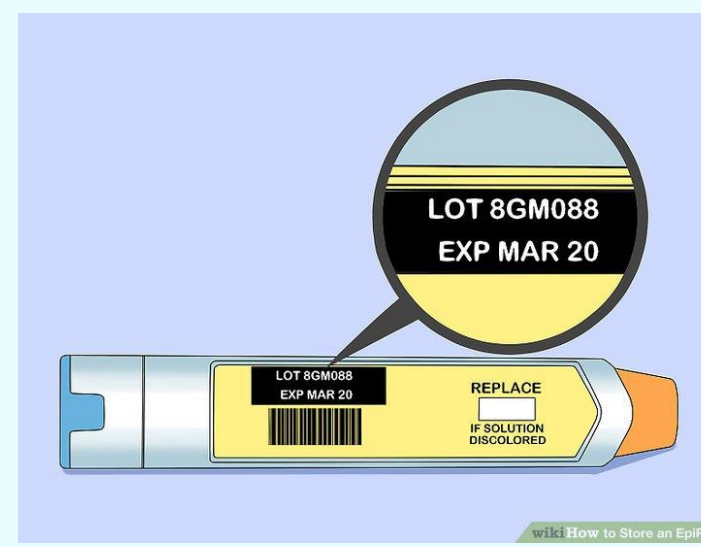


Use It or Lose It? A Systematic Review of Epinephrine Concentration in Auto-Injectors After Device Expiration

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Background

- Due to the risk of anaphylaxis, individuals must have a functional, in date, epinephrine auto-injector (EAI) with them at all times
- Each EAI should have > 12-18 months until expiration
- In 2018, the FDA issued a supply shortage alert for EAIs after which, certain EpiPen lots were extended 4 months past the expiration dates

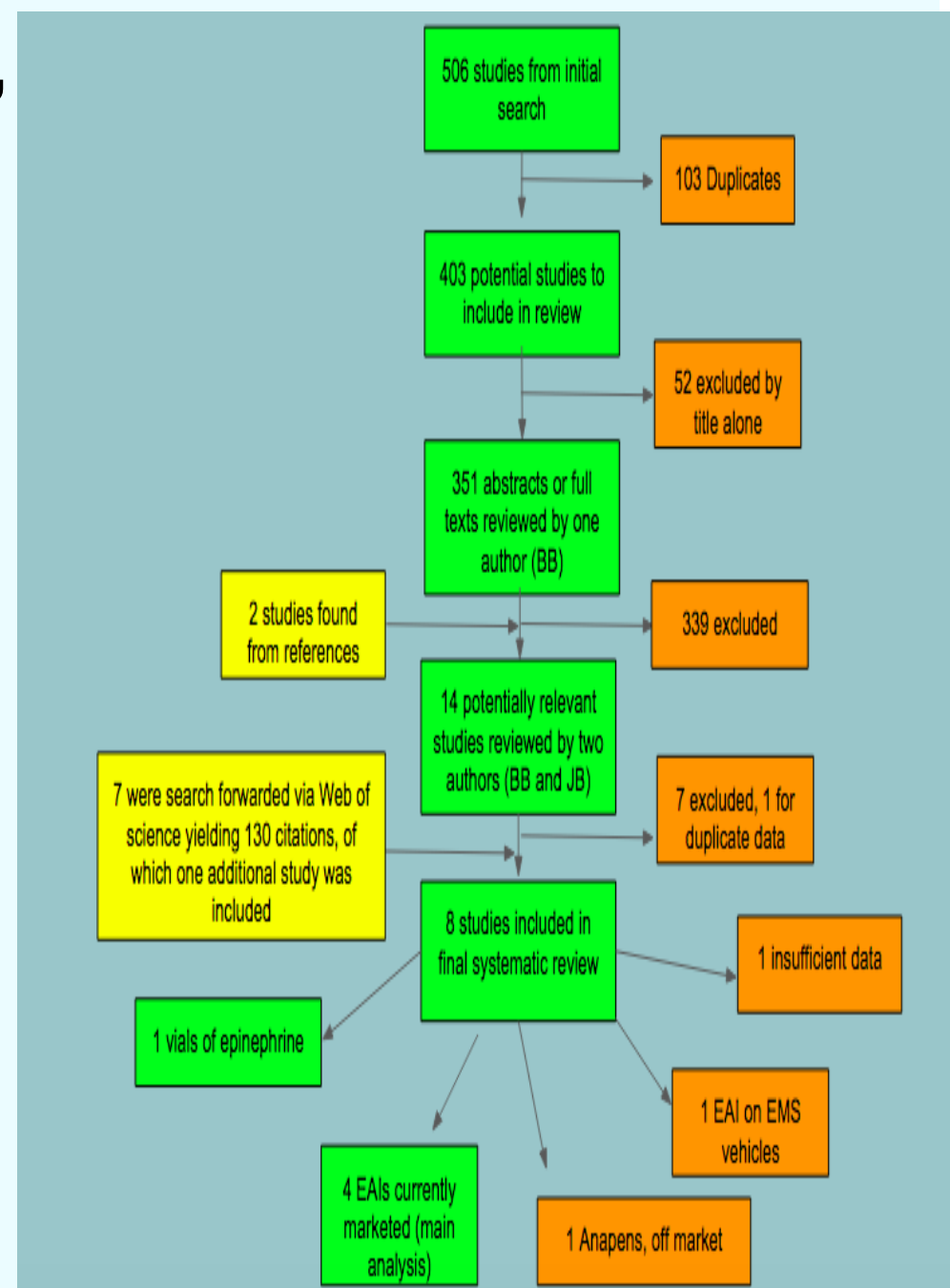


Objectives

- To systematically review all studies evaluating epinephrine content after device expiration
- To determine the proportion of devices that maintained Food and Drug Administration (FDA) standards of >90% labeled dose of epinephrine after device expiration

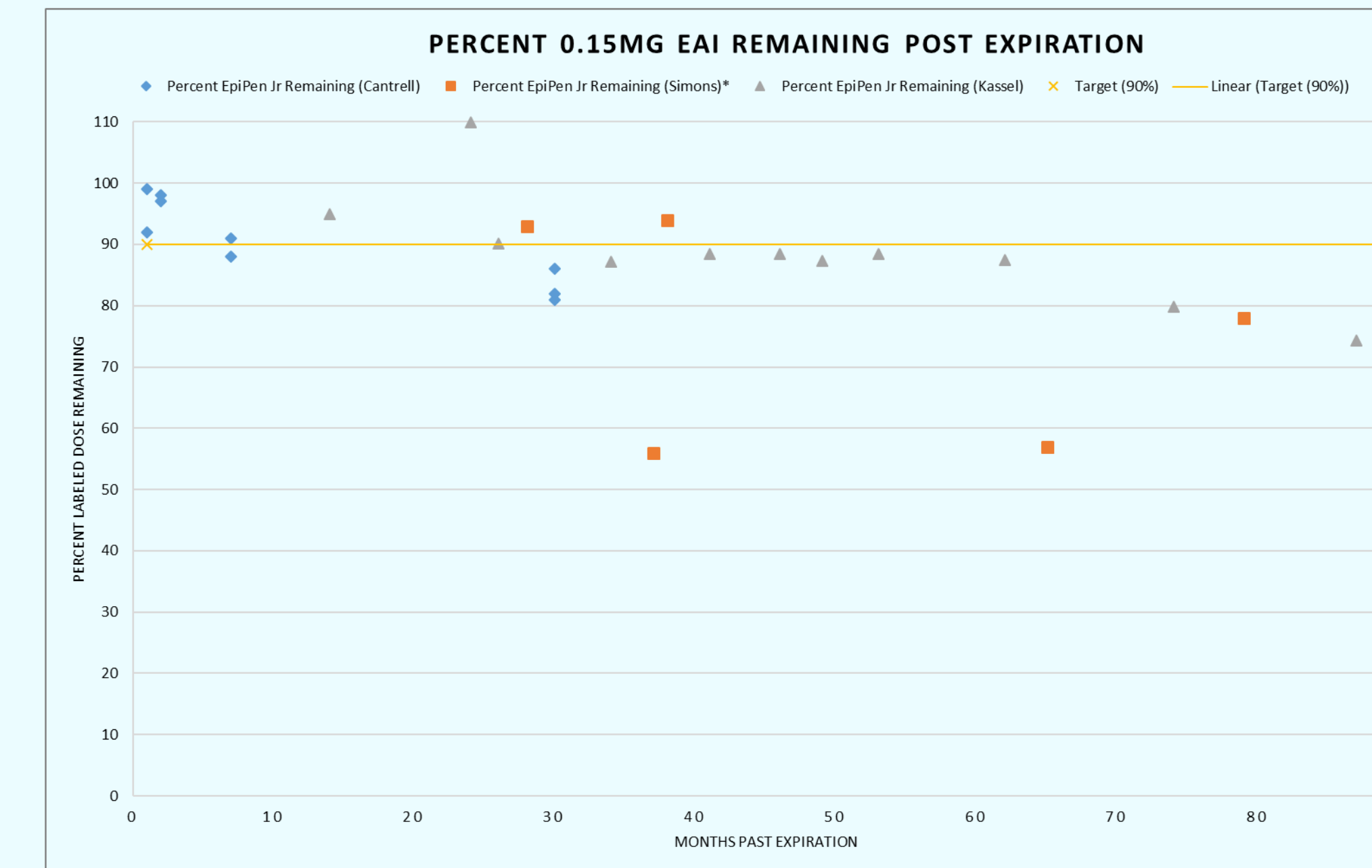
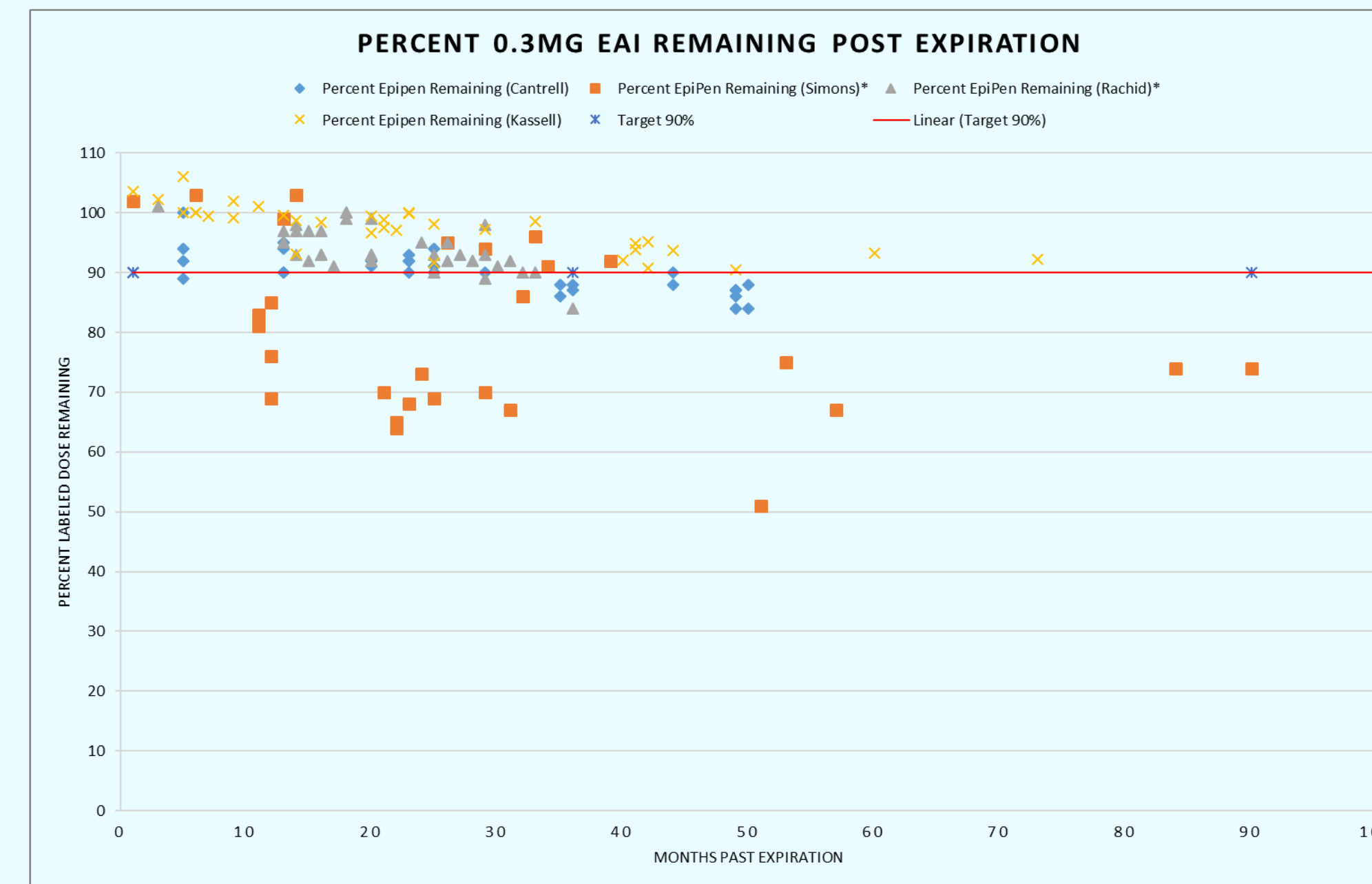
Methods

- We searched Embase, Medline, and Web of Science following PRISMA guidelines
- Included studies
 - measured epinephrine content post expiration
 - 0.1 mg/mL to 1 mg/mL epinephrine in syringes, vials, ampules or EAIs
- Primary outcome: % epinephrine remaining in currently marketed EAIs over time, compared to the FDA standard of >90% labeled dose



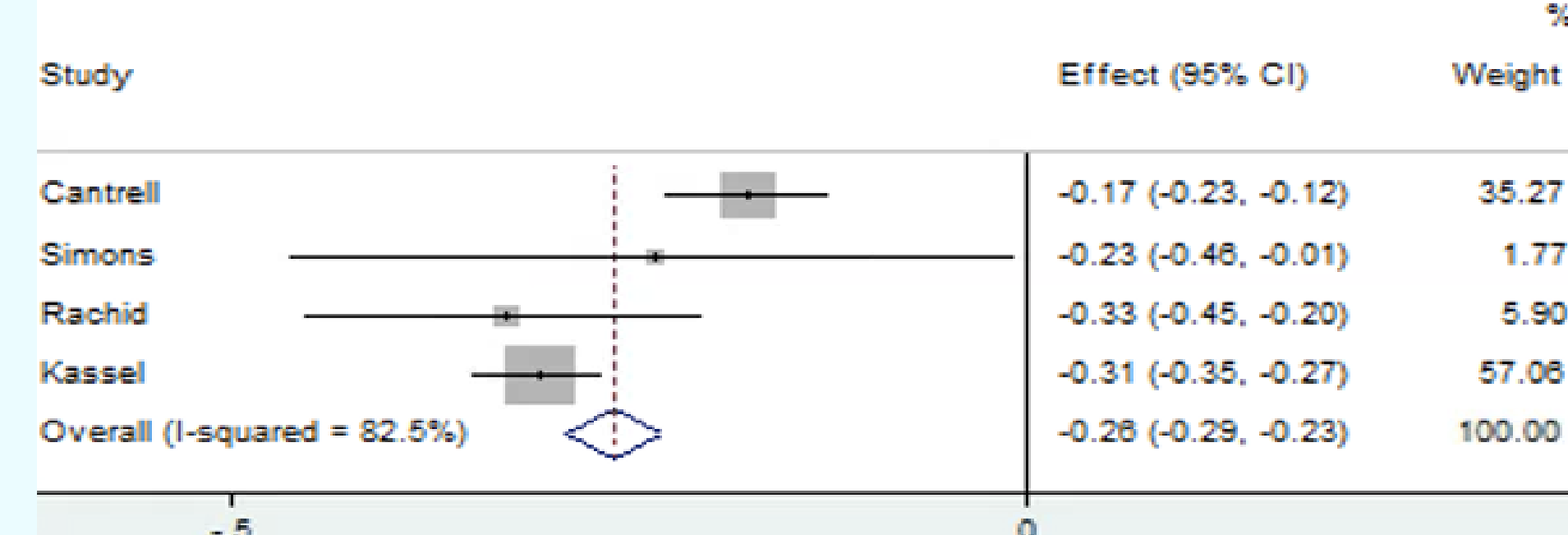
Results

- An individual patient data meta analysis using a linear mixed effects model derived an equation to estimate the rate of change of an EAI: Percent labeled dose of epinephrine remaining= Intercept + (B coefficient) x (months past expiration)

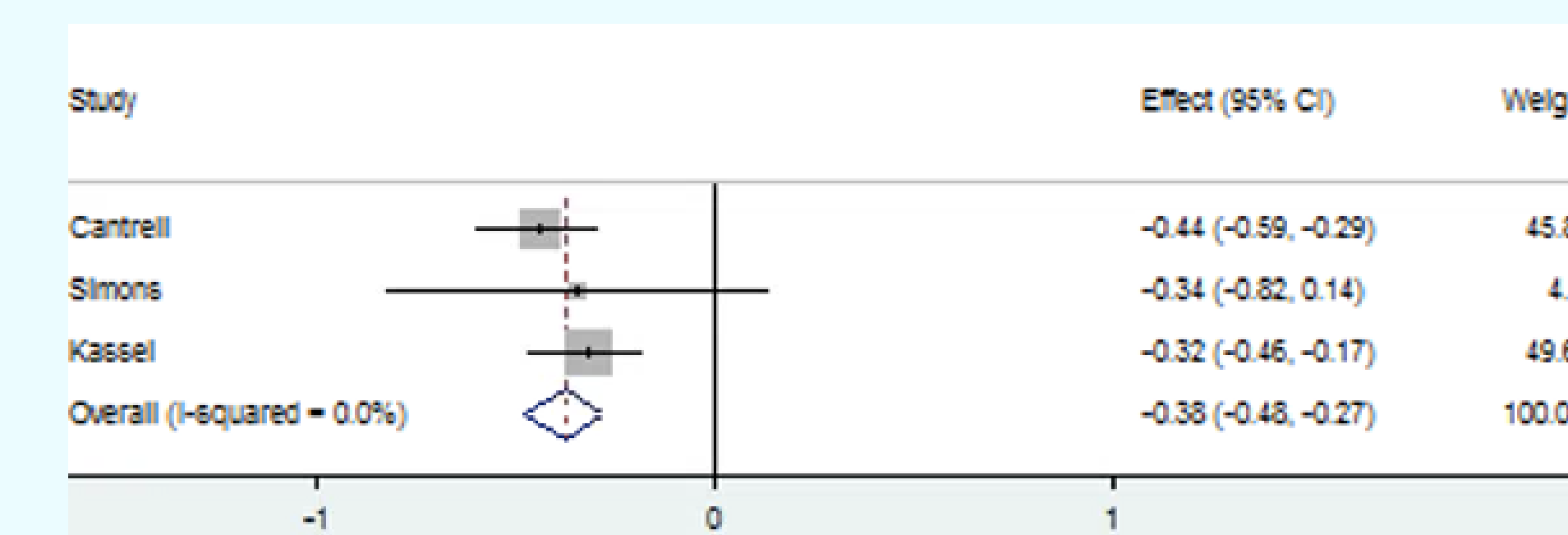


- At 4, 12, and 24 months past expiration, 100% (n=8), 75% (n=28), and 84% (n=77) of EAIs maintained >90% epinephrine
- Model-based average time to 90% epinephrine: 28.15 months (0.3mg, 95% CI=5.14, 57.17) and 18.87 months (0.15mg, 95% CI=0.00, 57.44)
- Average % at 4 months: 96.28% (0.3mg, 95% CI=90.33, 102.23) and 95.65% (0.15mg, 95% CI=86.90, 104.43)

0.3mg EAI	Coefficient (95% CI)	P-Value
Intercept	97.32 (91.49, 103.15)	< 0.001
Month	-0.26 (-0.29, -0.23)	< 0.001



0.15mg EAI	Coefficient (95% CI)	P-Value
Intercept	97.17 (88.82, 105.51)	< 0.001
Month	-0.38 (-0.48, -0.27)	< 0.001



- Meta-analysis of these 4 studies demonstrated a significant association between concentration remaining and months past expiration (Coefficient=- 0.28, 95% CI=-0.31, -0.25 p<0.001)

Discussion

- Short expiration dates and shortages of EAIs creates a burden for patients with allergies
- Given EAI shortages and recent extension of certain lots of EpiPen by 4 months, this information may be useful in extending more expiration dates
- More information is needed on the toxicity of epinephrine degradation products, which was not tested in these studies.
- More studies are needed to determine epinephrine pharmacokinetics and optimal dosing in anaphylaxis

Limitations:

- Small n of studies and devices per study
- Two authors did not respond to questions clarifying methodology and device data*
- Unclear of the conditions of the devices prior to testing (post consumer use)

Conclusions

- Many expired EAIs contain >90% epinephrine labeled dose for years, but devices tested below 90% as early as 5 months post-expiration.
- Based on this model, EAIs may maintain >90% expected epinephrine content 18 (0.15mg) and 28 (0.3mg) months past expiration
- Until further studies examine the possible toxicity of epinephrine degradation products, using in-date EAIs is preferred

