Risks and Alternatives to Gain-of-Function Studies

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MIDAS Models of Infectious Disease Agent Study

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Views are my own

Not necessarily the views of NIH or NIGMS, my funders

Key points

- Estimating risk: probability x consequence
  - *Example calculation*
- Alternative approaches to achieve science and public health goals
- Role of alternatives:
  - opportunity cost
  - MARGINAL benefit, not total benefit

Risk: Probability x consequence

Probability of pandemic from one “unit” of GOF research

x

Consequence of pandemic of GOF strain

Risk: Probability x consequence

Probability of pandemic from one “unit” of GOF research

= Pr (LAI | 1 unit of research)

x

Pr (Pandemic | 1 LAI)

Risk: Probability x consequence

Probability of pandemic from one “unit” of GOF research

>= 0.2% / BSL-3 year

x

Pr (Pandemic | 1 LAI)

2004-10 Henkel et al.
Applied Biosafety 2012

Risk: Probability x consequence

Probability of pandemic from one “unit” of GOF research

>= 0.2% / BSL-3 year

x

5%-60% for flu-like R_0

2004-10 Henkel et al. *Applied Biosafety* 2012

Merler, Ajelli et al. *BMC Med* 2014

J Lloyd-Smith et al. *Nature* 2005

M Lipsitch et al. *Science* 2003

Risk: Probability x consequence

Probability of pandemic from one "unit" of GOF research

>= 0.2% / BSL-3 year

x

5%-60% for flu-like R_0

~1 in 10,000 – 1 in 1000
per BSL3 lab-yr of GOF on flu

Adjustments to Probability Estimates

– Control measures (already factored into Merler study)

– Vaccination, prophylaxis of lab workers (imperfect)

– BSL3+ vs BSL3

– Molecular biocontainment

+ Undercounting of infections, overcounting lab-years in U.S. Select Agent program – limitations of Henkel et al.

+ Non-US standards in other countries

Risk: Probability x consequence

Mortality consequence of a pandemic =

Expected pandemic attack rate

x

Case-fatality risk

x

Global population

Risk: Probability x consequence

Mortality consequence of a pandemic =

24-38%

x

Case-fatality risk

x

Global population

Van Kerkhove et al. *IORV* 2013; USG Community Mitigation Guidance 2007

Risk: Probability x consequence

Mortality consequence of a pandemic =

24-38%

x

up to 60% (consider 1% if highly attenuated from H5N1)

x

Global population

Van Kerkhove et al. *IORV* 2013; USG Community Mitigation Guidance 2007
Van Kerkhove et al *Science* 2012; Toner et al. *CID* 2013

Risk: Probability x consequence

Consequence of an H5N1 pandemic (mortality) =

24-38%

x

1%-60%

x

7,000,000,000

= 2 million – 1.4 billion fatalities

Adjustments to Consequence Estimates

- Virulence reduced even below 1% (can't assume *a priori*)

+ Non-mortality costs: nonfatal health loss, $, loss of scientific credibility, school closures etc.

Risk: Probability x consequence

Probability of pandemic from one “unit” of GOF research

x

Consequence of pandemic of GOF strain

Risk: Probability x consequence

>= 10^{-4} to 10^{-3} / BSL-3 lab-year

x

$2x10^{6}$ to 1.4×10^{9} fatalities | GOF pandemic =

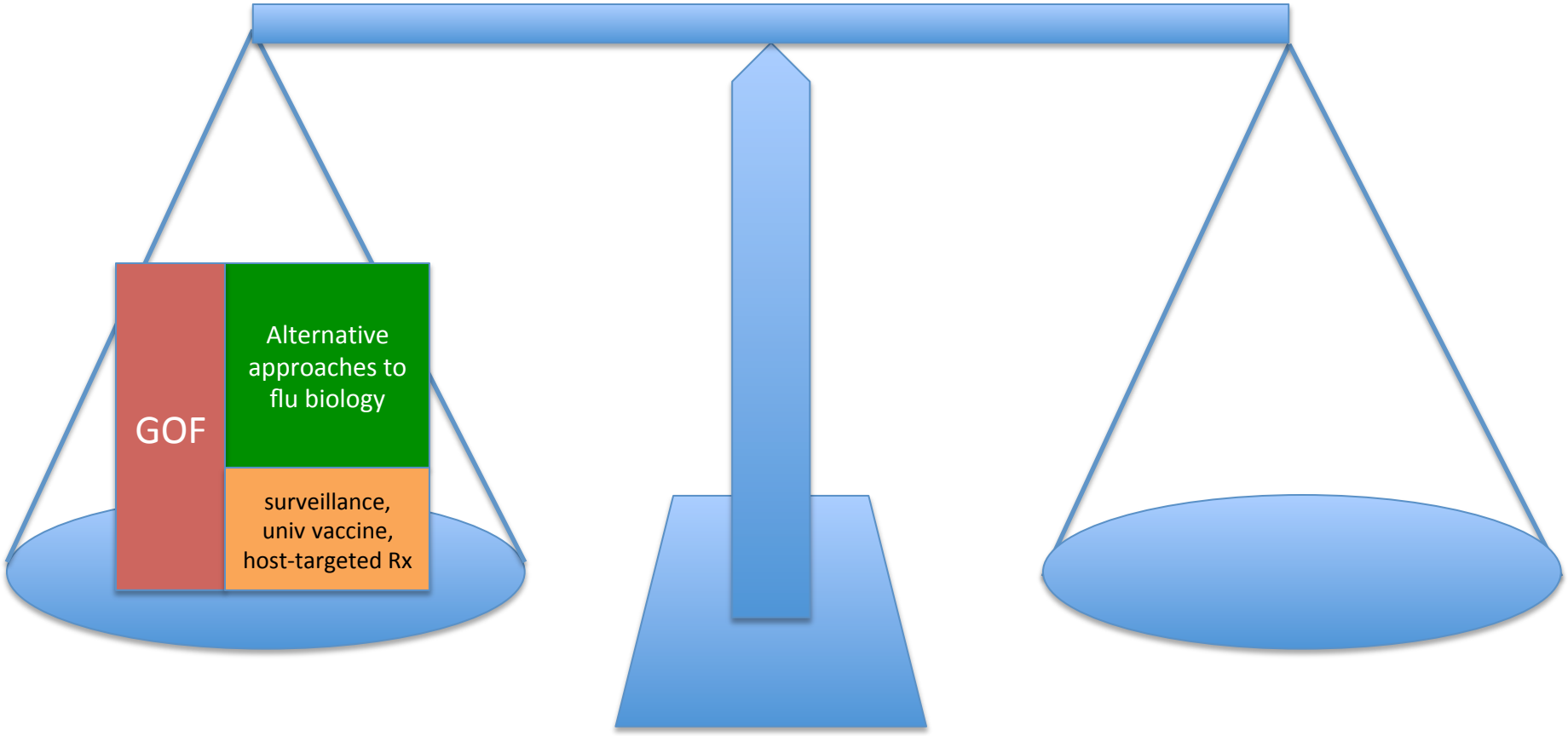
2,000-1,400,000 fatalities / BSL-3 lab-year using these (provisional) numbers

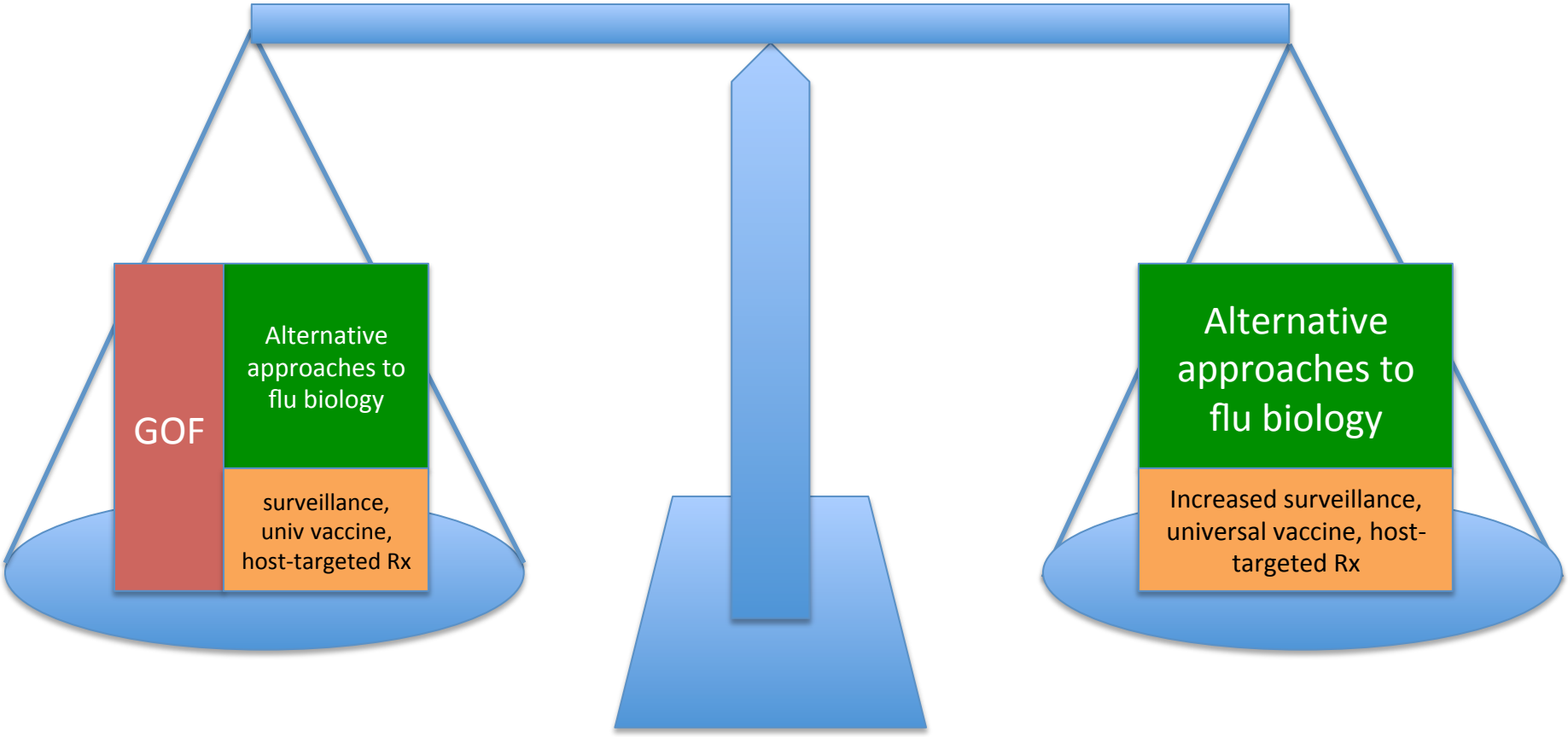
Alternative ways to study and *defeat* influenza

Approach	Risk to life	Cost	Throughput	Generalizability
PPP	High	$$$	-	-
Defective viruses in vitro	~0	$	+++	++
Analysis of natural bird vs. human strains	Low	$$	+	+
Universal vaccine	*~0*	*$$*	*++*	*+++*
Accelerate vaccine production	*~0*	*$$*	*++*	*+++*
Host-targeted therapeutics	*~0*	*$$$*	*?*	*+++*

More complete list with citations at Lipsitch & Galvani *PLoS Med* 2014

Why alternatives?


GOF
Alternative approaches to flu biology
surveillance, univ vaccine, host-targeted Rx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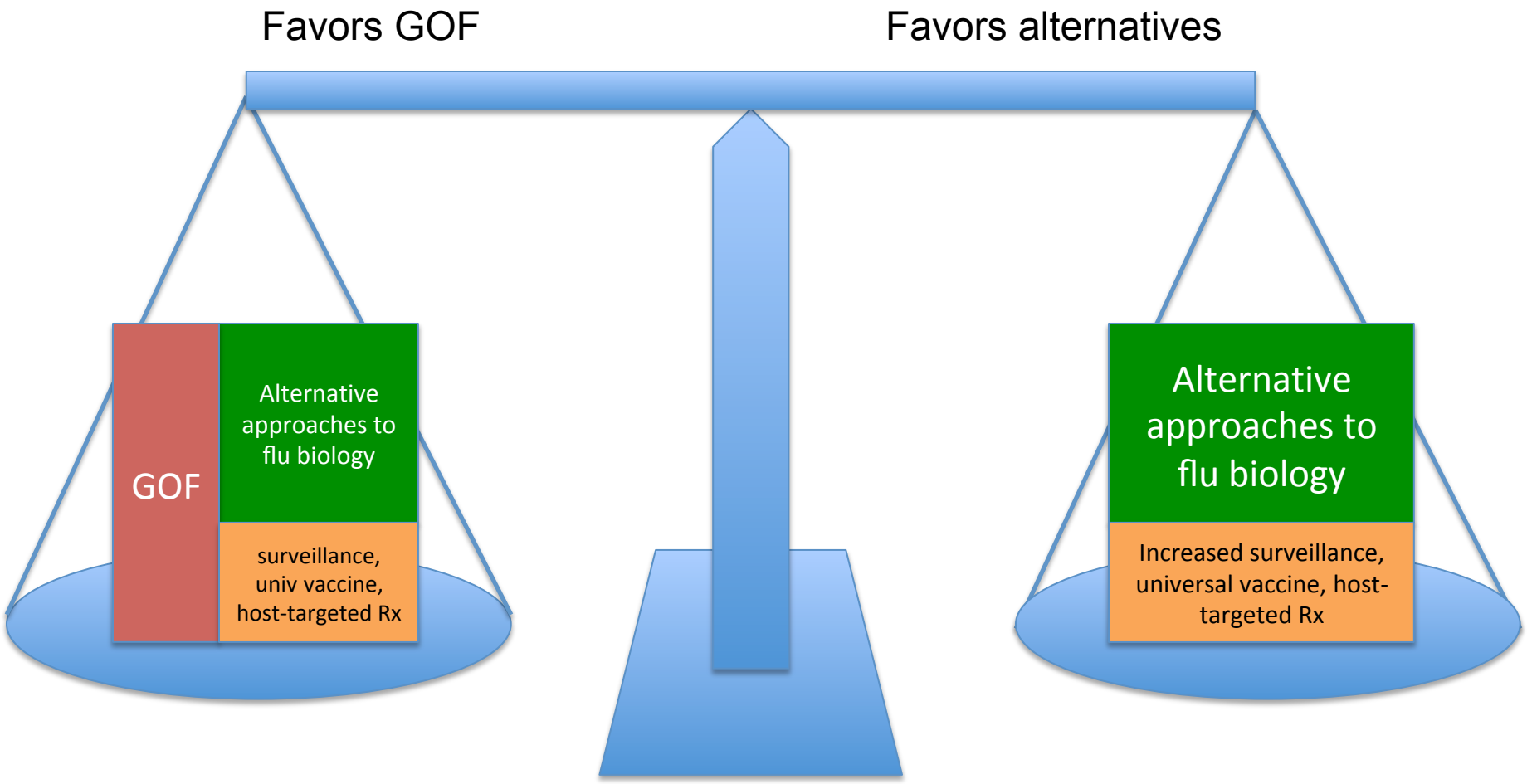
Alternative approaches to flu biology
Increased surveillance, universal vaccine, host-targeted Rx


Favors GOF
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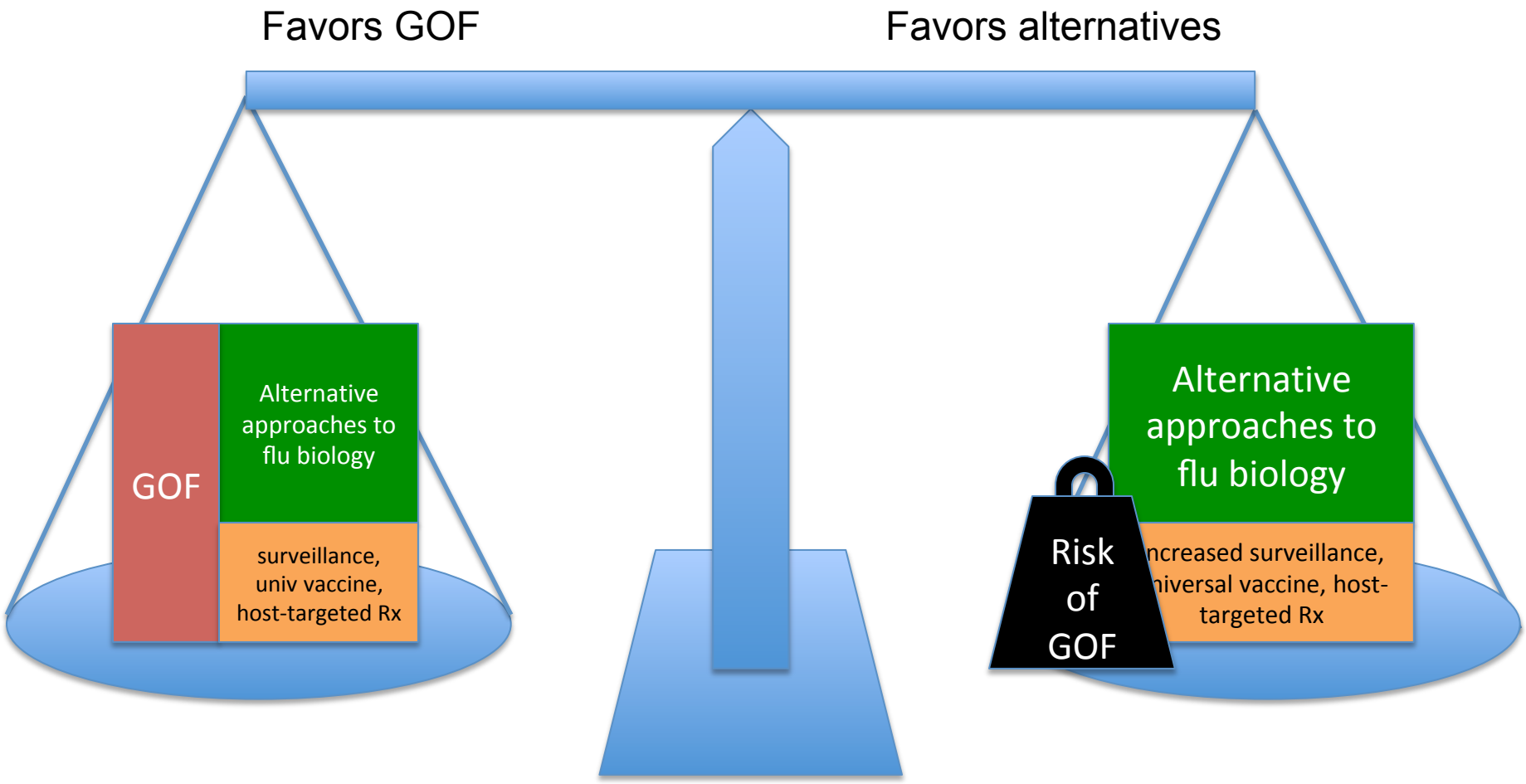
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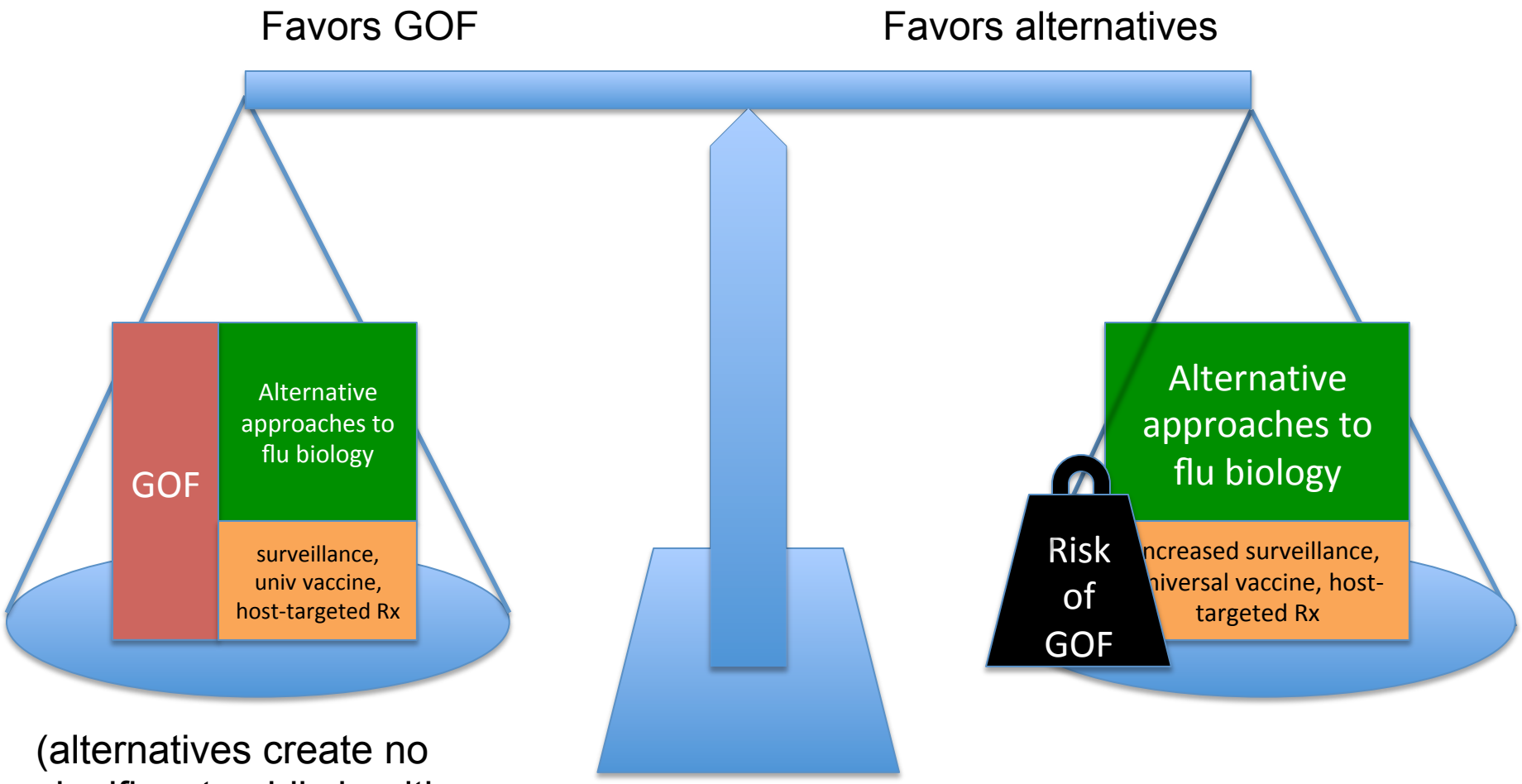

(alternatives create no significant public health risk)

Conclusions

- Open, quantitative, disinterested process needed to estimate risks
- Values exist for key elements of risk analysis, producing alarming risk estimates even if individual elements reduced by orders of magnitude
- Benefits should be considered as *marginal* benefits within a portfolio of investments in flu preparedness, accounting for opportunity cost – what do we gain by adding GoF and reducing other investments
- Risks should be considered in marginal terms too, but marginal = total risk when considering GoF. Alternatives present minimal risk.