



CARE-SEEKING IN FEMALES REPORTING SEVERE ADVERSE REACTIONS TO HPV VACCINE: RESEARCH AND POLICY PERSPECTIVES.

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- ❖ The signal consisted mainly of medically unexplained physical symptoms in vaccinated girls
- ❖ No evidence from analytical studies
 - No studies have demonstrated an increased risk among vaccinated girls compared with unvaccinated
- ❖ Difficult to analyse in epidemiological studies
 - CFS/ME and POTS are ill-defined conditions
- ❖ Reporting has been stimulated by media attention, social media and "infostorms"
 - Data from passive adverse events surveillance are biased



1. **Strength:** A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
2. **Consistency:** Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
3. **Specificity:** Causation is likely if there is a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
4. **Temporality:** The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
5. **Biological gradient:** Greater exposure should generally lead to greater incidence of the effect.
6. **Plausibility:** A plausible mechanism between cause and effect is helpful.
7. **Coherence:** Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
8. **Experiment:** "Occasionally it is possible to appeal to experimental evidence".[\[1\]](#)
9. **Analogy:** The effect of similar factors may be considered.

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- ❖ The aim:
 - To determine health care-seeking prior to the first HPV vaccination among females who suspected and reported adverse reactions to HPV vaccine.
- ❖ Case-control study
- ❖ Cases: 361 females with severe adverse reactions reported to DMA
- ❖ Controls: 163.910 matched on municipality, age, year of first HPV vaccine
 - Females
 - Vaccinated
 - No reports of adverse reactions
- ❖ Care seeking data obtained from:
 - National Health Insurance Service Register (primary health care)
 - National Patients Registry (hospital contacts)
- ❖ Only one exposure in each category

AGE DISTRIBUTION (361 CASES)

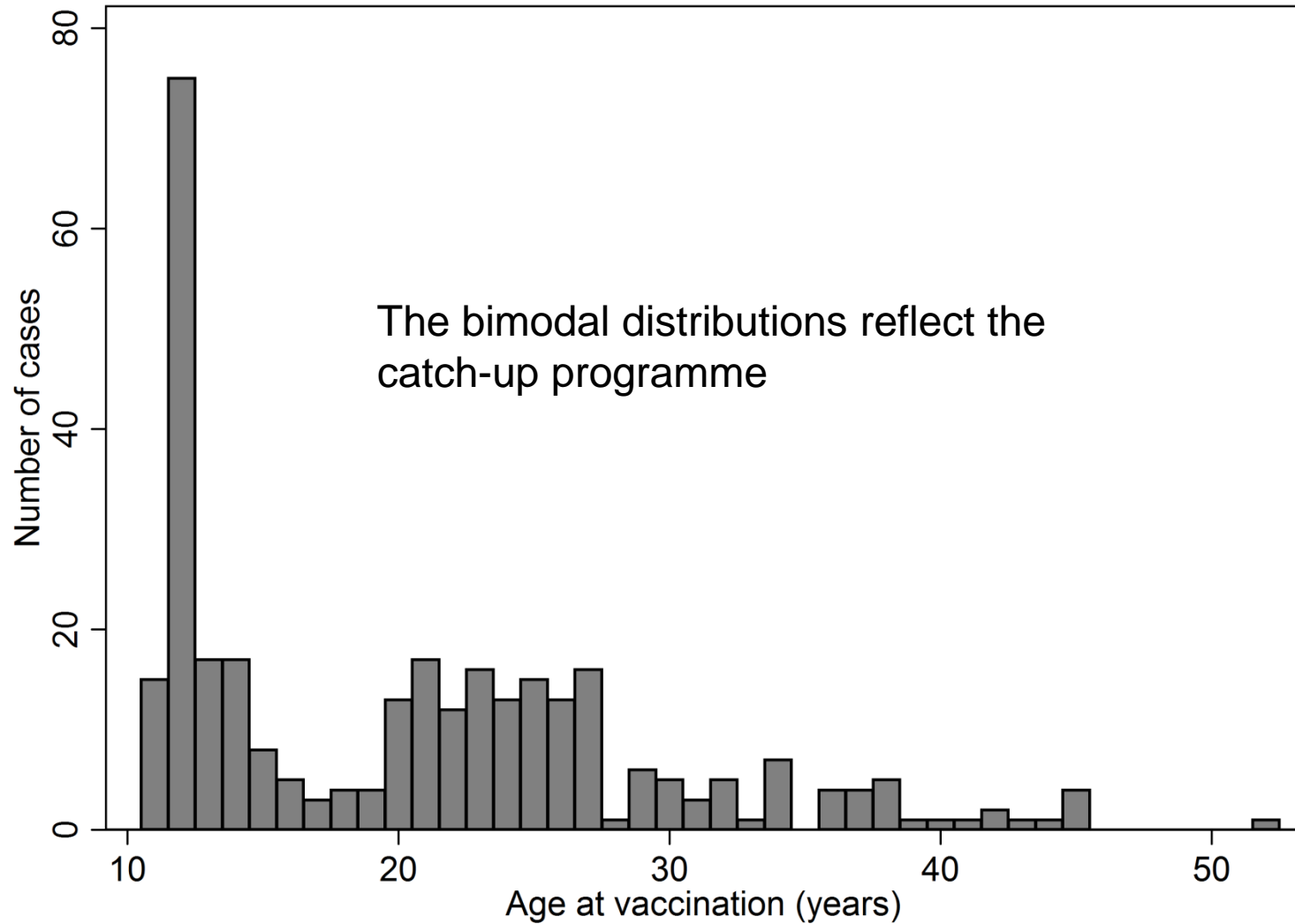


Table 1. Primary health care contacts (assessed by reimbursement codes) two year before the first HPV vaccination in 316 females who reported suspected adverse events to the vaccine and 163,910 matched controls.

Type of contact before first vaccination	Cases		Controls		Odds ratio	95% CI
	Number	Percent	Number	Percent		
Consultation at the office	310	98.1	157853	96.3	1.74	0.77–3.92
Consultation by phone or e-mail	299	94.6	142862	87.2	2.38	1.44–3.92
Laboratory analysis request	249	78.8	110092	67.2	1.73	1.29–2.32
Physiotherapy or related	96	30.4	20459	12.5	2.56	1.99–3.31
Psychologist, psy-chiartist etcetera	39	12.3	9751	5.9	2.18	1.54–3.11
Dentist	134	42.4	62590	38.2	0.94	0.65–1.35

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Table 2. Hospital contacts two year before the first HPV vaccination in 316 females who reported suspected adverse events to the vaccine and 163,910 matched controls.

Type of contact before first vaccination (ICD10 code and interpretation)	Cases		Controls		Odds ratio	95% CI
	Number	Percent	Number	Percent		
Z01.6, radiological examination, not elsewhere classified	68	21.5	18359	11.2	1.91	1.45–2.53
Z03.9, observation for suspected disease or condition, unsp.	26	8.2	5660	3.5	2.18	1.45–3.27
Z30–Z39, persons encountering health services related to reproduction	37	11.7	9413	5.7	1.35	0.92–1.98
Z00–Z99, factors influencing health status and contact with health services, <i>not included above</i>	80	25.3	21835	13.3	1.82	1.40–2.36
A00–B99, certain infections and parasitic diseases	5	1.6	2400	1.5	1.07	0.44–2.62
C00–D89, neoplasms, disease of the blood and blood forming organs and certain disorders involving immune mechanisms	6	1.9	2319	1.4	0.93	0.41–2.12
E00–E90, endocrine, nutritional and metabolic diseases	9	2.9	3368	2.1	1.18	0.60–2.30
F00–F99, mental and behavioural disorders	15	4.8	6450	3.9	1.20	0.71–2.03
G00–G99, the nervous system	9	2.9	2561	1.6	1.55	0.79–3.03
H00–H59, the eye and adnexa	7	2.2	1806	1.1	1.79	0.84–3.81
H60–H95, the ear and mastoid process	3	1.0	1483	0.9	1.01	0.32–3.19
I00–I99, the circulatory system	3	1.0	1094	0.7	0.92	0.29–2.92
J00–J99, the respiratory system	14	4.4	3958	2.4	1.81	1.05–3.10
K00–K93, the digestive system	23	7.3	5420	3.3	2.08	1.35–3.20
L00–L99, the skin and subcutaneous tissue	6	1.9	2555	1.6	1.14	0.50–2.57
M00–M99, the musculoskeletal system and connective tissue	38	12.0	8516	5.2	2.28	1.62–3.23
N00–N99, the genitourinary system	15	4.8	5875	3.6	0.93	0.55–1.59
O00–O00, pregnancy, childbirth and the puerperium	41	13.0	11037	6.7	1.37	0.95–1.98
P00–P96, conditions originating in the perinatal period	0	-	53	< 0.1	-	
Q00–Q99, congenital malformations, deformations and chromosomal abnormalities	5	1.6	2310	1.4	1.10	0.45–2.66
R00–R99, symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	44	13.9	9709	5.9	2.33	1.68–3.22
S00–T14, injuries	102	32.3	35693	21.8	1.81	1.42–2.30
T14–T98, other injuries, poisoning and certain other consequences of external causes not included in S00–T14	11	3.5	3952	2.4	1.36	0.74–2.49
X00–X90, various external causes of accidental injury	1	0.3	93	0.1	6.77	0.93–49.45

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Table 3. Final multivariable model showing health care-seeking in the two years prior to vaccination in 316 Danish females who reported suspected adverse events to HPV vaccination compared with 163,910 matched controls.

Type of contact before first HPV vaccination	Multivariable odds ratio for care-seeking	95% CI
Consultation at primary health care provider by phone or e-mail	1.91	1.15–3.16
Reimbursement of physiotherapy, chiropractor or related treatment	2.13	1.64–2.76
Reimbursement of psychologist, psychiatrist or related treatment	1.87	1.31–2.66
Hospital contact, ICD-10 code K00-K93, the digestive system	1.57	1.01–2.45
Hospital contact, ICD-10 code M00-M99, the musculoskeletal system and connective tissue	1.56	1.09–2.23
Hospital contact, ICD-10 code R00-R99, symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1.77	1.27–2.48
Hospital contact, ICD-10 code S00-T14, injuries	1.51	1.18–1.93

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- ❖ Females with reports of suspected adverse reactions from HPV vaccination already before their first vaccination had a health care-seeking pattern different from a matched population who did not report adverse events
- ❖ The “effect” did not occur before the “cause”
 - Less likely that the symptoms represent a true adverse events
- ❖ Other possibilities
 - Girls that are active in sport (and have injuries)
 - Girls that are otherwise vulnerable



Reporting of adverse events: Stimulated by the programme “The Vaccinated Girls” broadcasted 26 March 2015, by TV2

Features interviews with families and vaccinated girls with medically unexplained symptoms .



THREE MAJOR QUESTIONS

- ❖ Is there a cause for concern as regards the safety of HPV vaccines ?
 - Are there any safety issues not discovered in reviews of pre- and post-licensure data ?
- ❖ How can we explain the reported suspected adverse events ?
 - What is wrong with these girls ?
- ❖ The way forward
 - HPV vaccination policies ?
 - Communication strategies ?



❖ Attribution

- Temporal association between vaccination and symptoms
- The tendency to link disease to exposure is deeply anchored in human nature

❖ Iatrogenicity

- Artefact of medical specialization and poor research methodology
- “Blame-X syndrome”
 - Makes doctors and patients believe that they know the cause, which reduces anxiety for the unknown
- Avoids discussions of more fundamental issues

❖ The vaccine is a trigger for a Body Distress Syndrome

- BDS is a condition of autonomic arousal, gastrointestinal arousal, musculoskeletal tensions, and general symptoms
- Often triggered by injuries and trauma, e.g. whiplash lesion

❖ Adverse events