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Screening does not reduce cervical cancer deaths

The best and only protective measure is to have adequate nutrition and sleep

Pneumococcal and Hib vaccines for children

Harms may outweigh benefits: not recommended

CONTENTS （August 2017, Vol. 3, No. 8）

Editorial:

Is the intervention really necessary?
The importance of the epidemiologic evidence 13

Review

Screening does not reduce cervical cancer deaths 14
The best and only protective measure is to have adequate nutrition and sleep

Pneumococcal and Hib vaccines for children 20
Harms may outweigh benefits: not recommended

Is the intervention really necessary? The importance of the epidemiologic evidence

Translated from the editorial in Med Check-TIP (in Japanese) Jul 2017 : 17 (72)

In order to stress the need of an intervention (treatment or prevention) for a particular illness, such phrases are typically used: "The illness is increasing" "you should lower levels of this and that, which is the cause of the illness" or "the intervention is essential to prevent death from the illness".

Denosumab, a new product discussed in the Japanese issue (No72, July 2017), is one of the products used for reducing a fracture. It was developed not because osteoporosis is increasing. If you search epidemiologic evidence carefully, you will find a birth cohort study which clearly shows that osteoporosis has not been increasing, but rather decreasing. The reason why the manufacturers and their researchers stress the need of new products for prevention of osteoporosis, ignoring the fact that the disease has been decreasing, is only because they need to promote sales of these products.

The typical example for the phrase "you should lower levels of this and that, which is the cause of the illness" is "cholesterol, a cause of atherosclerosis (or arterial sclerosis which is preferred in Japan), should be lowered." However, cholesterol is actually not the cause of atherosclerosis or arterial sclerosis. On the contrarily, people with relatively high cholesterol level (or LDL - cholesterol level), who are considered to be ill or have high risk according to the current major guidelines, rather live longer.

A large number of epidemiologic studies have proven this as often discussed in this bulletin. The reasons why people with familial hypercholesterolemia (FH) are prone to myocardial infarction are not because their cholesterol (or LDL-cholesterol) level is extremely high, but because they are prone to inflammation and coagulation, and/or have sensitive vascular endothelium.

The phrase "the intervention is essential to prevent death from the illness" is used to strengthen the importance of vaccines. We carefully examined the vital statistics and compared mortality rates from bacterial meningitis and bacterial pneumonia, which are the target diseases of Hib vaccine and pneumococcal conjugate vaccines, before and after introduction of these vaccines. We found that the number of deaths (or mortality rate) after inoculation of both vaccines was higher than that reduced by the vaccines.

A drug always comes together with harm, but its benefit must outweigh the harm so that the use is justified. Such a drug may be used with caution so that harm would be minimized.

How should we deal with interventions that may save life but may also cause death? The use of such interventions is justified only after strictly weighing the number of deaths (rate) reduced and the number of deaths (rate) possibly induced by the interventions.

We are committed to continue evaluating interventions including vaccines based on this principle.

Review

Screening does not reduce cervical cancer deaths

The best and only protective measure is to have adequate nutrition and sleep

Translation from Japanese edition of Med Check-TIP 2017: May (No 71):54-57

Abstract:

• It is often argued that screening would prevent cervical cancer even if HPV vaccination is discontinued. However, this article reviewed thoroughly an English study which is believed to provide evidence for effectiveness of screening, and found that it has no basis.

• In addition, the only available randomized controlled trials (RCTs) comparing those with screening and control without screening were conducted in India where mortality from cervical cancer is 4-12 folds higher than that in Japan. Screening by cytological examination did not show any statistically significant efficacy even by the Indian RCT. As for other screening methods, some studies showed significant results while others did not. Even if the Indian RCTs showed significant results, extrapolation according to the mortality in Japan turns the results into "not significant", due to extremely low mortality rate from cervical cancer in Japan. Suppose that screening is effective, at least 240 million to 1.5 billion yen would be required in order to reduce one death from cervical cancer.

• Mortality from cervical cancer in Japan has been markedly decreasing, accompanying increase in fat intake. Excessive dieting among adolescent girls does not only lead to cervical cancer, but is also extremely risky for their general health. Enough fat and protein intake and adequate sleep without using hypnotics are essential for prevention of any kind of diseases.

Keywords:

cervical cancer, screening, randomized controlled trials, cytological examination, mortality, HPV detection, visual inspection with acetic acid (VIA), India,Japan, UK

Introduction

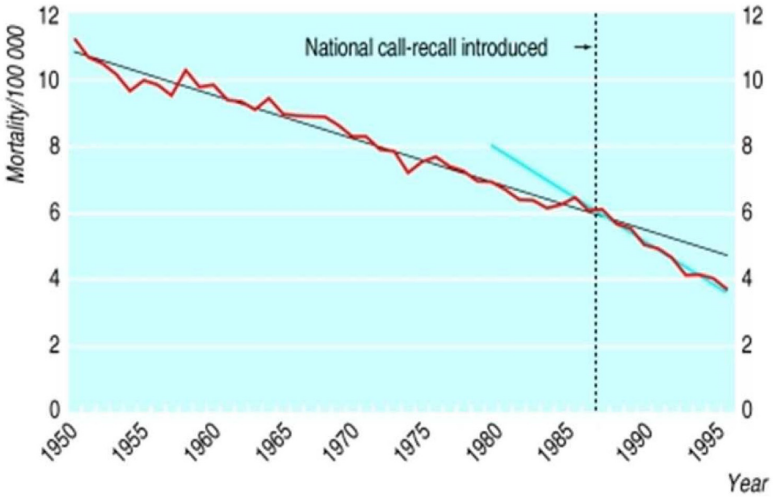
Harm of HPV vaccination outweighs its benefits. It is often argued that even if it is discontinued, cervical cancer can be prevented by screening, and thus HPV vaccine is not necessary [1,2]. Can screening really prevent cervical cancer, and reduce mortality from the disease as well as total mortality?

English Study: basis for effectiveness?

No randomized controlled study (RCT, fair comparative study) has been conducted in developed countries, including Japan, North America and Europe, to prove that the screening reduces mortality from cervical cancer and total mortality. Therefore, this article examined one study [3] (Ref. 1 is also based on ref.3), which is considered the most important evidence for efficacy of screening in developed countries.

In England, screening for cervical cancer has been actively recommended as a national project since 1987. The uptake of screening was 42% in 1988, and greatly increased up to 85% in 1994.

Figure 1: Age standardised mortality from cervical cancer, England, 1950-97



The straight lines show decreasing trends to highlight the difference between the 2 periods (The straight lines are original to Ref. 3).

Figure 2-a:Age specific mortality from cervical cancer, England,1950-97
(original figure)

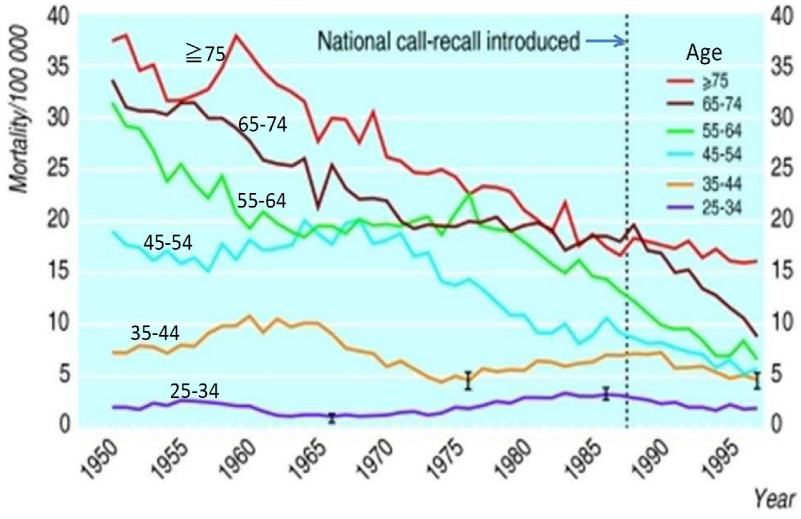


Figure 1 shows the change in mortality from cervical cancer in England. The mortality seems to have decreased since the screening project was launched. By only looking at this figure, active promotion of screening seems to have contributed successfully to the reduction of deaths from cervical cancer. It is understandable why this study is considered a basis for the efficacy. However, is this really true?

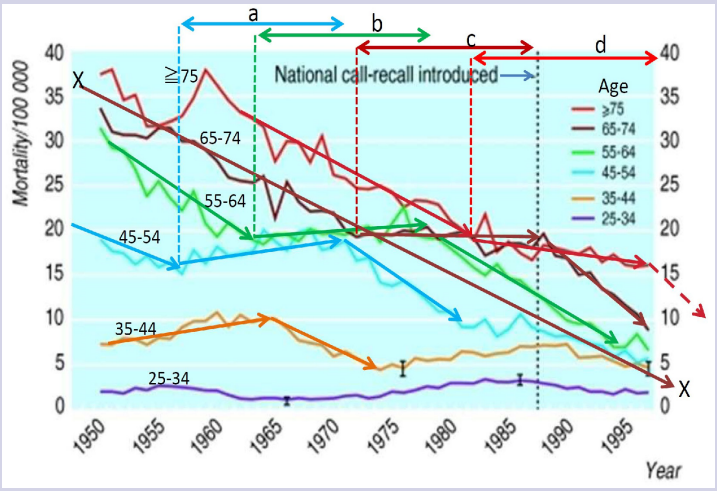
Now, let us take a look at the mortality by age groups in **Figure 2**. See the difference in the mortality between before and after 1987 for each age group. In the age group 45-54, the decreasing trend became milder after 1987. No change was observed in the age group 55-64. In the age 75 and older, the decrease became milder. No change was found in the age group 25-34. In the age group 35-44, the mortality slightly increased after the screening project started, and started decreasing slowly after a few years. After all, the mortality decreased only in the age group 65-74 while in other groups, almost no change or even slight increase was observed. The mortality among the age group 65-74, which had been plateaued, started decreasing around 1987. It seems that this timing happened to coincide with the time when the screening project was launched.

Therefore, this English study does not serve as evidence for the effectiveness of the screening.

By closely looking at the change by age groups (see **Fig. 2-b** and the commentary below for more details), it is clear that the

Commentary :

Figure 2-b : Age specific mortality from cervical cancer, England, 1950-97
(for comments in detail)



In the age group 65-74, mortality plateaued between 1970 and 1987 (Period C). In 1987, the mortality for this group became higher than that in people aged 75 and older. After that, it rapidly decreased, and approached the line X, which is an extension of the decreasing trend before 1970. In the age group 55-64 and 45-54, mortality plateaued or even increased between 1960-1977 (Period B) and 1955-1967 (Period A), respectively. In people aged 75 and older, the decreasing trend became very mild and almost plateaued, starting around 1980 (Period D).

This figures shows that people who were born between around 1905 and 1920 maintained high mortality from cervical cancer.

This suggests that people who had been malnourished in their adolescent during the First World War probably were persistently infected with HPV virus, and maintained high mortality from cervical cancer. Therefore, this data do not provide any evidence for the efficacy of screening in reducing mortality.

Only if early cryosurgery, electrocautery or conization are proven to reduce mortality, screening can be considered effective. However, screening was not effective, and thus early detection and intervention were practically not beneficial, either.

Table: Summary of the cluster randomized controlled studies on the efficacy of cervical screening (from ref 4 ~ 6)

ref 4: Effect of VIA Screening by Primary Health Workers: Cluster Randomized Controlled Study in Mumbai, India (Shastri et al 2014) [4]

Mumbai (urban): average 8 years since 1998 Visual inspection with acetic acid (VIA) subjects: healthy women aged 35 to 64			Screening N=75,360			Control (usual care) N=76,178			Crude odds ratio (OR) IRR (95%CI) *a Incidence Rate Ratio
			Person-years	n	Rate /100,000 p-y	Person-years	n	Rate /100,000 p-y	Crude OR (95%CI)
compared 10 clusters each for screening and control groups	Preinvasive case (HSIL+LSIL)*b		602,152	328	54.5	603,812	48	7.9	6.28 (4.39-8.97)
	Cervical cancer	Incidence	602,152	161	26.7	603,812	166	27.5	0.97 (0.78-1.21) 0.97 (0.80-1.19)
		Mortality	602,697	67	11.1	604,228	98	16.2	0.69 (0.50-0.94) 0.69 ((0.54-0.88)
	Mortality from other causes		602,697	4842	803.4	604,228	5177	856.8	0.94 (0.90-0.97)
	All cause mortality		602,697	4909	814.5	604,228	5275	873.0	0.93 (0.90-0.97) 0.93 ((0.79-1.10)
If applied in Japan	Cervical cancer	Mortality	602,697	16.6	2.8	604,228	24.3	4.02	0.69 (0.37-128)

*a: rate ratio of the mortality adjusted by world standard population

*b:HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesionn

ref 5: HPV Screening for Cervical Cancer in Rural India (Sankaranarayanan et al 2009) [5]

Rural: Since 1999, Total 52 clusters were randomized: 13 clusters each for 4 groups Screening methods: **HPV testing**			Screening **(HPV)** N=34,126			Control (usual care) N=31488			Odds ratio (OR)/hazard ratio (HR)
			Person-years	n	Rate /100,000 p-y	Person-years	n	Rate /100,000 p-y	Crude OR (95%CI) Age adjusted HR (95%CI)
Subjects: N=131,746 Healty women aged 30 to 59 year	CIN2,3 *c		268,185	245	91.4				
	Cervical cancer	Incidence	268,185	127	47.4	247,895	118	47.6	0.99 (0.77-1.28) **1.05 (0.77–1.43)**
		Mortality	268,674	34	12.7	248,175	64	25.8	0.49 (0.32-0.74) **0.52 (0.33–0.83)**
If applied in Japan	Cervical cancer	Mortality	268,674	5	2.0	248,175	10	4.02	**0.49 (0.17-1.41)**
Rural: Since 1999, Total 52 clusters were randomized: 13 clusters each for 4 groups Screening methods: cytologic testing **(PAP)**			Screening **(PAP)** N=32,058			Control (usual care) N=31488			odds ratio (OR)/hazard ratio (HR)
			Person-years	n	Rate /100,000 p-y	Person-years	n	Rate /100,000 p-y	Crude OR (95%CI) Age adjusted HR (95%CI)
Subjects: N=131,746 Healty women aged 30 to 59 year	CIN2,3 *c		250,523	262	104.6				
	Cervical cancer	Incidence	250,523	152	60.7	247,895	118	47.6	**1.27 (1.00-1.62) 1.34 (0.99–1.82)**
		Mortality	251,144	54	21.5	248,175	64	25.8	**0.83 (0.58-1.20) 0.89 (0.62–1.27)**
If applied in Japan	Cervical cancer	Mortality	251,144	8	3.4	248,175	10	4.02	**0.83 (0.33-2.09)**
Rural: Since 1999, Total 52 clusters were randomized: 13 clusters each for 4 groups Screening methods: Visual inspection **(VIP)**			Screening **(VIP)** N=34,074			Control (usual care) N=31488			odds ratio (OR)/hazard ratio (HR)
			Person-years	n	Rate /100,000 p-y	Person-years	n	Rate /100,000 p-y	Crude OR (95%CI) Age adjusted HR (95%CI)
Subjects: N=131,746 Healty women aged 30 to 59 year	CIN2,3 *c		267,326	195	72.9				
	Cervical cancer	Incidence	267,326	157	58.7	247,895	118	47.6	**1.23 (0.97-1.57) 1.30 (0.95–1.78)**
		Mortality	267,917	56	20.9	248,175	64	25.8	**0.81 (0.57-1.16) 0.86 (0.60–1.25)**
If applied in Japan	Cervical cancer	Mortality	267,917	9	3.3	248,175	10	4.02	**0.81 (0.33-2.01)**

*c:: CIN: Cervical Intraepithelial Neoplasia

It was reparted that there was no significant reduction in the rate of death from any cause in the intervention groups, as compared with the control group (data nc shown).

mortality had been basically decreasing in all groups before the active screening. This decreasing trend once plateaued for about 15 years, and then started decreasing again. The time at which the decreasing trend turned to plateau coincide with the time when people who had been adolescents during the First World War (1914-1918) reached that age group. It can be inferred that poor nutrition during the war led to persistent infection with HPV.

Indian Study: Inadequate Evidence

There are 3 long-term clinical trials that compared women who were observed without screening and those who were screened with any one of the 3 methods: cytological examination, HPV detection and visual inspection with acetic acid (VIA). These trials were conducted actively in India, involving women aged 30-64 [4-6].

These trials are not double blinded RCTs, but cluster-RCTs. In one cluster, all participants were screened while in another cluster, all were assigned to be given usual care as the controlled group. In the screened cluster, the participants were likely to be instructed and observed more intensively than those in the usual care control group. Therefore, this method tends to produce bias for favorable results for interventions. In fact, in one of the studies, not only total mortality and mortality from cervical cancer, but all kinds of mortality decreased in the intervention (screened) group

Table: Summary of the cluster randomized controlled studies on the efficacy of cervical screening (from ref 4-6)

ref 6: Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial (Sankaranarayanan et al 2007) [6]

Dindigul(Rural), average 5.6 years since 2000 Screening method: Visual inspection **(VIP)** Subjects: Healty women aged 30 to 59 year			Screening Group N=49,311 Screening done N=31,343			Control (usual care))N=30,958			Hazard ratio (HR)	
			Person-years	n	Rate /100,000 p-y	Person-years	n	Rate /100,000 p-y	Crude HR (95%CI)	Adjusted HR (95%CI)
compared 57 clusters each for screening and control groups	Cervical cancer	CIN2,3 *c	31343人	218						
		Incidence	274,023	167	60.9	178,394	158	88.6	0·67 (0·52–0·85)	0·75 (0·59–0·95)
		Mortality	274,430	83	30.2	178,781	92	51.5	0·59 (0·43–0·80)	0·65 (0·47–0·89)
	Mortality from other causes		274,430	1220	444.6	178,781	885	495.0	0.90 (0.82-0.98)	
	All cause mortality		274,430	1303	474.8	178,781	977	546.5	0.87 (0.80-0.94)	0·87 (0·78–0·96) ***d**
If applied in Japan	Cervical cancer	Mortality	274,430	6.5	2.4	178,781	7.2	4.02	**0.59 (0.20-1.70)**	

*c:: CIN: Cervical Intraepithelial Neoplasia) *d: Rate Ratio of the mortality adjusted by world standard population.

[6]. In another study, age-adjusted mortality rate ratio was not significant, but without age adjustment, mortality from other causes decreased [6]. Therefore, there were probably problems in the method of observation and how the participants were dealt with.

Mortality rate (/100,000 person-years) from cervical cancer without screening was 16 in urban areas [4] and approximately 50 to 25 in rural areas [5,6].

In Japan, mortality rate (/100,000 person-years) from cervical cancer among women aged 30-64 and 20-69 (target age group of the screening) was 4.5 and 4.02 in 2015, respectively (calculated based on the vital statistics [7]). This means that mortality from cervical cancer in India at the time of the studies was 3-12 folds higher than that in Japan in 2015.

In the Indian trials, when cervical intraepithelial neoplasia (CIN2 and CIN3), a precursor lesion of cervical cancer, was found by screening, treatments such as cryosurgery and electrocautery were given. Consequently, when the statistically significant results were yielded, the studies suggested that screening approximately 5,000 people [6], 8,000 people [5], or 20,000 people [4,5] reduced 1 cervical cancer death.

In Japan, cytological examination is the common method for screening. Only 1 of the Indian trials examined this method [5], and no significant reduction in mortality was observed. (The implication of this result will be explained below.)

There is also only 1 trial that studied HPV detection as a screening method [5]. In this RCT, the screening significantly reduced mortality.

Another method, in which acetic acid was applied to cervix to detect abnormality (VIA), was conducted in all 3 clinical trials. In the trials whose main objective was to demonstrate the efficacy of this method [4,6], mortality decreased significantly. However, in another trial whose main objective was to test the efficacy of HPV testing, screening using VIA did not significantly reduce mortality [5].

The results of the 3 trials are summarized in **Table**. For more details about the evidence, please refer to **Table**.

Screening in Japan

Extrapolation of the results of Indian studies to screening in Japan shows that by screening 40,000 – 150,000 persons would reduce 1 cervical cancer death. However, even if the same number of people are followed up for the same period of time, no significant reduction would be demonstrated (**Table**).

Screening by cytological examination requires about 6,000 yen per person just as a cost of testing. In order to reduce one death from cervical cancer, 240 million – 900 million yen (or 2.7 to 10 million dollars) would be needed.

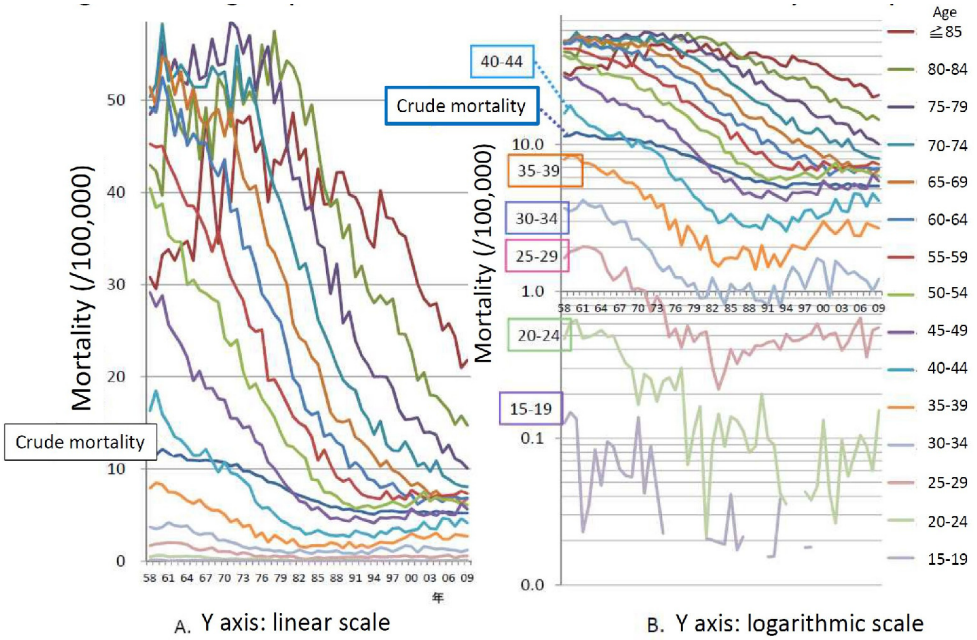
Moreover, this calculation rests on the premise that screening and surgical treatment on precursor lesions of cervical cancer are not harmful. Harms of surgeries and unnecessary anticancer agents are unknown as they were not reported in any of the 3 studies.

After all, the efficacy of the screening is unclear even in a country where uptake of screening was as high as 85% as shown in the English study.

Even if screening is proven to be effective in some countries where incidence of cervical cancer is very high, in countries like Japan and England, where mortality from cervical cancer has become low, no marked effectiveness of screening is observed.

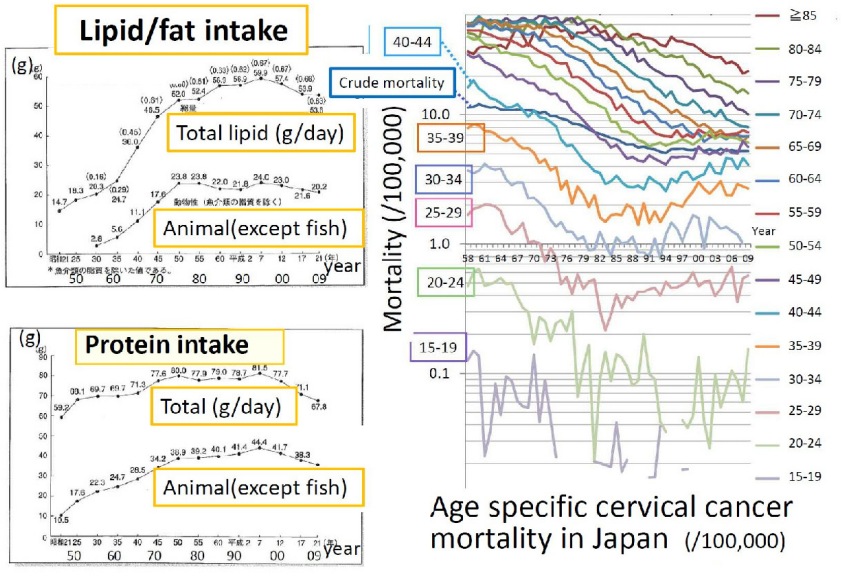
Screening takes money and time. In addition, if one is diagnosed with a preneoplastic lesion, she will continue to worry about it even if the lesion is removed by a simple surgery, electrocautery or cryosurgery. Even if screening might have minor benefits, various harms should be considered and carefully weighed against them.

Figure 3: Age specific cervical cancer mortality in Japan



1. Mortality from cervical cancer has decreased dramatically since 1958.
2. Why is HPV vaccine necessary?
3. Is it true that HPV vaccine is free from harm?

Figure 4: Lipid/fat intake and cervical cancer mortality in Japan



Inverse relation between fat intake and mortality

The TIP (Apr. 2013) [8] discusses relation between mortality from cervical cancer and nutritional intake in Japan in detail. In Japan, people who were adolescents during the Sino-Japanese War and the Russo-Japanese War seem to have the highest mortality from cervical cancer at whatever age they reach.

Except for this age group, mortality from cervical cancer rapidly decreased as fat intake increased after the Second World War. However, in 1990's after so-called the bubble economy had collapsed and the economy had declined due to bankruptcy of major corporations, fat intake decreased. Inversely, during this period, morality from cervical cancer in any age groups below age 60 plateaued or slightly increased (see **Figure 3** for more details). This inverse relationship is statistically significant in people aged 20-59 when analyzed by 5 year age group ($p<0.001$). It is also significant in people aged 15-19 and 60-74 when analyzed by 5 year age group ($p<0.05$).

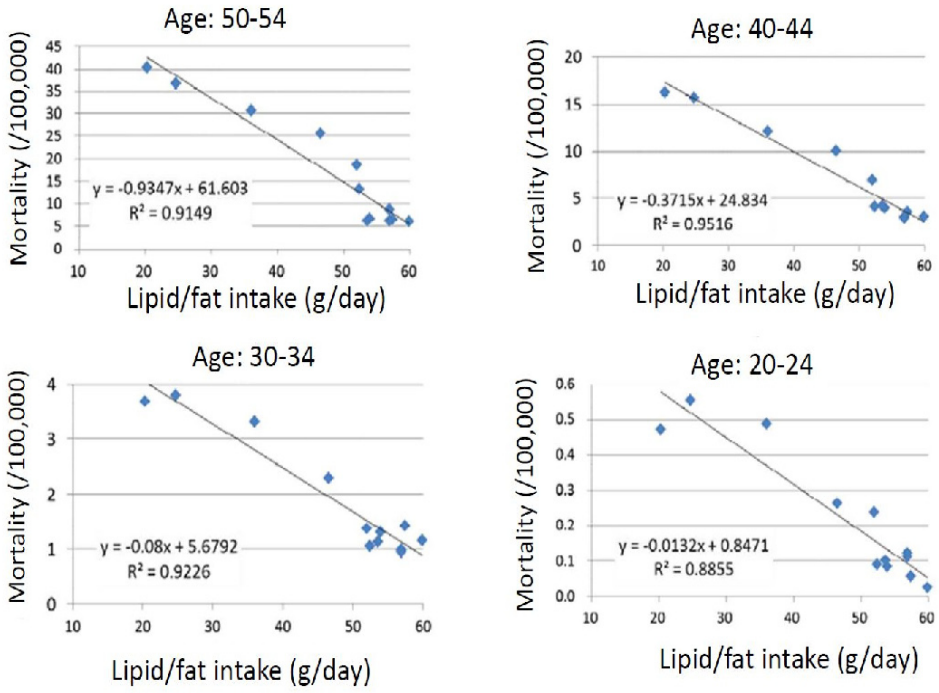
Similarly, inverse relationship was confirmed between mortality from cervical cancer and protein intake in many age groups. However, relationship with fat intake tends to be stronger.

Having adequate sleep without hypnotics is important for good health.

Sleep and screening are seemingly unrelated. However, it is more effective to have adequate sleep and nutrition than to spend billions of yen for screening to reduce 1 cervical cancer death. Here is the brief explanation.

According to a report that studied the relationship between the hours of sleep and life expectancy [9], most people usually

Figure 5: Inverse association between lipid/fat intake and cervical cancer mortality in various age groups (ref 8)



had about 8 hours of sleep. When they were allowed to sleep as much as they wanted, their hours of sleep increased by about 3 hours as compared with their usual hours of sleep. After reaching the peak, the hours of sleep gradually started decreasing and stayed at about 8.5 hours. Suppose this is how to identify optimal hours of sleep, it is 8.5-8.9 hours for people aged 18-32 and 7.4 hours for people aged 60-76 [10,11]. Measurements were made of hormone levels before and after the participants had secured the optimal hours of sleep. In the latter, levels of stress hormones was lower and insulin level was likely to be higher. Glucose level was also significantly lower [10].

According to this result, the optimal hours of sleep is longer than what we usually think, and securing the optimal hours of sleep might help reduce stress and contribute to better health. Risk ratio for death is high in people who usually sleep for 5-6 hours [9]. This is probably because a lack of sleep can be a great stressor.

Another study suggests that people who experience insomnia once or twice (or even 10 times) a month tend to live longer than those who never do. It also reports that using hypnotics for insomnia increases mortality risk by about 25%, and this is as risky as having one major illness [9].

For healthy living, it can be concluded that securing appropriate hours of sleep to reduce stress and taking nutritionally balanced diet are the best way [12].

In Practice

HPV vaccine should not be used. Moreover, no evidence suggests that screening reduces mortality from cervical cancer. We rather recommend to take proper nutrition, including enough fat and protein, and have adequate sleep (more than 8 hours) without using hypnotics.

References

1) Med Watcher Japan. Refutation_of_GACVS_statement (Dec 17 2015)_ on_the safety_of_HPV_ vaccines by WHO http://www.yakugai.gr.jp/topics/file/refutation_of_gacvs_statement_on_ safety_of_hpv_vaccines_20151217_japanese.pdf

2) 1. Gøtzsche PC, Jefferson T, Auken M, Brinth L. Complaint to the European ombudsman over maladministration at the European Medicines Agency (EMA) in relation to the safety of the HPV vaccines. http://nordic.cochrane.org/sites/nordic.cochrane.org/files/public/ uploads/ResearchHighlights/Complaint-to-ombudsman-over-EMA.pdf [accessed 27.01.17]

3) Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999 Apr 3;318(7188):904-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC27810/

4) Shastri SS, Mittra I, Mishra GA, Gupta S, Dikshit R, Singh S, Badwe RA. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. J Natl Cancer Inst. 2014 Mar;106(3):dju009. doi: 10.1093/jnci/dju0 https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/dju009

5) HPV screening for cervical cancer in rural India. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM, Hingmire S, Malvi SG, Thorat R, Kothari A, Chinoy R, Kelkar R, Kane S, Desai S, Keskar VR, Rajeshwarkar R, Panse N, Dinshaw KA. N Engl J Med. 2009 Apr 2;360(14):1385-94. doi: 10.1056/ NEJMoa0808516. http://www.nejm.org/doi/pdf/10.1056/NEJMoa0808516

6) Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, Fayette JM, Cherian J.Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet. 2007 Aug 4;370(9585):398-406. https://www.ncbi.nlm.nih.gov/pubmed/17679017

7) Japanese Vital Statistics http://www.e-stat.go.jp/SG1/estat/OtherList.do?bid=000001041646&cycode=7

8) Hama R et al、Epidemiology of cervical cancer and HPV vaccine. The Informed Prescriber 2013:28(2):27-31.(in Japanese) http://www.npojip. org/contents/link/tip-free/2013/2013_04.pdf

9) Kripke DF, Garfinkel L, Wingard DL et al. Mortality associated with sleep duration and insomnia. Arch Gen Psychiatry. 2002 Feb;59(2):131-6. https://www.ncbi.nlm.nih.gov/pubmed/11825133

10) Klerman EB, Dijk DJ. Age-related reduction in the maximal capacity for sleep--implications for insomnia. Curr Biol. 2008 Aug 5;18(15):1118-23. file:///C:/Users/Roku/Downloads/srep35812.pdf

11) Kitamura S, Katayose Y, Nakazaki K et al. Estimating individual optimal sleep duration and potential sleep debt. Sci Rep. 2016 Oct 24;6:35812. http://www.nature.com/articles/srep35812

12) Hama R、How to stop your medicines、San-go-kan、2017

Pneumococcal and Hib vaccines for children

Harms may outweigh benefits: not recommended

Translation from Japanese edition of Med Check-TIP 2017: Jul (No 72) :83-86

Abstract:

- Total 58 persons died shortly after inoculation of Hib vaccines and/or pneumococcal conjugate vaccine (PC vaccine) between 2010 and 2016 (average 9.3 deaths per year over about 6 years since 2011), and 48 of them died of sudden unexpected death (SUD). This figure (48 sudden deaths/58) suggests that sudden death occurs 27 times more frequently in the vaccinated persons, compared with the non-vaccinated (in 2009) of the same age group.
- The number of deaths due to bacterial meningitis had been already decreasing before the routine vaccination started in 2010. The actual number of deaths per year since 2010 was 4.5 while the number estimated based on the previous decreasing trend was 7.0. The actual number of death was smaller by average 2.5/year than that estimated by the decreasing trend.
- However, the number of deaths shortly after the vaccines was 9.3 persons/year. In other words, harm of vaccination might outweigh its benefits. Therefore, PC and Hib vaccines are not recommended for children.
- S. pneumoniae and Hib are normal bacterial flora. Development of serious infections caused by these bacteria are associated with inappropriate nutrition and environment, air pollution, and smokers in the household. It is necessary to explain to guardians that they can improve these factors and have a choice not to have their children vaccinated.

Keywords:
pneumococcal conjugated vaccine, Hib vaccine, bacterial meningitis, bacterial pneumonia, mortality, sudden death, SUD

Introduction

Pneumococcus (streptococcus pneumoniae) and H.influenzae type B (Hib) are normal bacterial flora that may transiently live in nose and throat of many people. However, they might occasionally cause bacterial meningitis, bacterial pneumonia and sepsis, and Hib might occasionally cause acute epiglottitis, which may lead to death or sequelae.

In order to prevent them, Hib vaccine (ActHIB) and pneumococcal conjugate (PC) vaccine (Prevenar, currently Prevenar 13) were developed. In March 2011, sudden deaths occurred in succession after administration of these vaccines, and the vaccination was temporarily withheld. However, it was resumed in April, within less than a month [1,2]. At that time, this was a controversial issue among editorial members and advisors of the Kusuri-no-Check (predecessor of the present Med Check-TIP). Clinical pediatricians argued that the vaccinations had been effective in reducing severe bacterial infections, and thus meaningful. Tanida, an expert in infectious diseases said that resuming the vaccinations was appropriate, but all the cases needed to be examined. Hama, an expert in pharmacovigilance insisted that although there were only limited data, it was too early to resume the vaccination at that time [2].

In order to have our subscribers to think together about efficacy and safety of PC vaccine and Hib vaccine for children, the Med Check-TIP No. 70 [3] introduced some data necessary for the review. However, since much had been already discussed in TIP [1] and Kusuri-no-check [2], the Med Check-TIP No. 70 did not present all the information. Because the information is important, in this article, some information is extracted and explained together with additional information.

Pneumococcus and Hib are normal bacteria

Pneumococcus (streptococcus pneumoniae) and Hib are carried by most infants for a while after birth. They carry and eliminate various types of pneumococcus and Hib, and repeat this cycle. After the first 6 months of life, they are carried by 20%-50% of infants [4-6] and are eliminated after some time [4]. However, because there are many types of pneumococcus

and Hib, even if one type is eliminated, another type is carried and is later eliminated, and this process is repeated. According to the reference 1, within the survey period of 6 months, at least 20 different types of bacteria were newly brought in, and 15 types of Haemophilus influenzae (this is bacteria and not influenza virus) disappeared in one group (a kindergarten for 4-6 year-old children).

The research also studied whether the children had had rhinitis, sinusitis and otitis media, and found almost no difference between the carriers and non-carriers [5]. Most children seem to get infected and develop mild rhinitis and sinusitis as they stay with other children, and this is part of their growth. Whether they develop chronic inflammation or not may greatly depend on their nutritional condition, environment, air pollution, and presence of smokers in the household such as their parents.

Causative organisms for bacterial meningitis and death

The three diseases, namely bacterial meningitis, bacterial pneumonia, and sepsis, are called invasive bacterial infections (IBI). In any of these, hospitalization and treatment with antibiotics are required. Sepsis and bacterial meningitis are especially serious infections that easily lead to death.

Types of causative organisms for bacterial meningitis are well documented. The most common causative organism is Haemophilus influenza (H. influenza). It is associated with approximately 50% of cases in any studies, and in most cases, type B (Hib) is involved [7-9].

For mortality from bacterial pneumonia (1996-2015), statics for pneumococcus and Hib as causative organisms are recorded separately. Pneumonia deaths caused by pneumococcus and Hib account for 4.5% and 1.5% of all pneumonia deaths, respectively (total 6%).

A recent study reported that after routine PC and Hib vaccines were launched, among bacterial meningitis patients, the numbers of patients whose causative organism was Hib and pneumococcus fell by 88% and 80%, respectively, as compared with the previous numbers [9]. Based on such a report, the vaccination is commonly believed to be effective.

Change in deaths due to sepsis, bacterial meningitis, and bacterial pneumonia

The number of deaths from sepsis, bacterial meningitis and bacterial pneumonia has been decreasing recently. Although a population of children aged 0-4 itself has been shrinking, the number of deaths is decreasing even when it is recalculated per population.

In the Med-Check-TIP No. 70 (p.31) and No. 71 (p.72), only the change in the number of deaths was shown. In this article, mortality rate (deaths/100,000 person-years) is shown (**Figure**: Note that in the figure, the vertical axis is logarithmic scale).

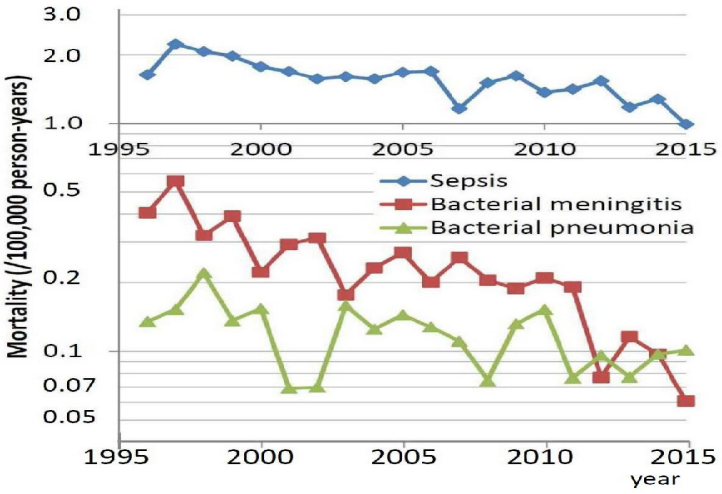
The figure shows that mortality from sepsis, bacterial meningitis, and bacterial pneumonia has been decreasing steadily year by year. Sepsis and meningitis are often caused by Hib. Therefore, if the decreasing trend after 2009, beginning of the routine vaccination, is more marked than that in and before 2008, Hib vaccination is presumed to have contributed to the decrease. Similarly, if marked change in mortality due to bacterial pneumonia is found between before and after 2009, pneumococcus vaccine presumably had a great impact on the change.

Hib vaccine (ActHIB) and Pneumococcus conjugate vaccine (Prevenar) were brought to market in 2009 and 2010, respectively. Assuming that previous decreasing trend in sepsis and bacterial meningitis continued after 2008, average mortality between 2012 and 2015 was calculated and compared with the actual number of deaths during the same period.

The average mortality from bacterial pneumonia was estimated based on the decreasing trend between 1996 and 2009. The summary is shown in the **Table 1**.

When discussed in the Med-Check-TIP No. 71, the average number of deaths per year between 2012 and 2015 from bacterial meningitis was 8.7, estimated by decreasing trends of the

Figure: Mortality trends of three invasive bacterial infections (1996-2015)



The Figure is constructed by the author using vital statistics [10]. Note that the vertical axis is logarithmic scale. Three invasive bacterial infections include sepsis, bacterial meningitis and bacterial pneumonia.

Table 1: Comparison of average mortality rate and annual number of deaths between 2012-2015 (estimated by the decreasing trends and observed data)

	Mortality rate (/100,000 person-years)		Number of death (/year)		
	Estimated	Observed	Estimated	Observed	P value *
Sepsis	1.20	1.25	61.6	63.8	0.8857
Bacterial meningitis	0.137	0.088	7.0	4.5	0.0286
Bacterial pneumonia	0.091	0.093	4.7	4.8	0.3429

* P values were calculated by Mann-Whitney U test

number of deaths per year, while the actual number was 4.5 in the same period. This means that the vaccine presumably contributed to reduce the number of deaths by average 4.2 per year. However, as a result of recalculation, considering the population of children, the estimated number of deaths per year from bacterial meningitis is 7.0 between 2012 and 2015. Therefore, the decrease is only by average 2.5 deaths per year. There was no significant difference in mortality from sepsis and bacterial pneumonia (**Table 1**).

Total 4 children and 2 children died from pneumonia due to streptococcus pneumoniae over 14 years between 1996 and 2009, and over 6 years between 2010 and 2015 respectively. Launching of PC vaccine did not have any impact.

Strong association between sudden death and vaccination

According to the Japanese vital statistics [10], the number of deaths among infants aged 2 months to 4 years old was 1,790 in 2015. Of these, when deaths from sudden infant death syndrome (SIDS) and deaths from unknown cause are classified as sudden unexpected death (SUD), the total number of deaths from SUD is 272 (this is the figure for a general population).

Total 62 deaths after inoculation of various types of vaccines were reported to the Adverse Reaction Working Group of the Immunization Vaccine Subcommittee, the Ministry of Health, Labour and Welfare Science Council between 2011 and May, 2017 [11]. Among them, 60 deaths were reported after vaccination for infants (two deaths were the cases after receiving HPV vaccine). Of the 60 deaths, 58 deaths occurred after Hib vaccine and/or PC vaccine (within approximately 6 years until Oct. 31, 2016). Among them, 48 deaths were due to SUD (***Note 1***).

> ***Note 1*** : *Proportions of deaths from SUD were not so different by the type of vaccines:. Recipients of 2 vaccines (Hib vaccine and PC vaccine) only= 84%(16/19), 2 vaccines + other vaccines= 82 % (22/25), Hib + others= 83%(5/6), Hib only= 75%(3/4), PC + others= 100%(2/2)、PC only= none、Vaccines other than 2 vaccines= 50% (1/2).*

The odds ratio of SUD/non-SUD in causes of death among a general population (odds=272/(1790-272)) and SUD/non-SUD in causes of death after inoculation of the 2 vaccines (odds=48/(58-48)) is 26.8 (95%CI: 13.4-53.6, p<0.0001). This suggests extremely strong association between the vaccinations and sudden unexpected death (SUD).

Total 4 deaths were reported after vaccinations other than Hib and PC vaccines. They include 2 deaths after HPV vaccine and another 2 deaths after other vaccinations. One SUD was reported each in HPV vaccine and other vaccines (total 2 deaths from SUD).

In 58 infants who died after Hib and/or PC vaccines, the duration between the inoculation and death was 1 day (approximately within 24 hours) in 25 infants, 2 days in 7 infants, 3 days in 8 infants, 4-7 days in 9 infants, 8-14 days in 4 infants, and 15 days or longer in 5 infants. The longest duration was 41 days (1 infant). More than half of SUDs concentrate on day 1 and 2, and more than two-thirds occurred by day 3. This also shows strong association between sudden unexpected death and the vaccination.

Suppose a half of infants of the same age group have received PC and/or Hib vaccines (immunization rate 50%), attributable risk to sudden death associated with these vaccines is approximately 93%. Therefore, 45 of 48 sudden deaths are presumed to be caused by the vaccination.

On the other hand, benefits of the vaccines include prevention of permanent injury due to bacterial meningitis. However, incidence of permanent injury due to the vaccines is unknown.

Many sudden deaths occurred after the vaccination, including SIDS, SUD and/or death after status epilepticus. In such cases as SIDS and/or SUD, respiration was suppressed during sleep because even under hypoxic conditions, respiratory drive was not activated. When cardiac arrest continues for over 4 minutes, it causes some kind of brain damage. Otherwise, the condition may seem to be resolved, but delayed hypoxic encephalopathy might occur after 2-3 days, which leads to developmental regression. This might be falsely diagnosed simply as developmental disorder, and might not be recognized as the harm of the vaccination.

Apart from sudden death, the vaccination is highly likely to be associated with seizure and anaphylaxis, and these can lead to death. Even if the 2 vaccines might reduce the number

of deaths from bacterial meningitis by average 2.5 persons/year, it is noteworthy that they might cause additional 9.3 deaths/year.

Types of vaccinations and mortality

Hib and PC vaccines were associated with the most cases of deaths after vaccination. This section examines whether mortality from Hib vaccine and PC vaccine is higher than that from other vaccines. (See ***Note 2*** and foot note of the **Table 2** for the method of these estimations)

> ***Note 2*** : *If a vaccine is routinely given for 3 times, the average number of doses given was presumed to be 2.5. Based on this, the number of vaccine recipients was estimated, and mortality per 100,000 recipients was calculated (See Table 2 for details).*

As a result of our examination, mortality rate (deaths/100,000 vaccine recipients) after Hib vaccine is 0.52, and is the highest. Mortality rate from PC vaccine is 0.45, and that after rota virus vaccines (both) is 0.39 and quadrivalent vaccine (DPT + inactivated polio) is 0.23, followed by other vaccines such as inactivated polio, hepatitis B vaccine, and BCG (**Table 2**).

We estimated the mortality rate from each vaccine adjusted by the influence of multiple simultaneous vaccinations. According to the adjusted methods, the mortality rate from Hib vaccine remained the highest (**Table 2**).

The Ministry of Health, Labour and Welfare considers that when the number of deaths exceeds 0.5 deaths/100,000 doses, safety of the vaccine is questionable [11]. This is equivalent to more than 1 death/100,000 recipients when one child receives average 2 doses.

However, as shown in the **Figure**, **Table 1** and **Table 2**, the standard safety cut off (0.5 deaths/100,000 doses or 1 death/100,000 recipients) set by the ministry is fundamentally wrong. Mortality rate (/100,000 person-years) from bacterial meningitis before the start of Hib vaccination (2009) was already 0.2-0.3 and that from bacterial pneumonia before 2009 was already as low as 0.08-0.15. These mortality rates are far lower than the mortality rate (deaths/100,000

Table 2 : Estimated number of inoculation, persons vaccinated, number of death, mortality rate after vaccines and mortality rate due to invasive bacterial infections with and without vaccination program

Name of vaccine	Periods surveyed	Inoculation of vaccine			death *c		Mortality (/100,000 persons)				Mortality (/100,000 person-years)		
		Total doses	Estimated number of pearsons inoculated		unadj.	adj.	denominator: method *a		denominator: method *b		(E) estimated by decreasing trend without vaccine *d	(O) after vaccination program introduced	E-O
			estimated by *a	estimated by *b			unadj.	adj.	unadj.	adj.			
all vaccines					60								
Hib vaccine	**2008/12~2016/10/31**	**26,710,835**	**10,684,334**	**14,516,758**	**56**	**24.0**	**0.52**	**0.22**	**0.39**	**0.17**	**0.14*e**	**0.09**	**0.05**
PC vaccine	**2010/2~2016/10/31**	**26,609,051**	**10,643,620**	**14,461,441**	**48**	**18.0**	**0.45**	**0.17**	**0.33**	**0.12**	**0.09*f**	**0.09**	**0.00**
DPT trivalent	2013/4/1~2016/10/31	1,144,913	457,965	622,235	2	0.67	0.44	0.15	0.32	0.11			
Rota vaccine (Rotatec)	2013/4/1~2016/10/31	2,368,179	947,272	1,287,054	6	1.23	0.63	0.13	0.47	0.10			
Rota vaccine (Rotarix)	2013/4/1~2016/10/31	2,685,661	1,611,397	2,189,398	4	0.98	0.25	0.06	0.18	0.04			
Rota vaccine (both)			2,558,668	3,476,451	10	2.21	0.39	0.09	0.29	0.06			
DPT-P quadrivalent	2012/10~2016/10/31	14,968,445	5,987,378	8,135,024	14	3.60	0.23	0.06	0.17	0.04			
Inactivated polio vaccine	2012/8~2016/10/31	5,719,146	2,287,658	3,108,232	3	0.75	0.13	0.03	0.10	0.02			
Hepatitis B vaccine	2013/4/1~2016/10/31	15,337,927	6,135,171	8,335,830	7	1.40	0.11	0.02	0.08	0.02			
BCG	2013/4/1~2016/10/31	3,497,916	3,497,916	3,497,916	2	0.70	0.06	0.02	0.06	0.02			

*a : Methods for estimating the number of recipients (Method a): For the vaccines which are routinely administered 3 times, the average number of doses per person was assumed to be 2.5 times, which was used to estimate the number of recipients. For those which are routinely administered twice, such as Rotarix and influenza vaccine, the number was calculated as 2.5 X 2/3. For BCG, which is routinely administered once, the number of doses was used as the number of recipients.

*b : Methods for estimating the number of recipients (Method b) : For the average number of initial doses of Hib vaccine, which is routinely given 3 times, 1.84 was used because the number is based on the estimate of the manufacturer and was used by the Ministry of Labour, Health and Welfare.

*c : Adjustment by multiple simultaneous vaccination: If a single kind of vaccine was given, one death was counted for one person. If 2 kinds or 3 kinds of vaccines were given simultaneously, it is considered that 1/2 death or 1/3 death occurred after each vaccination, respectively. The number of deaths was divided by the number of types of vaccines given simultaneously, and the total number of death was calculated for each vaccine.

*d : Estimated mortality rate (/100,000 person-years) without vaccination: mortality rate (/100,000 person-years) over 4 years between 2012-2015 was estimated based on the decreasing trend since 1996.

*e : Estimated mortality rate (/100,000 person-years) from bacterial meningitis (0.14) : Suppose that Hib vaccination was not introduced, the mortality rate was estimated based on the methods as described in *d. Mortality rate (/100,000 person-years) after the introduction of Hib vaccination (0.09) is lower than that estimated without vaccination (0.14). However, the mortality rates after vaccination (0.22, 0.17) are much greater than the reduction (0.05). It is also higher than the estimated mortality rate without vaccination (0.14). This clearly shows that the harm outweighs benefits.

*f : Estimated mortality rate (/100,000 person-years) from bacterial pneumonia (0.09): Suppose that pneumococcal vaccination was not introduced, the mortality was estimated based on the methods as described in *d. No difference was observed in mortality rate (/100,000 person-years) before and after introduction of the vaccine (0.09 for both before and after the introduction). Mortality rate (/100,000 persons inoculated) after inoculation of the vaccine (0.17 or 0.12) is much higher that the difference (0.0). It is also higher than the estimated mortality without introduction of the vaccine. This clearly shows that the harm outweighs benefits.

recipients) after inoculation of these vaccines (0.52 and 0.45) (***Note 3***) .

> ***Note 3:*** *Mortality rate from bacterial meningitis or bacterial pneumonia is expressed by the number of deaths per 100,000 person-years, while mortality rate after inoculation of a vaccine is expressed by the number of deaths per 100,000 recipients of vaccine: the units used are different in these mortality rates. However, the longest duration between inoculation and death was 41 days, which was far shorter than one year. Hence, mortality rate after inoculation of these vaccines expressed by "the number of deaths/100,000 recipient-years" may be far higher than the mortality rate (/100,000 person-years) from bacterial meningitis or bacterial pneumonia.*

In randomized controlled studies

In randomized controlled studies (RCT), efficacy of neither vaccination is adequately confirmed. Below is an article published in TIP [1]. (see the abstracted article below, reference numbers are different)。

In practice

In clinical setting, the vaccination for infants is practiced as if there is no other choice. However, while it slightly reduces deaths from infections, it causes more deaths. This situation should be considered, and these vaccines are not recommended for children. It is important to explain the following 3 points to guardians. ① Pneumococcus and Hib are both normal bacterial flora. ② These bacteria are transiently carried by children and are later eliminated. ③ Development of serious infection is associated with inappropriate nutrition and environment, air pollution, and smokers in the household, and thus these factors should be improved. It is also necessary to explain them that they have a choice not to have their children vaccinated.

The Abstract of TIP (Results of RCTs)

There are two randomized controlled trials (RCTs) for Hib vaccine in developed countries [12,13]. One trial, which was conducted in Finland, showed marked effect of the vaccine [12]. However, in another trial involving Alaska natives [13], it was proven ineffective because little increase in antibody titers was observed.

In RCTs and a meta-analysis of case controlled studies [14] in developing countries, relative reduction in (radiologically confirmed) pneumonia was 18% with Hib vaccination, and was not significant (combined risk ratio :0.82, 95%CI: 0.67-1.02). It was significant in clinical pneumonia and clinical severe pneumonia. However, protective effect was only 4% (95%CI: 3-6%) and 6% (95%CI: 1-9%), respectively, suggesting minimum clinical significance.

A systematic review on pneumococcal vaccine [15] showed a marked result; protective efficacy (relative risk reduction) in invasive pneumonia due to bacteria of vaccine serotypes was 80% (95%CI: 58-90%, p<0.0001). This is based mainly on data from developing countries. However, protective effect on clinical pneumonia, severe clinical pneumonia, and radiologically confirmed pneumonia was 6% [15] to 7% [14], 7% [14], and 26% [14] to 27% [15], respectively. The most influential study was conducted in Gambia, Africa, in which mortality in the controlled group was extremely high: 5.6% (491/8719). In a trial conducted in the Philippines [17], the vaccine did not show any effect on pneumococcal invasive pneumonia including those of vaccine serotypes and non-vaccine serotypes. Trials in developed countries [12, 18, 19] did not show any consistent result.

As for RCTs on pneumococcal vaccine in developed countries, the vaccine was proven effective in one trial in the U.S. [20]. However, in Finland, it was shown to be effective in preventing only otitis media, but not pneumonia [18, 19].

On the other hand, in a RCT for Hib vaccine, increased aseptic meningitis and SIDS were reported, but no data were included [12]. RCTs for pneumococcal vaccine, 2 deaths due to volvulus of the bowel were reported [18, 19], but they were regarded as "not related" to the intervention.

References

1) Hama R、Honzawa T. A review on the Hib vaccine, pneumococcal conjugate vaccine and death、The Informed Prescriber 2011: 26(4): 54-60 (In Japanese)

2) Feature "Hib and Pneumococcal Conjugate vaccine" Kusuri-no-Check 2011：(43):30-53、58-68. (In Japanese)

3) Editorial team of MedCheck TIP、Pneumococcal Conjugate vaccine and Hib vaccine MedCheck TIP 2017: 17(70):31. (In Japanese)

4) Takahashi J et al. Dynamics of Haemophilus Influenzae in pharyngeal flora of a certain population-. Is the Haemophilus Influenzae a normal flora? J Infect Dis 1992: 66: 956-963. (In Japanese)

5) Hashida K et al, A study on the H. Influenzae and Streptcoccus pneumoniae in the nasopharynx of children in a nursery. Jpn Ear & Nose. 2006: 109: 821-829. (In Japanese)

6) Asahi E et al. Carrier rate of Haemophilus influenzae type b and bacterial flora of nasopharynx of suckling infants.J Infect Dis 1997: 71: 236-240. (In Japanese)

7) Kamiya S and Nakano T. The nation-wide surveilance on the invasive bacterial infection in children、IASR 2010: 31; 94-6. (In Japanese)

8) Committee on Public Health of Japan Pediatric Association (Nakayama Y, et al). The results of a questionnaire survey on systemic infection due to H. Influenzae in 2008. J Jpn Pediatric Association 2009: 38: 195-9.

9) Shinjoh M, et al. Recent trends in pediatric bacterial meningitis in Japan--a country where Haemophilus influenzae type b and Streptococcus pneumoniae conjugated vaccines have just been introduced. J Infect Chemother. 2014 Aug;20(8):477-83

10) Vital Statistics of Japan (death), in e-Stat (Statistics by the Japanese Government) http://www.e-stat.go.jp/SG1/estat/OtherList.do?bid=000001041646&cycode=7

11) Adverse Reaction Working Group of the Immunization Vaccine Subcommittee, the Ministry of Health, Labour and Welfare Science Council 2011- 2017 http://www.mhlw.go.jp/stf/shingi/shingi-kousei.html?tid=284075

12) Eskola J, et al. A randomized, prospective field trial of a conjugate vaccine in the protection of infants and young children against invasive Haemophilus influenzae type b disease. N Engl J Med. 1990 Nov 15;323(20):1381-7.

13) Ward J, et al. Limited efficacy of a Haemophilus influenzae type b conjugate vaccine in Alaska Native infants. The Alaska H. influenzae Vaccine Study Group. N Engl J Med. 1990 Nov 15;323(20):1393-401.

14) Theodoratou E, et al. The effect of Haemophilus influenzae type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality.Int J Epidemiol. 2010 Apr;39 Suppl 1:i172-85.

15) Lucero MG, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD004977.

16) Cutts FT, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005;365(9465): 1139-46.

17) Lucero MG, et al. Efficacy of an 11-valent pneumococcal conjugate vaccine against radiologically confirmed pneumonia among children less than 2 years of age in the Philippines: a randomized, double-blind, placebo-controlled trial. Pediatr Infect Dis J. 2009 Jun;28(6):455-62.

18) Eskola J, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. New Engl J Med 2001; 344(6):403–9.

19) Kilpi T, et al. Protective efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Inf Dis 2003; 37(9):1155–64.

20) Black S, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatric Infectious Disease Journal 2000;19(3):187–95.

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