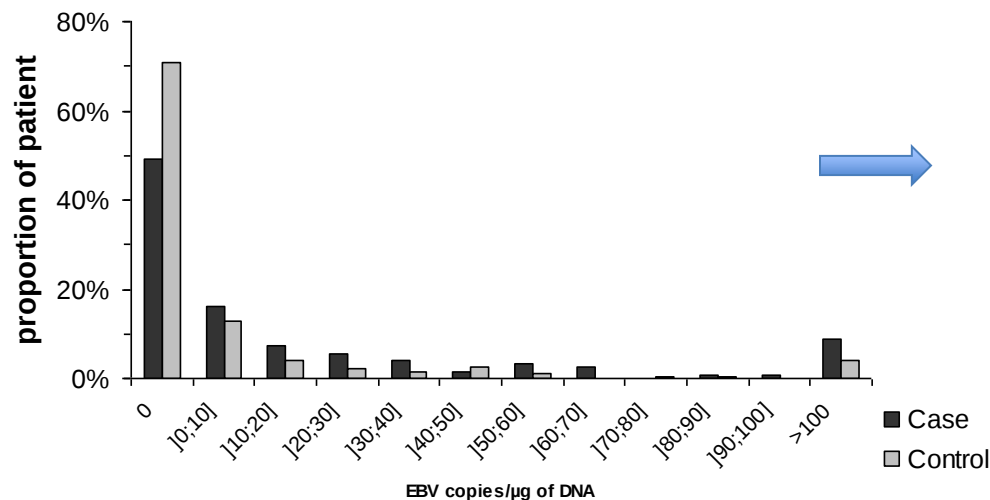


The NEPHROVIR study



- Link between viral infection and INS onset

PCR virus	INS (N=154)	Controls (N=196)	p (univariate)	p (multivariate)
EBV	51 %	29 %	<0.001	0.01
CMV	11 %	4 %	<0.05	NS
HHV6	55 %	61%	NS	NS
HHV7	83 %	72 %	<0.05	NS



**Association between
EBV and INS**

HLA DQA1-DQB1

A indirect link between EBV and INS

Gbadesin 2014

**HLA-DQA1 and PLCG2 Are
Candidate Risk Loci for
Childhood-Onset Steroid-
Sensitive Nephrotic Syndrome**
JASN 2014

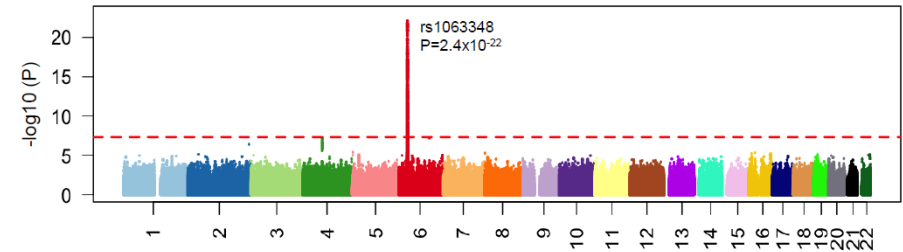
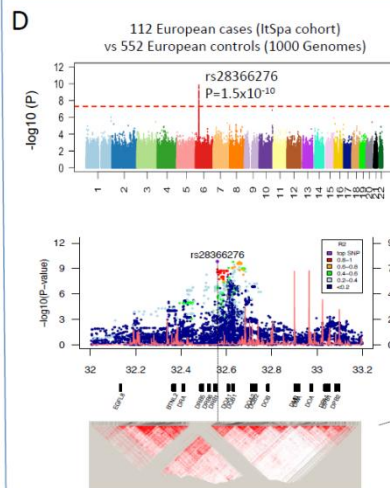
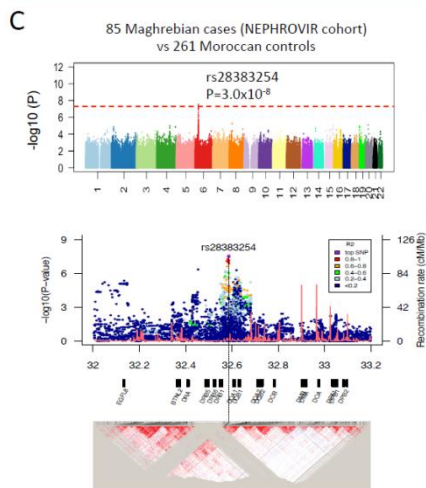
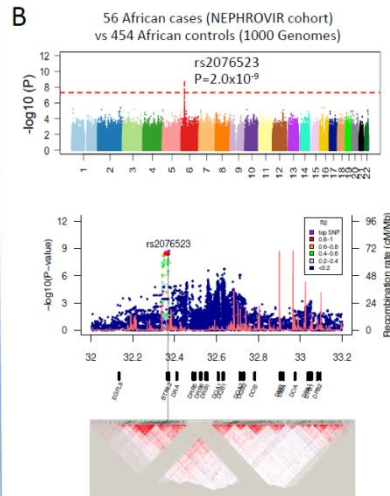
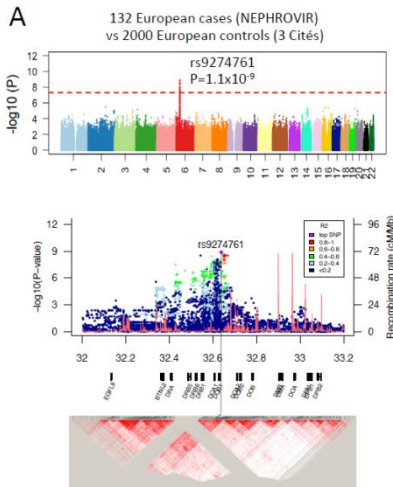
Rubicz 2013

Pederagnana 2014

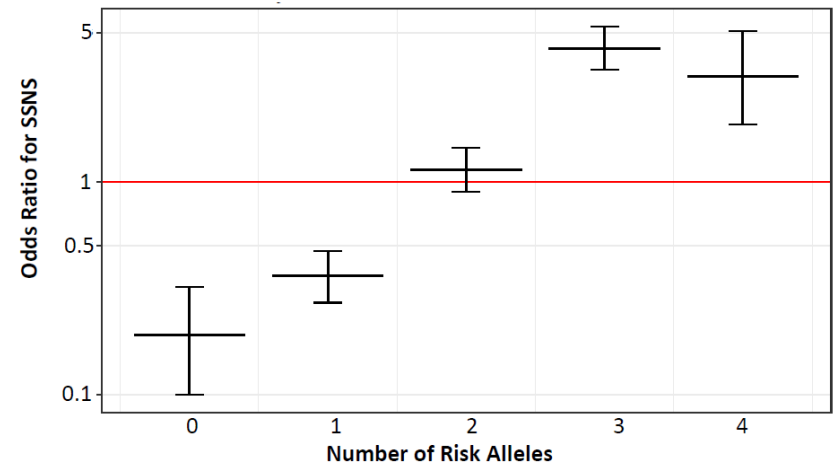
**A genome-wide integrative
genomic study localizes genetic
factors influencing antibodies
against Epstein-Barr virus
nuclear antigen 1 (EBNA-1)**
Plos Genet 2013
Plos Genet 2014

HLA DQA1-DQB1

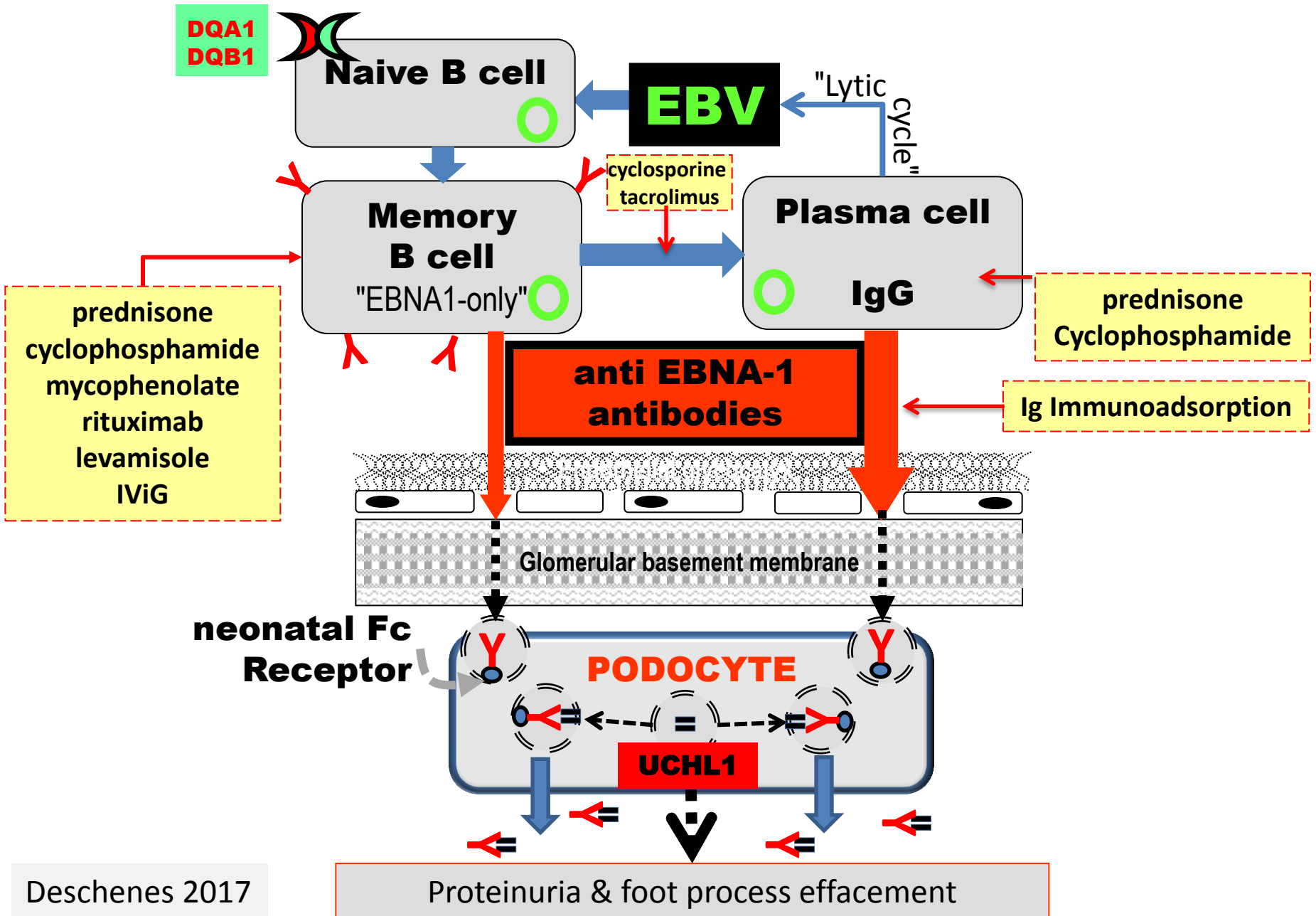
A indirect link between EBV and INS



Odds Ratio by Number of Risk Alleles –rs1063348 and rs28366266



The EBV model



Other viruses

Risk of Nephrotic Syndrome following Enteroviral Infection in Children: A Nationwide Retrospective Cohort Study



Jiun-Nong Lin^{1,2,3}, Cheng-Li Lin^{4,5}, Chi-Hui Yang⁶, Ming-Chia Lin⁷, Chung-Hsu Lai³, Hsi-Hsun Lin³, Chia-Hung Kao^{8,9,10*}

- 2000-2007, <18y, enterovirus infection and age at Dg
- N=280 000 + 280 000 controls match on time +/- 1y, age, gender, urbanisation, parents occupation
- End point : INS onset during an 8y follow-up

Table 2. The incidence and hazard ratio and 95% confidence intervals for nephrotic syndrome.

Variable	Event	Person-years	IR	Crude HR (95% CI)	p value	Adjusted HR (95% CI) †	p value
Enteroviral infection							
No	341	1,542,399	2.21	1 (Reference)		1 (Reference)	
Yes	410	1,548,686	2.65	1.20 (1.04–1.38)*	0.01	1.20 (1.04–1.39)*	0.01

Why the nephrotic hotspots?

A look at the epidemiology and demographics of nephrotic syndrome.

Modulators of INS incidence

- « Classical » factors associated to a higher incidence :

- Young age
- Gender (boys)
- Ethnicity (Asians)

Sharples 1985, Banh CJASN 2016

- « socio -geographic » factors

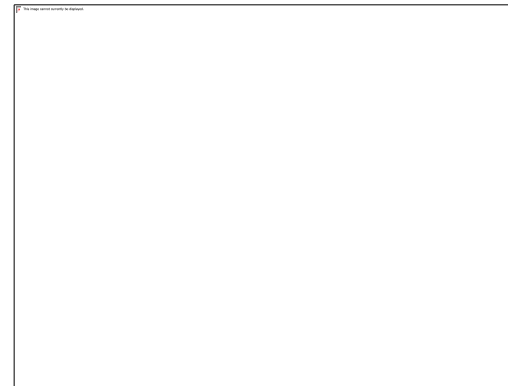
- Urban > rural areas
- Low socio-economic level

Feehally 1985

Schlesinger 1968

- Circannual variation in Japan

Toyabe 2005, Okada 2015



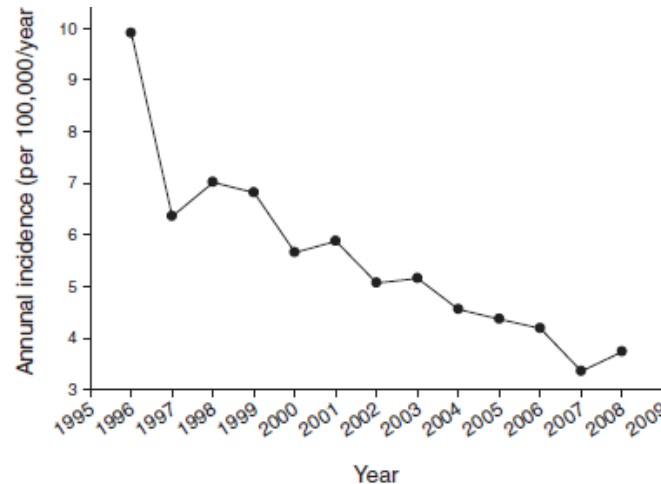
INS incidence around the world

** Prospective studies*

Author	country	date	incidence	N	Age (y)
Hodson*	Australia	1998-2000	1,15	135	<16
Franke	Germany	2005-2006	1,2	347	<18
El Bakkali*	Netherlands	2003-06	1,52	231	<18
Wong *	New Zeland	2001-04	1,9	49	<15
Schlesinger	USA, Erie County	1946-61	2,0	86	<16
McKinney	UK, Yorkshire	1987-98	2,3	194	<16
Pasini	Italy, Emilia Romagna	2007-2009	3,5	-	<15
Chang	Taiwan	1998-2006	9,91 -3,36	4083	<18
Kikunaga	Japan JP-SHINE	2010-2012	6,49	2099	<15
Palcoux*	France, Auvergne	1987-91	1,7	21	<16
Bouissou*	France, Midi-Pyrénées	1987-91	2,2	79	<16
Burguet	France, Franche Comté	1991-95	2,4	26	<16
Nivet	France, Indre et Loire	1985-94	2,4	23	<15
		1995-2004	3,4	32	
Harambat	France, Gironde	1992-2008	2,3	99	<15
Dossier*	France, Ile-de-France	2007-2010	3,35	188	<16

Epidemiology over the years

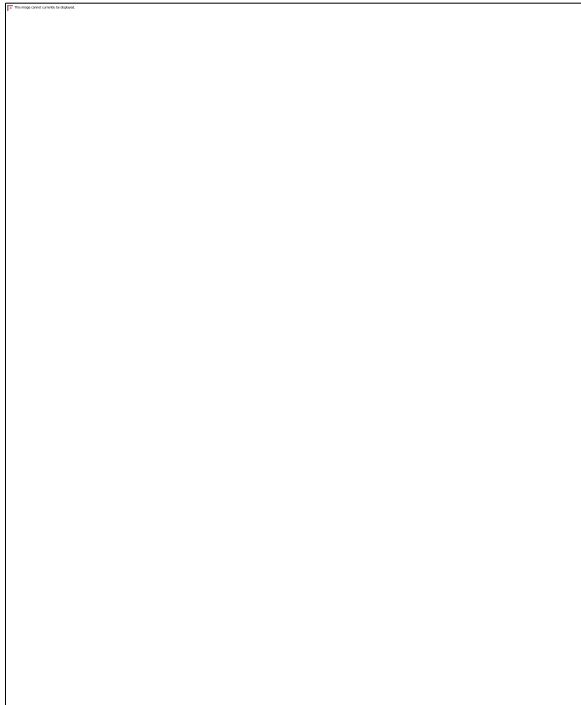
- Stable incidence
- Compared to other immune mediated diseases such as diabetes or asthma
- In Taiwan



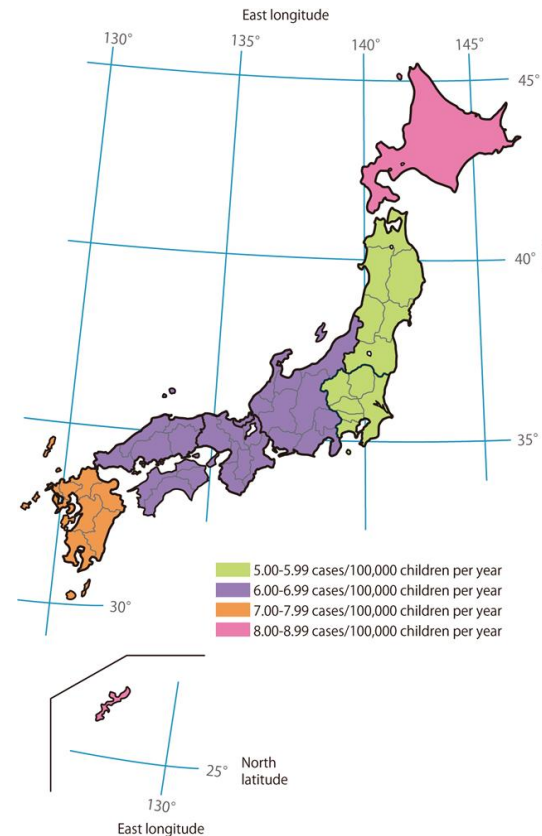
Chang J Epidemiol 2012

Spatial epidemiology

- The Netherlands



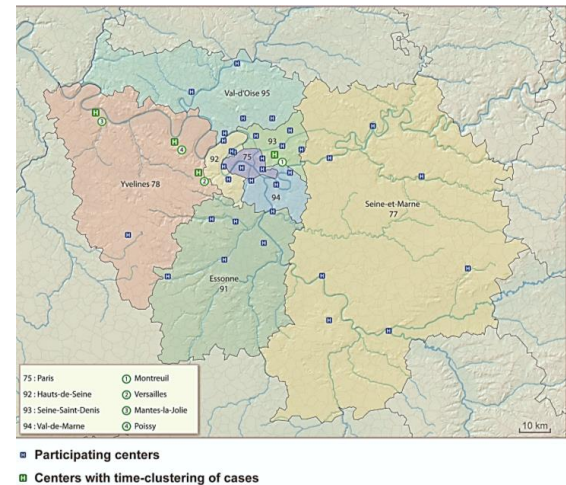
- Japan



The NEPHROVIR Cohort

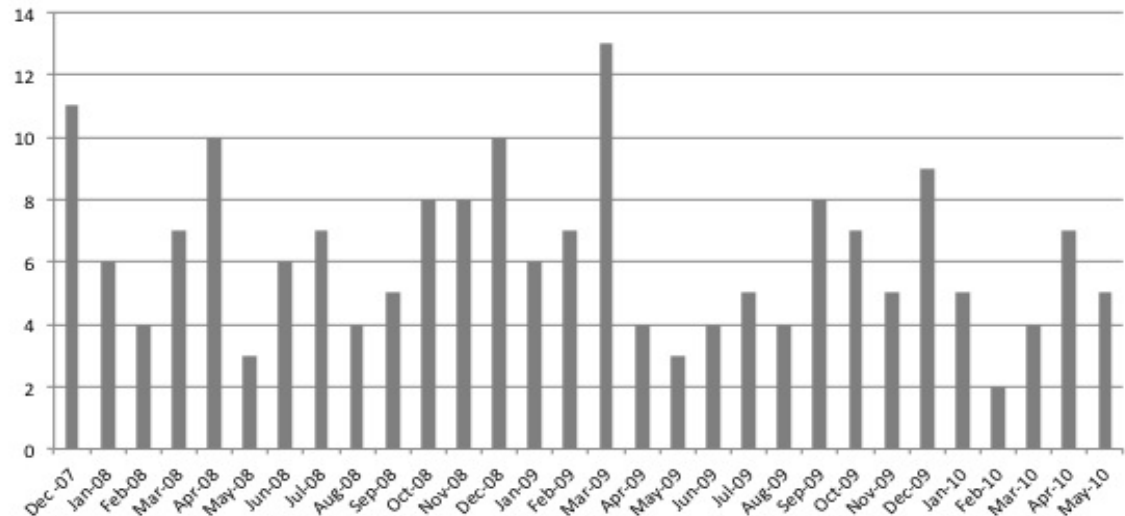


- NEPHROVIR-1 study
 - Prospective
 - Multicentric (N=39)
 - 30 months (2007-2010)
 - All children aged 6m-16y at onset of INS
 - Link between viral infection and INS onset
 - **N=188** new cases
 - Multi ethnic background
 - Annual incidence **3,35** / 100 000 children <16y
- 12,000 km²
 - 12 M inhabitants – 1000/km²
 - 2,7 M kids < 16 years
 - 8 counties - 1,276 townships
 - 35 general pediatric centers
 - 3 pediatric nephrology units
 - Free access to pediatric care

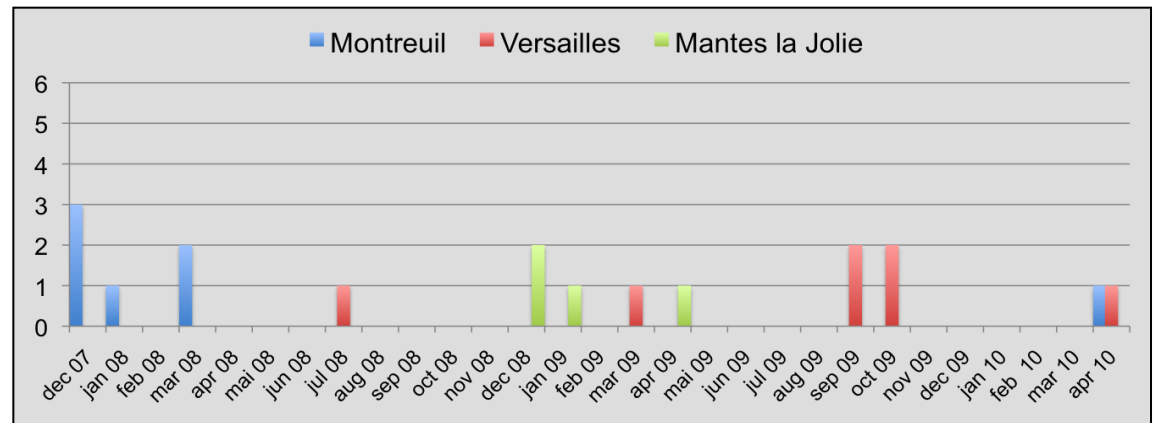


Epidemiology of INS in Paris area

- Monthly incidence

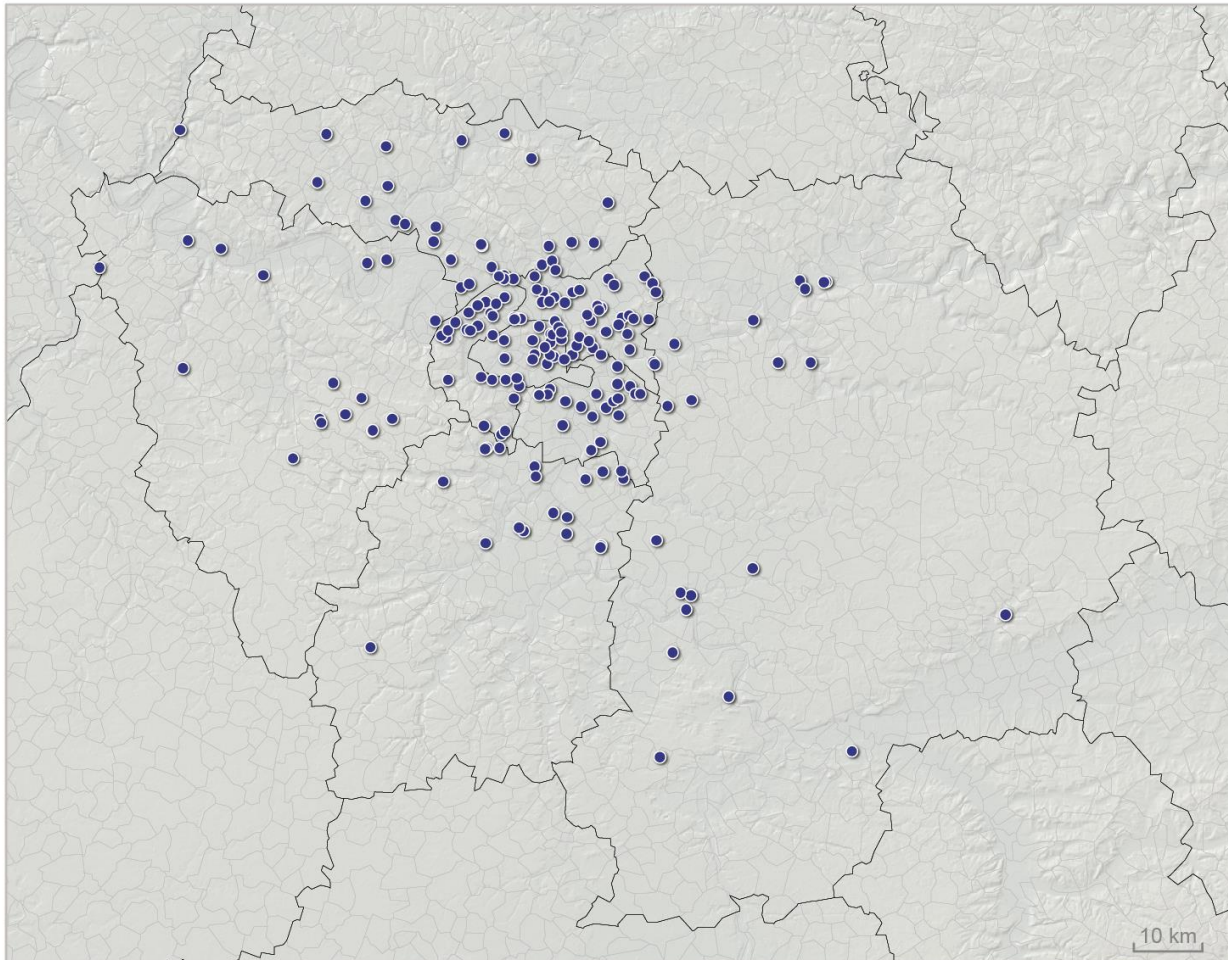


- « Clusters » in time and space



- Epidemic disease?

Temporo-spatial pattern ?

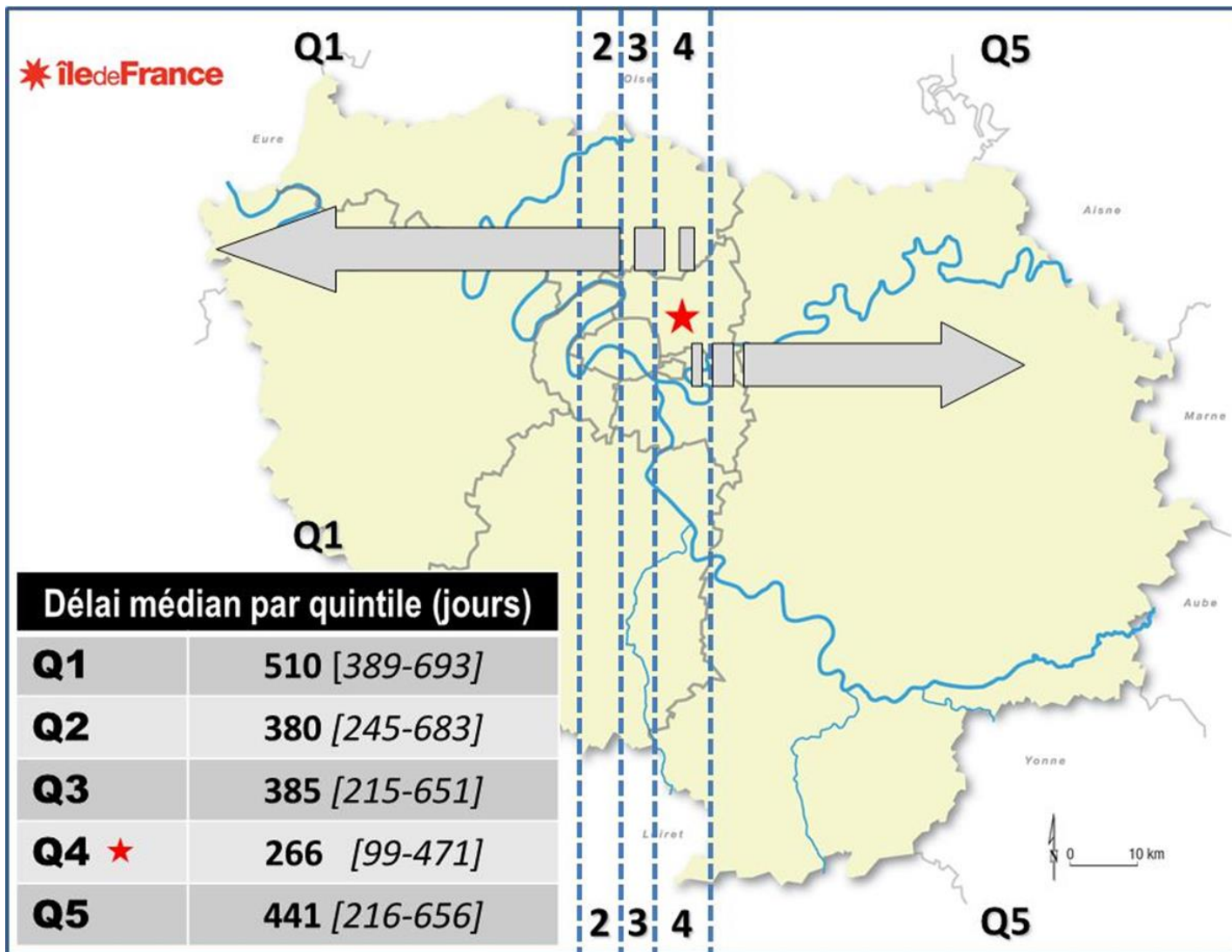


● Incident patient (n=188)

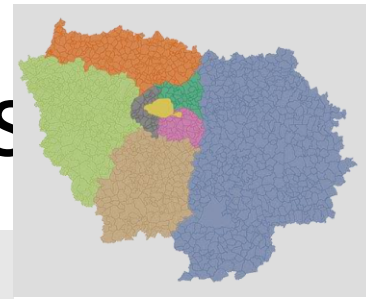
Source : CIAT-CSI (SRTM <http://srtm.csi.cgiar.org>) 2010



Longitudinal progression ?



Incidence within counties

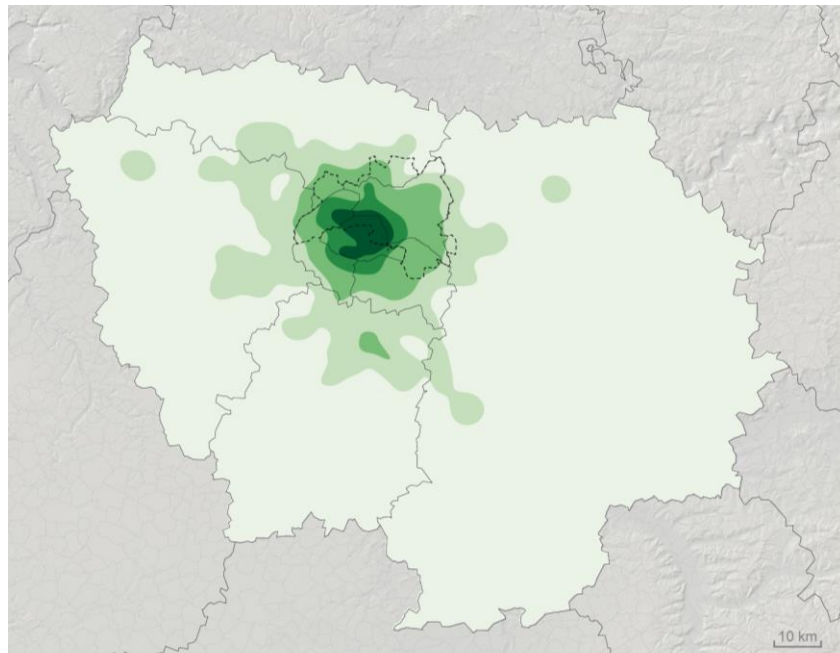


county	N observed / N expected	SIR [CI 95%]	p
75	13/21	0.61 [0.33; 1.05]	0.08
78	14/20	0.70 [0.38; 1.17]	ns
91	16/17	0.93 [0.53; 1.52]	ns
95	17/17	0.99 [0.58; 1.58]	ns
92	21/21	1.00 [0.62; 1.53]	ns
94	18/18	1.02 [0.60; 1.61]	ns
77	20/19	1.07 [0.65; 1.65]	ns
93	37/23	1.60 [1.13; 2.21]	0.009

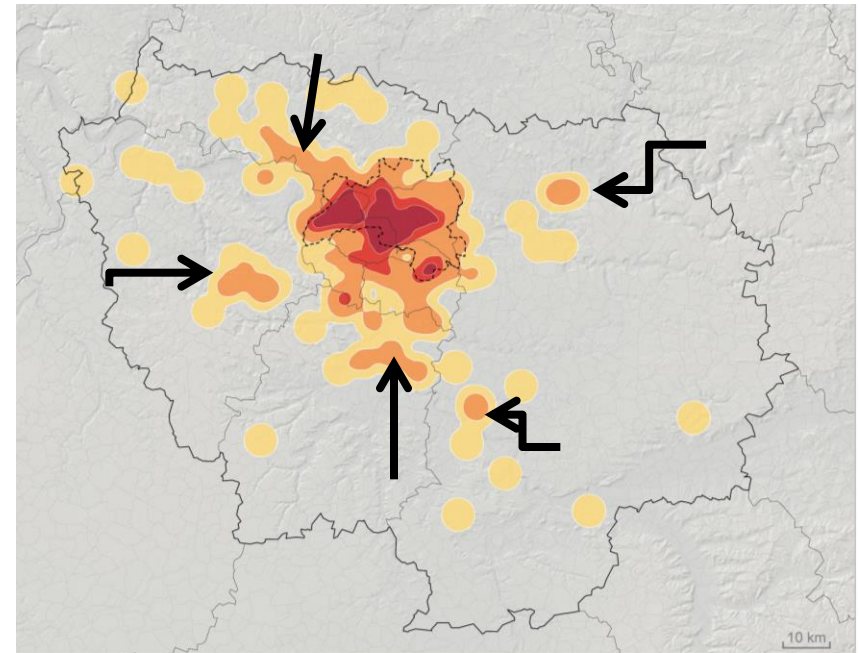
- Higher incidence in the 93

Kernel density map

Radius 5km

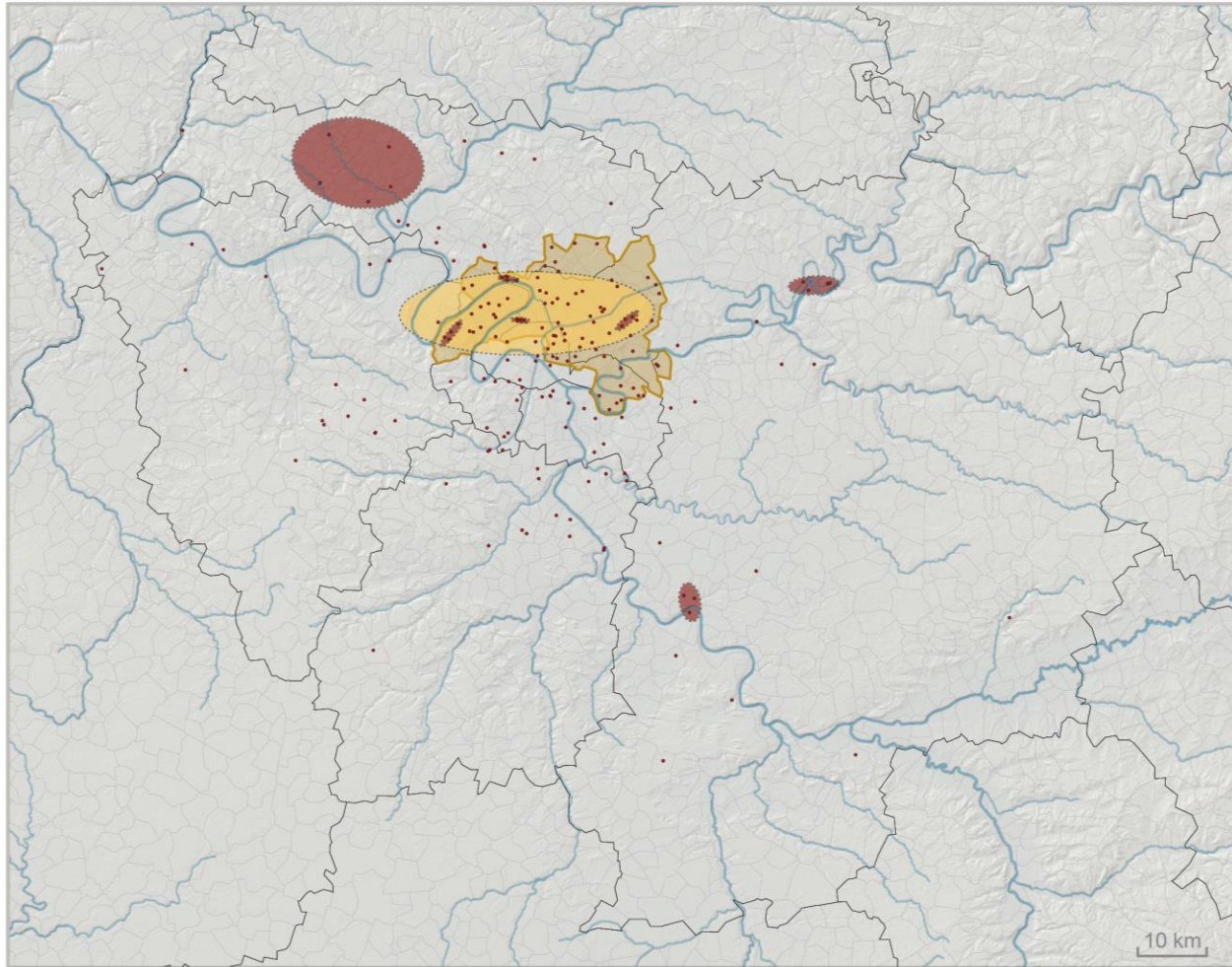


Density of population <16y



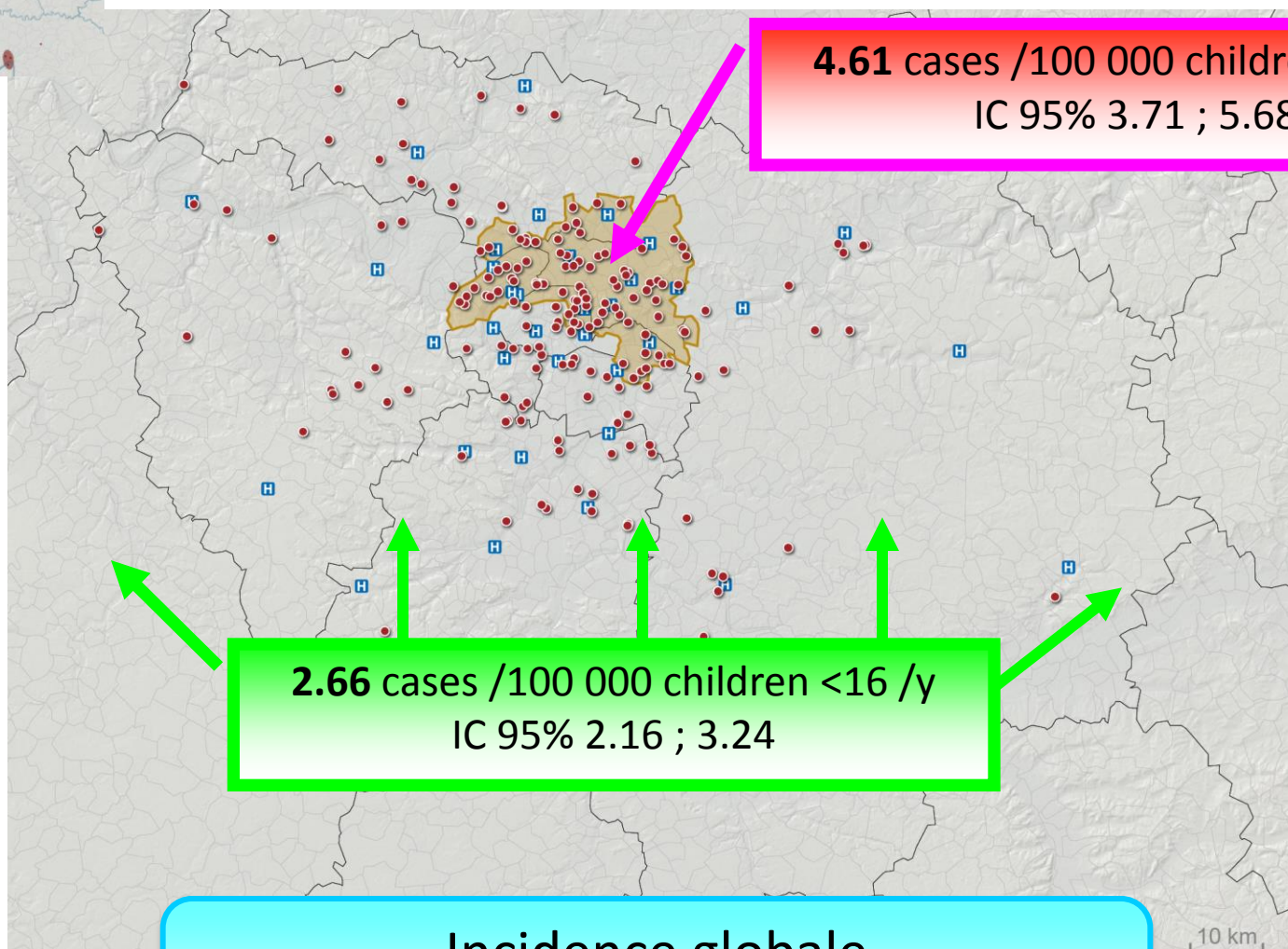
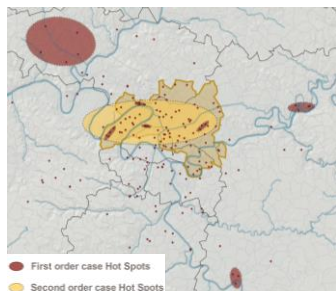
Density of cases

Nearest-neighbour hierarchical clustering

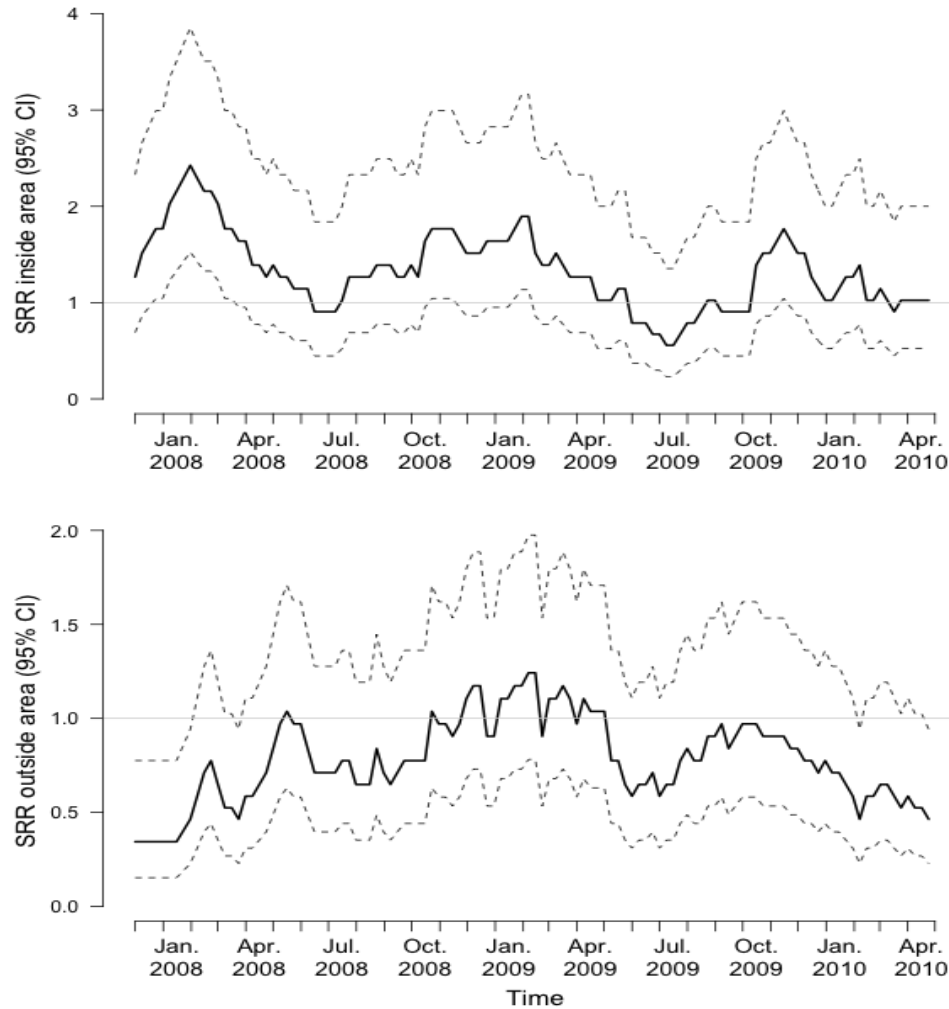


Source : CIAT-CSI (SRTM <http://srtm.csi.cgiar.org>) 2010

Overincidence area



Temporal pattern in the overincidence area



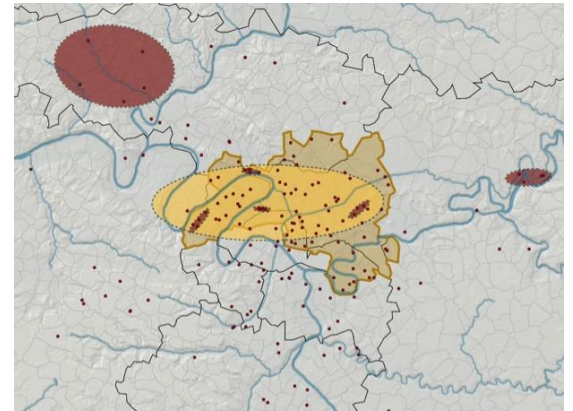
- Winter periodicity in the overincidence area

Environmental factor in this area ?

- Industrial area
- Winter periodicity

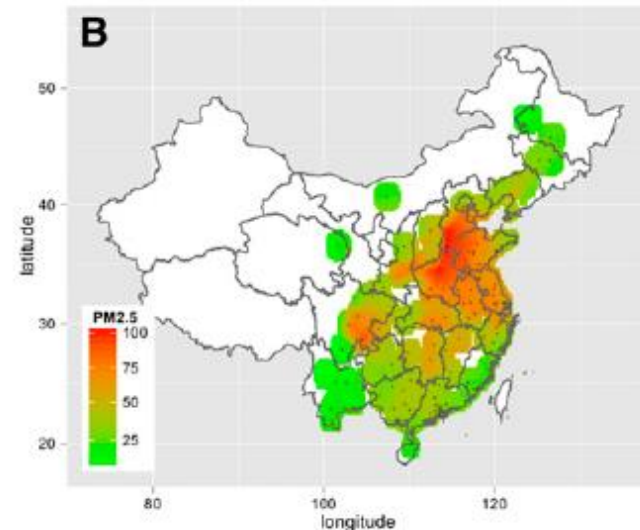
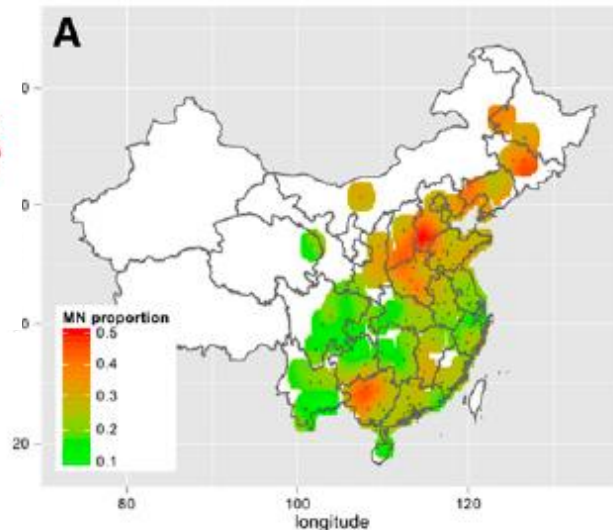
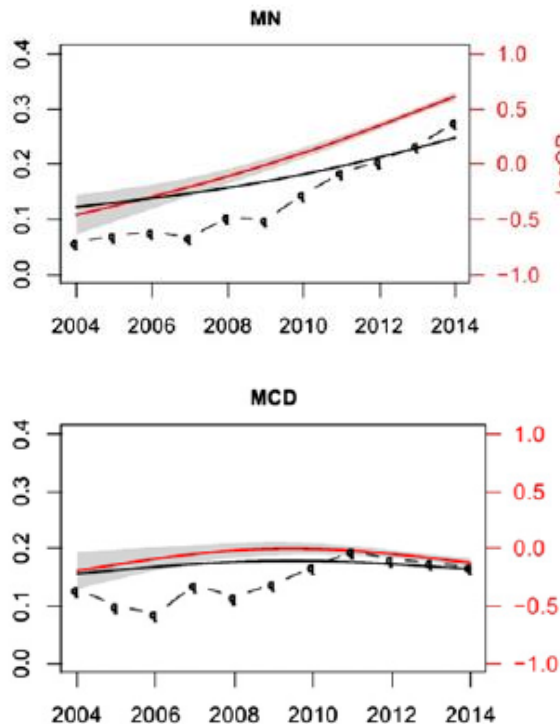


- Atmospheric pollution ?
- Winter peak of PAH (hydrocarbures aromatiques polycycliques)
 - Industries
 - domestic heating
 - Car circulation



Environment and renal disease

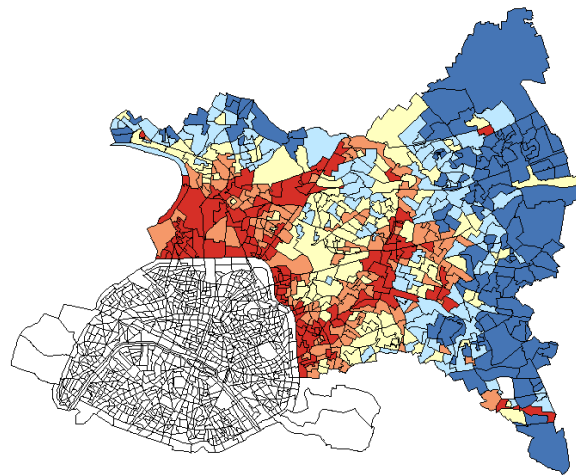
- Air pollution and nephropathies 2004-2014
- Correlation Membranous N. // exposition $PM_{2.5}$



- But no correlation in INS

Atmospheric pollution around Paris

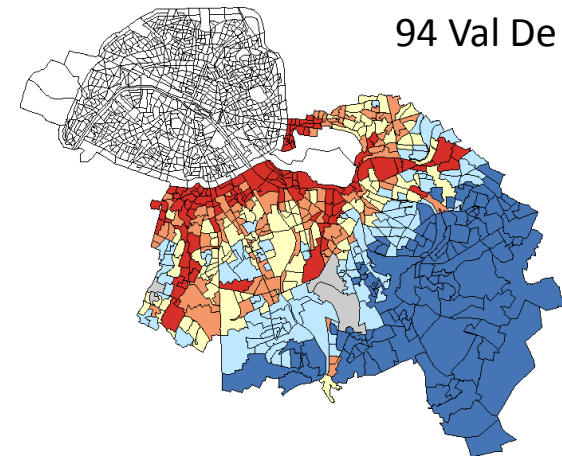
- O_3 , CO , NO_2 , Plomb, Particules Fines (PM_{10} , $PM_{2.5}$), composants organiques volatiles..
- « multi-polluant » approach
- Climatological cofactors (temperature, humidité)



93 Seine St Denis

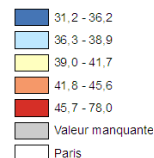
Etude Equit'air - Données Airparif 2002-2009

NO_2

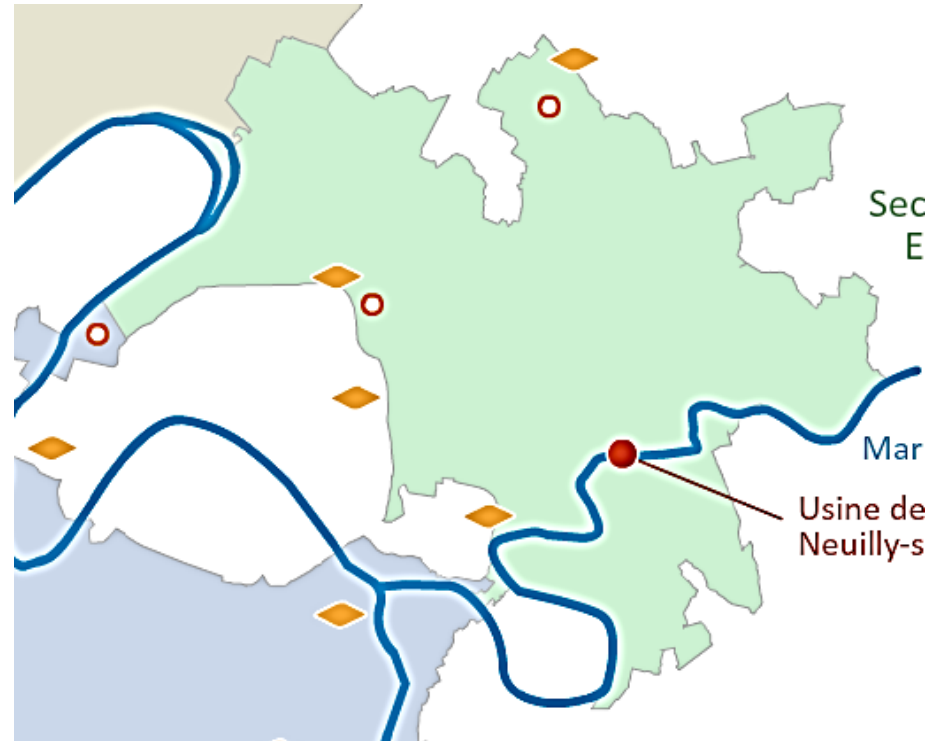
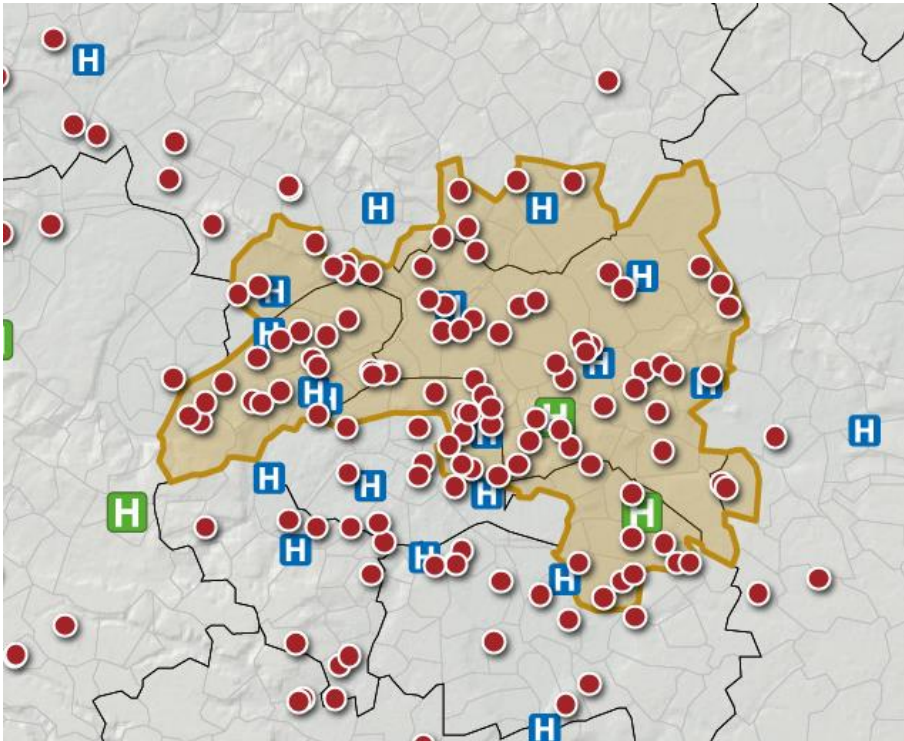


94 Val De Marne

Légende

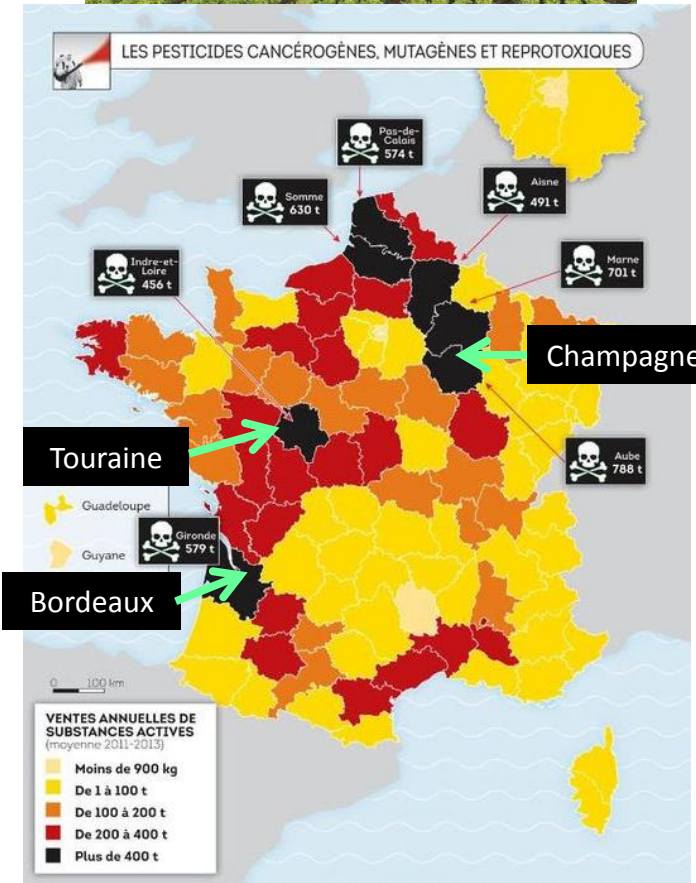
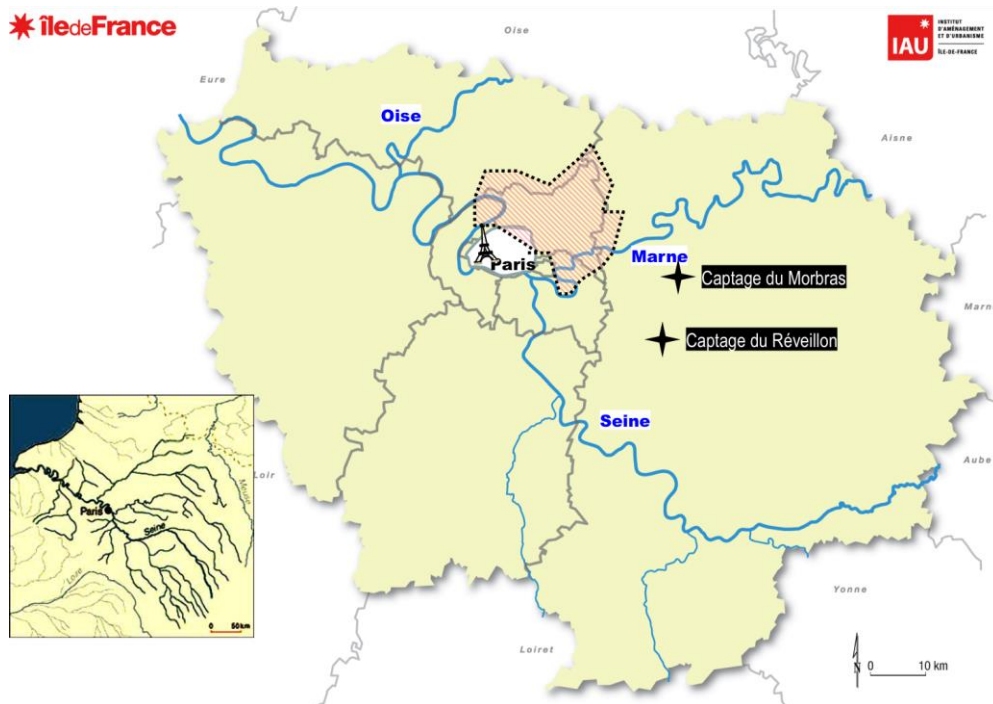


Overincidence area : another factor ?



Water ?

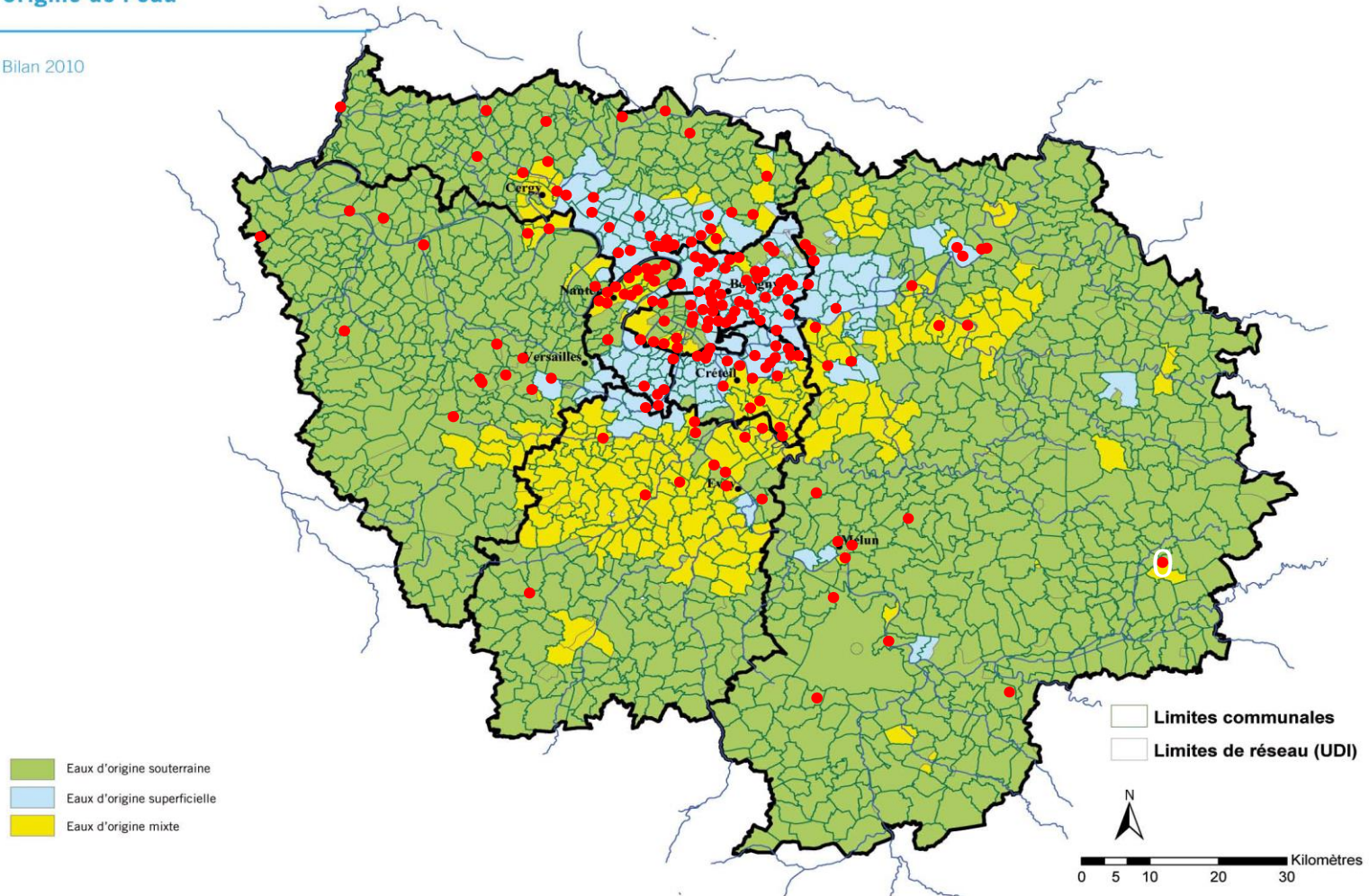
Environment and East-West progression ?



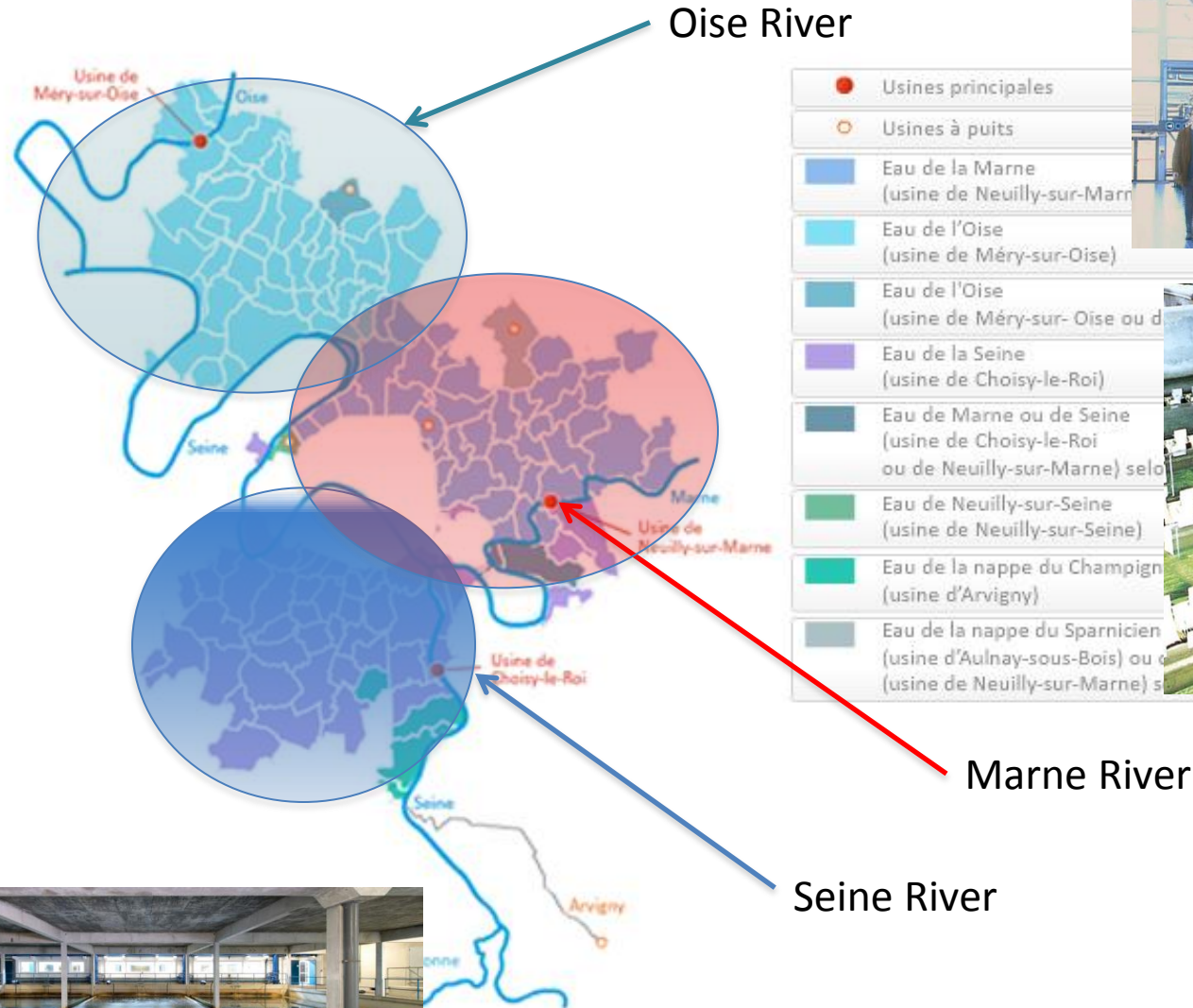
Drinking water origin in the Paris Area

Origine de l'eau

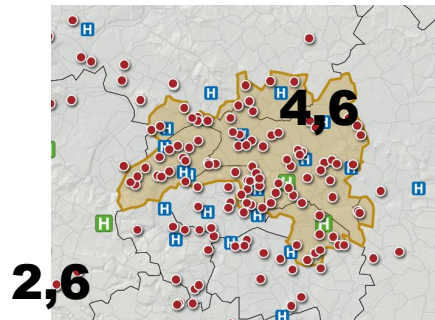
Bilan 2010



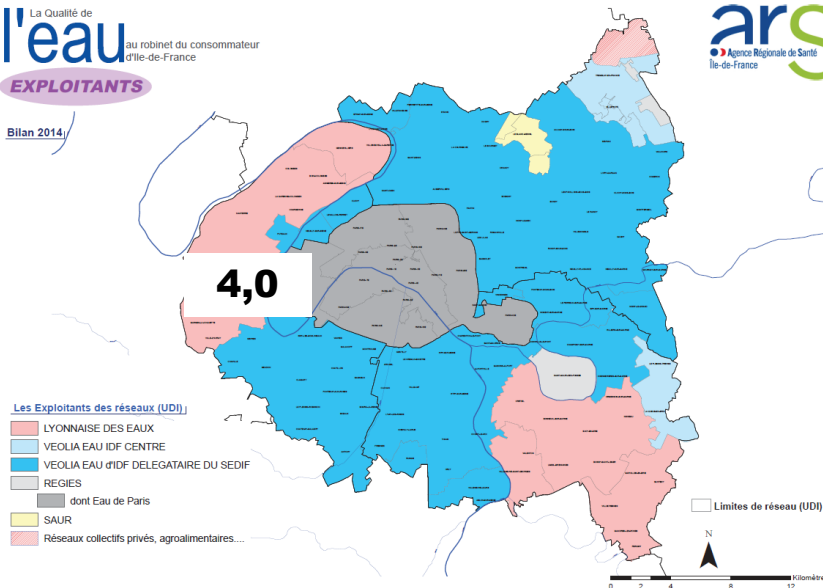
Drinking water supply around Paris



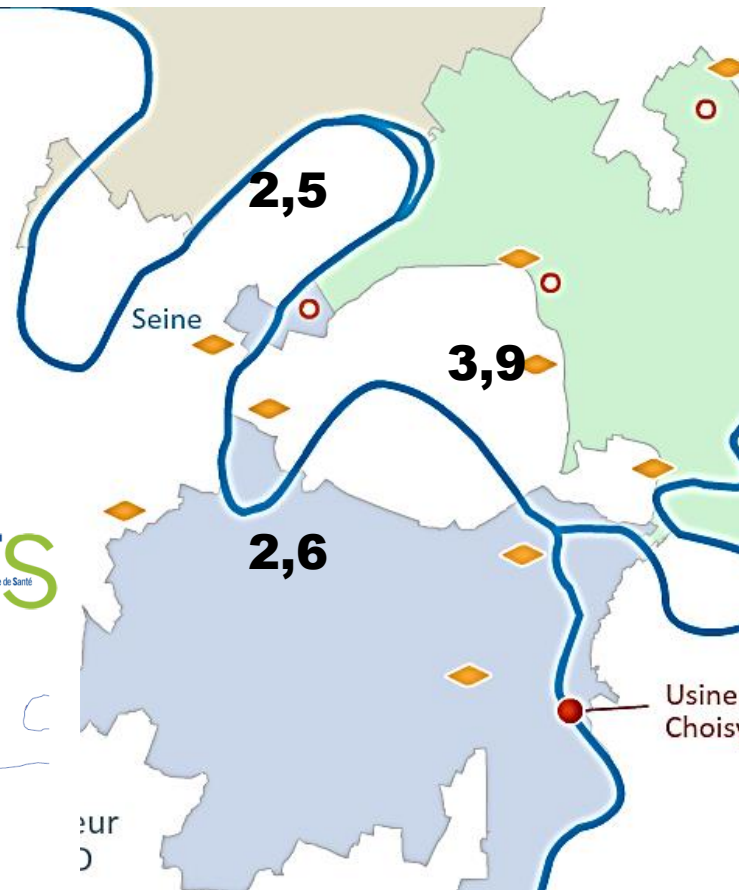
Drinking water and INS incidence



La Qualité de
l'eau
au robinet du consommateur
d'Ile-de-France
EXPLOITANTS
Bilan 2014



ars
Agence Régionale de Santé
Île-de-France



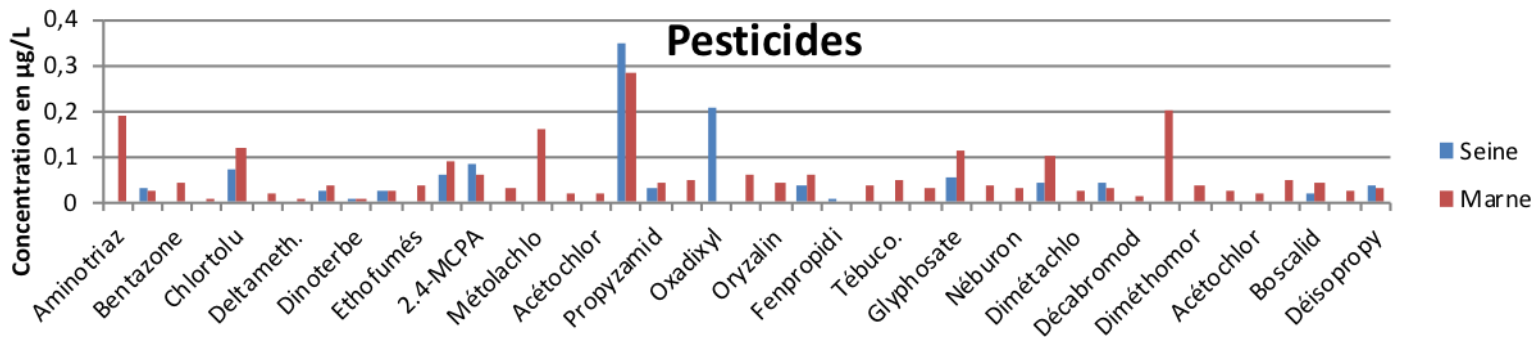
Réseaux Veolia-SEDIF



The WATER factor?

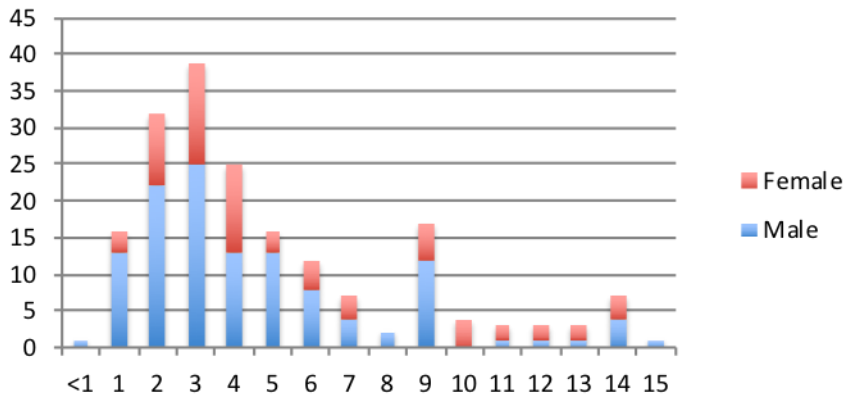
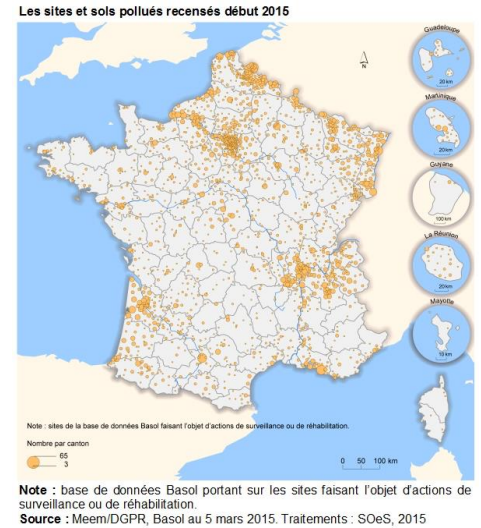
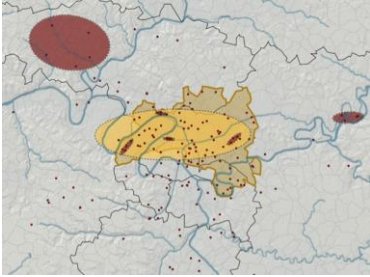


- Surface water as a vector
 - Drinking water ? Activities in contact with water ?
- Which kind of pollution ?
 - Microbiologic pollution
 - Chemical pollution : toxics, pesticides, ..
 - Comparaison river Seine / Marne



- Exposition ?
 - One hit or cumulative exposition?
 - Link to winter periodicity ? Viral infection = 2nd hit ?

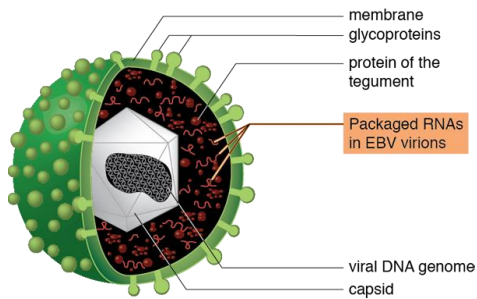
Soil pollution ?



Childhood Soil Ingestion: How Much Dirt Do Kids Eat?

- Frequent mouthing of objects and hands, play activities
- Soil/Dust Ingestion Rate is higher in toddlers (60-200mg/d)
- Houses/schools/playgrounds on former industrial sites

Why the nephrotic hotspots..



As a conclusion

- Epidemiology might bring missing keys to understand the pathophysiology of INS
- In the Paris area, clustering of cases, longitudinal progression and seasonal variation suggest that INS occurs on an epidemic mode
- Proximity to rivers, winter periodicity, spatial coincidence with tap-water distribution raise the question of environmental factors
- Individual factors/environmental factors
- Environmental epidemiology is the next step

Acknowledgements to
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Hélène Blanchoud, Georges Deschênes

&

Thank you for your attention

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