İnfluenza Aşıları: Yenilik var mı?

Dr. Serap Gençer

Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, İstanbul

EKMUD Çukurova Günleri – 18.03.2017

- Sürveyans verileri
- Mevcut aşılar
- İçeriği
- Etkinliği
- Gelecek aşılar

NEW

SG-03/2017


"BENİM ADIMI VERMİŞSİN. BEN AŞI OLMAYI DÜŞÜNMÜYORUM"


GRİP AŞISI TUZAĞINA DÜŞMEYİN
Prof. Küçükusta: Bu aşılar sağlığı korumaktan çok ilaç sanayicilerinin kasalarını dolduruyor


Başbakan aşı olmayacaksa vatandaş niye olsun


GRİP AŞISI OLALIM MI?
OLMAYALIM MI?


NEWS

NEW


ERİŞKİN BAĞIŞIKLAMA AKADEMİSİ
25-26 Şubat 2017

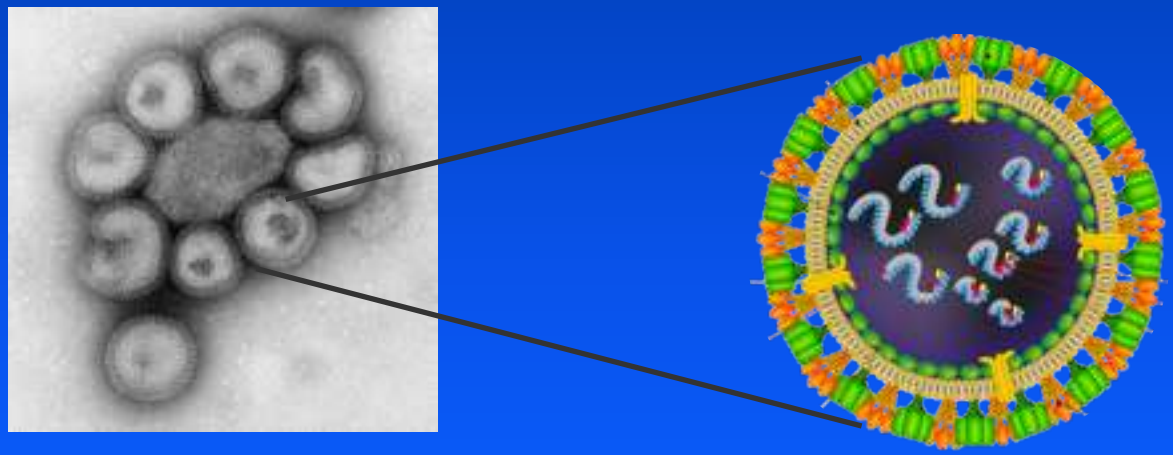

AHEF


TÜRKİYE ERMUD
ERİŞKİN BAĞIŞIKLAMA AKADEMİSİ


TÜRK HEMATOLOJİ DERNEĞİ
TÜRK İÇ HASTALIKLARI UZMANLIK DERNEĞİ

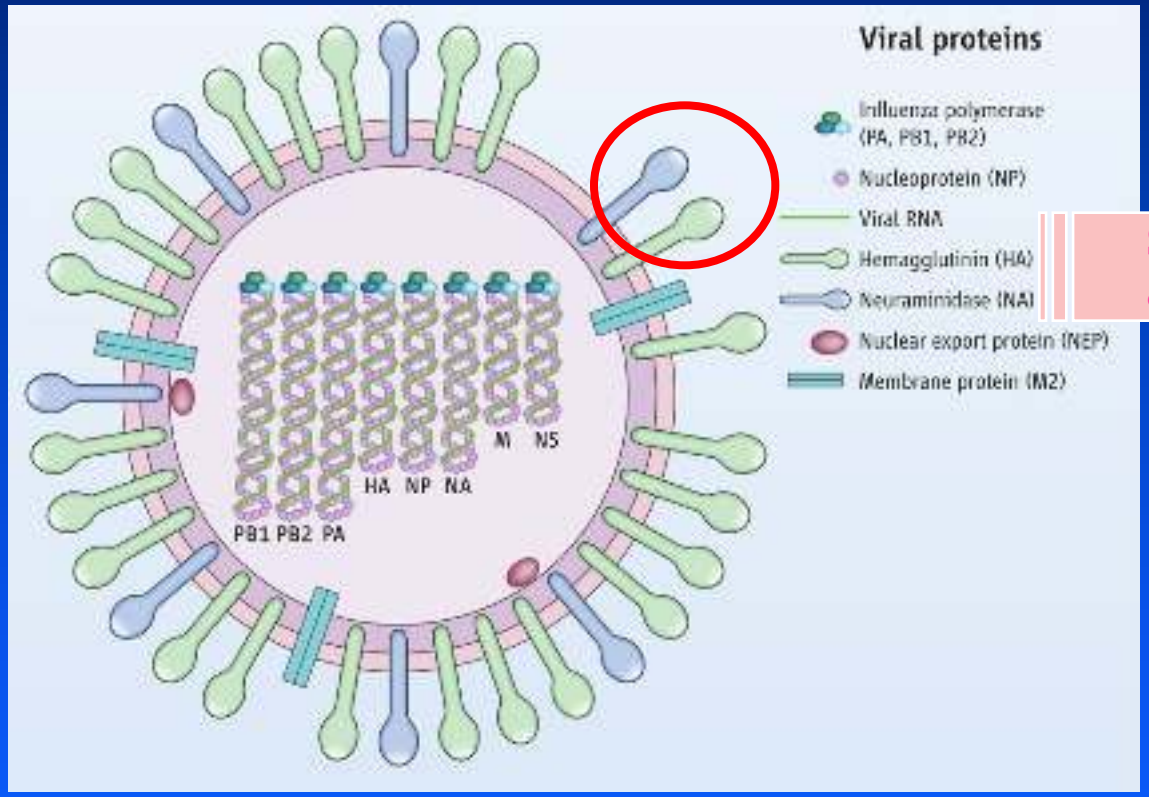
İnfluenza virusları

- *Orthomyxoviridae* ailesinden
- Pleomorfik, zarflı, tek sarmallı RNA virüsü
- A, B, C, D tipi influenza



İnfluenza virus genomunun kodladığı proteinler

- 8 segment ve bunların kodladığı 10 protein



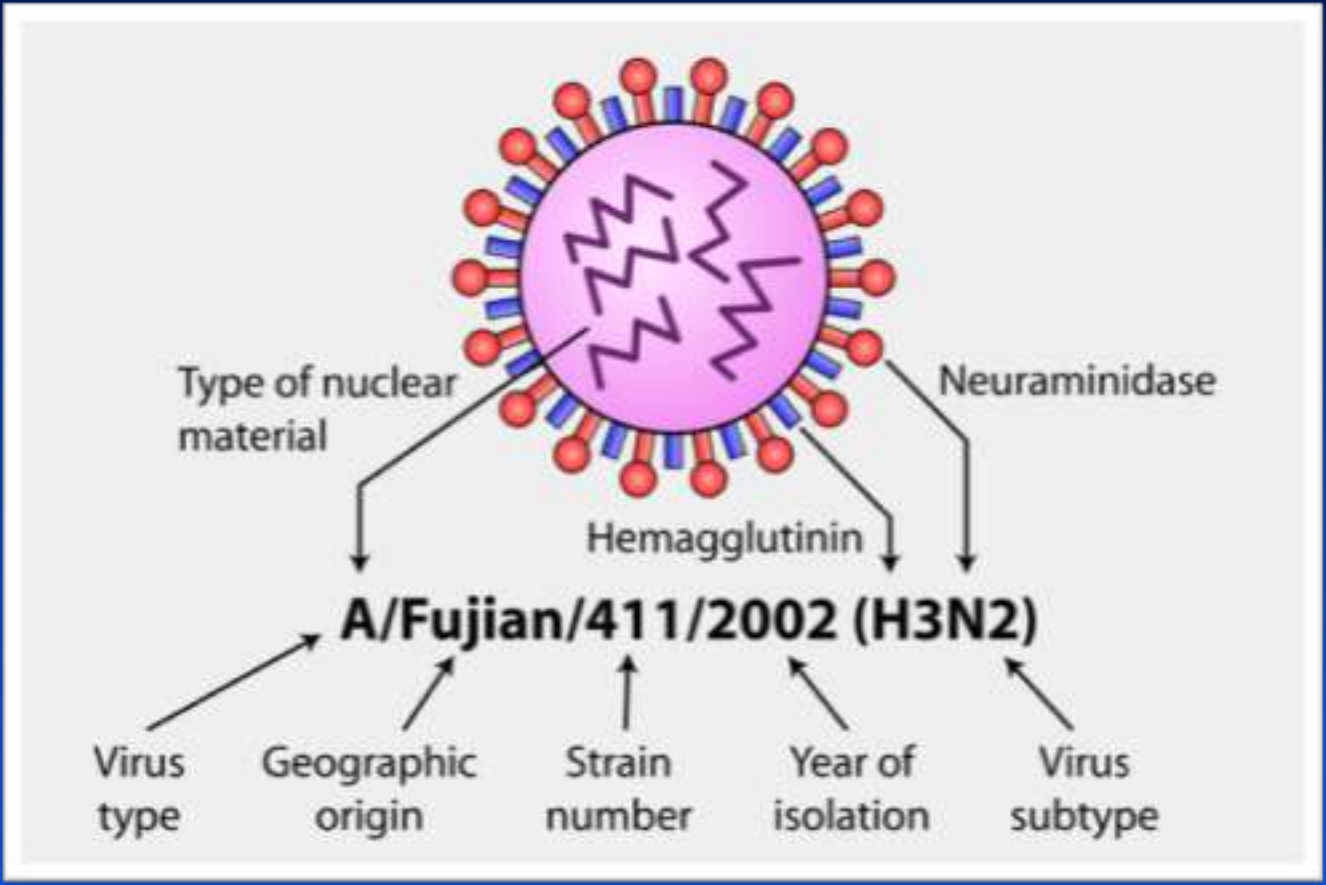
Subtiplerin adlandırılması

H1-H16

N1-N9

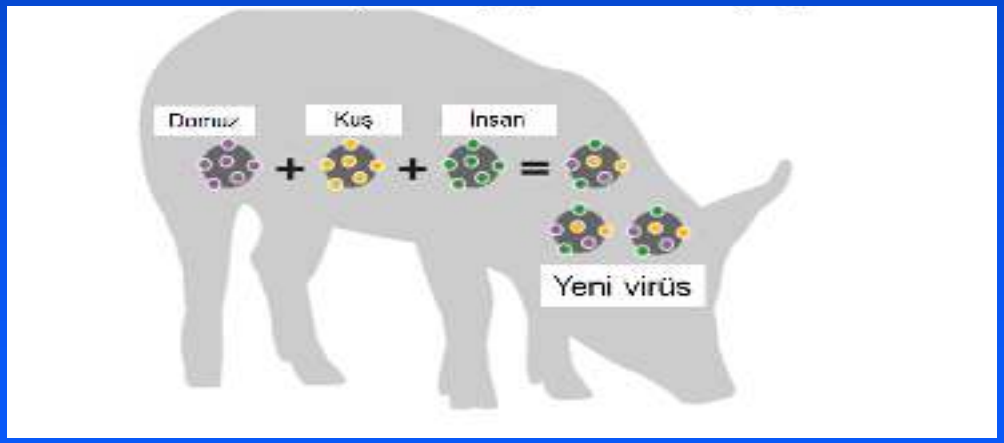
H1-H3, N1-N2 insanlarda yaygın, diğerleri sporadik

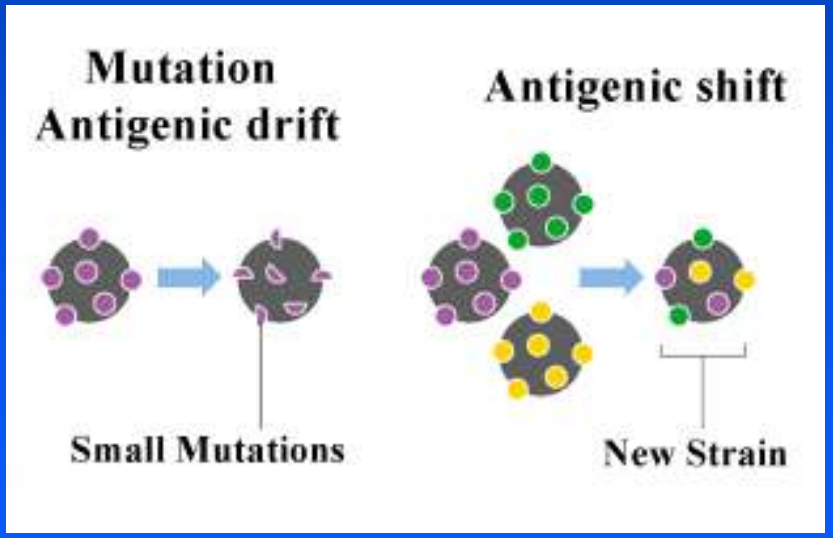
Subtipleri ve Adlandırma



Antijenik Değişim

- Antijenik drift (sürüklenme) → yıllık epidemiler
- Antijenik shift (kayma) → reassortment sonucu yeni bir influenza A alt tipi → pandemiler

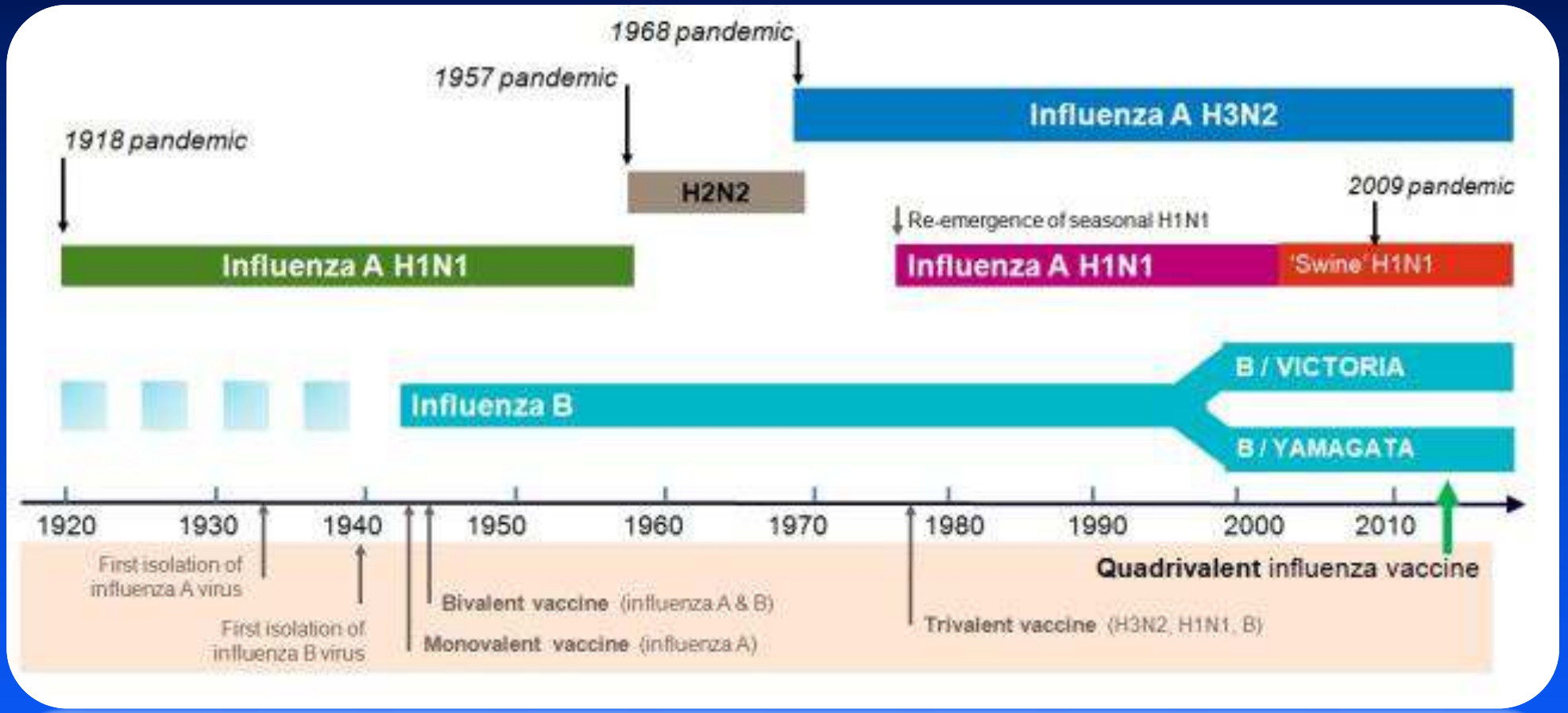




Uygulanacak Aşı

- Her grip sezonu için aşının içeriği DSÖ tarafından belirlenmekte, dolaşımdaki en sık 3 virüs tipi hedeflenerek üreticilere bildirilmekte
- Bu süreç en az 6 aylık bir süre gerektirir
  - Çoğunlukla embriyonlu yumurtada veya son yıllarda memeli hücrelerde üretilerek çoğaltılır
- ‘’*Tahmin et, üret*’’
- Dolaşımdaki suşların tiplendirilmesi önemli

Grip Aşılaması Geçmişi



Grip Aşısı İçeriği
(2017 sezonu için DSÖ önerisi)

- A/California/7/2009 (H1N1)-like virus
- A/Hong Kong/4801/2014 (H3N2)-like virus
- B/Brisbane/60/2008-like virus (from the influenza B/Victoria lineage)
- B/Phuket/3073/2013-like virus (Yamagata lineage)

http://www.who.int/influenza/vaccines/virus/recommendations/201609_qanda_recommendation.pdf?ua=1/

Neden Kuadrivalan?

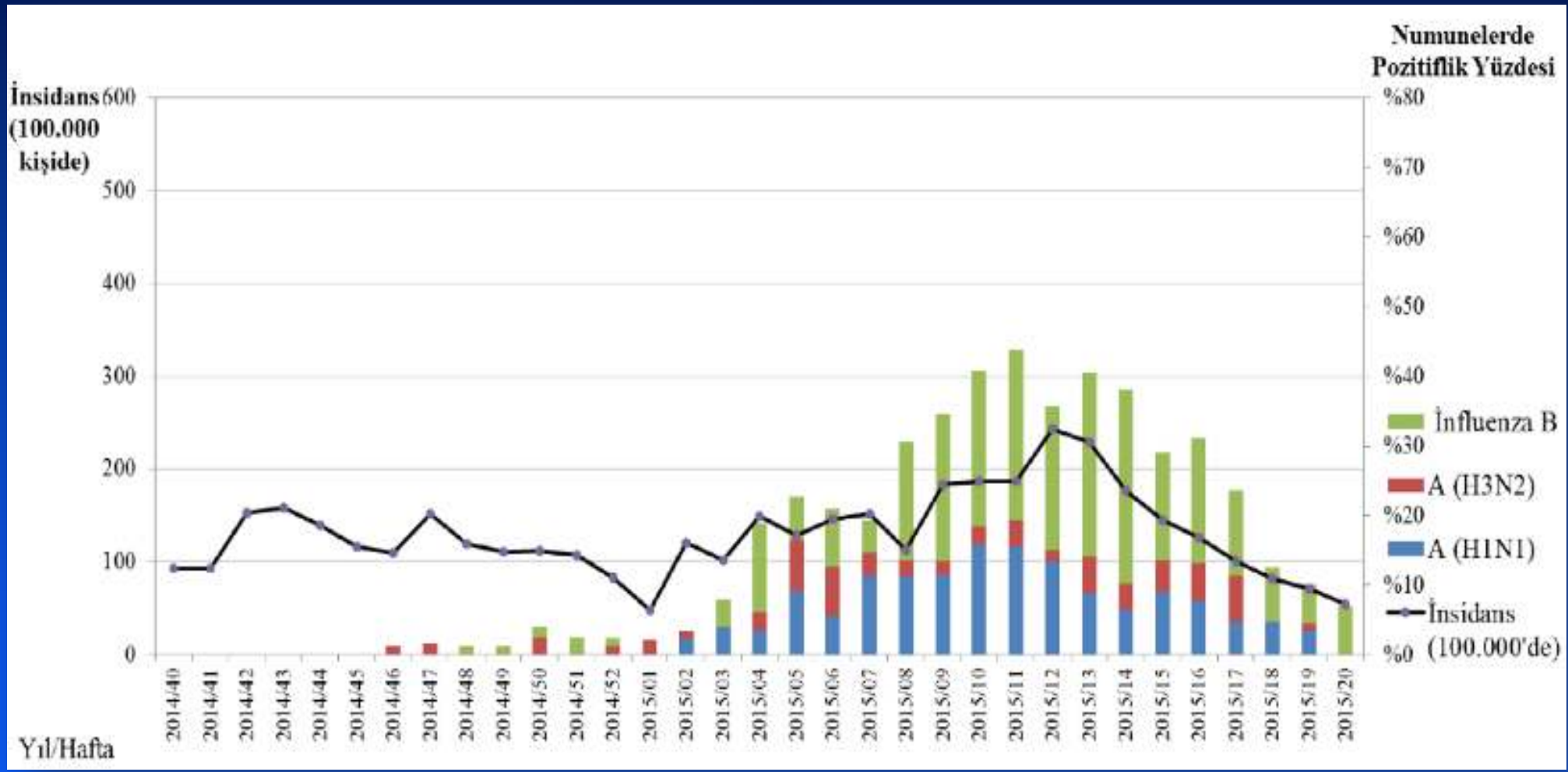
- 1999 ve 2012 arası sezonlarda mevsimsel grip epidemilerinin %26'sı influnza B.
- Tüm influenza B izolatlarının %42'si o sezondaki trivalan aşıda bulunmayan soylar.

Son 12 Sezona Ait Sürveyans Verileri

Sezon	Influenza A %	Hakim Alt tip	Influenza B %
2003-2004	100	H3N2	0
2004-2005	86	H1N1, H3N2	14
2005-2006	89	H3N2	11
2006-2007	64	H3N2	36
2007- 2008	68	H1N1	32
2008-2009	50	H3N2	50
2009-2010	100	pH1N1	0
2010-2011	46.4	pH1N1, H3N2	53.4
2011-2012	75.3	H3N2	24.6
2012-2013	95	H1N1, H3N2	5
2013-2014	94	H3N2	6
2014-2015	43.9	H1N1, H3N2	56

Prof. Dr. Selim Badur

Ülkemizde Sentinel İnfluenza Sürveyansı verileri (2014-2015)



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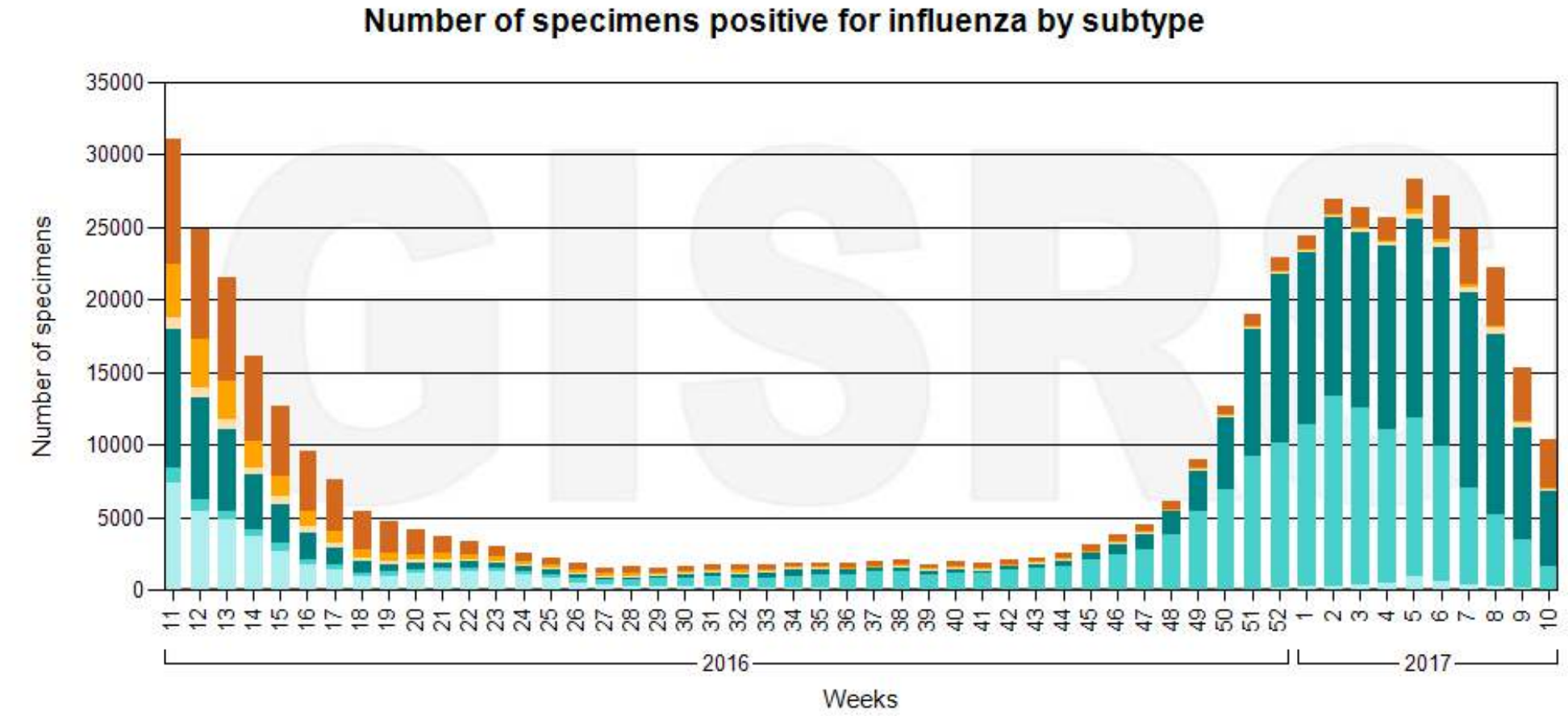
SB THSK Haftalık İnfluenza(Grip) Sürveyans Raporu 20 Mayıs 2015

Ülkemiz'de son dört sezona ait influenza virüslerinin oranları

Sezon	İnfluenza A(H1N1) pdm09	İnfluenza A(H3N2)	İnfluenza B
2012-2013	**%92,5**	%4,6	%2,7
2013-2014	%2,5	**%77**	%20,5
2014-2015	%38,0	%9,2	**%52,8**
2015-2016	%34.3	**%35.8**	**%28.5**

Prof. Dr. Selim Badur

Global circulation of influenza viruses



World Health Organization

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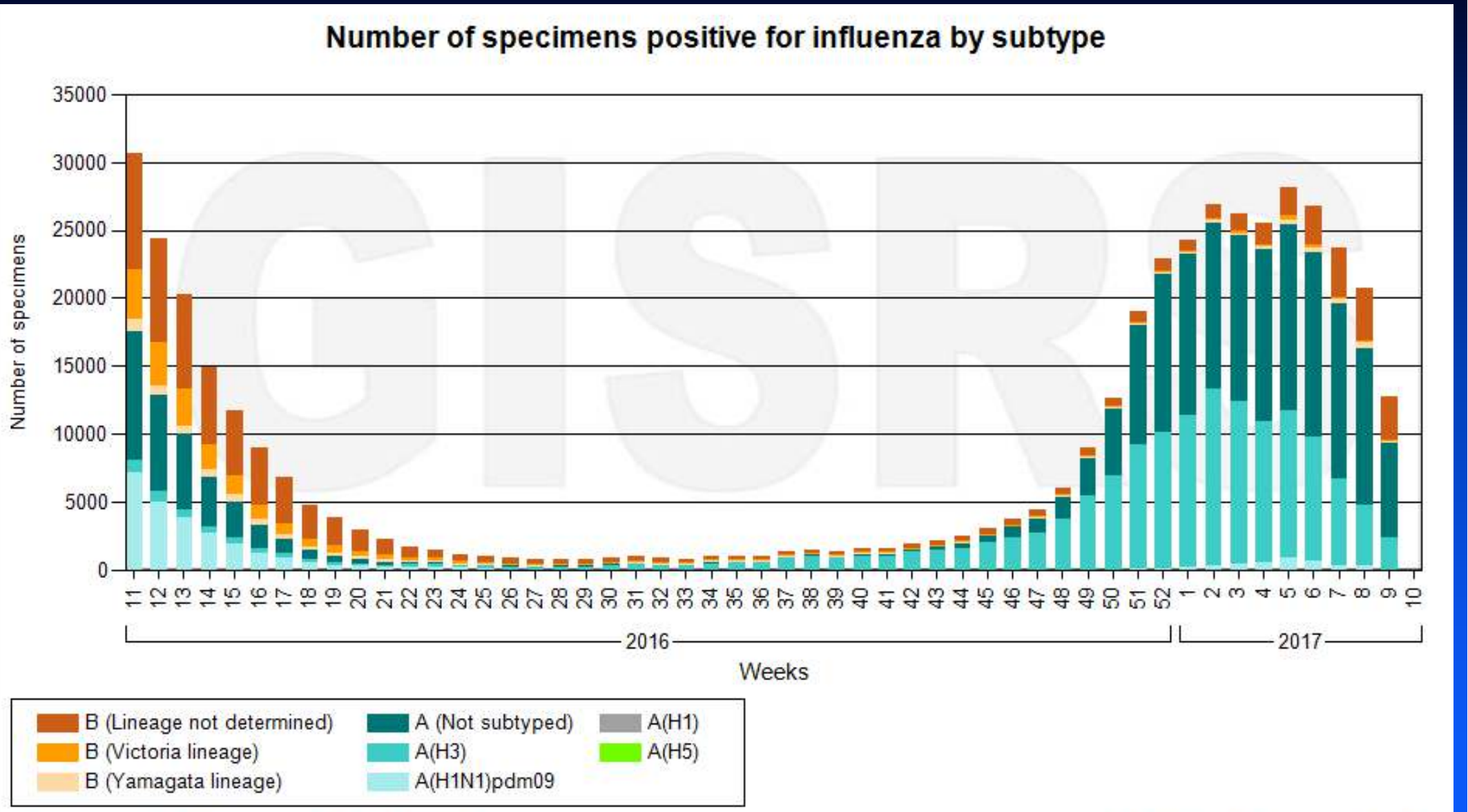
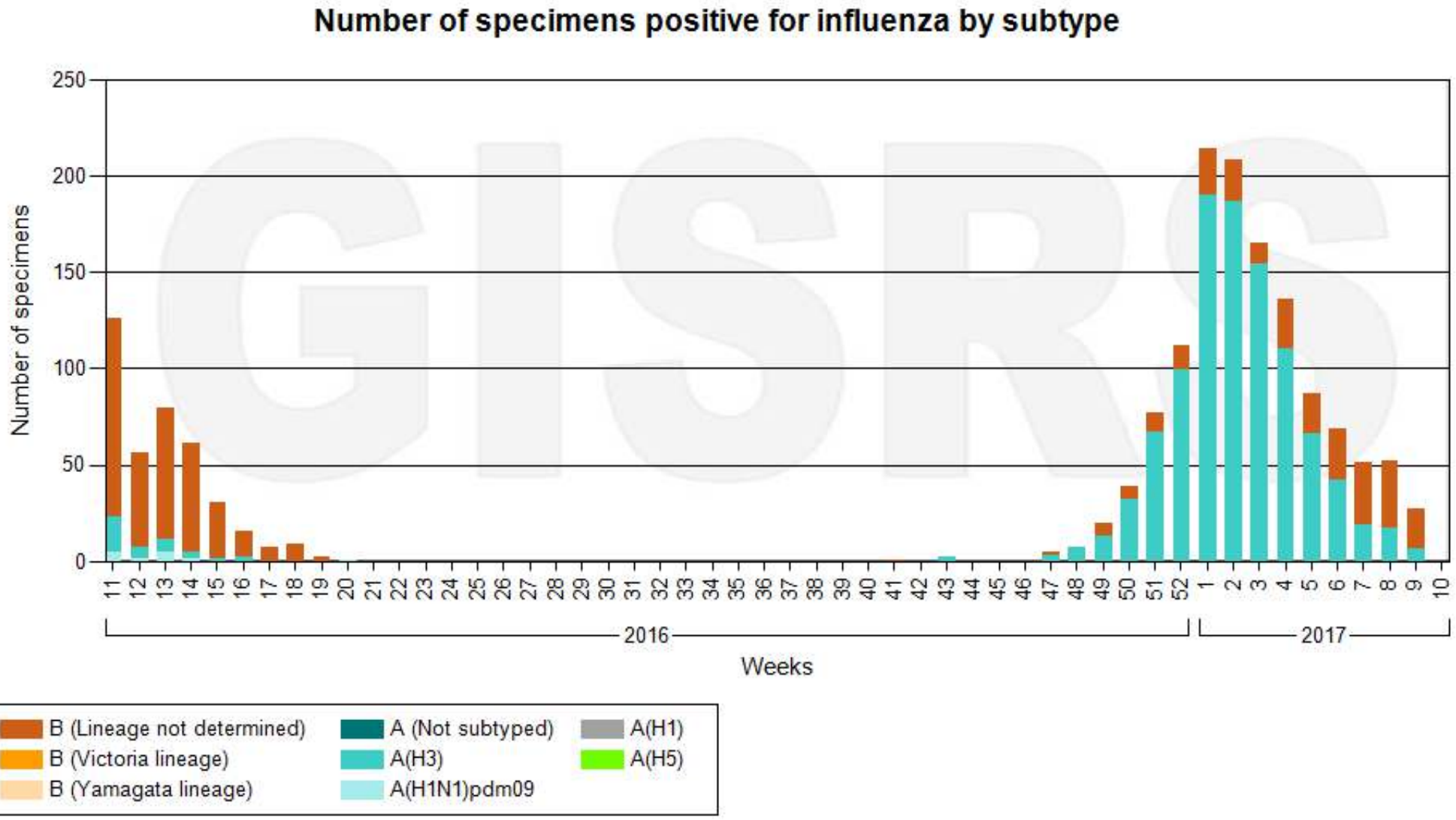
http://www.who.int/flunet

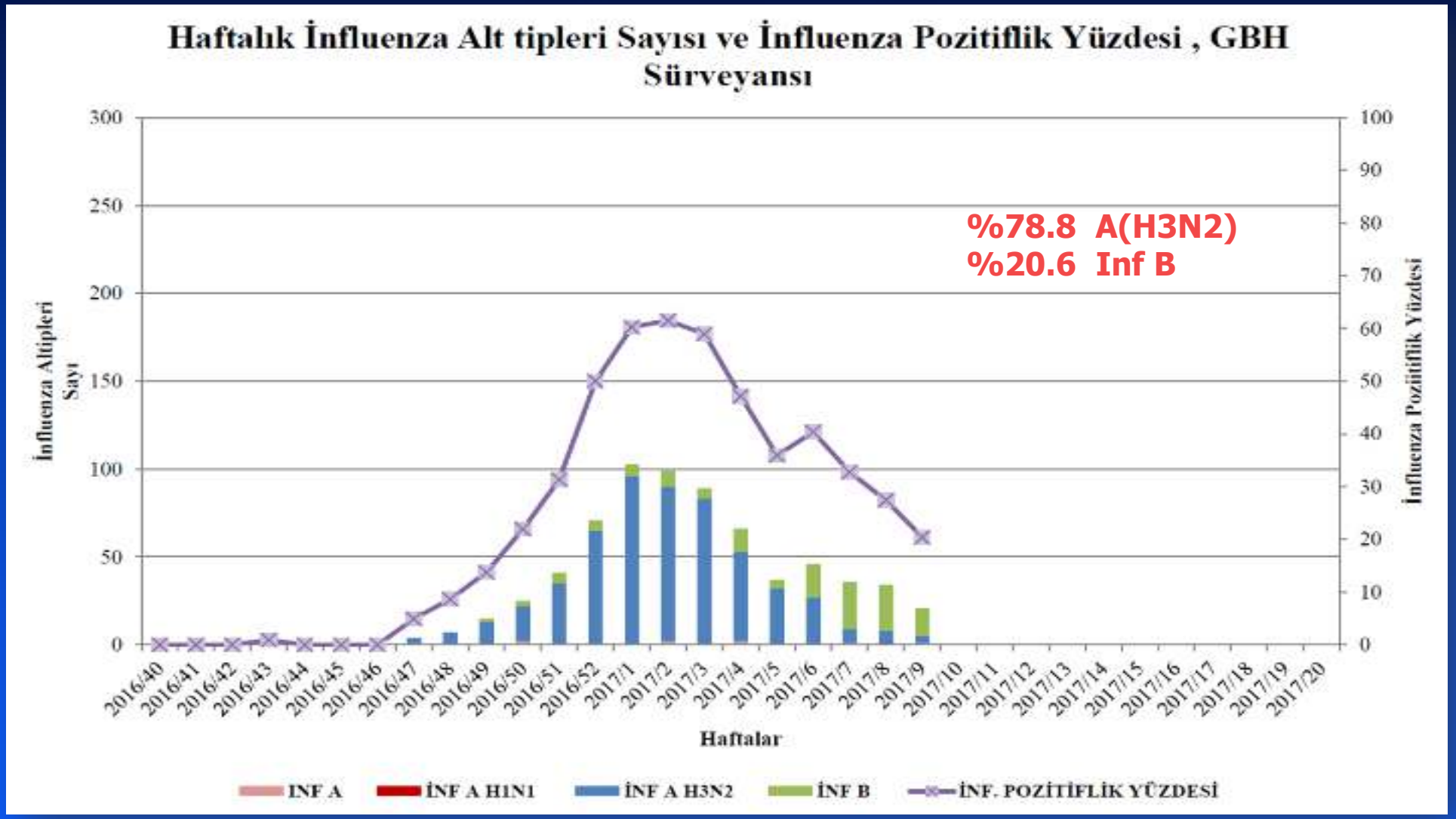
Northern hemishere circulation of influenza viruses generated on 13/03/2017



Turkey


Number of specimens positive for influenza by subtype
Number of specimens
250
200
150
100
50
0
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10
2016
2017
Weeks
B (Lineage not determined)
B (Victoria lineage)
B (Yamagata lineage)
A (Not subtyped)
A(H3)
A(H1N1)pdm09
A(H1)
A(H5)

Ülkemizde Sentinel İnfluenza Sürveyansı verileri (2016-2017)



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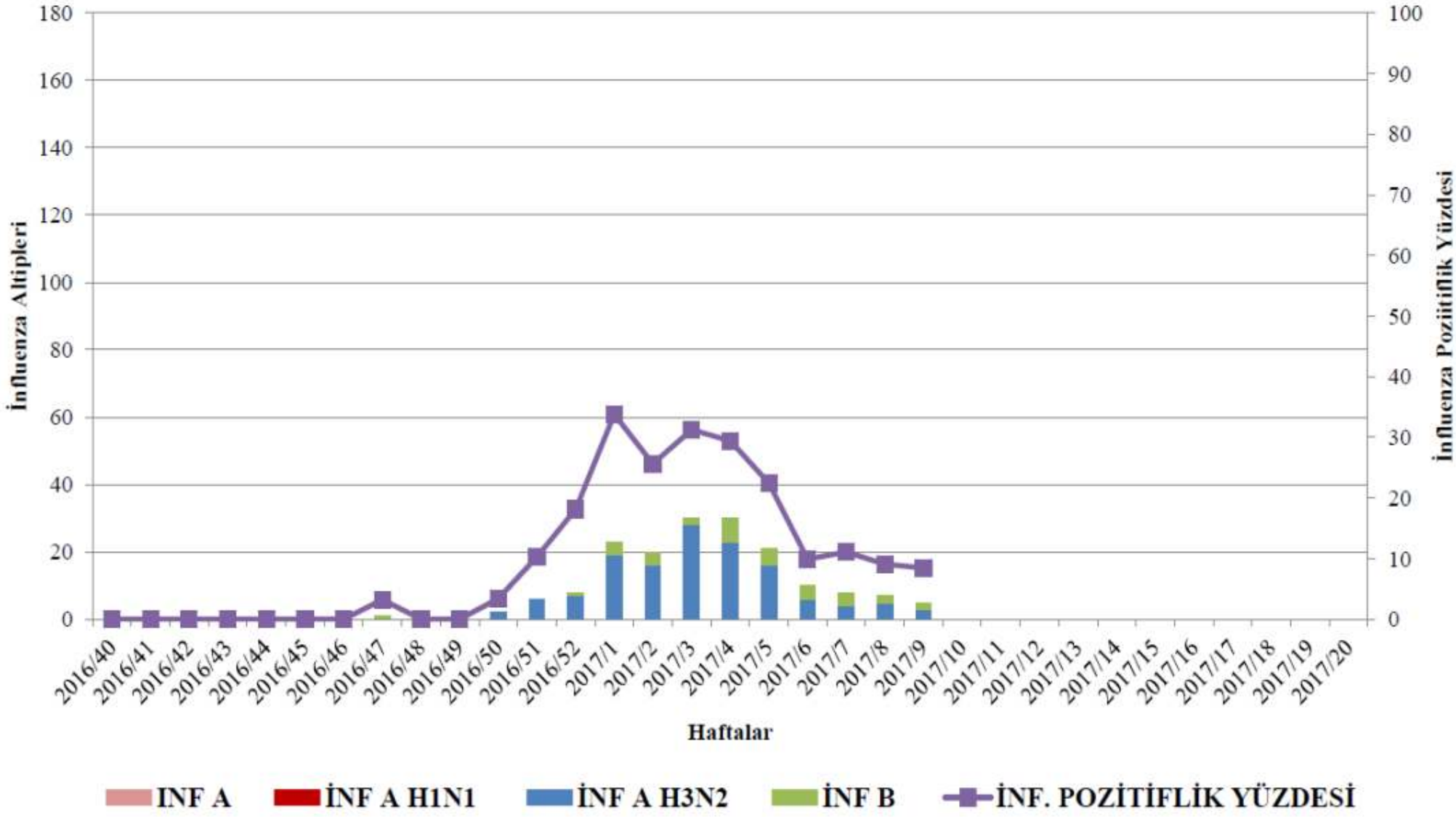
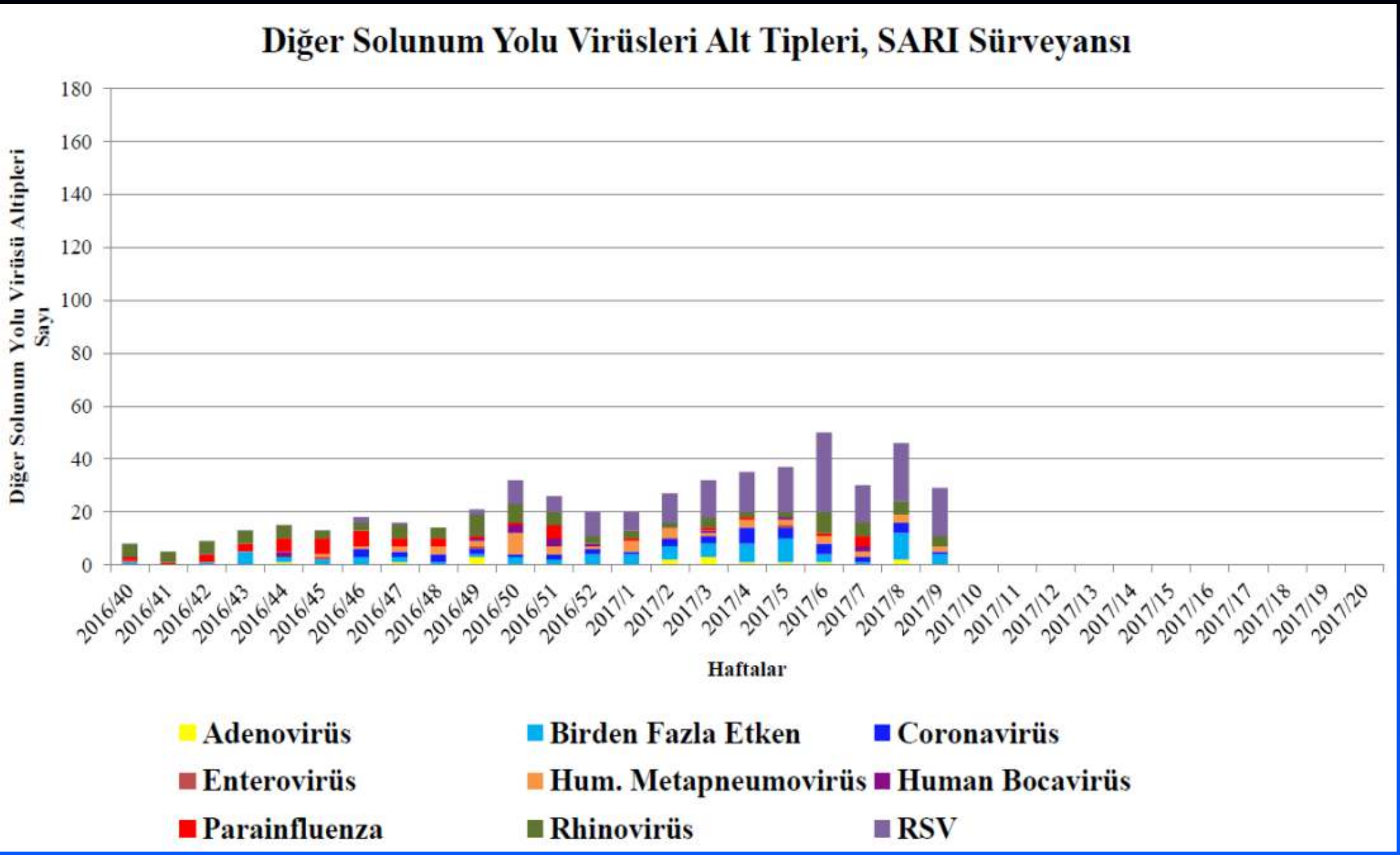
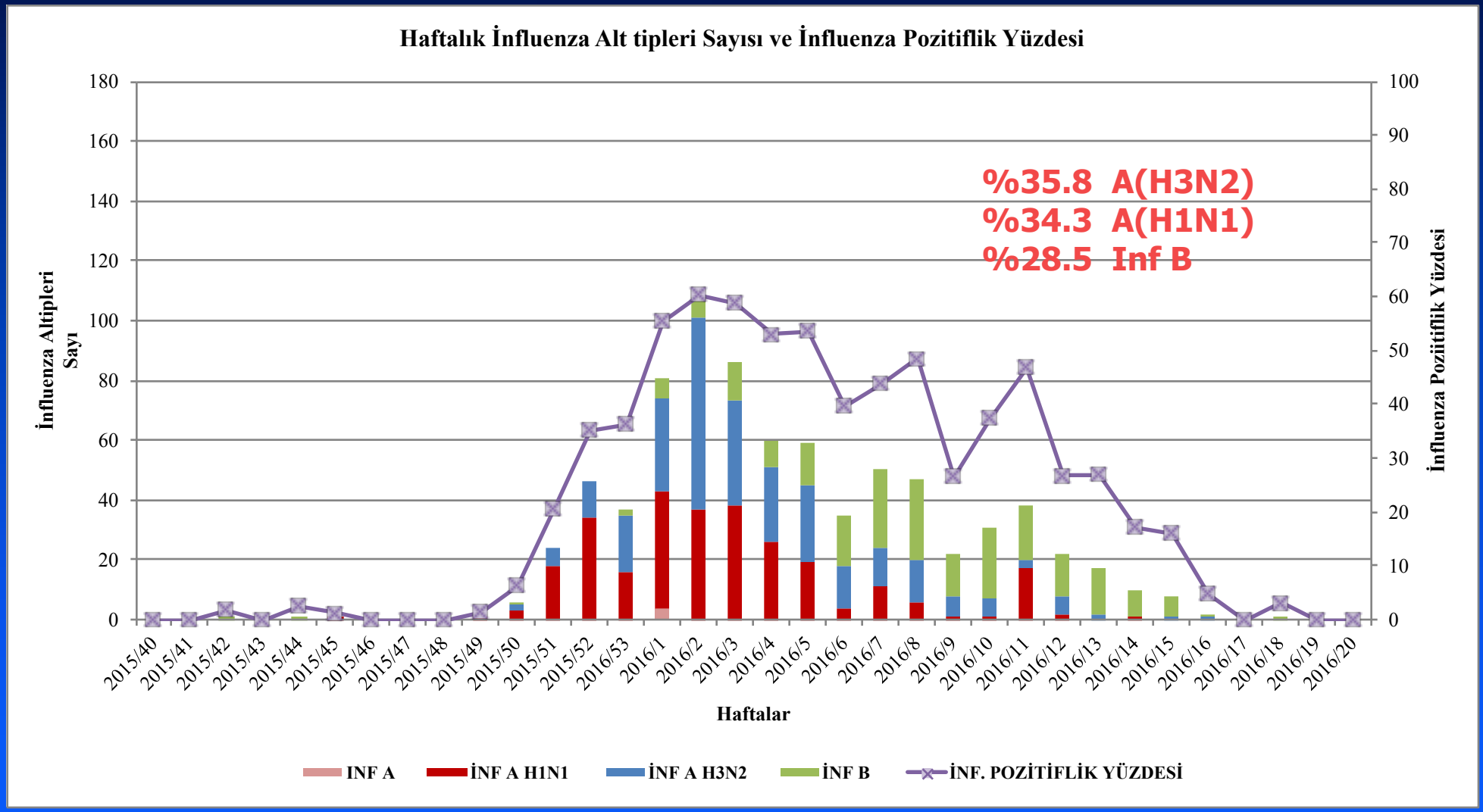
SB THSK Haftalık İnfluenza(Grip) Sürveyans Raporu 5 Mart 2017

Haftalık İnfluenza Alt Tipleri ve İnfluenza Pozitiflik Yüzdesi, SARI Sürveyansı




Diğer Solunum Yolu Virüsleri Alt Tipleri, SARI Sürveyansı
Diğer Solunum Yolu Virüsü Altipleri Sayı
180
160
140
120
100
80
60
40
20
0
2016/40
2016/41
2016/42
2016/43
2016/44
2016/45
2016/46
2016/47
2016/48
2016/49
2016/50
2016/51
2016/52
2017/1
2017/2
2017/3
2017/4
2017/5
2017/6
2017/7
2017/8
2017/9
2017/10
2017/11
2017/12
2017/13
2017/14
2017/15
2017/16
2017/17
2017/18
2017/19
2017/20
Haftalar
Adenovirüs
Birden Fazla Etken
Coronavirüs
Enterovirüs
Hum. Metapneumovirüs
Human Bocavirüs
Parainfluenza
Rhinovirüs
RSV

Ülkemizde Sentinel İnfluenza Sürveyansı verileri (2015-2016)



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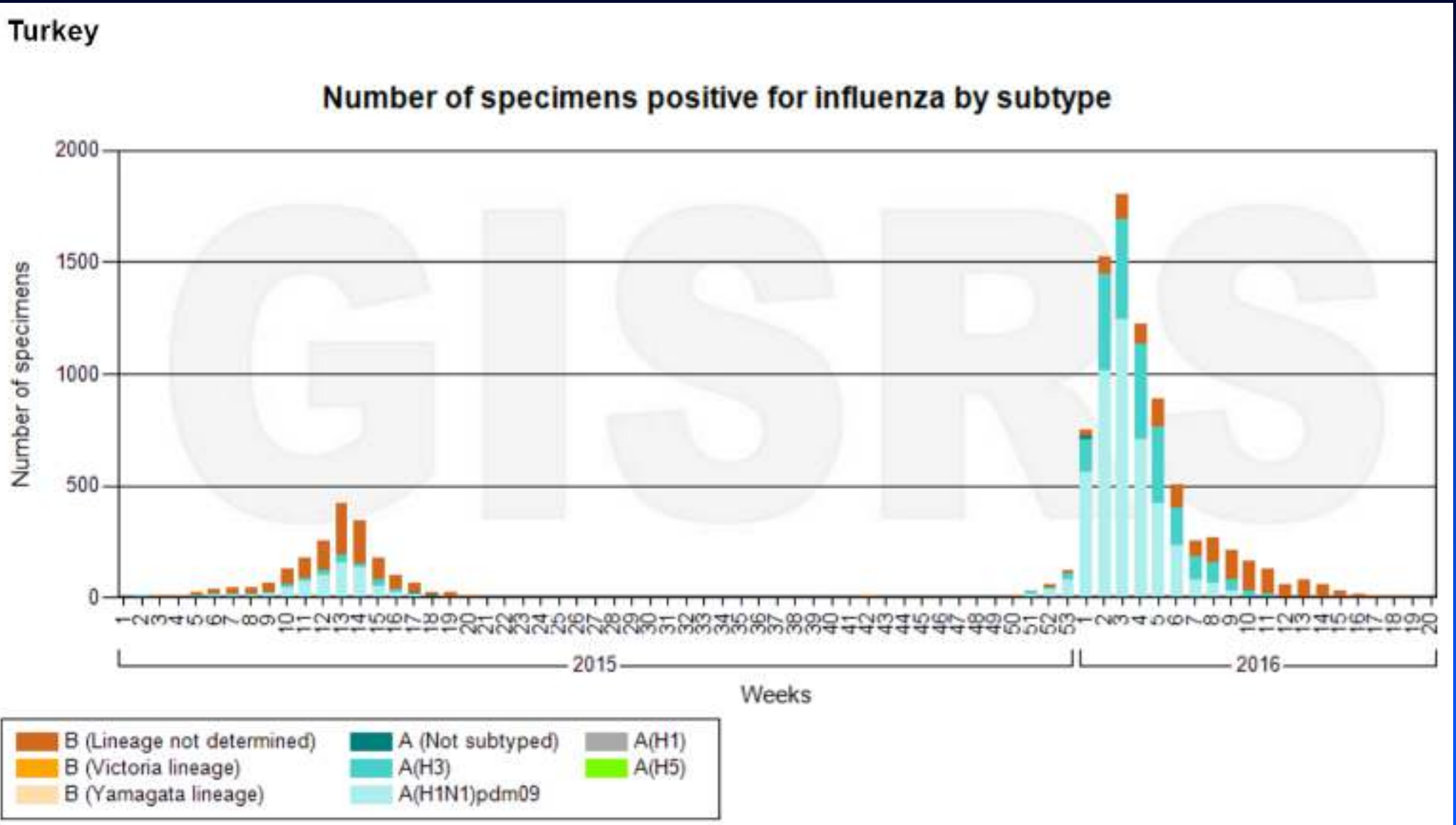
SB THSK Haftalık İnfluenza(Grip) Sürveyans Raporu 22 Mayıs 2016

Turkey



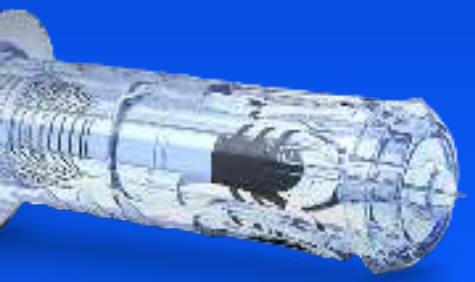
http://www.who.int/flunet

Mevcut Aşılar

- Standart doz trivalan ve kuadrivalan İnaktif İA
  - Her bir antijen 15 mcg

- ‘PharmaJet Stratis needle-free injection system’ standart doz İİA (2014)

- **İntradermal d**üşük doz kuadrivalan İİA (2014)
  - 18-64 y için.
  - Standart doz antijenin 1/5’i



- Yüksek doz trivalan İİA
  - ≥65 y için FDA onaylı.
  - Her bir antijen 60 mcg
- **Adjuvanlı trivalan İİA** (Kasım 2015)
  - ≥65 y için FDA onaylı

- Kültür hücrelerinde üretilen trivalan İİA
  - ≥18 y
- Rekombinan DNA teknolojisi ve bir baculovirus ekspresyon sisteminde üretilen trivalan İİA
  - ≥18 y
  - Kuadrivalan formu (2016)
  - Sadece hemagglutinin antijenleri

- Standart doz kuadrivalan Canlı Atenüe İA
  - Sağlıklı, gebe olmayan, 2-49 y için
  - 2016-2017 influenza sezonu için önerilmedi

LAIV and IIV vaccine effectiveness ages 2–17 years, by influenza type/subtype, 2015-16

	Any influenza		H1N1pdm09		B/Yamagata		B/Victoria	
	LAIV4	IIV3/4	LAIV4	IIV3/4	LAIV4	IIV3/4	LAIV4	IIV3/4
Total, Flu +	324	367	156	174	59	63	100	121
Vaccinated, Flu +	38	81	23	41	8	12	7	28

SG-03/2017

Flannery B, Chung J. Influenza Division, CDC For the US Flu VE Network

Aşı Etkinliğini Belirleme Kriterleri

- Anti-HA antikor titrelerini ölçmek
  - Koruyucu titre ?
- Hastalığa yakalanmama, komplikasyon oranlarının azalması gibi parametreler
  - Grip tanımı ?
  - Laboratuvar bulguları ile kanıtlanmış grip olgularının değerlendirilmesi

- TIIA'nın laboratuvar olarak doğrulanmış influenzayı önlemede etkinliği
  - %60 (%51-%67)
  - Aşı içeriği uyumluysa %62, uyum yoksa %55
- IBH'ı önlemede %16 etkili (aşı içeriğinle uyumlu ise)

Jefferson T, et al. Cochrane Database Syst Rev 2014;3:CD001269.

Table. Adjusted vaccine effectiveness estimates for influenza seasons from 2005-2016

Influenza Season†	Reference	Study Site(s)	No. of Patients‡	Adjusted Overall VE (%)	95% CI
2004-05	Belongia 2009	WI	762	10	-36, 40
2005-06	Belongia 2009	WI	346	21	-52, 59
2006-07	Belongia 2009	WI	871	52	22, 70
2007-08	Belongia 2011	WI	1914	37	22, 49
2008-09	Unpublished	WI, MI, NY, TN	6713	41	30, 50
2009-10	Griffin 2011	WI, MI, NY, TN	6757	56	23, 75
2010-11	Treanor 2011	WI, MI, NY, TN	4757	60	53, 66
2011-12	Ohmit 2014	WI, MI, PA, TX, WA	4771	47	36, 56
2012-13	McLean 2014	WI, MI, PA, TX, WA	6452	49	43, 55
2013-14	Gaglani 2009	WI, MI, PA, TX, WA	5999	52	44, 59
2014-15	Zimmerman 2016	WI, MI, PA, TX, WA	9311	19	10, 27
2015-16*	ACIP presentation, Flannery [332 KB, 26 pages]	WI, MI, PA, TX, WA	7563	47*	39, 53*

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https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm

Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies

Edward A Belongia, Melissa D Simpson, Jennifer P King, Maria E Sundaram, Nicholas S Kelley, Michael T Osterholm, Huong Q McLean

Summary

Background Influenza vaccine effectiveness (VE) can vary by type and subtype. Over the past decade, the test-negative design has emerged as a valid method for estimation of VE. In this design, VE is calculated as 100% x (1 – odds ratio) for vaccine receipt in influenza cases versus test-negative controls. We did a systematic review and meta-analysis to estimate VE by type and subtype.

Methods In this systematic review and meta-analysis, we searched PubMed and Embase from Jan 1, 2004, to March 31, 2015. Test-negative design studies of influenza VE were eligible if they enrolled outpatients on the basis of predefined illness criteria, reported subtype-level VE by season, used PCR to confirm influenza, and adjusted for age. We excluded studies restricted to hospitalised patients or special populations, duplicate reports, interim reports superseded by a final report, studies of live-attenuated vaccine, and studies of prepandemic seasonal vaccine against H1N1pdm09. Two reviewers independently assessed titles and abstracts to identify articles for full review. Discrepancies in inclusion and exclusion criteria and VE estimates were adjudicated by consensus. Outcomes were VE against H3N2, H1N1pdm09, H1N1 (pre-2009), and type B. We calculated pooled VE using a random-effects model.

Findings We identified 3368 unduplicated publications, selected 142 for full review, and included 56 in the meta-analysis. Pooled VE was 33% (95% CI 26–39; I^2=44·4) for H3N2, 54% (46–61; I^2=61·3) for type B, 61% (57–65; I^2=0·0) for H1N1pdm09, and 67% (29–85; I^2=57·6) for H1N1; VE was 73% (61–81; I^2=31·4) for monovalent vaccine against H1N1pdm09. VE against H3N2 for antigenically matched viruses was 33% (22–43; I^2=56·1) and for variant viruses was 23% (2–40; I^2=55·6). Among older adults (aged >60 years), pooled VE was 24% (–6 to 45; I^2=17·6) for H3N2, 63% (33–79; I^2=0·0) for type B, and 62% (36–78; I^2=0·0) for H1N1pdm09.

Interpretation Influenza vaccines provided substantial protection against H1N1pdm09, H1N1 (pre-2009), and type B, and reduced protection against H3N2. Vaccine improvements are needed to generate greater protection against H3N2 than with current vaccines.

Lancet Infect Dis 2016

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See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(16)00155-9

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belongia.edward@marshfieldclinic.org

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

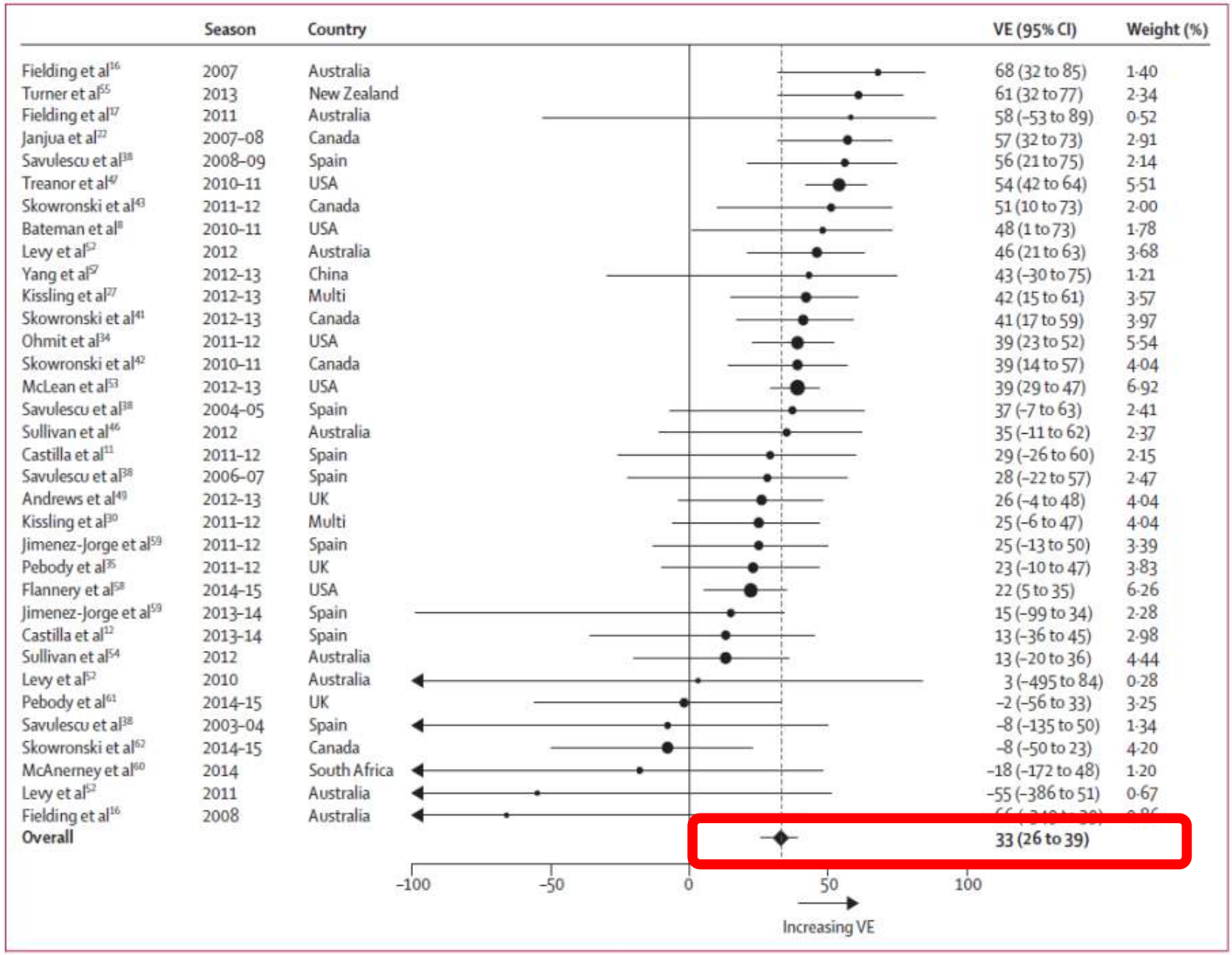


Figure 1: VE for H3N2 in studies without age restriction

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

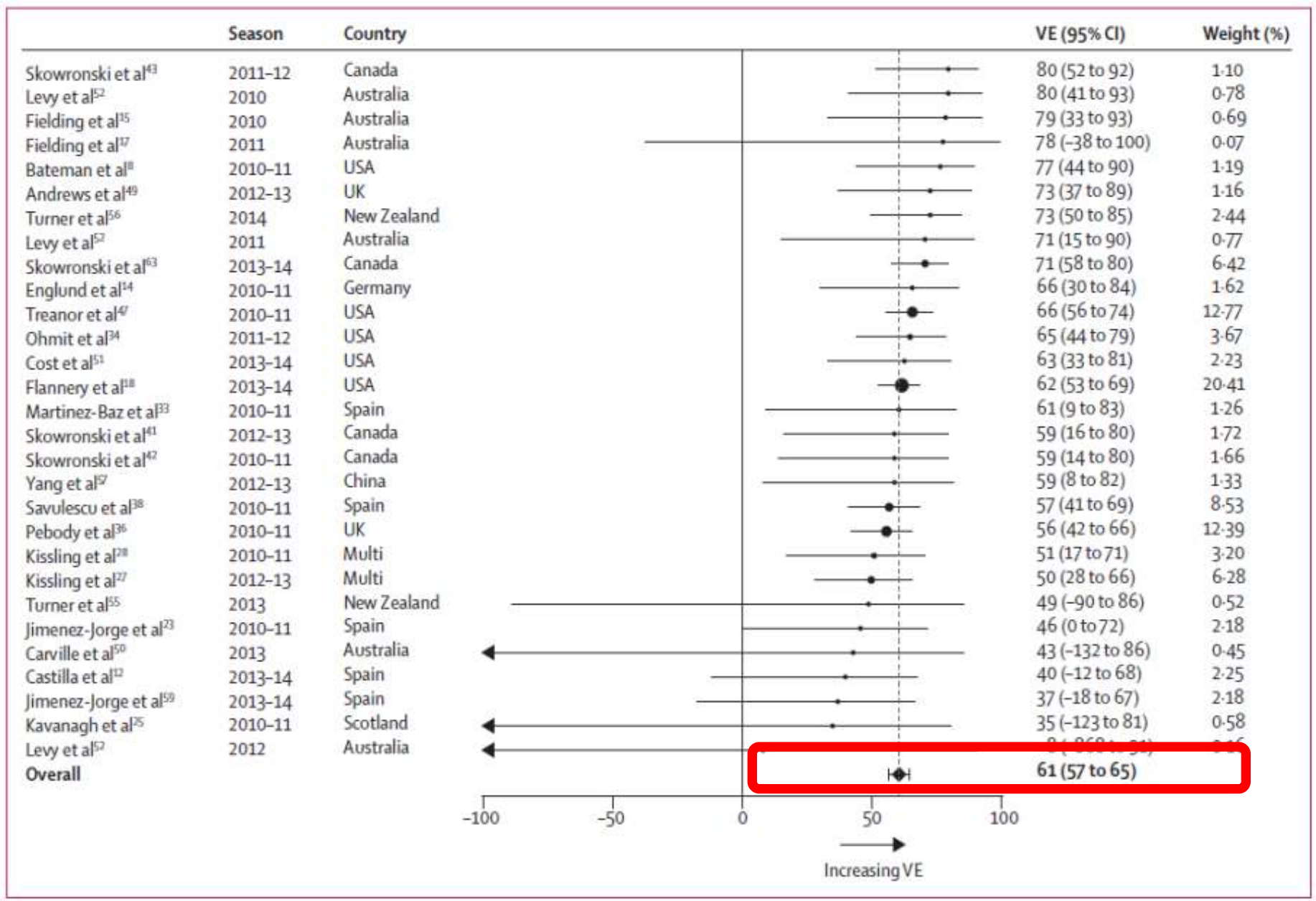


Figure 2: VE for H1N1pdm09 (seasonal vaccine) in studies without age restriction

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

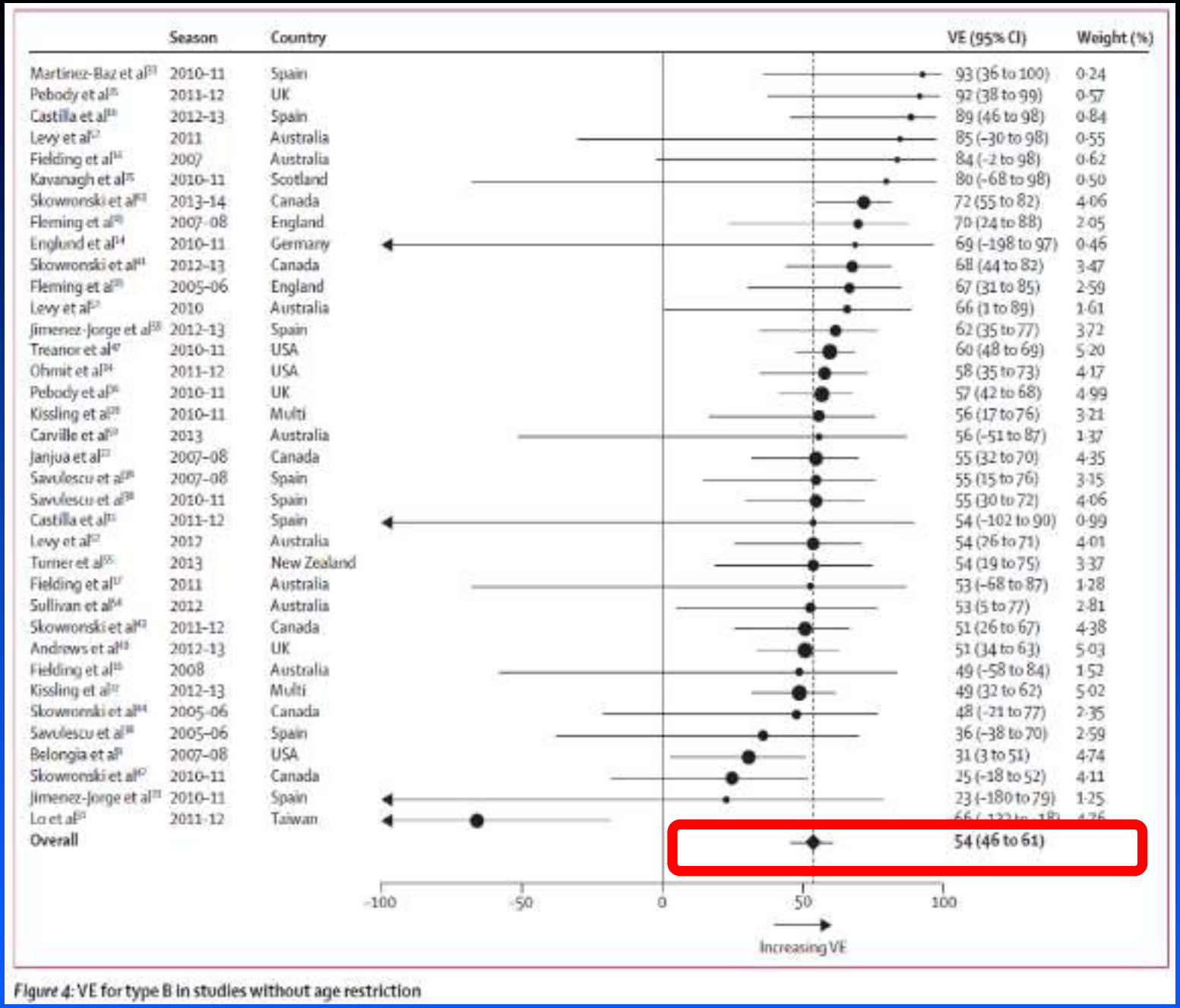


Figure 4: VE for type B in studies without age restriction

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

	Vaccine type	Pooled VE (%)	Pooled standard error	VE estimates (n)	p value for heterogeneity	I^2
Type B	Seasonal	54% (46–61)	0·083	36	<0·0001	61·3
H3N2	Seasonal	33% (26–39)	0·050	34	0·005	44·4
H1N1pdm09	Seasonal	61% (57–65)	0·048	29	0·783	0·0
H1N1pdm09	Monovalent	73% (61–81)	0·188	10	0·217	31·4
H1N1 (pre-2009)	Seasonal	67% (29–85)	0·397	5	0·093	57·6

Data in parentheses are 95% CIs. VE=vaccine effectiveness.

Table 2: Pooled VE by type and subtype in studies without age restriction

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

	Vaccine type	Pooled VE (%)	Pooled standard error	VE estimates (n)	p value for heterogeneity	I^2
Paediatric age groups*						
Type B	Seasonal	56% (38 to 69)	0·179	11	0·279	24·4
H3N2	Seasonal	43% (28 to 55)	0·119	10	0·251	28·2
H1N1pdm09	Seasonal	69% (49 to 81)	0·253	7	0·054	56·7
H1N1pdm09	Monovalent	62% (−5 to 87)	0·525	3	0·207	56·2
Working-age adults						
Type B	Seasonal	54% (16 to 75)	0·308	7	0·005	70·7
H3N2	Seasonal	35% (14 to 51)	0·146	9	0·078	48·4
H1N1pdm09	Seasonal	73% (52 to 84)	0·290	5	0·159	49·6
H1N1pdm09	Monovalent	74% (44 to 88)	0·391	3	0·852	0·0
H1N1 (pre-2009)	Seasonal	64% (29 to 82)	0·343	4	0·541	3·2
Older adults†						
Type B	Seasonal	63% (33 to 79)	0·295	3	0·989	0·0
H3N2	Seasonal	24% (−6 to 45)	0·166	6	0·416	17·6
H1N1pdm09	Seasonal	62% (36 to 78)	0·267	3	0·906	0·0

VE=vaccine effectiveness. *Pooled VE was not calculated for two studies reporting VE against H1N1 (pre-2009) in paediatric age groups. †One VE estimate for monovalent vaccine in older adults is not shown.

Table 3: Pooled vaccine effectiveness in paediatric age groups, working-age adults, and older adults

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

	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.

Table 4: Pooled VE estimates by season and reported antigenic similarity of H3N2 viruses to the vaccine strain

Belongia EA, et al. Lancet Infect Dis 2016; 16:942

Clinical Infectious Diseases

MAJOR ARTICLE

2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type

Richard K. Zimmerman,[1] Mary Patricia Nowalk,[1] Jessie Chung,[2] Michael L. Jackson,[3] Lisa A. Jackson,[3] Joshua G. Petrie,[4] Arnold S. Monto,[4] Huong Q. McLean,[5] Edward A. Belongia,[5] Manjusha Gaglani,[6] Kempapura Murthy,[6] Alicia M. Fry,[2] and Brendan Flannery[2]; for the US Flu VE Investigators*

[1]University of Pittsburgh, Pennsylvania; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Group Health Research Institute, Seattle, Washington; [4]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [5]Marshfield Clinic Research Foundation, Wisconsin; and [6]Baylor Scott and White Health, Texas A&M Health Science Center College of Medicine, Temple

(See the Editorial Commentary by Omer and Yildirim on pages 1574–6.)

Background. Circulating A/H3N2 influenza viruses drifted significantly after strain selection for the 2014–2015 vaccines. Also in 2014–2015, the Advisory Committee on Immunization Practices recommended preferential use of live attenuated influenza vaccine (LAIV) over inactivated influenza vaccine (IIV) among children aged 2–8 years.

Methods. Vaccine effectiveness (VE) across age groups and vaccine types was examined among outpatients with acute respiratory illness at 5 US sites using a test-negative design, that compared the odds of vaccination among reverse transcription polymerase chain reaction–confirmed influenza positives and negatives.

Results. Of 9311 enrollees with complete data, 7078 (76%) were influenza negative, 1840 (19.8%) were positive for influenza A (A/H3N2, n = 1817), and 395 (4.2%) were positive for influenza B (B/Yamagata, n = 340). The overall adjusted VE was 19% (95% confidence interval [CI], 10% to 27%) and was statistically significant in all age strata except those aged 18–64 years. The adjusted VE of 6% (95%CI, −5% to 17%) against A/H3N2-associated illness was not statistically significant, unlike VE for influenza B/Yamagata, which was 55% (95%CI, 43% to 65%). Among those aged 2–8 years, VE against A/H3N2 was 15% (95%CI, −16% to 38%) for IIV and −3% (CI, −50% to 29%) for LAIV; VE against B/Yamagata was 40% (95%CI, −20% to 70%) for IIV and 74% (95%CI, 25% to 91%) for LAIV.

Conclusions. The 2014–2015 influenza vaccines offered little protection against the predominant influenza A/H3N2 virus but were effective against influenza B. Preferential use of LAIV among young children was not supported.

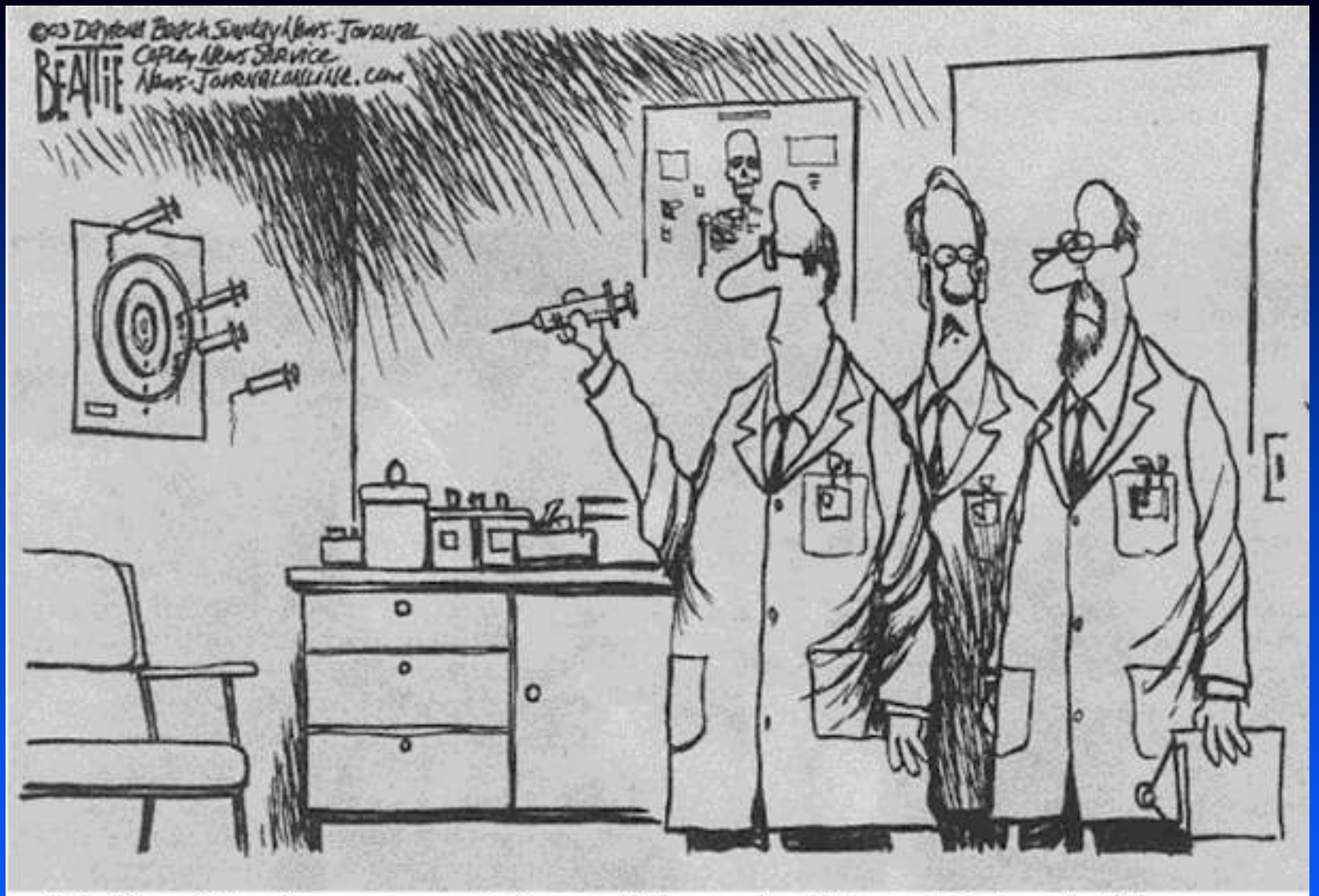
Keywords. influenza vaccine; vaccine effectiveness.

Zimmerman RK, et al. Clin Infect Dis 2016; 63:1564

Table 2. Percentage Vaccinated Among Influenza-Positive Cases and Test-Negative Controls and Unadjusted and Adjusted Vaccine Effectiveness Estimates by Age Group and Influenza Type/Subtype

Influenza Type/Age Group	Influenza Positive		Influenza Negative		VE		VE
	No. Vaccinated/ Total	%	No. Vaccinated/ Total	%	Unadjusted % (95% CI)	Adjusted[a] % (95% CI)	Fully Adjusted[b] % (95% CI)
Influenza A and B							
Overall	1098/2233	49.2	3866/7078	54.6	20 (12 to 27)	19 (10 to 27)	22 (13 to 30)
6 mo–8 y	186/473	39.3	1013/1946	52.1	40 (27 to 51)	25 (6 to 40)	26 (7 to 41)
9–17 y	137/392	35.0	391/950	41.2	23 (2 to 40)	25 (2 to 42)	26 (3 to 44)
18–49 y	272/642	42.4	996/2206	45.2	11 (–7 to 25)	7 (–12 to 33)	9 (–11 to 26)
50–64 y	229/378	60.6	739/1118	66.1	21 (0 to 38)	20 (–3 to 38)	25 (2 to 42)
≥65 y	274/348	78.7	727/858	84.7	33 (8 to 51)	32 (3 to 52)	33 (3 to 54)
Influenza A/H3N2							
Overall	939/1817	51.7	3866/7078	54.6	11 (2 to 20)	6 (–5 to 17)	11 (–1 to 21)
6 mo–8 y	160/396	40.4	1013/1946	52.1	38 (22 to 50)	20 (–3 to 37)	23 (1 to 40)
9–17 y	119/306	38.9	391/950	41.2	9 (–18 to 30)	7 (–26 to 31)	7 (–26 to 32)
18–49 y	236/531	44.4	996/2206	45.2	3 (–18 to 20)	–6 (–31 to 24)	–3 (–28 to 18)
50–64 y	176/281	62.6	739/1118	66.1	14 (–13 to 34)	12 (–19 to 34)	18 (–13 to 40)
≥65 y	248/303	81.9	727/858	84.7	19 (–15 to 42)	12 (–29 to 40)	15 (–28 to 43)
Influenza B/Yamagata							
Overall	128/340	37.7	3866/7078	54.6	50 (37 to 60)	55 (43 to 65)	54 (41 to 64)
6 mo–8 y	18/60	30.0	1013/1946	52.1	60 (31 to 77)	54 (17 to 74)	50 (9 to 72)
9–17 y	9/60	15.0	391/950	41.2	75 (48 to 88)	77 (51 to 89)	77 (50 to 89)
18–49 y	26/90	28.9	996/2206	45.2	51 (21 to 69)	55 (27 to 73)	53 (22 to 71)
50–64 y	52/90	57.8	739/1118	66.1	30 (–9 to 55)	24 (–20 to 52)	24 (–22 to 52)
≥65 y	23/40	57.5	727/858	84.7	76 (53 to 87)	74 (45 to 87)	74 (43 to 88)

Zimmerman RK, et al. Clin Infect Dis 2016; 63:1564



"Doğru virüse karşı aşı yaptığımızı bilmemek doğrusu hiç hoş değil...

Aşı İçeriği ile Dolaşan Suşun Uyumu ve Etkinliği

- 2004-2005 uyum %5, aşı etkinliği %10
- 2006-2007 ‘’ %91, ‘’ ‘’ %52

Belongia EA, et al. JID 2009;199(2):159-67.

- Kuzey yarımkürede 2014–2015 influenza sezonunda A(H3N2) subtipi baskın
  - Dolaşımdaki suşlar aşı içeriği ile uyumsuz
  - Diğer influenza tipleri/subtipleri ile karşılaştırıldığında öz.yaşlılarda ciddi sonuçlar
  - ≥65 yaşın 2/3'ü aşılanmasına rağmen influenzaya bağlı hastane yatışlarında artış

The Journal of Infectious Diseases

MAJOR ARTICLE

Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014–2015

Brendan Flannery,[1] Richard K. Zimmerman,[2] Larisa V. Gubareva,[1] Rebecca J. Garten,[1] Jessie R. Chung,[1,2] Mary Patricia Nowalk,[3] Michael L. Jackson,[4] Lisa A. Jackson,[4] Arnold S. Monto,[5] Suzanne E. Ohmit,[5] Edward A. Belongia,[6] Huong Q. McLean,[6] Manjusha Gaglani,[7] Pedro A. Piedra,[8] Vasiliy P. Mishin,[1] Anton P. Chesnokov,[1] Sarah Spencer,[1,2] Swathi N. Thaker,[1] John R. Barnes,[1] Angie Foust,[1] Wendy Sessions,[1] Xiyan Xu,[1] Jacqueline Katz,[1] and Alicia M. Fry[1]

[1]Influenza Division, Centers for Disease Control and Prevention, and [2]Atlanta Research and Education Foundation, Georgia; [3]University of Pittsburgh Schools of Health Sciences, Pennsylvania; [4]Group Health Research Institute, Seattle, Washington; [5]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [6]Marshfield Clinic Research Foundation, Wisconsin; [7]Baylor Scott & White Health, Texas A&M Health Science Center College of Medicine, Temple, and [8]Department of Molecular Virology and Microbiology, and Pediatrics, Baylor College of Medicine, Houston, Texas

(See the editorial commentary by Schotsaert and Garcia-Sastre on page 982.)

Background. During the 2014–2015 US influenza season, expanded genetic characterization of circulating influenza A(H3N2) viruses was used to assess the impact of the genetic variability of influenza A(H3N2) viruses on influenza vaccine effectiveness (VE).

Methods. A novel pyrosequencing assay was used to determine genetic group, based on hemagglutinin (HA) gene sequences, of influenza A(H3N2) viruses from patients enrolled at US Influenza Vaccine Effectiveness Network sites. VE was estimated using a test-negative design comparing vaccination among patients infected with influenza A(H3N2) viruses and uninfected patients.

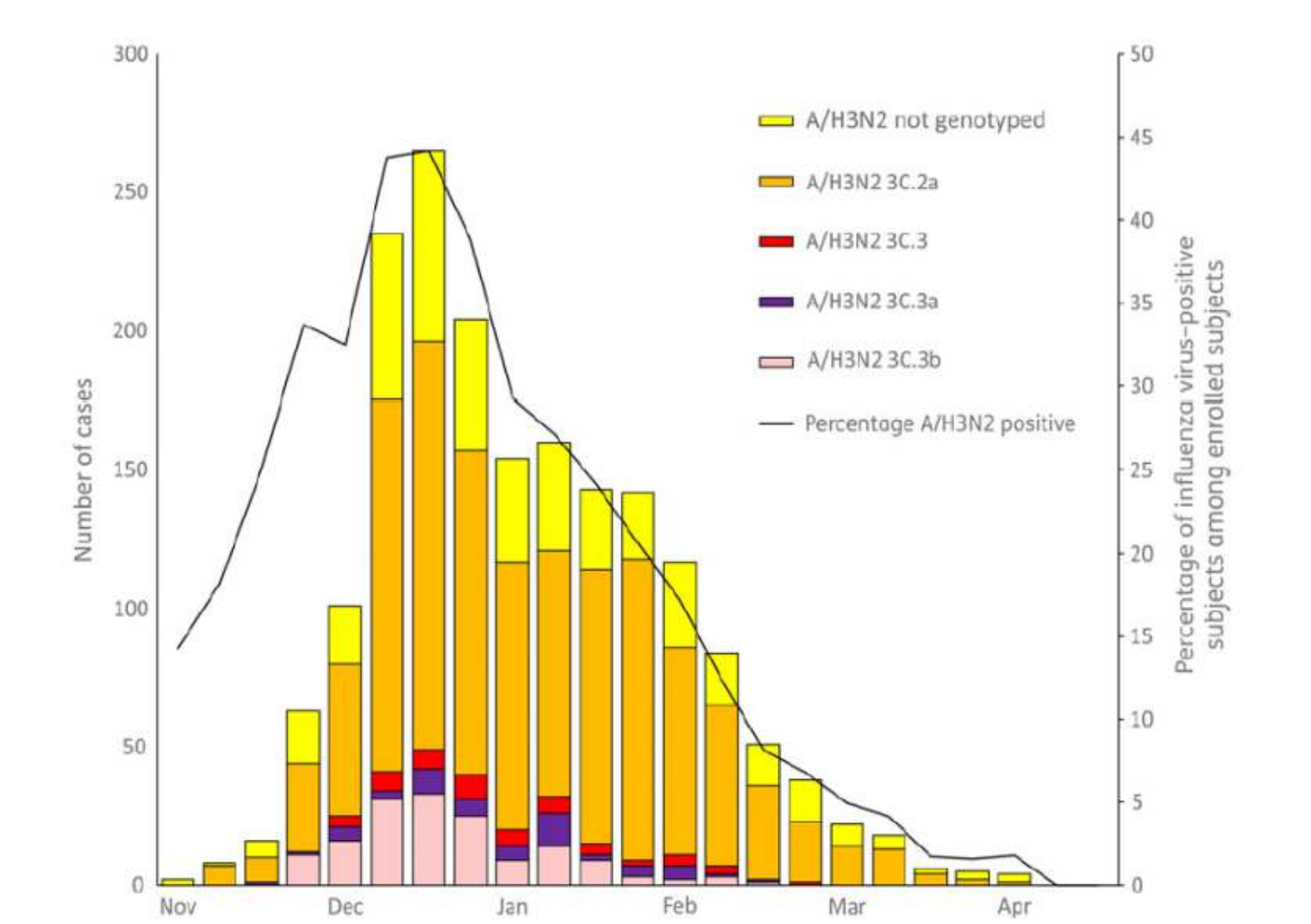
Results. Among 9710 enrollees, 1868 (19%) tested positive for influenza A(H3N2) virus; genetic characterization of 1397 viruses showed that 1134 (81%) belonged to 1 HA genetic group (3C.2a) of antigenically drifted influenza A(H3N2) viruses. Effectiveness of 2014–2015 influenza vaccination varied by influenza A(H3N2) virus genetic group from 1% (95% confidence interval [CI], −14% to 14%) against illness caused by antigenically drifted influenza A(H3N2) virus group 3C.2a viruses versus 44% (95% CI, 16%–63%) against illness caused by vaccine-like influenza A(H3N2) virus group 3C.3b viruses.

Conclusions. Effectiveness of 2014–2015 influenza vaccination varied by genetic group of influenza A(H3N2) virus. Changes in HA genes related to antigenic drift were associated with reduced VE.

Keywords. influenza; genetic characterization; pyrosequencing; influenza vaccine; vaccine effectiveness.

Flannery B, et al. J Infect Dis 2016; 214:1010

Influenza A (H3N2) viruses by genetic group and percentage influenza virus positivity (2014-15, USA)



Flannery B, et al. J Infect Dis 2016; 214:1010

- 2014–2015 aşı içeriği ve genetik grup:
  - A/Texas/50/2012(H3N2) (genetic group 3C.1)

Flannery B, et al. J Infect Dis 2016; 214:1010

- Sonuç:

İnfluenza viruslarının nükleotid sekanslama ve genetik grupların ortaya konması aşı suşunun seçimine ve aşı etkinliğinin belirlenmesine katkı sağlayacaktır.

Flannery B, et al. J Infect Dis 2016; 214:1010

Aşıya Yanıtı Etkileyen Faktörler

- Yaş
- Kullanılan ilaçlar (statinler…)

  Black S, et al. J Infect Dis 2016; 213:1224.
  Omer SB, et al. J Infect Dis 2016; 213:1216.
  McLean HQ, et al. J Infect Dis 2016; 214:1150.
- İmmün sistemin durumu
- Daha önceden sahip olduğu bağışıklık düzeyi

Clinical Infectious Diseases

MAJOR ARTICLE

A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season

Danuta M. Skowronski,[1,2] Catharine Chambers,[1] Suzana Sabaiduc,[1] Gaston De Serres,[3,4,5] Anne-Luise Winter,[6] James A. Dickinson,[7] Mel Krajden,[1,2] Jonathan B. Gubbay,[5,8] Steven J. Drews,[9,10] Christine Martineau,[3] Alireza Eshaghi,[6] Trijntje L. Kwindt,[1] Nathalie Bastien,[11] and Yan Li[11]

[1]British Columbia Centre for Disease Control, [2]University of British Columbia, Vancouver, [3]Institut National de Santé Publique du Québec, [4]Laval University, [5]Centre Hospitalier Universitaire de Québec, [6]Public Health Ontario, Toronto, [7]University of Calgary, [8]University of Toronto, [9]University of Alberta, [10]Alberta Provincial Laboratory, Edmonton, and [11]National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg

Background. The 2014–2015 influenza season was distinguished by an epidemic of antigenically-drifted A(H3N2) viruses and vaccine components identical to 2013–2014. We report 2014–2015 vaccine effectiveness (VE) from Canada and explore contributing agent–host factors.

Methods. VE against laboratory-confirmed influenza was derived using a test-negative design among outpatients with influenza-like illness. Sequencing identified amino acid mutations at key antigenic sites of the viral hemagglutinin protein.

Results. Overall, 815/1930 (42%) patients tested influenza-positive: 590 (72%) influenza A and 226 (28%) influenza B. Most influenza A viruses with known subtype were A(H3N2) (570/577; 99%); 409/460 (89%) sequenced viruses belonged to genetic clade 3C.2a and 39/460 (8%) to clade 3C.3b. Dominant clade 3C.2a viruses bore the pivotal mutations F159Y (a cluster-transition position) and K160T (a predicted gain of glycosylation) compared to the mismatched clade 3C.1 vaccine. VE against A(H3N2) was −17% (95% confidence interval [CI], −50% to 9%) overall with clade-specific VE of −13% (95% CI, −51% to 15%) for clade 3C.2a but 52% (95% CI, −17% to 80%) for clade 3C.3b. VE against A(H3N2) was 53% (95% CI, 10% to 75%) for patients vaccinated in 2014-2015 only, significantly lower at −32% (95% CI, −75% to 0%) if also vaccinated in 2013–2014 and −54% (95% CI, −108% to −14%) if vaccinated each year since 2012–2013. VE against clade-mismatched B(Yamagata) viruses was 42% (95% CI, 10% to 62%) with less-pronounced reduction from prior vaccination compared to A(H3N2).

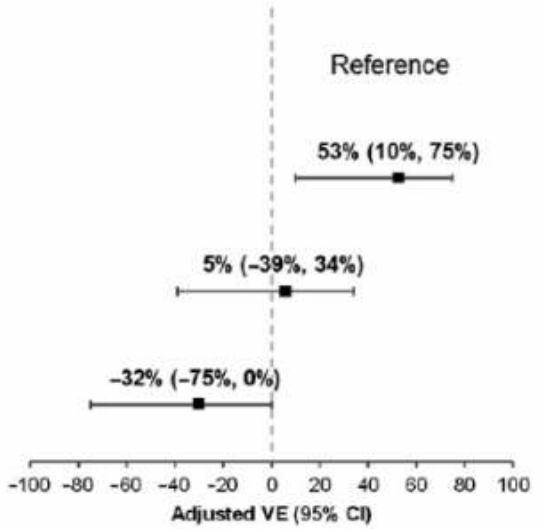
Conclusions. Variation in the viral genome and negative effects of serial vaccination likely contributed to poor influenza vaccine performance in 2014–2015.

Keywords. influenza vaccines; vaccine effectiveness; genomics; antigenic drift; sentinel surveillance.

Skowronski DM, et al. Clin Infect Dis 2016; 63:21.

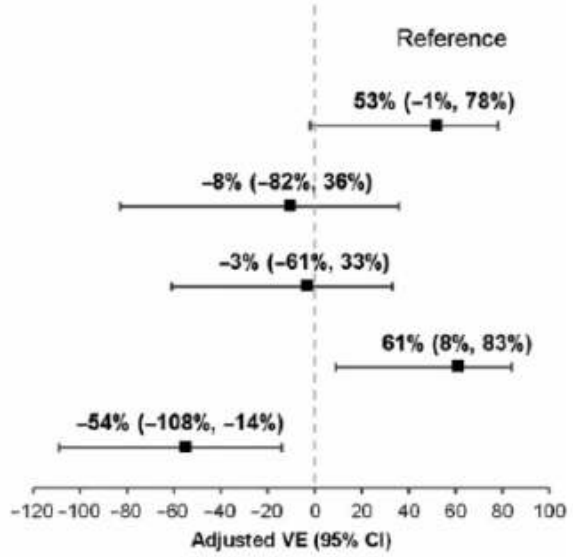
A

Vaccination History (2013–2014 and 2014–2015)	Case n (%)	Control n (%)
Unvaccinated both seasons	263 (48)	527 (52)
Current (2014–2015) but not prior (2013–2014)	13 (2)	67 (7)
Prior (2013–2014) but not current (2014–2015)	61 (11)	118 (12)
Both 2013–2014 and 2014–2015 vaccines	206 (38)	310 (30)



B

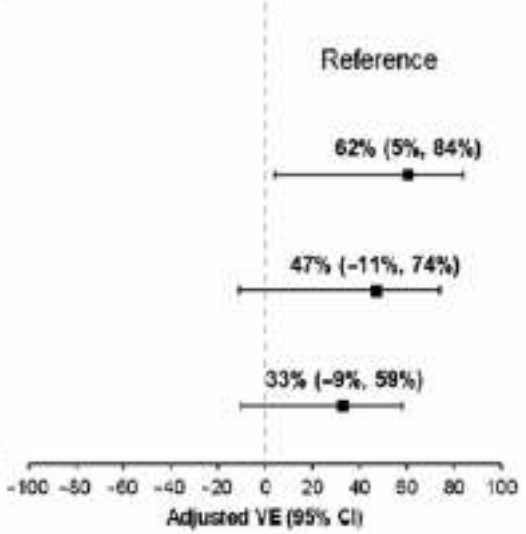
Vaccination History (2012–2013, 2013–2014, and 2014–2015)	Case n (%)	Control n (%)
Unvaccinated all 3 seasons	238 (46)	465 (49)
Current but neither prior (2012–2013 nor 2013–2014)	9 (2)	48 (5)
No current but 1 prior (2012–2013 or 2013–2014)	29 (6)	60 (6)
No current but both prior (2012–2013 and 2013–2014)	44 (8)	75 (8)
Current and 1 prior (2012–2013 or 2013–2014)	7 (1)	38 (4)
Current and both prior (2012–2013 and 2013–2014)	193 (37)	268 (28)



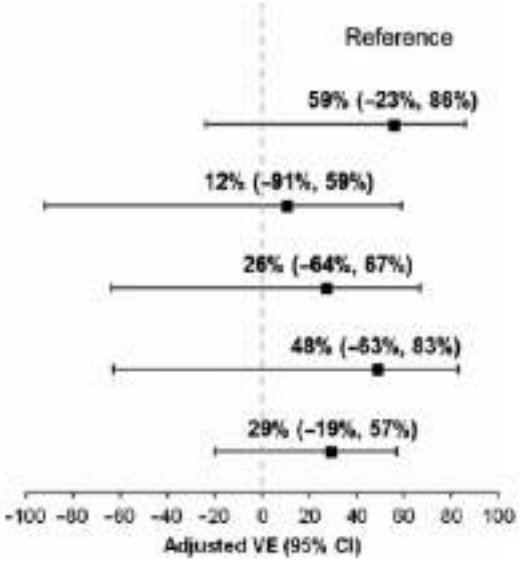
Effect of prior 2012–2013 and/or 2013–2014 season influenza vaccine receipt on current 2014–2015 influenza vaccine effectiveness for influenza A(H3N2)

Skowronski DM, et al. Clin Infect Dis 2016; 63:21.

A Vaccination History (2013–2014 and 2014–2015)	Case n (%)	Control n (%)
Unvaccinated both seasons	132 (70)	527 (52)
Current (2014–2015) but not prior (2013–2014)	6 (3)	67 (7)
Prior (2013–2014) but not current (2014–2015)	10 (5)	118 (12)
Both 2013–2014 and 2014–2015 vaccines	40 (21)	310 (30)



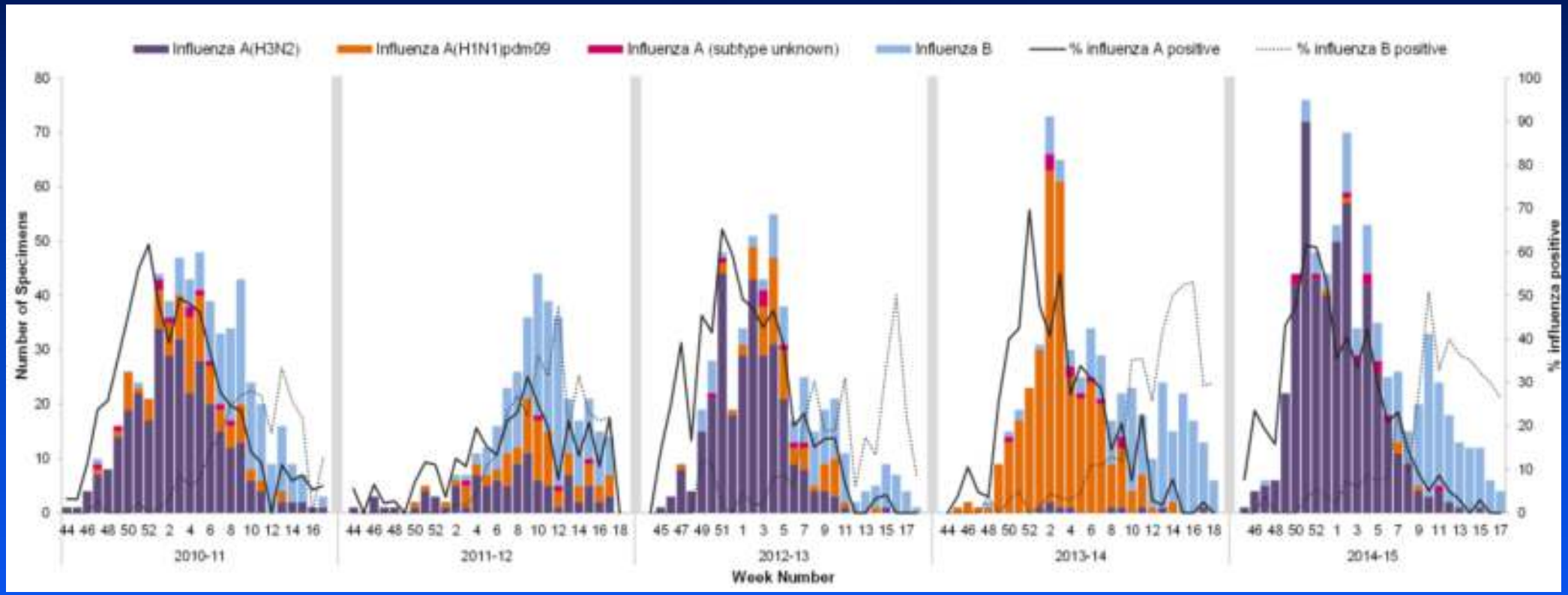
B Vaccination History (2012–2013, 2013–2014, and 2014–2015)	Case n (%)	Control n (%)
Unvaccinated all 3 seasons	123 (66)	465 (49)
Current but neither prior (2012–2013 nor 2013–2014)	4 (2)	48 (5)
No current but 1 prior (2012–2013 or 2013–2014)	10 (5)	60 (6)
No current but both prior (2012–2013 and 2013–2014)	9 (5)	75 (8)
Current and 1 prior (2012–2013 or 2013–2014)	4 (2)	38 (4)
Current and both prior (2012–2013 and 2013–2014)	37 (20)	268 (28)



Effect of prior 2012–2013 and/or 2013–2014 season influenza vaccine receipt on current 2014–2015 influenza vaccine effectiveness for influenza B(Yamagata)

Skowronski DM, et al. Clin Infect Dis 2016; 63:21.

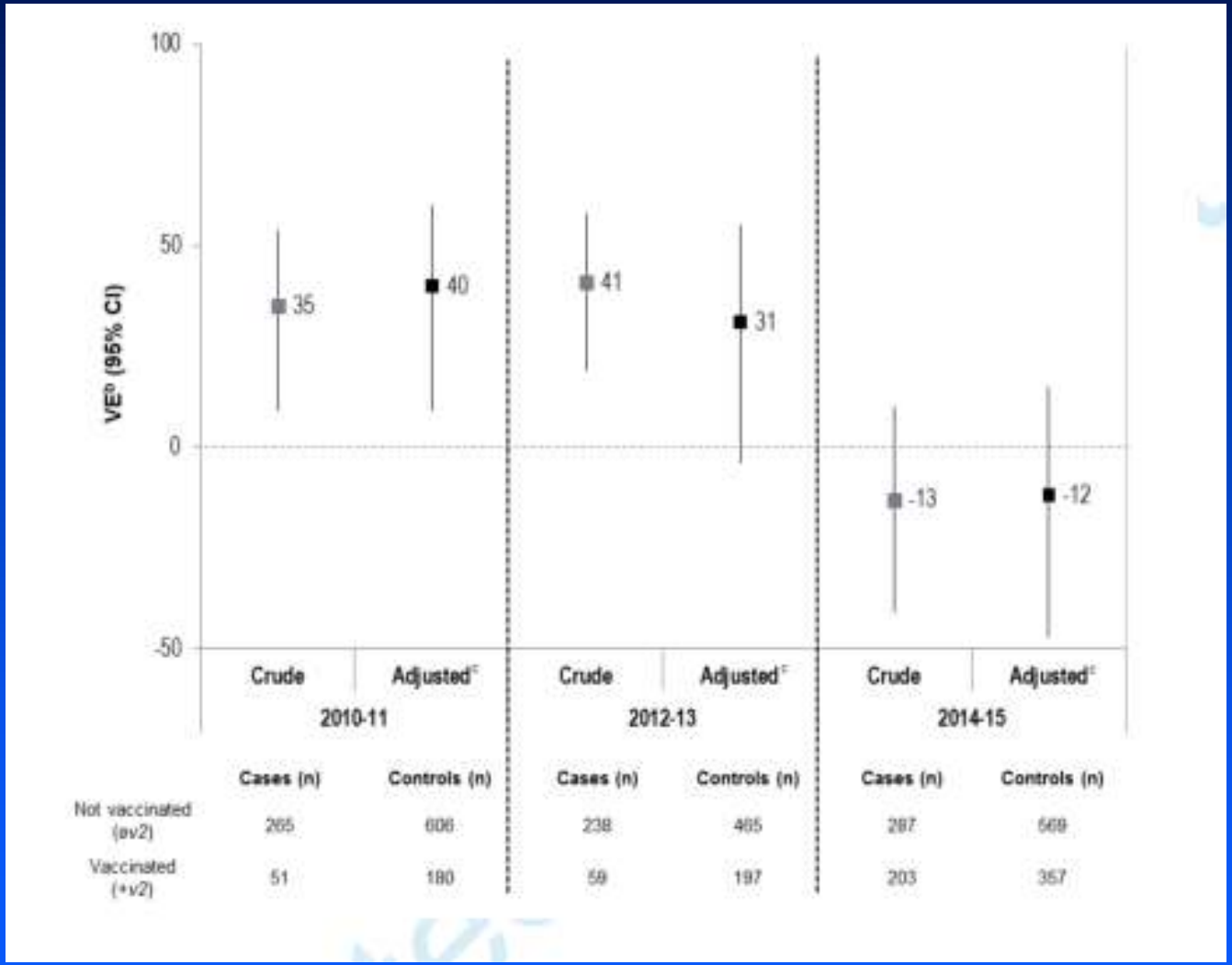
Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010-11 to 2014-15



SG-03/2017

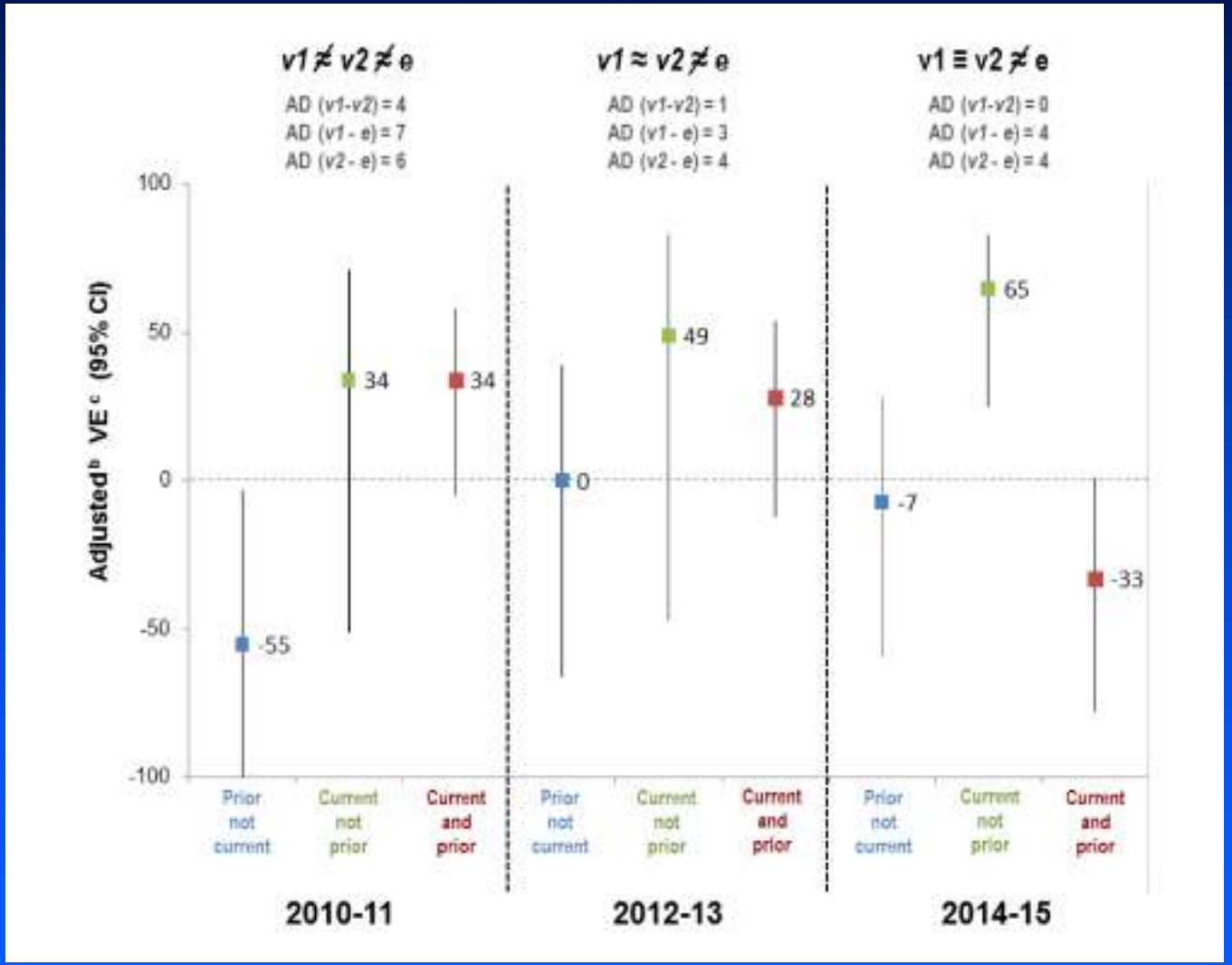
Skowronski DM, et al. J Infect Dis 2017

Crude and adjusted vaccine effectiveness (VE) estimates against influenza A(H3N2) among Canadian SPSN patients aged ≥ 9 years, for current season's vaccine (*v2*) regardless of prior season's (±*v1*, ±*v0*) vaccination status, 2010-2011, 2012-13, 2014-15 seasons



Skowronski DM, et al. J Infect Dis 2017

Adjusted vaccine effectiveness (VE) estimates against influenza A(H3N2) by current (*v2*) and/or prior (*v1*) season's vaccination history among Canadian SPSN patients aged ≥9 years, specified by vaccine-virus relatedness conditions and season (2010-11, 2012-13, 2014-15



Skowronski DM, et al. J Infect Dis 2017

- ‘’Antijenik mesafe hipotezi’’:
  - önceki ve şimdiki aşılar arasında antijenik mesafe küçük fakat önceki sezon aşısı ile şimdiki epidemik suşlar arasındaki genişse önceki sezon aşısı şimdiki sezon aşısı üzerinde negatif interferans gösterir

İmmünojenite ve Süresi

- Koruyuculuk süresi en az 4 ay
  - H3N2 ve H1N1 için >6 ay
  - Inf. B için daha erken
- >65 yaş ise 6. ayda titre azalmakta
  - Laboratuvar olarak doğrulanmış inf.da
    - İlk 100 gün etkinlik %61,
    - 100-119.gün %42
    - Sonrası %0

JID 2008;197:490.
Vaccine 2010;28:3929.
Euro Surveill 2013;18.

Clinical Infectious Diseases

MAJOR ARTICLE

Intraseason Waning of Influenza Vaccine Protection: Evidence From the US Influenza Vaccine Effectiveness Network, 2011–2012 Through 2014–2015

Jill M. Ferdinands,[1] Alicia M. Fry,[1] Sue Reynolds,[1,2] Joshua G. Petrie,[3] Brendan Flannery,[1] Michael L. Jackson,[4] and Edward A. Belongia[5]

[1]Influenza Division, Centers for Disease Control and Prevention, and [2]Battelle, Atlanta, Georgia; [3]University of Michigan School of Public Health, Ann Arbor; [4]Group Health Research Institute, Seattle, Washington, and [5]Marshfield Clinic Research Center, Marshfield, Wisconsin

Background. Recent studies suggest that influenza vaccine effectiveness (VE) may wane over the course of an influenza season, leading to suboptimal VE during late influenza seasons.

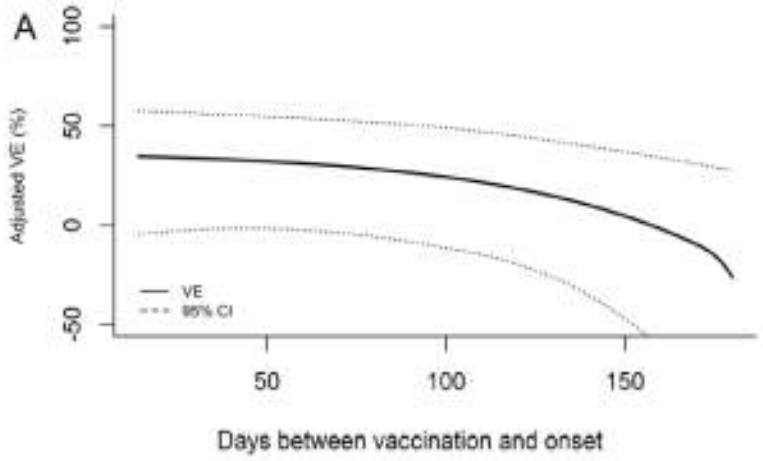
Methods. We examined the association between influenza VE and time since vaccination among patients ≥9 years old with medically attended acute respiratory illness in the US Influenza Vaccine Effectiveness Network using data pooled from the 2011–2012 through 2014–2015 influenza seasons. We used multivariate logistic regression with polymerase chain reaction–confirmed influenza infection as the outcome and vaccination status defined by days between vaccination and symptom onset as the predictor. Models were adjusted for calendar time and other potential confounding factors.

Results. We observed decreasing VE with increasing time since vaccination for influenza A(H3N2) ($P = .004$), influenza A(H1N1)pdm09 ($P = .01$), and influenza B viruses ($P = .04$). Maximum VE was observed shortly after vaccination, followed by a decline in VE of about 7% (absolute) per month for influenza A(H3N2) and influenza B and 6%–11% per month for influenza A(H1N1)pdm09 viruses. VE remained greater than zero for at least 6 months for influenza A(H1N1)pdm09 and influenza B and at least 5 months for influenza A(H3N2) viruses. Decline in VE was more pronounced among patients with prior-season influenza vaccination. A similar pattern of increasing influenza risk with increasing time since vaccination was seen in analyses limited to vaccinees.

Conclusions. We observed decreasing influenza vaccine protection with increasing time since vaccination across influenza types/subtypes. This association is consistent with intraseason waning of host immunity, but bias or residual confounding could explain these findings.

Keywords. case-control studies; influenza; influenza vaccine; vaccine effectiveness.

Ferdinands JM, et al. CID 2017; 64(5):544–50.



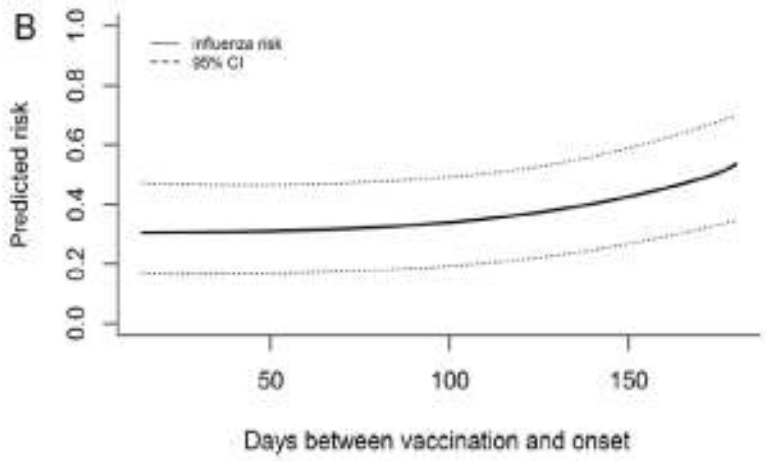
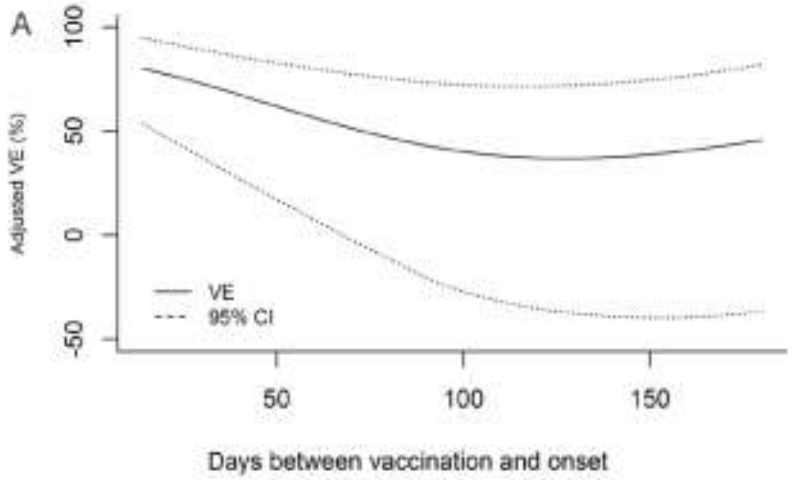


Figure 2. US Influenza Vaccine Effectiveness Network, 2011–2012 thr ess (VE) against influen a A(H3N2) irus infection by days since vaccination. Maximum VE was 35% at 14 days postvaccinati . VE reached zero at 158 days postvaccination Adjusted VE without inc since vaccination in the model was 24% (95% CI, 15%–32%). *B*, Predicted risk of influen ation in dataset limited to vaccinees. Abbreviations: CI, confidence interval, VE, vaccine effectiveness

Ferdinands JM, et al. CID 2017; 64(5):544–50



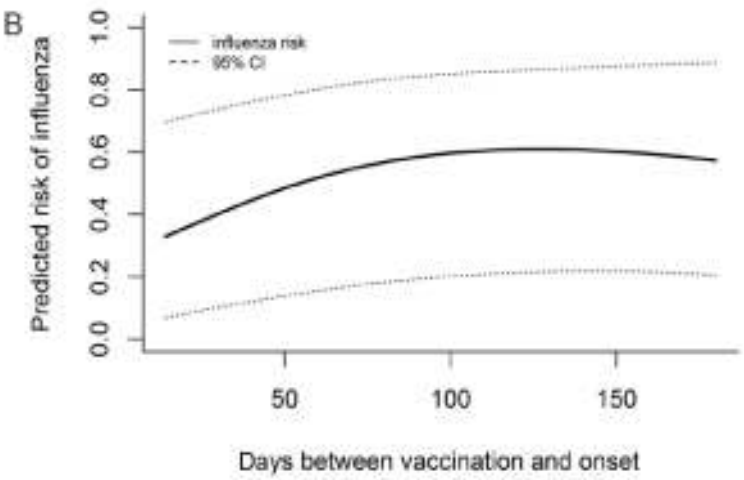


Figure 3. US Influenza Vaccine Effectiveness Network, 2011–2012 through 2013–2014. *A*, Adjusted vaccine effectiveness (VE) against influenza A(H1N1)pdm09 virus infection by days since vaccination. Maximum VE was 80% at 14 days postvaccination and minimum VE was 37% at 128 days postvaccination. VE was 46% at 180 days postvaccination. Adjusted VE without including time since vaccination in the model was 48% (95% confidence interval [CI], 36%–58%). *B*, Predicted risk of influenza A(H1N1) pdm09 virus infection by days since vaccination in dataset limited to vaccinees.

Ferdinands JM, et al. CID 2017; 64(5):544–50

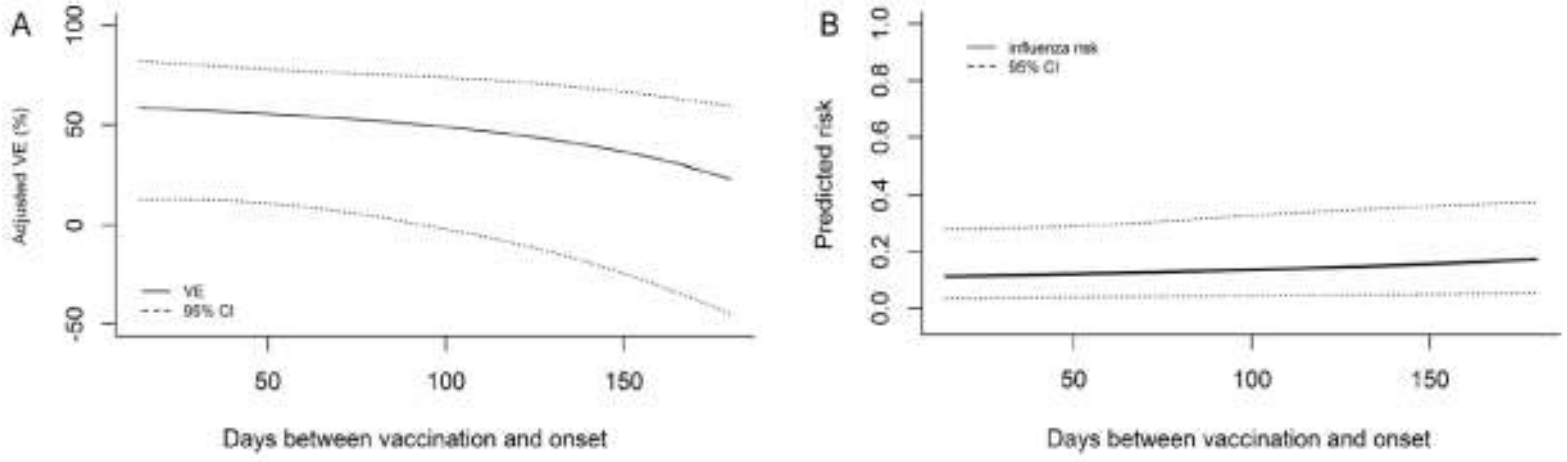


Figure 4. US Influenza Vaccine Effectiveness Network, 2011–2012 through 2014–2015. *A*, Adjusted vacci[illegible] influe[illegible]a B virus infe[illegible]tion by days since vaccination. Maximum vaccine effectiveness (VE) was 59% at 14 days postvaccination and minimum [illegible]E was 23% at 180 days pos[illegible]accination. Adjusted VE without including time since vaccination in the model was 45% (95% confidence interval [CI], 33%–54%). *B*, Predicted risk of influenza B virus infection by days since vaccination in dataset limited to vaccinees.

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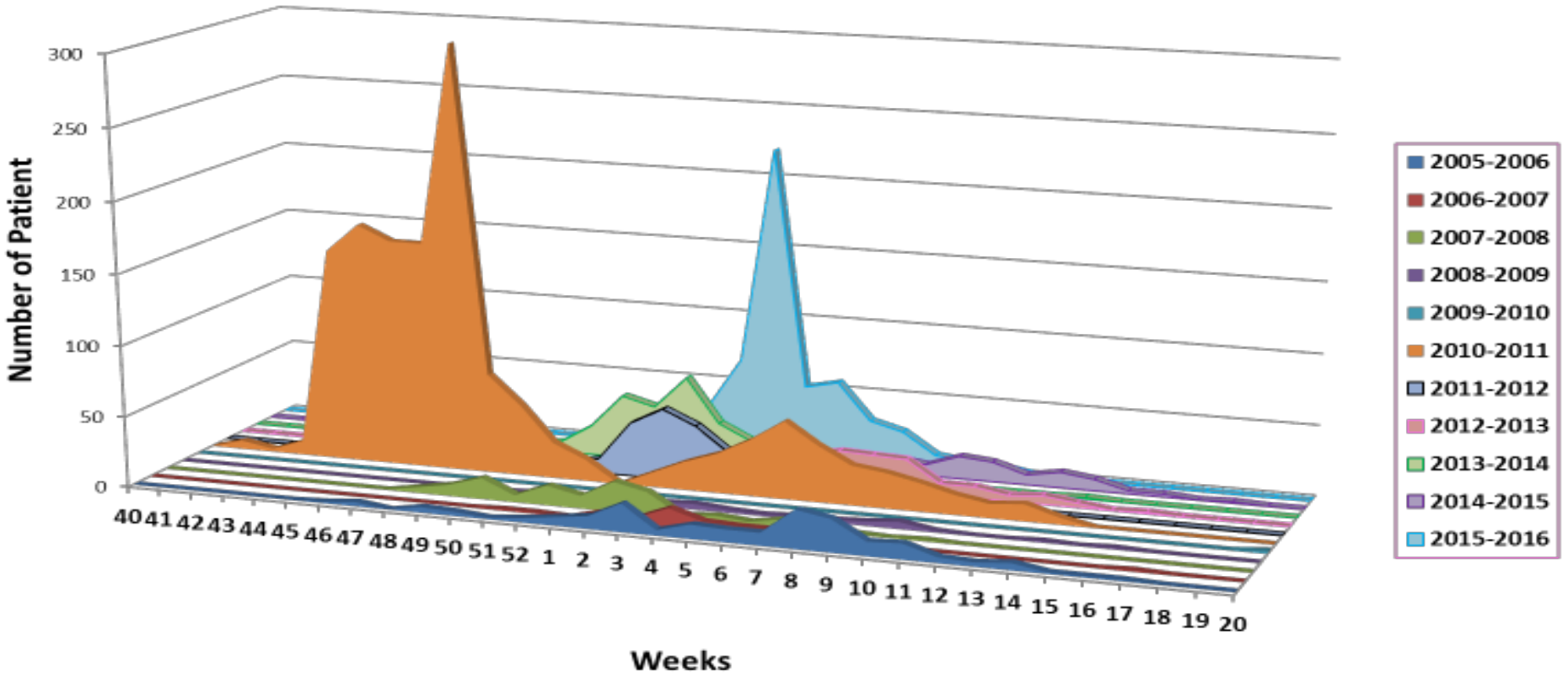
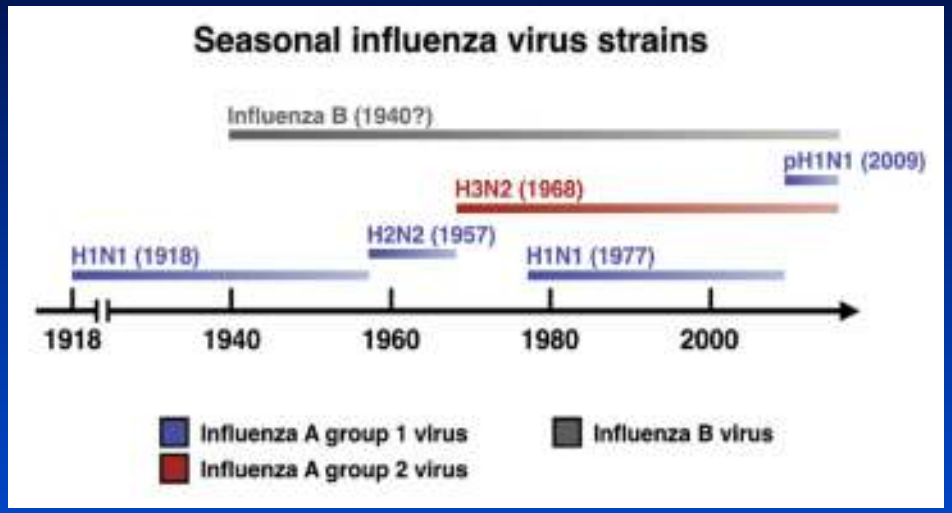
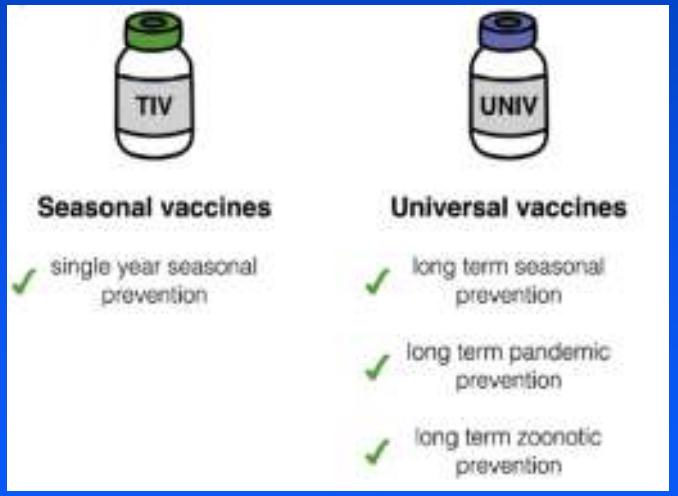
Ferdinands JM, et al. CID 2017; 64(5):544–50

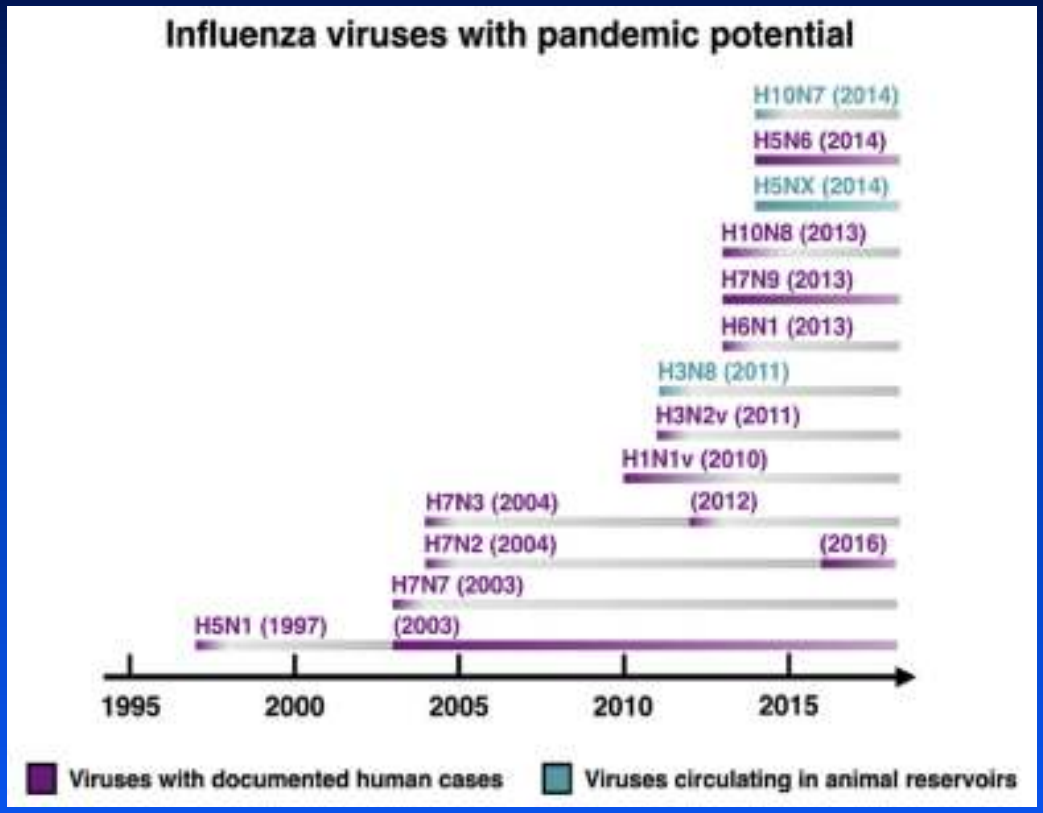
Mevsimsel İnfluenza A Değişiklikler



Geleceğin aşıları….







Nachbagauer R, Krammer F. CMI 2017.

Özetle…

- Hızla yayılabilen ve ne şekilde değişime uğrayacağı tam olarak kestirilemeyen bir virüs
  - Belli risk gruplarında yüksek ölümcül
- Etkinliği çok değişken
  - Aşı içeriği ile dolaşımdaki virüs uyumu önemli
  - Virusun genetik grubunu bilmek önemli
- Sürveyans önemli

Teşekkür Ederiz..