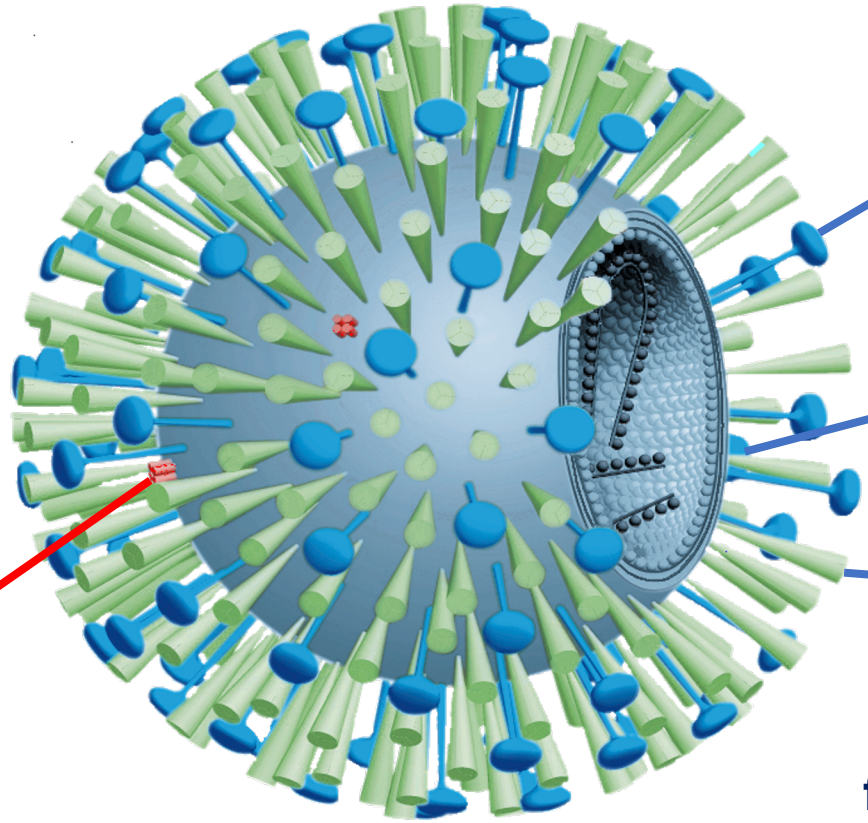
流行性感冒之
抗病毒藥物治療及疫苗預防

中山附醫 兒童感染科 潘蕙嫻

病毒結構



神經胺酸酶
(Neuraminidase)
11 subtypes
facilitates elution of progeny virions from infected cells

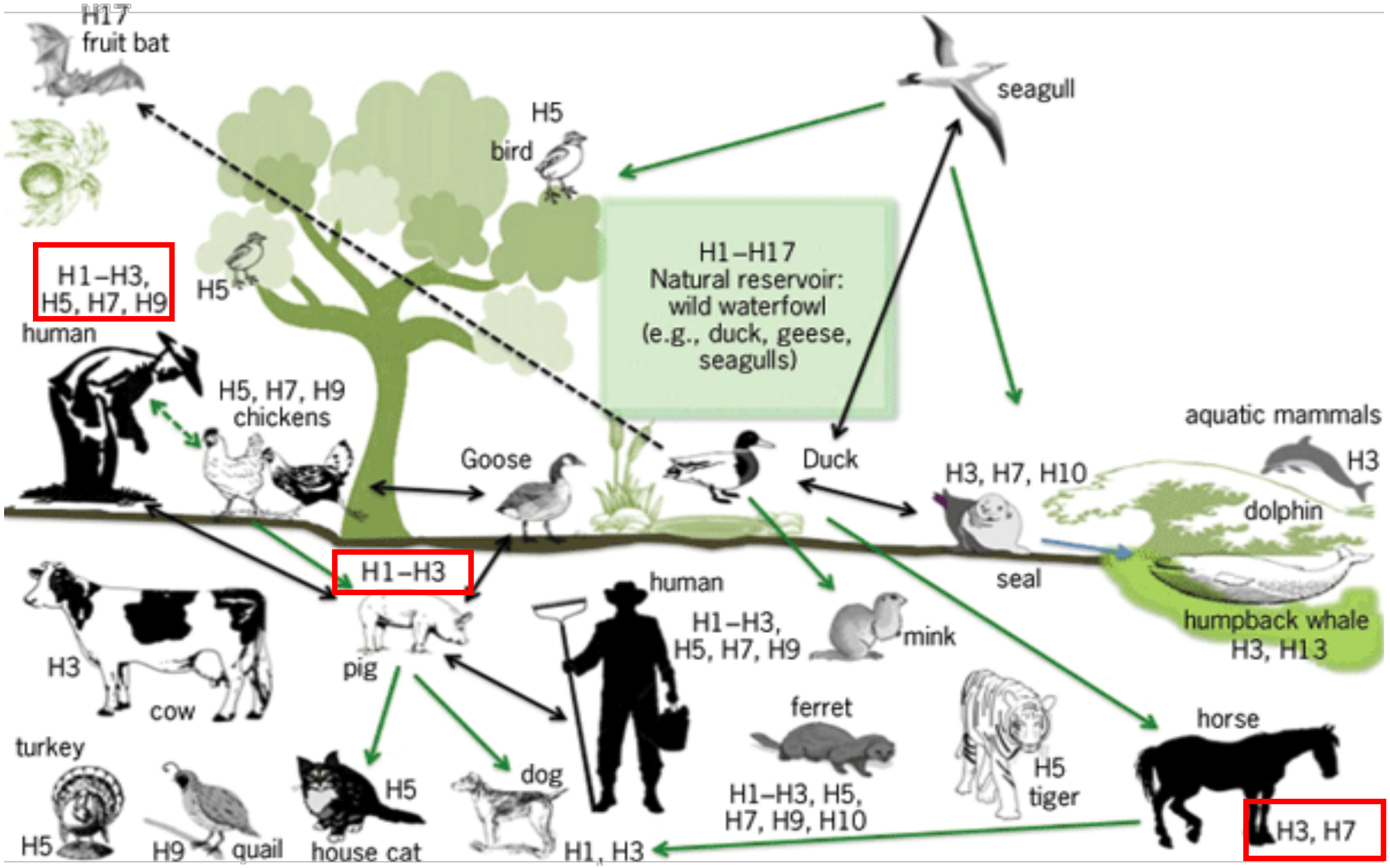
M1 protein

血球凝集素
(Hemagglutinin)
18 subtypes
functions in attachment & penetration

M2 protein

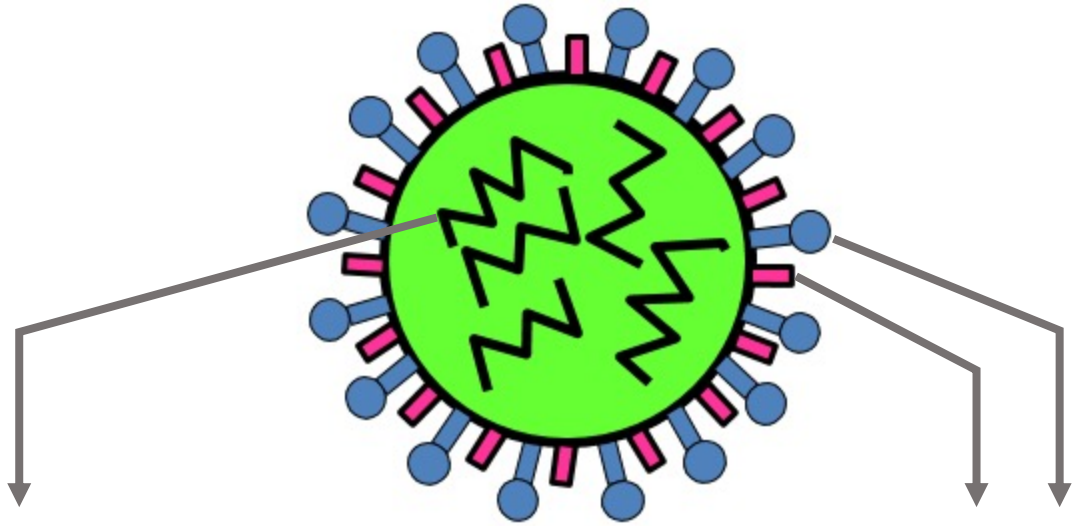
流感種類

	A型流感病毒	B型流感病毒	C型流感病毒
疾病嚴重程度	++++	++	+
帶原動物宿主	+	-	+
人類間的傳佈	大流行	地區性流行	偶發個案
抗原變異	Shift飄變/drift飄移	Drift 飄移	Drift 飄移
RNA片段數	8	8	7
病毒蛋白數	11	11	9



http://www.accessscience.com/search.aspx?rootID=802694

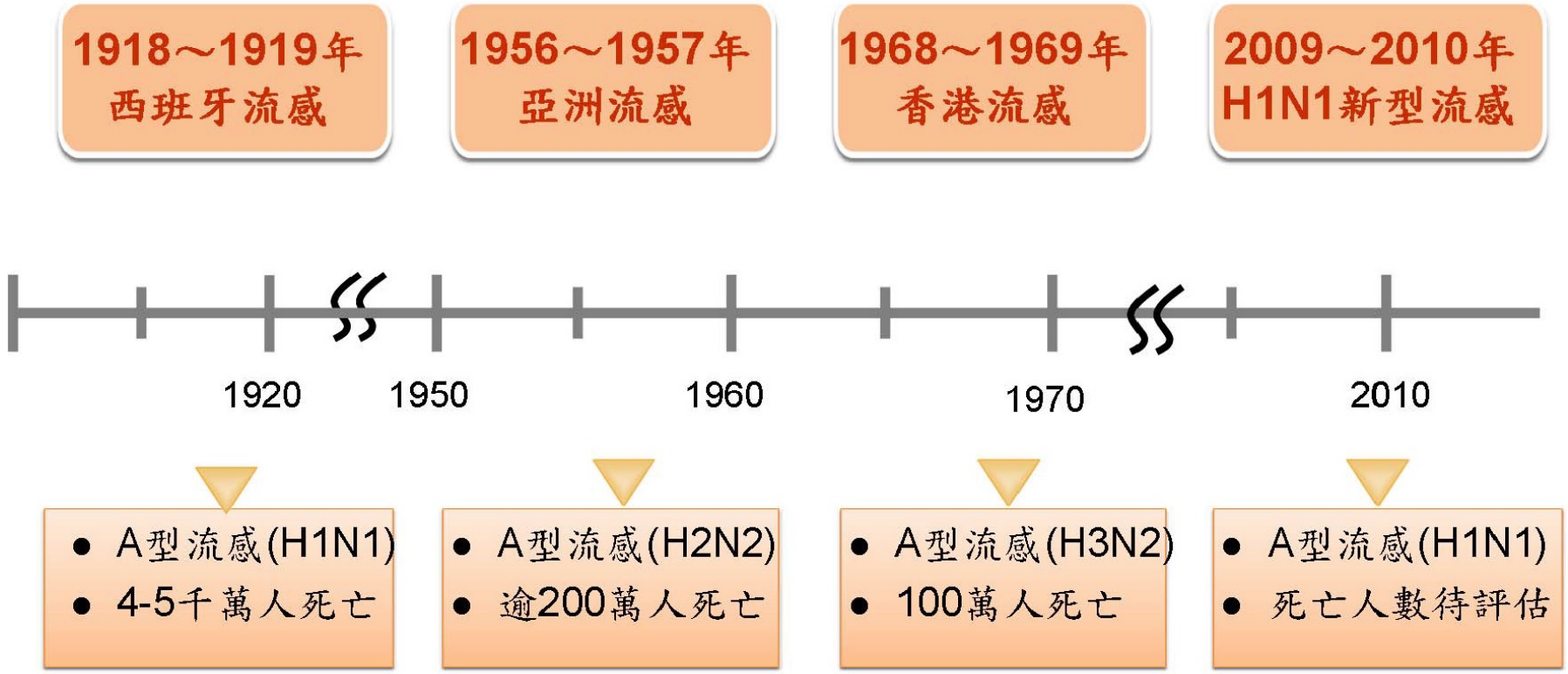
流感命名



A / California / 7 / 2009 (H1N1)

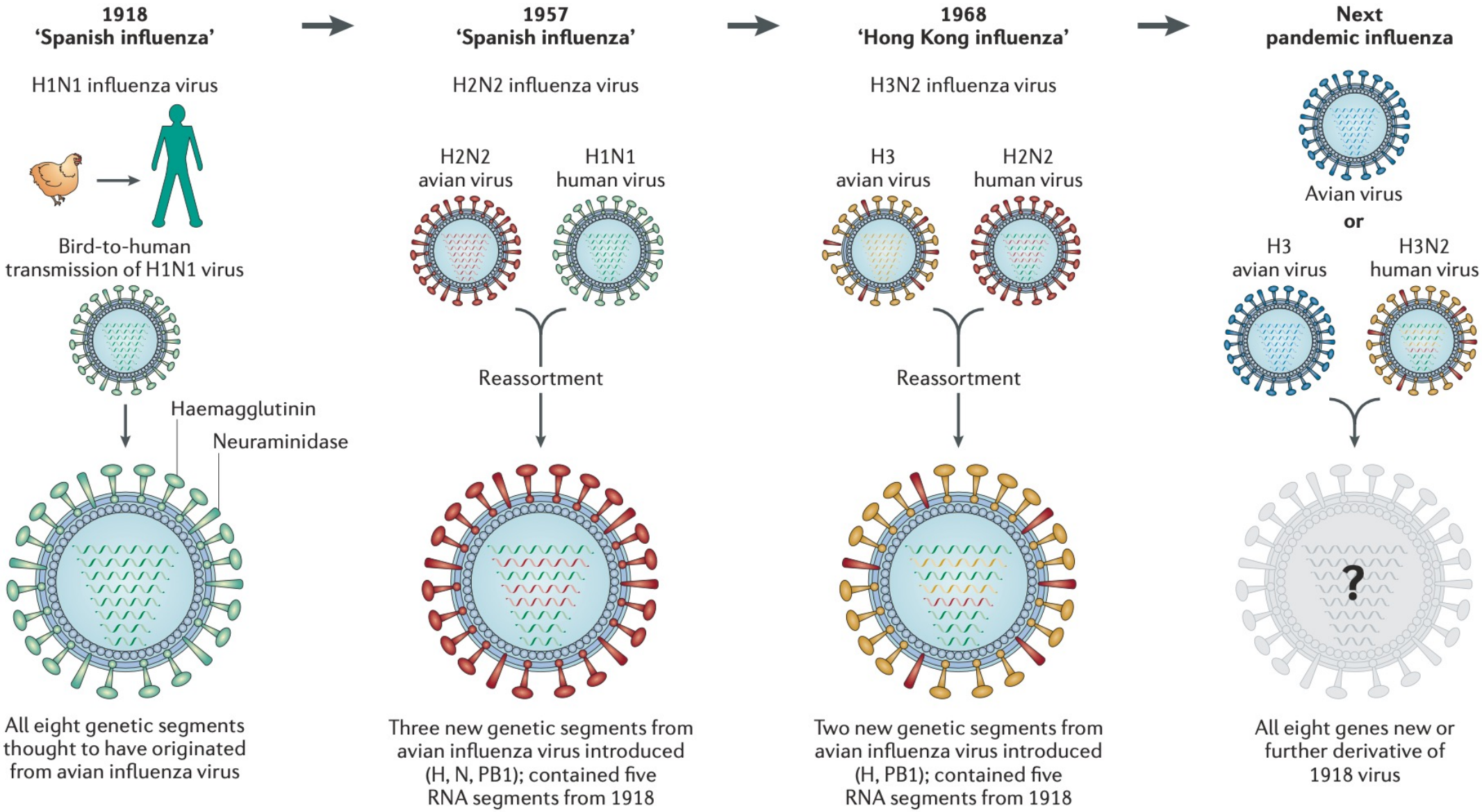
Virus type	Geographic origin	Strain number	Year of isolation	Virus subtype

二十世紀歷史上流感的大流行 (Influenza pandemics)



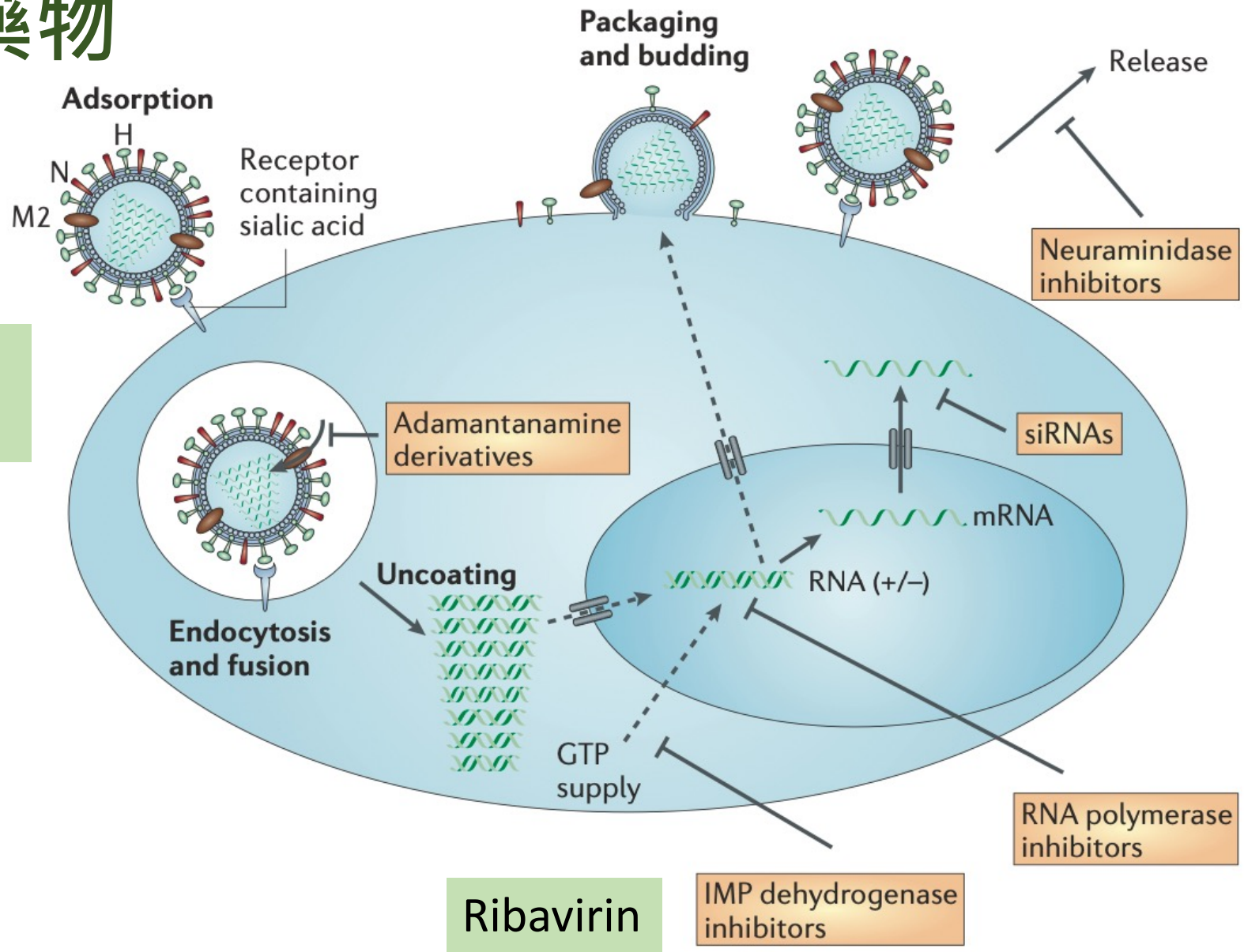
Year	Subtype	Estimate Death (million)	Origin of gene						
			NA	PA	PB1	PB2	NP	M	NS
1918	H1N1	50~100							
1957	H2N2	1~4							
1968	H3N2	1							
2009	H1N1	~0.018							

Reid et al 2004, SOIA Novel et al 2009, Taubenberger et al 2005, Zimmer and Burke, 2009



De Clercq E. Nat Rev Drug Discov. 2006.

抗病毒藥物



Amantadine
Rimantadine

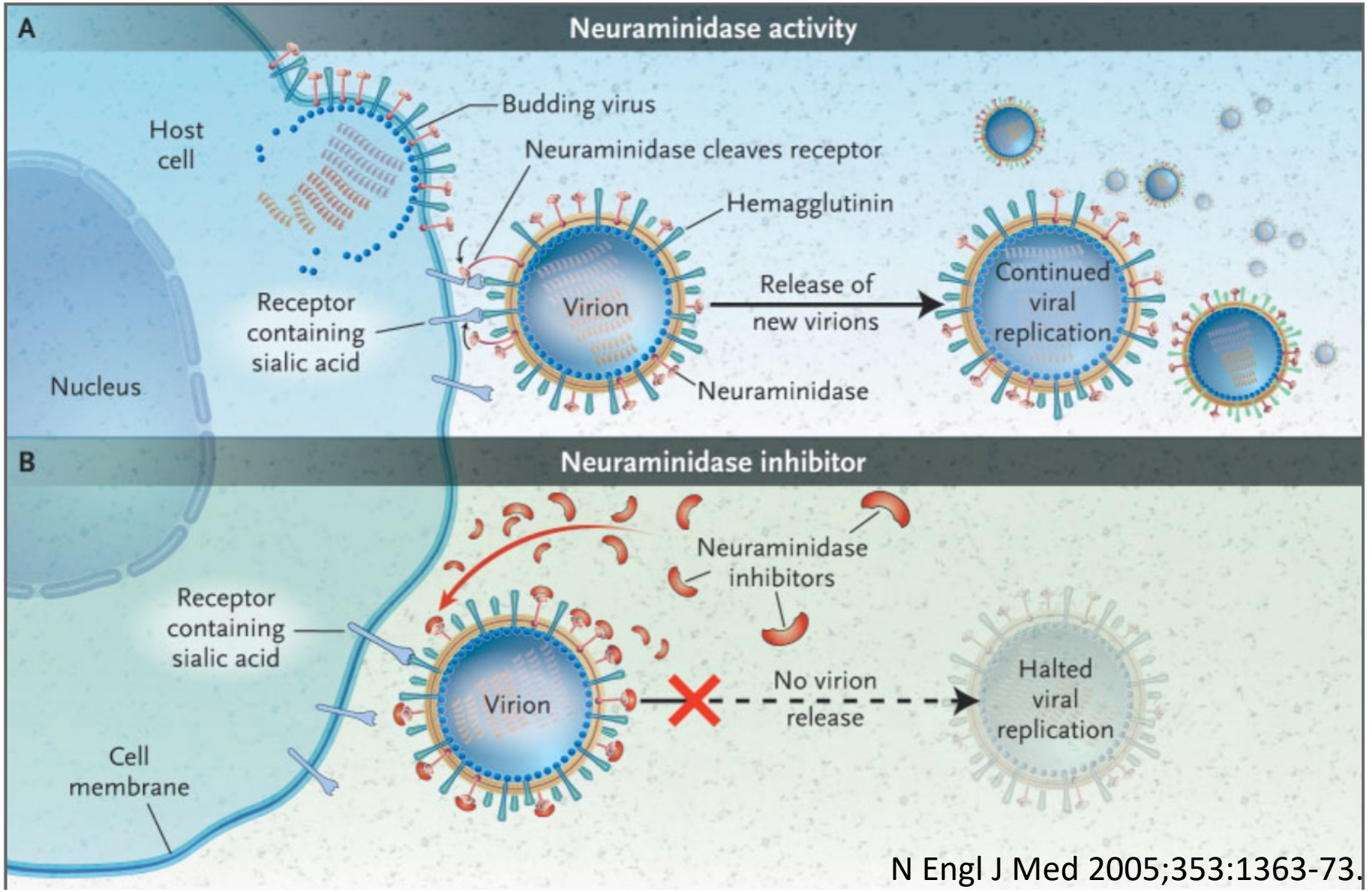
Zanamivir
Oseltamivir
Peramivir

Favipiravir

Ribavirin

De Clercq E. Nat Rev Drug Discov. 2006.

Mechanism of Neuraminidase Inhibitor



N Engl J Med 2005;353:1363-73.

抗病毒藥物

- **M2 protein inhibitor**
  - Amantadine/Rimantadine
  - 抗藥性問題嚴重，目前不適用
- **Neuraminidase inhibitor**
  - Oseltamivir (oral) / zanamivir (INH) / peramivir (IV)
  - 流感抗病毒藥物主流
  - 抑制病毒表面之神精氨酸酶，阻止複製完成之病毒自宿主細胞內釋出
  - 預防疾病、減輕症狀、縮短病程

- **RNA polymerase inhibitor**
  - Favipiravir (Avigan)
  - 干擾RNA病毒的複製過程，抑制感染細胞內的病毒基因複製以防止繁殖
  - 用於治療新型流感（限於其他抗流感病毒藥物無效）
  - 日本藥政許可
- **Polymerase Acidic Endonuclease inhibitor**
  - Baloxavir marboxi (Xofluza)
  - 作用於流感病毒複製過程所必需的Cap-snatching mechanism，可抑制流感病毒的複製增生，亦可阻斷流感病毒的傳播
  - 108年藥證許可

流感抗病毒藥劑種類

學名	Oseltamivir	Zanamivir	Peramivir	Favipiravir	Baloxavir marboxil
商品名	克流感/易剋冒	Relenza	Rapiacta	Avigan	Xofluza
包裝	75毫克膠囊	碟型吸入器x1 4孔間隔之泡囊x5	點滴用注射袋300mg	淡黃色膜衣錠，每錠200mg	20毫克膜衣錠
使用方式	口服	吸入	注射	口服	口服
對象	>=1個月	>=5歲	>=1個月	成人	>=12歲且體重>=40kg
劑量	75mg BID，5 days 2-3mg/kg BID	2孔 BID，5 days	成人：300mg（max 600mg） 兒童：10mg/kg	1600mg BID，1 day 600mg BID，4day	40-80公斤：口服單次40mg；大於80公斤：口服單次80mg
腎功能調整劑量	是	否	是	是	否

公費流感抗病毒藥劑儲備目的

- 因應全球新型流感大流行之整備需求，疾管署依世界衛生組織及國內專家建議，採購及儲備流感抗病毒藥劑
- 訂定公費藥劑使用對象，提供醫療使用於感染流感後容易併發重症的高危險群
- 於高峰期釋出效期最短的藥物，避免造成屆期銷毀之浪費情形

公費流感抗病毒藥劑使用對象

- 「流感併發重症」通報病例(需通報於法定傳染病通報系統)
- 「新型A型流感」通報病例(屬第五類法定傳染病需通報於法定傳染病通報系統) 註：選填此項者需填寫法傳編號
- 孕婦經評估需及時用藥者(領有國民健康署核發孕婦健康手冊之婦女)
- 未滿5歲及65歲以上之類流感患者
- 確診或疑似罹患流感住院(含急診待床)之病患 註：罹患流感因病況嚴重而需住院治療的病患，並不包括門診病人，依此條件使用公費藥劑者須備有「住院紀錄」
- 具重大傷病、免疫不全(含使用免疫抑制劑者)或流感高風險慢性疾病之類流感患者
- 肥胖之類流感患者(BMI>=30)

- 類流感等群聚事件經疾病管制署各區管制中心防疫醫師認定需用藥者 註：選填此項者需填寫群聚編號
- 新型A型流感極可能/確定病例之密切接觸者(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫所接觸之個案的法傳編號
- 動物流感發生場所撲殺清場工作人員(接觸者名冊經傳染病防治醫療網區正/副指揮官或其授權人員研判需給藥者) 註：選填此項者需填寫禽畜場名稱或編號

12月～3月

- 因應流感季高峰期防治需求之擴大用藥對象

公費流感抗病毒藥劑擴大使用對象

- 擴大使用期間：流感流行季
  - 每年12 月1日至隔年3月31日
  - 將視每年疫情狀況調整
- 擴大使用對象
  - 有發燒之類流感症狀，且家人/同事/同班同學有類流感發病者

- 經醫師評估符合公費流感病毒藥劑使用對象，無需進行快篩，即可依醫師專業判斷開立公費藥劑
- 公費藥劑使用對象須為本國籍，倘非本國籍人士，除通報流感併發重症及新型A型流感等法定傳染病患者外，應有居留證（18歲（含）以下孩童其父母需一方為本國籍或持有居留證

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

**Timothy M. Uyeki,[1] Henry H. Bernstein,[2] John S. Bradl
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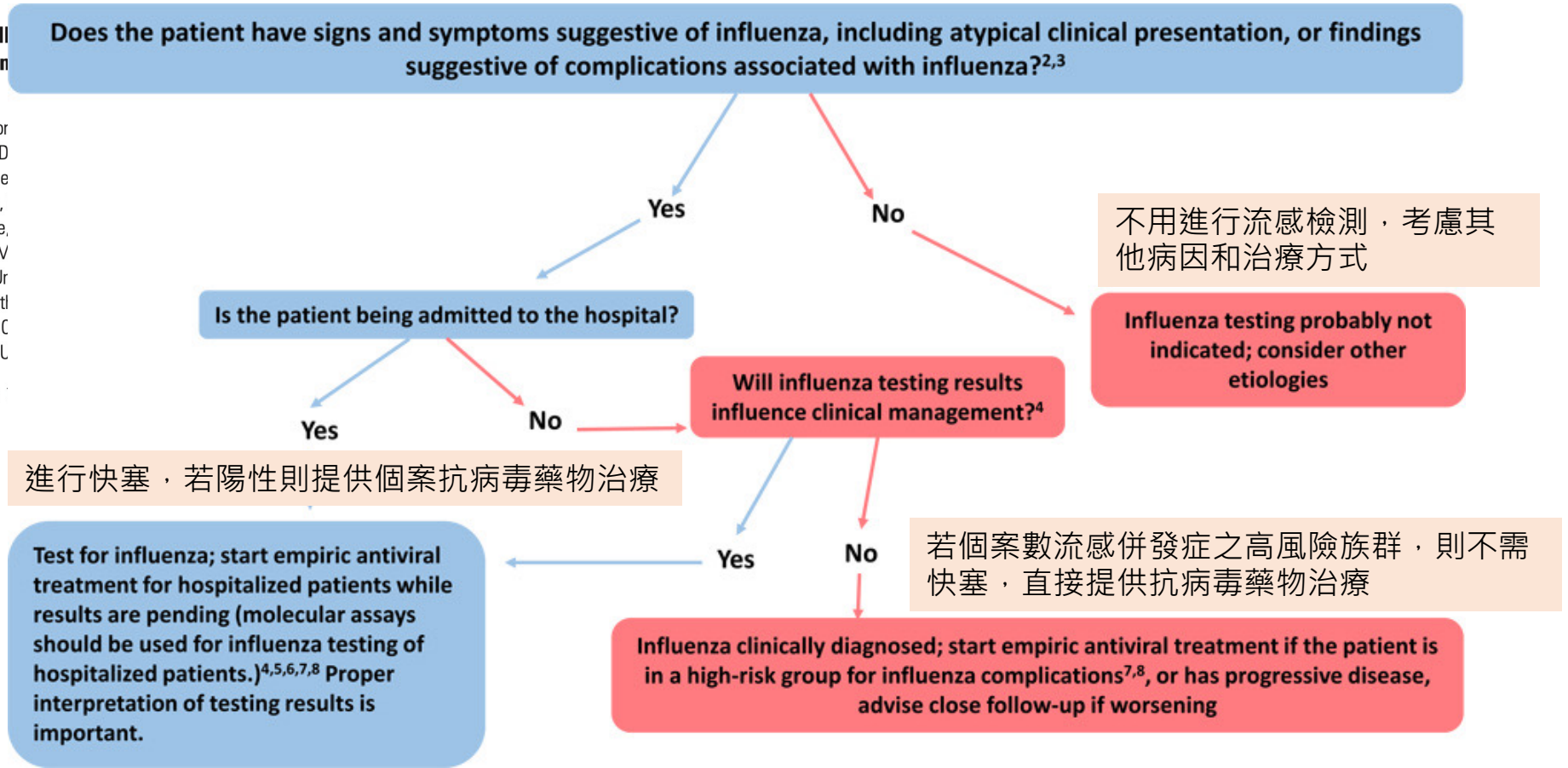
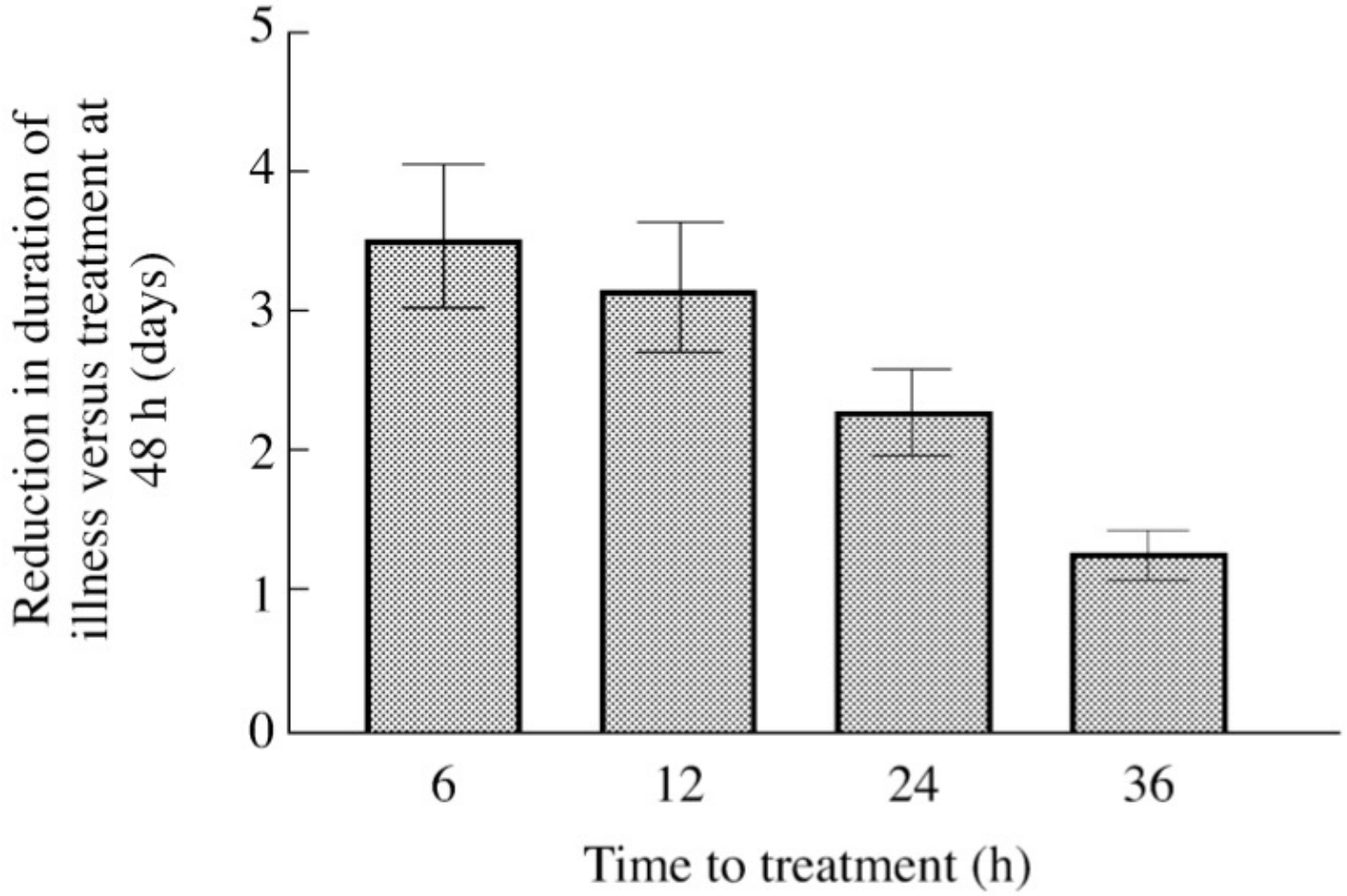
Keywords. influenza; diagnostic testing;

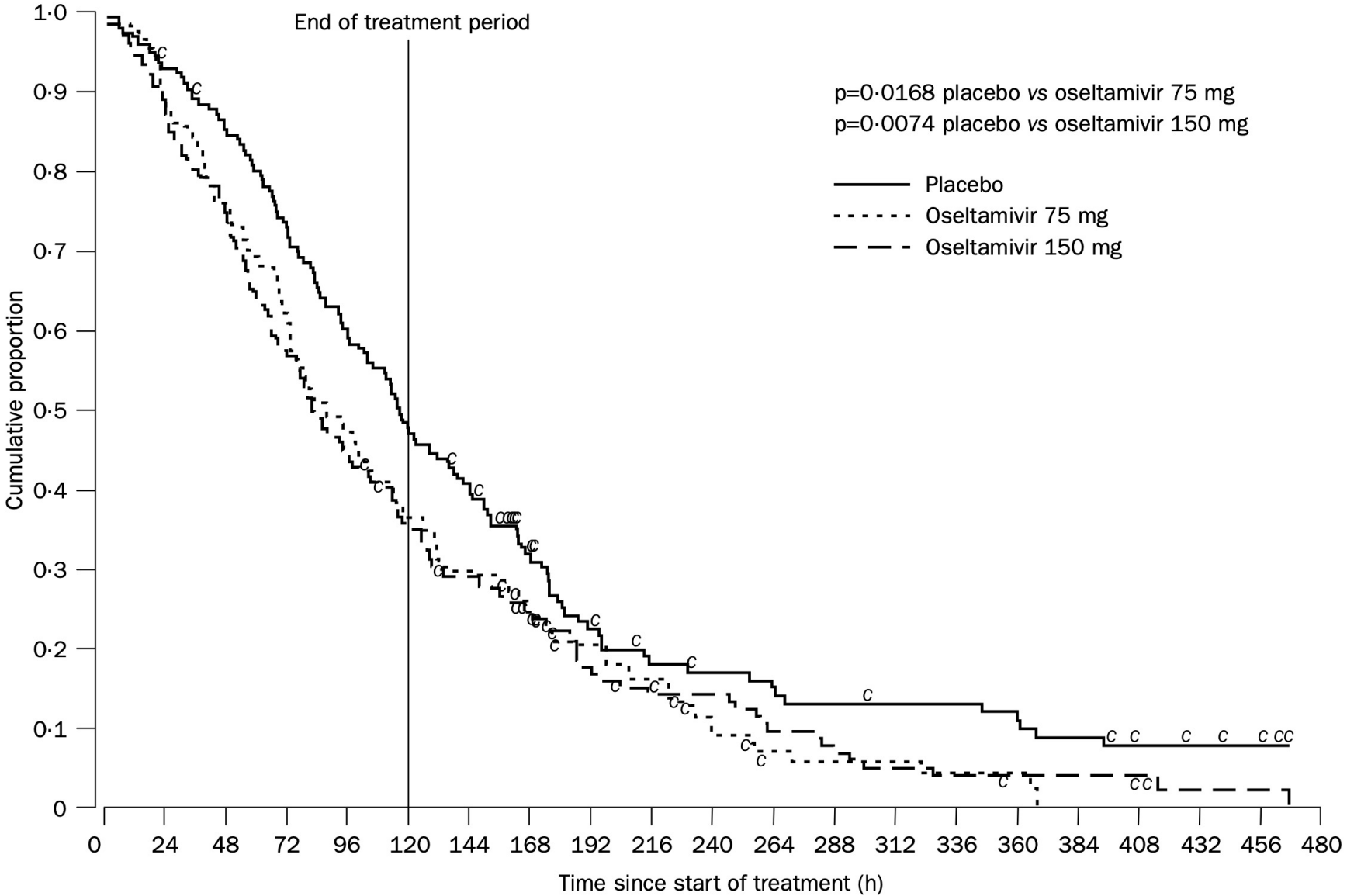


Efficacy of Oseltamivir



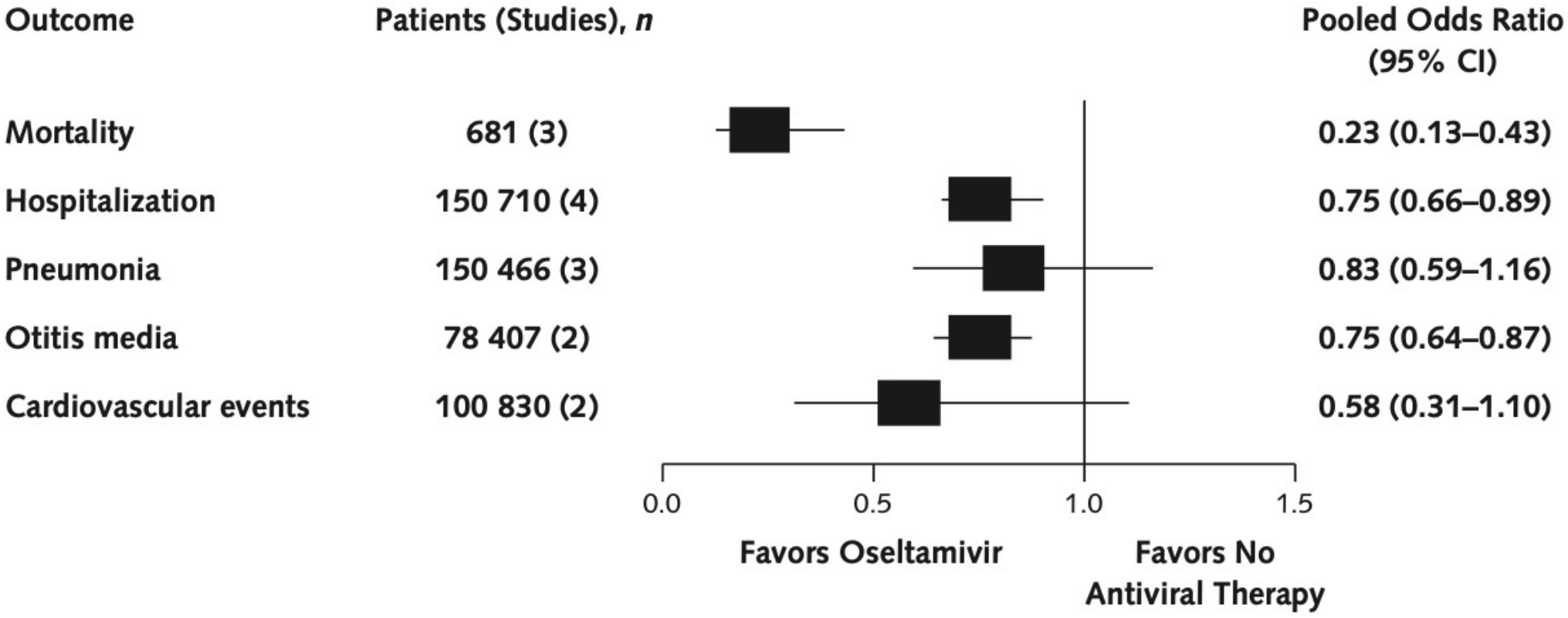
Journal of Antimicrobial Chemotherapy (2003) **51**, 123–129

Efficacy of Oseltamivir



Lancet 2000; **355:** 1845–50

Efficacy of Oseltamivir



Zanamivir

- Zanamivir(10mg BID for 5 days) inhaled early in the course in previously healthy adults and children 5-12 years old shortens the times to illness resolution and return to usual activities by **1-3 days**.
- In individuals with influenza B illness, zanamivir reduces the medial duration of fever by 32% from **53 hours to 36 hours**, compared to oseltamivir

Figure 1 Parts of the DISKHALER

Peramivir

- 何時考慮使用
  - Severe hospitalized patients (ICU with organ failure)
  - Poor response to the other NAIs
    - Poor GI absorption of oral medication
    - Lower respiratory tract infection, difficult to using inhaled anti-viral agents
  - Avian flu (H7N9 influenza)
- 通過衛福部藥證，自費使用
- 公費限新型流感，經轄區指揮官同意使用

Favipiravir

- RNA polymerase inhibitor
- 無藥證，限新型流感通報病例使用，經轄區指揮官同意使用
- 具致畸胎性，孕婦及有懷孕可能的婦人禁止使用

Baloxavir marboxil

- 抑制CAP依存性內切酶來終止病毒mRNA的轉錄
- 跟Oseltamivir比較，緩解流感**症狀**和**退燒**的程度，無顯著差異
- 抗病毒能力， Baloxavir在**抑制病毒數量**或者**效率**上都比對照組和Oseltamivir來的顯著
- 病毒本身有I38T/M/F取代變異的特性將會使得Baloxavir對於該病毒的抑制效果較不佳

Use of Ribavirin to Treat Influenza

TO THE EDITOR: Ribavirin, an antiviral drug with in vitro activity against both DNA and RNA viruses, is approved in the United States for the treatment of hepatitis C and respiratory syncytial virus.[1] Hepatitis C is treated with approved oral formulations in combination with interferon products; respiratory syncytial virus is treated with an aerosol formulation. Intravenous ribavirin is not curren

tion of therapy and the onset of symptoms (or viral inoculation in challenge studies), and the reporting of clinical outcomes, microbiologic data, and adverse events. Reported adverse events were consistent with the labeling of approved aerosol and oral formulations.[4,5]

Since the late 1980s, clinicians have requested access to intravenous ribavirin from the manu-

atening

Clinical data regarding its efficacy have been inconclusive; thus, it is not recommended for the treatment of influenza infection

N Engl J Med 361;17

Combination therapy

Oseltamivir, amantadine, and ribavirin vs. Oseltamivir

1. Lower nasopharyngeal swab polymerase chain reaction at day 3

2. No clinical endpoint improvements, including median duration of symptoms and duration of fever

	Total (n=454)	Combination group (n=230)	Monotherapy group (n=224)	p value
Day 0	454	230	224	..
Median viral count, log_{10} copies/mL	6·5 (5·4–7·4)	6·4 (5·6–7·2)	6·7 (5·1–7·7)	..
≥LLOQ	421 (93%)	221 (96%)	200 (89%)	..
≥LOD, < LLOQ	13 (3%)	4 (2%)	9 (4%)	..
<LOD	20 (4%)	5 (2%)	15 (7%)	..
Day 3	437	221	216	..
Median viral count, log_{10} copies/mL	3·4 (3·2–4·6)	3·4 (3·2–4·2)	3·9 (3·2–5·0)	0·004
≥LLOQ	152 (35%)	65 (29%)	87 (40%)	0·009
≥LOD, <LLOQ	47 (11%)	22 (10%)	25 (12%)	..
<LOD	238 (54%)	134 (61%)	104 (48%)	..
Day 7	431	216	215	..
Median viral count, log_{10} copies/mL	<3·2 (<3·2–3·4)	<3·2 (<3·2–3·4)	<3·2 (<3·2–3·4)	0·38
≥LLOQ	43 (10%)	19 (9%)	24 (11%)	0·24
≥LOD, <LLOQ	11 (3%)	4 (2%)	7 (3%)	..
<LOD	377 (87%)	193 (89%)	184 (86%)	..

Data are median (IQR) or n (%).Primary endpoint was the percentage of participants with virus detectable by PCR (ie, ≥LLOQ and ≥LOD, <LLOQ). LLOQ=lower limit of quantification of PCR assay. LOD=limit of detection of PCR assay.

Table 2: **Influenza virus over time in the efficacy population**

Lancet Infect Dis. 2017;17(12):1255

Vaccine

流感的預防

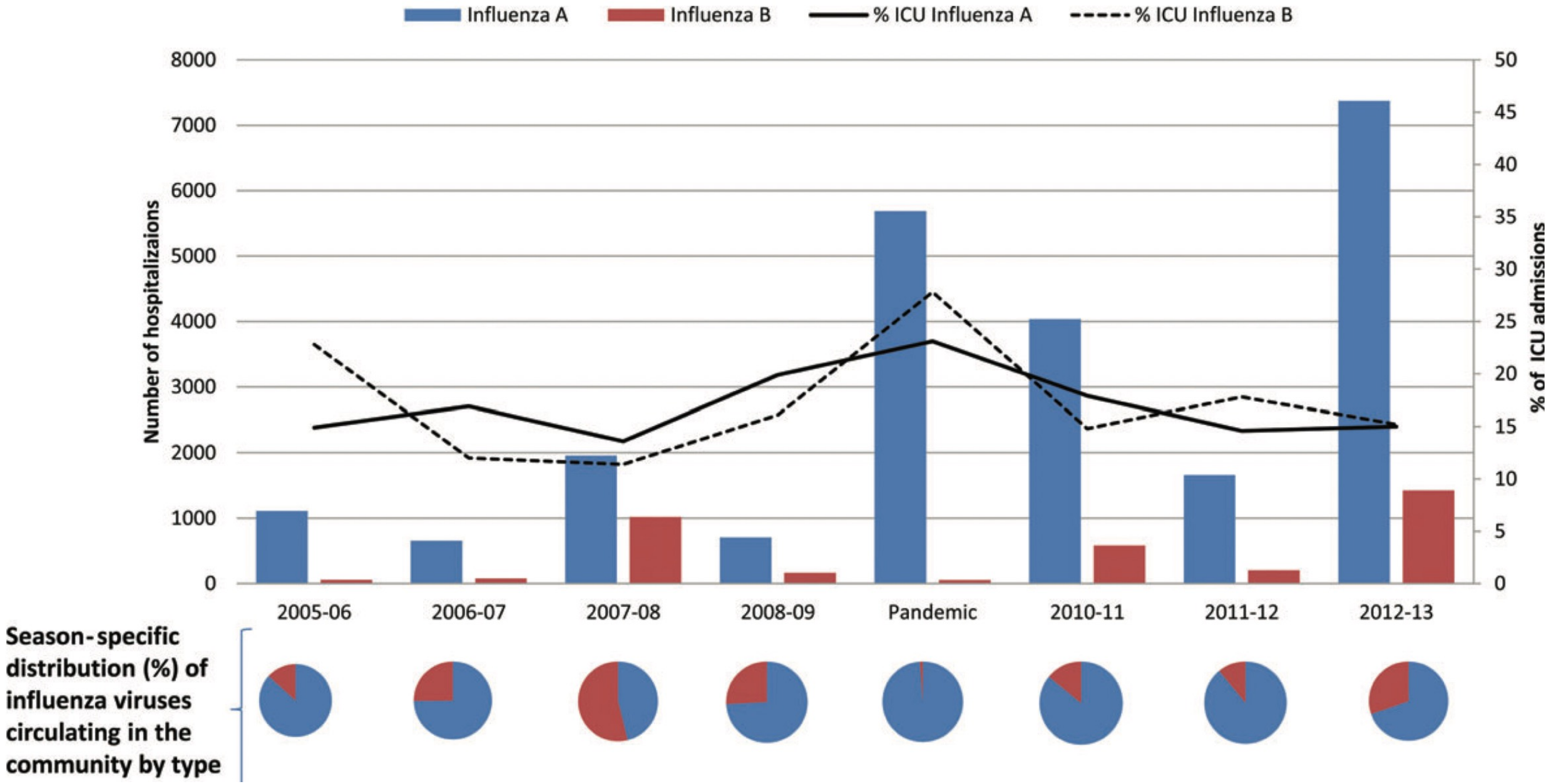
- 接種**疫苗**
  - 預防流感最有效的方式
- 暴露後預防藥物
  - 特殊高風險族群、群聚事件
- 感染管制措施
  - 醫療機構、長期照顧機構、人口密集機構
- 個人衛生
  - 咳嗽禮節、手部衛生、戴口罩

2021-2022年流感疫苗

- 不活化疫苗
- 四價疫苗
- 6個月以上均接種0.5mL
- 接種劑量與間隔
  - 8歲（含）以下首次接種2 劑，且間隔至少4週
  - 國小學童集中接種，全面施打1劑，若仍自覺需要，至醫療院所自費接種第2劑

2021-2022流感疫苗抗原成分

- 雞胚胎蛋培養疫苗
  - an A/Victoria/2570/2019 (H1N1) pdm09-like virus;
  - an A/Cambodia/e0826360/2020 (H3N2)-like virus;
  - a B/Washington/02/2019- like virus (B/Victoria lineage);
  - a B/Phuket/3073/2013-like virus (B/Yamagata lineage)
- 細胞培養疫苗
  - an A/Wisconsin/588/2019 (H1N1) pdm09-like virus;
  - an A/Cambodia/e0826360/2020 (H3N2)-like virus;
  - a B/Washington/02/2019- like virus (B/Victoria lineage);
  - a B/Phuket/3073/2013-like virus (B/Yamagata lineage).



Clin Infect Dis 2014 July 15

Match and Mismatch Between the Vaccine and Circulating Strains of Influenza B Viruses

Season	Vaccine B Lineage	Circulating B Lineages	Lineage-Level Vaccine Match, %	Lineage-Level Vaccine Mismatch, %
1999–2000	Yamagata	Yamagata (100%)	100	0
2000–2001	Yamagata	Yamagata (100%)	100	0
2001–2002	Yamagata	Yamagata (100%)	100	0
2002–2003	Victoria	Victoria (90%), Yamagata (10%)	90	10
2003–2004	Victoria	Yamagata (60%), Victoria (40%)	40	60
2004–2005	Yamagata	Yamagata (100%)	100	0
2005–2006	Yamagata	Victoria (95%), Yamagata (5%)	5	95
2006–2007	Victoria	Yamagata (100%)	0	100
2007–2008	Victoria	Yamagata (100%)	0	100
2008–2009	Yamagata	Victoria (100%)	0	100
2010–2011	Victoria	Victoria (90%), Yamagata (10%)	90	10
2011–2012	Victoria	Victoria (100%)	100	0

Clinical Infectious Diseases® 2014;59(11):1519–24

公費流感接種對象（暫定）

- **第一階段**
  - 醫事人員
  - 國小、國中、高中、高職、五專1至3年級學生等
  - 65歲以上長者
  - 滿6個月以上至國小入學前幼兒
  - 衛生防疫人員
  - 安養、養護、長照機構
  - 禽畜業及動物防疫人員
  - 孕婦及6個月內嬰兒之父母
  - 幼兒園托育人員及托育機構專業人員(含社區公共托育家園)
  - 具有潛在疾病者，包括高風險慢性病人、BMI大於等於30者、罕見疾病患者及重大傷病患者
- **第二階段**
  - 50-64歲成人

108年度流感疫苗接種計畫成果

統計日期：109/9/30

接種對象	應接種數	接種數	接種率
65歲以上長者/機構對象*	3,537,314	1,813,931	51.3%
50-64歲成人	5,289,099	990,641	18.7%
醫事執登人員	329,622	230,269	69.9%
防疫人員及醫院非執登工作人員	147,985	139,744	94.4%
禽畜養殖業等及動物防疫人員	8,386	8,386	100.0%
國小、國中、高中、高職、五專1至3年級學生	2,372,287	1,834,474	77.3%
3歲以上至入學前幼童--曾接種過	402,028	290,870	72.4%
3歲以上至入學前幼童--未曾接種過(第1劑)	238,153	39,948	16.8%
3歲以上至入學前幼童--未曾接種過(第2劑)		18,572	7.8%
罕見疾病/重大傷病患者			
19-49歲高風險慢性病人			
孕婦及6個月內嬰兒之父母	-	89,559	-
托育人員及托育機構專業人員	50,450	12,950	25.7%
6個月以上3歲以下幼兒--曾接種過	142,554	136,434	95.7%
6個月以上3歲以下幼兒--未曾接種過(第1劑)	365,480	155,579	42.6%
6個月以上3歲以下幼兒--未曾接種過(第2劑)		112,357	30.7%

近5 年醫事人員流感接種率：66-74%

*為安養等機構之住民及所屬直接照顧工作人員

Vaccine Efficacy

(1 - relative risk) x 100

- Relative risk was the ratio of the percentages of vaccine recipients with influenza to placebo recipients with influenza(P vaccine/P placebo)

Drugs (2019) 79:1337–1348

Vaccine Effectiveness: How Well Do the Flu Vaccines Work?

Questions & Answers

疫苗株與當季流行病毒株吻合時，流感疫苗降低疾病的風險只有40-60%

Español | Other Languages

How effective is the flu vaccine?

CDC conducts studies each year to determine how well the influenza (flu) vaccine protects against flu illness. While vaccine effectiveness (VE) can vary, recent studies show that flu vaccination reduces the risk of flu illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine. In general, current flu vaccines tend to work better against influenza B and influenza A(H1N1) viruses and offer lower protection against influenza A(H3N2) viruses. See "Does flu vaccine effectiveness vary by type or subtype?" and "Why is flu vaccine typically less effective against influenza A H3N2 viruses?" for more information.

FLU vaccine effectiveness varies by type or subtype

在此整合性研究分析中，
H3N2：33%；B：54%；
H1N1：67%

	Pooled VE (%)	Pooled standard error	VE estimates (n)*	p value for heterogeneity	I^2
H3N2 by season					
2010–11	46% (30 to 58)	0·131	5	0·368	26·1
2011–12	32% (23 to 40)	0·063	9	0·626	0·0
2012–13	40% (32 to 46)	0·059	6	0·644	0·0
2013–14	10% (–25 to 35)	0·164	3	0·913	0·0
2014–15	7% (–32 to 34)	0·179	3	0·051	74·3
H3N2 by antigenic similarity					
Variant	23% (2 to 40)	0·126	6	0·081	55·6
Similar	33% (22 to 43)	0·080	12	0·014	56·1
H1N1pdm09 by season					
2010–11	60% (54 to 65)	0·071	12	0·894	0·0
2011–12	68% (50 to 80)	0·239	3	0·541	7·2
2012–13	55% (41 to 66)	0·142	6	0·930	0·0
2013–14	62% (52 to 70)	0·117	6	0·260	35·2
Type B by season†					
2005–06	52% (25 to 70)	0·231	3	0·648	0·0
2007–08	50% (29 to 64)	0·172	5	0·235	41·2
2010–11	55% (48 to 62)	0·080	11	0·554	0·0
2011–12	49% (0 to 74)	0·343	7	<0·0001	89·7
2012–13	55% (46 to 62)	0·087	7	0·566	0·0

Data in parentheses are 95% CIs. VE=vaccine effectiveness. *Seasons with fewer than three VE estimates for a given subtype were not included. †2009–10 is not shown because only one estimate for type B during that season existed.

Ann Intern Med. 2012;156:512-524.

2019–20 Seasonal Influenza Vaccine Effectiveness — United States,

TABLE 2. Number and percentage of outpatients with acute respiratory illness and cough (N = 4,112) receiving 2019–20 seasonal influenza vaccine, by influenza real-time reverse transcription–polymerase chain reaction (RT-PCR) test result status, age group, and vaccine effectiveness* against all influenza A and B, B/Victoria and A(H1N1)pdm09 — U.S. Influenza Vaccine Effectiveness Network, October 23, 2019–January 25, 2020

	Influenza-positive		Influenza-negative		Vaccine effectiveness	
Influenza type/Age group	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted† % (95% CI)
Influenza A and B						
Overall	**1,060**	**390 (37)**	**3,052**	**1,682 (55)**	**53 (45 to 59)**	**45 (36 to 53)**
Age group						
6 mos–17 yrs	**462**	142 (31)	**934**	492 (53)	60 (50 to 69)	55 (42 to 65)
18–49 yrs	**413**	143 (35)	**1,084**	452 (42)	26 (6 to 42)	25 (3 to 41)
≥50 yrs	**185**	105 (57)	**1,034**	738 (71)	47 (27 to 62)	43 (19 to 60)
					60 (52 to 66)	**50 (39 to 59)**
					62 (51 to 71)	56 (42 to 67)
					54 (42 to 64)	32 (11 to 48)
Influenza A(H1N1)pdm09						
Overall	**326**	**138 (42)**	**3,052**	**1,682 (55)**	**40 (25 to 53)**	**37 (19 to 52)**
Age group						
6 mos–17 yrs	**98**	35 (36)	**934**	492 (53)	50 (23 to 68)	51 (22 to 69)
18–49 yrs	**125**	48 (38)	**1,084**	452 (42)	13 (-27 to 40)	5 (–45 to 37)
≥50 yrs	**103**	55 (53)	**1,034**	738 (71)	54 (31 to 69)	50 (20 to 68)

* Vaccine effectiveness was estimated as 100% x (1 – odds ratio [ratio of odds of being vaccinated among outpatients with CDC's real-time RT-PCR influenza-positive test results to the odds of being vaccinated among outpatients with influenza-negative test results]); odds ratios were estimated using logistic regression.

† Adjusted for study site, age group, sex, race/ethnicity, self-rated general health, number of days from illness onset to enrollment, and month of illness using logistic regression.

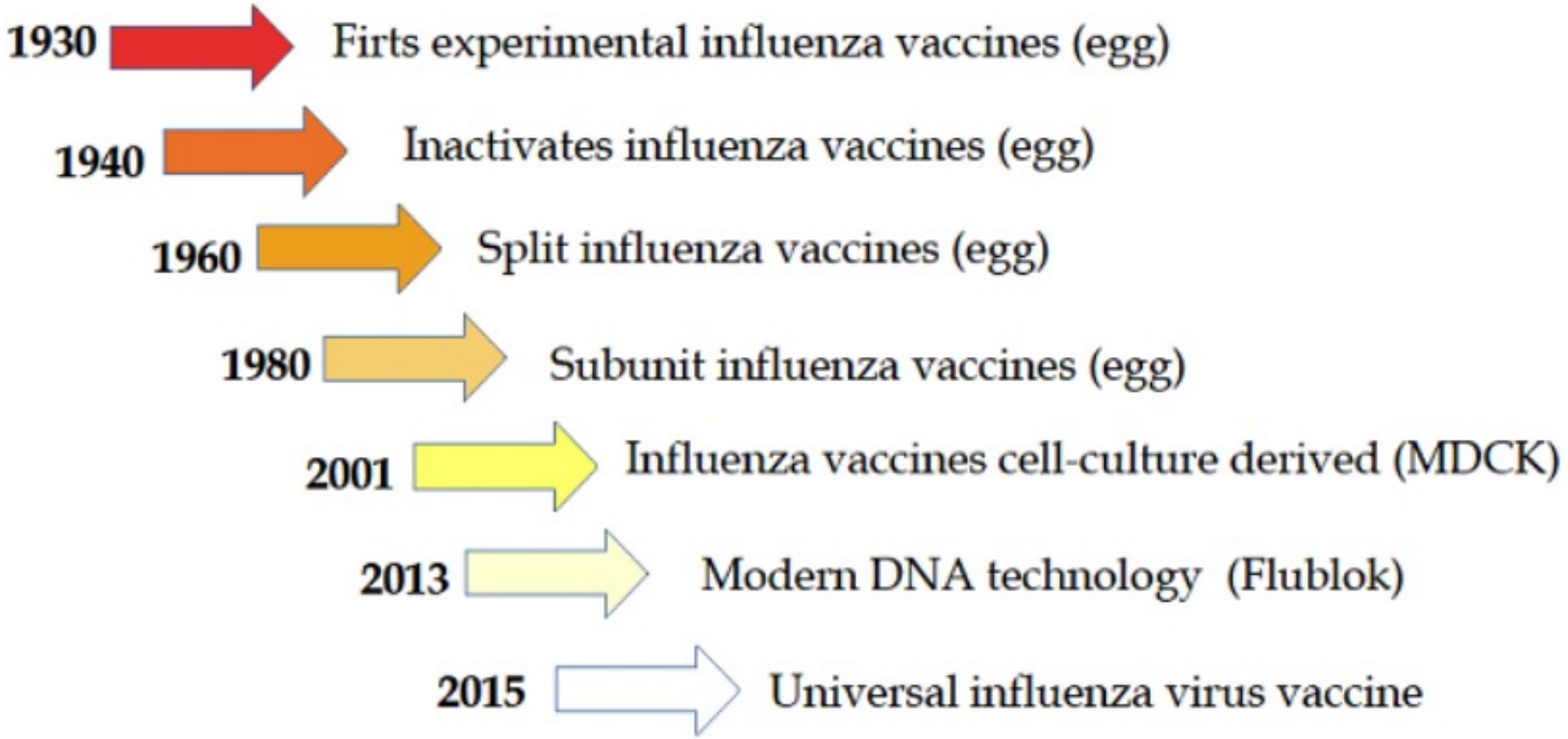
2019-2020年美國流感季流感疫苗效果45%，接種流感疫苗可降低快5成流感就醫風險

流感大事紀

1918	**Spanish Flu caused by H1N1**
1933	Isolation of influenza virus[36]
1935-1941	Early vacccination studies identified the importance of dose and matching strains[36]
1942-45	Trials with concentrated and inactivated vaccines[36]
1945	First commercial influenza vaccine available in the US[36]
1947	Global surveillance initiated by WHO
1957	**"Asian flu" caused by H2N2**
1960s	Attempts to generate attenuated viruses
1968	**Pandemic caused by H3N2**
1976-1977	Subunit influenza vaccine was developed and found to be less reactogenic than inactivated whole virus vaccines[47-49]
1976-1977	Swine flu (H1N1) outbreak in Fort Dix, US, prompting a short-lived mass vaccination campaign
1977-1978	**"Russian flu" outbreak (H1N1)**
1980s	Russians developed cold-adapted attenuated vaccine strains[64,65]
1997	**Outbreak of highly pathogenic H5N1 in Hong Kong**
1990s	Reverse-genetics system developed, leading to attenuated H5 vaccine strains[78,79]
2003	FluMist, intranasal LAIV licensed by FDA for adults*
2003-2004	**Outbreak of highly pathogenic H5N1 in Asia**
2007	H5 vaccine from Sanofi-Pastuer approved by FDA*
2007	Optaflu, MDCK-cell derived vaccine approved for use in Europe^
2009	**Swine Flu pandemic (swine origin H1N1)**
2009	FluZone High Dose licensed and recommeded by ACIP for elderly#
2009	Adjuvanted vaccines against 2009 swine flu strain approved under exceptional circumstance for use in Europe^
2010	ACIP recommends National Influenza vaccination for all ages 6 months and older#
2011	FluZone Intradermal licensed by FDA*
2012	Vepacel, Vero-cell derived influenza vaccine by GSK, licensed in Europe^, Flucelvax, MDCK-cell derived vaccine, Fluarix (quadrivalent TIV) and FluMist Quadrivalent, approved by FDA*
2013	FluBlok (baculovirus-derived) approved by FDA*

Clin Microbiol Rev. 2013 Jul;26(3):476-92.

Historical path of the development of influenza vaccine



Vaccines 2017, 5, 18

Influenza vaccine in 2020-21 in UK

Age Group	Recommended Vaccine	Live vaccine?	Types of flu strains protected	Reason for recommendation
Children aged 6 months to 2 years	Egg-grown quadrivalent vaccine (QIVe)	**No**	**Four**	LAIV is not suitable for children under two
Children aged 2 – 17 years	Live attenuated influenza vaccine (LAIV)	**Yes**	**Four**	Nasal vaccine helps to reduce spread of flu virus in children
Adults aged 18 – 64 years	Quadrivalent influenza vaccine: Egg-grown (QIVe) Cell-based (QIVc)	**No**	**Four**	Quadrivalent vaccines protect against four types of flu strain
Adults aged 65 or over	Adjuvanted trivalent influenza vaccine (aTIV)	**No**	**Three**	"Adjuvant" is added to the vaccine to make it more effective in older people

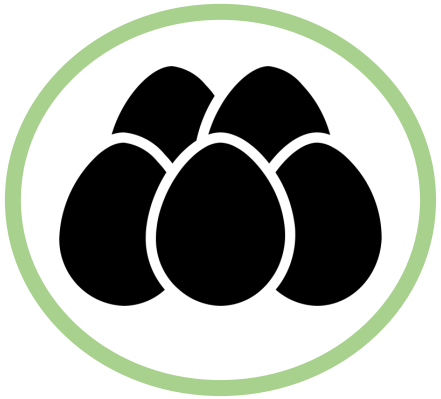
https://vk.ovg.ox.ac.uk/vk/inactivated-flu-vaccine

2020-21公費流感疫苗

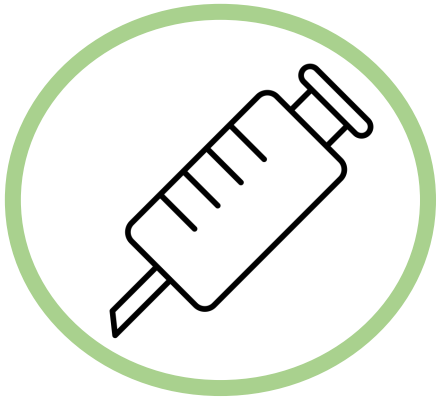
- 全面四價
- 增加細胞型流感疫苗

持有許可證廠商/品名	劑型	適用年齡
賽諾菲股份有限公司 / Vaxigrip Tetra巴斯德四價流感疫苗	0.5mL	提供6個月以上使用
國光生物科技股份有限公司 / AdimFlu-S(QIS)“安定伏”裂解型四價流感疫苗	0.5mL	提供3歲以上使用
台灣東洋藥品工業股份有限公司 /FLUCELVAX QUAD輔流威適流感疫苗	0.5mL	提供3歲以上使用

Disadvantages of egg-based vaccine



Supply of eggs
Egg allergies



Haemagglutinin proteins mutation
H3N2

1. ESMO Open. 2019;4(1):e000481
2. Vaccines. 2018;6(19):E19
3. NPJ Vaccines.2018;3:44

Cell based influenza vaccine

18-49yrs	TIVc/TIVe Phase 3, randomized, placebo-controlled, multicenter study (2007-2008) in the US, Finland, and Poland
18-64 yrs/ >65yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
4-17 yrs	TIVc/QIVc Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States
2/3-17 yrs	Phase 3, randomized, observer blind, multicenter study (2017-2019) in EUR, South America, AST, ASIA

Immunogenicity

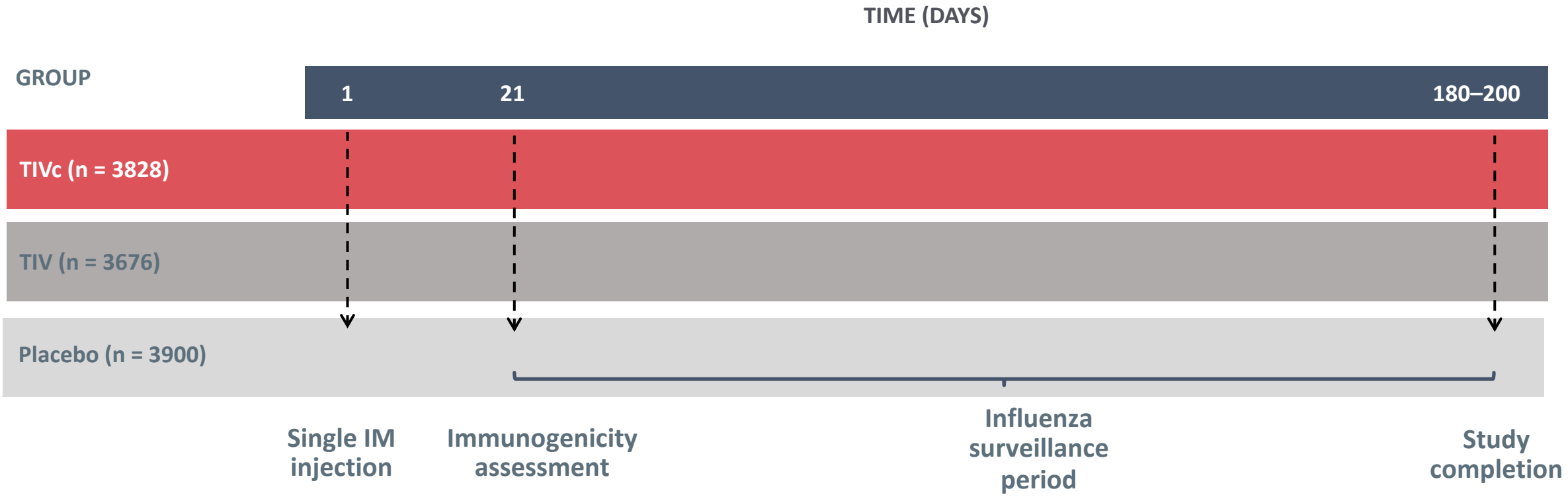
CBER (USA Center for Biologics Evaluation and Research) /CHMP immunogenicity criteria

- Lower limit of the 2-sided 95% CIs for the percentage of subjects achieving an **HI antibody titer 1:40** should be 70% and 60% for subjects aged 18 to <65 y and 65 y
- Lower limit of the 2-sided 95% CIs for the percentage of subjects achieving **seroconversion** should be 40% and 30% for subjects aged 18 to <65 y and 65 y
- **Seroconversion rate**
  - HI titer <1:10 → HI titer ≥1:40
  - HI titer ≥1:10 → at least a 4-fold increase

Drugs (2019) 79:1337–1348

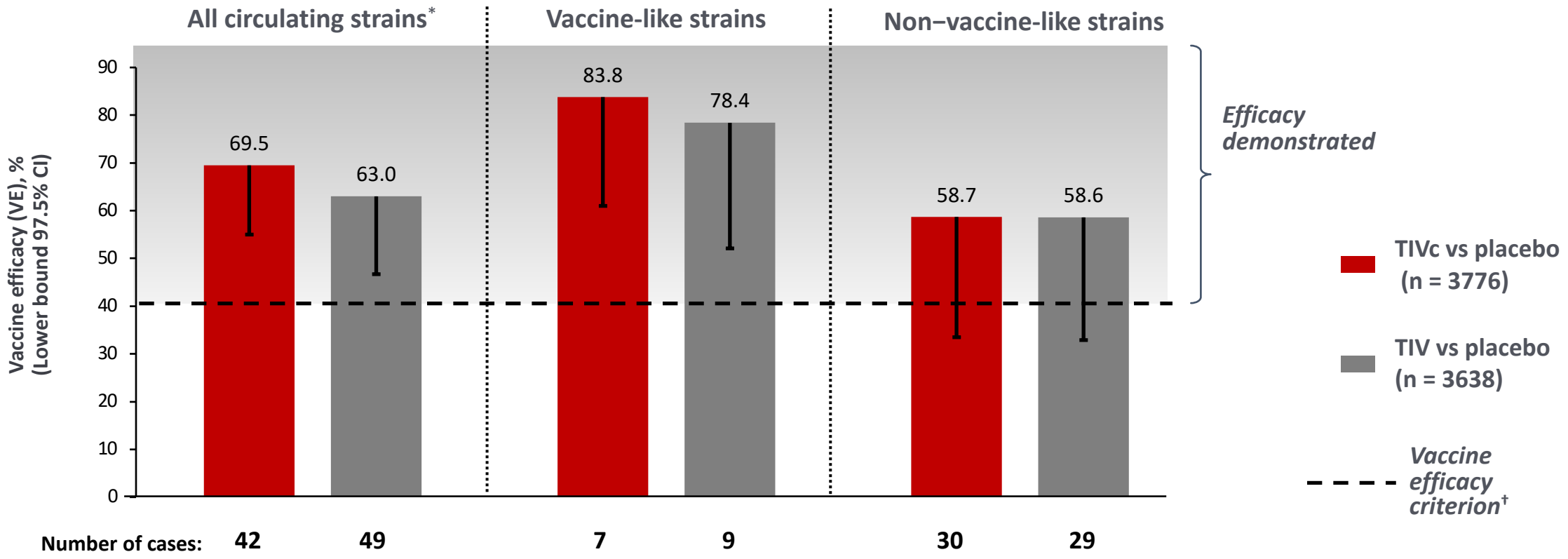
Efficacy study of TIVc and TIV vs placebo

Phase 3, randomized, placebo-controlled, multicenter study (2007-2008) in the United States, Finland, Poland



Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.

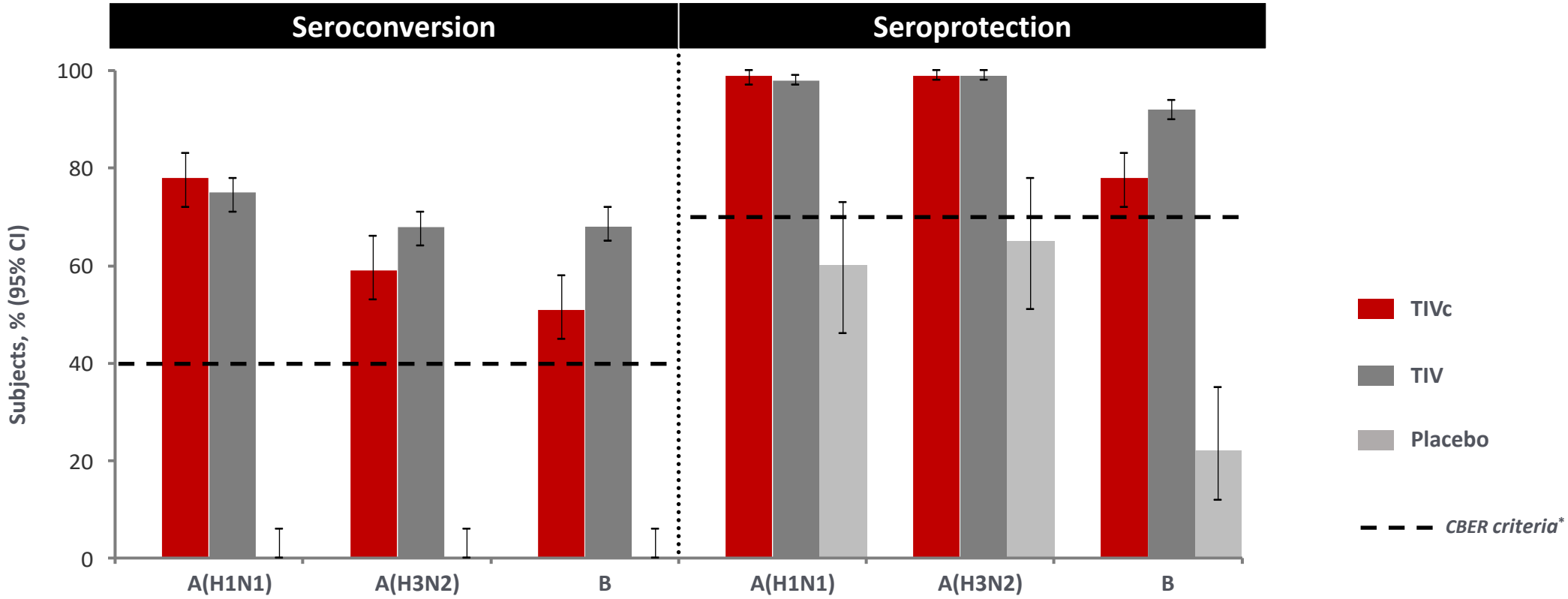
Efficacy of TIVc and TIV against circulating strains vs placebo in adults aged 18-49 years



Efficacy：(1 - P vaccine/P placebo) x 100

Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.

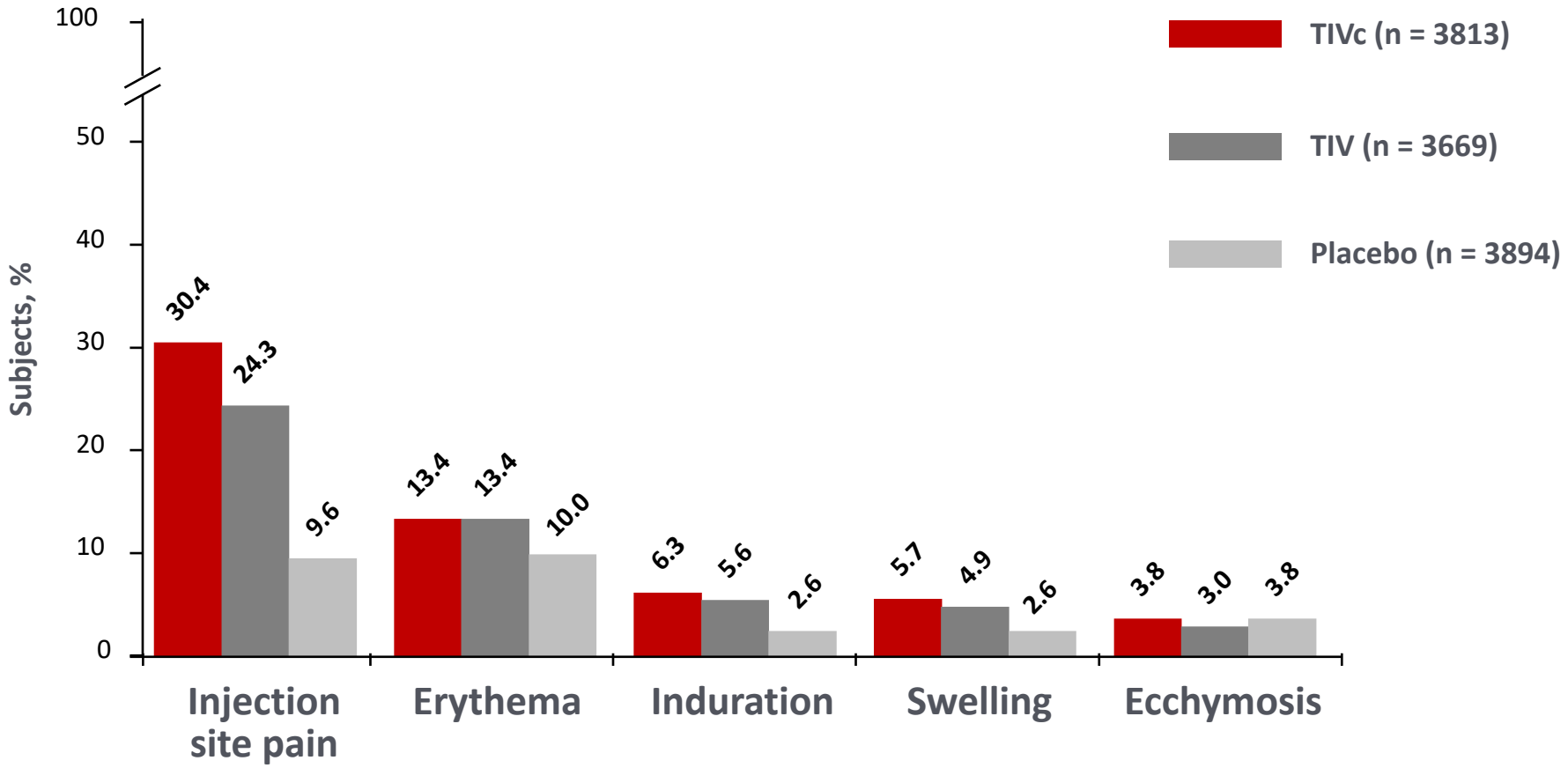
Seroconversion and seroprotection with TIVc and TIV vs placebo in adults aged 18-49 years



1) **Seroconversion** should be 40% 2) **HI antibody titer 1:40** should be 70%

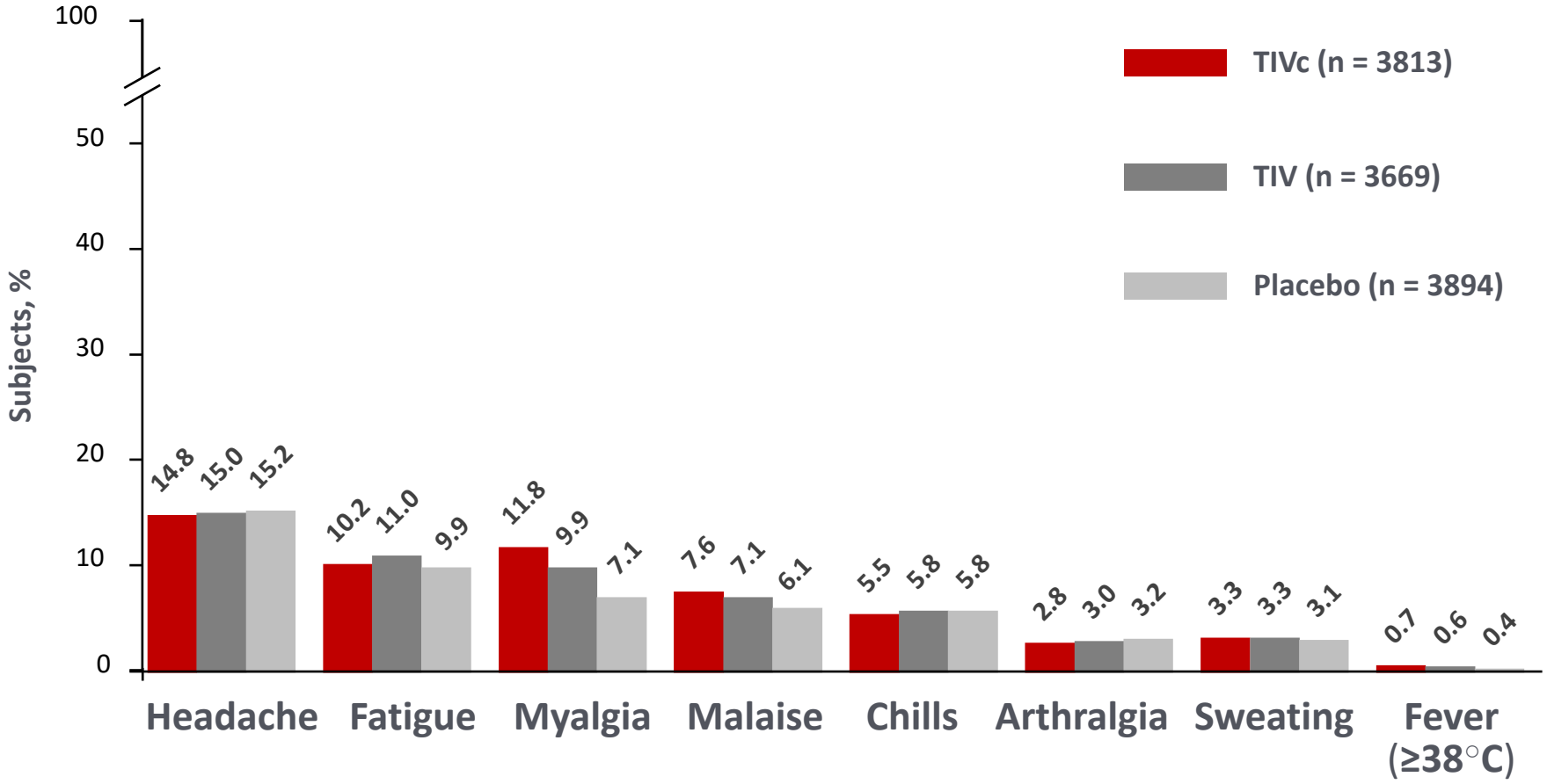
Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.

Solicited local reactions within 7 days post-vaccination in adults aged 18-49 years



1. Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00630331?view=results. Accessed May 11, 2019.

Solicited systemic reactions within 7 days post-vaccination in adults aged 18-49 years



1. Frey S et al. *Clin Infect Dis.* 2010;51:997-1004.
2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00630331?view=results. Accessed May 11, 2019.

COMPARATIVE TRIAL OF QIVC IN HEALTHY ADULTS

Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States

Primary objective(s)	Primary: To evaluate noninferiority of QIVc vs comparator TIVc Secondary: • To demonstrate superiority of QIVc against the unmatched B strain in TIVc • To evaluate immunogenicity of QIVc and TIVc according to CBER and CHMP criteria • To demonstrate safety and tolerability of each vaccine
Study population	Healthy adults (aged 18-64 years) and older adults (aged ≥65 years): N = 2680
Exposure(s)	**QIVc**
Comparator(s)	TIV1c (containing B/Yamagata lineage) or TIV2c (containing B/Victoria lineage)

Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

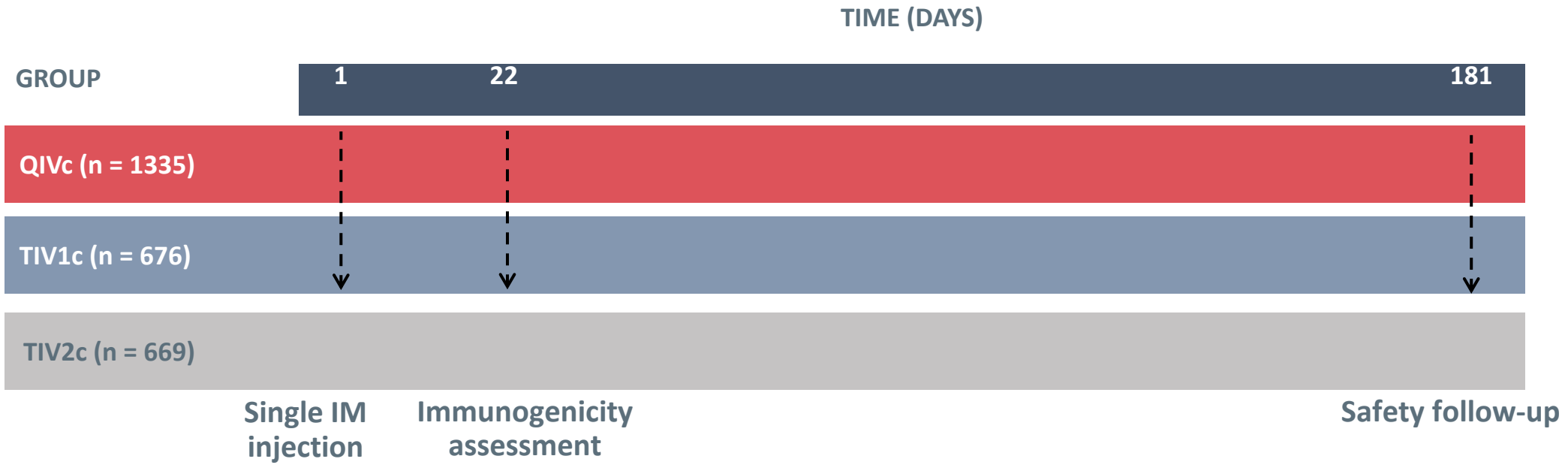
Non-Inferiority

- Upper limit (UL) of the 2-sided 95% confidence intervals (CI) of the vaccine group ratio of **GMTs** (TIV1c or TIV2c divided by QIVc) was <1.5
- UL of the 2-sided 95% CI for the difference in **SCR** (TIV1c or TIV2c minus QIVc) was <10%

Drugs (2019) 79:1337–1348

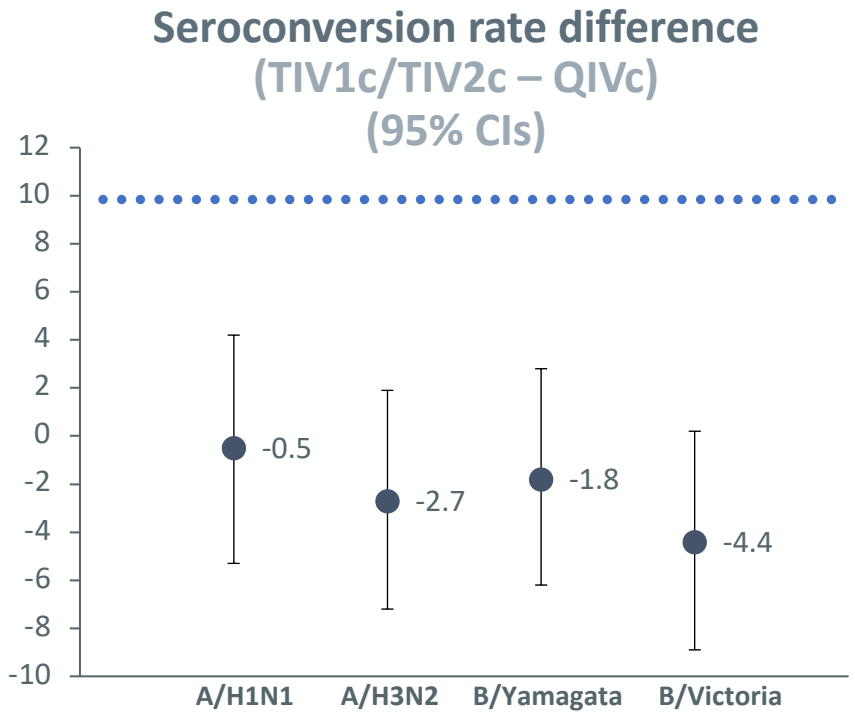
Comparative trial of QIVc in healthy adults

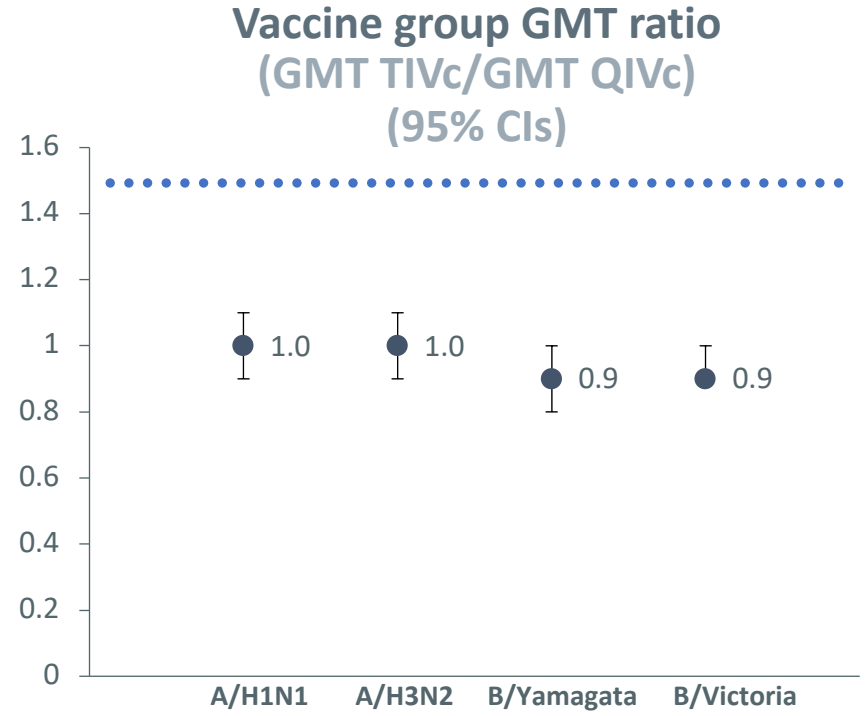
Phase 3, randomized, double blind, multicenter study (2013-2014) in the United States



Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

Immunogenicity of QIVc is non-inferior to TIVc on seroconversion rates and GMTs in adults



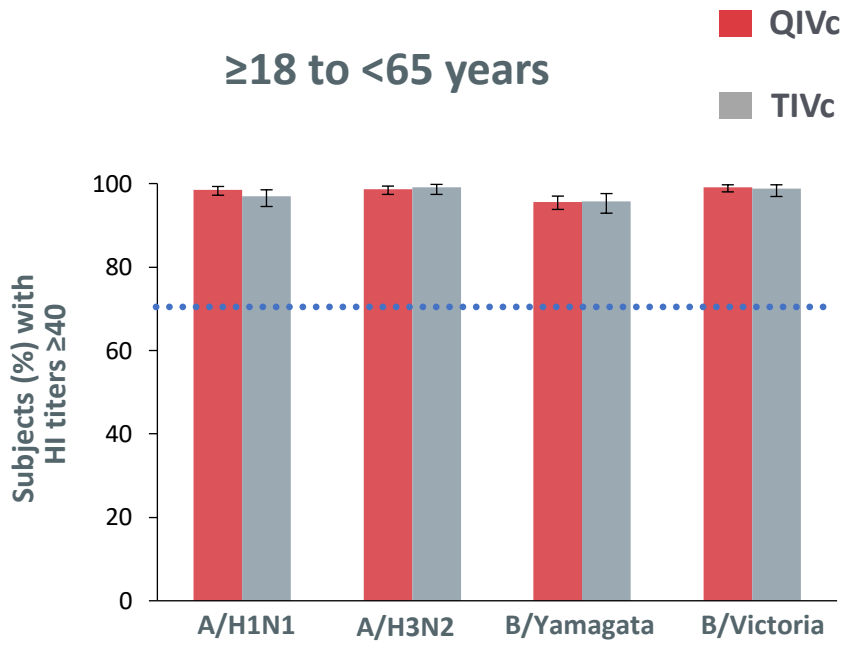


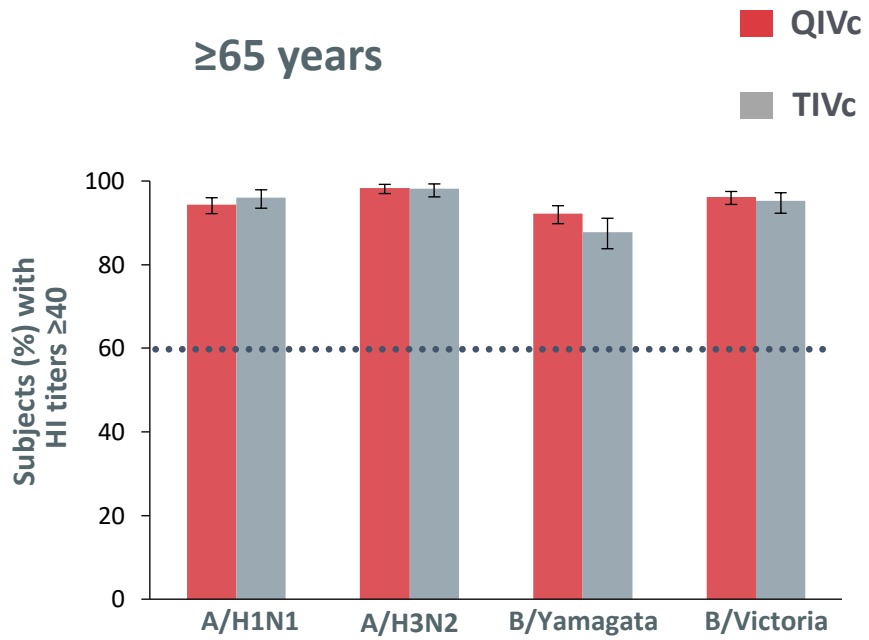
TIV1c or TIV2c minus QIVc <10%
TIV1c or TIV2c divided by QIVc <1.5

Noninferiority threshold

Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

QIVc induced immune response (seroprotection) comparable to TIVc in adults

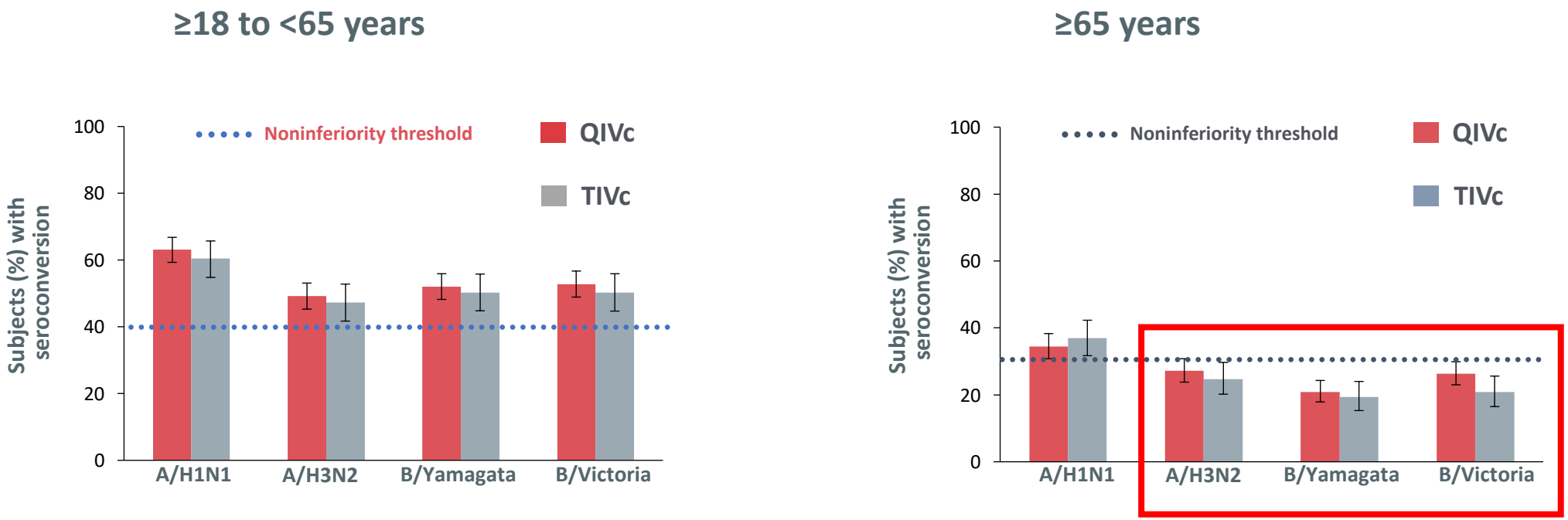




HI antibody titer 1:40 should be 70% and 60% for subjects aged 18 to <65 y and 65 y

Bart S et al. *Hum Vacc and Immuno.* 2016;9:2278-2288.

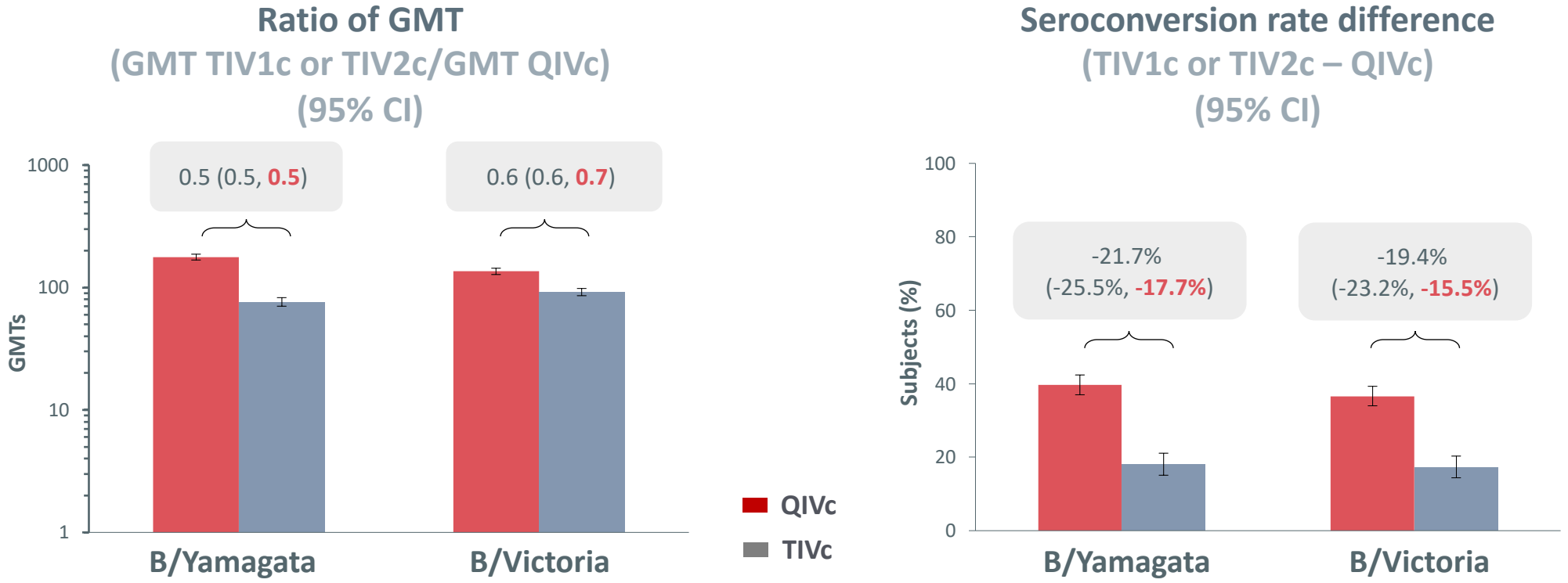
QIVc induced immune response (seroconversion) comparable to TIVc in adults



Seroconversion should be 40% and 30% for subjects aged 18 to <65 y and 65 y

Bart S et al. *Hum Vacc and Immuno.* 2016;9:2278-2288.

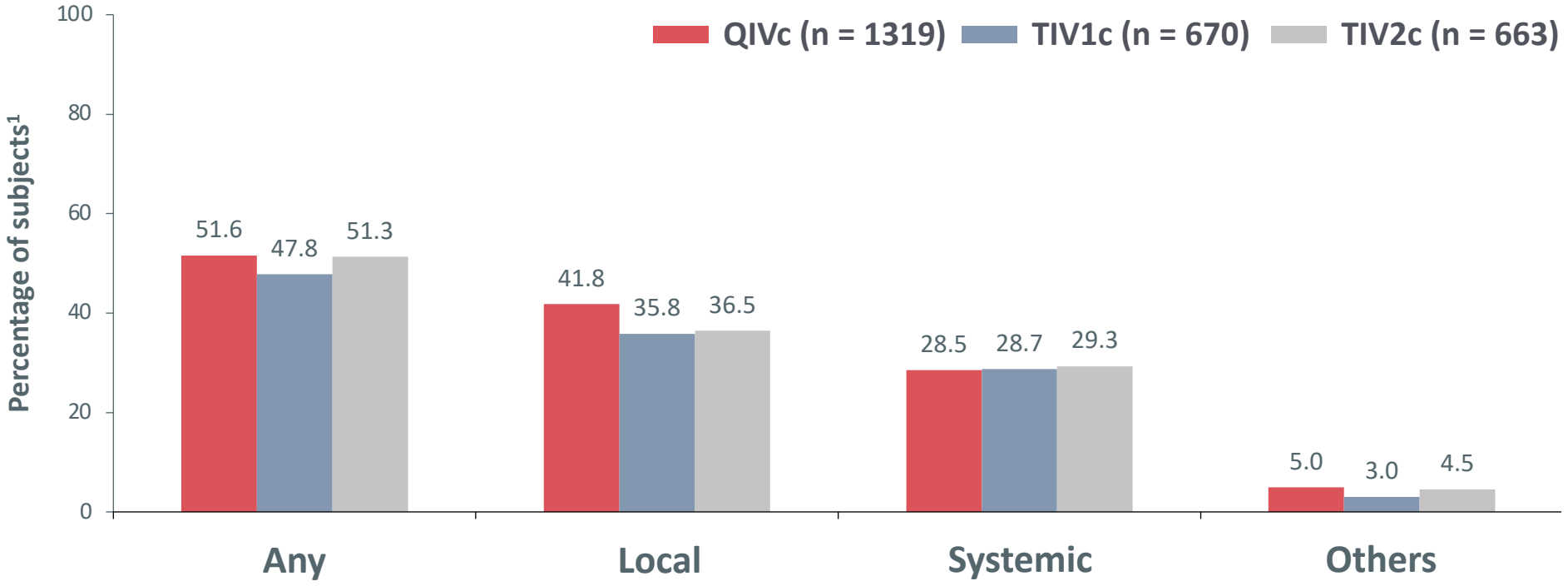
Superiority of QIVc relative to TIVc against unmatched B strains in adults



1) TIV1c or TIV2c divided by QIVc <1 2) TIV1c or TIV2c minus QIVc <0

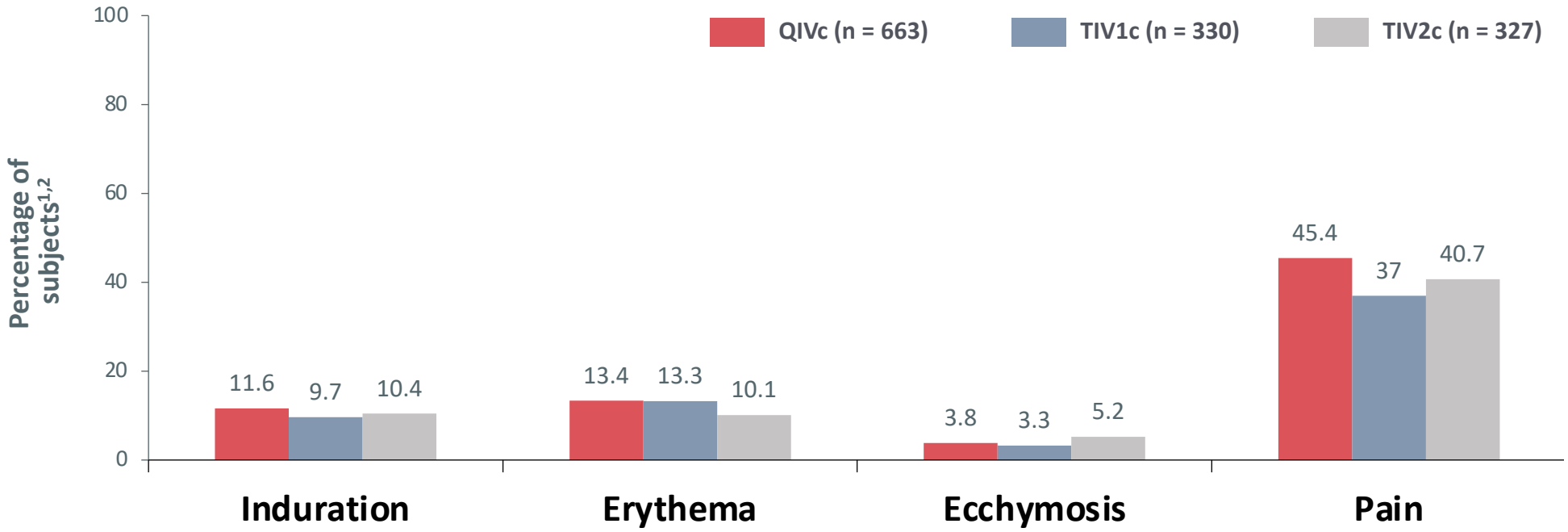
Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

Tolerability profiles of QIVc and TIVc were similar in adults



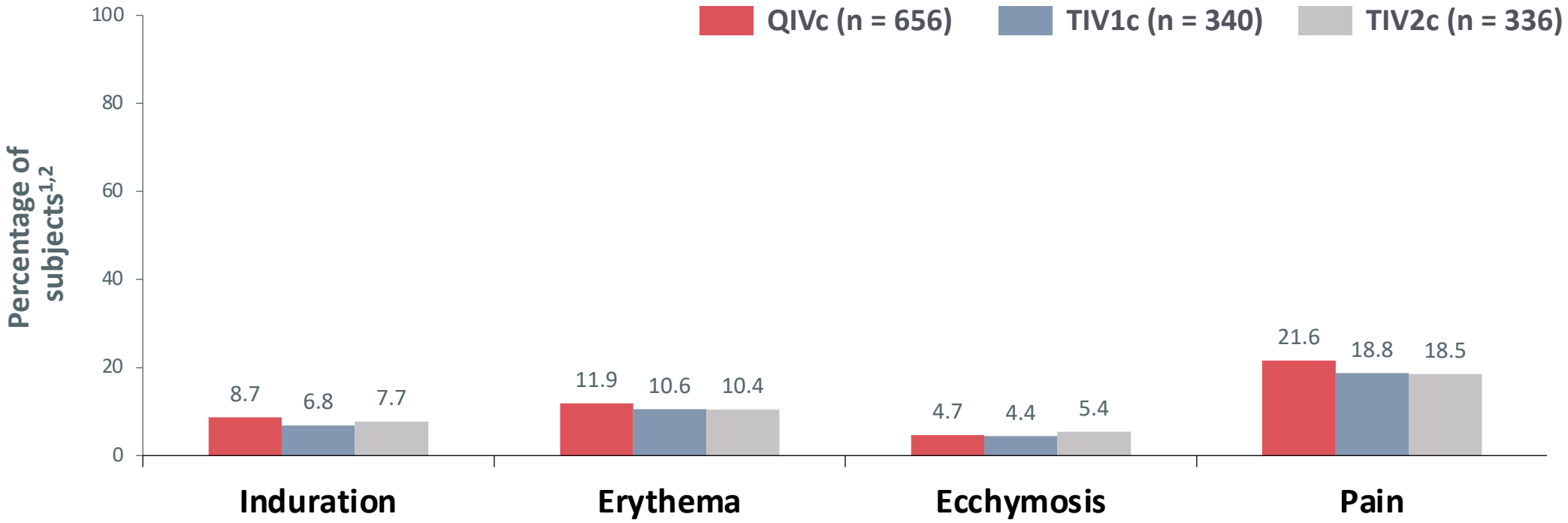
1. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/results/NCT01992094?term=NCT01992094&rank=1&sect=X301256#evnt. Accessed March 30, 2019. **2.** Bart S et al. *Hum Vaccin Immunother*. 2016;12(9):2278-2288.

Local adverse events within 7 days postvaccination with QIVc and TIVc in adults aged ≥18 to <65 years



Flucelvax Quadrivalent [package insert]. Summit, NJ. Seqirus, Inc. July 2018.

Local adverse events within 7 days postvaccination with QIVc and TIVc in adults aged ≥ 65 years



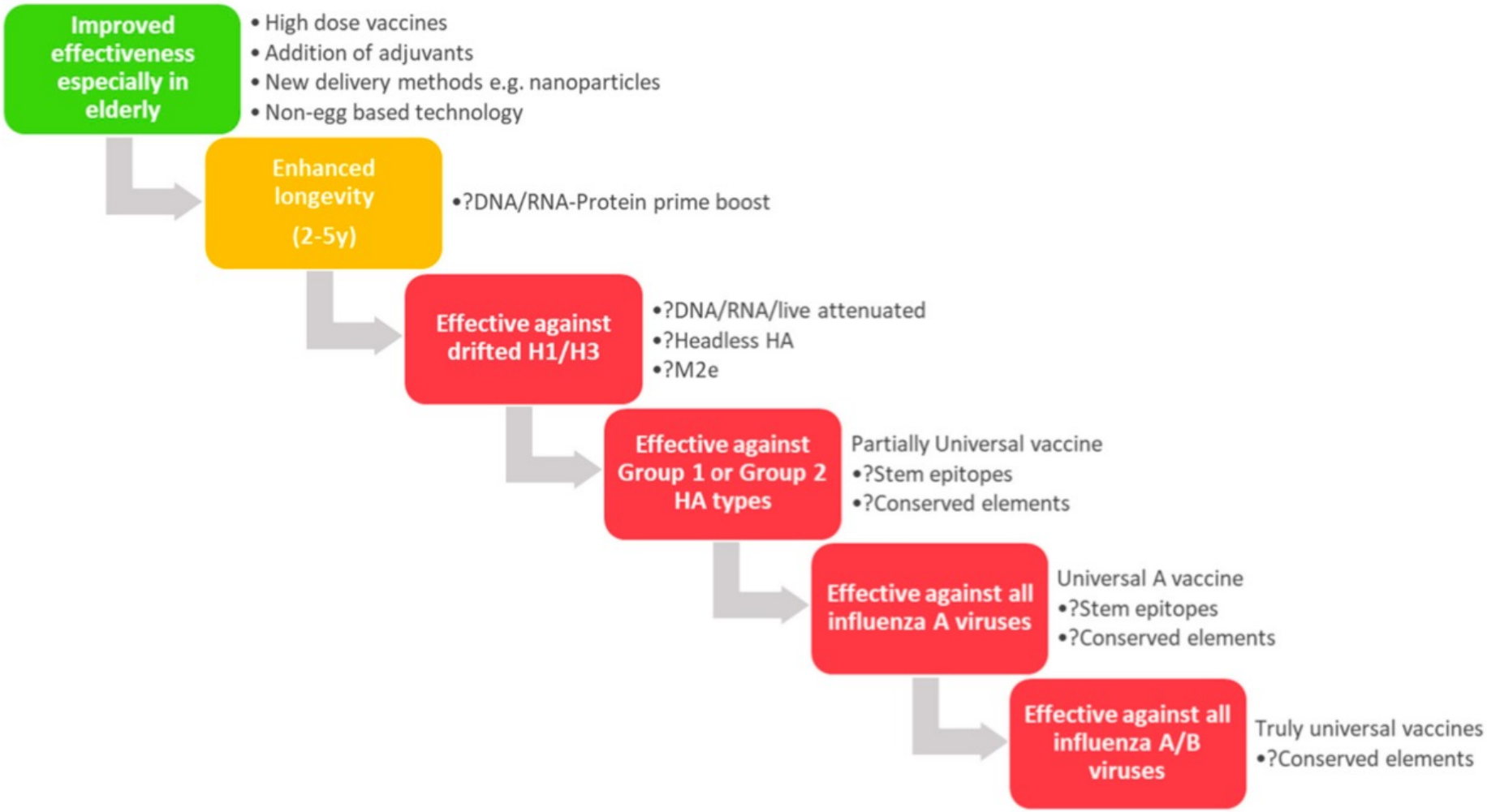
Flucelvax Quadrivalent [package insert]. Summit, NJ. Seqirus, Inc. July 2018.

Non-egg-based Influenza Vaccines

Company	Phase	Administration	Reference
Recombinant			
BiondVax	Phase III	Oral	[19]
Imutex	Phase II	SC	[20]
Recombinant—VLP			
Novavax	Phase III	IM	[21]
Osivax	Phase II	IM	[22]
Medicago	Phase III/discontinued	IM	[23]
Medigen	Phase II	IM	[24]
Recombinant—H5 protein fragment			
Generex	Phase I	Oral	[25]
Live attenuated			
Codagenix	Phase I	Nasal	[26]
FluGen	Phase II	Nasal	[27]
Vivaldi	Phase II	Nasal	[28]
Polymun	Phase I	Nasal	[29]
Vector—adenovirus			
Vaccitech	Phase II	IM	[30]
Vaxart	Phase II	Oral	[31]
Altimmune	Phase II	Nasal	[32]
Vector—alphavirus			
AlphaVax	Phase II	IM	[33]

Company	Phase	Administration	Reference
Adjuvant—novel			
BlueWillow	Phase I	Nasal	[34]
Nitto Denko	Phase I	Sublingual	[35]
Mercia	Phase II	IM	[36]
Adjuvant—toxin			
Mucosis	Phase I	Nasal	[37]
Eurocine	Phase I/II	Nasal	[38]
Advagene	Phase II	Nasal	[39]
mRNA			
Moderna Therapeutics	Phase I	IM	[40]
DNA vaccine			
Inovio	Phase I	IM	[41]
Virosomes			
Mymetics	Phase II	Nasal	[42]
Dendritic cells			
CEL-SCI	Phase I	IM	[43]

Potential steps and technologies to improve influenza vaccines



Microorganisms **2020**, *8*, 1745


THANK YOU