Kalp Krizi ve Felci Önleyen Aşılar

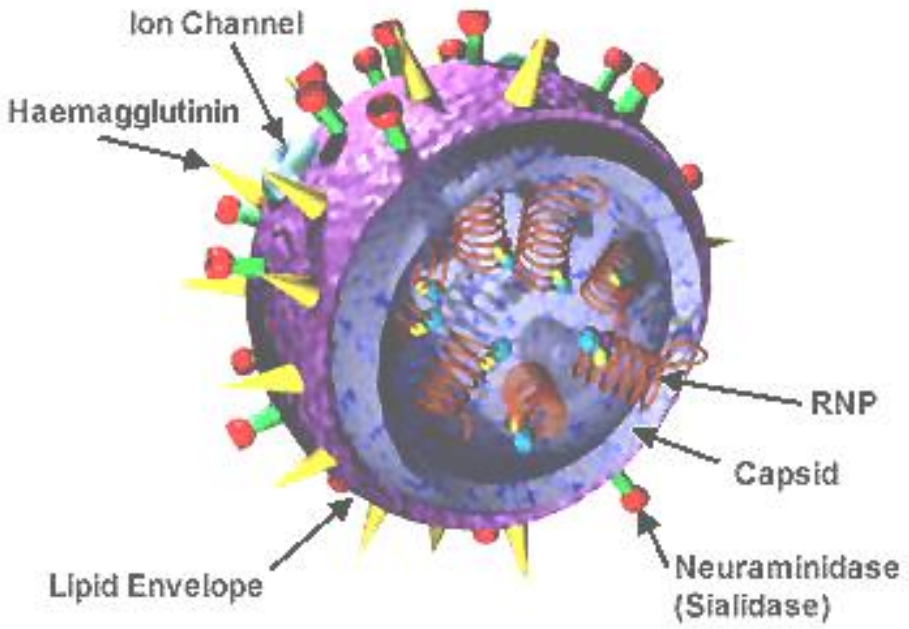
Dr. Alpay Azap

Ankara Üniversitesi Tıp Fakültesi

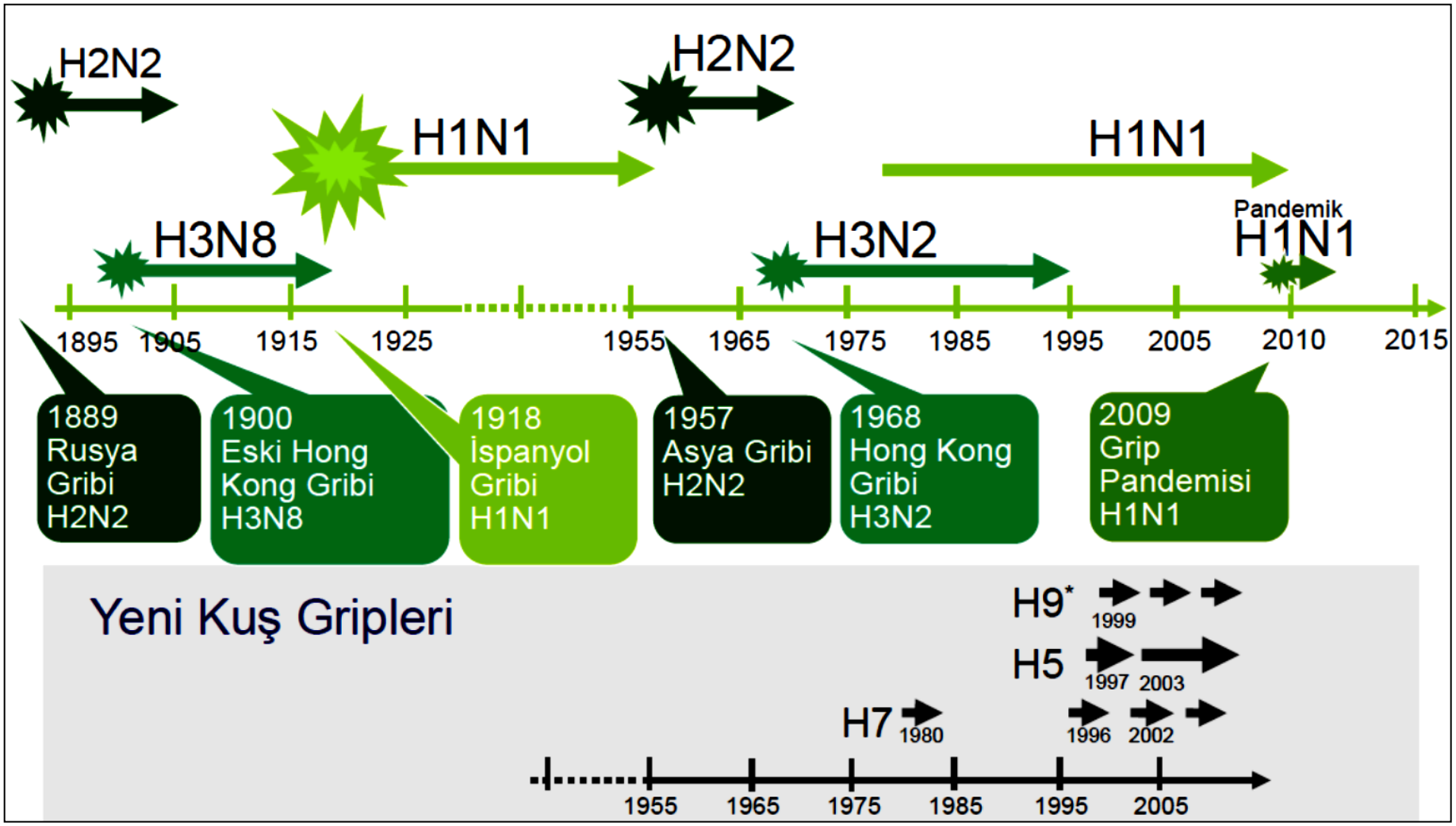
İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

Virus

- Ortomiksoviridae ailesinden
- Zarflı RNA virusu
- 3 farklı tipi mevcut:
  - A,B,C
    - A konak spektrumu geniş
    - B sadece insanda
    - C insan ve domuzda



1895-2010 Yılları Arasında Görülen Grip Pandemileri

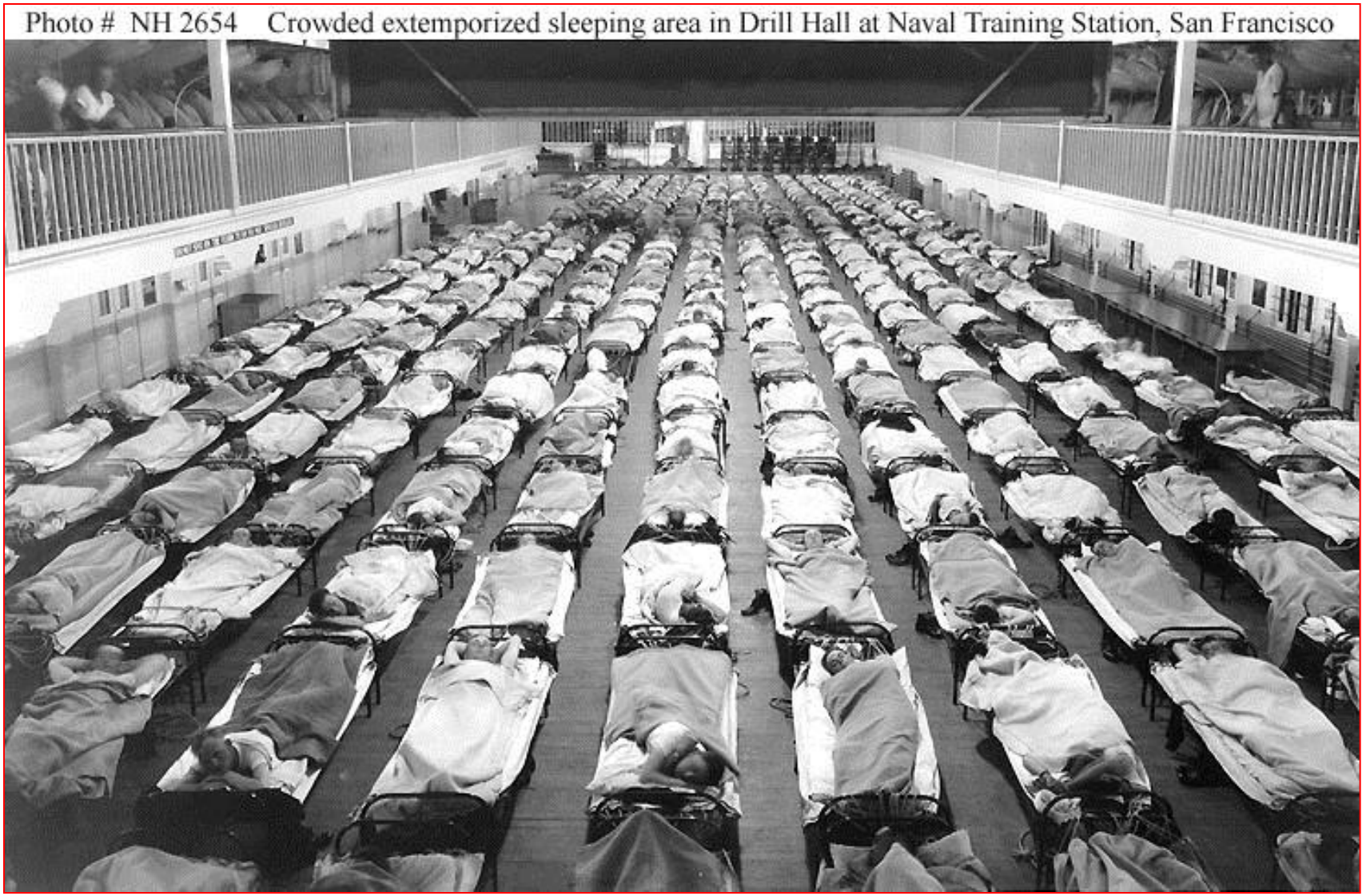


İnfluenza pandemileri

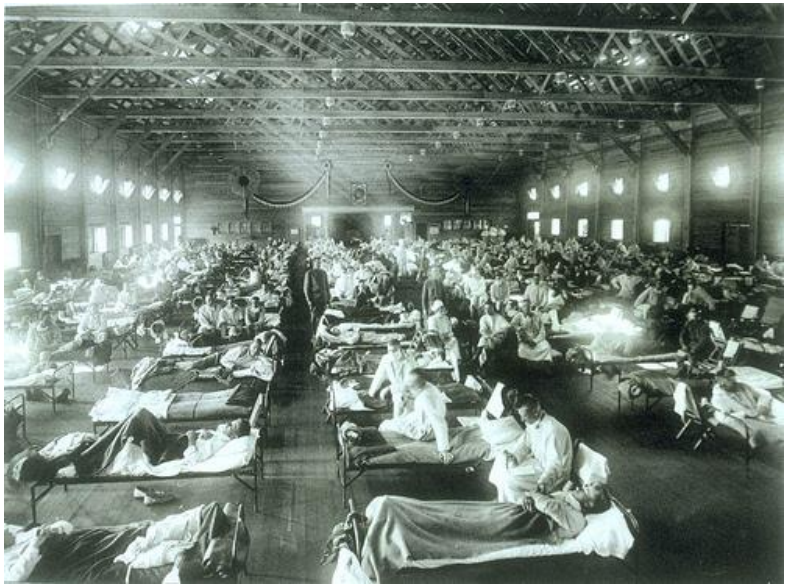
Yıl	Glikoprotein yapısı	Pandemi şiddeti	Ölüm
1889	H3N2	Orta	?
1918	H1N1 (“İspanyol")	Ağır	20-100 milyon
1957	H2N2 ("Asya")	Orta	1 milyon
1968	H3N2 ("Hong Kong")	Hafif	1 milyon
2009	H1N1	Hafif	+ 36.000

1918 - 1919

- Dünya nüfusu: Yaklaşık 1.6 milyar
- 1. Dünya Savaşı'nda ölen insan sayısı: Yaklaşık 8.5 milyon
- **"İspanyol gribi"**nden ölen kişi sayısı: **40 milyon**



1918, ABD, Askeri eğitim kampı



1918, ABD

Salgın 20-40 yaş arasındakileri öldürdü

Alaska “Yetimleri”, 1919

Approximate beginning of the epidemic, 1918

before sept. 14	between sept. 14 - 21	between sept. 21 - 28	between sept. 28 - oct. 5	after oct. 5

Source: America's Forgotten Pandemic - The Influenza of 1918 - 1989

Approximate beginning of the epidemic, 1918

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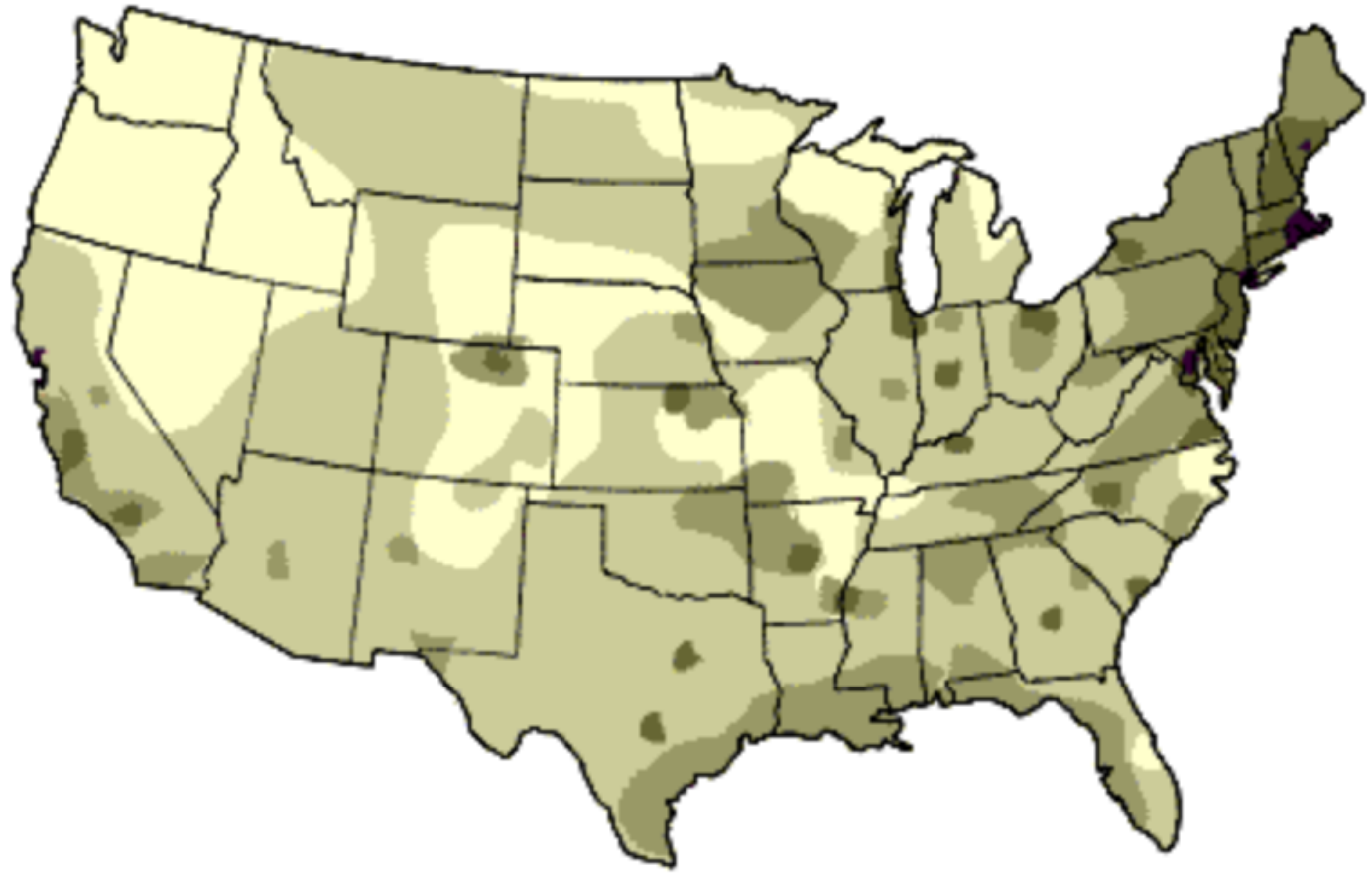
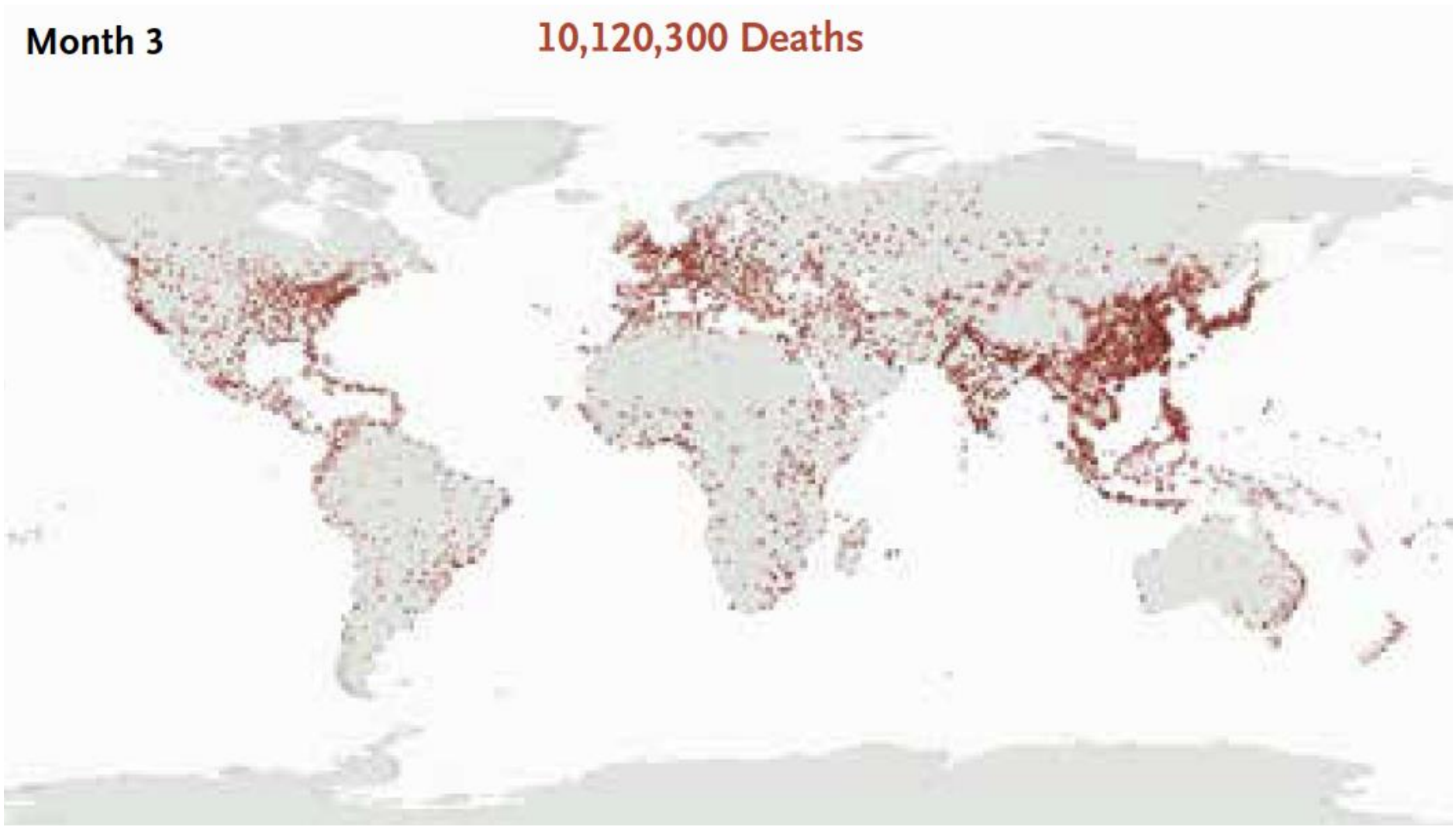
Approximate beginning of the epidemic, 1918



before sept. 14	between sept. 14 - 21	between sept. 21 - 28	between sept. 28 - oct. 5	after oct. 5

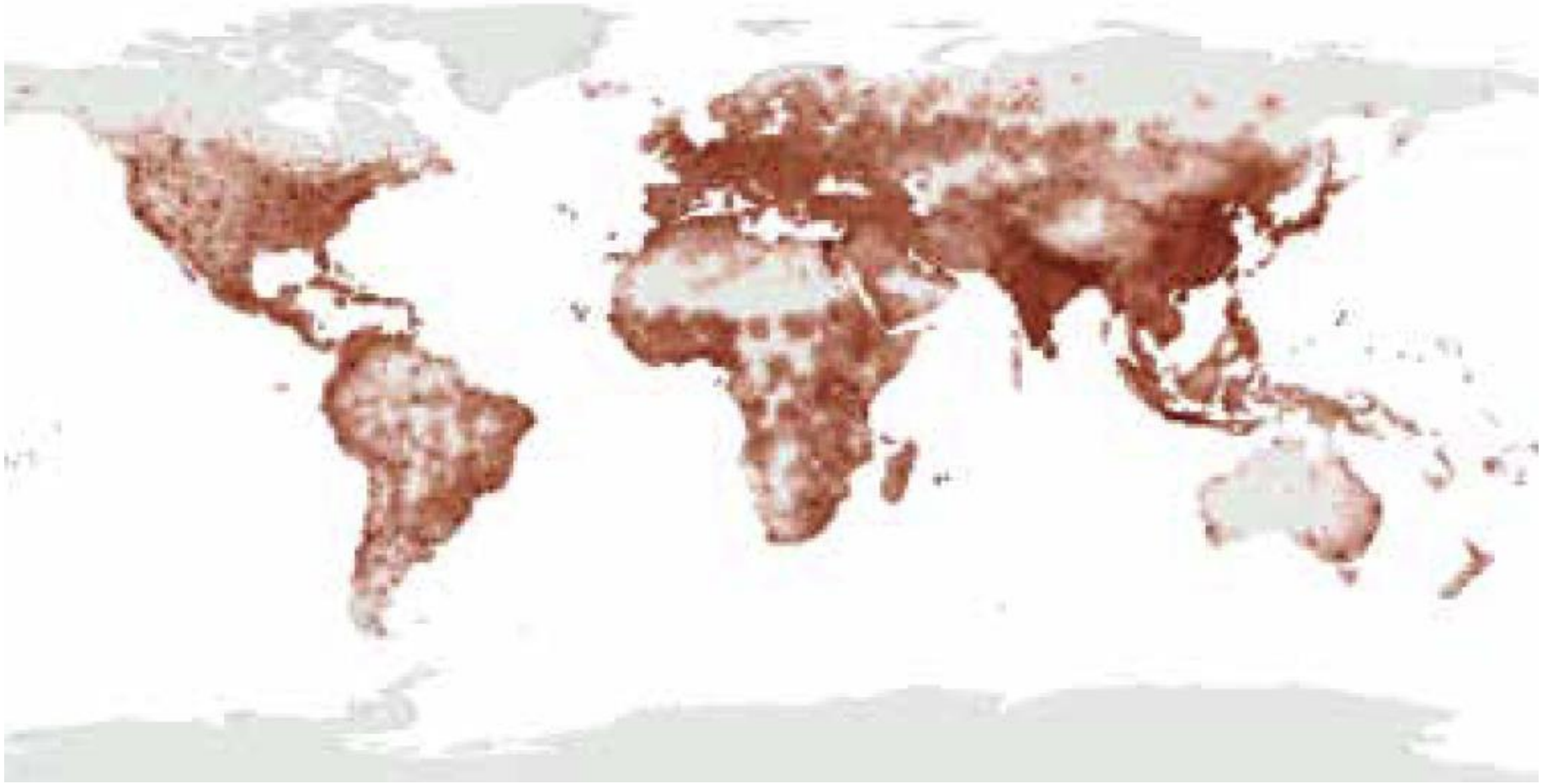
Source: America's Forgotten Pandemic - The Influenza of 1918 - 1989


A Month 1
28,600 Deaths


Month 3
10,120,300 Deaths

Month 6

32,918,500 Deaths



GRİP AŞILARI

	Quadrivalent *vs* trivalent*	Route	Approved age group	Comments
Inactivated	Quadrivalent or trivalent	Intramuscular	≥6 months	Contains 15 µg of each haemagglutinin
Inactivated: intradermal	Quadrivalent	Intradermal	18–64 years	Contains 9 µg of each haemagglutinin
Inactivated: derived from cell culture	Trivalent	Intramuscular	≥18 years	Contains 15 µg of each haemagglutinin; contains egg protein; manufacturing does not rely on eggs
Inactivated: high dose	Trivalent	Intramuscular	≥65 years	Contains 60 µg of each haemagglutinin
Live attenuated†	Quadrivalent	Intranasal	2–49 years	Cold adapted; uses a master donor virus plus the haemagglutinin and neuraminidase of the circulating viruses; generates a broader immune response (T-cell, mucosal); not approved for use in immunocompromised patients or pregnant women
Recombinant	Trivalent	Intramuscular	≥18 years	Made with recombinant DNA technology to produce full-length haemagglutinin; shorter manufacturing time than for egg-derived or cell-culture-derived vaccines; can be used in individuals with egg allergy

*Trivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and the dominant influenza B virus circulating at the time of vaccine strain selection. Quadrivalent vaccines contain antigens from the circulating H1N1 and H3N2 influenza A viruses and both lineages of influenza B. †Live attenuated vaccine not recommended by the US Advisory Committee on Immunization Practices for the 2016–17 season; this table represents the 2015–16 influenza season.

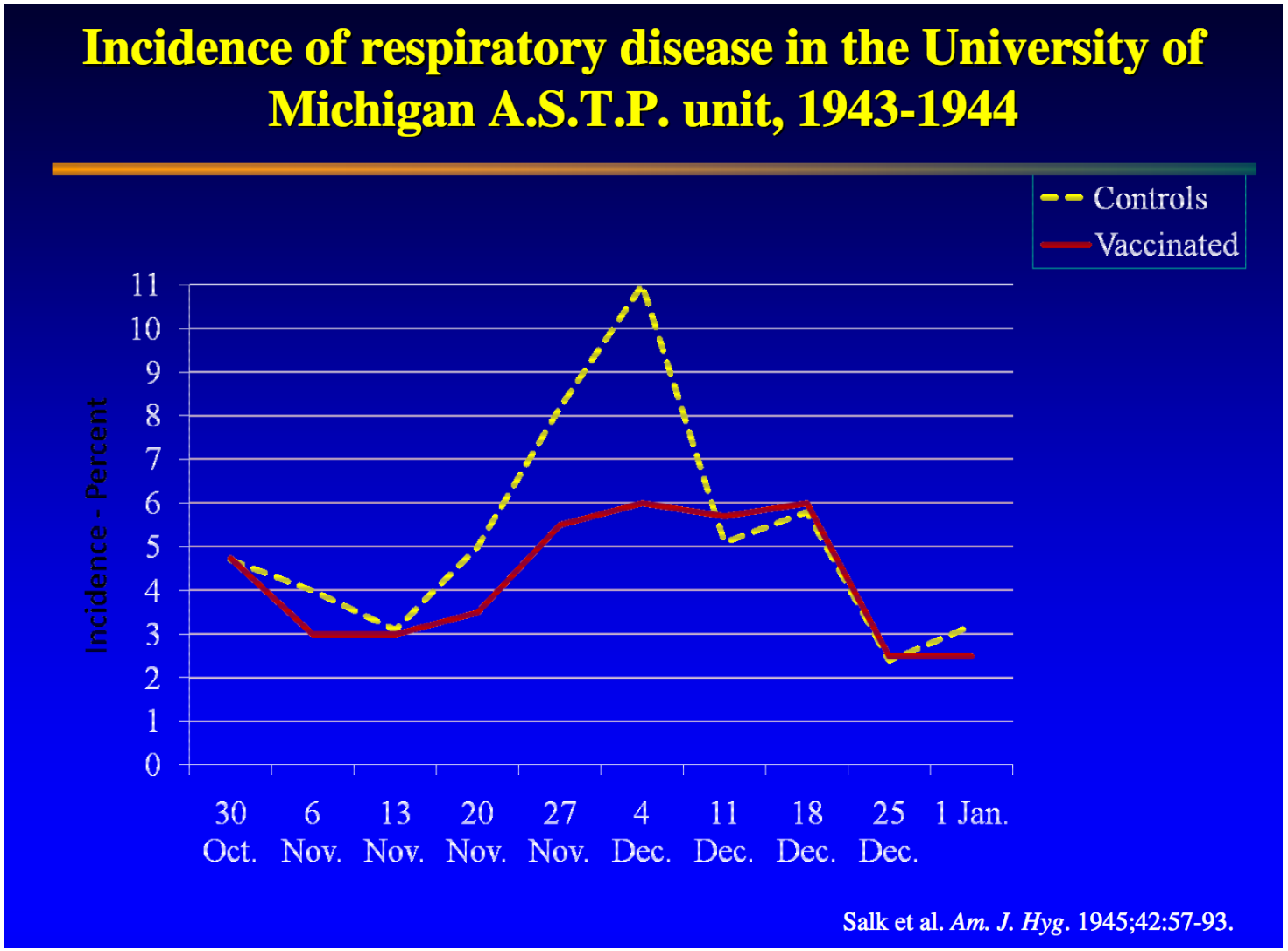
Table 4: **Types of influenza vaccine licensed for use in the USA 2015–16 influenza season**[40,93–97]

Lancet 2017; 390: 697–708

Aşı yeni bir aşı değil: Antijen yeni !!!

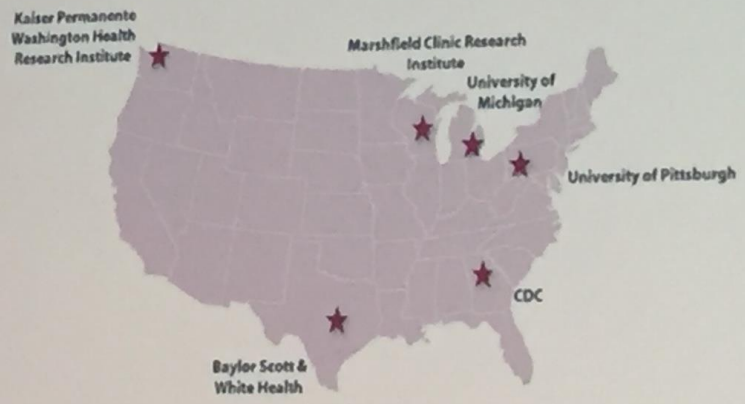
75 yıldır influenza aşısı aynı yöntemle üretiliyor

İlk grip aşısı: 1943

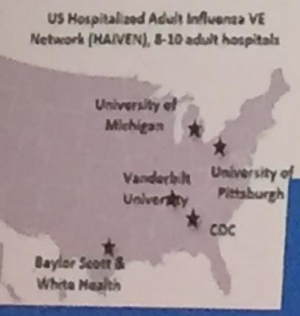


We monitor influenza Vaccine Effectiveness (VE) every year with the US Flu VE Network

US Flu VE Network*



*Enrolls outpatients aged ≥6 months old with acute respiratory illness from 66 clinics. Uses a test-negative case- control design where PCR positive flu = case and PCR negatives = control



Season	VE against A/B influenza viruses (95% CI)
2010-11	60% (53, 66)
2011-12	47% (36,56)
2012-13	49% (43, 55)
2013-14	52% (44,59)
2014-15	19% (10,27)
2015-16	48% (41, 55)
2016-17	40% (32, 46)
2017-18	40% (34, 46)

Mismatched

VE varies year to year but ranges between 40-60%

Aşı geliştirme aşamaları

Aşıya bağlı felç (Guillain-Barre Sendromu)

GBS:

Yıllık insidansı; 10-20/1 milyon kişi

Campylobacter jejuni, viral ÜSYE, influenza ile ilişkili

ABD'de 1976 aşılaması: 45 milyon kişi, GBS:4-8 kat artmış

Her 100.000 aşıda fazladan bir kişi GBS olmuş

"İnfluenzanın kendisine bağlı GBS riski aşınınkinden 4-7 kat daha fazla"

Clin Infect Dis 2009;48(1):48-56

"Aşının GBS ile ilişkisi yok veya zayıf (1 milyon doz için fazladan 1 olgu)"

MMWR;RR5850,2009

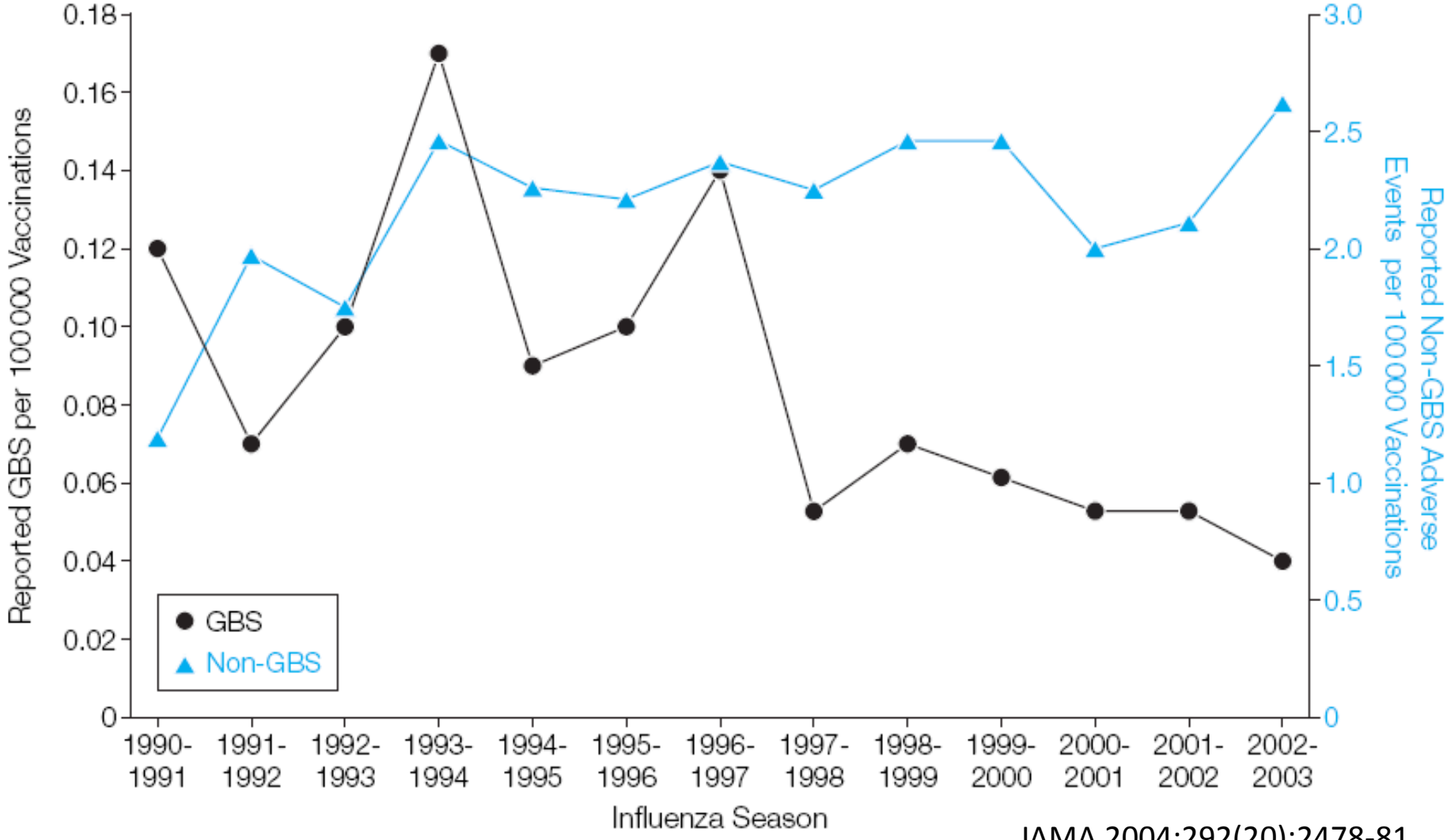
Emerg Infect Dis 2006;12(12):1880-87

JAMA 2004;292(20):2478-81

N Engl J Med 1998;339:1797-802

Drug Saf 2009;32(4):309-23

Figure 1. Rates of GBS and Non-GBS Reports Following Influenza Vaccination, VAERS 1990-2003



JAMA 2004;292(20):2478-81

GBS indicates Guillain-Barré syndrome; VAERS, Vaccine Adverse Events Reporting System.

The NEW ENGLAND JOURNAL of MEDICINE

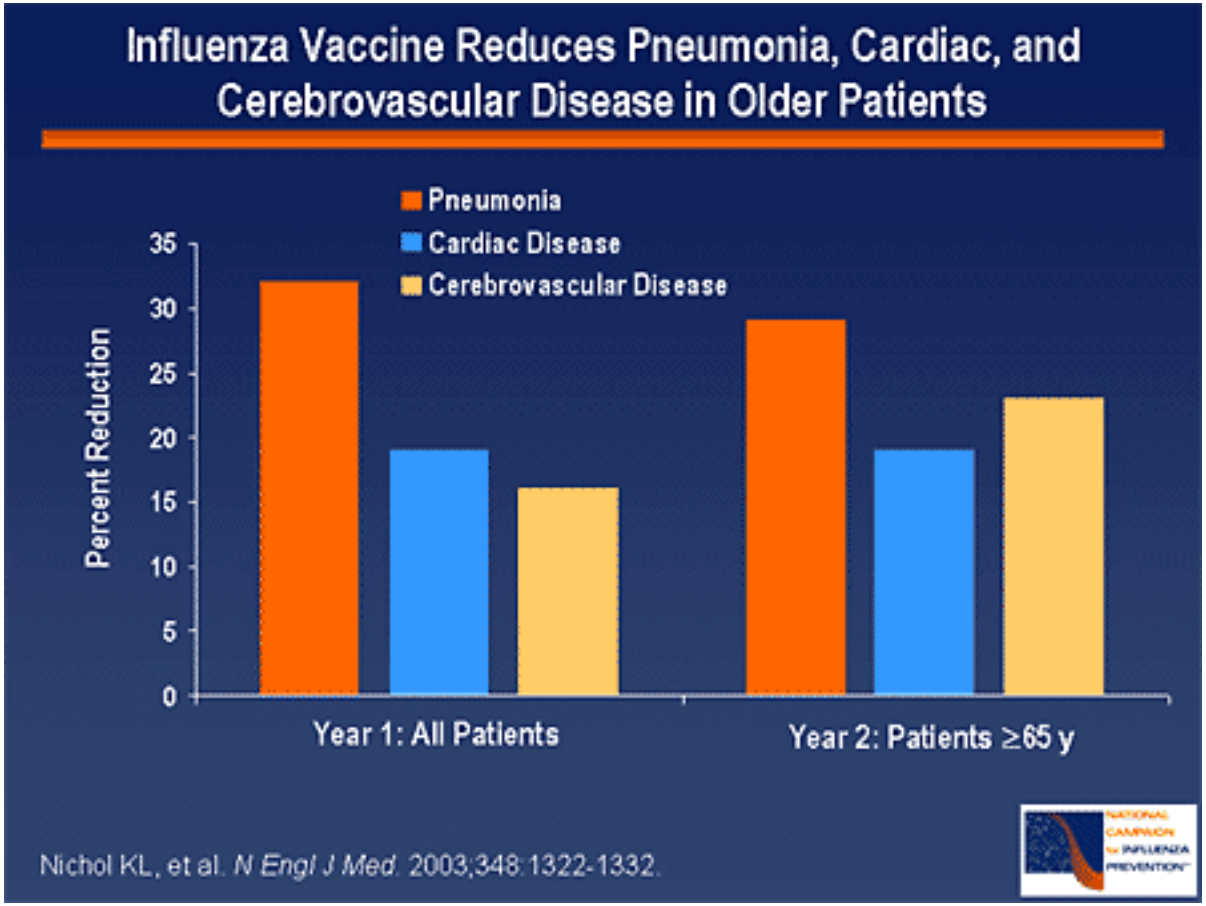
ORIGINAL ARTICLE

Influenza Vaccination and Reduction in Hospitalizations for Cardiac Disease and Stroke among the Elderly

3 ayrı bölgeden, >65y

1998–1999 :
140.055 kişi %55 aşılı

1999–2000:
146.328 kişi %59 aşılı



Effectiveness of MF59™-adjuvanted subunit influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly

Joan Puig-Barberà[a,b,*], Javier Díez-Domingo[b], Ángel Belenguer Varea[a],

İspanya'da 3 ayrı bölge hastanesinde >64 yaş hastaneye başvuranlarda vaka-kontrol çalışması

Üç ayrı vaka-kontrol grubu: AKS (144/258), SVO (134/246) ve Pnömoni (198/321)

Vaka ve kontrol gruplarında adjuanlı (MF59) İnfluenza aşısı ile aşılanma oranları karşılaştırılmış

Table 2

Risk (odds ratio and adjusted odds ratio) of hospitalisation for acute coronary syndrome, cerebrovascular accident and pneumonia in subjects who had received MF59™-adjuvanted subunit influenza vaccine

	Epidemiological week, 2005	Odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
ACS	7–14	0.89 (0.37–2.08)	0.786	0.13 (0.03–0.65)	0.013
CVA	3–10	0.66 (0.31–1.40)	0.276	0.07 (0.01–0.48)	0.007
Pneumonia	2–12	0.73 (0.40–1.35)	0.324	0.31 (0.14–0.71)	0.005

Vaccine 25 (2007) 7313–7321

Effectiveness of MF59™-adjuvanted subunit influenza vaccine in preventing hospitalisations for cardiovascular disease, cerebrovascular disease and pneumonia in the elderly

Joan Puig-Barberà[a,b,*], Javier Díez-Domingo[b], Ángel Belenguer Varea[a],

	>64 y 1000 kişide hastaneye yatıış hızı		Bir olayı önlemek için aşılanması gereken kişi sayısı
	Aşılanmayan	Aşılanan	
Akut Koroner Sendrom	1.07	0.14	1073
SVO	1.68	0.12	693
Pnömoni	2.55	0.79	567

Vaccine 25 (2007) 7313–7321

Prevention of Acute Myocardial Infarction and Stroke among Elderly Persons by Dual Pneumococcal and Influenza Vaccination: A Prospective Cohort Study

Ivan F. N. Hung,[1,2] Angela Y. M. Leung,[3] Daniel W. S. Chu,[5] Doris Leung,[3] Terence Cheung,[7] Chi-Kuen Chan,[2] Cindy L. K. Lam,[2] Shao-Haei Liu,[6] Chung-Ming Chu,[8] Pak-Leung Ho,[1] Sophia Chan,[3] Tai-Hing Lam,[4] Raymond Liang,[2] and Kwok-Yung Yuen[1]

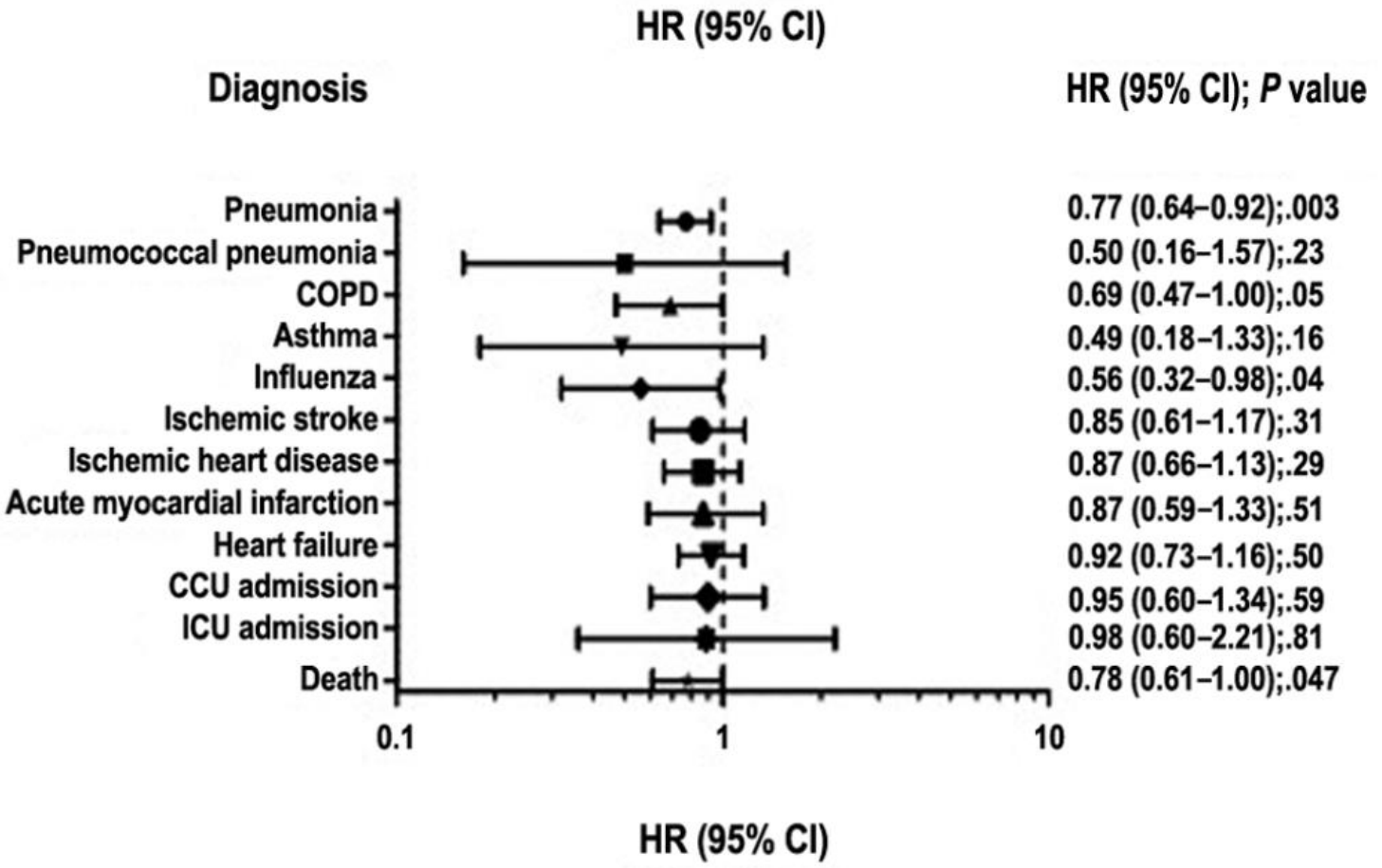
Clinical Infectious Diseases 2010; 51(9):1007–1016

Table 1. Baseline Characteristics of the 36,636 Study Subjects

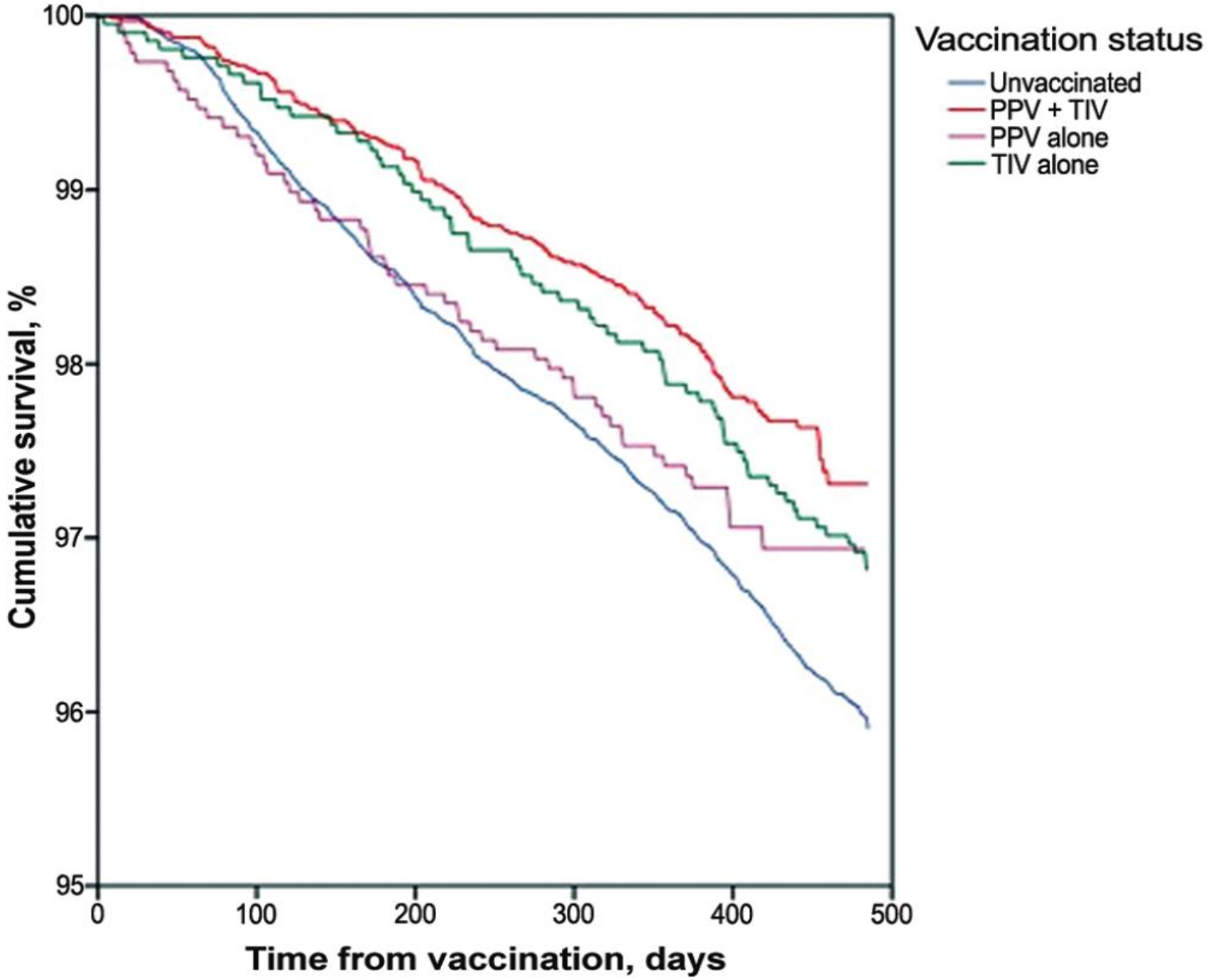
Characteristic	Unvaccinated persons (n = 25,393)	PPV-TIV group (n = 7292)	TIV-alone group (n = 2076)	PPV-alone group (n = 1875)	P
Age, median years (range)	75 (70–80)	77 (71–83)	75 (70–80)	75(71–80)	.81
Male sex	47	40	45	45	<.001
Asthma	2.2	2.2	2.2	2.8	.42
COPD	2.0	4.4	4.6	3.9	<.001
Ischemic heart disease	7.8	7.6	7.2	7.3	.64
Myocardial infarction	1.2	1.4	1.3	1.0	.33
Heart failure	7.9	7.6	7.9	8.7	.40
Hypertension	60.7	60.5	60.6	59.8	.91
Diabetes mellitus	24.1	25.5	24.6	24.5	.10
Ischemic stroke	7.1	7.8	7.5	7.4	.33
Chronic liver disease	0.3	0.2	0.1	0.3	.55
Chronic renal disease	2.3	2.4	2.5	2.6	.85
Cancer	5.9	5.2	6.7	5.4	.10
Smoker	13.5	14.2	13.8	14.8	.21

NOTE. Data are percentage of subjects, unless otherwise indicated. COPD, chronic obstructive pulmonary disease; PPV, 23-valent pneumococcal polysaccharide vaccine; TIV, trivalent influenza vaccine.

Sadece İnfluenza (TIV) Aşısı Yapılanlar



Clinical Infectious Diseases 2010; 51(9):1007–1016


Vaccination status
Unvaccinated
PPV + TIV
PPV alone
TIV alone
Cumulative survival, %
100
99
98
97
96
95
0
100
200
300
400
500
Time from vaccination, days

Association between influenza vaccination and reduced risks of major adverse cardiovascular events in elderly patients

Ming-Hsien Chiang [a] Hau-Hsin Wu [b] Chia-Jen Shih [c] Yung-Tai Chen [d,e,1] Shu-Chen Kuo [f,g,1] and Te-Li Chen [a,g]
Taipei, Miaoli County, Taiwan

Table II. Crude and adjusted ORs for the risk of MACEs among elderly participants

	Cases	Controls	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)*	*P*
MACEs	80,363	80,363				
No vaccination	51,317	47,078	Reference		Reference	
Vaccination	29,046	33,285	0.78 (0.77-0.80)	<.001	0.80 (0.78-0.82)	<.001
No ILI or vaccination	44,945	42,413	Reference		Reference	
ILI without vaccination	6372	4665	1.29 (1.24-1.34)	<.001	1.24 (1.18-1.29)	<.001
ILI after vaccination	1989	1825	1.02 (0.95-1.09)	.610	0.99 (0.92-1.07)	.834
Myocardial infarction	20,096	20,096				
No vaccination	12,843	11,722	Reference		Reference	
Vaccination	7253	8374	0.77 (0.74-0.81)	<.001	0.80 (0.76-0.84)	<.001
No ILI or vaccination	10,848	10,488	Reference		Reference	
ILI without vaccination	1995	1234	1.57 (1.45-1.69)	<.001	1.46 (1.34-1.59)	<.001
ILI after vaccination	587	513	1.10 (0.98-1.25)	.118	1.05 (0.92-1.21)	.440
Ischemic stroke	60,267	60,267				
No vaccination	38,474	35,356	Reference		Reference	
Vaccination	21,793	24,911	0.79 (0.77-0.81)	<.001	0.80 (0.77-0.82)	<.001
No ILI or vaccination	34,097	31,925	Reference		Reference	
ILI without vaccination	4377	3431	1.19 (1.14-1.25)	<.001	1.16 (1.10-1.22)	<.001
ILI after vaccination	1402	1312	0.99 (0.91-1.07)	.711	0.96 (0.89-1.05)	.398

*Adjusted for all significant covariates ($P < .05$) listed in Table I.

Am Heart J 2017;193:1-7

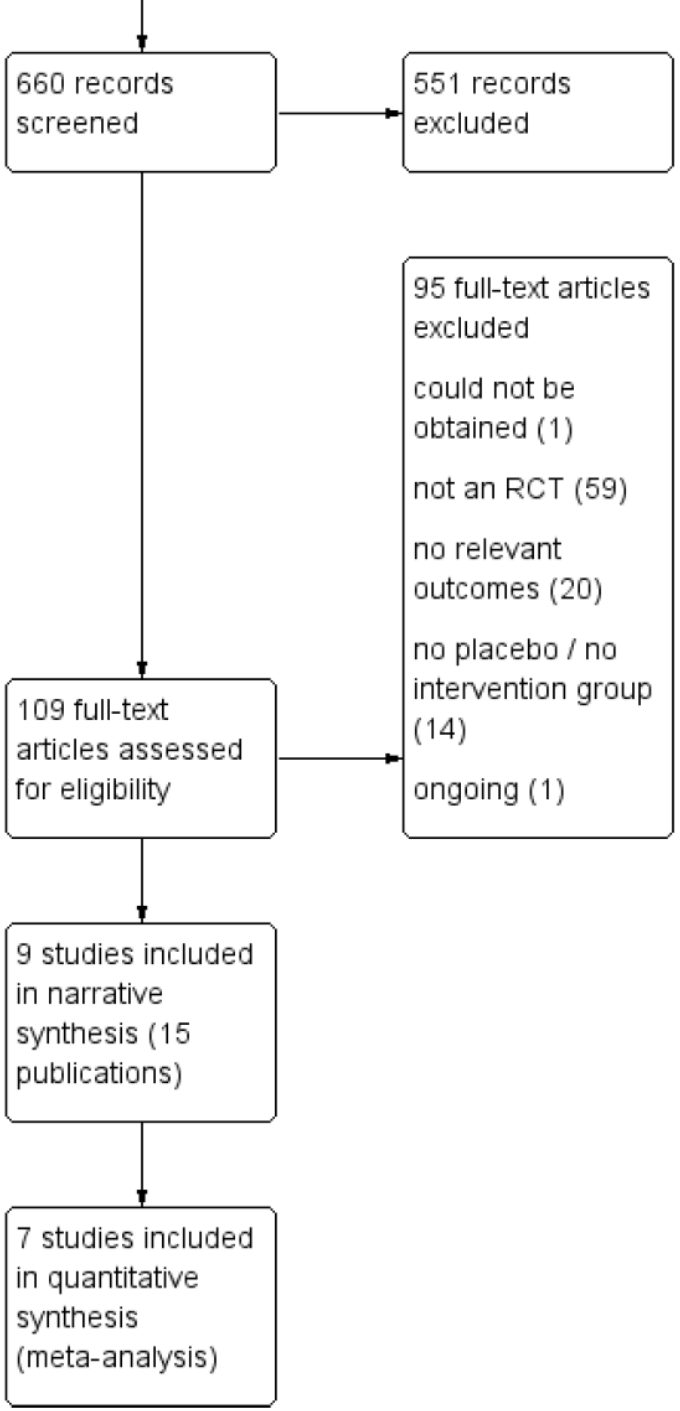
Cochrane Library

Cochrane Database of Systematic Reviews

Influenza vaccines for preventing cardiovascular disease (Review)

Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K

Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD005050.



Koroner arter hastalığı olanlarda İnfluenza aşılaması sonucunda;

RR: 0.45 (0.26-0.76), *P*=0.003

Avrupa'da 30 milyon KAH hastası var
Bağışıklama oranı %45,6'dan %75'e çıkarsa

42.000 kardiyovasküler ölüm engellenebilir

SEPSİSTE ENDOTEL HASARI

SİTOKİNLER

TNF-α, IL-1, IL-6, IL-18, IL-12, IL-15, MIF, HMGB-1

KEMOKİNLER

IL-8, MIP-1α, MIP-1β, MCP-1, MCP-3

LİPİD MEDİYATÖRLER

Tromboksan A2

PAF

Prostaglandinler

Lökotrienler

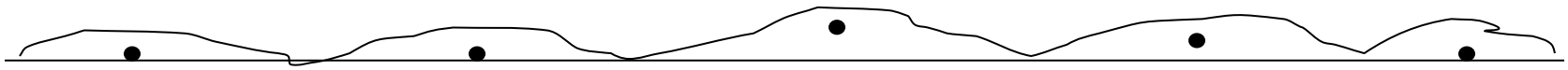
Doku faktörü (DF)

OKSİJEN RADİKALLERİ

Superoksit ve hidroksil radikaller

NO

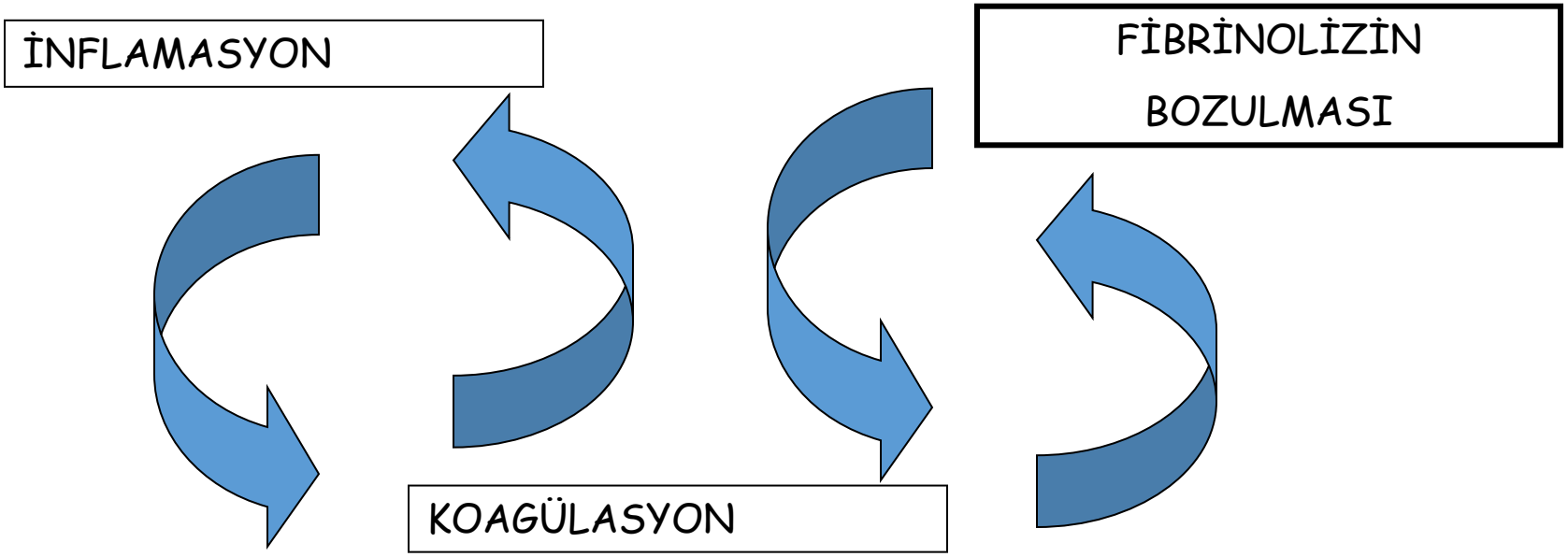
ENDOTEL HASARI



TF

PAI-1

PROKOAGÜLAN ETKİ



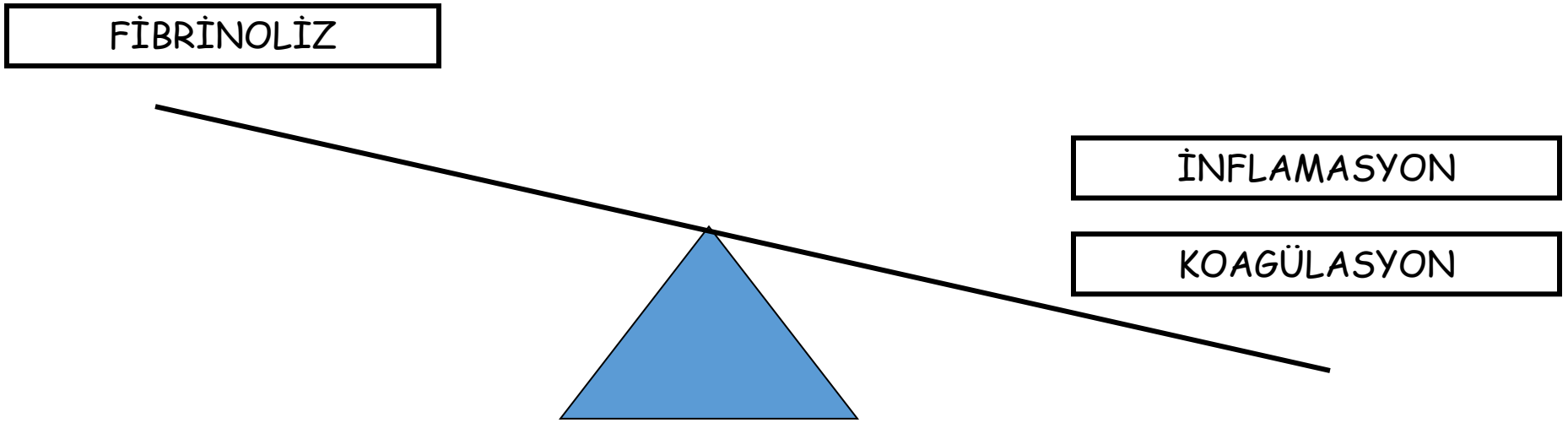
Crit Care 2001; 5: 1

Scand J Infect Dis 2003; 35: 545

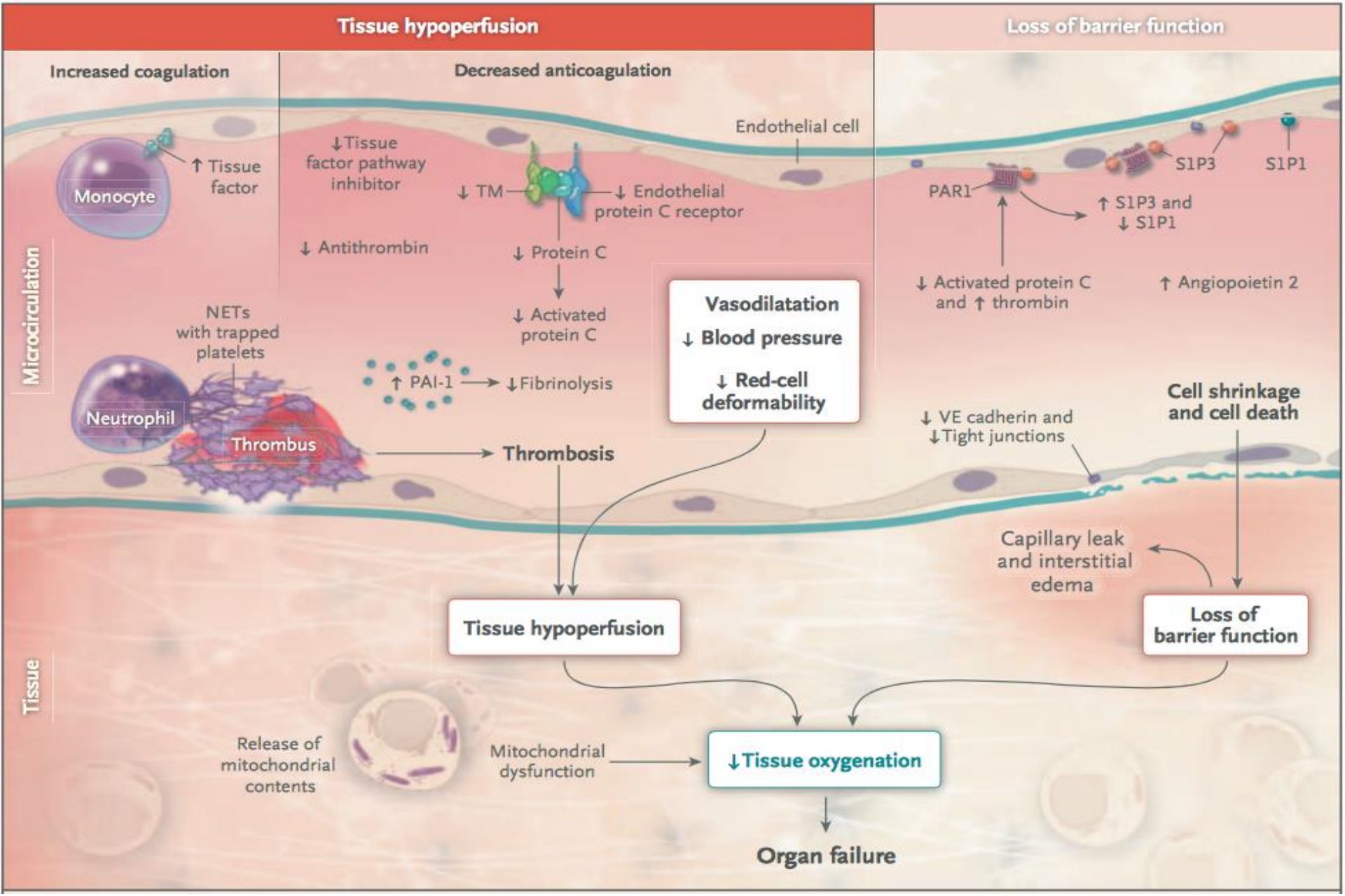
CID 2003; 36

N Engl J Med 2001; 344: 759

CİDDİ SEPSİS



N Engl J Med 2013;369:840-51


Tissue hypoperfusion
Loss of barrier function
Increased coagulation
Decreased anticoagulation
Endothelial cell
↑ Tissue factor
Monocyte
↓Tissue factor pathway inhibitor
↓ TM
↓ Endothelial protein C receptor
↓ Antithrombin
↓ Protein C
↓ Activated protein C
PAR1
S1P3
S1P1
↑ S1P3 and ↓ S1P1
↓ Activated protein C and ↑ thrombin
↑ Angiopoietin 2
Microcirculation
NETs with trapped platelets
Neutrophil
Thrombus
↑ PAI-1
↓Fibrinolysis
Vasodilatation
↓ Blood pressure
↓ Red-cell deformability
Thrombosis
↓ VE cadherin and ↓Tight junctions
Cell shrinkage and cell death
Capillary leak and interstitial edema
Tissue hypoperfusion
Loss of barrier function
Tissue
Release of mitochondrial contents
Mitochondrial dysfunction
↓Tissue oxygenation
Organ failure

Kimler aşılanmalı?

- 50 yaş üzerindeki herkes
- 6 aydan büyük, 18 yaştan küçük tüm çocuklar
- Altta yatan hastalığı olanlar

  KOAH, kanser, organ nakli, KBY, steroid kullanımı, kalp hastalığı, DM..vb
- Sağlık çalışanları
- Gebeler
- Morbid obez olanlar (VKİ≥40)
- 6 aydan küçük bebeğe bakanlar
- İmmünsupresif (kanser, organ nakli..vb) yakını olanlar
- Aspirin kullanmak zorunda olan 6ay-18 yaş arası kişiler
- Aşılanmak isteyen herkes

AŞI

- Epidemi öncesi, sonbaharda (Ekim ayı ideal!) uygulanmalı
  - Yetişkinlere tek doz
  - 9 yaş ve altı çocuklara bir ay arayla 2 doz
  - 3 yaş ve altı çocuklara yarım doz, bir ay arayla iki kez
  - İntramüsküler uygulanır
  - **Her yıl tekrarlanması gerekiyor**

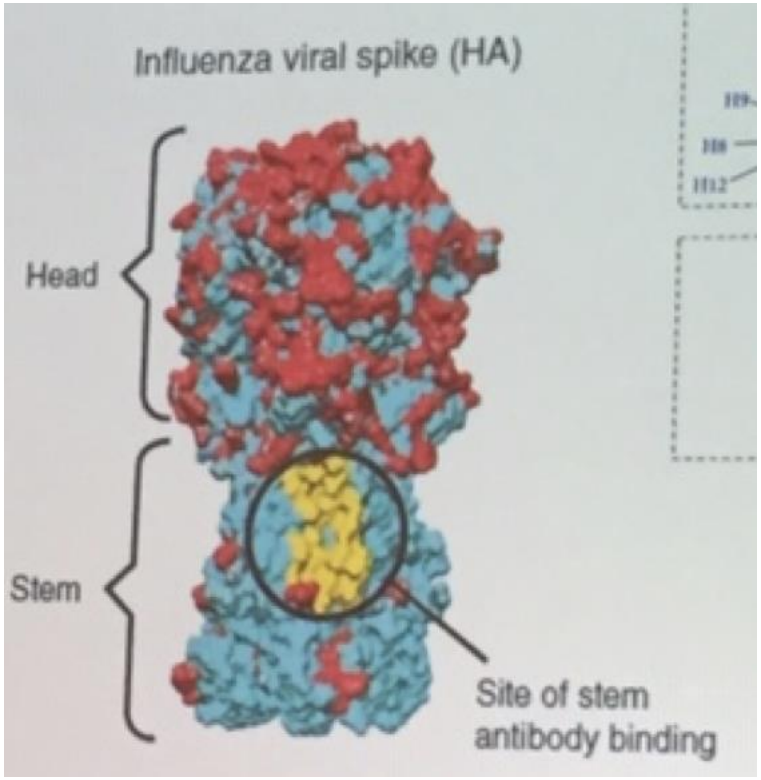
Daha iyi bir grip aşısı için;

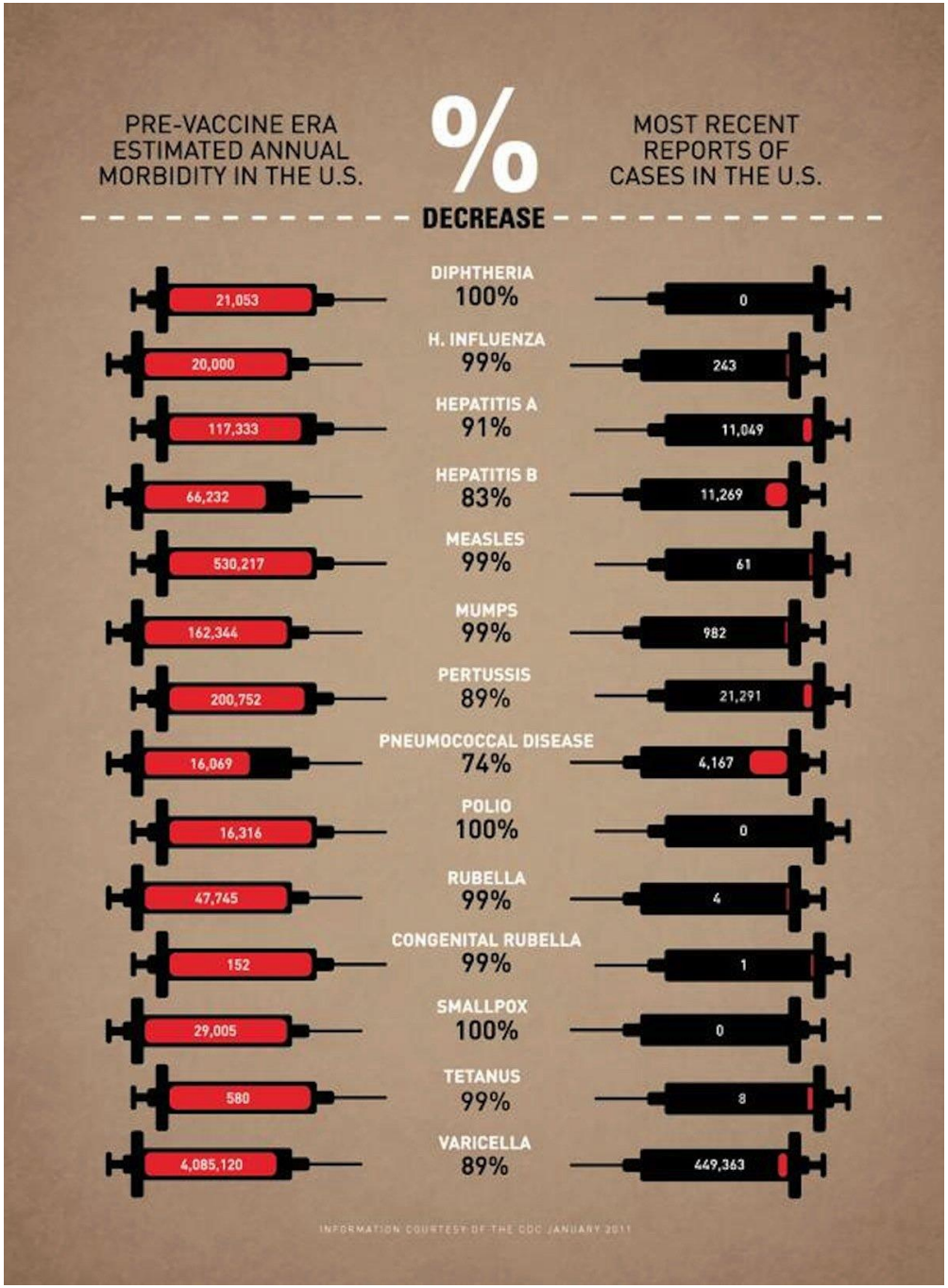
Daha uzun süren ve yüksek doz antikor yanıtı sağlayacak aşılar

- Yüksek doz antijen içeren aşı
- Antikor yanıtını artıran proteinler (M-001)
- Rekombinan aşılar

Daha geniş etkili aşılar

- Nöraminidazı hedefleyen aşılar
- HA'nin sap kısmına yönelik aşılar





teşekkürler