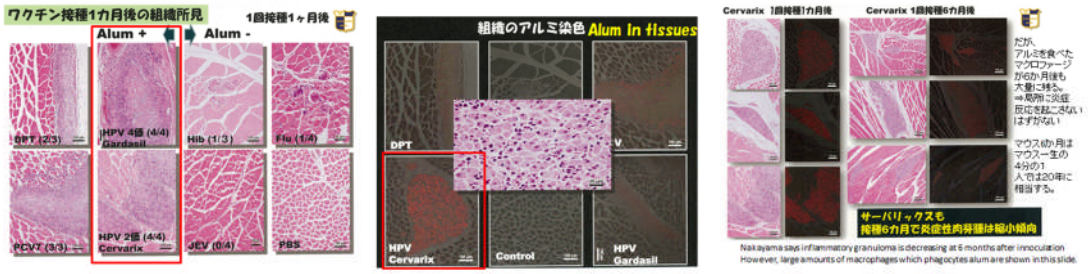
**Harm of HPV vaccine: Causal Inference, Underlying Mechanisms (2014.2.25 Abstract)**

Director NPO pharmacovigilance Center (Kusuri-no-Check) Rokuro Hama M.D. http://npojip.org

**Part 1: Toxicity testing: Clinical doses show long term toxicity**

MHLW says that long term safety is proved by Nakayama's mice experiments. I examined the relevance of this study and toxicity testing done by pharmaceutical companies.

Dr Nakayama used a single dose of intramuscular (im) 0.1mL/20g of HPV vaccine (5mL/kg) and other vaccines to mice and observed acute phase cytokines including IL-6, TNF-alpha. He examined histology of muscles on month 1, month 3 and month 6 after inoculation. 1/3 to 1/2 of this dose (according to his explanation confirmed by Mr Fukushima) induces acute reactions observed by clinical human dose of Cervarix or Gardasil (5mL). So this dose is about 2 to 3 times higher than the human clinical dose. He observed granuloma consisting mainly macrophages at M1, M3 and M6.




He says that inflammatory granuloma is decreasing at 6 months after inoculation. However, large amounts of macrophages phagocyting alum are shown in his slides even after 6 month which is quarter whole life span of mice (for human about 20 yeas).

Standard methods of a toxicity test usually consist of four dose groups: 1) high dose (definite toxic dose to know cause of death), 2) intermediate dose, 3) low dose (non-toxic dose to determine NOAEL: non-observable adverse effect level) and 4) control (Only vehicle or no treatment) (if additives has any toxicities, then non-treatment control should be used.

Adjuvants in HPV vaccine: DNA-alum and MPL-alum have extensive toxicities which are intentionally added to enhance immunity to achieve continuously high level of antibody. Hence in order to confirm safety of these products, it is essential to compare these final products, adjuvant and no-treatment control (or saline injection). Hence, totally 5 groups are needed.

Nakayama says no differences were observed in serum cytokine levels between Cervarix and other vaccines. However his logic is very poor. 1) this is only for acute phase. It is not known 6 months or more after inoculation. 2) Local increase of cytokines may induce various reactions. 3) DNA-alum or MPL-alum nano-particle could directly stimulate TLR-4 and other TLRs of various cells including various inflammatory cells and nodose ganglion (a major vagus ganglion at neck) may act like cytokines in local tissues. 4) It cannot deny that there may be girls who induce higher serum level of cytokines

His test consists of one dose level without control, without high, intermediate dose, without adjuvant only and "no-treatment" group. Moreover chronic inflammations (granuloma) with large amount of macrophage phagocyting alum-particles were observed even at 6 months after injection.

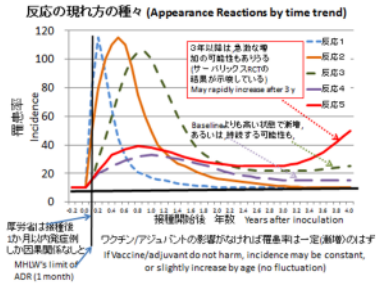
Toxicity tests for Gardasil consist of two groups: one dose for Gardasil and one dose for alum adjuvant. Toxicity tests for Cervarix consisted more (two dose groups for Gardasil, one AS04 adjuvant and saline). These were better than Nakayama's experiment but not adequate for determining safety. Moreover these show toxicity of HPV vaccine. PMDA's examination report shows that Gardasil final aqueous products contains pg/mL level of DNA and μg/mL level of RNA.

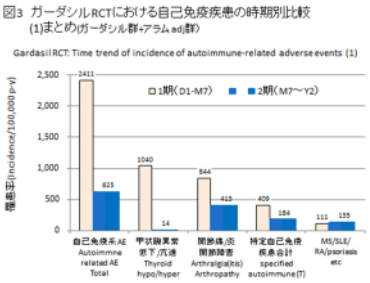
**Hence safety level (NOAEL) is not determined and possible toxicities were shown.**

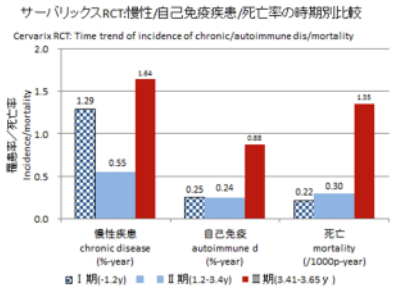
## Part 2　Epidemiological Association and underlying mechanisms: All show causality

MHLW's Denial of causality by between HPV vaccine and chronic pain and/or autoimmune, neurological events after HPV vaccine injection is based on the results from 1) RCT, systematic review of RCTs, 2) observational studies (mainly retrospective cohort studies) and 3) comparison with incidence of autoimmune general populations. Evidence of the claim is extremely poor, because

1) RCTs are all those with adjuvanted controls. Systematic review of RCTs reviewed only RCTs with adjuvanted controls. Adjuvants themselves have toxicities. Incidence trend after inoculation have been fluctuating as shown RCTs of Gardasil and Cervarix. (slides)



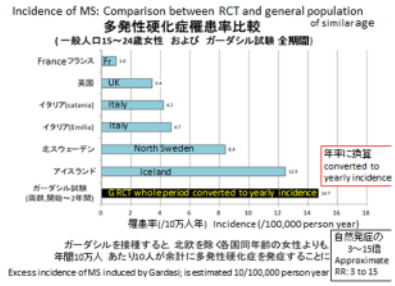



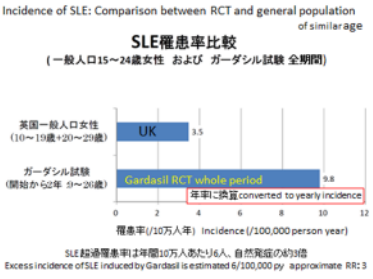



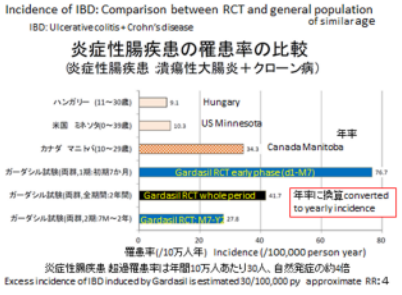

2) Observational studies are mainly retrospective cohort studies: These are all biased by "healthy vaccinee effects". Having these biases, one study reported increased risk of 3 autoimmune disease (Raynaud's D, Behcet syndrome and type 1 diabetes) .

3) "No difference to general population" claimed by MHLW is the comparison with prevalence. Adequate comparison revealed higher incidence(slides). Excess incidence of MS induced by Gardasi; is estimated 10/100,000 person year(py). Approximate RR: 3 to 15. Excess incidence of SLE induced by Gardasil is estimated 6/100,000 py. Approximate RR : 3. Excess incidence of IBD induced by Gardasil is estimated 30/100,000 py, approximate　RR : 4

**MS　(RR :3～15)　　SLE (RR: 3)　　IBD(UC+CD) (RR:4)**




### 2.　underlying mechanisms

1) Intoxication/poisoning (classification by cause) : Adjuvants are all toxic.
2) Immune/inflammation (classification by pathogenesis): persistence of granuloma of macrophages induce inflammation and immunological stimuli.
3) Nerve disorders (classification by organ): Inflammation/immune disease may cause thromboembolism, cause nerve diseases. Circulating DNA/MPL-Alum may be trapped by various parts of body which may cause local inflammation and may cause local pain as if moving without systemic reaction of inflammation.
4) Psychosomatic disease MHLW claims are somatization or conversion disorders which have been called "hysteria" for many years. These diagnoses are often used when physician cannot diagnose well by their own previous knowledge. Hence new and unknown disease may well be missed if these are the conclusion of the apparent unknown disorder. These diagnoses are used to conceal the real harm of new products.