Lower efficacy vaccines – what is acceptable and how to integrate more public health interventions and vaccines

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Terveyden ja hyvinvoinnin laitos

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Conflicts of Interest

- Governmental employee - public health
- PI in Finland of (i) covid-19 vaccines immunogenicity study, (ii) influenza vaccine multiple dose immunogenicity study among HCWs, (iii) Avian influenza immunogenicity study
- WP co-lead of the IMI-DRIVE and IMI-PROMISE consortiums (public-private-partnership projects)
- Private practitioner @Aava Travel Medicine clinic – individual health
- Member of the Finnish THL NITAG
- Chair of WHO SAGE

Agenda / Objectives

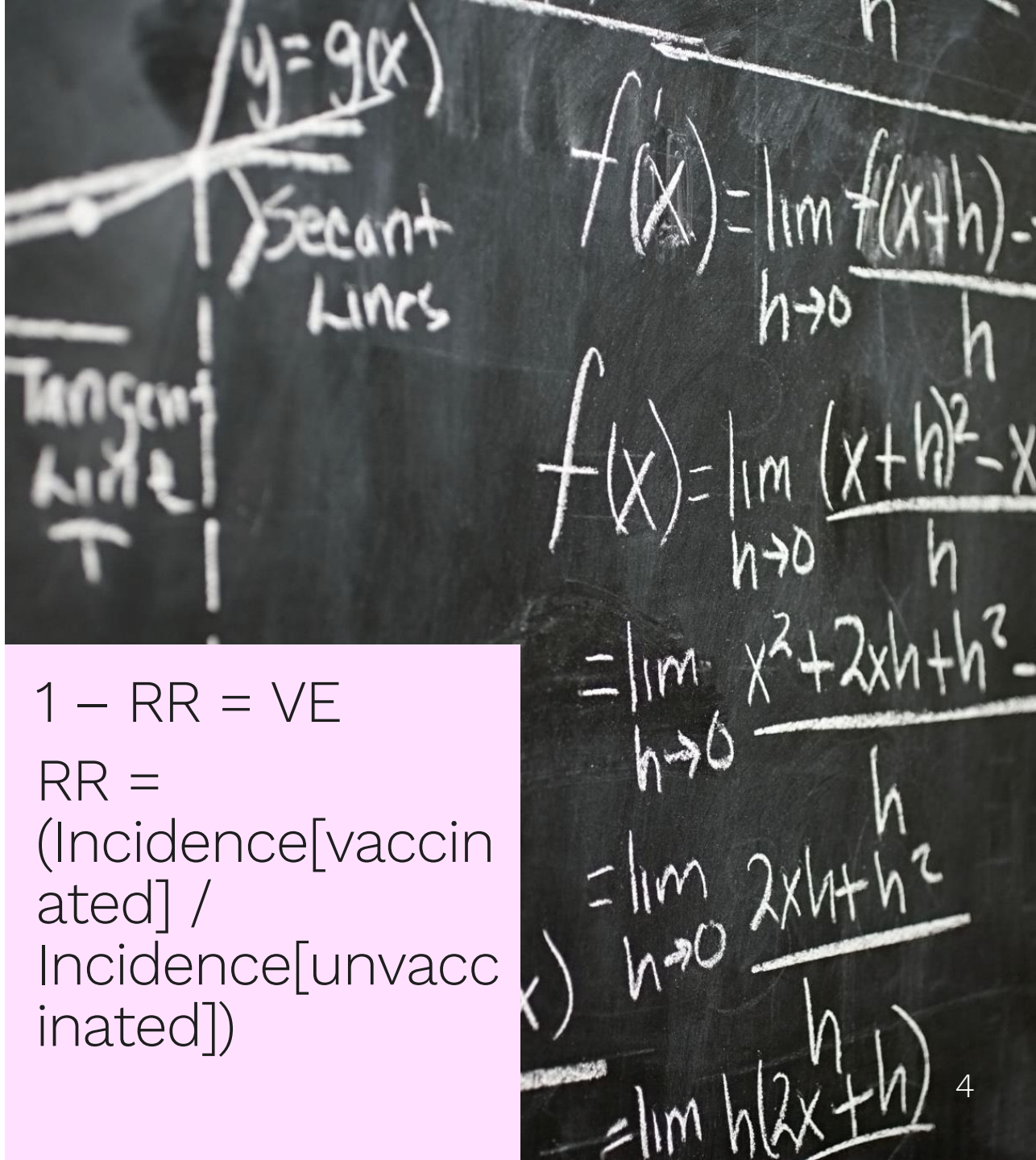
- The concept of efficacy and effectiveness
- The evolution of vaccines efficacy over the years
- How low-efficacy vaccines have a place in the overall vaccine-preventable diseases prevention strategies
- Example malaria vaccine

Definitions

Efficacy vs Effectiveness

Degree of efficacy

- High
- Medium
- Modest / Low



1 – RR = VE

RR = (Incidence[vaccinated] / Incidence[unvaccinated])

Vaccine efficacy VE

$= 1 - (\text{Incidence}_{[\text{vaccinated}]} / \text{Incidence}_{[\text{unvaccinated}]})$

Limitations of iRandomized Controlled Trials

- Indirect effects cannot be measured
- Insufficient power for rare outcomes such as mortality
- Usually insufficient duration for some outcomes such as asthma/wheezing for RSV; neurologic sequelae for meningococcal disease
- Focus on etiologically defined (lab+) disease, which may greatly underestimate all disease burden caused by the pathogen

Vaccine effectiveness

- A measure of how well a vaccine works in the real world.
- How well a vaccine works to protect communities as a whole
- In Analytic terms = Analysis Intent to treat ITT ?

  ? what was the total impact of vaccine in the population?

  Vs. VE = analysis per protocol PP

  ? did the vaccine work when delivered as intended?

Different viewpoints

Events, outcomes, endpoints

Randomized Controlled Clinical trial questions

- Emphasis on first events: did the vaccine prevent disease in a high percent of individuals?
- Outcomes = VE, safety: did the vaccine work as intended and is it safe?
- Endpoints = Etiologically confirmed: did the vaccine work against the target etiology?

Public health questions

- Emphasis on all events: how many events can the vaccine prevent?
- Outcomes = Incidence rate reduction: what is the efficiency of the vaccine against important outcomes?
- Endpoints clinical = how much disease is preventable regardless of etiologic confirmation at presentation?

Beyond VE

Measure of public health value

Vaccine preventable disease incidence and NNV

- Vaccine attributable risk reduction
- Incidence rate reduction

Number of cases averted per unit of vaccinated people per year

= $Incidence_{[unvaccinated]}$ - $Incidence_{[vaccinated]}$

= $Incidence_{[unvaccinated]}$ x VE

- Number needed to be fully vaccinated (NNV) to prevent an outcome

= 100 000 / VPDI / length of follow-up for VPDI

Examples of lower efficacy vaccines

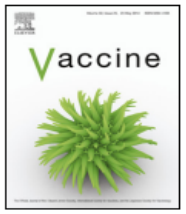
comparison of VE with VPDI

Vaccine 32 (2014) 3133–3138

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Review

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

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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.

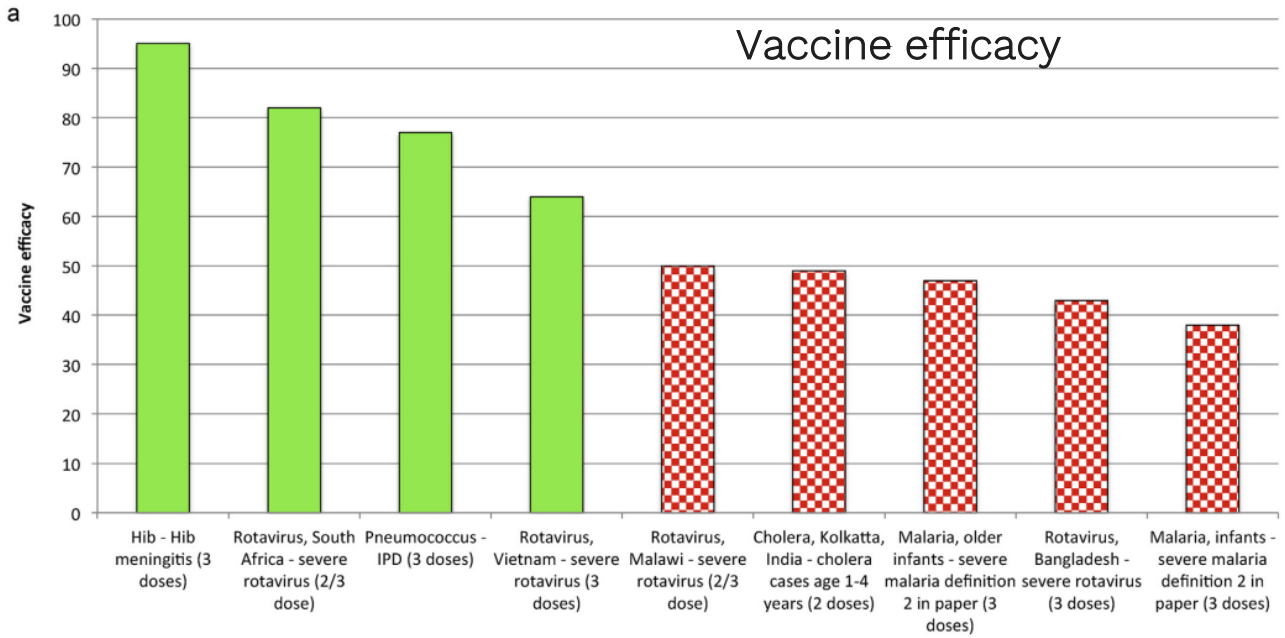
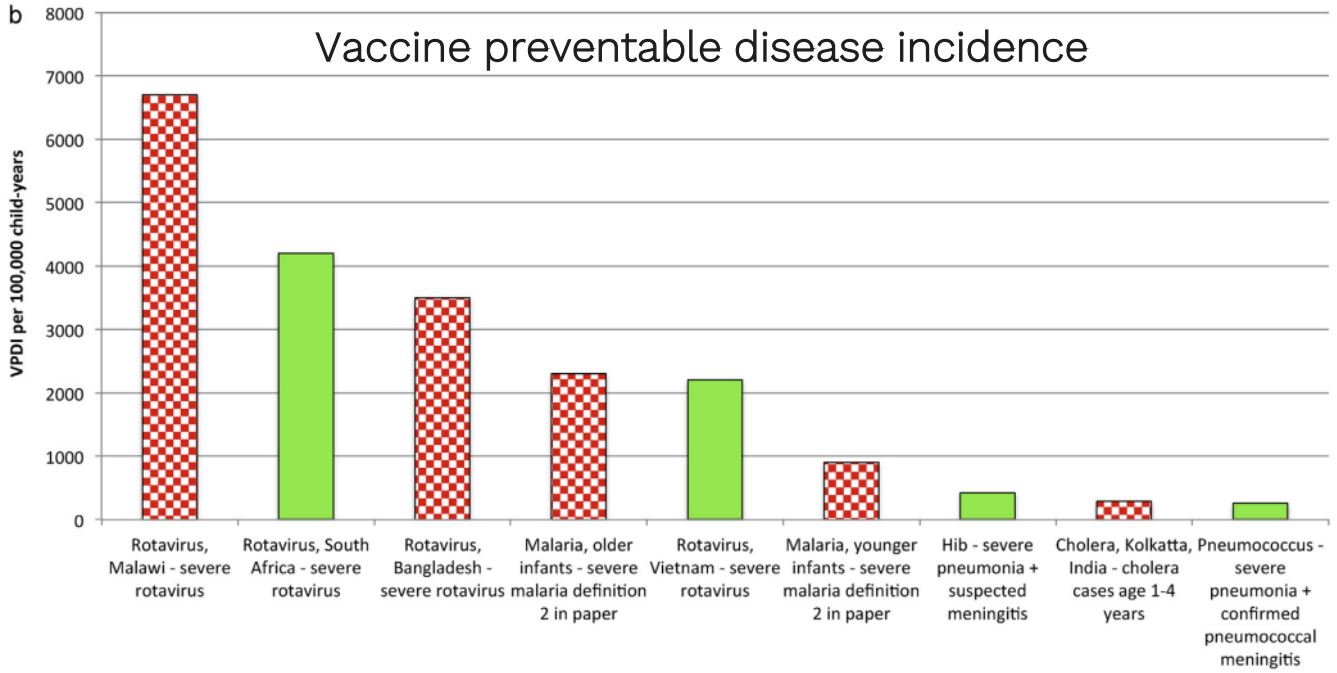


Fig. 1. (a) Vaccine efficacy against various severe outcomes from randomized controlled trials of vaccines (Table 2). (b) Vaccine preventable disease incidence (VPDI) against various severe outcomes from randomized controlled trials of vaccines. Fig. 1a and b report data from the same nine trial sites with Fig. 1a in descending order of VE and Fig. 1b in descending order of VPDI. Green bars indicate >60% VE and red cross-hatched bars 50% or less VE.

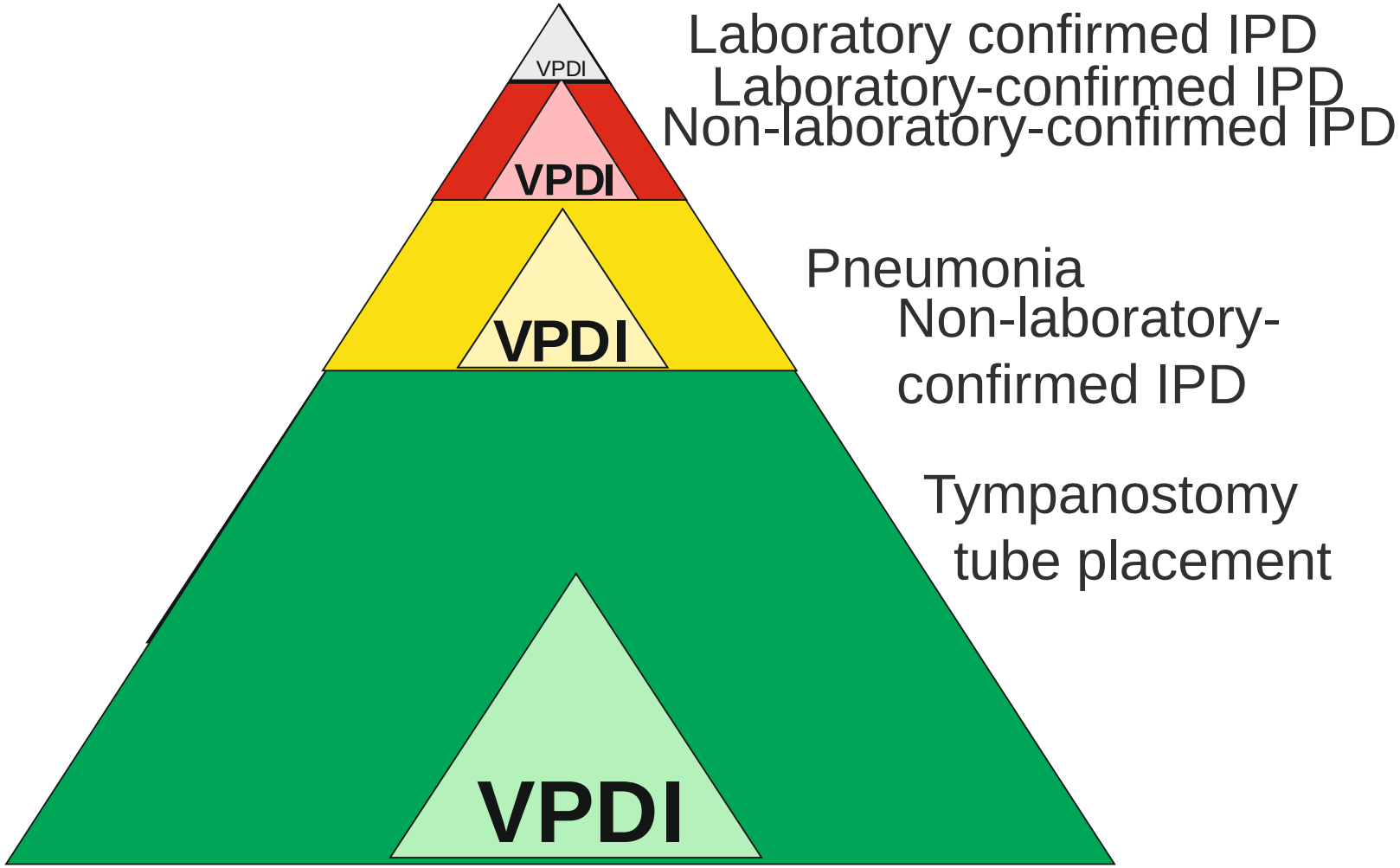
Focus on vaccine efficacy may lead to underestimation of the public health significance of the vaccine, thus non-acceptance and failure to introduce the vaccine



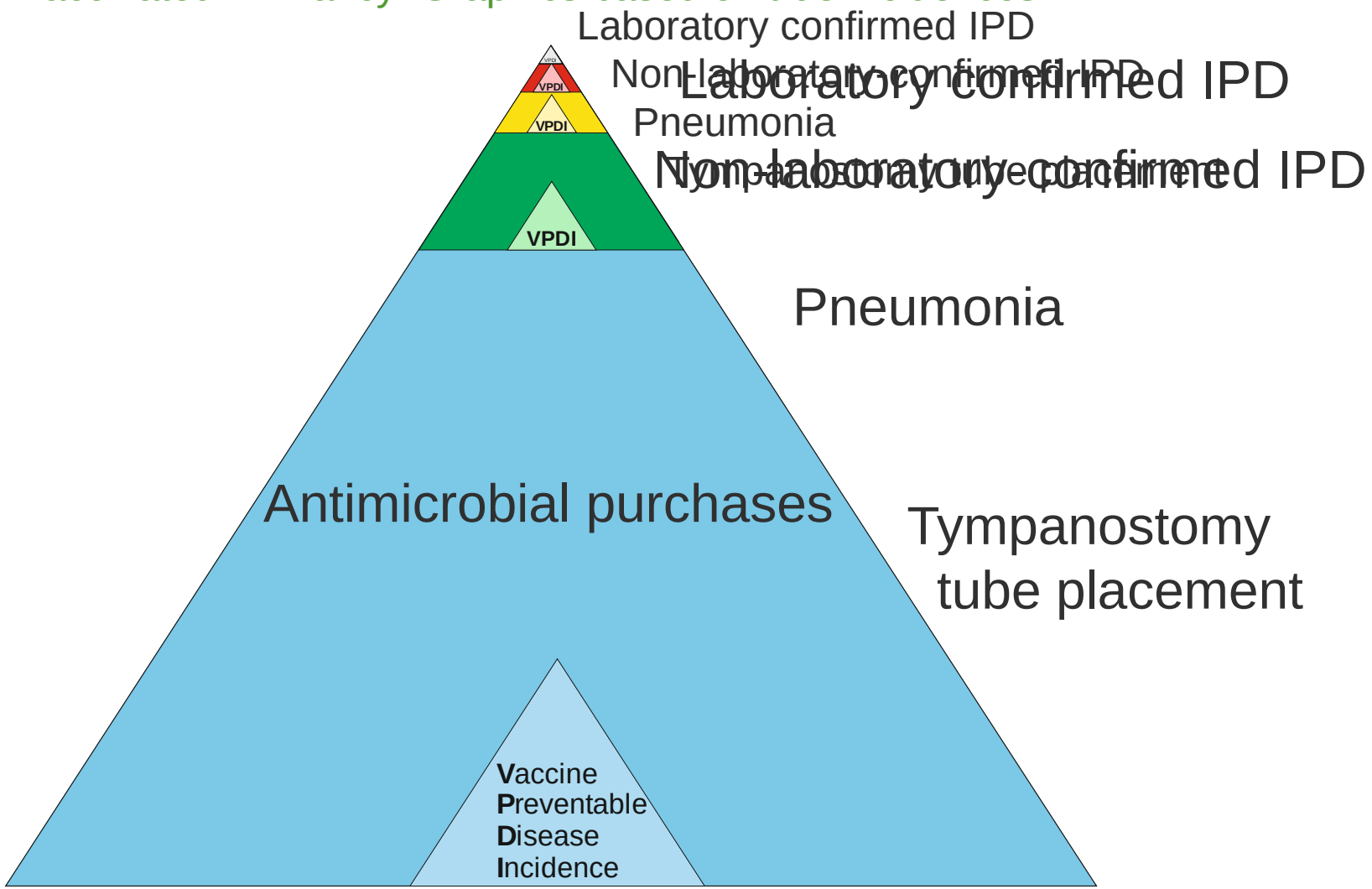
thl

Gessner & Feikin 2014 6.6.2024

Disease burden and vaccine-preventable disease incidence (VPDI) in children vaccinated in infancy. Graphics based on true incidences.



Disease burden and vaccine-preventable disease incidence (VPDI) in children vaccinated in infancy. Graphics based on true incidences.

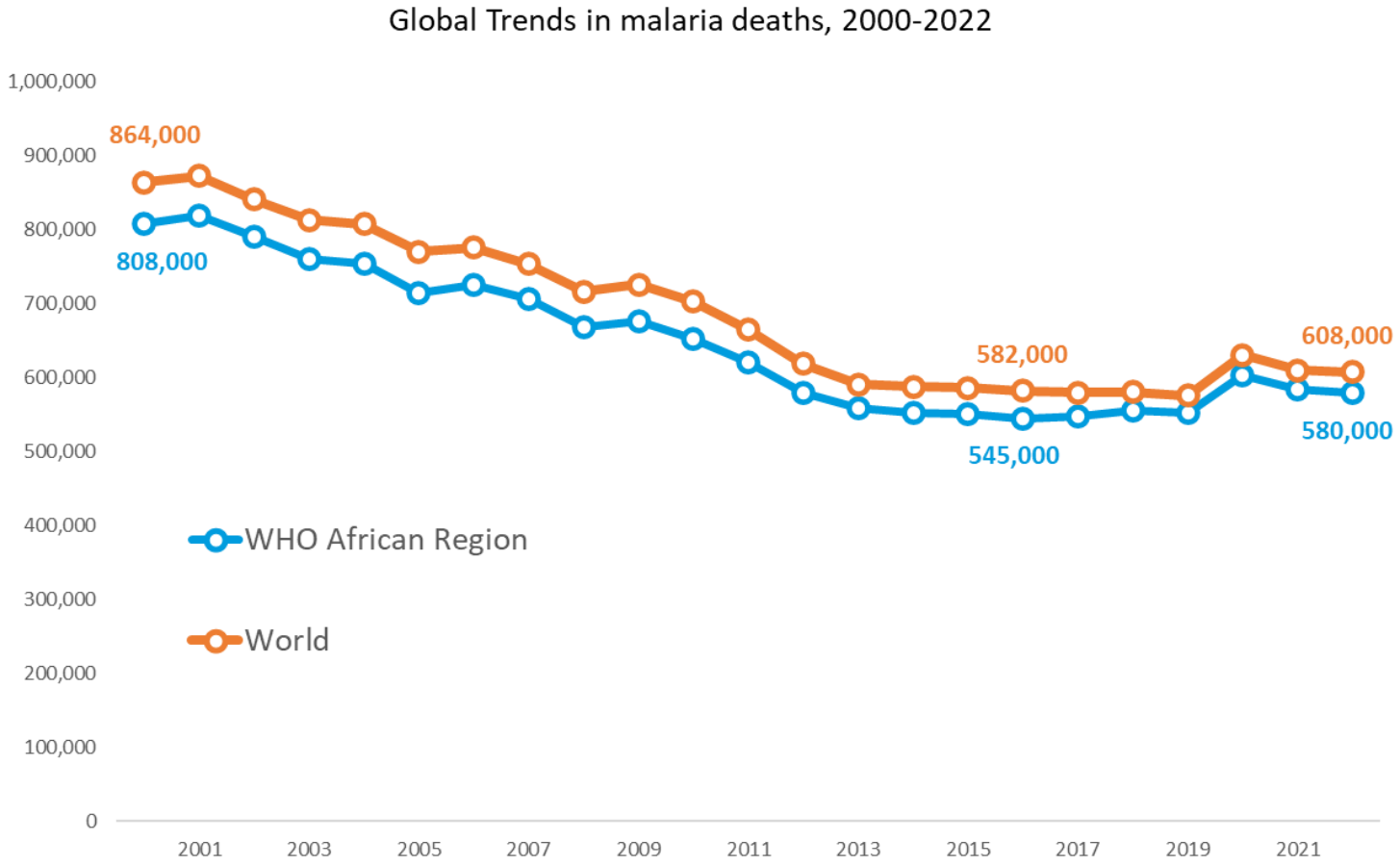


Case study Malaria vaccines

World Health Organization

Credit: WHO/M.Nieuwenhof

Although a preventable and curable illness, malaria continues to be a major cause of child morbidity and mortality



Global (2022)

- 249 million cases
- 640,000 deaths

Highest Burden in Africa

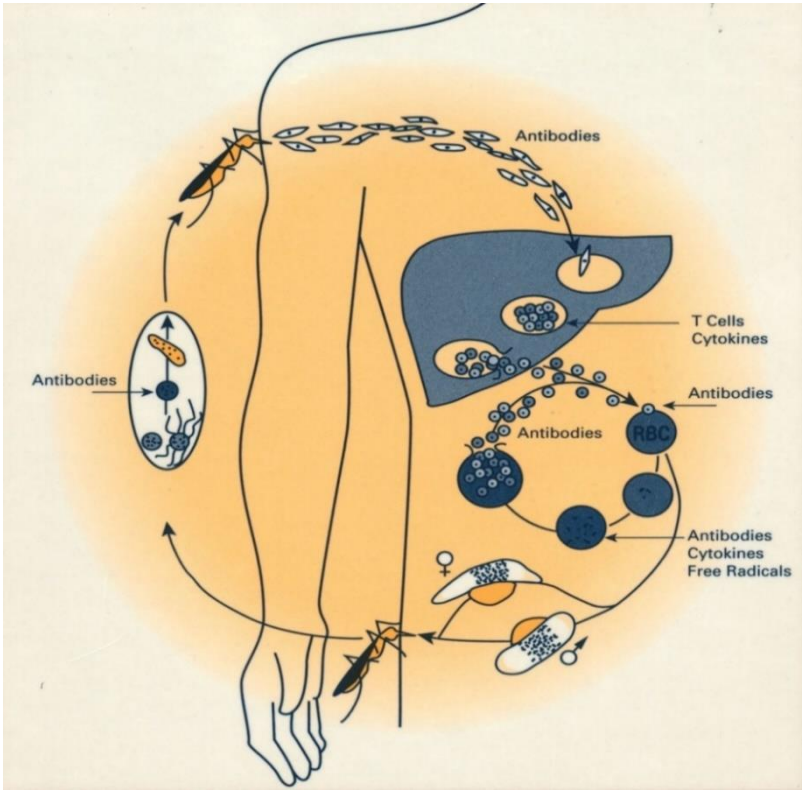
- 233 million cases
- 580,000 deaths
- ~95% of deaths are in African children
- **Progress has stalled**

World Health Organization

World Malaria Report 2022

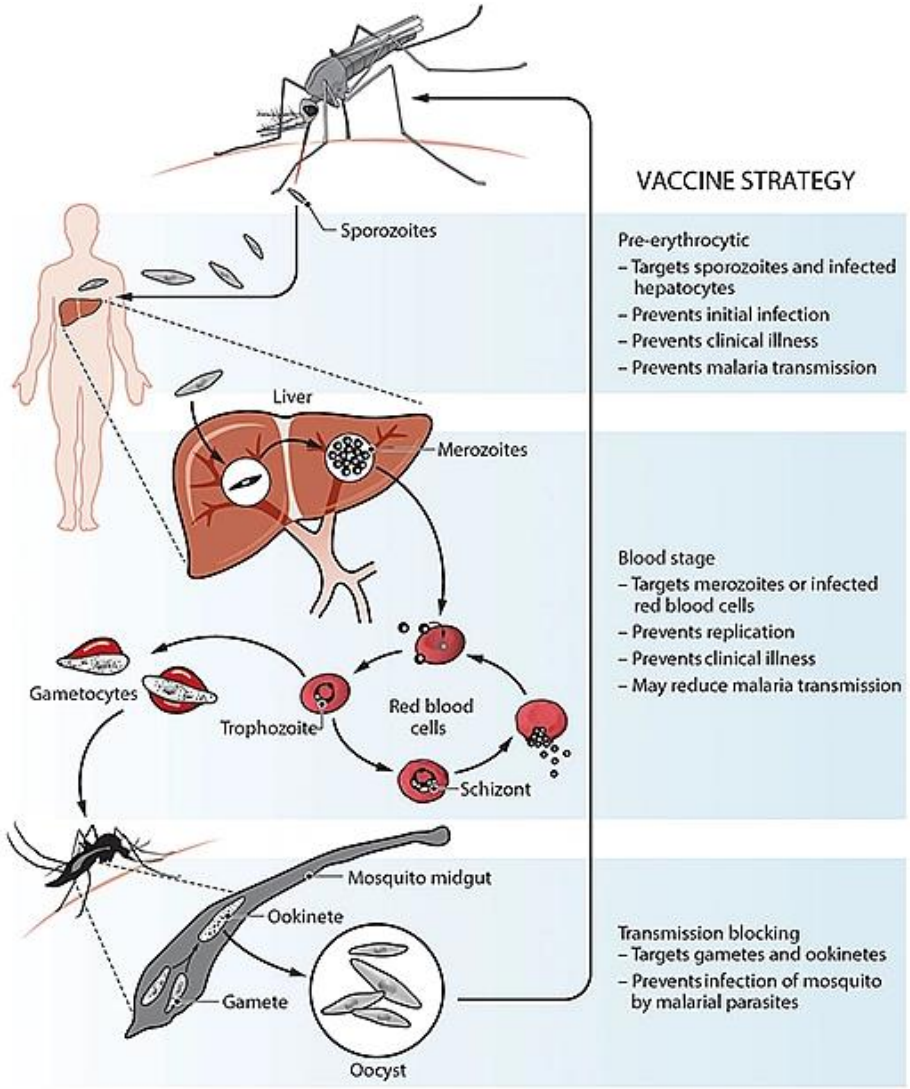
More than 60 years of research and development to bring the first malaria vaccine to African children

- Complex parasite with over 5000 genes
  - large proportion devoted to immune evasion
  - In nature, the malaria parasite efficiently establishes repeated new and chronic clinical and sub-clinical infections
  - Multiple parasite stages; multiple strains
  - Multiple antigens, high antigenic variation
- Immune response
  - Acquired immunity is stage-specific and strain-specific (with cross-reactivity)
- Vaccine development challenges
  - No validated correlate of protection
  - Human challenge model, important addition
    - Variable correlation with field efficacy
  - Costly clinical development pathway with little incentive to manufacturers (lack of high-income market)



Malaria vaccine targets and strategies

Combination vaccines may be key, and may provide synergy



Recommended vaccines:
RTS,S/AS01 and R21/MatrixM

Most advanced candidate:
RH5 completed Ph 2

Most advanced candidate:
PfS230 in Ph 2

The development pathway of the first malaria vaccine, RTS,S/AS01, and the Malaria Vaccine Implementation Programme (MVIP)

World Health Organization

• Credit: WHO/M.Nieuwenhof

The RTS,S/AS01 malaria vaccine: 30+ years of development

2015
EMA positive scientific opinion granted

2016
WHO recommendation for pilot implementation: ***feasibility of delivery, safety, impact***

Oct 2021
WHO recommends broad use

Dec 2021
Gavi Board decision to fund malaria vaccine roll-out

2022
Gavi IRC reviews and approves first applications

Oct 2023
WHO recommends R21/Matrix-M

Discovery | Pre-clinical | Phase 1 | Phase 2 | Phase 3 | **Malaria Vaccine Implementation Programme 2017-2023** | Vaccine introduction planning and roll-out

1984
GSK team established to find a malaria vaccine

1987
WRAIR & GSK Candidate vaccine with immune response

1995
First clinical trials in adults begin in US, followed by trials in adults in Africa

2004
Proof of concept demonstrated in African children, then in infants

2009
Phase 3 trial in 11 sites in 7 African countries

2015
Phase 3 final results published

2019
National Regulatory Approval; Vaccine launch in routine programme in Ghana, Kenya, Malawi

2021
Pilot evaluations 24-month analysis on safety and impact

2023
Pilot evaluations 46-month analysis on safety, feasibility, impact; many lessons learned

2024
First countries outside of pilot areas have introduced vaccine

VE = 31.3%
(97.5% CI, 23.6 to 38.3) clinical malaria

Summary results from the MVIP evaluation, 46 months of vaccine scale-up through routine immunization system, 2019 - 2023

- **High uptake and high impact*:**

→ **13% vaccine-attributable reduction in all-cause mortality** excluding injury [0.87 (95% CI: 0.78, 0.98)]

- Demonstrates the magnitude of the contribution of malaria to mortality in children

→ **22% reduction** in hospitalized severe malaria [0.78 (95%CI: 0.64, 0.96)]

- **Impact measured during scale up when ~70% had received 3 doses, and ~40% had received 4 doses**
- Vaccine confirmed to be safe
- No reduction in ITN use, care-seeking behavior, uptake of other vaccines
- Equitable; extends reach of malaria preventive tools

World Health Organization

*Statistical Analysis Report available: Immunization, Vaccines and Biologicals (who.int)

Malaria Vaccine Implementation Programme 2019-2023:
> 2 million children vaccinated with RTS,S
> 6 million doses administered

Funded by Gavi, Global Fund, Unitaid

WHO recommendation for malaria vaccines in 2021, updated 2023

WHO recommends the use of malaria vaccines for the prevention of *P. falciparum* malaria in children living in malaria endemic areas, prioritizing areas of moderate and high transmission

- The malaria vaccine should be provided in a schedule of **4 doses** in children from around 5 months of age
- Primarily in areas of seasonal transmission: a **5 dose** schedule can be used to optimize impact
- Vaccine introduction should be considered in the context of comprehensive national malaria control plans

As of October 2023, WHO recommendation now includes two malaria vaccines:

- **RTS,S/AS01**
- **R21/Matrix-M**

World Health Organization

[1] Vaccination programmes may choose to give the first dose at a later or earlier age, based on operational consideration.

Summary of modelling work

MRC Centre for Global Infectious Disease Analysis

Imperial College London

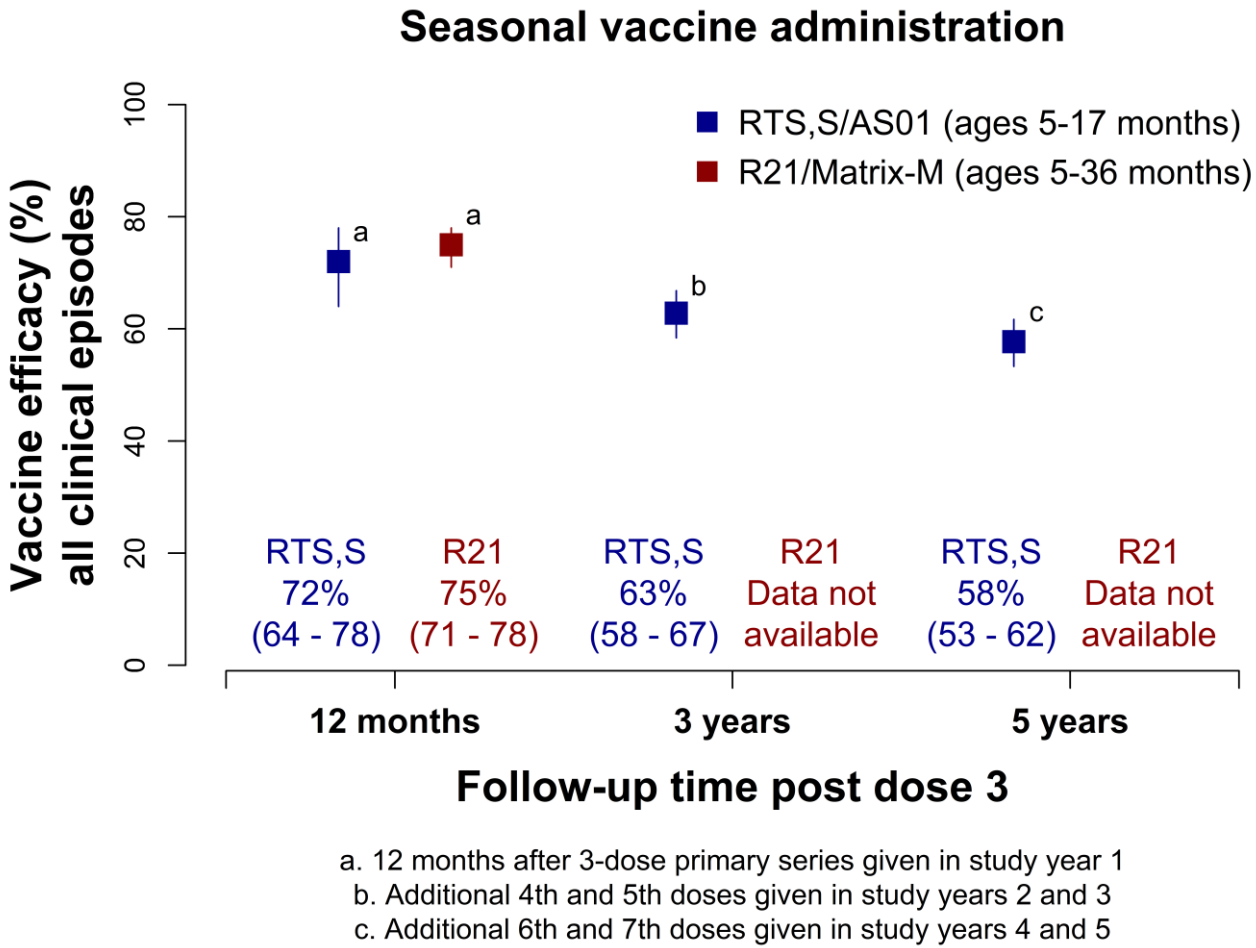
- Modelling predictions indicate a significant public health impact across a wide range of settings, including lower transmission areas.

- Cost-effectiveness estimates are comparable with other malaria interventions and other childhood vaccines and are additional to the impact of other widely deployed control measures.

- Future work will refine model estimates, including using additional follow up data.

Optimizing vaccine efficacy with strategic seasonal vaccination in areas of highly seasonal transmission

- Both vaccines have waning VE, with highest VE in first 6 months after delivery
- Age-based delivery RTS,S and R21 provide moderate vaccine efficacy
  - RTS,S VE = 50% against clinical malaria
    R21 VE = 66% against clinical malaria
- By strategically administering vaccine just just prior to malaria season, increase VE
- VE with seasonal delivery in areas of highly seasonal malaria transmission
  - R21 VE = 75% (95% CI 71 - 78)
  - RTS,S VE = 72% (95% CI 64 - 78)



a. 12 months after 3-dose primary series given in study year 1
b. Additional 4th and 5th doses given in study years 2 and 3
c. Additional 6th and 7th doses given in study years 4 and 5

World Health Organization

1. Chandramohan N Engl J Med 2021: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2026330?articleTools=true
2. R21 Phase 3 results from R21 Full Evidence Report: https://terrance.who.int/mediacentre/data/sage/SAGE_eYB_Sept2023.pdf
3. Dicko Lancet 2023: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00368-7/fulltext

Highest impact achieved when mix of malaria interventions used together

- Case management
- Vector control (ITNs, IRS, LSM)
- Chemoprevention (SMC, IPTp, PMC, MDA)
- Vaccines (RTS,S, R21)

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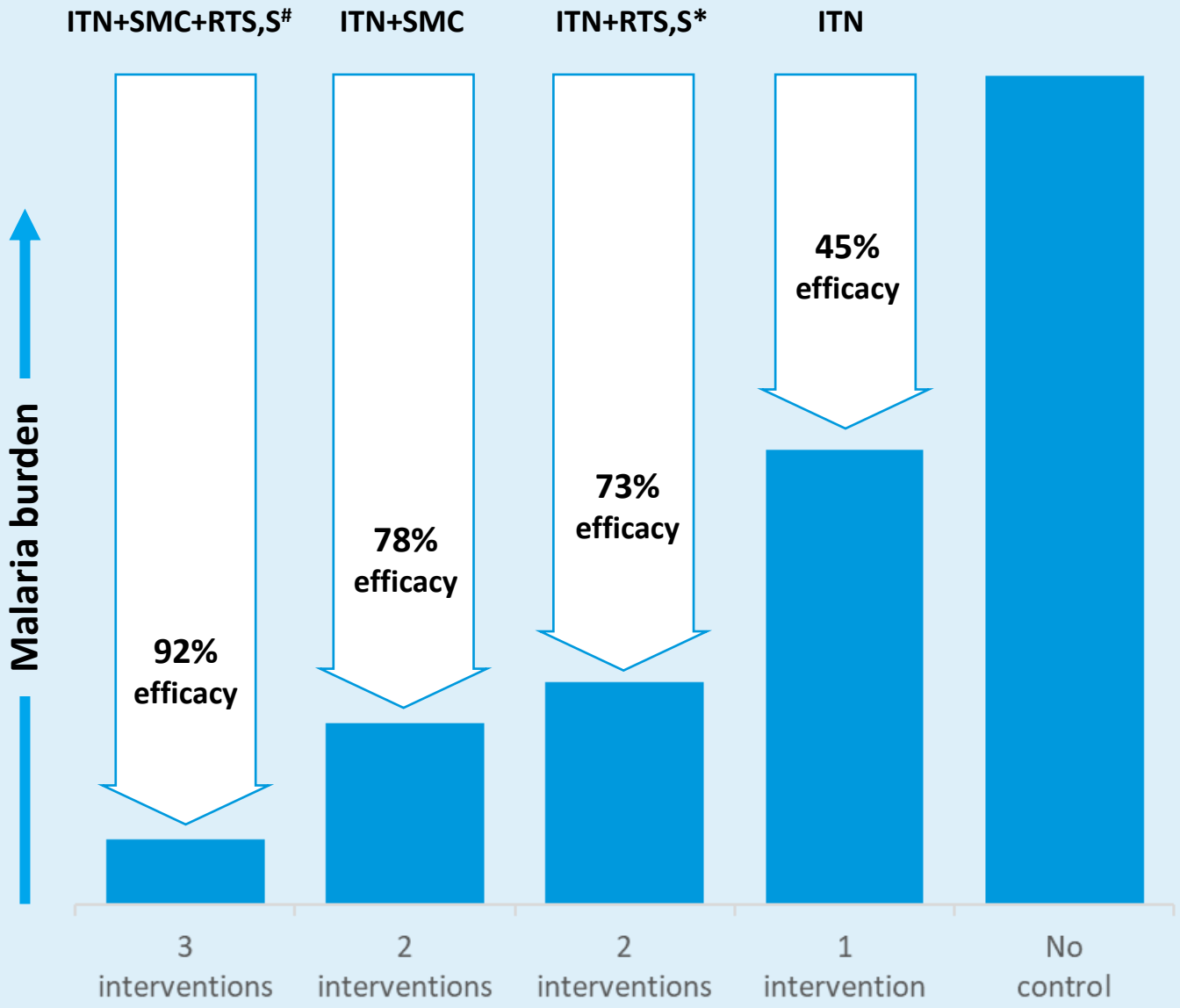
Potential impact in areas of highly seasonal transmission

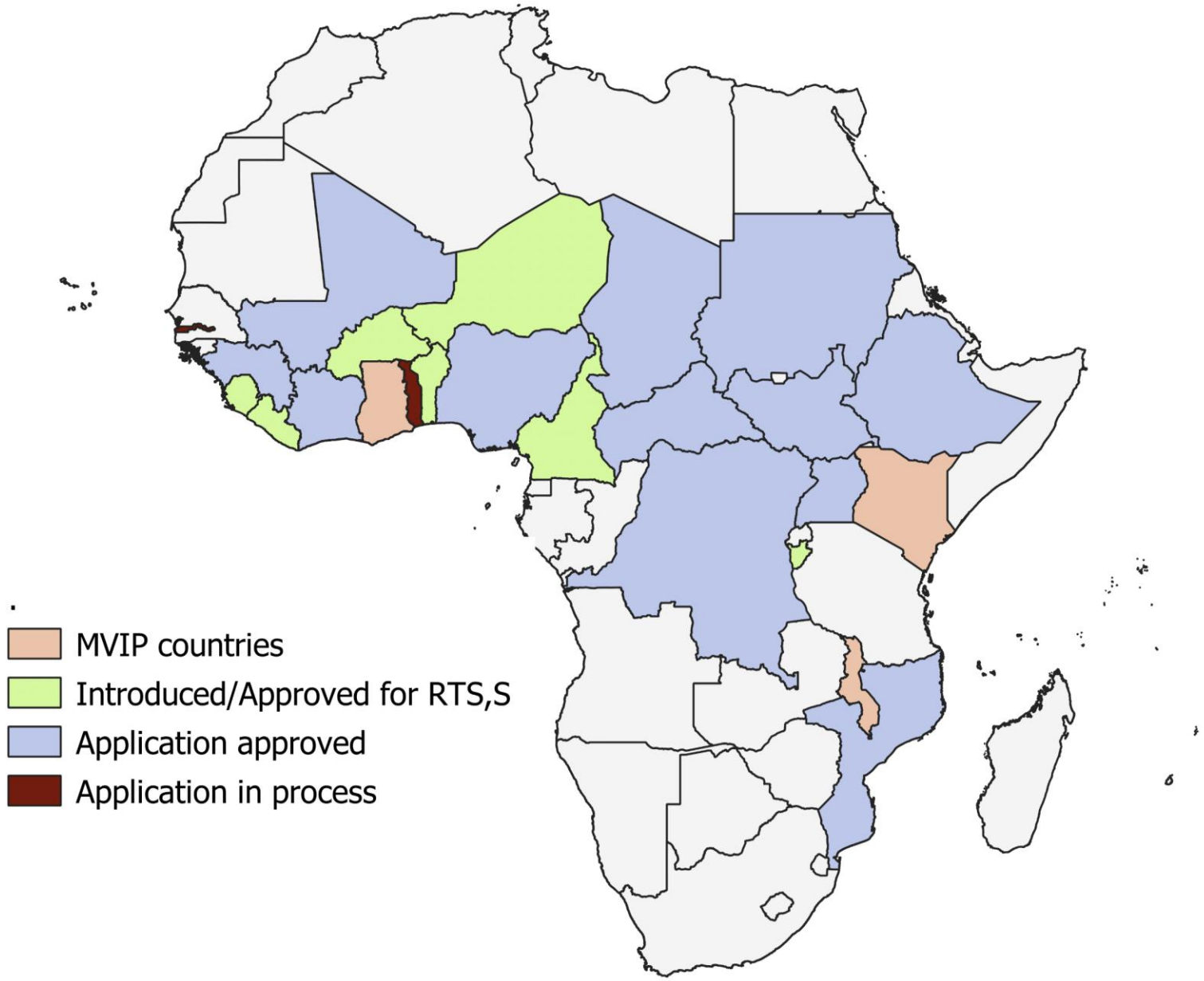


Source:Professor Paul Milligan, LSHTM

seasonal vaccination, over 3 years
*assumes seasonal vaccination equivalent to efficacy of 4 SMC cycles

Malaria Vaccine Introduction Unprecedented demand

- **22 Countries approved** by Gavi to receive support for malaria vaccine introduction
- **First introductions outside of pilot Jan 2024**
- **As of mid-May 2024: 8 Countries implementing RTS,S/AS01 malaria vaccine sub-nationally:**
  - Benin, Burkina Faso, Cameroon, Ghana, Kenya, Malawi, Liberia, Sierra Leone
- More introductions and applications expected this year



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Summary

1. The complexity of the malaria parasite, immune evasion strategies, lack of a correlate of protection complicate development of malaria vaccines
2. Malaria Vaccine Pilot Implementations have shown that the RTS,S/AS01 vaccine is safe, feasible to deliver, and has important impact even in the setting of good coverage with other malaria control tools, and established a policy pathway for subsequent malaria vaccines
3. The pilots resulted in rich learning, support from global financing bodies, but delayed wide introductions and resulted in challenges in manufacturing, supply
4. At a time when progress in malaria control has stalled, the malaria vaccine will play an important role, and can help change the trajectory of malaria illness and deaths

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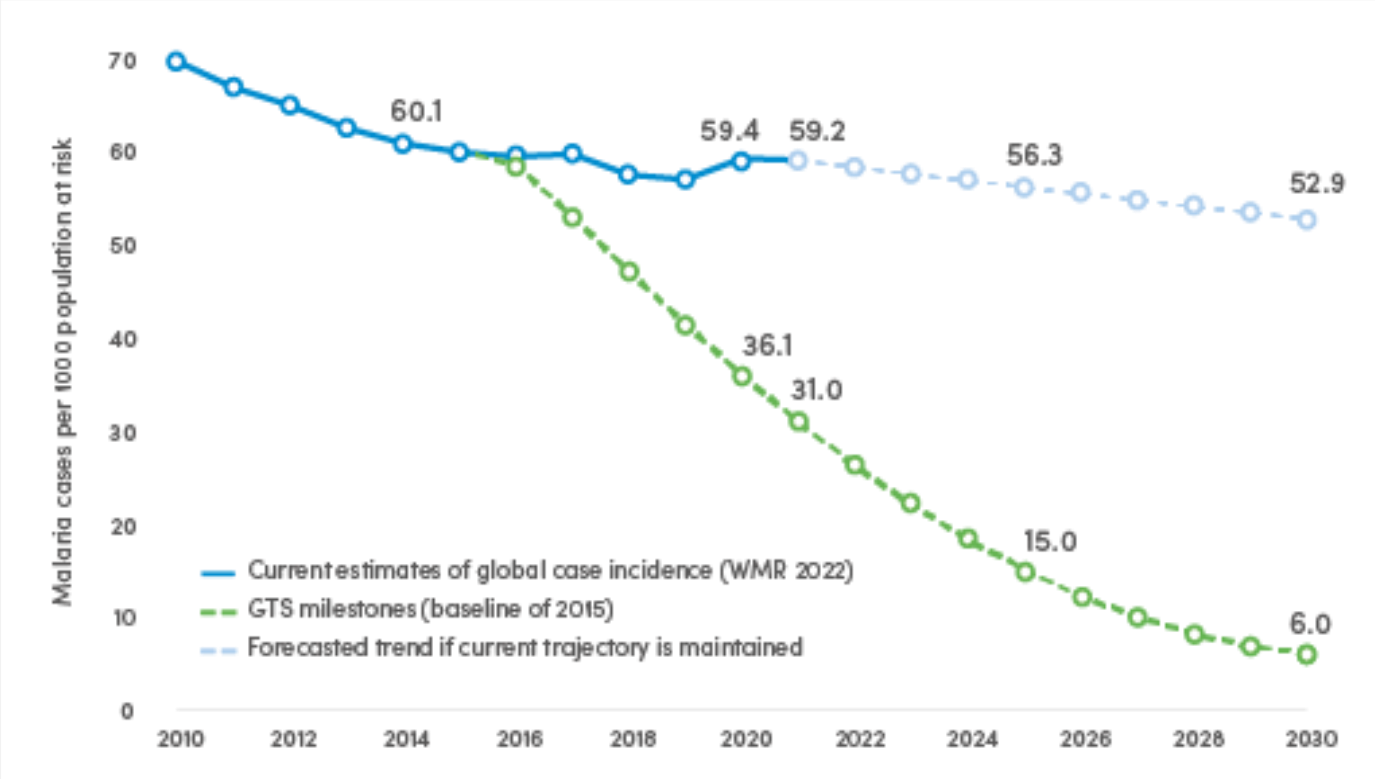
Global malaria case incidence (and mortality) are off track to achieve the targets in the Global Technical Strategy for Malaria (GTS)



- In 2021, off track by 48%
- Vaccines essential part of malaria preventive measures to reduce cases and death and achieve the GTS targets
- Need to scale up existing and new vaccines once recommended

Effective malaria interventions are available

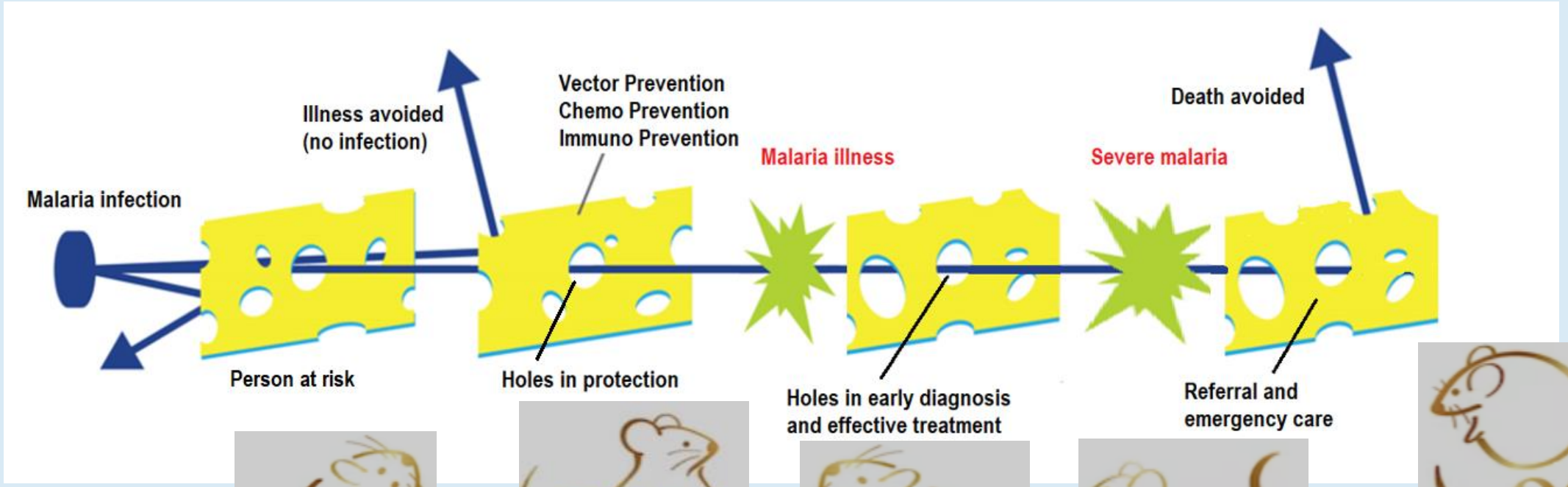
- Vector control
- Chemoprophylaxis
- Malaria vaccines

- Diagnosis & treatment of uncomplicated malaria
- Referral
- Hospital-based management of severe malaria

- Intermittent preventive therapy in pregnant women, infants, school-children
- Seasonal malaria chemoprevention
- Post-discharge malaria chemoprevention

Slide provided by Dr. Andrea Bosman, WHO

All malaria interventions are partially effective: Swiss model of hazard mitigation for malaria



Limited resources

Poverty

Education

Gender

Weak health systems

… many other

Slide provided by Dr. Andrea Bosman, WHO

Literature

- Gessner BE, Feikin DR. Vaccine preventable disease incidence as a complement to vaccine efficacy for setting vaccine policy. Vaccine 2014;32:3133-3138.

Thank you !

Thank you to ADVAC lecturers Brad Gessner, Annelies Wilder-Smith, Mary Hamel

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6.6.2024

Example from SARS-CoV-2 vaccines

2022 May;27(2):300-319.
doi: 10.1111/bjhp.12546. Epub 2021 Jul 11.

Efficacy information influences intention to take COVID-19 vaccine

Colin J Davis[1], Matt Golding[2], Ryan McKay[3]

PLoS One. 2022; 17(5): e0267840.
Published online 2022 May 12. doi: 10.1371/journal.pone.0267840
PMCID: PMC9097986
PMID: 35552553

Efficacy versus abundancy: Comparing vaccination schemes

Omar El Deeb, Conceptualization, Formal analysis, Methodology, Writing – original draftcorresponding author# 1 , 2 ,* and Maya Jalloul, Conceptualization, Formal analysis, Methodology, Writing – review & editing# 3