KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

Bilimle Sağlıkla 33 Yıl

Aşıların **Bilinenden Öte** Etkileri

Dr. H. Selçuk Özger

Gazi Üniversitesi Tıp Fakültesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı

Bilinegelmek; Önceden beri bilinmek
Öte; Daha fazla

Aşılar **bilinen** misyonlarını **tamamladı mı?**

Scroll of the Declaration of Smallpox Eradication.

Aşılar **bilinen** misyonlarını **tamamladı mı?**


PLOS ONE

RESEARCH ARTICLE

Health system capacity in Sydney, Australia in the event of a biological attack with smallpox

Chandini Raina MacIntyre[1,2], Valentina Costantino[1], Mohana Priya Kunasekaran[1]*

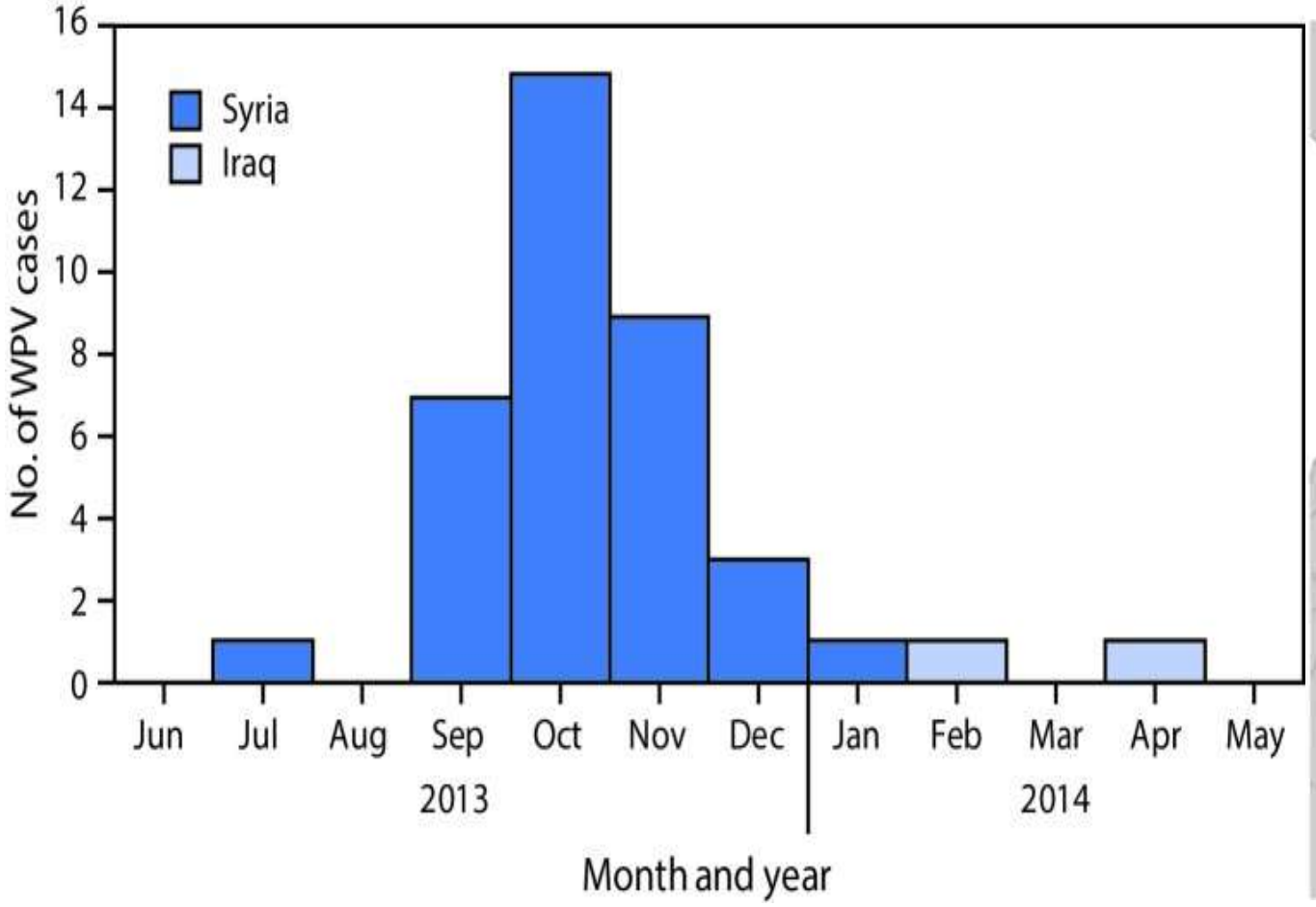
1 Biosecurity Program, Kirby Institute, Faculty of Medicine, The University of New South Wales, Sydney, New South Wales, Australia, **2** College of Public Service and Community Solutions, Arizona State University, Tempe, Arizona, United States of America

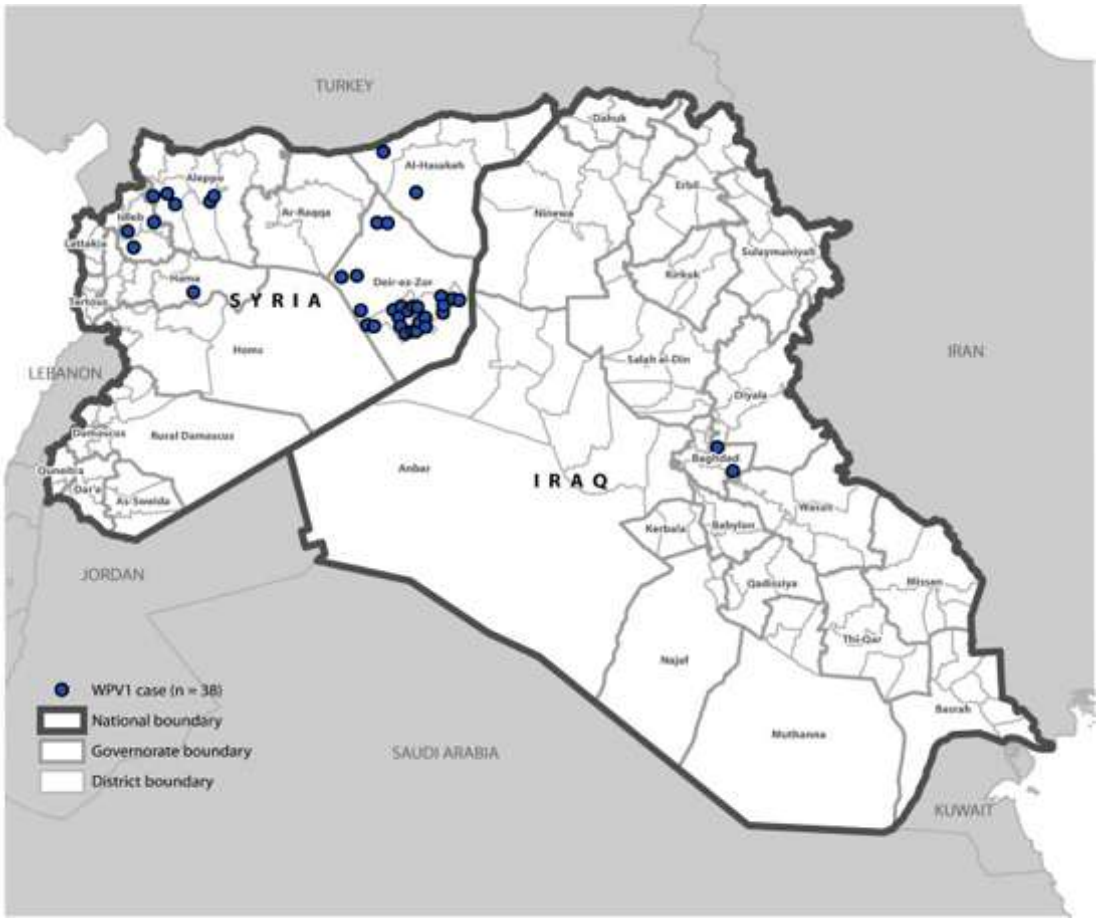
Ya geri dönerse?


SPIN THE WHEEL!
CHINA
IRAN
RANDOM
FAKE NEWS
DEMOCRATS
twitter
Investing.com

Aşılar **bilinen** misyonlarını **tamamladı mı?**

The Syrian conflict and infectious diseases





Ozaras Et Al.Expert Review Of Anti-infective Therapy, 2016

Mbaeyi et al. MMWR / March 3, 2017 / Vol. 66 / No. 8

FRANCIS R. MALASIG/EPA-EFE/SHUTTERSTOCK

Children with measles in an overcrowded hospital ward in the Philippines, where an outbreak occurred in Manila and central Luzon in February 2019.

LINDSEY WASSON/REUTERS

Parents on a march protesting against mandatory vaccinations in Washington state earlier this year.

Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative Review

Developing the concept of beneficial non-specific effect of live vaccines with epidemiological studies

P. Aaby [1, *], C.S. Benn [2, 3]

Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

TIPICO IX: report of the 9th interactive infectious disease workshop on infectious diseases and vaccines

Federico Martinón-Torres, Xavier Bosch, Rino Rappuoli, Shamez Ladhani, Esther Redondo, Timo Vesikari, Adolfo García-Sastre, Irene Rivero-Calle, José Gómez-Rial, Antonio Salas, Carlos Martín, Adam Finn & Robb Butler

Aşıların **heterolog** etkileri
Aşıların **hedef dışı** etkileri
Aşıların **ikincil** etkileri

Vaccine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

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

Conference report

Heterologous vaccine effects

Mitra Saadatian-Elahi [a,*], Peter Aaby [b], Frank Shann [c], Mihai G. Netea [d], Ofer Levy [e], Jacques Louis [f], Valentina Picot [f], Michael Greenberg [g], William Warren [h]

Bazı aşılar ile patojen spesifik **kullanım amacının ötesinde koruyucu etki** sağlanması olarak tanımlanmaktadır.

Historical studies of non-specific effects of vaccines

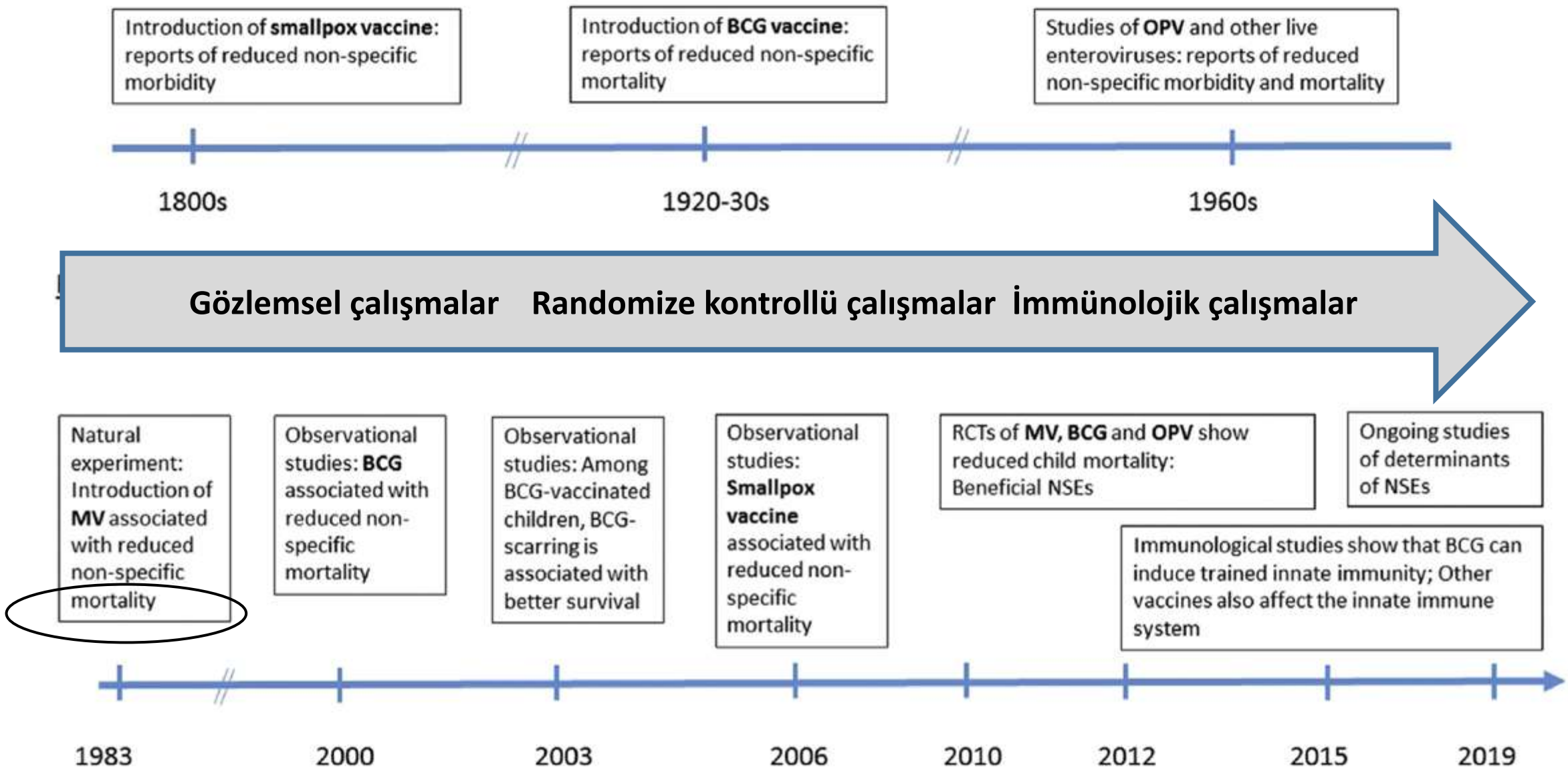


Fig. 1. Time lines in the study of the non-specific effects of vaccines.

Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Çiçek (1800)
BCG (1920)
Oral polio (1960)
Kızamık (1970)

ncept of beneficial non-specific effect of live
emiological studies

Bu aşılar **beklenilenin ötesinde** mortalite azalmasına neden oldular...

Smallpox

Jenner vaccinating James Phipps
National Library of Medicine

Smallpox için aşılama ile mortalite

(Aşılı/aşısız; Mortalite sıklık oranı; 0.22 (%95 CI; 0.05-0.61))

Etkinin kadın cinsiyette daha belirgin

Jensen ML et al.PLoS ONE.2006

Smallpox için aşılama ile mortalite

(Aşılı/aşısız; Mortalite sıklık oranı; 0.60 (% 95 CI; 0.41-0.87))

Etki kadın cinsiyette belirgin

Her ek doz için etkide artma

P. Aaby et al. Vaccine .2006

Hastane yatış sıklıklarında aza| (HR 0.84; (%95 CI: 0.72–0.98))

Bu koruyucu etkinin aşı sonrası sürenin ile giderek azaldığı gösterilmiştir. (her yıl için % 6)

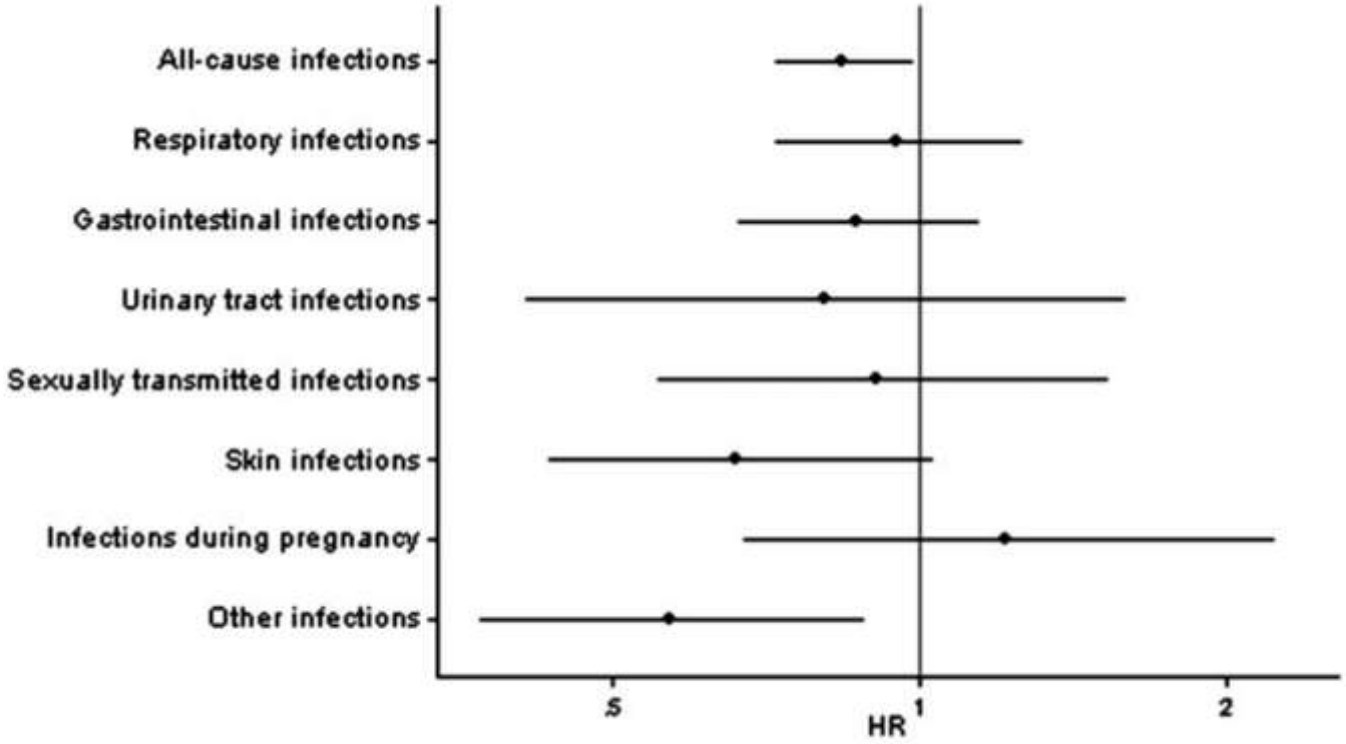


Figure 3 Estimated HRs (dot) of subgroups of infectious disease hospitalization with 95% CIs (lines) for smallpox-vaccinated vs smallpox-unvaccinated (HR = 1).

Signe Sørup etal. International Journal of Epidemiology, 2011

The Temple of Vaccinia at Dr Jenner's House Museum and Garden.

International Journal of Epidemiology, 2017, 695–705
doi: 10.1093/ije/dyw120
Advance Access Publication Date: 5 July 2016
Original article

Miscellaneous

Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971–2010

Andreas Rieckmann,[1,3,*] Marie Villumsen,[1] Signe Sørup,[1] Line Klingen Haugaard,[4,5] Henrik Ravn,[1,3] Adam Roth,[6,7] Jennifer Lyn Baker,[4,5] Christine Stabell Benn[1,3] and Peter Aaby[1,2,3]

Smallpox ± BCG aşılarının **non-spesifik etkisi**

Doğal sebeplerden ölüm sıklığında azalma

(aHR; 0,54 (% 95 CI: 0,36 - 0,81)

Daha az allerjik hastalık (astım) ve multipl skleroz

Bager Pel al. Clin Immunol, **2003**

Daha az malign melanom ve non-hodgkin lenfoma

Lankes HA, et al. Control, **2009**

Krone B, Eur J Cancer, **2005**

T-hücre CCR5 down regülasyonu

Vanpouille C et al. J Virol., 2007

Aşılı bireylerden elde edilen periferik mononükleer hücrelerde CCR5 tropik HIV-1 virusunun replikasyonunun baskılanması

Weinstein RS et al.BMC Immunol., 2010

HIV-1 zarf glikoprotein ile benzerlik çapraz-reaktif immün yanıt

Carter CJ.. Immunopharmacol Immunotoxicol, **2012**

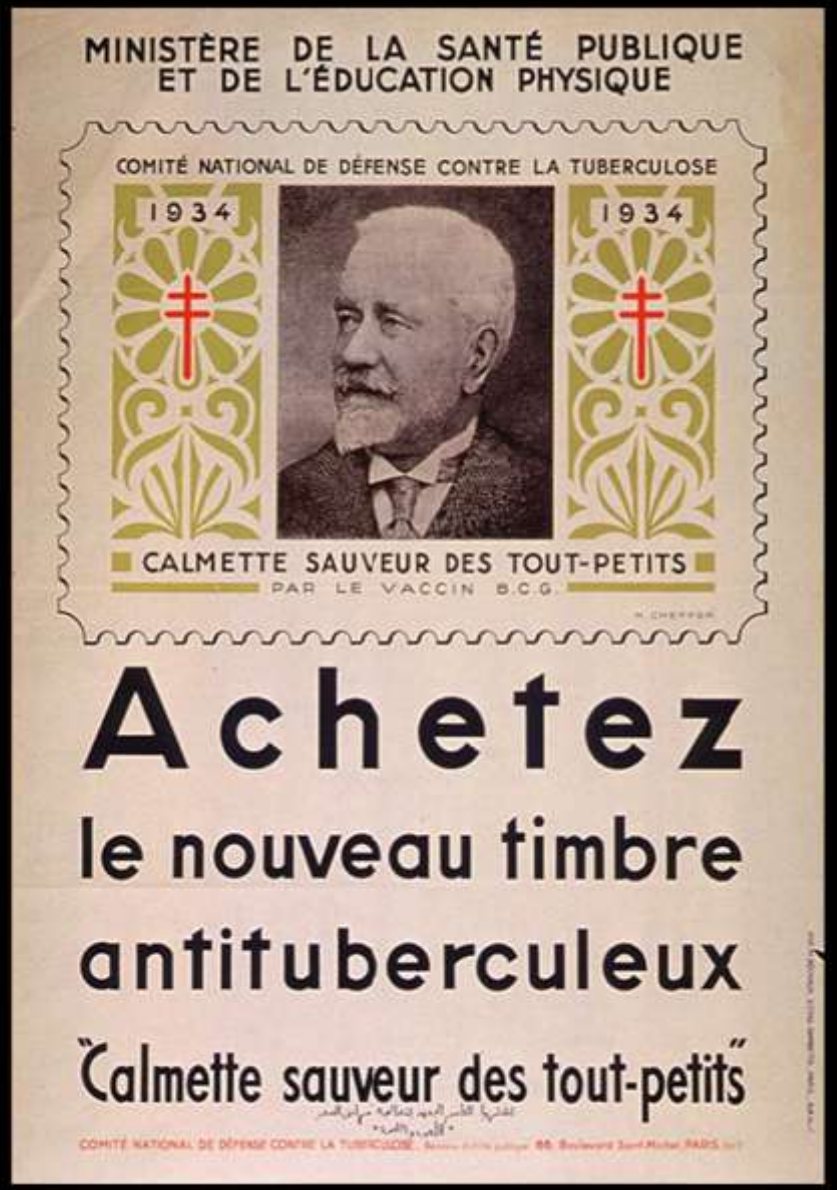
HIV-1 enfeksiyonun (kadınlarda) seksüel geçişinin azalması

Rieckmann A et al. Open Forum Infect Dis.,2017

Acele mi ediyoruz ?

Key messages

- Studying the cohort of Copenhagen schoolchildren who experienced the phase-out of both BCG and smallpox vaccinations in the 1970s, we found that having received both of these vaccines was associated with a 46% (19–64%) reduction in the hazard rate for death from natural causes.
- BCG and smallpox vaccinations were not associated with deaths due to non-natural causes (accidents, suicides and murders).
- Live attenuated vaccines, such as BCG and the smallpox vaccine, may have long-term beneficial non-specific effects on mortality.
- Caution should be observed before phasing out live attenuated vaccines after eradication of the disease, as is currently planned for oral polio vaccine and possibly for measles vaccine.



BCG

The Health Committee of the League of Nations adopted BCG as a recommended tuberculosis vaccine

Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines

Higgins JPT, Soares-Weiser K, Reingold A

13 March 2014

BCG aşılaması
Doğal nedenlerden kaynaklanan **ölüm sıklıklarında azalmaya neden olabilir.**
Cinsiyet farklı saptanmamıştır.
Erken aşılama etkiyi artırmaktadır.
A vitamin düzeyinin aşı etkinliği üzerine etkisi gösterilememiştir.

Randomized Trial of BCG Vaccination at Birth to Low-Birth-Weight Children: Beneficial Nonspecific Effects in the Neonatal Period?

Peter Aaby,[1,2] Adam Roth,[3,6] Henrik Ravn,[3] Bitiguida Mutna Napirna,[2,a] Amabelia Rodrigues,[1] Ida Maria Lisse Lone Stensballe,[3] Birgitte Rode Diness,[1] Karen Rokkedal Lausch,[1] Najaaraq Lund,[1] Sofie Biering-Sørensen,[1] Hilton Whittle,[5] and Christine Stabell Benn[1,3]

Ateş
Solunum yolu enfeksiyonları
Sepsis

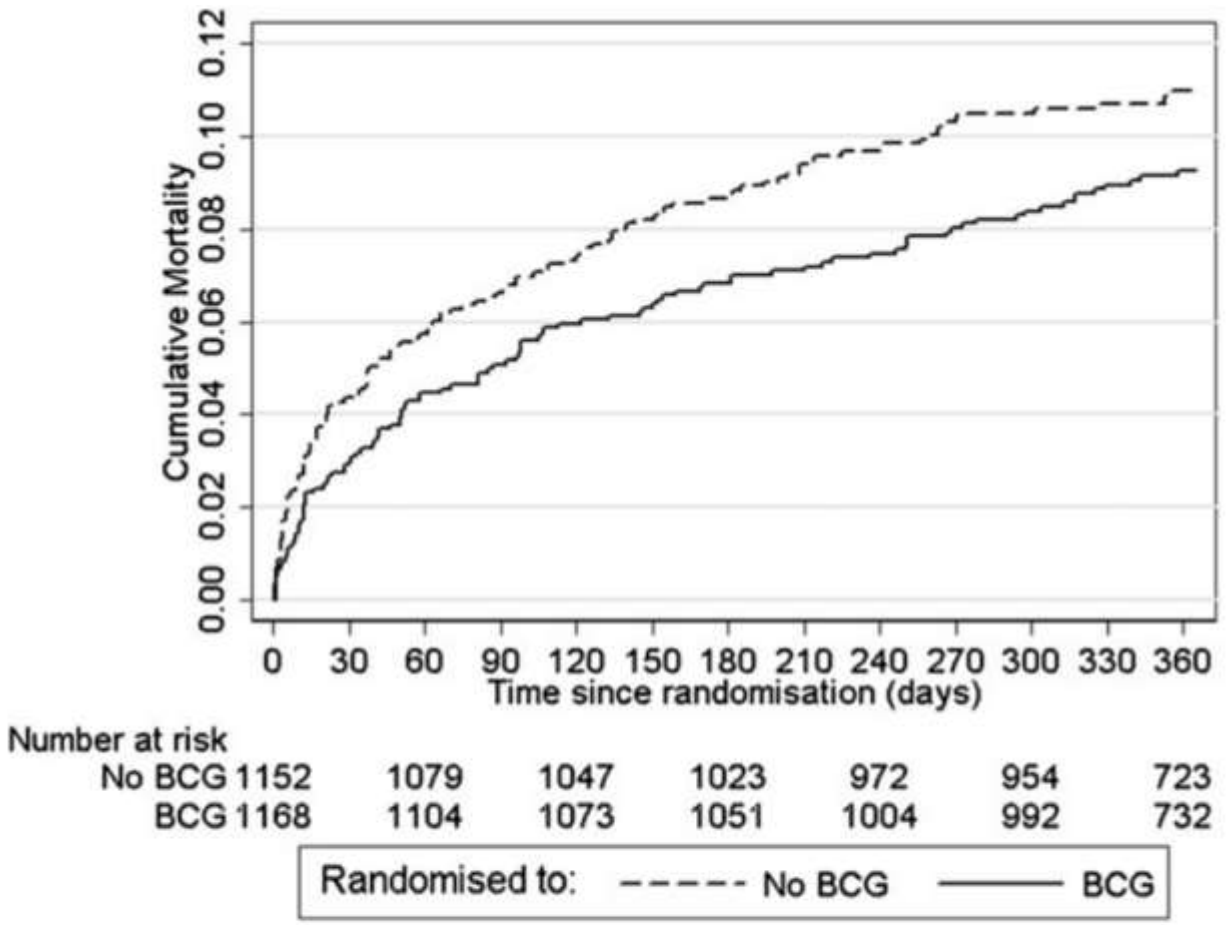
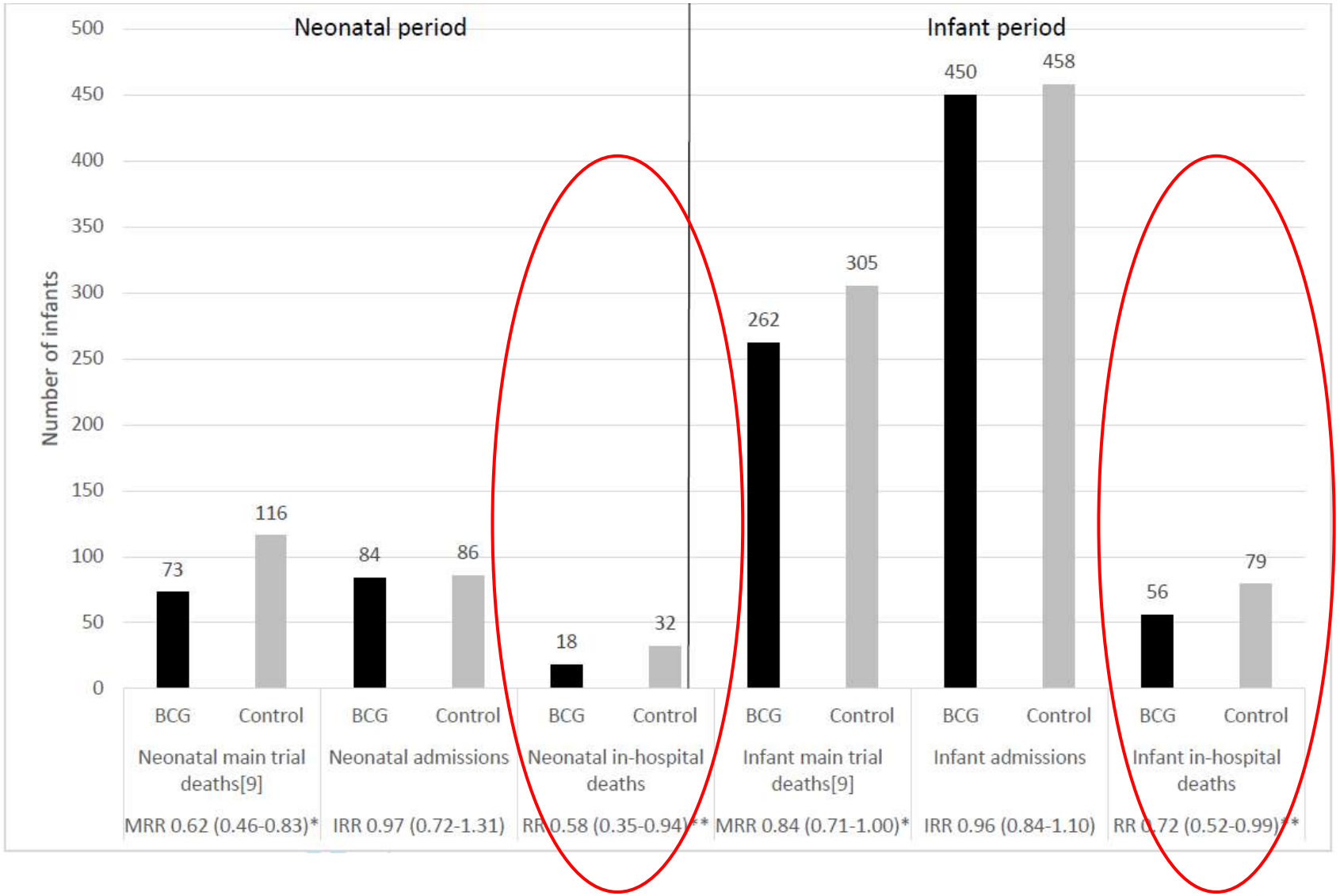
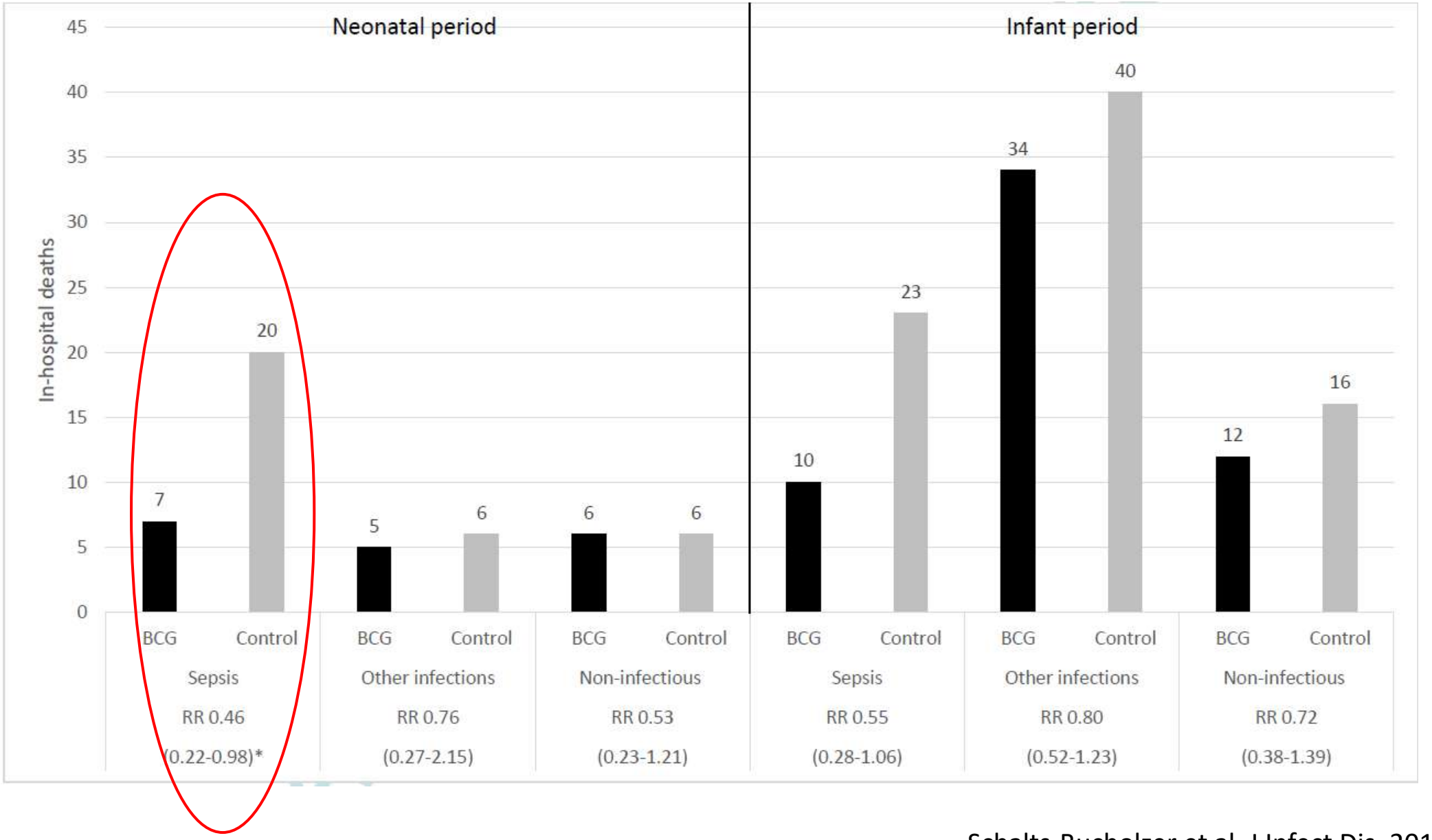


Figure 2. Cumulative mortality curves during the first year of life according to randomization group.

Figure 3. Mortality, hospitalization and in-hospital mortality across the three RCTs of BCG versus no BCG



Schalts-Bucholzer et al. J Infect Dis. 2019.



Schalts-Bucholzer et al. J Infect Dis. 2019.

REVIEWS

The mechanism of action of BCG therapy for bladder cancer—a current perspective

Gil Redelman-Sidi, Michael S. Glickman and Bernard H. Bochner

Abstract | Bacillus Calmette–Guérin (BCG) has been used to treat non-muscle-invasive bladder cancer for more than 30 years. It is one of the most successful biotherapies for cancer in use. Despite long clinical experience with BCG, the mechanism of its therapeutic effect is still under investigation. Available evidence suggests that urothelial cells (including bladder cancer cells themselves) and cells of the immune system both have crucial roles in the therapeutic antitumour effect of BCG. The possible involvement of bladder cancer cells includes attachment and internalization of BCG, secretion of cytokines and chemokines, and presentation of BCG and/or cancer cell antigens to cells of the immune system. Immune system cell subsets that have potential roles in BCG therapy include $CD4^+$ and $CD8^+$ lymphocytes, natural killer cells, granulocytes, macrophages, and dendritic cells. Bladder cancer cells are killed through direct cytotoxicity by these cells, by secretion of soluble factors such as TRAIL (tumour necrosis factor-related apoptosis-inducing ligand), and, to some degree, by the direct action of BCG. Several gaps still exist in our knowledge that should be addressed in future efforts to understand this biotherapy of cancer.

Redelman-Sidi, G. *et al. Nat. Rev. Urol.* **11**, 153–162 (2014); published online 4 February 2014; doi:10.1038/nrurol.2014.15

Yaklaşık 40 yıldır, kas invazyonu göstermeyen mesane kanserlerinde primer immünoterapi ajanı kullanılmaktadır.

İmmün yanıt indükleme ve anti-tümör aktivitesi nedeniyle tedavi ve rekürrensin önlenmesinde etkin olarak kullanılmaktadır.

Redelman-Sidi, G. *et al. Nat. Rev. Urol.* 2014

M. Saadatian-Elahi et al. Vaccine, 2016

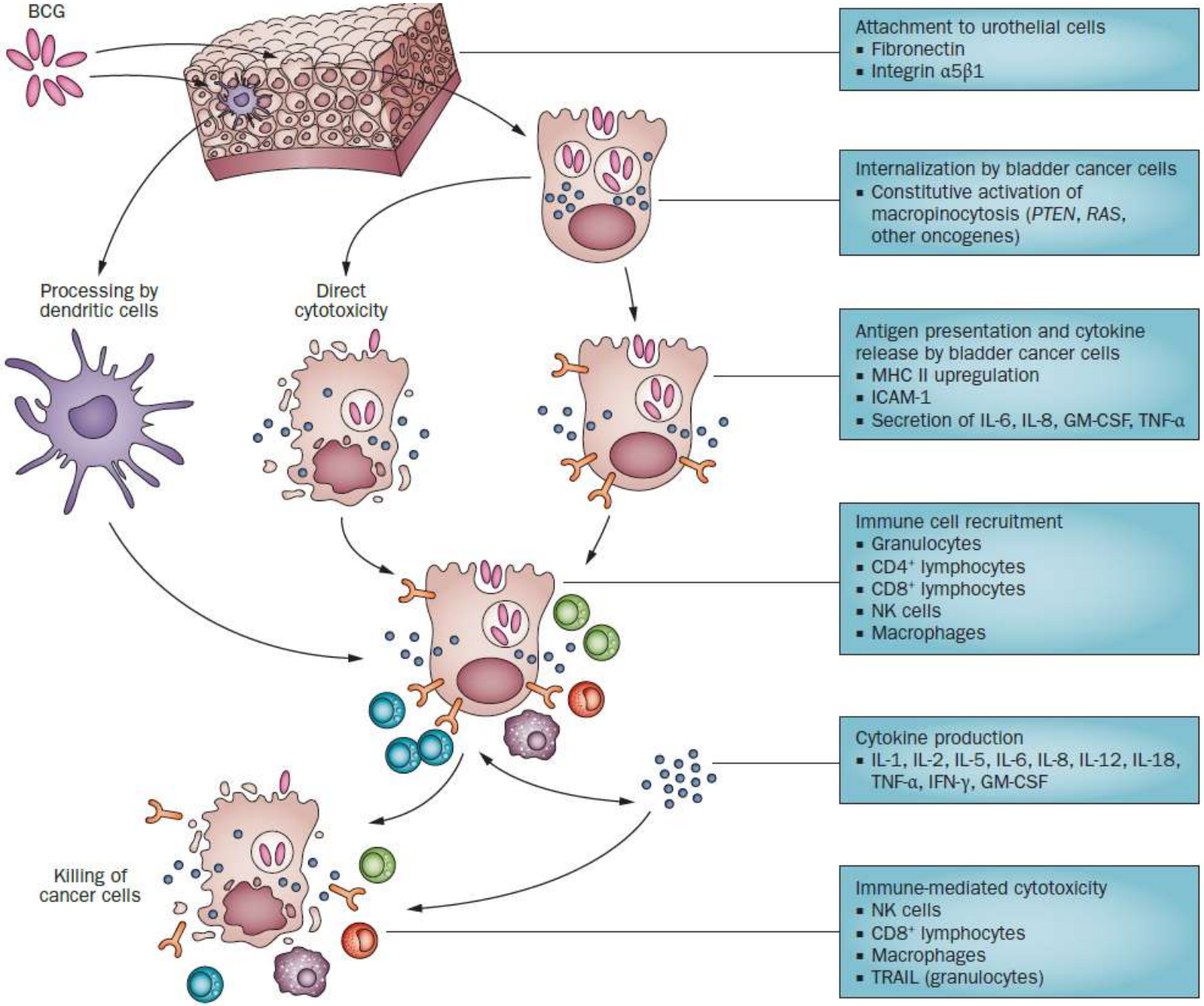


Figure 1 | Tentative model of the mechanism of action of BCG in bladder cancer. According to this model, live BCG attaches

Mortalitenin azaltılması
Solunum yolu enfeksiyonu ve sepsis nedeniyle hastane yatışlarının azaltılması
Mesane kanser tedavileri
Ekzama ve diğer alerjik hastalıklar
Otoimmün hastalıklar
İmmunmodülatör

Petra Zimmermann,Nigel Curtis *Expert Review of Vaccines,2018*

ARTICLE IN PRESS

Clinical Microbiology and Infection xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

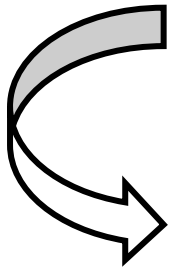
journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

Non-specific effects of BCG vaccine on viral infections

S.J.C.F.M. Moorlag [1, *], R.J.W. Arts [1], R. van Crevel [1], M

[1] Department of Internal Medicine, Radboud University Medical Centre, Nijmegen, the Net
[2] Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIM



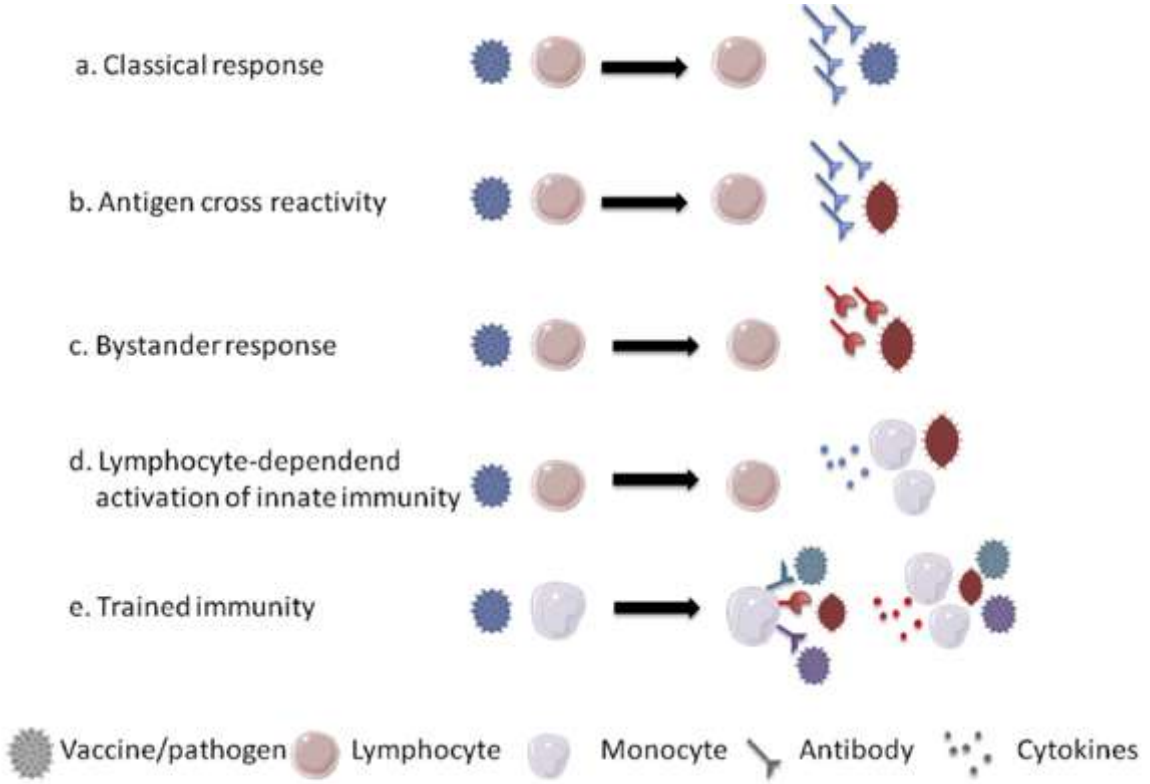


Fig. 1. Heterologous or non-specific effects of vaccination. (a) Classical vaccination response, which induces specific antibodies. (b) Antigen cross reactivity with cross-reactivation antibodies to related antigens on other pathogens. (c) Bystander response, with activation and antibody production by other lymphocytes. (d) Cytokines produced by lymphocytes after vaccination activate the innate immune system. (e) Trained immunity, with epigenetic and metabolic reprogramming of monocytes resulting in enhanced immune responses, such as enhanced cytokine and Reactive oxygen species (ROS) production, to related and non-related pathogens.

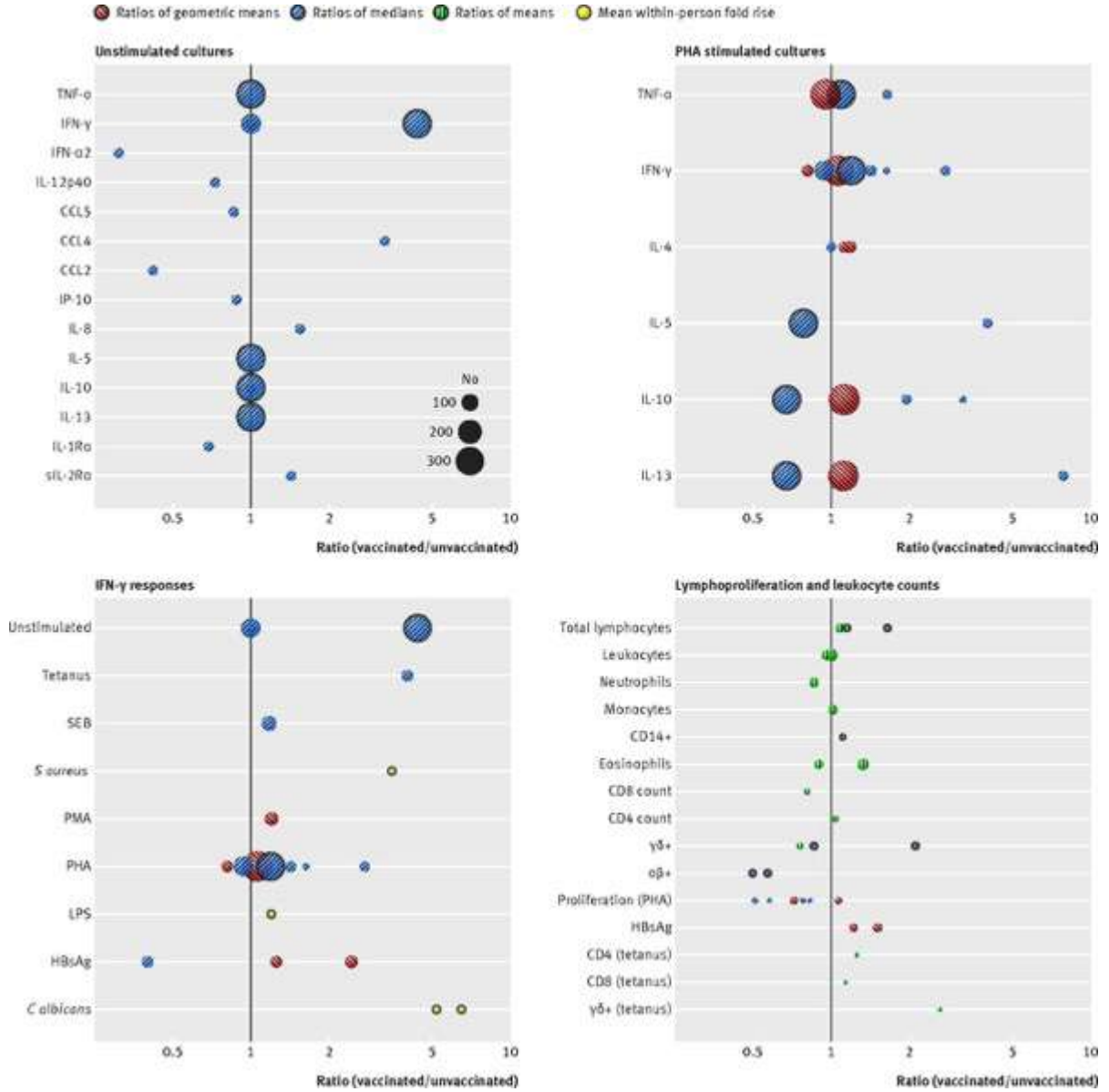
Fig 2 Non-specific immunological responses to BCG vaccination for unstimulated cultures, PHA stimulated cultures, IFN-γ responses, and lymphoproliferation and leukocyte counts from included BCG studies.

Proinflamatuar sitokin ⇧
Antiinlamatuar sitokin ⇩

IFN-γ ⇧

Nötrofil, CD8 lenfosit ⇩

CD4 lenfosit, monosit ⇧



Rama Kandasamy et al. BMJ 2016

Review

Cell PRESS

A small jab – a big effect: nonspecific immunomodulation by vaccines

Christine S. Benn[1], Mihai G. Netea[2], Liisa K. Selin[3], and Peter Aaby[4]

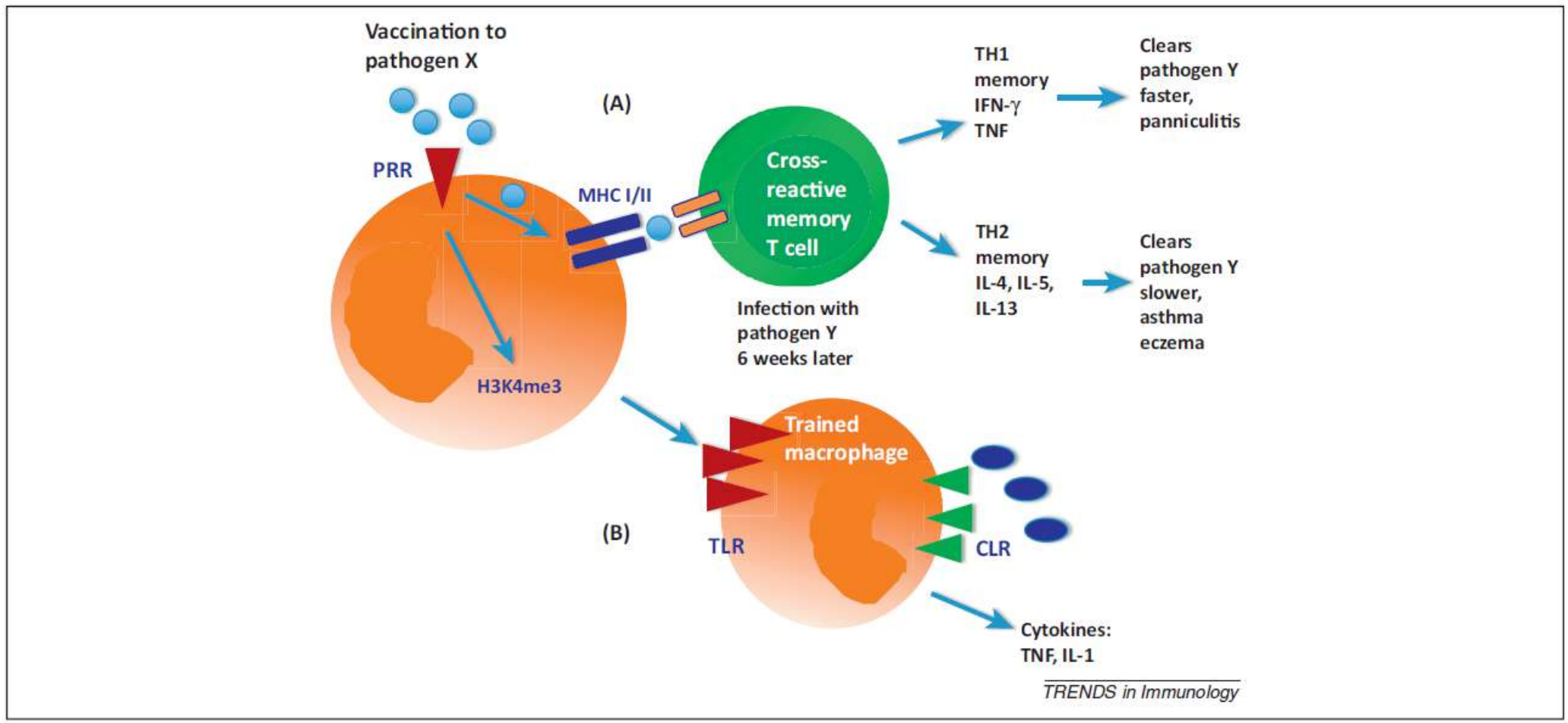


Table 1
Overview of non-specific effects of BCG vaccine described for various viral infections

	Virus	Study type	Effect of BCG	References
Human studies	Yellow fever vaccine	RCT	Reduced yellow fever vaccine titres correlating with IL-1β	Arts et al. [42]
	HPV	RCT		
		Case series		
		Case series		
	RSV	Case–control study		
	Influenza A (H1N1)	RCT		
	HSV	Case series		
		Case series		
Animal studies	HSV 1	CD-1 mice		
	HSV 2	—		
		CD-1 mice		
	Influenza A	—		
		C57Bl/6 mice		
		CD-1 mice		
	Influenza A (H7N9)	BALB/c mice		
	Hepatitis B	C57Bl/6 mice		
	Japanese encephalitis	BALB/c mice		
	Encephalomyocarditis virus	C57B1/10		
	Ectromelia virus	DDN mice		
		DDN mice		
	Vaccinia	BALB/c mice		
		C57Bl/6 mice		

Strain of mice unknown; BCG, Bacillus Calmette–Guérin; IL, interleuki
virus; MDP, muramyl dipeptide; RSV, randomized controlled trial.

Viral enfeksiyonlara karşı koruma

Lantent virüs reaktivasyonu engelleme

Viral baskılama (yeni aşı çalışmaları)

Viral enfeksiyon ilişkili morbidite ve mortalitenin azaltılması

Moorlag et al.Clinical Microbiology and Infection ,2019

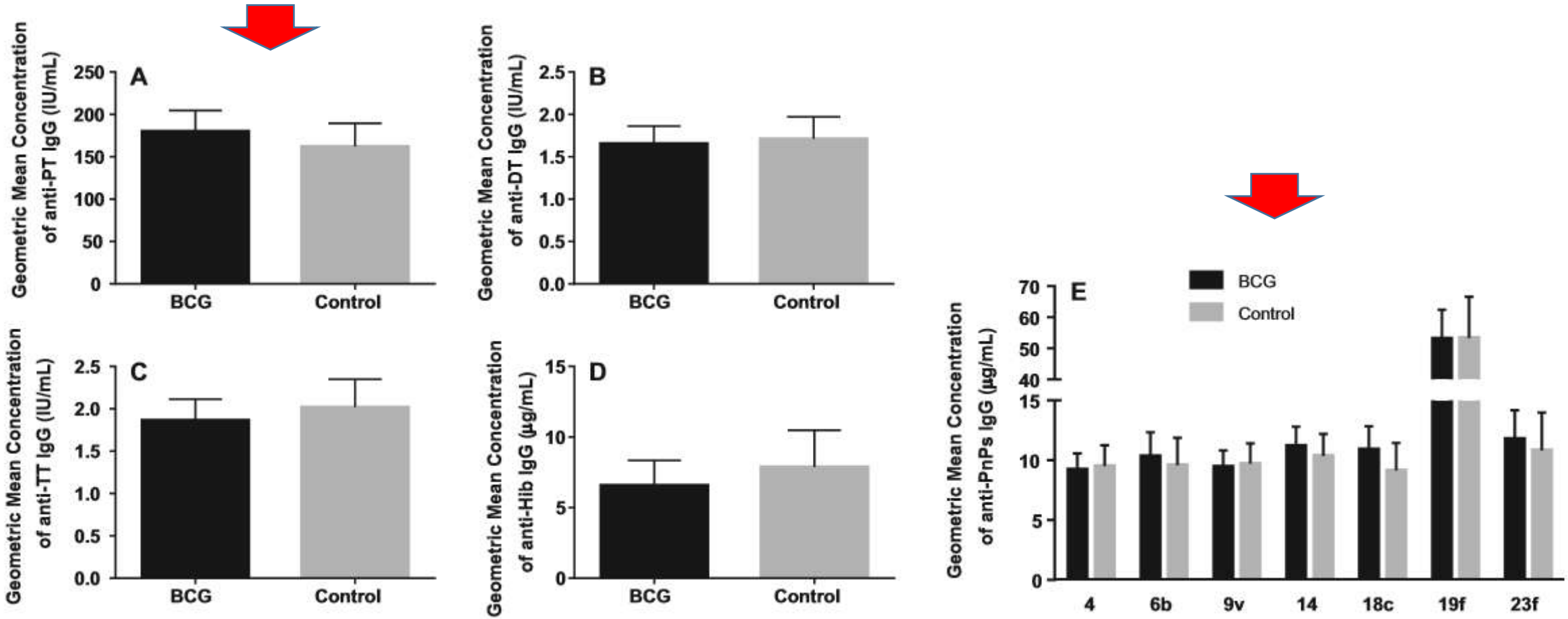


Fig. 1. Geometric mean concentrations (GMCs) of antibodies against A: anti-pertussis toxin (anti-PT), B: anti-diphtheria toxin (anti-DT), C: anti-tetanus toxin (anti-TT), D: anti-haemophilus influenzae type b, E: pneumococcal capsular polysaccharide antigens (anti-Pn Ps IgG) for each pneumococcal serotype. Error bars depict 95% CI.

Expert Review of Vaccines

ISSN: 1476-0584 (Print) 1744-8395 (Online) Journal homepage: http://www.tandfonline.com/loi/ierv20

The influence of BCG on vaccine responses – a systematic review

Petra Zimmermann & Nigel Curtis

Diğer aşılar öncesinde veya eş zamanlı uygulanan BCG aşısı diğer aşılara immün yanıtı artırmaktadır .

(Hepatit B, polio, pnömokok ve influenza)

Aşı etkinliği ve koruyuculuk süresinin geliştirilmesi için **BCG suşu** ve **optimal zamanlama** konusunda çalışmalara ihtiyaç vardır.

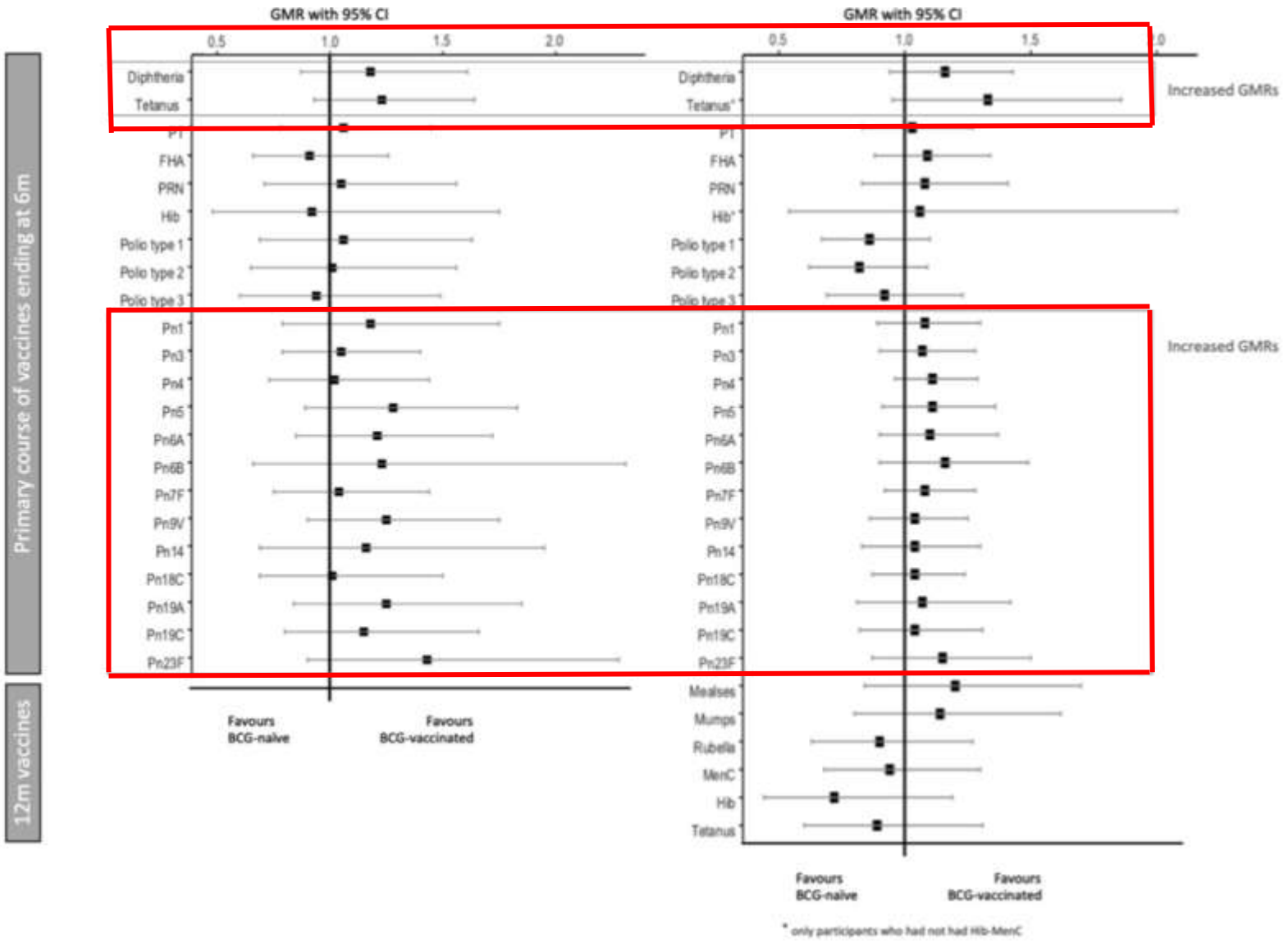
EDITORIAL COMMENTARY

Different Strains of Bacillus Calmette–Guérin Vaccine Have Very Different Effects on Tuberculosis and on Unrelated Infections

Frank Shann

Department of Paediatrics, Intensive Care Unit, Royal Children's Hospital, University of Melbourne, Parkville, Australia

Farklı aşı suşların kullanılması (± üretim farklılıkları) ile spesifik ve non - spesifik etkilerin değişkenlik gösterebileceği belirtilmektedir.



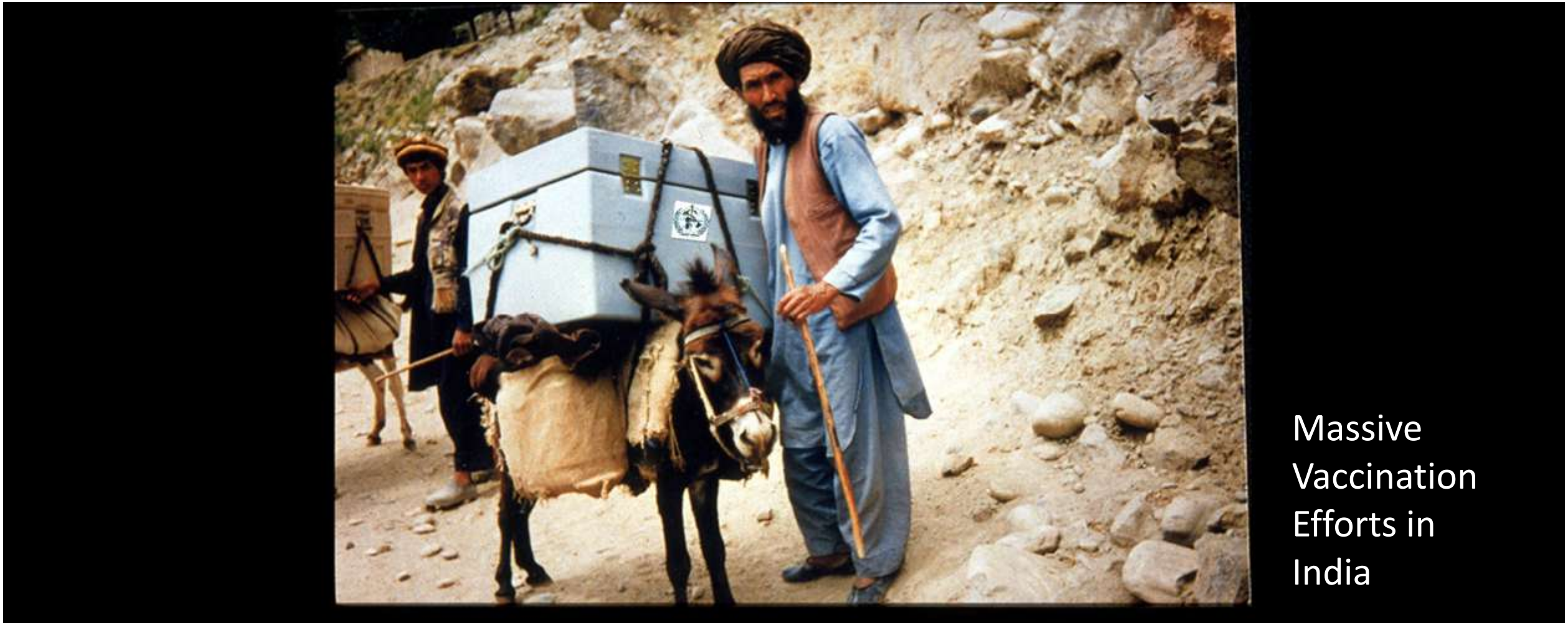
Zimmermann et al. Vaccine,2019

BCG uygulanması ile Difteri, tetanoz aşı yanıtı ⇧

BCG uygulanması ile pnömokok aşı yanıtı ⇧

Yaşamın ilk günü uygulanan aşıda etki belirgin

Kızamık Aşılaması



Çocukluk döneminde (3 veya 5 yıla kadar) % 30-86 arasında değişen mortalite azalmasına neden olduğu gösterilmiştir.

Table 2
Mortality rate ratios for measles-vaccinated and measles-unvaccinated children with and without measles cases/measles deaths in the survival analysis

Study	Design; age at vaccination; who compared; follow-up period	Vaccine efficacy against death (95% CI)	
		Including measles cases in survival analysis	Excluding measles cases in survival analysis
Bissau, 'Natural experiment' [16]	7–24 month; effective MV vs ineffective MV; 24 months	67% (3–89%)	35% (−162 to 84%)
Guinea-Bissau [19]	9–23; vaccinated vs unvaccinated in same area; 19 months	64% (37–79%)	65% (35–81%)
Senegal [17]	9–18 months; vaccinated vs unvaccinated same area; 23 months	40% (19–55%)	40% (18–55%)
Burundi [18]	9–23 months; vaccinated vs unvaccinated same community	75% (55–86%)	74% (48–87%)

CI, confidence interval; MV, measles vaccine.

P. Aaby, C.S. Benn. Clinical Microbiology and Infection,2019

MMR uygulanması ile **hedeflenen enfeksiyon dışı enfeksiyon gelişiminin** (özellikle alt solunum yolu enfeksiyonları) ve **ilişkili hastane yatış sıklıklarının** azaltıldığı gösterilmiştir.

Barbara H Bardenheier et al. Clin Infect Dis. 2017

Doğal bağışıklık üzerine etkileri (induction Trained-innate immune memory)

Kızamık ilişkili immun baskılanma ve immun amnezinin engellenmesi

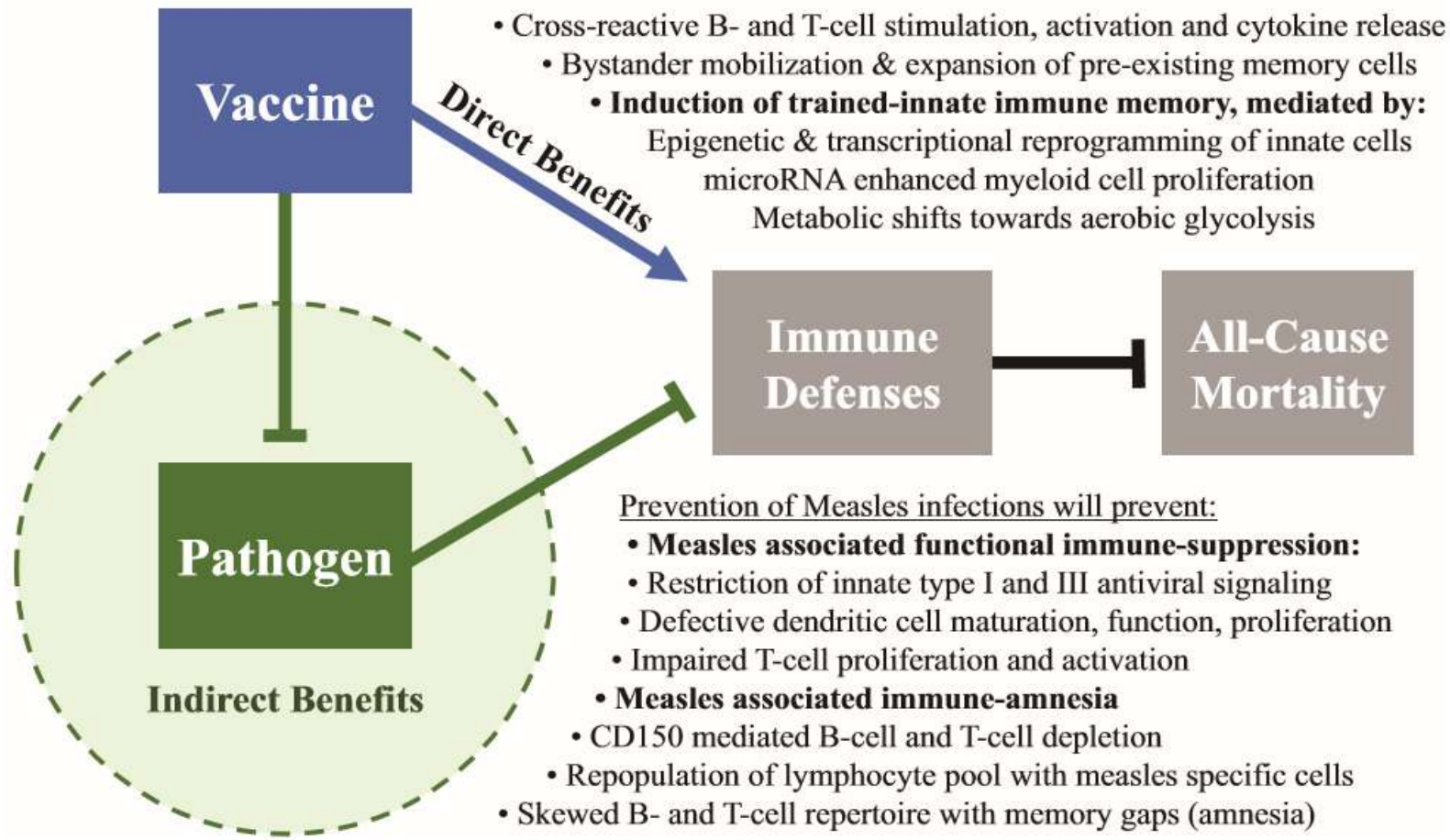


Figure 1 Direct and indirect benefits of measles vaccination.

Mina Mj.J Infect Dis. 2017

Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines

Higgins JPT, Soares-Weiser K, Reingold A

13 March 2014

Kızamık Aşılaması
Tüm nedenlerden kaynaklanan ölüm sıklıklarında azalmaya neden **olabilir.**
Kadın cinsiyette etki daha belirgin saptanmıştır.
Eş zamanlı veya sonrasında DTP uygulanmasının etkiyi azaltabileceği belirtilmektedir.
A vitamin düzeyinin etkinlik üzerine etkisi gösterilememiştir.

Kızamık aşısı ile elde edilebilecek non-spesifik etkinin, **MMR sonrası inaktive** aşı uygulanması veya **inaktive/canlı aşının birlikte** uygulanması ile azaldığı belirtilmektedir.

Aşı şemalarının gözden geçirilmesi mi gerekli?

S. Sørup et al. Vaccine 2016 S. Sørup et al. JAMA, 2014

Table 2. Risk of bias summary applying ROBINS-I.

ROBINS-I risk of bias	Sorup et al., 2014	Sorup et al., 2015	Sorup et al., 2016	Tielemanns et al., 2017	Bardenheier et al., 2017
Bias due to confounding	Critical	Serious	Serious	Critical	Serious
Bias in selection of participants into the study	Low	Low	Low	Low	Low
Bias in classification of interventions	Moderate	Moderate	Moderate	Moderate	Moderate
Bias due to deviations from intended interventions	Low	Low	Low	Low	Low
Bias due to missing data	Low	Low	Low	Low	Low
Bias in measurement of outcome	Moderate	Moderate	Moderate	Moderate	Moderate
Bias in selection of the reported result	Low	Low	Low	Low	Low
Overall risk of Bias	Critical	Serious	Serious	Critical	Serious

Kontrol grubunda da azalma

Müdahale ve kontrol grupları arasındaki eşitsizlik

A. X. Sınzınger Et Al. Human Vaccınes & Immunotherapeutıcs, 2019

HUMAN VACCINES & IMMUNOTHERAPEUTICS
https://doi.org/10.1080/21645515.2019.1663119

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Non-specific effects of MMR vaccines on infectious disease related hospitalizations during the second year of life in high-income countries: a systematic review and meta-analysis

Andrea Xaver Sinzinger [a], Rüdiger Von Kries[a], Anette Siedler[b], Ole Wichmann[b], and Thomas Harder[b]

[a]Institute of Social Paediatrics and Adolescents Medicine, Division of Epidemiology, Ludwig-Maximilians-University Munich, Munich, Germany; [b]Immunization Unit, Robert Koch Institute, Berlin, Germany

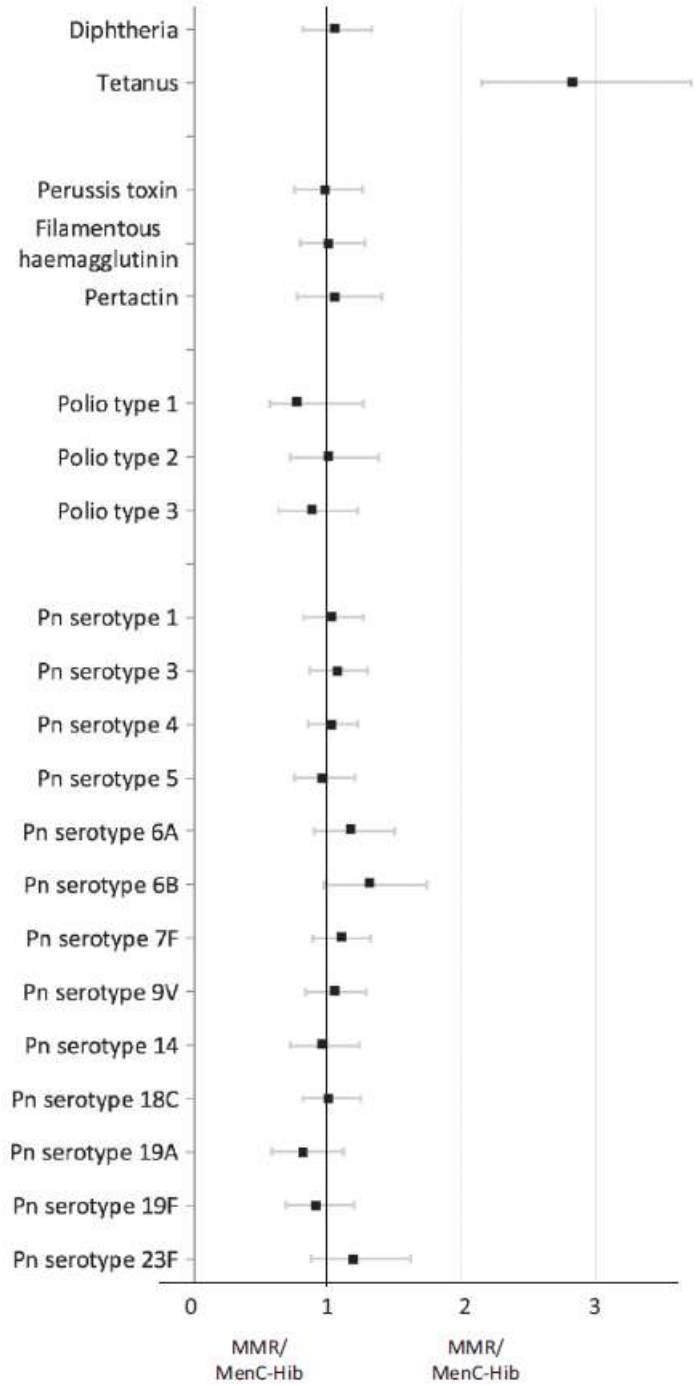
ABSTRACT

Children who had received MMR as the most recent vaccine had a pooled 35% (95%CI: 12–53%) lower risk for hospitalization due to any infectious disease, compared to children who had received DTaP as the most recent vaccine (three studies, 1,919,192 children). The effect was stronger for respiratory tract infections than for gastrointestinal infections. Two studies investigated MMR alone, compared to concurrent administration of MMR and DTaP vaccines. Here, the pooled estimate for reduction in risk of hospitalization for any infectious disease was smaller and not significant (15%; 95%CI: −9% to 34%). Risk of bias was serious to critical in all studies. Moreover, two of the five studies demonstrated a significantly reduced risk for a control outcome (hospitalization for injuries), strongly indicating healthy vaccinee bias or residual confounding. The available evidence is insufficient to support a change in current vaccination schedules.

ARTICLE HISTORY
Received 16 April 2019
Revised 12 August 2019
Accepted 26 August 2019

KEYWORDS
Non-specific effects of vaccines; MMR; DTaP; Review; child hospitalization; high-income countries

Mevcut kanıt düzeyi güncel aşı şemalarını değiştirmek için yetersiz



MMR/ Hib + MenC aşısının aşı yanıtları üzerine etkisi var mı?

Tetanoz dışında diğer aşılar ile elde edilen antikor yanıtlarında bir farklılık saptanmamıştır.

Petra zimmermann et al., Immunology & Cell Biology 2019

Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

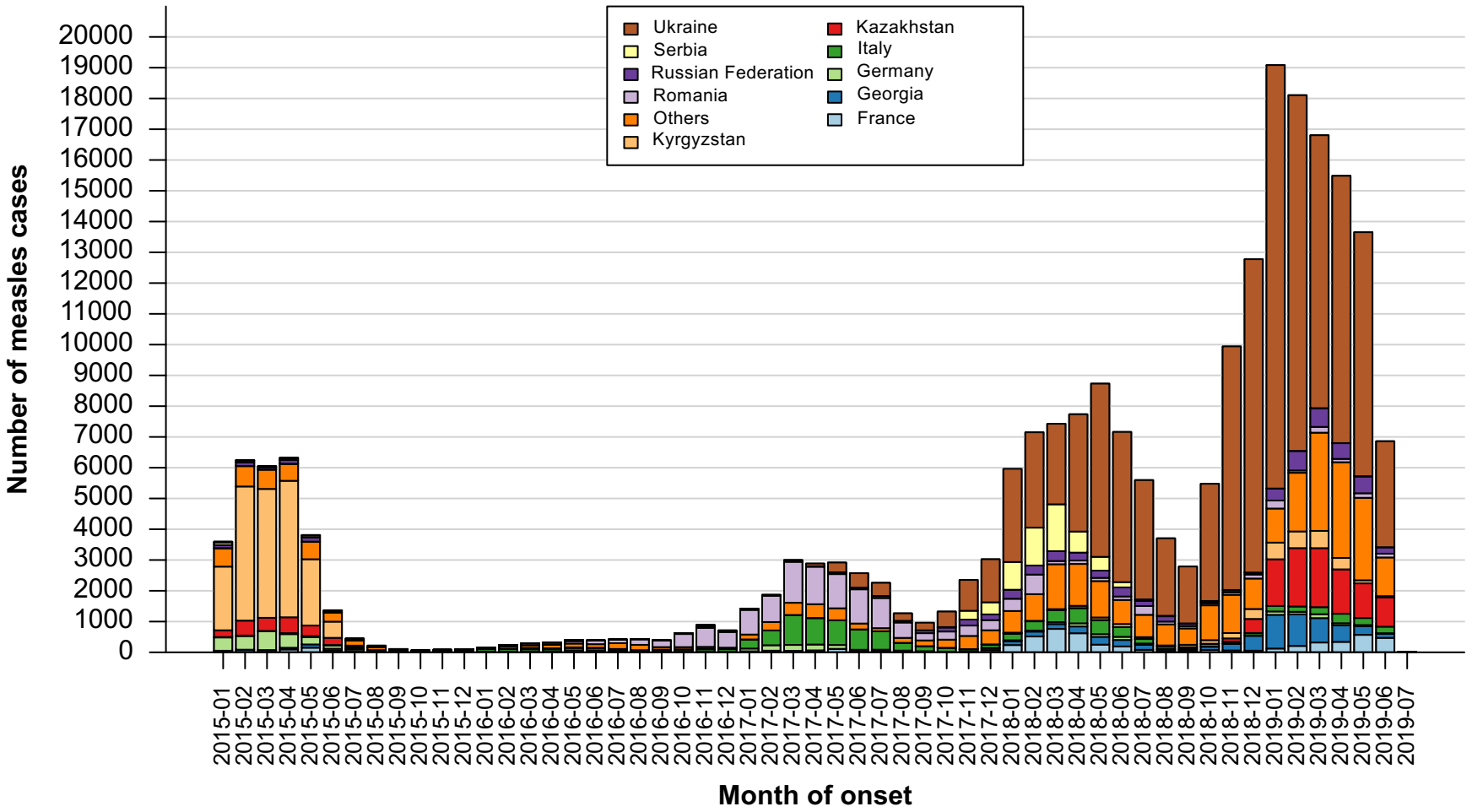
journal homepage: www.elsevier.com/locate/vaccine

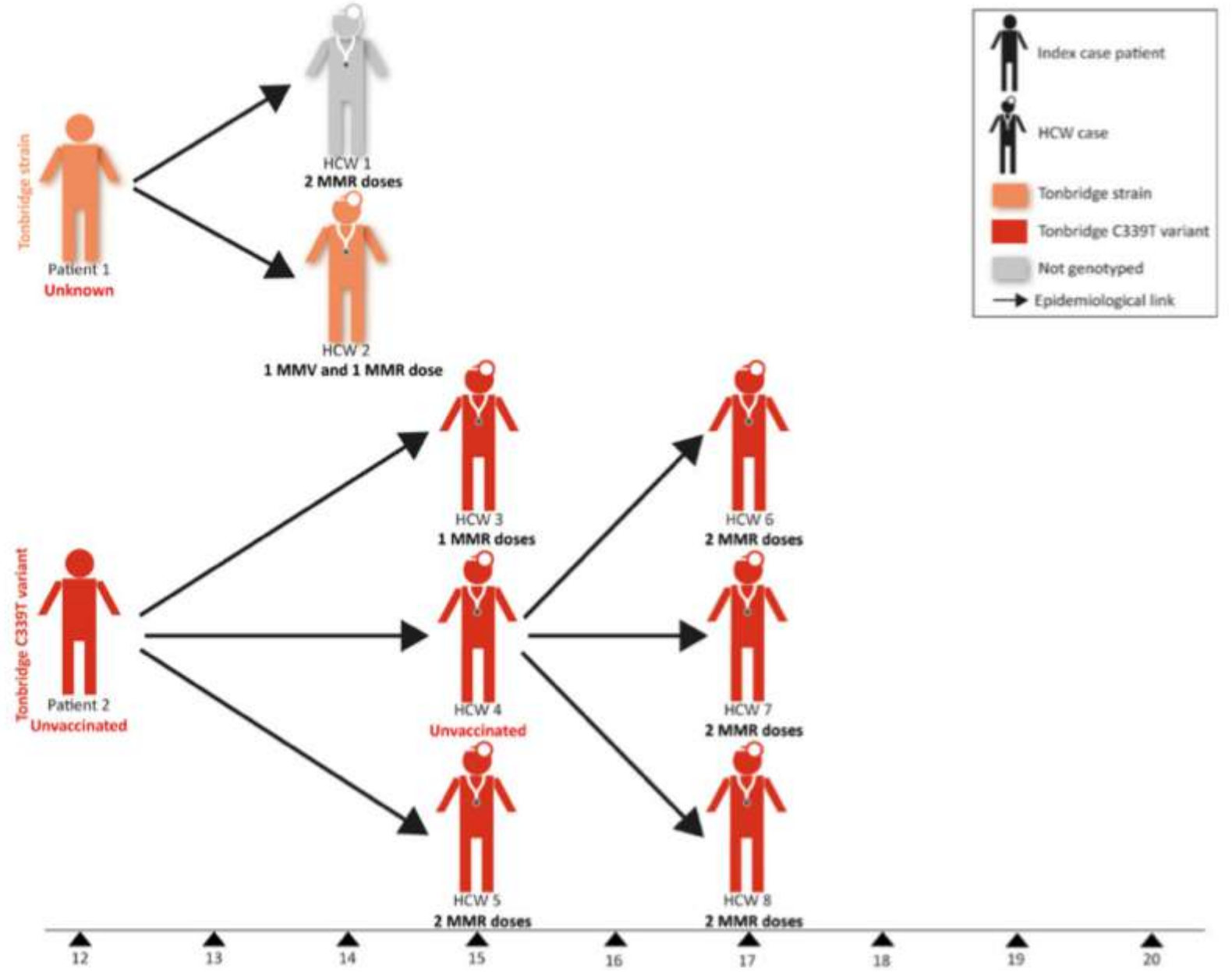
The risk of non-specific hospitalised infections following MMR vaccination given with and without inactivated vaccines in the second year of life. Comparative self–controlled case-series study in England

Nick Andrews [a,*], Julia Stowe [c], Sara L. Thomas [b], Jemma L. Walker [a,b], Elizabeth Miller [c]

MMR aşısının tek başına uygulanması ve/veya inaktive aşılar (Hib/MenC/PVC) ile birlikte uygulanmasının non-spesifik enfeksiyon gelişimine etkisi saptanmamıştır.

İnaktive aşı uygulamaların non-spesifik enfeksiyon sıklığını artırıcı bir etkisi saptanmamıştır.


Ukraine
Serbia
Russian Federation
Romania
Others
Kyrgyzstan
Kazakhstan
Italy
Germany
Georgia
France
Number of measles cases
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2015-01
2015-02
2015-03
2015-04
2015-05
2015-06
2015-07
2015-08
2015-09
2015-10
2015-11
2015-12
2016-01
2016-02
2016-03
2016-04
2016-05
2016-06
2016-07
2016-08
2016-09
2016-10
2016-11
2016-12
2017-01
2017-02
2017-03
2017-04
2017-05
2017-06
2017-07
2017-08
2017-09
2017-10
2017-11
2017-12
2018-01
2018-02
2018-03
2018-04
2018-05
2018-06
2018-07
2018-08
2018-09
2018-10
2018-11
2018-12
2019-01
2019-02
2019-03
2019-04
2019-05
2019-06
2019-07
Month of onset



Daha önce aşılananlarda;

-Ağır vaka yok

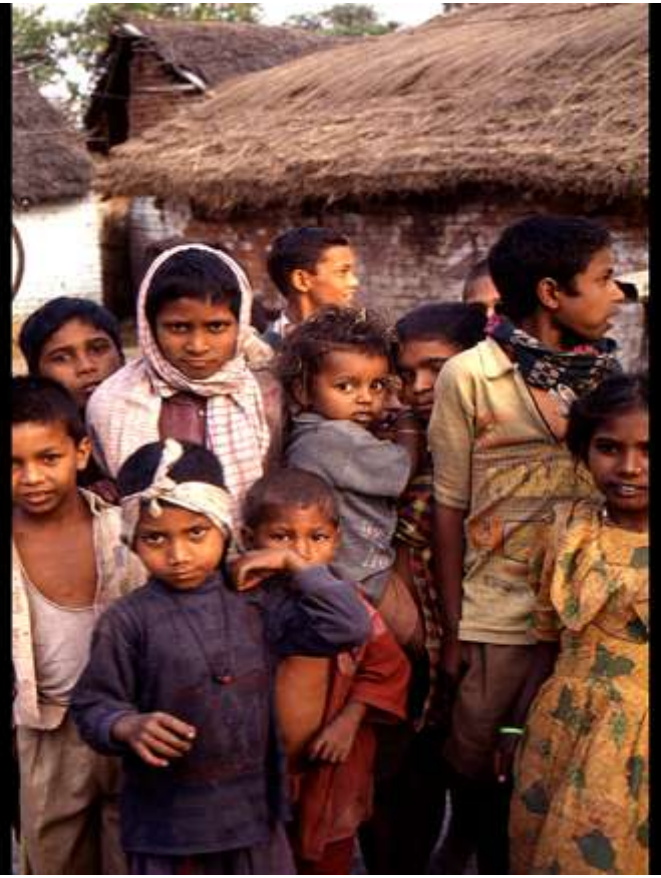
-Virus yayılımına neden olmadılar

Salgının sınırlı olmasını sağladılar

Susan J. M. Hahné et al. JID 2016

Luojun Yang et al. European Journal of Epidemiology

Oral polio aşılaması



Children waiting to be vaccinated against polio in 2000 during a Stop Polio Transmission campaign

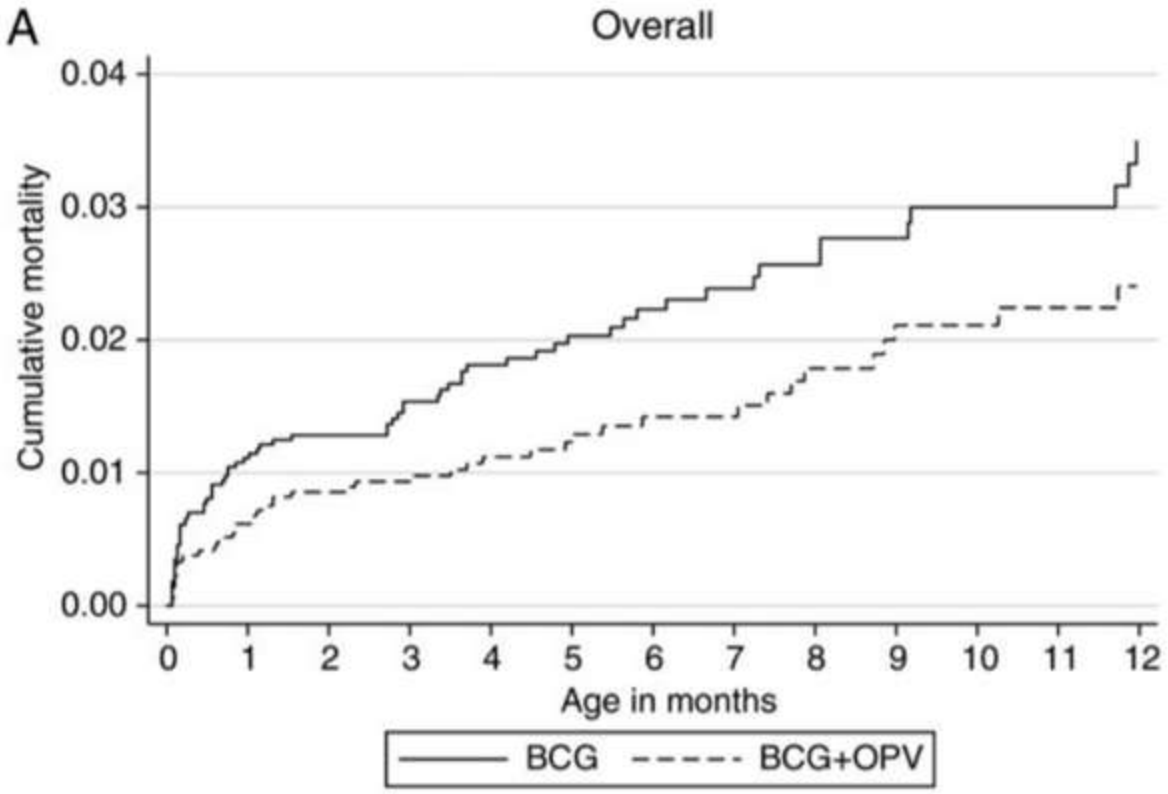
MAJOR ARTICLE

The Effect of Oral Polio Vaccine at Birth on Infant Mortality: A Randomized Trial

Najaaraq Lund,[1,2] Andreas Andersen,[1] Anna Sofie K. Hansen,[3] Frida S. Jepsen,[3] Amarildo Barbosa,[3] Sofie Biering-Sørensen,[3] Amabelia Rodrigues,[3] Henrik Ravn,[1,4] Peter Aaby,[1,3] and Christine Stabell Benn[1,4]

[1]Research Center for Vitamins and Vaccines, Statens Serum Institut, Copenhagen, and [2]Department of Pediatrics, Kolding Hospital/University of Sou Denmark, Kolding; [3]Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau; and [4]Institute of Clinical Research, University of Southern Den Odense University Hospital

Oral Polio Aşılaması
Oral polio aşılaması **mortalite azalmasına** neden olmaktadır.
Etki **yaşamın ilk günlerinde** uygulandığında belirgindir.
Etki **erkek cinsiyette** daha belirgindir.



frontiers in Public Health

ORIGINAL RESEARCH
published: 02 February 2018
doi: 10.3389/fpubh.2018.00013

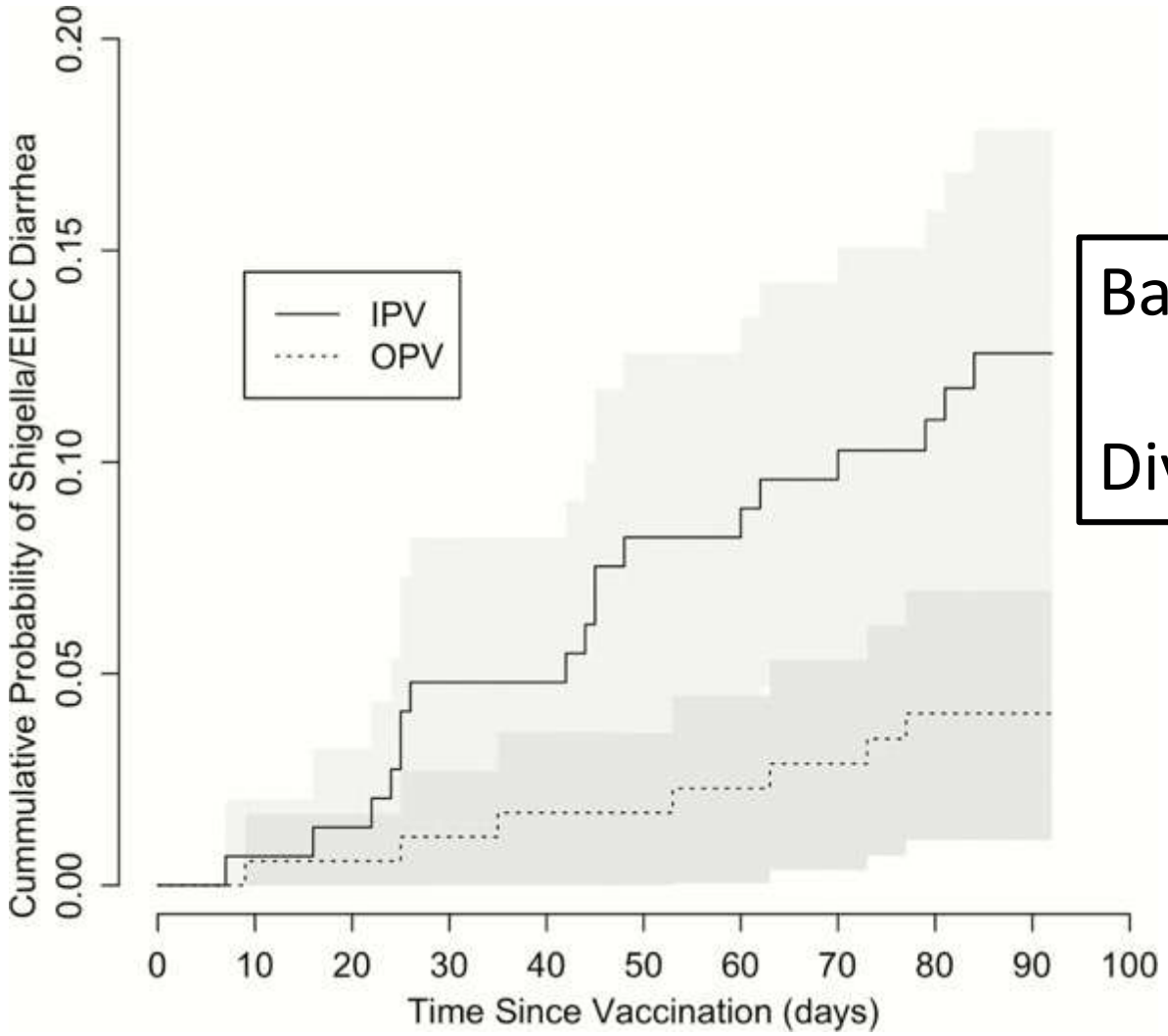
National Immunization Campaigns with Oral Polio Vaccine Reduce All-Cause Mortality: A Natural Experiment within Seven Randomized Trials

*Andreas Andersen[†], Ane Baerent Fisker[†], Amabelia Rodrigues[2], Cesario Martins[2], Henrik Ravn[1,3], Najaaraq Lund[1], Sofie Biering-Sørensen[1], Christine Stabell Benn[1,3] and Peter Aaby[1,2,3]**

Mortalite (Aşılı/aşısız; 0.81, 0.68-0.95) ⇩

Her booster dozda mortalite azalması ⇩

(0.87 (95% CI: 0.79–0.96)



Bakteriyel etkenlerle gelişen diyare ⇩

Diyare süresi ⇩

Alexander Upfill-Brown et al. CID 2017:65

Canlı olmayan aşılar (**DTP**, kuduz) ve **non-spesifik etkileri**

Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines

Higgins JPT, Soares-Weiser K, Reingold A

13 March 2014

DTP aşılaması
Genel mortaliteye etkisinin tartışılması için yeterli veri **yoktur.** (10 Gözlemsel çalışma meta-analiz)

DTP aşısı uygulanmayan grup (kadın cinsiyet) ile karşılaştırıldığında mortalite artışına neden olmaktadır.(HR: 2.56; 95% CI:1.74–3.76)

Table 1
Systematic review of the sequence/order of DTP, BCG and MV vaccination and all-cause mortality in children: WHO Working-Group review [4].

Comparison (model)	Effect (95% CI)	I^2
BCG vs unvaccinated[a] (Random)	0.53 (0.40–0.72)	62%
DTP-after-BCG vs BCG[a,b] (Random)	1.38 (0.92–2.08)	71%
MV-after-DTP vs DTP[a] (Random)	0.54 (0.45–0.64)	49%
DTP-after-BCG[a] vs DTP-with-BCG (Fixed)	1.92 (1.25–2.93)	0%
DTP-after BCG[a] vs BCG-after-DTP (Fixed)	1.37 (0.84–2.25)	0%
MV-with-DTP vs MV-after-DTP[a] (Fixed)	2.30 (1.56–3.38)	0%
DTP-after-MV vs MV-after-DTP[a] (Random)	2.66 (1.04–6.81)	57%

www.who.int/immunization/sage/meetings/2014/April/3_NSE_Epidemiology_review_Report_to_SAGE_14_Mar_FINAL.pdf.

[a] As in the WHO immunization schedule.

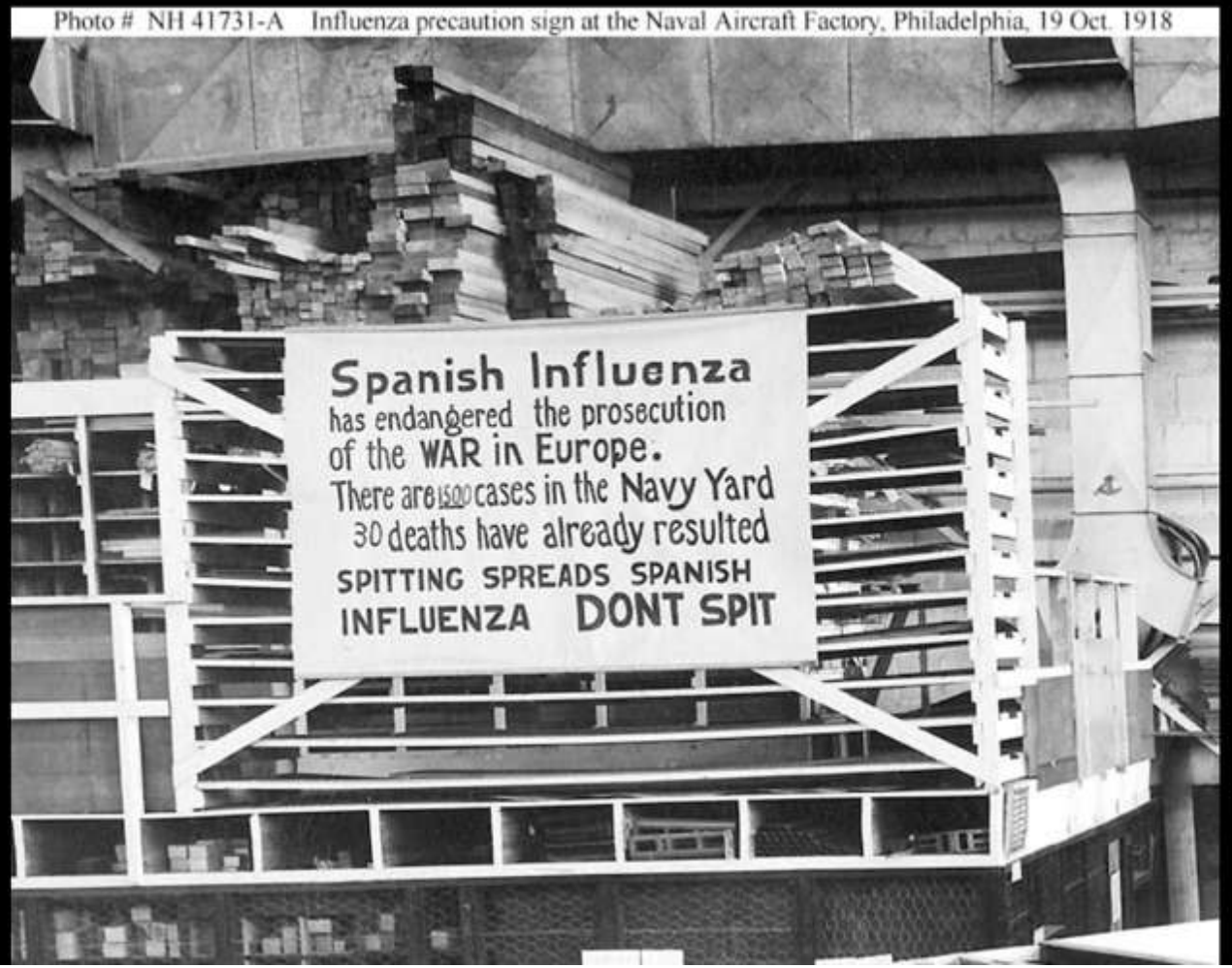
[b] Subsequent analysis excluding studies with a poorly-defined control group, severe frailty bias or severe survival bias gives an effect of 2.56 (95% CI 1.74–3.76) in girls.

P. Aaby, C.S. Benn. Clinical Microbiology and Infection,2019

Canlı aşıların faydalı non-spesifik etkileri varken, canlı olmayan aşıların ‘zararlı’ non-spesifik etkileri (özellikle kadın cinsiyet) vardır.

P. Aaby, C.S. Benn. Clinical Microbiology and Infection,2019

İnfluenza aşılaması



A sign warning about Spanish Influenza at the Naval Aircraft Factory, Philadelphia, Pennsylvania, on 19 October 1918.

MAJOR ARTICLE

Administration of $AS03_B$-adjuvanted A(H1N1)pdm09 Vaccine in Children Aged <3 Years Enhances Antibody Response to H3 and B Viruses Following a Single Dose of Trivalent Vaccine One Year Later

Katja Hoschler,[1] Nick J. Andrews,[1] Saul N. Faust,[2] Adam Finn,[3] Andrew J. Pollard,[4] Matthew D. Snape,[4] Woolf T. Walker,[2] Maria Zambon,[1] and Elizabeth Miller[1]

Canlı olmayan-Adjuvanlı-Monovalan H1N1 aşınının H3N2 ve influenza B için, aşıdan 1 yıl sonra, çapraz-reaktif bir antikor yanıtına neden olduğu gösterilmiştir.

VIRAL IMMUNOLOGY
Volume 32, Number 3, 2019

Pp. 1–13
DOI: 10.1089/vim.2018.0118

A Novel Role for PDZ-Binding Motif of Influenza A Virus Nonstructural Protein 1 in Regulation of Host Susceptibility to Postinfluenza Bacterial Superinfections

Kelly Shepardson,[1] Kyle Larson,[1] Hanbyul Cho,[1] Laura Logan Johns,[1] Zeynep Malkoc,[1] Kayla Stanek,[1] Julia Wellhman,[1] Sarah Zaiser,[2] Jaelyn Daggs-Olson,[2] Travis Moodie,[2] Joshua M. Klonoski,[2] Victor C. Huber,[2,*] and Agnieszka Rynda-Apple[1,*]

IFN yanıt modülasyonu
Makrofaj ve nötrofil aracılı bakteriyel klirensinin baskılanması Antimikrobial peptid salınımının inhibisyonu T ve NK hücre yanıtının baskılanması

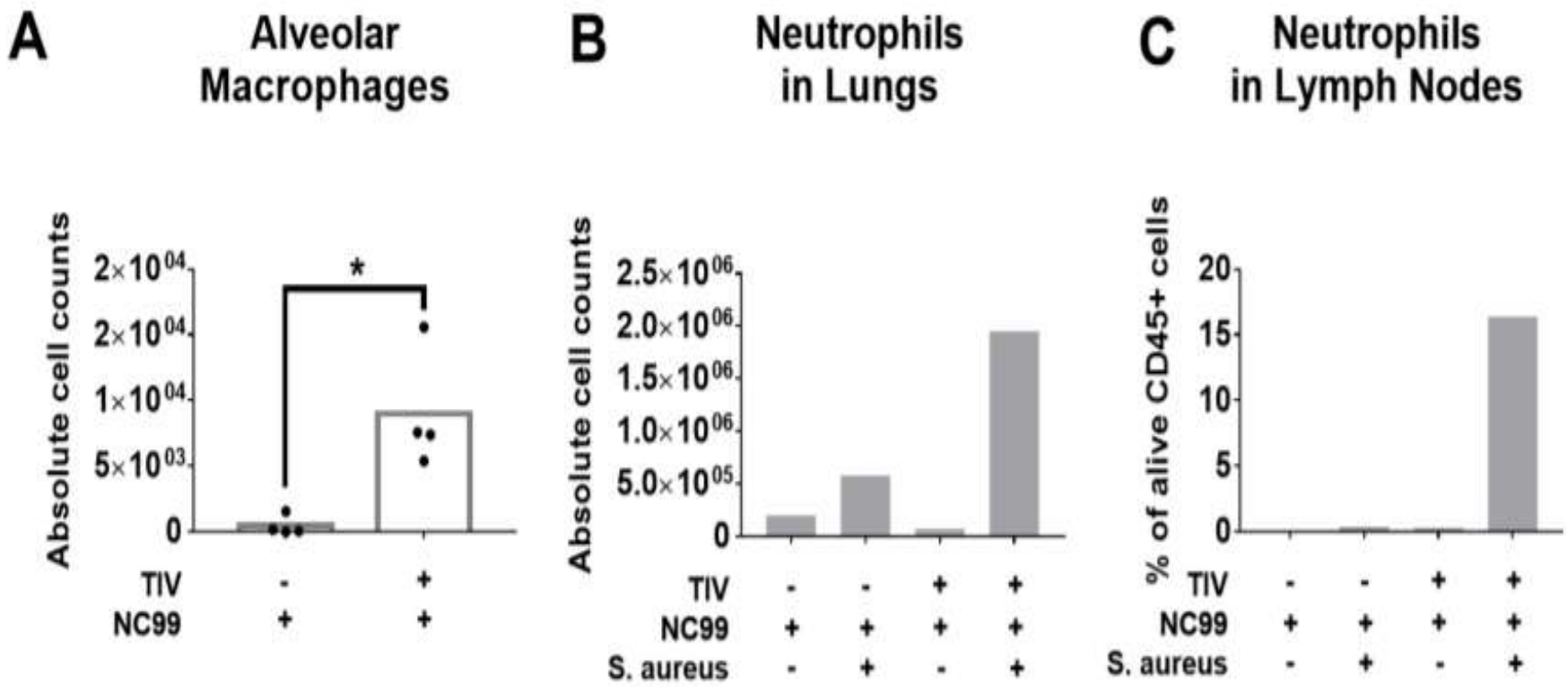


Figure 7. TIV vaccination affects levels of alveolar macrophages and neutrophils after NC99 H1N1 infection and bacterial superinfection (Experiment 1). (**A**) Absolute numbers of alveolar macrophages

Choi et al.Vaccines ,2019

Journal of Infection (2012) 65, 231–238

ELSEVIER

BIAM British Infection Association

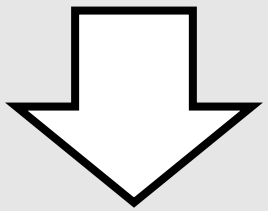
www.elsevierhealth.com/journals/jinf

Additive benefits of pneumococcal and influenza vaccines among elderly persons aged 75 years or older in Taiwan — A representative population-based comparative study

Yu-Chia Chang [a], Yiing-Jenq Chou [b], Jen-Yin Liu [a], Te-Feng Yeh [c], Nicole Huang [d,*]

Mortalite

Hastane yatış
(influenza, bakteriyel pnömoni, KOAH, kalp yetmezliği)



Hastane harcamaları

Kardiovasküler sistemi koruyan aşılar

İnfluenza Aşılaması
Kardiovasküler hastalık ilişkili mortalite azalma (RR 0.45; 95%CI 0.26–0.76)
Kardiak yetmezliği olan popülasyonda hastane yatış sıklığında azalma (RR 0.73; 95% CI 0.71–0.76)

A. Ciszewski et al. Vaccine 2018

Ren S et al. Open Heart 2015

Wu WC et al. Am Heart J2014

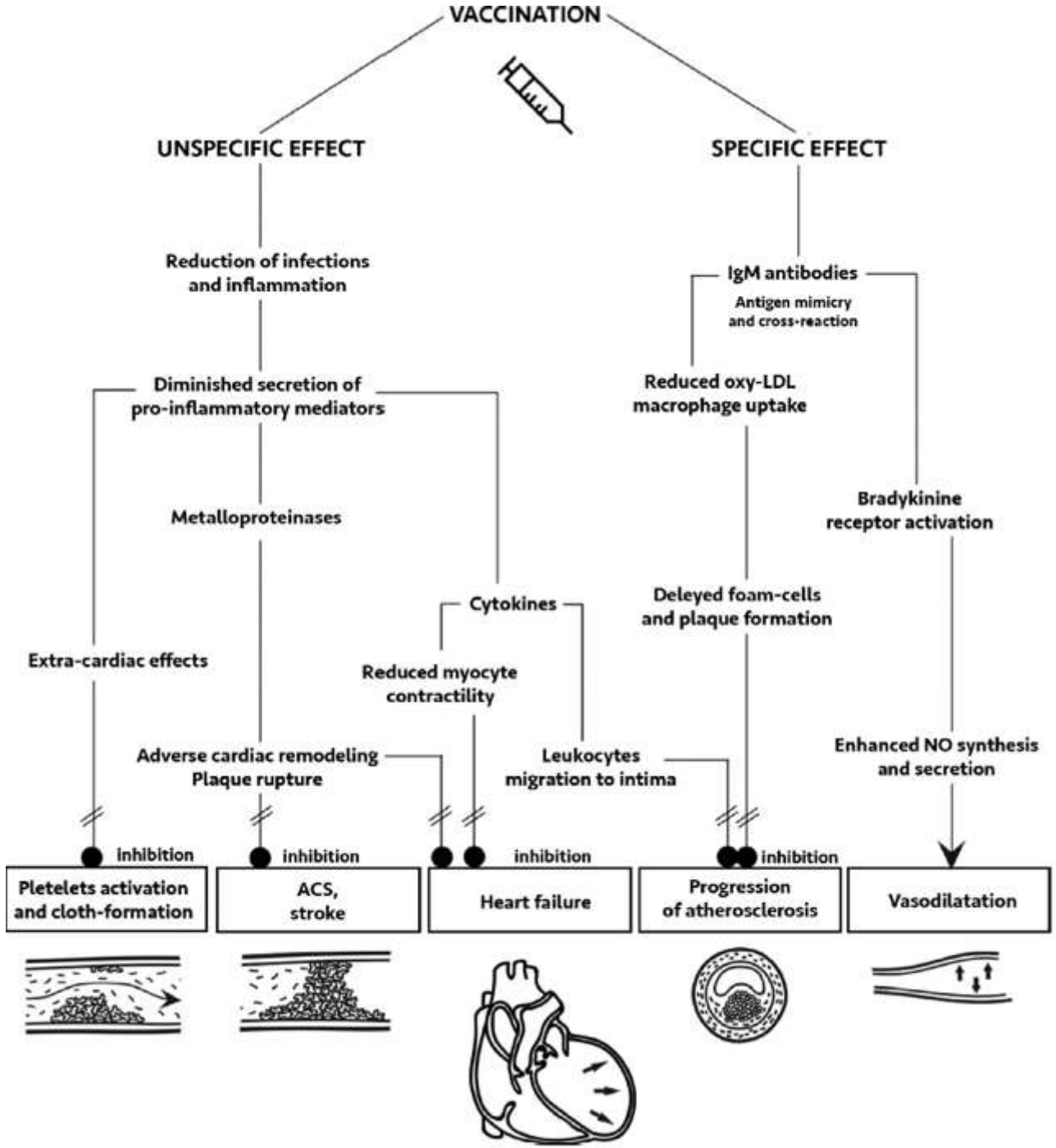
Kardiovasküler sistemi koruyan aşılar

Pnömokok Aşılaması

≥ 65 yaş üstü popülasyonda akut koroner sendrom riskinde azalma
(RR=0.83; 95% CI 0.71 to 0.97)

Kalp yetmezliği olan popülasyonda 1 yıllık mortalite sıklıklarında azalma
(RR 0.77, 95%CI:0.62–0.96)

A. Ciszewski et al. Vaccine 2018 Ren S et al. Open Heart 2015 Wu WC et al. Am Heart J2014

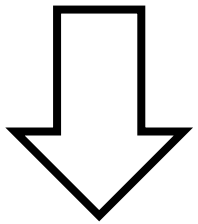


A. Ciszewski et al. Vaccine 2018

İnfluenza aşılaması

Mortalite (19.3% versus 18.8%; aHR,0.92; 95% CI 0.89–0.95)

Serobrovasküler olay riskinde (aHR, 0.84; 95% CI 0.78–0.92)



İskemik SVO riskinde (RR=0.87, 95%CI: 0.79–0.96)

Aynı etki pnömokok aşısında saptanmamıştır

A.N. Siriwardena et al. Vaccine, 2014

G. Tsivgoulis et al. *Journal of the Neurological Sciences.2018*

Christian Fynbo Christiansen et al. Intensive Care Med,2019

Ren S, Newby D, Li SC, et al. Open Heart 2015

CARDIOLOGY

Turning Basic Research into Clinical Success

Cardiology 2018;141:98–106
DOI: 10.1159/000493572

Received: April 23, 2018
Accepted after revision: September 10, 2018
Published online: November 14, 2018

Beneficial Effects of Vaccination on Cardiovascular Events: Myocardial Infarction, Stroke, Heart Failure

Katerina Fountoulaki[a] Sotirios Tsiodras[b] Eftychia Polyzogopoulou[c]
Christophoros Olympios[a] John Parissis[d]

Bu etki artırılabilir mi?

Doz ?

Süre ?

Periferik mono-nükleer hücrelerdeki ß**2-adrenerjik reseptör sayısı** ile serum

IFNγ ve IL-6 seviyesi arasında negatif bir korelasyon saptanmıştır

CD8 T hücre yanıtını azalttığı gösterilmiştir

M. Wahle et al. Journal Of Interferon & Cytokine Research,2005

Kalp yetmezliğinin **semptatik sinir sistem aktivasyonunu** artırdığı gösterilmiştir.

Katerina Fountoulaki et al. Cardiology, 2018

Sağlıklı-benzer yaş grubu ile karşılaştırıldığında **influenza aşı yanıtının**

azalmasına neden olduğu saptanmıştır

McElhaney JE. Et al.Vaccine, 2004

Beta-blokörler influenza aşı yanıtını artırır mı?

Table 5: Multivariable hazard ratios and 95% confidence intervals of influenza vaccination and beta-blocker for hospitalization due to HF.

Influenza vaccine	Beta-blocker	HR	95% CI	*P* value
No	No	Reference		
No	Yes	1.29	0.27–6.16	0.750
Yes	No	2.46	0.40–15.22	0.334
Yes	Yes	0.05	0.01–0.71	0.027

Note. All analyses were adjusted for gender, dyslipidemia, SCr, and LVEF, which are independent prognostic indicators for hospitalization due to HF.

Apirak Sribhutorn et al. Cardiology Research and Practice,2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.

IIV3 influenza
Yüksek doz (60 µg) & standart doz (15 µg)

Antikor yanıtı ⇧
İnfluenza benzeri hastalık sıklığı ⇩

Human Vaccines & Immunotherapeutics

ISSN: 2164-5515 (Print) 2164-554X (Online) Journal homepage: https://www.tandfonline.com/loi/khvi20

Immunogenicity and safety of high-dose quadrivalent influenza vaccine in Japanese adults ≥65 years of age: a randomized controlled clinical trial

Leilani Sanchez, Osamu Matsuoka, Satoshi Inoue, Takahiro Inoue, Ya Meng, Takahiro Nakama, Kumiko Kato, Aseem Pandey & Lee-Jah Changfor the QHD00008 Study Team

IIV4 influenza
Yüksek doz (60 µg) & standart doz (15 µg)

Antikor yanıtı ⇧
Yan etki gelişimi açısından benzer
IM daha etkin ve güvenilir

Yüksek doz influenza aşı uygulamalarının kardiovasküler komorbiditesi olan popülasyona etkisi nedir?

American Heart Journal 202 (2018) 97–103

Contents lists available at ScienceDirect

American Heart Journal

Trial Design

High-dose influenza vaccine to reduce clinical outcomes in high-risk cardiovascular patients: Rationale and design of the INVESTED trial

Orly Vardeny, PharmD MS [a,*,1], Jacob A. Udell, MD, MPH [b,1], Jacob Joseph, MD [c], Michael E. Farkouh, MD, MSc [d], Adrian F. Hernandez, MD [e], Alison J. McGeer, MD [f], H. Keipp Talbot, MD MPH [g], Deepak L. Bhatt, MD [h], Christopher P. Cannon, MD [h], Shaun G. Goodman, MD [i], Inder Anand, MD [j], David L. DeMets, PhD [k], Jon Temte, MD, PhD [l], Janet Wittes, PhD [m], Kristin Nichol, MD [a], Clyde W. Yancy, MD [n], J. Michael Gaziano, MD [c], Lawton S. Cooper, MD, MPH [o], KyungMann Kim, PhD [k], Scott D. Solomon, MD [c]

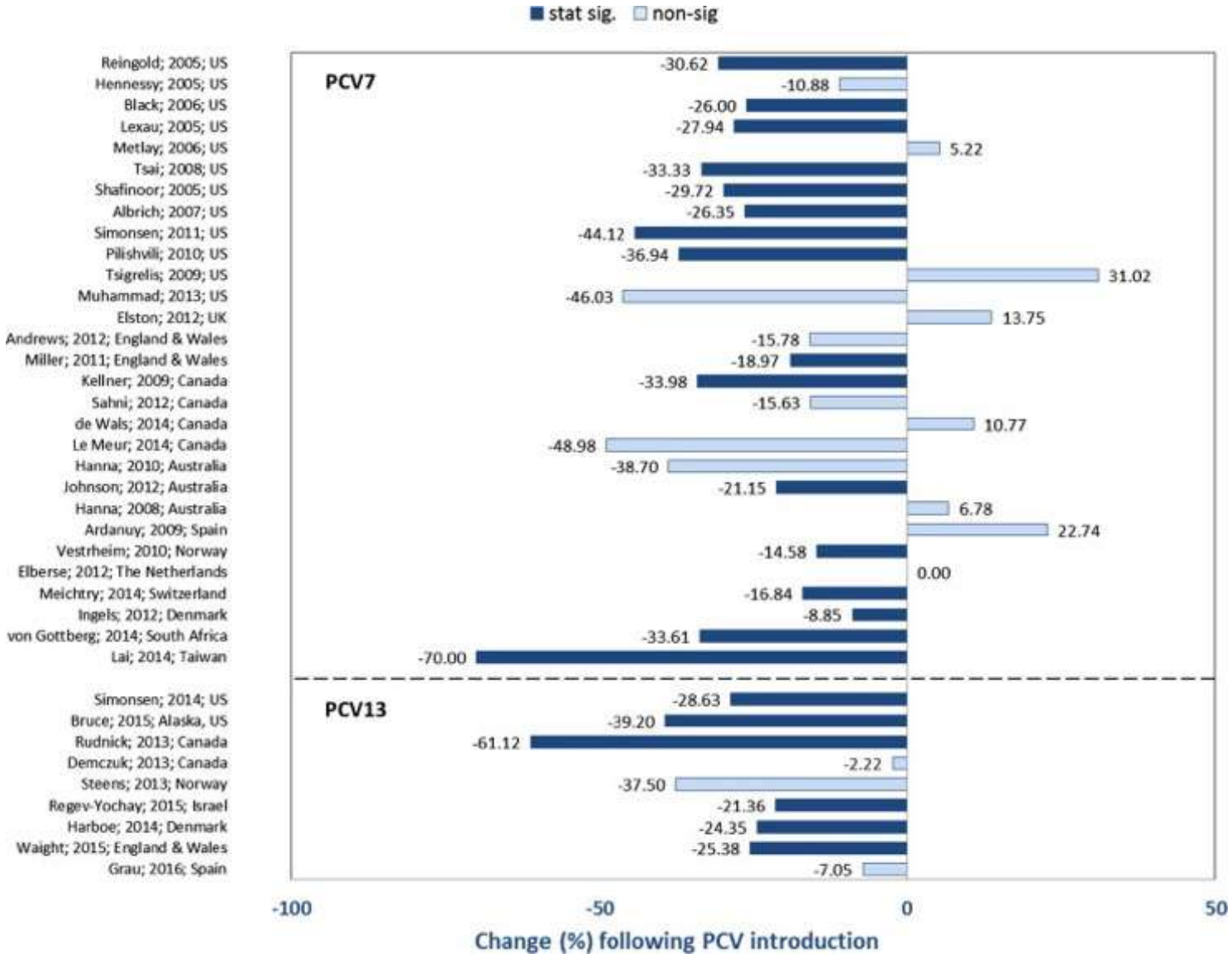


Fig. 2. Invasive pneumococcal disease in adults change (%) of incidence following the introduction of PCV.

Pnömokok aşılarının indirek erişkin etkisi

İnvaziv pnömokokal hastalık sıklığında (özelliklede ≥65 yaş)

Pnömoni nedeniyle hastane yatış sıklığında

G. Tsaban et al.Vaccine (2017)

Andrew D. Wiese et al. Expert Review of Vaccines,2019

Cochrane Library

Cochrane Database of Systematic Reviews

Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease (Review)

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

Pnömokok aşı UYGULANMASI ile

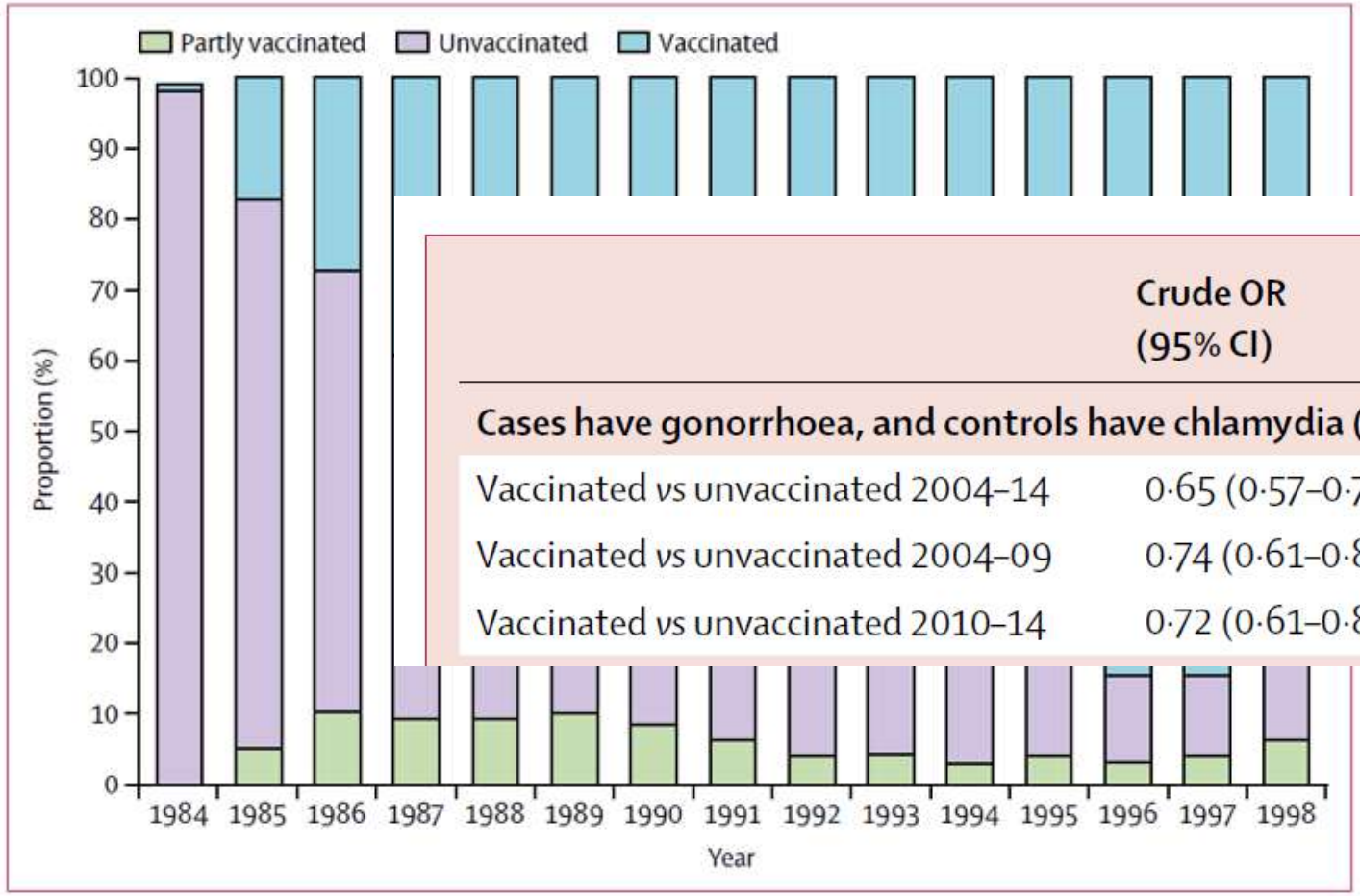
Toplum kökenli pnömoni ⇩

KOAH alevlenme ⇩

Meningokok aşısı ile gonokok enfeksiyonlarını engelleyebilir miyiz?

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black



	Crude OR (95% CI)	Adjusted OR* (95% CI)	Vaccine effectiveness (95% CI)
Cases have gonorrhoea, and controls have chlamydia (co-infected excluded)			
Vaccinated *vs* unvaccinated 2004–14	0·65 (0·57–0·72)	0·69 (0·61–0·79)	31% (21–39)
Vaccinated *vs* unvaccinated 2004–09	0·74 (0·61–0·89)	0·80 (0·66–0·98)	20% (2–34)
Vaccinated *vs* unvaccinated 2010–14	0·72 (0·61–0·86)	0·91 (0·75–1·11)	9% (0–25)

Figure 2: Vaccination status of participants by year of birth

vaccines

MDPI

Article

Effectiveness of a Group B Outer Membrane Vesicle Meningococcal Vaccine in Preventing Hospitalization from Gonorrhea in New Zealand: A Retrospective Cohort Study

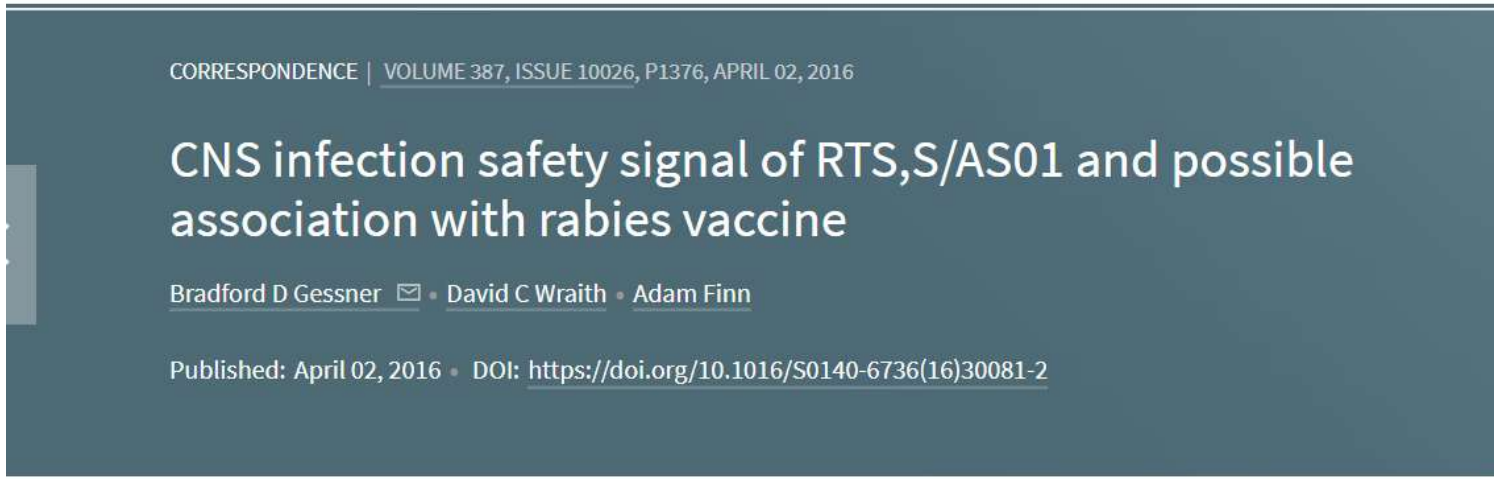
Janine Paynter [1,*], Felicity Goodyear-Smith [1], Jane Morgan [2], Peter Saxton [3], Steven Black [4] and Helen Petousis-Harris [5]

Meningokok aşısı ile gonokok enfeksiyonlarını engelleyebilir miyiz?

Table 3. Cox's proportional hazards with Firth correction for rare events estimates and 95% confidence intervals (CI) for the primary outcome (hospitalization with gonorrhea was specified).

Vaccination Status					
Unvaccinated	129	(0.028)	466,710		Ref
Partial	S	S	S	0.42 (0.08–2.12)	0.31 (0.06–1.57)
Vaccinated	132	(0.019)	677,190	0.89 (0.69–1.16)	0.76 (0.58–0.99)

THE LANCET



CORRESPONDENCE | VOLUME 387, ISSUE 10026, P1376, APRIL 02, 2016

CNS infection safety signal of RTS,S/AS01 and possible association with rabies vaccine

Bradford D Gessner • David C Wraith • Adam Finn

Published: April 02, 2016 • DOI: https://doi.org/10.1016/S0140-6736(16)30081-2

5-17 ay/ yaş grubunda grupta kontrol grubu ile karşılaştırıldığında serabral sıtma ve SSS enfeksiyonu gelişme sıklığının düşük saptanması

6-12 hafta/yaş grubunda benzer bir farklılığın saptanmaması

Table 1
Vaccine schedules for children enrolled in the RTS,S/AS01 malaria vaccine clinical trial.

Age group	Intervention group			Control group	
	Primary series	Active booster (R3R group)	Control booster (R3C group)	Primary series	Control booster (C3C group)
Age 5–17 months at enrollment	RTS,S/AS01 at 0, 1, 2 months	RTS,S/AS01 at 20 months	MCV-C[a] at 20 months	Verorab rabies vaccine at 0, 1, 2 months	Verorab rabies vaccine at 20 months
Age 6–12 weeks at enrollment	RTS,S/AS01 at 0, 1, 2 months	RTS,S/AS01 at 20 months	MCV-C[a] at 20 months	MCV-C[a] at 0, 1, 2 months	MCV-C[a] at 20 months

[a] Menjugate serogroup C meningococcal conjugate vaccine.

Kontrollü randomize çift-kör bir çalışma
Rastlantı
Sistematik bir bias
Yan etki (AS01- Kan beyin bariyeri, koroid pleksus)
Uygulanan **kuduz aşısının SSS enfeksiyonu açısından non-spesifik bir koruma** sağlamış olabileceği

B.D. Gessner et al. Vaccine, 2017

Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, 3720 BA Bilthoven, Netherlands

Susanne M A J Tielemans,[1] Hester E de Melker,[1] Susan J M Hahné,[1] Anna G C Boef,[1] Fiona R M van der Klis,[1] Elisabeth A M Sanders,[1,2] Marianne A B van der Sande,[1,3] Mirjam J Knol[1]

Table 3 | Hazard … or poisoning (ne… …erest) and for injuries

Outcome	Most recent vaccination	Events/person years	HR (95% CI)* Age adjusted	HR (95% CI)* Fully adjusted†
Infections	Fourth DTaP-IPV-Hib+PCV	4111/284 786	1.00	1.00
	MMR+MenC	6850/776 456	0.60 (0.55 to 0.65)	0.62 (0.57 to 0.67)
Injuries or poisoning	Fourth DTaP-IPV-Hib+PCV	3605/285 676	1.00	1.00
	MMR+MenC	5150/782 738	0.81 (0.71 to 0.93)	0.84 (0.73 to 0.96)
Infections	Third DTaP-IPV-Hib+PCV	10 654/639 484	1.00	1.00
	Fourth DTaP-IPV-Hib+PCV	3185/231 001	0.66 (0.60 to 0.72)	0.69 (0.63 to 0.76)‡

* Hazard ratios from Cox regression with age as underlying time scale and stratified for date of birth.
† Adjusted for sex, chronic disease, admission for any reason at age 8 months, birth weight, gestational age, maternal age and parity, parental country of birth, and postcode.
‡ Adjusted for sex, chronic disease, birth weight, gestational age, maternal age and parity, parental country of birth, and postcode.

RESEARCH

Non-specific effects of measles, mumps, and rubella (MMR) vaccination in high income setting: population based cohort study in the Netherlands

[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, 3720 BA Bilthoven, Netherlands

Susanne M A J Tielemans,[1] Hester E de Melker,[1] Susan J M Hahné,[1] Anna G C Boef,[1] Fiona R M van der Klis,[1] Elisabeth A M Sanders,[1,2] Marianne A B van der Sande,[1,3] Mirjam J Knol[1]

Çalışma katkısı

MMR aşısının düşük hastane başvurusu ile ilişkisi gösterilmiştir ancak bu etki farklı bir ek doz aşı ile de elde edilebilir, kızamık aşısına indirgenmemelidir.

Kızamık aşının non-spesifik etkisi dışlanmamalıdır ancak bu etki bias'tan ayırt etmekte güç olabilir.

Aşılamanın non-spesifik etkileri konusunda gözlemsel çalışmalardan elde edilen verilerin yorumlanmasında dikkatli olunmalıdır.

Non-specific effects of vaccines: plausible and potentially important, but implications uncertain

Andrew J Pollard,[1,2] Adam Finn,[3] Nigel Curtis[4]

Pollard AJ, et al. Arch Dis Child 2017

Box 1
Key observations historical trials and epidemiological studies.

(Live-attenuated) vaccines are associated with possible non-specific effects

- BCG, measles, OPV, and vaccinia

Sex-differential effects observed for non-specific effects

- In favor of girls: BCG, MV, and vaccinia
- In favor of boys: OPV

Additional effects observed after revaccination

- BCG, MV, OPV, and vaccinia

Maternal priming affects outcome of non-specific effects in newborns

- BCG and measles

Other observations or applications

- BCG bladder instillation reduces risk of recurrence of bladder cancer
- BCG vaccination reduces incidence of atopy

Acele mi ediyoruz?

Cinsiyet farklılığı

Aşılama zamanlamaları

Enfeksiyon dışı etkiler

Küresel bırakma öncesi OPV aşısının non-spesifik etkilerinin **daha fazla araştırılması** gereklidir.

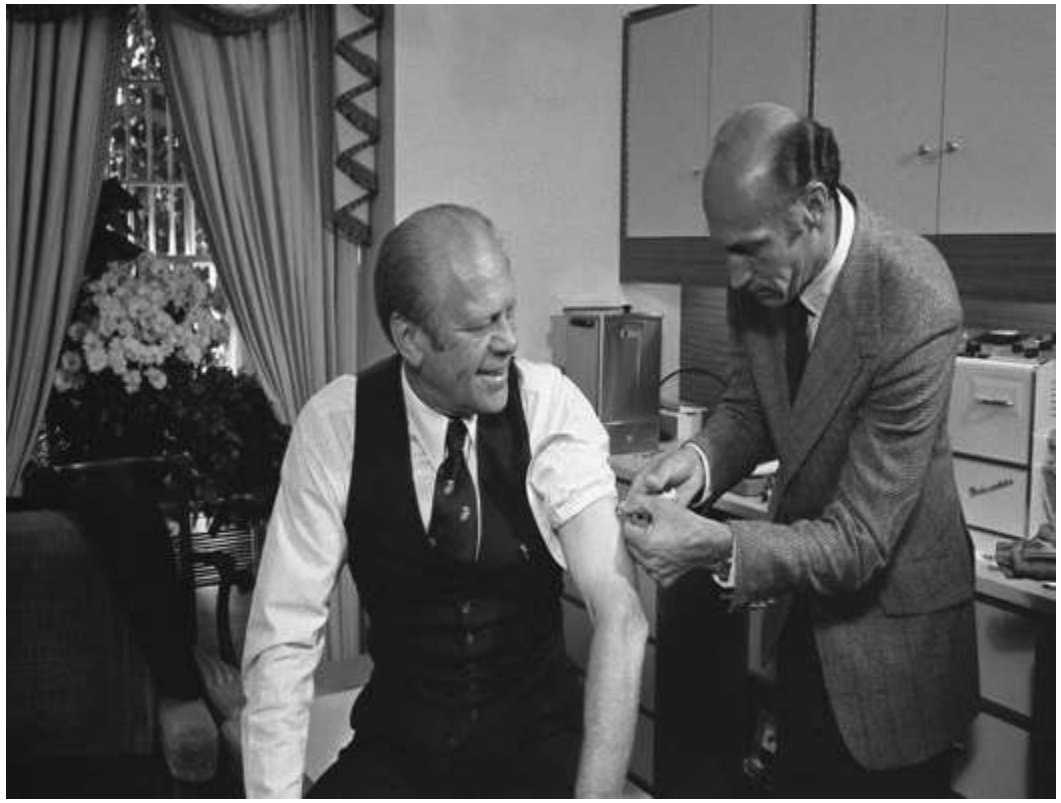
Alexander Upfill-Brown et al. CID 2017:65

BCG'nin non-spesifik etkilerini belirleyerek, viral enfeksiyonlarla ilişkili ciddi morbidite ve mortalite azalmalarına yol açabilecek **yeni tedavi seçeneklerine** ve **aşılama stratejilerine** doğru önemli bir adım atacağız.

. Moorlag et al.Clinical Microbiology and Infection ,2019

Epidemiyolojik gözlemleri destekleyen **immünolojik çalışmalar** nedeniyle **aşı programlarının planlanmasında hem spesifik hem de non-spesifik etkilerin dikkate alınması** gereklidir.

P. Aaby, C.S. Benn. Clinical Microbiology and Infection,2019



U.S. President Gerald Ford receiving his vaccine for the Swine Flu-1976

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 110, No 2

Printed in U.S.A

Original Contributions

GUILLAIN-BARRE SYNDROME FOLLOWING VACCINATION IN THE NATIONAL INFLUENZA IMMUNIZATION PROGRAM, UNITED STATES, 1976–1977[1]

LAWRENCE B. SCHONBERGER, DENNIS J. BREGMAN, JOHN Z SULLIVAN-BOLYAI, RICHARD A. KEENLYSIDE, DONALD W. ZIEGLER, HENRY F. RETAILLIAU, DONALD L EDDINS AND JOHN A. BRYAN