# Immunizations

**Second Only to Clean Water!**

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

*CD. 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
Immunizations
Second Only to Clean Water!

Reported Cases of Vaccines Preventable Diseases,
United States, 1950-2010
So How Are We Doing?

Healthy People 2020 Goal 80%

2011 National rates* for 19-35 month olds

68.50%

*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
  - By 18 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
Population-Based Versus Practice-Based Recall for Childhood Immunizations: A Randomized Controlled Comparative Effectiveness Trial

**Objectives:** We compared the effectiveness and cost-effectiveness of population-based versus practice-based recall for childhood immunizations among preschool-aged children. Immunization compliance was measured in a field study among Colorado residents. In a randomized controlled trial, the Colorado Immunization Network (CIN) was responsible for maintaining a database of immunizations, linking these records to electronic health records, and sending immunization notifications. Patients seen in CIN clinics received electronic reminders, while those in practice-based recall received printed reminders. The percentage of immunizations up to date was compared between the groups.

**Methods:** A randomized controlled trial was conducted among preschool-aged children. Immunization rates were assessed over a 6-month period. The study was a cluster-randomized trial with 10 clusters per arm. The primary outcome measure was the percentage of immunizations up to date. Covariates included age, gender, and the number of immunizations received.

**Results:** The population-based recall group had a higher percentage of immunizations up to date compared to the practice-based recall group. The difference was statistically significant (p = 0.03). The cost of the population-based recall was lower than the practice-based recall (p = 0.02).

**Conclusions:** Population-based recall for childhood immunizations is more effective and cost-effective than practice-based recall, as demonstrated in this randomized controlled trial.
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 counties 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

14 Colorado Counties

6 Urban counties with similar income, race-ethnicity, population & CIIS saturation

3 counties practice-based R/R

3 counties population-based R/R

8 Rural counties with similar income, race-ethnicity, population & CIIS saturation

4 counties practice-based R/R

4 counties population-based R/R
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 were used.
  - Two models were conducted to assess the association between the intervention group and whether or not 1) the 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 the site of the 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

- 85% received ≥1 Reminder Notice (assuming 85% received R/R)
- 15% did not receive a R/R notice

- 10,907 eligible children
- n=1,925 eligible children

Practice-based R/R Reach
195 practice sites

- 95% received ≥1 Reminder (assuming 100% received R/R)
- 5% did not receive R/R

- n=17,848 eligible children
- n=887 eligible children
Percent Receiving Any Vaccine within 6 months
(of those needing vaccines at baseline)

32%  
$n=12,832$

23%  
$n=18,735$

Absolute Effect
Difference
9%
$p<.0001$
Percent Brought Up-to-Date within 6 months
(of those needing vaccines at baseline)

19% for Pop-R/R counties
13% for Practice-based R/R

Absolute Effect Difference
6% p<.0001
Subgroup Analysis w/in Practice-based Counties Percent Brought Up-to-Date
R/R vs no R/R

- Practice-based Recall (n=10 practices) - 24%
- No Practice-based R/R (n=185 practices) - 12%
Subgroup Analysis w/in Practice-based Counties

Percent Brought Up-to-Date

R/R vs no R/R

Practice-based Recall (n=10 practices)
- Population Based: 24% (n=887)
- No Practice-based R/R (n=185 practices): 12% (n=17848)

No significant difference between groups (p=.0001)
## Results: Multivariable Models

### Association of Intervention Group with Two Outcomes

<table>
<thead>
<tr>
<th>Outcomes Modeled</th>
<th>Adjusted OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becoming <strong>up-to-date</strong> in population-based versus practice-based county</td>
<td>1.24 (1.11-1.38)</td>
<td>.0002</td>
</tr>
<tr>
<td>Receiving <strong>any vaccine</strong> in population-based versus practice-based county</td>
<td>1.27 (1.15-1.39)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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

- Population-based R/R (n=188 practices $40,367) = $215
- Practice-based R/R (n=10 practices $13,153) = $1,315
Cost of R/R Per Child who Received ≥1 Vaccine

Population-based R/R

- $10
- n = 4,083

Practice-based R/R

- $38
- n = 348
Cost of R/R Per Child Brought Up-to-Date

Population-based R/R
- $17
- n = 2,394

Practice-based R/R
- $62
- n = 212
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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The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Library of Medicine or the National Institutes of Health.
Questions?
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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rural and Urban Counties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>Min, max</td>
</tr>
<tr>
<td>Number of children age 19-35 months</td>
<td>4197 (4432)</td>
</tr>
<tr>
<td>% Up-to-date at baseline</td>
<td>40.8% (8.3)</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>22.3% (12.9)</td>
</tr>
<tr>
<td>% African American</td>
<td>2.9% (2.7)</td>
</tr>
<tr>
<td>Average Income ($)</td>
<td>$53481 (15793)</td>
</tr>
<tr>
<td>Pediatric to Family Medicine ratio</td>
<td>0.28 (0.25)</td>
</tr>
<tr>
<td># CHCs</td>
<td>4.4 (3.5)</td>
</tr>
</tbody>
</table>
Distribution of Balance Criterion

Balance criterion by optimal group

# Magnitude of differences in means on raw variables

## Differences Between Study Groups on Raw Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Optimal Mean (Max)</th>
<th>Remaining Randomizations Mean (Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children age 19-35 months</td>
<td>223 (613)</td>
<td>1264 (6325)</td>
</tr>
<tr>
<td>% Up-to-date at baseline</td>
<td>2.1% (5.0)</td>
<td>4.9% (15.0)</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>5.6% (11.3)</td>
<td>7.9% (23.3)</td>
</tr>
<tr>
<td>% African American</td>
<td>&lt;1% (1.0)</td>
<td>1.4% (4.5)</td>
</tr>
<tr>
<td>Average Income ($)</td>
<td>$3659 (9702)</td>
<td>$9731 (27131)</td>
</tr>
<tr>
<td>Pediatric to Family Medicine ratio</td>
<td>0.20 (0.40)</td>
<td>0.15 (0.40)</td>
</tr>
<tr>
<td># CHCs</td>
<td>1.3 (2.8)</td>
<td>1.6 (4.8)</td>
</tr>
</tbody>
</table>

*absolute value of differences taken for each randomization*
## Worst Randomization from Optimal Set

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rural</th>
<th>Urban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm 1 Mean (SD)</td>
<td>Arm 2 Mean (SD)</td>
</tr>
<tr>
<td>Number of children age 19-35 months</td>
<td>682 (695)</td>
<td>618 (465)</td>
</tr>
<tr>
<td>% Up-to-date at baseline</td>
<td>39.0 (7.5)</td>
<td>36.3 (6.5)</td>
</tr>
<tr>
<td>% Hispanic</td>
<td>26.5 (17.6)</td>
<td>22.3 (12.1)</td>
</tr>
<tr>
<td>% black</td>
<td>1.3 (.5)</td>
<td>2.3 (2.2)</td>
</tr>
<tr>
<td>Average Income $</td>
<td>47115 (16755)</td>
<td>49493 (15475)</td>
</tr>
<tr>
<td>Pediatric to Family Medicine ratio</td>
<td>.43 (.38)</td>
<td>.10 (.16)</td>
</tr>
<tr>
<td># CHCs</td>
<td>2.5 (2.6)</td>
<td>1.8 (1.5)</td>
</tr>
</tbody>
</table>
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?