

KOAH'da immünizasyon işe yarıyor mu?

Yrd.Doç.Dr.Özlem Erçen Diken
Hitit Üniversitesi Tıp Fakültesi
Göğüs Hastalıkları ABD, Çorum

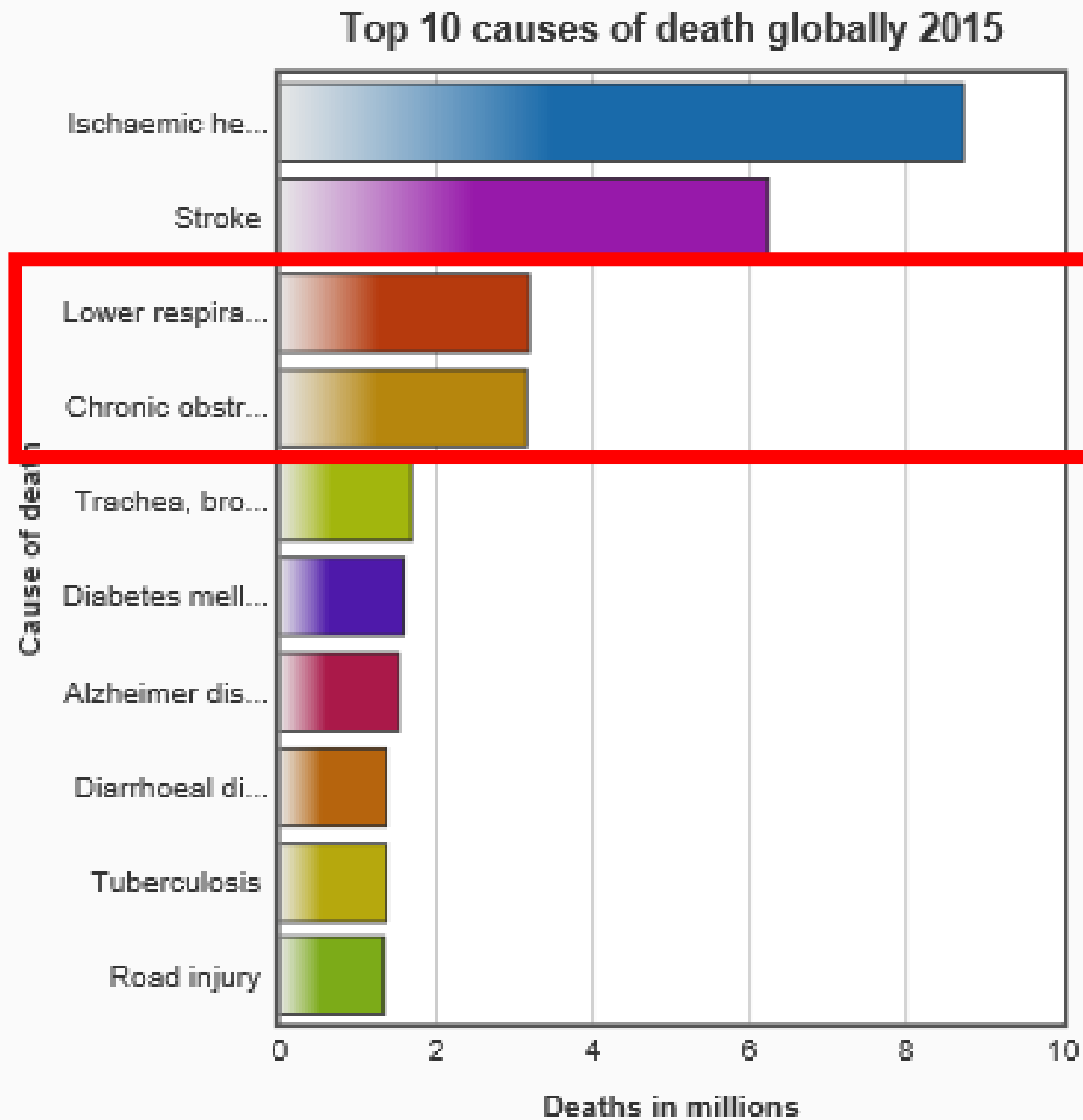


**KOAH'TA GÜNCEL
TARTIŞMALAR**

3 Mart 2018, Cumartesi

CVK Park Bosphorus Hotel, İstanbul

DSÖ



İnfluenza

➤ İnfluenza A- mevsimsel salgın ve pandemiler

Hemaglutinin (HA)

Nöraminidaz (NA)

İnsanda üç tip HA (H1, H2, H3) ve iki tip NA (N1 ve N2)

➤ İnfluenza B- mevsimsel salgınlar

➤ İnfluenza C- sporadik olgulara ve kısıtlı bölgesel salgınlar, klinik açıdan hafif



0.5 ml
IM

Tablo 3. Kullanımda olan ve FDA tarafından onaylanmış grip aşuları

Aşı tipi	Hedef Populasyon	Uygulama yolu	Notlar
Trivalan inaktive aşı*	Genel (6 ay ve üstü)	IM	İki influenza A, bir influenza B suşu içerir.
Kuadrivalan inaktive aşı*	Genel (6 ay ve üstü)	IM	İki influenza A, iki influenza B suşu içerir.
Canlı aşı	Sağlıklı, 2-49 yaş	Nazal sprey	Hamileler, ilaç veya hastalığa bağlı olarak bağışıklık sistemi baskılanmış kişiler de önerilmez.
İntradermal aşı	Genel (18-64 yaş arasında onaylanmıştır)	İntradermal	İntramuskülere göre daha fazla bağışıklık uyarabilir.
Rekombinan aşı	Yumurta alerjisi olanlar (18-49 yaş arasında onaylanmıştır)	IM	Yumurta proteini içermez.
Hücre kültürü bazlı aşı	18 yaş üstü	IM	Pandemi sırasında hızlı aşı üretimine olanak sağlar.
Yüksek doz aşı	65 yaş üstü ve bağışıklık sistemi zayıflamış olanlar	IM	Yüksek dozun klinik sonuçlarına ilişkin veriler henüz yetersizdir.

*Ülkemizde 2015 yılı itibarı ile var olan aşılar

İnfluenza

➤ Türkiye

- 2014 yılına kadar standart olarak iki tip A (**H3N2 ve H1N1**) ve bir tip B (Victoria veya Yamagata suşundan birisi) hemaglutininini içeren **inaktive trivalan** aşı
- 2014 yılından itibaren iki tip A ve iki tip B içeren **kuadrivalan aşının** da kullanıma girmesi ile B tipine karşı aşı uyumsuzluğu ortadan kalkmıştır.

2004

hedef riskli gruplar SGK geri ödeme

2010

tüm sağlık çalışanlarına ücretsiz

İnfluenza aşısı

5 yaşından küçük (özellikle ≤ 2 yaş) çocuklar (≥ 6 . ay)

*65 yaşından büyük erişkinler

*Gebeler

*Bakım evinde yaşayanlar

*Kronik sağlık sorunu olanlar

-Kronik pulmoner hst. (astım, KOAH, KF)

- Kardiyovasküler (tek başına hipertansiyon hariç) hst.

- Böbrek hst., Karaciğer hst.

- Kan hastalıkları (OHA dahil)

- Endokrin hastalık (DM gibi)

- Metabolik hastalık (genetik metabolik hastalıklar gibi)

*Nörolojik veya nörogelişimsel bozukluğu olanlar (beyin, spinal kord, periferik sinir ve kas hastalıkları, serebral palsi, epilepsi, inme, mental retardasyon, büyüme-gelişme geriliği, musküler distrofi, spinal kord hasarı dahil)

*Hastalık veya ilaca bağlı olarak bağışıklık sistemi baskılanmış kişiler (kanser, uzun süreli steroid kullanımı, HIV gibi)

*19 yaşından küçük olup uzun süredir aspirin tedavisi alanlar

*Morbid obezler (Vücut kitle indeksi >40)

*Sağlık çalışanları

*Grip açısından riskli grupta tanımlanan kişilere bakım verenler ve aynı evde yaşayanlar (çocuklar dahil)

KOAH ve İnfluenza

İNFLUENZA AŞISI SONRASI HASTANE BAŞVURUSU VE YATIŞLAR AZALIR

Aşıdan önce

Akut solunum infeksiyonları ve akut atak nedeniyle başvuru

%28.6 kişi-yıl

Hafif, orta, ağır olgularda başvurular

%16; %42; %**33 kişi-yıl**

Aşıdan sonra

• Akut solunum infeksiyonları ve akut atak nedeniyle başvuru

%9.7 kişi-yıl

• Hafif, orta, ağır olgularda başvurular

%6.5; %18.5; %**8.42 kişi-yıl**



Aşının etkinliği

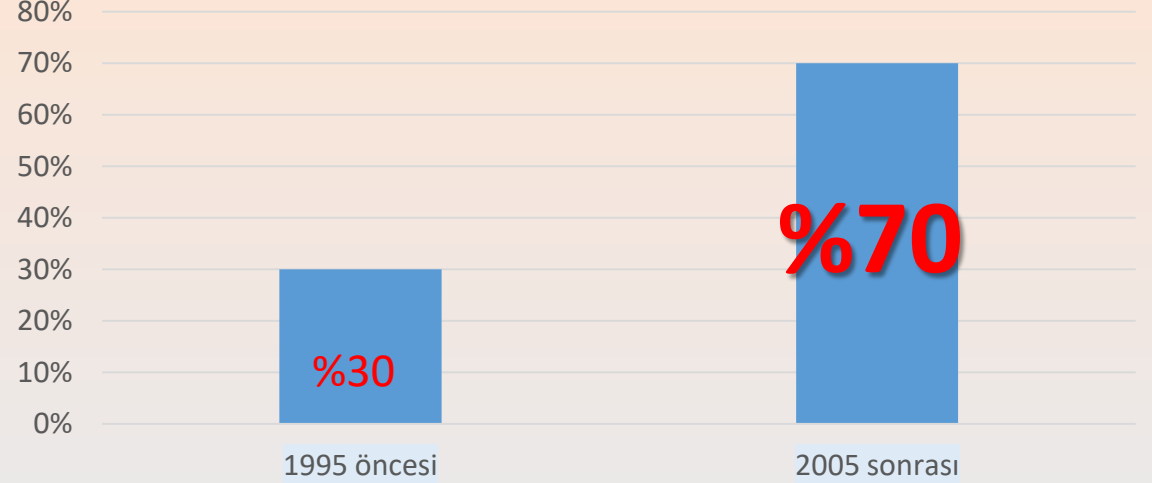
- Hafif KOAH'ta (FEV1 > %70) %60
- Orta derecede KOAH'ta (FEV1: %50-69) %60
- Ciddi KOAH'ta (FEV1 < %50) %75

%67

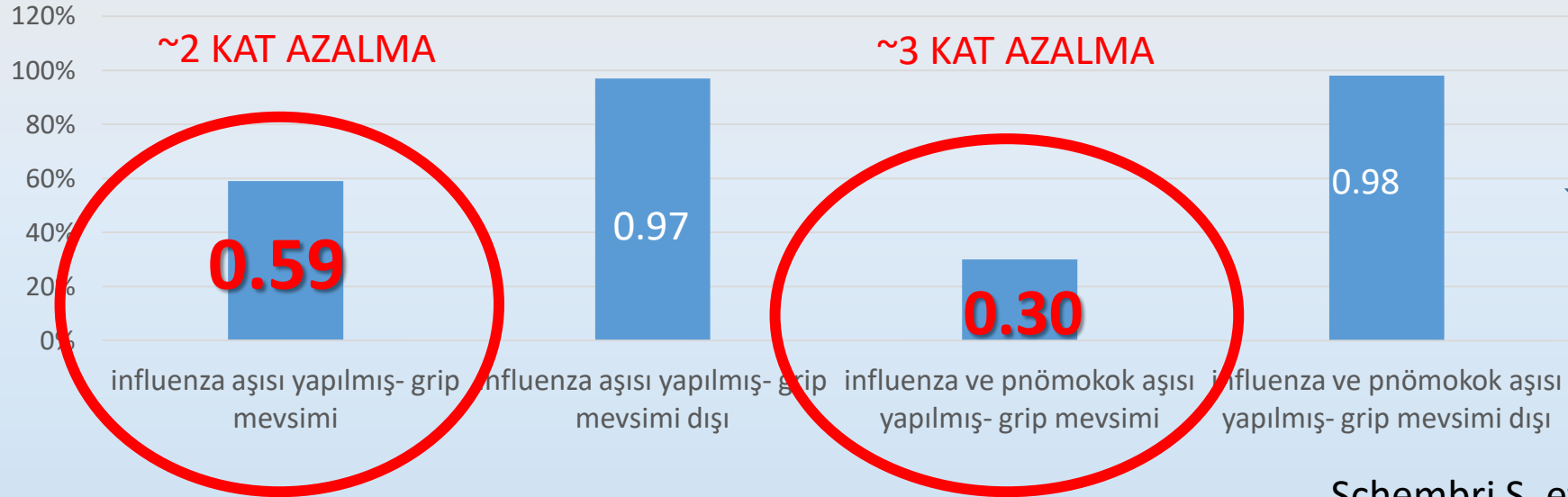
KOAH ve İnfluenza

- “The Health Improvement Network (THIN)”
- Veritabanı 177,120 hasta
- **İngiltere** - 18 yıl (1988-2006)

KOAH'da aşılama oranı



İnfluenza ilişkili tüm ölüm nedenleri



**İnfluenza
aşıları
KOAH'da tüm
nedenlere
bağlı
mortalitede
azalma**

Evaluation of clinical data and antibody response following influenza vaccination in patients with chronic obstructive pulmonary disease

Ceyda Anar¹, Can Bicmen², Sena Yapicioglu¹, Ipek Unsal¹, Huseyin Halilcolar¹, Ufuk Yilmaz¹

¹Dr. Suat Seren Training and Research, Hospital for Chest Diseases and Surgery, Department of Chest Diseases, Izmir, Turkey;

²Dr. Suat Seren Training and Research, Hospital for Chest Diseases and Surgery, Department of Microbiology, Izmir, Turkey

TÜRKİYE VERİLERİ

KOAH ve İnfluenza

KOAH + influenza AŞILI

- 44 hasta
- Hastanede yatış günü 7.7 gün
- Atak nedeniyle hastaneye başvuru %38.6
- Pnömoni gelişimi %25
- Yoğun bakım ihtiyacı %15.9



KOAH + AŞISIZ

- 38 hasta
- Hastanede yatış günü 17.5 gün
- Atak nedeniyle hastaneye başvuru %76.3
- Pnömoni gelişimi %34.2
- Yoğun bakım ihtiyacı %31.6

Changes in COPD mortality rate after amendments to the Preventive Vaccination Law in Japan.

Kiyohara K¹, Kojimahara N, Sato Y, Yamauchi N.

KOAH ve İnfluenza

- Japonya'da
- Kasım 2011- 65 yaşından sonra **aşılama kanunu**
- Bu aşı kanundan önce ve sonra KOAH'ta mortalite değişikliğini inceleyen bir çalışma
- Kanundan sonra 65 yaş ve üzeri KOAH'lı kişilerde ocak, şubat, mart aylarında **mortalitede anlamlı bir düşüş** (RR sırasıyla 0.84, 0.85, 0.92).

KOAH ve aşılar- steroid

- Steroidin aşılarla olan yanıtı etkileyip etkilemediği tartışmalı
- KOAH hastalarında MF59-adjüvanlı aşıya immün cevapta steroidin etkinliğinin değerlendirildiği bir çalışma
- Sistemik steroid alanlar hastalar, inhale steroid alan hastalar ve hiç steroid kullanmayan hastalar
- **Antikor titrelerinde, serokonversiyon oranlarında anlamlı fark tespit edilmemiş**

Influenza aşısının KOAH'lı hastalarda güvenilirliği

- Aşılı 293 hasta - 293 kontrol
- Aşı sonrası iki haftalık dönemde
 - **aşılanan grupta 11 KOAH akut atak**
 - **aşılanmayan grupta 21 KOAH akut atak**

OR: 0.52

Aşı erken dönemde atakları arttırmaz,
güvenle uygulanabilir

İnfluenza aşısının KOAH'lı hastalarda yan etkileri

- Lokal reaksiyonlar fazla (p= 0.002)
- Sistemik reaksiyonlar açısından anlamlı fark yok (p= 0.5).

- akciğer fonksiyonları
- egzersiz kapasitesi
- akut solunumsal hastalık

1. ve 4. haftada influenza aşısı ve plasebo grupları arasında fark yok.



available at www.sciencedirect.com

ScienceDirect

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



Influenza vaccination among Canadians with chronic respiratory disease

Nicholas T. Vozoris ^{a,*}, M. Diane Lougheed ^b

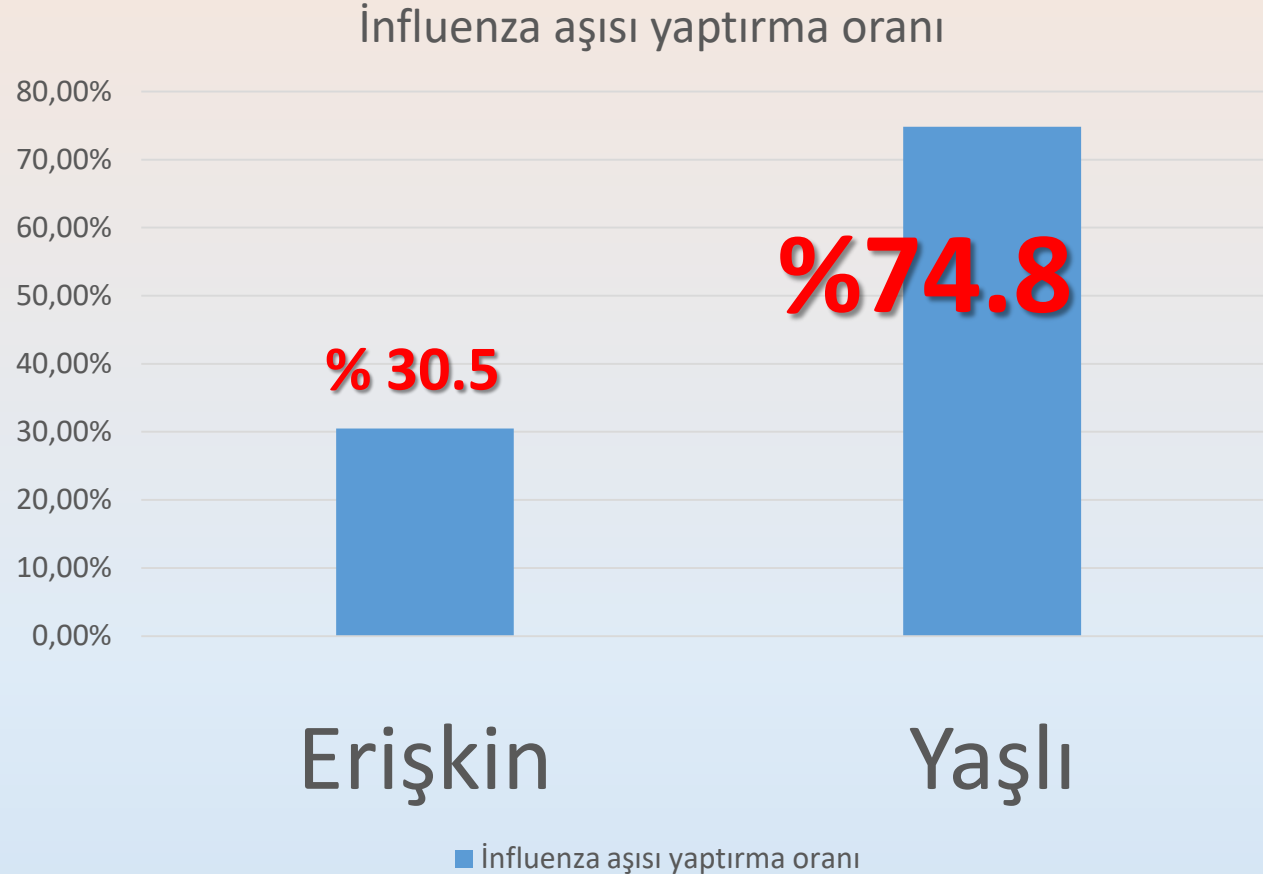
- Kanada'da KOAH'lı hastalarda aşılama oranları **%47.9**
- Aşılama oranlarını etkileyen faktörler;

Aşı olmayan grup

- erkek cinsiyet
- halen sigara içicisi olmak
- aile doktorlarının olmaması

“Italian National Institute of Statistics (ISTAT)” veritabanı

➤ Son 12 ayda mevsimsel influenza aşısı yaptırma oranları



Aşı olmayan grup

- bekar olmak,
- sigara içicisi olmak,
- son 30 gün içinde aile doktoru viziti olmamak
- komormid bir hastalığın olmaması

Doğu Karadeniz Bölgesinde Kronik Obstrüktif Akciğer Hastalığı: Hastalık Özellikleri ve İnfluenza-Pnömomokok Aşılama Sıklığı

Chronic Obstructive Pulmonary Disease in Eastern Black Sea Region: Characteristics of the Disease and the Frequency of Influenza-Pneumococcal Vaccination

Yılmaz BÜLBÜL^a, Funda ÖZTUNA^a, Ayhan GÜLSOY^a, Tefrik ÖZLÜ^a

^aGöğüs Hastalıkları AD, Karadeniz Teknik Üniversitesi Tıp Fakültesi, Trabzon

Turkiye Klinikleri J Med Sci 2010;30(1):24-9

- hastaların bir önceki yıl **grip aşısı** yaptırama oranı **%33.3**
- ömür boyu bir kez **pnömokok aşısı** yaptırama oranı **%12**
- Hastalık şiddeti ile pnömokok aşısı yaptırama arasında ilişki (p= 0.002)
- Sigaraya devam edenlerde aşı yaptırama oranı bırakanlara göre düşük saptanmış (p= 0.011)

KOAH Hastalarında İnfluenza ve Pnömomokok Aşılama Sıklığı

The Frequency of Influenza and Pneumococcal Vaccination in COPD

Savaş Özsu¹, Ergün Uçar², Yakup Arslan², Emin Maden³, Hayati Bilgiç²

¹ Karadeniz Teknik Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları, Trabzon

² Gülhane Askeri Tıp Akademisi, Göğüs Hastalıkları AD, Ankara

³ Selçuk Üniversitesi Tıp Fakültesi, Göğüs Hastalıkları, Konya

- KOAH'lı hastalarda **grip aşısı** yaptırma oranı **%37**
- **Pnömomokok aşısı** yaptırma oranı **%15**
- Hastalık süresi uzun olanlarda grip aşısı uygulanma sıklığı daha fazla (p< 0.001)

KOAH ve İnfluenza

- Akut atakları önleme
- Geç oluşan atakları (üç-dört hafta) önleme
- İnfluenza ilişkili solunum infeksiyonlarını azaltma
- Cost efektifite

Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review.

Sehatzadeh S.

Summary of Efficacy of the Influenza Vaccination in Immunocompetent Patients With COPD

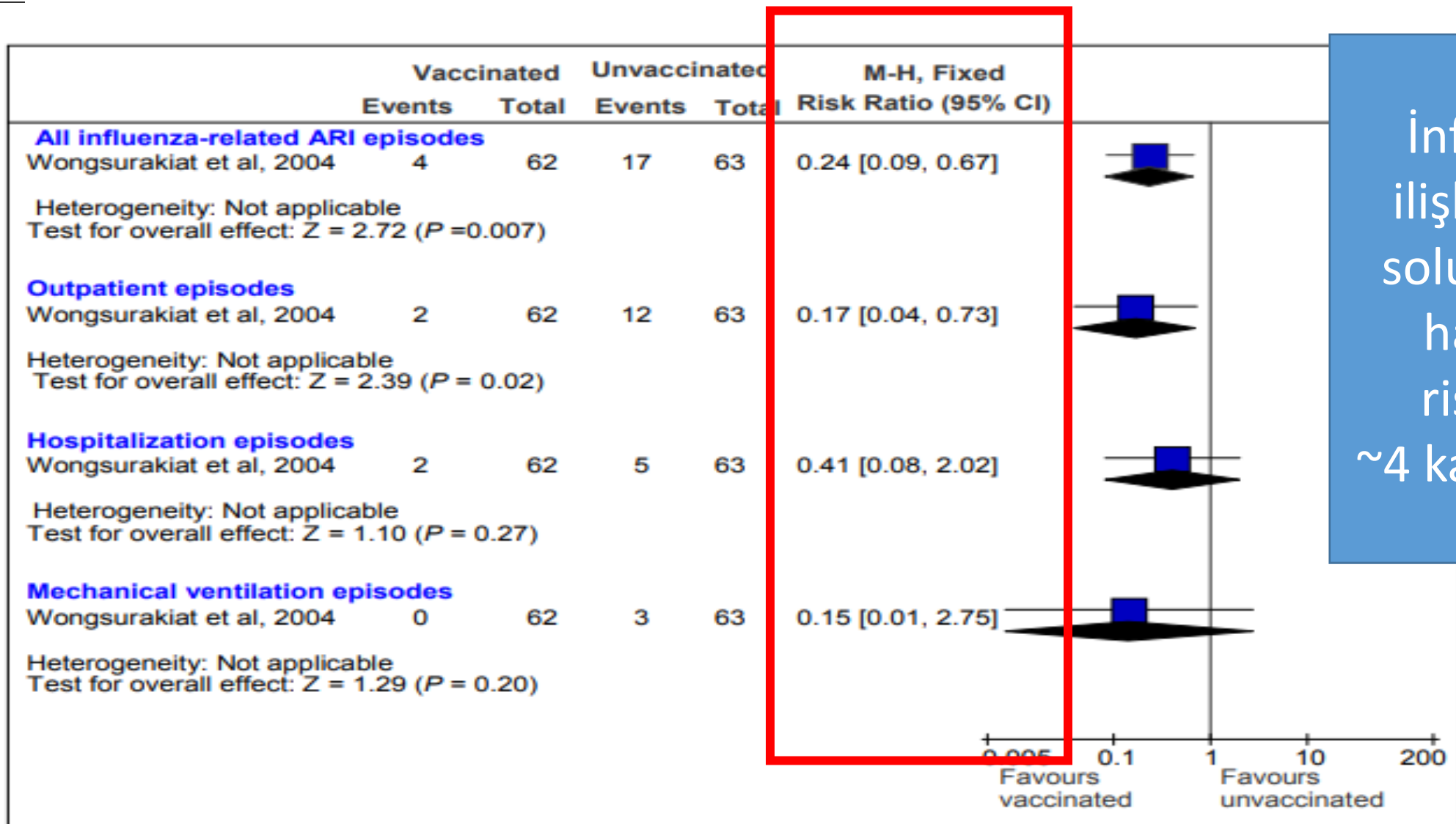
Clinical Effectiveness The influenza vaccination was associated with significantly fewer episodes of influenza-related acute respiratory illness (ARI). The incidence density of influenza-related ARI was:

- All patients: vaccine group: (total of 4 cases) = 6.8 episodes per 100 person-years; placebo group: (total of 17 cases) = 28.1 episodes per 100 person-years, (relative risk [RR], 0.2; 95% confidence interval [CI], 0.06–0.70; $P = 0.005$).
- Patients with severe airflow obstruction (forced expiratory volume in 1 second [FEV₁] < 50% predicted): vaccine group: (total of 1 case) = 4.6 episodes per 100 person-years; placebo group: (total of 7 cases) = 31.2 episodes per 100 person-years, (RR, 0.1; 95% CI, 0.003–1.1; $P = 0.04$).

**AŞI
etkinliği
%76**

Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review.

Sehatzadeh S.



İnfluenza ilişkili akut solunumsal hastalık riskinde ~4 kat azalma

Figure 1: Incidence and Severity of Influenza-Related ARI in Patients with COPD*

*Abbreviations: ARI, acute respiratory illness; CI, confidence interval; COPD, chronic obstructive pulmonary disease; M-H, Mantel-Haenszel.

Guidance for Use in Specific Populations and Situations

Populations at Higher Risk for Medical Complications Attributable to Severe Influenza

All persons aged ≥ 6 months without contraindications should be vaccinated annually. However, vaccination to prevent influenza is particularly important for persons who are at increased risk for severe complications from influenza and for influenza-related outpatient, ED, or hospital visits. When vaccine supply is limited, vaccination efforts should focus on delivering vaccination to the following persons at increased risk for medical complications attributable to severe influenza who do not have contraindications (no hierarchy is implied by order of listing):

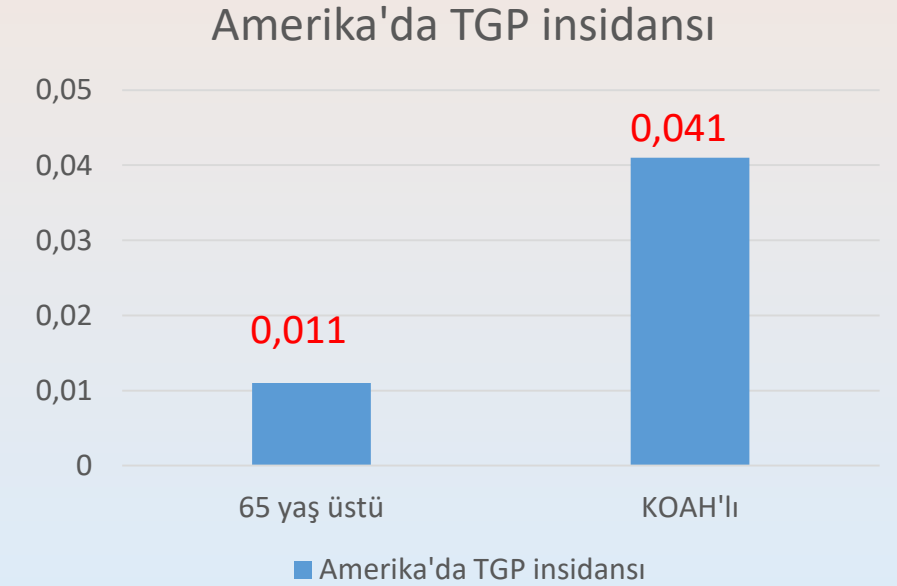
- all children aged 6 through 59 months;
- all persons aged ≥ 50 years;
- adults and children who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);
- persons who are immunocompromised due to any cause (including immunosuppression caused by medications or by HIV infection);
- women who are or will be pregnant during the influenza season;
- children and adolescents (aged 6 months through 18 years) who are receiving aspirin- or salicylate-containing medications and who might be at risk for experiencing Reye syndrome after influenza virus infection;
- residents of nursing homes and other long-term care facilities;
- American Indians/Alaska Natives; and
- persons who are extremely obese (BMI ≥ 40).

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2017–18 Influenza Season

KOAH - PNÖMOKOK

KOAH ve Pnömonok

- KOAH'lı pnömokok infeksiyonu insidans?
- Toplumda gelişen pnömoni (TGP)'li hastalar arasında KOAH siktir
- Pnömonili KOAH hastalarının **hastaneye yatışları** da hava akımı kısıtlanmasına paralel artar.
- TGP'li kronik akciğer hastalıklı hastalar arasında da en sık izole edilen etken *S. pneumoniae*'dir.



Pnömonokok aşısı

- ❖ Virülans- kapsül
- ❖ 90 farklı pnömokok serotipi
- ❖ Erişkinlerde en ciddi enfeksiyonlardan sorumlu serotipler 14, 3, 9, 19, 1, 6, 23 ve 7'dir.
- Biri polisakkarit (PPSV23) diğeri konjuge (PCV13) olmak üzere iki tip pnömokok aşısı bulunmaktadır.

POLİSAKKARİT AŞI- PPSV23

İnvaziv pnömokok enfeksiyonlarından sorumlu serotiplerin %90'dan fazlasını kapsayan **23 farklı serotip**

1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

Ekinliği %50-85

KONJUGE AŞI- PCV13

Toksik olmayan difteri toksinine (CRM197) bağlı (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14,18C, 19A, 19F, 23F) **on üç serotip**

Bu aşı T lenfosit bağımlı bağışık hafıza oluşturabilir- protein içerir- uzun bağışıklık

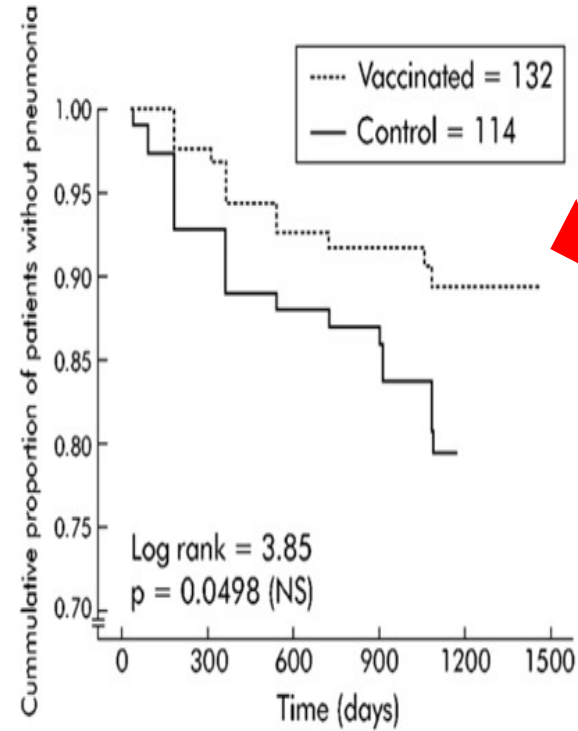
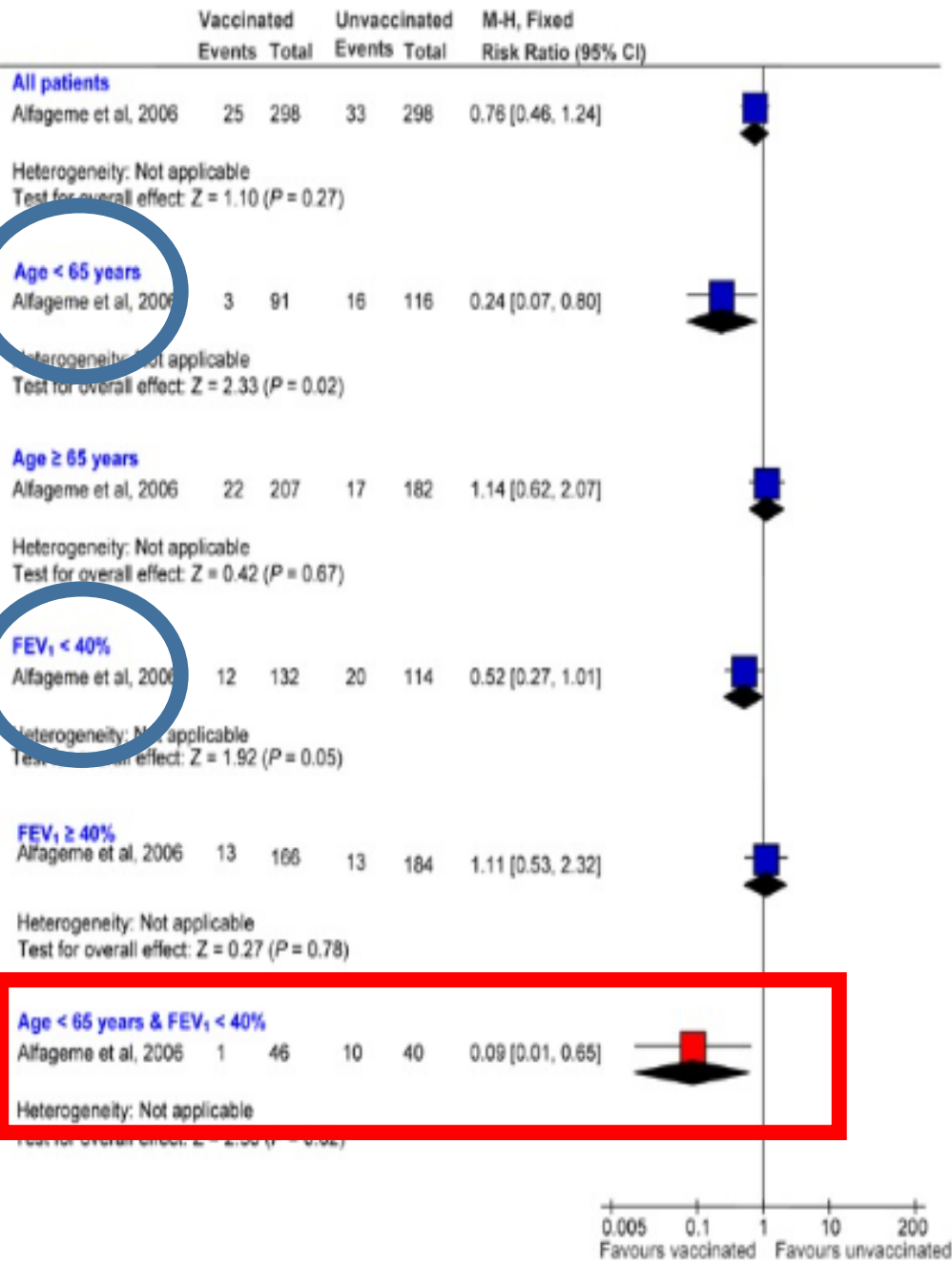
Etkinliği % 45- 75

**Konjuge aşığı takiben polisakkarit aşı kullanılması en etkin yöntem
Antikor yanıtı daha geniş**

Influenza and pneumococcal vaccinations for patients with chronic obstructive pulmonary disease (COPD): an evidence-based review.

Sehatzadeh S.

AĞIR KOAH'LI HASTALARDA
AŞILI GRUPTA PNÖMONİSİZ
HASTALARIN KÜMÜLATİF
DAĞILIMI



Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients with Severe COPD Without Pneumonia Over the Follow-up Period[‡]

**FEV₁ < %40
< 65 YAŞ
NNT 10**

Table 9: Efficacy of the 23-Serotype Pneumococcal Vaccine in Reducing the Incidence of Community-Acquired Pneumonia of Unknown Etiology and due to Pneumococcus*

Subgroups	Vaccine Efficacy (%)	P value
All patients	24 (-24 to 54)	0.333
Age < 65 years	76 (20 to 93)	0.013
Age ≥ 65 years	-14 (-107 to 38)	0.801
FEV ₁ < 40%	48 (-7 to 80)	0.076
FEV ₁ ≥ 40%	-11 (-132 to 47)	0.945
Age < 65 years & FEV ₁ < 40%	91 (35 to 99)	0.002

*Abbreviation: FEV₁, forced expiratory volume in 1 second.

Source: Alfageme et al, 2006 (45)

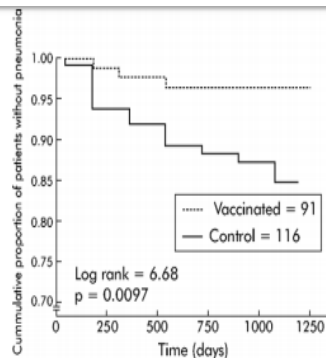


Figure 6: Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients Less Than 65 Years of Age Without Pneumonia Over the Follow-up Period

**Aşı etkinliği
%24**

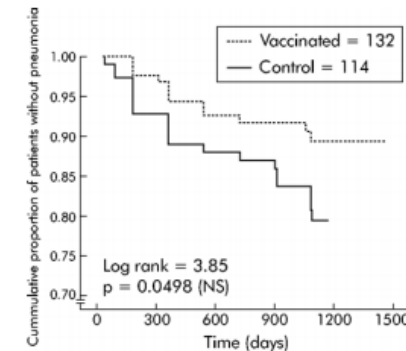





Figure 7: Kaplan-Meier Survival Curve Demonstrating the Cumulative Proportion of Patients with Severe COPD Without Pneumonia Over the Follow-up Period*

KOAH ve Pnömonokok Aşıları

Sağlıklı
erişkinlerde
pnömonokok
aşısının
etkinliği

%60

- KOAH'lı hastalarda aşıya karşı immün yanıt net değildir.
- KOAH'lı hastalarda aşıya **antikor** cevabı genel popülasyonla karşılaştırıldığında benzer, **gözlemsel çalışmalarda klinik yanıt düşük** 
- Aşı yapılmadan **antikor** titreleri sık ataklar nedeniyle yüksek 
- KOAH'lı hastalarda aşı cevabının değerlendirmek güç 

Walters JAE, Tang JNQ, Poole P, Wood-Baker R.

Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease.
Cochrane Database of Systematic Reviews **2017**, Issue 1. Art. No.: CD001390.

7 studies included in review
version 2010

160 records
identified through

5 additional
records identified

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each study (JW, JT), using criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook). We resolved disagreements by discussion or by consultation with another review author. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias(es).

We graded each potential source of bias as high, low or unclear and provided a quote from the study report, together with a justification for our judgement, in the 'Risk of bias' table. We summarised risk of bias judgements across different studies for each of the domains listed. When information on risk of bias was related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for studies that contributed to those outcomes.

2171 KOAH'lı hasta

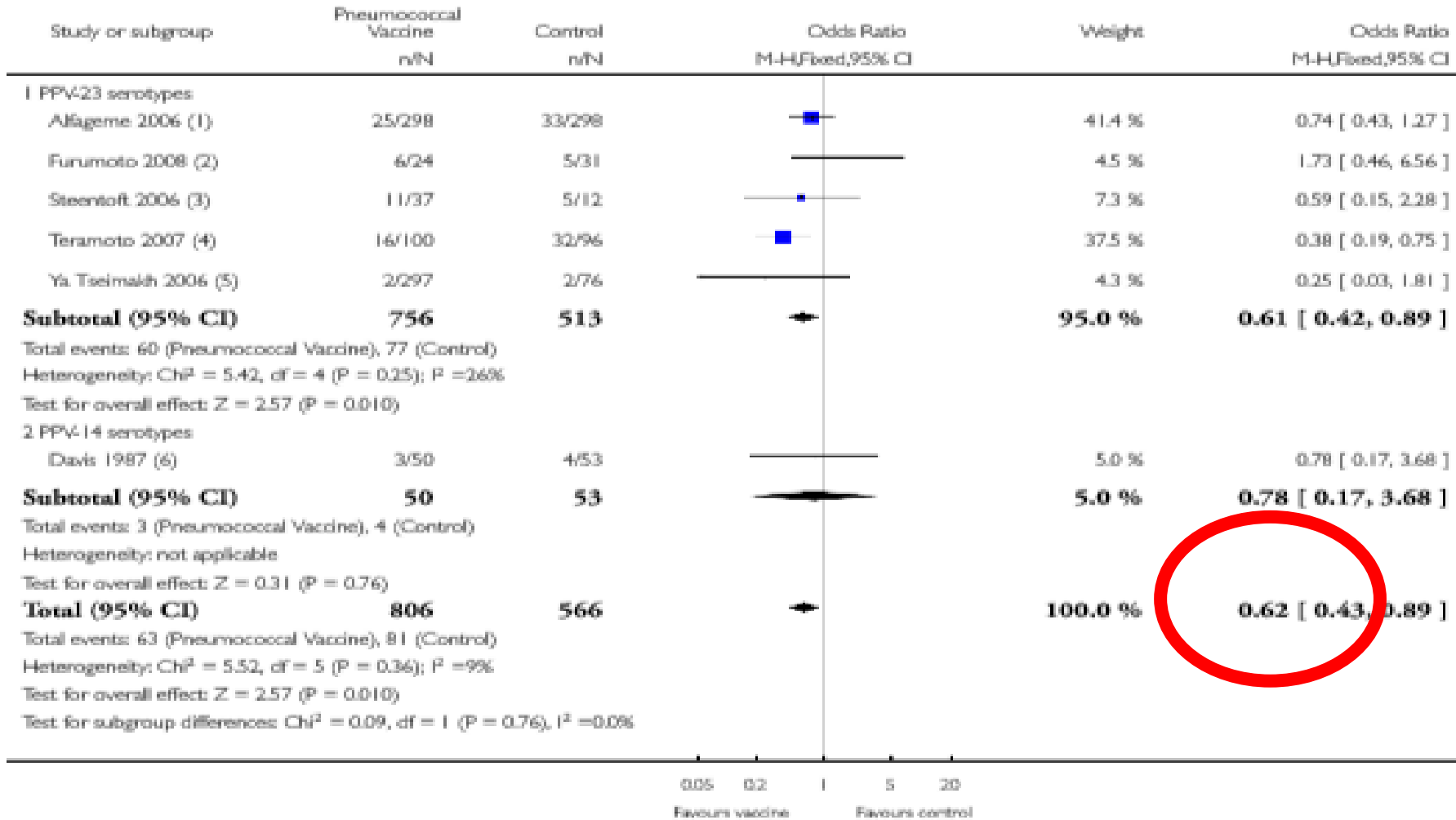
Toplam 12 çalışma

Ortalama 66 yaş

Ortalama FEV1 1.2 L (5 çalışma), %54 (4 çalışma)

12 studies
included in
quantitative
synthesis
(meta-analysis)

1 epizodda TKP/ pnömokok aşısı+/-



TKP olma riskini 1.61 kat azaltır

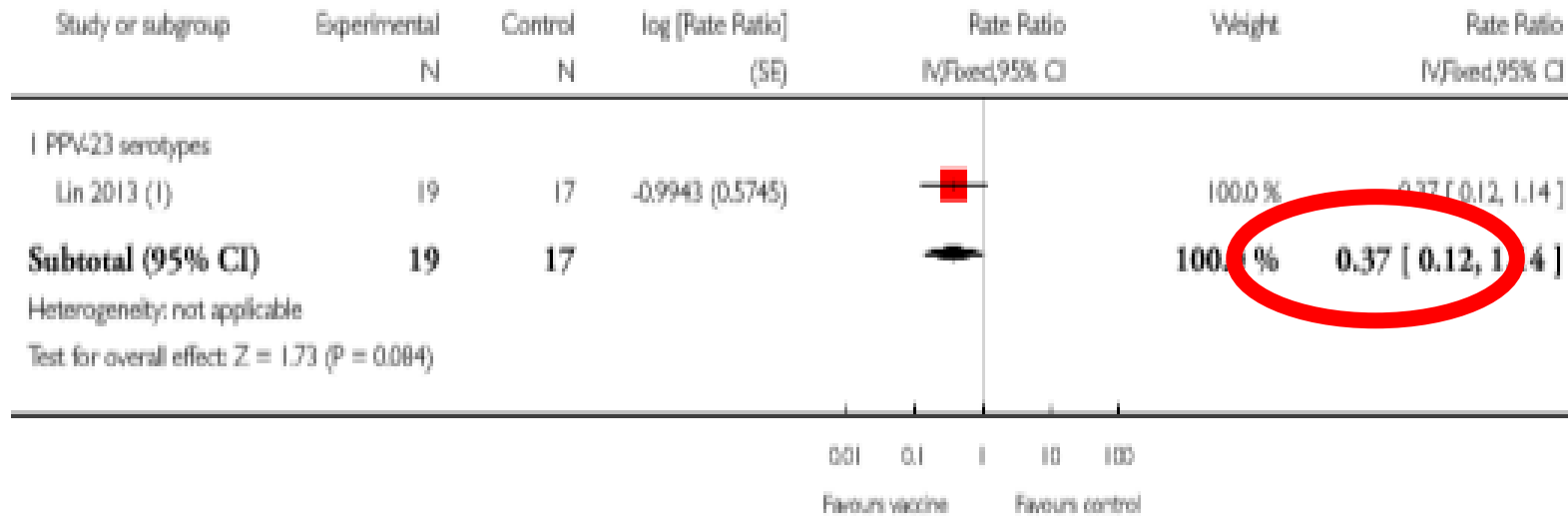
- (1) 32 months median
- (2) 24 months
- (3) 6 months
- (4) 24 months
- (5) 6 months
- (6) 24 months

1 yılda TKP/ pnömokok aşısı +/-

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 2 Community-acquired pneumonia: rate per person-year

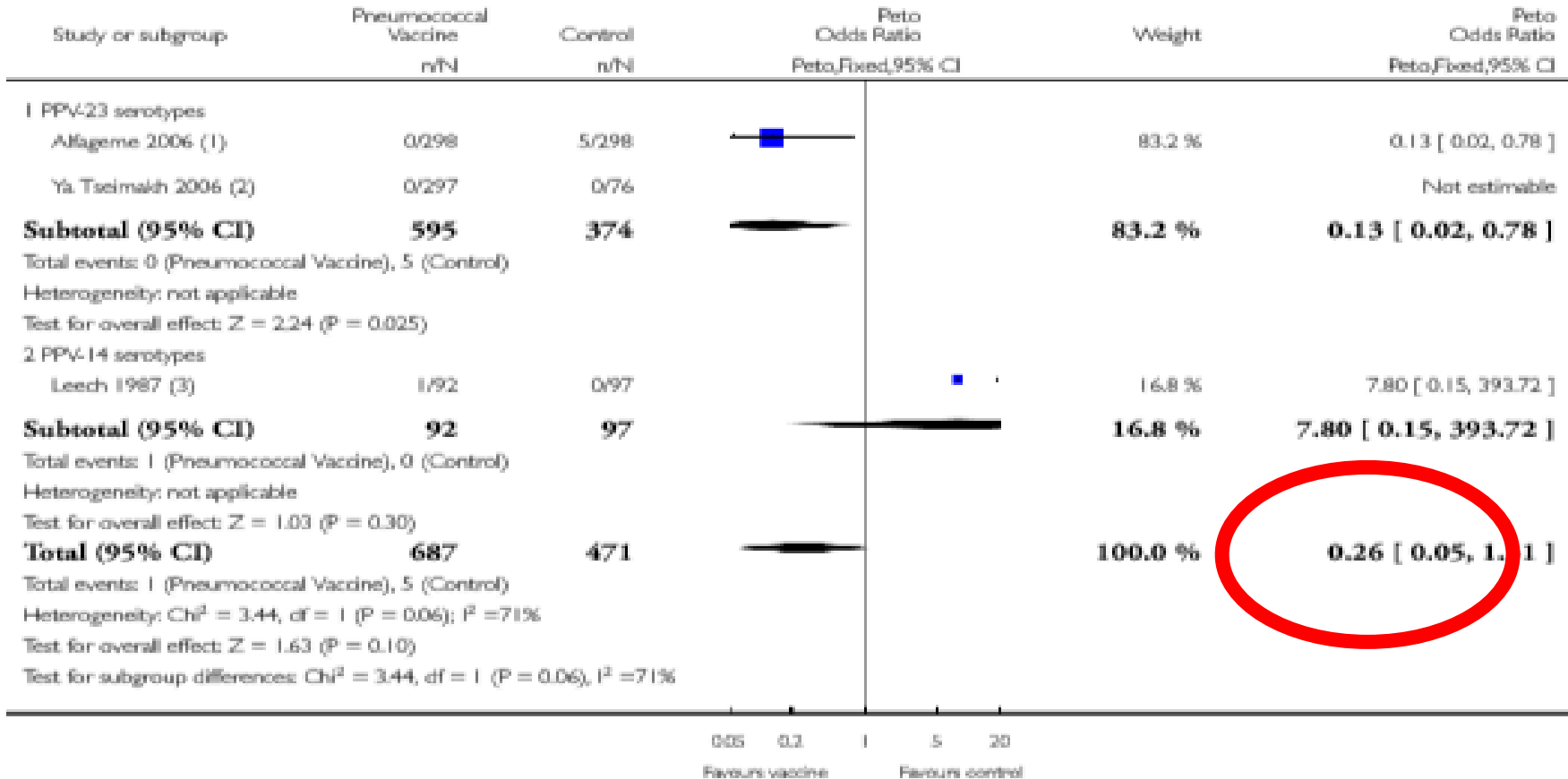


TKP olma
riskini
2.7 kat
azaltır

(1) 12 months

Pnömonok pnömonisi riski/ pnömonok aşısı +/-

Outcomes: 3 Pneumococcal pneumonias at least 1 episode



Pnömonok
pnömonisi
riskini
4 kat azaltır

(1) 32 months median

(2) 6 months

(3) 24 months

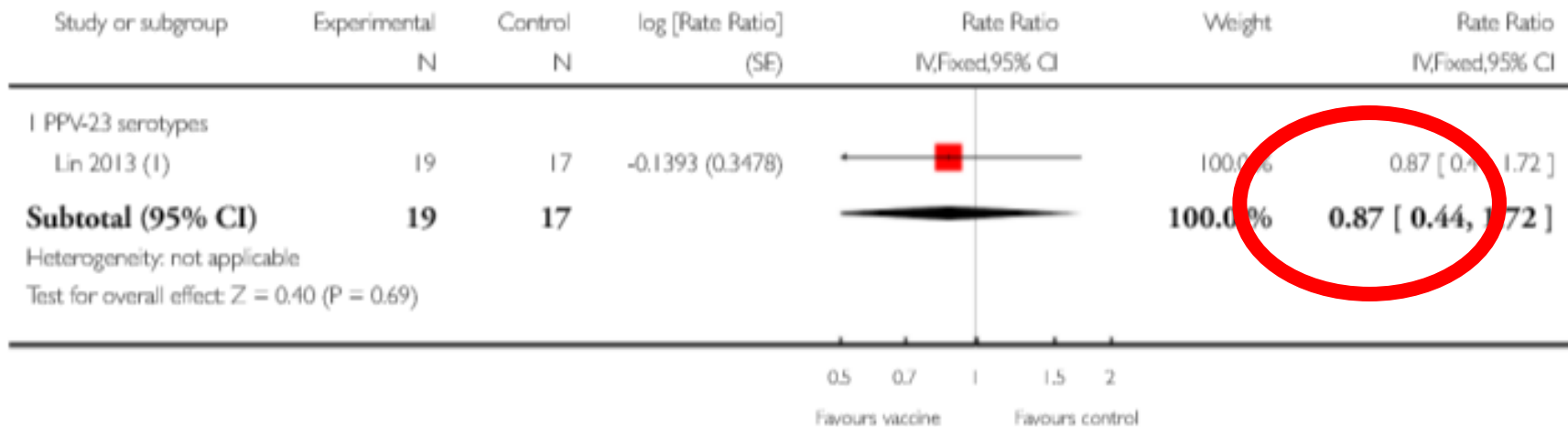
Yılda KOAH atak riski/ pnömokok aşısı +/-

Analysis 1.12. Comparison 1 Pneumococcal vaccine versus control, Outcome 12 COPD exacerbations: rate/person-year.

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 12 COPD exacerbations: rate/person-year



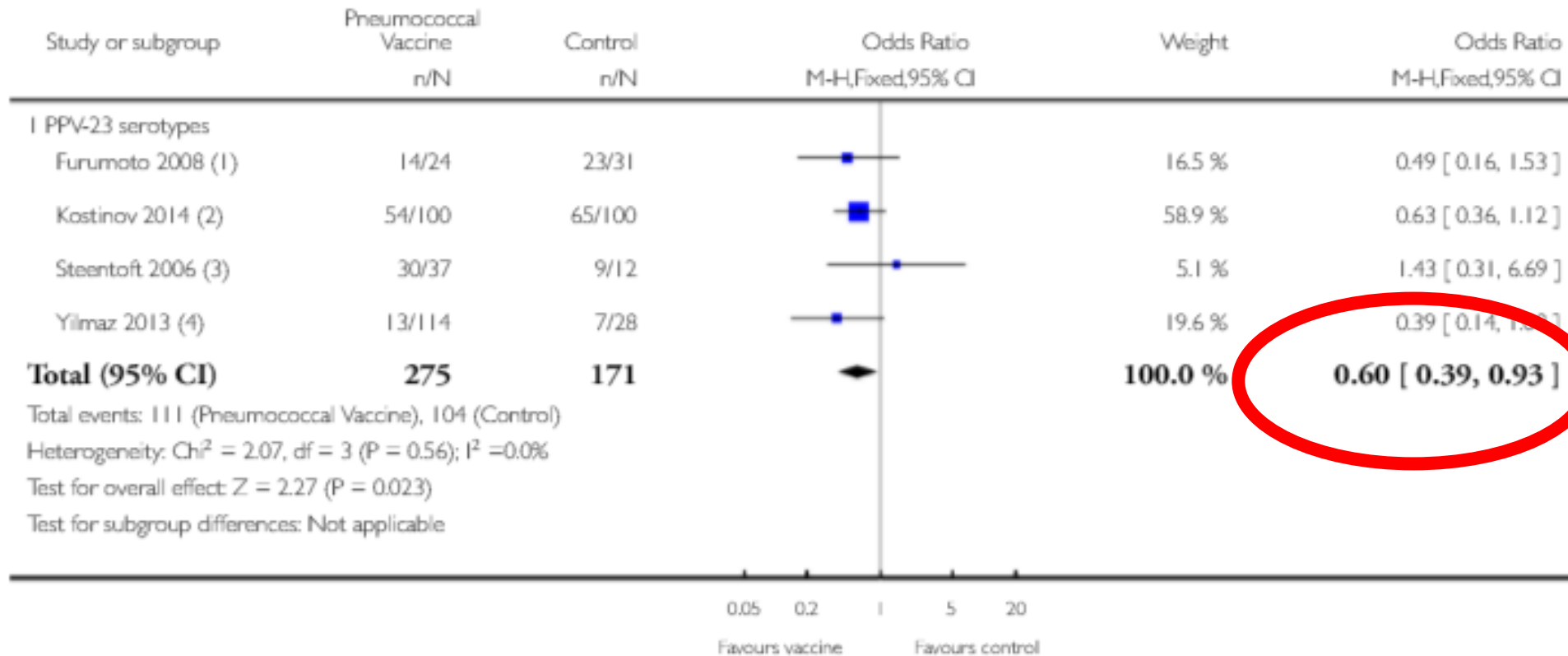
(I) 12 months

En az 1 KOAH atağı riski/ pnömokok aşısı +/-

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 10 At least 1 COPD exacerbation

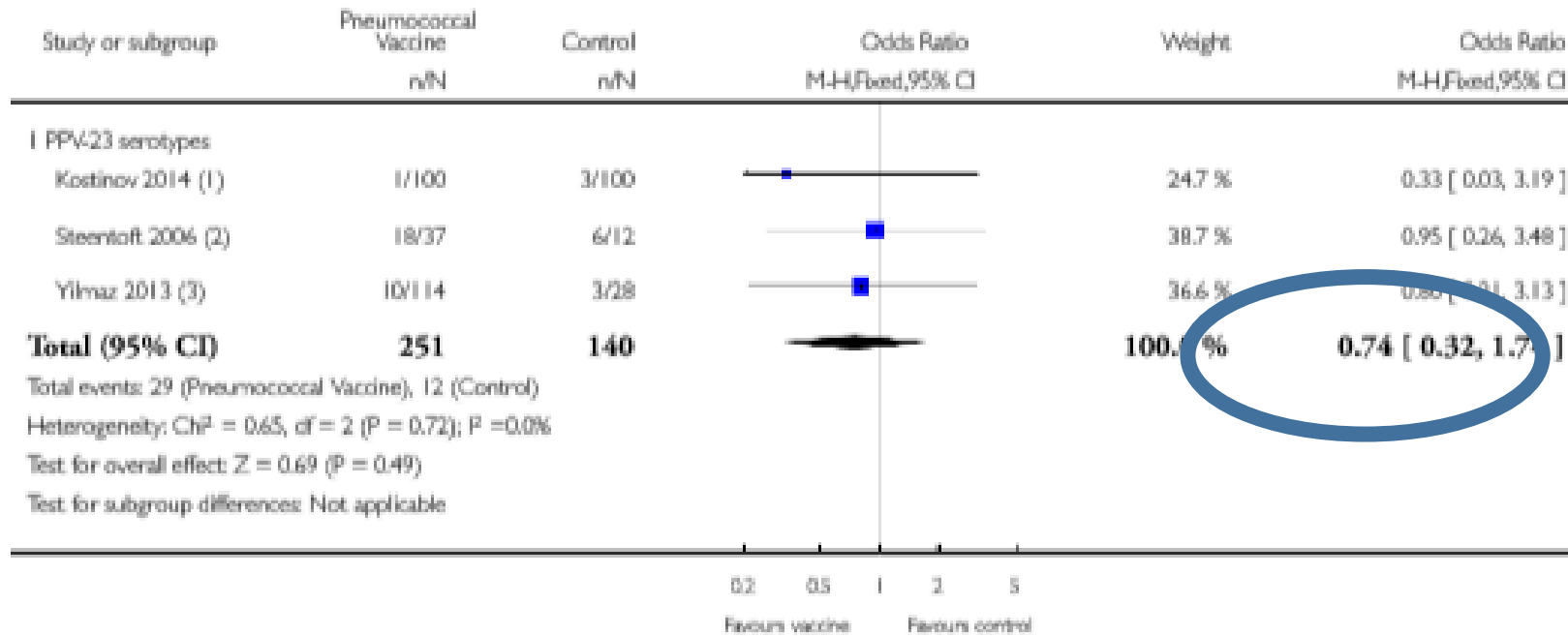


1 epizodda herhangi bir nedenle hastaneye başvuru /pnömokok aşısı +/-

Review: Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease

Comparison: 1 Pneumococcal vaccine versus control

Outcome: 6 Hospital admission, any cause: at least 1 episode



(1) 12 months

(2) 6 months

(3) 3-12 months

Walters JAE, Tang JNQ, Poole P, Wood-Baker R.
Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease.
Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD001390.

181 olguluk PCV ve PPSV-23 aşıyı karşılaştıran çalışmada TKP, Tüm nedenlerden mortalite, hastane başvurusu, KOAH atak olasılığı arasında fark yok.

PPSV-23 ile bazı hafif yan etkilerin olasılığını daha fazla bulmuşlar.

12 çalışmanın
analizinde
AŞILI VE AŞISIZ
GRUPTA

Kardiyopulmoner ölüm,
Tüm nedenlerden ölüm,



FARK YOK

Pnömonokok aşısı endikasyonları

* **Kronik pulmoner hastalık (astım dışında)**

- * Kronik kardiyovasküler hastalık
- * Diabetes mellitus
- * Kronik karaciğer hastalığı veya nefrotik sendrom
- * Fonksiyonel veya anatomik aspleni (Orak hücreli hastalık veya splenektomi)
- * Elektif splenektomi- cerrahiden en az iki hafta öncesinde aşılanmalıdır
- * İmmüsupresif hastalıklar
- * Koklear implantlar
- * Beyin-omurilik sıvısı (BOS) kaçıkları
- * HIV tanısı alan hasta
- * Bakım evinde kalan kişiler
- * Lösemi, Hodgkin hastalığı, multiple myelom gibi hematolojik hastalıklar
- * Yaygın malignite
- * Uzun süreli immün supresif tedavi
- * Solid organ nakli



0,5 ml

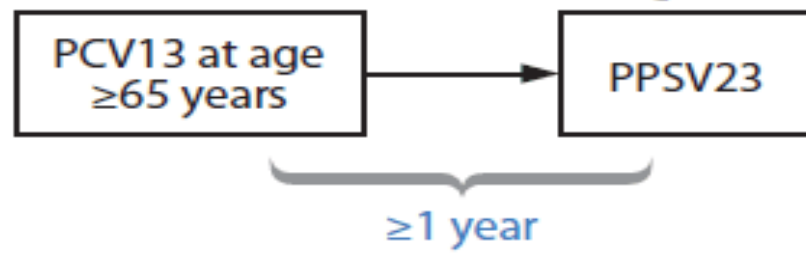
IM

CDC, sigara içen ve astımı olanlarda da pnömonokok aşısını önermektedir.

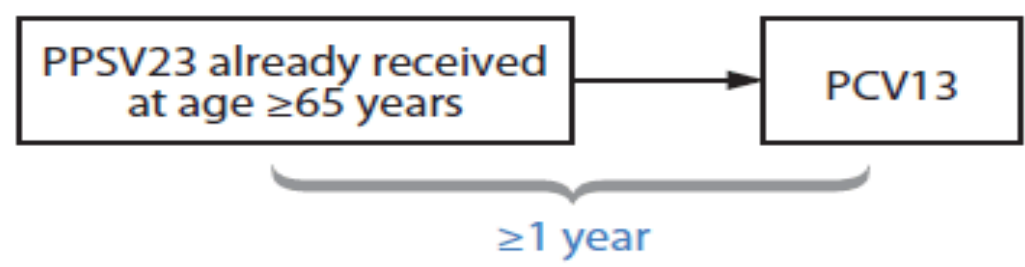
Tablo 4. Risk durumlarına göre pnömokok aşuları arasındaki olması gereken süre

Risk durumu	Önce konjuge aşı yapıldıysa polisakkarit aşı için gereken süre		Önce polisakkarit aşı yapıldıysa konjuge aşı için gereken süre	
	19-64 yaş	≥ 65 yaş	19-64 yaş	≥ 65 yaş
Riskli durum yok*	≥ 1 yıl*	≥ 1 yıl	≥ 1 yıl*	≥ 1 yıl
-Kronik kalp hastalığı				
-Kronik akciğer hastalığı				
-Diabetes mellitus				
-Alkolizm	≥ 8 hafta	≥ 1 yıl	≥ 1 yıl	≥ 1 yıl
-Kronik karaciğer hastalığı				
-Siroz				
-Sigara içiciliği				
-BOS kaçağı	≥ 8 hafta	≥ 8 hafta	≥ 1 yıl	≥ 1 yıl
-Kohlear implant				
-Fonksiyonel ya da anatomik aspleni	≥ 8 hafta	≥ 8 hafta	≥ 1 yıl	≥ 1 yıl

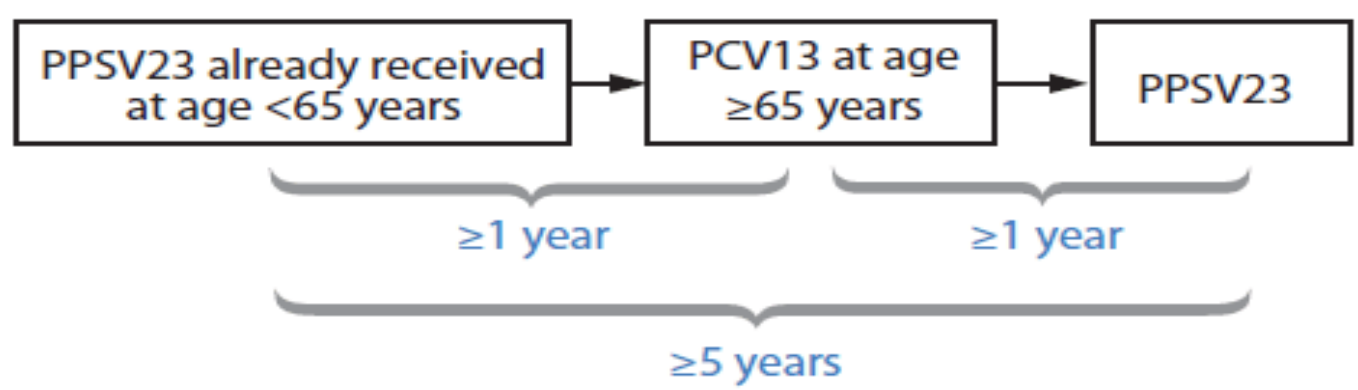
Pneumococcal vaccine-naïve persons aged ≥ 65 years



Persons who previously received PPSV23 at age ≥ 65 years



Persons who previously received PPSV23 before age 65 years who are now aged ≥ 65 years





Review

Prevention of Community-Acquired Pneumonia with Available Pneumococcal Vaccines

Significantly less optimistic is the protection of adult people, particularly those aged ≥ 65 years with PPV23 alone or in association with PCV13. Real effectiveness of PCV13 and PPV23 in prevention of adult CAP is not precisely defined. It is not clarified whether sequential administration of the two vaccines is significantly more effective than a single administration. Moreover the interval between the two injections is not precisely defined. In addition, the cost-effectiveness of PCV13 use, alone or in combination, must be better established [84].

Further studies in this regard are urgently needed and ACIP's decision to reevaluate the present recommendations in 2018 in light of new epidemiological evaluations and ad hoc studies seems particularly wise.

	All pneumococcal pneumonia			PPV23-type pneumococcal pneumonia		
	Number of cases vs number of controls	Adjusted vaccine effectiveness* (95% CI)	p value (test for interaction)	Number of cases vs number of controls	Adjusted vaccine effectiveness* (95% CI)	p value (test for interaction)
Overall	419 vs 1617	27.4% (3.2 to 45.6)	..	272 vs 1617	33.5% (5.6 to 53.1)	..
Stratified by sex	0.117	0.117
Male	261 vs 1002	16.4% (-19.8 to 41.7)	..	176 vs 1002	20.9% (-21.7 to 48.6)	..
Female	158 vs 615	42.9% (6.4 to 65.2)	..	96 vs 615	52.0% (10.4 to 74.3)	..
Stratified by age group (years)	0.657	0.563
65-74	132 vs 315	32.2% (-20.7 to 61.9)	..	100 vs 315	39.8% (-15.5 to 68.6)	..
≥75	287 vs 1302	24.3% (-5.9 to 45.9)	..	172 vs 1302	28.2% (-9.4 to 52.9)	..
Stratified by underlying disorders	0.891	0.706
With chronic respiratory diseases	135 vs 500	27.0% (-18.7 to 55.1)	..	82 vs 500	34.6% (-20.8 to 64.6)	..
Without chronic respiratory diseases	284 vs 1117	26.3% (-5.7 to 48.6)	..	190 vs 1117	32.4% (-3.9 to 56.0)	..
Stratified by chest radiograph findings	0.394	0.49
Lobar pneumonia	42 vs 186	67.3% (-0.5 to 89.4)	..	23 vs 186	71.4% (-29.9 to 93.7)	..
Bronchopneumonia	377 vs 1431	25.4% (-0.7 to 44.8)	..	249 vs 1431	32.7% (3.2 to 53.2)	..
Stratified by pneumonia type	0.19	0.605
Community-acquired pneumonia	293 vs 957	13.4% (-23.0 to 39.0)	..	202 vs 957	24.1% (-15.2 to 50.0)	..
Health-care-associated pneumonia	126 vs 660	42.9% (3.1 to 66.4)	..	70 vs 660	44.3% (-10.3 to 71.8)	..

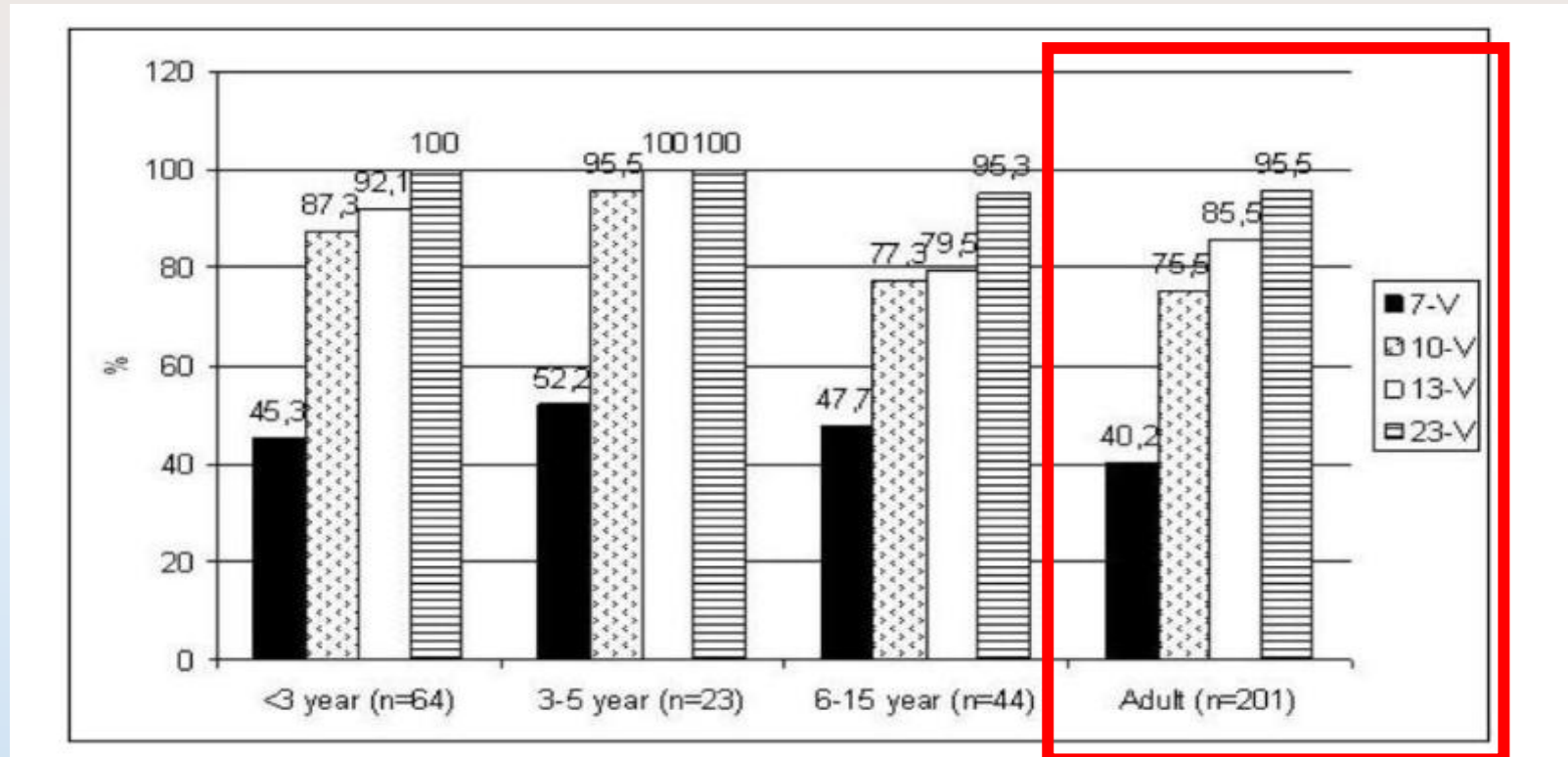
*Adjusted for study site, sex, age, underlying disorder, smoking status, pre-hospital antibiotic treatment, and year of hospital visit.

PCV13 vs PPSV23

Türkiye’de invaziv *S. pneumoniae* izolatları ve aşıların içerdiği serotiplerle uygunluğunun değerlendirildiği 10 yıllık bir çalışma (n=332)

PPSV23 %96

PCV13 %96.4



Türkiye'de PCV13 KOAH'ı içeren riskli hasta grubunda ruhsat almış, ancak henüz geri ödeme kapsamına alınmamıştır.

PCV 13 daha costefektif bulunmuş*.

GOLD 2017- KOAH aşılama öneriler

Table 3.2. Vaccination for stable COPD

- Influenza vaccination reduces serious illness and death in COPD patients (**Evidence B**).
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community-acquired pneumonia in COPD patients aged < 65 years with an FEV₁ < 40% predicted and in those with comorbidities (**Evidence B**).
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia and serious invasive pneumococcal disease (**Evidence B**).

TÜRKİYE VERİSİ

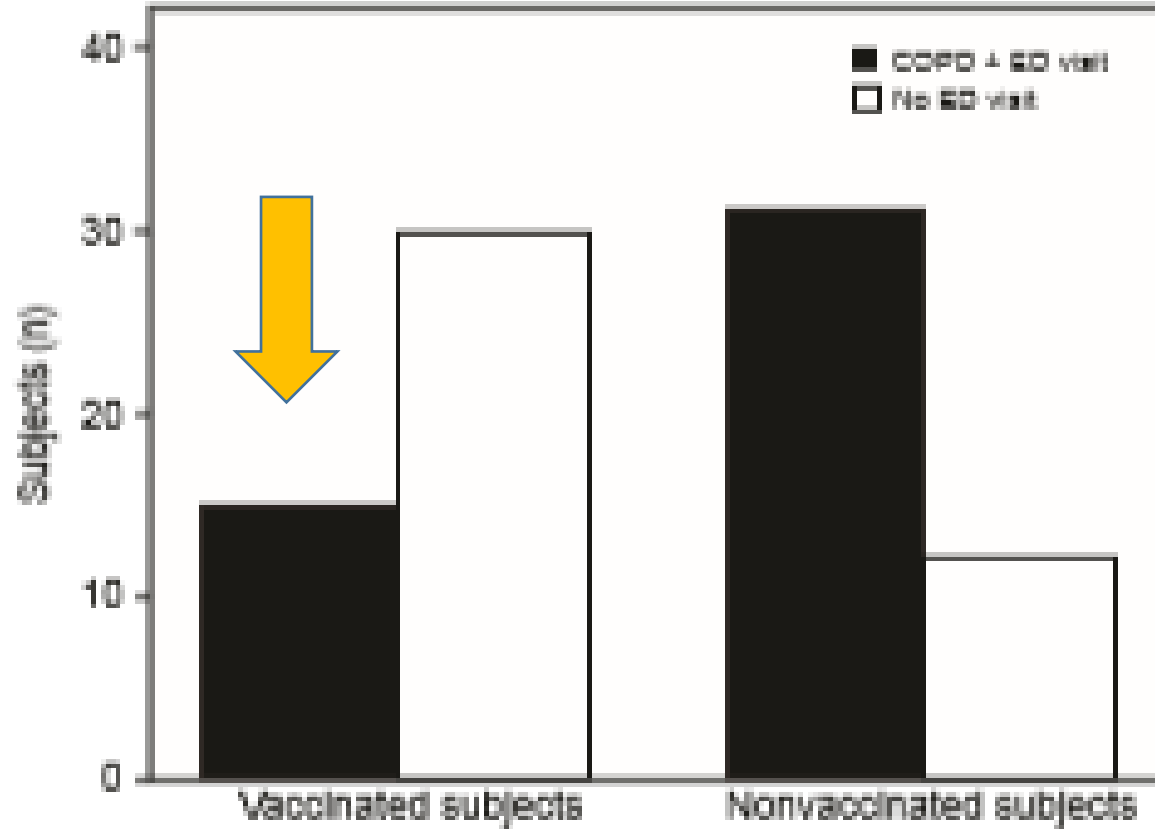


Fig. 1. Relationship between vaccination status and COPD-related emergency department visits. $P < .001$.

KOAH İLİŞKİLİ ACİLE BAŞVURU

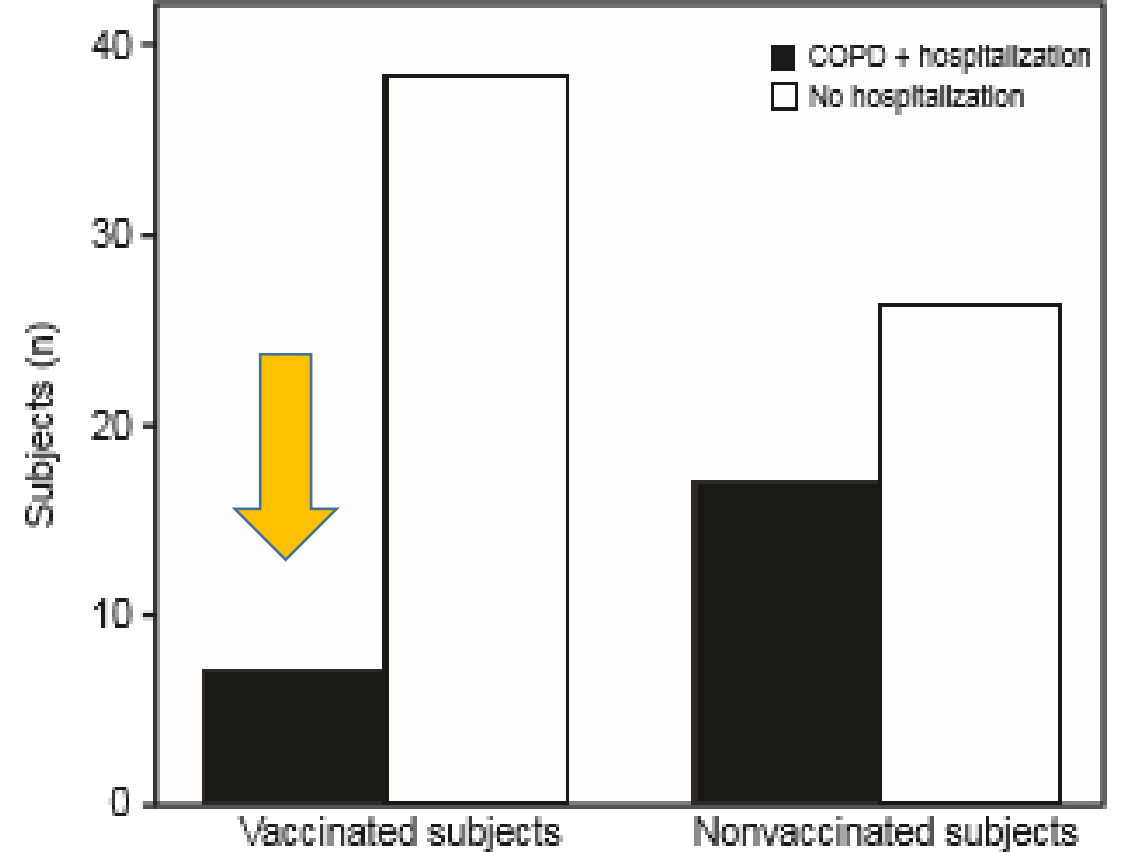


Fig. 2. Relationship between vaccination status and COPD-related hospitalizations. $P = .02$.

KOAH İLİŞKİLİ HASTANEYE YATIŞ

DUAL İNFLUENZA+PNÖMOKOK AŞISI

REVIEW

 OPEN ACCESS

Comparison of dual influenza and pneumococcal polysaccharide vaccination with influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly.

Yan-Yang Z...

emia.²³ Furthermore, while an additive effect of dual pneumococcal and influenza vaccination on infectious acute exacerbations was seen in the first year after vaccination, the effect did not persist into the second year and was only significant in patients with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD).²⁴

Table 1. Char...

1st author
(publication)

Chan (2012)

Chang (201...

Kawakami (2010)²³

Hung (2010)²⁵

Christenson
(2004)²⁴

Honkanen (1999)¹⁹

RCT	Enrollment during October to November 2005; 2 years (24 months) of follow up	391	FV+PV	78.5 ± 7.3	38%	n/a	n/a
		387	FV	77.7 ± 7.2	32%	n/a	n/a
Prospective study	December 3, 2007 to March 31, 2009 (16 months)	7292	FV+PV	77 (71–83) ^a	40%	4.40%	2.20%
		2076	FV	75 (70–80) ^a	45%	4.60%	2.20%
Prospective study	December 1999 to November 2000; 1 year (12 months) of follow up.	72107	FV+PV	≥65 ^b	n/a	n/a	n/a
		29346	FV				
Retrospective	Cohort I: start in November 30, 1992; Chort II: start in November 15, 1993; followed until December 31, 1994 (13 months) for pneumonia, and December 31, 1995 (25 months) for bacteremia	13980	FV+PV	Cohort I: 74.1 ± 6.8 Cohort II: 72.8 ± 6.5	38%	6.10%	
		12,945	FV	Cohort I: 73.9 ± 7.0 Cohort II: 73.6 ± 6.5	38%	6.30%	

COPD, chronic obstructive pulmonary disease; FV, influenza vaccination; n/a, not available; PV, pneumococcal vaccination; RCT, randomized controlled trial. ^aMedian (range). ^bNo mean age was reported, and the population was stratified by age.

İNFLUENZA+PNÖMOKOK vs TEK İNFLUENZA



REVIEW

OPEN ACCESS

Comparison of dual influenza and pneumococcal polysaccharide vaccination with influenza vaccination alone for preventing pneumonia and reducing mortality among the elderly: A meta-analysis

Table 2. Outcomes of studies included in the meta-analysis.

1st Author (publication year)	Intervention	Vaccine status and ascertainment	Incidence(per person years) ^b	PNÖMONİ		MORTALİTE	
				RR (95% CI) ^c	N (%)	RR (95% CI) ^c	N (%)
Chan (2012)	FV+PV	Record of nursing home showed the vaccination status of each resident.	n/a	n/a	42 (17.1)	FV+PV vs. FV: aHR = 0.54 (0.35–0.84)	
				n/a	57 (27) 1.30%	FV+PV vs. FV: aOR = 0.74 (0.57–0.96)	
					1.70%		
					23 (5.9)	n/a	
					25 (6.5)		
						Vaccinated vs. unvaccinated: aHR = 0.65 (0.55–0.77)	
						FV+PV vs. FV: aHR = 0.86 (0.64–1.16)	
						Vaccinated vs. unvaccinated: HR = 0.78 (0.61–1.0)	
						Vaccinated vs. unvaccinated: aOR = 0.29 (0.06–1.31)	
						FV+PV vs. FV: aOR = 0.41 (0.047–3.64)	
						Vaccinated vs. unvaccinated: aOR = 0.70 (0.15–3.21)	
Honkanen (1999)	FV+PV FV	Records from local health centers in 23 administrative districts in northern Finland (cohort I) showed trivalent FV and 23-valent PV or trivalent FV alone in autumn 1992, and this was extended to a further 12 districts (cohort II) in 1993.	0.74% (0.0074 per person years)				
			0.63% (0.0063 per person years)				

In conclusion, the results of this study support concomitant pneumococcal and influenza vaccination of the elderly. A dual vaccination strategy is associated with lower pneumonia and mortality rates. Sequential PCV13 and PPV23 vaccination for adults ≥ 65 years has been recommended by ACIP of US FDA. Though the findings of this study are promising, the value of concomitant pneumococcal and influenza vaccination of the elderly needs to be confirmed by large scale clinical trials.

PNÖMONİ

MORTALİTE

RİSK AZALMASI

FV, Influenza vaccination; PV, pneumococcal vaccination; RR, relative risk; aHR, adjusted hazard ratio; aOR, adjust odds ratio; n/a, not available.

^aPneumonia refer to ICD-9-CM: 480–486 or ICD-10-CM: J12–18.

^bThe incidence of all-cause pneumonia were converted to per person years for all studies.

^cAO RR > 1 indicates that influenza + pneumococcal vaccination is associated with a higher pneumonia or all-cause mortality rate than influenza vaccination alone, whereas an RR < 1 indicates that dual vaccination is associated with a lower pneumonia or all-cause mortality rate than influenza vaccination alone. A RR = 1 indicates the rates are similar between the 2 treatment groups.

^dThe definition of RR in Honkanen et al.¹⁹ was irrelevant to either OR or HR. The RR in this study was calculated based on the ratio between outcome rates per 1,000 person-years of the influenza+pneumococcal group and the influenza alone group.

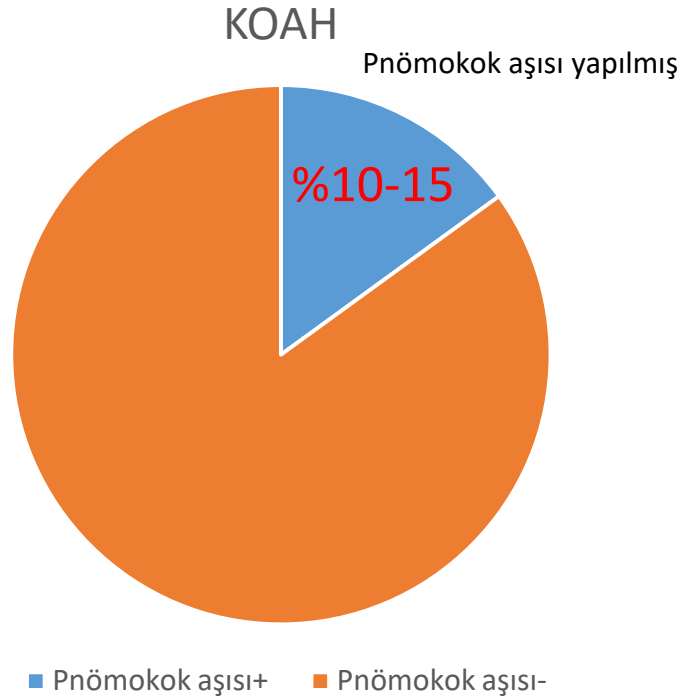
COMMENTARY

 OPEN ACCESS

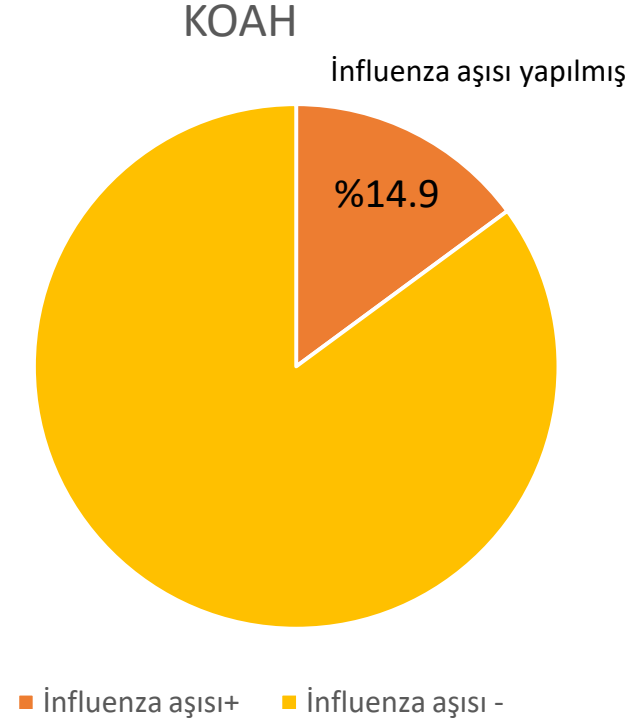
Barriers to adult immunization and solutions: Personalized approaches

Devrim Emel Alici^a, Abdullah Sayiner^b, and Serhat Unal^c

^aMedical Department, Pfizer PFE, Istanbul, Turkey; ^bDepartment of Chest Diseases, Ege University Faculty of Medicine, Izmir, Turkey; ^cDepartment of Infectious Diseases and Clinical Microbiology, Hacettepe University Faculty of Medicine, Ankara, Turkey



PNÖMOKOK AŞISI



İNFLUENZA AŞISI

RESEARCH ARTICLE

Pneumococcal Conjugated Vaccine Reduces the High Mortality for Community-Acquired Pneumonia in the Elderly: an Italian Regional Experience

Vincenzo Baldo^{1*}, Silvia Cocchio^{1*}, Tolinda Gallo², Patrizia Furlan¹, Pierantonio Romor², Chiara Bertoncetto¹, Alessandra Buja¹, Tatjana Baldovin¹

¹ Department of Cardiac, Thoracic, and Vascular Sciences, Hygiene and Public Health Unit, University of Padua, Padua, Italy, ² EuroHealth Net, Friuli Venezia Giulia Region Health Directorate, Udine, Italy

© These authors contributed equally to this work.

* vincenzo.baldo@unipd.it

Abstract

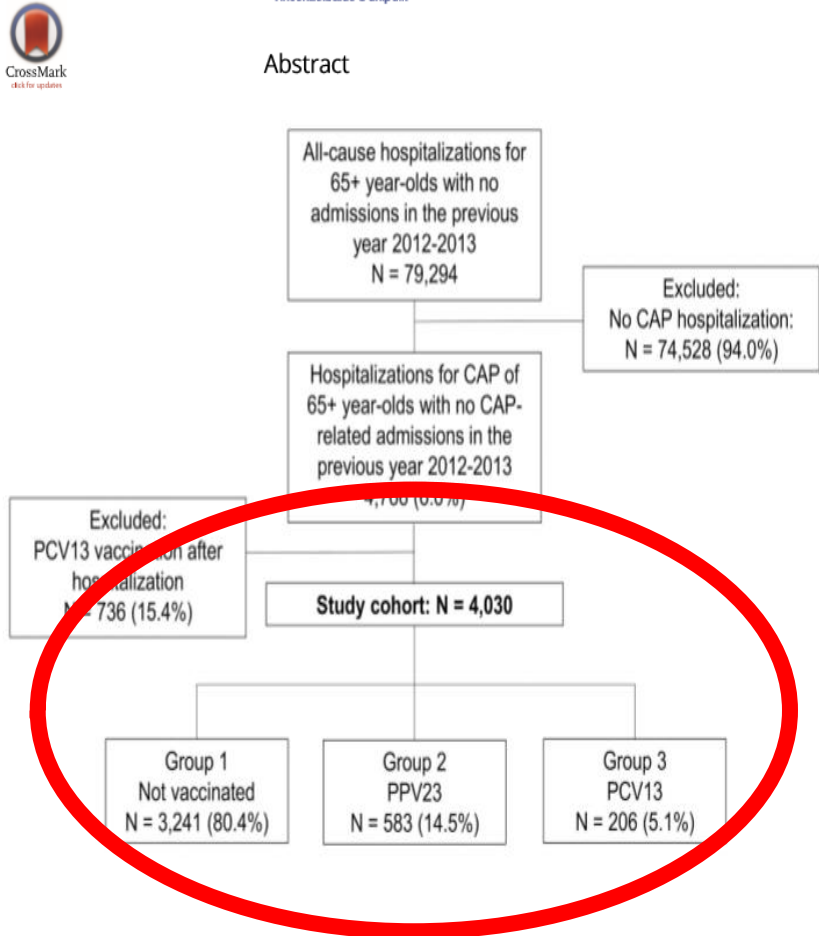


Table 3. Characteristics of the study population by pneumococcal vaccination status.

Variables	Pneumococcal vaccination status					
	Not vaccinated		PPV23		PCV13	
	n	(%)	n	(%)	n	(%)
Gender [n(%)]						
Males	1,577	(48.7)	293	(50.3)	107	(51.9)
Females	1,664	(51.3)	290	(49.7)	99	(48.1)
Age groups [n(%)]						
65–69	112	(3.5)	29	(5.0)	3	(1.5)
70–74	339	(10.5)	87	(14.9)	21	(10.2)
75–79	479	(14.8)	96	(16.5)	34	(16.5)
80–84	643	(19.8)	91	(15.6)	41	(19.9)
85+	1,668	(51.5)	280	(48.0)	107	(51.9)
At least one comorbidity [n(%)]	2,380	(73.4)	440	(75.5)	169	(82.0)
Asthma	1,253	(38.7)	235	(40.3)	94	(45.6)
COPD	583	(18.0)	116	(19.9)	48	(23.3)
Chronic heart diseases	1,237	(38.2)	233	(40.0)	78	(37.9)
Diabetes	792	(24.4)	162	(27.8)	56	(27.2)
Malignant neoplasms	518	(16.0)	99	(17.0)	30	(14.6)
Influenza vaccination [n(%)]	2,251	(69.5)	526	(90.2)	204	(99.0)
All-cause mortality						
in-hospital	803	(24.8)	133	(22.8)	36	(17.5)
at 30 days	282	(8.7)	52	(8.9)	14	(6.8)
at 1 year	772	(23.8)	147	(25.2)	52	(25.2)
cumulative	1,857	(57.3)	332	(56.9)	102	(49.5)

RESEARCH ARTICLE

Pneumococcal Conjugated Vaccine Reduces the High Mortality for Community-Acquired Pneumonia in the Elderly: an Italian Regional Experience

Vincenzo Baldo^{1*}, Silvia Cocchio^{1*}, Tolinda Gallo², Patrizia Furlan¹, Pierantonio Romor², Chiara Bertonecello¹, Alessandra Buja¹, Tatjana Baldovin¹

¹ Department of Cardiac, Thoracic, and Vascular Sciences, Hygiene and Public Health Unit, University of Padua, Padua, Italy, ² EuroHealth Net, Friuli Venezia Giulia Region Health Directorate, Udine, Italy

© These authors contributed equally to this work.
* vincenzo.baldo@unipd.it

Abstract



SAĞKALIM

PCV-13

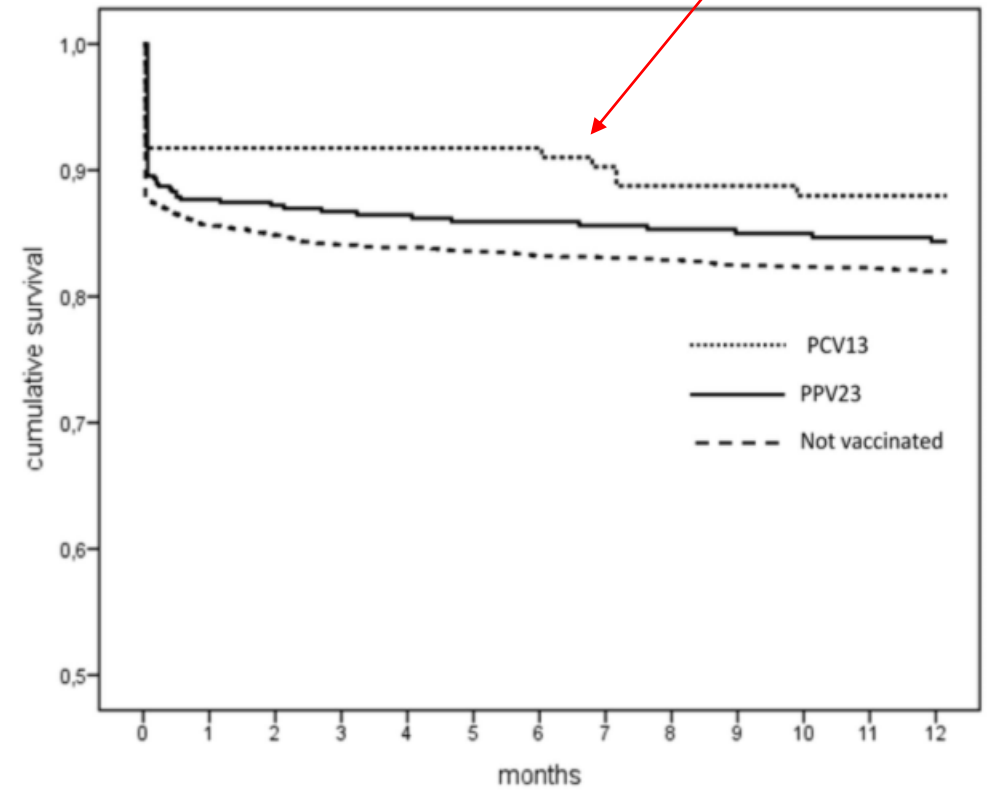


Fig 3. One-year survival after pneumonia by patients' vaccination status.

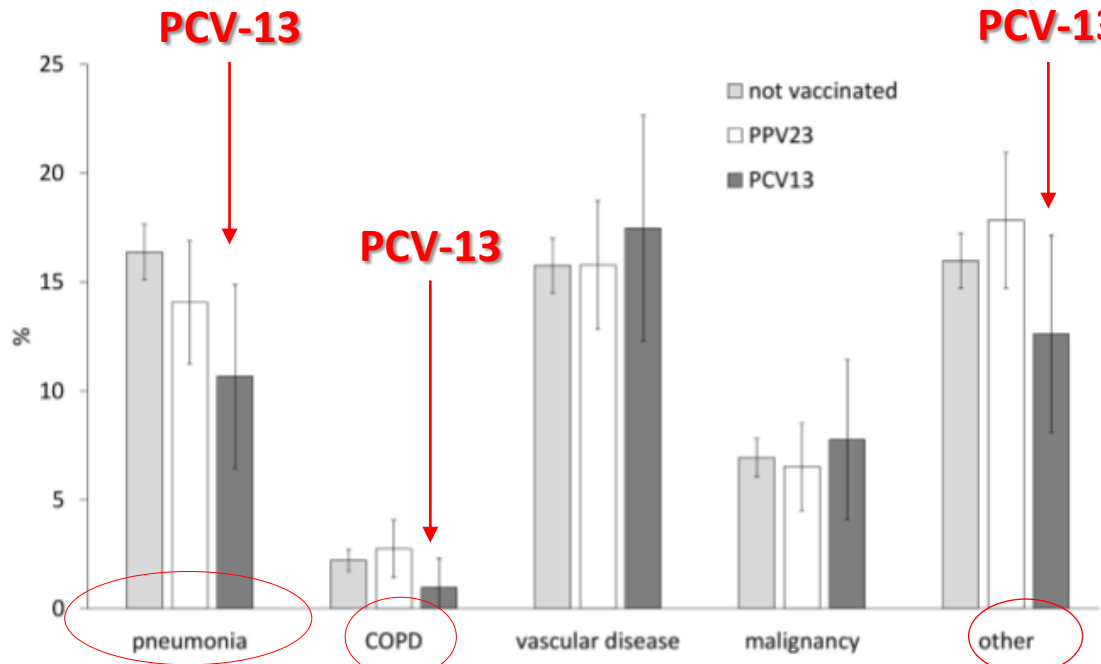


Fig 2. Mortality rate (%) by cause of death and pneumococcal vaccination status.

MORTALİTE ORANI

Field effectiveness of elderly immunization with pneumococcal conjugate vaccine in Northern Italy

Filippo Ansaldi^{1,2}, Andrea Orsi^{1,2*}, Paolo Durando^{1,2}, Cristiano Alicino¹, Cecilia Trucchi¹, Chiara Paganino¹, Ilaria Barberis¹, Daniela De Fiorentiis³, Monica Zacconi¹, Erika Albanese¹, Valter Turello⁴, Sergio Schiaffino⁵, G Icardi^{1,2}

¹Department of Health Sciences, University of Genoa, Genoa, Italy

²I.R.C.C.S. University Hospital San Martino - IST National Institute for Cancer Research, Genoa, Italy

³Office of Maritime Health, Air and Border (USMAF), Ministry of Health, Genoa, Italy

⁴Local Health Unit ASL 3 Genovese, Genoa, Italy

⁵Department of Health and Social Services - Prevention, Public Health and Vulnerable Social Groups - Liguria Region, Genoa, Italy



PCV13

Results

During pre-PCV period, annual cumulative incidence of ED accesses for LRTI was equal to 7/1000 and 2% in ≥ 65 and ≥ 85 year adults, respectively. In ≥ 65 years adults, more than 70% of subjects identified by the SSS has at least one risk condition, with a peak of 87% in ≥ 80 year cohort.

Preliminary results, based on an observation period of 155,274 and 74,419 person-months, respectively before and after pneumococcal vaccination (n=3,782, median age 75 years, 10th-90th percentile 71-78 years), showed a reduction in the incidence of ED accesses for LRTI in the vaccinated population, compared to not vaccinated: the preventive fraction, adjusted for age and seasonality, was estimated to be 24.5%, with a decrease in ED access incidence of 1.5/10,000 person-months.

**RISK
GRUPLARIN
DA VE YAŞLI
GRUPTA
ÖNERİYOR**

AŞI ETKİNLİĞİ %24.5

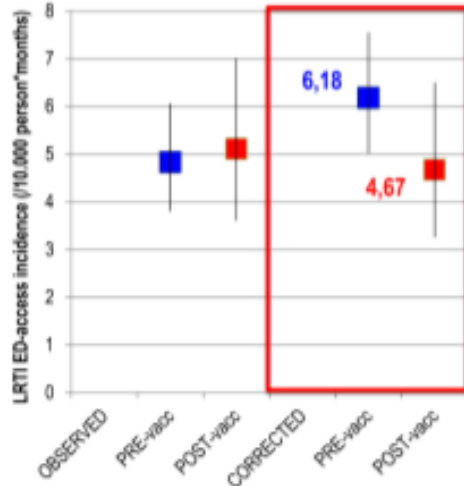
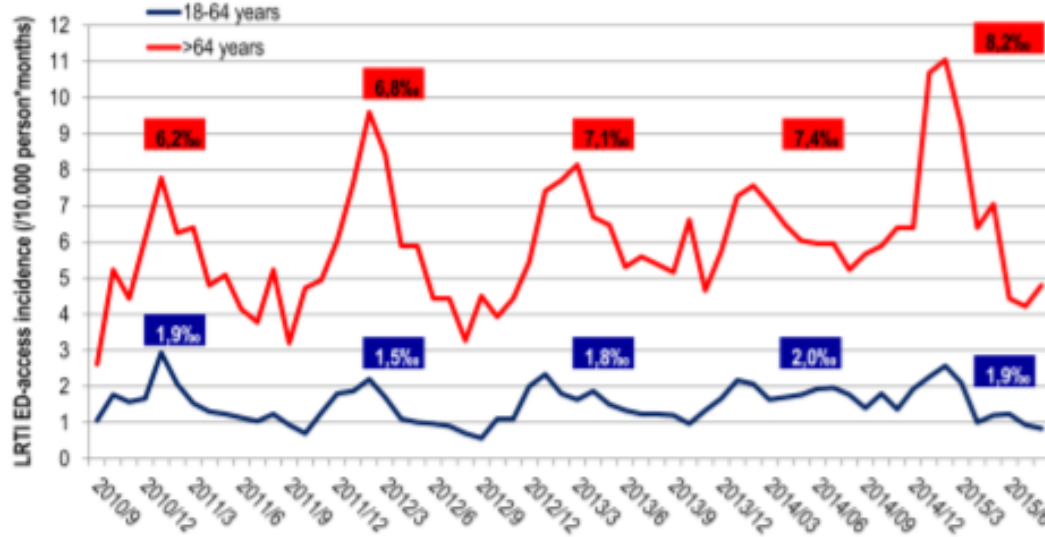
Backgrounds

Liguria, an Italian administrative region characterized by an unusual picture in Europe of pneumococcal conjugate vaccine (PCV) coverage in pediatric age group, $>80\%$ and $>90\%$ since 2004 and 2007, respectively, has issued new PCV13 recommendations for free active immunization in at risk adults and elderly in 2013.

To assess the impact of this new immunization program, particularly in subjects aged 70-75 years or with risk factors, two different studies have been implemented among elderly dwelling in the metropolitan area of Genoa, the capital city of Liguria Region.

Materials/methods

A descriptive epidemiology of the clinical burden of lower respiratory tract infections (LRTI) in adults ≥ 18 years and a crossover evaluation of the effect of PCV13 introduction in elderly aged ≥ 70 years, in terms of emergency department (ED) accesses for LRTI, obtained by a Syndrome Surveillance System operating from 2007, have been performed.



Δ Incidence = -1.5/10,000 person*months
[95%CI: -3.5 \rightarrow 0.5/10,000 person*months]

Vaccine effectiveness = 24.5%
[-11.3 \rightarrow 47.8%]

P-value = 0.081

Conclusions

This population-based approach showed the effectiveness of current Liguria region recommendations for the prevention of pneumococcal disease in adults and high risk groups and the beneficial impact of PCV13 vaccination in adults under "real world" clinical and epidemiological settings.

PR

2012-2014 YILLARI

COCCAL

160 HASTA

AŞI ÖNCESİ HASTA BAŞINA **2.67 ATAK**
AŞI SONRASI **1.79 ATAK**

ARR 0.211

NNT 4.72

Intro
is a m
pneur

Objet

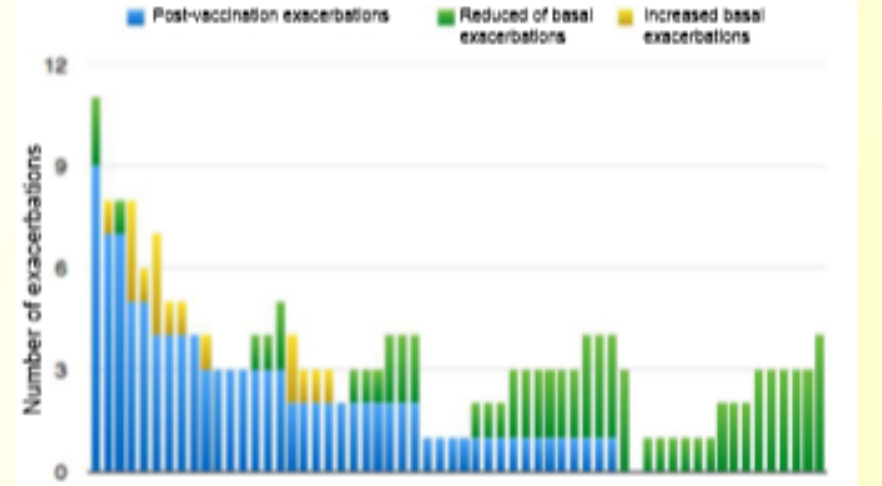
Meth
(COP
hypop
inform
calcul
hospi

hypothesis (H0) that the average differences with respect to the reduction in the population exacerbations before and after application of a single dose of the vaccine, is equal to 0 (zero).

Results. A total of 160 patients were enrolled from July 2012 to May 2014, of which have only been analyzed data from patients who have completed a period of 1 year follow-up after administration of the vaccine. In the studied population, prior to vaccination, was recorded a total of 166 events, with an average of 2.67 +/- 0.24 exacerbations per patient, with maximum of 11 exacerbations; then after vaccination, was recorded total of 108 events, with an average of 1.79 +/- 0.25 exacerbations patients with a maximum of 9 exacerbations, obtaining a Odds Ratio (OR) of 1,53 [95% CI 1,14-1,92], with a Absolute Risk Reduction (ARR) of 0,211 [95% CI -0,183 – 0,605] and a Number Needed to Treat (NNT) of 4,72 in vaccinated patients.

Conclusion. We conclude that PCV13 is effective in reducing exacerbations in patients with COPD and other chronic respiratory diseases.

Keywords: chronic lung disease, S. pneumoniae, exacerbation, control, pneumococcal conjugate vaccination, PCV13, pneumococcus.

S. pneumoniae
emory against thePulmonary Disease
eases, Apnea and
asencia, for which
lence density was
tions and/or

KOAH ATAK - PCV13, SION ÇALIŞMASI

RESEARCH PAPER

Burden of community-acquired pneumonia in adults

Filiz Kosar^a, Devrim Emel Alici^b, Basak Hacibedel^c, Burcu Arpinar Yigitbas^a

^aYedikule Chest Diseases and Chest Surgery, Pulmonary Medicine, Istanbul, Turkey; ^bPfizer P
^cPfizer Pharmaceuticals, Health Economics and Outcomes Research, Istanbul, Turkey; ^dAciba
 Diseases, Istanbul, Turkey

Table 2. Comparison of costs in the patients with community-acquired pneumonia regarding age group

Costs per patient, €	Inpatients		p
	<65 y n = 107 Mean ± SD	≥ 65 y n = 101 Mean ± SD	
Specialist visit	23.87 ± 17.09	27.41 ± 18.78	0.079
Imaging	25.90 ± 23.67	27.7 ± 28.68	0.745
Laboratory	42.11 ± 36.95	56.18 ± 57.98	0.014
Medication	203.6 ± 400.24	432.29 ± 1,110.98	0.004
Hospitalization	117.84 ± 88.39	165.31 ± 189.62	0.034
Total	412.37 ± 506.75	708.34 ± 1,331.19	0.014

SD, standard deviation.

Table 1. Demographic and clinical characteristics of the patients with community-acquired pneumonia and the costs per patient.

	Inpatients n = 208	Outpatients n = 211
Age, year, mean ± SD	61.56 ± 17.87	53.78 ± 17.46
Age group, n (%)		
<65	107 (51.4)	150 (71.1)
≥ 65	101 (48.6)	61 (28.9)
Gender, n (%)		
Female	101 (48.6)	98 (46.4)
Male	107 (51.4)	113 (53.6)
Hospitalization duration day, mean ± SD	6.81 ± 4.68	—
Comorbid diseases, n (%)		
COPD	76 (36.5)	48 (22.7)
Hypertension	38 (18.3)	15 (7.1)
Diabetes Mellitus	28 (13.5)	7 (3.3)
Heart diseases	25 (12.0)	6 (2.8)
Asthma	14 (6.7)	43 (20.4)
Costs per patient, €, mean ± SD		
Specialist visit	25.59 ± 17.98	7.63 ± 2.71
Imaging	26.78 ± 26.19	15.12 ± 14.8
Laboratory	48.94 ± 48.71	17.04 ± 22.37
Medication	314.65 ± 831.52	25.12 ± 23
Hospitalization	140.89 ± 148.11	—
Total	556.09 ± 1,004.77	51.16 ± 40.92

COPD, chronic obstructive pulmonary disease; SD, standard deviation.

CAPITA

ORIGINAL ARTICLE

Rationale and design of CAPITA: a RCT of 13-valent conjugated pneumococcal vaccine efficacy among older adults

E. Hak^{1,2*}, D.E. Grobbee¹, E.A.M. Sanders², T.J.M. Verheij¹, M. Bolkenbaas¹, S.M. Huijts¹, W.C. Gruber³,
S. Tansley¹, A. McDonough¹, B. Thoma¹, S. Patterson³, A.J. van Alphen⁴, M.J.M. Bonten^{1,5}

¹Julius Center for Health Sciences and Primary Care, Departments of ²Pediatric Immunology and Infectious Diseases, and ³Medical Microbiology, University Medical Center Utrecht, the Netherlands, ⁴Wyeth Vaccines Research, Wyeth, Pearl River New York, USA, ⁵Netherlands Vaccine Institute, Bilthoven, the Netherlands, *corresponding author: tel.: +31 (0)88-756 82 14, fax: +31 (0)88-76 80 99, e-mail: e.hak@umcutrecht.nl

ABSTRACT

The burden of community-acquired pneumonia (CAP) among the elderly is high and has increased over the last decades. *Streptococcus pneumoniae* is the most common cause of CAP and in 10% the infection may be fatal. Although the 23-valent polysaccharide pneumococcal vaccine (23-PSV) is considered effective in the prevention of invasive

PNEUMOCOCCAL INFECTIONS AMONG OLDER ADULTS

The burden of community-acquired pneumonia (CAP) among the elderly is high with an estimated million cases and between 350,000 and 620,000 hospitalisations in the United States alone, whereas CAP ranks among the top 7 causes of death¹. Of note, hospitalisations and death

PCV13

13-valanlı pnömokokal konjuge aşı etkinliği
Faz 4, Randomize,
Plasebo kontrollü klinik çalışma

84,496 gönüllü
≥ 65 yaş üstü

**AS-TGP: Aşı Serotipi Toplumda Gelişen
Pnömoni %45 etkinlik**

**AS-NB TGP : Aşı Serotipi Non
Bakteriyemik Toplumda gelişen**

Pnömoni %45 etkinlik

**AS-İPH: Aşı Serotipi İnvaziv Pnömokokal
Hastalık %75 etkinlik**

TABLE 1. Vaccination situations of the patients

	Influenza vaccination n (%)	Pneumococcal vaccinations n (%)
Vaccination rate	106 (36.5)	40 (14.1)
Non-vaccination rate	190 (63.5)	256 (85.9)
Recommended by		
Chest specialist	57 (54.0)	15 (38.1)
Internal medicine and family doctor	19 (18.0)	5 (11.3)
Family	6 (5.3)	2 (5.0)
Pharmacists	4 (3.8)	1 (2.5)
Media	4 (3.8)	1 (2.5)
Reasons for non-vaccination*		
My doctor didn't advise me to	108 (57.2)	119 (46.8)
I never catch flu/pneumonia	30 (15.7)	40 (15.7)
I don't see myself in the risk group	3 (1.7)	2 (0.9)
I don't need to get vaccinated	18 (9.5)	12 (4.9)
I'm afraid of the needle	5 (2.8)	45 (17.6)
I don't believe that flu or pneumonia is a dangerous disease	10 (5.7)	2 (0.9)
I believe that the vaccines include harmful material, such as mercury	10 (5.7)	-
There are specialists that are against vaccination	4 (2.3)	2 (0.9)
Vaccine may cause flu	2 (1.1)	-
It's boring to get vaccinated every year	1 (0.6)	1 (0.6)
Vaccines may cause allergic reactions	4 (2.3)	6 (2.3)
I believe that vaccination is ineffective	3 (1.7)	4 (1.4)
I don't know what vaccination is for	-	136 (53.3)

*Patients could mark more than one choice in this question

A close-up photograph of a field of white daffodils with bright yellow centers. The flowers are in various stages of bloom, with some fully open and others as buds. The background is a soft-focus field of more daffodils. Overlaid in the center of the image is the word "TEŞEKKÜRLER" in a bold, red, sans-serif font.

TEŞEKKÜRLER