

# Vaccination and Narcolepsy Causal or Not ?

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Advanced Course in Vaccinology  
Annecy 14 May 2014

Vaccine Programme Unit



NATIONAL INSTITUTE FOR HEALTH AND WELFARE, FINLAND



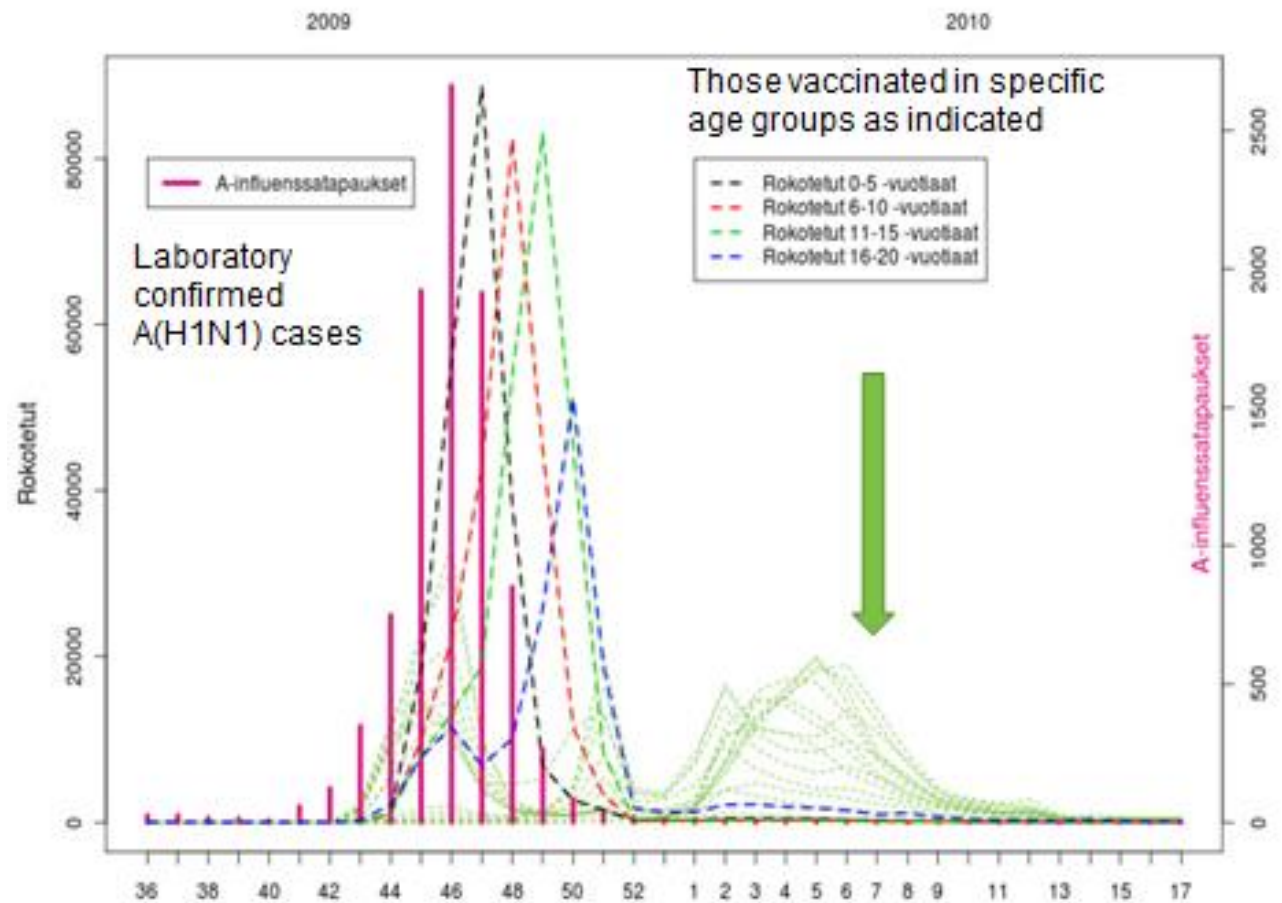
# Disclosures

- THL has strong public health inclination
- THL holds a major research contract with GSK on 10-valent pneumococcal conjugate
- HN: scientific coordination of ARIVAC consortium on phase III with PCV10 with sanofi pasteur as one of members
- HN: Advisory board of PCV – GSK, Pfizer, ECDC
- HN: Payments for lecturing - Crucell and GSK

No personal payments from industry since 2011.

# Narcolepsy vs Pandemrix

... "so is it true"? narcolepsy .... Zzzzzzzzz -----



# The only pandemic vaccine available for Finland in 2009 = Pandemrix<sup>R</sup> =A(H1N1) virusantigen and AS03 adjuvant



EMA licensed;  
Safety profile  
acceptable  
in Phase II

A similar  
vaccine  
Arepanrix<sup>R</sup>  
used in  
Canada



# Narcolepsy-cataplexy

ICSD-2 2005, ICD10 G47.4

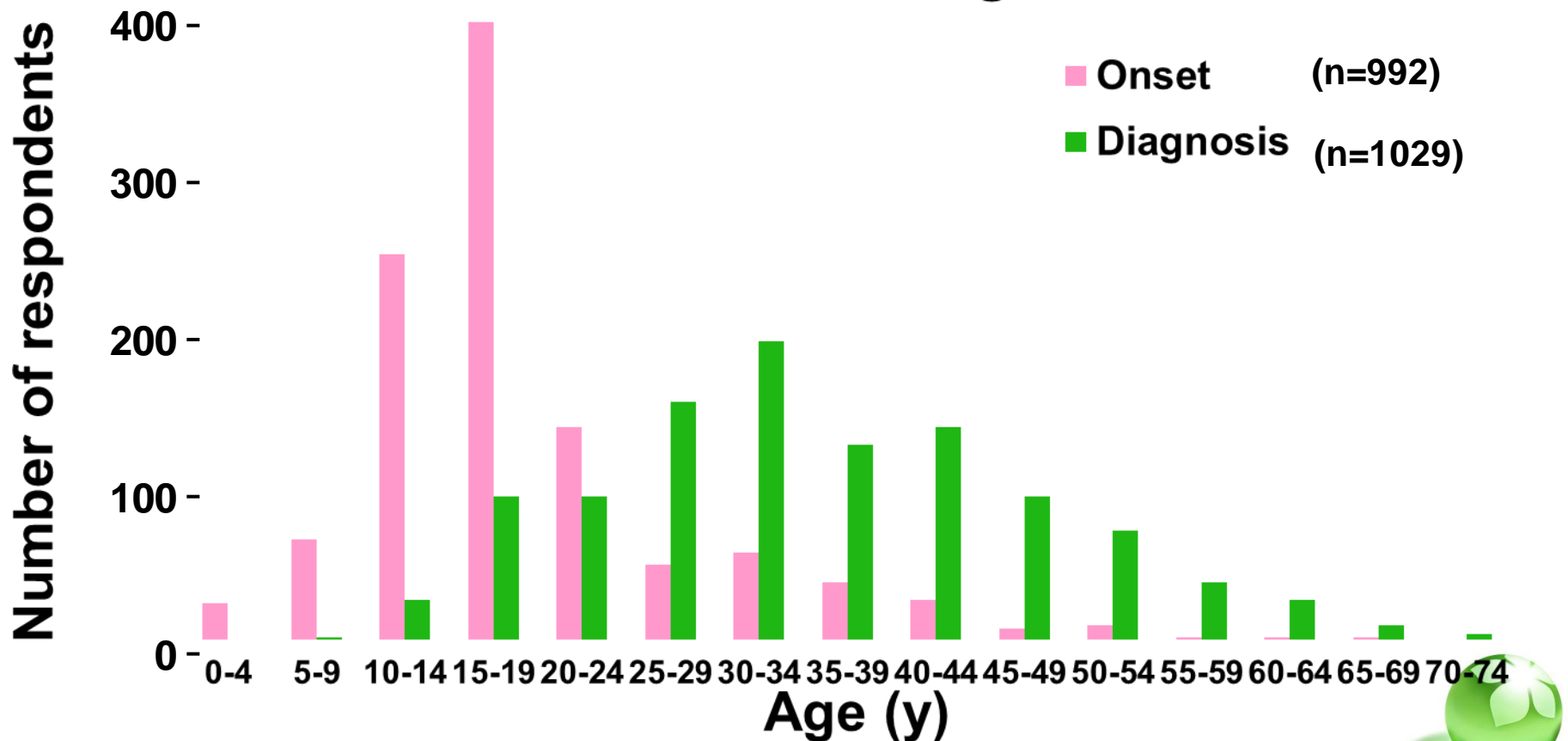
rare chronic disease, 1/100 000

- A. Excessive day time sleepiness >3 mo, daily
- B. Cataplexy (= abrupt temporary loss of muscle tension in association with emotional / tense situations)
- C. Diagnosis confirmed with polysomnography and multiple sleep latency test MSLT / alternatively Li-hypocretin (orexin) concentration  $\leq 110$  pg/mL
- D. No other better explanation



Peak age at onset is ~15 years of age.  
But diagnosis is often delayed.

## Total Onset vs Total Diagnosis



# Clinical forms of narcolepsy

	Prevalence among narcoleptic patients	<b>HLA DQB1*0602 positive</b>	Li-Hypocretin / Orexin Low ≤110 pg/mL
<b>Narcolepsy - cataplexy</b>	>50 %	<b>&gt; 90 %</b>	> 90 %
Narcolepsy without cataplexy	10-50 %	41 %	10-21 %
Symptomatic narcolepsy <sup>1</sup>	116 patients (review)	17 %	most
Population	-	11-35 %	0

ICSD-2 2005; <sup>1</sup>Nishino and Kanbayashi 2005; Knudsen et al. 2010; Ritchie et al. 2010  
According to Hublin 2010

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# DQB1\*0602

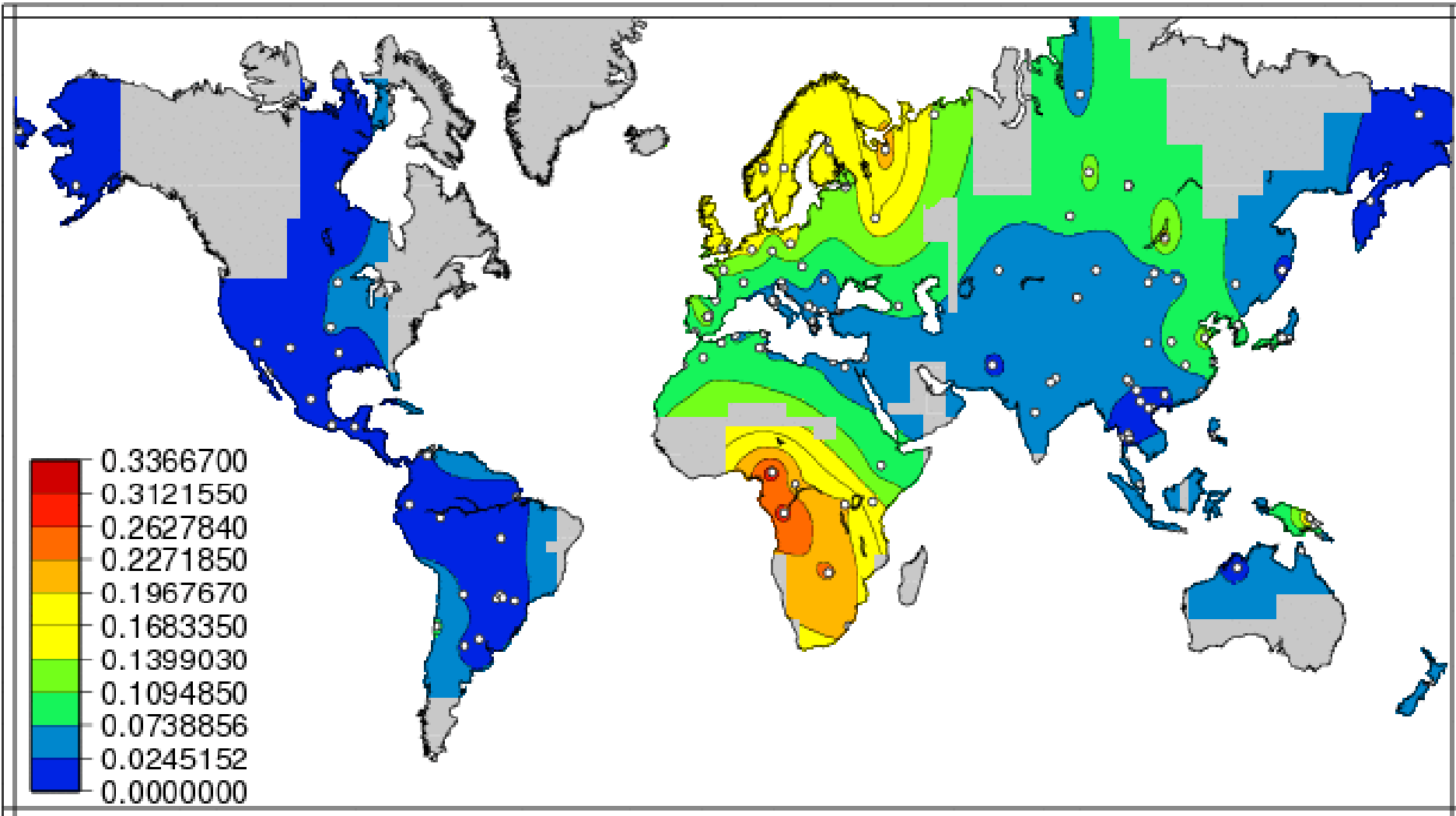


Image from Solberg et al. (2008) – see [www.pypop.org/popdata](http://www.pypop.org/popdata) for more info.



# Etiology of narcolepsy ?

## The multifactorial model



# So what happened ?



17.8.2010



## Sweden opens inquiry into suspect flu vaccine

AFP / STOCKHOLM — Sweden's Medical Products Agency opened an inquiry Wednesday into vaccinations for swine flu made by British pharmaceutical company GlaxoSmithKline, suspected of provoking narcolepsy.

"The MPA has received **six reports** from health care professionals regarding narcolepsy as suspected adverse drug reaction following Pandemrix flu vaccination," it said in a statement.

"The agency will, in consultation with external experts, assess the possible relationship between the vaccination and the reported reactions."

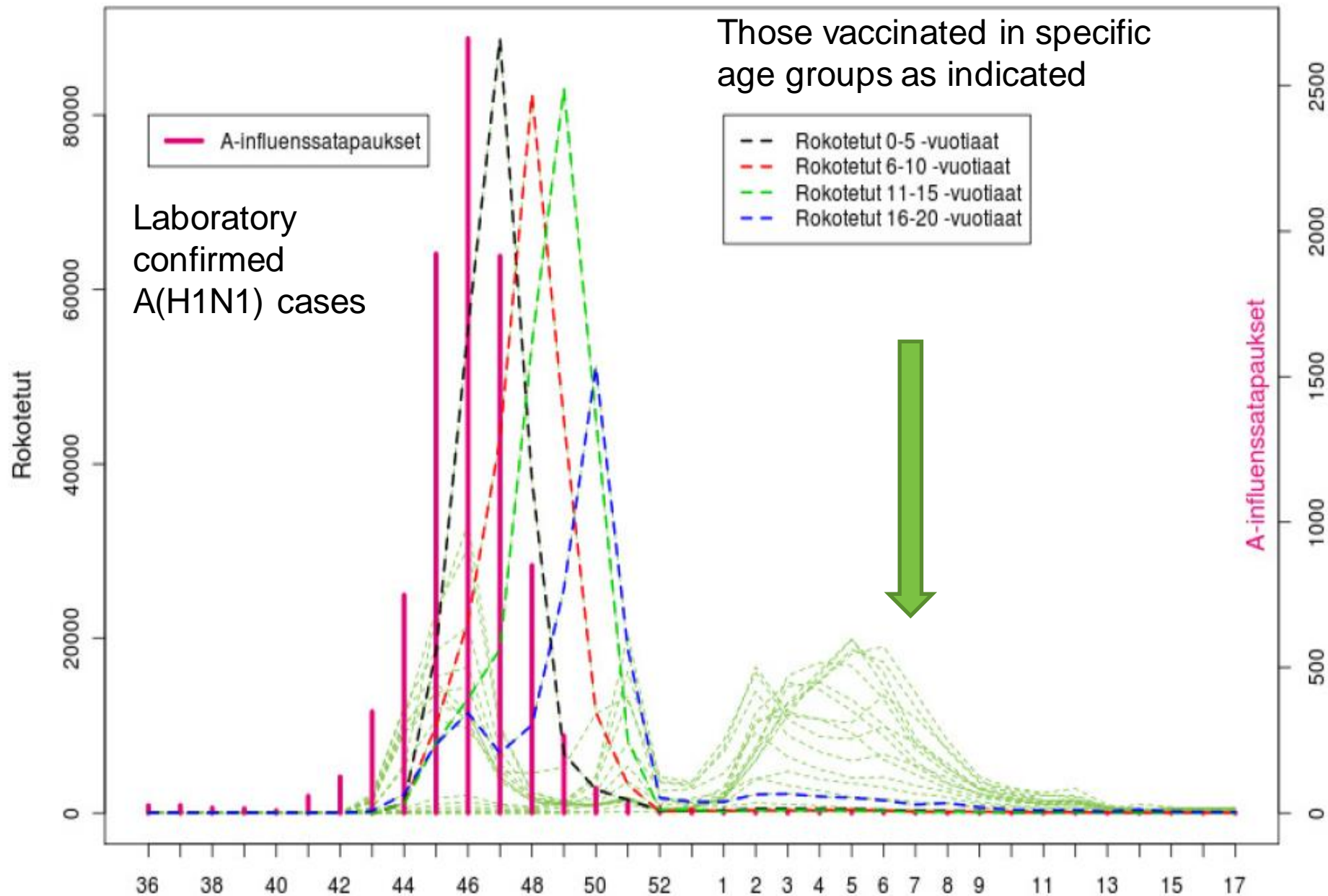
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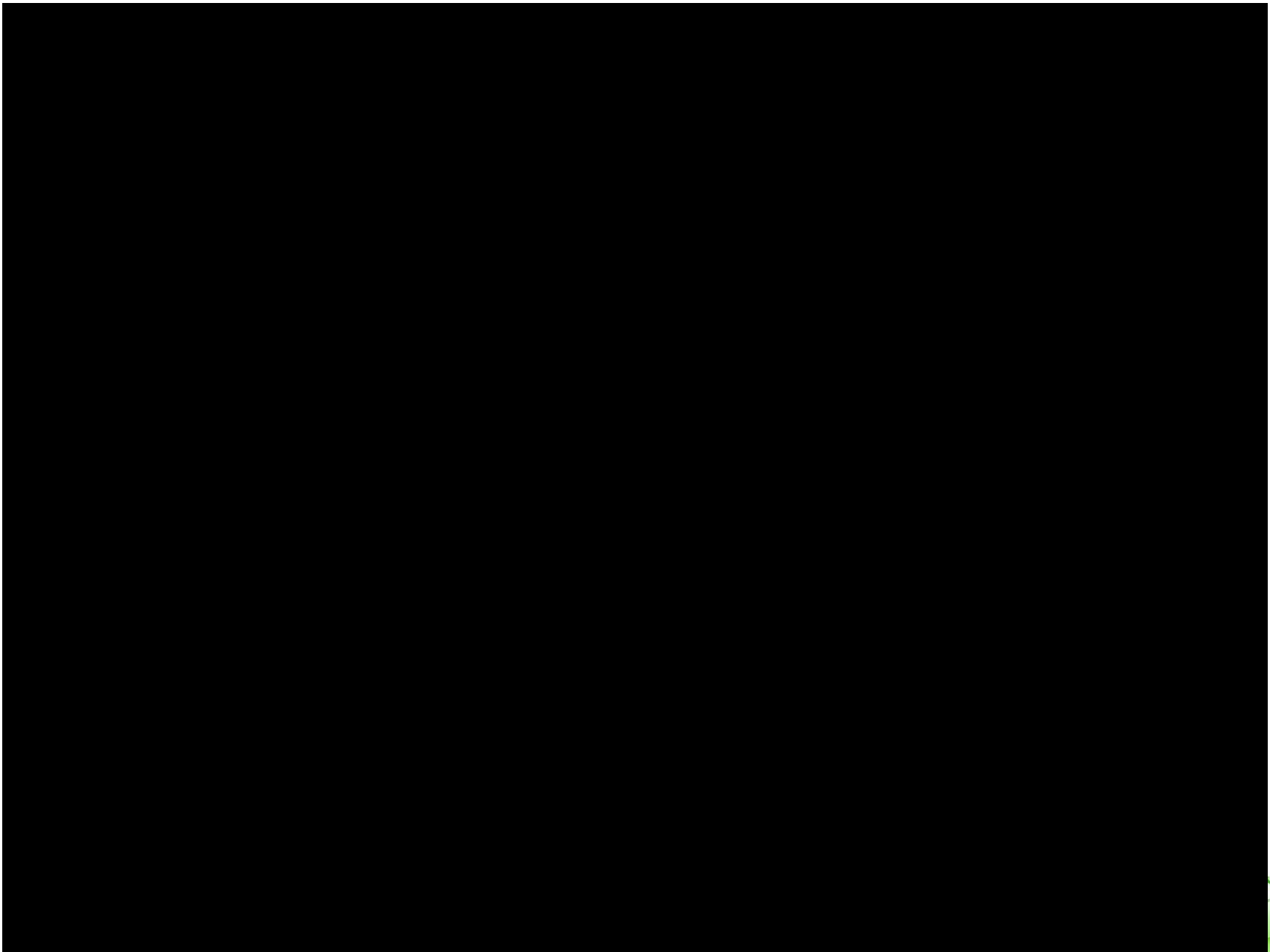


2009

2010

Those vaccinated in specific age groups as indicated





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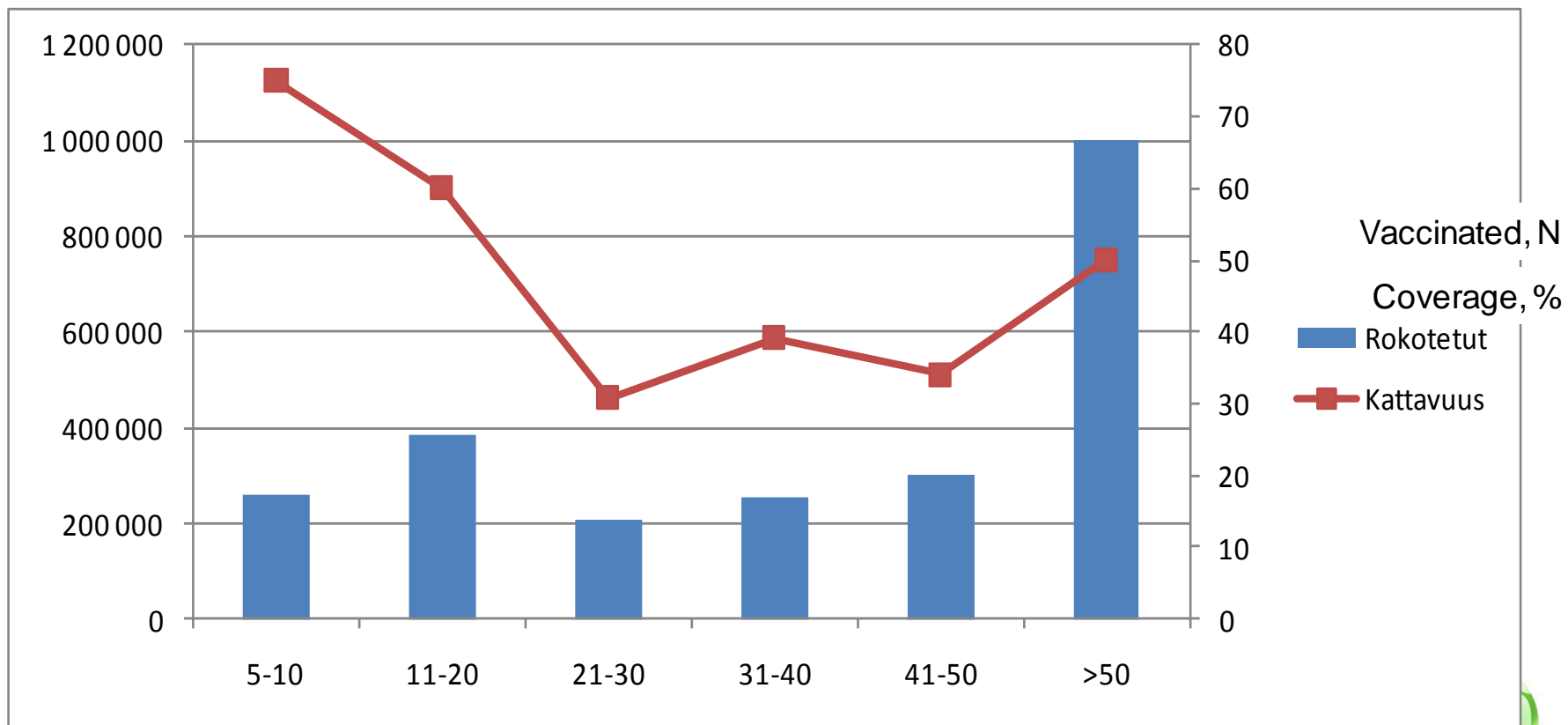


# Exposure

## The number of Pandemrix<sup>R</sup> vaccinated in Finland

Number of vaccinated

Vaccine coverage, %

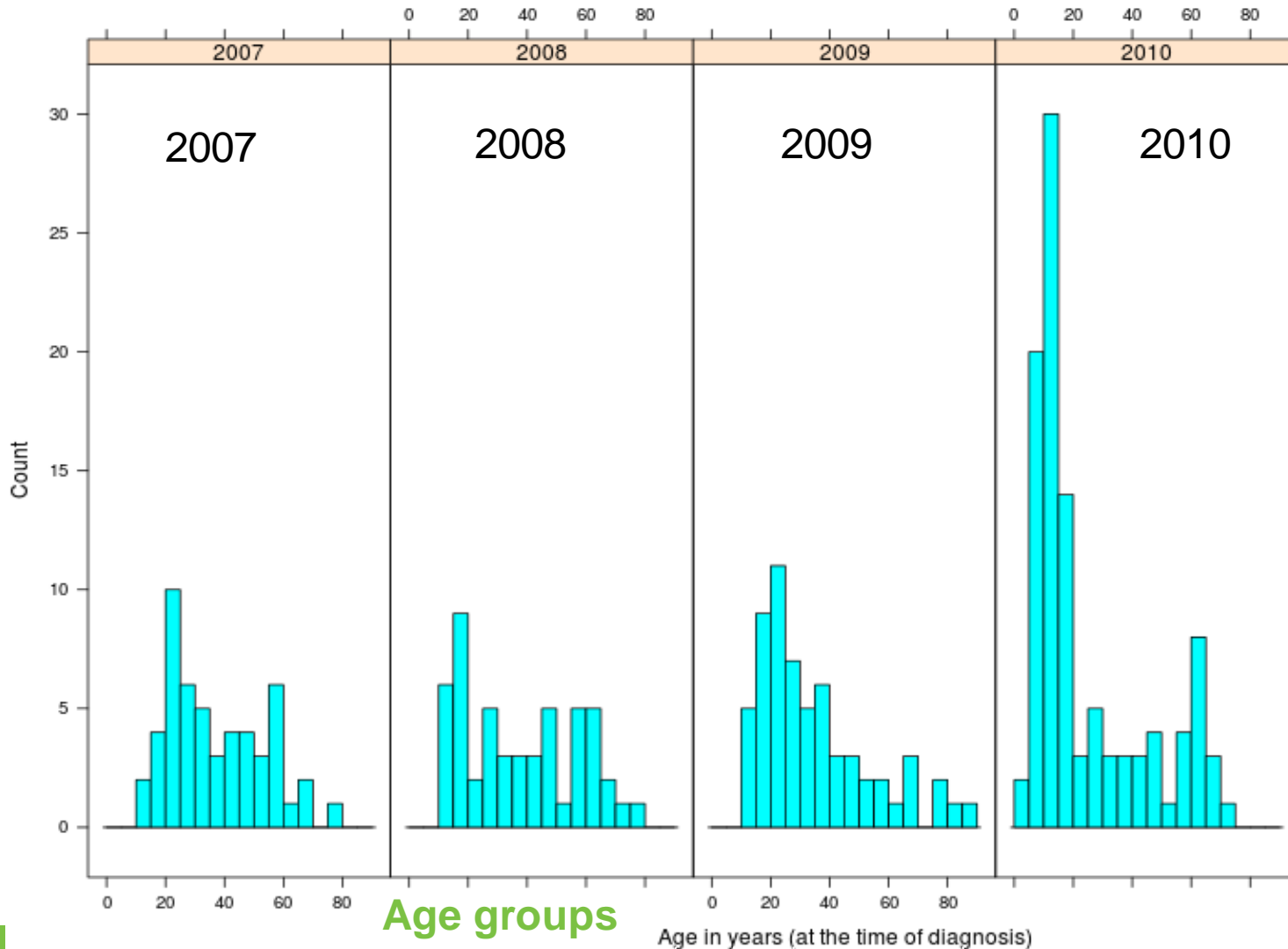


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# Is there a signal ?

## Based on hospital discharge register data

Years of observation **Narcolepsy cases by age and calendar time**



**Among those  
4-19 yrs**

**Expected =  
1 / 100 000**

**Observed =  
8 / 100 000**

Are others seeing a signal? Should we alert others ?

# How many individuals in the susceptible age group were exposed ?

Country	Pandemrix <sup>R</sup> Doses given to 4-19 yr old	Comment
Sweden	~1 000 000	
Finland	668 000	
Ireland	339 312	
Norway	470 000	5-18 year olds
France	?	
Germany	~700 000	
Great Britain	~295 000	5-16 year olds
Canada, entire country	~ 1 200 000	Pandemrix-like Arepanrix <sup>R</sup>
Canada, Quebec	793 448	5-18 year olds



# Studies initiated to verify signal

- In Sweden
- In Finland
- The European Medical Agency EMA
  - ECDC contracted the VAESCO consortium study in 8 European countries,
  - GSK contracted a study in Canada with Arepanrix<sup>R</sup>



# In Finland, Retrospective cohort study

## Materials and methods (1)

- Cohort = born  $\geq 1991$  & officially living in Finland
- Primary follow up period 1.1.2009 - 16.8.2010
- Variables entered into analysis
  - Pandemrix<sup>R</sup> vaccination
  - Onset of narcolepsy
- Pandemrix vaccination records systematically collected from primary health care
- 1000 vaccination records validated



# Retrospective cohort study

## Materials and methods (2)

- Listings of all newly diagnosed narcoleptic cases (ICD10 code **G47.4**) registered during years 2009-10 in the central hospital registers
- Two sleep medicine experts independently of each other reviewed all the patient records of these cases
- Brighton Collaboration narcolepsy-cataplexy diagnostic criteria were used (Poli F et al. Vaccine 2013)
- Disagreement solved by a panel of 3 other sleep medicine experts = final decision



# Narcolepsy

## Brighton Collaboration case definition

- Level 1
  - Excessive daytime sleepiness and/or suspected cataplexy AND
  - CSF hypocretin-1 deficiency
- Level 2
  - Excessive daytime sleepiness AND
  - Definite cataplexy AND
  - Level 1 or 2 MSLT abnormalities
- Level 3
  - Excessive daytime sleepiness AND
  - Level 1 MSLT abnormalities
  - Absence of other mimicking disorders

**Levels 1-3 included as cases**



# A disease with usually an insidious start

## What dates to be used for onset of narcolepsy ?

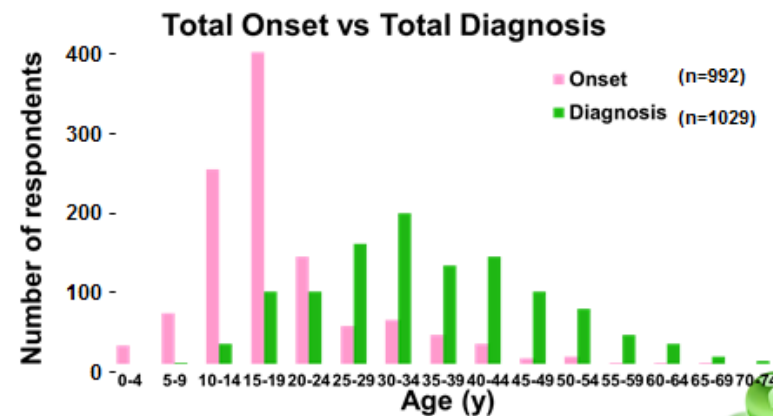
- Onset of EDS

Estimate from medical records

= information mainly obtained from parents

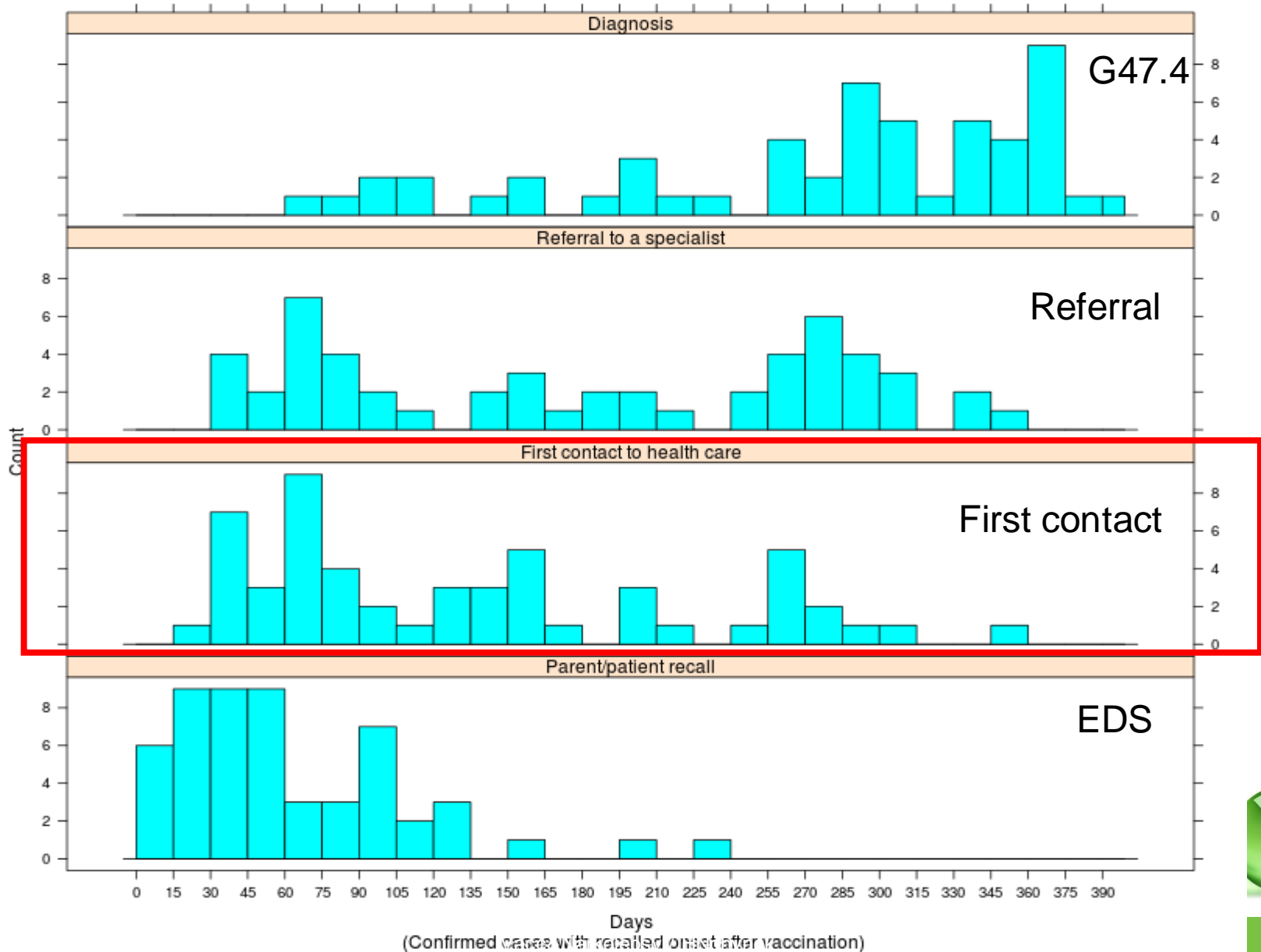
- First documented contact to health care
- Referral to specialist / neurologist
- Diagnosis G47.4

Peak age at onset is ~15 years of age.  
But diagnosis is often delayed.



# Retrospective cohort study final results

## Onset time differences related to date of vaccination



# Relative risk of narcolepsy among Pandemrix vaccinated vs. not vaccinated in Finland

Register based, retrospective cohort study

Follow-up period	Narcolepsy cases		Follow-up years		Relative Risk		
	Not vacc	Vacc	Not vacc	Vacc	Risk ratio	95% LCL	95% UCL
First contact: 2009-01-01 to 2010-12-31	7	57	1069247	762461	11.4	5.6	27.5
<b>First contact: 2009-01-01 to 2010-08-15</b>	7	46	986195	510874	<b>12.7</b>	<b>6.1</b>	<b>30.8</b>

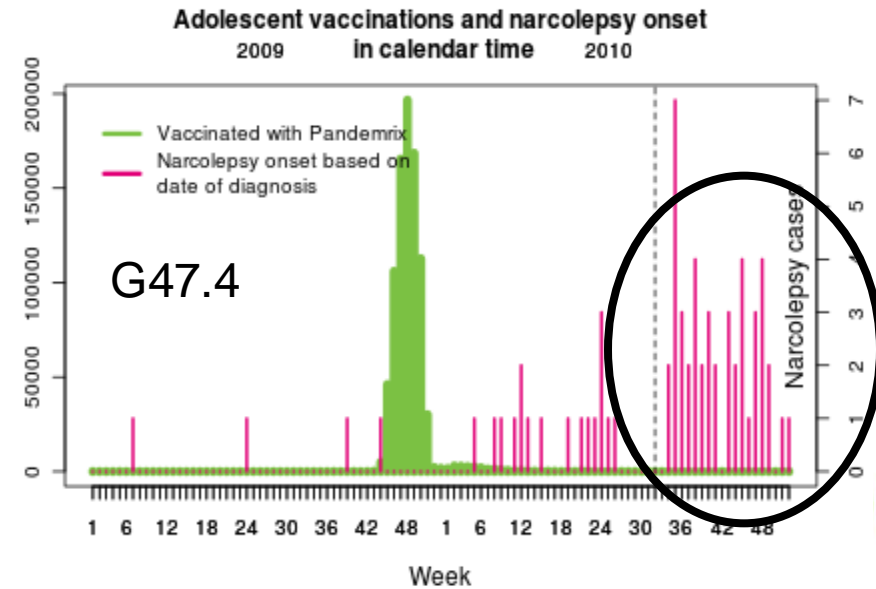
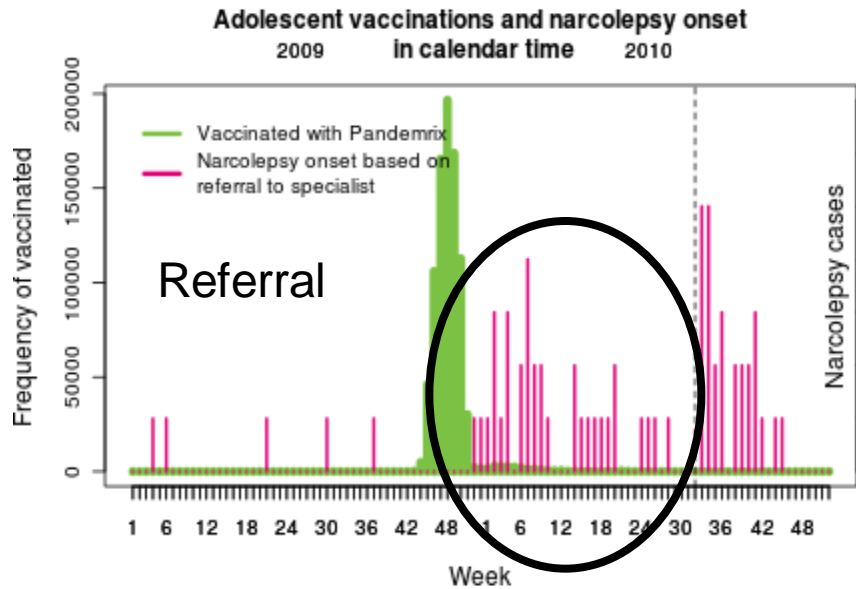
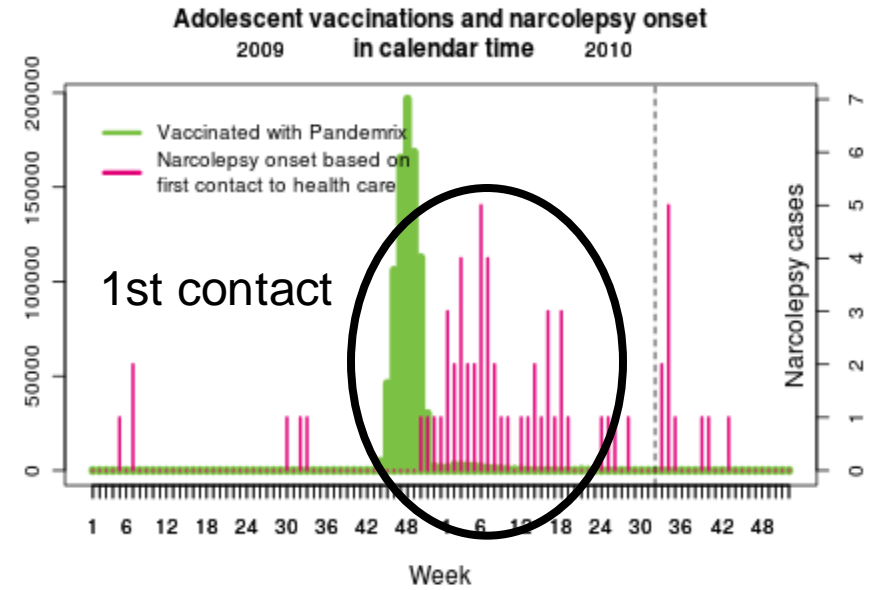
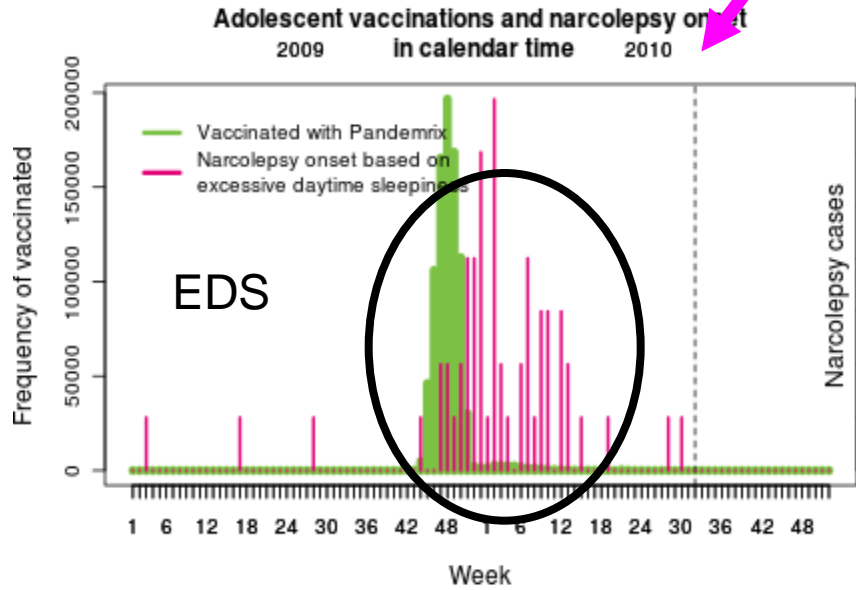
**Vaccine attributable risk for developing narcolepsy  
= 6 / 100 000 among those vaccinated 4-19 years of age**

**= 1 / 16 000 ”**



THL Final Report 31.8.2011  
NATIONAL INSTITUTE FOR HEALTH AND WELFARE FINLAND  
Nohynek et al PLOS One 2012

# MPA Sweden press release on association





# EMA precautionary recommendation July 2011



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

27 July 2011  
EMA/CHMP/568830/2011 corr\*<sup>1</sup>  
Press Office

## **Press release**

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### European Medicines Agency recommends restricting use of Pandemrix

In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.

# The letter from the Lancet Editor

Email 24 October 2011

Dear Dr. Nohynek,

... After a detailed and long discussion, the feeling among the rest of the editorial board was that it is best to let go the two narcolepsy papers due to **lack of known mechanism to explain it** and **recall bias**. I am so, so very sorry....

The official **Lancet** email will be arriving shortly.

BMJ – also **NoGo**

# AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland

Hanna Nohynek<sup>1\*</sup>, Jukka Jokinen<sup>1</sup>, Markku Partinen<sup>2</sup>, Outi Vaarala<sup>1</sup>, Turkka Kirjavainen<sup>3</sup>, Jonas Sundman<sup>1</sup>, Sari-Leena Himanen<sup>4</sup>, Christer Hublin<sup>5</sup>, Ilkka Julkunen<sup>6</sup>, Päivi Olsén<sup>7</sup>, Outi Saarenpää-Heikkilä<sup>8</sup>, Terhi Kilpi<sup>1</sup>

OPEN ACCESS Freely available online

 PLOS ONE

## Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland

Markku Partinen<sup>1,2,15\*</sup>, Outi Saarenpää-Heikkilä<sup>3</sup>, Ismo Ilveskoski<sup>4</sup>, Christer Hublin<sup>5</sup>, Miika Linna<sup>6</sup>, Päivi Olsén<sup>7</sup>, Pekka Nokelainen<sup>8</sup>, Reija Alén<sup>9</sup>, Tiina Wallden<sup>10</sup>, Merimaaria Espo<sup>10</sup>, Harri Rusanen<sup>11</sup>, Jan Olme<sup>12</sup>, Heli Sättilä<sup>13</sup>, Harri Arikka<sup>14</sup>, Pekka Kaipainen<sup>15</sup>, Ilkka Julkunen<sup>16</sup>, Turkka Kirjavainen<sup>17</sup>

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**Could the association be  
verified in other than  
the signaling countries  
Sweden and Finland ?**



Could other countries verify the signal ?

## Exposure

Those 4-19 years of age vaccinated with Pandemrix<sup>R</sup>/Arepanrix<sup>R</sup> and narcolepsy cases spontaneously notified to AEFI registers by 24 January 2011

Country	Notified cases	Vaccinated 4-19 year olds	Cases / 100 000 vaccinated
Island	3	31 958	9,4
Finland	54	668 000	8,1
Sweden	58	1 193 000	4,9
Norway	8	510 000*	1,6
The Great Britain	2	295 000**	0,7
Germany	5	928 000***	0,5
Canada	2	~ 2 000 000	0,1

\*5-19-year olds / \*\*5-16 –year olds / \*\*\* 0-17-year olds

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# In all countries where Pandemrix<sup>R</sup> was used in large numbers in susceptible age group, association was observed

	Age group yrs	Study design	Definition of onset	Follow up period	Risk (RR/OR)	95 % CI
<b>Finland</b>	4-19	Cohort	1. contact with HC	1.1.2009-15.8.2010	12.7	6.1 - 30.8
<b>Sweden</b>	≤19	Cohort	Date of dg G47.4	1.10.2009-31.12.2010	4.06	2.87 - 5.58
	21- 30	Cohort		1.10.2009 – 31.12.2011	2.18	1.00-4.75
	31- <40				1.58	0.68-3.44
<b>Ireland</b>	5-19	Cohort	1. contact with HC	1.4.2009-31.12.2010	13.0	4.6 - 34.7
<b>France</b>	<19	Case-Control	Date of referral MSLT	1.4.2009-30.4.2011	5.1	2.11 - 12.3
	≥19			3.9	1.4 - 11.0	
<b>Norway</b>	4-19	Cohort	Date of EDS by patient	1.10.2009 - 30.6.2010	14.5	
<b>UK</b>	4-19	CaseCohort SCCS	Date of EDS recorded by GP/centre	6 months post vaccination	16.2	3.1 – 84.5
					9.9	2.1 – 47.9

# ADULTS

## Association between Pandemrix and narcolepsy

Country	Age group yrs	Study design	Definition of onset	Follow up period	Risk (RR/OR)	95 % CI
France	≥19	C-C	Date of referral MSLT	1.4.2009- 30.4.2011	3.9	1.4 - 11.0
Ireland	20-	RC	1. contact with HC	1.4.2009- 31.12.2010	NA	NA
Sweden	21- 30 31- <40	RC	Date of dg G47.4	1.10.2009 – 31.12.2011	2.18 1.58	1.00-4.75 0.68-3.44
Finland	20-	RC	1. contact with HC	1.1.2009- 31.12.2011	2.8 – 5.5	1.6 – 14.1
UK	20-	SCCS CaseC	Date of EDS recorded by GP/centre	6 months post vaccination	NA	NA

# Conclusions from the epidemiological studies

- Pandemrix vaccination is associated with an abrupt increase in narcolepsy-cataplexy among children and teens, and possibly also in adults
- The relative risk varies between 3 to 14 / 100 000 in the susceptible age group
- The vaccine associated absolute risk is small (<7 /100 000) but consistently seen in different populations where Pandemrix was used in large numbers in susceptible age group
- Most likely such a rare event would not have been picked up in prelicensure trials
- In most countries, the postlicensure passive safety surveillance did not pick up the signal either



## Innovation in vaccines: Preparing for the next generation vaccines

Pieter NEELS, MD  
CHMP member,

Vice-chair Vaccine Working Party



.be



Eurovaccine.net, 2012

Barcelona 22.11.2012

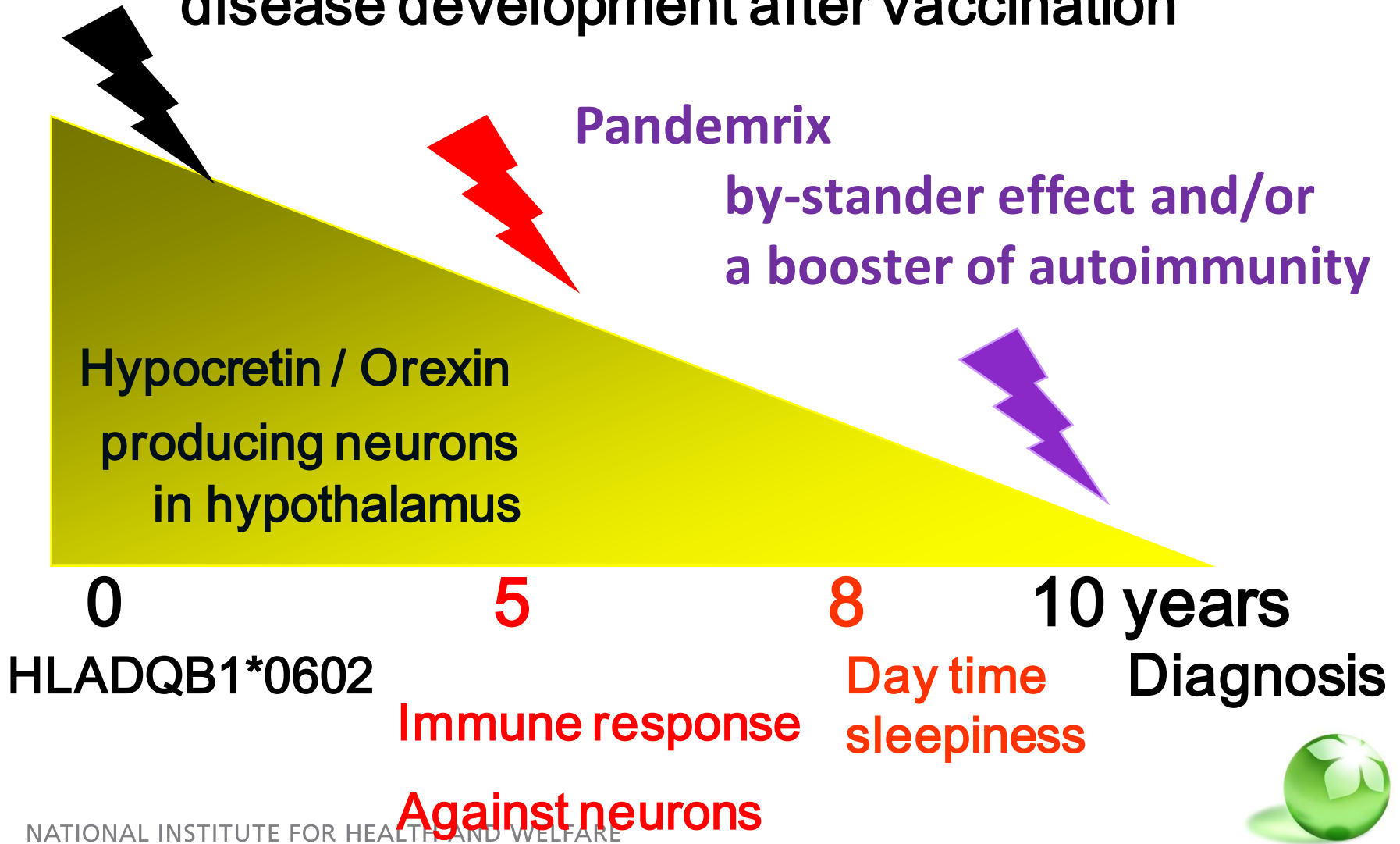
- This vaccine was associated with narcolepsy first in Finland
- Debate on causality is not over:
  - Epidemiology data versus immunology data
  - Is it the Adjuvant, or H1N1 antigene, or the combination, or the combination of wild virus infection and vaccination?



**If the association is causal,  
what could be  
the biological mechanism?**



# Suggested biological mechanism: immune mediated. Pandemrix as an accelerator of narcolepsy: rapid disease development after vaccination



# All those fallen ill with narcolepsy have the know risk factor HLA DQB1\* 0602: Biological explanation to the onset of narcolepsy triggered by the vaccine

Näyte-nro	Haplotype 1	Haplotype 2
N001	(DR15)-DQB1*0602	(DR11/12/13)-DQA1*05-DQB1*0301
N002	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N003	(DR15)-DQB1*0602	(DR8)-DQB1*04
N004	(DR15)-DQB1*0602	(DR11/12/13)-DQA1*05-DQB1*0301
N005	(DR15)-DQB1*0602	(DR11/12/13)-DQA1*05-DQB1*0301
N006	(DR15)-DQB1*0602	DRB1*0404-DQB1*0302
N007	(DR15)-DQB1*0602	(DR9)-DQA1*03-DQB1*0303
N008	(DR15)-DQB1*0602	DRB1*0401-DQB1*0302
N009	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N010	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N011	(DR15)-DQB1*0602	DRB1*0404-DQB1*0302
N013	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N014	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N015	(DR15)-DQB1*0602	DRB1*0401-DQB1*0302
N021	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N024	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N025	(DR15)-DQB1*0602	(DR8)-DQB1*04
N026	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N027	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N028	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N029	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N030	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N031	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N033	(DR15)-DQB1*0602	DRB1*0401-DQB1*0302
N035	(DR15)-DQB1*0602	(DR3)-DQA1*05-DQB1*02
N038	(DR15)-DQB1*0602	DRB1*0401-DQB1*0302
N039	(DR15)-DQB1*0602	(DR7)-DQA1*0201-DQB1*0303
N040	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N042	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N043	(DR15)-DQB1*0602	(DR7)-DQA1*0201-DQB1*0303
N044	(DR15)-DQB1*0602	(DR16)-DQB1*0502
N047	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N048	(DR15)-DQB1*0602	(DR8)-DQB1*04
N049	(DR15)-DQB1*0602	(DR11/12/13)-DQA1*05-DQB1*0301
N050	(DR15)-DQB1*0602	(DR14)-DQB1*0503
N051	(DR15)-DQB1*0602	(DR4)-DQA1*03-DQB1*0301
N052	(DR15)-DQB1*0602	DRB1*0404-DQB1*0302
N053	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N056	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N059	(DR15)-DQB1*0602	(DR13)-DQB1*0603
N060	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N061	(DR15)-DQB1*0602	(DR11/12/13)-DQA1*05-DQB1*0301
N062	(DR15)-DQB1*0602	(DR8)-DQB1*04
N063	(DR15)-DQB1*0602	(DR1/10)-DQB1*0501
N064	(DR15)-DQB1*0602	(DR15)-DQB1*0602
N067	(DR15)-DQB1*0602	DRB1*0401-DQB1*0302
N069	(DR15)-DQB1*0602	(DR8)-DQB1*04

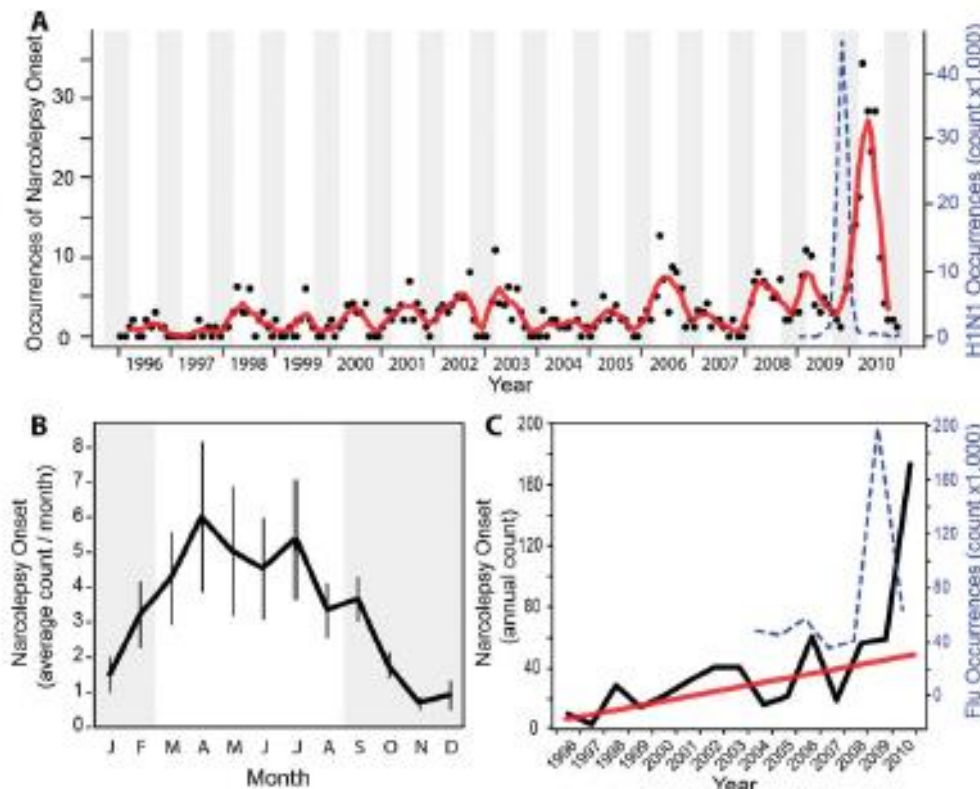


# What is the role of A(H1N1) infection?

## Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han, MD,<sup>1</sup> Ling Lin, MD, PhD,<sup>2</sup> Simon C. Warby, PhD,<sup>2</sup> Juliette Faraco, PhD,<sup>2</sup> Jing Jia, MD,<sup>1</sup>

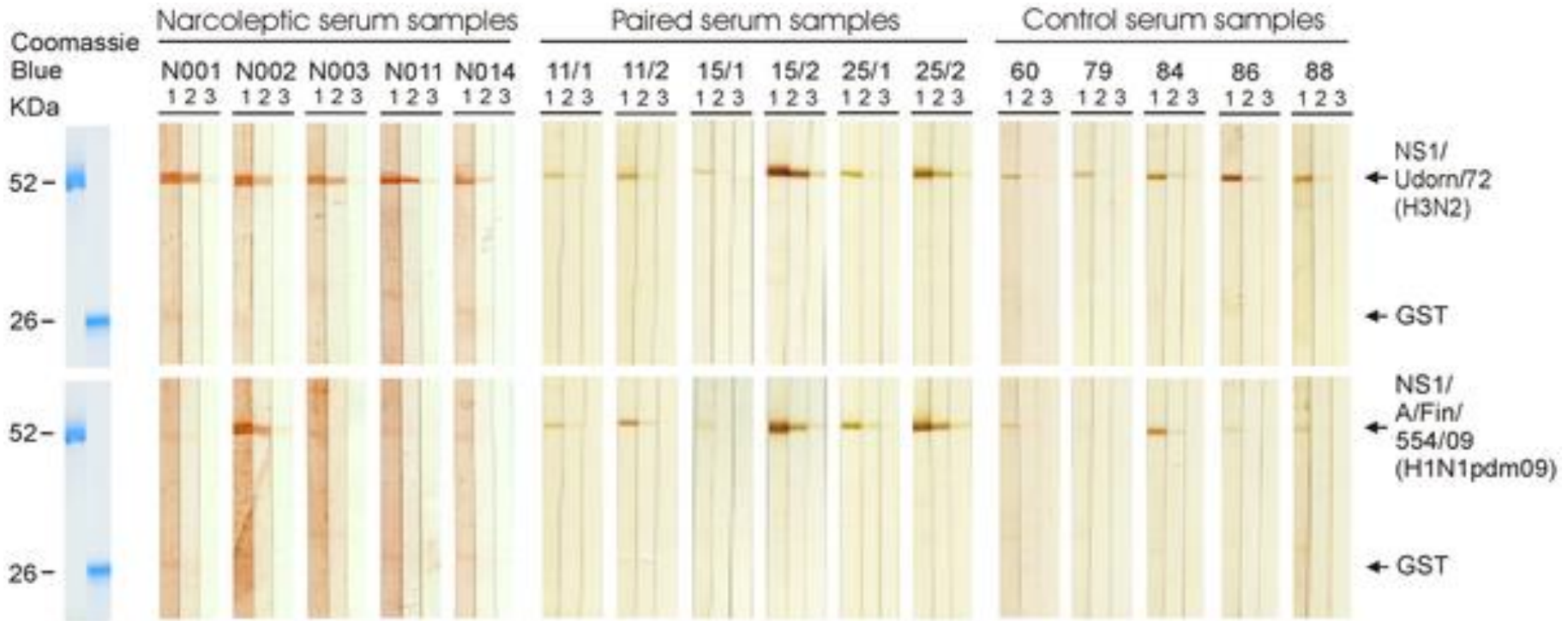
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 enough to peak.  
 H1N1 winter  
 of 142 (5.6%)  
 1-month delay  
 cases.  
 respiratory infections,  
 sensitive to winter  
 11;70:410-417



# Analysis of NS1 protein-specific antibody responses in human sera by using recombinant influenza A virus NS1 proteins.



Melén K, Partinen M, Tynell J, Sillanpää M, et al. (2013) **No Serological Evidence of Influenza A H1N1pdm09 Virus Infection as a Contributing Factor in Childhood Narcolepsy after Pandemrix Vaccination Campaign in Finland.** PLoS ONE 8(8): e68402. doi:10.1371/journal.pone.0068402

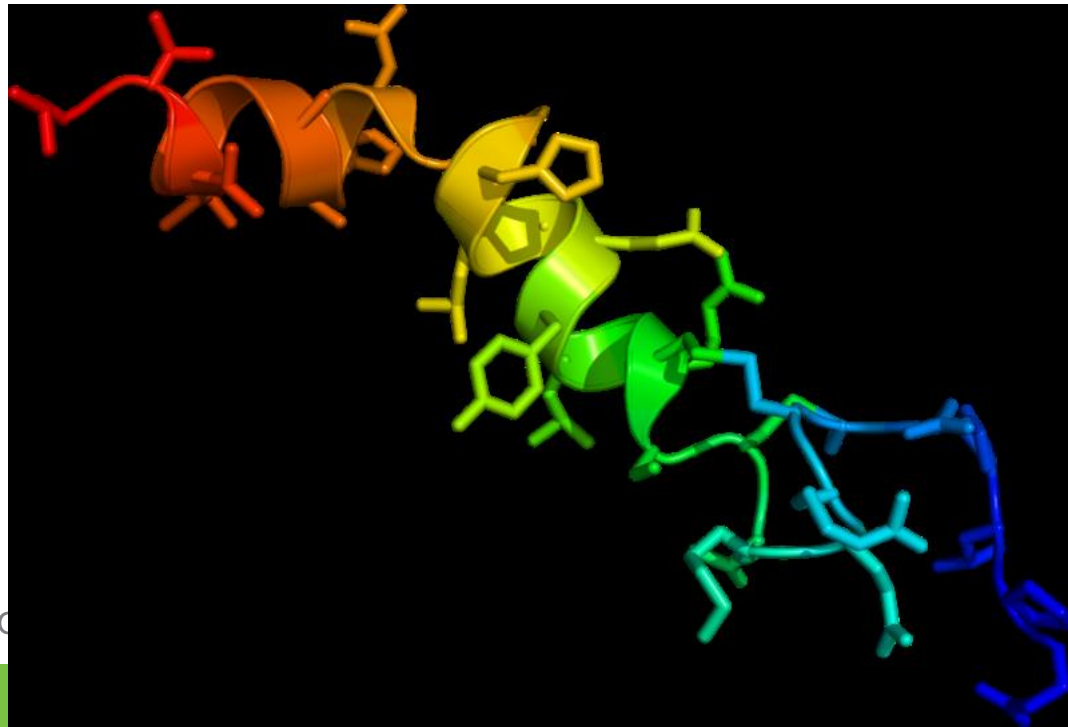
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0068402>

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# Hypothesis I by Prof. Outi Vaarala, THL

In the process of manufacturing Pandemrix<sup>R</sup> vaccine AH1N1 antigen, a structure is formed which resembles the autoantigen of narcolepsy.

The immune response associated with narcolepsy was caused by the virus antigen suspension of Pandemrix<sup>R</sup> and the adjuvant strengthened this response



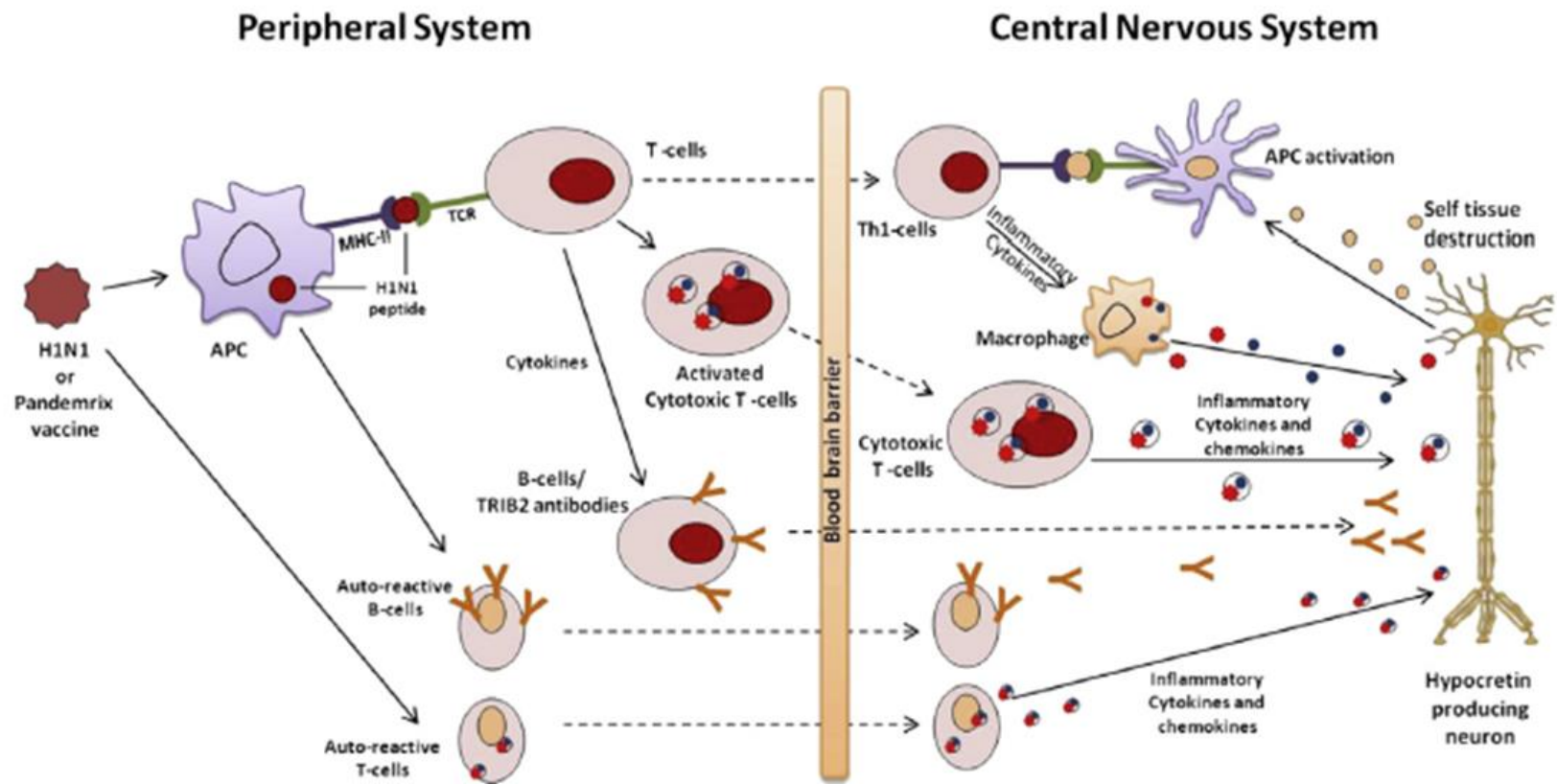


# Hypothesis II on the pathogenesis by Emmanuel Mignot. Science 18.12.2013

RESEARCH ARTICLE

NARCOLEPSY

A.K Singh et al. / Journal of Autoimmunity 43 (2013) 26–31





# Gaps in knowledge – significance to vaccine development and NVPs

- What is the biologically plausible mechanism; how can we study it ?
- How long will those Pandemrix vaccinated with HLA DQB1\*0602 be at risk?
- What does this incident mean to the future development of adjuvanted influenza / pandemic / other influenza vaccines ?
- What does this mean to the future seasonal influenza vaccination of those Pandemrix<sup>R</sup> exposed ?
- How to contain the negative safety messages and impact to influenza vaccination / vaccinations in general ?
- How to help those chronically affected ?



Commissioner  
Tonio Borg  
© European Union



Horizon2020projects  
February 2014

**Borg to consult on possible narcolepsy research  
European Health Commissioner Tonio Borg is set to discuss  
with Máire Geoghegan-Quinn the possibility of funding of  
research narcolepsy.**

Borg will consult with the European Commissioner for Research, Innovation and Science after an EU-wide group representing at least 1,000 victims met with the European Health Commissioner in Brussels. The group are advocating research for treatments, as well as to raise awareness and promote best practice in managing the condition. Gathering data on those affected is also thought to be a priority.

Borg said he would discuss with Geoghegan-Quinn how money could be used from the Health programme and how data could also be collected.



# In summary

- New adjuvants are needed for vaccine development
- Safety of adjuvants can be tested in preclinical studies, clinical trials and in postlicensure
- However, rare events can only be observed in wide scale use, and even then they may go unnoticed
- Regulators, vaccine developers and public health scientist need to work together
- With the rare AEFI narcolepsy-cataplexy associated with Pandemrix, it is unlikely that the ASO3 adjuvant played any major role



# Acknowledgements

- The Finnish Narcolepsy Task Force clinicians – Markku Partinen, Christer Hublin, Outi Saarenpää-Heikkilä, Sari-Leena Himanen, Tuukka Kirjavainen, Päivi Olcén
- The THL Narcolepsy Research Team - Jukka Jokinen, Terhi Kilpi, Outi Vaarala, Ilkka Julkunen, Pirjo-Riitta Saranpää, Jonas Sundman



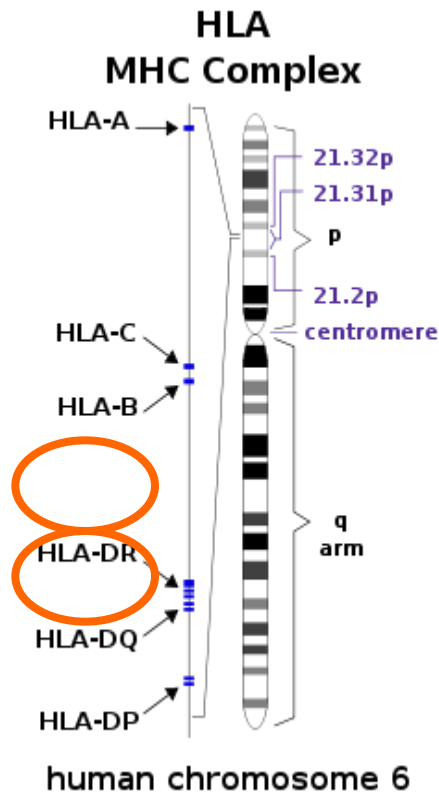


# Conclusions from the immunological and virological studies in Finland on Pandemrix and narcolepsy

- **Children who developed narcolepsy after Pandemrix vaccination**
  - 1) Show similar HLA related susceptibility as earlier reported for narcolepsy without Pandemrix association**
  - 2) Did not show clinical or immunological evidence of H1N1 infection (NS1 protein assay)**
  - 3) Reacted abnormally to Pandemrix vaccination:**
    - **Developed narcolepsy with cataplexy**
    - **Developed increased levels of antibodies binding to AS03 and to H1N1 antigen suspension of Pandemrix**
    - **React differently to Pandemrix vs Arepanrix H1N1 antigen suspension, which could be a possible explanation to the lack of signal – so far - from Canada ?**



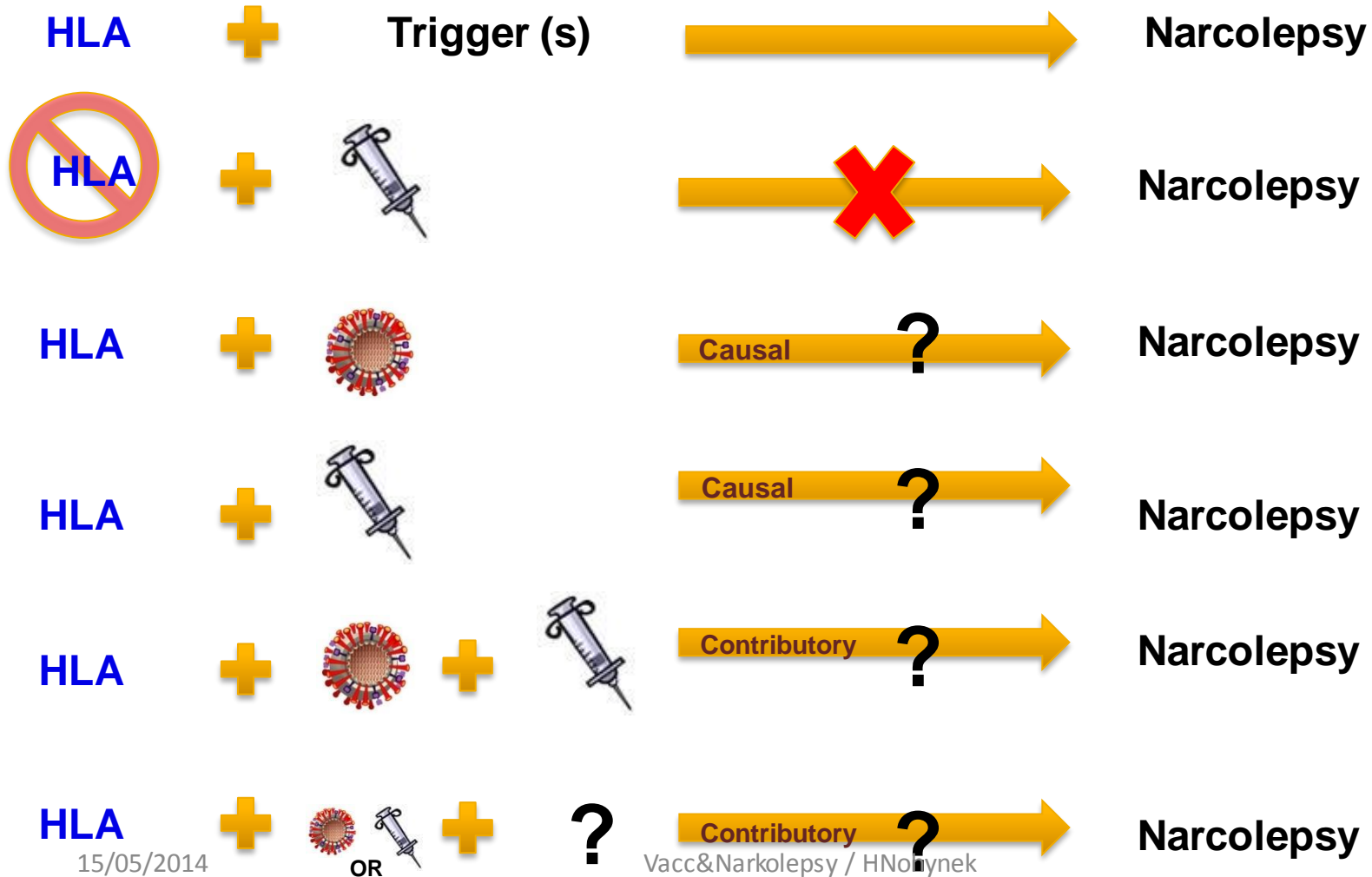
# The association of the HLA DR and DQ –gene region alleles with autoimmune diseases



- Diabetes mellitus, type 1
  - HLA DQB1\*0302 ja HLA DQB\*02 ↑
- MS-disease
  - HLA DRB1\*1501 ↑
- Coeliacia
  - HLA-DQA1\*05 and HLA-DQB1\*02 ↑
- Narcolepsy-cataplexy
  - HLA DQB1\*0602 ↑



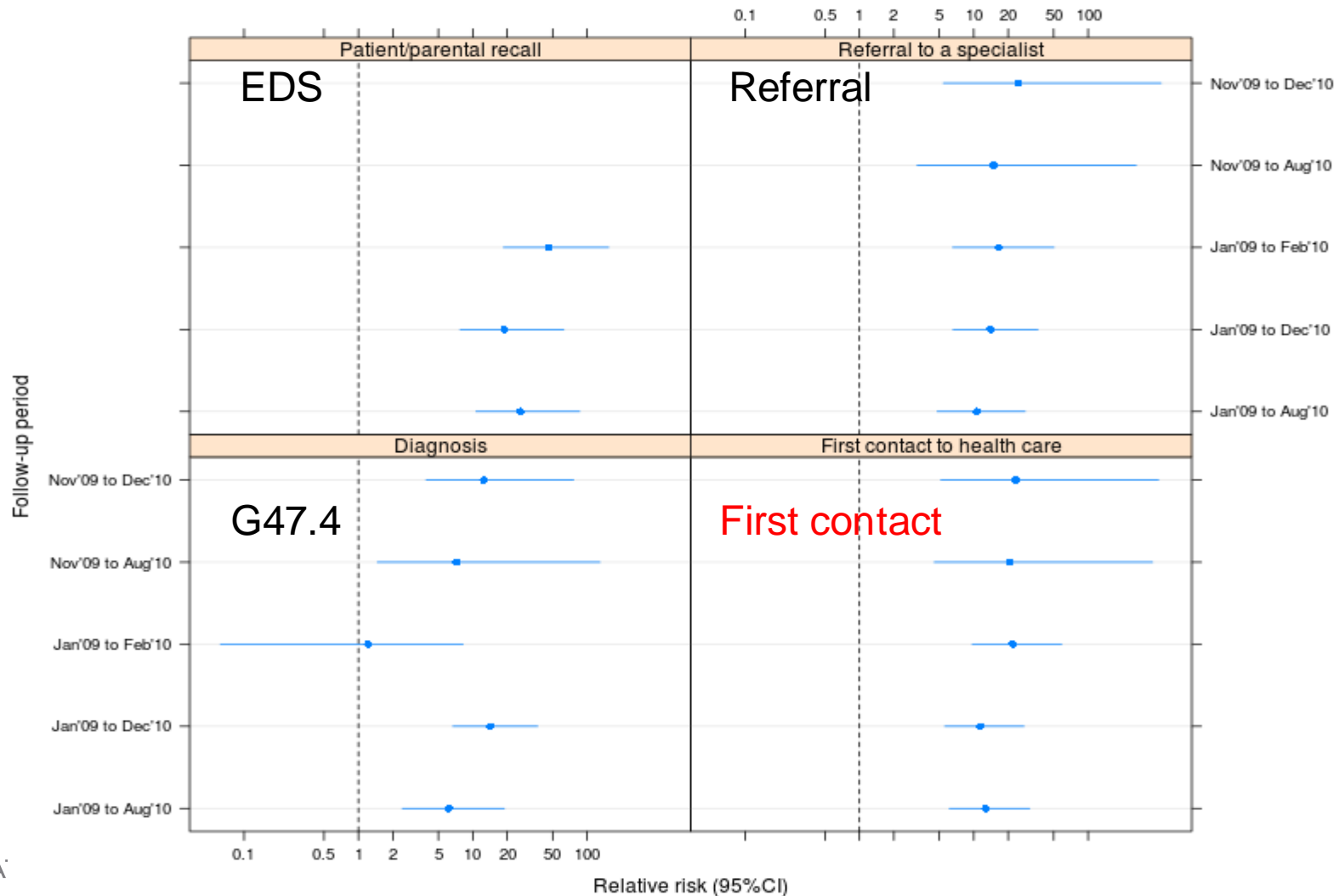
# GSK - Currently available evidence does not yet allow to distinguish between potential mechanisms





# Sensitivity analysis of RR: onset dates vs. follow-up times

among those with DG G47.4 given by 31.12.2010



NA



# Onset of immune mediated disease Analogy to Type 1 Diabetes Mellitus

