Dying Cochrane: Could it be resuscitated?

Herpes zoster subunit vaccine Shingrix:

Baloxavir (Xofluza®) for Influenza: No Value

No difference from Tamiflu in efficacy, and suppresses immunity

Cochrane review on HPV vaccine should be revised:

Due to missing trials, adjuvant toxicity, mortality and healthy user bias

CONTENTS （December 2018, Vol. 4, No. 12）

Dying Cochrane: Could it be resuscitated?

Cochrane's systematic reviews are an important source of information while fake information on drugs and therapeutics is rampant. The recent incident of expulsion of Dr. Peter Gøtzsche, one of the cofounders of Cochrane is a critical issue that has shaken the credibility of the organization(see p41 and 50). It is an unprecedented event in the 25-year history of Cochrane Collaboration.

Initially, Cochrane used to be "Cochrane Collaboration", but recently "Collaboration" was removed, and it is now registered as a Charity, a Limited Liability Company whose headquarter is based in the UK. The organizational structure is complex. It includes a Central Executive Team which is headed by a CEO. Apart from them, Governing Board is responsible for overseeing the development and implementation of Cochrane's strategic direction. The board also has the right to decide on expulsion of its members. The board (trustees of the charity and directors of the company) is comprised of at least 13 members (but according to the Articles of Association, the number of the board members should not be less than three, and this is largely inconsistent), and decisions are made by majority vote. More than half of the board members are elected by Cochrane's members; with the rest appointed by the board.

Before this incident, the governing board consisted of eight elected members and five appointed members. Among the eight elected members, four remained in the board while three resigned in protest. The remaining one is Dr. Gøtzsche. Among the five appointed officers, two remained, and one resigned in protest followed by resignation of another officer who opposed the decision. The other one abstained from voting, but later resigned so that there would be less appointed members in the board. This means that six members were in favor of the expulsion while the other six, including Dr. Gøtzsche, were against it. By excluding Dr. Gøtzsche from the process, the board decided on the expulsion. Based on the minimum number stipulated by the Articles of Association, six board members are enough to run the board. However, if at least 13 members are needed as explained in Cochrane's website (now it has been changed), the current board is illegitimate. Moreover, the current governing board does not represent the opinions of the entire organization at first place. Therefore, it should be dissolved and totally reelected.

The direct reason why Dr. Gøtzsche had to be expelled was that he has been criticizing CEO's top-down approach and acceptance of distorted reviews by researchers with conflict of interest. However, there have been criticisms against CEO even before the incident. Nine of the 12 Cochrane centers have been raising concern over the management. The US Cochrane Center closed down, and a director of Cochrane France resigned in frustration over lack of transparency and poor leadership. German, Canadian and Austrian centers expressed their opposition by voting against the expulsion. In addition, all 31 Directors form the Iberoamerican Cochrane Network have expressed their support for Dr. Gøtzsche.

In 2016, ISDB (International Society of Drug Bulletins) adopted a policy that will be totally implemented in 2019, in which members are not allowed to have conflict of interest with the healthcare industry. Those who have not fulfilled the criteria will be removed from the full membership list. Med Check-TIP fulfills it.

Now it is clear that the information independent of pharmaceutical companies is reliable. What is important is not simply the transparency, but the fact that conflict of interest distorts scientific information. If conflict of interest is not eliminated, Cochrane will no longer be trusted by patients and medical professionals. We support the views of Dr. Gøtzsche and the ISDB Committee that the current board should be dissolved and reelected. In addition, we believe that the Articles of Association should be amended as well.

New Products

Herpes zoster subunit vaccine *Shingrix:*
Judgment Reserved
The effect is certain, but the evaluation of harm is flawed

MedCheck-TIP Editorial team

Summary

• Relative preventive efficacy of a herpes zoster subunit vaccine (brand name: Shingrix, approved in March 2018) is 97% in people aged 50 and over and 90% in people aged 70 and over. There was no hospitalization nor death due to herpes zoster, and the effect to prevent them was not proven. In order to prevent 1 postherpetic neuralgia, 1276 persons need to be vaccinated.

• When 1276 people are vaccinated, over 800 people would additionally experience local pain, and 171 people would suffer from serious adverse reactions which lead to hospitalization or limit activity of daily living. Although it was reported that there was no difference in serious adverse events, immunologic disorders and death between the two groups, the report is not reliable. This is because in a phase II study, mortality rate increased by about six-fold in the second year after the vaccination as compared with that in other years. However, in subsequent pivotal clinical trials, most serious adverse reactions were not followed after the first year. Moreover, since toxicity studies are incomplete, safety is not guaranteed.

• Herpes zoster is a benign disease. If it is detected early, it can be cured by treatment with antivirals. Until harm is appropriately assessed, the judgement of Shingrix for preventing herpes zoster and postherpetic neuralgia in the elderly is reserved.

Conclusion: Judgment Reserved

Keywords:

herpes zoster subunit vaccine, Shingrix, HZ/su vaccine, relative prevention rate, local adverse reaction, systemic adverse reaction, muscle pain, fatigue, fluctuation of mortality, adjuvant, AS01B

Introduction

An attenuated varicella vaccine, for which prevention of herpes zoster was approved as an additional indication in 2016, almost halves the incidence of herpes zoster in people aged 50 and over. However, the effect is reduced in people aged 70 and over. Moreover, the preventive effect diminishes 5 years after the inoculation, and the booster is ineffective. These facts raise concern over the effectiveness in the elderly, the population which has high need for the vaccination (MedCheck-TIP No.71).

Meanwhile, a new herpes zoster subunit vaccine (HZ/su vaccine) was approved on March 23, 2018 for the prevention of herpes zoster (recombinant zoster vaccine: Shingrix® for intramuscular injection, Japan Vaccine Co.,Ltd.) This article summarizes its efficacy and harm.

A novel adjuvant in this vaccine is called AS01B and contains the main ingredient of the adjuvant in HPV vaccine. The toxicity studies for the adjuvant were incomplete (see the boxed column).

Results of international joint clinical trials of Shingrix

Table 1 shows the results of randomized controlled clinical trials that examined the preventive efficacy of Shingrix on herpes zoster.

The report no. 1 [1] is a summary of an international joint phase III trial conducted by 18 countries, including

Table 1: Summary of preventive efficacy on herpes zoster [1, 2]

Reference	Group	HZ patients /Participants	Incidence rate (/1000 pys)	RPR %[95%CI]	NNTB (/year)
1	Vaccine	6/7344	0.3	97.2 [94, 99]	114
	Control	210/7415	9.1	ARR:0.88%/year	
2	Vaccine	23/6541	0.9	89.8 [84, 94]	120
	Control	223/6622	9.2	ARR:0.83%/year	

* a: incidence rate (/1000 person-years)

NNTB: number needed to treat to benefit   ARR: absolute risk reduction

Japan, involving adults aged 50 years and older. The participants were randomly allocated and received 0.5 mL of test vaccine or saline (control) intramuscularly twice in total; at the beginning and the second month. Since both preparations were distinguishable by appearance, investigators other than those who had administered the substances were assigned for assessment in order to ensure the blindness (so-called PROBE method).

Total 7698 participants received at least one dose in the vaccine group and 7713 in the control group. The following participants were excluded from the analysis; those who received only one dose, those who deviated from the vaccination schedule and those who developed herpes zoster within 30 days after vaccination. After the exclusion, 7344 participants in the vaccine group and 7415 in the control group were subjected to the analysis of the efficacy. The median follow-up was 3.1 years.

The report no. 2 is the result of an international joint phase III clinical trial conducted by 18 countries including Japan, for adults aged 70 years old and over [2]. Total 6950 participants in the vaccine group and 6950 in the control group were analyzed. This study followed the same exclusion criteria as that of the report no. 1, and 6541 participants in the vaccine group and 6622 participants in the control group remained. The median follow-up was 3.7 years. In the report no. 1 [1], relative preventive effect was 97.2% (p <0.001), and the number needed to treat to benefit (NNTB) was 114. In the report no. 2, the relative preventive effect was 89.8% (p <0.001), and NNTB was 120 [2].

In 16,596 participants aged 50 years old in the reports no. 1 and 2 combined, the relative preventive effect was 91.3% (p <0.001) [2]. In the both reports, the preventive effect in each age group was almost the same. In addition, the result of subgroup analysis of Japanese who were included in these clinical trials [3, 4] was similar to the result of the whole study.

Table 2 summarizes the preventive effect on postherpetic neuralgia (sustained for 90 days or more) [2]. The median follow-up was 3.8 years, and the relative preventive effect on neuralgia was 91.2% (p <0.001) in all age groups. Postherpetic neuralgia did not occur in the vaccinated participants aged 70 years old and below. Relative preventive effect of postherpetic neuralgia was 88.8% (95% CI: 68.7-97.1; p <0.001) when the analysis was restricted to those aged 70 years old and over. However, in those who had already developed herpes zoster, there was no difference in the incidence

Table 2: Preventive efficacy on postherpetic neuralgia (PHN) [2, 3]

Group	HZ patients /Participants	Patients with PHN		RPR % [95%CI]	NNTB (/year)
		Number	rate (/1000 pys)		
Vaccine	32/13881	4	0.1	91.2 [76, 98]	1276
Control	477/14035	46	0.9	ARR:0.08 %/year	

* a: incidence, NNTB, ARR: see the footnote for Table 1

PHN: postherpetic neuralgia was defined as a worst pain score of 3 or higher for pain (on a scale of 0 to 10, with higher numbers indicating worse pain) that persisted or developed more than 90 days after the onset of herpes zoster rash.

Person-years of observation: vaccine group: 53171.5 person-years, control group: 53545.0 person-years

of neuralgia between the two groups (12.5% in the vaccine group and 9.6% in the control group, p = 0.54).

The absolute preventive effect was 0.08% annually. This means that the vaccine can prevent one postherpetic neuralgia by inoculating 1276 people.

The rise of antibody titer persisted at 3.8-fold to 7-fold 6 years after inoculation as compared to the baseline [4].

Because there was no hospitalization nor death due to herpes zoster, reduction in such cases was not proven [4].However, reportedly, it was possible to use Shingrix for recipients of autologous peripheral blood stem cell transplant and patients with HIV [5,6].
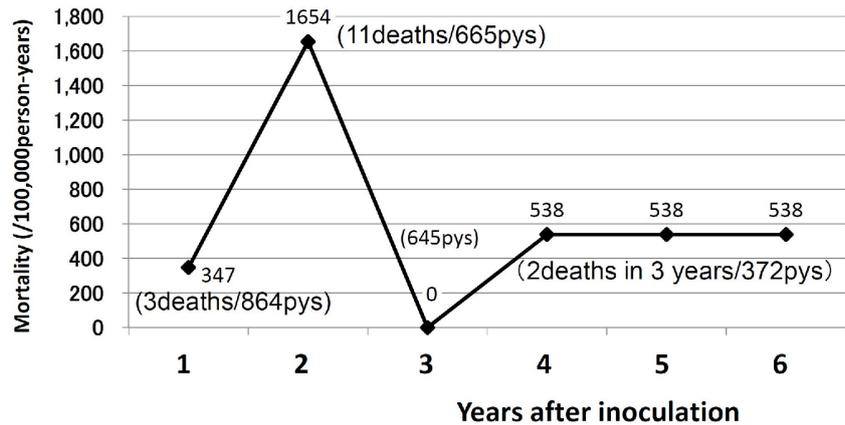
In phase II trials, mortality peaked in the second year (Figure 1)

Two phase II trials for dose finding were carried out before the pivotal phase III trials [1, 2]. They were namely trial no. 003 for finding the dose of vaccine antigenic component (follow-up for 6 years) and trial no. 010 for finding the dose of adjuvant [4].

In trial no. 003, the antigenic component was used in all 5 groups; 4 groups were treated with antigen + adjuvant twice (3 groups) or once (1 group), and the other group received antigen + saline twice. In a long-term follow-up, all serious adverse events (serious AE) and deaths were followed until the third year, after which the vaccine adopted as a commercial product was followed until the sixth year.

There is no report on the number of nonfatal severe AEs (238 persons, 328 events) and death (1st year: 1 case, 2nd year: 11 cases, 3rd year: 0) per each group after 3 months from the first inoculation, but only on the number for all groups combined. The number of deaths was reported by year. Based on this, the annual mortality rate was calculated for each year after inoculation. As a result, the mortality peaked in the second year (after 1 year until the end of second year), and it was about 6 times higher than all other time periods

Figure 1: Annual variation of mortality in Phase II study (trial no.003)

(odds ratio 6.3, p = 0.0001: **Figure 1**).

If the vaccine is harmless and does not affect death, the mortality rate should remain constant from beginning to the end. Therefore, the marked peak of the mortality rate in the second year strongly suggests the harmful effect of the vaccine. On the contrary, in the third year, the number of death was 0 (mortality rate 0), and after that it stayed at the relatively low level. Incidentally, the mortality rate in the second year, approximately 1700/100,000 person years, is at the same level as the mortality rate of the general population which includes people with sickness. (Japan's mortality rate among people aged 60 to 84 years old in 2008 was 1846/100,000 people). Considering that the trial no. 003 was a clinical trial for healthy people, it can be said that the mortality rate in the second year is remarkably high.

Fatal flaw in reporting serious AEs after 14 months (Figure 2)

In phase III trials [1, 2], serious AEs were collected up to 1 year and 2 months after the inoculation, and after that, only serious AEs that were considered to be related to study agents were collected. Moreover, in the phase II trials, all serious AEs were considered "not related". Even in the phase III trials, most serious AEs were considered "not related". Therefore, it is highly likely that serious AEs in the second year, when the incidence is highest, were not collected. It is also unknown how death was processed.

Strong tissue toxicity is suggested in humans (Figure 3)

In phase III trials, local reaction and systemic reactions up to 7 days after the inoculation of Shingrix occurred more frequently in vaccine groups than in control groups [1-4] (Figure 3).

AEs that led to hospitalization or limited self care

Shingrix is not safe: Evidence from nonclinical studies

1. Components of Shingrix

Shingrix (HZ/su vaccine) is a subunit vaccine in which glycoprotein component (gE) of varicella-zoster virus (HZV) is used as an antigen and a novel adjuvant is added. Therefore, the advantage is claimed that it can be used for people with lowered immunity who cannot use attenuated live varicella vaccines.

The novel adjuvant is called AS01B. It is a substance in which MPL (MonoPhosphoryl-Lipid A), a derivative of the lipid A, which is the main component of endotoxin (or lipopolysaccharide), and a surfactant called purified Quillaja saponin (QS-21) are bound to liposome. Both MPL and QS-21 have cytotoxicity and stimulate/enhance natural immunity, which is essential for induction of acquired immunity. MPL is also the main component of adjuvant AS04 in bivalent HPV vaccine Cervarix.

2. The purpose and method of general toxicity test

In order to predict possible toxicity in humans, using a small number of animals, toxicity studies for medicines use markedly higher doses over a prolonged period. More specifically, the studies are conducted with at least four dose groups: 1) High-dose group to find out organs and lesions that may cause death, 2) the intermediate-dose group, 3) Low-dose group to find out NOAEL (No Observed Adverse Effect Level) and 4) One control group. Animals in the control group are usually treated with vehicle (solvent) alone. However, if the additive(s) such as adjuvants are toxic, the studies should also have two control groups; one with saline and the other with the additive(s). Such studies should be conducted with 2 or more different animal species. Adjuvants are toxic to tissues. Therefore, intrinsically, novel adjuvants and vaccines should be tested as new substances, and the procedures for general toxicity studies should be followed.

3. Toxicity studies of Shingrix

However, the EMEA's guidance and Good Laboratory Practice (GLP) for vaccines and adjuvants do not follow the standard methods of toxicity studies for new products. EMEA's guidance and GLP only require one dose level in one animal species even for new adjuvants and new vaccines containing new adjuvants.

In accordance with GLP, only one dose level was investigated in the toxicity studies for Shingrix. The doses tested were 0.1 mL in rat (400 g) and 0.5 mL in rabbit (about 4 kg); Human equivalent dose (HED) on the basis of body surface area was only 4 times higher than human dose.

• **In a single-dose toxicity study**, extensive inflammation was observed: With saline control, inflammatory cell infiltrations were observed locally in some rabbits, but inflammatory cell infiltrations occurred extensively with AS01B (up to moderate) and Shingrix (up to serious), respectively. Therefore, the tissue toxicity in order of severity is as follows; Shingrix > AS01B >> saline.
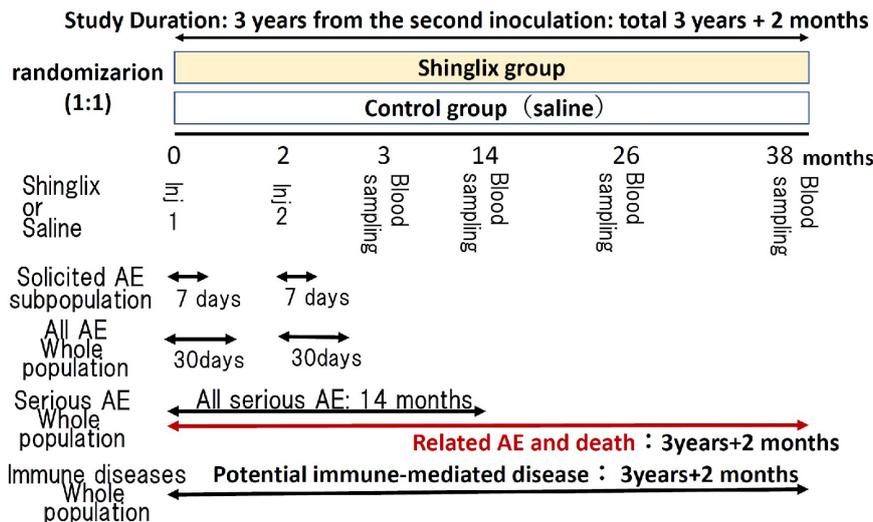
• **In repeated-dose AS01B toxicity studies with rats**, inflammation occurred in most animals: AS01B at the dose 4-time higher than the human dose was intramuscularly administered to rats on the peroneal muscle for 7 times, once every 2 week. No abnormal finding was observed with saline control. With AS01B, swelling of the peroneal muscle and up to "marked" inflammatory reactions occurred extensively in most of the 10 animals.

• **Extensive inflammation with vaccine/adjuvant:** Shingrix was administered subcutaneously and intramuscularly to rabbits for 4 times, once every 2 weeks. Three days after the last dose, mild inflammatory reactions occurred extensively in all cases with Shingrix, and moderate inflammatory reactions and extensive or multiple inflammatory reactions were observed in some animals treated with AS01B. At days 28/29 after the final administration, there was no histological changes caused by Shingrix nor AS01B. However, it is not mentioned that all the findings resolved.

4. Summary of nonclinical findings

Since vaccines are basically administered to healthy people, higher safety is required for inoculation. However, the standard imposed on toxicity study of vaccines and adjuvants is absolutely incomplete, compared to that for medicines in general. Even in such an incomplete toxicity study, Shingrix and the new adjuvant AS01B showed strong tissue toxicity. Therefore, it can be concluded that use of Shingrix is not clinically safe.

Figure 2: Schedule for evaluation of harm: Phase III pivotal trials [1, 2]

Study Duration: 3 years from the second inoculation: total 3 years + 2 months

randomizarion (1:1)
- Shinglix group
- Control group (saline)

| 0 | 2 | 3 | 14 | 26 | 38 months |

Shinglix or Saline: Inj. 1 — Inj. 2 — Blood sampling — Blood sampling — Blood sampling — Blood sampling

Solicited AE subpopulation: 7 days — 7 days

All AE Whole population: 30days — 30days

Serious AE Whole population: All serious AE: 14 months

Related AE and death：3years+2 months

Immune diseases Whole population: Potential immune-mediated disease：3years+2 months

Solicited report of injection-site AE within 7 days: based on the daily record (pain, redness, swelling) and solicited report of systemic reactions within 7 days (fatigue, fever, gastrointestinal symptoms, headache, myalgia, shivering) were collected.
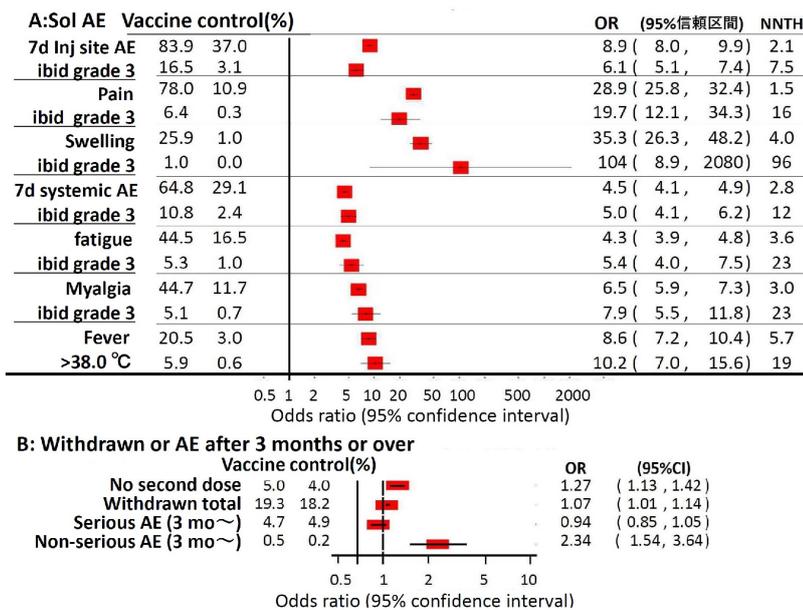
All AE: all AEs observed for 30 days: no specification, but all AEs were collected for 30 days.

activity of daily living (grade 3 and above) occurred in 16.5% of the participants in the vaccine group and 3.1% in the control group within 7 days after the inoculation. This means that the vaccine may cause harm in 1 in 7.5 people.

The incidence of pain at injection site which occurred within 7 days after receiving 2 doses was 11% in the

Figure 3: Summary of vaccination and AEs [1-4]

A:Sol AE

	Vaccine	control(%)	OR	(95%信頼区間)		NNTH
7d Inj site AE	83.9	37.0	8.1 (8.0,	9.9)		2.1
ibid grade 3	16.5	3.1	6.1 (5.1,	7.4)		7.5
Pain	78.0	10.9	28.9 (25.8,	32.4)		1.5
ibid grade 3	6.4	0.3	19.7 (12.1,	34.3)		16
Swelling	25.9	1.0	35.3 (26.3,	48.2)		4.0
ibid grade 3	1.0	0.0	104 (8.9,	2080)		96
7d systemic AE	64.8	29.1	4.5 (4.1,	4.9)		2.8
ibid grade 3	10.8	2.4	5.0 (4.1,	6.2)		12
fatigue	44.5	16.5	4.3 (3.9,	4.8)		3.6
ibid grade 3	5.3	1.0	5.4 (4.0,	7.5)		23
Myalgia	44.7	11.7	6.5 (5.9,	7.3)		3.0
ibid grade 3	5.1	0.7	7.9 (5.5,	11.8)		23
Fever	20.5	3.0	8.6 (7.2,	10.4)		5.7
>38.0 ℃	5.9	0.6	10.2 (7.0,	15.6)		19

0.5 1 2 5 10 50 100 500 2000
Odds ratio (95% confidence interval)

B: Withdrawn or AE after 3 months or over

	Vaccine	control(%)	OR	(95%CI)
No second dose	5.0	4.0	1.27	(1.13 , 1.42)
Withdrawn total	19.3	18.2	1.07	(1.01 , 1.14)
Serious AE (3 mo〜)	4.7	4.9	0.94	(0.85 , 1.05)
Non-serious AE (3 mo〜)	0.5	0.2	2.34	(1.54, 3.64)

0.5 1 2 5 10
Odds ratio (95% confidence interval)

Solicited AE: see the footnote for Figure 2   AE: Adverse event

NNTH: Number needed to treat to harm

Grade 3 or more AE: hospitalization is required, daily living is disrupted or more serious cases (almost equivalent to serious AE)

control group while it was 78% in the vaccine group; total 2 in 3 people additionally suffered from local pain. The incidences of redness and swelling were very high in the vaccine group, as well. Systemic symptoms within 30 days after the inoculation included fatigue, muscle pain and fever, as shown in **Figure 3**. In addition, headache, chills, and gastrointestinal disorders also occurred frequently.

It was reported that there was no difference between the two groups in the incidences of serious AEs and immune-related disorders and the number of deaths. However, it is highly likely that most of serious AEs in the second year, when marked difference is expected, are not reported, and thus the report cannot be trusted. Furthermore, it is extremely unnatural that while non-serious AEs were reported 2.3 time more frequently in the vaccine group, no difference was found in serious AEs (**Figure 3, B**).

The incidence of AEs showed almost similar trend in the study for Japanese with that in the whole study.

Balance between harm/benefit and cost

In order to prevent postherpetic neuralgia in 1 person, 1276 persons had to be treated. Moreover, preventive effect for hospitalization and death due to herpes zoster was not proven.

On the other hand, as far as we know, additional 2 in 3 persons developed local pain and 1 in 7.5 people experienced local reactions that required hospitalization or disturbed their activities of daily living as compared with the control group. In other words, in order to prevent postherpetic neuralgia in 1 person, 833 people would

experience local pain, and 171 people would suffer from various harms, such hospitalization or local reactions that disrupt activity of daily living.

Furthermore, in the phase II trials, death after vaccination clearly increased in the second year, but in the phase III trials, even if any serious AEs occurred after the second year, most of them might not have been included because they might have been considered "not related". , Therefore, their conclusion that there was no difference in serious AEs and death is not reliable.

QALYs (quality-adjusted life-year: 1 QALY corresponds to 1 year in perfect health) is adopted as an indicator to measure cost-effectiveness. The cost-effectiveness of Shingrix was calculated as 50,000 USD (about 5.6 million yen)/1QALY, and it was considered high [7]. However, the computation is based on the assumption that there is no difference in adverse reactions between treatment and control groups.

If the agent is marketed in Japan at the same price as that in the U.S., 280 USD (about 31,500 yen) for 2 doses, about 40 million yen would be required for the pharmaceutical cost alone in order to prevent postherptic neuralgia in one person. If the cost for inoculation is included, about 50 million yen would be needed. Adjuvant is indispensable because the immunogenicity of Shingrix is significantly lowered without it [4]. The whole picture should be clarified whether the adjuvant, which itself is toxic, causes harm after the second year or not.

Herpes zoster is a benign disease that can be cured without feeling much pain by early detection and swift antiviral treatment. This also undermines the need for developing new vaccines.

Conclusion

The relative preventive effect for postherpetic neuralgia of two doses of Shingrix is 97% in people aged 50 years old and older and 90% in people aged 70 years and older. However, over 1200 persons must be vaccinated in order to prevent potsherpetic neuralgia in one person. At the same time, additional 800 persons would develop local pain, and 171 persons would experience hospitalization or harm that disrupts their activity of daily living. In the second year, mortality is suspected to increase, and safety studies, including animal studies, are extremely insufficient. Herpes zoster is a benign disease that can be cured by early detection and swift antiviral treatment. Unless harm is assessed more appropriately, the judgement on Shingrix should be reserved.

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Baloxavir (Xofluza®) for Influenza: No Value
No difference from Tamiflu in efficacy, and suppresses immunity

Introduction

Baloxavir marboxil ("baloxavir" in short; brand name: Xofluza®) is priced high as patients need to take the drug only once, and viral shedding stops almost on the following day. The cost for one course of baloxavir treatment is about 4800 yen (approximately 42 USD) in adults (body weight 40 kg-79 kg) while that for oseltamivir (Tamiflu®), laninamivir (Inavir®) and zanamivir (Relenza®) is 2720 yen (24 USD), 4280 yen (38 USD) and 2942 (26 USD), respectively. During the influenza season of 2019, the drug is expected to be prescribed for 3.3 million patients with influenza and the estimated sales is 14.1 billion yen (124 million USD) in Japan[1]. Is baloxavir really worth it?

Viral growth is suppressed

Baloxavir inhibits an enzyme called cap dependent endonuclease (CEN) [2-5]. It is reported that CEN is an enzyme unique to influenza virus and synthesizes mRNA (messenger RNA), which is like a design drawing of each part of the virus. Because of this characteristic, when this enzyme is inhibited, synthesis of mRNA is disrupted, and growth of influenza virus is suppressed. However, it does not kill the influenza virus.

Oseltamivir (Tamiflu) and other neuraminidase inhibitors do not inhibit viral growth, but simply prevent the virus from leaving the surface of the epithelial cells of the respiratory mucosa. Viral load is reduced in nasal discharge, but not in the lung [6].

However, baloxavir seems to suppress viral growth even in the lung of animals as well [2, 3]. Furthermore, in humans, no influenza virus was detected in the nasal mucosa on the following day after taking baloxavir. After taking placebo or oseltamivir, it took 4-5 days or 3 days, respectively for influenza virus to disappear. Therefore, viral load was reduced much faster with baloxavir.

No difference in time to symptomatic improvement between oseltamivir and baloxavir
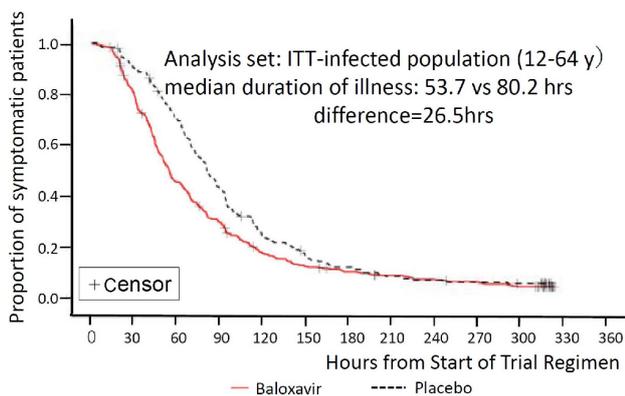
However, time to flu-symptom disappearance was only one day earlier with baloxavir than with placebo. The median time was 53.7 hours with baloxavir and 80.2 hours with placebo; there was only 26.5 hours difference (**Figure-a**) [2,3,7]. Baloxavir and oseltamivir (Tamiflu) were also compared (**Figure-b**). In the comparison between subgroups aged 20 years old or over with baloxavir or oseltamivir, no difference was observed. The median time to symptomatic disappearance was 53.5 hours with baloxavir and 53.8 hours with oseltamivir; difference is only 0.3 hours (**Figure-b**) [2, 3]. Although the difference was not significant, there were more patients whose symptoms continued for 4 days or longer in baloxavir group than in Tamiflu group. There was no difference in the proportion of patients who required hospitalization or antibiotics [7].

As we repeatedly mentioned in previous articles, apparent symptomatic improvement by oseltamivir and other neuraminidase inhibitors is not due to reduction of the virus, but because the agents simply let patients abstain from fighting against the virus. Therefore, it does not really improve symptoms [6].
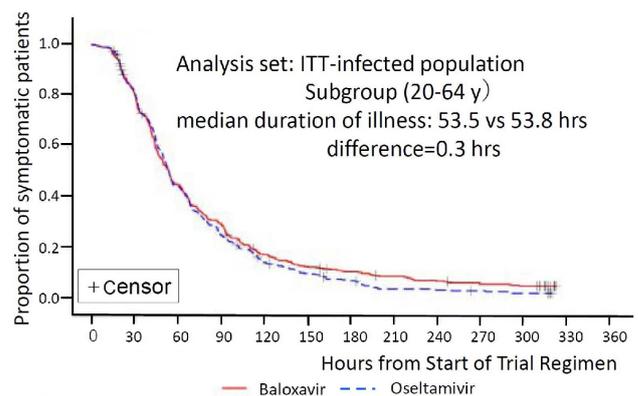
Although baloxavir has a mechanism of action different from that of oseltamivir and other neuraminidase inhibitors and strongly inhibits viral growth, the outcome is substantially the same with that of oseltamivir and other neuraminidase inhibitors.

Figure: Summary of Results: Phase III Trial of baloxavir

a) baloxavir versus placebo

Analysis set: ITT-infected population (12-64 y)
median duration of illness: 53.7 vs 80.2 hrs
difference=26.5hrs

b) baloxavir versus oseltamivir

Analysis set: ITT-infected population
Subgroup (20-64 y)
median duration of illness: 53.5 vs 53.8 hrs
difference=0.3 hrs

Unknown effect on patients with severe influenza or high-risk factors

In non-clinical studies, animals were infected with lethal dose of influenza virus, and mortality was lower in baloxavir group than in controlled group or oseltamivir group. However, the effect of the agent in people with severe influenza, diabetes or impaired immunity is unknown, as no study has been conducted to investigate it [2]. This is similar to the case of oseltamivir and other neuraminidase inhibitors [6].

Antibody production is reduced by 30%

The problem is that antibody production might be insufficient, since the virus disappears quickly. No animal study has confirmed that the agent does not interfere with antibody production [2,3]. In clinical trials, the effect on serum antibody level was investigated, but it is not mentioned in the documents for approval [2,3]. The recently published study [7] is the only literature that reported the results of the serum antibody production. The main text of the study reported that there was no difference on antibody production compared with placebo. However, detailed analysis (meta-analysis) of the appendix of the study revealed that odds of patients with a four-fold or more rise in serum antibody titre decreased by 28% in baloxavir group compared to in placebo group (odds ratio 0.72, p=0.014).

Meta-analysis results on treatment trials of oseltamivir showed that odds of those with a 4-fold or more rise in serum antibody decreased by 18% compared to placebo (odds ratio 0.82, p=0.004). Hence attenuation in serum antibody production by baloxavir is rather greater than that by oseltamivir.

Attenuation of secretory IgA (sIgA) by neuraminidase inhibitors is more marked [6] Sawabuchi et al [8] reported that lower induction of sIgA against the influenza A virus was observed in children treated with oseltamivir in comparison with children treated without oseltamivir. The odds of a child's sIgA level increasing more than 10-fold were non-significantly lower in children treated with oseltamivir (2/12) than in children without oseltamivir (3/3): odds ratio is 0.17 (95%CI: 0.01, 2.39, p=0.13) (calculated from the data shown in the **Figure 1** of Ref [8])[6].

These findings are consistent with evidence from animal tests using subclinical dose of oseltamivir in influenza infected mice in which sIgA antibody decreased by 80 % (1/5 of control) [6,9]. Indeed, re-infection is remarkable in the patients who were treated with neuraminidase inhibitors including oseltamivir [6,8,10].

It is totally unknown about baloxavir whether the secretory IgA in respiratory mucosa is affected or not and the risk of reinfection by baloxavir is greatly concerned. If secretory IgA antibody production is insufficient, patients might be easily re-infected in the same season or following years [6,8-10].

Even if the virus disappears quickly, 10%-20% of the virus remains as resistant (mutated) virus. In this case, the virus regrows on around day 6, delaying overall recovery [2,3]. The median time to recovery was 43 hours without resistant virus and 80 hours with resistant virus (phase II study).

Further concern

① Effect on human enzymes and their receptors

CEN is believed to be a virus-specific enzyme. As far as we have researched, it is unknown whether humans have a similar enzyme. However, in toxicity studies, the liver and the coagulation system (PT and APTT) were affected. The possibility that coagulopathy was caused by liver injury cannot be ruled out. In addition, "no observed adverse effect level" (NOAEL) is only 2 to 3 times higher than the human dose.

② Large individual difference in metabolism by CYP3A

Baloxavir is metabolized by a drug-metabolizing enzyme CYP3A, which has a large individual difference. If the drug is used by many patients, intense toxicity may be experienced by those with slow metabolism. Moreover, it interacts with many substances. When a serious adverse reaction occurs, harm is unavoidable as the blood concentration remains high for a long time after taking just one dose.

In practice (conclusion)

Baloxavir (Xofluza) demonstrated no difference in symptomatic improvement as compared with oseltamivir, and shortened the time to symptom disappearance by only one day as compared with placebo. Because influenza is a self-limiting infection or an infectious disease that can be cured naturally, no medication is needed. Furthermore, much is still unknown with baloxavir. If a serious harm occurs, even if it is rare, it may be very difficult to save. The drug is not worth its high price, and various concerns remain. Baloxavir (Xofluza) should not be used.

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Adverse Reactions

New evidence of severe abnormal behaviors/ psychiatric reactions to oseltamivir(Tamiflu)

MedCheck-TIP Editorial team

Serious abnormal behaviors occurred 29 times more frequently

From a prospective cohort study by Fujita et al. [1], Fukushima et al. (Hirota team) [2] extracted "abnormal behavior A", serious cases that could lead to accidents (24 persons in Tamiflu group and 4 persons in non-Tamiflu group) to examine the risk of Tamiflu use by self-controlled case series method.

The risk ratios for Tamiflu use compared to non-use were determined by adjusting various factors. They were between 1.9-fold and 29-fold (95%CI: 4.21-201) depending on the duration of Tamiflu use and non-use that was utilized in their analysis. The greatest risk ratio was yielded when the duration of about six hours after taking Tamiflu was utilized in the analysis. Fukushima et al. concluded that they could not deny the possibility that abnormal behavior was induced by influenza itself, since the duration overlapped with the early period of influenza where high fever was observed.

On the contrary, according to the data by Fujita et al. [1], the incidence rate of delirium per 1000 person-days during high fever phase (until about 24 hours after start of fever) was about 5 persons before Tamiflu use while exceeding 30 persons at most after Tamiflu use. Therefore, it should be considered that Tamiflu causes "abnormal behavior A".

References

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https://www.jstage.jst.go.jp/article/jjpe/15/2/15_2_73/_pdf/-char/ja
2) Fukushima W et al. Oseltamivir use and severe abnormal behavior in Japanese children and adolescents with infuenza: Is a self-controlled case series study applicable? Vaccine 2017: 35: 4817-24

Severe psychiatric reactions occurred 35 times more frequently

In Cochrane's systematic review [1], the risk of psychiatric symptoms increased dose-dependently in treatment trials of oseltamivir (Tamiflu), and in the prophylaxis trials it was significantly higher in the Tamiflu group than in the placebo group. The review reported that psychiatric symptoms were induced in about 1 person per 100 persons. However, the risk ratio was 1.8 and not so high.

Jones et al. used logistic regression method and analyzed psychiatric symptoms taking duration and intensity of symptoms into account. The odds ratio was 3.46 (95% CI: 1.28 - 9.32) for overall intensities. Analysing the intensity of the symptoms showed little difference between groups for mild ones (OR 1.23, 95% CI: 0.30 - 5.04), but a statistically nonsignificant increase for moderate symptoms (OR 4.34, 95% CI: 0.79 - 24.0), and a large, significant increase for severe psychiatric events (OR 34.5, 95% CI: 3.66 - 325).

Based on these results, Jones et al. stated that their analysis shows evidence of a causal effect of oseltamivir on psychiatric symptoms.

There was little difference between both groups for mild cases, even when symptom duration was taken into account. However, Tamiflu induced moderate and severe psychiatric symptoms 1 per 210 persons and 1 per 230 persons, respectively which show that Tamiflu induces moderate or severe psychiatric symptoms rather frequently.

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https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD008965.pub4/full?highlightAbstract=oseltamivir
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Cochrane review on HPV vaccine should be revised :

Due to missing trials, adjuvant toxicity, mortality and healthy user bias in observational studies

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Summary

Tovey's comments on a paper by Jøorgensen et al. published in BMJ Evidence-Based Medicine related to the recently published Cochrane Review on HPV vaccines has many flows. The Cochrane review should be revised by including all identified clinical trial data, considering adjuvant toxicity, significantly high mortality in mid-adult women and confounding bias with "healthy vaccinee effect" in observational studies. Before the revision is completed, I strongly recommend the Cochrane review should be suspended.

This is a revised article based on a letter as a rapid response **[a]** to Dr. David Tovey on a paper by Jørgensen et al **[b]**

a) Hama R. https://ebm.bmj.com/content/23/5/165.responses#cochrane-review-should-be-revised-due-to-overlooked-trials-toxicity-of-adjuvant-mortality-in-mid-adult-women-and-lack-of-discussion-on-observational-studies-with-serious-healthy-vaccinee-effect

b) Jørgensen L, Gøtzsche PC, Jefferson T. The Cochrane HPV vaccine review was incomplete and ignored important evidence of bias. BMJ Evidence-Based Medicine 2018 July 27 https://doi.org/10.1136/bmjebm-2018-111012 2

Keywords:

Cochrane review, HPV vaccine, adjuvant, mortality, heaithy vaccinee effect,

Introduction

Tovey (Cochrane's Editor in Chief) et al **[1,2]** commented on a paper by Jøorgensen et al. **[3]** published in BMJ Evidence-Based Medicine related to the recently published Cochrane Review on HPV vaccines **[4]**. I would like to give my feedback on this issue. The key findings of Tovey's investigations are as follows:

1. The Cochrane Review did not miss "nearly half of the eligible trials". A small number of studies were missed due to the primary focus on peer-reviewed reports in scientific journals, but addition of these data makes little or no difference to the results of the review for the main outcomes;

2. The trials comparators were unambiguously, transparently, and accurately described;

3. The selection of outcomes for benefits was appropriate and was consistent with World Health Organization guidance;

4. The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly;

5. The review was compliant with Cochrane's current conflict of interest policy;

6. Cochrane's media coverage was cautious and balanced, but we recognize that there could be improvements in relation to transparency where external experts are quoted;

7. The BMJ Evidence-Based Medicine article substantially overstated its criticisms.

I would like to comment on Tovey's findings 1, 2, 4 and lastly, I added comments as 8. Most observational studies neglect "healthy vaccine effect/healthy user bias".

1. On "The Cochrane Review did not miss nearly half of the eligible trials".

Tovey explained "A small number of studies were

missed due to the primary focus on peer-reviewed reports in scientific journals." However, the abstract of the Cochrane review reports: "We searched MEDLINE ----- for reports on effects from trials.

We searched trial registries and company results' registers to identify unpublished data for mortality and serious adverse events."

For the serious adverse events, the Cochran review described in the sensitivity analysis as follows: "We assessed the robustness of data collected for serious adverse events, all-cause mortality and pregnancy outcomes based on the source of data. The primary analysis for these outcomes included data that we considered to represent the most complete follow-up. As a sensitivity analysis we used data for these same outcomes that had only been reported in the published trial reports."

It is evident that the Cochrane review recognized the importance of clinical study reports (CSRs) and partially gathered the unpublished data for mortality and serious adverse events.

Jørgensen et al. pointed out that there were many missed trials which Cochrane review did not included because they were not published.

As for the analysis of oseltamivir, we, the Cochrane neuraminidase inhibitor team, used all CSRs and found significantly increased psychiatric events in the 4 CSRs for prophylaxis of influenza. However, if we restricted to use peer reviewed published journals, we would not have detected the psychiatric harm even if CSRs for published trials were used. This is the most important point that Jørgensen et al. emphasized.

Summary of this section

The review should be revised by including all CSRs identified and other points described in the following sections. Before the revision is completed, the Cochrane review should be suspended.

2. Description of the comparators and the unavoidable toxicity of adjuvants
2-1. The safety of adjuvants is not established.

Tovey wrote "The trials comparators were unambiguously, transparently, and accurately described". However, the problem is not the descriptions but the real toxicity of adjuvants.

It is true that the Cochrane review by Arbyn et al. described the comparators unambiguously, transparently, and accurately. However, the problem is not the accuracy and transparency of the description of the comparators. It is that adjuvants as the comparators conceal the true harm of HPV vaccines because the safety of the vaccine adjuvant has never been established clinically [5] nor non-clinically. Instead, harm of adjuvant is rather unavoidable as indicated by laboratory tests and toxicity tests shown in the followings.

2-2. Non-clinical tests strongly suggest the harm of adjuvant.

It is revealed that true adjuvant is the DNA of the recipient which is produced by tissue damage by the administered adjuvant, such as alum adjuvant. This suggests that the bigger the damage, the stronger the stimulation of innate immunity and work as adjuvant [6,7], and autoimmune diseases [8], including those in the central nervous system [9] may be induced.

GlaxoSmithKline conducted several animal toxicity tests, although they did not fulfil the standard toxicity testing method for the ordinary pharmaceutical products.

In the third toxicity test, single or repeated i.m., Cervarix, and ASO4 adjuvant induced item-related local degeneration, necrosis, and regeneration of muscle fibers with hemorrhage and mild-to-moderate subacute inflammation at 4 days and 5 months after the first inoculation, unlike saline [10]. The extent and proportion of animals with these lesions were the same between Cervarix and ASO4 group and immediately after the single dose but more prominent in the Cervarix group than ASO4 adjuvant group after 4 repeated doses [10].

Summary of this section

In a randomized controlled trial, saline control is appropriate as the comparator for the analysis of both efficacy and harm. For efficacy analysis, active control such as adjuvant or vaccines with/without adjuvant may not be necessarily inappropriate as the comparator. However, these active controls are definitely inappropriate for the harm analysis. The other approach should be applied for the harm analysis, if no saline control trials are available.

4. On "The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly";
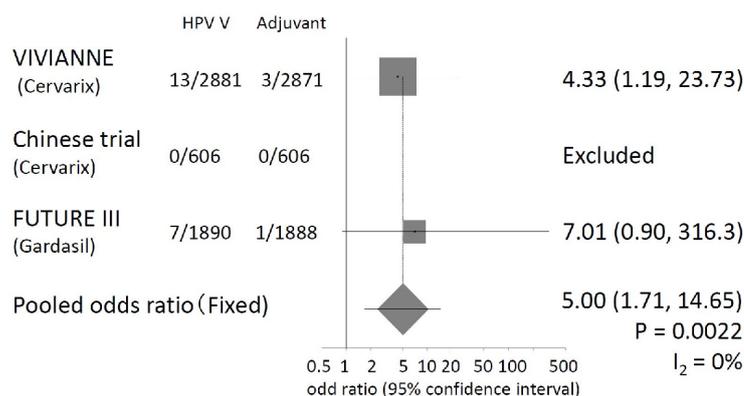
4-1. Meta-analysis of mortality in the trials targeting mid-adults women

You wrote "The review included published and unpublished data on serious harms, and the findings on mortality were reported transparently and responsibly." According to my meta-analysis using the extracted data from the reference peer reviewed papers in which subjects' ages were 25 (or 26) to 45 year or older [11-14], the pooled odd ratio was 5.00 (95%CI: 1.71, 14.65), P = 0.0022 (I2 = 0%) (**Figure 1**).

- For the VIVIANE trial [11,12], I used 13 deaths in Cervarix group and 3 deaths in adjuvant group within 4 years, because after that period there was no difference between these groups.
- For the FUTURE III trial [13], the numbers of deaths described in the published paper were 7 in the Gardasil group and 1 in the adjuvant group as shown in its sensitivity analysis of death. However, in the Cochrane review, the numbers are 8 and 4, respectively, presumably based on the data including after 4 years from unpublished CSR.
- For the Chinese trial [14], my extraction was HPV vaccine 0 and adjuvant 0 while the Cochrane review data were 1 and 0, respectively, also in the sensitivity analysis.

Figure 1 indicates that HPV vaccines increase mortality in woman aged 25 or older by 5 times within 4 years after the first injection. Moreover, Tovey described that after adding the mortality data from newly included trial NCT00834106 (targeted 20 to 45 years of age), RR of death increased from 1.54 (95% CI 0.73 to 3.23) to 1.65 (95% CI 0.80 to 3.38). It is highly probable that substantial difference of death risk may be reported in this added study. Tovey should clarify the number of deaths in both groups (Data from Clinicaltrial.gov suggest that the number of deaths are estimated 2/1499 and 0/1498 for Gardasil and adjuvant group respectively).

Figure 1: Mortality risk within 4 years after the first injection (Meta-analysis of 3 trials targeted mid-adult women)

Risk of death in women aged 25 to 45 years may be further robust by adding this trial.

Summary of this section

Pooled odd ratio of death for mid-adult women was 5.00 (95%CI: 1.71, 14.65), while no difference on mortality for younger women was observed. Serious adverse event and mortality should be separately analysed for different age groups: namely under the age of 25 years and mid-adults (approximately 25 or older) in addition to the analysis as the whole ages.
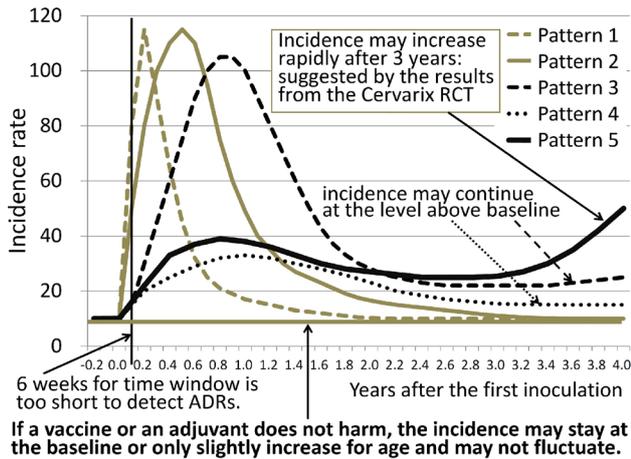
4-2. Fluctuation of mortality and adverse events

If a vaccine does not cause harmful effects, the incidence rate of adverse events may stay at the baseline or increase only slightly as age increases. However, if the incidence rate of adverse events fluctuates substantially, then it may be the result of the harmful effect of the vaccine. Several patterns of theoretical trend of incidence rate are shown (**Figure 2A**).
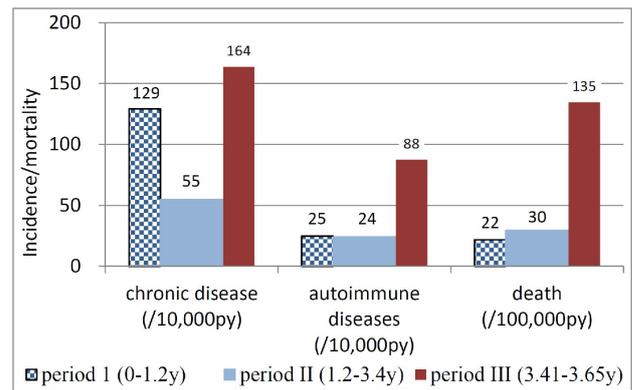
In the pivotal RCT of Cervarix (PATRICIA), no difference in the adverse events between Cervarix group and adjuvanted HA vaccine group was observed. Hence, I calculated the overall (both groups) trend of incidence rates of adverse events, including chronic diseases (CD), autoimmune diseases (AD) and death (D) dividing 3 periods: 1: 0-1.2 year, 2: 1.2-3.4 year, 3:3.4-3.65 year. Incidence rate (/100,000 person-year) of CD, AD and D fluctuate as follows: CD: 129-55-164, AD: 25-24-88, D:22-30-135 respectively. These data show that the incidence rates or mortality rates greatly fluctuate and increase even after about 3.5 years from the first

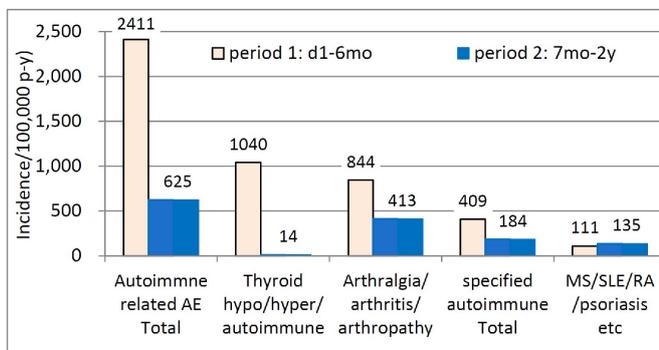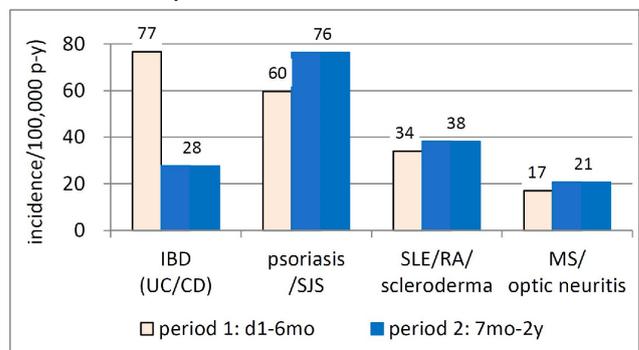## Figure 2: Fluctuation of adverse events

A: Theoretical pattern

6 weeks for time window is too short to detect ADRs.

Years after the first inoculation

If a vaccine or an adjuvant does not harm, the incidence may stay at the baseline or only slightly increase for age and may not fluctuate.

B. Cervarix trial (PATRICIA)

C. Gardasil (1) Autoimmune diseases

D. Gardasil (2) Specified autoimmune diseases

■ Period 1: day 1 to 6 months, ■ Period 2: 7 months to 2 years. Data were derived from Gardasil RCTs in the Japanese Summary Basis of Approval. Grouped specified autoimmune diseases: Inflammatory bowel diseases (IBD: ulcerative colitis and Crohn's disease), psoriasis/Stevens–Johnson syndrome (SJS), systemic lupus erythematosus (SLE)/rheumatoid arthritis (RA)/scleroderma, multiple sclerosis (MS)/optic neuritis.

inoculation (**Figure 2B**).

For Gardasil studies, I calculated the incidence rates (/100,000 person-years) of various autoimmune-related adverse events (AE) among participants from both Gardasil and control (almost all received alum-adjuvant) groups (**Figure 2C** and **2D**). Incidence rates (/100,000 person-years) of total autoimmune related adverse events are 2441 at the first period (day 1 to 6 months) and 625 at the second period (7-24 months) and that of inflammatory bowel disease are 77 and 28 respectively.

These also indicate that the incidence rates of various autoimmune diseases greatly fluctuate over time and suggest Gardasil affected these fluctuations (included studies were all phase II and III trials targeted women aged 9 to 24).

VIVIANE trial shows high mortality rate during the first 4 years and low mortality rate after 4 years in the Cervarix group, but this was not evident in the control adjuvant group (**Figure 3**). These data show fluctuations are greater in the HPV vaccine group.
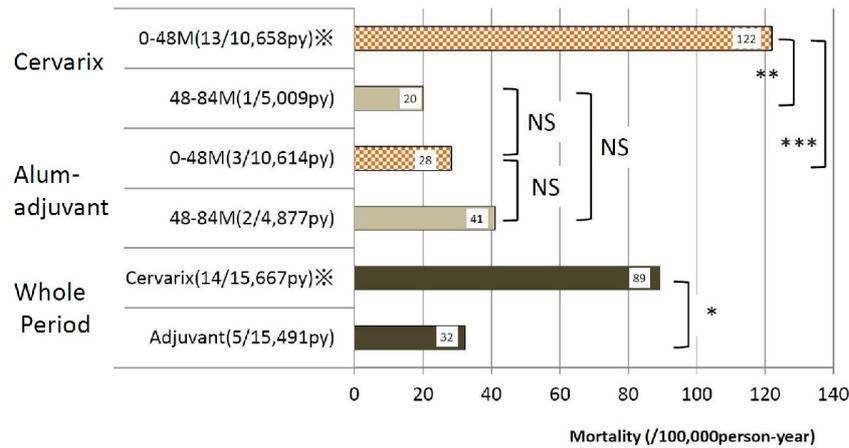
If the numbers of deaths for FUTURE III trial are 8 for Gardasil group and 4 for adjuvant group, 1 and 3 deaths may be observed after 4 years, respectively. Person-years at risk is not estimated, but 7 in the first 4 years and 1 thereafter indicate similar fluctuation, and less fluctuation is observed in the adjuvant group. This may be a very similar phenomenon as shown in the VIVIANE trial.

Summary of this section

Fluctuation of serious adverse events including death should be considered in the RCTs using adjuvant as comparator. Analysis of high risk and low risk periods together may conceal true harm of HPV vaccines. Analysis should be conducted separately for the different risk periods.

Figure 3 Fluctuation of mortality in Cervarix group in VIVIANE trial

※ : A patient died from breast cancer at M52 is excluded in the first period (0-48 M) but included in
the second period (48-84 M). *:p=0.041, **:p=0.047, ***:p=0.013, NS: not significant.

4-3. Comparison of incidence rates of specific autoimmune diseases between RCT and general population of women of similar age group

The incidences rates of some autoimmune diseases examined, such as multiple sclerosis (MS), systemic lupus
erythematosus (SLE), and inflammatory bowel diseases (IBD), calculated from the data in the "SBA" of Gardasil (age ranged 9–26 years, mainly 16–23 years) were all higher than those in the general female population of similar age (15 to 25 years old).

For example, the incidence rate (per 100,000 person-year) of MS in Gardasil RCTs (14.7) was about 3–15 times higher than that of general population in Italy (4.2–4.7), the United Kingdom (3.4), and France (1.0). Notably, MS incidence reported in Gardasil RCTs was even higher than the highest reported in the general population, namely, in north Sweden (8.4) and Iceland (12.5) (**Figure 4A**).

Incidence rates of IBD in the RCTs are also higher than that of the general female population of similar age, though the age range is a little broader (0 to 39 years old) (**Figure 4B**).
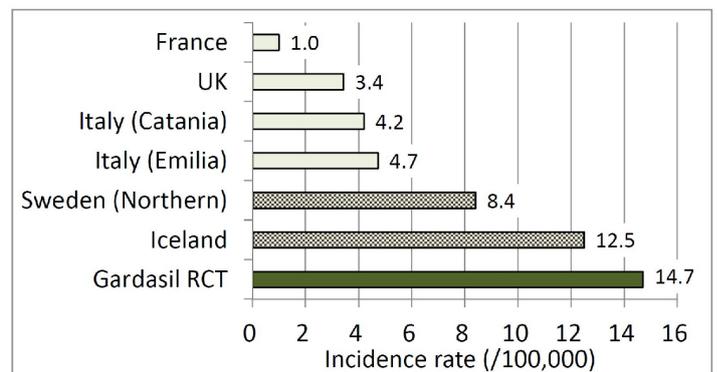
Summary of this section

Annual incidence rates for typical adverse events such as specific autoimmune diseases in the RCTs should be compared with that of general population of similar age.
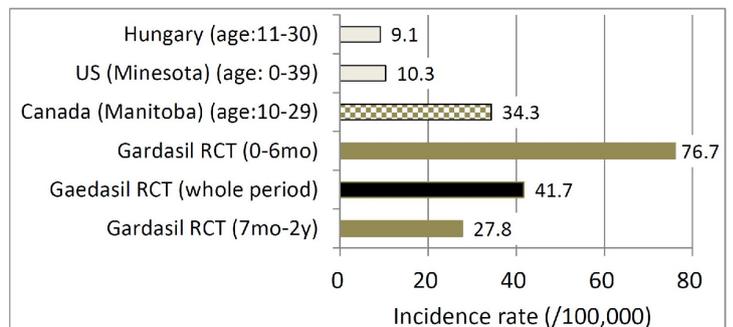
In the discussion section, the Cochrane review discussed the Adverse effects of HPV vaccines citing

Figure 4 : Comparison of incidence rates of MS and IBD between RCTs and general female population of similar age

A: Muitiple Sclerosis(MS)

B: Inflammatory Bowel Disease(IBD)

8. Most observational studies neglect "healthy vaccine effect/healthy user bias"

many observational studies.

However, most observational studies have fundamental flaws:

• Negligence of healthy vaccine effect (healthy user bias),
• Negligence of time dependent bias in the self-control case-series method and
• Confusion of incidence with prevalence.

Here I only discuss the Negligence of healthy vaccine effect (healthy user bias) which most observational studies neglected, affect the results seriously and sometimes reverse the association.

Negligence of healthy vaccinee effect (healthy user bias)
i) Theoretical basis

It is important that confounding bias is avoided in epidemiologic studies. In particular, confounding bias from "healthy vaccinee effect" always affects results in favour of an intervention, leading to overestimation of its effectiveness and safety.

People who have any diseases and/or are prone to have fever/infection tend to avoid vaccination. Autoimmune diseases often follow infection. Unless unvaccinated people who are sicklier or frailer than vaccinated people at baseline were not adequately adjusted, the results of the high incidence rate of autoimmune diseases in the vaccinated people may be offset by the disease incidence in the sickly unvaccinated people. This is "healthy-vaccinee effect," "frailty selection bias," or "frailty exclusion confounding bias." [15]

Bias from "healthy-vaccinee effect" becomes more impactful as the coverage of vaccination becomes higher, namely 80% or higher [15]. Theoretically in the unvaccinated, odds ratio for having symptoms at a certain vaccine coverage (%) compared with the lowest coverage group increases as the percent coverage increases.

ii) Nagoya study

Nagoya study is a questionnaire survey on symptoms after HPV vaccination, involving about 70,000 girls (born between 2 April 1994 and 1 April 2001: approximately aged 14 to 21 in September 2015) living in Nagoya City Japan. Of these, about 30,000 girls responded: 20,748 girls were vaccinated and 9,098 girls were unvaccinated [16].

Suzuki et al. [16] concluded "the results suggested no causal association between the HPV vaccines and their alleged harmful symptoms".

However, according to my logistic regression analysis using the disclosed PDF data, odds ratios (ORs) of positive symptoms before vaccination were significantly (p<0.05) lower than 1.0 in 15 of 24 symptoms ranging from 0.16 (Dependent on stick or wheel chair) to 0.86 (Irregular menstrual cycle). ORs for symptoms leading to hospital visit were significantly lower than 1.0 in 7 of 24 symptoms, especially in severe symptoms, such as "Unable to walk normally" (0.22), "Dependent on stick or wheel chair" (0.21), "Sudden loss of strength" (0.28) and "Weak in the extremities" (0.30). OR for "Difficulties in calculation" is not significant (P=0.148), but point estimate of OR was very low (0.25, p=0.15).

The trends of the proportion of the frail, by coverage both in the unvaccinated and the vaccinated groups fit well to the theoretical trends expected in each group.

On the other hand, odd ratios of positive symptoms after vaccination leading to hospital visit were generally higher than 1.0 (no symptom was less than 1.0) and significantly higher than 1.0 in 11 of 24 symptoms: for example, "Weak in the extremities" (2.76, p=0.014) and "Difficult to remember Chinese characters" (8.46, p=0.047). "Dependent on stick or wheel chair leading to hospital visit" were reported in 13 girls in the vaccinated group, while none in the unvaccinated group: odds ratio = 9.61 (95%CI: 1.21- infinity, p=0.027) by the exact-like logistic regression using "R" software.

Considering the low odds ratio of health status before inoculation, each odds ratio after inoculation should be divided by the corresponding odds ratio before inoculation. Hence point odds ratio after vaccination of HPV vaccine for the symptoms leading to hospital visit are estimated as follows (those above 5.0 are shown): Dependent on stick or wheel chair: 46.7, Difficult to remember Chinese character: 24.8, Difficult to calculate: 15.5, Unable to walk normally: 11.0, Weak in the extremities: 9.2, Sudden loss of strength: 8.6 and Involuntary movement: 5.7

Among many observational studies, French study is a study which apparently adjusted the health status prior to vaccination [17,18]. However, it has some limitations as follows:

iii) French study: apparently incorporating prior health status but not actually

1) The authors did not restrict the health status prior to vaccination as covariate for adjustment. They adjusted the health status after inclusion up to 3 months before the event or censoring as covariate. Hence, the health

French study [17,18] is a retrospective cohort study based on national healthcare administrative databases. Total 2.25 million girls aged 13 to 16 years between 2008 and 2013 were included: 0.84 million (37.3%) were exposed to HPV vaccine and 1.41 million were not exposed. Proportion of girls vaccinated was the highest in those included in 2008 (45.4%) and subsequently decreased 43.3%, 35.0%, 26.0% and 15.1% for 2009, 2010, 2011 and 2012 respectively. Outcome events were 14 autoimmune diseases (AID), including central nervous system (CNS) demyelinating diseases (MS: multiple sclerosis etc.), Guillain-Barres syndrome (GBS), and inflammatory bowel diseases (IBD). Hazard ratios of any of the14 AIDs or of individual AID were estimated by Cox regression analysis adjusting age, year of vaccination as time dependent variable. Vaccination other than HPV vaccine, hospitalisations, health-care seeking behaviour indicators, year of inclusion, geographic area of residence and socioeconomic level were also adjusted. "Health-care seeking behaviour indicators" include all-causes hospitalizations, outpatient primary care and specialist visits. Hospitalizations were considered in the model as a time-dependent binary variable, indicating if at least one hospitalisation occurred over the 12-month period running from 15 months to 3 months prior to each time point. Outpatient visits were considered as time-fixed variables: binary variables indicating the occurrence during the year prior inclusion, and quantitative variables indicating the mean annual frequency of visits during follow-up (ratio of the total number of visits after inclusion until 3 months before the event or censoring). A statistically significant association with HPV vaccine was shown in 2 autoimmune diseases: adjusted HR of inflammatory bowel diseases (IBD) was 1.18 (95%CI: 1.01-1.38) and that of Guillain-Barré syndrome (GBS) was 3.78 (95%CI: 1.79-7.98). The sensitivity analysis showed that the association of both autoimmune diseases were the strongest for the period from 0 to 3 months and tended to decrease subsequently without significance for IBD, but it remained significant for GBS. Risk of GBS is robust as suggested by the sensitivity and subgroup analysis.

status they adjusted included that after vaccination, which may be affected by the HPV vaccination. They analysed without adjusting health status as sensitivity analysis and did not show the results.

2) The health status they adjusted as that prior to inclusion (or vaccination) was at least one outpatient visit during the year prior to inclusion and not prior to vaccination. Vaccinated girls had more outpatient primary care than unvaccinated girls (94.2% vs 86.5%) and visited more specialists (75.9% vs 65.2%). This phenomenon contradicts the common tendency that unvaccinated people are usually sicklier or frailer than vaccinated people at baseline as explained in the section of "Theoretical basis of healthy vaccinee effect". Low proportion of outpatient visit in the unvaccinated may not indicate that unvaccinated girls are healthier but may be related to their lower socioeconomic level. Hence, adjusting the status of outpatient visit could not adjust the true health status of the vaccinated and unvaccinated.

3) They also adjusted age, year of vaccination and year of inclusion. Proportion of the vaccinated is closely related to the year of inclusion. As shown in the section of "Theoretical basis for healthy vaccinee effect (healthy user bias)", in the unvaccinated people, odds of having illness prior to vaccination increases as the percent coverage of vaccination increases.

As shown by Jackson et al. [19], risk of death for vaccinated persons compared with unvaccinated persons was lower before influenza season than during and after influenza season. The reductions in risk before influenza season indicate preferential receipt of vaccine by relatively healthy seniors, and adjustment of diagnosis code variables did not control this bias. Hence, unless true health status prior to vaccination is adjusted, the adjustment is flawed in the French study.

In fact, crude rate ratios (RRs) calculated by the number of patients with any autoimmune diseases (AIDs) and 12 individual AIDs were higher than the adjusted hazard ratios (HRs); for example, any AID: 1.14 (P<0.001) vs 1.07 (p=0.10), inflammatory bowel diseases (IBD): 1.54 (P<0.001) vs 1.18 (P=0.032) and CNS demyelinating diseases: 1.28 (P=0.059) vs 1.06 (P=0.72).

Moreover, incidence rate (/105 py) of CNS demyelinating diseases in the unvaccinated group (4.6

or 5.9) is very high compared with that of multiple sclerosis (0.99 [95% CI: 0.94–1.04]) in the general female population of the same age group (aged 15 to 24 years) in France between 2001 and 2007 [19]. Hence incidence rate (/105py) of CNS demyelinating diseases after HPV vaccine in the HPV vaccinated group in the French pharmacovigilance study [17] is far higher than that in the general population in France [19]. The high incidence rate in the unvaccinated girls may be the result of healthy user bias and exclusion of frailty from vaccination due to the high vaccination coverage.

These suggest that frail girls had been included in the unvaccinated group at the time of inclusion. Therefore, it should be considered that "healthy vaccinee effect" or "frailty exclusion bias" may not have been completely excluded even in this French pharmacovigilance study [17,18].

Moreover, significantly high incidence of events after inclusion such as frequent consultation (≧ 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 needing frequent medical care and/or hospitalisation (9% of the girls per year needed additional hospitalization compared with prior vaccination and unvaccinated girls) may be related to some adverse outcomes of HPV vaccination other than autoimmune diseases.

For the discussion of harm comparing the results with those from observational studies, it is essential to consider the "healthy vaccinee effect". Unless the health status before vaccination (pseudo vaccination date for unvaccinated group) is adjusted in observational studies, the findings should not be used as evidence of safety.

Conclusion

1) The review should be revised by including all ASRs identified and other points described below. Before the revision is completed, I strongly recommend the Cochrane review should be suspended.

2) In a randomized controlled trial, saline control is appropriate as the comparator for the analysis of both efficacy and harm. For efficacy analysis, active control such as adjuvant or vaccines with/without adjuvant may not be necessarily inappropriate as the

comparator. However, these active controls are definitely inappropriate for the harm analysis. The other approach should be applied to the harm analysis, if no saline control trials are available.

3) Pooled odd ratio of death for mid-adult women was 5.00 (95%CI: 1.71, 14.65), while no difference on mortality for younger women was observed. Serious adverse event and mortality should be separately analysed for different age groups: namely under the age of 25 years and mid-adults (approximately 25 or older) in addition to the analysis as the whole ages.

4) Fluctuation of serious adverse events including death should be considered in the RCTs using adjuvant as comparator. Analysis of high risk and low risk periods together may conceal true harm of HPV vaccines. Analysis should be conducted separately for the different risk periods.

5) Annual incidence rate for typical adverse events such as specific autoimmune diseases in the RCTs should be compared with that of general population of similar age.

6) For the discussion of harm comparing the results with those from observational studies, it is essential to consider the "healthy vaccinee effect". Unless the observational studies adjust the health status before vaccination (pseudo vaccination date for unvaccinated group), the findings from such studies should not be used as evidence of safety.

It is my sincere hope that Tovey et al. would consider this feedback seriously in order to further improve the quality of the Cochrane review.

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Conflict of interest

No conflict of interest with industries including pharmaceutical companies.

Rokuro Hama (RH) has been a member of the Cochrane neuraminidase inhibitor team headed by Tom Jefferson since January 2010. RH has met Dr. David Tovey (DT) and discussed the methods for conducting the systematic review of neuraminidase inhibitors [20] at the Oxford meeting in April 2011. RH explained DT and other members of the Cochrane neuraminidase inhibitor team how Tamiflu lowered the antibody production in the treatment trial and that ITTI population was

inappropriate for the assessment of efficacy. Instead, RH proposed that ITT population should be used to assess efficacy and harm of Tamiflu. The method using ITT population was agreed by the Cochrane neuraminidase inhibitor team at the meeting in April 2011.

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NEWS

Cochrane Out of Control: Expulsion of the Prominent Member

On September 13, 2018, Cochrane's Governing Board announced that it would expel Dr. Peter Gøtzsche, one of its founders, from the organization. The decision was made with a slim margin; with six officers in favor, five members against and one abstinence. Dr. Gøtzsche was excluded from the discussion. Four officers resigned in protest against the decision [1].

Dr. Peter Gøtzsche was the director of the Nordic Cochrane Centre and one of the 13 board members. He conducted 18 systematic reviews, and exposed that breast cancer screening programs (see MedCheck-TIP No.63 and No.66) and comprehensive medical examinations (MedCheck-TIP No.76) were ineffective. He has made major contributions as a leader of Cochrane's Methods Groups. His important achievements also include research on overuse and harm of psychotropic drugs [2].

Dr. Gøtzsche severely criticized Cochrane's systematic review on HPV vaccine published in May this year [3], indicating that the review had analyzed only about half of the studies, and raising a question of conflicts of interest with the manufacturers [4].

Cochrane's Editor in Chief and his Deputy refuted the criticism [5], but their argument is flawed [6, 7].

Governing Board simply explained that Dr. Gøtzsche was expelled for causing "disrepute" to the organization, but no concrete reason was provided. The board did not allow him to defend himself in the discussion, and it even threatened to close the Nordic Cochrane Centre [8]. Dr. Gøtzsche has been fired from his job as the director of Nordic Cochrane Centre at Rigshospitalet [9,10].

These events greatly undermined the founding spirit of the Cochrane Collaboration; that is to exclude influence from the pharmaceutical industry and to build truly reliable information about roles and benefits/harm of therapeutic and diagnostic medicine by voluntary efforts of researchers. However, now Cochrane itself has become commercialized and influence from the pharmaceutical industry is increasing. This seems to be the cause of the crisis today. There is a growing concern now that Cochrane is a "sinking ship" [8, 11]. (Related articles: pages 30 and p41~)

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See also: Editorial of this issue (p.30), Critical Review (p.41)

France has delisted anti-dementia agents

From August 1, 2018, the French government has decided to totally discontinue reimbursement of four drugs for dementia of the Alzheimer type (hereinafter anti-dementia agents), such as donepezil, by health insurance. Anti-dementia agents can be used only at patients' own expense.

The four drugs are, namely, donepezil (Aricept® in Japan), galantamine (Reminyl®), rivastigmine (Rivastatch® patch, Exelon® patch) and memantine (Memary®).

The French Pharmacoeconomic Committee has been scientifically evaluating the benefit of the anti-dementia agents, and the policies they introduced in the past 10 years have prepared the ground for this decision [1].

First of all, in 2007, the committee stated that agents for Alzheimer's disease provide no "therapeutic advantage", downgrading them from the level IV (minor) to the level V (no therapeutic advantage). This measure was taken based on the committee's judgement that there was no evidence on the long-term benefit, but only on transient efficacy [1]. This coincides with the conclusion of Med Check No. 27 published in July 2007; "there is no effective medicines for treatment of dementia". This decision was made four years before three anti-dementia agents, except for donepezil, were approved in Japan.

In September 2011, the committee recommended that the reimbursment rate for anti-dementia agents would be lowered from the regular rate of 65% to 15% because they were considered less useful.

In 2012, subscribing to this recommendation, the rates for these agents were actually lowered. However, since the expenses for donepezil and memantin were covered 100% by the other source, this measure was practically ineffective.

However, on August 1, 2018, a new measure was introduced, which provides totally no reimbursement for the agents. According to Dr. Christophe Kopp, Managing Editor of Prescrire International, France, no other source would cover the cost.

In Japan, over 150 billion yen is spent annually for these ineffective drugs. Half of it is wastefully prescribed for people aged 85 years or over, and three-fourth is for people aged 80 years or over [3]. This situation should be seriously reconsidered.

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