Son Literatürlerden Seçmeler

Prof. Dr. Volkan Korten
Yrd. Doç. Dr. Elif Tükenmez Tigen

Literatürler

1. Sistematik Derleme: Ig E aracılı Penisilin veya Sefalosporin alerjisi olan hastalara Karbapenem verilebilir mi?
2. Tetravalan Deng aşısının etkinliği
3. Duyarlı Tüberküloz tedavisinde 4 aylık Moxifloksasin bazlı rejimin etkinliği

MAJOR ARTICLE

A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

Brittany Kula, Gordana Djordjevic, and Joan L. Robinson

Department of Pediatrics, University of Alberta and Stollery Children's Hospital, Edmonton, Canada

CID 2014:59 (15 October) •

A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

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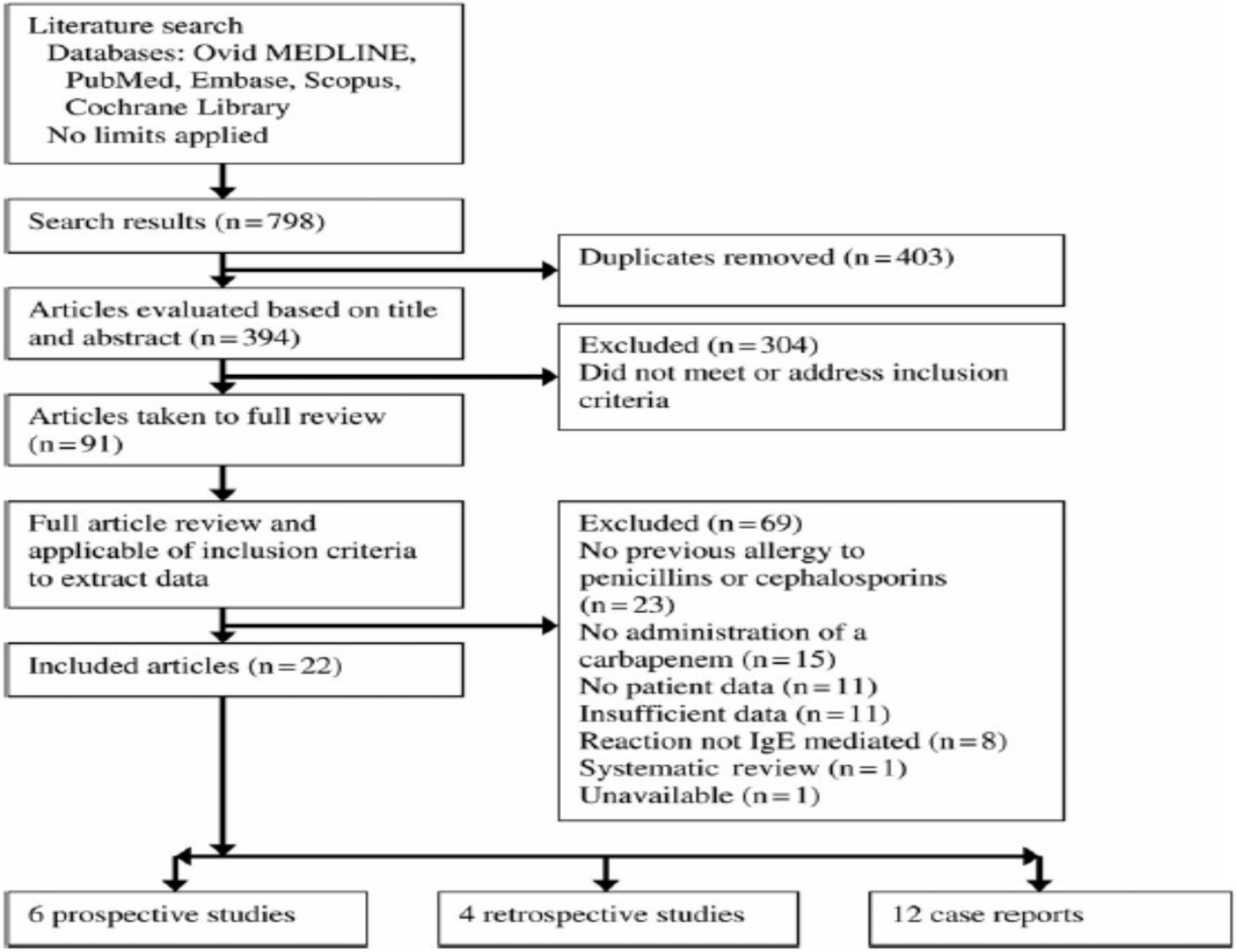
- Penisilin ve Sefalosporin arası çapraz reaksiyon→%10→Yeni sefalosporinler %1
- Penisilin ve karbapenemler arası çapraz reaksiyon düşük olmalı????

A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

- Hipersensitivite, çapraz reaksiyon, penisilin, sefalosporin, karbapenem kelimeleri ile taratıldı.


Literature search
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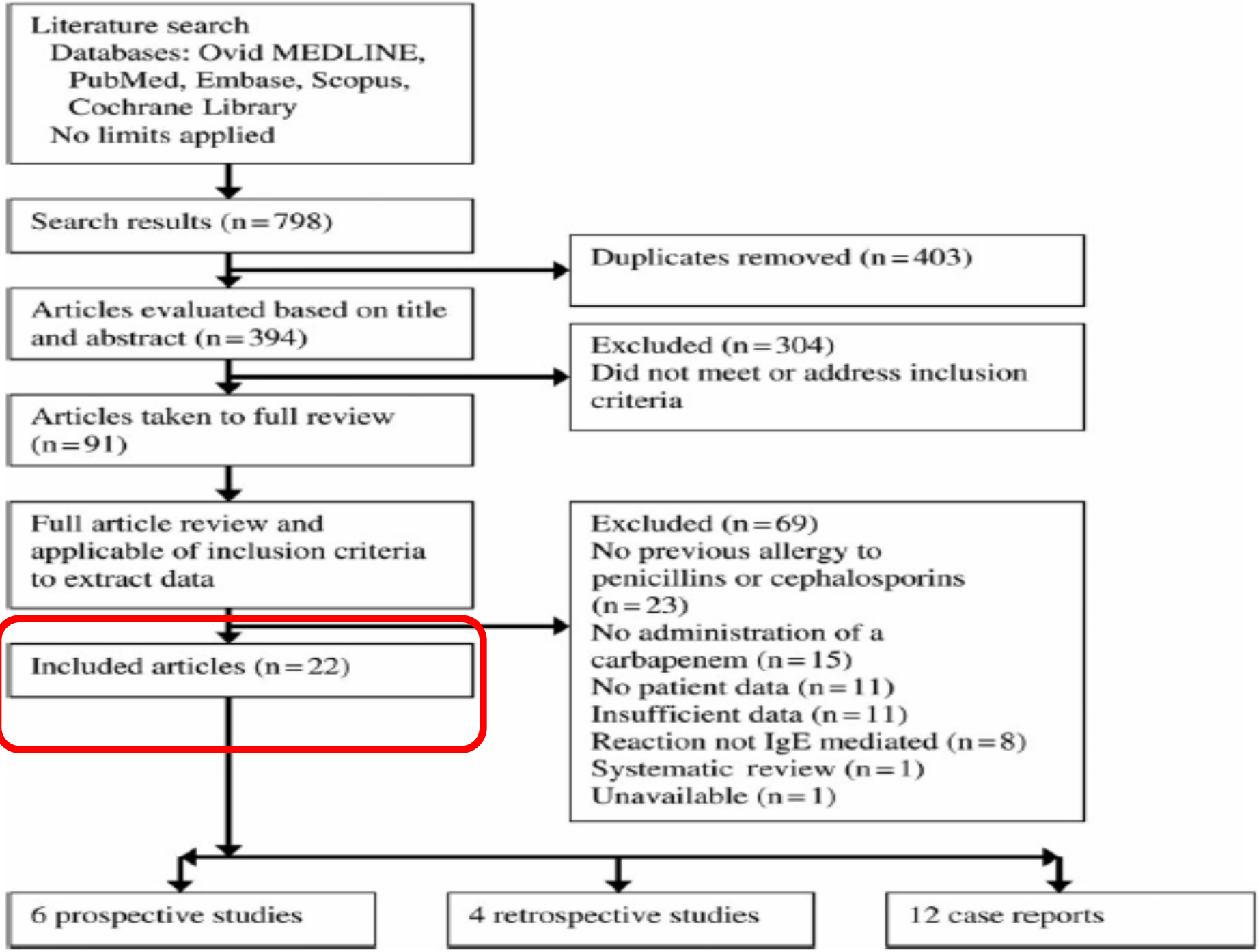
Search results (n = 798)
Duplicates removed (n = 403)
Articles evaluated based on title and abstract (n = 394)
Excluded (n = 304)
Did not meet or address inclusion criteria
Articles taken to full review (n = 91)
Full article review and applicable of inclusion criteria to extract data
Excluded (n = 69)
No previous allergy to penicillins or cephalosporins (n = 23)
No administration of a carbapenem (n = 15)
No patient data (n = 11)
Insufficient data (n = 11)
Reaction not IgE mediated (n = 8)
Systematic review (n = 1)
Unavailable (n = 1)
Included articles (n = 22)
6 prospective studies
4 retrospective studies
12 case reports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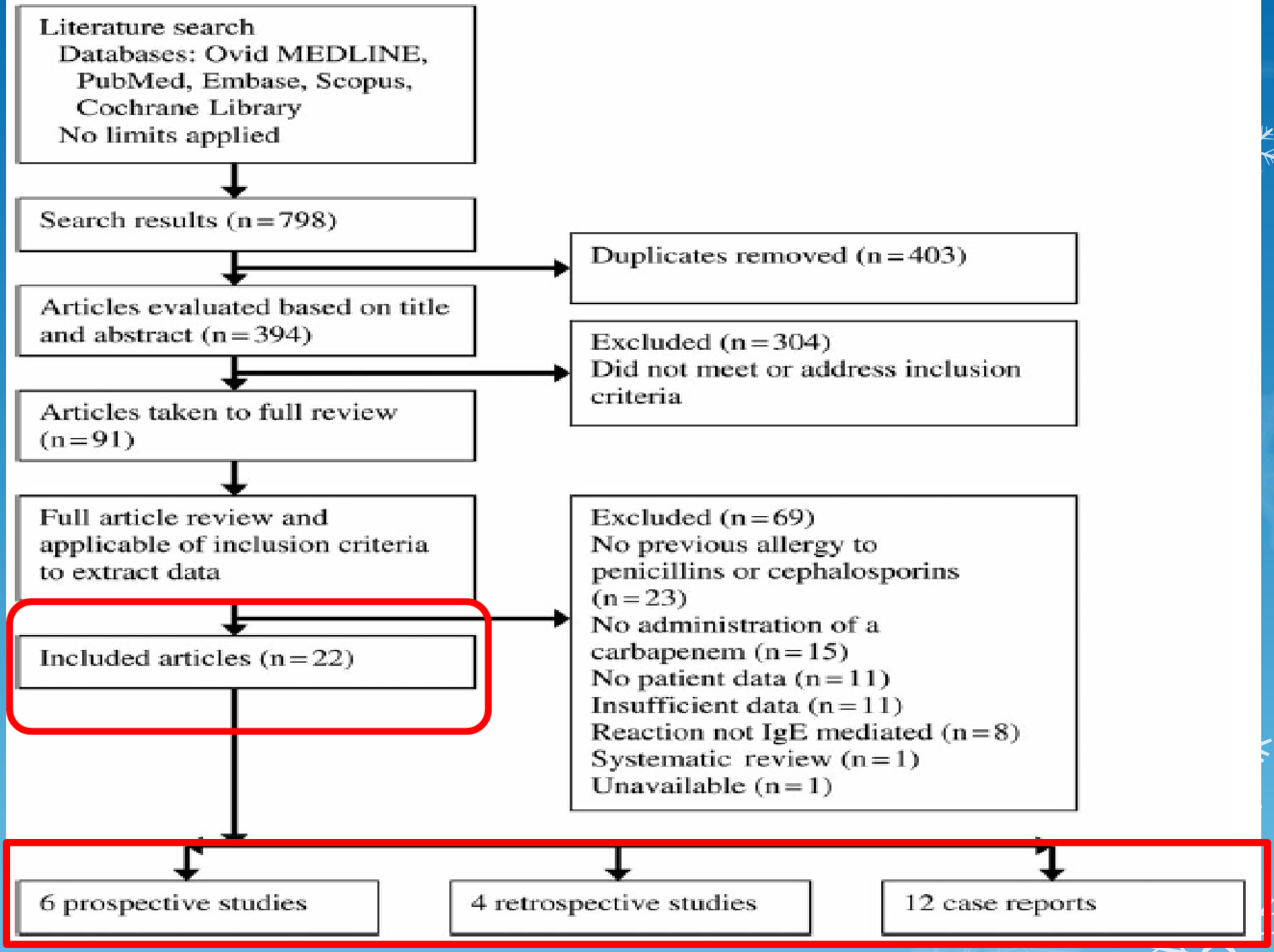
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A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

- *Dahil edilme kriterleri:*
  - Penisilin/Sefalosporin'e karşı Ig E aracılı hipersensitivite (+)→ Karbapenem
- *Dışlama kriterleri:*
  - Cilt testi (+) olup hiç antib. verilmemiş olma

A Systematic Review: Can One Prescribe Carbapenems to Patients With IgE-Mediated Allergy to Penicillins or Cephalosporins?

- Reaksiyonlar → Olası, şüpheli, kanıtlanmış.
- *Tanımlar:*
  - Kanıtlanmış allerjik reak: 4 saat içinde ciddi anafilaksi gelişmesi(anjiyoödem, laringeal ödem, hospitalizasyon)
  - Şüpheli: Cilt reaksiyonları (kaşıntı, döküntü)
  - Olası: 4 saatten sonra ve tam tariflenemeyen semptomlar

Table 1. Case Series of Children or Adults With Previous Immunoglobulin E-Mediated Reactions to Penicillins or Cephalosporins Subsequently Given Carbapenems

Source	Study Design	Class of Drug Causing Previous Reaction	Number of Patients Meeting Inclusion Criteria	Age Range (Years)	Classification of Penicillin/ Cephalosporin Reaction	Carbapenem Administered
Atanasković-Marković et al (2008) [9]	Prospective	Penicillin	107	4–13	Proven IgE-mediated	Meropenem
Atanasković-Marković et al (2009) [7]	Prospective	Penicillin	123	4–13	Proven IgE-mediated	Imipenem
Cunha et al (2008) [11]	Prospective	Penicillin	110	28–94	51 proven and 59 possible IgE-mediated	Meropenem
Patriarca et al (1999) [6]	Prospective	Penicillin	9	17–63	4 possible, 2 suspected, and 3 proven IgE-mediated	Imipenem
Romano et al (2006) [8]	Prospective	Penicillin	110	45.56 ± 15.66	Proven IgE-mediated	Imipenem
Romano et al (2007) [10]	Prospective	Penicillin	103	14–83	Proven IgE-mediated	Meropenem
Lager et al (2009) [12]	Retrospective	Penicillin	94	>18	7 proven, 32 suspected, and 55 possible IgE-mediated	Imipenem, meropenem or ertapenem
McConnell et al (2000) [13]	Retrospective	Penicillin	63	20–74	Possible IgE-mediated	Imipenem
Prescott et al (2004) [14]	Retrospective	Penicillin	100	2–86	Possible IgE-mediated	Imipenem or meropenem
Sodhi et al (2004) [15]	Retrospective	Penicillin	163	32–91	10 proven and 153 possible IgE-mediated	Imipenem or meropenem

- 854 hasta çalışmaya alındı.
- 838 penisilin, 12 sefalosporin, 4 penisilin/sefalosporin reaksiyon.
- Karbapenem reaks→ 40/854 (%4.7) vakada gelişti.

Table 2. Reactions to Carbapenems in Children and Adults With Previous Immunoglobulin E-Mediated Reactions to Penicillins

Reference	Evidence for Allergy	Skin Test	Country	Age of Population (Years)	N	Type of Carbapenem	Number With Proven IgE-Mediated Reactions to Carbapenem	Number With Suspected IgE-Mediated Reactions to Carbapenem	Number With Possible IgE-Mediated Reactions to Carbapenem	Number With Non–IgE-Mediated Reactions to Carbapenem	Total Number With Reactions to Carbapenem
Atanasković-Marković et al (2009, 2008) [7, 9]	Proven IgE-mediated	Positive	Serbia	3–14	81	Imipenem and meropenem	0	0	0	0	0
Cunha et al (2008) [11]	Proven IgE-mediated	NR	United States	28–94	51	Meropenem	0	0	0	0	0
Atanasković-Marković et al (2009) [7]	Proven IgE-mediated	Positive	Serbia	3–14	42	Imipenem	0	0	0	0	0
Atanasković-Marković et al (2008) [9]	Proven IgE-mediated	Positive	Serbia	3–14	26	Meropenem	0	0	0	0	0
Sodhi et al (2004) [15]	Proven IgE-mediated	NR	United States	32–91	10	Imipenem or meropenem	0	0	0	1	1
Lager et al (2009) [12]	Proven IgE-mediated	NR	United States	>18	7	Imipenem, meropenem, or ertapenem	0	0	0	0	0
Patriarca et al (1999) [6]	Proven IgE-mediated	Negative	Italy	23–60	3	Imipenem	0	0	0	0	0
Gorman et al (2003) [18]	Proven IgE-mediated	Positive	Canada	40	1[a]	Imipenem	0	0	1	0	1
Romano et al (2007) [10]	Suspected IgE-mediated	Positive	Italy	14–83	35	Meropenem	0	0	0	0	0
Romano et al (2006, 2007) [8, 10]	Suspected IgE-mediated	Positive	Italy	NR	68	Imipenem and meropenem	0	0	0	0	0
Romano et al (2006) [8]	Suspected IgE-mediated	Positive	Italy	44.56 ± 15.66	42	Imipenem	0	0	0	0	0

- Karbapenem'e karşı reaks→36/838 (%4.3)
  - Kanıtlanmış→1/838
  - Şüpheli→0/838
  - Olası→19/838

  } Ig-E aracılı
  - 16 vaka→ Non Ig-E aracılı
  - 295 cilt testi (+) olanların arasında reaks. gelişen sadece 1 kişi var.
  - **Ig-E aracılı karbapenem allerjik reaksiyon→% 0.5**

- Sefalosporin'e Ig E aracılı reaksiyon gelişen 12 hastanın;
  - Olası allerjik reaksiyon→1 hasta Ig-E aracılı reaksiyon
  - Non-Ig E aracılı reaksiyon→ 2 hasta
  - Şüpheli Karbapenem reaksiyon→%50
  - Olası Karbapenem reaksiyon→%20

- Sayı çok az

Sonuç

- Ig E aracılı penisilin alerjisi olan bir hastada beta-laktam verilmesi gerekirse karbapenem güvenli olabilir ama yine de dikkatli vermek gerekir.
- %1 dozu önce denenmeli, 1 saat sonra %10'u reaksiyon gelişmezse tam doz verilmesi önerilmekte.
- Karbapenem cilt testi çok güvenilir değil.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

- Plasebo-kontrollü çift kör randomize faz 3 çalışma
  - Çalışma hastaları:
  - ≥18yaş yeni tanı daha önce tedavi almamış ve kx de üremesi olan ve rifampisin ve kinolon duyarlı olan hastalar çalışmaya alınmış
  - HIV (+) hastalar CD4>250 ve ART almıyorlarsa çalışmaya dahil edilmişler.

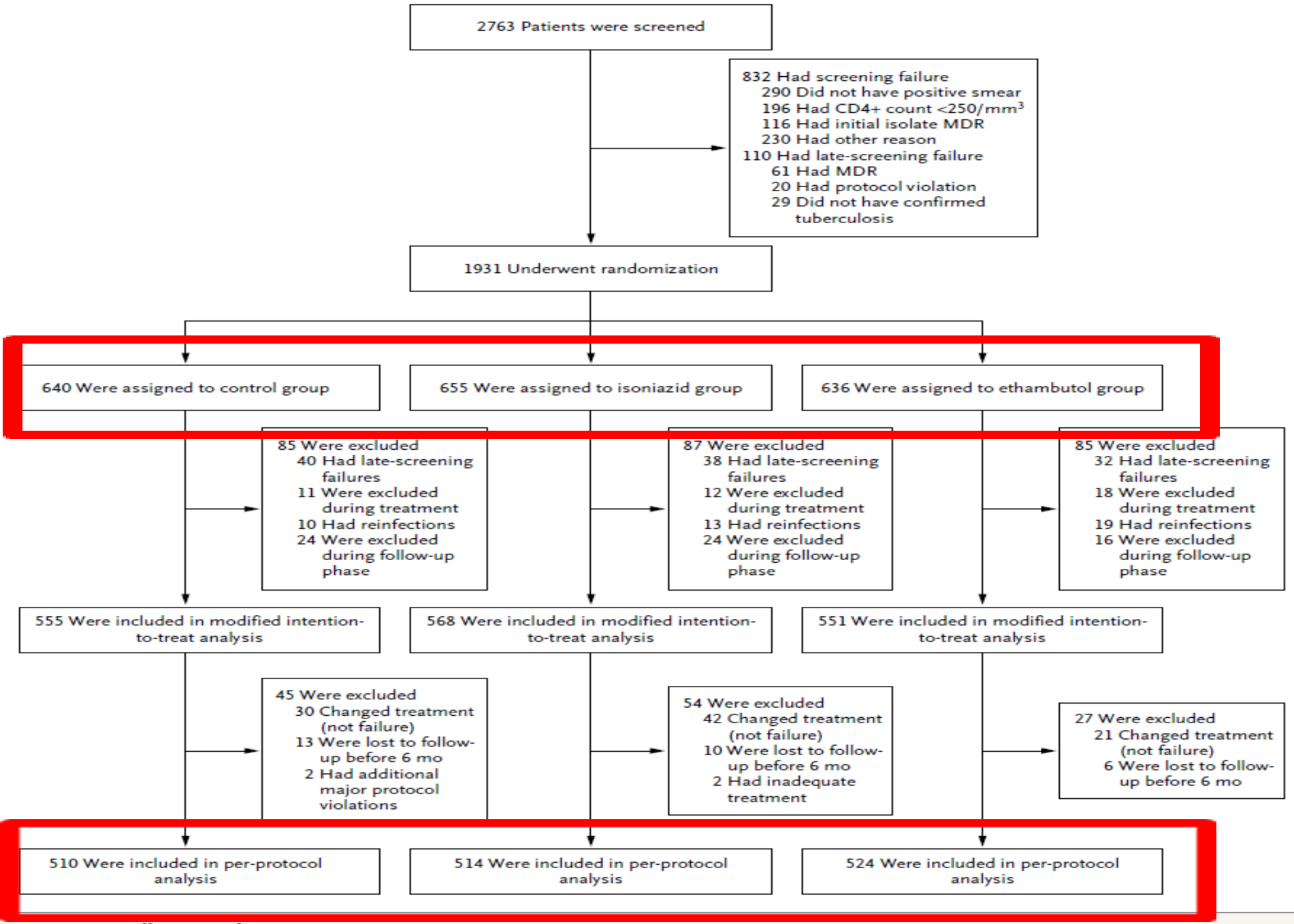
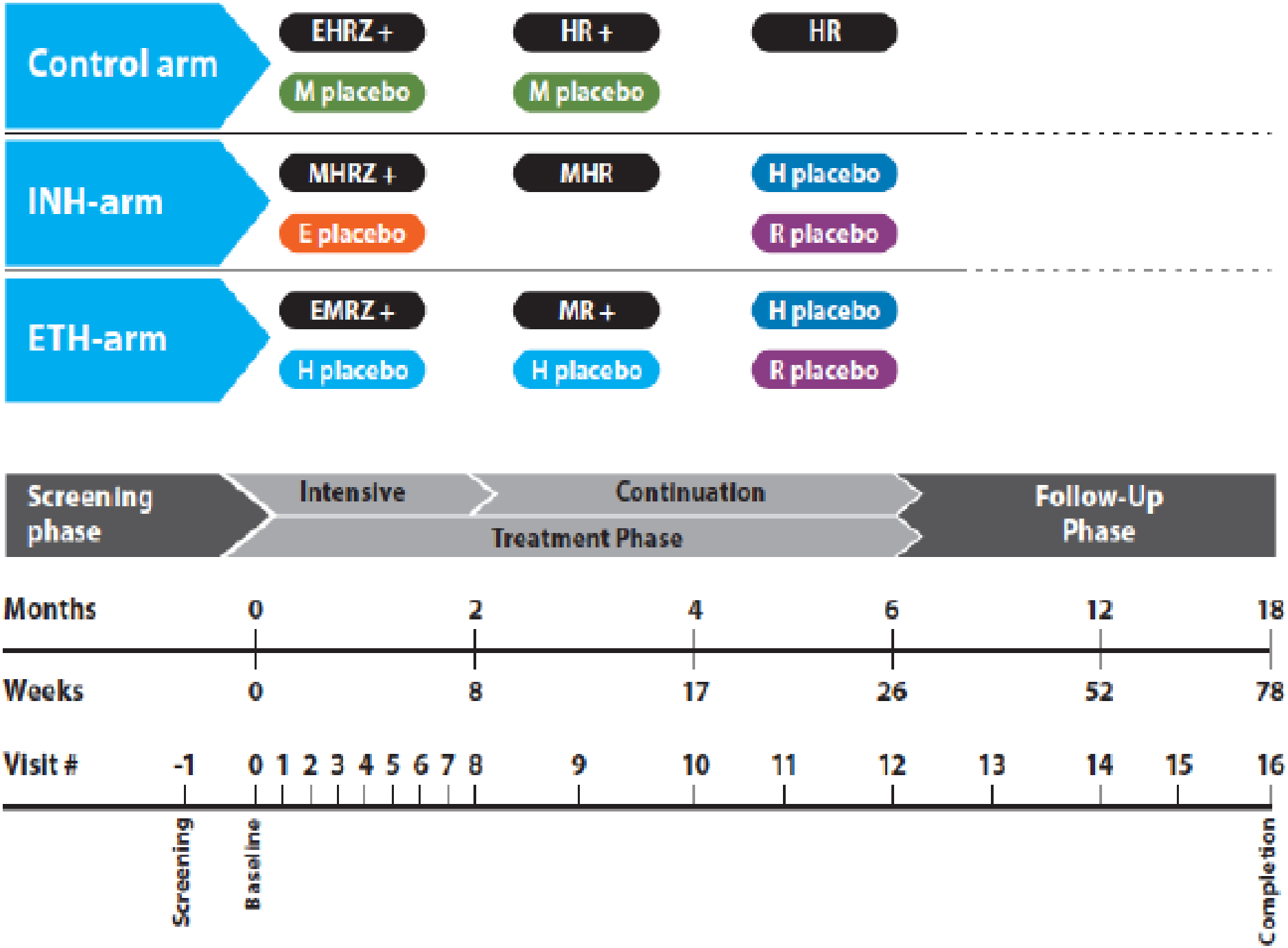


Figure 1. Enrollment and Outcomes.

MDR denotes multidrug resistance.

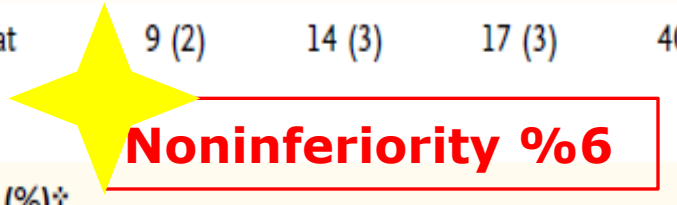

Control arm
EHRZ +
M placebo
HR +
M placebo
HR
INH-arm
MHRZ +
E placebo
MHR
H placebo
R placebo
ETH-arm
EMRZ +
H placebo
MR +
H placebo
H placebo
R placebo
Screening phase
Intensive
Continuation
Treatment Phase
Follow-Up Phase
Months 0 2 4 6 12 18
Weeks 0 8 17 26 52 78
Visit # -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
Screening
Baseline
Completion

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

- Hastalar 8 haftalık vizitlerde değerlendirilmek üzere ayrıldılar.
- PA Akciğer, fizik muayene, iki balgam kültürü, görme muayenesi, idrar tetkikleri, karaciğer fonk. testleri
- *Çalışma sonlanım noktaları:*
  - Primer etki sonuçu:
  - Randomizasyondan sonraki 18 ay içinde klinik ya da bakteriyolojik başarısızlık ya da relaps
  - Primer güvenlik sonlanım noktası: grade 3-4 yan etki olması (Division of AIDS of the National Institute of Allergy and Infectious Diseases.)

Table 2. Primary Efficacy Analysis in Per-Protocol and Modified Intention-to-Treat Populations.*

Variable	Per-Protocol Analysis				Modified Intention-to-Treat Analysis			
	Control Group (N=510)	Isoniazid Group (N=514)	Ethambutol Group (N=524)	All Patients (N=1548)	Control Group (N=555)	Isoniazid Group (N=568)	Ethambutol Group (N=551)	All Patients (N=1674)
Favorable outcome — no. (%)								
Patients with outcome	467 (92)	436 (85)	419 (80)	1322 (85)	468 (84)	436 (77)	419 (76)	1323 (79)
Culture-negative status at 18 mo	409 (80)	389 (76)	367 (70)	1165 (75)	410 (74)	389 (68)	367 (67)	1166 (70)
Unable to produce sputum	0	2 (<1)	0	2 (<1)	0	2 (<1)	0	2 (<1)
Unable to produce sputum at 18 mo but culture-negative status earlier	49 (10)	31 (6)	35 (7)	115 (7)	49 (9)	31 (5)	35 (6)	115 (7)
Missing data on L–J culture at 18 mo and MGIT negative	9 (2)	14 (3)	17 (3)	40 (3)	9 (2)	14 (2)	17 (3)	40 (2)
Unfavorable outcome — no. (%)†								
Patients with outcome	43 (8)	78 (15)	105 (20)	226 (15)	87 (16)	132 (23)	132 (24)	351 (21)
6-Mo treatment phase								
Nonviolent death	5 (1)	6 (1)	7 (1)	18 (1)	5 (1)	6 (1)	7 (1)	18 (1)
Treatment failure‡								
Culture-confirmed	3 (1)	4 (1)	1 (<1)	8 (1)	3 (1)	4 (1)	1 (<1)	8 (<1)
Not culture-confirmed	4 (1)	1 (<1)	4 (1)	9 (1)	4 (1)	1 (<1)	4 (1)	9 (1)

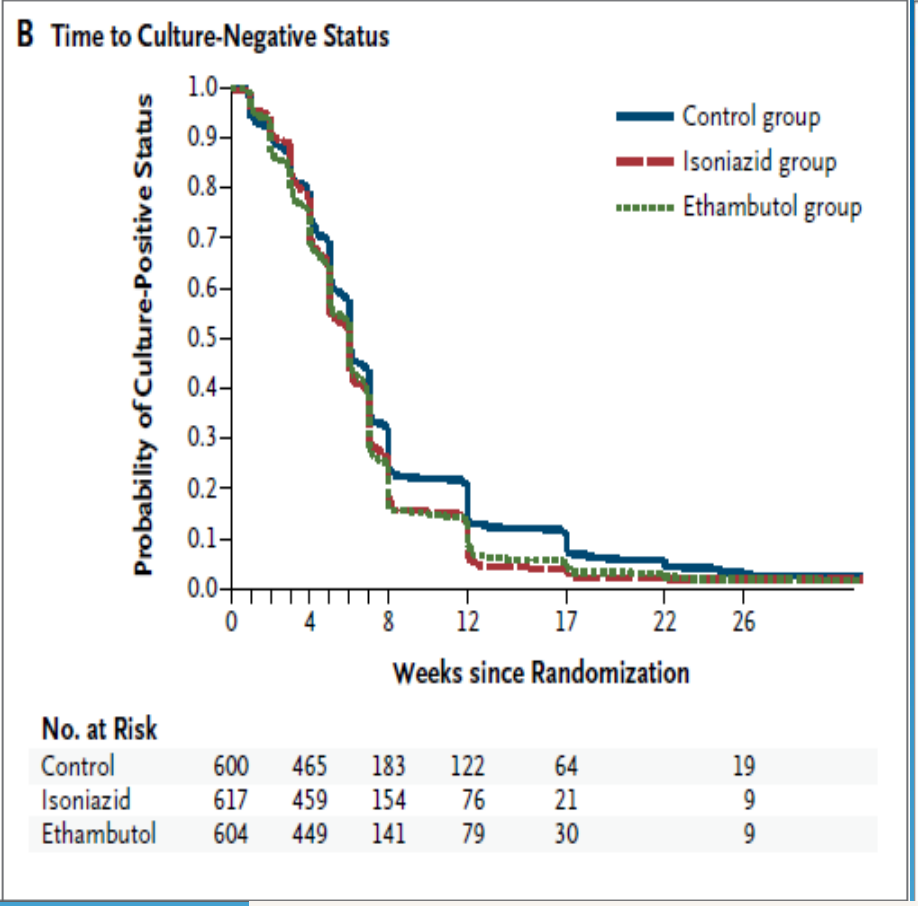


Adverse reaction	NA	NA	NA	NA	18 (3)	15 (3)	9 (2)	42 (3)
Withdrawal of consent	NA	NA	NA	NA	8 (1)	18 (3)	8 (1)	34 (2)
Relocation	NA	NA	NA	NA	2 (<1)	4 (1)	4 (1)	10 (1)
Other investigator decision	NA	NA	NA	NA	2 (<1)	5 (1)	0	7 (<1)
No completion of treatment	NA	NA	NA	NA	13 (2)	10 (2)	6 (1)	29 (2)
Follow-up								
Relapse after culture-negative status	12 (2)	46 (9)	64 (12)	122 (8)	13 (2)	46 (8)	64 (12)	123 (7)
Retreated for tuberculosis	14 (3)	17 (3)	27 (5)	58 (4)	14 (3)	18 (3)	27 (5)	59 (4)
Death from tuberculosis or respiratory distress	2 (<1)	0	0	2 (<1)	2 (<1)	0	0	2 (<1)
No culture-negative status								
Ever	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)	2 (<1)	0	3 (<1)
At last visit	2 (<1)	3 (1)	2 (<1)	7 (<1)	2 (<1)	3 (1)	2 (<1)	7 (<1)
Adjusted difference from control in rate of unfavorable outcome — percentage points (97.5% CI)	NA	6.1 (1.7–10.5)	11.4 (6.7–16.1)	NA	NA	7.8 (2.7–13.0)	9.0 (3.8–14.2)	NA

* The treatment phase was defined as any time from randomization to 32 weeks after randomization (26 weeks plus 6-week window). L–J denotes Lowenstein–Jensen solid medium, and NA not applicable.

† During follow-up, the relapse and retreatment categories include patients during the scheduled end of active treatment (after month 4 for the moxifloxacin-containing groups and month 6 for the control group). In the per-protocol analysis, data from 24-locus mycobacterial-interspersed-repetitive-unit analysis were missing for 9 of 17 patients with treatment failure, 42 of 122 patients with relapse, and 38 of 58 patients who were retreated for tuberculosis.

‡ Listed are patients who were receiving active treatment in whom treatment failed.



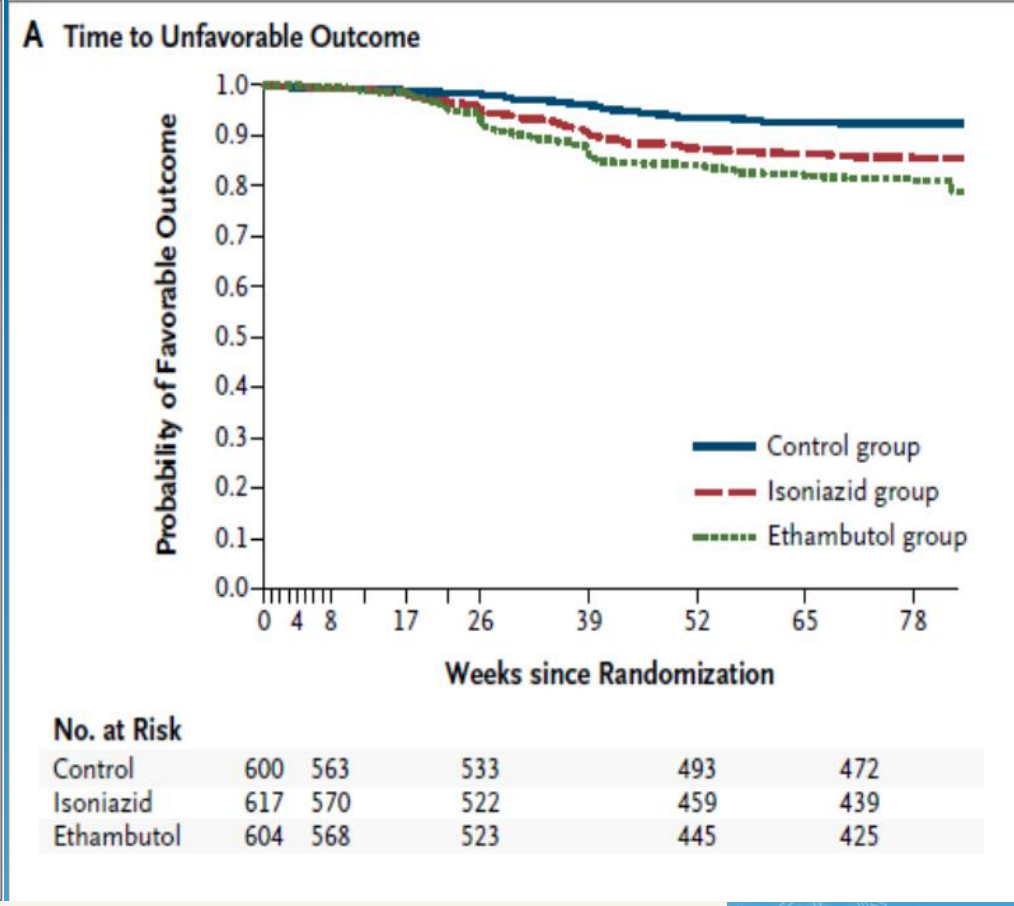


Figure 2. Kaplan–Meier Estimates of the Time to an Unfavorable Outcome and Conversion to Culture-Negative Status.

Panel A shows that the time until patients had an unfavorable outcome was shorter in the isoniazid group than in the control group (hazard ratio, 1.25 [97.5% CI, 1.08 to 1.42]) and was further reduced in the ethambutol group (hazard ratio, 1.21 [97.5% CI, 1.05 to 1.37]). Panel B shows the time until conversion to culture-negative status, which occurred sooner in the isoniazid group and the ethambutol group than in the control group, according to analyses of sputum samples cultured in Lowenstein–Jensen solid medium. Patients who were excluded from the primary per-protocol analysis were included in this analysis, but data were censored at the time of exclusion from the per-protocol analysis.

- Yan etkiler açısından gruplar arasında anlamlı fark yokmuş.

Sonuç

- Komplike olmayan kültür (+) tuberkuloz olgularında moksifloksasin içeren rejimlerin hızlı bakterisidal etkinlik sağladığı kanıtlandı.
- Fakat 4 aylık tedavi rejimleri ile klasik 6 aylık tedavi sonuçları benzerlik göstermedi.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

Luis Villar, M.D., Gustavo Horacio Dayan, M.D., José Luis Arredondo-García, M.D., Doris Maribel Rivera, M.D., Rivaldo Cunha, M.D., Carmen Deseda, M.D., Humberto Reynales, M.D., Maria Selma Costa, M.D., Javier Osvaldo Morales-Ramírez, M.D., Gabriel Carrasquilla, M.D., Luis Carlos Rey, M.D., Reynaldo Dietze, M.D., Kleber Luz, M.D., Enrique Rivas, M.D., Maria Consuelo Miranda Montoya, M.D., Margarita Cortés Supelano, M.D., Betzana Zambrano, M.D., Edith Langevin, M.Sc., Mark Boaz, Ph.D., Nadia Tornieporth, M.D., Melanie Saville, M.B., B.S., and Fernando Noriega, M.D., for the CYD15 Study Group*

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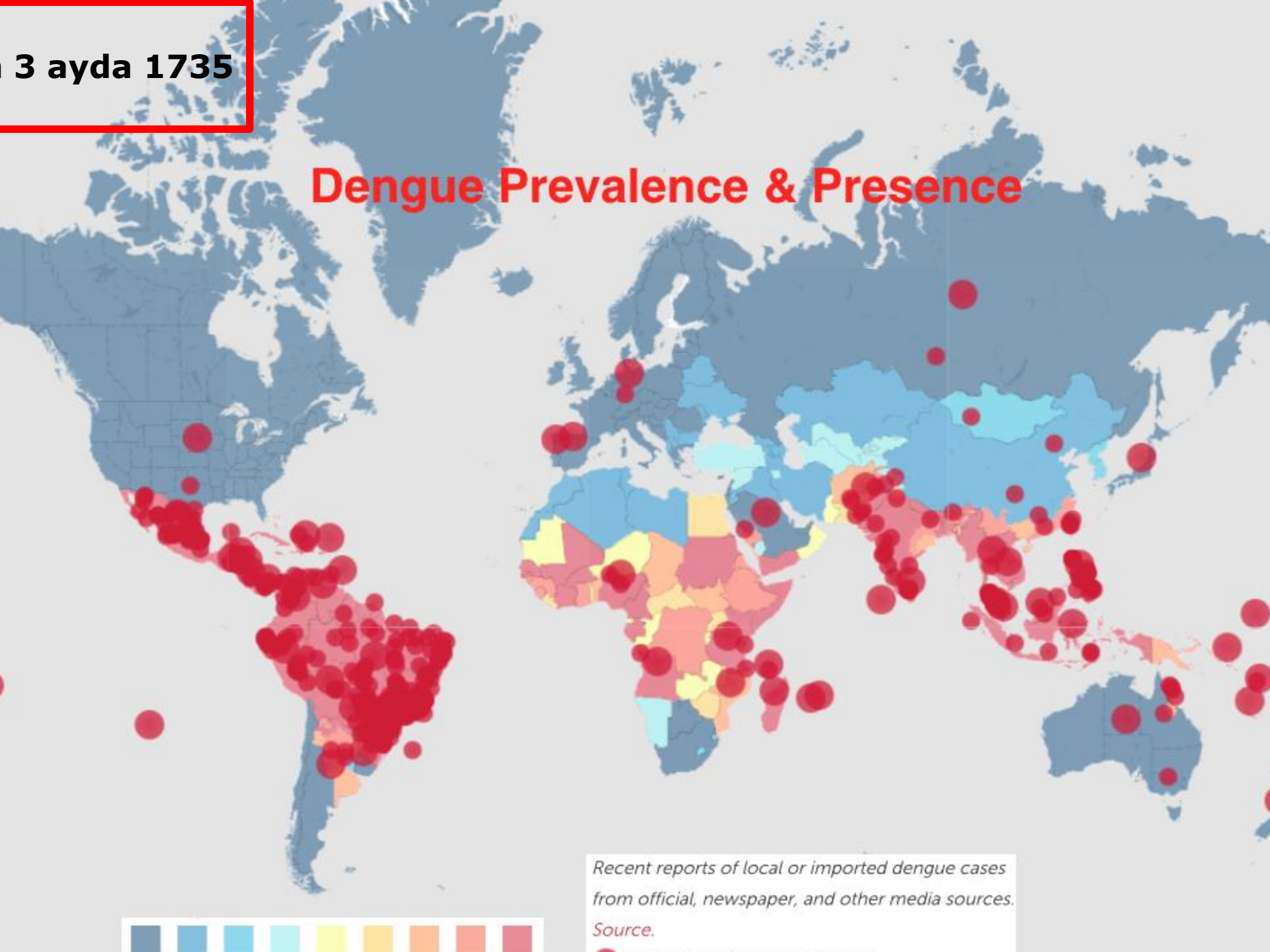
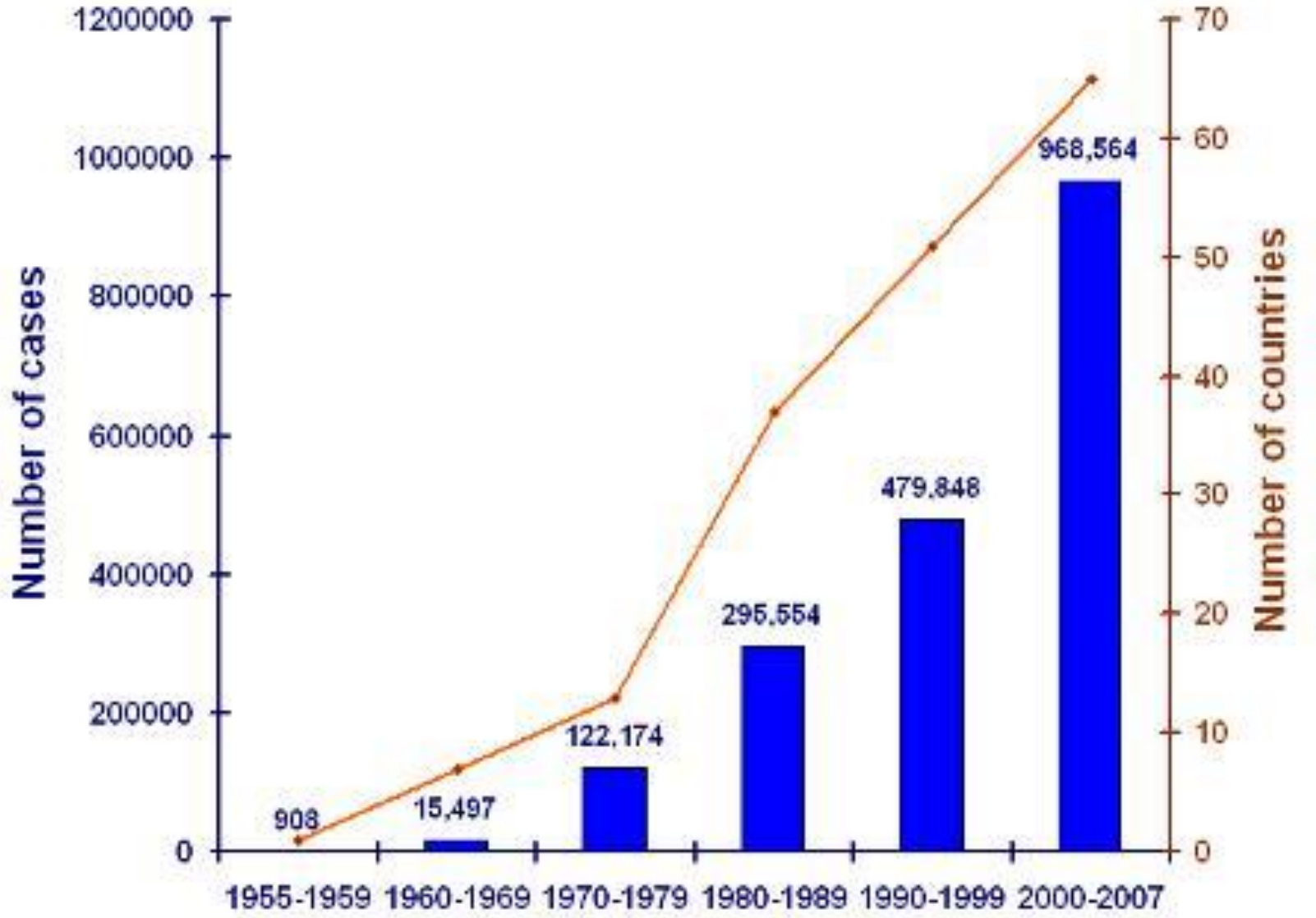
3 ayda 1735


Dengue Prevalence & Presence
Recent reports of local or imported dengue cases from official, newspaper, and other media sources.
Source.

Average annual number of DF/DHF cases reported to WHO & average annual number of countries reporting dengue



Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

- Deng virüsü hastalığı tropikal bölgelerde yaşayanlarda görülen ve sivirineklerden bulaşan bir hastalıktır.
- Deng virüsünün endemik olduğu Latin Amerika ülkelerinde 9-16 yaş çocuklarda tetravalen deng aşısının etkinliğinin değerlendirildiği faz 3 çalışma.
- Randomize kör, plasebo kontrollu calışma
- 3 doz Rekombinan, canlı, attenue, tetravalen aşı veya placebo 0. 6. 12. ay aşıları yapılmış.
- Bu çocuklar 25 ay takip edilmiş.
- 3. aşıdan 28 gün sonrasında gelişen Deng enfeksiyonu da sonlanım noktası.

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

- Aşı grubunda 176 VCD, kontrol grubunda 221 VCD gelişmiş.
- Serotype 1→ %50
- Serotype 2→%42
- Serotype 3→%74
- Serotype 4→%77

etkinlik saptanmış.

- Bu aşı ile deng nedeniyle hastaneye yatış oranları **%80 azalmış**.
- Takipte çocuklardan 0, 7,13, 25. aylarda kan örnekleri alınarak deng serotip antikorlar açısından bakılmış.
- Takipte ateş gelişen çocuklardan ilk 5 gün içinde ve sonrasında 7. 14. günlerde kan örnekleri alınarak antikor durumu bakılmış.
- PCR ve ELİSA ile deng varlığı araştırılmış.

Table 2. Vaccine Efficacy against Any Serotype of Dengue.

Analysis	Vaccine Group			Control Group			Vaccine Efficacy (95% CI)
	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	Cases/ Events*	Person-Yr at Risk†	Incidence Density (95% CI)‡	
	no.		*no./100 person-yr*	*no.*		*no./100 person-yr*	%
Per-protocol analysis	176/176	11,793	1.5 (1.3–1.7)	221/221	5,809	3.8 (3.3–4.3)	60.8 (52.0–68.0)
Intention-to-treat analysis	277/280§	26,883	1.0 (0.9–1.2)	385/388§	13,204	2.9 (2.6–3.2)	64.7 (58.7–69.8)

* A case was defined as a first episode of virologically confirmed dengue (VCD) by means of enzyme-linked immunosorbent assay for dengue nonstructural protein 1 antigen, dengue screening on quantitative reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, or serotype-specific RT-PCR assay. Among the VCD cases, 90% had positive results for both dengue RNA and nonstructural protein 1 antigen, 6% for dengue RNA only, and 2% for nonstructural protein 1 antigen only.

† Data for person-years at risk are the cumulative time in years until VCD was diagnosed or until the end of the active follow-up period, whichever came first. This value is the sum of individual units of time for which the participants contributed to the analyses.

‡ Incidence density was calculated as the number of cases divided by the cumulative person-years at risk.

§ Six participants (3 in each group) who had two episodes of VCD had the following serotypes: 2 participants, unknown serotype and serotype 2; 1 participant, serotypes 1 and 2; 1 participant, serotypes 1 and 3; 1 participant, serotypes 3 and 1; and 1 participant, two unknown serotypes. A total of 14 participants (6 in the vaccine group and 8 in the control group) had two serotypes detected during the same febrile episode, with all episodes except two occurring after the third injection; 7 participants had serotypes 1 and 2 (1 after the first injection), 5 participants had serotypes 1 and 3 (1 after the second injection), and 2 participants had serotypes 2 and 3.

Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America

- 12 vaka ciddi denge olmuş 1 tanesi aşı grubunda 11 tanesi kontrol grubunda
- Aşıya bağlı yan etkiler açısından iki grup arasında anlamlı fark yok
- Bu çalışmada bu aşının etkinliği %60.8 olarak bulunmuş.
- %80 hastane yatışı olmamış
- %95.5 ciddi deng olmamış