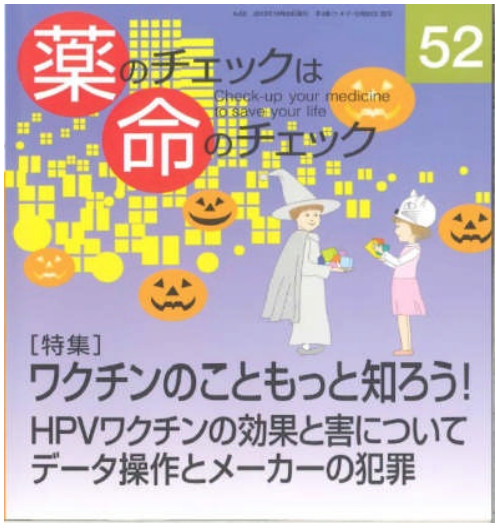
Harm assessment of HPV vaccine and “frailty exclusion bias” or “healthy vaccinee effect”: A theoretical basis and practical influences on Nagoya City Study 2016.5.11



Rokuro Hama M.D.

NPO Japan Institute of Pharmacovigilance

Med Check TIP

Frailty exclusion bias
or
Healthy-vaccinee effects

A theoretical basis and practical influences on Nagoya City Study

Abstract (1)

- It is essential to take **"Frailty exclusion bias" or "Healthy-vaccinee effects"** into account in assessing efficacy and/or harm of vaccine by observational studies.
- Theoretically, proportion (or odds of frailty) **increases in non vaccinated** and **decreases in vaccinated** as the coverage increases.
- Consequently, even if a vaccine has no efficacy and no harm, **odds ratio** for having symptoms/diseases in vaccinated compared with non-vaccinated become **less than 1.0.**
- If vaccine coverage increase, **due to this type of bias**, a vaccine without efficacy looks like effective and **a harmful vaccine looks like safe.**
- Theoretically, if the coverage of vaccine increased up to 80 to 90 %, the bias get extremely serious.
- In fact, symptoms such as "difficulty in simple calculation" or "need stick or wheel chair" etc were reported as if these increase by 30 to 40 % every year but these were due to extremely high vaccine coverage namely 88 % to 90 %.
- In order to eliminate this type of bias, health status prior to vaccination should be adjusted.

Abstract(2)

- No information for health status prior to vaccination was collected in Nagoya City Study. However, it may be possible to reduce bias by the following methods:
- Odds ratio for each symptom and the 95% confidence interval (95%CI) should be calculated by using the number of subjects, number of responders, number of women with symptoms, by symptom, by birth year (age)
- These odds ratios are the ones comparing those within the same age. Hence no age adjustment is needed.
- Theoretically the **frailty exclusion bias is the least** in the girls who were born in 2000 (about age 15-years) because of **the least coverage (15%).** Odds ratio in the women with other ages, should be adjusted by the the most reliable odds ratio with the least coverage of vaccination (15%).
- The odds ratios obtained by the methods above may be far more reliable than the interim results. However, it is still biased by exclusion of frailty.

Conclusion

- The preliminary data in the Nagoya City Study suggest the highly possibility of harmful effect of HPV vaccine.
- We recommend that Nagoya City should withdraw the interim report and disclose raw data so that the third party could analyse the data.
- We also recommend that Nagoya City should also re-analyse the data by themselves using appropriate methods.

Observational studies comparing cohorts vaccinated with HPV vaccine and non-vaccinated

Papers that claimed “no association”

1.Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human Papilloma Virus Immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. *Pediatr Infect Dis J* 2007;26: 979-84

2.Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. *Vaccine* 2011:29: 8279-82.

3.Arnheim-Dahlström L, Pasternak B et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ.* 2013; 347: f5906.

4.Donegan K, Beau-Lejdstrom R, King B, Seabroke S et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31: 4961-7

5.Scheller NM, Arnheim-Dahlström L et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA.* 2015;313:54-61

Papers that reported association or with data suggesting association

3.Arnheim-Dahlström (having data suggesting association)

6. Geier DA, Geier MR. A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events. *Clin Rheumatol.* 2015;34:1225-31.

7. Baril L, Rosillon D, Willame C, Angelo MG, Zima J, van den Bosch JH et al Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom.. *Vaccine.* 2015:33(48): 6884-91 [Epub 2015 Jul]

8.Agence nationale de sécurité des medicaments et des produits de santé. Vaccins anti-HPV et risque de maladies autoimmunes : étude pharmacoépidémiologique.

http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

(explanation about the paper 1 and 4～8 will be on the slides37～42)

9. Interim report of Nagoya City Study will be criticized in the slides **9～34** precisely.

Papers claiming “no association” without taking “frailty exclusion bias” into account (2) Paper by Gee et al

- In the (2) Gee article, selection criteria for the control group are not clearly stated.
- This alone is enough to make the study unreliable.
- Additionally, it is likely that outpatients who consulted for any reasons other than vaccination were selected for the control group.
- This may mean that the control group included many patients with infections, increasing the incidence of autoimmune diseases at the start of follow-up.
- Therefore, they are unsuited as a control group of healthy vaccinated people.

Papers claiming “no association” without taking “frailty exclusion bias” into account
(3) Paper by Arnheim-Dahlström et al

- A cohort study following-up approximately 1.0 million girls aged 10-17 years old between 2006 and 2010, utilizing a database in Sweden and Denmark. Some 300,000 girls received at least one dose of Gardasil (average 2.35 doses), and were observed for 180 days after inoculation.
- After adjusting for their age, educational background of parents, and the year of inoculation, incidences of 53 neurological disorders, autoimmune diseases and venous thrombosis were analysed, and the risk ratio (RR) with the control was calculated.
- As a result, among 29 diseases analysed, 23 autoimmune diseases appeared in 5 or more vaccinees. Of these, there was no significant difference for 20 diseases.
- Even though a “frailty exclusion bias” was not taken into account, the incidence was significantly higher in the Gardasil group for 3 diseases, namely Behcet’s disease (RR=3.37), Raynaud's disease (RR=1.67), and type I diabetes mellitus (RR=1.29).

Nagoya City Survey

- Subjects: about 70,000 women who were born in the fiscal year 1994 to 2000: they were in the 3rd grade of junior high school (about 14or 15 year old) to 21-year-old at September 2015
- Questionnaire survey asking:

1) Experience of HPV vaccine injection at least once.

2) Whether they have 24 different symptoms and other symptoms or not.

Hence, this survey may be considered as a retrospective cohort study comparing present symptoms between HPV vaccinee group and non-vaccinee group.

Nagoya City Survey (2) Preliminary report

Nagoya City Survey on HPV vaccine: preliminary report of analysis

Table 1 Response rate of questionnaire

Distributed	not delivered	net distributed	response	rate
71,177	217	70,960	30,793	43.4%

Table 2 Proportion of vaccinated and non-vaccinated

non-vaccinated	Vaccinated	(%)	Total	unknown	grand total
9,245	21,034	(69.47%)	30,279	514	30,793

Nagoya City Survey (3)
Birth year (age) and vaccination coverage (%)

Table 5 birth year (fiscal year) and vaccination coverage

Birth year	2000	1999	1998	1997	1996	1995	1994
approximate age	15	16	17	18	19	20	21
Vaccine +	3,761	2,038	1,260	663	452	428	496
−	662	2,123	3,158	3,766	3,725	3,749	3,565
Total	4,423	4,161	4,418	4,429	4,177	4,177	4,061
Coverage (%)	15.0%	51.0%	71.5%	85.0%	89.2%	89.8%	87.8%

Coverage of vaccination among those born in 1994 through 1997 were very high with more than 85%. However, the coverage decreased subsequently and was only 15 % among those born In 2000.

Comment by Hama: Coverage is extremely high (88 to 90 %) among those who were born in 1994-96. These must have been heavily influenced by “frailty exclusion bias”.

Nagoya City Survey (4)

Odds ratio with symptoms by vaccination status

Table 3 cross tabulation by (vaccinated vs non-vaccinated) and (symptom positive vs negative)

30,279: excluding unknown vaccination status

	Non-vaccinated Symptom (−)	(+)	Vaccinated Symptom (−)	(+)	Symptom unknown	Odds ratio	95% CI
Irregular menstrual cycle 01	6,812	2,330	15,354	5,515	268	1.05	(0.99 - 1.11)
Abnormal menstrual volume 02	8,569	565	19,205	1,638	302	1.29	(1.17 - 1.43)
Arthralgia 03	8,412	729	19,324	1,522	292	0.91	(0.83 - 1.00)
Severe headache 04	8,232	928	18,714	2,168	237	1.03	(0.95 - 1.11)
Fatigue 05	8,116	1,047	18,587	2,291	238	0.96	(0.88 - 1.03)
Easy to be tired 06	8,163	996	18,578	2,297	245	1.01	(0.94 - 1.10)
Unable to concentrate 07	8,433	728	19,407	1,448	263	0.86	(0.79 - 0.95)
Abnormal visual field 08	8,986	171	20,470	388	264	1.00	(0.83 - 1.19)
Too glaring 09	8,802	359	19,964	915	239	1.12	(0.99 - 1.27)
Sudden visual acuity decrease 10	8,358	799	19,466	1,400	256	0.75	(0.69 - 0.82)

The red marked items are those with significantly more symptoms in vaccinated and the green marked items are those with significantly less symptoms in vaccinated.

Table 3 continued: Odds ratio with symptoms by vaccination status

	Non-vaccinated Symptom (−)	(+)	Vaccinated Symptom (−)	(+)	Symptom unknown	Odds ratio	95% CI
Dizziness 11	8,060	1,095	18,564	2,299	261	0.91	(0.84 - 0.98)
Cold foot 12	8,004	1,155	18,317	2,536	267	0.96	(0.89 - 1.03)
Difficult to sleep 13	8,454	698	19,379	1,492	256	0.93	(0.85 - 1.02)
Sleep too long 14	8,080	1,073	18,357	2,488	281	1.02	(0.95 - 1.10)
Rough skin 15	8,076	1,076	18,789	2,081	257	0.83	(0.77 - 0.90)
Hyperventilation 16	8,834	333	20,183	704	225	0.93	(0.81 - 1.06)
Difficult to remember 17	8,944	220	20,257	632	226	1.27	(1.09 - 1.48)
Difficulty in simple calculation 18	9,082	81	20,697	189	230	1.02	(0.79 - 1.33)
Difficult to remember simple kanji 19	8,986	185	20,471	417	220	0.99	(0.83 - 1.18)
Involuntary move 20	9,107	58	20,689	200	225	1.52	(1.13 - 2.04)
Cannot walk normally 21	9,135	22	20,811	73	238	1.46	(0.90 - 2.35)
Need stick or wheel chair 22	9,139	16	20,853	33	238	0.90	(0.50 - 1.64)
Sudden loss of power 23	9,054	100	20,586	284	255	1.25	(0.99 - 1.57)
Weakness in extremities 24	9,007	124	20,461	357	330	1.27	(1.03 - 1.56)
Others 1(free writing) 25	2,641	118	5,539	528	21,453	2.13	(1.74 - 2.62)
Others 2 ‘free writing) 26	2,467	28	5,201	89	22,494	1.51	(0.98 - 2.31)

The red marked items are those with significantly more symptoms in vaccinated and the green marked items are those with significantly less symptoms in vaccinated.

Nagoya City Survey (5)
Birth year (age) and odds ratio of symptoms compared with those born in 2000 (Non-vaccinated only)

Table 4: Birth year (age) and risk ratio of symptoms (Non-vaccinated only)

Birth year approximate age	00 15	99 16	98 17	97 18	96 19	95 20	94 21	Increment Per year
Irregular menstrual cycle 01	1.00	1.05	1.10	1.12	1.09	1.63	1.63	7.4%
Abnormal menstrual volume 02	1.00	1.08	1.15	1.39	0.97	1.51	1.86	8.9%
Arthralgia 03	1.00	0.83	0.91	1.31	1.04	1.54	1.65	8.5%
Severe headache 04	1.00	1.18	1.18	1.48	1.32	1.79	1.68	9.4%
Fatigue 05	1.00	1.18	1.40	1.56	1.39	2.14	2.26	14.2%
Easy to be tired 06	1.00	1.22	1.46	1.36	1.34	2.12	1.95	11.9%
Unable to concentrate 07	1.00	1.12	1.40	1.52	0.94	1.75	1.50	7.6%
Abnormal visual field 08	1.00	0.75	0.98	1.30	1.93	2.05	2.53	17.9%
Too glaring 09	1.00	0.86	1.32	1.10	1.79	2.56	2.16	16.7%
Sudden visual acuity decrease 10	1.00	0.95	0.83	0.74	0.91	1.12	1.29	0.9%

Odds ratios of positive symptom by various birth year compared with those born in 2000 are shown. The red marked odds ratios are significant (95% confidence intervals are not shown in this table). All symptoms except “sudden visual acuity decrease” increased as age increased.

Table 4 (continued): Birth year and odds ratio of symptoms compared with those born in 2000 (Non-vaccinated only)

Birth year approximate age	00 15	99 16	98 17	97 18	96 19	95 20	94 21	Increment Per year
Dizziness 11	1.00	1.00	1.18	1.21	1.24	1.54	1.53	7.5%
Cold foot 12	1.00	1.13	1.19	1.40	1.47	1.81	1.88	11.2%
Difficult to sleep 13	1.00	0.85	1.06	1.06	1.91	2.84	2.65	20.0%
Sleep too long 14	1.00	1.26	1.13	1.20	1.34	1.85	1.92	10.4%
Rough skin 15	1.00	0.97	0.96	1.17	1.26	1.09	1.34	4.5%
Hyperventilation 16	1.00	1.22	1.73	1.27	2.08	3.12	2.37	18.3%
Difficult to remember 17	1.00	0.85	1.97	2.00	1.96	3.02	4.63	29.5%
Difficulty in simple calculation 18	1.00	0.52	1.57	3.29	1.98	4.27	5.52	38.9%
Difficult to remember simple kanji 19	1.00	0.77	0.83	2.00	2.05	4.37	3.27	29.7%
Involuntary move 20	1.00	0.91	1.32	1.88	0.46	4.44	2.51	22.4%
Cannot walk normally 21	1.00	0.96	0.52	0.98	7.32	3.09	5.29	37.9%
Need stick or wheel chair 22	1.00	0.77	1.25	NA	5.25	1.85	4.74	30.9%
Sudden loss of power 23	1.00	1.05	1.04	0.89	3.22	2.84	2.67	20.9%
Weakness in extremities 24	1.00	1.21	1.24	1.24	1.84	2.18	1.66	11.0%
Others 1 (free writing) 25								
Others 2 (free writing) 26								

Odds ratios of positive symptom by various birth year compared with those born in 2000 are shown. The red marked odds ratios are significant (95% confidence intervals are not shown in this table). All symptoms except “sudden visual acuity decrease” increased as age increased.

Nagoya City Survey (6) Age adjusted odds ratio

Table 6: Age adjusted odds ratio

(odds ratio in the Table 3 were adjusted by age using logistic regression analysis

	Before adjustment		age adjusted	
	OR	95%CI	OR	95%CI
Irregular menstrual cycle 01	1.05	(0.99 - 1.11)	0.94	(0.88- 1.01)
Abnormal menstrual volume 02	1.29	(1.17 - 1.43)	1.11	(0.98- 1.25)
Arthralgia 03	0.91	(0.83 - 1.00)	0.86	(0.77- 0.96)
Severe headache 04	1.03	(0.95 - 1.11)	0.91	(0.83- 1.00)
Fatigue 05	0.96	(0.88 - 1.03)	0.80	(0.73- 0.88)
Easy to be tired 06	1.01	(0.94 - 1.10)	0.87	(0.79- 0.95)
Unable to concentrate 07	0.86	(0.79 - 0.95)	0.81	(0.72- 0.90)
Abnormal visual field 08	1.00	(0.83 - 1.19)	0.84	(0.67- 1.04)
Too glaring 09	1.12	(0.99 - 1.27)	0.92	(0.80- 1.07)
Sudden visual acuity decrease 10	0.75	(0.69 - 0.82)	0.80	(0.71- 0.89)

Table 6 (continued): Age adjusted odds ratio

	Before adjustment OR	95%CI	age adjusted OR	95%CI
Dizziness 11	0.91	(0.84 - 0.98)	0.83	(0.75- 0.91)
Cold foot 12	0.96	(0.89 - 1.03)	0.79	(0.72- 0.86)
Difficult to sleep 13	0.93	(0.85 - 1.02)	0.73	(0.65- 0.81)
Sleep too long 14	1.02	(0.95 - 1.10)	0.90	(0.82- 0.98)
Rough skin 15	0.83	(0.77 - 0.90)	0.80	(0.73- 0.88)
Hyperventilation 16	0.93	(0.81 - 1.06)	0.73	(0.63- 0.86)
Difficult to remember 17	1.27	(1.09 - 1.48)	0.99	(0.82- 1.19)
Difficulty in simple calculation 18	1.02	(0.79 - 1.33)	0.68	(0.50- 0.93)
Difficult to remember simple kanji 19	0.99	(0.83 - 1.18)	0.75	(0.61- 0.93)
Involuntary movement 20	1.52	(1.13 - 2.04)	1.15	(0.81- 1.62)
Cannot walk normally 21	1.46	(0.90 - 2.35)	0.89	(0.51- 1.56)
Need stick or wheel chair 22	0.90	(0.50 - 1.64)	0.49	(0.24- 0.99)
Sudden loss of power 23	1.25	(0.99 - 1.57)	1.01	(0.77- 1.33)
Weakness in extremities 24	1.27	(1.03 - 1.56)	1.13	(0.88- 1.44)
Others 1 (free writing) 25				
Others 2 (free writing) 26				

Nagoya City Survey
(7) Conclusion

- Of the 24 symptoms, there was no symptom that was significantly more reported among those vaccinated, after age adjustment.
- In the contrarily, there were several symptoms that were significantly less reported among those vaccinated compared with non-vaccinated.
- These might have occurred because those who had symptoms did not receive vaccine and it may be difficult to consider that HPV vaccination reduced such symptoms.

  (This point is deleted in the formally disclosed preliminary report on Dec 14 2015)
- This is the statistical analysis hence, the causality of individual case should be assessed very carefully.

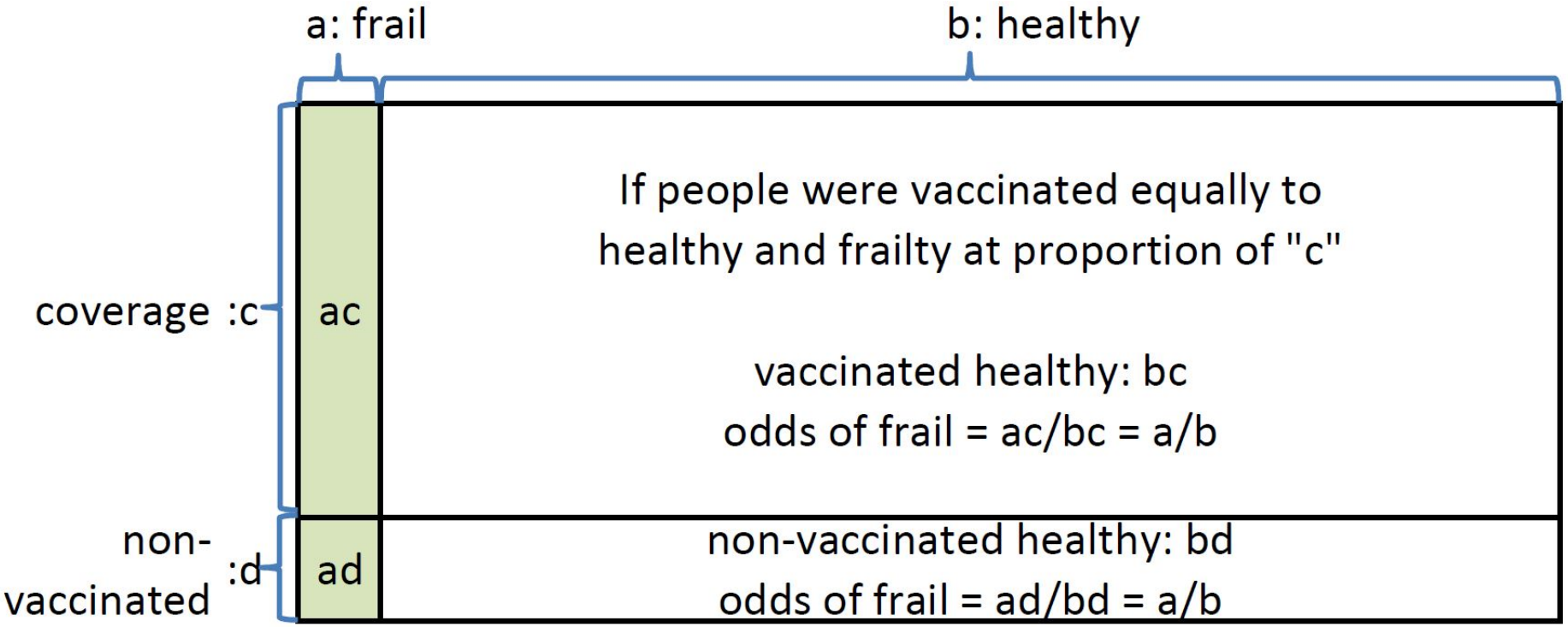
Nagoya City Survey

(8)the most serious limitations

- Highly biased by “the frailty exclusion bias”
- They misunderstand the increase of odds ratio of positive symptoms among those born in 1994 to 1997 due to “the frailty exclusion bias” derived by the very high coverage of vaccination as the increase of age.
- They yield very strange results in that significantly low odds ratio in the vaccinated compared to the non-vaccinated by adjusting age.

Theoretical basis of “frailty exclusion bias” (1) no exclusion

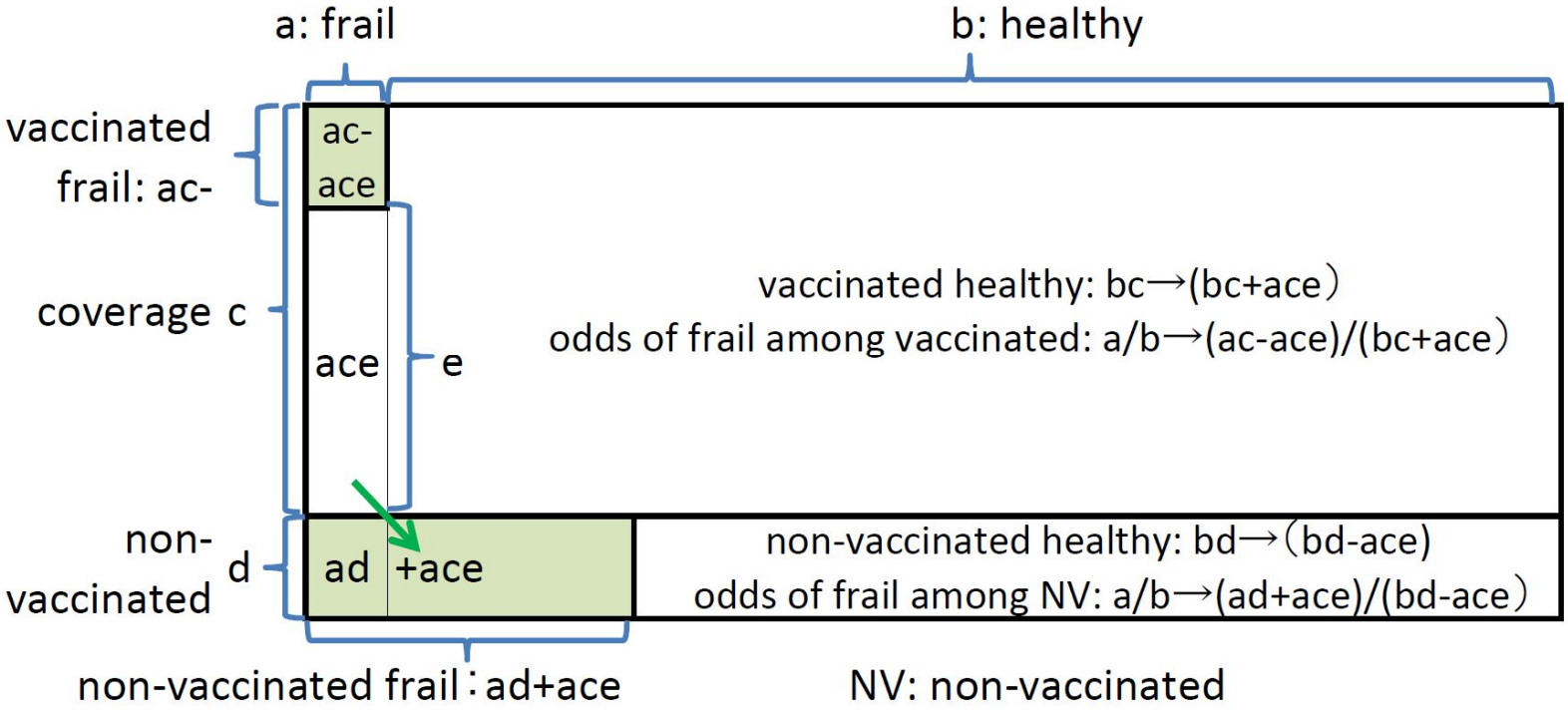
Fig 1 No exclusion of frailty



- Imagine a population in which high risk people (the frailty) are living by the proportion of "a".
- People are vaccinated by the coverage "c".
- If the frailty (people with high risk) or the healthy are equally vaccinated, and the vaccine do not cause any adverse effect, the odds of frailty is a/b for both in the vaccinated and non-vaccinated.
- Hence the odds ratio of frailty in vaccinated compared with non-vaccinated is 1.0.

Theoretical basis of “frailty exclusion bias” (2) with exclusion

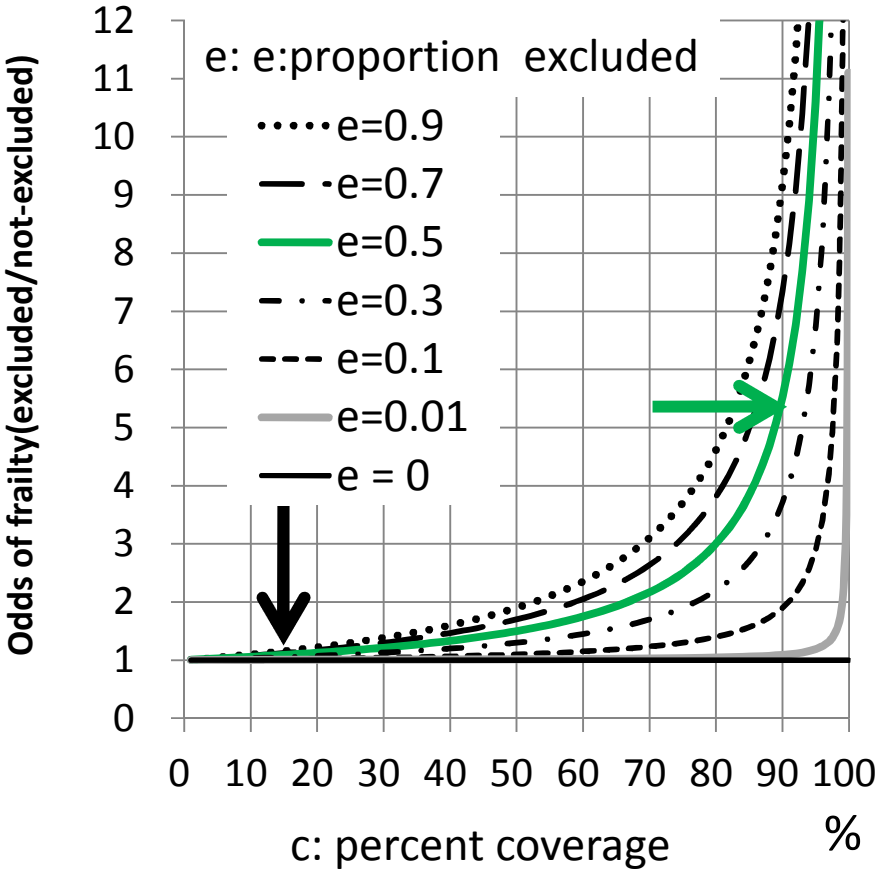
Fig 2: If frail people were excluded for vaccination



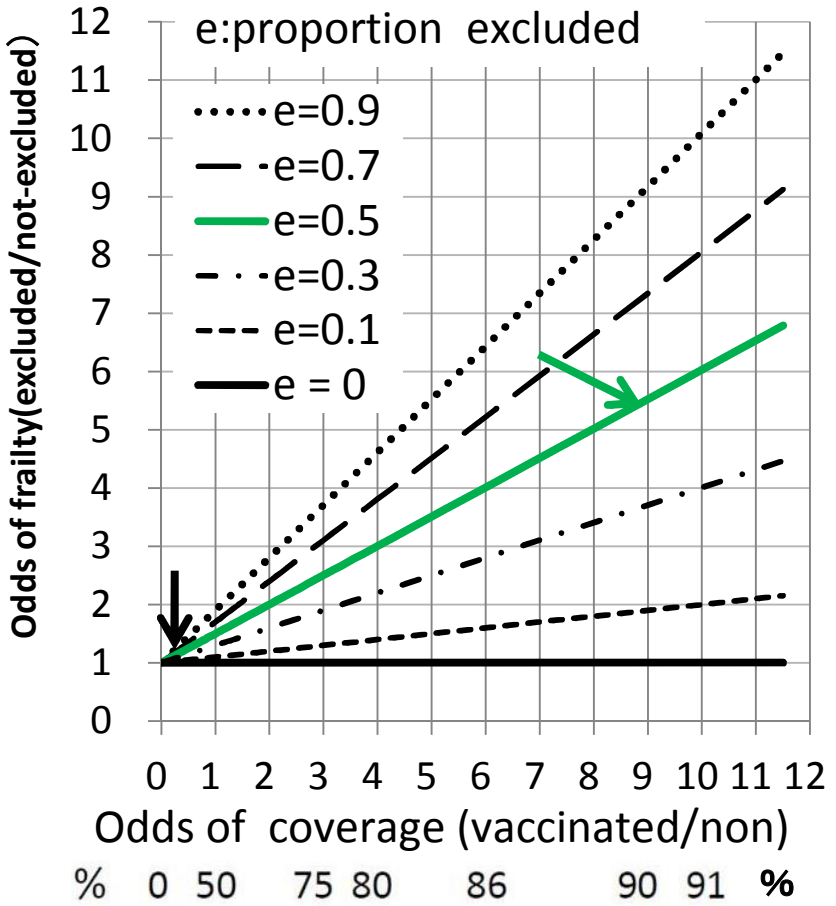
- If the frailty were excluded for vaccination by the proportion of "e“ and if the vaccine do not cause any adverse effect, odds of frailty is (ac-ace)/(bc + ace)) among vaccinated and (ad + ace)/(bd - ace)) among non-vaccinated.
- Hence the odds ratio of frailty in vaccinated compared with non-vaccinated = ((ac - ace)/(bc + ace))／((ad + ace)／(bd - ace))
- Unless "e" is 0, odds ratio of frailty in the vaccinated compared with unvaccinated will be always less than 1.0 theoretically.
- This is the theoretical basis of "frailty exclusion bias“, "frailty selection bias" or "healthy vaccinee effect".

Influence of frailty exclusion bias on non-vaccinated group
Odd of frailty in the case “excluded” versus “not excluded”

A : percent of coverage

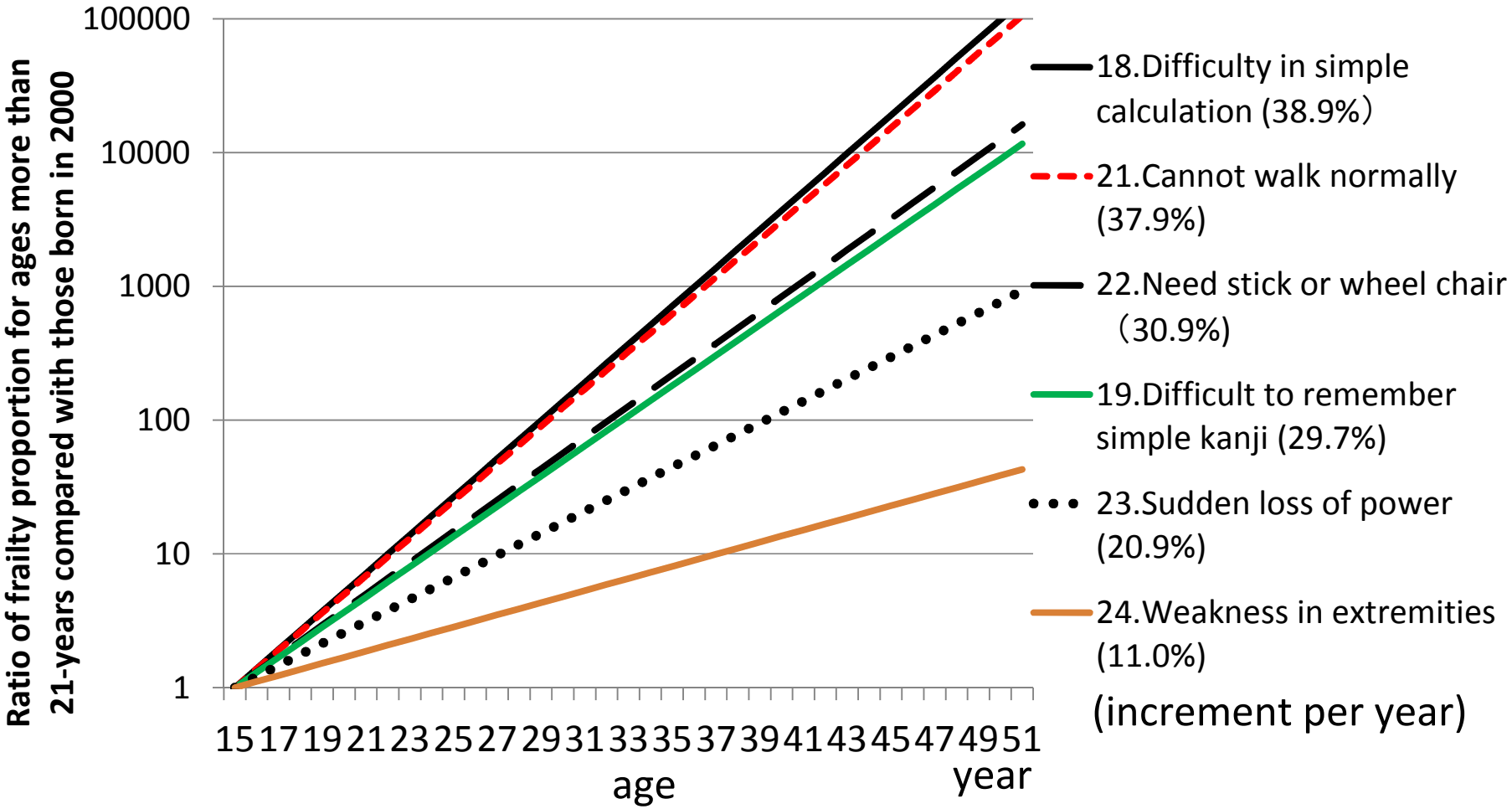


B : odds of coverage (vaccinated/non)



If the coverage is 15%(odds=0.18)(↓), influence of exclusion on the non-vaccinated group is small in any proportion of exclusion . However, if the coverage is nearly 90 % (odds = 9) as in the Nagoya City Survey, the influence is extreme (odds ratio increase to 5(→), if one half of frailty were excluded (e=0.5)

Proportion of women aged 22 year or more with positive symptoms will increase impossibly high if the increase were simply due to age



If the apparent increasing tendency of positive symptoms were simply due to age, the proportion of women with positive symptoms have to increase dramatically high: That's impossible.

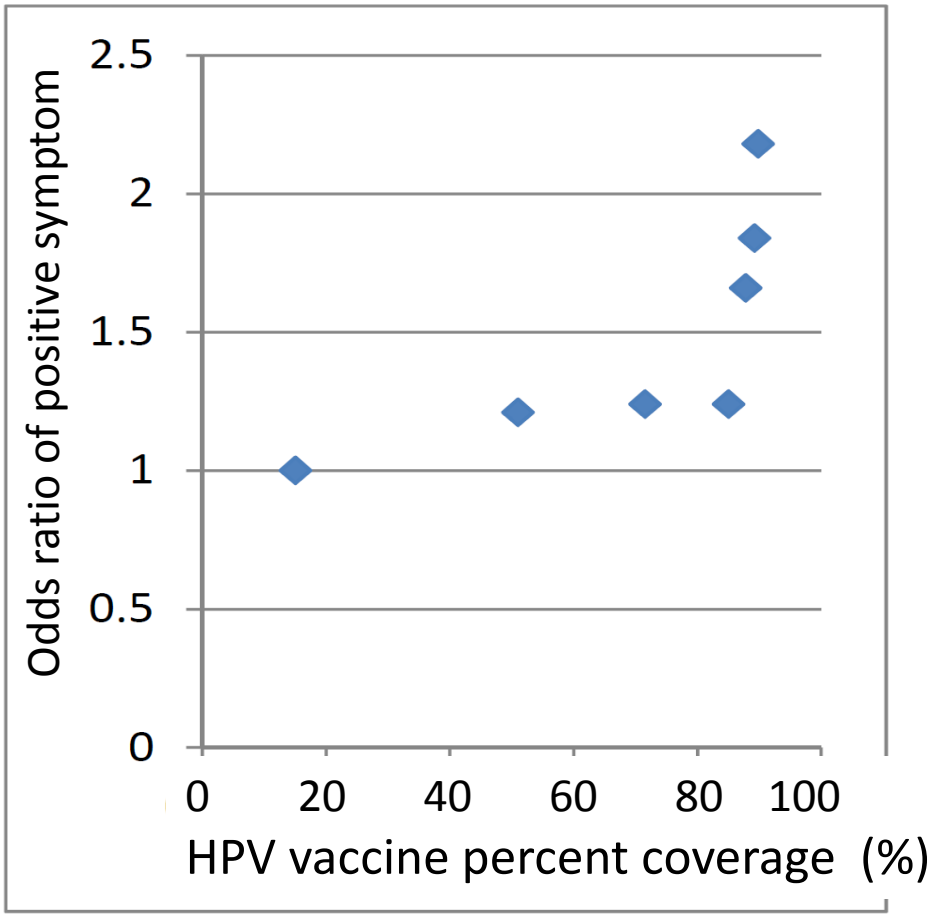
Example of influence：24. Weakness in extremities

Vaccination coverage and odds ratio of positive symptom in non-vaccinated（compared to those born in 2000: coverage=15%）

HPV vaccination coverage

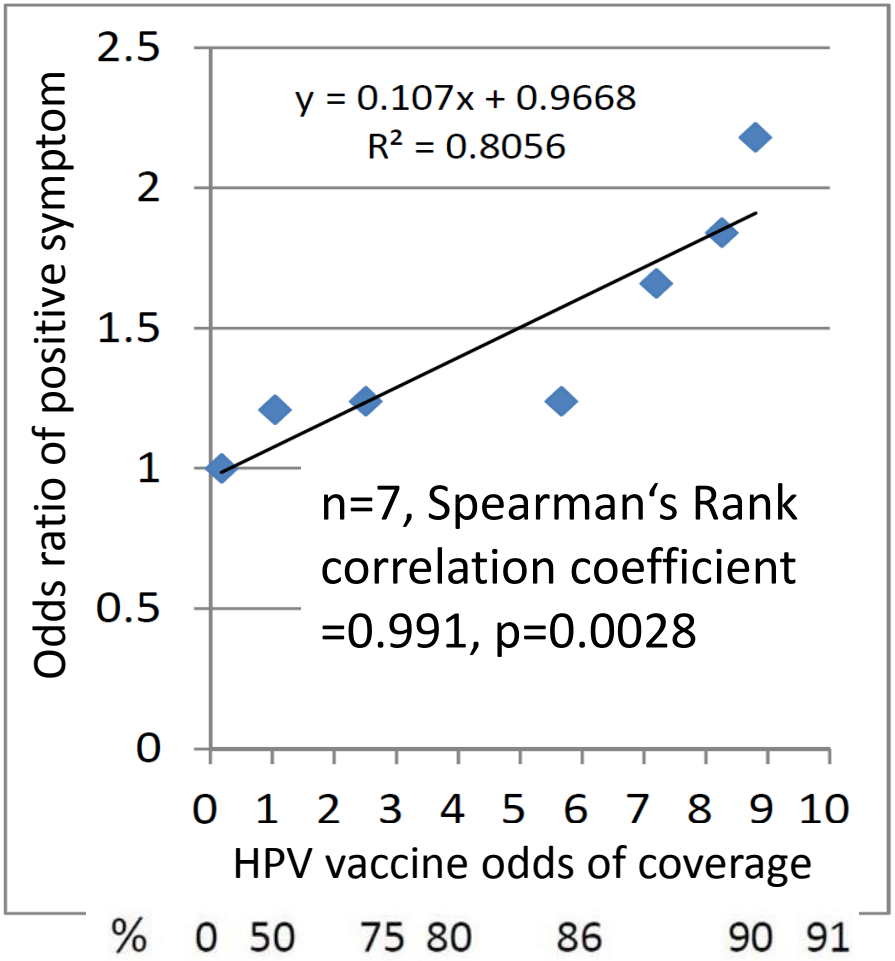
(A) shown in percent coverage

Pattern is similar to slide 22-A



(B) shown in odds of coverage

Pattern is similar to slide 22-B



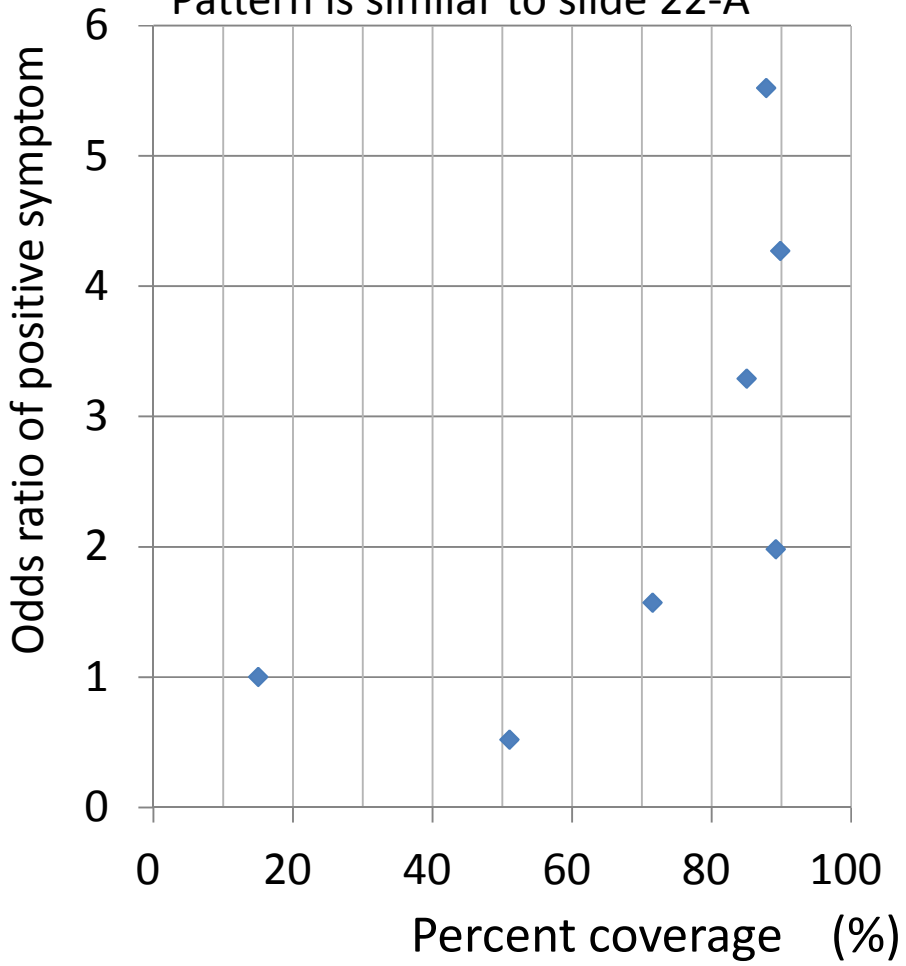
Example of influence : 18. Difficulty in simple calculation

Vaccination coverage and odds ratio of positive symptom in non-vaccinated（compared to those born in 2000: coverage=15%）

HPV vaccination coverage

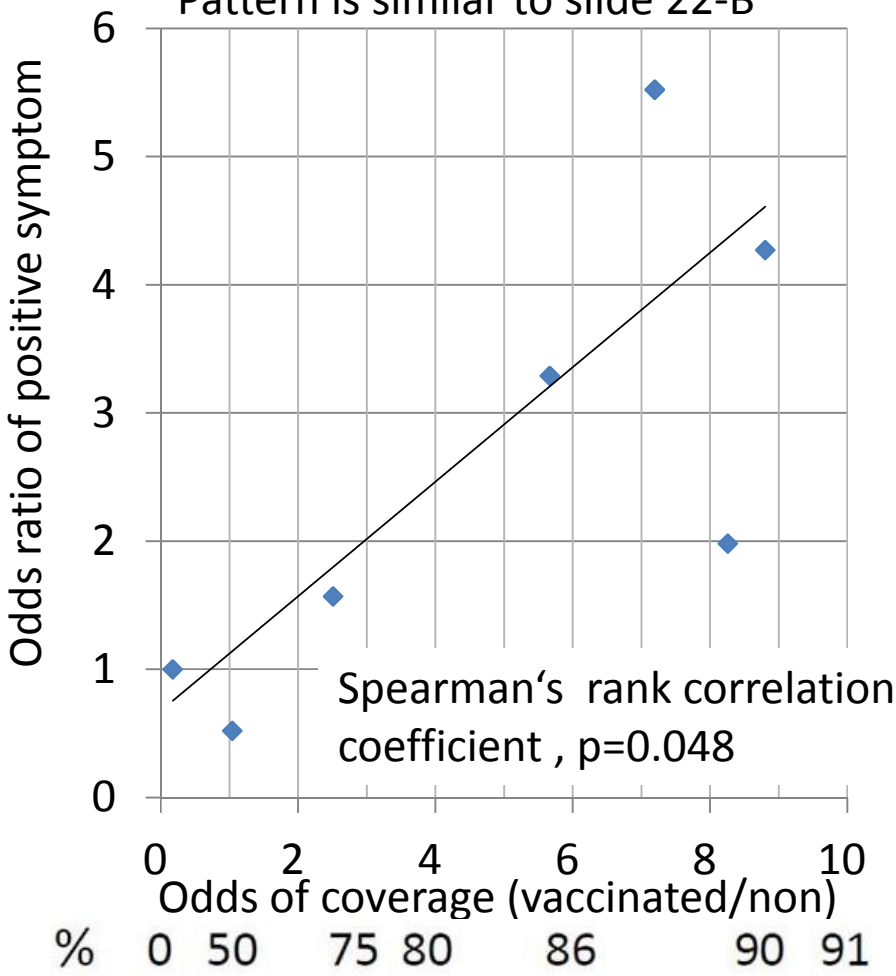
(A) shown in percent coverage

Pattern is similar to slide 22-A



(B) shown in odds of coverage

Pattern is similar to slide 22-B



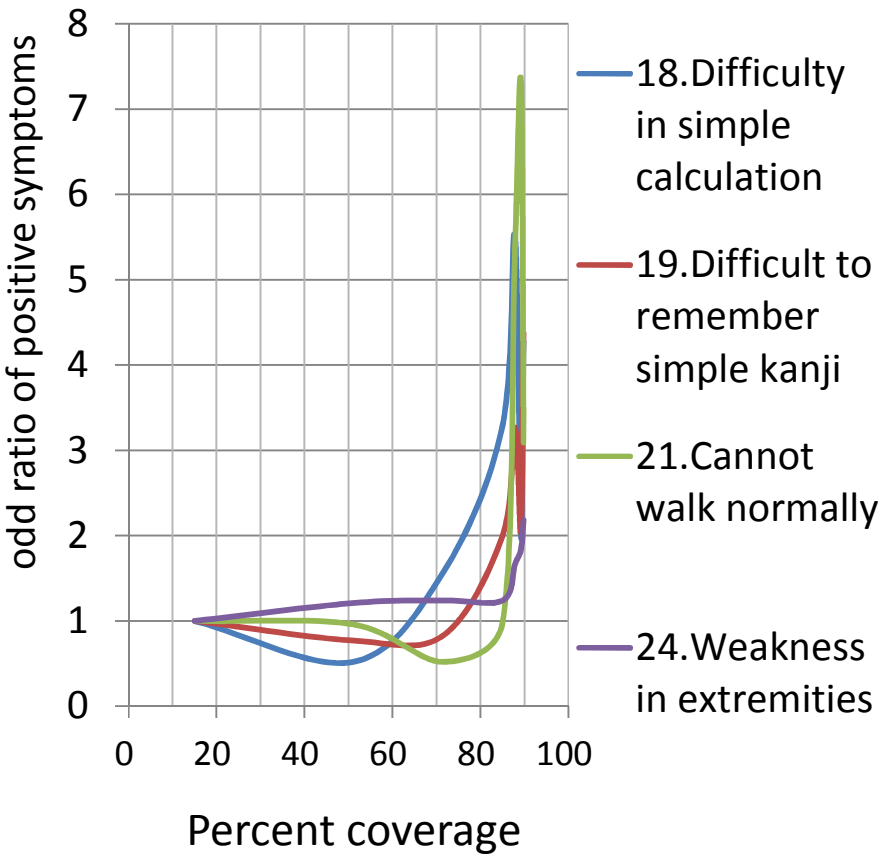
Example of influence：Symptoms (18, 19, 21, 24)

Vaccination coverage and odds ratio of positive symptom in non-vaccinated（compared to those born in 2000: coverage=15%）

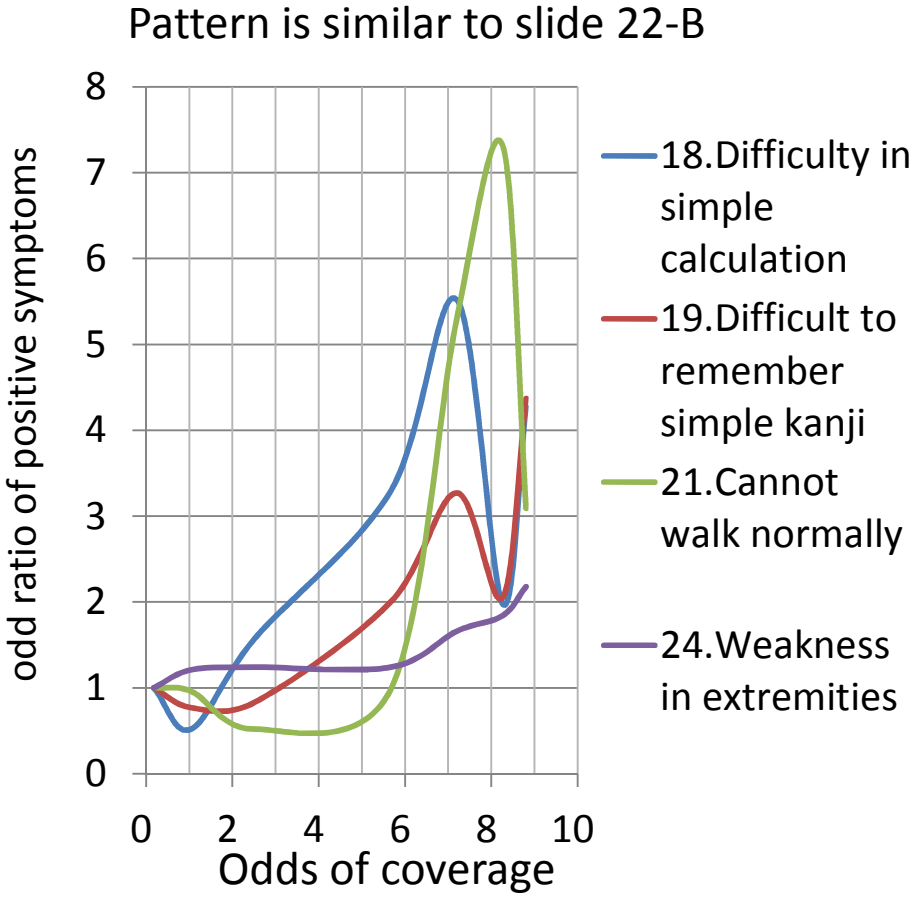
HPV vaccination coverage

(A) shown in percent coverage　　(B) shown in odds of coverage

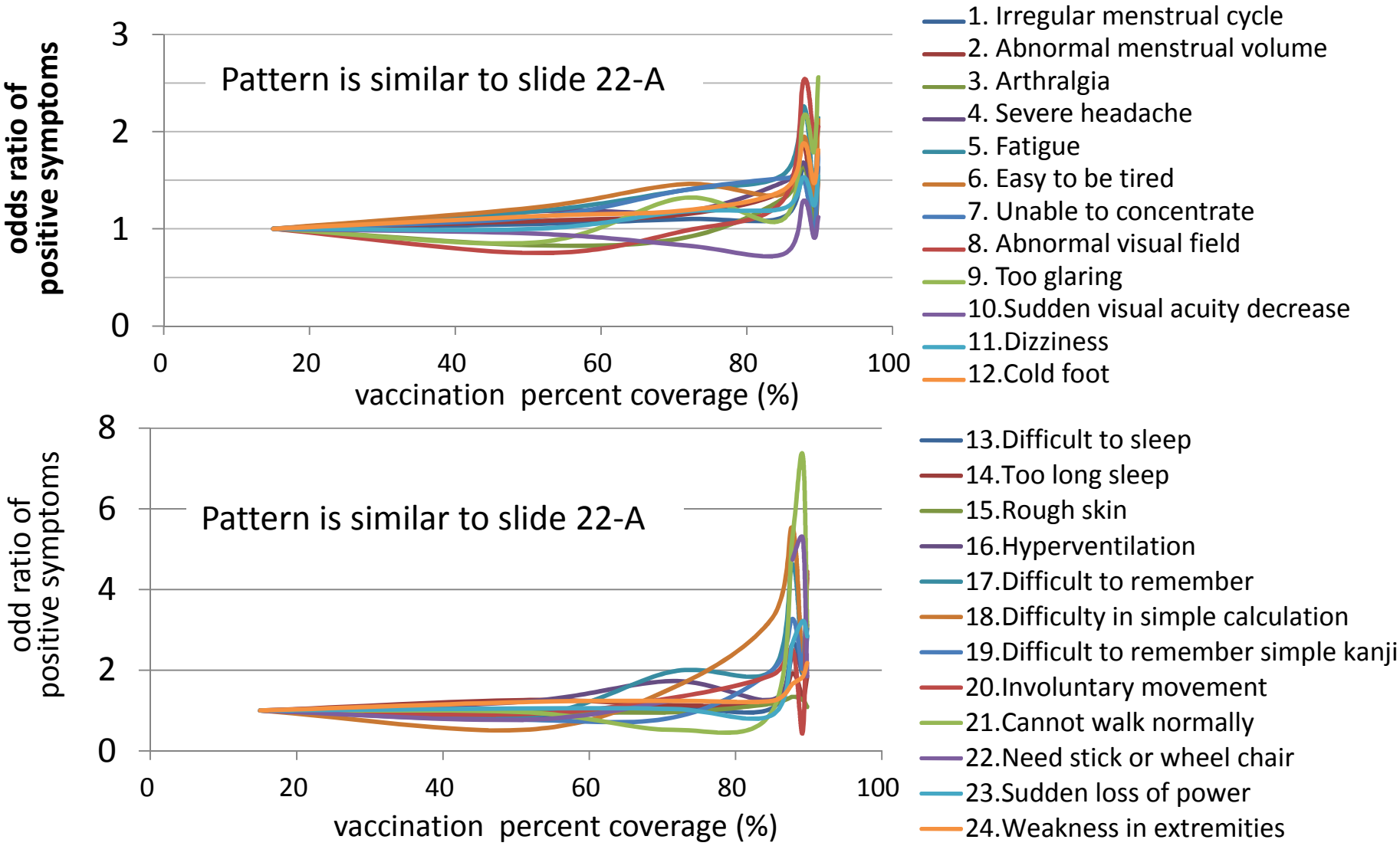
Pattern is similar to slide 22-A



Pattern is similar to slide 22-B



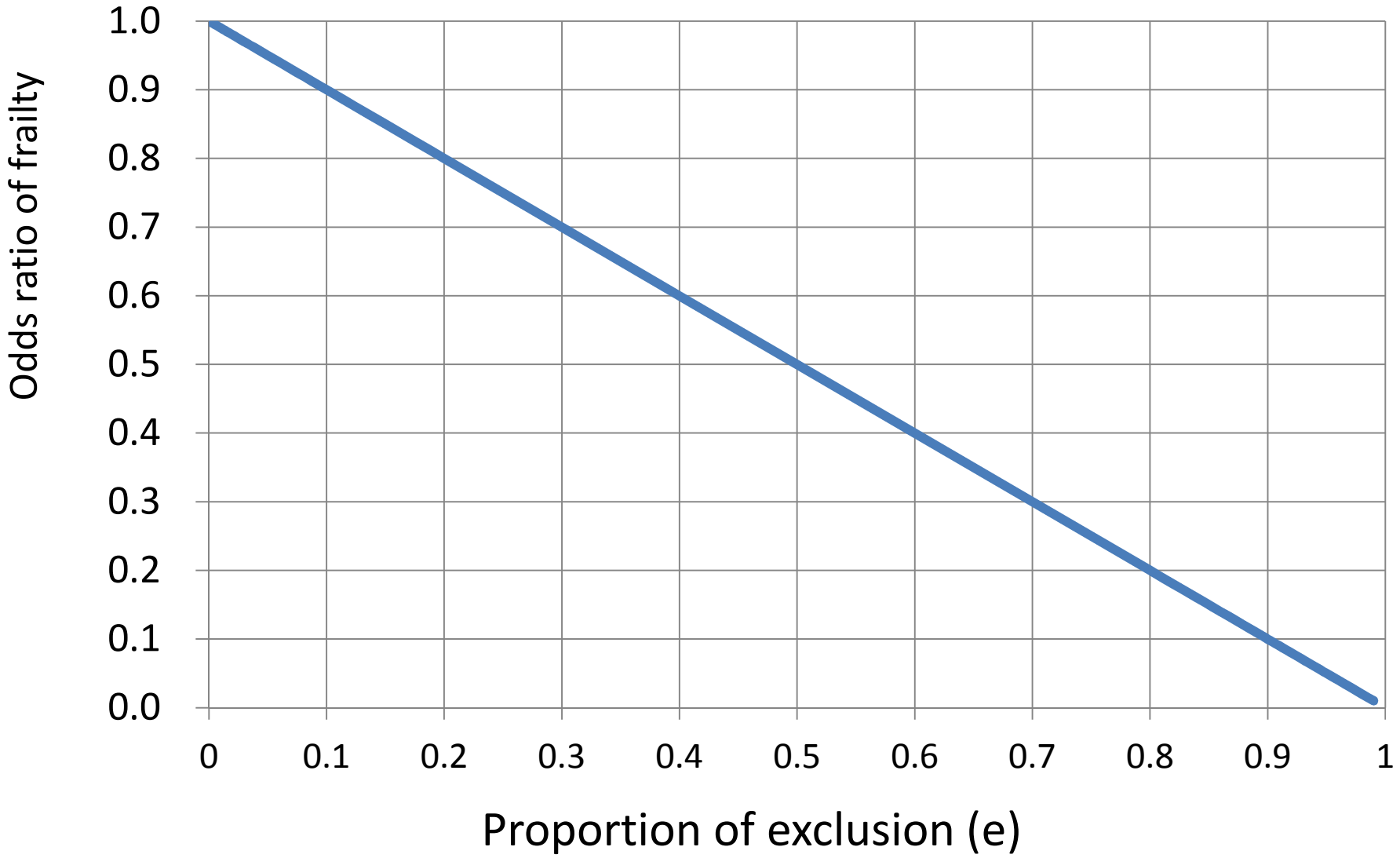
Vaccination coverage and odds ratio of positive symptom in non-vaccinated（compared to those born in 2000: coverage=15%) Graphic illustration of the Table 4 of Nagoya City survey



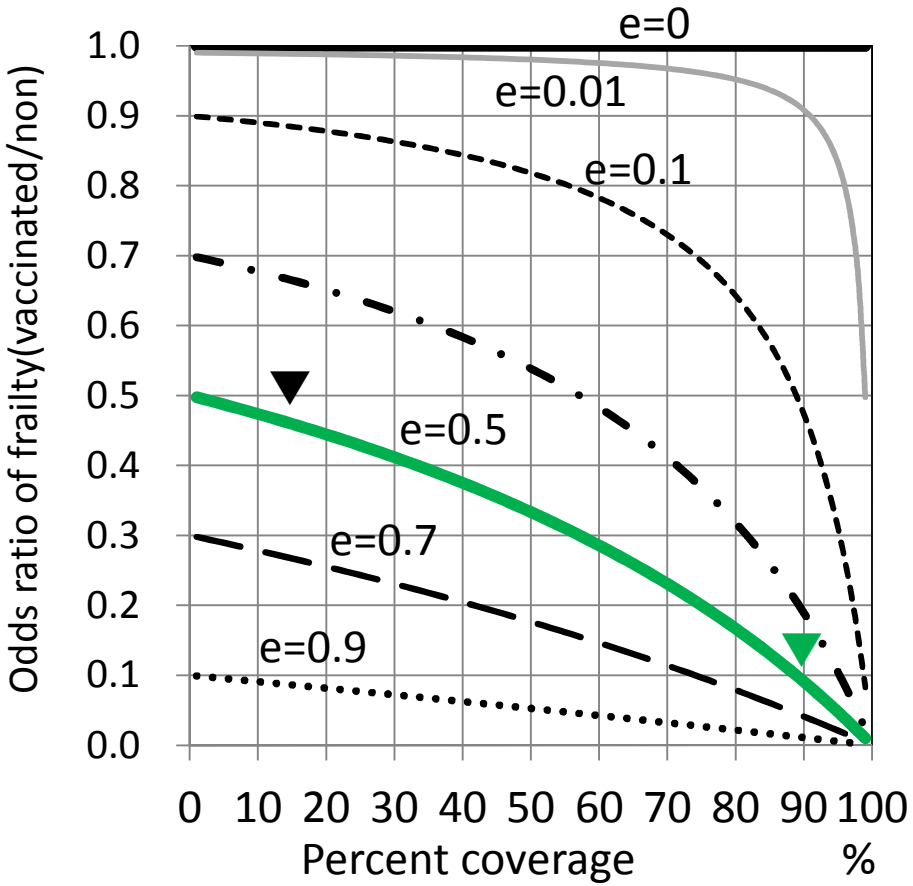
Odds ratios of positive symptoms go up to 3 to 7 for those born in 1994 to 96 in table 4. The major reason may be due to frailty exclusion bias rather than age.

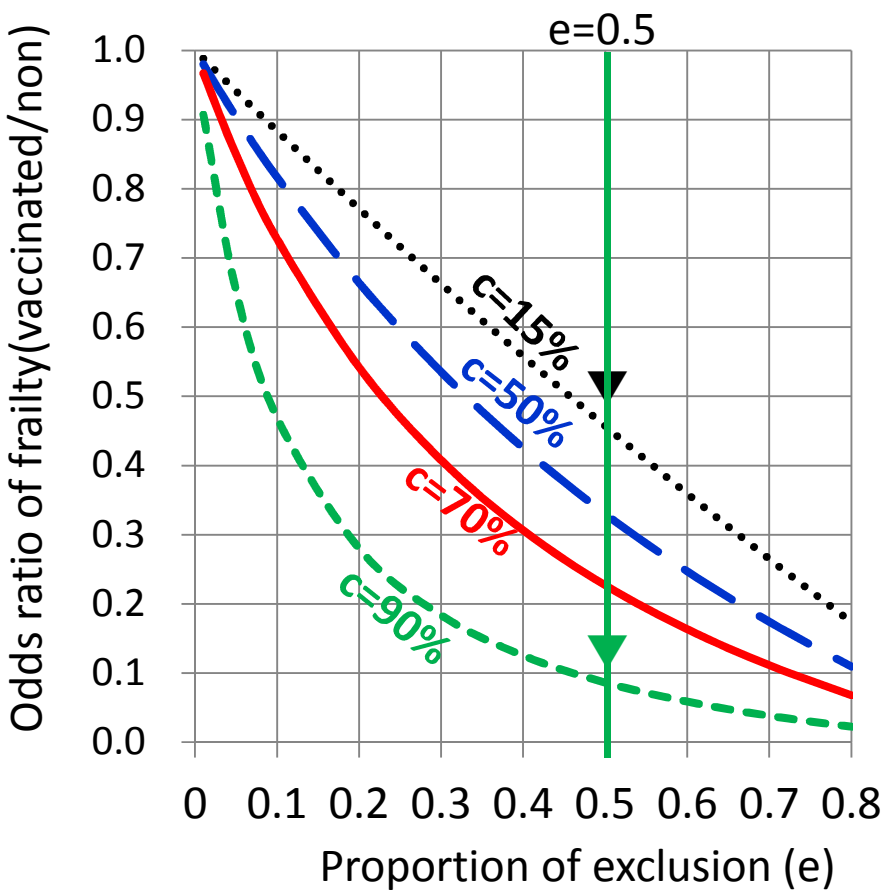
Odds ratio of frailty compared with no exclusion

In case when a=0.001(0.1%). However, if a=<0.01 (1%), the results are almost similar



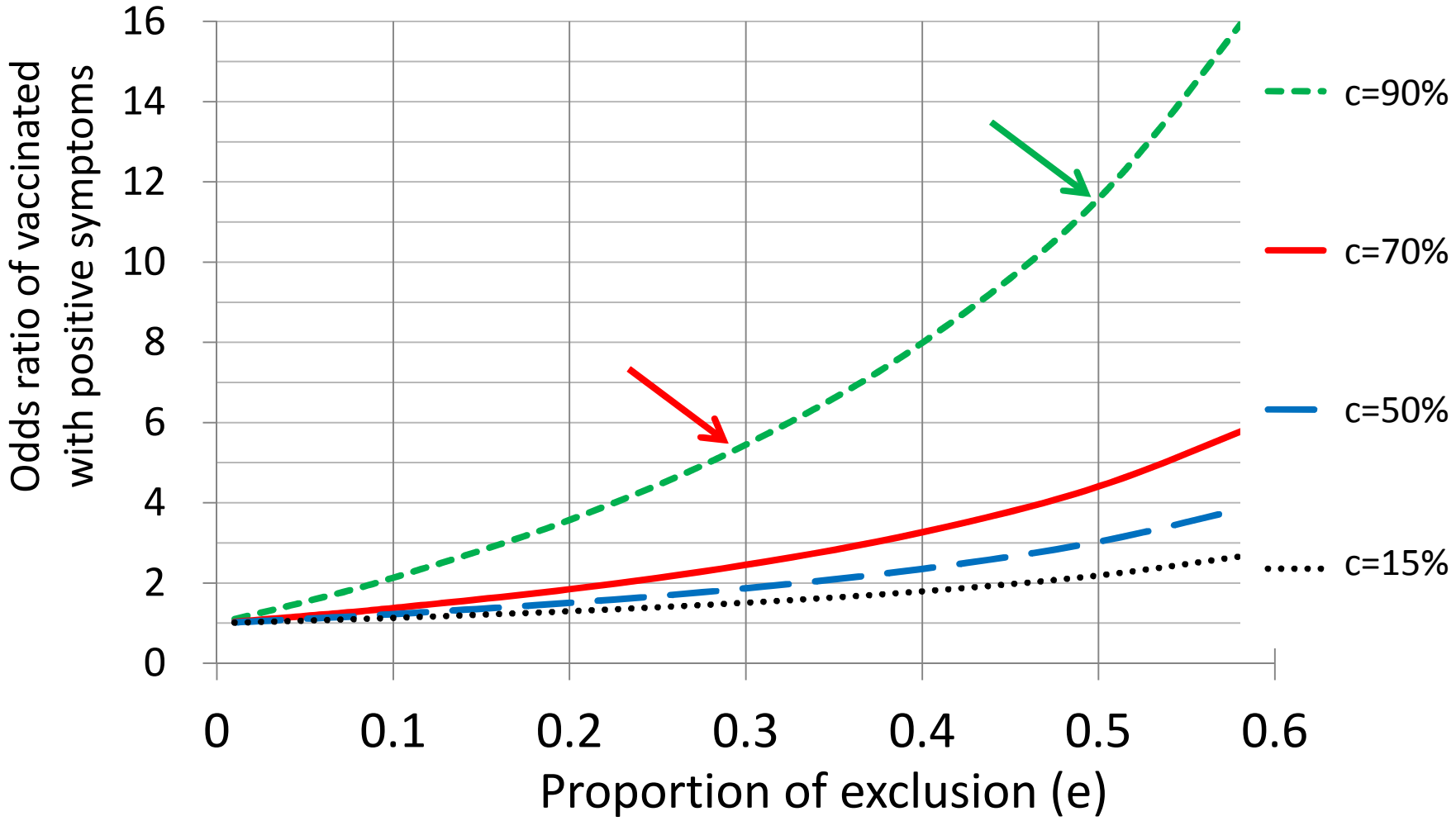
Theoretical influence on the odds ratio of frailty by the percent coverage and the proportion of exclusion (vaccine has no efficacy nor harm)





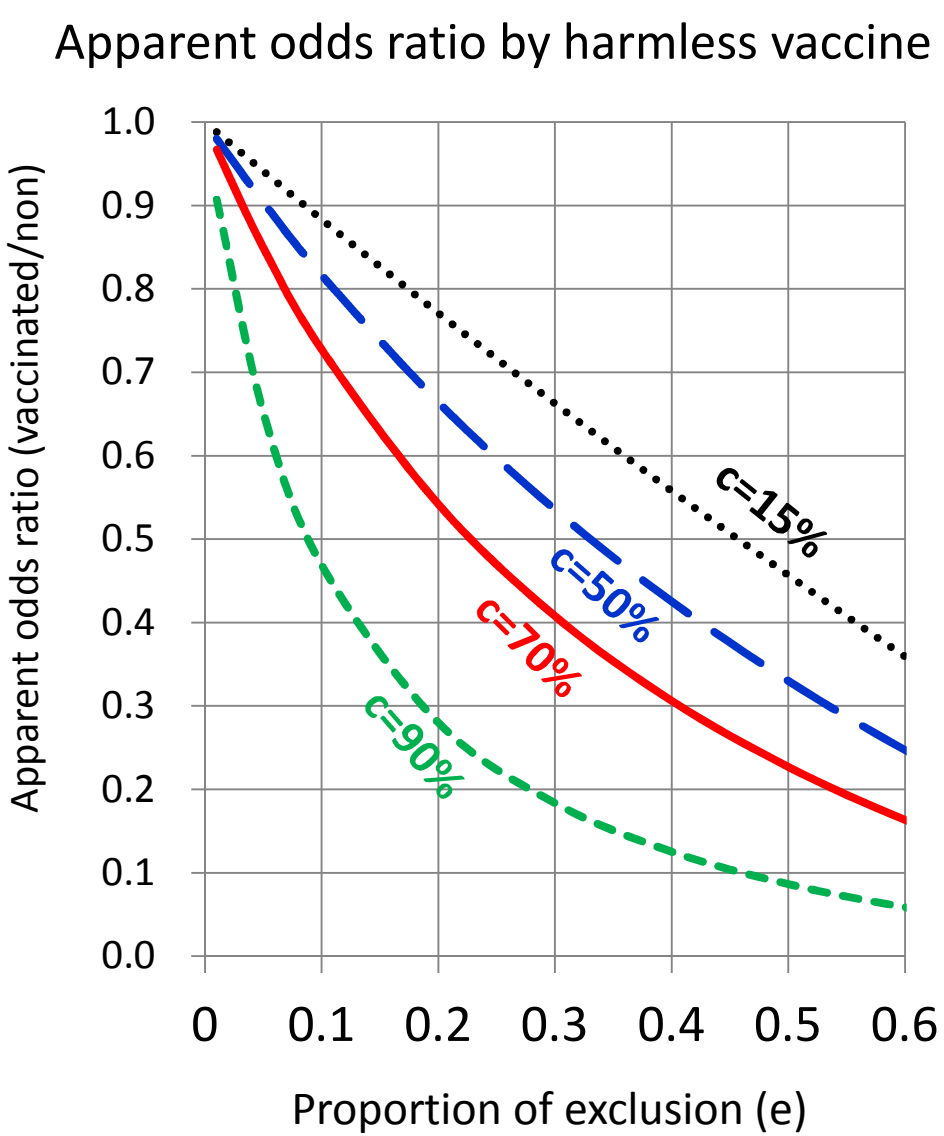
If e=0.5, odds ratio of frailty of vaccinated compared to non-vaccinated is calculated less than 0.5 (▼), even if coverage is low (15%). If coverage increase up to 90%, odds ration fell to less than 0.1(▼). Apparent odds ratio in vaccinated compared with non-vaccinated is calculated one tenth although the vaccine has no harmful effect.

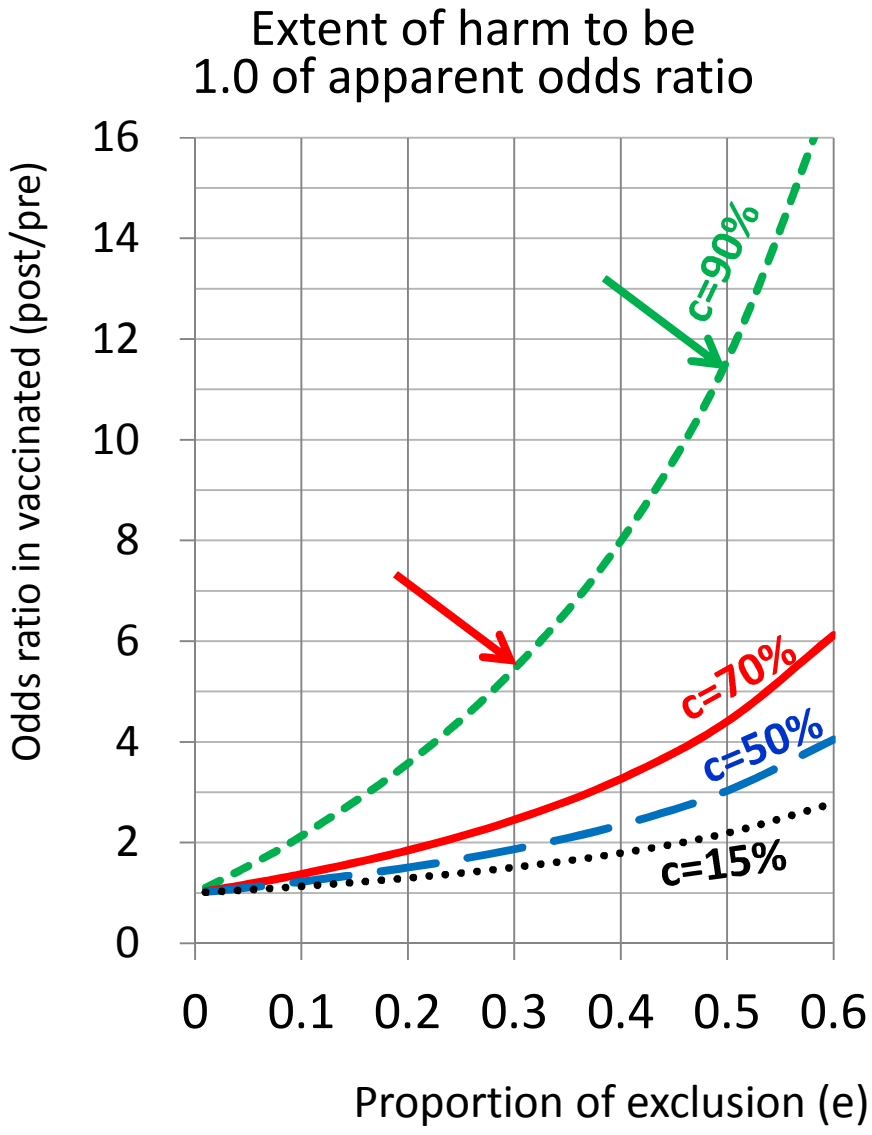
Influence of frailty exclusion bias : How harmful a vaccine must be in order to be odds ratio = 1.0



If coverage is 90% (c=0.9----), **5.5 times** more diseases (symptoms) are needed when e=0.3**(→)**, and **11 times** more diseases are needed when e=0.5 **(→)** in order to be 1.0 of odds ratio.

Influence of frailty exclusion bias : comparison of apparent odds ratio and extent of harm to be 1.0 of odds ratio





Note: see the foot note of slide 36

How can we know from the raw data of Nagoya City Survey:

- Odds ratio should be adjusted by the health status before vaccination instead of age, because the age difference may be very small if any.
- However, Nagoya City Survey did not collect such information.
- The second best estimation may be as follows:
- Odds ratio and its 95 % confidence interval in vaccinated compared to non-vaccinated should be calculated by birth year for each 24 symptom (see slide 39）.
- The odds ratios calculated by birth year is not needed for age adjustment.
- Odds ratio among those born in 2000 (OR_{2000}) may be the least biased by the frailty exclusion bias, as the coverage is the least (15%).
- Then, odds ratios among other ages should be adjusted by the OR_{2000}.
- Note that odds ratio adjusted by OR_{2000} is still biased (see slides 35） and we should consider that the true odds ratio may be higher.
- Hence if odds ratio by these methods show statistical increase, we should at least consider that HPV vaccine increased symptoms in vaccinated women.

Necessary data for calculation of odd ratio by birth year

Example : 24. Weakness in extremities

birth year (age)	vaccinated					non-vaccinated				odds ratio (OR)			
	coverage (%)	responded	answered N2	number of positive symptom n	%	responded N1	answered N2	number of positive symptom n	%	OR	95% CI		P
											LL	UL	
2000 (15)	15.0	662	N2	n		3761	N2	n					
1999 (16)	51.0	2123	N2	n		2038	N2	n					
1998 (17)	71.5	3158	N2	n		1260	N2	n					
1997 (18)	85.0	3766	N2	n		663	N2	n					
1996 (19)	89.2	3725	N2	n		452	N2	n					
1995 (20)	89.8	3749	N2	n		428	N2	n					
1994 (21)	87.8	3565	N2	n		496	N2	n					
all ages	69.47		20818	357	1.7		9131	124	1.4				

1) Data in the above table for symptoms 1～25(26) are necessary.

2) Odds ratios for each birth year should be adjusted by OR_{2000} .

3) Odds ratio having at least one of the symptoms No8 or No17～No26 which are considered several typical symptoms after HPV vaccination should be calculated.

Conclusion

- It is highly suspected that the interim report of Nagoya City Survey indicates harmful effect of HPV vaccines.
- We recommend that Nagoya City withdraw the interim report and disclose raw data
- so that the third party could analyse the data.
- We also recommend that Nagoya City itself reanalyse the data by appropriate methods.

Observational studies comparing cohorts vaccinated with HPV vaccine and non-vaccinated (reprint)

Papers that claimed “no association”

1.Siegrist CA, Lewis EM, Eskola J, Evans SJ, Black SB. Human Papilloma Virus Immunization in Adolescent and Young Adults: A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions. *Pediatr Infect Dis J* 2007;26: 979-84

2.Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: Findings from the Vaccine Safety Datalink. *Vaccine* 2011:29: 8279-82.

3.Arnheim-Dahlström L, Pasternak B et al. Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. *BMJ.* 2013; 347: f5906.

4.Donegan K, Beau-Lejdstrom R, King B, Seabroke S et al. Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. *Vaccine* 2013; 31: 4961-7

5.Scheller NM, Arnheim-Dahlström L et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA.* 2015;313:54-61

Papers that reported association or with data suggesting association

3.Arnheim-Dahlström (having data suggesting association)

6. Geier DA, Geier MR. A case-control study of quadrivalent human papillomavirus vaccine-associated autoimmune adverse events. *Clin Rheumatol.* 2015;34:1225-31.

7. Baril L, Rosillon D, Willame C, Angelo MG, Zima J, van den Bosch JH et al Risk of spontaneous abortion and other pregnancy outcomes in 15-25 year old women exposed to human papillomavirus-16/18 AS04-adjuvanted vaccine in the United Kingdom.. *Vaccine.* 2015:33(48): 6884-91 [Epub 2015 Jul]

(explanation about the paper 1 and 4～7 will be on the slides38～41)

Papers claiming “no association” without taking “frailty exclusion bias” into account (2) Paper by Gee et al

- In the (2) Gee article, selection criteria for the control group are not clearly stated.
- This alone is enough to make the study unreliable.
- Additionally, it is likely that outpatients who consulted for any reasons other than vaccination were selected for the control group.
- This may mean that the control group included many patients with infections, increasing the incidence of autoimmune diseases at the start of follow-up.
- Therefore, they are unsuited as a control group of healthy vaccinated people.

Papers claiming “no association” without taking “frailty exclusion bias” into account
(3) Paper by Arnheim-Dahlström et al

- A cohort study following-up approximately 1.0 million girls aged 10-17 years old between 2006 and 2010, utilizing a database in Sweden and Denmark. Some 300,000 girls received at least one dose of Gardasil (average 2.35 doses), and were observed for 180 days after inoculation.
- After adjusting for their age, educational background of parents, and the year of inoculation, incidences of 53 neurological disorders, autoimmune diseases and venous thrombosis were analysed, and the risk ratio (RR) with the control was calculated.
- As a result, among 29 diseases analysed, 23 autoimmune diseases appeared in 5 or more vaccinees. Of these, there was no significant difference for 20 diseases.
- Even though a “frailty exclusion bias” was not taken into account, the incidence was significantly higher in the Gardasil group for 3 diseases, namely Behcet’s disease (RR=3.37), Raynaud's disease (RR=1.67), and type I diabetes mellitus (RR=1.29).

A paper confused prevalence with incidence (Siegrist et al)

- Siegrist et al used a prevalence as follows as the control of incidence after HPV vaccination.
- **Denominator:** the number of health insured females aged 9-18 and 19-30 years old
- **Numerator:** the number of persons who consulted a doctor (outpatient, emergency and hospitalization) at least once in 2005.

  "prevalence"= a proportion of persons having a disease among certain population at a certain point in time.
- **"incidence rate" =** newly occurred diseases among certain population within a certain period of time.
- Since autoimmune diseases do not easily remit, "prevalence" is about 10-30 times higher than "incidence rate" in general. For instance, the ratio of prevalence to incidence of MS is about twenty on average.
- Siegrist et al reported prevalence of MS = 5.1 per 100,000 →incidence = 0.25/100,000 person-years (py) →0.03 per 100,000 person-6 weeks.

  → 1/3,300,000 person-6 weeks. In Japan, incidence of MS is about 1/10 of that in the Western countries.
- In Japan, three cases with MS were already reported.
- The Japanese MHLW calculated that 30 cases are expected to occur in 3.3 million persons inoculated with HPV vaccine in Japan based on the prevalence reported by Siegrist

self-controlled case series (SCCS) is also problematic

- **4.Donegan et al**
- **5.Scheller et al**

both used the methods of self-controlled case series (SCCS)

・The self-controlled case series (SCCS) method was developed to investigate **associations between acute outcomes and transient exposures**, using only data on cases (individuals who have experienced the outcome of interest)

・Double peaked trends were suggested and incidence rates of chronic diseases including autoimmune diseases and mortality rates seem to increase after 3.5 years from the first inoculation.

●Donegan used the incidence 1year after inoculation as control and reported no association: incident rate ratio (IRR) 1.07 (95%CI: 0.57-2.00, p=0.84).

・However, sensitivity analysis by the prolonged time window (18 months) yielded IRR 1.47 (p=0.25). What might be the estimated risk ratio if the time window had been prolonged to 24 and/or 48 months in Donegan's study?

Papers that reported association or with data suggesting association: **6.** Geier et al and **7.** Baril et al both are free from frailty exclusion bias

6. Geier et al

・Using the vaccine adverse event reporting system (VAERS) database, Geier et al reported positive and significant associations between HPV vaccines use and serious autoimmune adverse events (SAAE):

・odds ratios (95%CI) were:

gastroenteritis: 4.6 (1.3-18.5), arthritis: 2.5 (1.4-4.3),

SLE: 5.3 (1.5-20.5), vasculitis: 4.0 (1.01-16.4),

alopecia: 8.3 (4.5-15.9) and CNS conditions: 1.8 (1.04-2.9).

・In addition, those who had positive rheumatoid factor, antinuclear antibody or **antiphospholipid antibodies** were significantly more likely to be exposed to HPV vaccine than the unexposed (OR:4.8, 95%CI=2.7-8.7, $p<0.0001$).

7. Baril et al denied association but data shows association

Purpose: To assesse the risk of spontaneous abortion after inadvertent exposure to HPV-16/18-vaccine during pregnancy

Participants：Pregnant women aged 15～25.

Exposed：women who had the first day of gestation between 30 days before and 45 days (90 days for the extended exposure period) after any HPV-16/18-vaccine dose.

Non-exposed: women who had the first day of gestation 4-18 months after the last dose

Results：the hazard ratio (HR) (95%CI) adjusted for age at first day of gestation was 1.30 (0.79-2.12) →No evidence of risk of abortion.

Problems：

1)Dose-response was observed: 1 dose → HR 1.11 (0.64-1.91)

2 dose → HR 2.55 (1.09-5.93, p=0.03)

2)The first day of gestation between **4 to 18 months** after the last dose of vaccine may **never be free from risk** of spontaneous abortion.

3)Considering the association with **anti-phospholipid antibodies**,

4)HR of **2.55** should be considered as **underestimation** for spontaneous abortion.

8. French National Agency for Medicines and Health Products Safety : A Cohort study on autoimmune conditions following HPV vaccination

http://ansm.sante.fr/content/download/80841/1023043/version/1/file/Ansm_Gardasil-Hpv2_Rapport_Septembre-2015.pdf

Participants and methods: A retrospective **c**ohort study utilizing database of national health system. 2.25 million girls aged 13 to 16 years between 2008 to 2012 were included : 0.84 million (37.3%) were exposed with HPV vaccine and 1.41 million were not exposed.

Inclusion criteria: At least one visit for medical care during 2 years prior to inclusion, no HPV vaccination nor history of autoimmune diseases before inclusion. Vaccine coverages were variable with the highest in 2008 (45%) and the lowest in 2012 (15%).

Available information：Reimbursement data for medical care (medication, other cares), hospitalisation (including purpose of hospitalisation), comorbidities, chronic illness etc.

Follow-up period:2008.1.1(or birthday of 13 year)～2013.12.31(or birthday of 17 year): Median duration of follow-up: vaccinated girls: 19.8m（1.4million person-years）, non-vaccinated girls: 25.3m (4.7million person-years).

Outcome events (14 autoimmune diseases: AD): 1) Central demyelinating diseases (multiple sclerosis etc), 2) Guillain-Barres syndrome, 3) SLE, 4) DLE, 5) vasculitis, 6) rheumatic arthritis, 7) Myositis/dermatomyositis, 8) Shogren Syndrome, 9) ITP, 10) Type 1 diabetes, 11) Thyroiditis, 12) Pancreatitis, 13) IBD, 14) Celiac disease

Analysis methods：Hazard ratios of any 14 AD or of individual AD were estimated by Cox regression analysis adjusting age, year of vaccination as time dependent variable. Geometric data, other diseases, level of care before inclusion, vaccination other than HPV vaccine were also adjusted**.** Subgroup analysis and sensitivity analysis were performed to make sure of the robustness of the results.

Table 3: Characteristics of cohort according to exposure of HPV vaccine

Inclusion year	total		vaccinated		non-vaccinated	
	N	%	N	%	N	%
2008	1,096,378	100	497,275	45.4	599,103	54.6
2009	290,252	100	125,671	43.3	164,581	56.7
2010	285,188	100	99,919	35.0	185,269	65.0
2011	289,457	100	75,192	26.0	214,265	74.0
2012	291,441	100	44,063	15.1	247,378	84.9
total	2,252,716	100	842,120	37.4	1,410,596	62.6

Outcome Events after inclusion	vaccinated		non-vaccinated		odds ratio (OR)			
	N	%	N	%	OR	95%CI		NNTH
						LL	UL	
N	842,120	100	1,410,596	100				
Consultation≧4/year	403,877	48.0	347,940	24.7	2.81	2.80	2.83	4
person-year	1,400,000	100	4,700,000	100				
Hospitalization *a	195,936	14.1	207,812	4.4	3.54	3.52	3.56	10

*a: odds of hospitalisation during two years prior to inclusion were slightly frequent in the HPV vaccinated group (OR=1.11 (1.10, 1.12). However after receiving HPV vaccine, hospitalization frequency increased greatly (OR= 3.5), and one among 10 girls/year vaccinated were necessary to hospitalise additionally compared to those without vaccine.

Main results and comparison of incidence (/10^5py) in non-vaccinated: Original data by French agency (FA) and re-analysis by Hama (RH)

Autoimmune diseases (AD)	Vaccinated		non- Vaccinated			Odds ratio (OR)		excess incidence	Hazard ratio (HR)			
									uni-variate		multi-variate	
	Events	/10^5 py	Events	/10^5 py								
				RH	FA	OR	p	/10^5 py	HR	p	HR	p
CNS demyelinating diseases	82	5.9	219	**4.7**	**5.8**	**1.26**	**0.07**	**1.2**	**0.98**	**0.89**	**1.05**	**0.72**
Guillain Barre Syndrome	19	1.4	21	0.4	0.4	3.05	<0.001	**1.0**	3.62	<0.001	4.00	<0.001
SLE or DLE	45	3.2	139	3.0	3.4	1.09	0.60		0.97	0.87	1.02	0.93
Systemic/local sclerosis	11	0.8	44	0.9	1.1	0.84	0.61		0.7	0.31	0.69	0.32
Vasculitis	69	5.0	220	4.7	4.8	1.06	0.68		1.07	0.64	1.05	0.75
Rheumatoid arthritis	99	7.1	308	6.6	6.7	1.09	0.48		1.07	0.58	0.98	0.86
Myositis/dermatomyositis	15	1.1	36	0.8	1.1	1.41	0.26		1.04	0.91	0.82	0.56
Sjögren syndrome	5	0.4	13	0.3	0.3	1.30	0.62		1.08	0.9	1.00	0.99
ITP	37	2.7	168	3.6	3.7	0.74	0.10		0.68	0.044	0.72	0.11
IBD	293	21.0	647	**13.8**	**16.9**	**1.53**	**<0.001**	**7.3**	**1.27**	**0.002**	**1.19**	**0.032**
Celiac disease	40	2.9	148	3.1	3.2	0.91	0.61		0.97	0.88	0.87	0.48
Type 1 diabetes	149	10.7	652	13.9	11.5	0.77	0.004		0.95	0.64	1.08	0.45
Thyroiditis	87	6.2	272	5.8	5.8	1.08	0.53		1.08	0.58	1.05	0.75
Pancreatitis	68	4.9	190	4.0	4.8	1.21	0.18		0.96	0.8	0.85	0.31
At least one AD	996	71.6	2,978	**63.4**	**66.8**	**1.13**	**<0.001**	**8.2**	**1.08**	**0.05**	**1.07**	**0.10**

Total person-years (py) of follow-up for vaccinated group was reported about 1.4 million. If more accurate estimate(1,392,030) were used, re-calculated incidence rates per 100,000 py are all the same as in the report by French agency. However, incidence rates in the non-vaccinated group are greatly different, especially CNS demyelinating diseases, inflammatory bowel diseases (IBD) and at least one autoimmune disease (AD). It is very difficult to understand the reasons why such large discrepancies occurred, but our calculation methods may be valid, because the incidence rates in vaccinated group are all the same as in the original report.

Reported results by French agency and opinion of WHO

Results reported by French Agency:

1. Any AD: Adjusted HR (HRa) =1.07 [95 %CI:0.99, 1.16] No difference. But,

2. IBD: HRa=1.19 [1.02, 1.39]: significantly higher in the vaccinated group until 3 months but decreased subsequently without significance.

3. GBS: HRa=4.00 [1.84, 8.69] significantly higher in the vaccinated group until 3 months and decreased subsequently but still significant.

Risk of GBS is robust by sensitivity analysis and subgroup analysis.

Incidence of GBS attributable to HPV vaccine is 1 to 2 per 100,000 person-years

4.This is the first study in which association between HPV vaccine and AD was observed.

WHO's Opinion on the results of French study

This risk (of GBS) in the first few months after vaccination was very small (~1 per 100,000 vaccinated children) and has not been seen in other smaller studies.

Strength and Limitations of the French study (1)

1. Vaccination coverage is the highest (45%) in 2008 and the lowest (15%) in 2012. HR was analysed by Cox regression analysis adjusting age and vaccinated year and health condition prior to inclusion. This means the "Frailty exclusion bias" was taken into account at least partially.

2. But it is unclear how it affected the results that girls with at least one visit for medical care prior to inclusion were included.

3. If more accurately estimated person-year (1,392,030) is used, re-calculated incidence rates per 100,000 py are all the same as in the table in the abstract reported by the French agency. Hence this estimate and calculation of incidence rate is correct.

4. However, incidence rates per 100,000 py in the non-vaccinated group are greatly different: especially CNS demyelinating diseases (4.7 vs 5.8), inflammatory bowel diseases (IBD) (13.8 vs 16.9) and at least one autoimmune disease (AD) (63.4 vs 66.8).

5. If our estimate of incidence rate in the non-vaccinated group is correct,

OR for CNS demyelinating diseases may be nearly significant (P=0.07),

OR for IBD may increase much more up to 1.53 (P<0.001) and

OR for having at least one autoimmune diseases= 1.13 (P<0.001).

6. Excess incidence rates (HPV vaccine attributable incidence rate/100,000py) are: CNS demyelinating diseases (1.2), GBS (1.0), IBD (7.3) and any AD 8,3).

Strength and Limitations of the French study (2)

5. These annual incidence rate may exceed the maximum benefit expected (but unproven) with HPV vaccine by preventing cervical cancer mortality.

6. Moreover, incidence rate per 100,000 py of CNS demyelinating diseases in the non-vaccinated group (4.7 or 5.8) is very high compared with that of multiple sclerosis including optic neuritis (1.0) in the general population of the same age group (women aged 15 to 24 years) in France [ref].

7. This suggest that non-vaccinated group had included frail girls at the time of inclusion. Therefore "Frailty exclusion bias" or "healthy vaccinee effect" may not be completely excluded in this French pharmacovigilance study. (Even if it is taken into account that included girls were those who visited medical facilities at least once , incidence rate of CNS demyelinating diseases in the non-vaccinated group may be too high).

8. However, Risks were significant for 2 autoimmune diseases (ADs).

9. Moreover, frequent consultation ($\geqq$4/year): Odds ratio (OR) = 2.81 (2.80,2.83) and at least one hospitalization: OR = 3.54 (3.52, 3.56) (based on person-year) should be taken into account. This is because high odds ratio for need of frequent medical care and/or hospitalisation may be related to some adverse outcome of HPV vaccination other than autoimmune diseases.

10. More comprehensive approach for analysis is necessary, because symptoms after HPV vaccination may be more complicated and difficult to be described by classical diagnosis.