# Influenza vaccines: Safety considerations

**Hanna Nohynek**
**MD PhD Professor**
**Chief physician**
**Chair, WHO SAGE**

Terveyden ja
hyvinvoinnin laitos

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# What do we know of the safety of influenza vaccines in general ?

Any adverse events, AEFI

- Local = redness pain oedema
- Systemic = fever myalgia headache

Depends on

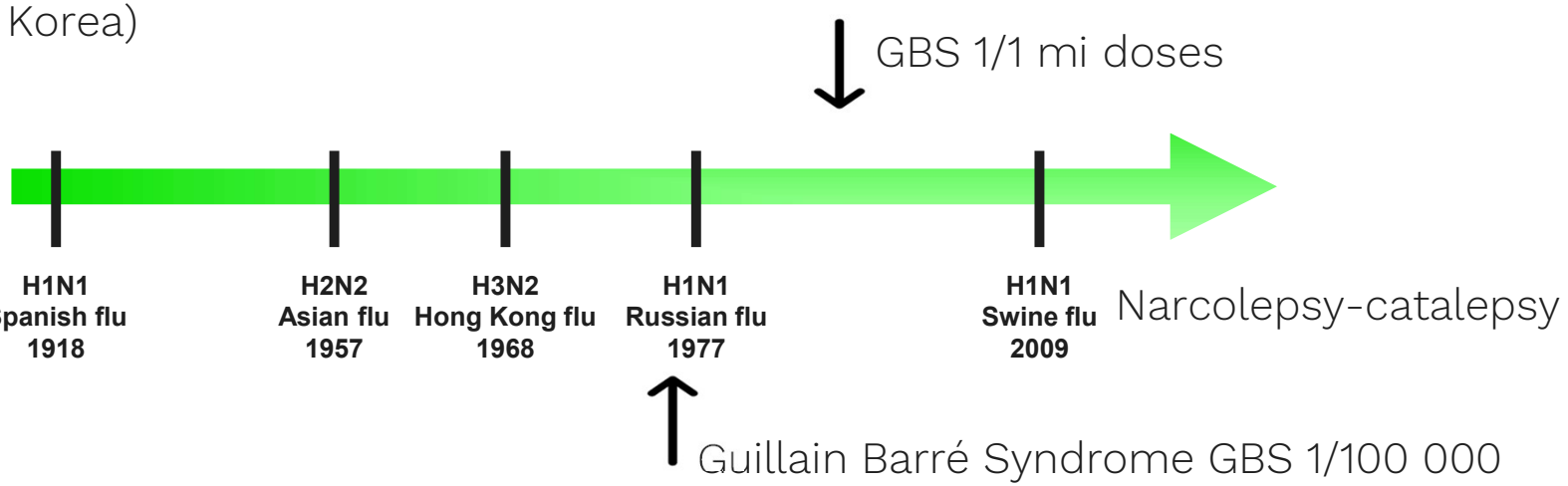
- the amount of antigen
- if adjuvanted or not

Serious Adverse Events

- Rare

# SAEs observed with different seasonal / pandemic influenza vaccines

In national studies, SAE reported in approximately <1 - 3,4 / 1 mi doses of vaccine (USA, South Korea)




Other SAEs reported = optic neuritis, transverse myelitis, Bell's palsy, multiple sclerosis, tics, oculo-respiratory syndrome ORS – although causality not always established

Patel et al. Plotkin Orenstein Vaccines 2022

Julkunen / Kakkola et al. Encyclop. Virol. 2021

# How can we study vaccine safety in the context of developing a new HXNX vaccine ?

- Preclinical
- Clinical
- Extrapolation from experience with previous products

# The relation of the statistical power of the trial and the ability to observe AEFI risk increase two-fold

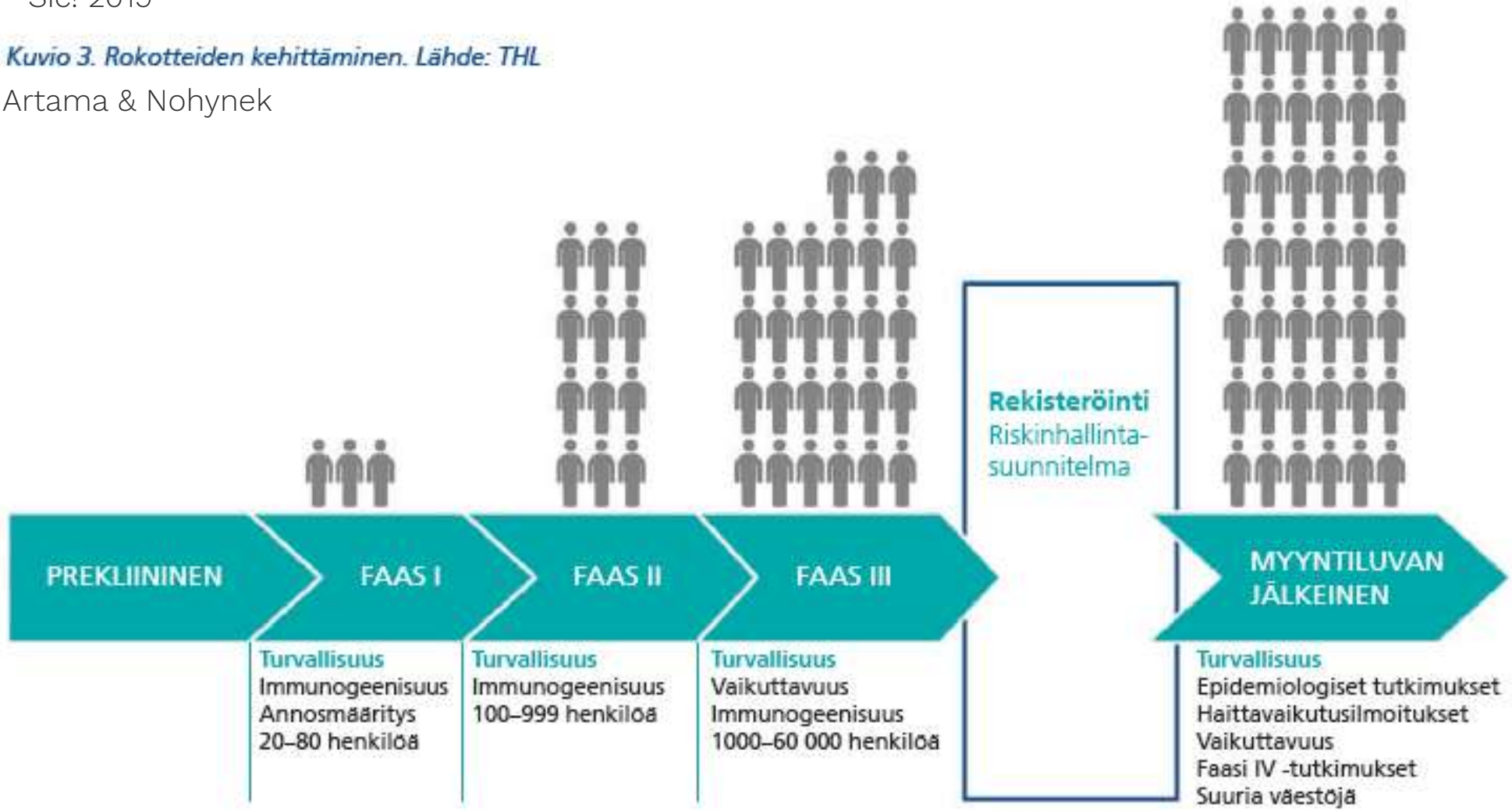
| Number subjects | 5 -> 10 % | 1 -> 2 % | 0,1 -> 0,2 % |
|---|---|---|---|
| 1 000 | 0,82 | 0,17 | 0,05 |
| 5000 | 0,99+ | 0,80 | 0,07 |
| 10 000 | 0,99+ | 0,98+ | 0,17 |
| 50 000 | 0,99+ | 0,99+ | 0,79 |

S.Ellenberg

Sic! 2019

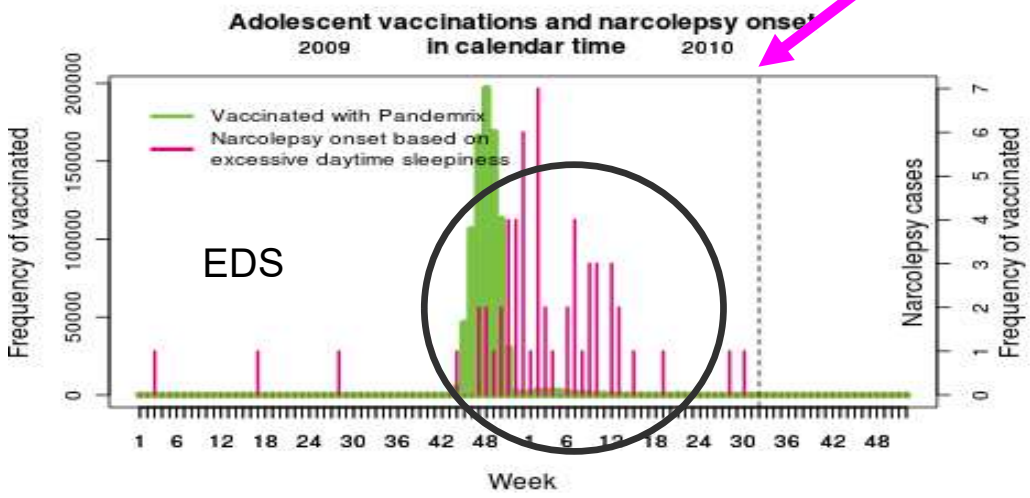
*Kuvio 3. Rokotteiden kehittäminen. Lähde: THL*

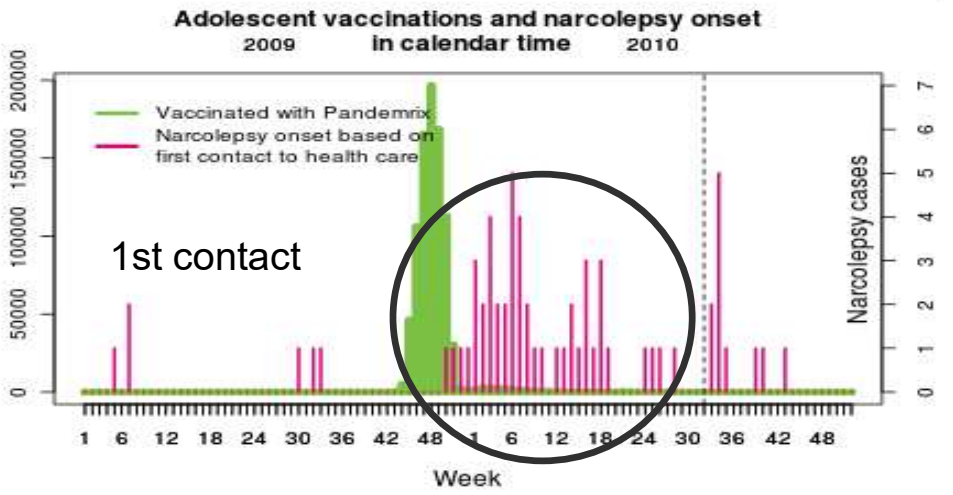
Artama & Nohynek

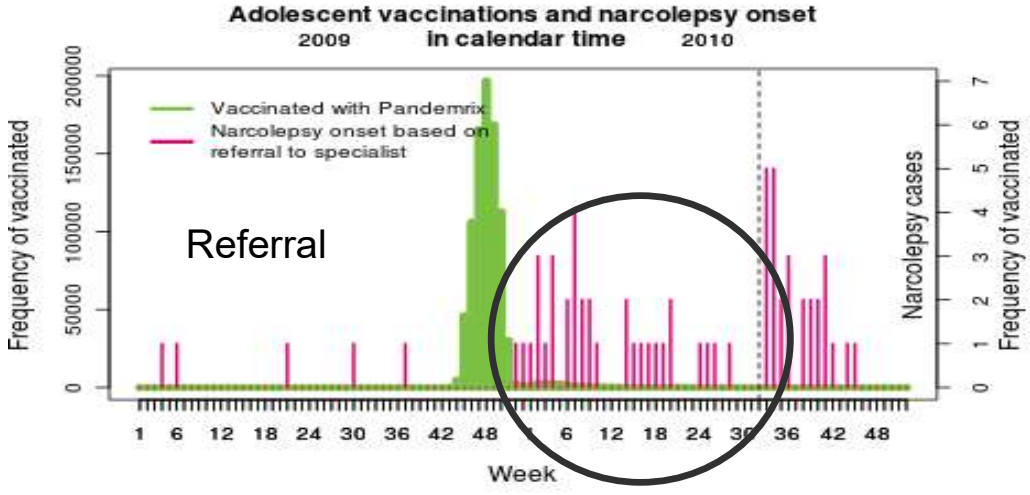


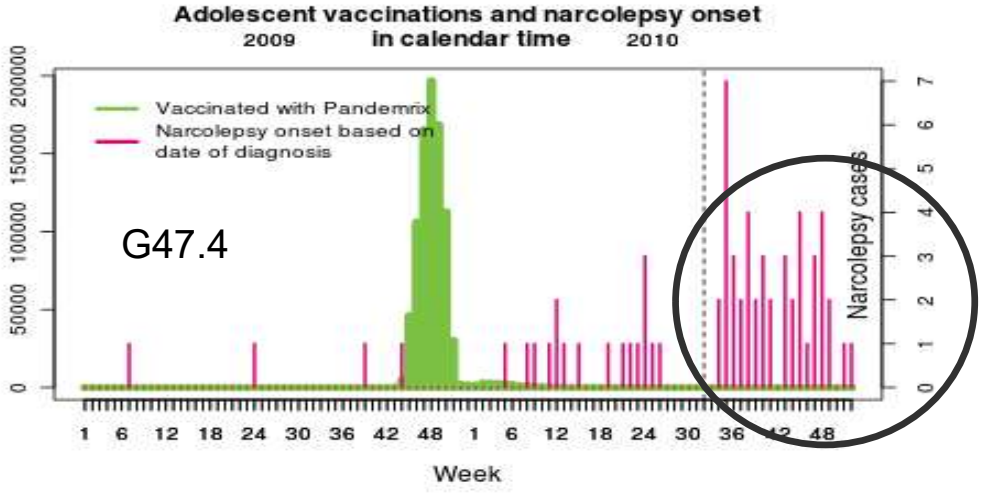
Example Narcolepsy-cataplexy post H1N1 vaccination (PandemrixR)

MPA Sweden press release on association



# Conclusions from the first set of epidemiological studies (case-control, register based cohort) on Pandemrix$^{R}$

- Pandemrix vaccination **is associated** with an abrupt increase in narcolepsy-cataplexy among children and teens, and also, to lesser degree, in adults
- The **relative risk varies between 3 to 14 / 100 000** in the susceptible age group in children and teens
- 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
- Of the **Bradford Hill criteria for causality**, fulfilled are at least 4: strength, consistency, specificity and temporality
- 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

# EMA precautionary recommendation July 2011

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 July 2011
EMA/CHMP/568830/2011 corr*[1]
Press Office

**Press release**

## 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.

tni

# Update on narcolepsy studies - Europe

Sleep Medicine Reviews 38 (2018) 177–186

Contents lists available at ScienceDirect

Sleep Medicine Reviews

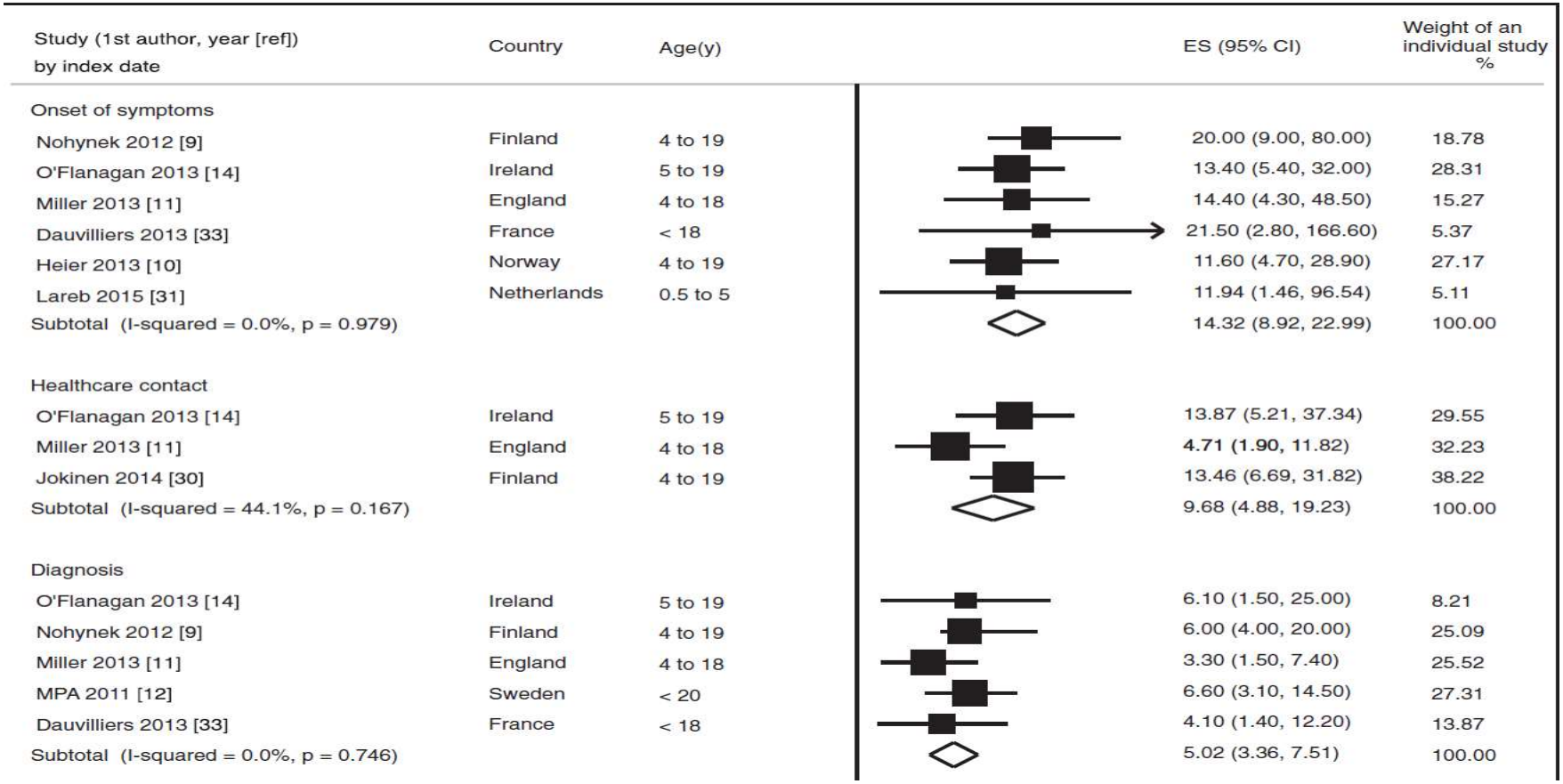
journal homepage: www.elsevier.com/locate/smrv


CLINICAL REVIEW

## Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis

Tomi O. Sarkanen [a, b, *], Anniina P.E. Alakuijala [b, c], Yves A. Dauvilliers [d, e], Markku M. Partinen [b, f]

# Sarkanen et al (Sleep Med Rev. 2018): Systematic review
# Risk in children and adolescents. Attributable risk 1 in 18,400 doses



| Study (1st author, year [ref]) by index date | Country | Age(y) | ES (95% CI) | Weight of an individual study % |
|---|---|---|---|---|
| Onset of symptoms | | | | |
| Nohynek 2012 [9] | Finland | 4 to 19 | 20.00 (9.00, 80.00) | 18.78 |
| O'Flanagan 2013 [14] | Ireland | 5 to 19 | 13.40 (5.40, 32.00) | 28.31 |
| Miller 2013 [11] | England | 4 to 18 | 14.40 (4.30, 48.50) | 15.27 |
| Dauvilliers 2013 [33] | France | < 18 | 21.50 (2.80, 166.60) | 5.37 |
| Heier 2013 [10] | Norway | 4 to 19 | 11.60 (4.70, 28.90) | 27.17 |
| Lareb 2015 [31] | Netherlands | 0.5 to 5 | 11.94 (1.46, 96.54) | 5.11 |
| Subtotal (I-squared = 0.0%, p = 0.979) | | | 14.32 (8.92, 22.99) | 100.00 |
| Healthcare contact | | | | |
| O'Flanagan 2013 [14] | Ireland | 5 to 19 | 13.87 (5.21, 37.34) | 29.55 |
| Miller 2013 [11] | England | 4 to 18 | 4.71 (1.90, 11.82) | 32.23 |
| Jokinen 2014 [30] | Finland | 4 to 19 | 13.46 (6.69, 31.82) | 38.22 |
| Subtotal (I-squared = 44.1%, p = 0.167) | | | 9.68 (4.88, 19.23) | 100.00 |
| Diagnosis | | | | |
| O'Flanagan 2013 [14] | Ireland | 5 to 19 | 6.10 (1.50, 25.00) | 8.21 |
| Nohynek 2012 [9] | Finland | 4 to 19 | 6.00 (4.00, 20.00) | 25.09 |
| Miller 2013 [11] | England | 4 to 18 | 3.30 (1.50, 7.40) | 25.52 |
| MPA 2011 [12] | Sweden | < 20 | 6.60 (3.10, 14.50) | 27.31 |
| Dauvilliers 2013 [33] | France | < 18 | 4.10 (1.40, 12.20) | 13.87 |
| Subtotal (I-squared = 0.0%, p = 0.746) | | | 5.02 (3.36, 7.51) | 100.00 |

**Not included: German CC study Oberle et al Sleep Medicine 2017 aOR in <18 year olds 4.1 (1.4 – 12.6)**
**Norwegian cohort study Trogstad et al Vaccine 2017 aHR <30 yr olds onset <1yr 8.71( 4.03-18.82)**

# In summary

- HXNX vaccines are usually very safe, and rarely cause serious adverse events, however,
- Rare and even unknown SAEs are possible, and they most likely are observed only post-licensure;
- Therefore, we need to be prepared and have a good AEFI surveillance system in place and readiness to study any concerning safety signal

# Thank you !