The Dilution of Efficacy in Microbicide Trials

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Statistical Center for HIV/AIDS Research & Prevention
SCHARP

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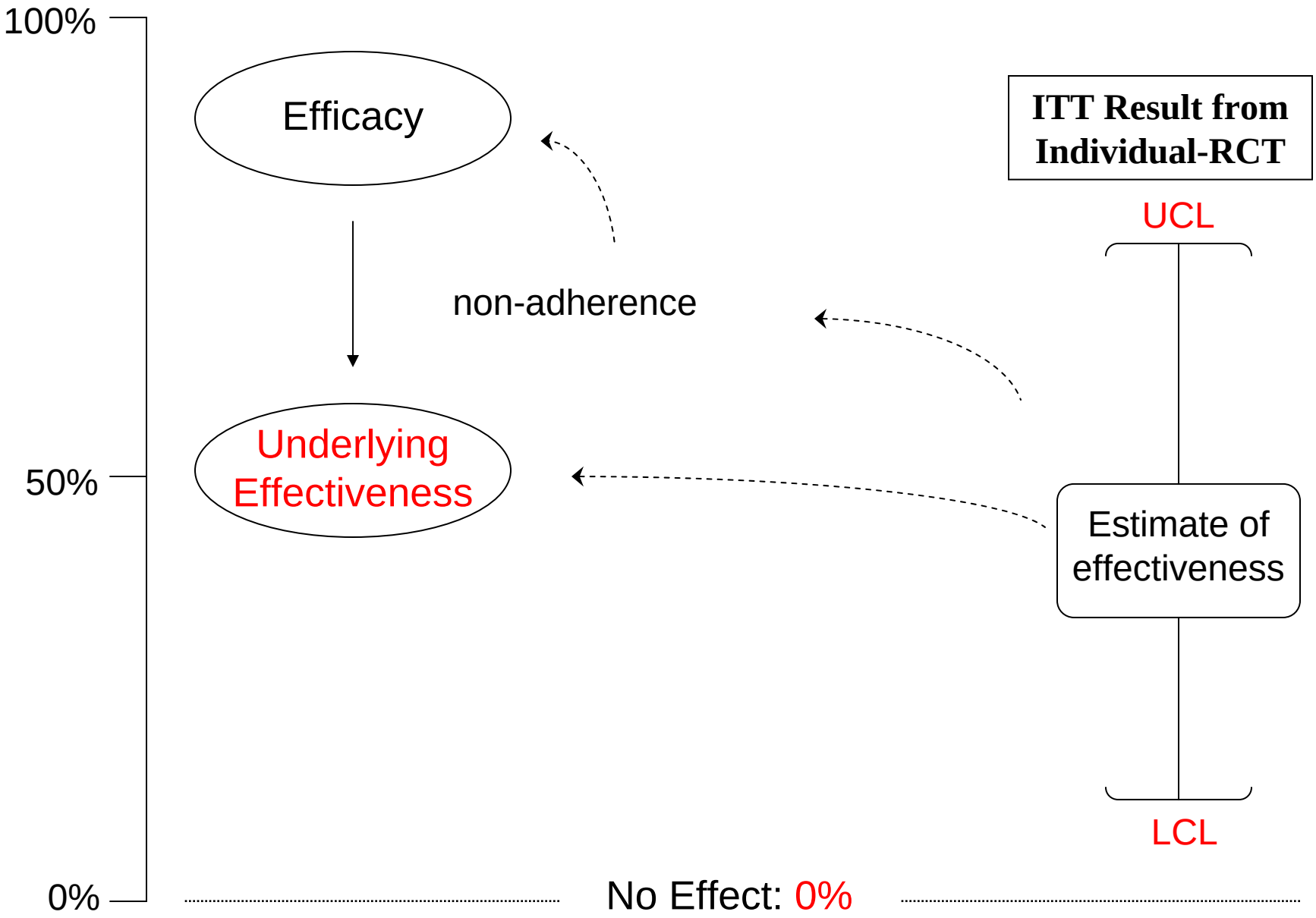
VACCINE AND INFECTIOUS DISEASE INSTITUTE

MTN
microbicide trials network

Overview

- Definition of efficacy dilution
- Sources of dilution in microbicide trials
- Overall impact of dilution
- Case in point: The Carraguard Trial
- Conclusions



Family Health International

Slide courtesy of Dr. Doug Taylor

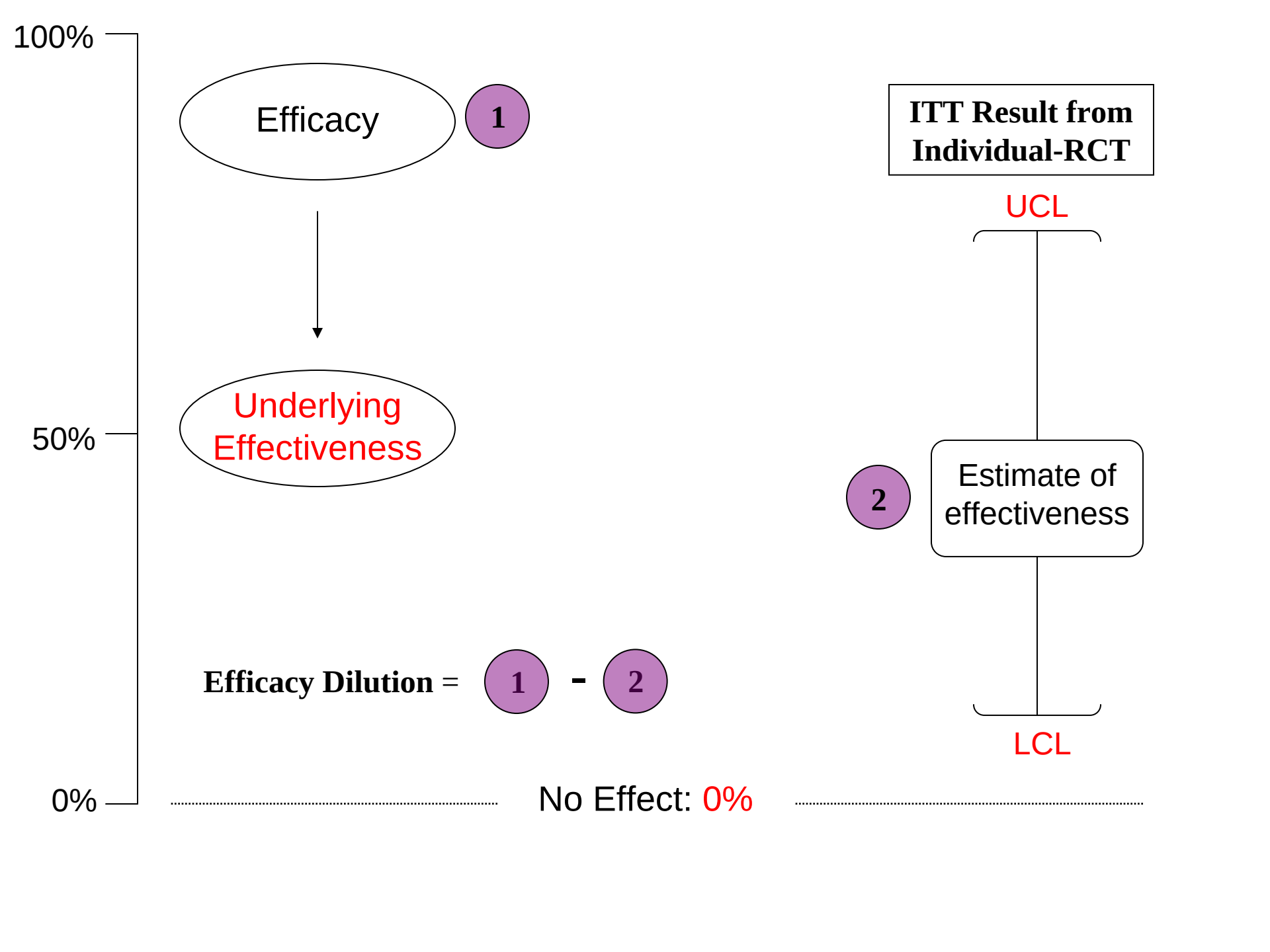
How do we define efficacy dilution?

Difference between:

1. The true efficacy of a candidate microbicide with respect to a "*no gel*" comparator group
   - with no bias associated with the open-label nature of this hypothetical treatment comparison

and

2. Observed effectiveness under an ITT analysis in a well conducted RCT


100%
50%
0%
Efficacy
1
Underlying Effectiveness
ITT Result from Individual-RCT
UCL
2
Estimate of effectiveness
LCL
Efficacy Dilution = 1 - 2
No Effect: 0%

Sources of Efficacy Dilution

- Why (2) lower than (1) ?
  - Many sources of dilution in microbicide RCT
    - Product adherence
    - Time off-product due to
      - pregnancy
      - other emerging condition post-randomization e.g., AEs
    - HIV infections from other sources
      - e.g., from anal intercourse
    - Non-inertness of placebo gel
    - Others

Emerging Themes in Epidemiology

BioMed Central

Analytic perspective

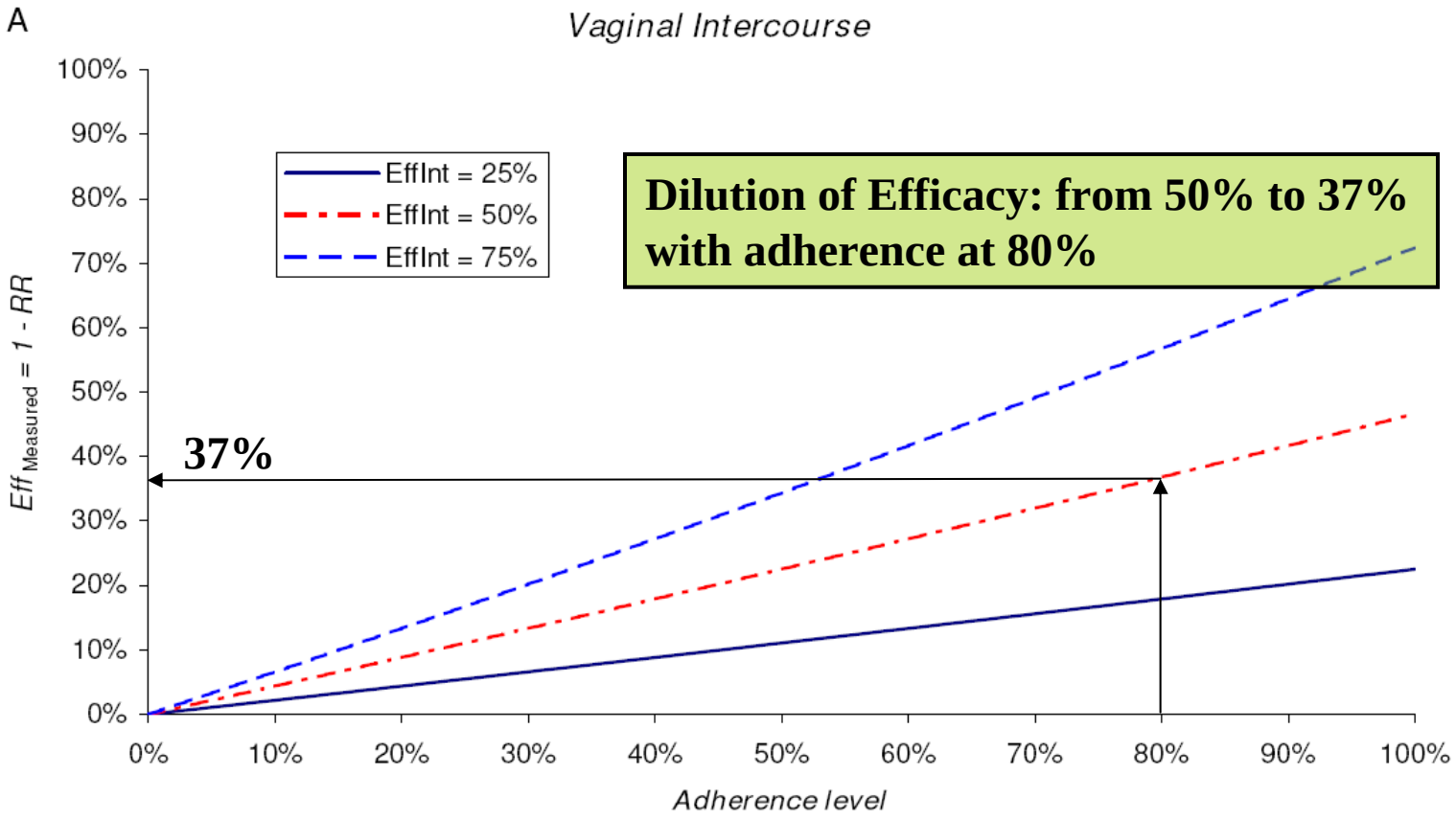
Open Access

Persisting with prevention: The importance of adherence for HIV prevention

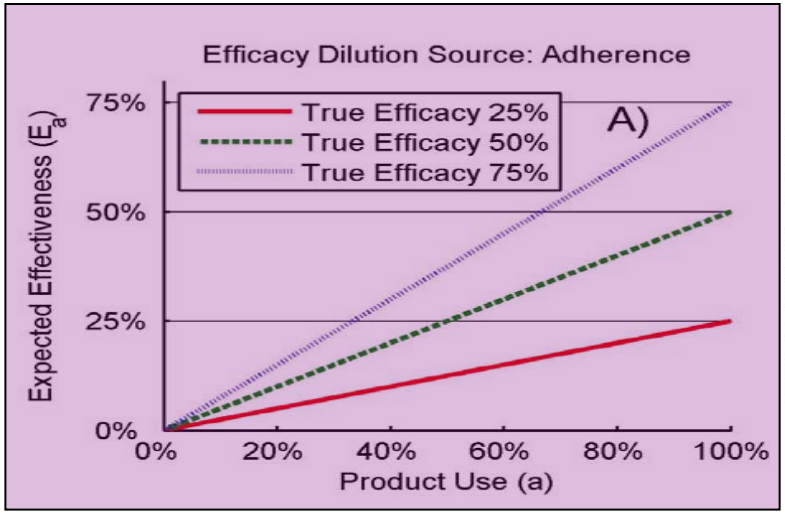
Helen A Weiss*[1], Judith N Wasserheit[2], Ruanne V Barnabas[3], Richard J Hayes[1] and Laith J Abu-Raddad[4]

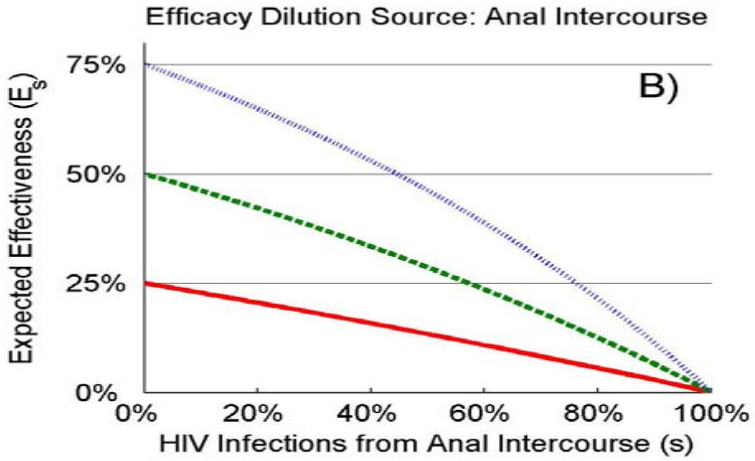
Emerg Themes Epidemiol. 2008 Jul 11;5:8.

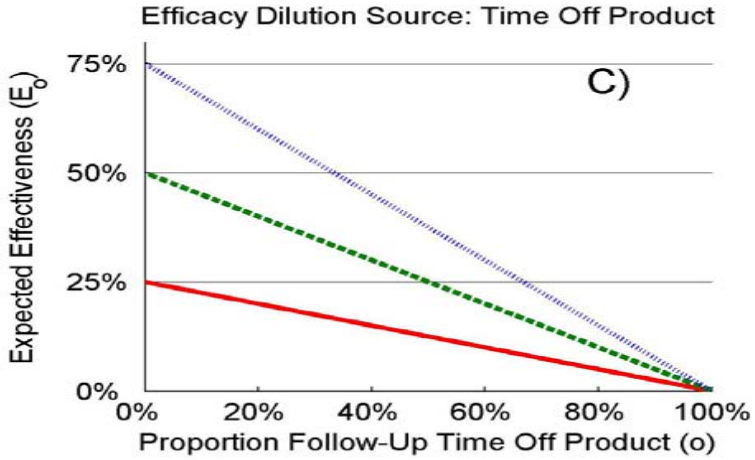
Dilution of Efficacy: Adherence

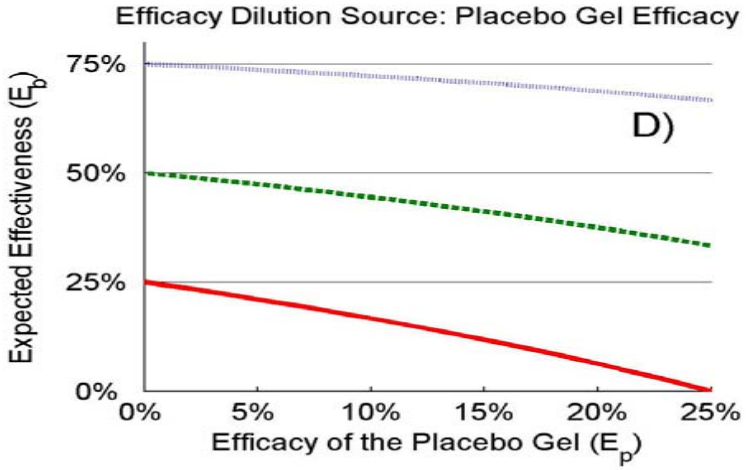


Dilution of Efficacy from Different Sources









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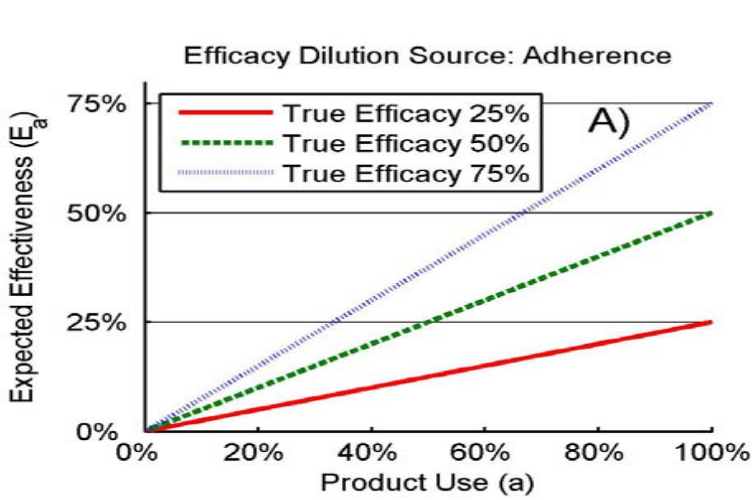

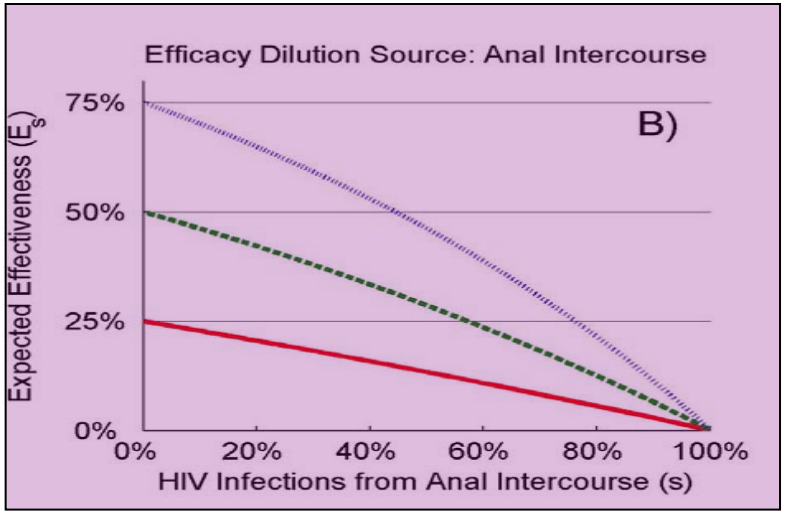

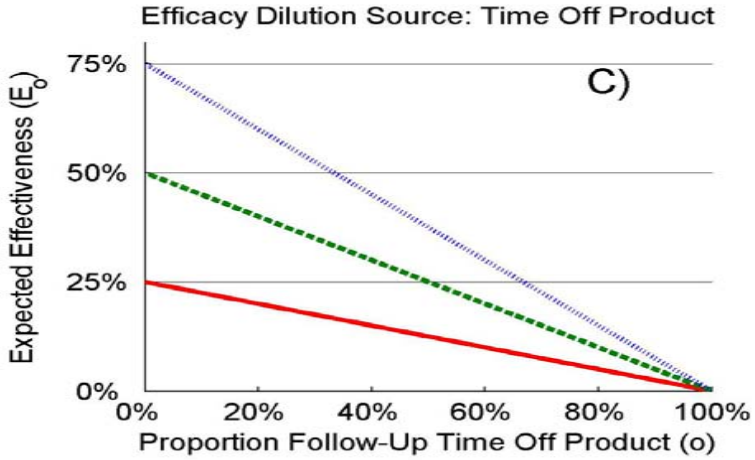

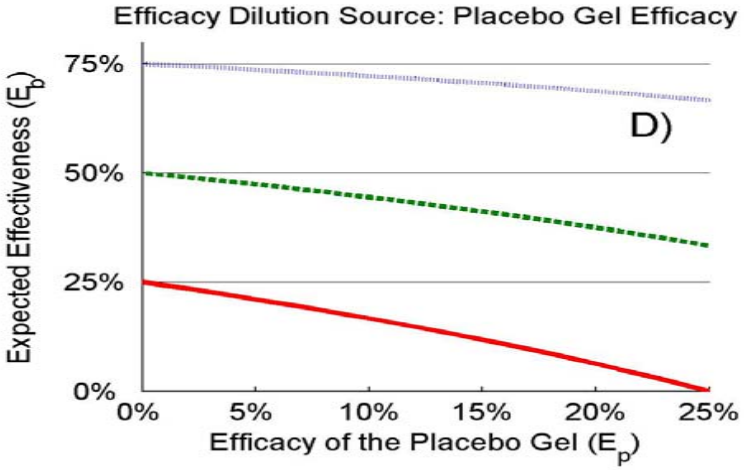

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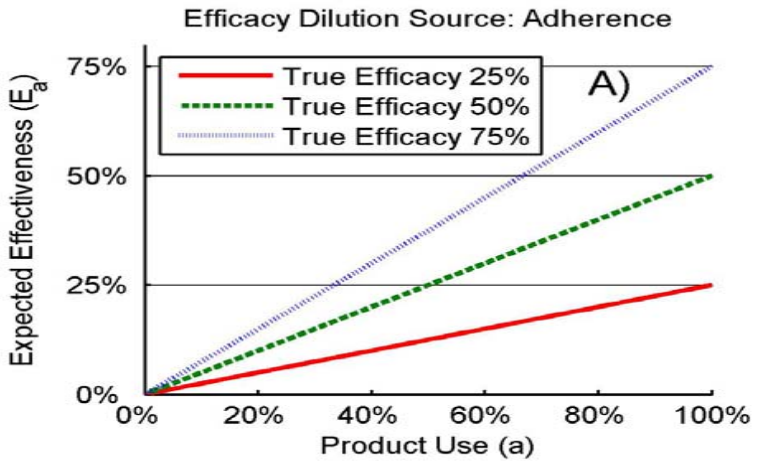

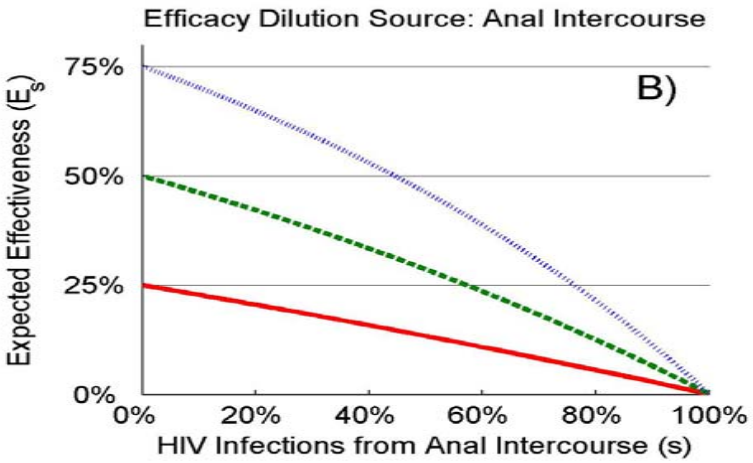

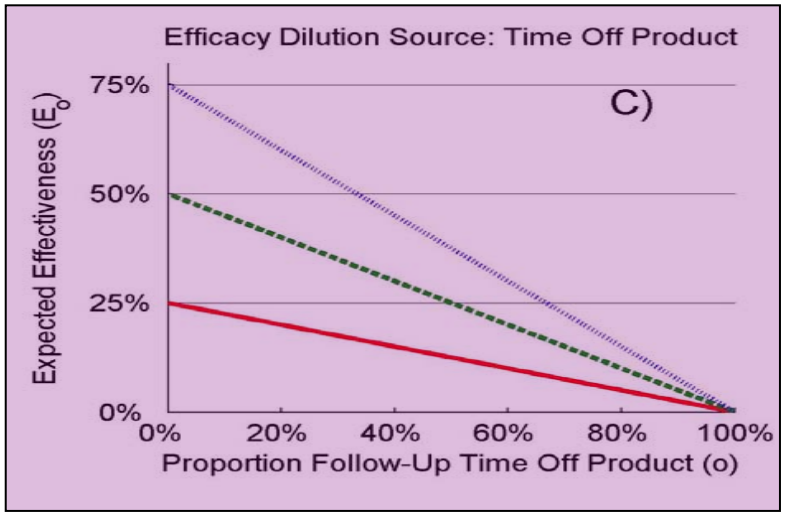

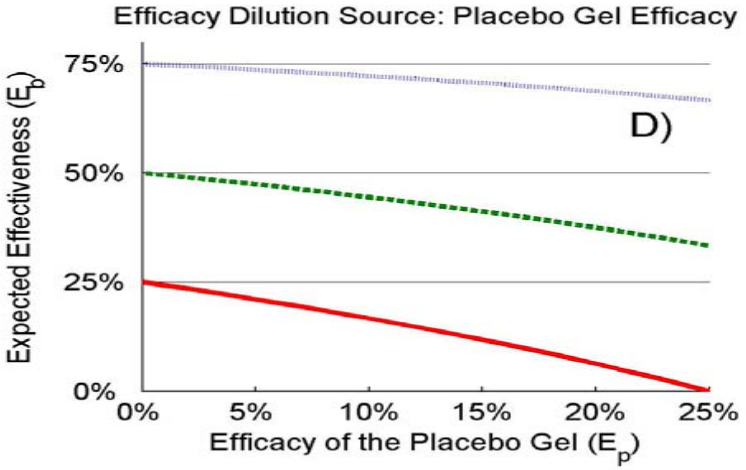

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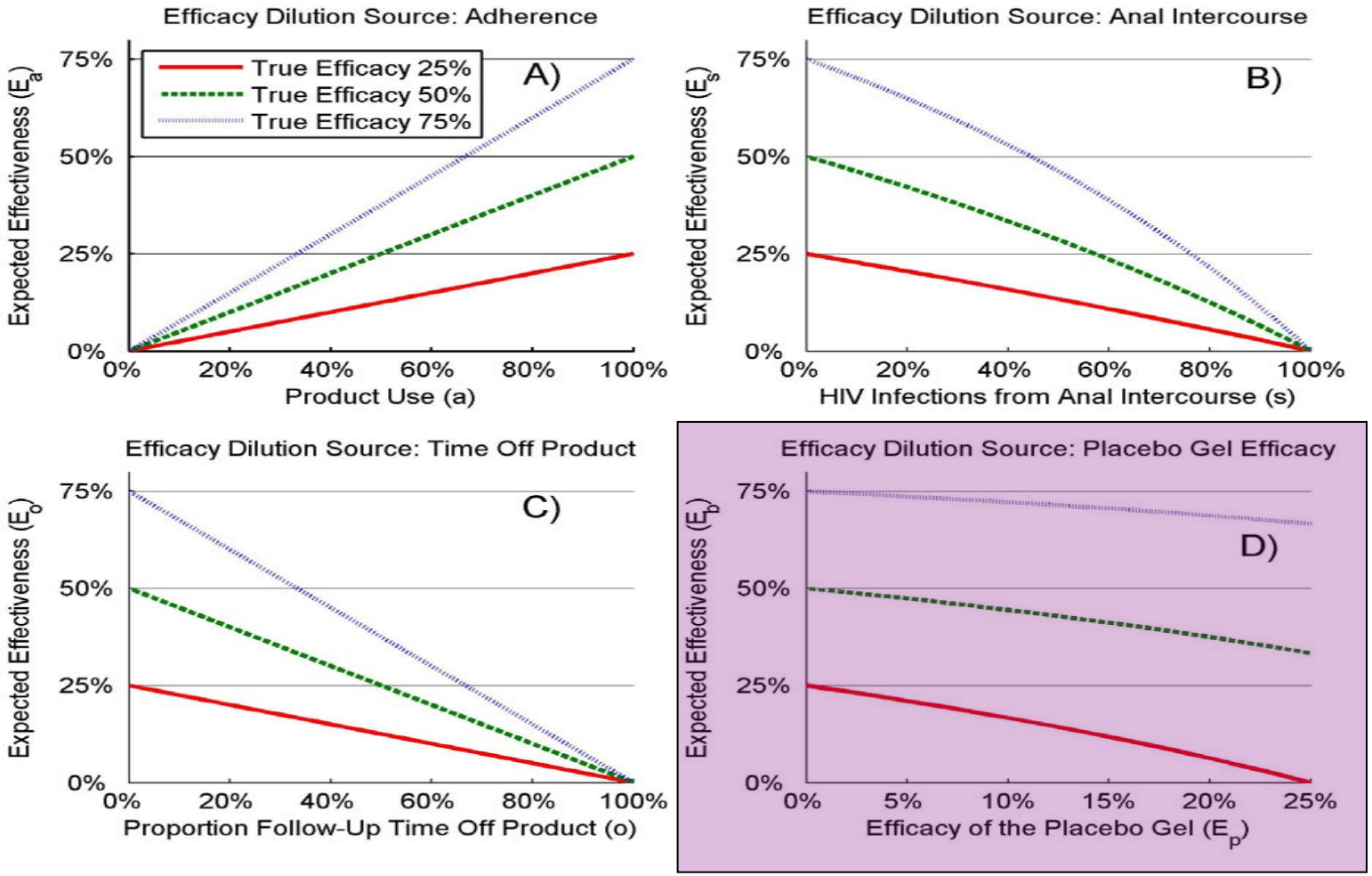


Question:

What is the level of dilution when all sources of potential dilution are present in a RCT?

- Typical microbicide trials have several sources of dilution ... not just one (ie adherence)

Look at Four Scenarios:

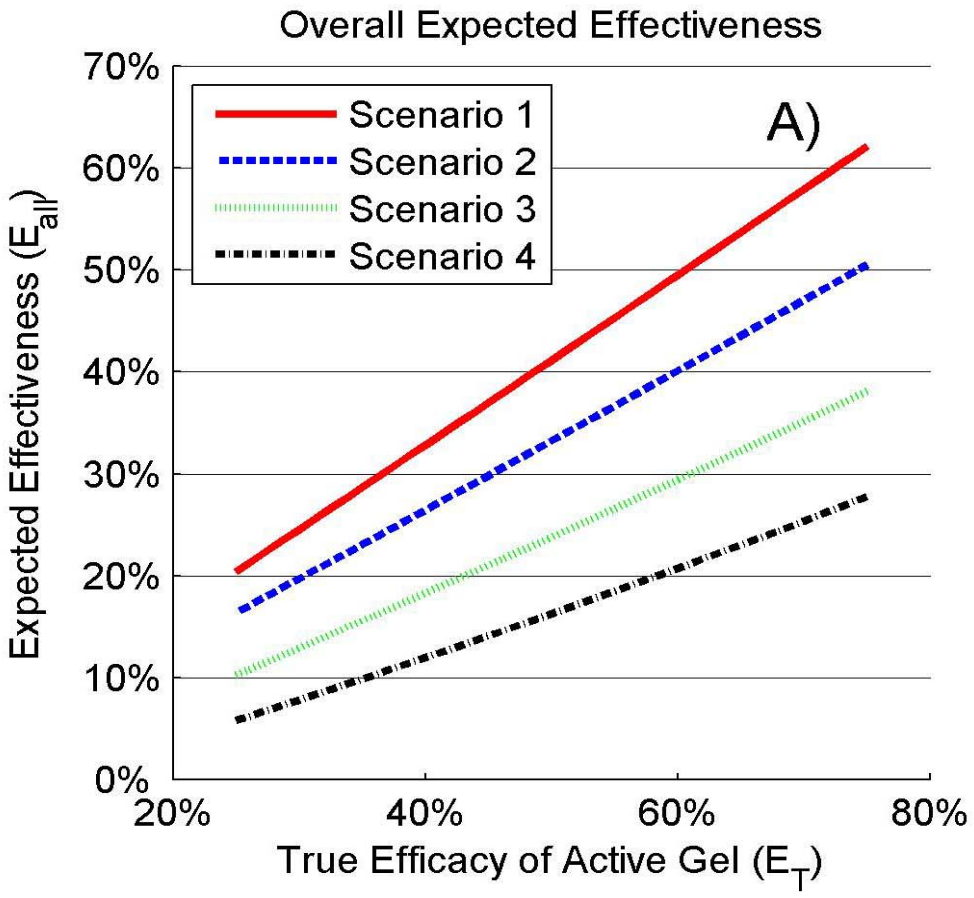
Scenario 1: Ideal RCT (most likely unrealistic)

Scenario 2 & 3: More typical of what we have observed in first wave of microbicide RCT

Scenario 4: Slightly more extreme but not unrealistic

	Scenario			
Source of Dilution	**1**	**2**	**3**	**4**
Adherence/Product Use	90%	80%	70%	60%
Time off product due to: pregnancy and/or AEs	5%	10%	15%	20%
Source of infection: Anal Intercourse	5%	10%	20%	30%
Placebo gel efficacy	0%	0%	5%	10%

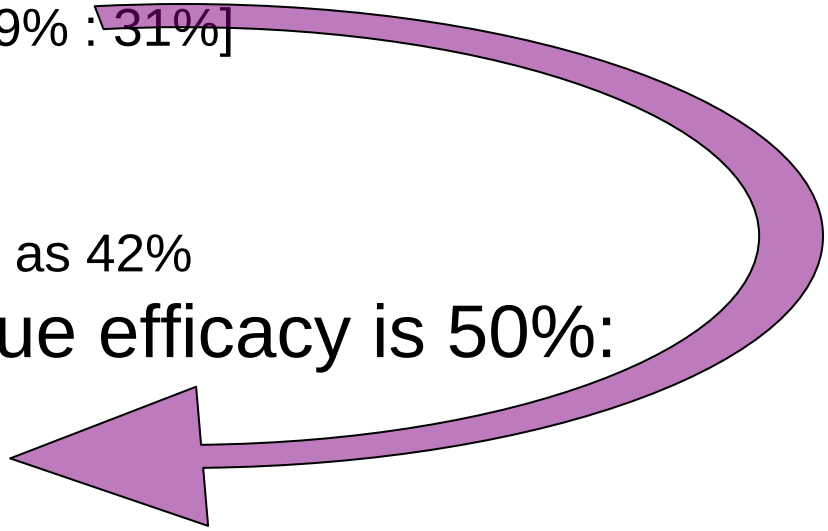
Dilution of Efficacy from All Sources: Overall Impact



	Scenario			
True Efficacy	**1**	**2**	**3**	**4**
25%	20%	16%	10%	6%
50%	41%	33%	24%	16%
75%	62%	50%	38%	28%

Case in Point: The Carraguard Trial

- Observed effectiveness in the trial:
  - 13.0% 95% CI [-9% : 31%]
- Sources of dilution in trial
  - Non inertness of placebo gel
  - Adherence … could be as low as 42%
- Expected effectiveness if true efficacy is 50%:
  - 14.9%



Assumption:

True efficacy 50%, 20% of HIV infection from AI, 40% adherence, 10% efficacy of placebo gel, 0% time off-product due to pregnancy

Is Carraguard effective?

If Carraguard is truly effective:

- In the 40%-60% range
  - The trial had very little chance of detecting it given the potential amount of efficacy dilution in the trial
- In the range of 75%
  - In that case the overall expected effectiveness under our model would be only 25%, which remains much lower than the 33% the trial was powered to detect
    - The trial had only 51% power to detect a 25% effectiveness

Conclusions

- Dilution of efficacy is potentially quite large
  - When all potential sources of dilution are taken into account
  - First generation of microbicide trials had potentially large amount of dilution
- **Important note:**

  The dilution effect will also dilute the effect of a (truly) harmful product which is increasing the risk of HIV infections. Given that a few candidate microbicides have been show to increase the risk of HIV acquisition, our results imply that these products may even be more harmful than what was observed in these trials.

Conclusions

- Use of complex statistical models
  - Need valid data on adherence and sexual behaviors (eg anal intercourse)
  - Difficult to foresee how a candidate microbicide could be marketed solely based on its favorable results on a ‘per-protocol’ analysis with somewhat much weaker ITT results

Conclusions

- Adherence
  - Optimize by counseling, counseling, & counseling
  - Develop '*valid*' measurement tools
- Source of Infections: HIV infection from anal intercourse
  - Prevent by counseling, counseling, & counseling
  - Develop '*valid*' measurement tools
- Time off-product
  - Select women with '*great care*' ie that will not become pregnant during the trial which will reduce the impact of time off-product due to pregnancy
  - Eventually, allow product use for pregnant women
- Placebo
  - Select an inert placebo gel
  - Universal placebo gel -a hydroxyethylcellulose (HEC)