

Assessing the Evidence for Potential Benefits and Risks of Removing the Age Restrictions for Rotavirus Vaccination

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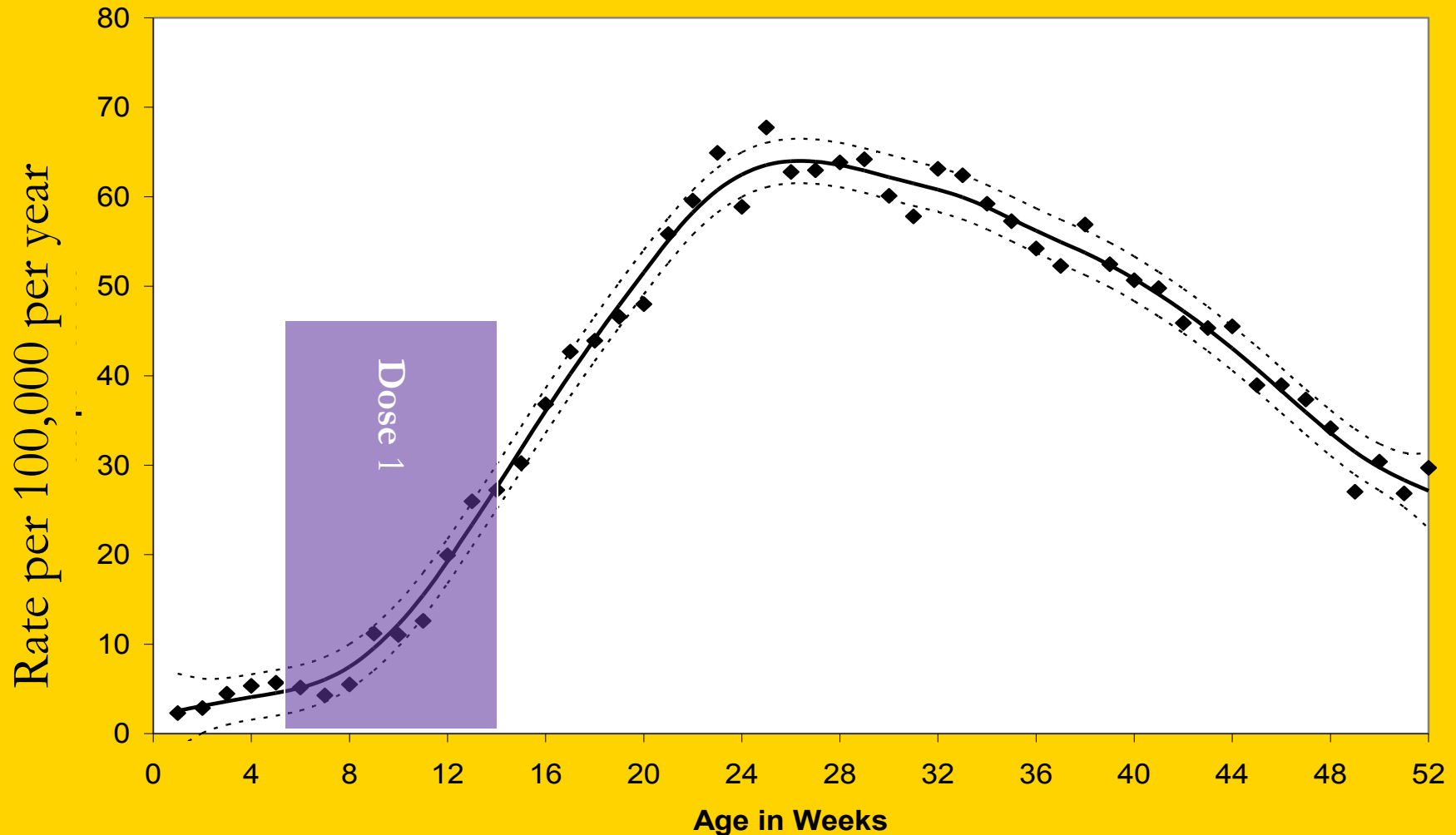
Overview

- Update new inputs for benefit risk analysis of current WHO age recommendations
 - Err on the side of safety
- Results of the analysis
- Discussion

Rotashield Experience

- Rotashield
 - Rhesus-human reassortant rotavirus vaccine
 - Licensed in US in 1998
- Associated with risk of intussusception
 - ~1 intussusception per 10,000 vaccinees
- Withdrawn in 1999

Background Rates of Intussusception by Week of Age during First Year of Life



Benefit-risk Analysis

158 countries in the analysis

- 99.9% of the rotavirus deaths
- WHO child & adult mortality strata
 - B & C (low mortality)
 - D: Americas (high mortality)
 - D: Asia (high mortality)
 - D&E: Africa (high mortality)

Data Inputs

Benefits	Risks
Vaccination coverage & age at immunization	Vaccination coverage & age at immunization
Rotavirus death estimates	Intussusception rates, and case-fatality
Age distribution of deaths	Age distribution of intussusception
Vaccine efficacy	Risk of intussusception associated with vaccination

Assumptions

- **Coverage:** timing to 158 countries extrapolated from 48 countries with DHS and MICS data
- **Age distribution of RV deaths** approximates age distribution of RV hospitalizations
- **Efficacy:** pooled estimates from trials/studies
 - includes waning during second year of life

Assumptions on Risk

- Err on the side of risk
- **Risk estimates pooled from studies with risk**
 - Relative risk of 5.5 (4.1-7.5) in 7 days of dose 1
 - Relative risk of 1.7 (1.2-2.7) in 7 days of dose 2
- **Doubled published case-fatality for IS**
 - 25% in D: Asia & D-E Africa
 - 10% in D: Americas, B&C countries
- **Alternate scenario**
 - Double relative risk when dose 1 after 15 wks of age
 - 20% increase in background rates and fatality of IS

Background Intussusception Rate in the Absence of Vaccination

- 18 population-based studies w/ high quality data

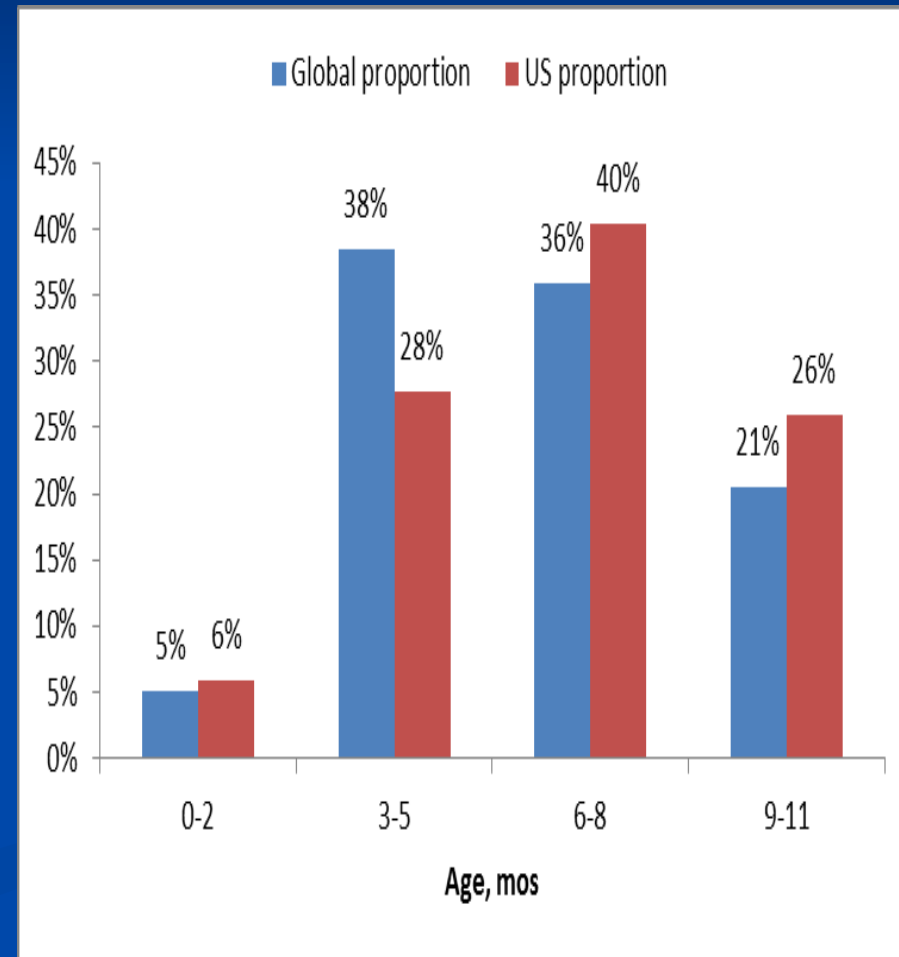
- >5 hospitals with known catchment population or national data

- age-specific rates needed by week of age

- 8 studies by month of age

- 1 US study by week of age

- applied age distribution from US to global rates



No Risk of Intussusception with Either RV5 or RV1 in Large Clinical Trials

Outcome	RV1 N=31,673	Placebo N=31,552	Relative Risk (95% CI)
<31 days any dose	6	7	0.85 (0.30-2.42)

*Ruiz-Palacios et al. NEJM 2006;354(1)

*Vesikari et al. NEJM 2006;354(1)

Post-Licensure Intussusception Data

- Low-level risk of intussusception identified within week 1 after dose 1 and/or dose 2 in some countries (Australia, Mexico, Brazil)
 - ~1-2 cases per 100,000 vaccinated (5-10 times lower than Rotashield risk)
- Risk not documented in US to date
 - Insufficient data to exclude risk seen in other countries
- *Excellent compliance with age restrictions*
 - *Thus, limited ability to generate data on intussusception risk with first dose given after 15 weeks of age*

Documented Benefits vs. Risk of Rotavirus Vaccination Under Routine Use

	RV hospitalizations (deaths) prevented	Intussusceptions (deaths) caused
Mexico ¹	11,600 (663)	41 (2)
Brazil ¹	69,600 (640)	55 (3)
Australia ²	7,000 (0)	6 (0)
US ³	53,000 (16)	48 (0)

1: Patel, NEJM 2011;364(24):2283-2292

2: TGA: <http://www.tga.gov.au/safety/alerts-medicine-rotavirus-110225.htm#results>

3: Cortese, US ACIP, October 2010

Model estimates of benefit vs risk

Restricted schedule

- *Dose 1 by 15 weeks of age*
- *Last dose by 32 weeks*

Unrestricted schedule

- *No age restriction*

- **Benefits:** rotavirus mortality reduction
vs.
- **Risks:** excess fatal intussusception, under current risk estimates
- No catch up

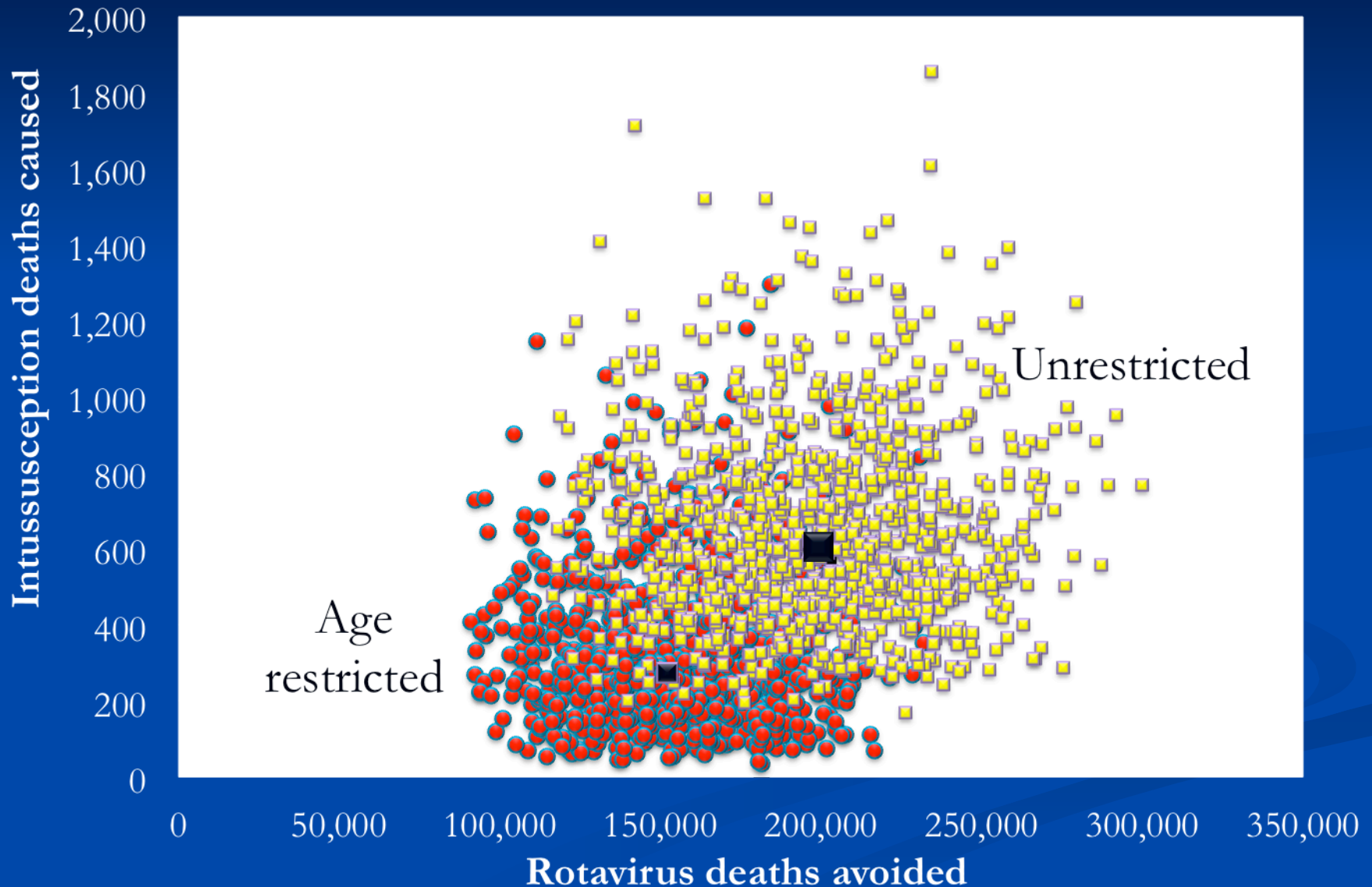
Rotavirus Deaths Averted versus Excess Intussusception Deaths

Rotavirus Vaccine: estimated deaths averted vs. estimated associated IS deaths

Global RV deaths = 453,000

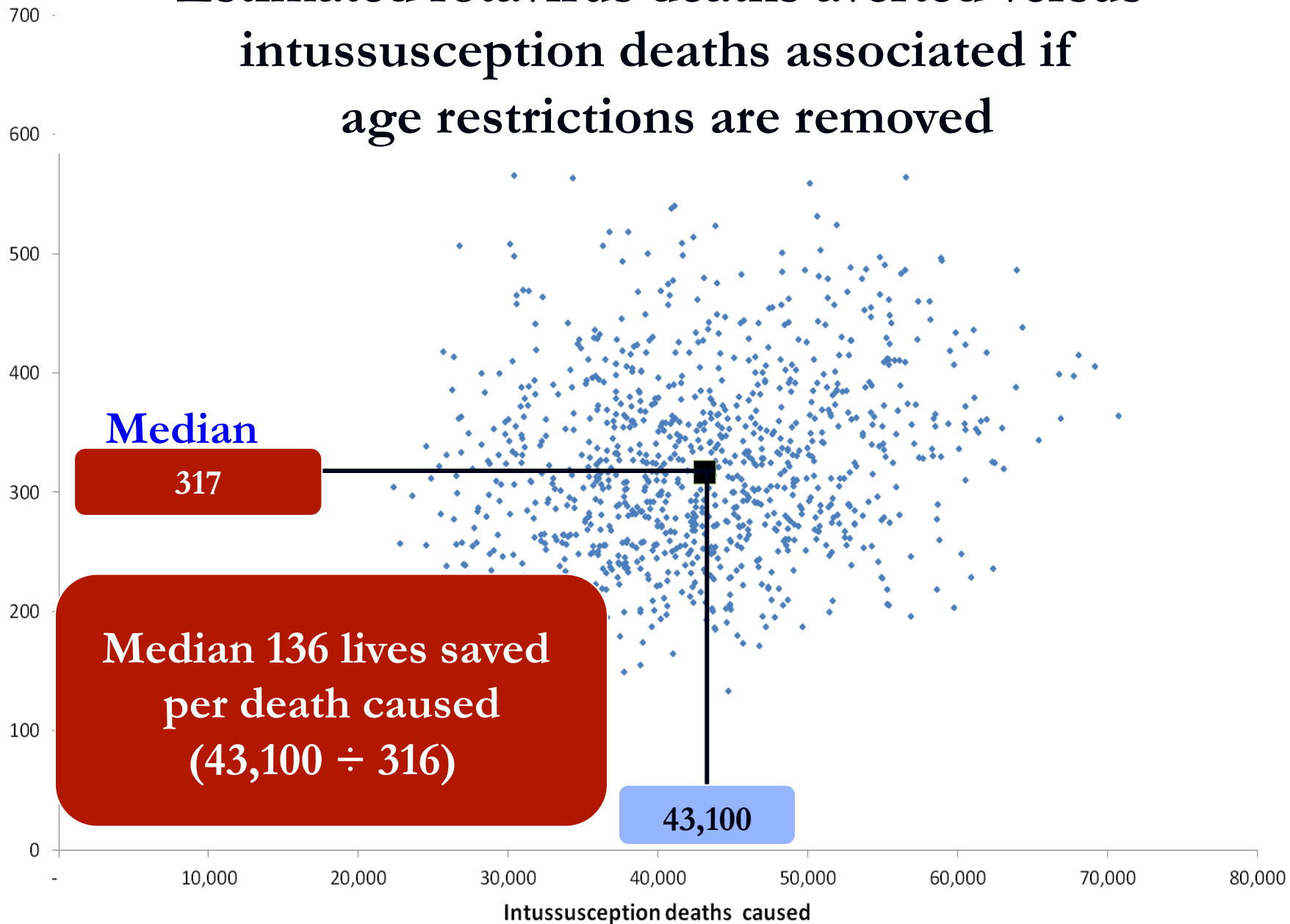
	Median (5 th and 95 th percentiles)	
	Rotavirus Deaths Averted	Associated Intussusception Deaths
Restricted	156,100 (110,100 to 201,800)	288 (99 to 688)*
No age restriction	199,200 (140,700 to 255,400)	605 (310 to 1,133)*
No age restriction (vs. age restriction)	43,100 additional rotavirus deaths averted (30,600 to 53,500)	317 additional IS deaths associated (211 to 445)

Estimated global rotavirus deaths averted and IS deaths associated



Estimated rotavirus deaths averted versus intussusception deaths associated if age restrictions are removed

Rotavirus deaths averted



**What if risk of
intussusception increases
with age at vaccine
administration?**

Estimated increased Relative Risk of IS with Age*

	Median (5 th and 95 th percentiles)	
	Rotavirus Deaths Averted	Associated Intussusception Deaths
Restricted	156,100 (110,100 to 201,800)	288 (99 to 688)*
No age restriction	199,200 (140,700 to 255,400)	929 (513 to 1,579)*
No age restriction vs. age restriction	43,100 additional rotavirus deaths averted (30,600 to 53,500)	641 additional IS events caused (224 to 991)

Comparison of Results by Region

● Rotavirus deaths averted versus intussusception deaths caused by removing age restrictions

Africa

Median

18,405

Median 147 lives saved
per death caused
($18,405 \div 125$)

125

Rotavirus deaths averted

Intussusception deaths caused

30,000
25,000
20,000
15,000
10,000
5,000
-

0 50 100 150 200 250

● Rotavirus deaths averted versus intussusception deaths caused by removing age restrictions

- Median 119 lives saved per death caused

Asia

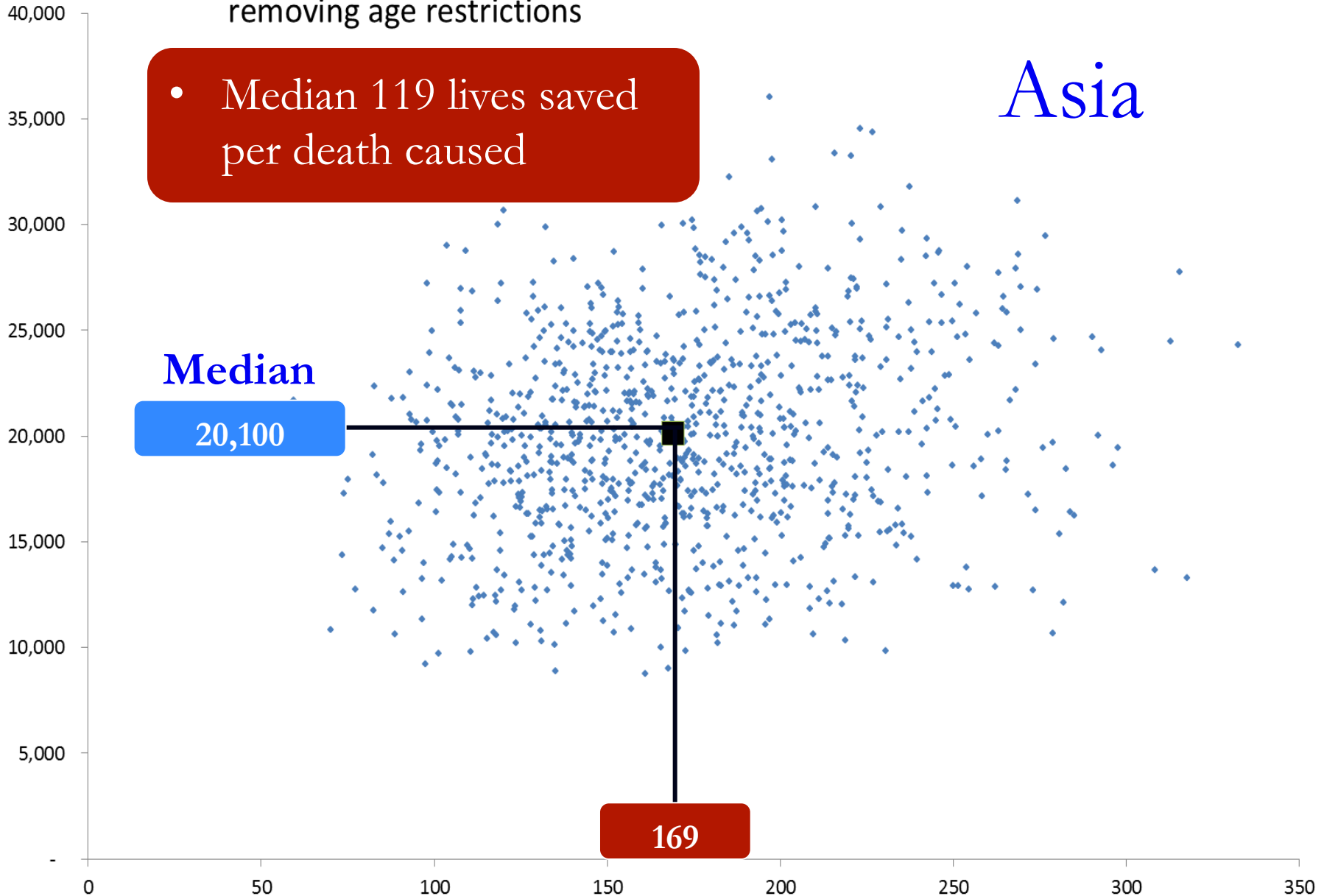
Median

20,100

169

Rotavirus deaths averted

Intussusception deaths caused



● Rotavirus deaths averted versus intussusception deaths caused by removing age restrictions

- Median 195 lives saved per death caused

B&C

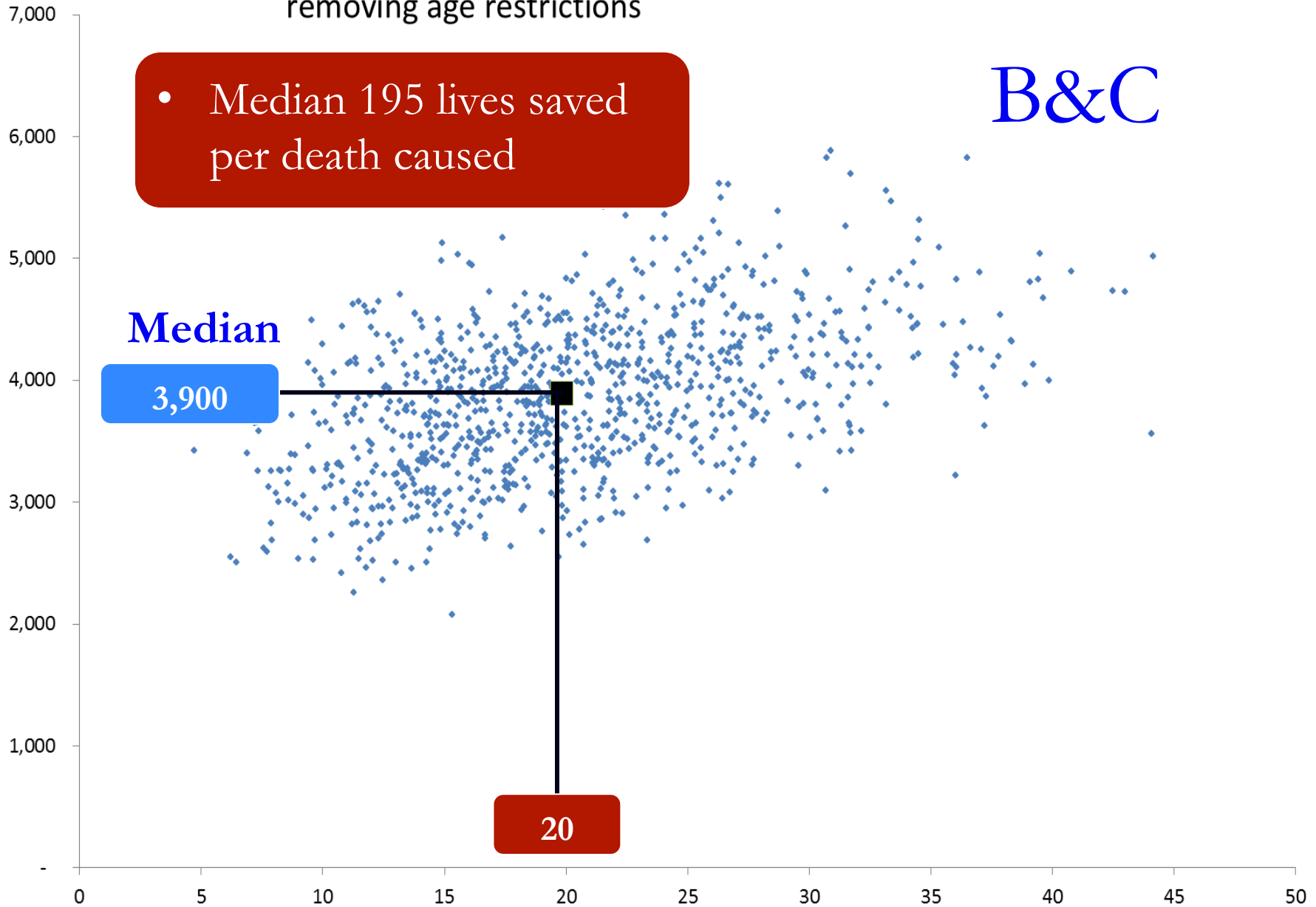
Rotavirus deaths averted

Median

3,900

20

Intussusception deaths caused



● Rotavirus deaths averted versus intussusception deaths caused by removing age restrictions

Americas

- Median 250 lives saved per death caused

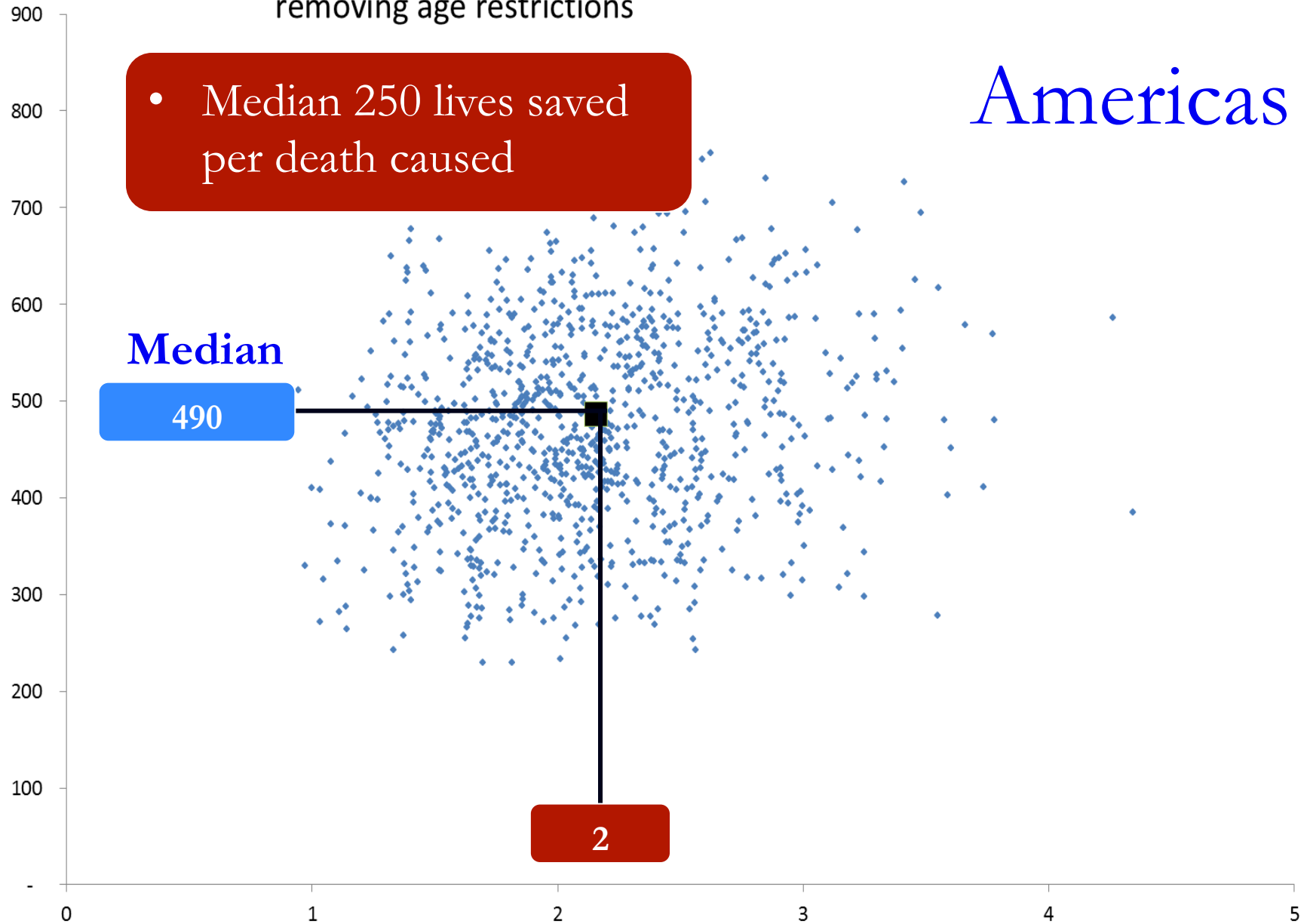
Rotavirus deaths averted

Median

490

2

Intussusception deaths caused



Limitations

- Relative risk of vaccine-related intussusception beyond 15wks speculative
- Limited data on risk of background and vaccine associated intussusception in Africa/Asia
- Extrapolating timing to countries without DHS or MICS surveys
- Herd effects ignored: would favor vaccine
- Relative coverage ignored: would reduce benefits
 - Higher mortality among infants without access to vaccines

Summary

- Trade-offs exist for the age restrictions
- On the benefits side, unrestricted schedule may prevent additional 43,100 (30,600-53,500) rotavirus deaths due to ~23-25% absolute increase in vaccine coverage
- On the risk side, unrestricted schedule may cause ~317 (211-445) excess intussusception deaths compared to current age restricted schedule

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