

Antimikrobiyal Yönetim için Araştırma Tasarımları

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Öğrenme Hedefleri

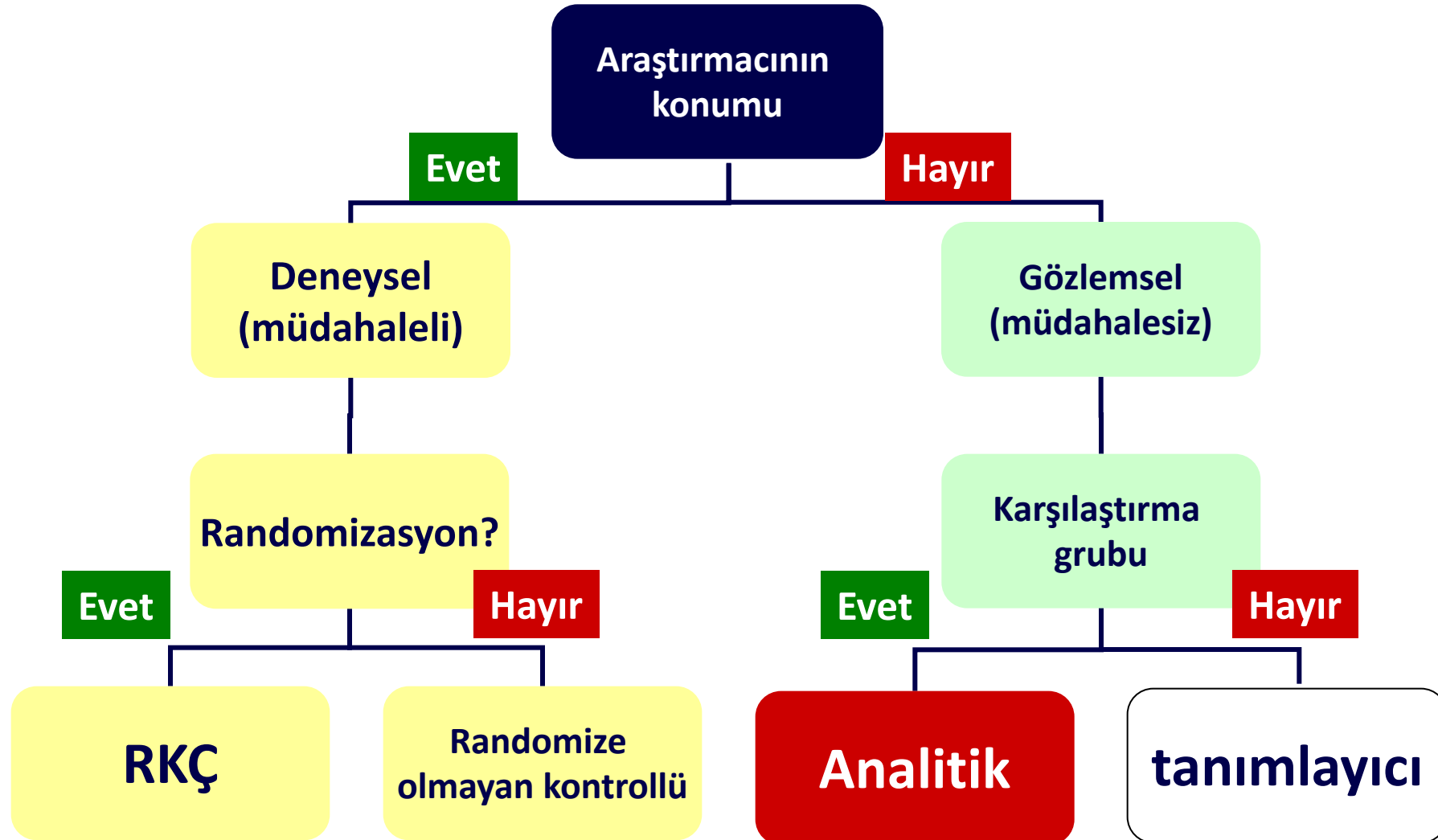
- Çalışma tasarımları türleri
- Antibiyotik uygunluğunun ölçülmesi
 - Reçetelerin değerlendirilmesi
- Müdahalenin etkisi nasıl ölçülür?
- Antimikrobiyal yönetimde araştırma yöntemlerinin tanımlanması
- Kesintili zaman serisi analizi

Çalışmanın Aşamaları

1. Arkaplan/Giriş
2. Hipotez
3. Tasarım
4. Veri toplama
5. Analiz
6. Raporlama



Çalışma Tasarımları

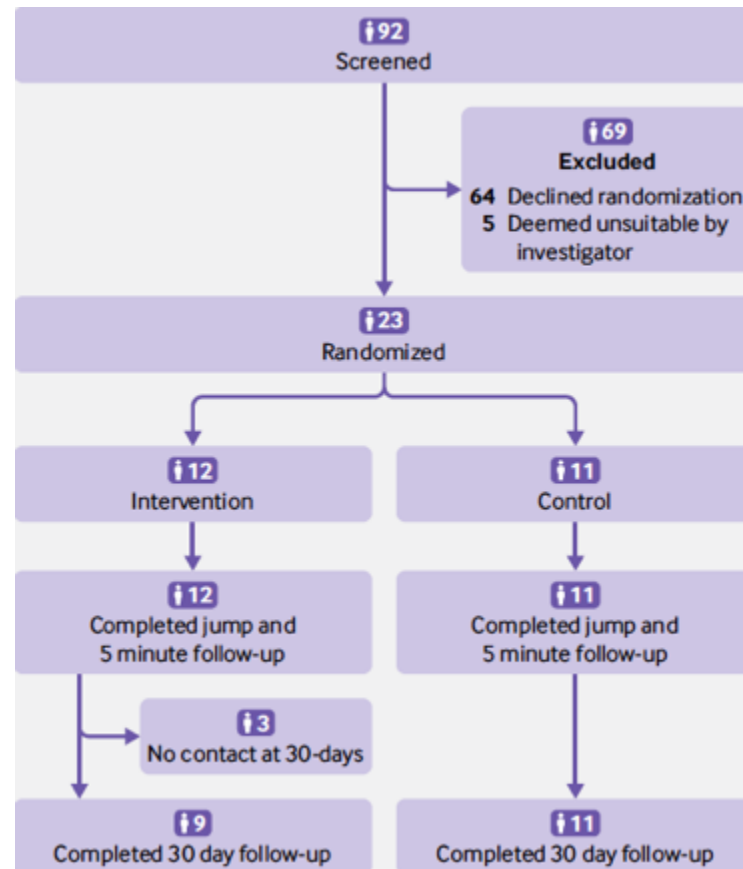


Çalışmalar Nasıl Değerlendirilmeli?

1. Sonuçların Uygunluğu (İçsel uygunluk/geçerlilik)
 - Tasarım uygun mu?
 - Yanlılık kontrol edilmiş mi?
 - İstatistik analizler doğru mu?
2. Sonuçların doğruluğu
 - Etki uyumlu ve doğru mu?
3. Genelleme (Dışsal uygunluk/geçerlilik)
 - Sonuçları pratikte uygulayabilir miyiz?

Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial

Robert W Yeh,¹ Linda R Valsdottir,¹ Michael W Yeh,² Changyu Shen,¹ Daniel B Kramer,¹ Jordan B Strom,¹ Eric A Secemsky,¹ Joanne L Healy,¹ Robert M Domeier,³ Dhruv S Kazi,¹ Brahmajee K Nallamothu⁴ On behalf of the PARACHUTE Investigators



Yeh RW, BMJ 2018

Conclusion

Parachute use compared with a backpack control did not reduce death or major traumatic injury when used by participants jumping from aircraft in this first randomized evaluation of the intervention. This largely resulted from our ability to only recruit participants jumping from stationary aircraft on the ground. When beliefs regarding the effectiveness of an intervention exist in the community, randomized trials evaluating their effectiveness could selectively enroll individuals with a lower likelihood of benefit, thereby diminishing the applicability of trial results to routine practice. Therefore, although we can confidently recommend that individuals jumping from small stationary aircraft on the ground do not require parachutes, individual judgment should be exercised when applying these findings at higher altitudes.



Yeh RW, BMJ 2018

Chocolate Consumption, Cognitive Function, and Nobel Laureates

Messerli

N Engl J Med

2012

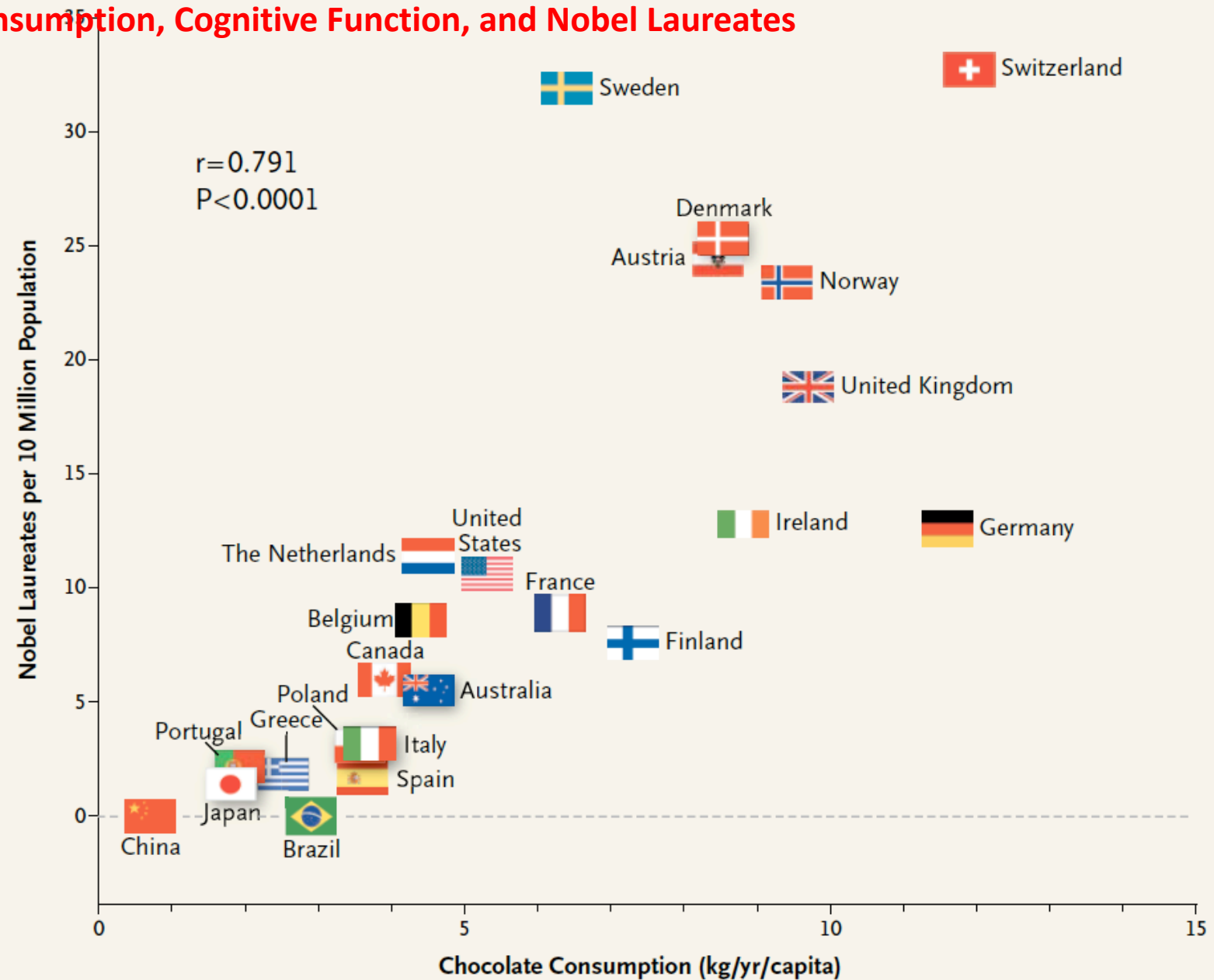
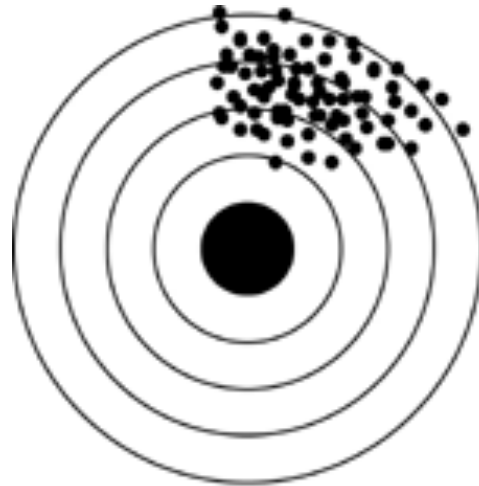
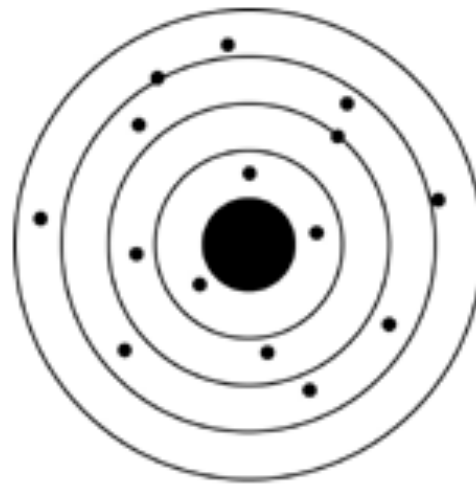


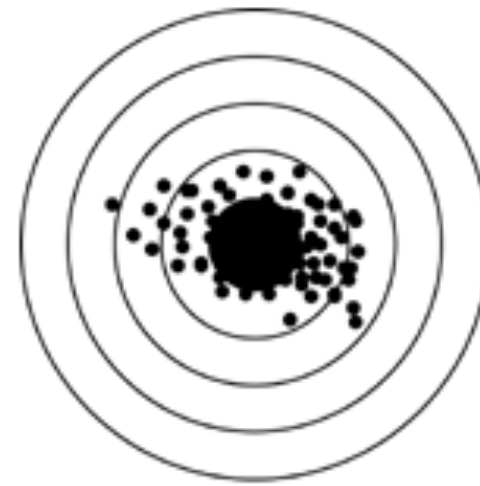
Figure 1. Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates per 10 Million Population.



Reliable but Not Valid

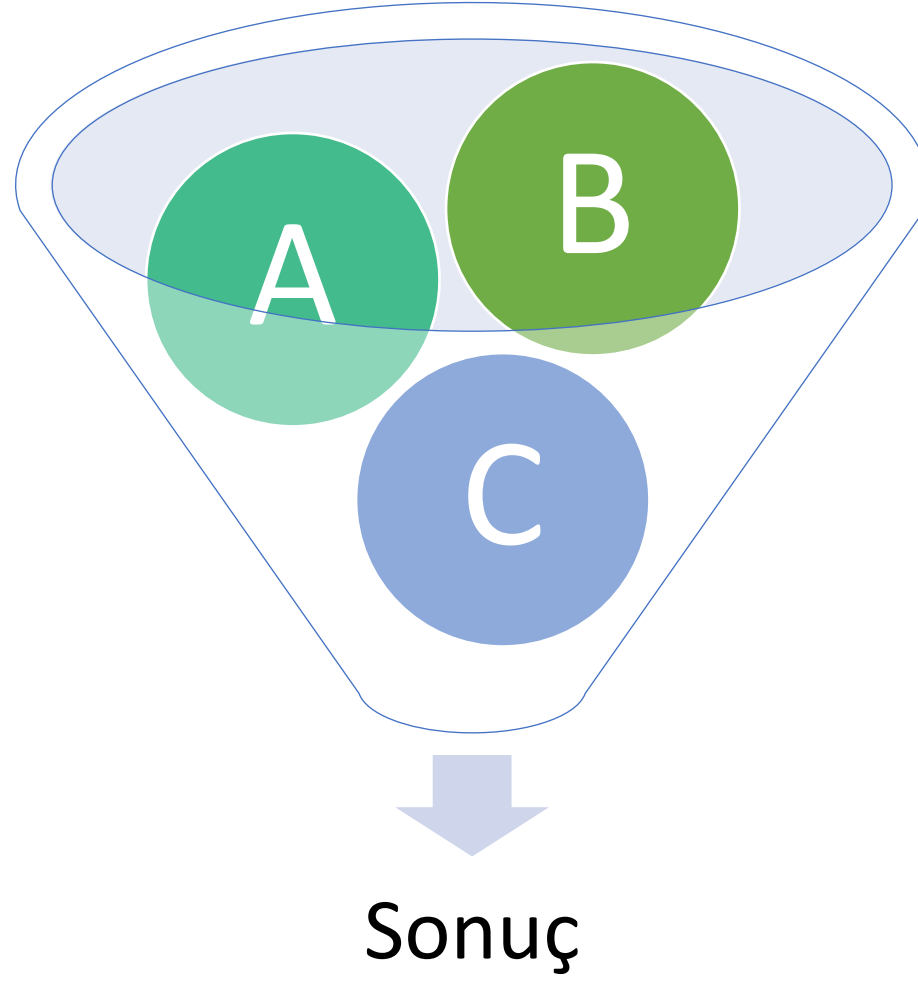


Valid but Not Reliable



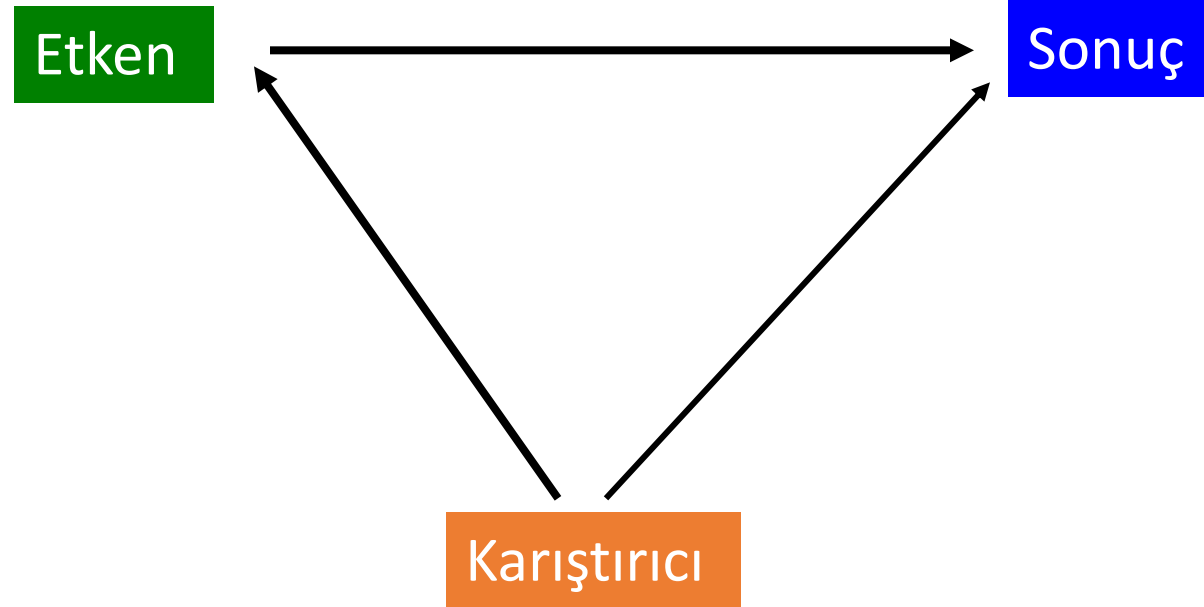
Valid and Reliable

Nedensellik: Hangi Etken Ne Kadar Önemli?



Karıştırıcı Etken

- Baktığınız etkenle sonuç arasında, başka bir etkenden dolayı bir ilişki varmış gibi sonuç çıkması

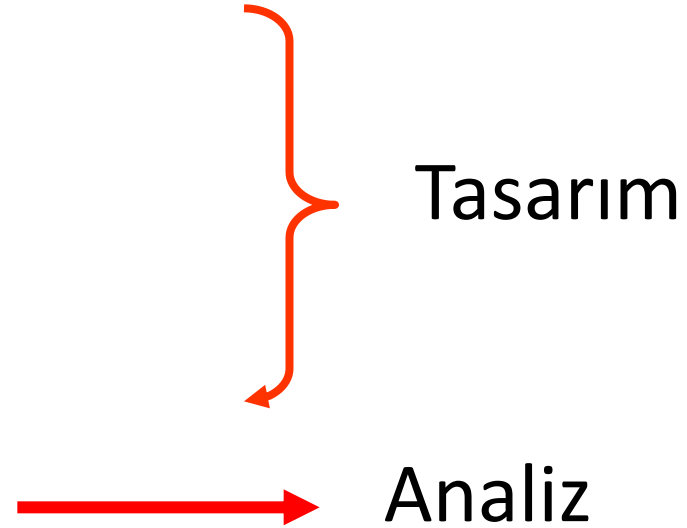


Araştırma Sonuçları

1. Hata/Yanlılık (Bias)

2. Karıştırıcı etken
(Confounder)

3. Şans faktörü



Evaluation of antibiotic use in a hospital with an antibiotic restriction policy

Ayşe Erbay^{a,*}, Aylin Çolpan^a, Hürrem Bodur^a, Mustafa A. Çevik^a, Matthew H. Samore^b, Önder Ergönül^b

^a *Ankara Numune Education and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Ankara, Turkey*

^b *University of Utah, School of Medicine, Department of Internal Medicine, Division of Clinical Epidemiology, Salt Lake, UT, USA*

Received 14 May 2002; accepted 29 August 2002

- 1) Agree with choice of antibiotic, but dosage was inappropriate per literature
- 2) Disagree with choice of antibiotics because the spectrum of the antibiotics were overlapped
- 3) Disagree with choice of antibiotic because the spectrum was not broad enough
- 4) Disagree with choice of antibiotic because the spectrum was overly broad
- 5) Disagree with choice of antibiotic because an equally effective drug was available at a lower cost
- 6) Disagree with need for an antibiotic.

Table 1

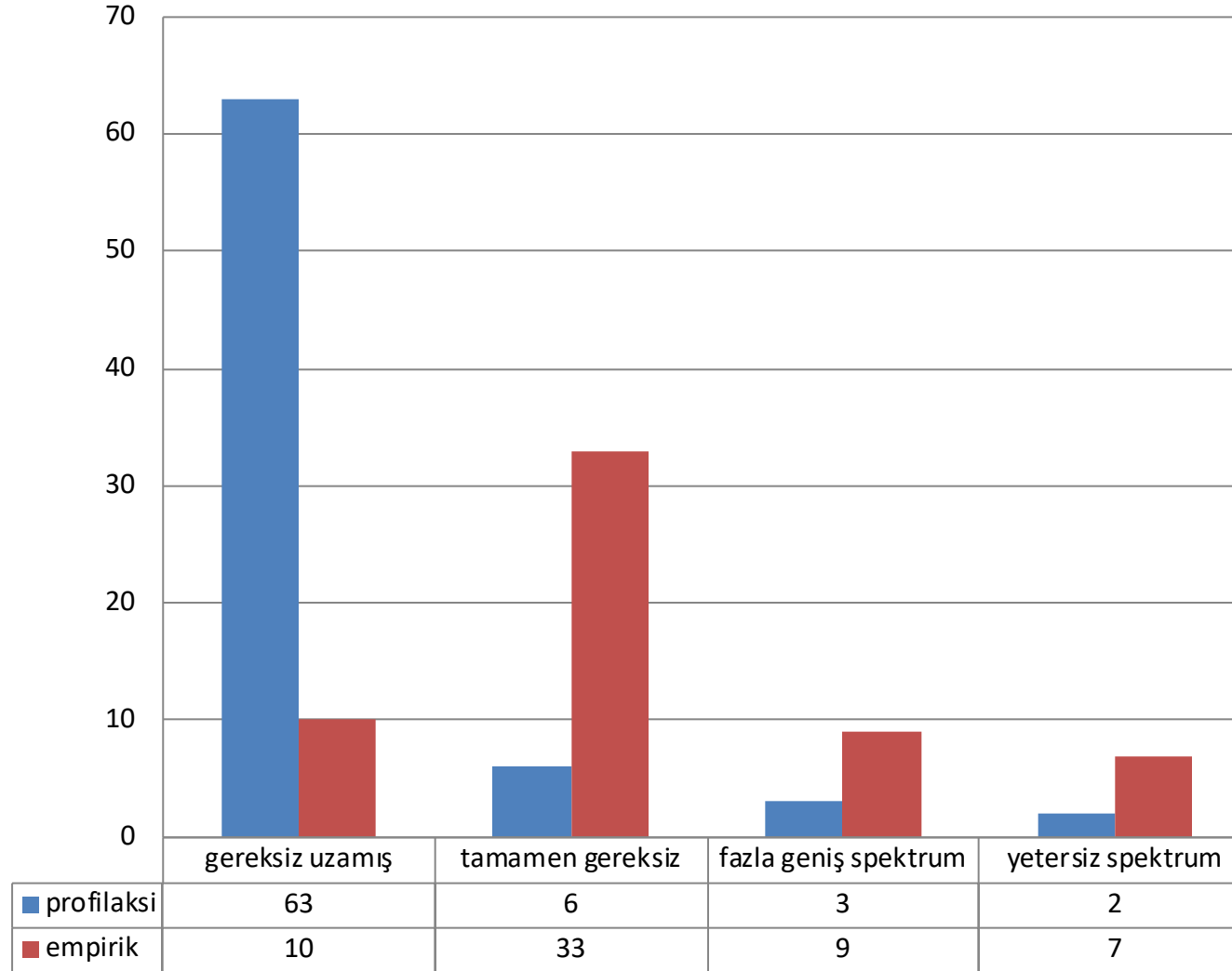
Resistance rates of some Gram-negative microorganisms in ANERH in 2000

	<i>Klebsiella</i> spp. (%)	<i>E. coli</i> (%)	<i>Pseudomonas</i> spp. (%)	<i>Acinetobacter</i> spp. (%)
Cefotaxime	80.0	56.0	93.4	100
Ceftazidime	76.3	49.3	62.6	96.3
Cefoperazone–sulbactam	59.4	50.0	50.0	50.0
Ticarcillin–clavulanate	84.8	81.4	76.7	85.7
Piperacillin–tazobactam	57.1	25.7	42.6	82.8
Cefepime	56.9	39.5	57.1	71.9
Imipenem	6.9	2.4	31.4	39.2
Gentamicin	66.6	58.0	65.2	88.0
Amikacin	45.7	20.0	36.9	70.3
Ciprofloxacin	56.6	57.6	46.5	80.0

Categories of inappropriate antibiotic use

Categories of inappropriate antibiotic use	<i>n</i>	%
Unnecessary use (no evidence of an infection or indication of prophylaxis)	86	63.7
Overly broad	15	11.1
Not broad enough	12	8.9
Agree with choice of antibiotic, but dosage was inappropriate	12	8.9
Overlap of spectrum (> 1 agents used at the same time)	8	5.9
More expensive than the equivalent	2	1.5
Total	135	100

En Sık Uygunsuz Antibiyotik Kullanma Nedenleri



EHU Onayı Başarılı mı?



Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

The need for an antibiotic stewardship program in a hospital using a computerized pre-authorization system



Buket Ertürk Şengel^{a,*}, Hüseyin Bilgin^a, Beyza Ören Bilgin^b, Tolga Gidener^c, Simge Saydam^c, Aslıhan Pekmezci^c, Önder Ergönül^d, Volkan Korten^a

Table 3
Univariate and multivariate analyses for the predictors of appropriate antibiotic use.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Prospective audit and feedback	1.4	1.02–1.84	0.036	1.5	1.09–2.04	0.011
Antibiotics restricted by NARP	2	1.51–2.82	<0.001	1.7	1.2–2.31	0.002
Medical vs. surgical wards (excluding ICU)	3.2	2.34–4.28	<0.001	3	2.2–4.11	<0.001

OR, odds ratio; CI, confidence interval; NARP, nationwide antibiotic restriction program; ICU, intensive care unit.

1. Uygun antibiyotik kullanımını anlamlı olarak etkiler
2. Ancak, prospektik gözlem ve geri bildirim ile desteklenmesi gerekir.

Research Paper

The Impact of a Nationwide Antibiotic Restriction Program on Antibiotic Usage and Resistance against Nosocomial Pathogens in Turkey

Adalet Altunsoy¹, Cenk Aypak^{2✉}, Alpay Azap¹, Önder Ergönül³, İsmail Balık¹

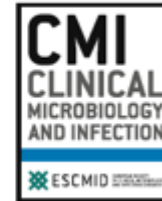
Table 2: Comparison of antibiotic consumption two years before and after the initiation of NARP*

Restricted Antibiotics	Antibiotic consumption (grams)		% difference
	2001+2002	2003+2004	
Meropenem	113362	85236	-24.8
Imipenem	50532	45935.2	-9.1
Ceftazidim	60074	38129	-36.5
Ceftriaxone	300955	190281	-36.8
PIP-TAZO*	270594	417114	+54.1
Cefepime	100588	121799	+21.1
Vancomycin	113362	85236	-17.8
Teicoplanin	50532	45935.2	-1.4
Total	60074	38129	-11.3

*nationwide antibiotic restriction program, **piperacillin-tazobactam

Çalışmalar Neden Yayınlanır?

- Sorunun “önemi”
 - Popüler konu: yaygın etki
 - Yaşamsal: öldürücü
- Farklı yaklaşım
- Farklı sonuç
- Denek sayısının çokluğu
- Yazarların ünü
- Büyük resim sunması



Systematic review

The quality of studies evaluating antimicrobial stewardship interventions: a systematic review

V.A. Schweitzer^{1,*}, I. van Heijl², C.H. van Werkhoven¹, J. Islam³, K.D. Hendriks-Spoor², J. Bielicki⁴, M.J.M. Bonten⁵, A.S. Walker⁶, M.J. Llewelyn³ on behalf of the Consensus on Antimicrobial Stewardship Evaluations (CASE) study group[†]

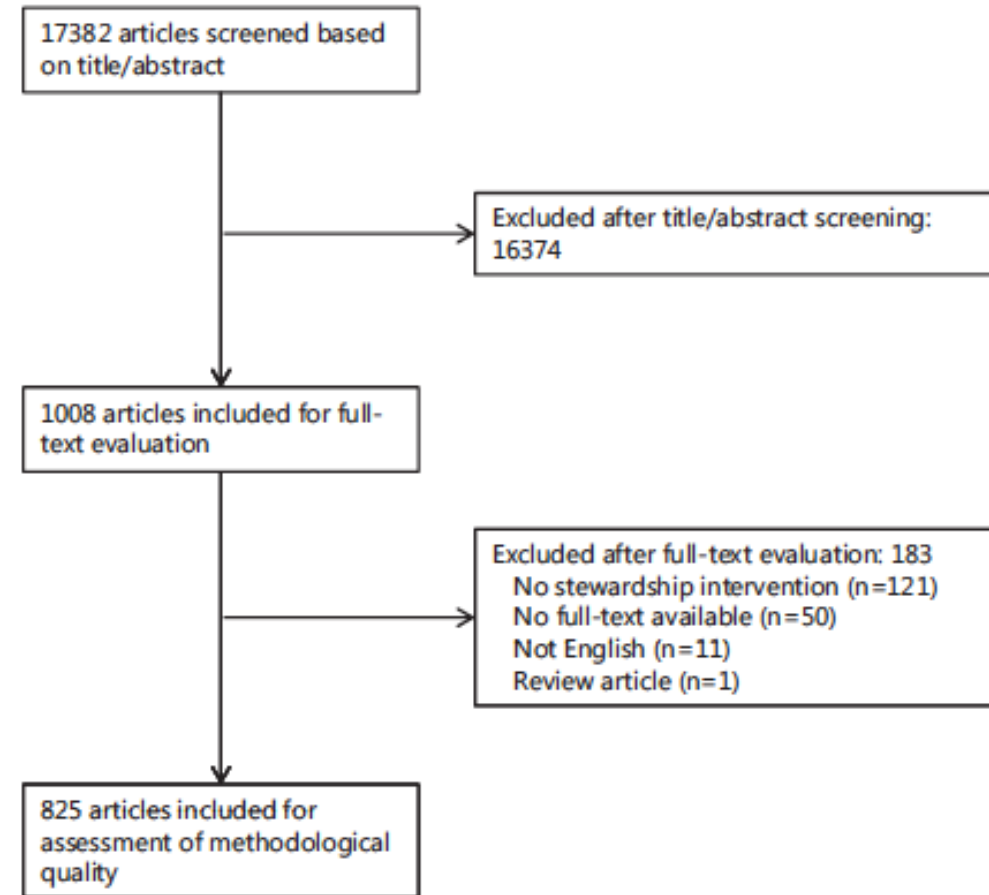


Fig. 1. Flowchart of the studies included in the systematic literature review.

Table 2

Outcomes reported in the included antimicrobial stewardship studies stratified by studies performed in the community and the hospital setting

Process measure outcomes	Community (n = 205), n (%)	Hospital (n = 620), n (%)
Costs/cost-effectiveness	36 (18)	200 (32)
Appropriateness	34 (17)	178 (29)
Defined daily doses (DDD)	34 (17)	156 (25)
Proportion treated with antibiotics	121 (59)	131 (21)
Recommendation acceptance	6 (3)	114 (18)
Guideline adherence	27 (13)	100 (16)
Duration of treatment	5 (2)	93 (15)
Days on therapy (DOT)	6 (3)	62 (10)
Time to appropriate therapy	3 (1)	71 (11)
Antibiotic knowledge	17 (8)	14 (2)
None	2 (1)	5 (1)
Other	58 (28)	166 (27)
Clinical outcome measures		
None	144 (70)	283 (46)
Mortality	9 (4)	203 (33)
Length of stay	5 (2)	201 (32)
Infection	10 (5)	75 (12)
Hospital readmission	0 (0)	76 (12)
Adverse effects	5 (2)	52 (8)
Revisits	22 (11)	0 (0)
Clinical cure	12 (6)	27 (4)
Intensive care unit admission	0 (0)	24 (4)
Hospital admission	9 (4)	0 (0)
Time to clinical stability	3 (1)	6 (1)
Other	16 (8)	49 (8)
Microbiological outcome measures		
None	188 (92)	447 (72)
Colonization/infection resistant pathogens	17 (8)	146 (24)
<i>Clostridium difficile</i> infections	5 (2)	62 (10)
Other	2 (1)	12 (2)

Belirli Bir Hastalık Seçimi

Table 1

Characteristics of included studies stratified by studies performed in the community and the hospital setting

Study characteristics	Community (<i>n</i> = 205), <i>n</i> (%)	Hospital (<i>n</i> = 620), <i>n</i> (%)
Number of patients included (median, IQR)	1255 (278–11,230)	423 (186–1398)
Number of centres involved (median, IQR)	27 (8–90)	1 (1–1)
Age		
Adults	64 (31)	285 (46)
Children	33 (16)	68 (11)
Both	108 (53)	267 (43)
Specific disease targeted		
No specific disease targeted	63 (31)	342 (55)
Upper respiratory tract infections	106 (52)	25 (4)
Lower respiratory tract infections	57 (28)	70 (11)
Bacteraemia	0 (0)	42 (7)
Urinary tract infections	18 (9)	27 (4)
Prophylaxis	2 (1)	39 (6)
Sepsis	0 (0)	17 (3)
Skin and soft tissue infections	1 (1)	8 (1)
Abdominal infections	3 (1)	10 (2)
Other	16 (8)	62 (10)

Belirli Bir Antibiyotik Seçelim mi?

Antibiotic class targeted		
No specific antibiotic class targeted	177 (86)	427 (69)
Cephalosporins	4 (2)	66 (11)
Fluoroquinolones	10 (5)	54 (9)
Carbapenems	0 (0)	48 (8)
Vancomycin	0 (0)	31 (5)
Aminoglycosides	0 (0)	28 (5)
Penicillins	10 (5)	15 (2)
Macrolides	8 (4)	5 (1)
Other	17 (8)	89 (14)

Nasıl Bir Müdahale?

Antimicrobial stewardship interventions

Education	149 (73)	260 (42)
Audit and feedback – individual patient	12 (6)	245 (40)
Audit and feedback – periodic	59 (29)	82 (13)
Restriction	13 (6)	113 (18)
Clinical decision support	31 (15)	112 (18)
Rapid diagnostic testing	24 (12)	68 (11)
Therapeutic drug monitoring	0 (0)	15 (2)
Guideline implementation	20 (10)	95 (15)
Delayed prescribing	9 (4)	0 (0)
Other	42 (20)	78 (13)

En Sık Yapılan Araştırma Tasarımları

Research designs		
Before–after study	48 (23)	365 (59)
Before–after study (ITS)	22 (11)	82 (13)
Cohort without control group	6 (3)	75 (12)
Controlled before-after study	22 (11)	19 (3)
Randomized controlled trial (RCT)	28 (14)	40 (6)
Parallel cluster randomized trial	30 (15)	6 (1)
Parallel cluster randomized trial with baseline period	26 (13)	2 (1)
Controlled before-after study (ITS)	7 (3)	12 (2)
Non-randomized parallel cluster study	5 (2)	8 (1)
Factorial cluster randomized trial	7 (3)	0 (0)
Cluster randomized cross-over trial	2 (1)	3 (1)
Stepped wedge cluster randomized trial	0 (0)	1 (1)
Non-randomized cluster cross-over study	0 (0)	3 (1)
Factorial randomized controlled trial (RCT)	1 (1)	2 (1)
Non-randomized stepped wedge study	0 (0)	2 (1)
Adaptive RCT	1 (1)	0 (0)



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Consensus statement

Optimizing design of research to evaluate antibiotic stewardship interventions: consensus recommendations of a multinational working group

V.A. Schweitzer¹, C.H. van Werkhoven¹, J. Rodríguez Baño², J. Bielicki³, S. Harbarth⁴, M. Hulscher⁵, B. Huttner⁴, J. Islam⁶, P. Little⁷, C. Pulcini⁸, A. Savoldi^{9,10}, E. Tacconelli^{9,10}, J.-F. Timsit^{11,12}, M. van Smeden¹³, M. Wolkewitz¹⁴, M.J.M. Bonten¹⁵, A.S. Walker^{16,17}, M.J. Llewelyn^{7,*}, on behalf of Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) Working Group on Design of Antimicrobial Stewardship Evaluations

(a)

Intervention Rationale

Justification in evidence informs outcome selection
Needs assessment data will inform interpretation and implementation of findings



Intervention Aims

Will be informed by the Intervention Rationale and by the Intervention Setting (e.g. needs assessment)
Will inform selection of outcomes

Intervention Setting

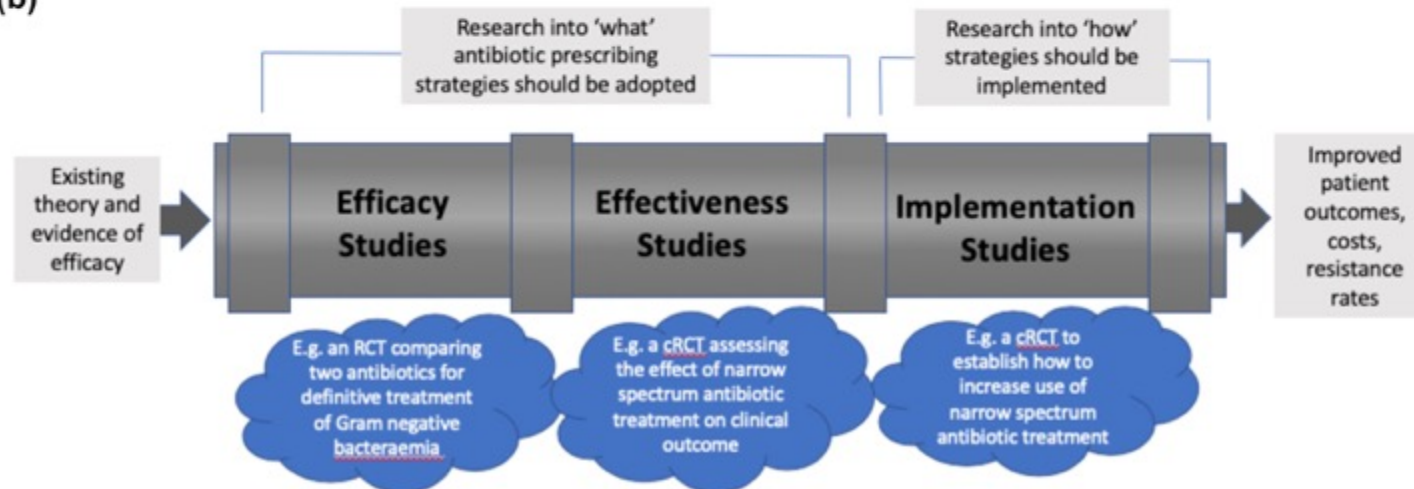
Will inform selection of sites / clusters and feasibility of different study designs

Intervention Features

Will inform selection of outcomes and of sites / clusters and may determine feasibility of blinding

Hybrid Designs

(b)



Glossary of terms

Term	Explanation
Intervention rationale	The theory and evidence behind the stewardship intervention which is to be evaluated encompassing external factors (e.g. behavioural theory, evidence from previous research) and the clinical setting
Clinical setting	The environment in which the intervention is evaluated, both physical (e.g. ICU, emergency room, hospital type, primary care, long-term care) and practical (e.g. prescribing practice, team structures, staffing, behaviour)
Intervention aim(s)	The improvement being sought (e.g. reduction in inappropriate antimicrobial prescribing, reduction in use of specific antimicrobial classes or reduced <i>Clostridium difficile</i> infection)?
Features of the intervention	The different elements which make up a multifaceted intervention (e.g. education, decision support)
Cluster	A unit representing a group of smaller components, at which an intervention is delivered (e.g. a hospital ward representing all the doctors working in it, a group of primary care physicians working in a practice)
Outcomes of interest	The outcomes measured to determine effectiveness, safety and costs of the intervention
Experimental design studies	Studies which use randomization to allocate the stewardship intervention and control, either to individual patients/professionals or clusters of patients/professionals
Quasi-experimental design studies	Studies which don't use randomization to allocate the stewardship intervention but rather use as controls different time period(s) and/or site (s), either external (controlled before-after studies) or internal (interrupted time series analyses, before-after studies)
Contamination	Unintended exposure of patients in the control phase or cluster to some or all of the intervention
Efficacy study	A study which assesses whether an antimicrobial use intervention produces the expected result under ideal and controlled conditions
Effectiveness study	A study which assesses whether an antimicrobial use intervention produces the expected result under 'real-world' pragmatic conditions
Implementation Study	A study which assesses the impact of an antimicrobial use improvement strategy in daily practice
Mediator analyses	Techniques to investigate mechanisms through which complex interventions achieve an observed effect
Superiority analysis	An analysis which sets out to determine if the intervention or strategy being assessed is better than comparator
Non-inferiority analysis	An analysis which sets out to determine whether the intervention or strategy being assessed not worse (by a prespecified amount, the non-inferiority margin) than comparator
Process Indicators	Measures of the care that is actually delivered to the patients (e.g., empirical regimen according to guideline)
Structure indicators	Measures of the organization of the healthcare system (e.g., the availability of a stewardship team)
Ecological assessment (of antimicrobial resistance)	Measurement of burden of antimicrobial resistant organism(s) or gene(s) in the environment or aggregated patient samples

Tanımlar

Efficacy: Etkin

İdeal ve kontrollü ortamda antimikrobiyal kullanımını ölçmeyi hedefler.
İçsel tutarlılık (internal validity)

Effectiveness: Etkili

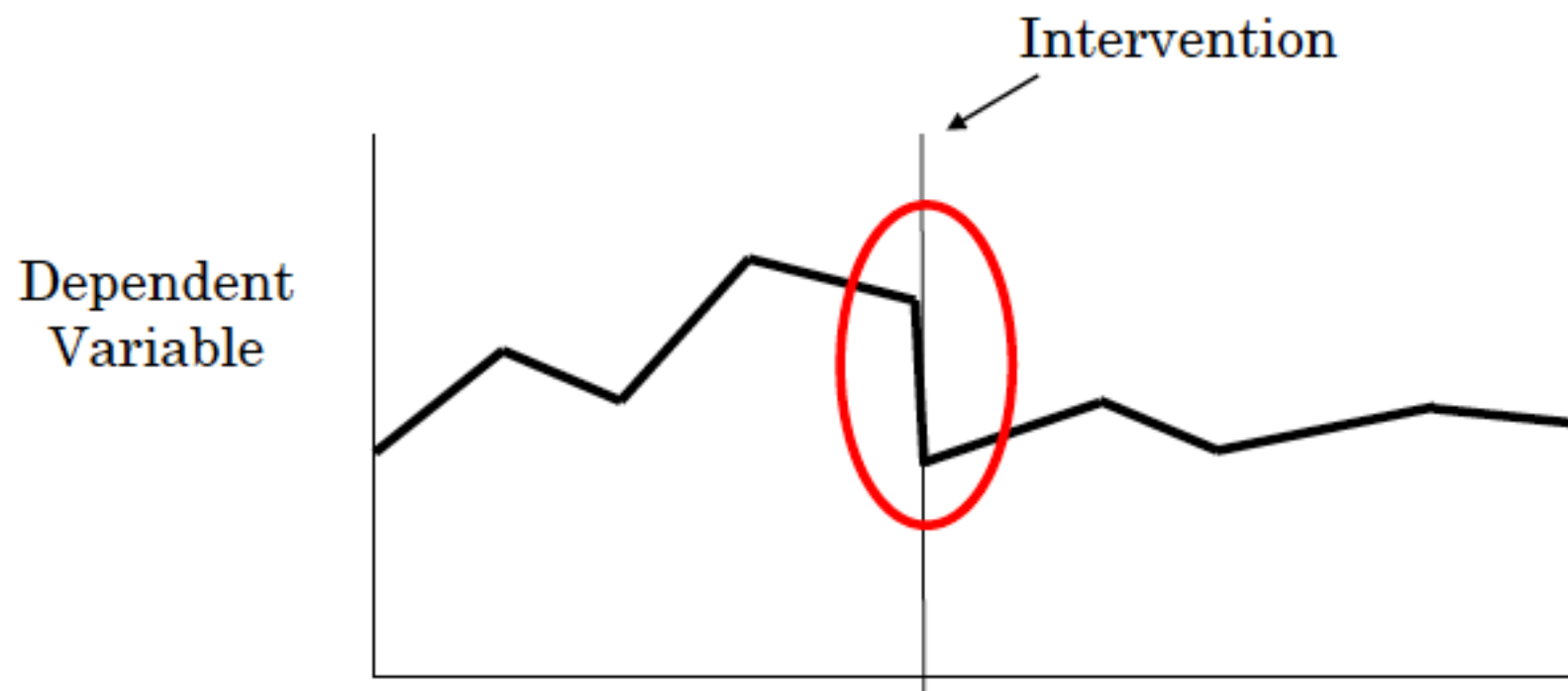
Gerçek yaşamda antimikrobiyal kullanımı ölçmeyi hedefler.
Dışsal geçerlilik (external validity)

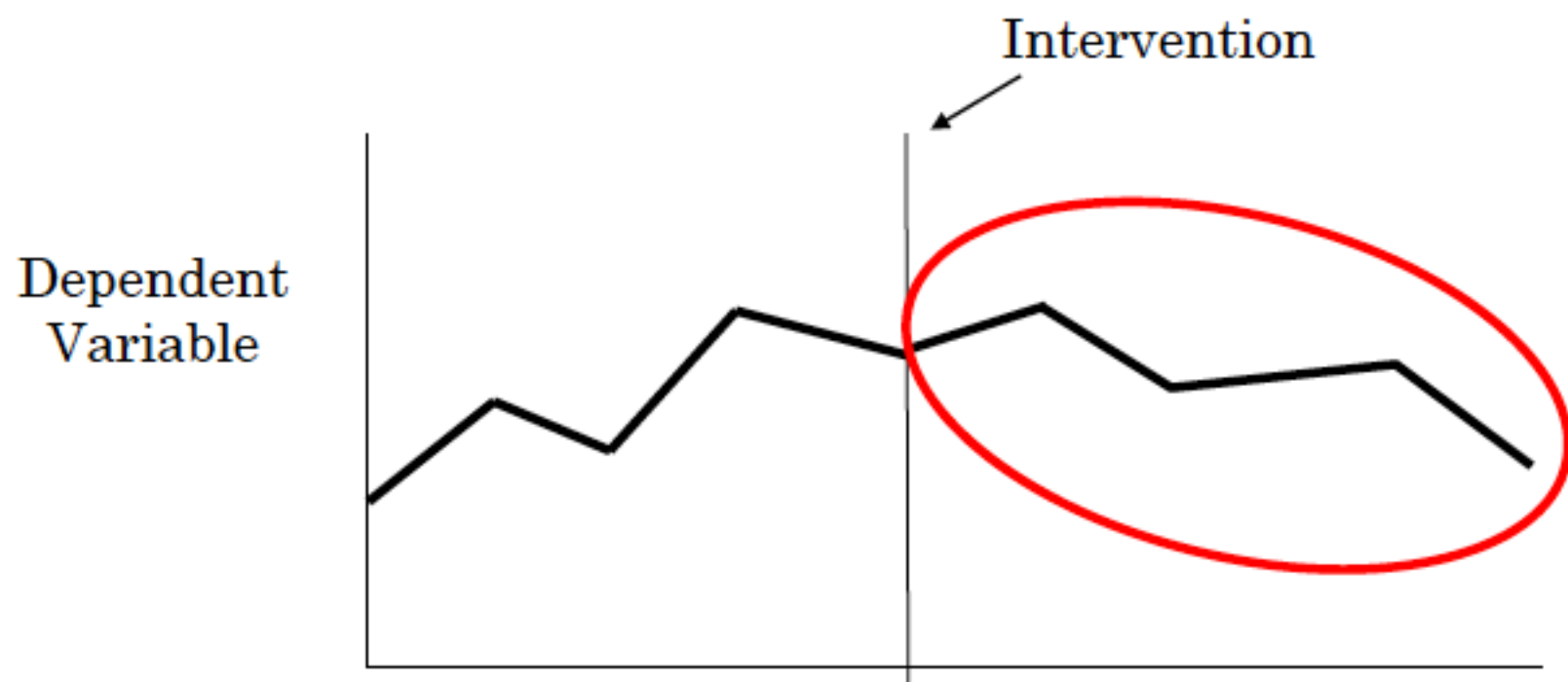
Ecological: Ortam/çevre

Genel (aggregated) hasta ve/veya mikroorganizmaların yükünü ölçmeyi hedefler.

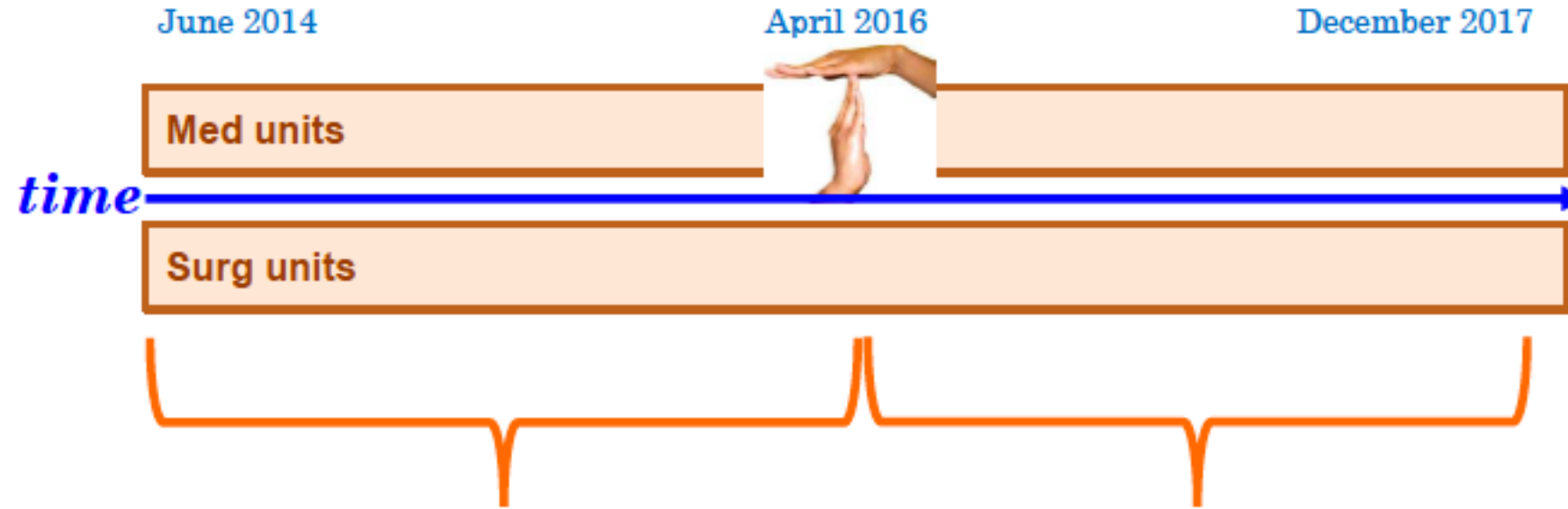
Yarı Deneyssel Çalışmalar

- Quasi experimental
- Randomizasyon yok
- Farklı zamanlarda
- Kontrol kullanımı mümkün
- Öncesi/sonrası çalışması
- Kesintili zaman serisi (interrupted time series analyses)



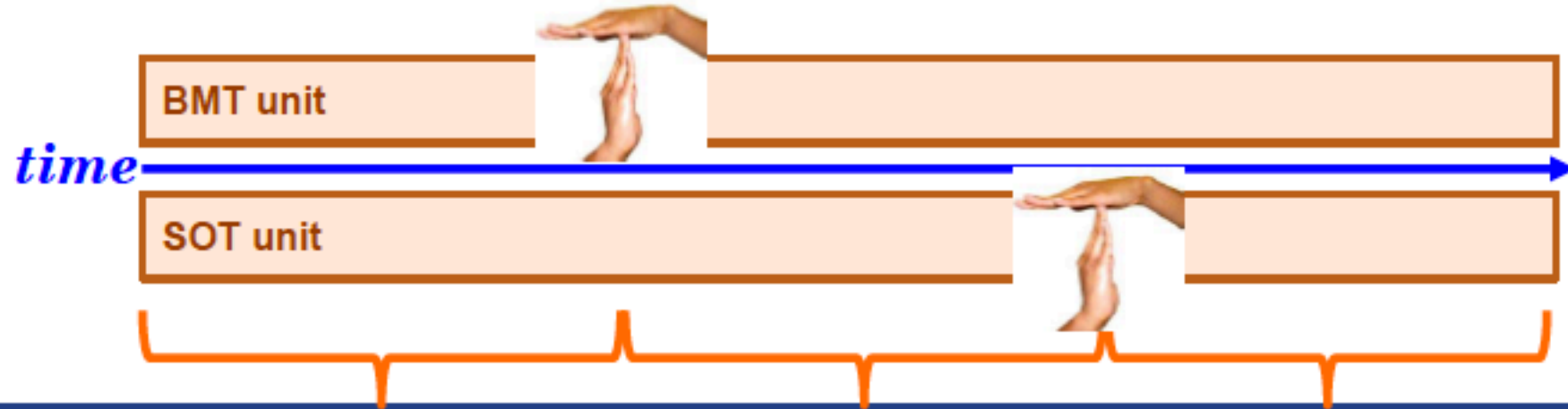


Kontrol Grubunun Eklenmesi



Kontrol grubunun özellikleri

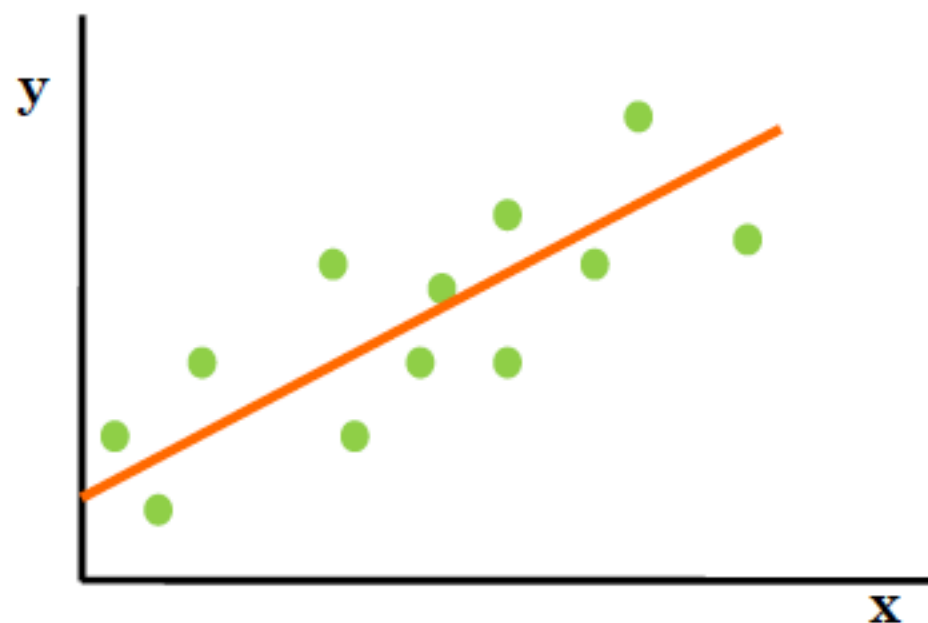
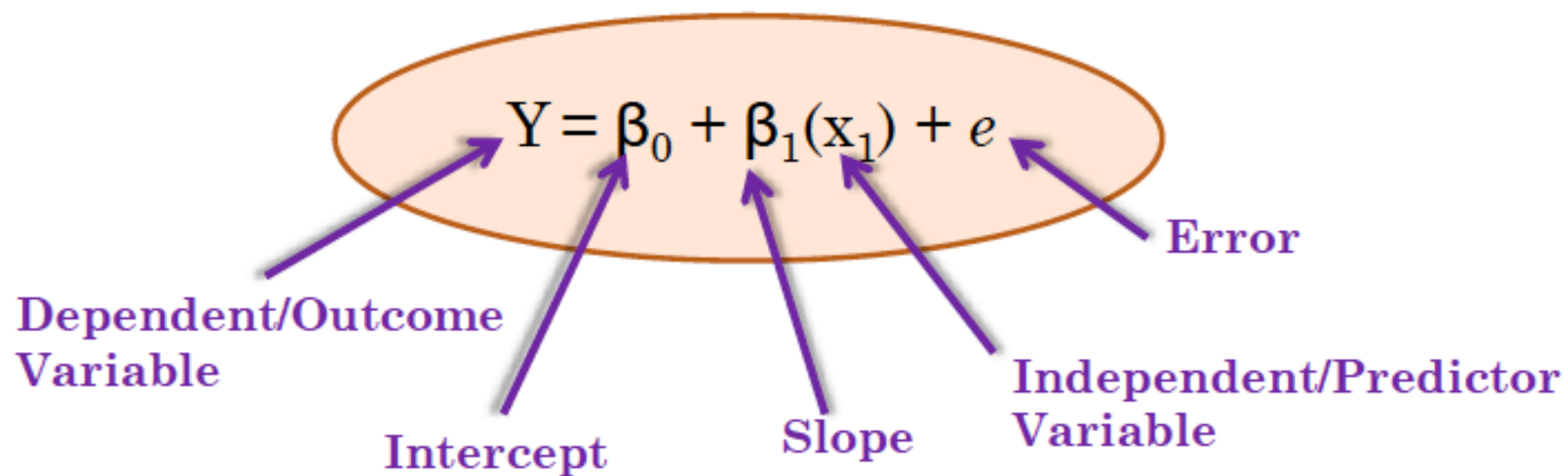
Öncesi/Sonrası ve Kontrol



CDI per 10,000 patient days

	Pre-intervention	Post-intervention I	Post-intervention II
BMT unit	7.24	4.63	3.69
SOT unit	6.35	5.99	2.99

REGRESSION



SEGMENTED REGRESSION FOR ITS

$$Y_t = \beta_0 + \beta_1(\text{time}_t) + \beta_2(\text{intervention}_t)$$

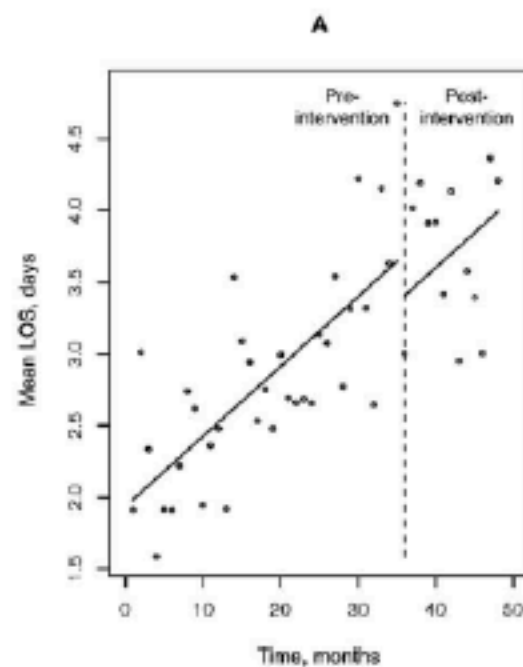
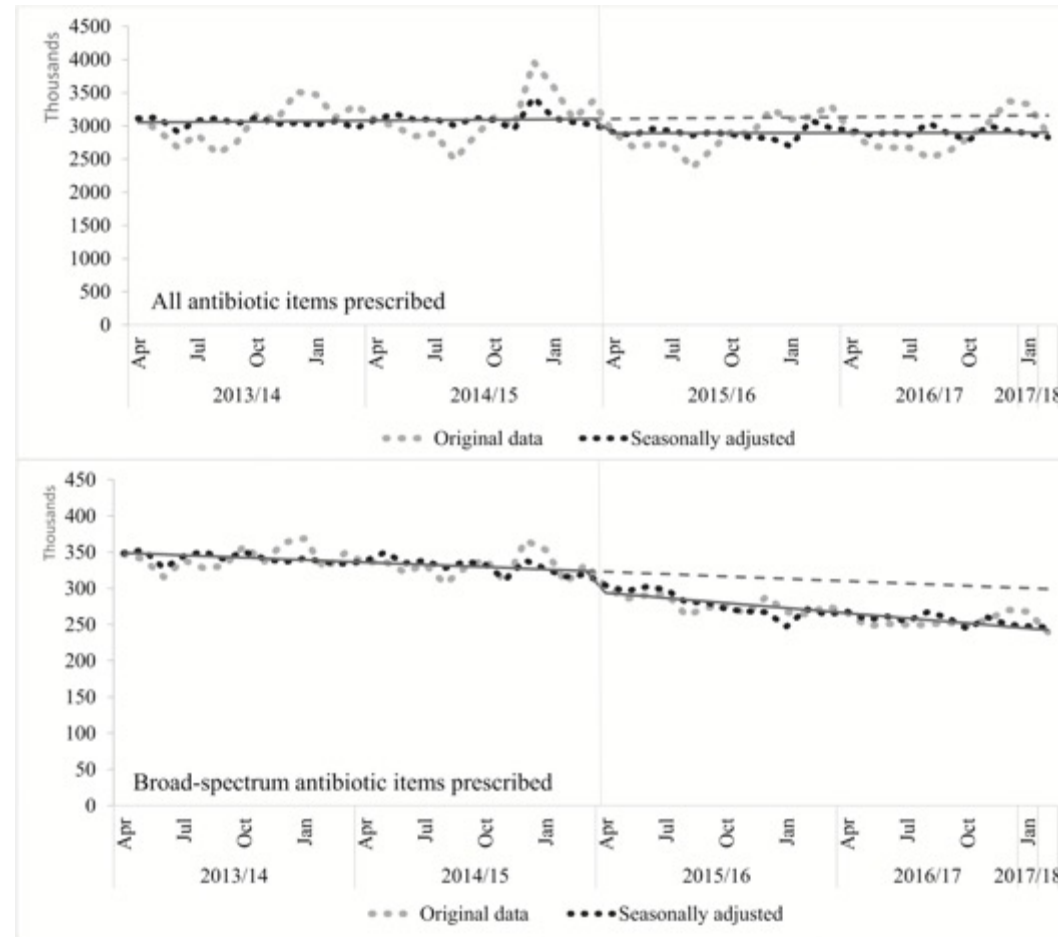


Figure 2. Interrupted time-series data regarding length of hospital stay (LOS) simulated from a segmented linear regression model with a change in slope (before vs. after the intervention), fit with a nonsegmented linear regression model that cannot estimate a change in slope (A) and a segmented linear regression model that can estimate a change in slope (B). The intervention was implemented at month 36.

Figure 2. Segmented regression analysis for all antibiotic and broad-spectrum antibiotic items prescribed. The solid ...



Yarı DeneySEL Çalışmaların Avantaj ve Dezavantajları

Avantajları

RKÇ'dan daha ucuz

Pratik

Retrospektif olsa da politikaları gözden geçirme
Nedenselliği (causality) kısmen açıklar

Kontrol gruplarının eklenmesiyle
güçlendirilebilir.

Dezavantajları

Retrospektif veriler eksik olabilir ve toplamak
zordur.

Randomize değil

Notlar

Randomizasyon gerekmez

RKÇ'de dışlanan hastalar dahil edilebilir. Etkinliği değil,
etkililiği ölçebilir. Dış geçerliliği yüksek.

Strateji oluşturma her zaman elimizde olmayabilir.

Yarı deneySEL; nedensellik için zamansallık (temporality),
ilişkinin gücü (strength of association) ve doz yanıtı

Nedensellik için altın standart değil ama güçlendirilebilir.

Notlar

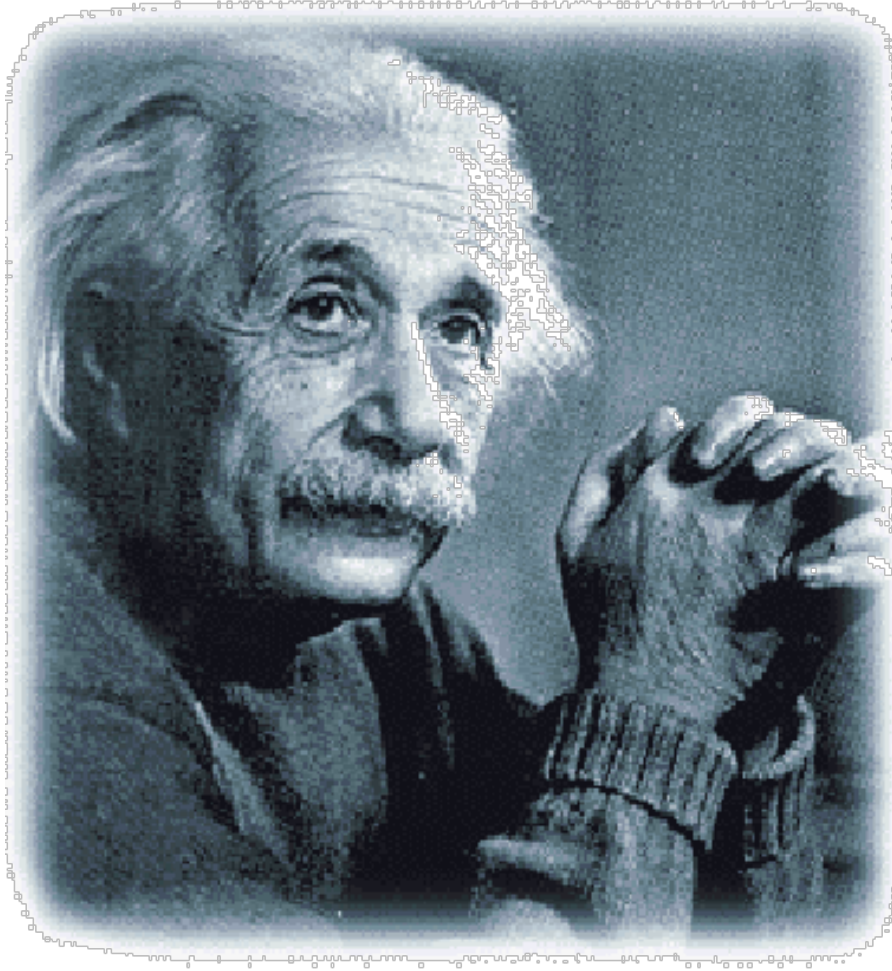
Verilerin uygunluğu, doğruluğu, tam olması kontrol
edilmelidir.

İçsel tutarlılığı düşük

Nedenselliği tam olarak açıklayamaz.

Yanlılık (Bias) Türleri

Seçim (Selection)	Çalışma ve kontrol gruplarının yanlış seçimi
Olgunlaşma (Maturation)	Çalışmanın doğal ilerleyişi sırasında değişiklikler: mevsimsel, yorgunluk, yaşlanma ve sıkılma gibi.
Hawthorne Etkisi	Çalışma ilerledikçe iyileşmenin olması
Tarihsel	Çalışma sırasında başka gelişmelerin olması
Ortalamaya çekmek (Regression to the Mean)	Uç değerler zamanla normale yaklaşabilir
Ölçme aracı (instrumentation)	Ölçme aracının zamanla değişmesi
Değerlendirme	Sonuçların değerlendirmesinde sistematik hata
Raporlama/yayınlama	Olumlu sonuçlar daha çok yayınlanır



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