VACCINE IMPACT AND VALUE OF VACCINATION
LOOKING AT BENEFITS BEYOND EFFICACY AND SAFETY

Bradford D. Gessner

Vaccinology 2017
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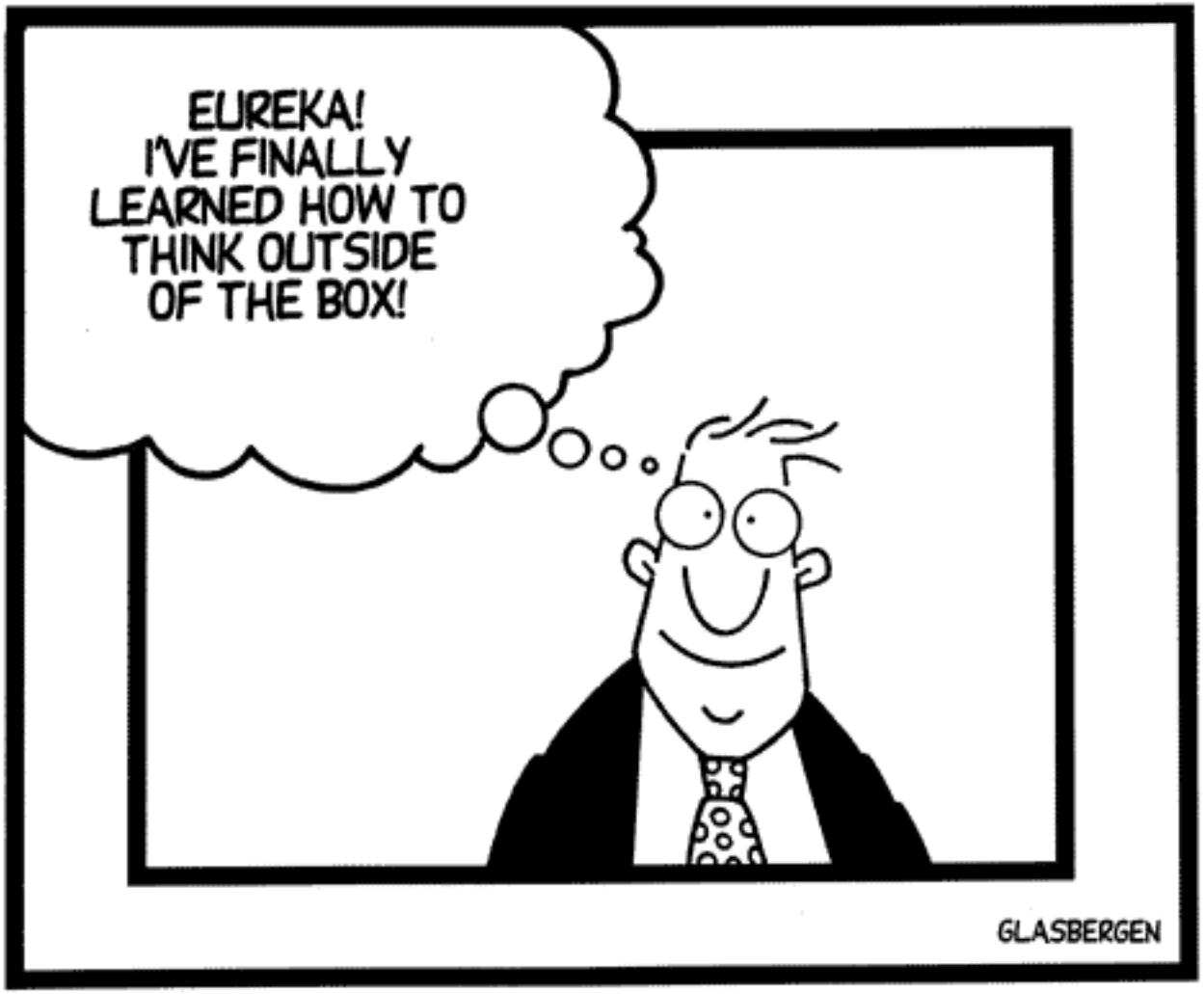
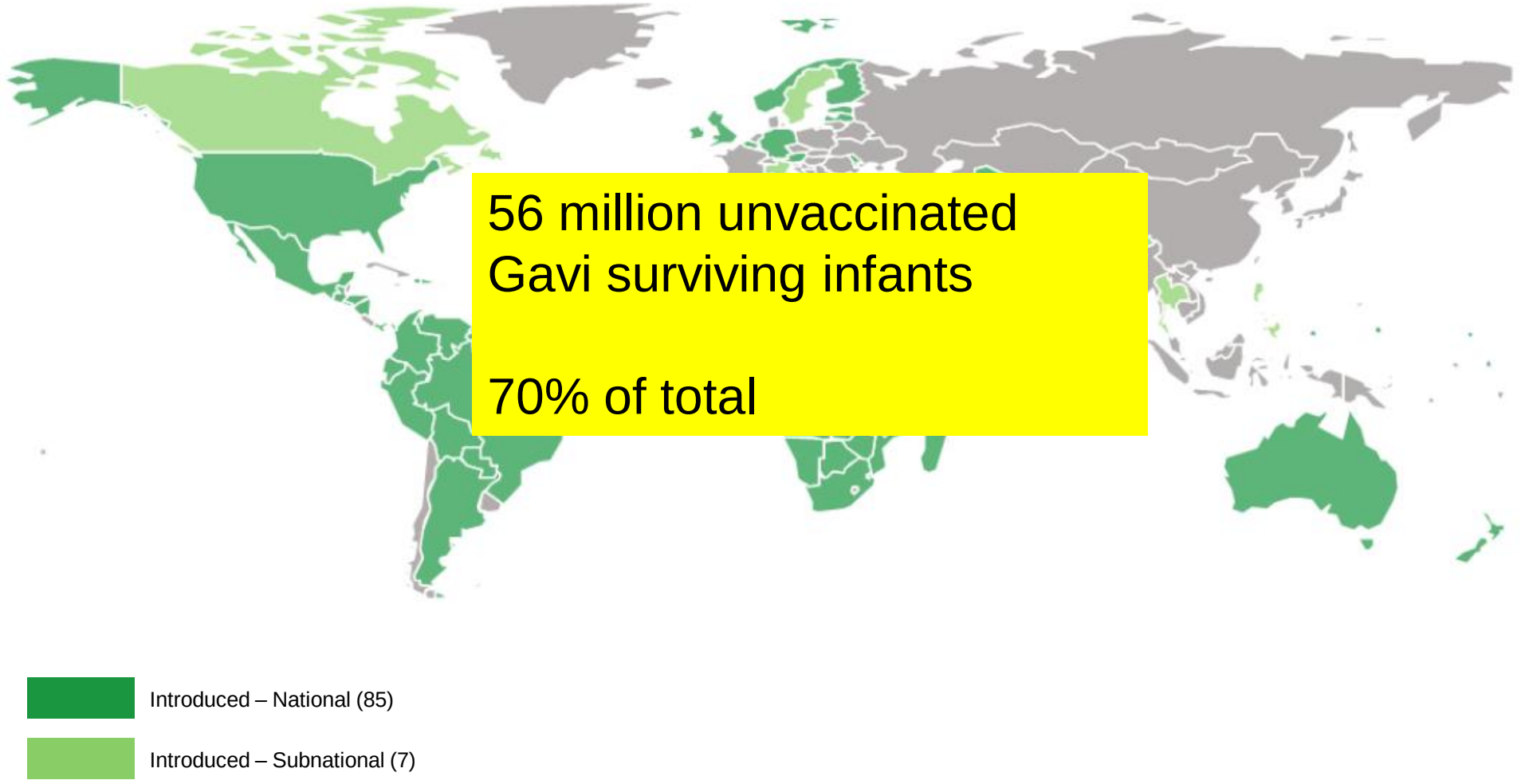
Declarations

- Worked for AMP for 20 years, funding from:
  - Crucell, GSK, Hilleman, Merck, Novartis, Pfizer, Sanofi
  - US and French Governments
  - BMGF
  - Gavi, the Vaccine Alliance
  - WHO, Unicef
- Consultant
  - Sanofi, dengue
- Affiliations
  - Pfizer: Global Lead for PCV
  - AMP: Board
  - U. Maryland: Adjunct professor



SETTING THE STAGE

Global Introduction Status of Rotavirus Vaccine



Source: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub Global Vaccine Introduction and Implementation Report, March 2017.

Countries introducing HPV in NIPs as of Nov. 2016

Cervical Cancer Action: http://www.cervicalcanceraction.org/comments/comments3.php

National programs

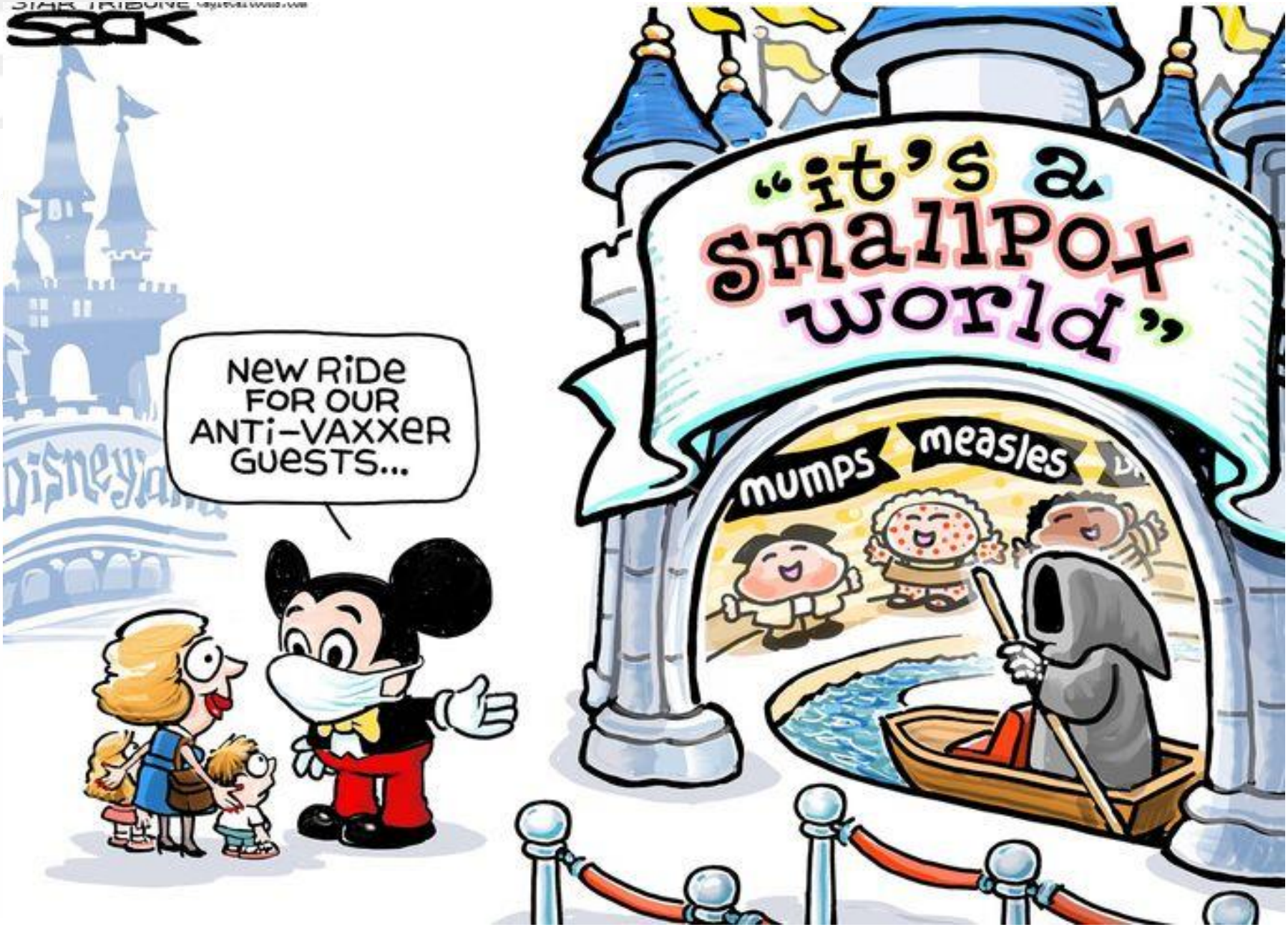
American Samoa
Andorra
Argentina
Aruba
Australia
Austria
Bahamas
Barbados
Belgium
Belize
Bermuda
Bhutan
Bonaire
Botswana
Brazil
Brunei
Bulgaria
Canada
Cayman Islands
Chile
Colombia
Cook Islands
Curacao
Czech Republic
Denmark
Dominican Republic
Ecuador
Fiji
Finland
France
French Polynesia
Germany
Greece
Guam
Guyana
Honduras
Hungary
Iceland
Ireland
Israel
Italy
Japan
Kiribati
Latvia
Lesotho
Libya
Lichtenstein
Luxembourg
Macedonia
Malaysia
Malta
Marshall Islands
Mexico
Micronesia
Monaco
Netherlands
New Caledonia
New Zealand
Niue
Northern Marianas
Norway
Palau
Panama
Paraguay
Peru
Philippines
Portugal
Romania
Rwanda
San Marino
Seychelles
Singapore
Slovenia
South Africa
Spain
St. Eustatius
Suriname
Sweden
Switzerland
Trinidad and Tobago
Uganda
United Arab Emirates
United Kingdom
United States
Uruguay
Uzbekistan
Vanuatu

Pilot programs

Angola
Bangladesh
Benin
Bolivia
Burkina Faso
Burundi
Cambodia
Cameroon
Cote d'Ivoire
Ethiopia
Gambia
Georgia
Ghana
Haiti
India
Indonesia
Kenya
Lao PDR
Liberia
Madagascar
Malawi
Mali
Moldova
Mongolia
Mozambique
Nepal
Niger
Papua New Guinea
Sao Tome
Senegal
Sierra Leone
Solomon Islands
Tanzania
Thailand
Togo
Vietnam
Zambia
Zimbabwe

Foundation is fragile

- Relative value of vaccines critical in every country
- Cost of vaccine transparent and a fact on the ground
- But vaccine benefits need a more robust approach


SACK
NEW RIDE FOR OUR ANTI-VAXXER GUESTS...
"it's a smallpox world"
mumps
measles

FRAMEWORK

Framework

	Clinical trial perspective	Public health perspective
Context	Conservative: should this vaccine be licensed and produced?	Balanced: Should this vaccine be used in my setting?
Endpoints	Etiologically confirmed: did the vaccine work against the target etiology?	Clinical: how much disease is preventable regardless of etiologic confirmation at presentation?
Outcomes	VE, safety: did the vaccine work and is it safe?	Burden reduction, incidence rate reduction, number needed to vaccinate: what is the efficiency of the vaccine against important outcomes?
Design	Individually randomized: does the vaccine provide direct protection?	Cluster randomized: what is the total impact of the vaccine in a population?
Implementation	Tightly controlled allocation and intensive disease monitoring: is it certain the vaccine worked?	Public health allocation and routine disease monitoring: what is the expected real world impact?
Trial length	Long enough to get trial endpoints : what is the shortest trial that will get endpoints?	Long enough to assess total impact on population health: what does the vaccine prevent over time?
Analysis	Per protocol: did vaccine work when delivered to maximize assessment of whether product had biological effect?	ITT + total impact: what was the total (direct + indirect) impact of vaccine in the population when given in real world setting?
First vs. all events	First: did the vaccine prevent disease in a high percent of individuals?	All: how many events can the vaccine prevent over the whole follow-up period?

ENDPOINTS:
CLINICAL INSTEAD OF ETIOLOGICALLY CONFIRMED

Between the idea and the reality, falls the shadow… OR why reliance on etiologic outcomes fails public health

- **Field issues**
  - Lack of referral
  - Lack of transportation
  - Economic barriers
- **Investigator issues**
  - Outcome not suspected
  - Staff not at work 24/7
  - Lack of diagnostic equipment
- **Laboratory issues**
  - Transportation (delay or loss)
  - Improperly trained staff
  - Variable test specificity/sensitivity
  - Insufficient blood volume
  - Pre-treatment with antibiotics
- **Epidemiological issues**
  - Imperfect entry criteria case definition sensitivity/specificity
  - Imperfect understanding of outcomes associated with infection (e.g., measles and malnutrition)
  - Organism might be part of causal chain and not present

The above may vary by age group, risk group (HIV, marginalized, etc.), geography; often will impact most those most at risk of vaccine preventable disease

OXFORD
UNIVERSITY PRESS

From: **Impact of Widespread Introduction of Pneumococcal Conjugate Vaccines on Pneumococcal and Nonpneumococcal Otitis Media**

Clin Infect Dis. 2016;63(5):611-618. doi:10.1093/cid/ciw347

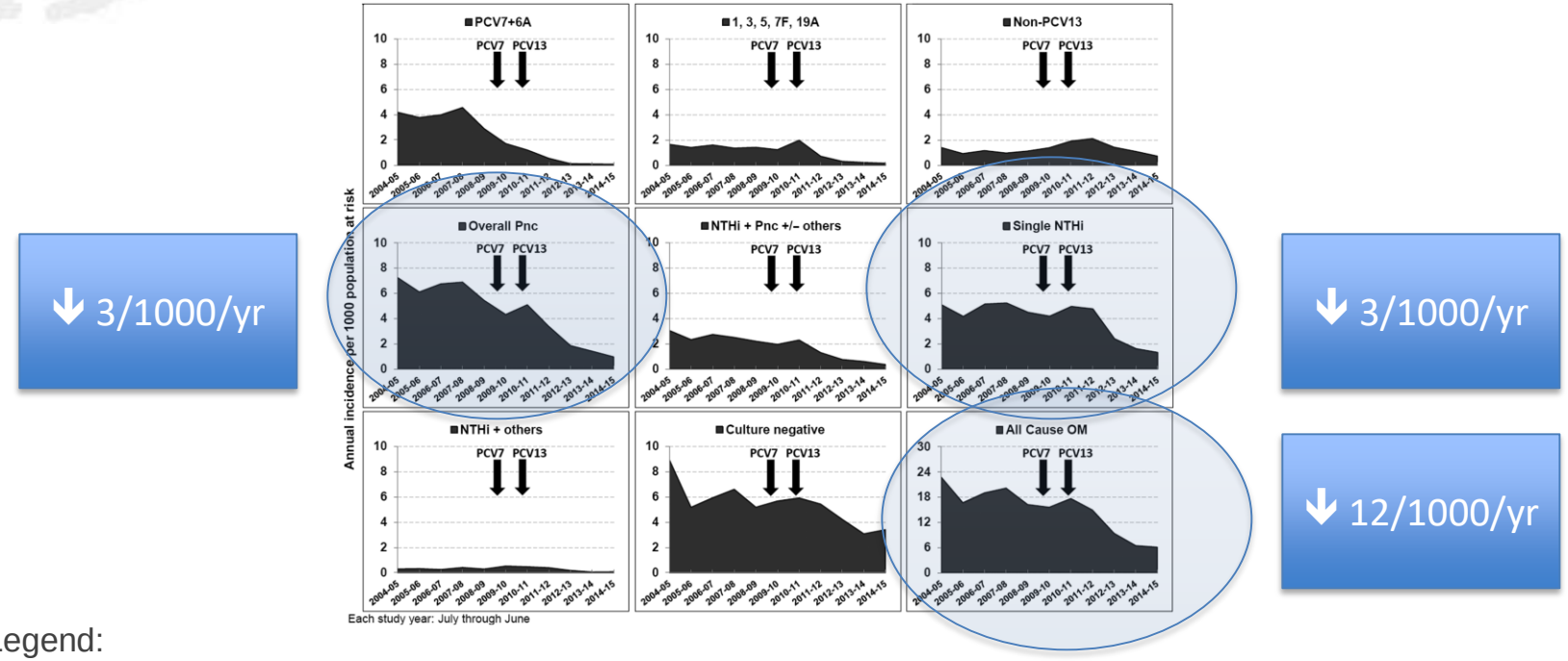


Figure Legend:

Incidence dynamics of pneumococcal, nontypable Haemophilus influenzae, culture-negative, and all-cause otitis media episodes during which middle ear fluid culture was obtained in children aged <36 months in southern Israel, July 2004 through June 2015. Abbreviations: NTHi, nontypable Haemophilus influenzae; OM, otitis media; PCV, pneumococcal conjugated vaccine; Pnc, Streptococcus pneumoniae.

OUTCOMES:
PUBLIC HEALTH MEASURES OF DISEASE BURDEN

Why does burden matter?

ELSEVIER

Social Science & Medicine 65 (2007) 1751–1764

SOCIAL SCIENCE & MEDICINE

www.elsevier.com/locate/socscimed

What influences government adoption of vaccines in developing countries? A policy process analysis

Syarifah Liza Munira[a,*], Scott A. Fritzen[b]

"Disease burden has been consistently mentioned by policymakers in countries to be the number one factor in setting priorities for vaccines to be introduced into immunization programs; the higher the burden, the more attractive a potential addition to the immunization regime of the country would be."

- Gates Foundation, Gavi, NITAGs, and WHO SAGE all emphasize primacy of burden as a criteria for decision making.
- Not burden per se, but the amount of burden a vaccine can reduce

Public health outcome measures

VACCINE PREVENTABLE DISEASE INCIDENCE (VPDI)

- Same as vaccine attributable risk or incidence rate reduction
- = Incidence [unvaccinated] – Incidence [vaccinated]
- = Incidence [unvaccinated] x VE
- = number of cases averted per unit of vaccinated people per year

NUMBER NEEDED TO VACCINATE (NNV)

- The number of people that must be vaccinated to prevent one outcome
- Not a rate so incorporates length of trial (or duration of immunity)
- If VPDI is reported as cases prevented per 100,000 vaccinated persons per year, NNV = 100,000/VPDI/length of study

Use of vaccines as probes to define disease burden

Daniel R Feikin, J Anthony G Scott, Bradford D Gessner

Vaccine probe studies have emerged in the past 15 years as a useful way to characterise disease. By contrast, traditional studies of vaccines focus on defining the vaccine effectiveness or efficacy. The underlying basis for the vaccine probe approach is that the difference in disease burden between vaccinated and unvaccinated individuals can be ascribed to the vaccine-specific pathogen. Vaccine probe studies can increase understanding of a vaccine's public health value. For instance, even when a vaccine has a seemingly low efficacy, a high baseline disease incidence can lead to a large vaccine-preventable disease burden and thus that population-based vaccine introduction would be justified. So far, vaccines have been used as probes to characterise disease syndromes caused by *Haemophilus influenzae* type b, pneumococcus, rotavirus, and early infant influenza. However, vaccine probe studies have enormous potential and could be used more widely in epidemiology, for example, to define the vaccine-preventable burden of malaria, typhoid, paediatric influenza, and dengue, and to identify causal interactions between different pathogens.

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International Vaccine Access Center, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (D R Feikin MD); Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA (D R Feikin); KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya (Prof J A G Scott); London School of Hygiene and Tropical Medicine, London, UK (Prof J A G Scott); and Agence de Médecine Préventive, Ferney-Voltaire, France (B D Gessner MD)

Correspondence to:
Dr Daniel R Feikin, International Vaccine Access Center, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
dfeikin@jhsph.edu

Introduction

Traditionally, vaccine studies have focused on characterising the vaccine's efficacy. By contrast, vaccine probe studies characterise the disease. A vaccine probe study is a randomised clinical trial of a vaccine of known efficacy; the difference in the incidence of disease between vaccinated and unvaccinated people represents the vaccine-preventable disease incidence (VPDI). Vaccine probe studies also estimate the aetiological fraction (ie, the proportion of cases of a disease syndrome caused by the pathogen), which is often difficult to define through other study designs. Vaccines have already been used as probes to characterise disease syndromes caused by *Haemophilus influenzae* type b (Hib), pneumococcus, influenza, and rotavirus. However, vaccine probe studies have much potential and could be used more widely in epidemiology, for example, to define the vaccine-

surveillance to be sufficient to justify introduction of Hib vaccine.[3] By contrast, most Hib pneumonia episodes in Asia are non-bacteraemic and therefore invisible to normal clinical surveillance methods. This inability to easily diagnose Hib pneumonia generated an impasse whereby the investment case for Hib vaccine in Asia was contingent on an epidemiological parameter that could not easily be estimated.

The solution was to use the vaccine itself as a probe to reveal how much pneumonia could be prevented by Hib vaccine.[4,7] The focus of this new trial was not vaccine efficacy, which was already well established, but the difference in pneumonia incidence between vaccinated and unvaccinated populations. This study, which took place in Lombok, Indonesia, was the first prospectively designed vaccine probe study. Subsequently, this approach of designing, or interpreting, vaccine studies from the perspective of disease effect has been used for

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Review

Vaccine preventable disease incidence as a complement to vaccine efficacy for setting vaccine policy

Bradford D. Gessner[a,*], Daniel R. Feikin[b,c]

[a] Agence de Médecine Preventive, 164 Rue de Vaugirard, 75015 Paris, France
[b] International Vaccine Access Center, Department of International Health, Johns Hopkins School of Public Health, Baltimore, MD, USA
[c] Division of Preparedness and Emerging Infections, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

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Vaccine

ABSTRACT

Traditionally, vaccines have been evaluated in clinical trials that establish vaccine efficacy (VE) against etiology-confirmed disease outcomes, a measure important for licensure. Yet, VE does not reflect a vaccine's public health impact because it does not account for relative disease incidence. An additional measure that more directly establishes a vaccine's public health value is the vaccine preventable disease incidence (VPDI), which is the incidence of disease preventable by vaccine in a given context. We describe how VE and VPDI can vary, sometimes in inverse directions, across disease outcomes and vaccinated populations. We provide examples of how VPDI can be used to reveal the relative public health impact of vaccines in developing countries, which can be masked by focus on VE alone. We recommend that VPDI be incorporated along with VE into the analytic plans of vaccine trials, as well as decisions by funders, ministries of health, and regulatory authorities.

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Conference report

Estimating the full public health value of vaccination

Bradford D. Gessner[a,*,1,2], David Kaslow[b], Jacques Louis[c], Kathleen Neuzil[d], Katherine L. O'Brien[e], Valentina Picot[c], Tikki Pang[f], Umesh D. Parashar[g], Mitra Saadatian-Elahi[h], Christopher B. Nelson[i]

[a] Agence de Médecine Préventive, Paris, France
[b] PATH, Seattle, WA, United States
[c] Fondation Mérieux, 17 rue Bourgelat, 69002 Lyon, France
[d] Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, United States
[e] Department of International Health & Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, United States
[f] Lee Kuan Yew School of Public Policy, National University of Singapore, Singapore
[g] Division of Viral Diseases, US Centres for Disease Control and Prevention, Atlanta, GA, United States
[h] Hospices Civils de Lyon, Groupement Hospitalier Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France
[i] Sanofi Pasteur, Vaccination Policy Department, 2 Avenue du Pont Pasteur, 69367 Lyon cedex 07, France

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Immunization programs
Public health

ABSTRACT

There is an enhanced focus on considering the full public health value (FPHV) of vaccination when setting priorities, making regulatory decisions and establishing implementation policy for public health activities. Historically, a therapeutic paradigm has been applied to the evaluation of prophylactic vaccines and focuses on an individual benefit-risk assessment in prospective and individually-randomized phase III trials to assess safety and efficacy against etiologically-confirmed clinical outcomes. By contrast, a public health paradigm considers the population impact and encompasses measures of community benefits against a range of outcomes. For example, measurement of the FPHV of vaccination may incorporate health inequity, social and political disruption, disruption of household integrity, school absenteeism and work loss, health care utilization, long-term/on-going disability, the development of antibiotic resistance, and a range of non-etiologically and etiologically defined clinical outcomes.

Following an initial conference at the Fondation Mérieux in mid-2015, a second conference (December 2016) was held to further describe the efficacy of using the FPHV of vaccination on a variety of prophy-

Wilder-Smith et al. BMC Medicine (2017) 15:138
DOI 10.1186/s12916-017-0911-4

BMC Medicine

OPINION Open Access

The public health value of vaccines beyond efficacy: methods, measures and outcomes

A. Wilder-Smith[1,2,3*], I. Longini[4], P. L. Zubeir[5], T. Bärnighausen[2], W. J. Edmunds[3], N. Dean[4], V. Massey Spicher[6], M. R. Benissa[7] and B. D. Gessner[8]

Abstract

Background: Assessments of vaccine efficacy and safety capture only the minimum information needed for regulatory approval, rather than the full public health value of vaccines. Vaccine efficacy provides a measure of proportionate disease reduction, is usually limited to etiologically confirmed disease, and focuses on the direct protection of the vaccinated individual. Herein, we propose a broader scope of methods, measures and outcomes to evaluate the effectiveness and public health impact to be considered for evidence-informed policymaking in both pre- and post-licensure stages.

Discussion: Pre-licensure: Regulatory concerns dictate an individually randomised clinical trial. However, some circumstances (such as the West African Ebola epidemic) may require novel designs that could be considered valid for licensure by regulatory agencies. In addition, protocol-defined analytic plans for these studies should include clinical as well as etiologically confirmed endpoints (e.g. all cause hospitalisations, pneumonias, acute gastroenteritis and others as appropriate to the vaccine target), and should include vaccine-preventable disease incidence and 'number needed to vaccinate' as outcomes.
Post-licensure: There is a central role for phase IV cluster randomised clinical trials that allows for estimation of population-level vaccine impact, including indirect, total and overall effects. Dynamic models should be prioritised over static models as the constant force of infection assumed in static models will usually underestimate the effectiveness and cost-effectiveness of the immunisation programme by underestimating indirect effects. The economic impact of vaccinations should incorporate health and non-health benefits of vaccination in both the vaccinated and unvaccinated populations, thus allowing for estimation of the net social value of vaccination.

Conclusions: The full benefits of vaccination reach beyond direct prevention of etiologically confirmed disease and often extend across the life course of a vaccinated person, present outcomes in the wider community, stabilise health systems, promote health equity, and benefit local and national economies. The degree to which vaccinations provide broad public health benefits is stronger than for other preventive and curative interventions.

Keywords: Vaccine efficacy, Effectiveness, Overall effectiveness, Vaccine-preventable disease incidence, Public health impact, Dynamic modelling, Cluster randomised controlled trial, Pre-licensure, Post-licensure, Quasi-experiments

* Correspondence: annelieswn@gmail.com
[1] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore
[2] Institute of Public Health, University of Heidelberg, Heidelberg, Germany
Full list of author information is available at the end of the article

EXAMPLES

VPDI (per 1000 CYO) and NNV for etiologically confirmed vs. clinical outcomes

Study	Syndrome	Etiology confirmed			Clinical outcome		
		VE	VPDI	NNV	VE	VPDI	NNV
Gambia, PCV Lancet 2005;365:1139-46	Radiological pneumonia	70%	1.4	357	37%	13	38
Indonesia, Hib Lancet 2005;365:43-52	Hospitalized meningitis	86%	0.16	3125	22%	1.6	313
Kenya, rotavirus Vaccine 2012;30 (suppl 1):A52-60	AGE (conf. in hosp vs. all cause in comm)	84%	33	15	34%	190	3

;;

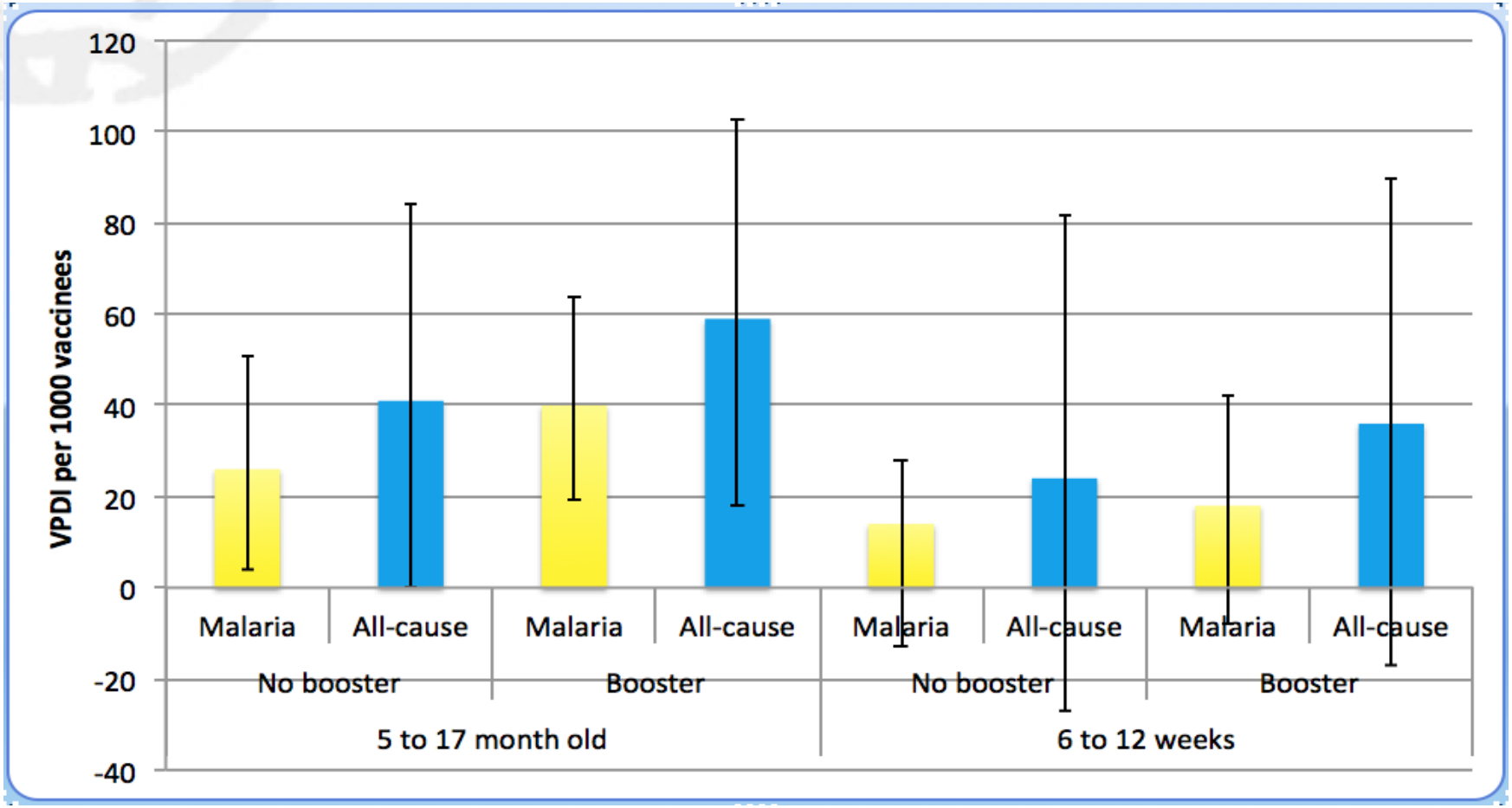
Clinical outcomes show greater VPDI outside of developing country settings

Study	VE	VPDI (per 1000 CYO)
Finland (Vaccine 2012;31:176-82)		
Confirmed inpatient AGE	80%	3.9
All cause inpatient AGE	54%	10.7
Kenya (Vaccine 2012;30 Supp 1:A52-60)		
Confirmed severe	84%	33
Community severe AGE	34%	190

Clinical outcomes and public health measures can be particularly helpful where burden higher/VE lower

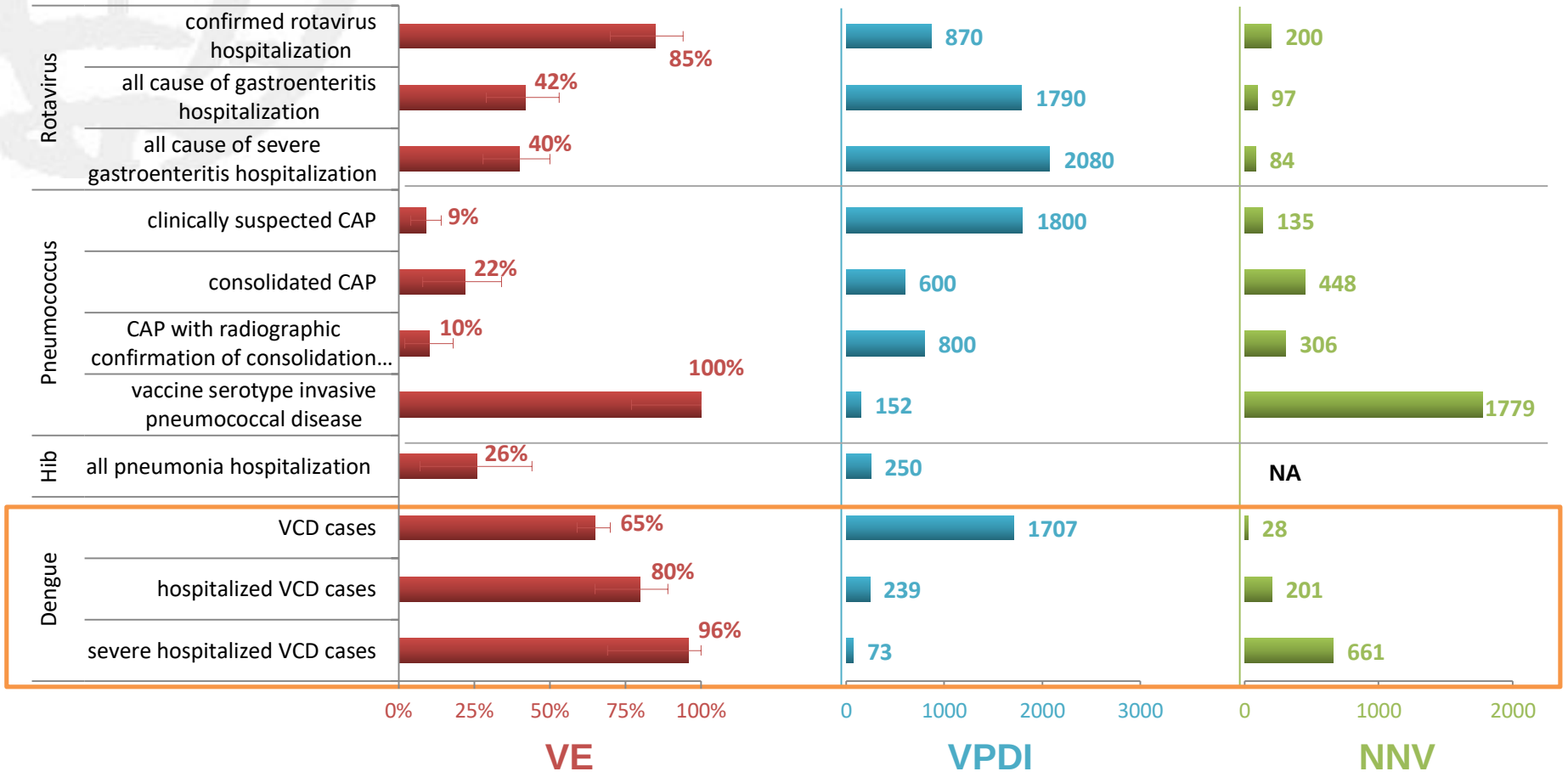
Outcome/study	VE	VPDI (per 1000 CYO)	NNV
Severe rotavirus AGE (NEJM 2010;362:289-98)			
S. Africa	77%	42	24
Malawi	49%	67	15
Severe rotavirus AGE (Lancet 2010;376:615-23)			
Vietnam	64%	22	33
Bangladesh	43%	35	21

RTS,S VPDI against malaria-specific and all-cause hospitalization



VPDI and NNV facilitate vaccine comparisons: CYD TDV dengue vaccine compared to other vaccines

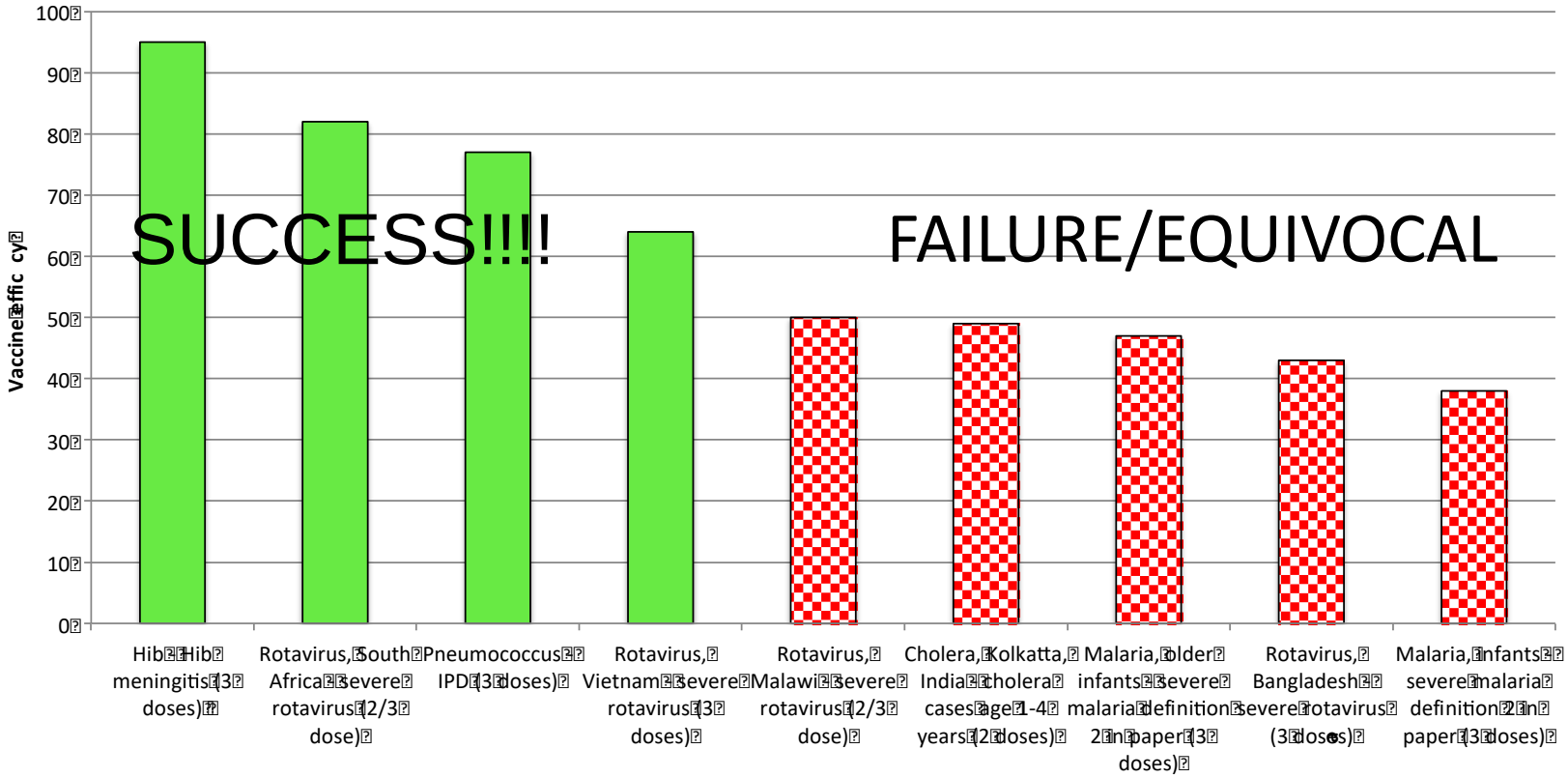
Latin America



In Latin America, while severe disease VPDI was relatively low, the VPDI for all hospitalized dengue was approximately equal to the sum of invasive Hib disease and severe pneumonia

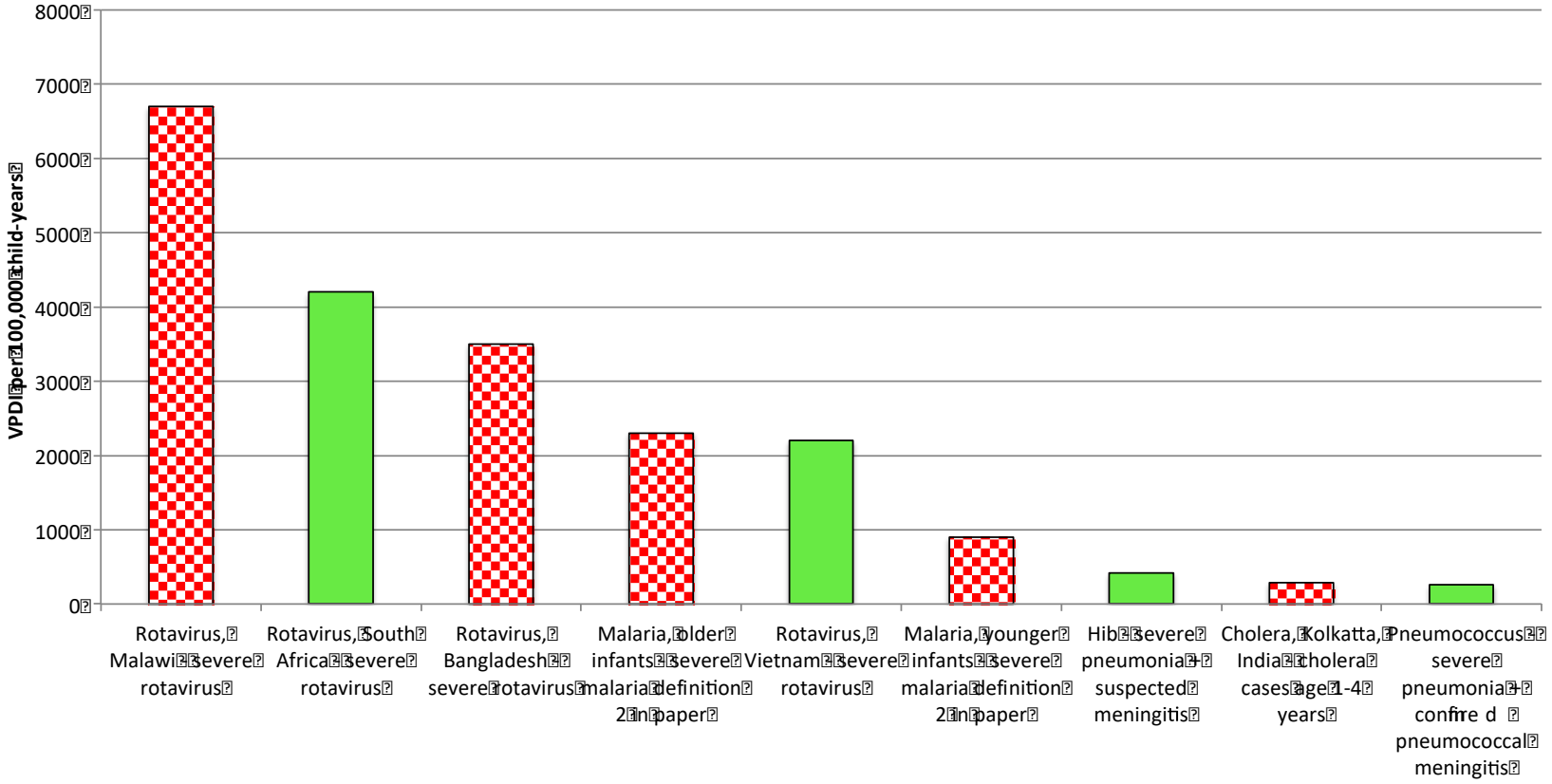
CAP: consolidated community acquired pneumonia; NA: not available

PER PROTOCOL ANALYSIS OF VE



Vaccine 2014;32:3133-8

PER PROTOCOL ANALYSIS OF VPDI



Vaccine 2014;32:3133-8

VACCINE VALUE IS EXTENSIVE

Vaccine preventable burden is more than incidence rate reduction

[non-severe + severe + sequelae] * [direct + indirect] * [duration of protection] * [total age groups possible to protect]

PLUS

Outbreak reduction

PLUS

Political and health system stabilization

PLUS

Equity improvements

PLUS

Ancillary issues (e.g., antibiotic use reduction, fear, stigma)

Severity

	Sp/Hib meningitis	Sp/Hib pneumonia	Malaria	Rotavirus	Cholera	Dengue	HPV
Mortality	++++	++	+++	+	++	+	+++
Hospitalization	++++	+++	+++	++	+++	++	+
Outpatient disease	--	+	++++	++++	+	++++	--

Sequelae

	Sp/Hib meningitis	Sp/Hib pneumonia	Malaria	Rotavirus	Cholera	Dengue	HPV
Cognitive (MR, DD, LD, language)	++++	--	+++	--	--	--	--
Mental health	++++	--	?	--	--	--	++++
Sensory (hearing, vision)	++++	--	--	--	--	--	--
Physical (CP, seizures)	++++	--	+++	--	--	--	--
Stunting	?	?	+++	+	+	?	--

Indirect effects

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Indirect against unvaccinated same target age cohorts	X	?	X	X	?	X
Indirect against unvaccinated outside of target age cohorts	X	?		X	?	X

Duration of immunity

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Relatively long +/- booster	X					X
Moderately long (based on existing data)				X	X	
Short		X				
Less relevance (almost all disease at young age)			X			

Age distribution

	Age <5 yrs disease	All age disease	Post sexual initiation disease
Age <5 yrs severity/sequelae	Rotavirus, Hib	Malaria, dengue	
All age severity/sequelae		Pneumococcus, cholera	
Post sexual initiation severity/sequelae			HPV

Equity

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Occurrence higher in disadvantaged between countries	--	++++	--	++++	++	--
Occurrence higher in disadvantaged within countries	--	++	--	+++	++	--
Severity higher in disadvantaged	+	+++	+++	++	+	+++
Mortality higher in disadvantaged	+++	++++	++++	+++	+	+++

Outbreaks and politics

	Sp/Hib	Malaria	Rotavirus	Cholera	Dengue	HPV
Massive outbreaks	--	--	--	++/++++	++/++++	--
Disruption of health system	--	--	--	++/++++	++/++++	--
Politically sensitive	--	+++	--	++++	+++	--
Impact on tourism	--	+++	--	++++	+++	--

28,639 Ebola cases
11,316 direct deaths

10,600 additional deaths due to HIV, TB, malaria
Unknown number due to maternal deaths, vaccine preventable deaths

Liberia lost 8% of health workers
Sierra Leone lost 7% of health workers

17,300 orphaned children
All schools closed

$2.2 billion loss in GDP
$3.6 billion donated

https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/cost-of-ebola.html

http://cepi.net

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Commentary

Informing vaccine decision-making: A strategic multi-attribute ranking tool for vaccines—SMART Vaccines 2.0

Stacey Knobler [a,*], Karin Bok [b], Bruce Gellin [b]

[a] Fogarty International Center, National Institutes of Health, USA
[b] National Vaccine Program Office, US Department of Health and Human Services, USA

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ABSTRACT

SMART Vaccines 2.0 software is being developed to support decision-making among multiple stakeholders in the process of prioritizing investments to optimize the outcomes of vaccine development and deployment. Vaccines and associated vaccination programs are one of the most successful and effective public health interventions to prevent communicable diseases and vaccine researchers are continually working towards expanding targets for communicable and non-communicable diseases through preventive and therapeutic modes. A growing body of evidence on emerging vaccine technologies, trends in disease burden, costs associated with vaccine development and deployment, and benefits derived from disease prevention through vaccination and a range of other factors can inform decision-making and investment in new and improved vaccines and targeted utilization of already existing vaccines. Recognizing that an array of inputs influences these decisions, the strategic multi-attribute ranking method for vaccines (SMART Vaccines 2.0) is in development as a web-based tool—modified from a U. S. Institute of Medicine Committee effort (IOM, 2015)—to highlight data needs and create transparency to facilitate dialogue and information-sharing among decision-makers and to optimize the investment of resources leading to improved health outcomes. Current development efforts of the SMART Vaccines 2.0 framework seek to generate a weighted recommendation on vaccine development or vaccination priorities based on population, disease, economic, and vaccine-specific data in combination with individual preference and weights of user-selected attributes incorporating valuations of health, economics, demographics, public concern, scientific and business, programmatic, and political considerations.

Attributes available on SMART Vaccines

Category	Specific attribute
Health consideration	Premature deaths/year, incident cases/year, QALYs gained/DALYs averted
Economic considerations	Directs costs/savings of vaccine use; workforce productivity gained; one-time costs; cost-effectiveness ($/QALY or DALY)
Population that benefits	Children, women, disadvantaged, military, other
Public concerns	Alternative measures, adverse events, fear of or stigma from disease, pandemic potential
Scientific/business	Profitability for manufacturer, new production platforms, existing manufacturing techniques, litigation barriers, NGO interest
Programmatic	Improvement in delivery methods, fits existing schedule, reduces cold-chain
Intangible	Eradication/elimination of disease, increase public awareness
Policy	Interest for national security, foreign policy goals

Screenshot from SMART Vaccines software

https://www.nap.edu/smartvaccines/

CONCLUSIONS

- Vaccines have large effects beyond direct prevention of first-event etiology-confirmed disease in individuals
  - But…effects poorly captured
- Areas for improvement:
  - Different trial designs
  - More extensive use of clinical endpoints and public health outcome measures
    - Incorporation into phase III and IV trials
  - Broader assessment of social and household consequences of disease/vaccine impact
  - Inclusion of ancillary outcomes like equity
- Good data are not good enough
  - Vaccine community must care about fully assessing a vaccine's value
  - Vaccine community should accurately communicate this value
  - Solutions should be found to overcoming misinformation and pre-existing biases


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Dave Carpenter
CARTOONSTOCK .com
Search ID: dcrn1221