衛生福利部
Ministry of Health and Welfare

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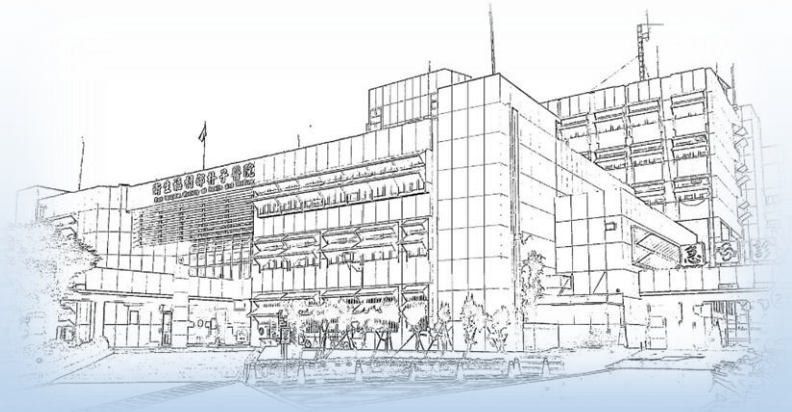

流感預防新契機- Adjuvanted Seasonal Influenza Vaccines

衛生福利部朴子醫院

醫務秘書 感染科

曾政尹 M.D., Ph.D.

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Ministry of Health and Welfare

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大綱

- Epidemiology & Burden of Influenza (including 65y+ Population)
- Vaccination & Immunosenescence
- Adjuvant Technology and Product (MF59)
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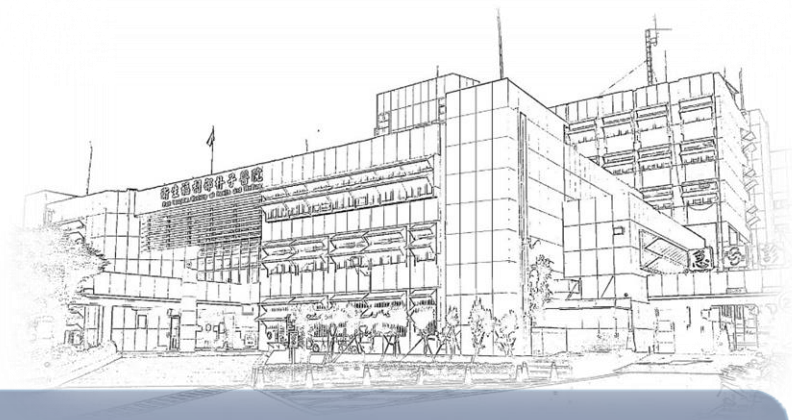

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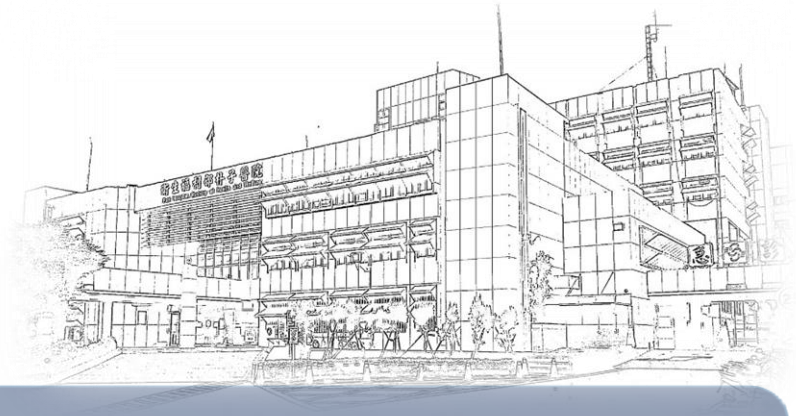
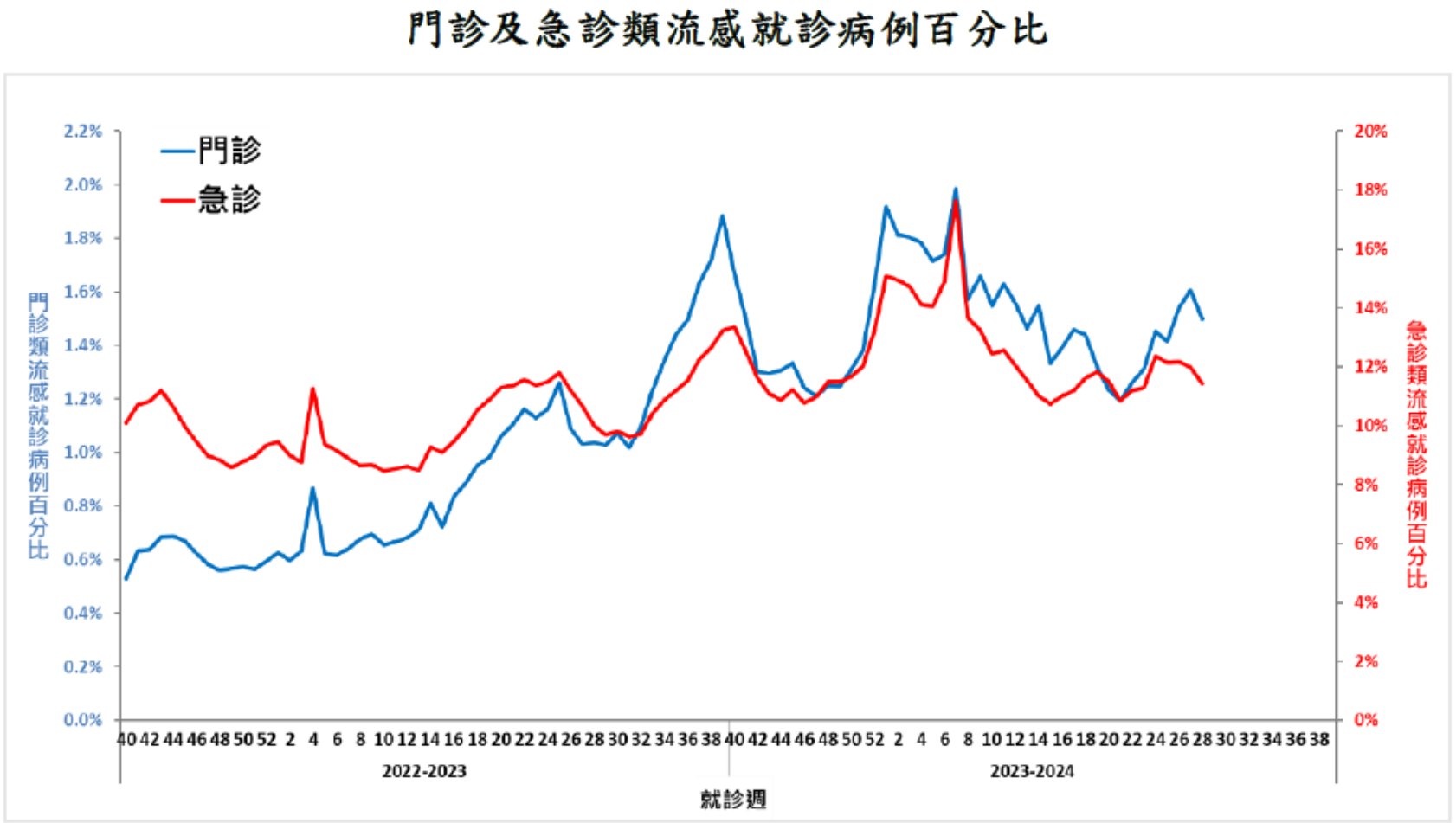
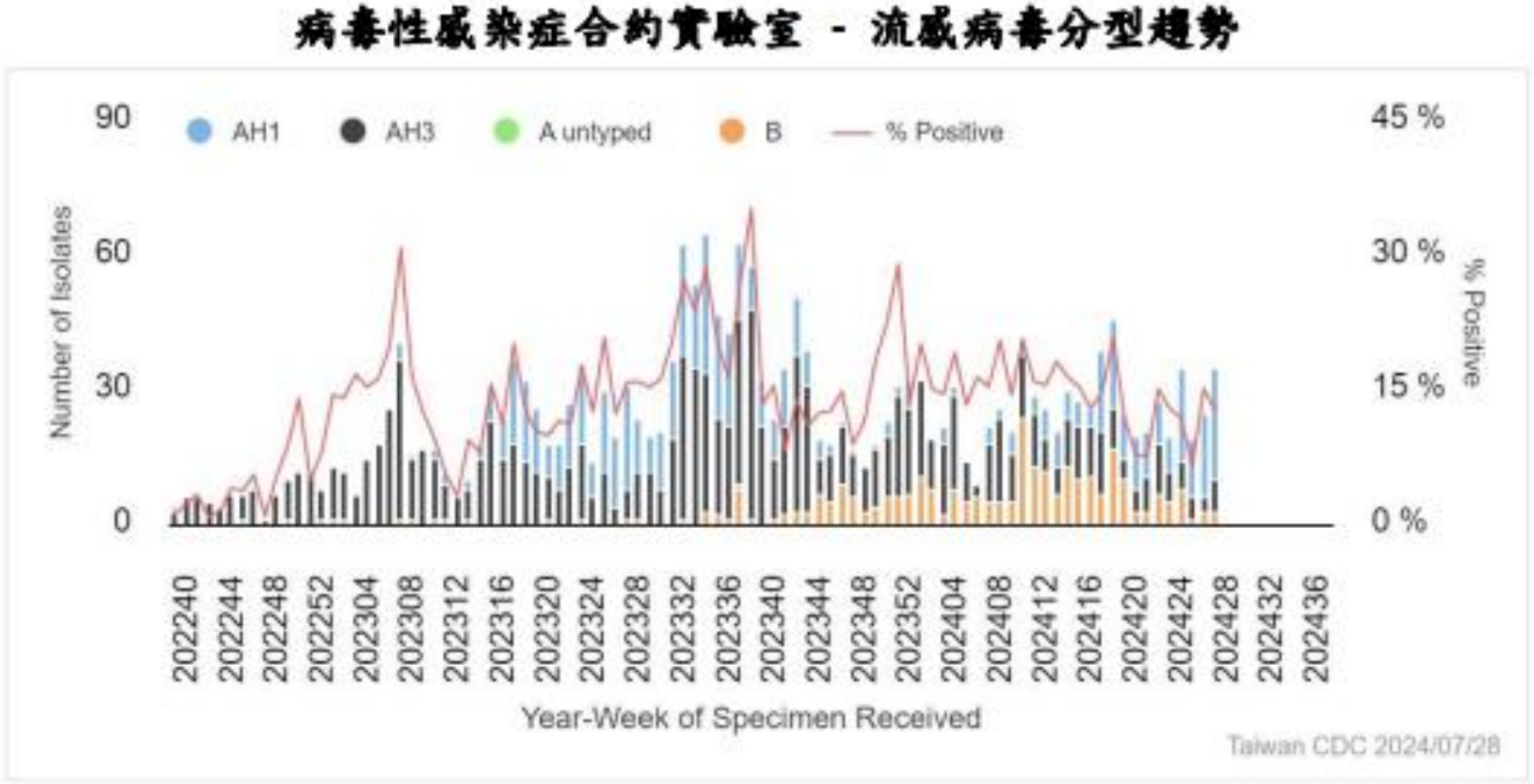


Epidemiology–近三年類流感就診趨勢



2024年第25週至第28週流感病毒分離件數A型高於B型，A/H1N1型占68.4%、A/H3N2型占18.3%、B型占13.2%。



流感併發重症比率(依年齡層)

2023-2024 流感季流感併發重症發生率及死亡率統計

年齡別	病例數	死亡數	每十萬人口累積發生率	每十萬人口累積死亡率
小於 3 歲	6	1	1.35	0.23
3-6 歲	29	3	3.89	0.40
7-18 歲	72	6	2.94	0.25
19-24 歲	8	1	0.52	0.06
25-49 歲	195	31	2.24	0.36
50-64 歲	298	42	5.63	0.79
65 歲以上	825	213	19.70	5.09
總計	1,433	297	6.13	1.27

- 疾管署統計，本流感季(2023年10/1起)截至2024/7/27，累計**1,433例流感併發重症。**
- 年齡層以**65歲以上**長者占**57%**為多
- **死亡297例，65歲以上**長者占**71%** (其中七成以上未接種流感疫苗)。

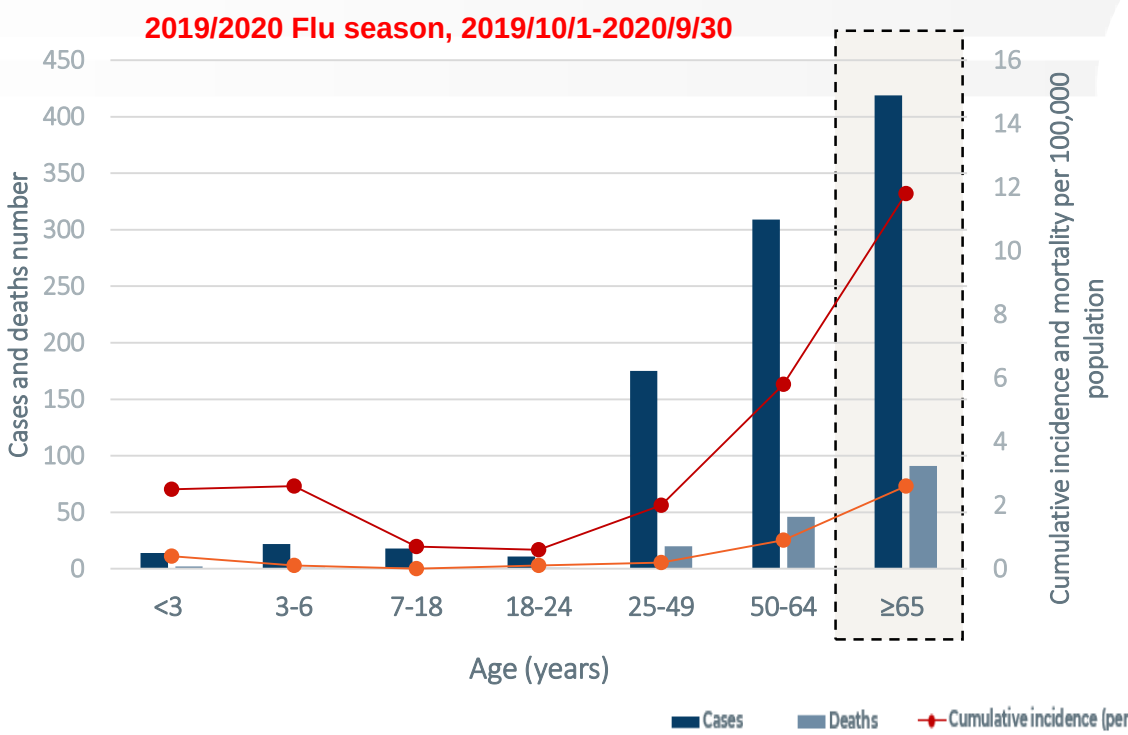
資料來源: 衛生福利部疾病管制署流感速訊 2024年第30週 (2024/7/21– 2024/7/27)

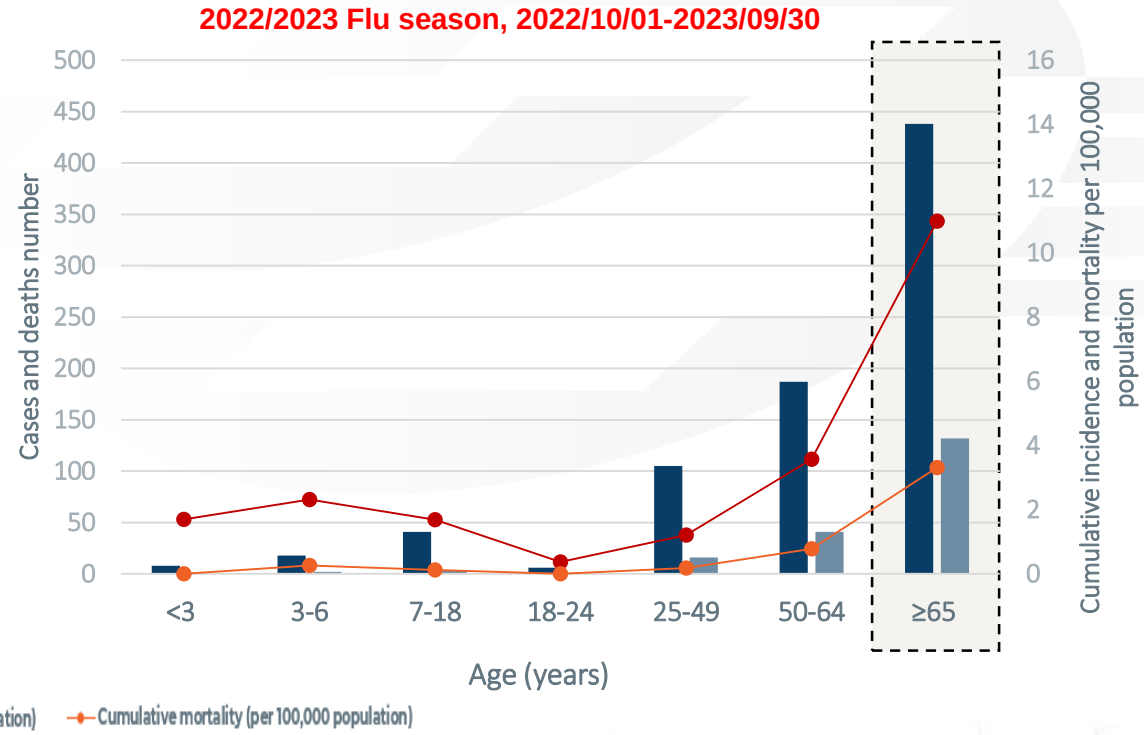
Influenza case with severe complications in Taiwan

(流感併發重症發生率及死亡率統計)

Adults ≥65 years of age experience the **highest influenza-related mortality and morbidity risk**.[1]

Influenza cases with severe complications. Cases and deaths number & incidence and mortality rate[2]

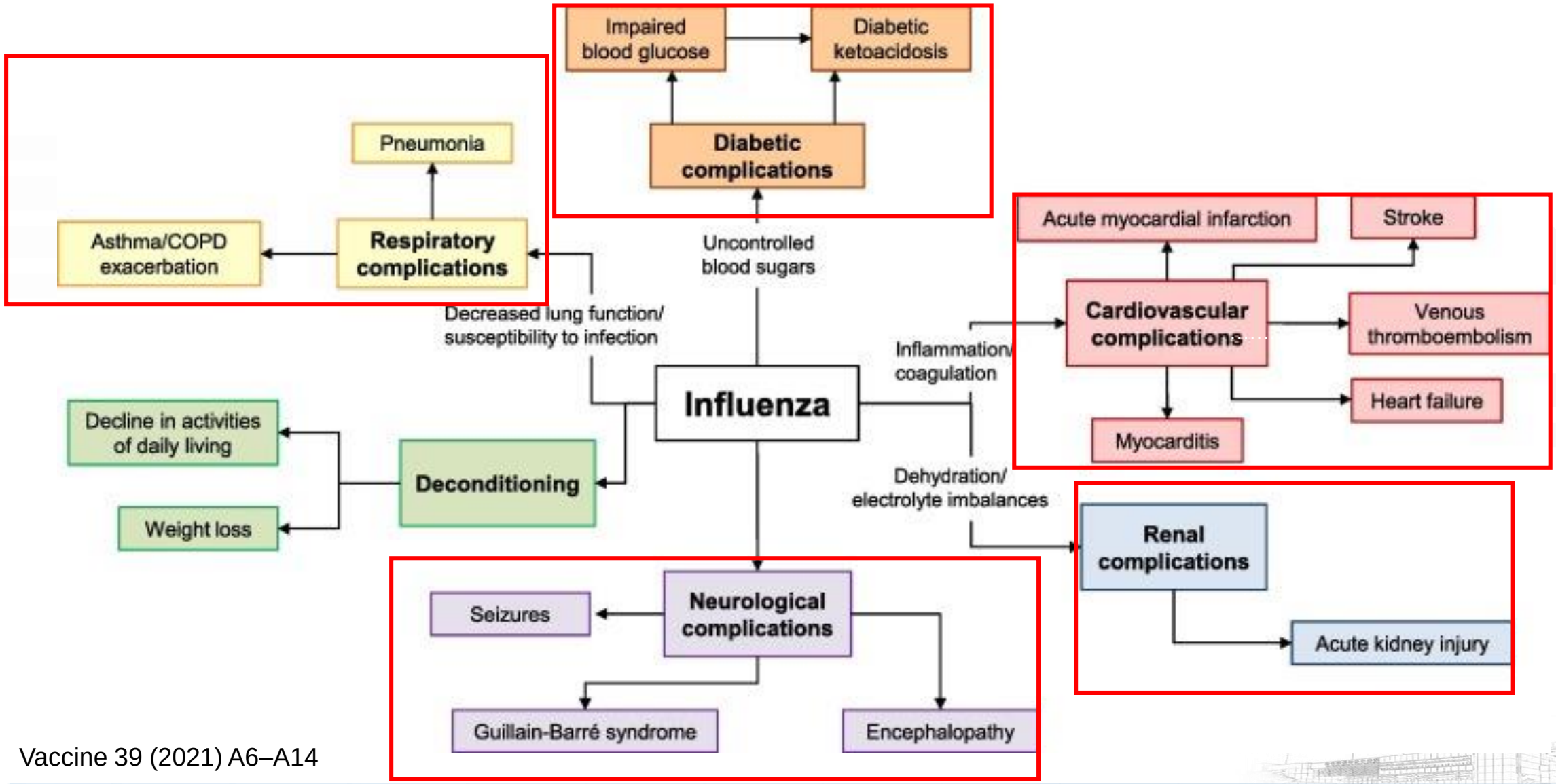




Length of influenza season is not constant and varies each year; data cut off for the above seasons are based on Influenza Express website

1.Taiwan Centers for Disease Control. Practical Guidelines for Prevention and Control of Seasonal Influenza. https://www.tda.org.tw/upload/NewsData/6388/6088.pdf?v=20237314928 Last accessed: 28 June,2023
2. Taiwan Centers for Disease Control. Influenza Express, Available from: https://www.cdc.gov.tw/En/Category/MPage/Utv3lzlSnTK-t6inZrBZsw Last accessed: 8 Nov, 2023

流感併發症



Vaccine 39 (2021) A6–A14

Seasonal influenza results in significant morbidity and mortality worldwide

Influenza is responsible for significant morbidity and mortality across the globe, regardless of national wealth[1]

It is estimated that **290 000 to 650 000 influenza-related respiratory deaths** occur annually worldwide, equivalent to 4.0–8.8 per 100 000 individuals per year[2] and around **2% of all respiratory deaths** each year[3]

Symptoms are typically respiratory in nature, but the infection can also trigger other outcomes such as:

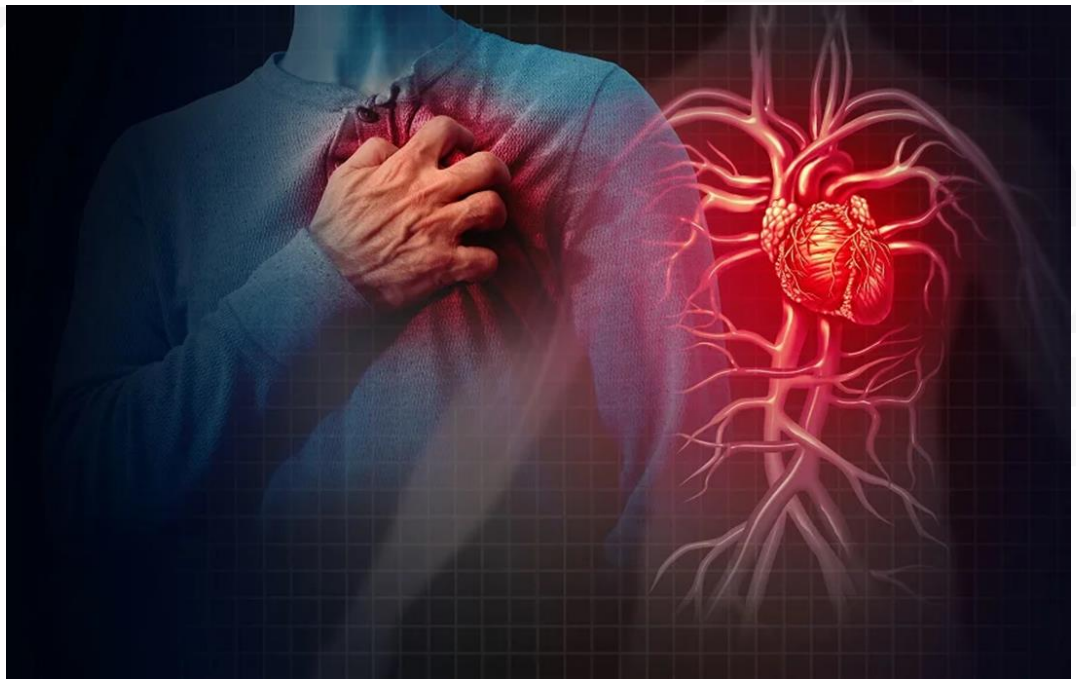
stroke[4]

acute myocardial infarction[4–6]

1. Sullivan SG, Cowling BJ. *Lancet Respir Med*. 2019;7(1):8–9; **2.** Iuliano AD, et al. *Lancet*. 2018;391(10127):1285–1300; **3.** Paget J, et al. *J Glob Health*. 2019;9(2):020421; **4.** Blackburn R, et al. *Clin Infect Dis*. 2018;67(1):8–17; **5.** Kwong JC, et al. *N Engl J Med*. 2018;378(4):345–353; **6.** Warren-Gash C, et al. *J Infect Dis*. 2012;206(11):1652–1659.

流感併發症

- 流感後的30天內，產生中風的事件的風險會提高。
- 急性呼吸道疾病(例如：流感)對心輸出量和功能有更直接的影響，增加了心肌梗塞和其他心臟事件的風險。



Published online 2020 Oct 8. doi: 10.1161/JAHA.120.016213

流感與肺癌風險增加有關–台灣研究

- 流感患者肺癌風險增加，1.09 倍相關(aOR 1.09，p<0.0001)
- 肺癌風險隨著累積接觸流感而略有增加(1-2次暴露：aOR 1.05；3-4次接觸：aOR 1.12；5次以上暴露：aOR 1.25)

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Association between the risk of lung cancer and influenza: A population-based nested case-control study

Ching-Fu Weng[a,b], Li-Ju Chen[c], Chih-Wan Lin[d], Ho-Min Chen[c], Henry Hsin-Chung Lee[e,f], Thai-Yen Ling[b,**], Fei-Yuan Hsiao[d,g,h,*]

Table 4
Sex differences in adjusted odds ratios for lung cancer and exposure to influenza.

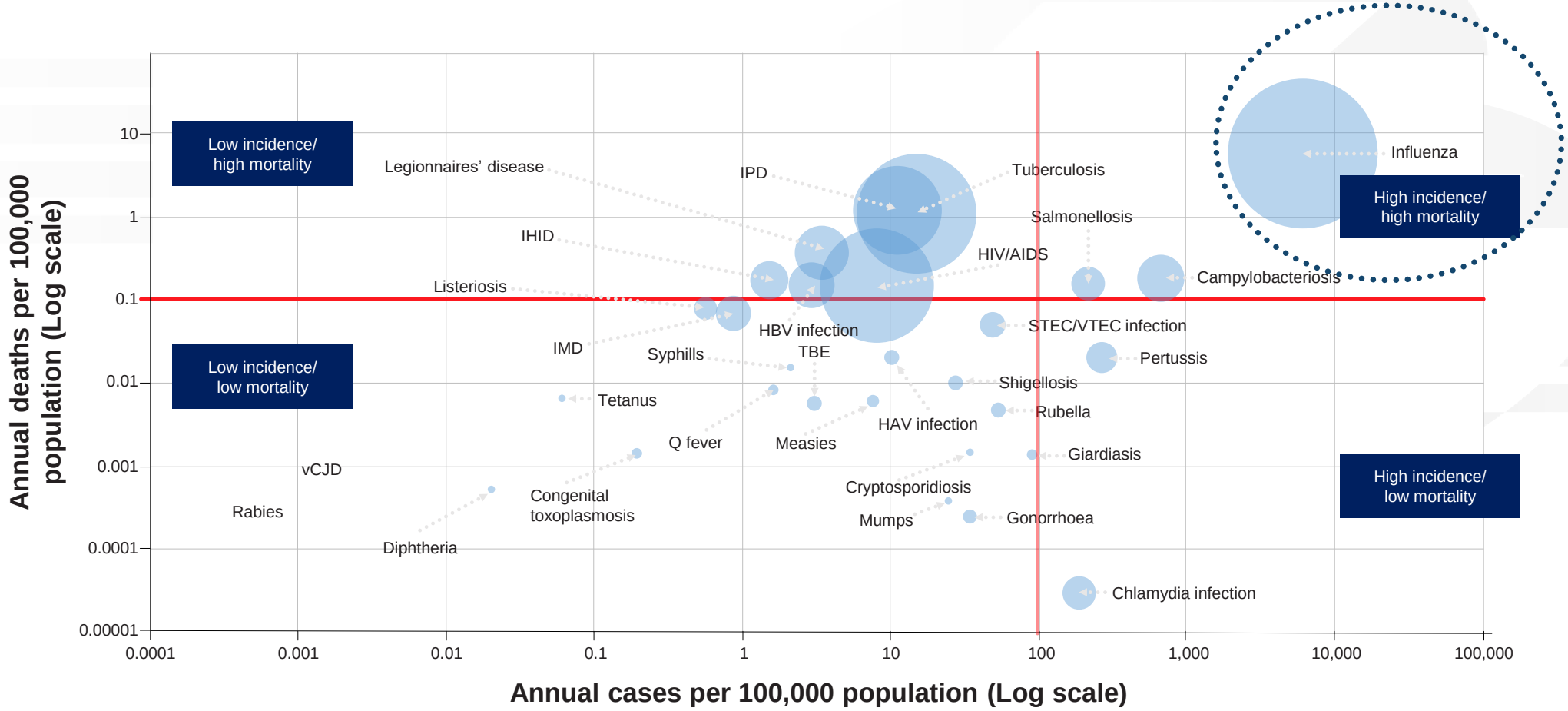
Variable	Men			Women		
	Adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Influenza			0.0015			0.0172
Non-exposure	ref			ref		
Exposure	1.09	1.04–1.16		1.08	1.01–1.15	
Timing of influenza			<0.0001			0.0050
Non-exposure	ref			ref		
Recent exposure	1.24	1.14–1.35		1.18	1.07–1.31	
Former exposure	1.01	0.94–1.08		1.02	0.94–1.11	
Counts of Influenza episodes			<0.0001			0.1208
Non-exposure	ref			ref		
1-2	1.04	0.97–1.11		1.07	1.00–1.16	
3-4	1.13	0.98–1.31		1.11	0.94–1.32	
5+	1.37	1.20–1.56		1.09	0.92–1.30	

Table 3
Adjusted odds ratio for lung cancer and counts of exposure to influenza.

Variable	Adjusted OR	95 % CI	*p*-Value
Influenza			<0.0001
Non-exposure	ref		
1-2	1.05	1.00–1.11	
3-4	1.12	1.00–1.25	
5+	1.25	1.13–1.39	
Charlson comorbidity index			<0.0001
0	ref		
1-2	1.08	1.05–1.10	
3 and above	1.01	0.97–1.06	
Tuberculosis	2.01	1.76–2.28	<0.0001
Pneumonia	1.45	1.37–1.54	<0.0001
Bronchiectasis	1.08	0.94–1.24	0.2753
Pneumoconiosis	1.04	0.80–1.36	0.7580
Pulmonary alveolar pneumonopathy	2.43	1.51–3.92	0.0003
Chronic Obstructive Pulmonary Disease	1.80	1.71–1.89	<0.0001
Asthma	1.41	1.33–1.50	<0.0001

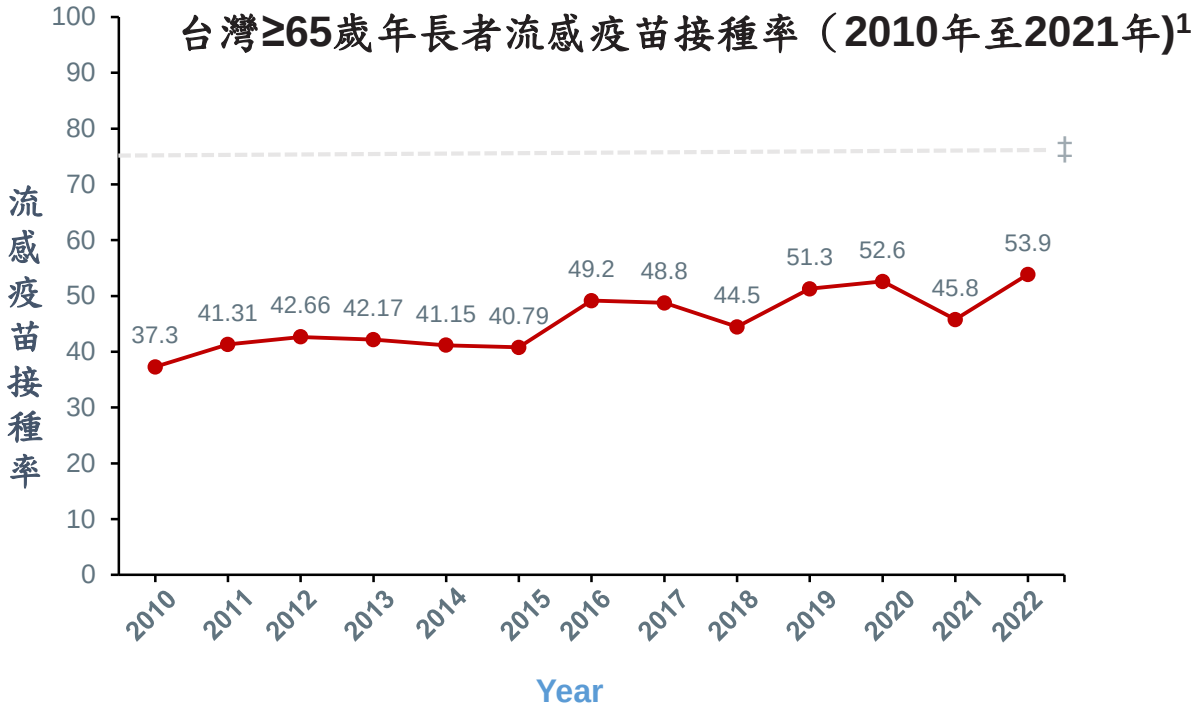
International Journal of Infectious Diseases 88 (2019) 8–13

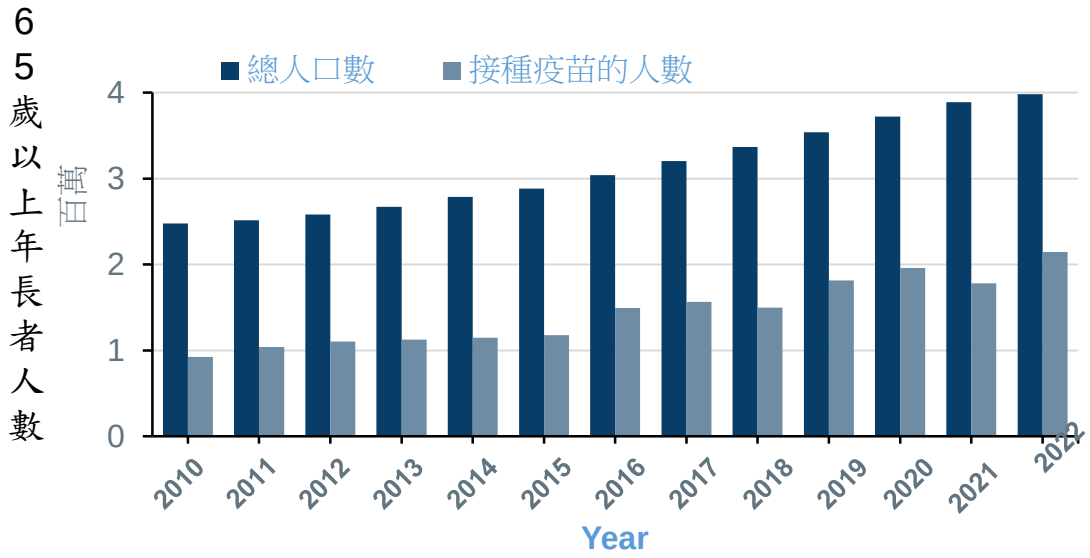
Influenza is associated with the highest incidence and mortality than any other pathogens against which we immunize



Cassini Alessandro, Colzani Edoardo, Pini Alessandro, Mangen Marie-Josee J, Plass Dietrich, McDonald Scott A, Maringhini Guido, van Lier Alies, Haagsma Juanita A, Havelaar Arie H, Kramarz Piotr, Kretzschmar Mirjam E, on behalf of the BCoDE consortium. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro Surveill. 2018;23(16):pii=17-00454. https://doi.org/10.2807/1560-7917.ES.2018.23.16.17-00454 *last accessed on 14 Jun 2021*

台灣65歲以上年長者公費流感疫苗接種率不佳





台灣邁入超高齡社會

1993年：老化社會，老年人口>7%

2018年：老化社會，老年人口>14%

2025年：預計進入超老齡社會，老年人口>20%

WHO建議將年長者流感疫苗接種覆蓋率提高到 75%。

由於老年人口比例增加，流感負擔預計將逐年為台灣社會帶來重大影響[4]

1.衛生福利部疾病管制署-歷年度流感疫苗接種計畫成果available from:https://www.cdc.gov.tw/Category/MPage/JNTC9qza3F_rgt9sRHqV2Q.

2. Jorgensen P, Mereckiene J, Cotter S, Johansen K, Tsolova S, Brown C. How close are countries of the WHO European Region to achieving the goal of vaccinating 75% of key risk groups against influenza? Results from national surveys on seasonal influenza vaccination programmes, 2008/2009 to 2014/2015. Vaccine. 2018 Jan 25;36(4):442-452. doi: 10.1016/j.vaccine.2017.12.019. Epub 2017 Dec 26. PMID: 29287683; PMCID: PMC5777640.

3. National Development Council Population Projection for the R.O.C (Taiwan) Available from: https://pop-proj.ndc.gov.tw/download.aspx?uid=70&pid=70 , Last accessed June 15, 2023

4. Taiwan Centers for Disease Control, Practical Guidelines for Prevention and Control of Seasonal Influenza. (Nov 2022)
Available from: https://www.tda.org.tw/upload/NewsData/6388/6088.pdf?v=20237314928, Last accessed: 8 Nov, 2023

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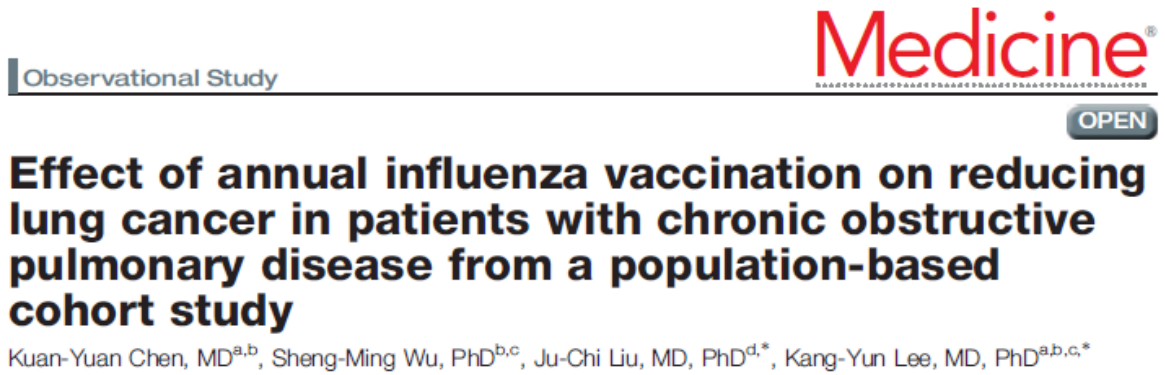
可能降低COPD 患者發生肺癌的風險

- 接種流感疫苗的慢性阻塞性肺病患者，發生肺癌的風險**顯著低於未接種**疫苗的患者(相對風險比 [aHR]：0.56)
- **疫苗接種次數越多，觀察到的潛在保護作用就越大**
- 接種1次疫苗aHR：0.65 (0.55,0.77)，接種2-3次疫苗aHR: 0.48 (0.40,0.54)，接種≥4次疫苗aHR： 0.24 (0.20,0.29)


Observational Study

Medicine

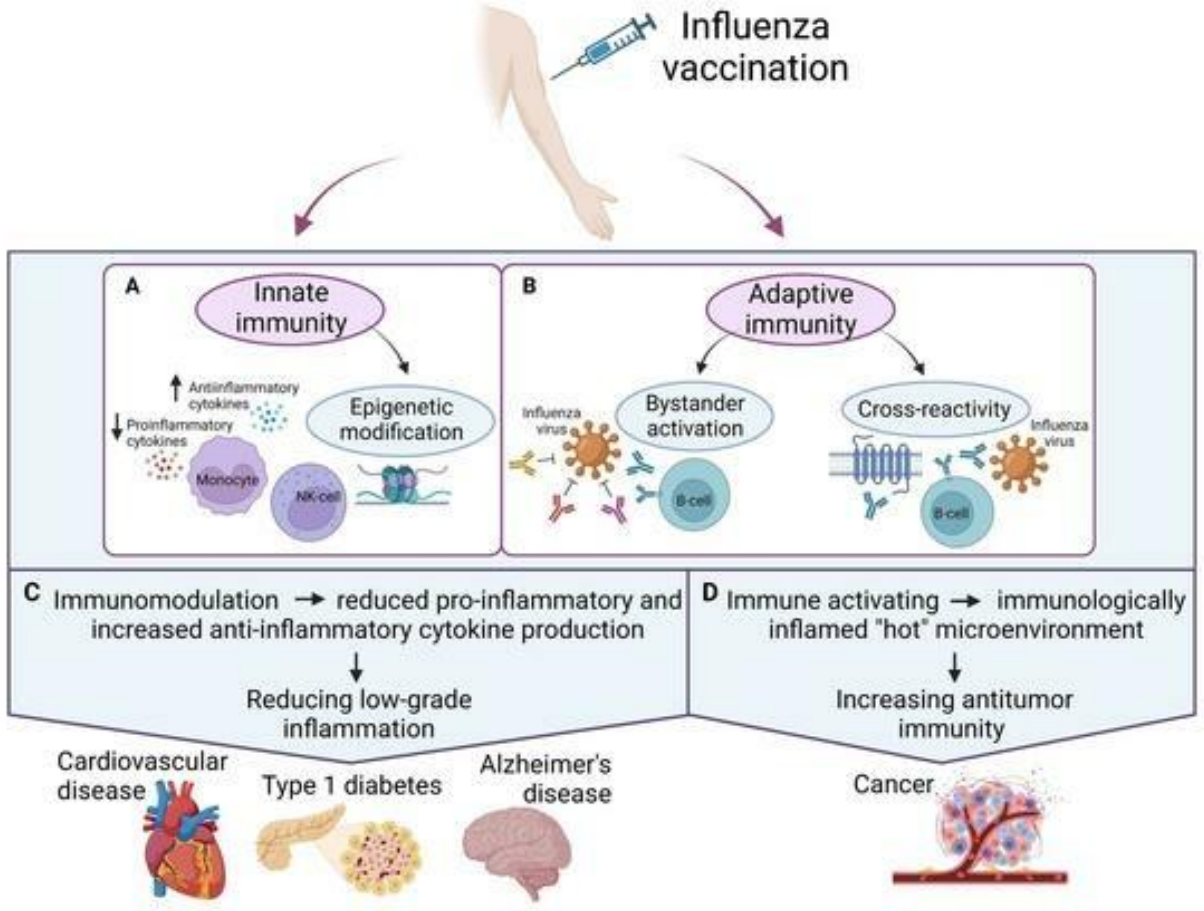
OPEN

Effect of annual influenza vaccination on reducing lung cancer in patients with chronic obstructive pulmonary disease from a population-based cohort study

Kuan-Yuan Chen, MD[a,b], Sheng-Ming Wu, PhD[b,c], Ju-Chi Liu, MD, PhD[d,*], Kang-Yun Lee, MD, PhD[a,b,c,*]

Medicine 2019;98:47(e18035)

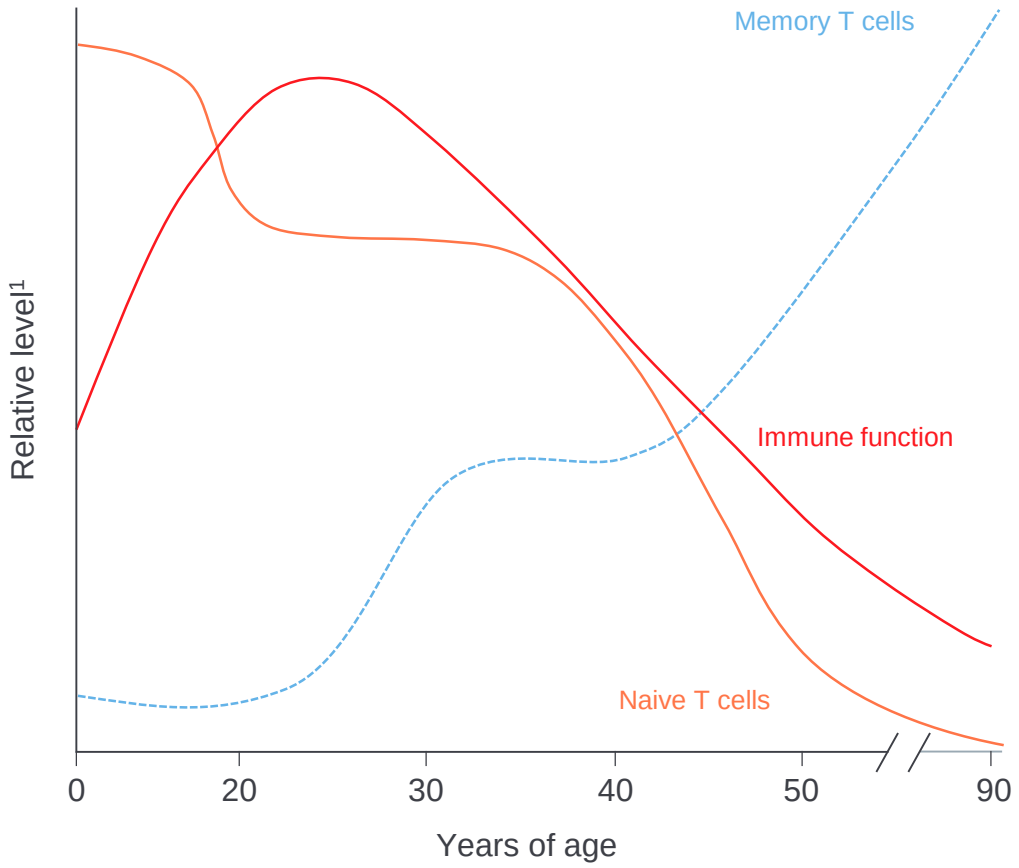
接種流感疫苗的益處



- 流感疫苗除了保護免受流感感染之外，還有其他重要疾病預防的潛力。
- 接種流感疫苗後，對於心血管疾病、第一型糖尿病、癌症和阿茲海默症等疾病，可能減少其事件的風險。

https://www.mdpi.com/2076-393X/11/9/1419

Age-related Changes in the Immune System



T Cells

- With increasing age, the body's pool of T cells changes from predominantly naive T cells to predominantly memory T cells because of lifelong exposure to antigens and decreased T-cell production in the thymus.[1]
- This shift may contribute to a decreased ability of the aging immune system to mount an effective response to novel infections.[1]

B Cells

- In the aging immune system, B cells may exhibit a **decrease in diversity and range of specific antibodies**.[2]

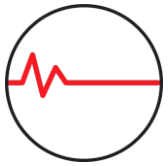
Adapted from Experimental Gerontology, Vol. 40, Abedin S, Michel JJ, Lemster B, Vallejo AN. Dissemination of increased Risk of Influenza in the Elderly Across the United States, 537-548, 2005, with permission from Elsevier.
1. Abedin S, et al. Diversity of NKR expression in aging T-cells and in T-cells of the aged: the new frontier into the exploration of protective immunity in the Elderly. Exp Gerontol. 2005;40:537-548. 2. Weinberger B, et al. Biology of immune responses to vaccines in elderly persons. Clin Infect Dis. 2008;46:1078-1084.

Immunosenescence is the progressive degradation of immune function accompanying the ageing process

- Underlying the **reduced natural- and vaccine-induced immunity** in **older** individuals is the phenomenon known as **immunosenescence**[1–3]
- Although the mechanism of Immunosenescence is not fully understood, it is linked to the erosion of **adaptive immunity** with advancing age[4] and is associated with:

Declining T- and B-cell responses[5,6]

More severe outcomes[3,5]

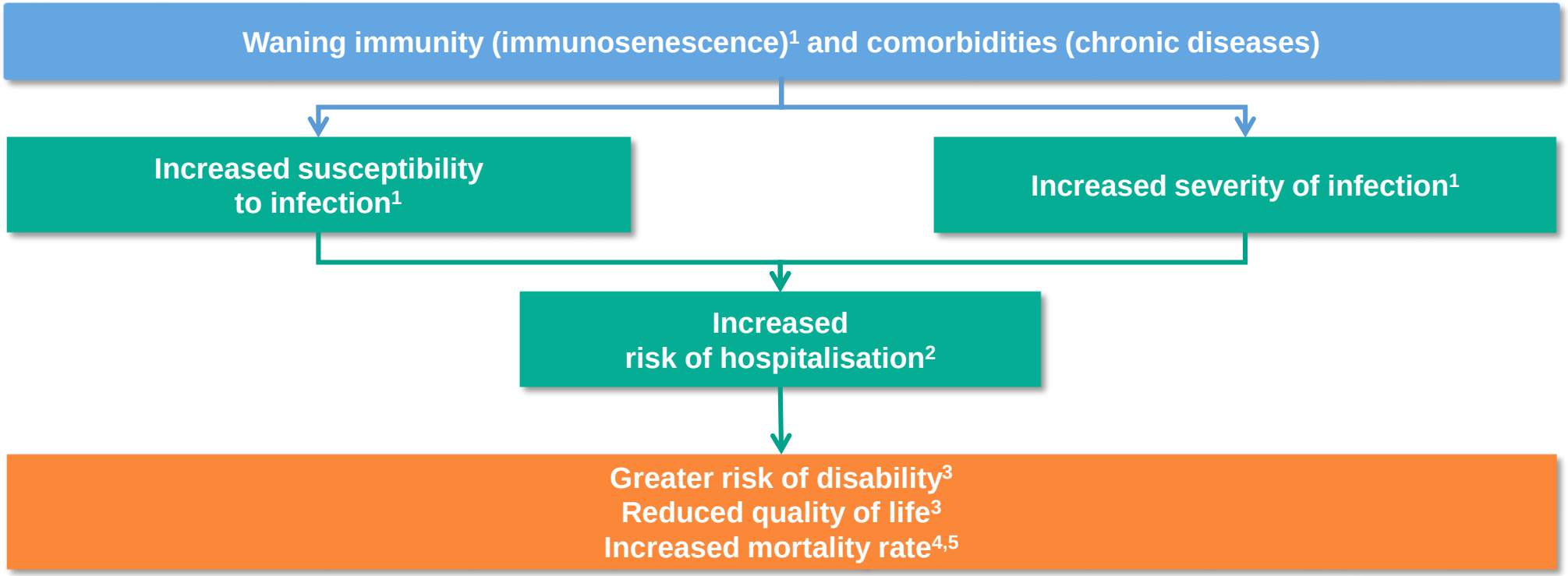


Higher mortality[3]

The **reduced diversity** in antibody repertoire associated with immunosenescence is implicated in the **poor responsiveness** of older individuals to vaccination[5,6]

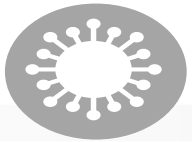
1. Targonski PV, et al. *Vaccine*. 2007;25(16):3066–3069; **2**. Nikolich-Zugich J. *Nat Immunol*. 2018;19(1):10–19; **3**. Lee KA, et al. *Front Aging*. 2022;3:900028;
4. Gustafson CE, et al. *J Allergy Clin Immunol*. 2020;145(5):1309–1321; **5**. Crooke SN, et al. *Immun Ageing*. 2019;16:25; **6**. Del Giudice G, et al. *NPJ Aging Mech Dis*. 2018;4:1.

The effects of aging on the immune system: Impacts on infection and outcomes



1. Gavazzi G, et al. Lancet Infect Dis. 2002;2:659-666. 2. Thompson WW, et al. JAMA. 2004;292:1333-1340. 3. McElhaney JE. Vaccine. 2005;23(suppl 1):S10-S25.
4. Thompson WW, et al. JAMA. 2003;289:179-186. 5. Sprenger MJ, et al. Int J Epidemiol. 1993;22:334-340.

Multiple factors influence the disease burden and influenza vaccine effectiveness in adults ≥65 years of age



Influenza virus

e.g. antigenic drift or shift *(natural mutation in circulating flu strains)*

Antigenic mismatch may lead to reduced vaccine efficacy[1]

Vaccine

Vaccine type
e.g. egg-adaptation
(changes introduced during egg-based manufacturing)

Conventional influenza vaccines may offer limited protection[2]

Population/ Patient

e.g. Age-related immunosenescence
(declining immune function in the elderly)

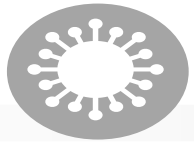
Potential for reduced immune response to the vaccination[3]

UNMET NEEDS

Reducing disease burden requires surveillance for improved burden-targeting and **vaccines capable of broader immune responses to help protect against influenza infection**[4]

1. Beran J, et al. *Lancet Infect Dis*. 2021;20:1473–3099; 2. Cocchio S, et al. *Vaccines (Basel)*. 2020;8(3):344; 3. Dugan HL, et al. *Cell Immunol*. 2020;348:103998 ; 4. Molinari NAM, et al. *Vaccine*. 2007;25(27):5086–5096; 4. Noh JY, Kim WJ. *Infect Chemother*. 2013;45(4):375–386.

Multiple factors influence the disease burden and influenza vaccine effectiveness in adults ≥65 years of age

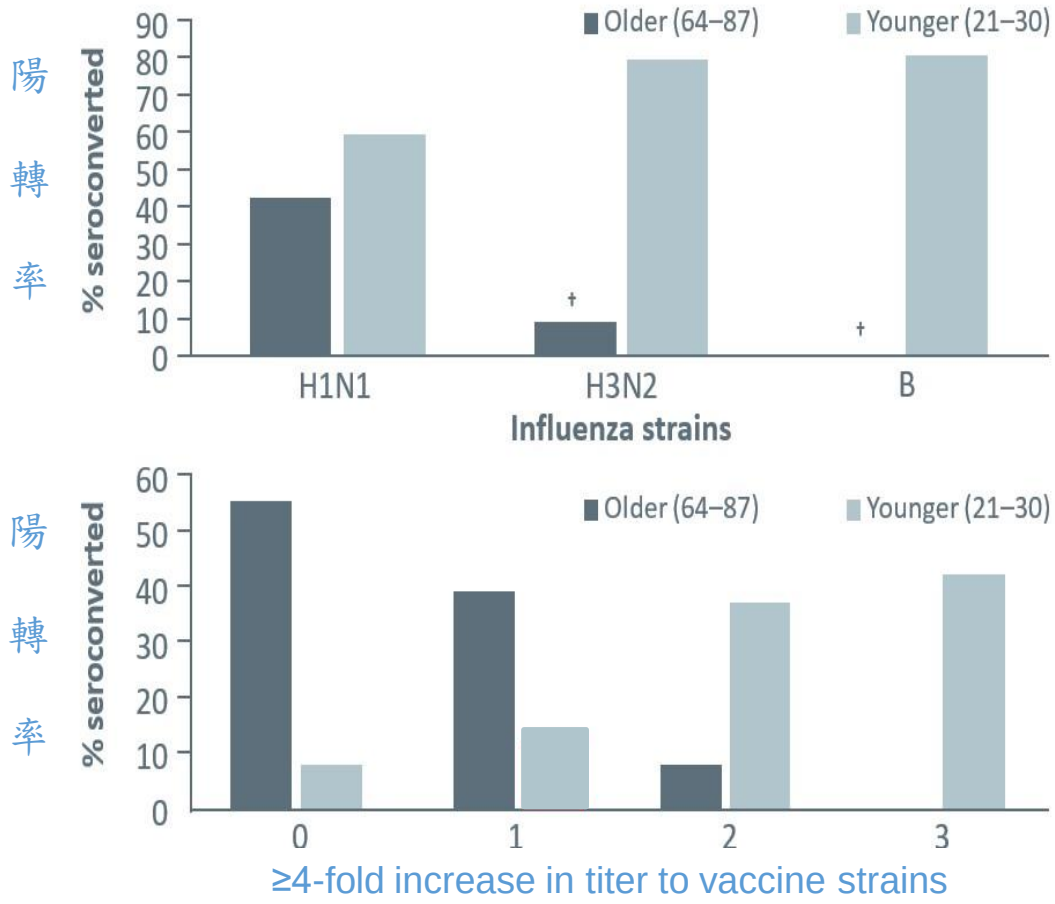


	Influenza virus	Vaccine	Population/ Patient
	e.g. antigenic drift or shift *(natural mutation in circulating flu strains)*	***Vaccine type e.g. egg-adaptation*** *(changes introduced during egg-based manufacturing)*	***e.g. Age-related immunosenescence*** *(declining immune function in the elderly)*
	Antigenic mismatch may lead to reduced vaccine efficacy[1]	*Conventional influenza vaccines may offer limited protection[2]*	*Potential for reduced immune response to the vaccination[3]*
Opportunities to improve vaccine effectiveness	**Annual strain update**	**Non-egg-based vaccines[4]**	**Adjuvanted & high-antigen vaccines[5]**

1. Beran J, et al. *Lancet Infect Dis*. 2021;20:1473–3099; 2. Cocchio S, et al. *Vaccines (Basel)*. 2020;8(3):344; 3. Dugan HL, et al. *Cell Immunol*. 2020;348:103998 ; 4. Molinari NAM, et al. *Vaccine*. 2007;25(27):5086–5096; 4. Skowronski DM et al. PLoS One. 2014;9(3):e92153. ; 5. ATAGI. Australian Immunisation Handbook, Australian Government Department of Health, Canberra, 2020, immunisationhandbook.health.gov.au. Accessed December 2022

年長者接種傳統流感疫苗抗體免疫生成力不佳

50 名年輕人和 54 名年長者



- H1N1陽轉率：年長者低於40%
- H3N2陽轉率：年長者低於10%
- B型陽轉率：年長者沒有反應

- 無血清陽轉: 55%年長者沒有產生抗體
- 產生一種抗體的血清陽轉率：40%年長者
- 產生兩種抗體的血清陽轉率：8%年長者
- 產生三種抗體的血清陽轉率：0%年長者

Published in final edited form as:
J Immunol. 2010 March 1; 184(5): . doi:10.4049/jimmunol.0901022.

Age-associated Decrease in Toll-like Receptor Function in Primary Human Dendritic Cells Predicts Influenza Vaccine Response[1]

*Samples were obtained from Yale University Health Services vaccination clinics in October and November 2007. Fifty younger adults (aged 21–30 years) and 54 older adults (aged ≥65 years) were included in the analysis. †P<0.0001. Panda A, et al. J Immunol. 2010;184(5):2518–2527.

年長者接種傳統流感疫苗抗體免疫生成力不佳

- 2014~2015台灣觀察流感疫苗對年長者保護成效的世代追蹤
- 透過PSM(Propensity Score Matching)匹配,比較有接種流感疫苗和沒接種流感疫苗的差異共272,896人
- **傳統流感疫苗在預防流感死亡有30%的保護效果**

未接種流感疫苗　　有接種流感疫苗

Variables	Total (N = 272,896)		Without IV (N = 136,448)		With IV (N = 136,448)		With IV vs. without IV (Ref.)							
	Event	Incident (‰)	Event	Incident (‰)	Event	Incident (‰)	cOR	95% CI		p-Value	aOR#	95% CI		p-Value
★Death	24,368	89.29	13 918	102.00	10,450	76.59	0.72	0.70	0.74	<0.001	0.70	0.68	0.72	<0.001
Hospitalization														
★Influenza and pneumonia	29,556	108.30	14,296	104.77	15,260	111.84	1.08	1.05	1.11	<0.001	0.98	0.95	1.01	0.111
★Respiratory diseases	41,131	150.72	20,228	148.25	20,903	153.19	1.04	1.02	1.06	<0.001	0.96	0.94	0.99	0.004
★Respiratory failure	12,636	46.30	6589	48.29	6047	44.32	0.91	0.88	0.95	<0.001	0.85	0.82	0.89	<0.001
Heart disease	24,589	90.10	12,422	91.04	12,167	89.17	0.98	0.95	1.00	0.085	0.96	0.93	0.99	0.004
Hemorrhagic stroke	1103	4.04	605	4.43	498	3.65	0.82	0.73	0.93	0.001	0.85	0.75	0.97	0.014
Ischemic stroke	4249	15.57	2291	16.79	1958	14.35	0.85	0.80	0.91	<0.001	0.89	0.84	0.95	0.001
Any one of above disease	53,622	196.49	26,631	195.17	26,991	197.81	1.02	1.00	1.04	0.075	0.96	0.94	0.98	<0.001

Abbreviations: IV, Influenza vaccination; ref., reference group; cOR, crude odds ratio; aOR, adjusted odds ratio; CI, confidence interval # All models were analyzed via the generalized estimating equation. Extraneous factors adjusted in the model contained disability severity, type of disability, age, sex, premium salary, urbanization level, CCI score, catastrophic illness status, long-term care facility residents, outpatient utilization, hospital admission, and preventive care service utilization.

Chang YC, et al. Vaccines. 2020;8(1):140

長者接種疫苗後免疫生成性較低[1]，且流感疫苗疫苗效力隨時間而減弱的現象也比較顯著[2]

流感疫苗對長者保護力較低

- 根據國際研究顯示，對因確診流感而住院的保護力約有41%，

  其中對**18至64歲以下病患的保護力約為51%，對65歲以上長者的保護力則為37%**[1,3]

- 流感疫苗在預防流感和重症病例中，提供健康成年人約 70-90% 的保護，為老年人約 50-60%的保護`

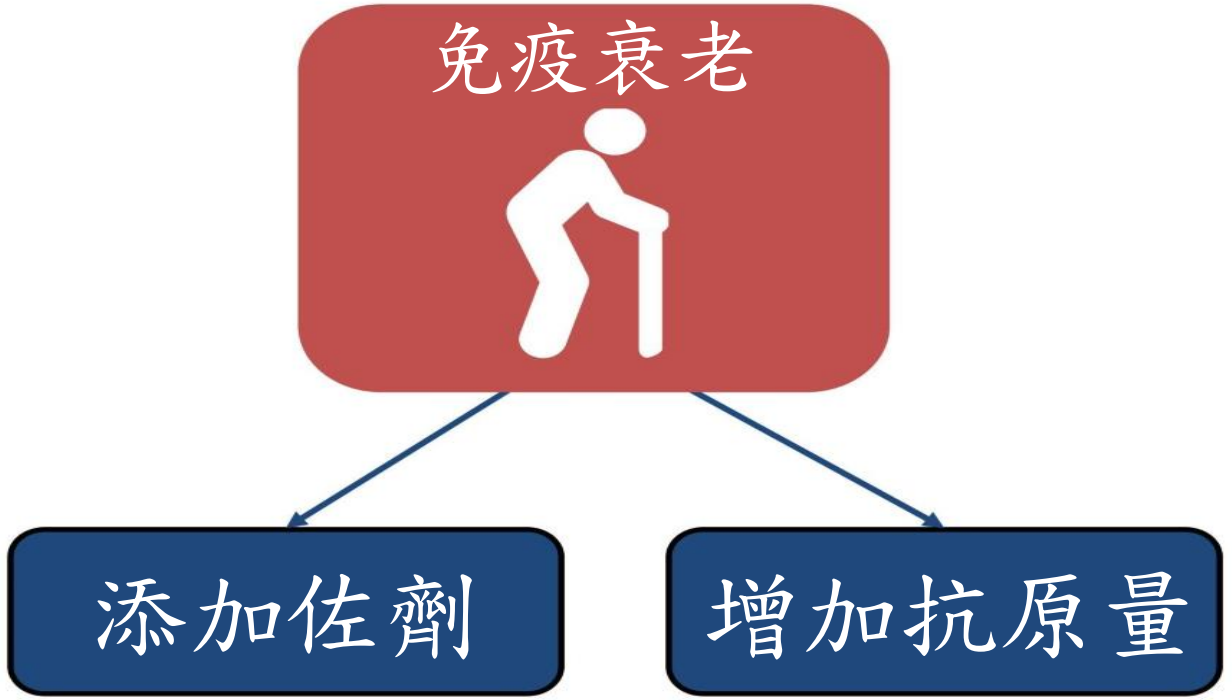
長者接種後抗體消退速度較快[2]

- 接種後抗體消退與疫苗保護效力息息相關。

  各病毒株抗體消退速度並不一致，**在高齡的成年人有較快消退速度**，進而減弱流感疫苗的保護效力[2]

1. Taiwan Centers for Disease Control, Practical Guidelines for Prevention and Control of Seasonal Influenza.. Available from: https://www.tda.org.tw/upload/NewsData/6388/6088.pdf?v=20237314928, (Dec 2022 version) Last accessed: Nov 13, 2023. ;
2. 許玉龍、黃高彬（2020）。接種季節流感疫苗後的保護效力與抗體減退之探討。感染控制雜誌，30(3)，179-187。https://doi.org/10.6526/ICJ.202006_30(3).0003
3. Rondy M et al. J Infect. 2017;75(5):381-394. doi:10.1016/j.jinf.2017.09.010
;4. Taiwan Centers for Disease Control, Disease and Conditions- Influenza, Available from : https://www.cdc.gov.tw/En/Category/ListContent/bg0g_VU_Ysrgkes_KRUDgQ?uaid=Zvnt3Ff941PorUmUD0-leA , Last accessed: Nov 9, 2023
5. Castilla J et. Al. Euro Surveill. 2013;18(5):pii=20388. https://doi.org/10.2807/ese.18.05.20388-en
6. Belongia EA et al: Vaccine. 2015 Jan 1;33(1):246-51

流感疫苗新科技，改善65 歲以上成人免疫衰老問題



Dorrington MG, Bowdish DME.Frontiers in Immunol 2013;4(171):1 10.

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MF-59®-adjuvanted Influenza Vaccine

➢ **MF59® As An Adjuvant, Is Added To An Influenza Vaccine With The Intended Purpose Of Creating A Strong, Broad, And Durable Immune Response**[1-3]

MF-59® adjuvanted **trivalent** inactivated influenza vaccine

- **Since 1997**: MF-59® adjuvanted trivalent inactivated influenza vaccine, was first approved for use in older adults **in 1997**[5]
- **65Y+**: MF-59® adjuvanted trivalent inactivated influenza vaccine was specifically **designed for use in those 65 years** and older to improve the immune response in this population[1,4]
- **~ 10mg squalene**: Single dose of MF-59® adjuvanted trivalent inactivated influenza vaccine[7] contains **~10 mg squalene**

MF-59® adjuvanted **quadrivalent** inactivated influenza vaccine

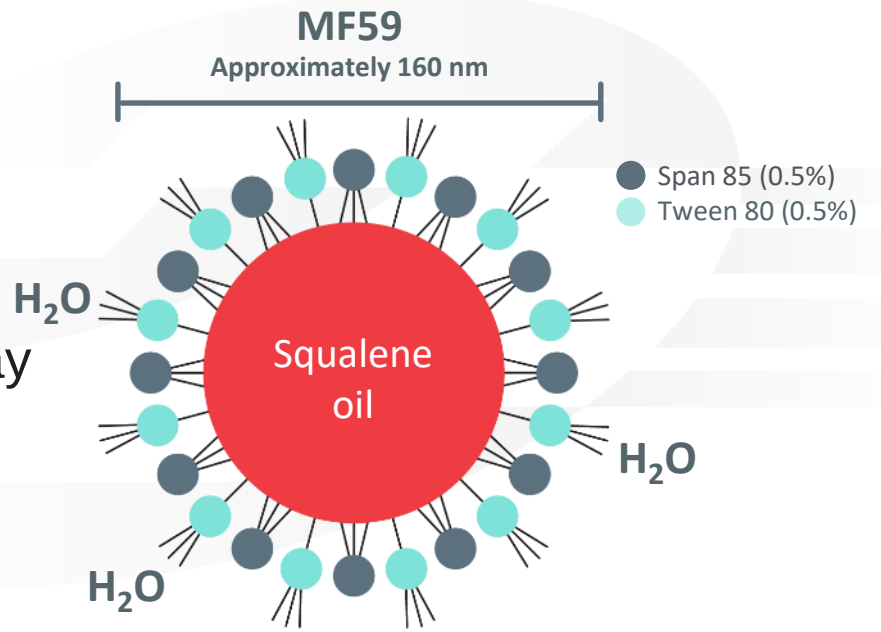
- **2020 US Approval**: MF-59® adjuvanted quadrivalent inactivated influenza vaccine, received **FDA approval on February 21, 2020**[6]

1. Garçon N, Leroux-Roels G, Cheng WF. Vaccine adjuvants. Understanding Modern Vaccines: Perspectives in Vaccinology. 2011;1(1):89-113. 2. O'Hagan DT, Ott GS, Nest GV, Rappuoli R, Giudice GD. The history of MF59® adjuvant: a phoenix that arose from the ashes. Expert Rev Vaccines. 2013;12:13-30. 3. O'Hagan DT, Ott GS, De Gregorio E, Seubert A. The mechanism of action of MF59 – an innately attractive adjuvant formulation. Vaccine. 2012;30:4341-4348. 4. Frey SE, Aplasca-De Los Reyes MR, Reynales H, et al. Comparison of the safety and immunogenicity of an MF59®-adjuvanted with a non-adjuvanted seasonal influenza vaccine in elderly subjects. Vaccine. 2014;32:5027-5034 5. Seqirus Inc, Fluad US Package Insert; 2020. 6. Seqirus Inc, Fluad Quadrivalent US Package Insert; 2020. 7. Fluad [package insert]. Summit, NJ: Seqirus Inc: 2020.

Oil-in-water adjuvant: MF59®

MF59 is an oil-in-water emulsion composed of squalene, which is stabilized by Tween 80 and Span 85[1]

- **Squalene (角鯊烯)**[1]
  - **Biodegradable** and **biocompatible** oil
  - Intermediate precursor in the **cholesterol** biosynthetic pathway
  - Synthesized in the **liver** (>1 g/day) and derived from **dietary sources** (50 mg–200 mg/day)
- Single dose of FLUAD®[2] contains ~10 mg squalene

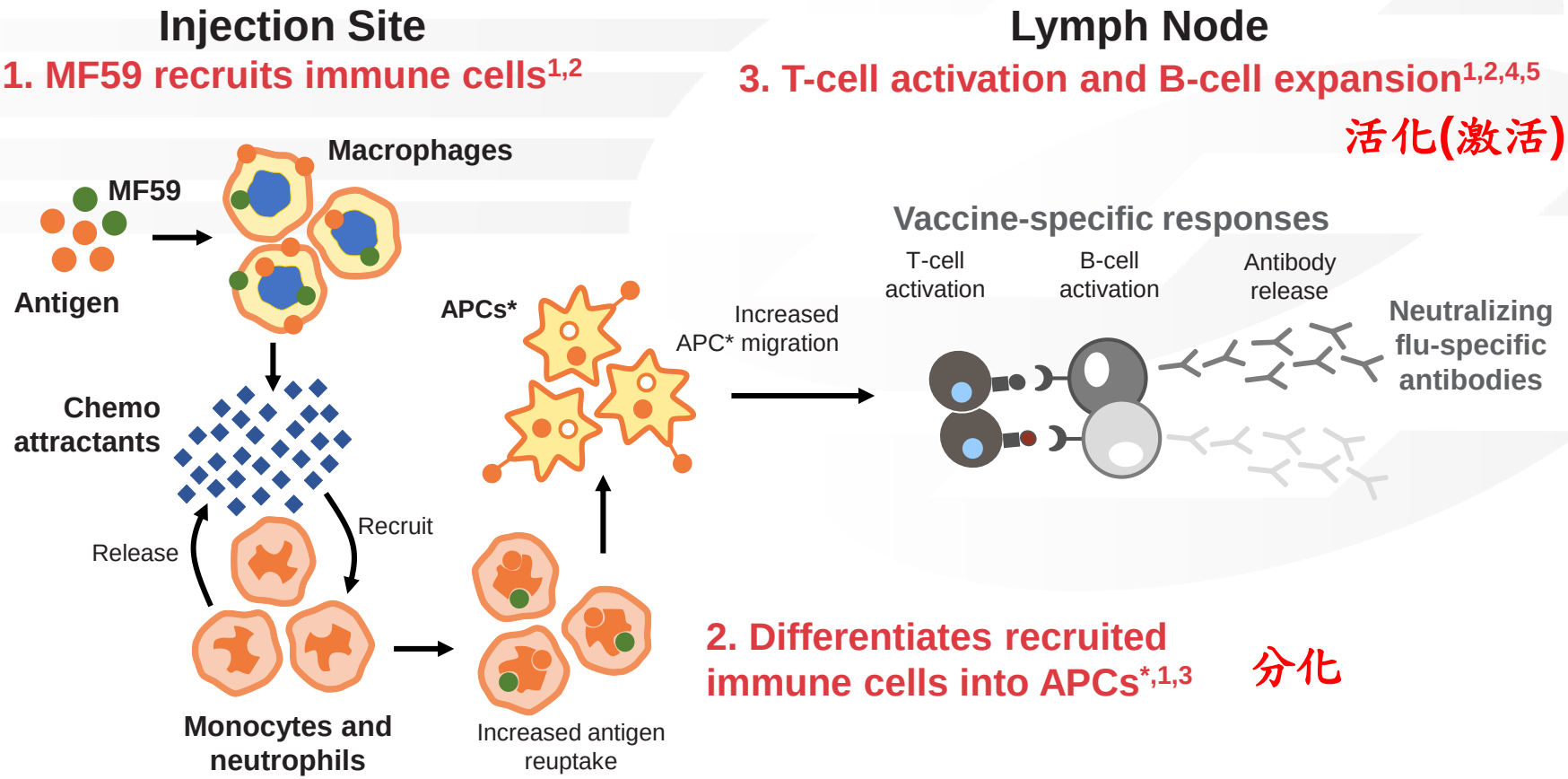


角鯊烯(Squalene)是一種人體可自行產生的天然脂質，最早在鯊魚的肝臟中被科學家發現，也可從橄欖、甘蔗等植物萃取中獲得，近年市面上絕大部分的角鯊烯都是植物性來源，主要存在於皮膚中，可以幫助肌膚保濕、鎖水。

FLUAD® and MF59® are registered trademarks of Seqirus UK Limited or its affiliates.

1. O'Hagan DT, et al. *Expert Rev Vaccines*. 2013;12(1):13-30. 2. Fluad [package insert]. Summit, NJ: Seqirus Inc: 2020.

MF59®: Proposed mode of action (增強免疫三步驟)



*APC = antigen-presenting cell.

1. Seubert A, et al. *J Immunol*. 2008;180(8):5402-5412. 2. Calabro S, et al. *Vaccine*. 2011;29(9):1812-1823. 3. Schultze V, et al. *Vaccine*. 2008;26(26):3209-3222.
4. Khurana S, et al. *Sci Transl Med*. 2010;2(15):1-8. 5. Vono M, et al. *Proc Natl Acad Sci USA*. 2013;110(52):21095-21100.

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aTIV vs. TIV: significantly higher antibody responses in a meta-analysis of 23 Phase I-III trials

- **Study Design:**
  - Meta-analysis from 23 Phase I through III trials (1992-2013) from interventional trials database
  - Comparator: aTIV vs. TIV
  - Subject number: **11,105** subjects ≥65 years old
- **Results: (immunogenicity, first dose)**

Measure	Difference, aTIV > TIV (95% CI)*		
	H1N1	H3N2	B
Seroconversion rate	9.5% (5.2 – 13.9)	10.5 % (6.6-14.5)	12.7% (8.6-16.8)
GMT ratio	1.15 (1.01-1.31)	1.30 (1.18-1.44)	1.23 (1.15-1.31)
% of Subjects HI titre ≥1:40	2.4% (0.8-4.0)	2.7% (0.9-4.5)	4.5% (1.8-7.1)

*Lower bounds of 95% CIs for all results met criteria for statistical significance

aTIV: adjuvanted trivalent influenza vaccine; GMT, geometric mean titer; TIV, trivalent influenza vaccine.

Nicolay et al. 2019. Immunogenicity of aIIV3, MF59-adjuvanted seasonal trivalent influenza vaccine, in older adults > 65 years of age: Meta-analysis of cumulative clinical experience. Int J Infect Dis 85S:S1-S9.

H3N2抗體效價是一般流感疫苗的1.6倍；H1N1抗體效價為1.4倍

- 共7,082位受試者隨機分組接受接種佐劑流感疫苗(N=3,541)與傳統流感疫苗(N=3,541)。
- 與傳統流感疫苗比較，FLUAD 可獲得更強效的免疫反應。

Table 2a: Immune Responses to Each Antigen 22 Days after Vaccination with FLUAD or AGRIFLU in Adults 65 Years and Older[a]

GMTs Against FLUAD and AGRIFLU Vaccine Strains	FLUAD N[b]= 3225-3227 GMT (95% CI)	AGRIFLU N[b] =3256-3259 GMT (95% CI)	FLUAD and AGRIFLU GMT Ratio[c] (95% CI)
A/California/7/2009-like (H1N1)	99 (93-106)	70 (66-75)	1.4 (1.32-1.49)
A/Perth/16/2009-like (H3N2)	272 (257-288)	169 (159-179)	1.61 (1.52-1.7)
B/Brisbane/60/2008- like	28 (26-29)	24 (23-26)	1.15 (1.08-1.21)

Safety and Immunogenicity of MF59C.1 Adjuvanted Trivalent Subunit Influenza Vaccine in Elderly Subjects. ClinicalTrials.gov Identifier: NCT01162122

aTIV vs. TIV: significantly greater GMT ratios for heterologous strains, mainly H3N2, in a meta-analysis

Study Design:

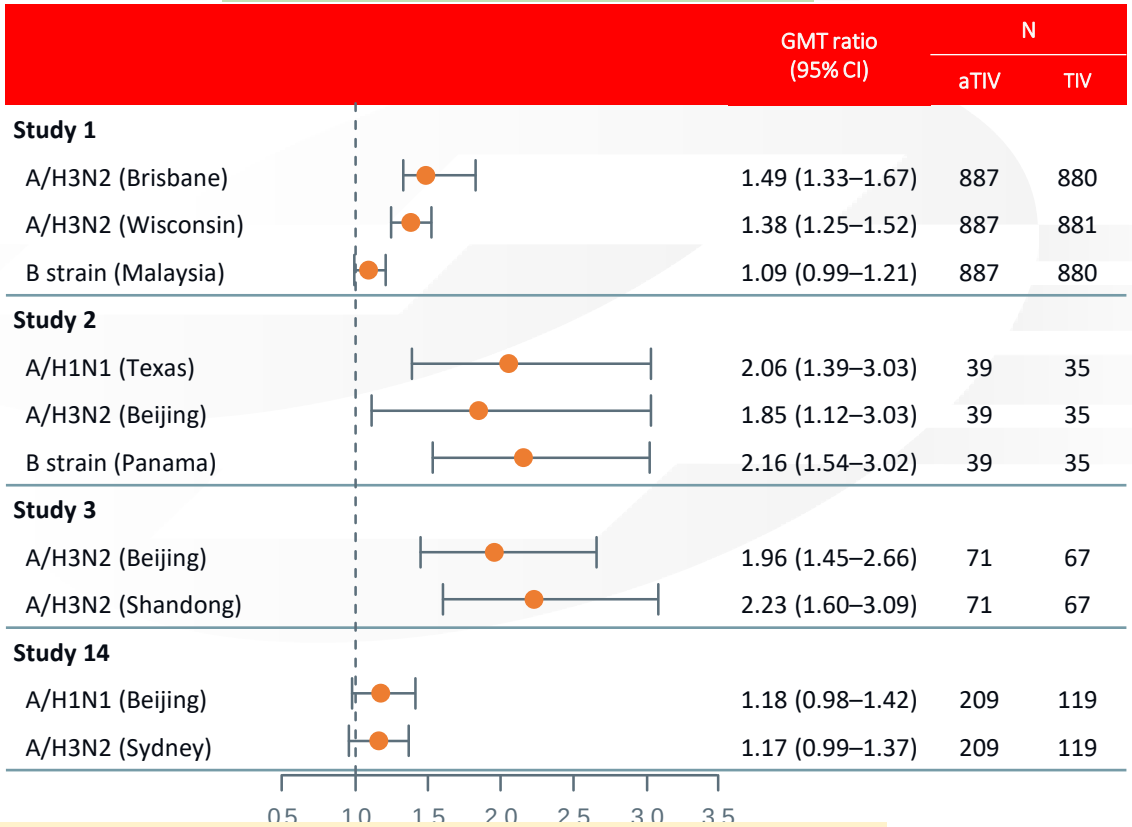
- Meta-analysis from 23 Phase I through III trials (1992-2013)
- aTIV vs. TIV
- 11,105 subjects ≥65 years old

Results:

- **Antibody vs. heterologous strains significantly greater for aTIV in 7 out of 10 strains** (5x H3N2, 1x B, 1x H1N1)

MF59 associations with increased **breadth** of immune response suggest potential for greater protection against vaccine-mismatched virus strains

GMT ratios geometric mean HI antibody titer (GMT)



於Meta analysis中，非疫苗型別病毒株(主要是H3N2)的抗體效價比率明顯高於傳統疫苗

Nicolay et al. 2019. Immunogenicity of aIIV3, MF59-adjuvanted seasonal trivalent influenza vaccine, in older adults ≥ 65 years of age: Meta-analysis of cumulative clinical experience. Int. J Infect Dis 85S: S1-S9.

aTIV vs. TIV: elevated antibody response to 1 year for H3N2 strain

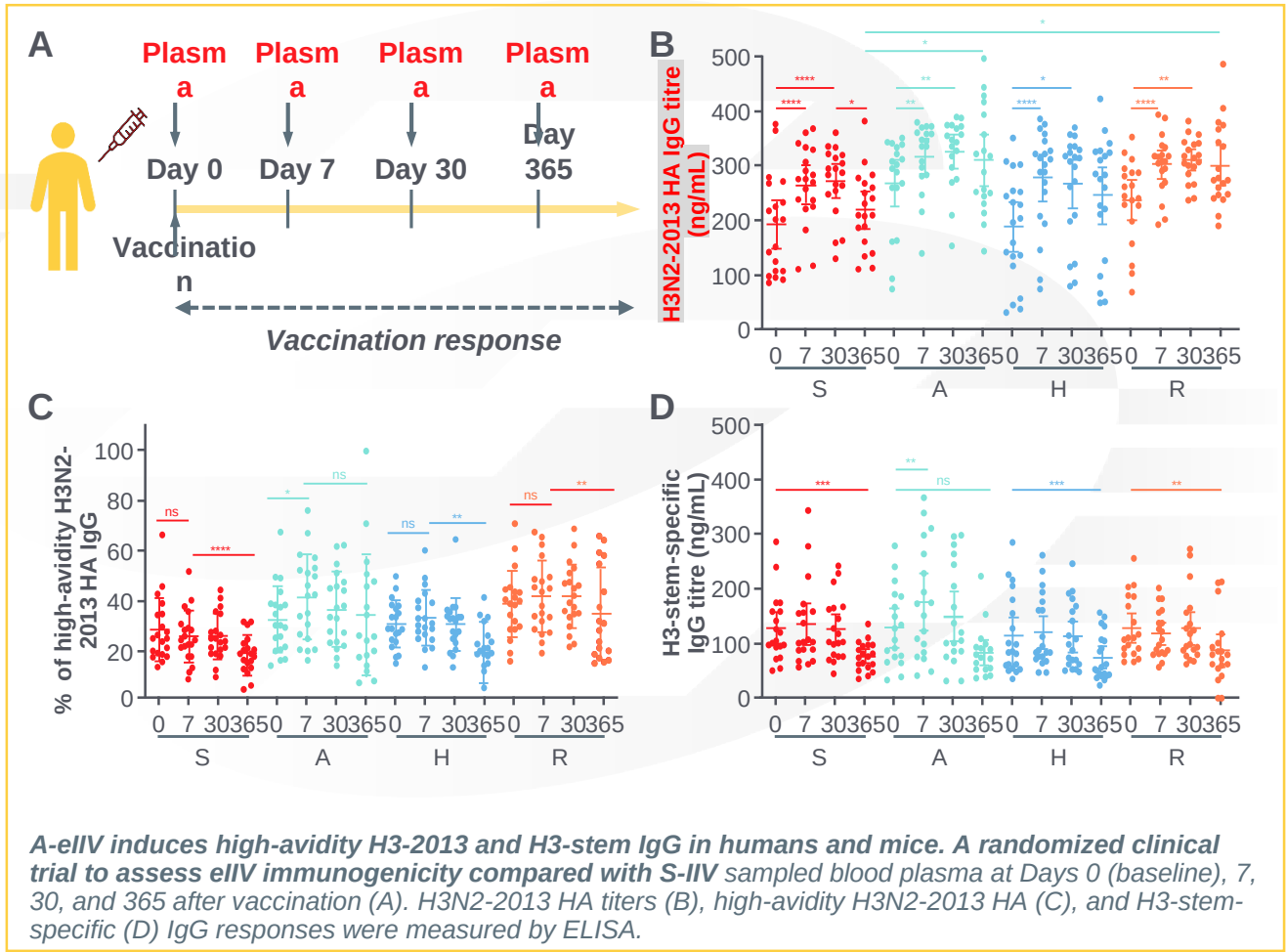
Study Design:

- **Design:** Randomized trial in **Hong Kong**, 2017/2018 formulation
  - TIV vs. aTIV/HD-TIV/rQIV
- **Population:** Community-dwelling older adults (**65 - 82 years**)
- **Endpoint:** Immunogenicity (anti-HA titers and avidity) vs. H3N2-2013 (representative strain)

Results:

- Antibody responses were equivalent between all vaccine groups at Days 7 and 30

aTIV and rQIV H3N2-2013 HA IgG responses were elevated **1 year** after vaccination compared with TIV **(p < 0.05)**, suggesting **increased long-term memory**



A-eIIV induces high-avidity H3-2013 and H3-stem IgG in humans and mice. A randomized clinical trial to assess eIIV immunogenicity compared with S-IIV *sampled blood plasma at Days 0 (baseline), 7, 30, and 365 after vaccination (A). H3N2-2013 HA titers (B), high-avidity H3N2-2013 HA (C), and H3-stem-specific (D) IgG responses were measured by ELISA.*

A, adjuvant vaccine; aTIV, adjuvanted trivalent influenza vaccine; eIIV, enhanced inactivated influenza vaccine; ELISA, enzyme-linked immunosorbent assay; HA, hemagglutinin; HD-TIV, high-dose trivalent influenza vaccine; IgG, immunoglobulin G; R, recombinant; rQIV, recombinant quadrivalent influenza vaccine; S, standard vaccine.

Kavian et al. 2020. Assessment of enhanced influenza vaccination finds that FluAd conveys an advantage in mice and older adults. Clin Transl Immunol 9:E1107.

真實世界保護力驗證

MF59 佐劑疫苗可顯著改善長者對流感的保護效果，保護效果約為63%

研究目標:
評估接種佐劑流感疫苗和傳統流感疾病在實驗室確診病例的相對有效性，同時，也與未接種疫苗的人進行比較。

人群
共有 282 名符合條件的參與者被納入研究中，其中近一半的參與者(**136** 人)住在**長期護理機構**，且年齡均在 **85 歲或以上**

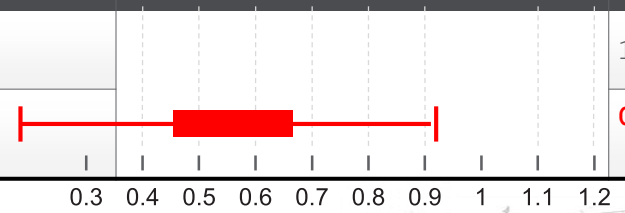
實驗設計
前瞻性病例對照設計，進行一項基於社區的病例對照研究，納入老年人作為研究對象。病例檢測呈陽性，對照檢測呈流感陰性。已知免疫抑制的者被排除在外。

研究期間:
橫跨個流感季節, 2011/2012

P.G. VanBuynderetal./Vaccine31(2013)6122–6128

rVE 相對疫苗有效性多變量分析

Vaccine	Adjusted** Odds Ratio (95% CI)	P-value
傳統流感疫苗	1.00 (Ref.)	0.04
MF59-佐劑流感疫苗	**0.37** (0.14-0.96)	



aTIV reduced risk of all-cause hospitalization vs. TIVe or QIVe in ≥65 years in Italy over 18 seasons

Objective

To **evaluate the rVE for aTIV vs. TIVe or QIVe**† in preventing all-cause hospitalisation across 18 seasons in Italy

Design

Nested case–control analysis using the Italian **HSD** primary care medical records database

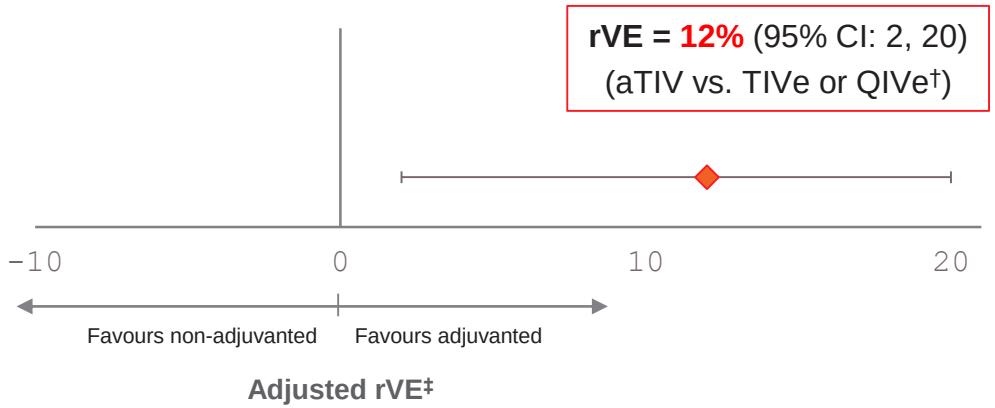
Timing

Across **18 influenza seasons** 2002/2003 to 2018/2019

Population

58,252 adults aged ≥65 years included in the analysis

Association between vaccine type and all-cause hospitalisation



†QIVe available only for the 2018/2019 season; ‡adjusted for cardiovascular risk, other cerebrovascular diseases, gastrointestinal disorders, heart failure, depression, asthma, chronic obstructive pulmonary disease, polypharmacy, lower respiratory tract infection.

aTIV, adjuvanted trivalent influenza vaccine; HSD, Health Search Database; QIVe, quadrivalent influenza vaccine; rVE, relative vaccine effectiveness; TIVe, trivalent influenza vaccine.

Lapi F et al. *Expert Rev Vaccines*. 2022;19:2.

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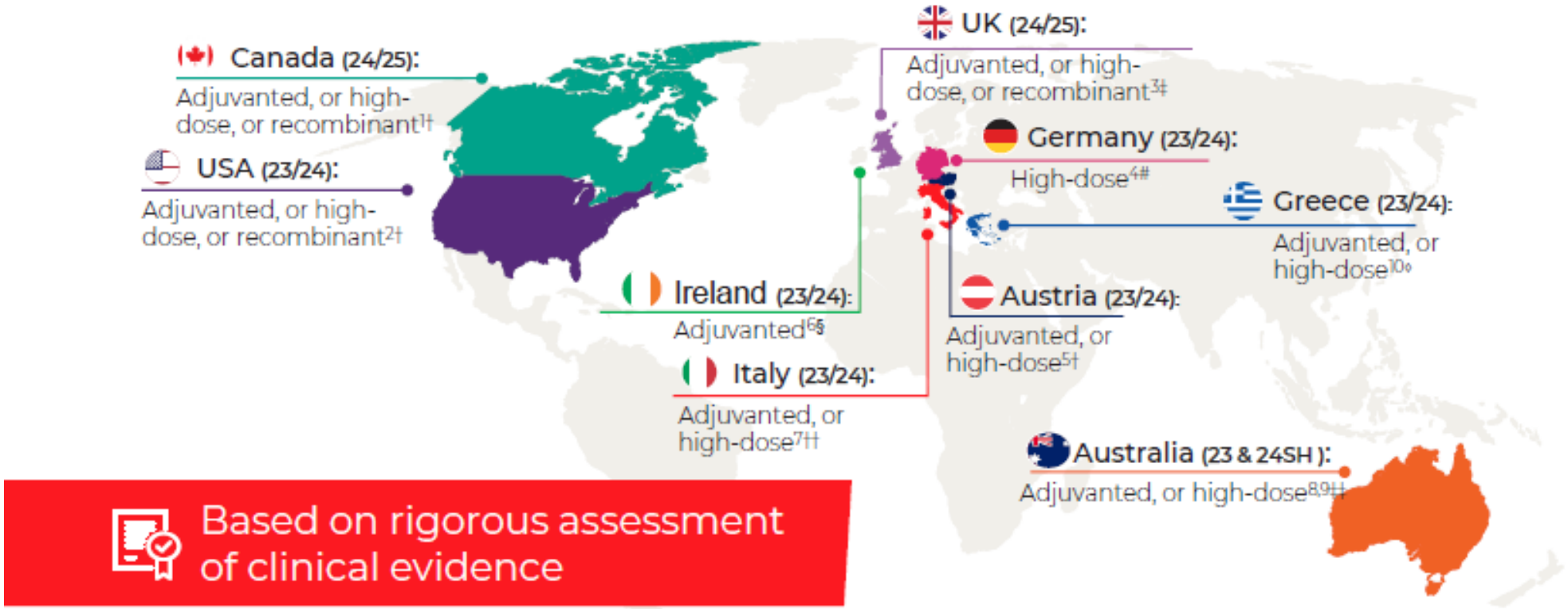
各國政府建議推薦接種的流感疫苗

美國、英國、澳洲等國家政府疫苗接種委員會，推薦65歲以上長者優先接種



SH: Southern hemisphere
†If none of these are available, then any other age-appropriate influenza vaccine should be used. ‡If aQIV, QIV-HD or QIVr are not available, QIVc is considered an acceptable alternative. #If QIV-HD is not available, QIVc, QIVr, aQIV, and QIV split virus and subunit vaccines are recommended alternatives. ††QIV, QIVr, and QIVc are also available for adults aged ≥65 but are not specifically recommended. §QIV is recommended if aQIV is not available. ‡‡Both aQIV and QIV-HD are equally recommended, but only aQIV is funded by the National Immunisation Program. ◊Both aQIV and QIV-HD are equally recommended. aQIV, adjuvanted quadrivalent influenza vaccines; QIV-HD, high-dose quadrivalent influenza vaccines; QIVr, recombinant quadrivalent influenza vaccines; QIVc, cell-based quadrivalent influenza vaccines; TIVe/QIVe, standard egg-culture influenza vaccines.

英國政府建議

Summary table of influenza vaccines for 2024/25

Programme	Age/Risk group	Preference	If the preferred vaccine is not available
Routine	≥65 years	aQIV, QIVr, QIV-HD	QIVc
	18-64 years in risk groups	QIVc or QIVr	QIVe
	2-17 years	LAIV	
	2-17 years in risk groups but unable to have LAIV†	QIVc	QIVe
	6 months-2 years in risk groups	QIVc (off label)	QIVe

† LAIV the vaccine of choice for the children's programme 2- to 17-year-olds

Adults 65 years of age and over

For vaccination of those aged 65 years and over JCVI advises the use of the following vaccines:

- Adjuvanted quadrivalent inactivated influenza vaccine (aQIV)
- High-dose quadrivalent inactivated influenza vaccine (QIV-HD)
- Quadrivalent recombinant influenza vaccine (QIVr)

The quadrivalent influenza cell-culture vaccine (QIVc) can also be considered for use in this age group if the above options are not available subject to the considerations below.
The quadrivalent influenza egg-culture vaccine (QIVe) is not advised for use in this age group.

Reference:https://www.gov.uk/government/publications/national-flu-immunisation-programme-plan-2024-to-2025/national-flu-immunisation-programme-2024-to-2025-letter

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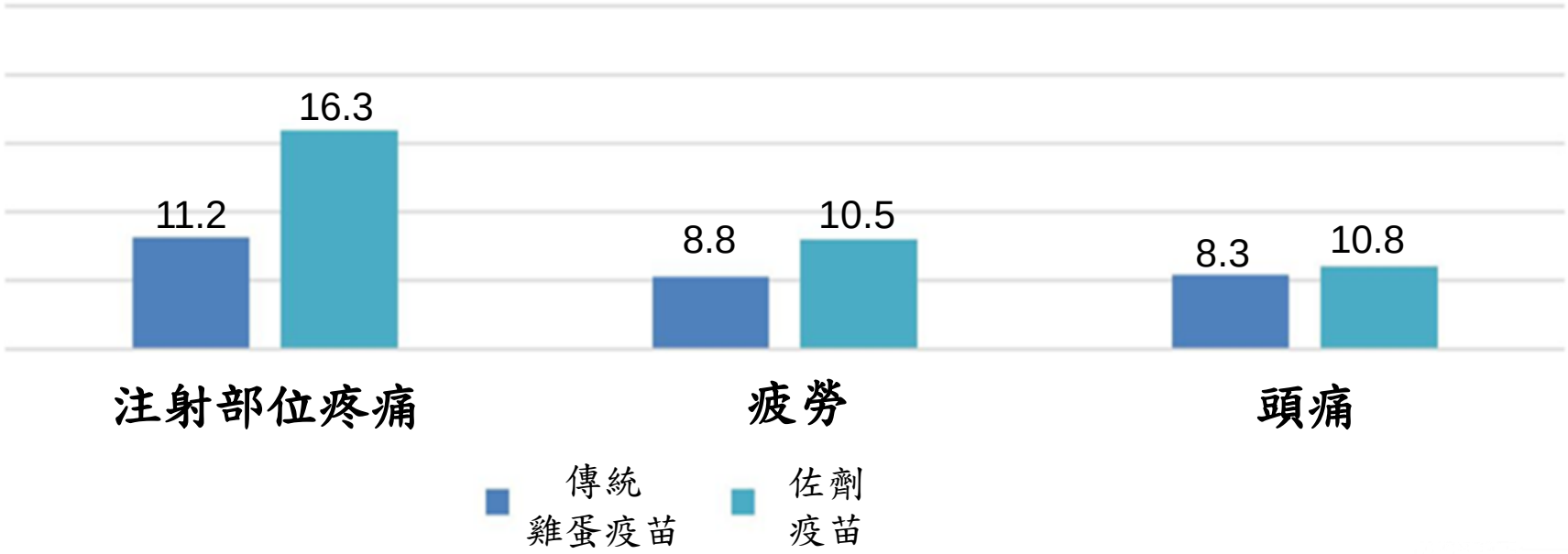
Fluad Tetra增強免疫

- 佐劑添加到疫苗可產生更強、更廣泛和更持久免疫反應的物質。
- 近年來，疫苗經常添加佐劑以提高其有效性。
- Fluad Tetra，使用MF59佐劑，主要由角鯊烯油製成(原來存在於人類、植物和動物體內的天然油脂)。

Fluad® Tetra 安全性(V118_18和V118_20)

- 兩項臨床試驗研究中對4,269 名年齡≥65 歲的受試者進行安全性評估，收集疫苗接種7 天後局部和全身不良反應事件，多數是**輕度或中度**的不良反應，且 **3 天內**會恢復。
- 在兩項研究中，發生率(**≥10%**)，最常通報的不良反應:



輔流安四價流感疫苗 FLUAD TETRA Suspension for Injection 仿單, 衛部菌疫輸字 第 001230 號, 版本日期 2023-09-05

接種流感疫苗 守護你我

Holodinsky JK, Zerna C, Malo S, Svenson LW, Hill MD. Association between influenza vaccination and risk of stroke in Alberta, Canada: a population-based study. Lancet Public Health. 2022 Nov;7(11):e914-e922. doi: 10.1016/S2468-2667(22)00222-5. Erratum in: Lancet Public Health. 2022 Dec;7(12):e991. PMID: 36334607.

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謝 謝 指 教