Assessing and Balancing Risks in the Formulation and Dating Period of Vaccines

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Purpose of this talk

Provide ideas for a **framework** to assess and balance **risks** (and benefits?) in the formulation and dating period of vaccines
What I WON’T discuss

- Prescriptive recommendations
- My opinion on who’s got it right or wrong...
- Or if everyone got it wrong
- That’s because (among other reasons) I am not a vaccine expert
What is risk analysis?

• Risk is usually defined as a triplet:
  1. What can go wrong (event)?
  2. How likely is it (probability)?
  3. How big is the impact?
    o 2 & 3 can be combined into a probability distribution

• Provides an informative assessment of probability, so decision-maker does not have to deal with an event/impact is being simply “possible”

• Opportunities (risks that we would like to happen) or benefits can also be quantified

• Quantitatively balancing risk and benefits requires a common “currency”
Key to consider

- Provides method to make decision under uncertainty - is a decision tool

- Uses what is currently known about the risk issue

- It makes no scientific judgment, i.e. keeps neutral

- It has to respond to decision questions - often has to make approximations and assumptions

- Has to deal with data available
  - Not a wish list
  - So analyses need to be constructed around available data
  - Uncertainty can be considered and its impact on the estimates assessed
Variability and uncertainty

Variability/randomness:
- The effects of chance - a function of the system
- Not reducible through study or further measurement

Uncertainty:
- Lack of knowledge - a function of the observer
- Reducible through further measurement or study

Variability only:  
\[ N(\mu, \sigma) \]

Variability and parameter uncertainty:  
\[ N(\mu, \sigma) \]
Unbiased estimate when no systematic error
Value of parameter

Biased estimate (systematic error)

Bias?
Bias in efficacy estimates from current challenge trials. Where are we?
Why do we need to balance risks and benefits?

Because they said so....
Relevant executive orders (EOs)

Executive order 12866 – 1993 (Clinton)

- “Significant regulatory actions” be submitted for review to the Office of Information and Regulatory Affairs (OIRA).
- What is “significant’’?
  - Annual effect on Economy of >$100M (in 93’ dollars), or
  - Adversely affect economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities
- Thus, net cost/benefit analysis needed

Executive Order 13563 – 2011 (Obama)

- Encourages agencies to consider regulatory approaches that reduce the burden of regulation while maintaining flexibility and freedom of choice for the public
- Requires agencies to quantify anticipated benefits and costs of proposed rulemakings as accurately as possible using the best available techniques

Non-lawyer-readable summary of relevant EOs here http://www2.epa.gov/laws-regulations/summary-executive-order-12866-regulatory-planning-and-review
Risk-benefit analysis – many methods

- i.e. **Net clinical benefits analysis**: quantitative framework to evaluate tradeoffs between **benefits and harms** of therapy

**Conceptually:**

\[
Net \text{ benefit} = \sum \text{Treatment benefit} - \sum \text{Treatment harms}
\]

- Benefit – Efficacy
- Harms – usually Adverse Events (AEs)

Often expressed using **disease burden metrics** (e.g. QUALYs), but can also be $ or even **clinical** outcomes

**Typically** used to evaluate **single therapy**, but framework could be modified to evaluate **policy changes**
Assessing risk-benefit of policy changes

Net benefit = (Individual risk * reduction relative risk) – harms

Benefits - absolute risk reduction (ARR)

- Risks differences: often expressed as relative risk (RR): risk treatment/risk baseline
  
  In our case
  
  Baseline: present policy,
  “Treatment”: proposed policy

  e.g. if RR = .5, disease risk in treated is half from baseline

  Thus, reduction in RR (RRR) = 1-RR
  
  - Also called vaccine efficacy in RCTs

...but initial efficacy should be similar at production (i.e. RR=1)

  Thus, interest might be RR of efficacy at end of dating

Interference with other vaccines? Increase in RR (i.e. < efficacy)

Individual risks

\[ \text{Net benefit} = \text{(Individual risk} \times \text{reduction relative risk)} - \text{harms} \]

- **Individual risk (IR)** - Normally risk of contracting condition treated (without treatment)
- **Vaccines**: often infectious disease prevalence \((p)\) (or incidence) in target population

\(p\) is same for present and proposed policy, so theoretically **could** also consider probability of individuals being exposed to vaccines at end of dating \((P_{\text{expEnd}})\) e.g. proportion of doses administered/left at end of dating

\[ \text{IR} = \text{disease prevalence} \times \text{Prob. exposure end of dating} \]

Example: \(RR=.5\), prevalence=.2, \(P_{\text{expEnd}}=.1\)
\(RRR=.5 \times (1-RR)\), then absolute risk reduction (Benefit) = 1\% \((.5 \times .1 \times .1)\)

If IR is higher (say prevalence is .4 and \(P_{\text{expEnd}}=.3\)), then ARR = 7.5\%
Harms

Typically Adverse events
- Due to increased potency
- Due to synergism with concurrent vaccines

Metrics same as to benefits (RR, IR, etc)

...but unlike for efficacy, AEs might be different at start (higher potency), not just at end of dating, so harms not constant (but possible to incorporate too)
Balancing benefits and harms (Assuming constant harms)

Net harm < Average > Net benefit
Balancing benefits and harms (harms increase)

Net harm <  > Net benefit
How to weigh R/B?

- We need a **common “currency”** to compare costs and benefits ("utilities")
  - E.g. what %increase in harm is equivalent to 1% increase in benefits. Or: How many additional AEs are equivalent to 1 extra infection due to vaccine failure?

- Production animals: $ (easier than for humans!)
- Companion animals: ??
  - In humans, unified utility “currency” exist e.g. Quality Adjusted Life Years (QUALYs) and Disability-adjusted life years (DALYs)
  - Alternative: clinically relevant statistics e.g. NNT, NNH, no utilities
Limitations of traditional risk-benefit

- **Primary stakeholder**: consumer (efficacy/safety main consideration), no indirect costs, no externalities

- Doesn’t measure overall cost to society

- Utility metrics – QoL metrics in vet world?

- RR constant (but can be relaxed)
How about a societal cost-benefit analysis?

- Not only direct cost/benefit health outcomes, but can potentially consider all stakeholders

- However, we need to know:
  - Who are we giving standing
  - Who bears the direct costs (e.g. increase cost of production)
  - Who bears the indirect costs – potential decreases in new vaccine development? Effect in society.
  - Price elasticities
  - Changes in consumer behavior (beyond price)
  - Externalities,
  - etc
  - In summary, **lots of information (thus assumptions required)**

However, it can be (and is done) when impact is high (as per EO 13563)
Example direct and indirect risks/benefits potency

**Lower potency**

**Benefits**
- Less admin burden
- Less AEs?

**Risks**
- Less batches with target potency/efficacy

**Higher potency**

**Benefits**
- More batches with target potency/efficacy

**Risks**
- Safety: increased AEs?
- Synergism AEs concurrent vaccines?
- Interference in efficacy?
- Upper bound limitations for new products?
- Manufacturing cost?
- Off label dilution?
- Costs
- Administrative burden
Conclusions

- Benefits and risks can be quantitatively assessed using a common framework

- **But, estimates** of direct benefits (efficacy) and risks (AEs) for present and proposed policy **required**

- No common “currency” (e.g. QUALYs) likely available for companion species, so alternative interpretation of net-benefits/harms might be needed. $ easier to quantify in production animals

- Much more information is needed if societal cost-benefit analysis required (e.g. )
Thanks for your time!

Please feel free to contact me if you have any questions

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