KLIMIK 2019

HIV, EBOLA, Sarı Humma ve Bakteri Aşıları

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Enfeksiyon Hastalıkları ve Klinik Mikrobiyoliji Servisi

HIV Epidemisi

HIV aşı geliştirilmesindeki zorluklar

- Bulaş yolları çeşitli
- HIV enfeksiyonun doğal eradikasyonu yok
- HIV immün yanıt, HIV enfeksiyonun önlenmesinde etkili değil
- HIV immün hücreleri öldürür
- Hızlı replikasyon ve kronikleşme
- HIV'in aşırı çeşitliliği

HIV Aşı Çalışmaları

YILMMS	AŞI	ÇALIŞMA ADI/ ÜRÜN/CLADE	LOKASYON	ÖRNEKLEM	SONUÇ
1998-2003	Bivalan gp120	VAX003 AIDSVAX B/B	Kanada, Hollanda, Porto Riko, ABD, MSM	5,417	Etki yok
1999-2003	Bivalan gp120	VAX004 AIDSVAX B/E	Tayland IV User	2,546	Etki yok
2004-2007	Ad5, internal proteinler (Gag, Pol, Nef)	STEP (HVTN 504)	Avustralya, Brezilya, Kanada, Dominik, Haiti, Jamaika, Peru, Porto Riko, ABD, MMS	3,000	Erken sonlandırıldı, Ad5 seropozitiflerde ve sünnetsizlerde HIV riskini artırdığı bulundu
2004-2007	Ad5, internal proteinler	Phambili (HVTN 503)	G. Afrika, heteroseksüel	801	STEP sonuçları dikkate alınarak, sonlandırıldı
2003-2009	**Canarypox/bivalan gp120**	**RV144 ALVAC-HIV (vCP1521) ve AIDSVAX B/E**	**Tayland**	**16,402**	**Orta derece etkinlik(31.2%)**
2009-2013	DNA/Ad5, internal proteinler+Env A/B/C (trimer)	HTVN 505	ABD MSM,18-50 yaş	2500	Etki yok

RV144 Çalışması

- Randomize, çift-kör, Plesebo kontrollü
- 2003-2009 Tayland
- US Askeri HIV Araştırma ve Tayland Sağlık Bakanlığı
- 16 000 katılımcı
- Prime-Boost Strateji
  - ALVAC-HIV (vCP1521); 4 priming doz (0,1,3,6. ay)
  - AIDSVAX B/E (bivalan gp120 protein) 2 booster doz (3,6.ay)

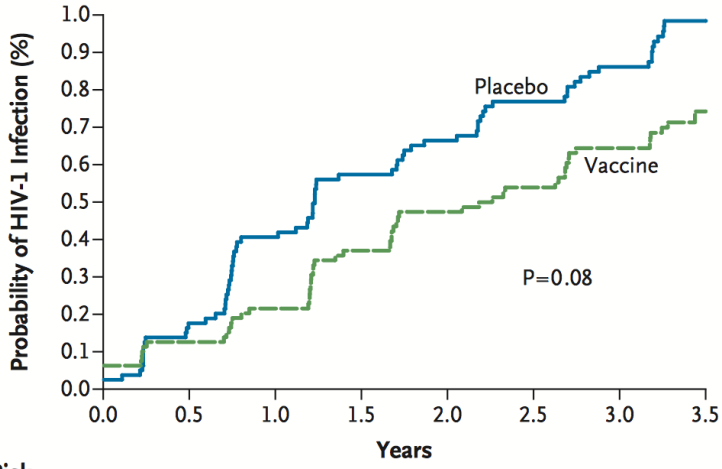
ClinicalTrials.gov Identifier: NCT00223080

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 3, 2009 VOL. 361 NO. 23

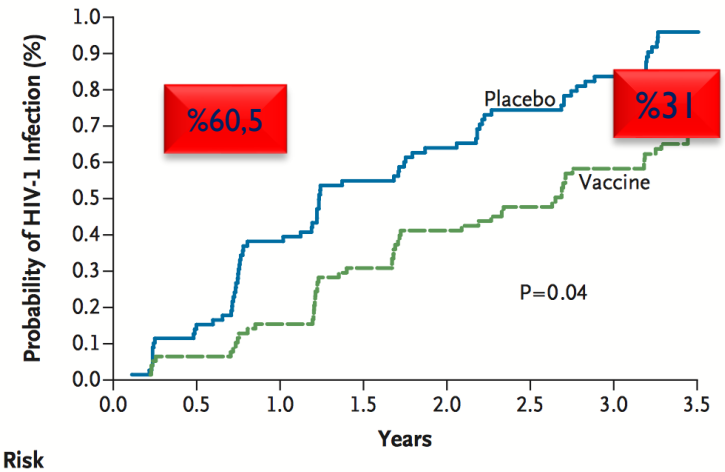
Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

A Intention-to-Treat Analysis



No. at Risk					
Placebo	8200	7775	7643	7441	7325
Vaccine	8202	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		32	52	67	76
Vaccine		17	37	50	56

C Modified Intention-to-Treat Analysis

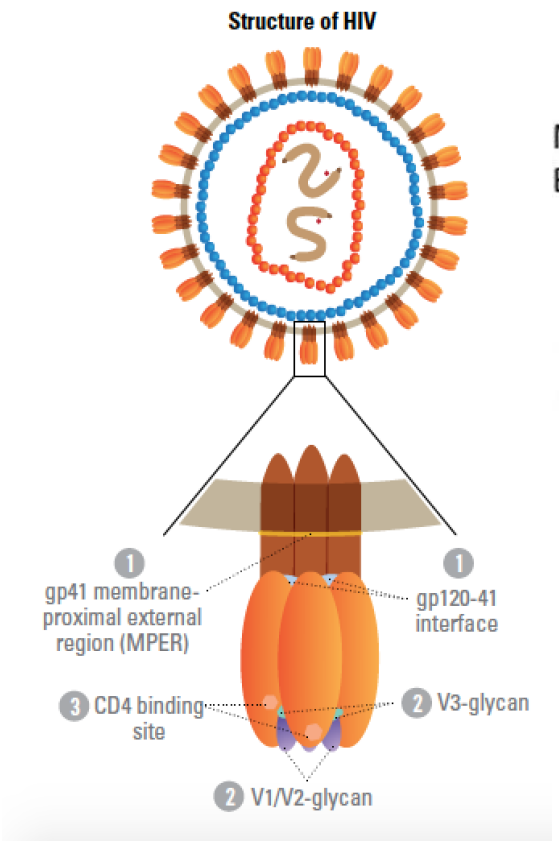


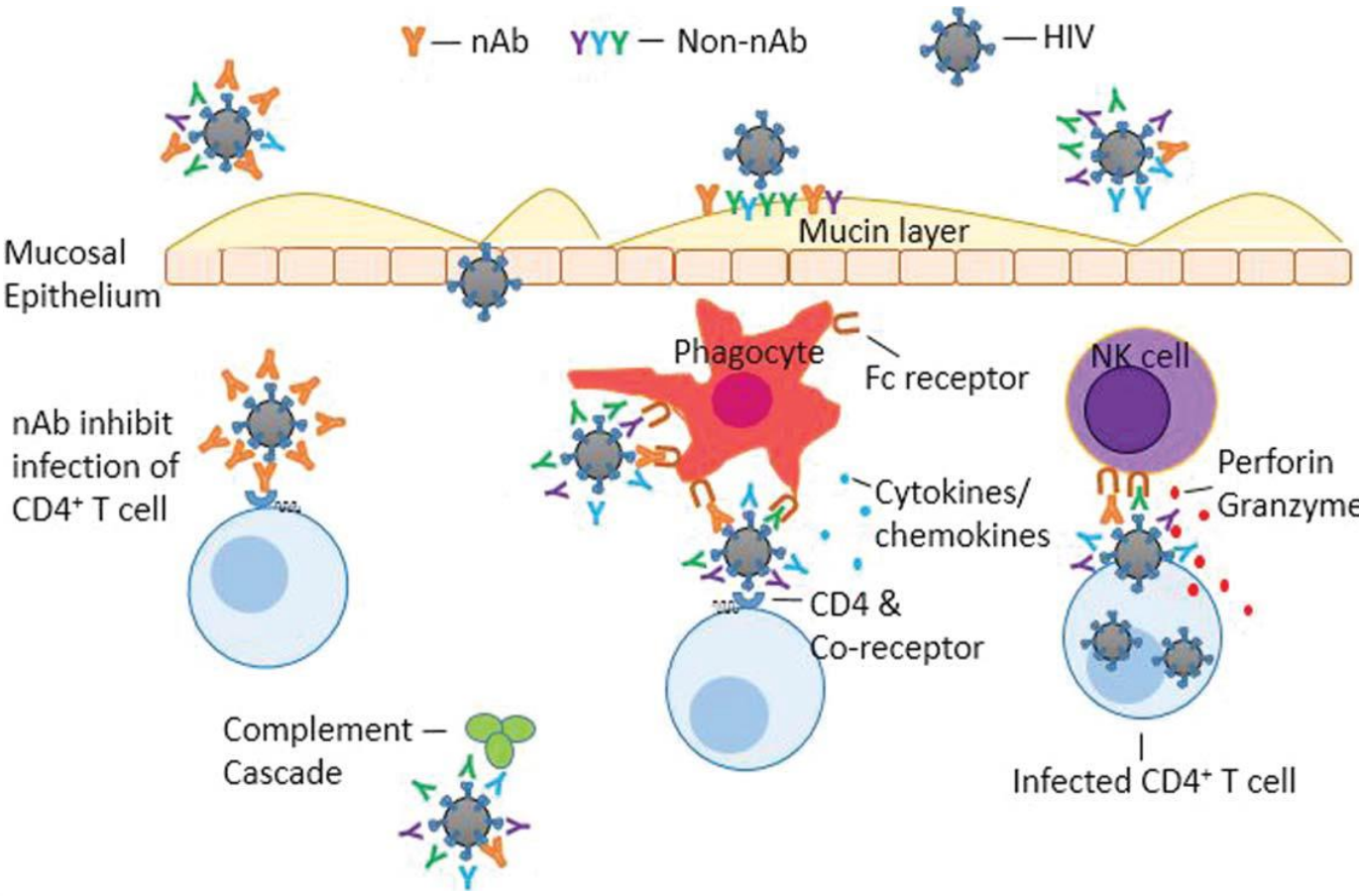
No. at Risk					
Placebo	8198	7775	7643	7441	7325
Vaccine	8197	7797	7665	7471	7347
Cumulative No. of Infections					
Placebo		30	50	65	74
Vaccine		12	32	45	51

RV144 Çalışması
HIV riskini azaltan NEDENLER

- **Non-n Ab IgG;**
  - Env proteinin gp70 değişken bölgeleri (V1V2) HIV
    - Hem yapısal he de lineer epitopları tanıyor
    - HIV-1 subtipleri ile çapraz reaktivite
    - Kompleman aktivasyonu
    - ADCVI (ADCC , ADCP)
    - Ab bağımlı sitokin ve kemokin salınımı
- Zayıf nAb IgG ⟶ V1V2
- Env spesifik IgA
  - Yüksek olanlarda infeksiyon koruma yok
- Env spesifik Cd4 Th
- Gp120 spesifik
  - IgG1 Ab; VAX003'de etkisiz bulumuştu
  - IgG3 Ab; VAX003'e göre daha yüksek oranda
    - Spesifik efektör fonksiyonları artırıyor ; ADCC ve ADCP

RV144 Çalışması
HIV riskini azaltan NEDENLER

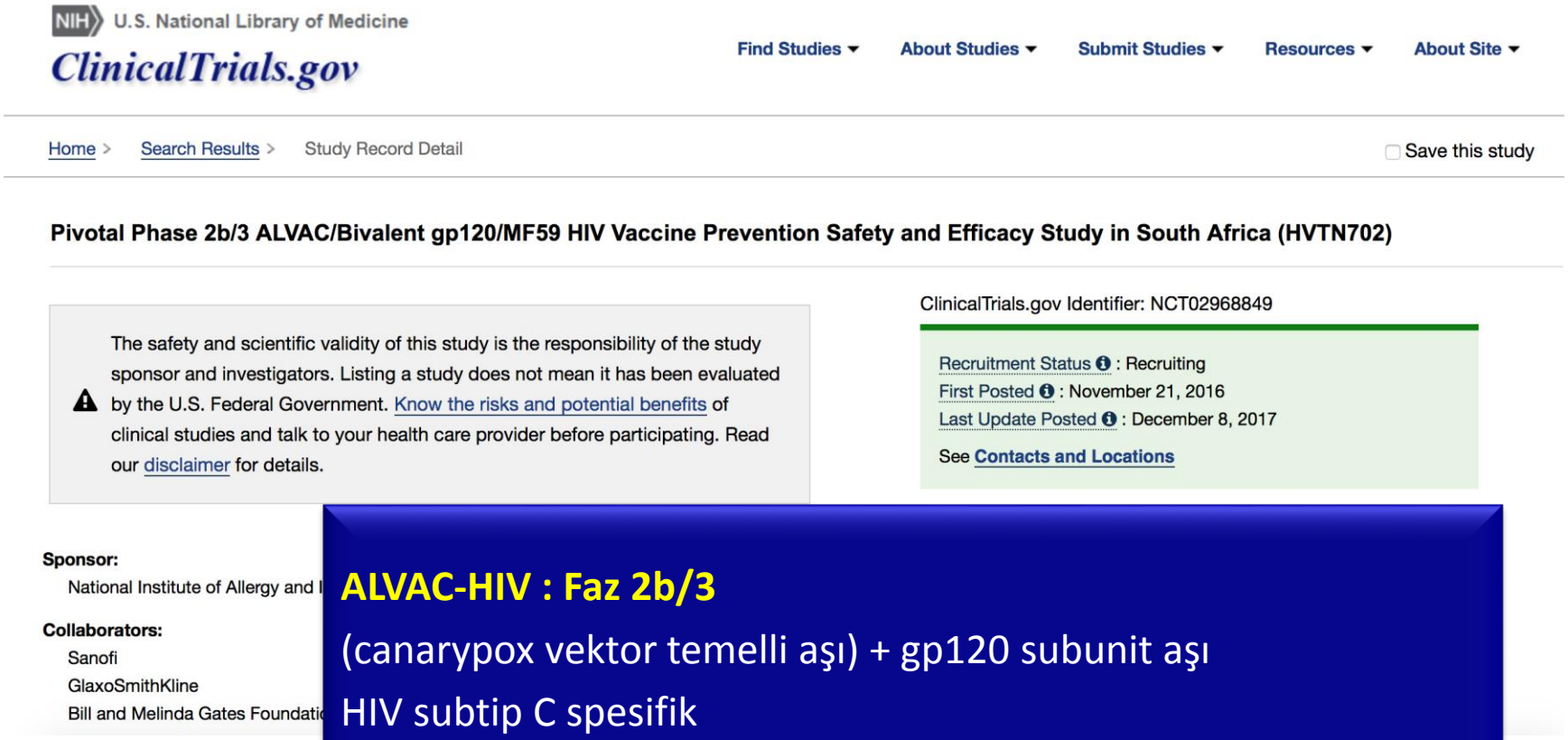




Pox-Protein Public-Private Partnership
(P5; Pox Protein Kamu-Özel Ortaklığı)

- **2010 ; P5 kuruldu**
- RV144 bulgularına dayanan araştırmalar başlatıldı
  - 2012 RV305
  - 2013 RV306
    - Booster doz ile RV144 etkinliği artar
  - 2015 HVTN 100 Faz1/2
    - 252 kişi (Adjuvan MF59)
  - Sonuç: Geniş Serili Klinik Araştırmalar Başlanabilir

HVTN 702



ALVAC-HIV : Faz 2b/3

(canarypox vektor temelli aşı) + gp120 subunit aşı

HIV subtip C spesifik

Adjuvan MF59

Heteroseksüel 18-35 yaş, 5400 kadın ve erkek

Mozaik Aşı Stratejileri

- **Primat çalışmaları**
  - Ad/MVA (modified vaccine Ankara) veya Ad/Ad aşılarının
  - HIV-1 mozaik yapısal ve zarf antijenleri ekspresyonu
  - prime—boost rejimi
    - Nötralizan Ab
    - Fonksiyonel Ab
    - Etkili T h yanıtı
    - Intrarektal SHIV bulaşını engelliyor
  - Ad26 mozaik prime/gp140 boost
    - 6 intrarektal maruziyet sonra %50 koruyucu
    - ADCC (ADCP, ADNKA, ADCD)

Barouch DH,. Protective efficacy of a global HIV-1 mosaic vaccine against heterologous SHIV challenges in rhesus monkeys. Cell 2013, 155:531-539.

Mozaik Aşı Stratejileri

- APPROACH çalışması; 2014-**2022, Faz1/2, 400 gönüllü**
  - Prime:
    - Ad26.Mos.HIV 0,12 hft
  - Boost:
    - Ad26.Mos.HIV+C calade gp140 24 ve 48 hft veya
- **SONUÇ**
  - Ad26/Ad26 plus yüksek doz gp140 en immünojenik form
  - 52. haftada
    - %100 Env spesifik Ab yanıtı
    - %80 Ab bağımlı hücresel fagositoz yanıtı
    - %83 Th yanıtı

Barouch DH. Lancet. 2018 Jul 21;392(10143):232-243.

Imbokoda
(HTVN 705/HPX2008) Faz 2b

A Study to Assess the Efficacy of a Heterologous Prime/Boost Vaccine Regimen of Ad26.Mos4.HIV and Aluminum Phosphate-Adjuvanted Clade C gp140 in Preventing Human Immunodeficiency Virus (HIV) -1 Infection in Women in Sub-Saharan Africa

ClinicalTrials.gov Identifier: NCT03060629

Status	Ongoing
Phase	IIb
Objective	
Prevention Option(s)	HIV Vaccine
Study Design	Randomized Double-blind
Arms and Assigned Interventions	

Description	Participants will receive Ad26.Mos4.HIV 5*10^10 virus particles (vp) as 0.5 milliliter (mL) via Intramuscular (IM) injection into the left deltoid on Months 0, 3, 6, and 12 and Clade C gp140 (250 [microgram] mcg) co-formulated with Aluminum phosphate adjuvant as 0.5 mL IM into the right deltoid on Months 6 and 12.
Mode of Delivery	Intramuscular
Products	Ad26.Mos.HIV gp140
ARMs	Experimental
Clade	C

NOVEMBER 2017 → FEBRUARY 2022

Enrollment 2 600

Age Range 18 Years ↔ 35 Years

Population Women

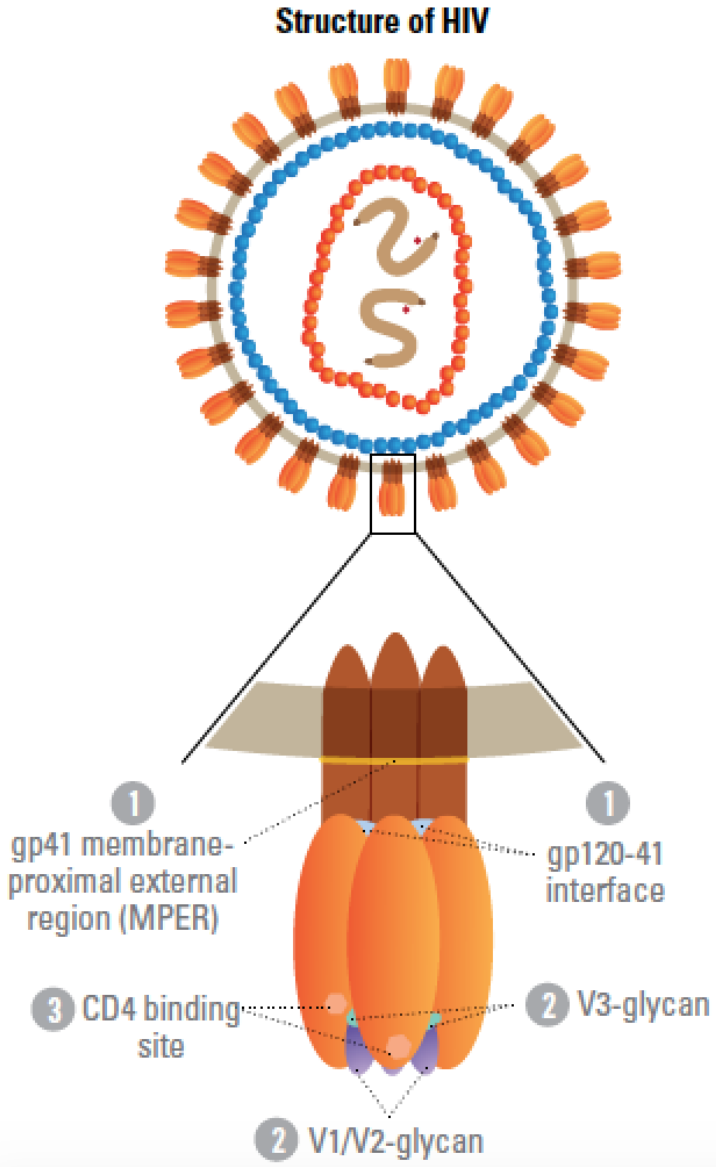
Sites

UNC Lilongwe CRS
Lilongwe
Malawi

Centro de Investigação e Treino em Saúde de Polana Caniço
Maputo
Mozambique

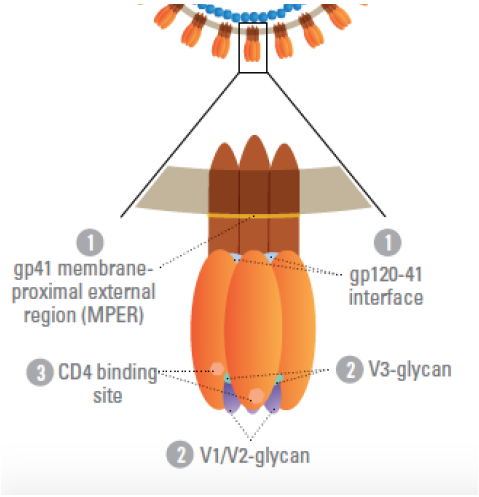
Josha Research Center
Josha, Bloemfontein
South Africa

Nötralizan-Antikor Stratejileri



HIV envelope target	Antibody	Status			
		Pre-clinical	Phase I	Phase II	Phase IIb/III
CD4 binding site	3BNC117		●		
	VRC01		●		●
	VRC07-523		●		
	N6		●		
gp41 membrane proximal external region (MPER)	10e8		●		
	4e10	●			
gp120-41 interface	8ANC195	●			
	PGT151	●			
V1/V2-glycan	CAP256-VRC26		●		
	PGDM1400		●		
	PG9		●		
	CH01	●			
V3-glycan	PGT121		●		
	PGT128	●			
	PGT135	●			
	10-1074		●		
CD4 binding / V3-glycan	3BNC117+ 10-1074		●		
	CAP256-VRC26 +PGT121			●	
	CAP256-VRC26 + VRC07		●		

Nötralizan-Antikor Stratejileri



- Pasif immünizasyon
- VRC01 Faz-1 çalışması
  - CD4 bağlanma bölgesine nAb
  - Güvenli ve Tolere edilebilir
  - Invitro virüs nötralizasyonu
    - *Ledgerwood JE.. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol 2015; 182:289-301*
- AMP (antibody mediated prevention) 2016 Faz2
  - VRC01; gp120'nin Cd4 bağlanma bölgesine karşı bnAb
  - ABD, G. Amerika ; 2700 MSM
  - Safra Altı Afrika, 1500 kadın
    - Clinicaltrials.gov NCT02716675/NCT02569215

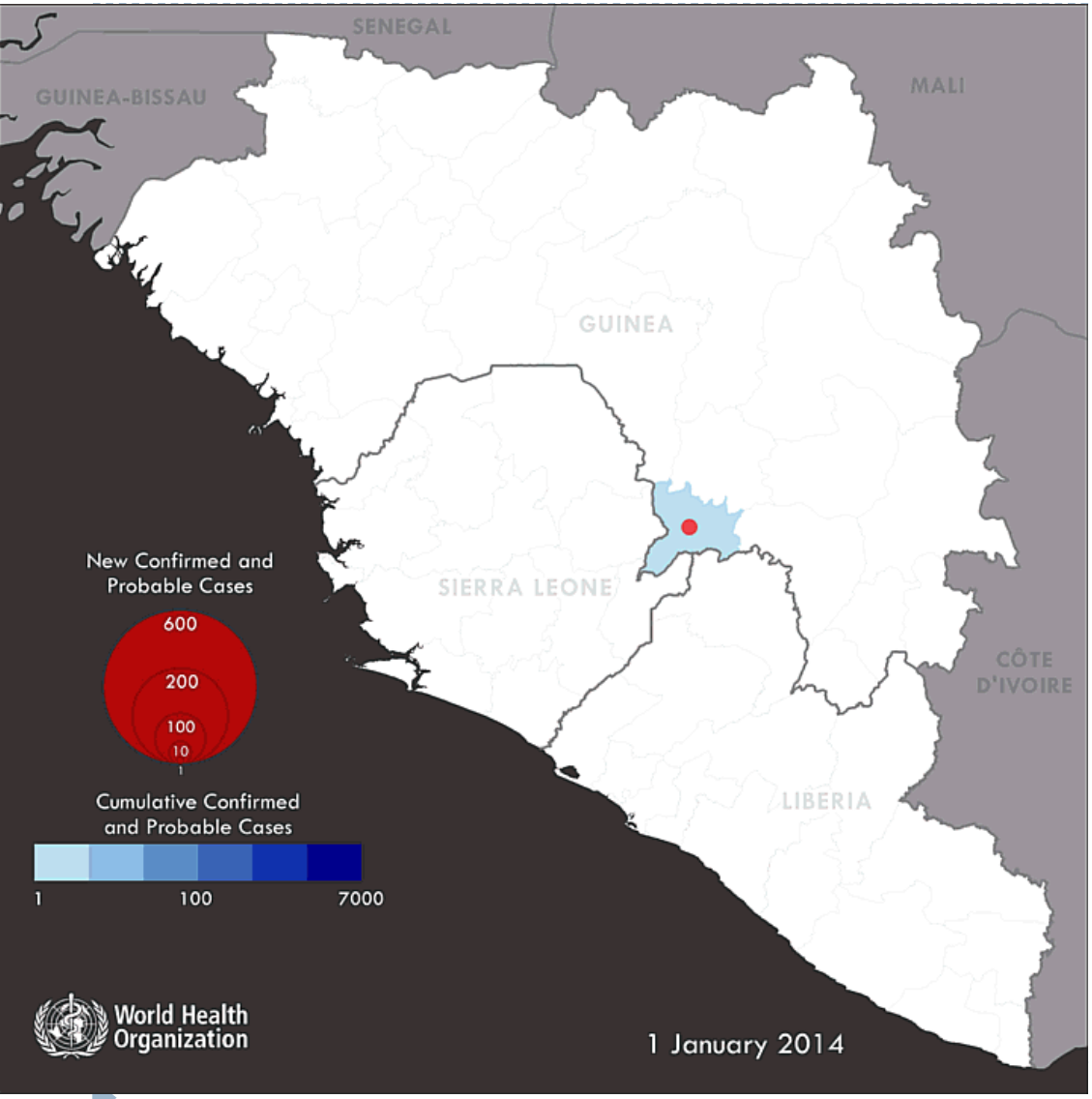
Nötralizan-Antikor Stratejileri

- Vektör aracılıklı immünoprofilaksi
  - Deney hayvanları Kimerik farelerde ve Primatlarda
    - Adeno-associated virus (AAV); bnAB ekspresyonu
    - Yüksek doz IV ve Mukozal bulasa karşı koruyucu
      - Nature 2012; 481:81-4
      - Nat Med 2014
  - IAVI A003, faz 1,
    - rAAV vektör, PG9 Ab (V1V2 glikan Ab) kodluyor
    - Randomize, kör, doz azaltmalı çalışma
    - 24 sağlıklı erkek
      - Clinicaltrials.gov NCT01937455

HIV aşıları özet

- V2 spesifik Ab geliştiren modeller
  - ALVAC/AIDSVAX B/E
- Polifonksiyonel Ab geliştiren modeller
  - Ad26 vektorler
  - Mosaik immünojenler
  - Trimerik gp140 protein rejimleri
- bnAb uyarımı veya taşınması
  - Immünizasyon
  - Gen transferi
  - Pasif immünizasyon
- Efektör hafıza hücreleri oluşturulması
  - Replikatif vektör (CMV)

EBOLA



- Batı Afrika 2014
  - Liberya, Gine ve Sierra Leone
  - 29 000 (şüpheli, olası veya kesin)
  - 15 000 Lab. doğrulanmış
  - Olgu/fatalite %40

Primatlarda Aşı Etkili

- Vesiküler stomatit virüs
- DNA plazmidleri
- Rekombinant adenovirus (rAd)
- Virüs benzeri partiküller
  - %100 koruyuculuk

Hoenen T, Groseth A, Feldmann H. Current ebola vaccines. Expert Opin Biol Ther. 2012 Jul;12(7):859-72. Epub 2012 May 5.

İnsan Klinik Çalışmaları

- 3 aday aşı rejimi

- rVSV-ZEBOV aşı adayı (V920) tek doz (Merck)
- Ad26-ZEBOV/MVA-BN-Filo aşı adayı; prime-boost rejim (Janssen Vaccines & Prevention B.V. in collaboration with Bavarian Nordic GmbH)
- ChAd3-EBO-Z aşı adayı Tek doz (GlaxoSmithKline) veya MVA-BN-Filo aşı adayı booster olarak kombine (Bavarian Nordic GmbH).

Ebola ça Suffit ("Ebola this is enough")

Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial

Ana Maria Henao-Restrepo, Ira M Longini, Matthias Egger, Natalie E Dean, W John Edmunds, Anton Camacho, Miles W Carroll, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Stefanie Hossmann, Mandy Kader Kondé, Souleymane Kone, Eeva Kuisma, Myron M Levine, Sema Mandal, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, Conall H Watson, Sakoba Kéïta, Marie Paule Kieny, John-Arne Røttingen**

Summary

Background A recombinant, replication-competent vesicular stomatitis virus-based vaccine expressing a surface glycoprotein of Zaire Ebolavirus (rVSV-ZEBOV) is a promising Ebola vaccine candidate. We report the results of an interim analysis of a trial of rVSV-ZEBOV in Guinea, west Africa.

Methods For this open-label, cluster-randomised ring vaccination trial, suspected cases of Ebola virus disease in Basse-Guinée (Guinea, west Africa) were independently ascertained by Ebola response teams as part of a national surveillance system. After laboratory confirmation of a new case, clusters of all contacts and contacts of contacts were defined and randomly allocated 1:1 to immediate vaccination or delayed (21 days later) vaccination with rVSV-ZEBOV (one dose of 2×10^7 plaque-forming units, administered intramuscularly in the deltoid muscle). Adults (age ≥18 years) who were not pregnant or breastfeeding were eligible for vaccination. Block randomisation was used, with randomly varying blocks, stratified by location (urban *vs* rural) and size of rings (≤20 *vs* >20 individuals). The study is open label and masking of participants and field teams to the time of vaccination is not possible, but Ebola response teams and laboratory workers were unaware of allocation to immediate or delayed vaccination. Taking into account the incubation period of the virus of about 10 days, the prespecified primary outcome was laboratory-confirmed Ebola virus disease with onset of symptoms at least 10 days after randomisation. The primary analysis was per protocol and compared the incidence of Ebola virus disease in eligible and vaccinated individuals in immediate vaccination clusters with the incidence in eligible individuals in delayed vaccination clusters. This trial is registered with the Pan African Clinical Trials Registry, number PACTR201503001057193.

Findings Between April 1, 2015, and July 20, 2015, 90 clusters, with a total population of 7651 people were included in the planned interim analysis. 48 of these clusters (4123 people) were randomly assigned to immediate vaccination with rVSV-ZEBOV, and 42 clusters (3528 people) were randomly assigned to delayed vaccination with rVSV-ZEBOV. In the immediate vaccination group, there were no cases of Ebola virus disease with symptom onset at least 10 days after randomisation, whereas in the delayed vaccination group there were 16 cases of Ebola virus disease from seven clusters, showing a vaccine efficacy of 100% (95% CI 74·7–100·0; p=0·0036). No new cases of Ebola virus disease were diagnosed in vaccinees from the immediate or delayed groups from 6 days post-vaccination. At the cluster level, with the inclusion of all eligible adults, vaccine effectiveness was 75·1% (95% CI −7·1 to 94·2; p=0·1791), and 76·3% (95% CI −15·5 to 95·1; p=0·3351) with the inclusion of everyone (eligible or not eligible for vaccination). 43 serious adverse events were reported; one serious adverse event was judged to be causally related to vaccination (a febrile episode in a vaccinated participant, which resolved without sequelae). Assessment of serious adverse events is ongoing.

Interpretation The results of this interim analysis indicate that rVSV-ZEBOV might be highly efficacious and safe in preventing Ebola virus disease, and is most likely effective at the population level when delivered during an Ebola virus disease outbreak via a ring vaccination strategy.

Funding WHO, with support from the Wellcome Trust (UK); Médecins Sans Frontières; the Norwegian Ministry of Foreign Affairs through the Research Council of Norway; and the Canadian Government through the Public Health Agency of Canada, Canadian Institutes of Health Research, International Development Research Centre, and Department of Foreign Affairs, Trade and Development.

Lancet 2015; 386: 857-66

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See Comment page 831

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Lancet. 2017 Feb 4;389(10068)505-518.

- 23 Mart 2015- 20 Temmuz 2015
- Faz 3
- Halka aşılama modeli (Temaslılar, Temaslılara temaslılar)
- 5837 gonullu

- Küme randamizasyonu
- İlk gün ve gecikmiş (randimizasyon 21 gün sonra) tek Doz IM rVSV-ZEBOV

EBOLA

- EBOLA aşısı yapılan ilk kişi
- Mohamed Soumah
- 27 yaşında

"It wasn't easy. People in the village said that the injection was to kill me. I was afraid. I was the first one to be injected, the very first, here in my village on 23 March 2015. I've been monitored for 3 months and I've had no problems. The last follow-up, 84 days after the vaccination, was all clear".

Ebola ça Suffit ("Ebola this is enough")

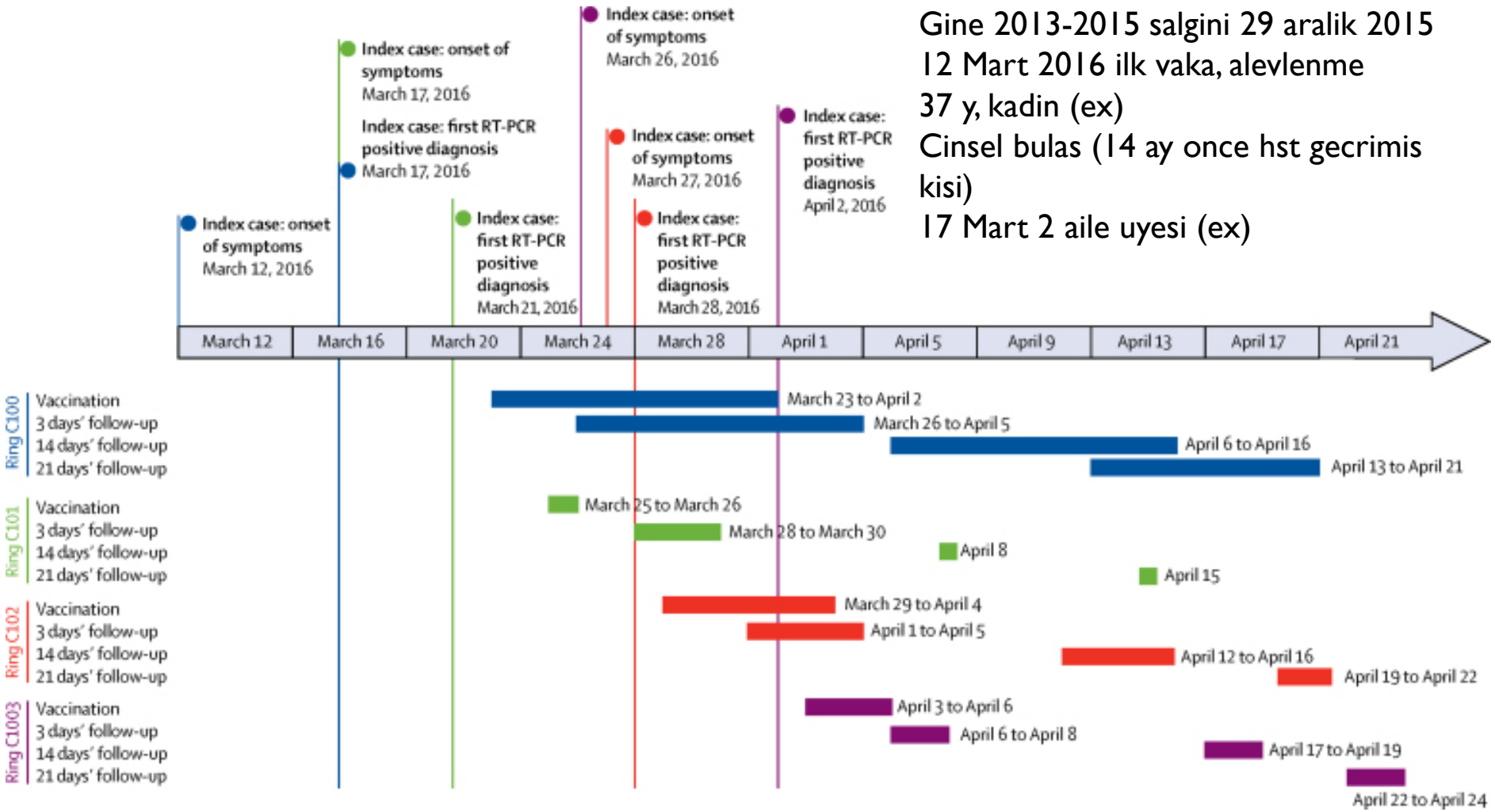
	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented	All eligible (eligible adults, contacts and contacts of contacts)	All (all contacts and contacts of contacts)
Number of individuals (clusters)				
Immediate	2014 (48)	2048 (48)	3035 (48)	4123 (48)
Delayed	2380 (42)	1930 (42)	2380 (42)	3528 (42)
Number of cases at <10 days (affected clusters)				
Immediate	9 (4)	10 (5)	18 (9)	21 (9)
Delayed	16 (12)	6 (5)	16 (12)	25 (13)
Number of cases at ≥10 days (affected clusters)				
Immediate	0 (0)	0 (0)	6* (3)	8* (4)
Delayed	16† (7)	11† (5)	16† (7)	21† (7)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74·7 to 100)	100% (70·8 to 100)	75·1% (−7·1 to 94·2)	76·3% (−15·5 to 95·1)
p value§	0·0036	0·0194	0·1791	0·3351

*All cases occurred in unvaccinated individuals. †Four cases were vaccinated and developed symptoms on day 0, 2, 6, or 6 after vaccination. ‡From fitting a β-binomial distribution to the cluster-level numerators and denominators and using an inverted likelihood ratio test to identify the lower bound for vaccine efficacy (first two columns); from Cox proportional hazards model to estimate vaccine effectiveness (last two columns). §From Fisher's exact test (two-sided).

Table 2: **Calculations of vaccine efficacy and vaccine effectiveness based on different study populations**

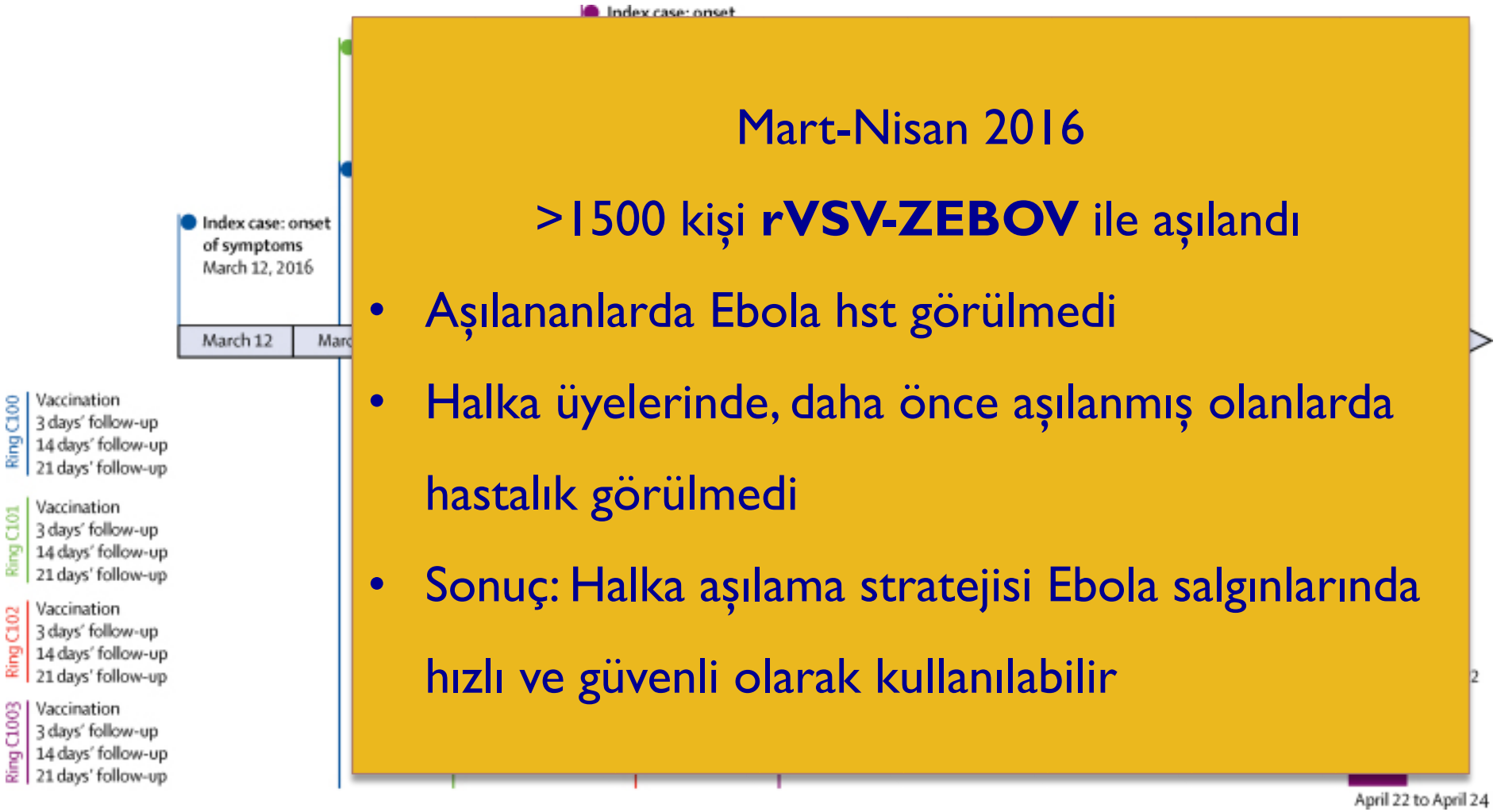
Henao-Restrepo AM. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open label, cluster-randomised trial (Ebola Ça Suffit!). Lancet. 2017 Feb 4;389(10068)505-518.

Mart 2016 Gine Salgını



Gine 2013-2015 salgini 29 aralik 2015
12 Mart 2016 ilk vaka, alevlenme
37 y, kadin (ex)
Cinsel bulas (14 ay once hst gecrimis kisi)
17 Mart 2 aile uyesi (ex)

Mart 2016 Gine Salgını



Mart-Nisan 2016

>1500 kişi **rVSV-ZEBOV** ile aşılandı

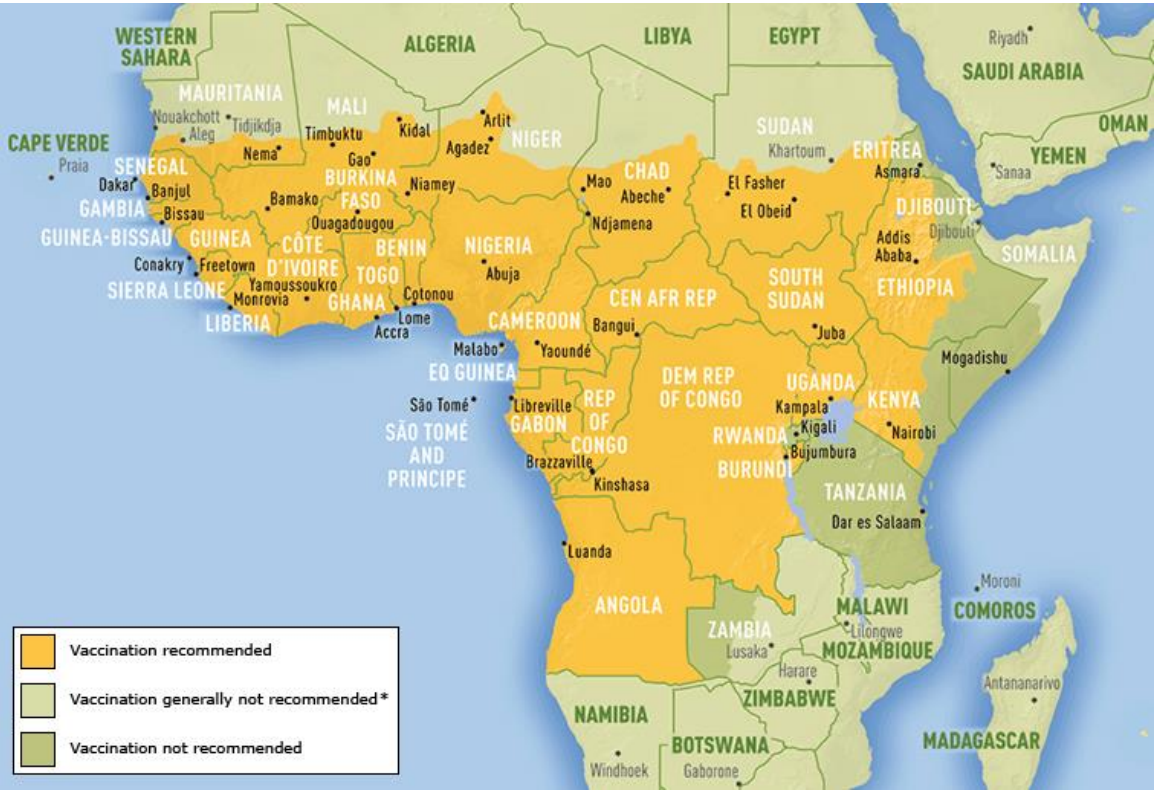
- Aşılananlarda Ebola hst görülmedi
- Halka üyelerinde, daha önce aşılanmış olanlarda hastalık görülmedi
- Sonuç: Halka aşılama stratejisi Ebola salgınlarında hızlı ve güvenli olarak kullanılabilir

EBOLA Aşıları

- **rVSV-ZEBOV güvenli ve immünojenik**

- Dünya genelinde, Ebola aşıları iki ülkede, Çin ve Rusya'da onaylanmıştır.
- Çin, CANSINOBIO tarafından üretilen Ad4-EBOV aşısını 2017'de onaylamıştır.
- Rusya, Gamaleya Federal Epidemiyoloji ve Mikrobiyoloji Araştırma Merkezi tarafından üretilen iki vektörde aynı Ebola virus glikoproteini eksprese den aşı (GamEvac-Combi; heterolog VSV ve Ad5 vektorel prime-boost Ebole aşı) 2017 yılında onaylandı.

Sarı Humma



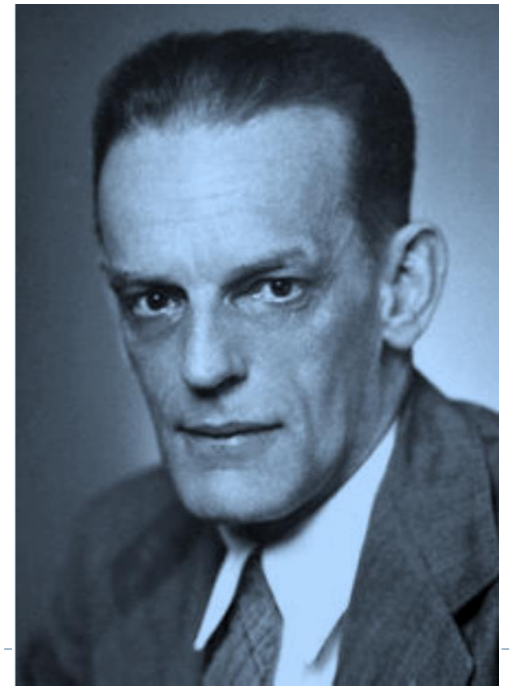
2013
130000 olgu
78000 mortalite

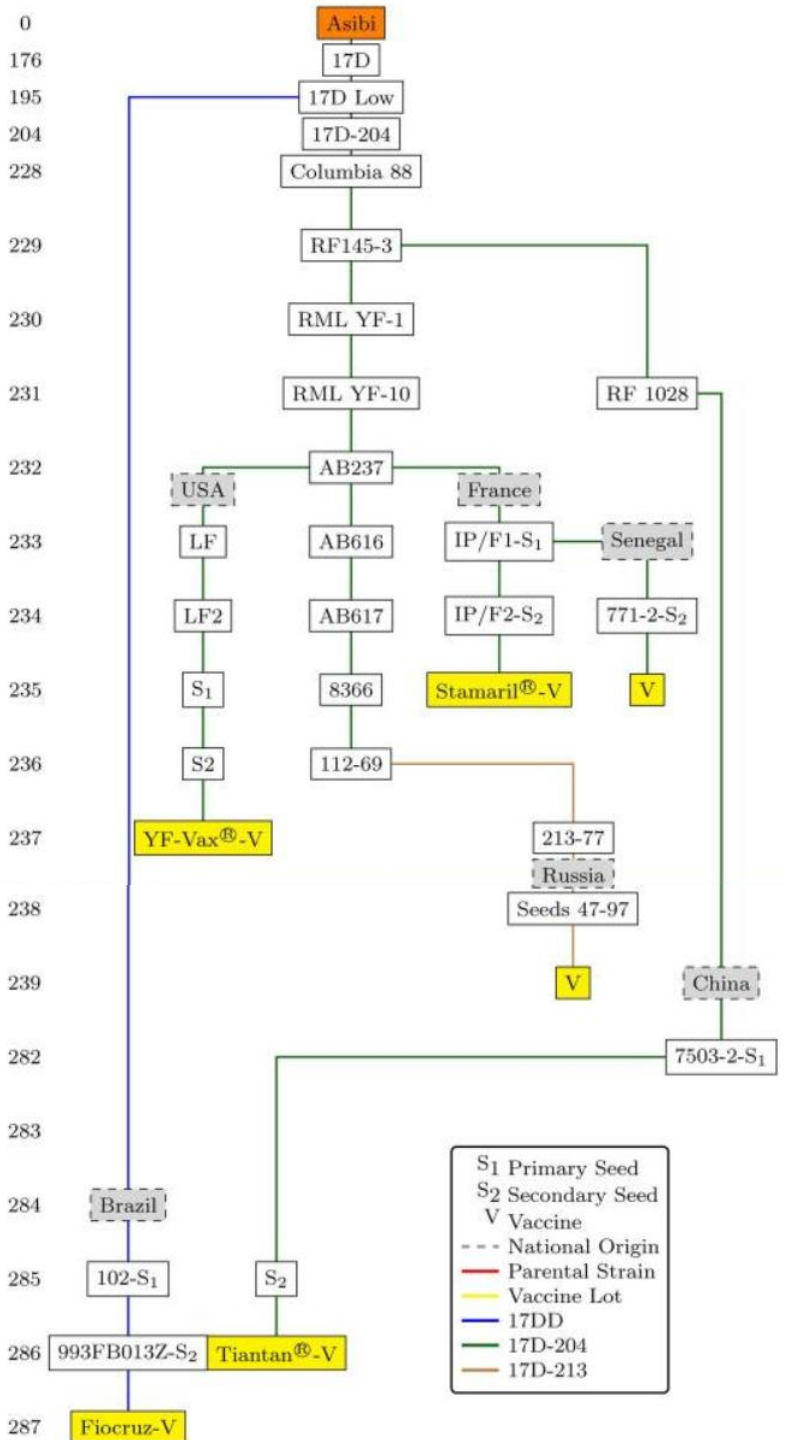
2016 Angiola, DRC
2900 olgu
253 mortalite

2018 Brezilya
464 olgu
154 mortalite

Sarıhumma aşısı

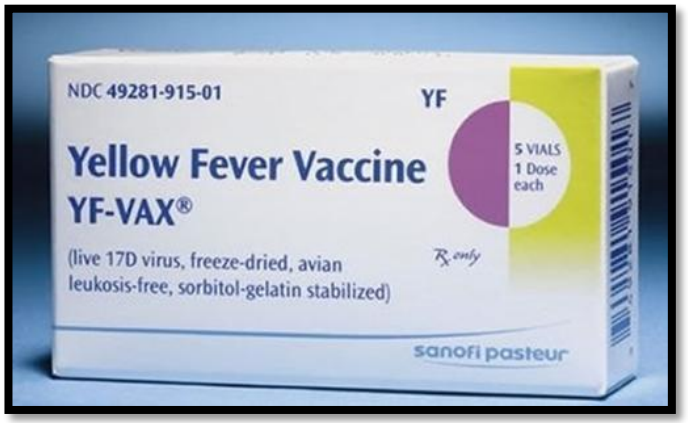
- Max Theiler, 1937, 17D suşu
- Canlı-atenüe aşı
  - 17D-204
  - 17DD





Sarıhumma aşısı

- ABD (17D-204, YF-Vax, SP)
- Fransa (17D-204, Stamaril, SP)
- Senegal (17D-204, Pasteur, Dakar)
- Çin (17D-204, Tiantan, WIBP)
- Rusya (17D-213, Poliyo ve viral ensefalit enst)
- Brazil (17DD, BM/FIOCRUZ)



Sarı Humma aşısı

- Endikasyon
  - Endemik bölgelerde yaşayanlar
    - Rutin infant immünizasyonu
    - Kitlesel aşılama (salgında hedef ≥%80 popülasyon)
  - Endemik bölgelere seyahat eden >9 y bireyler

- Kontrendikasyon
  - <9 ay (≥6 - <9 ay risk değerlendirilmesi)
  - Gebe ve emziren anne; salgın varlığında risk yüksek ise yap
  - Yumurta proteinlerine karşı ciddi alerji
  - Ağır immün yetmezlik, timus yetmezliği

Düşük doz aşı (1/5) etkili

- DRC 490 seronegatif ≥2 y
  - 17DD 1/5 doz (0,1 ml)
  - 482 (98%; 95% CI, 96 to 99) serokonversiyon

Table 3. Seroconversion or Immune Response and Geometric Mean Titer at Follow-up, According to Serostatus at Baseline.*

Subgroup	Seroconversion or Immune Response at Follow-up		P Value	Geometric Mean Titer (95% CI)		P Value
				At Baseline	At Follow-up	
	no./total no.	*% (95% CI)*				
Seronegative at baseline						
All participants	482/493	98 (96–99)	NA	NA	1340 (1117–1607)	NA
Age group			0.06†			<0.001‡
2–5 yr	73/77	95 (87–98)		NA	487 (293–810)	
6–12 yr	114/114	100 (97–100)		NA	1234 (911–1673)	
13–49 yr	157/162	97 (93–99)		NA	2255 (1604–3171)§	
≥50 yr	138/140	99 (95–100)		NA	1368 (999–1872)¶	
Sex			0.03†			0.61‡
Male	251/253	99 (97–100)		NA	1469 (1154–1870)	
Female	231/240	96 (93–98)		NA	1215 (924–1600)	

N Engl J Med. 2018 Feb 14. doi: 10.1056/NEJMoa1710430. [Epub ahead of print] Immunogenicity of Fractional-Dose Vaccine during a Yellow Fever Outbreak - Preliminary Report.

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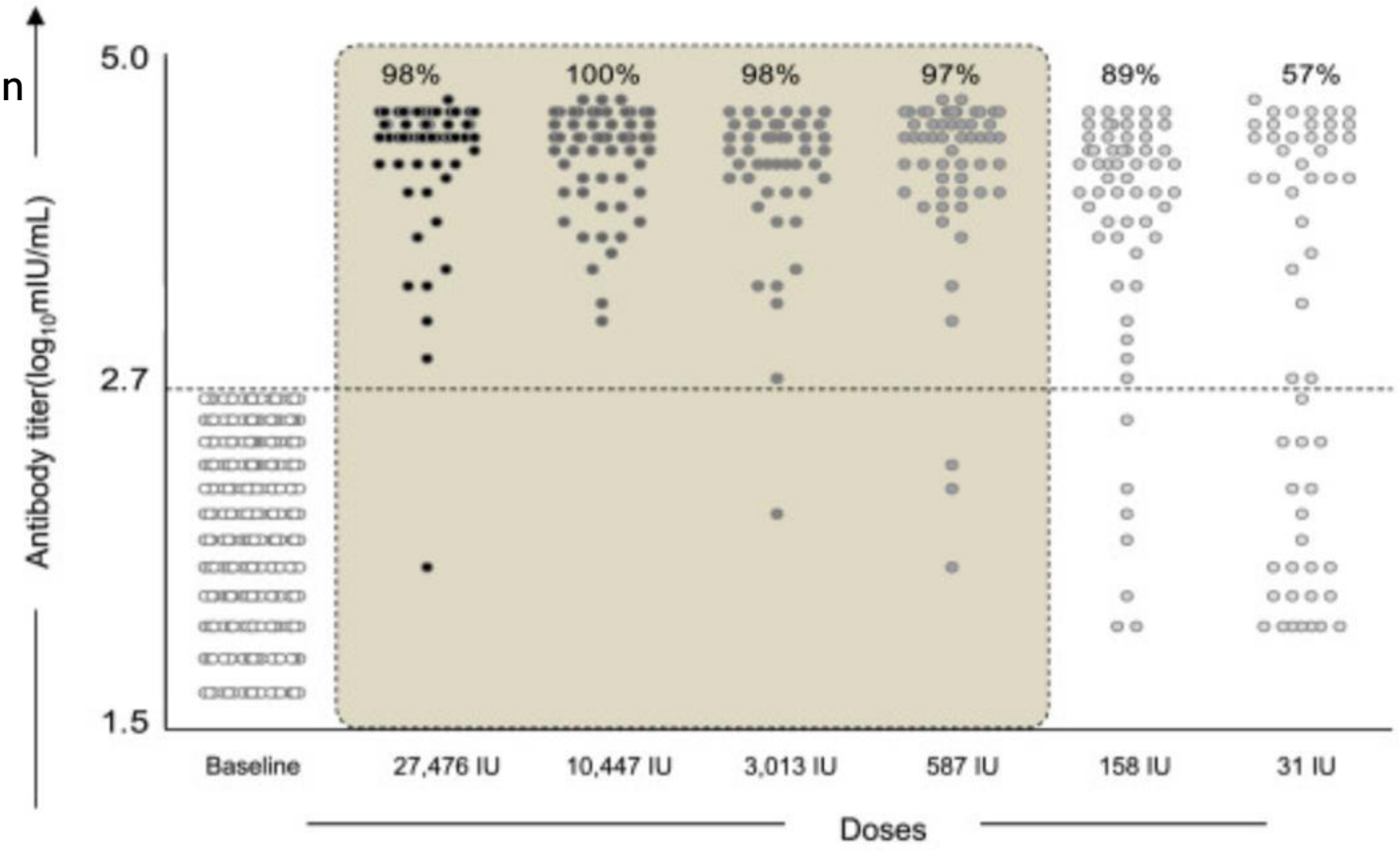
BMC Infectious Diseases
this article | search | submit a manuscript | register

BMC Infect Dis. 2014; 14: 391.
Published online 2014 Jul 15. doi: 10.1186/1471-2334-14-391
PMCID: PMC4223624
PMID: 25022840

Subdoses of 17DD yellow fever vaccine elicit equivalent virological/immunological kinetics timeline

Ana Carolina Campi-Azevedo,[#1] Paula de Almeida Estevam,[#1] Jordana Grazziela Coelho-dos-Reis,[1]
Vanessa Peruhype-Magalhães,[1] Gabriela Villela-Rezende,[1] Patrícia Flávia Quaresma,[1]

900 sağlıklı yetiskin
1/10 doz yeterli



YELLOW FEVER

STRATEGIC RESPONSE PLAN

JUNE-AUGUST 2016

World Health Organization

Jul 2016 – version three

WHO 2016; acil durumlarda 0,1 ml SC uygulanabilir

< 2 yas, gebeler, HIV hastalarında denenmedi

Booster Gerekli Değil-Temmuz 2016

Yellow fever vaccination booster not needed

World Health Organization | Health Topics | Countries | News | Emergencies | About Us

- International travel and health
- Disease information
- Vaccines
- Other travel health risks
- General precautions
- Mode of travel considerations

New yellow fever vaccination requirements for travellers

Amendment to the period of validity of the international certificate of vaccination against yellow fever, which is now extended to the life of the person vaccinated

27 July 2016

In May 2014, The World Health Assembly adopted an amendment to Annex 7 of the International Health Regulations (2005) (IHR), which stipulates that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate will change from 10 years to the duration of the life of the person vaccinated. On 11 July 2016, the amended IHR Annex 7 entered into force and is legally binding upon all IHR States Parties. The revised Third Edition of the IHR includes this amended text.

Thus, **from 11 July 2016 the certificate of vaccination against yellow fever is valid for the life of the person vaccinated.** This lifetime validity applies automatically to all existing and new certificates, beginning 10 days after the date of vaccination. Accordingly, as of 11 July 2016, revaccination or a booster dose of yellow fever vaccine will not be required for international travellers as a condition of entry into a State Party, regardless of the date that their international certificate of vaccination was initially issued.

ACIP - Haziran 2015

- Tek doz SH aşı yeterli
- **ANCAK**
  - Gebelik esnasında aşılananlar, sonrasında ilave doz
  - Aşıdan sonra HSC transplantlılar, immünrekonstruksiyon sonrası
  - HIV enfeksiyonlular 10 yılda bir
  - >10 aşılı bir kişinin;
    - Endemik bölgede uzun sure kalacak olması,
    - Yüksek endemik bölgeye (Bati Afrika kirsal kesim) bulaş sezonunda seyahat etmesi,
    - Salgın esnasında seyahat
    - Laboratuvar çalışanları

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

18-49 y 60 gönüllü, Faz 1
pürifiye tam-virüs XRX-001
24 kişi 0,48 µg,
24 kişi 4,8 µg,
12 kişi plesebo

($PRNT_{50}$>10)

An Inactivated Cell-Culture Vaccine against Yellow Fever

Thomas P. Monath, M.D., Elizabeth Fowler, Ph.D., Casey T. Johnson, D.O., John Balser, Ph.D., Merribeth J. Morin, Ph.D., Maggie Sisti, B.S., and Dennis W. Trent, Ph.D.

ABSTRACT

BACKGROUND

Yellow fever is a lethal viral hemorrhagic fever occurring in Africa and South America. A highly effective live vaccine (17D) is widely used for travelers to and residents of areas in which yellow fever is endemic, but the vaccine can cause serious adverse events, including viscerotropic disease, which is associated with a high rate of death. A safer, nonreplicating vaccine is needed.

From Xcellerex, Marlborough, MA (T.P.M., E.F., M.J.M., M.S., D.W.T.); Johnson City Clinical Trials, Lenexa, KS (C.T.J.); and Veristat, Holliston, MA (J.B.). Address reprint requests to Dr. Monath at Kleiner, Perkins, Caufield, and Byers, 2750 Sand Hill Rd., Menlo Park, CA 94025, or at tmonath@kpcb.com.

N Engl J Med 2011;364:1326-33.

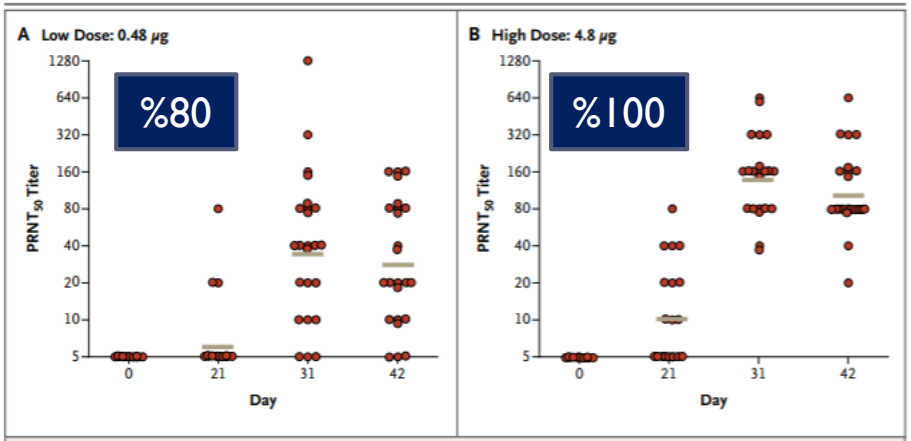


Figure 1. Plaque-Reduction Neutralization Test (PRNT) Titers of Neutralizing Antibody through Day 42 in the Two Vaccination Groups, According to Dose.

Panel A shows data for the low-dose vaccination group, and Panel B data for the high-dose vaccination group. The $PRNT_{50}$ titer is the highest serum dilution inhibiting 50% or more of the plaques. Values for each subject and the geometric mean titers (horizontal gray lines) are shown.

PLOS | NEGLECTED TROPICAL DISEASES

- FARE deneyi
- DNA plazmid, vektör
  - p/YFE; i veya
  - LAMP-1 pL/YFE
- 17DD suşu
- Boş vektör
- PBS

RESEARCH ARTICLE

A DNA Vaccine against Yellow Fever Virus: Development and Evaluation

Milton Maciel, Jr.[1¤], Fábia da Silva Pereira Cruz[2], Marli Tenório Cordeiro[2,3], Márcia Archer da Motta[4], Klécia Marília Soares de Melo Cassemiro[2], Rita de Cássia Carvalho Maia[5], Regina Célia Bressan Queiroz de Figueiredo[2], Ricardo Galler[4], Marcos da Silva Freire[4], Joseph Thomas August[1], Ernesto T. A. Marques[1,2,6]*, Rafael Dhalia[2]

1 Johns Hopkins University, School of Medicine, Department of Pharmacology & Molecular Sciences, Baltimore, Maryland, United States of America, **2** Oswaldo Cruz Foundation (FIOCRUZ), Aggeu Magalhães Research Centre, Department of Virology, Laboratório de Virologia e Terapia Experimental (LAVITE), Universidade Federal de Pernambuco (UFPE), University City, Recife, Pernambuco, Brazil, **3** Health Secretariat of the State of Pernambuco, Central Public Health Laboratory-LACEN, Boa Vista, Recife, Pernambuco, Brazil, **4** Oswaldo Cruz Foundation (FIOCRUZ), Oswaldo Cruz Institute, Bio-Manguinhos, Laboratório de Tecnologia Viro
University of Pernambuco, Dep
6 University of Pernambuco, Cen

¤ Current address: ETEC Vac

CrossMark
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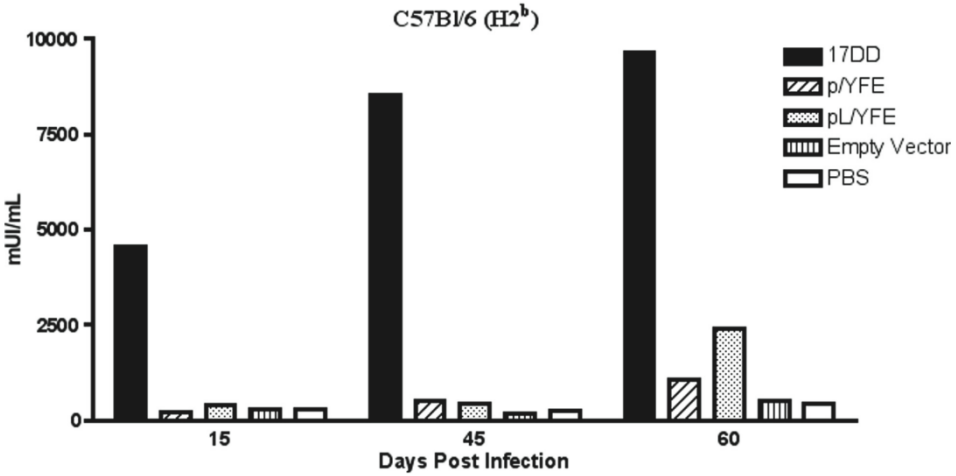
Table 5. C57Bl/6 and BALB/c mouse challenge experiments after immunization with the YF 17DD vaccine or the DNA constructs.

Immunization	Challenge (10^5 PFUs)	C57Bl/6		BALB/c	
		Mortality (deaths/ total number inoculated)	Average survival time (days ± SD)	Mortality (deaths/ total number inoculated)	Average survival time (days ± SD)
YF 17DD vaccine	YF 17DD virus	0/10	-	0/10	-
p/YFE	YF 17DD virus	0/10	-	0/10	-
pL/YFE	YF 17DD virus	0/10	-	0/10	-
Empty vector	YF 17DD virus	10/10	12.8±0.92	8/10	10.3±0.46
PBS	YF 17DD virus	10/10	12.4±0.97	9/10	10.9±1.17
PBS	PBS	0/5	-	0/5	-

doi:10.1371/journal.pntd.0003693.t005



Staphylococcus aureus

Development status of *Current* vaccine candidates.

Candidate name/Identifier	Developer	Vaccine approach	Pre-clinical	Phase I	Phase II	Status
Active prophylactic vaccines						
PF-06290510/SA4Ag	Phizer	ClfA/MntC/CP5/CP8 conjugated to CRM_{197}			X	Safety and Efficacy of SA4Ag Vaccine in Adults Having Elective Posterior Instrumented Lumbar Spinal Fusion Procedure (STRIVE): NCT01827358
					X	SA4Ag Safety, Tolerability, and Immunogenicity Study in Japanese Adults: NCT02492958
GSK2392103A	GSK	CP5/CP8/TT/AT/ClfA plus AS03B		X		No longer under active development. A Study to Evaluate the Safety, Reactogenicity and Immunogenicity of GSK Biologicals' Staphylococcal Investigational Vaccine in Healthy Adults: NCT01160172 [34]
NDV3	NovaDigm Therapeutics	rAls3p-N (C.albicans surface protein that cross reacts with *S. aureus*) plus Alum		X		Under development. Safety and Immunogenicity Study of a Recombinant Protein Vaccine (NDV-3) Against *S. aureus* and Candida: NCT01273922. Clinical development for Vulvovaginal candidiasis (VVC) ongoing: NCT01926028
Glycosylated CP5, CP8, and Hla_{H35L}	GSK (Glycovaxyn)		X			[33]
SA75	Vaccine Research International	Whole cell vaccine		X		No longer under active development http://www.vri.org.uk/PhaseITrial.pdf
4C-Staph	Novartis	FhiD2, EsxAB, Hla, Sur-2	X			[35]
SAG	Pan Chai University	*S. aureus* ghosts	X			[36]
various	IBT/NIAID	Multi-valent attenuated toxoid	X			[37]
Passive prophylactic immunization						
MEDI4893	Medimmune	mAb binding to S. aureus toxin			X	Dose-ranging efficacy and safety in mechanically Ventilated Adults: NCT02296320
AR-301	Aridis	mAb			X	Phase I/II Safety, Pharmacokinetics and Efficacy of KBSA301 in Severe Pneumonia (*S. aureus*) as an adjunctive therapy to standard of care antibiotics in hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) patients: NCT01589185

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 11, 2682–2691
https://doi.org/10.1080/21645515.2018.1496764

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RESEARCH PAPER

Safety, tolerability, and immunogenicity of a novel 4-antigen *Staphylococcus aureus* vaccine (SA4Ag) in healthy Japanese adults

Megumi Inoue[a], Takuma Yonemura[b], James Baber [c], Yasuko Shoji[d], Masakazu Aizawa [d], David Cooper[e], Joseph Eiden[e], William C. Gruber[e], Kathrin U. Jansen[e], Annaliesa S. Anderson[e], and Alejandra Gurtman[e]

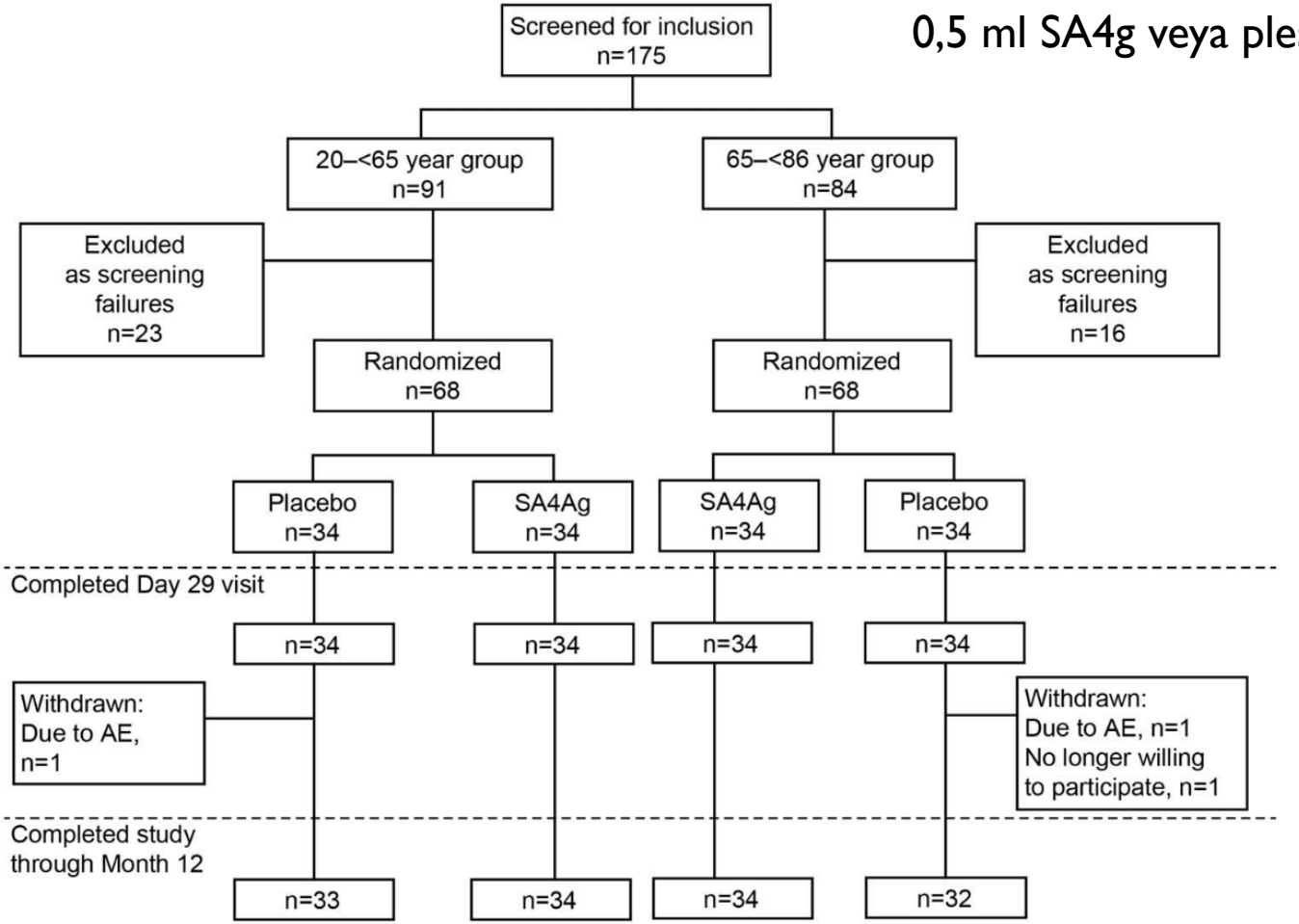
[a]SOUSEIKAI PS Clinic, Fukuoka, Japan; [b]SOUSEIKAI Sumida Hospital, Tokyo, Japan; [c]Pfizer Vaccine Research and Development, Sydney, NSW, Australia; [d]Pfizer Vaccine Research and Development, Tokyo, Japan; [e]Pfizer Vaccine Research and Development, Pearl River, NY, USA

SA4Ag;

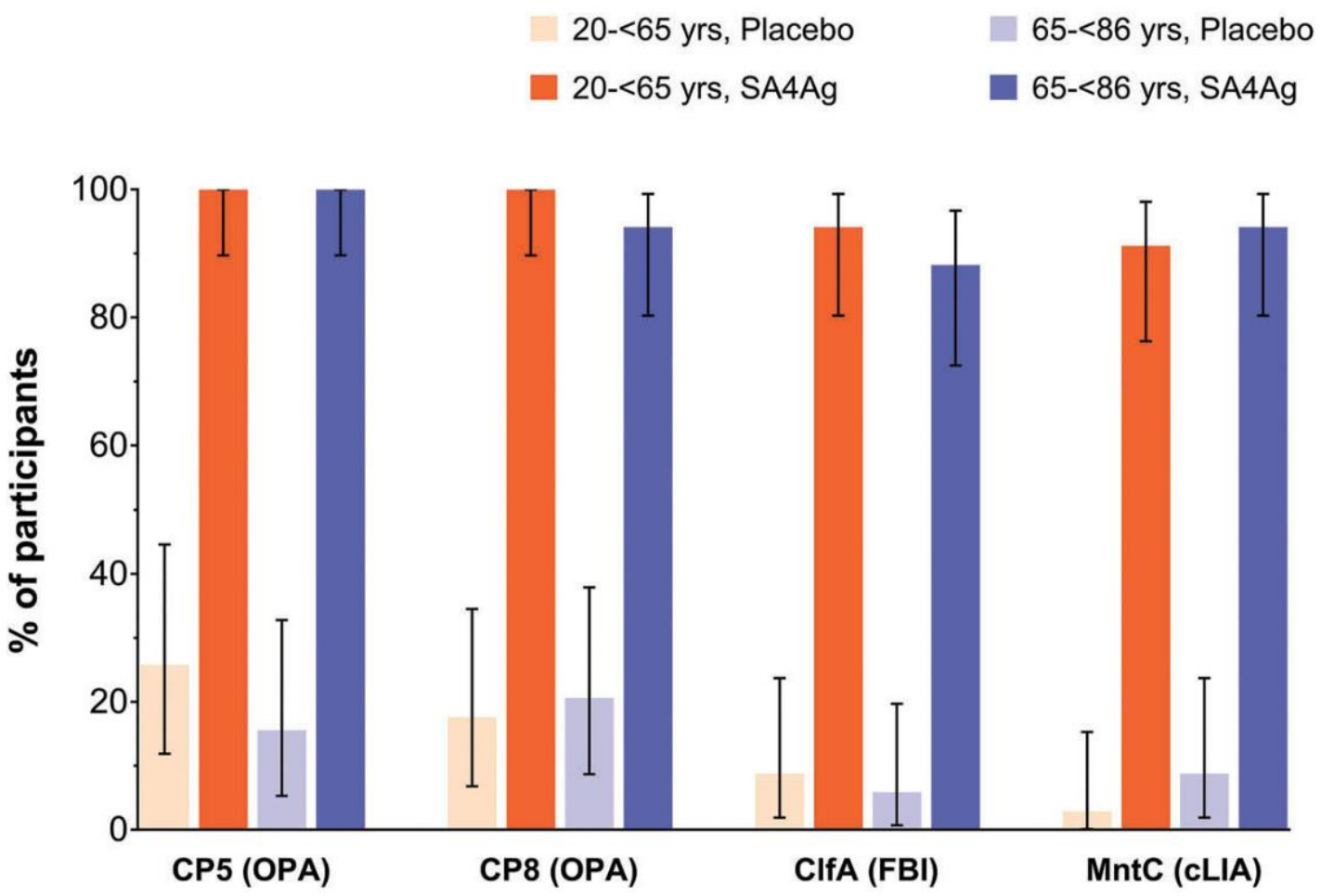
- CRM197 ile konjuge kapsüler serotip tip 5 ve 8 (CP5 30µg ve CP8 30µg),
- rekombinant clumping faktör A (ClfA 60µg),
- lipoprotein mangan trasnporter C (MntC)'den geliştirilen rekombinant protein P305A (rP305A 200µg)

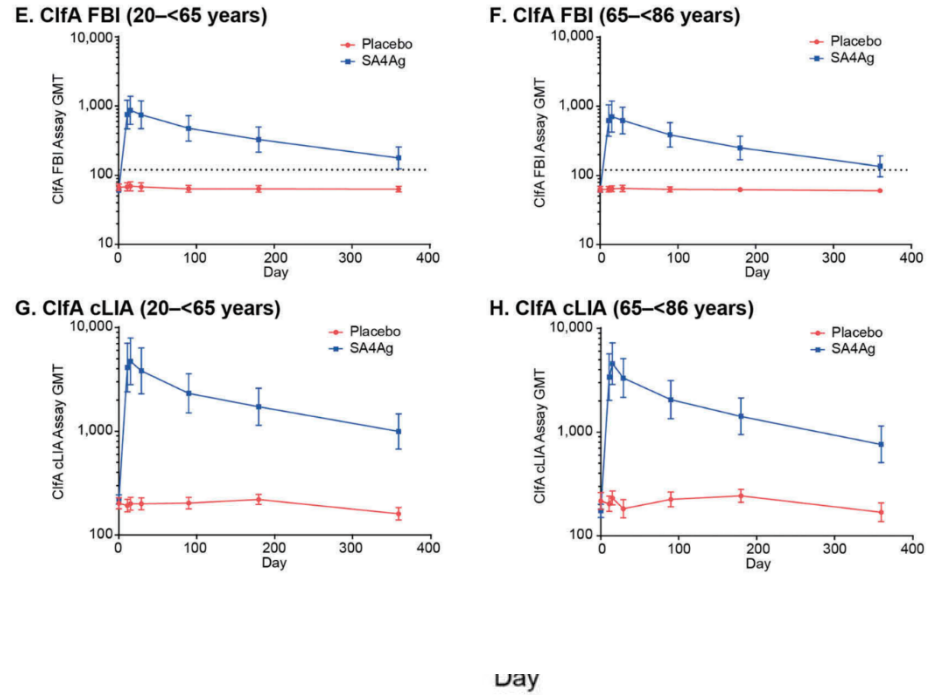
- Faz 1/2a; çok merkezli, paralel grup, plesebo kontrol
- 2015-2016

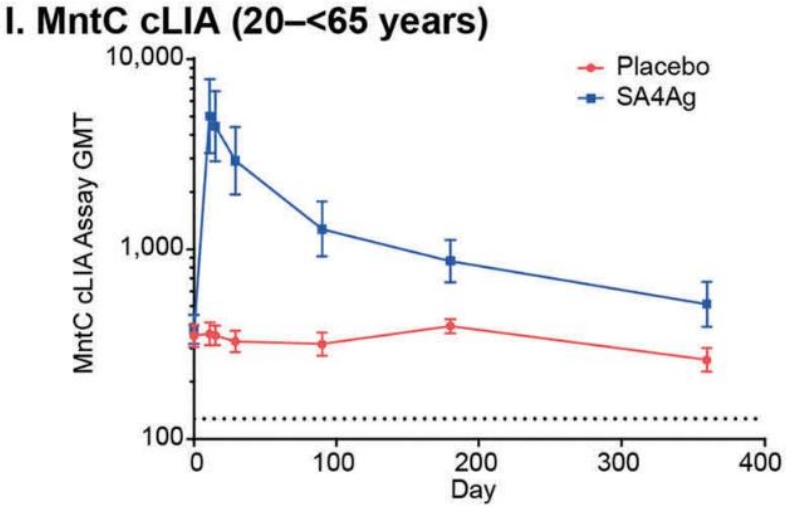
0,5 ml SA4g veya plesebo IM



Hedef antijenlere 29. günde Ab yanıtları




E. ClfA FBI (20–<65 years)
F. ClfA FBI (65–<86 years)
A. CP5 OPA (20–<65 years)
B. CP5 OPA (65–<86 years)
G. ClfA cLIA (20–<65 years)
H. ClfA cLIA (65–<86 years)
C. CP8 OPA (20–<65 years)
D. CP8 OPA (65–<86 years)
Placebo
SA4Ag
ClfA FBI Assay GMT
ClfA cLIA Assay GMT
CP5 OPA Assay GMT
CP8 OPA Assay GMT
Day


I. MntC cLIA (20–<65 years)
J. MntC cLIA (65–<86 years)
Placebo
SA4Ag
MntC cLIA Assay GMT
Day

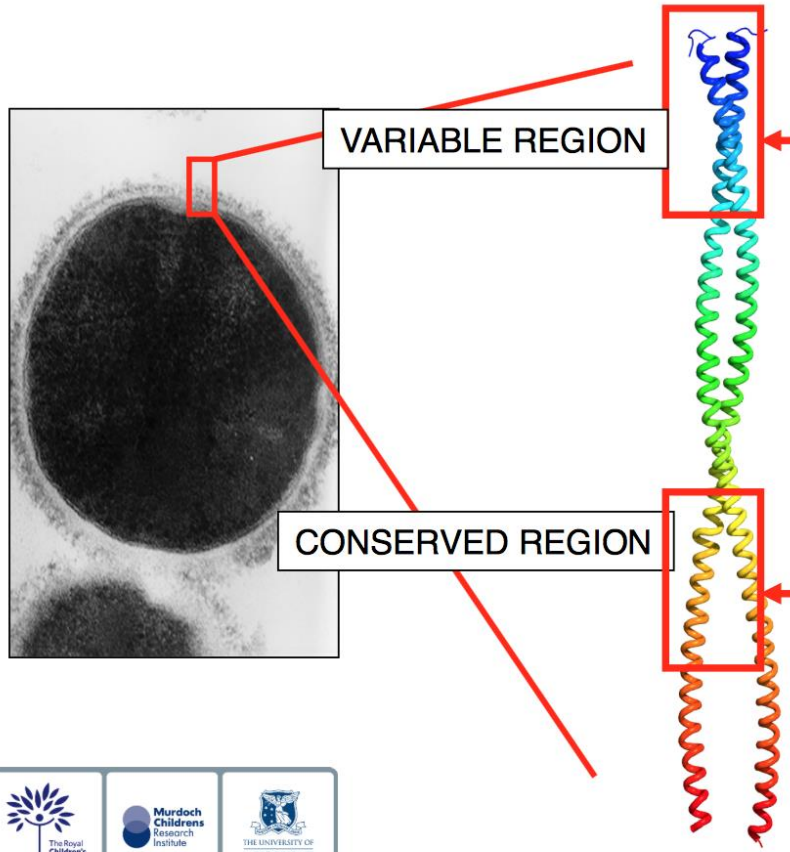
Sonuç

- SA4Ag hızlı ve güçlü immün yanıt oluşturuyor
- Ab etkinliği 12 ay sureyle devam ediyor
- Avustralya ve ABD çalışmalarıyla benzer sonuç
- Güvenlik profili iyi

Streptococcus pyogenes

30-valent vaccine (StreptAnova)	M protein (HVR region)	Jim Dale, PREVENT, USA	Phase 1 complete (awaiting results)
J8 vaccine	M protein (C-terminal peptide)	Michael Good, Australia	Phase 1 of reformulated vaccine (planned)
StreptinCor	M protein (C-terminal peptide)	Luiza Guilherme, Brazil	Phase 1 (planned)
"Combo"	Non-M protein multi-antigen	Novartis/GSK	Under development

M-based designs / non M-based



M proteini/*emm* tiplemesi (223 tip)

-J8 asisi
-StretinCor

Melbourne Children's
Excellence in clinical care, research and education
The Royal Children's Hospital Melbourne
Murdoch Childrens Research Institute
The University of Melbourne

Safety and Immunogenicity of 26-Valent Group A Streptococcus Vaccine in Healthy Adult Volunteers-Faz 1

- 4 rekombinant protein; 26 serotip N terminal peptit ve Spa (yüzey antijeni)
- 30 sağlıklı yetişkin, IM 400 µg 26 valan GAS aşı
- 0,1,4. ay IM 0,5 mL
- 26/27 ag >4 kat Ab artışı
- Log2 serum Ab artışı, tüm 27 ag için 3,67+/-0,21
- Log2 serum örneklerinde strepotokokal bakteriyel miktarında azalma anlamlı
- Sonuç: aşı güvenli ve etkili

Clinical Infectious Diseases, Volume 41, Issue 8, 15 October 2005, Pages 1114–1122, https://doi.org/10.1086/444458

30 valanlı Aşı (StreptAnova)

- Prekilinik çalışmalar
  - Aşıda yer alan Tüm emm tiplerine fonksiyonel ab yanıtı
  - Aşı içeriğinde olmayan emm tiplerine çapraz opsonizasyon
  - Faz 1 başlatıldı
  - 45 sağlıklı
  - 6 ay ara ile 3 aşı
  - Aşı sonrası 1 yıl immün yanıt ve güvenlik izlemi

J 8 Aşısı

- M prt C-tekrar bölgesi B hücre epitop
- Opsonik Ab üretimini uyarır (Fare)
- İntra peritoneal enfeksiyon modelinde koruma (paranteral aşı)
- İntranazal bulaş modelinde koruma (IN aşı)
- Faz1 çalması, tek doz, immünojenik ve güvenli
- CXC kemokin proteaz içeren formülasyonu fare modelinde impetigoya karşı koruyucu

Batzloff MR. Protection against Group A Streptococcus by immunization with J8-diptheria toxoid: contribution of J8- and diptheria toxoid-specific antibodies to protection. J Infect Dis 2003;187:1598–608.