Immunizations Second Only to Clean Water!

Disease	Pre-Vaccine Era Estimated Annual Morbidity*	Most Recent Estimates‡ of U.S. Cases	Percent decrease
Diphtheria	21,053	0†	100%
H. influenzae (invasive, <5 years of age)	20,000	243† §	99%
Hepatitis A	117,333	11,049‡	91%
Hepatitis B (acute)	66,232	11,269‡	83%
Measles	530,217	61†	>99%
Mumps	162,344	982†	99%
Pertussis	200,752	13,506†	93%
Pneumococcal disease (invasive, <5 years of age)	16,069	4,167‡	74%
Polio (paralytic)	16,316	0†	100%
Rubella	47,745	4†	>99%
Congenital Rubella Syndrome	152	1†	99%
Smallpox	29,005	0†	100%
Tetanus	580	14†	98%
Varicella	4,085,120	449,363‡	89%

*CDC. JAMA, November 14, 2007; 298(18):2155–63
†CDC. MMWR, January 8, 2010; 58(51,52):1458–68
‡2008 estimates, *S. pneumoniae* estimates from Active Bacterial Core Surveillance
§ 25 type b and 218 unknown

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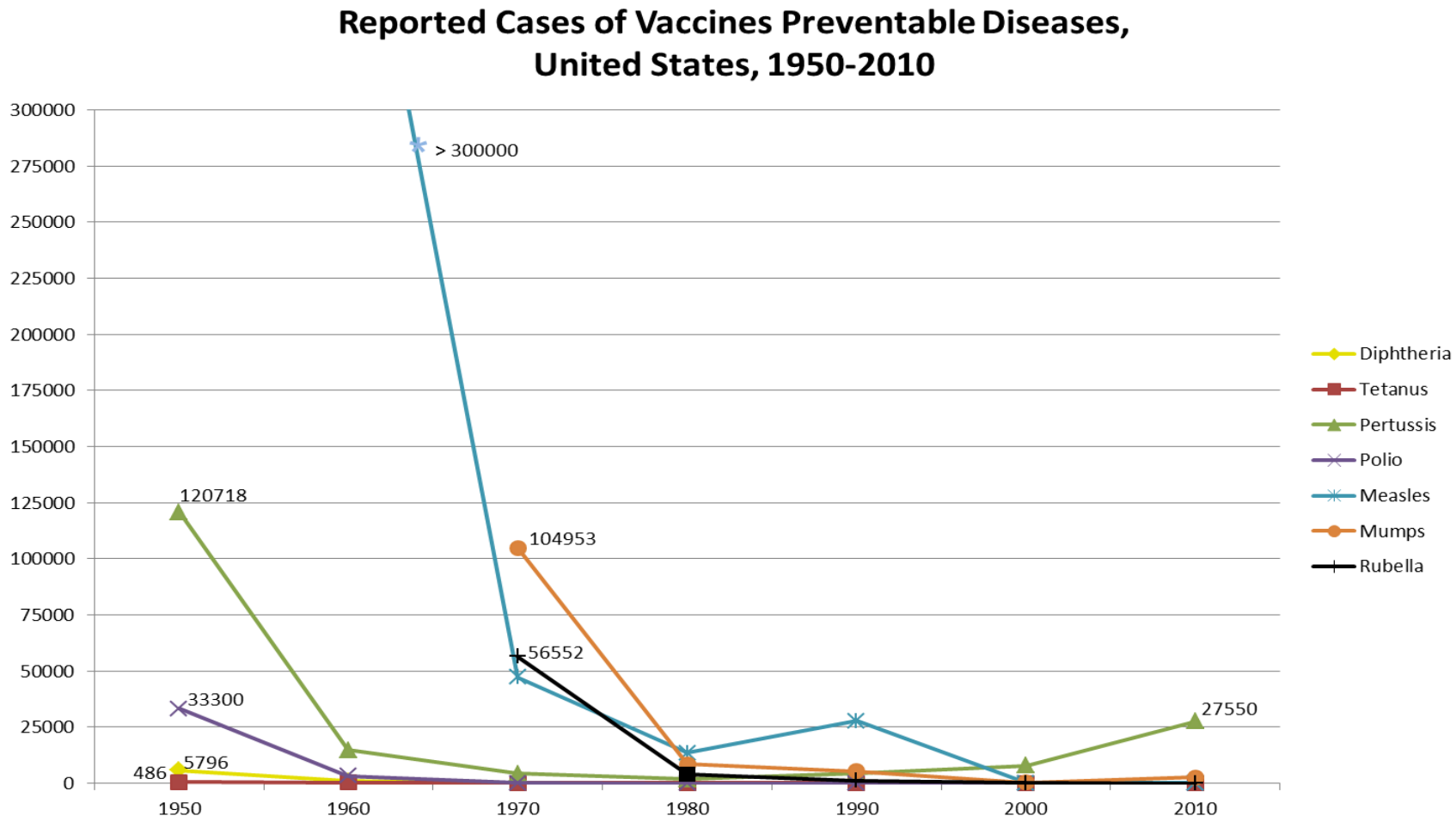
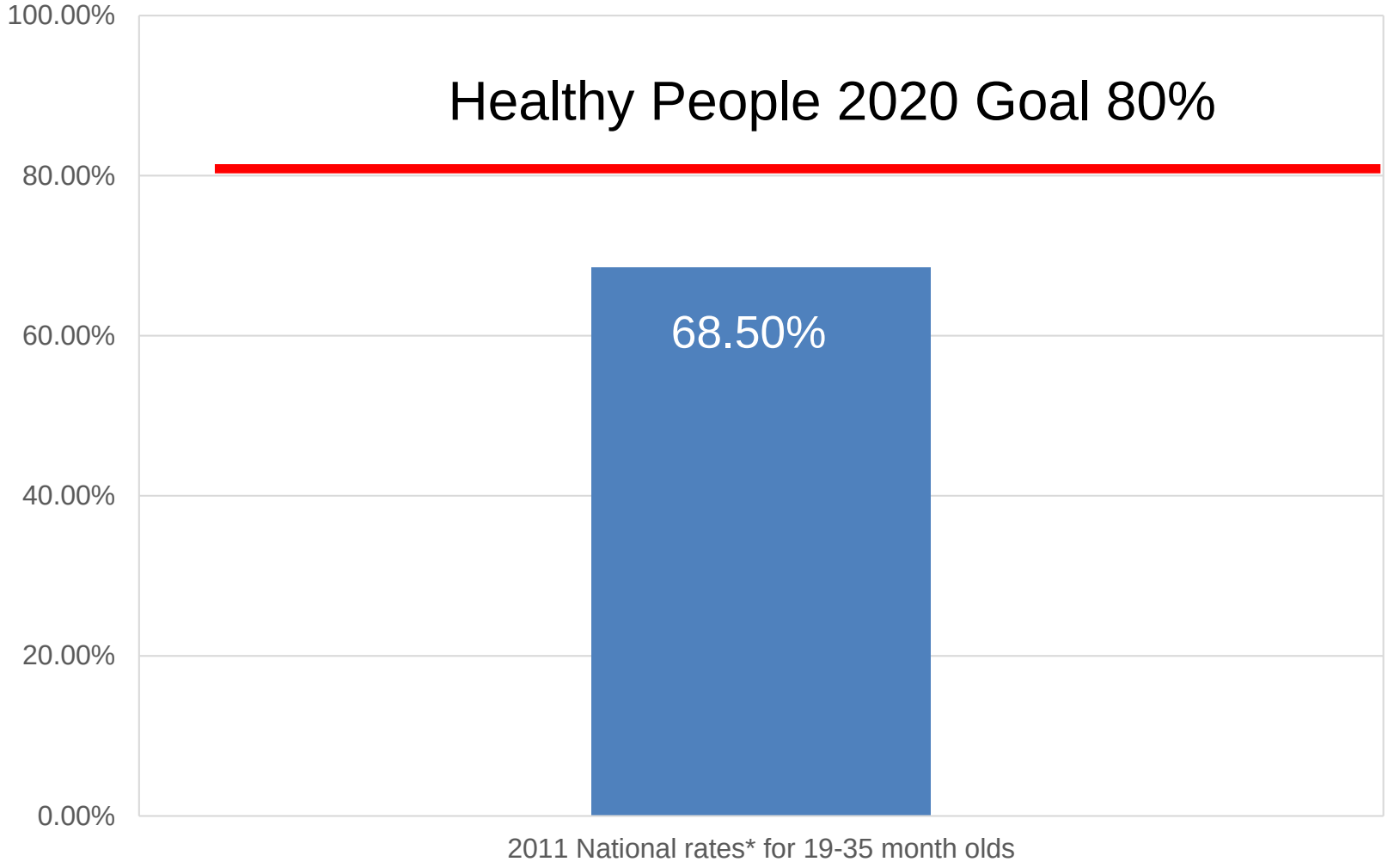
Immunizations Second Only to Clean Water!



So How Are We Doing?



*Routinely recommended vaccines: ≥4 doses of DTaP/DT/DTP, ≥3 doses of poliovirus vaccine, ≥1 doses of measles-containing vaccine, full series of Hib (3 or 4), ≥3 doses of HepB, ≥1 dose of varicella vaccine, ≥4 doses of PCV

What's the Problem?!

Barriers to optimal immunization delivery

- Financial
- Access to care issues
- Lack of awareness
- Infrastructure and regulatory issues
- Complexity and expansion of vaccination schedule
  - # of vaccines more than doubled in past 25 years
  - By18 months of age U.S. children recommended to receive vaccines against 14 different diseases, requiring up to 26 different vaccine doses
- Vaccine hesitancy
  - Misinformation
  - Safety concerns

American Journal of PUBLIC HEALTH

Population-Based Versus Practice-Based Recall for Childhood Immunizations: A Randomized Controlled Comparative Effectiveness Trial

Allison Kempe, MD, MPH, Alison Saville, MSPH, MSW, L. Miriam Dickinson, PhD, Sheri Eisert, PhD, Joni Reynolds, RN, MSN, Diana Herrero, MS, Brenda Beaty, MSPH, Karen Albright, PhD, Eva Dibert, MHA, Vicky Koehler, MPH, Steven Lockhart, BA, and Ned Calonge, MD

Objectives. We compared the effectiveness and cost-effectiveness of population-based recall (Pop-recall) versus practice-based recall (PCP-recall) at increasing immunizations among preschool children.

Methods. This cluster-randomized trial involved children aged 19 to 35 months needing immunizations in 8 rural and 6 urban Colorado counties. In Pop-recall counties, recall was conducted centrally using the Colorado Immunization Information System (CIIS). In PCP-recall counties, practices were invited to attend webinar training using CIIS and offered financial support for mailings. The percentage of up-to-date (UTD) and vaccine documentation were compared 6 months after recall. A mixed-effects model assessed the association between intervention and whether a child became UTD.

Results. Ten of 195 practices (5%) implemented recall in PCP-recall counties. Among children needing immunizations, 18.7% became UTD in Pop-recall versus 12.8% in PCP-recall counties (*P* < .001); 31.8% had documented receipt of 1 or more vaccines in Pop-recall versus 22.6% in PCP-recall counties (*P* < .001). Relative risk estimates from multivariable modeling were 1.23 (95% confidence interval [CI] = 1.10, 1.37) for becoming UTD and 1.43 (95% CI = 1.15, 1.38) for receipt of any vaccine. Costs for Pop-recall versus PCP-recall were $215 versus $1981 per practice and $17 versus $62 per child brought UTD.

Conclusions. Population-based recall conducted centrally was more effective and cost-effective at increasing immunization rates in preschool children. *American Journal of Public Health.* 2013;103:1116–1123. doi:10.2105/AJPH.2012.301035

Vaccination is recognized as one of the greatest public health achievements of the 20th century.[1] Childhood vaccines developed in the previous century were associated with declines in the incidence of major childhood infectious diseases by 98% or more compared with baseline 20th century annual morbidity rates.[2,3] Despite this, only 44.3% of children aged 19 to 35 months received all recommended vaccines in 2009.[4] Because of the importance of timely vaccination in young children, one of the nation's top health goals as outlined in Healthy People 2020, is to increase the proportion of children aged 19 to 35 months who receive all recommended doses of childhood vaccines to 80%.[4]

Based on strong evidence of effectiveness, the Community Preventive Services Task Force[5,6] recommends the use of reminder/recall for increasing immunization rates, including notification for upcoming immunizations (reminders) or recall notices for overdue immunizations (recall). The use of regional or state immunization information systems (IISs) can greatly facilitate reminder/recall because such systems cannot only identify children who need immunizations but often can also generate reminder postcards or electronic data that can be used to produce autodialer messages. Current national data suggest that despite strong national recommendations, few providers are doing any type of reminder/recall for immunizations.[7] Because of this, there has been interest in determining whether reminder/recall efforts might be more feasible and less costly to conduct centrally by health departments using a regional or state IIS.

We conducted a population-based, cluster-randomized pragmatic trial comparing the effectiveness of practice-based recall versus population-based recall conducted by the state health department using the Colorado Immunization Information System (CIIS) in increasing immunization rates among children aged 19 to 35 months as well as the cost-effectiveness of each method.

METHODS

This study was a stratified cluster-randomized pragmatic trial in 14 counties (8 rural, 6 urban) in Colorado with randomization at the county level within rural and urban strata. We followed the criteria established for National Institutes of Health–funded pragmatic trials.[8,9]

Settings and Study Participants

Colorado Immunization Information Sy
(CIIS). CIIS receives client and vaccine

through live data ent
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JAMA Pediatrics

Collaborative Centralized Reminder/Recall Notification to Increase Immunization Rates Among Young Children: A Comparative Effectiveness Trial

Allison Kempe, MD, MPH; Alison W. Saville, MSPH, MSW; L. Miriam Dickinson, PhD; Brenda Beaty, MSPH; Sheri Eisert, PhD; Dennis Gurfinkel, MPH; Sarah Brewer, MPH; Heather Shull, MA; Diana Herrero, MS; Rachel Herlihy, MD, MPH

IMPORTANCE Reminder/recall notifications used by primary care practices increase the rates of childhood immunizations, but fewer than 20% of primary care practitioners nationally deliver such reminders. A reminder/recall notification conducted centrally by health departments in collaboration with primary care practices may reduce practice burden, reach children without a primary care practitioner, and decrease the cost of reminders/recalls.

OBJECTIVE To assess the effectiveness and cost-effectiveness of collaborative centralized (CC) vs practice-based (PB) reminder/recall approaches using the Colorado Immunization Information System (CIIS).

DESIGN, SETTING, AND PARTICIPANTS We performed a randomized pragmatic trial from September 7, 2012, through March 17, 2013, including 18 235 children aged 19 to 35 months in 15 Colorado counties.

INTERVENTIONS In CC counties, children who needed at least 1 immunization were sent as many as 4 reminders/recalls by mail or autodialed telephone calls by the CIIS. Primary care practices in these counties were given the option of endorsing the reminder/recall notification by adding the practice name to the message. In PB counties, primary care practices were invited to web-based reminder/recall training and offered financial support for sending notifications.

MAIN OUTCOMES AND MEASURES Documentation of any new immunization within 6 months constituted the primary outcome; achieving up-to-date (UTD) immunization status was secondary. We assessed the cost and cost-effectiveness of each approach and used a generalized linear mixed-effects model to assess the effect of the intervention on outcomes.

RESULTS In PB counties, 24 of 308 primary care practices (7.8%) attended reminder/recall training and 2 primary care practices (0.6%) endorsed the reminder/recall notifications. Within CC counties, 129 of 229 practices (56.3%) endorsed the reminder/recall letter. Documentation rates for at least 1 immunization were 26.9% for CC vs 21.7% for PB counties ($P < .001$); 12.8% vs 9.3% of patients, respectively, achieved UTD status ($P < .001$). The effect of CC counties on children's UTD status was greater when the reminder/recall notification was endorsed by the primary care practice (19.2% vs 9.8%; $P < .001$). The total cost of the CC reminder/recall was $28 620 or $11.75 per child for any new immunization and $24.72 per child achieving UTD status; the total cost to the 2 practices that conducted PB reminders/recalls was $74 000 per child for any immunization and $124.45 per child achieving UTD status. The modeling resulted in an adjusted odds ratio of 1.31 (95% CI, 1.16-1.48) for any new immunization in CC vs PB counties.

CONCLUSIONS AND RELEVANCE A CC reminder/recall notification was more effective and more cost-effective than a PB system, although the effect size was modest. Endorsement by practices may further increase the effectiveness of CC reminder/recall.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01557621

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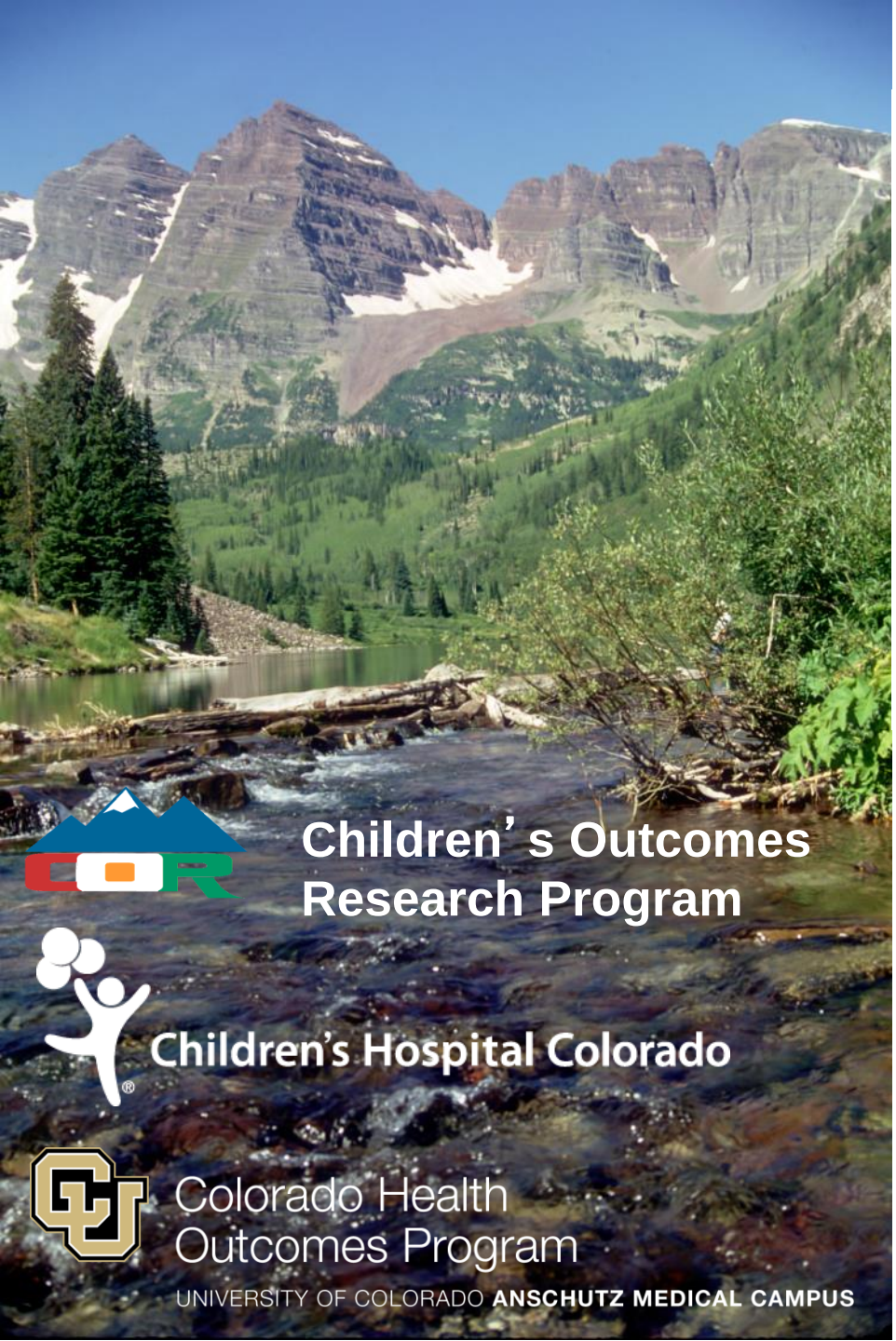
Editorial page 314
Author Audio Interview at jamapediatrics.com
Supplemental content at jamapediatrics.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Allison Kempe, MD, MPH, Children's Outcomes Research Program, Children's Hospital Colorado, 13199 E Montview Blvd, Ste 300, Aurora, CO 80045 (allison.kempe@childrenscolorado.org).



Population-based vs. Practice-based Reminder/Recall: a Pragmatic Comparative Effectiveness Trial

Allison Kempe, MD, MPH

Background

- Reminder/recall (R/R): postcards, letters or telephone calls to inform patients they are due or overdue for immunizations
- Can be automated using Immunization Information System (IIS)
- R/R conducted in practice settings shown effective in increasing rates but only 16% of physicians nationally are conducting
- Population-based R/R if conducted centrally by public health departments could offer advantages of:
  - Reducing burden of conducting R/R by practices
  - Reaching children without usual source of primary care

Objectives

To compare the *effectiveness* and *cost-effectiveness* of conducting R/R using two methodologies:

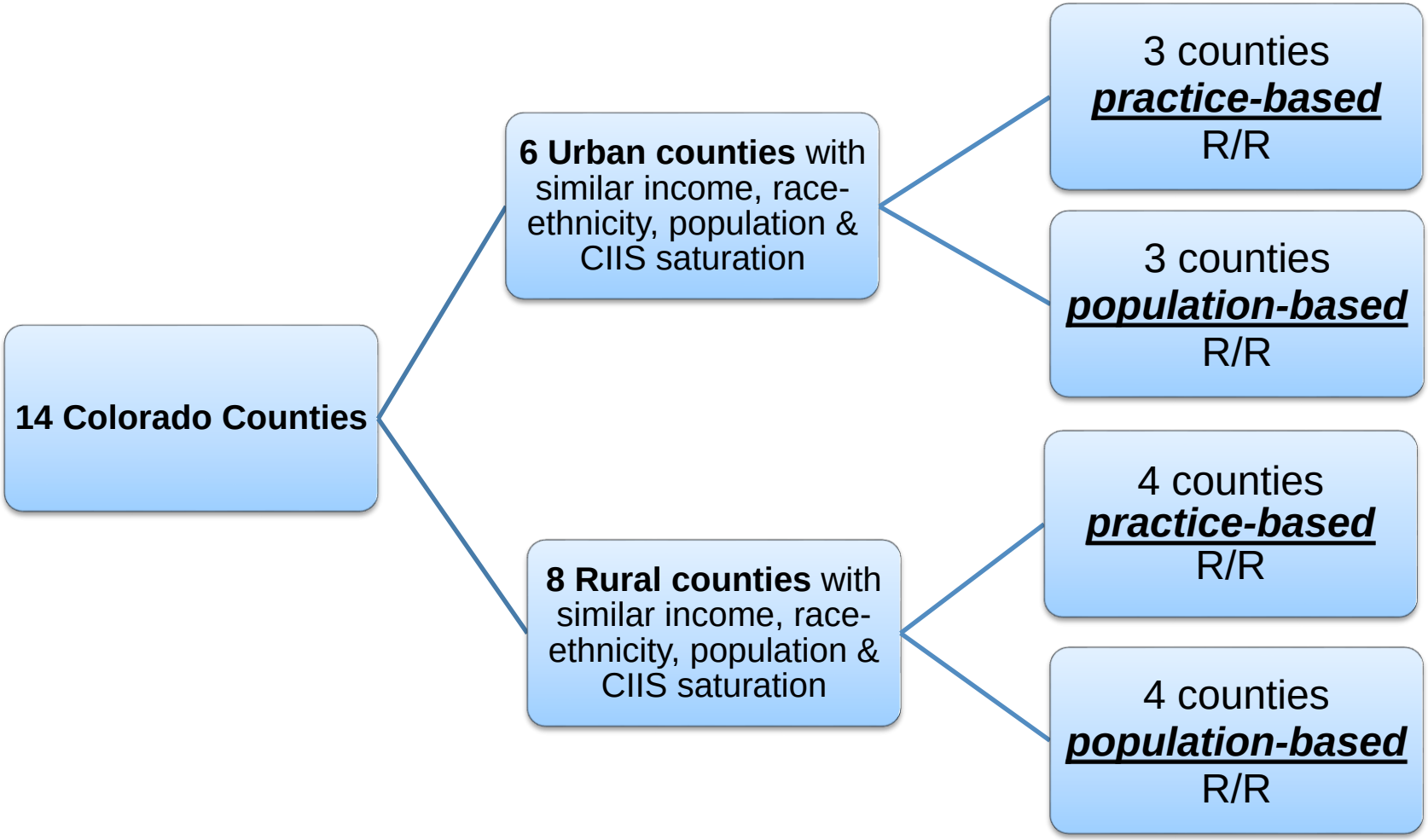
1. ***Population-based R/R:*** conducted centrally by the State Health Department using the Colorado Immunization Information System (CIIS)

2. ***Practice-based R/R:*** conducted at the level of the primary care practice using CIIS

Randomization Procedures

- Counties first stratified into Urban or Rural based on Colorado Rural Health Center Designation
- Within these strata, covariate constrained randomization used to optimize balance between study arms with respect to baseline variables of <u>counties</u> including:
  - % Minority race and ethnicity
  - % 19-35 month olds with ≥2 Iz in IIS
  - # Pediatricians, # FM, Pediatric/FM ratio
  - Median income
  - # Children 19-35 months
  - # Community Health Centers

Methods: Randomization of Counties



Study Populations for Both Intervention Arms

Patient names, addresses and immunization data automatically uploaded from Birth Vital Statistics to

Colorado Immunization Information System (CIIS)

Downloaded names and addresses of children 19-35 months old needing ≥1 immunization within all 14 counties

Methods: Intervention Strategies

- Population-based recall counties:
  - Centralized R/R conducted by the State Public Health Department June – September 2010
  - Up to 3 mailings to children 19-35 months needing immunizations
  - R/R notices suggested patients go to primary care provider for immunization or, if they did not have one, to public health immunization site

Methods: Intervention Strategies

- Practice-based recall counties:
  - All practices invited to attend web-based R/R training in May/June 2010
  - R/R methodology suggested
    - 3 mailings to children 19-35 months needing immunizations
    - June – September 2010
  - Financial support for mailings offered to practices who did R/R in this timeframe

Methods: Statistical Analysis

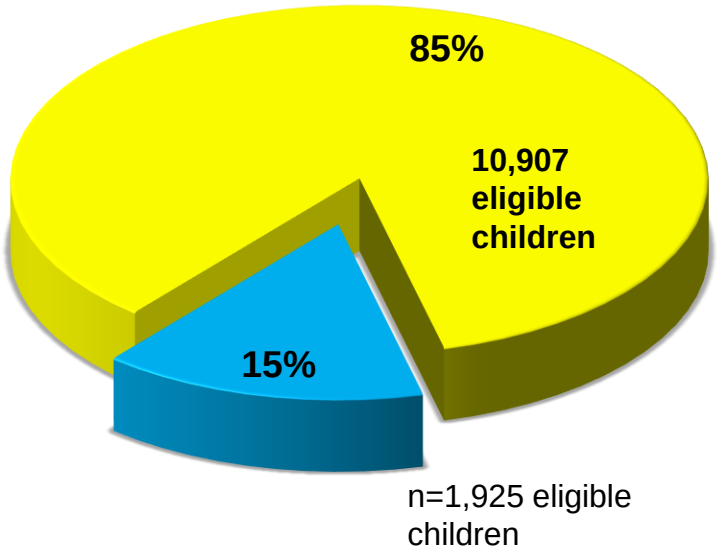
- To account for clustered nature of the data mixed effects models used
  - Two models conducted to assess association between intervention group and whether or not 1) child became UTD or 2) received any shot during the study period
  - Fixed effects for both models included county baseline UTD rate, rural/urban status of county, and whether or not site of last service did R/R
  - The random effect in both models was site of last service

Methods: Cost Assessment

- Population-based R/R (performed centrally)
  - Staff time for training and implementation
  - Staff time for updating bad mailing addresses
  - Mailing and printing costs for up to 3 mailings
- Practice-based R/R (performed differently at each practice)
  - Average staff time among practices conducting R/R
  - Average mailing costs or costs of phone calls

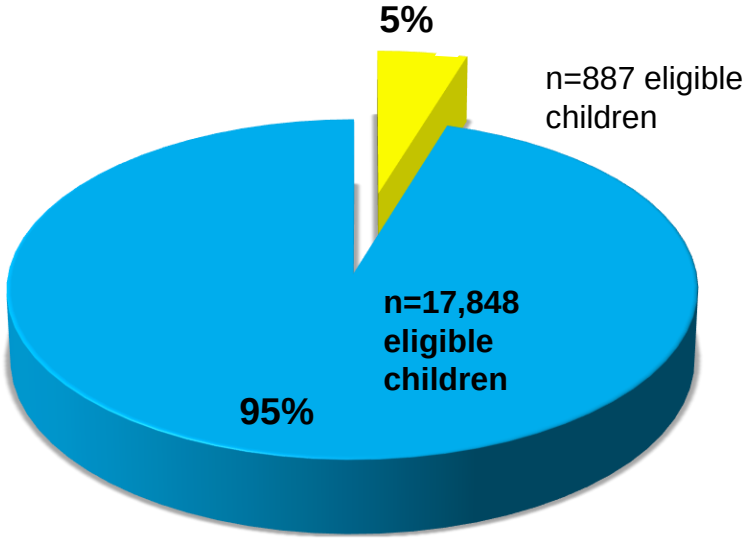
Comparison of "Reach" of Intervention

Population-based R/R Reach
188 practice sites



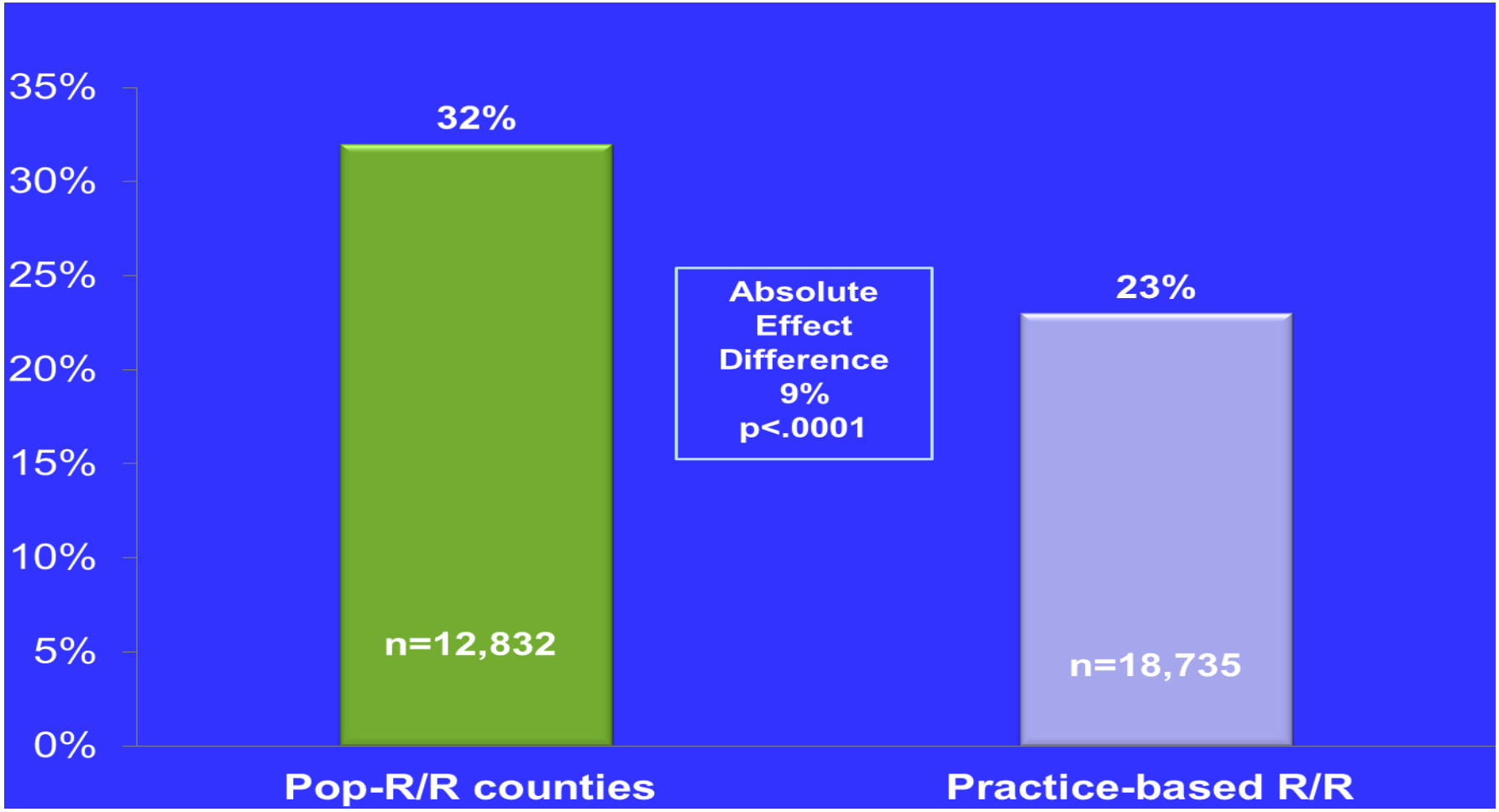
- Received >=1 Reminder Notice (assuming 85% received R/R)
- Did not receive a R/R notice

Practice-based R/R Reach
195 practice sites

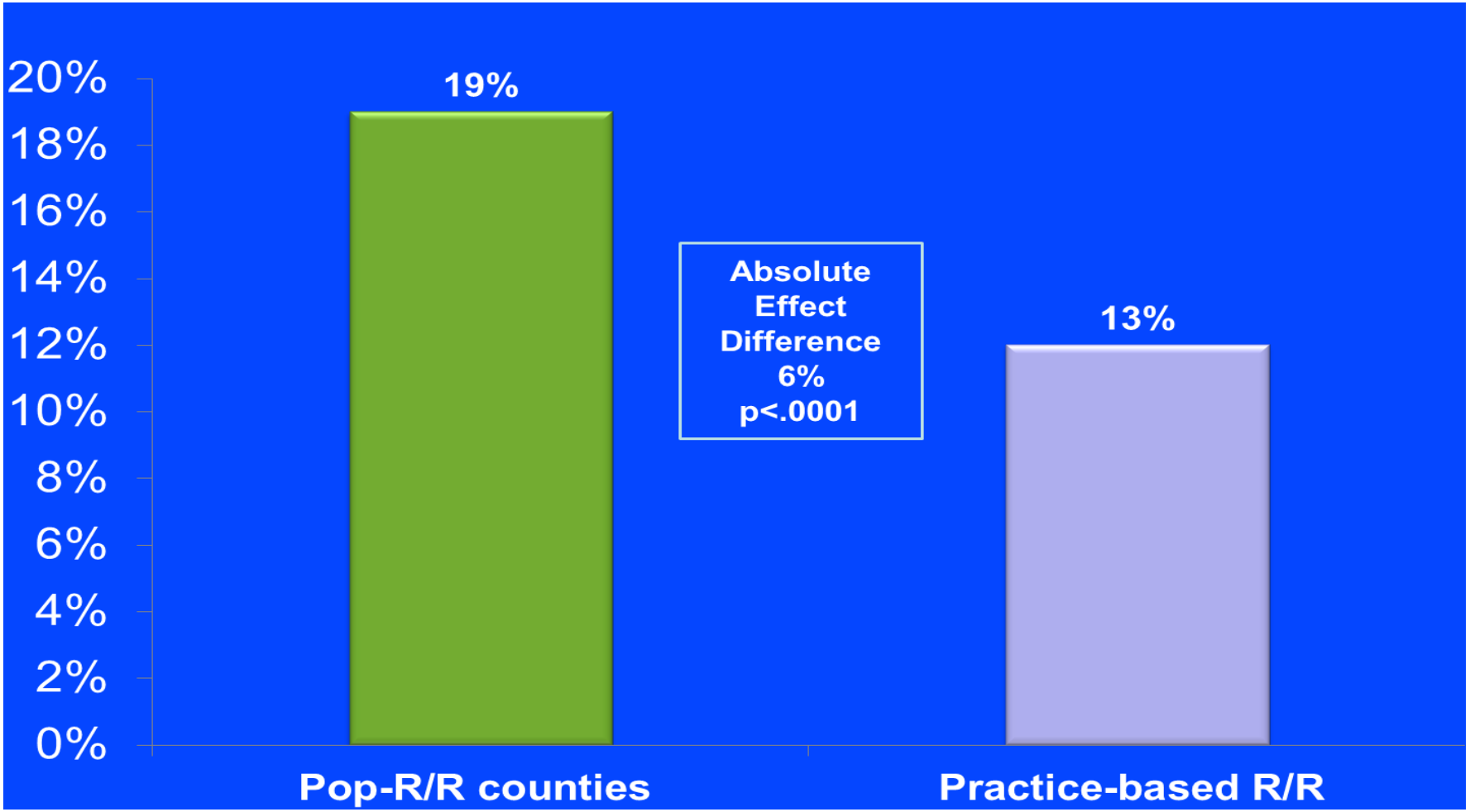


- Received >=1 Reminder (assuming 100% received R/R)
- Did not receive R/R

Percent Receiving Any Vaccine within 6 months
(of those needing vaccines at baseline)



Percent Brought Up-to-Date within 6 months
(of those needing vaccines at baseline)



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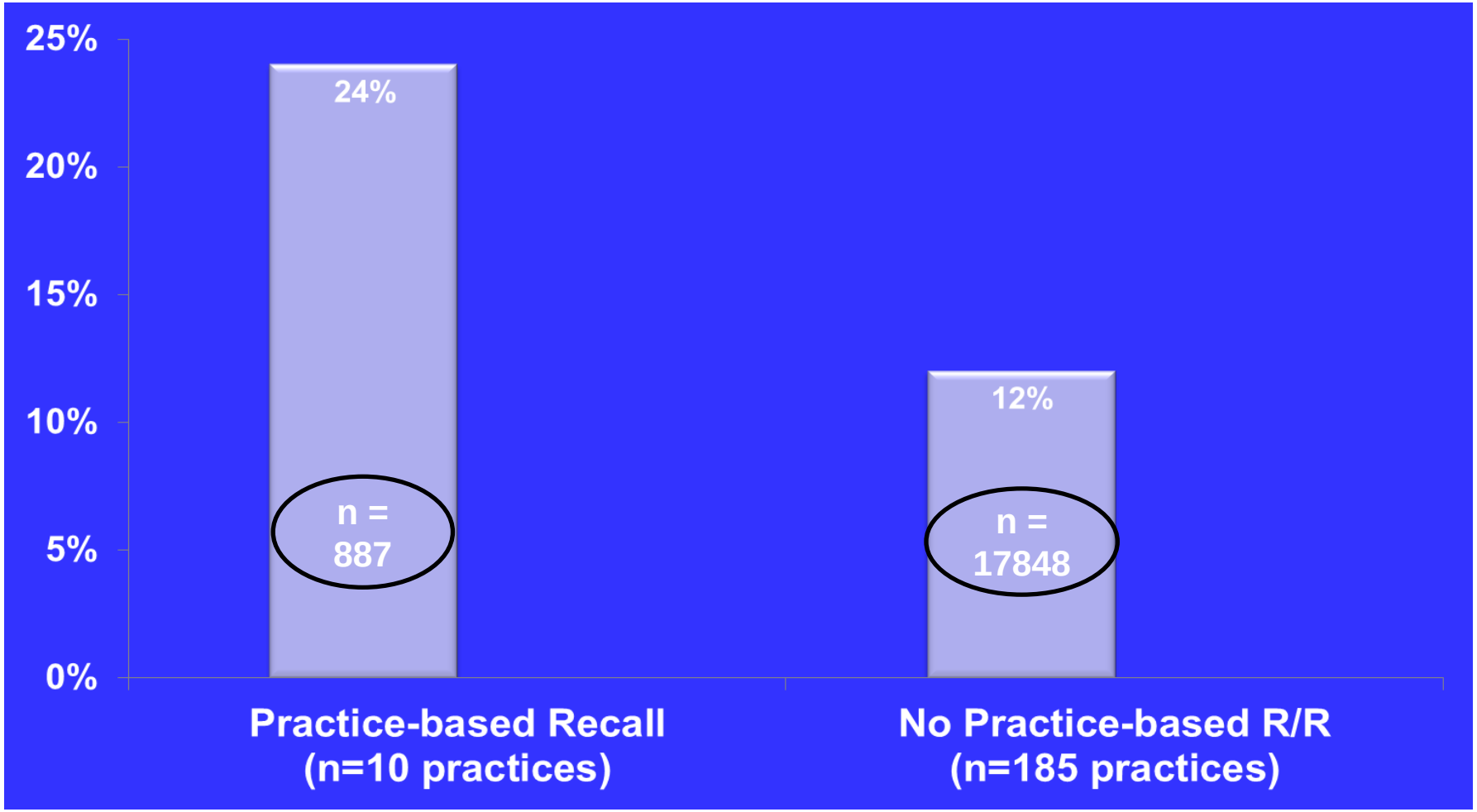
Subgroup Analysis w/in Practice-based Counties Percent Brought Up-to-Date R/R vs no R/R



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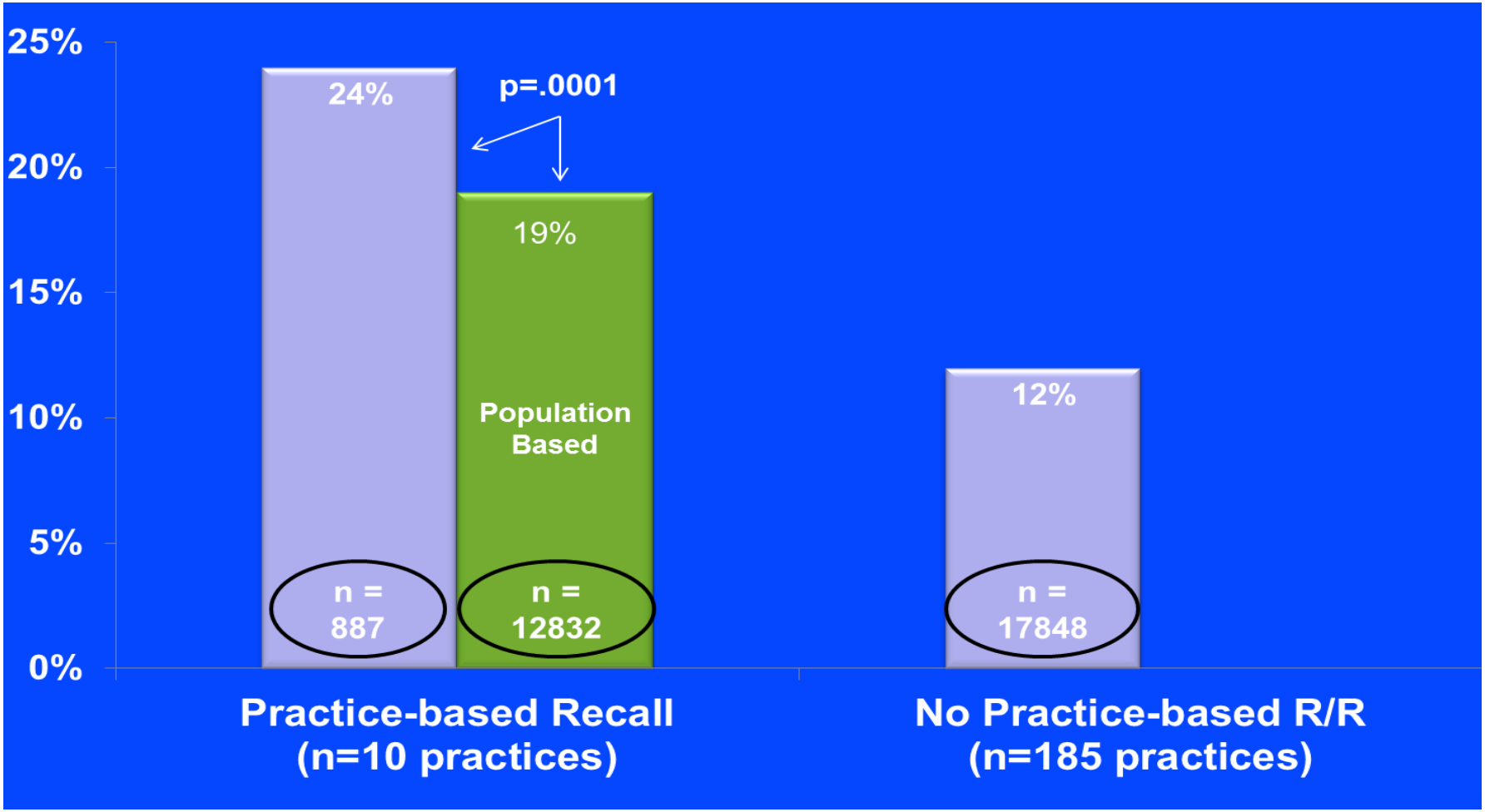
Subgroup Analysis w/in Practice-based Counties
Percent Brought Up-to-Date
R/R vs no R/R



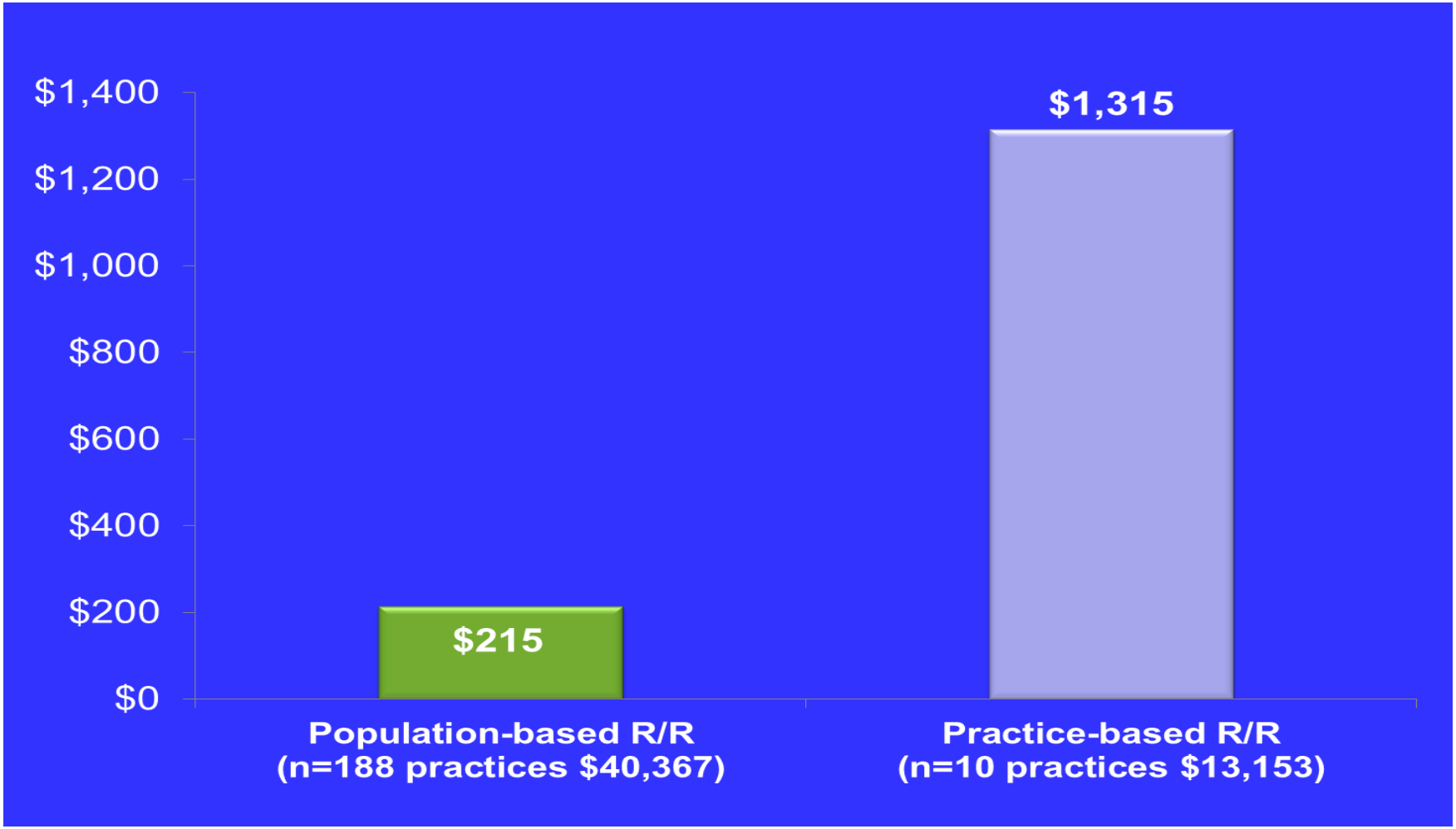
Results: Multivariable Models

Association of Intervention Group with Two Outcomes

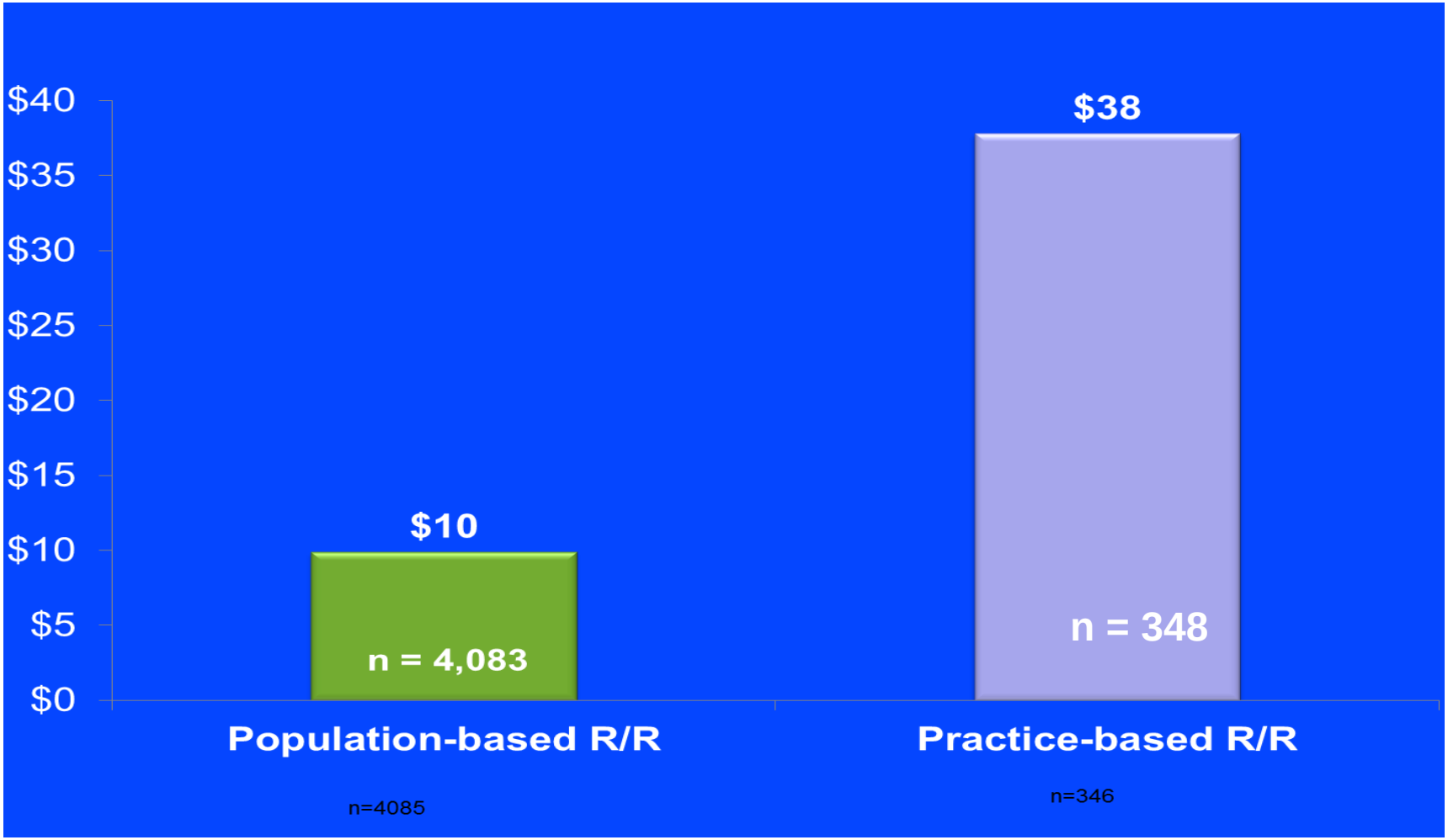
Outcomes Modeled	Adjusted OR (95% CI)	P-value
Becoming up-to-date in population-based versus practice-based county	1.24 (1.11-1.38)	.0002
Receiving any vaccine in population-based versus practice-based county	1.27 (1.15-1.39)	<.0001

Other variables included in the model were baseline county UTD rate, rural/urban status of county, site of last service and whether or not site of last service did R/R, all of which were not statistically significant

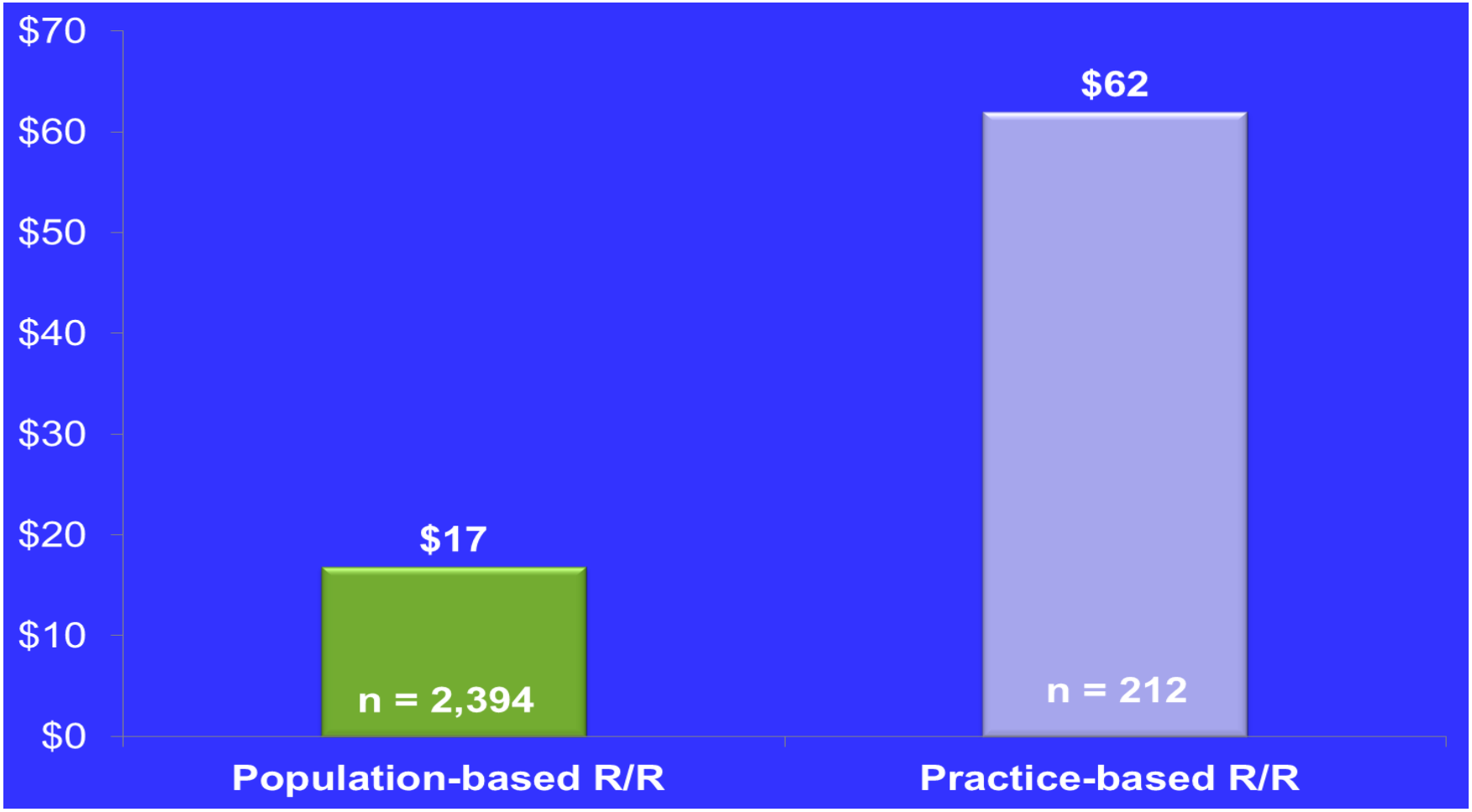
Cost of Conducting R/R per Practice



Cost of R/R Per Child who Received ≥1 Vaccine



Cost of R/R Per Child Brought Up-to-Date



Limitations

- Population impossible to accurately denominate in all counties—but same method of approximation used in both intervention arms
- Population-based R/R hampered by many inaccurate addresses from vital statistics
- Practices may have conducted R/R after the 6 month period of F/U despite incentives
- Costs were based on personnel report, rather than direct observation

Conclusions

- Both practice-based and population-based R/R effective—practice-based slightly more effective when practices participated
- Overall, at a county level population-based R/R was more effective than practice-based R/R because of lack of participation of practices even when incentives provided
- Costs per practice or per child vaccinated were much lower for population-based R/R

Study Team

University of Colorado Denver

Principal Investigator – Allison Kempe, MD, MPH

- Alison Saville, MSPH, MSW
- L. Miriam Dickinson, PhD
- Brenda Beaty, MSPH
- Sheri Eisert, PhD
- Karen Albright, PhD
- Eva Dibert, MHA
- Vicky Koehler, MPH

CDPHE & CIIS Collaborators

- Ned Calonge, MD
- Joni Reynolds, RN, MSN
- Diana Herrero, MS

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Questions?

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Population-based vs Practice-based Reminder/Recall Trial:

Study Design, Data, and Analytic Challenges

L. Miriam Dickinson, PhD

Study Design Challenges

- Early decisions involved unit of randomization
- Treatment Arms
  - *Population-based R/R*
    - *Intervention delivered at the level of the population*
  - *Practice-based R/R*
    - *Intervention targeted eligible practices (training for R/R) and delivered to patients by practices*
- Cluster Randomized Trial
  - Individual level randomization not feasible and didn't fit the goals of the study
  - Power and sample size had to account for clustering

Cluster Randomized Trials

- Unit of randomization is a group rather than an individual
  - Groups can be defined in a variety of ways
    - Geographic location (e.g. communities, counties, etc)
    - Organizational units (schools/classrooms, hospitals, medical practices)
    - Families
- Reasons for cluster randomized design
  - Intervention is at the level of the group
  - Potential contamination makes individual-level randomization problematic
  - Feasibility – convenience, economic considerations

Common issues with CRTs

- Generally, the number of units to be randomized is much smaller than trials in which individuals are randomized
- Recruiting groups from a larger pool can be challenging
  - Self-selection
- Heterogeneity among groups
- Individuals within groups are more similar to each other than members of other groups
  - Violation of independence assumption
- Potential for covariate imbalance between study arms
  - Simple, or even stratified randomization of groups can result in study arms that are very different from each other
- More complex analyses
- Reduced power

Study Design Challenges

- Deciding on the unit of randomization
  - County
  - Baseline data could be obtained from CIIS database by county of residence
- All children in age range with at least 2 immunization records in CIIS, residing in selected counties, would be included in the trial if they needed 1 or more vaccines

Study Design Challenges

- Implications of using a county-based population
  - PB arm
    - All eligible practices in PB intervention counties would be invited to participate in training, thus eliminating potential selection bias
    - But practice participation was not a requirement
    - Individual affiliation with a practice was not a requirement for data to be included
  - Population-based arm
    - All eligible children, regardless of practice affiliation (or not) would be included in the trial
  - Analysis: population-based sample

County Selection

- Pre-specified criteria for selecting counties
  - Minimum 70% in CIIS
  - Urban or rural (frontier counties with <10,000 excluded)
  - No ongoing existing county-wide reminder/recall efforts
  - Other county-specific exclusions (e.g. high refusal rates, smaller population relative to other urban)

Study Design Challenges: concerns about covariate imbalance

- Relatively few units for randomization and heterogeneity among clusters
- Imbalance in clinical trials is not a new problem
- Stratification is not always sufficient to overcome this problem
  - Motivating factor to explore alternatives to simple (or stratified) randomization came from experience with a previous cluster randomized trial (type 2 diabetes) and imbalanced study arms
- Minimization methods for randomization of individuals were first described in the 1960's and 1970's
- Extended to CRTs in early 2000s

Methods for Randomization

- Raab and Butcher (2001) consider the effects of covariate imbalance on an optimal design criterion: difference between crude and adjusted treatment effect
  - Showed that differences between crude and adjusted treatment effect are minimized when differences in treatment group means on covariates to be included in the analysis are small
- Covariate constrained randomization methods described
  - Moulton LH. Covariate-based constrained randomization of group-randomized trials. Clinical Trials 2004
  - Glynn RJ, Brookhart A, Stedman M, Avorn J, Solomon DH. Design of cluster-randomized trials of quality improvement interventions aimed at medical care providers. Medical Care. 2007
- But relatively few CRTs had used these approaches at the time we planned this trial

Procedure for Covariate Constrained Randomization

- Baseline data on units of randomization must be available
- All possible randomizations of units into study groups are generated (for 2 arm trial)
- A balance criterion (B), defined as the sum of squared differences between study groups on relevant standardized variables, is calculated for each randomization
  - $B=(w_1(x_{11} - x_{21})^2 + w_2(x_{12} - x_{22})^2 + \ \ldots\ )$
  - Where w is the weight for each selected variable, x_{11} is the mean for study arm 1, variable 1, x_{21} is the mean for arm 2, variable 1, etc.
- Establish a criterion for maximum allowable difference between study arms and define a set of "optimal randomizations" in which the differences between treatment groups on covariates are minimized
- A single randomization is then chosen from the set of "optimal randomizations"

Covariate Constrained Randomization for R/R trial

- All possible randomizations generated using SAS Proc IML
- Standardize randomization variables (z-scores)
- Generate a file containing data on each randomization and calculate group means on all randomization variables
- Variables weighted equally
- For each randomization
  - Balance criterion calculated (sum of total squared differences across all variables)

Covariate Constrained Randomization for R/R trial

- Stratification variable (urban/rural) can be included in the process by limiting possible randomizations to those that are balanced
- In this case, each study arm should include exactly 4 rural counties; all other combinations are eliminated
- This results in smaller set of possible randomizations that are already balanced on rural/urban location

Covariate Constrained Randomization for R/R trial

- Variables for balance criterion (county level)
  - Total number of children in age range
  - Up-to-date rates for early childhood immunizations
  - % African American in county
  - % Hispanic in county
  - Average income
  - Pediatric to family medicine ratio
  - # of community health clinics
- For each randomization balance criterion calculated (total squared difference)
  - $B = (nKIDSg1 - nKIDSg2)^2 + (UTDg1 - UTDg2)^2 + (\%blackG1 - \%blackG2)^2 + (\%HispG1 - \%HispG2)^2 + (incomeG1 - incomeG2)^2 + (pedsfmratioG1 - pedsfmratioG2)^2 + (nchcG1 - nchcG2)^2$

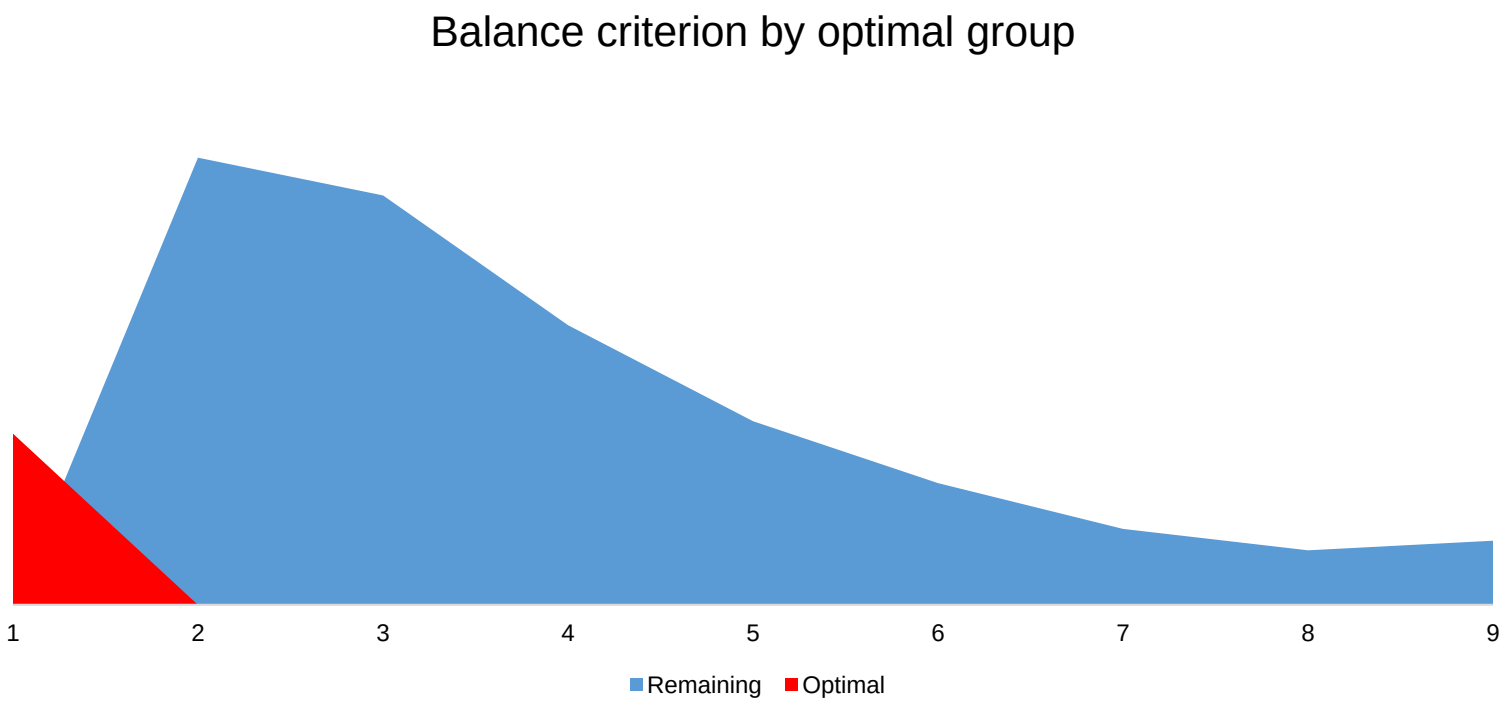
Covariate Constrained Randomization for R/R trial

- Examined the distribution of the balance criterion and set a value for defining the optimal set
  - Target is approximately the best 10% but there are no set rules
- Optional: compare differences in means on raw variables for "optimal set" vs others
- Randomly selected a final randomization from the optimal set and assigned counties to study arms

County Level Characteristics

	County-Level Variables for Randomization	
Variable	Rural and Urban Counties Mean (SD)	Min, max
Number of children age 19-35 months	4197 (4432)	234, 12354
% Up-to-date at baseline	40.8% (8.3)	27.0%, 54.0%
% Hispanic	22.3% (12.9)	6.0%, 44.0%
% African American	2.9% (2.7)	0%, 10.0%
Average Income ($)	$53481 (15793)	$29738, $93819
Pediatric to Family Medicine ratio	0.28 (0.25)	0, 1.0
# CHCs	4.4 (3.5)	0, 11

Distribution of Balance Criterion



Dickinson LM, Beaty B, Fox C, Pace W, Dickinson WP, Emsermann C, Kempe A.. Pragmatic cluster randomized trials using covariate constrained randomization: A method for practice-based research networks (PBRNs). J Am Board Fam Med. 2015 Sep-Oct;28(5)

Magnitude of differences in means on raw variables

Differences Between Study Groups on Raw Variables		
Variable	Optimal Mean (Max)	Remaining Randomizations Mean (Max)
Number of children age 19-35 months	223 (613)	1264 (6325)
% Up-to-date at baseline	2.1% (5.0)	4.9% (15.0)
% Hispanic	5.6% (11.3)	7.9% (23.3)
% African American	<1% (1.0)	1.4% (4.5)
Average Income ($)	$3659 (9702)	$9731 (27131)
Pediatric to Family Medicine ratio	0.20 (0.40)	0.15 (0.40)
# CHCs	1.3 (2.8)	1.6 (4.8)

+absolute value of differences taken for each randomization

Worst Randomization from Optimal Set

Variable	Arm 1 Means of County-Level Variables (SD)	Arm 2 Means of County-Level Variables (SD)
Number of children age 19-35 months	4275 (4628)	4118 (4546)
% Up-to-date at baseline	40.1% (8.8)	41.5% (8.3)
% Hispanic	23.8% (14.8)	20.9% (11.6)
% African American	2.5% (2.4)	3.3% (3.1)
Average Income $	$56264 (18004)	$50699 (13877)
Pediatric to Family Medicine ratio	0.33 (0.33)	0.23 (0.15)
# CHCs	4.8 (4.5)	4.0 (2.4)

Selected Randomization by Location

Variable	Rural		Urban	
	Arm 1 Mean (SD)	Arm 2 Mean (SD)	Arm 1 Mean(SD)	Arm 2 Mean(SD)
Number of children age 19-35 months	682 (695)	618 (465)	7467 (3915)	8049 (3855)
% Up-to-date at baseline	39.0 (7.5)	36.3 (6.5)	44.8 (9.1)	43.3 (10.1)
% Hispanic	26.5 (17.6)	22.3 (12.1)	18.3 (14.5)	22.3 (11.1)
% black	1.3 (.5)	2.3 (2.2)	4.3 (3.9)	3.8 (3.1)
Average Income $	47115 (16755)	49493 (15475)	61298 (23090)	56019 (5326)
Pediatric to Family Medicine ratio	.43 (.38)	.10 (.16)	37.8 (18.8)	21.3 (10.9)
# CHCs	2.5 (2.6)	1.8 (1.5)	5.3 (2.9)	8.0 (3.6)

Data and Analytic Challenges

- Establishing a cohort
  - Baseline cohort: data obtained from CIIS database in June 2010
  - Follow-up CIIS database obtained December 2010
  - Final analytic database involved matching baseline and follow-up records: 98.3% match

Data and Analytic Challenges

- Generalized linear mixed effects models
  - Study arm, county baseline up-to-date rates and rural/urban location included as fixed effects
- Clustering
  - Clustering within practice was important so we used site of last service used as random effect (most children assigned to a cluster this way)
  - For children with no practice affiliation or very small clusters we aggregated and created an "unaffiliated" cluster for each county
    - Convergence problems with numerous singletons and very small clusters
- Secondary analysis within PB arm
  - Used R/R vs not

Conclusions and Acknowledgements

- Cluster randomized pragmatic trials present unique challenges but, in most situations, reasonable solutions to study design, data and analytic challenges can be found
- I would like to acknowledge Brenda Beaty for her collaboration on this project

Questions? Thoughts?