

# THE DANISH VACCINATION PROGRAMME AND SPONTANEOUS REPORTED ADVERSE DRUG REACTIONS (ADRS)



Anja Poulsen

MD PhD

Department of Paediatrics, Rigshospitalet, and  
Medical Secretary at The Danish Health and Medicine Authority

2014

DIPS Meeting Klarskovgaard

# AGENDA

- The Danish Vaccination Programme – 2014
  - Serious Adverse Events related to vaccines in Denmark
    - Vaccination and granulomas
    - HPV vaccine – adverse events
-

# THE DANISH VACCINATION PROGRAMME 2013

- 3 months Diphtheria-Tetanus-Pertussis-Polio-Hib 1 og PCV-1
- 5 months Diphtheria-Tetanus-Pertussis-Polio-Hib 2 og PCV-2
- 12 months Diphtheria-Tetanus-Pertussis-Polio-Hib 3 og PCV-3
- 15 months Morbilli-Parotitis-Rubella 1 (live attenuated)
- 4 years Morbilli-Parotitis-Rubella 2 (live attenuated)
- 5 years Diphtheria-Tetanus-Pertussis-Polio booster
- 12 years Morbilli-Parotitis-Rubella 2<sup>1</sup> and girls Human Papilloma Virus (HPV) 1, 2 og 3<sup>2</sup>
  
- All women can be vaccinated for free against Rubella.
  - 1) For children older than 4 years 1st of April 2008. Will stop 2016.
  - 2) All girls born in the years 1985-1992 freely HPV vaccinated in 2012 and 2013

I GUESS YOU ALL CAN MENTION  
THE CHANGES IN THE PROGRAMME 2014 ?

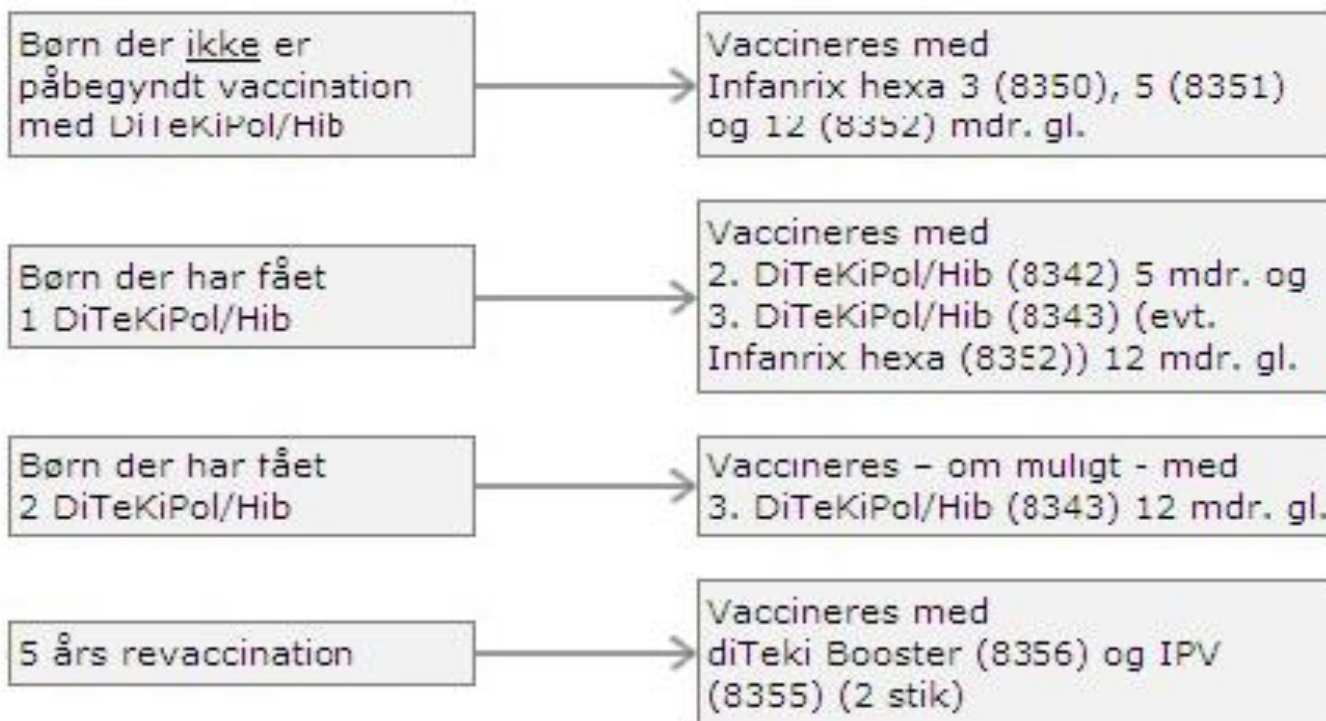
- How many – please vote?
    - 1
    - 2
    - More
-

# THE DANISH VACCINATION PROGRAMME 2014

1. 14th of January introduction of Infanrix Hexa®<sub>(GSK)</sub> Instead of DTP-IPV+Hib temporary change due to manufacturing challenges <sub>(SSI)</sub>:
  - Includes hepatitis B Vaccine
  - Will probably be changed back -when ?
2. From 1st of January 2014 to end of 2015 catch up vaccination for girls born : 1993-1997 for free.
3. From 6 th of August Gardasil® reduced to 2 doses for 12 and 13 years old girls
  - Still 3 doses for girls above 14 years of age.

# RATHER COMPLICATED – LOOK IN EPI-NYT

**Figur 1. Vaccination af børn under det midlertidige vaccineskift  
(ydelseskoder anført i parentes)**



# ADVERSE REACTIONS

Reporting of ADRs has been **obligatory in Denmark since 1968**.

All reports of ADRs are **categorized as serious or not serious**.

Furthermore, they will be **classified as listed or unlisted** according to presence of the ADR in Summary of Product Characteristics (SPC).

Not all ADRs are reported.

## **Definition of serious adverse drug event :**

Any untoward medical occurrence that at any dose results in :

- 1. Death
- 2. Is life-threatening
- 3. Requires inpatient hospitalization or
- 4. Prolongation of existing hospitalization
- 5. Results in persistent or significant disability/incapacity
- 6. Is a congenital anomaly/birth defect,
- 7. Requires intervention to prevent permanent impairment or damage.

# CAUSALITY ASSESSMENT

- Will not prove or disprove any association. It is meant to assist in determining the level of certainty of such an association.
- The Danish health and medicine Agency will classify:
  - Possible (muligt)
  - Less likely (mindre sandsynligt)
  - Not possible to classify/evaluate (ikke muligt at vurdere)
- **Signal:** if several of one or related unknown disorders are reported
  - This will lead to report to EMA (European Medicine Agency), they will then decide further steps (f.ex ask for review etc).
  - Periodic Safety Update Reports



WHAT SHOULD I EXPECT ???



# SECOND HALF YEAR 2013 – EXAMPLE

## NUMBER OF ADVERSE EVENTS REPORTED (NOT HPV)

Vaccine	Serious	Non-serious	Totally
DiTeKiPol	0	1	1
DiTeKiPol booster	1	5	6
DiTebooster	1	7	8
DiTeKiPol/Act-Hib og Prevenar13	5	6	11
Prevenar 13	2	2	4
<b>DiTeKiPol/Act-Hib</b>	<b>16</b>	<b>12</b>	<b>28</b>
DiTeKiPol/Act-Hib og Prevenar	0	2	2
DiTeKiPol booster og Prevenar	1	2	3
<b>Priorix/MMR</b>	<b>6</b>	<b>5</b>	<b>11</b>
Gardasil og Priorix	2	0	2
Priorix	1	4	5
Pneumovax	1	0	1
M-M-RVAXPRO	1	8	9
<b>Totalt</b>	<b>37</b>	<b>54</b>	<b>91</b>

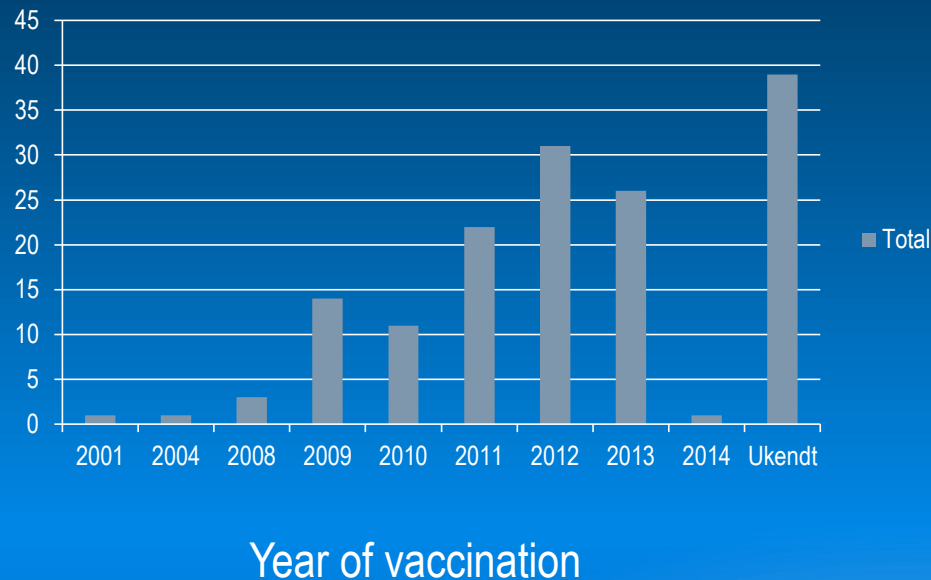
# EXAMPLE OF THE "CLASSIC" SERIOUS ADVERSE EVENTS TO VACCINES

- **Fever and admission** of a 3 month old baby
- **Febrile convulsions** (especially DTP-IPV+Hib and MMR)
- **Hypotonic-Hyporesponsive Episode** (described: Jan Bonhoeffer et al:Vaccine 22 (2004) 563–568)
  - Sudden onset of reduced muscle tone, hyporesponsiveness and change of skin color (paleness or cyanosis)
  - Most reports of HHE follow pertussis component vaccines but can be seen after others
- **Discolored leg syndrome** (described: Jeanet M. Kemmeren et al: Eur J Pediatr (2009) 168:43–50)
  - defined as an even or patchy red, blue or purple discoloration of the leg(s) and/or leg petechiae with or without swelling (after DTP-IPV+Hib)
- **Encephalitis**, MMR (rare)
- **Trombocytopenia** ; MMR
- **Vaccine failure** (Pertussis, Haemophilus)

# GRANULOMA – AND ALUMINIUM ALLERGY A CAUSE OF MANY REPORTS

In average reported 1,7 years after vaccination

**Total**



January 2009 - June 2014	Totally
DITEBOOSTER	3
DITEKIPOL	1
DITEKIPOL BOOSTER	3
DITEKIPOL/ACT-HIB	123
GARDASIL	6
PREVENAR 13	4
PREVENAR	
INJ.VÆSKE,SUSPENSION	1
PRIORIX	8
I alt	149

# GRANULOMA DUE TO ALUMINIUM ADJUVANS

- The majority of children with a granuloma after vaccination will have a positive test for allergy to aluminium (patch)
- After 5 years the test will be negative in 77% of the children
  - ( described in Anette Gente Lidholm et al: Contact Dermatitis, 68, 286–292,2013)
- DiTeKiPol- Act Hib has a content of 1 mg Aluminium per vaccine, the other vaccines 0 mg(MMR) and 0,8 mg (Infanrix hexa), Prevenar 0,125 mg
- Can be annoying but will probably disappear – does not cause of general allergy

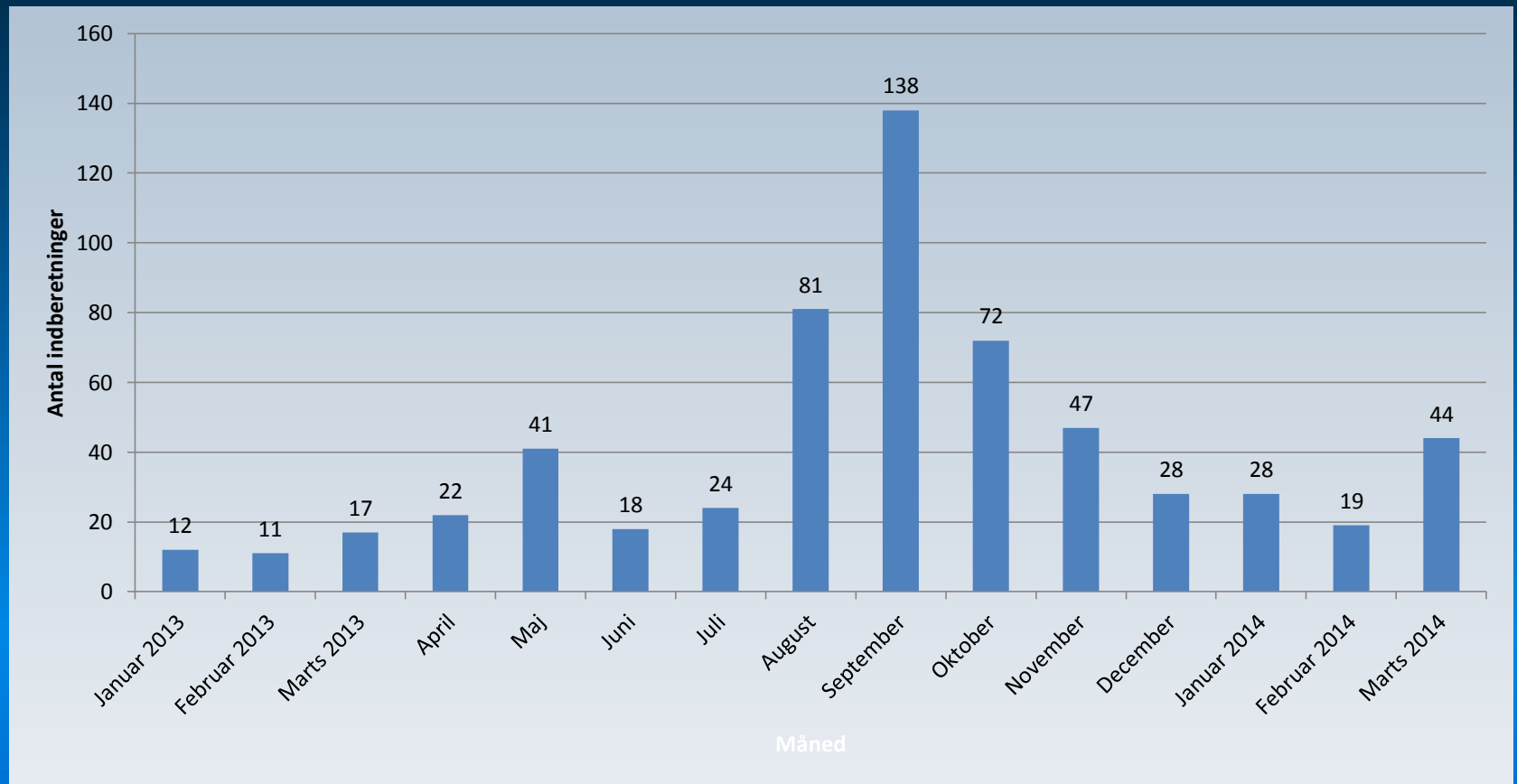
<b>First 6 months of life – how much aluminium in</b>	<b>Milligram</b>
Breast milk	10 mg
Infant formula	40 mg
Soya.based formula	120 mg
Vaccines	ca 2 mg
Parenteral nutrition	16,7 mmol/L* every day

# DISTRIBUTED DOSES OF HPV VACCINE 2009-2014

HPV-vaccine	2009	2010	2011	2012	2013	1.halvår 2014 *	Total
Total ADR's	288	66	43	96	511	125 (91)	
Serious ADR's	25	5	6	18	177	38 (24)	
Sold doses	347.690	151.476	163.374	349.730	488.224	69.161 (38.640)	1.569.655
<u>Ratio</u>	<u>1:13.880</u>	<u>1:30.295</u>	<u>1:27.229</u>	<u>1:19.429</u>	<u>1:2.758</u>	<u>1:1.820</u>	

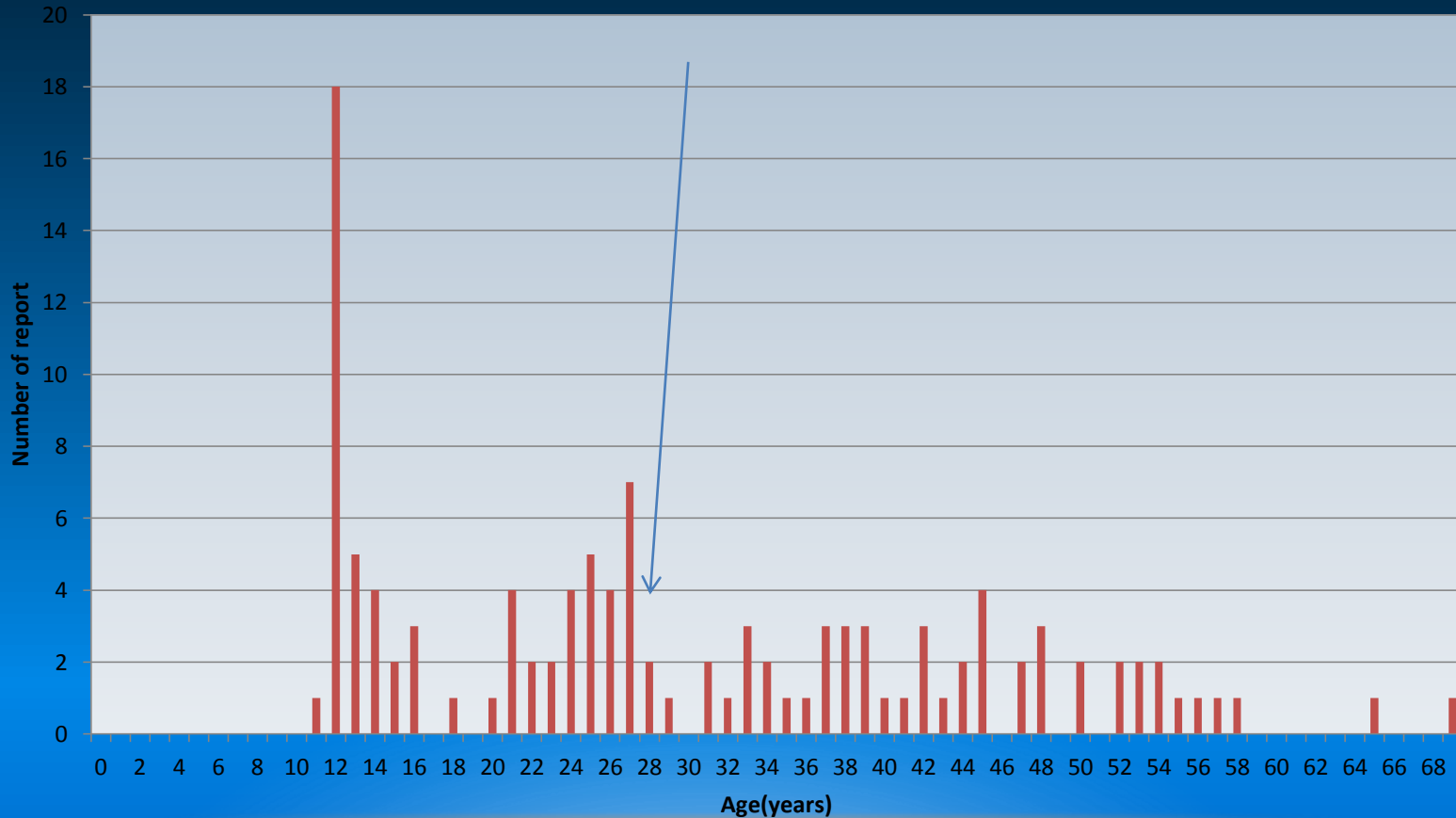
\* First trimester in brackets

# GARDASIL AND REPORTED ADVERSE EVENTS



34 reports in 2nd trimester 2014

# AGE DISTRIBUTION ADR AND HPV VACCINE



28 years maximum age for having received free vaccinations  
(born after 1985 in the end of 2013)



# EXAMPLE OF A REPORT

- 17 years old female vaccinated with HPV vaccine
  - 3-4 months after second vaccine tired, dizzy, pain and parasthesias in both arms, headache, not been able to follow school
  - Examinations: lumbar puncture, MRI, blood test – seen at local department of neurology - no explanation
  - Diagnosis, further examinations ?
  - Considered serious by the reporter (GP).
  - How to evaluate ?
- The literature describes case reports with POTS (postural orthostatic tachycardia syndrome) and from Japan with Complex Regional Pain Syndrome – no signal, when analysed further, so far.
- Autoimmune disorders not more frequent in several studies
- 27 cases of POTS have been recorded so far in Denmark until 1.7.2014 – only very few from other countries (May 2013 cumulated 33 cases).
- Signal ? - Media (The **Secular Effect** describes increased reporting when a drug becomes subject to media exposure )?

# SUMMARY

- Granulomas increasingly frequent reported – new phenomenon ???
- Gardasil has an increased number of reports
  - Important to be open for new signals (POTS)
  - Gardasil introduced to new age groups-
  - Important to secure population-specific and age-specific baseline rates of specific conditions in the relevant age-group (for example, rates of autoimmune diseases)
- [www.meldenbivirkning.dk](http://www.meldenbivirkning.dk)
- ”Nyt om bivirkninger”

- Questions ?

