



Malaria Landscape: Update on Research and Product Development

Chris Hentschel

13th RBM Partnership Board Meeting
November 2007, Addis Ababa, Ethiopia

Curing Malaria Together www.mmv.org



Medicines for Malaria Venture

Two parts:



- Short-term; RBM Board guidance sought:
 - The case of Coartem[®] Dispersible – a major potential change to the ACT landscape
- Long-term; for information only:
 - The R&D pipeline is healthier than ever and realising its potential will be crucial for our long-term elimination/eradication goals
- Conclusions

I. Background

Current Standard of Care



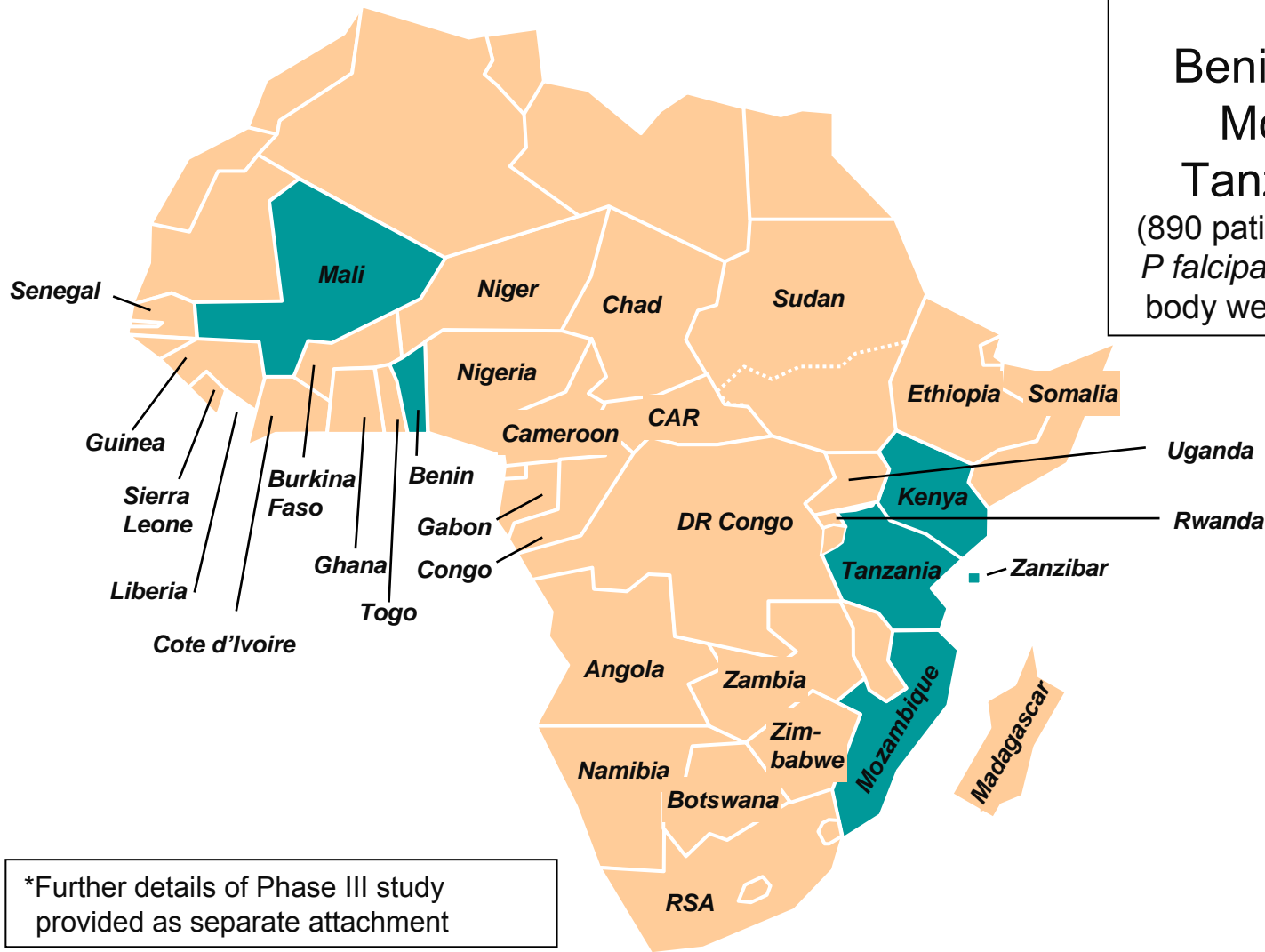
Currently Coartem[®] tablets are being crushed for infants and small children, which could lead to:

- Inaccurate dosing – danger of under dosing
- Bitter taste
- Difficulty in administration
- Less than optimal compliance



In 2004, MMV & Novartis partnered to develop a pediatric formulation of Coartem[®] - a 'line extension' product

Participating countries in Phase III Study



*Further details of Phase III study provided as separate attachment

II. Summary of Results

Coartem® Dispersible – specifically designed for children



- Phase III results confirm >97% parasitological cure rate, with similar safety to standard crushed tablet formulation
- Suitable for infants and children
- Sweetened cherry flavor preferred and adopted
- Rapidly dispersible in water/liquid
- Dossier review by Swissmedic imminent

Dispersible tablet administration



Summary data set available as PDF file



2260 Efficacy and Safety of a New Dispersible Tablet Formulation of Artemether-Lumefantrine in Pediatric Patients with Acute Uncomplicated *Plasmodium Falciparum* Malaria – Randomized, Investigator-Blinded, Multicenter Comparison with the Crushed Tablet

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⁶Malaria Branch, Center for Disease Control and Prevention/Kenya Medical Research Institute, Kisumu, Kenya; ⁷Walter Reed Project/Kenya Medical Research Institute, Kisumu, Kenya; ⁸Zanzibar Malaria Research Unit of the Karolinska Institute, Tanzania; ⁹Novartis, Basel, Switzerland & East Hanover, USA; ¹⁰Medicines for Malaria Venture, Geneva, Switzerland

Introduction

- A high adherence to the 6-dose regimen of artemether-lumefantrine (A-L) has been reported irrespective of whether given under supervision or under unsupervised conditions of routine clinic practice in Africa.^{1,2}
- Nevertheless, young children may not be able to swallow whole tablets and the crushed tablet (CT) may be expelled because of the bitter taste of A-L. In addition, crushing the tablet might be a cumbersome procedure.
- A sweetened cherry-flavored A-L dispersible tablet (DT) formulation has been developed to make administration to pediatric patients more convenient.
- We evaluated the efficacy and safety, and pharmacokinetics of DT in African infants and children with *P. falciparum* malaria.

Objectives

Primary objective:

- To demonstrate non-inferiority based on PCR-corrected 28-day cure rates (using a margin of -5%) of a DT 6-dose regimen vs. the 6-dose regimen of CT at standard dosages.

Key secondary / exploratory objectives:

- To compare 42-day PCR-corrected parasitological cure rates, time to fever clearance (FCT) and time to parasite clearance (PCT) between treatments.
- To compare the safety and tolerability profiles (including QTc) of DT and CT.
- To investigate drug plasma concentrations with the aim to assess potential relationships between A-L exposure and safety and/or efficacy variables.

Methods

Design:

- Randomized (1:1), investigator-blinded, multicenter, parallel-group 42-day study in children with uncomplicated *P. falciparum* malaria from Benin, Kenya, Mali, Mozambique, and Tanzania/Zanzibar.
- Children (≤ 12 years) were stratified into 3 different dosing groups and received DT or CT for 3 days according to body weight:

Figure 2. PCR-corrected 28-day cure rate by body weight group

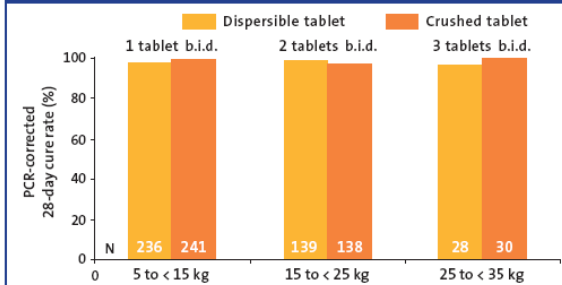


Figure 3. Mean \pm SD lumefantrine plasma concentration-time profiles in pediatric patients treated with crushed or dispersible artemether-lumefantrine tablets (body weight groups pooled)

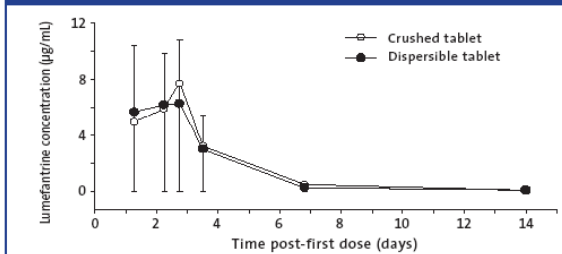


Table 1. PCR-corrected 28-day cure rate by analysis population

Population	Dispersible tablet	Crushed tablet
Primary analysis		
% patients cured (n/N)	97.8% (394/403)	98.5% (403/409)
95% CI	96.3 - 99.2	97.4 - 99.7
ITT*		
% patients cured (n/N)	95.0% (397/418)	96.2% (407/423)
95% CI	92.9 - 97.1	94.4 - 98.0
Per protocol		
% patients cured (n/N)	98.7% (391/396)	98.5% (400/406)

Results

- 899 patients were randomized (447 to DT and 452 to CT) and >85% in each group completed the study (Figure 1); 3.7% withdrew during the 3-day treatment period (DT, 3.6%; CT, 3.8%).
- 812 (90.3%) patients qualified for primary analysis (DT, 90.2%; CT, 90.5%); main reason for exclusion was a missing day 28 parasite count without being a treatment failure before that day (DT, 7.6%; CT, 7.5%).
- Both treatment groups were comparable in terms of baseline demographic and clinical characteristics. The majority of patients were < 6 years old.

Efficacy:

- PCR-corrected 28-day cure rates were high and comparable between treatment groups for the primary analysis population (Table 1).
- The results for the ITT and PP population were supportive for claiming non-inferiority of DT to CT (Table 1).
- The lower bound of the 1-sided 97.5% CI was -2.7% and thus greater than the prespecified non-inferiority limit of -5%.
- Corrected 28-cure rates were generally comparable between body weight groups for both DT and CT (Figure 2).
- Uncorrected 28-day cure rates were 92.1% in the DT and 90.5% in the CT group (primary analysis population).
- Corrected 42-day cure rates considering patients with unclear or missing PCR results as recrudescence were high in both groups (Table 2).
- Median FCT (DT, 7.9 h; CT, 7.8 h) and median PCT (DT, 34.3 h; CT, 34.9 h) were similar between groups (95% CIs overlapped).

Safety and tolerability:

- Tolerability was good in both treatment groups, with no difference in the overall incidence of adverse events (AEs). Most common AEs were related to malaria (Table 3).
- The most frequent drug-related AE was vomiting (DT, 7.4%; CT, 9.3%) but only a fraction of those switched to rescue medication due to vomiting of study medication (DT, 1.3%; CT, 2.4%).
- No signs of clinically relevant neurotoxicity were observed during the study; no hearing loss was reported.
- SAEs were experienced by 1.6% and 1.3% of patients in the DT and CT group, respectively, the majority were infections.
- There were 3 deaths during the trial (DT, 2; CT, 1) unrelated to study drug.

Current situation



- We (the Novartis-MMV Coartem[®] D Steering Committee) are currently evaluating options for switching between standard and dispersible tablets in the public market; namely a complete switch for all weight categories up to 35Kg versus a switch for smallest infants and children
- Fewer dosage forms allow economies of scale and other potential benefits

III. & IV. Requested Board Action and Next Steps



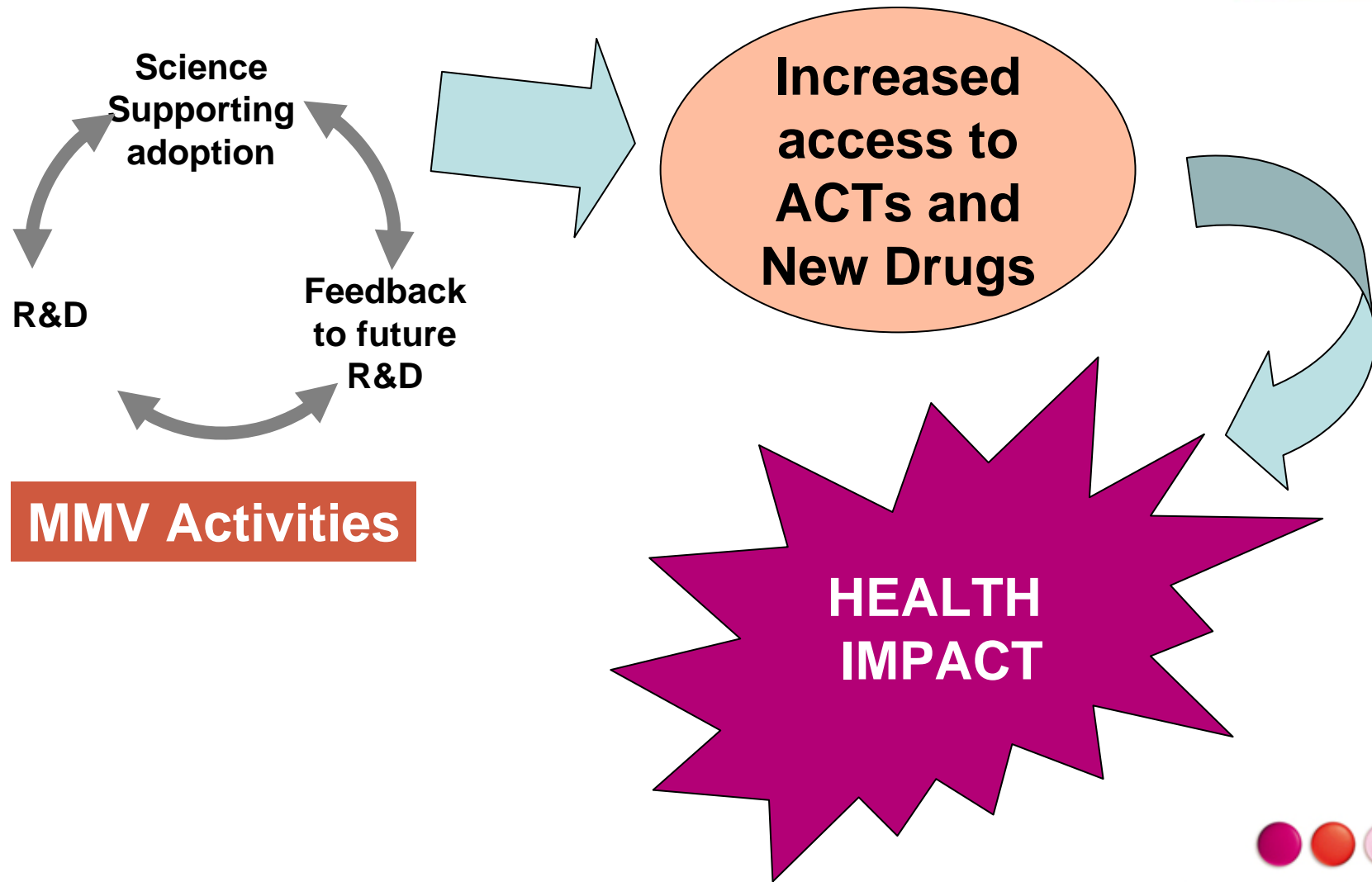
- RBM guidance sought on standard vs. dispersible tablet switch options as we prepare and finalise our plans
- MMV will provide final switch plan, incorporating feedback, by next RBM Board meeting in May 2008

V. Contacts for clarification of this document or discussion of these issues or proposals

Dr Chris Hentschel

VI. Attachment Coartem Dispersible Phase III Study ASTMH 2007 Poster

Need to close the cycle

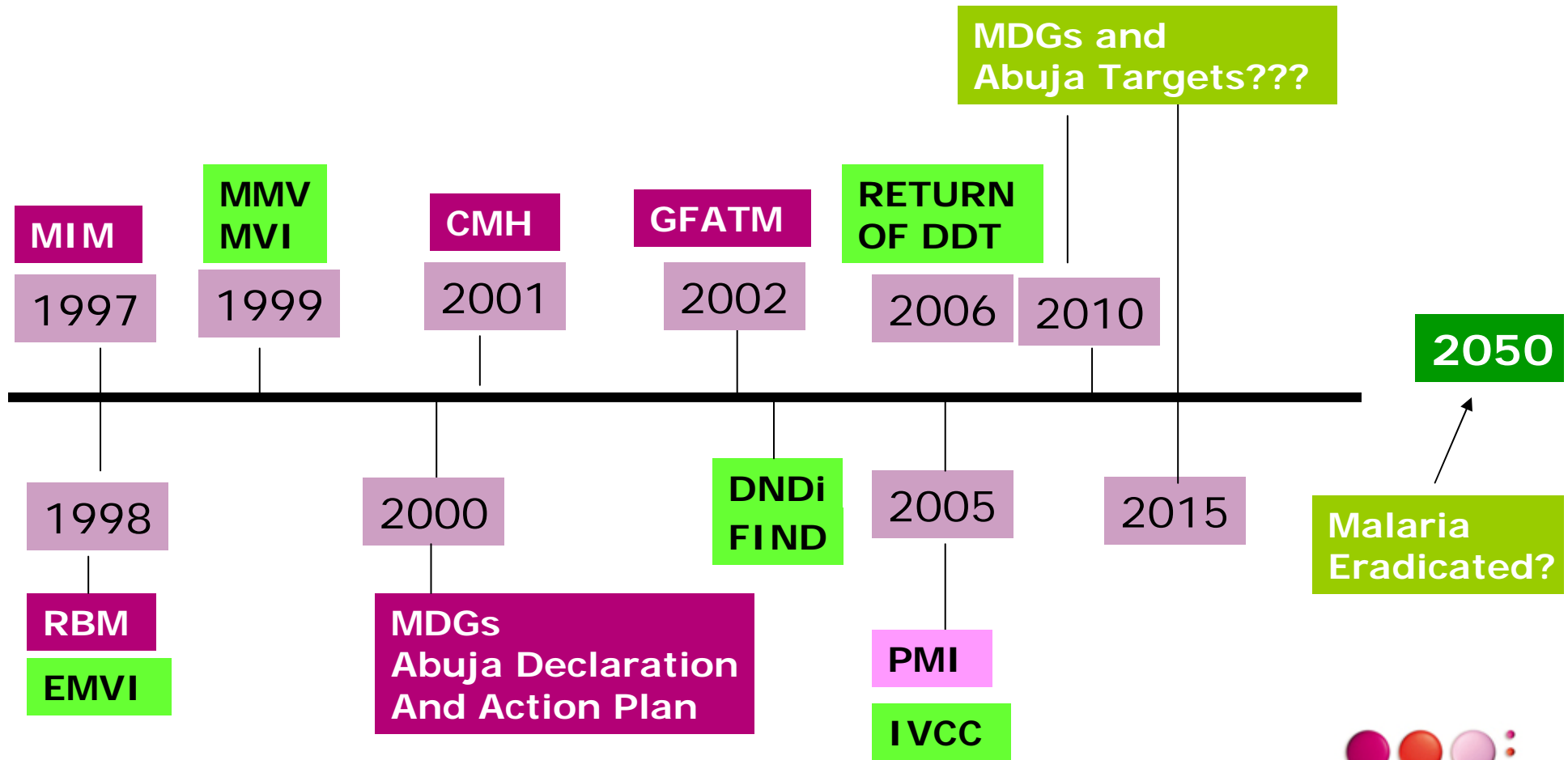


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Modern R&D era started around 2000



Modern eradication era started around 2000 with 2007 as the 'tipping point'



Gates Fights To Eradicate Malaria

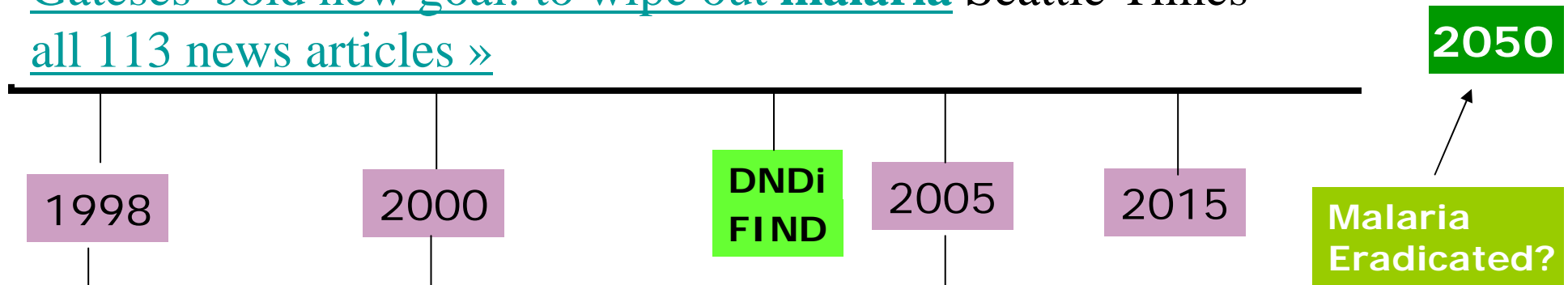
Forbes, NY - 20 hours ago

Edlund said **malaria eradication** is a critical first step towards making the African economy productive. "Ten dollars buys a bed net, delivers it to Africa, ...

Gates Foundation Looks to Fight Malaria The Associated Press

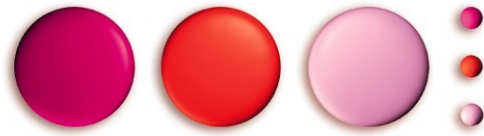
Gateses' bold new goal: to wipe out malaria Seattle Times

[all 113 news articles »](#)



"I dare you to come along with us," said Dr. Margaret Chan, head of the WHO, speaking at a malaria conference organized by the Bill & Melinda Gates Foundation.

PDPs positioned as part of the solution



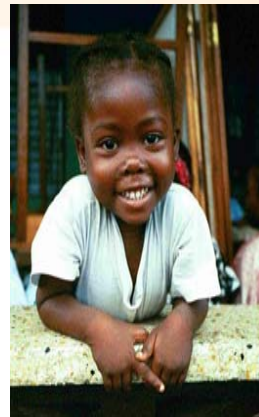
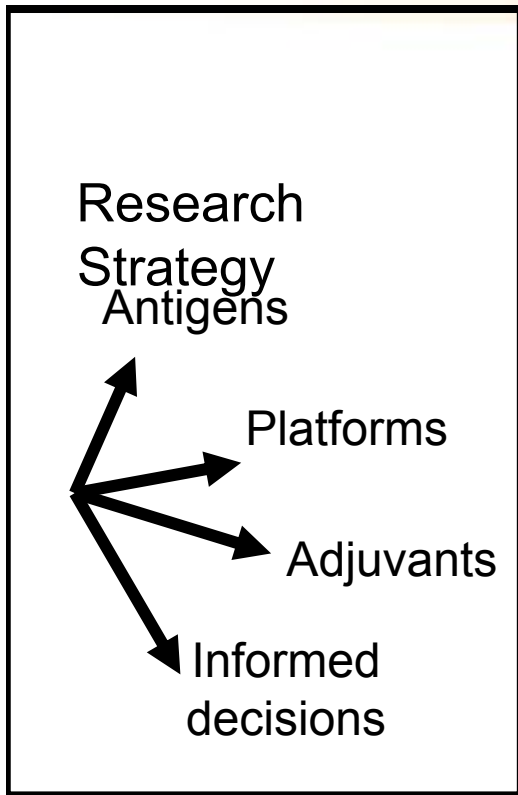
Medicines for Malaria Venture



PATH Malaria Vaccines Initiative



To accelerate the development of promising vaccine candidates and ensure their availability and accessibility in developing countries



RTS,S
GSK, Manhica, Phase 3,
10 sites, 7 countries

Portfolio
8 vaccine candidates

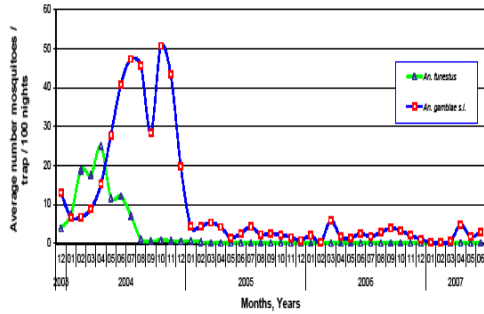
Decision-making framework
Regulatory pathways
Manufacturing
Communities
Resources

Recombinant proteins
Adenovector

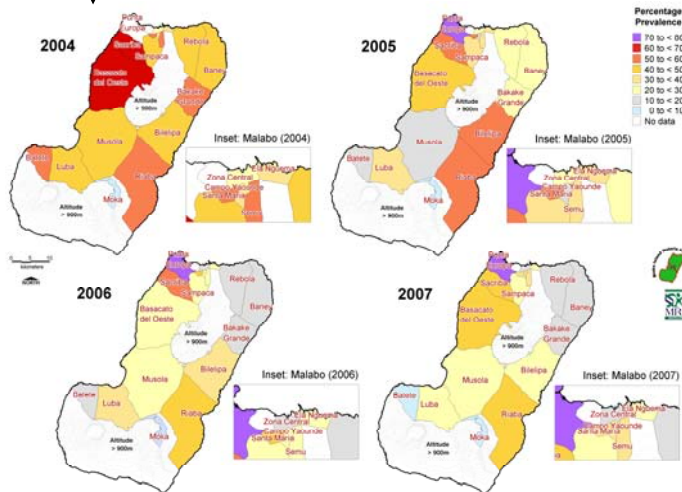
Sanaria
Live attenuated sporozoites
Process development



Innovative Vector Control Consortium



IVCC
COMBATING INSECT BORNE DISEASE
 The Innovative Vector Control Consortium



FIND's goal: provide an efficient malaria diagnostic tool for each level of health.

Malaria diagnostic tool for field use.

Way to succeed: Improve malaria RDTs's quality :

-Assess the RDTs on the market with references materials : conduct a standard testing

-Improve thermostability of RDTs: better sensitivity and sensibility on field.

-Provide quality control tool for RDTs: regain user self-confidence.

Develop a molecular tool easier and faster than PCR.

Medicines for Malaria Venture



- **Mission:** Discover Develop & Deliver safe, effective and affordable antimalarials
- **Operating model:** effective partnership; portfolio management, high standard development, quality product and global reach
- **Achievement:** Pipeline of over 30 projects ranging from discovery stage to Phase III and beyond
- **Vision:** public health impact with new antimalarials



Working in Partnership – a few figures



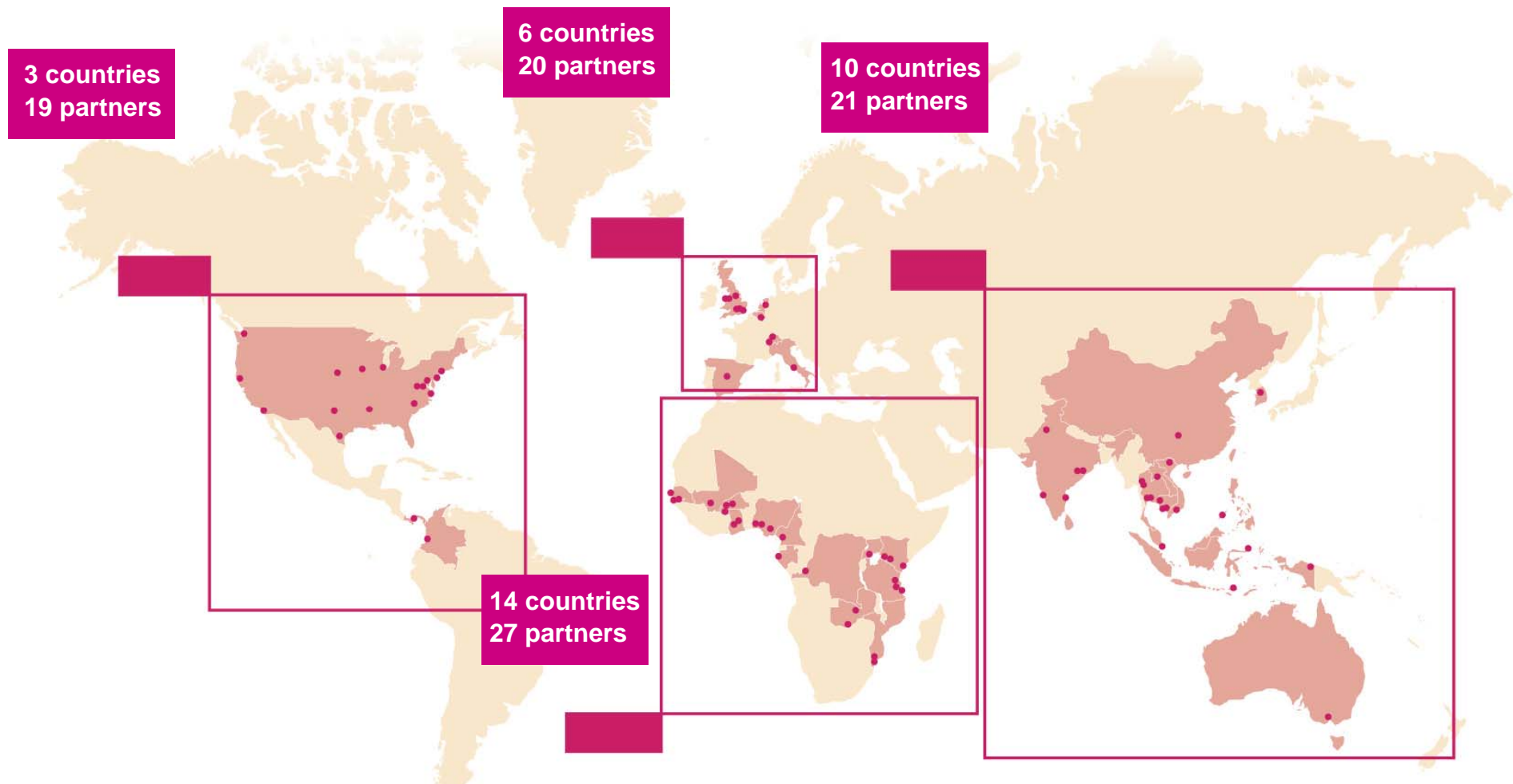
- Over 80 academic, industry and endemic country partners
- More than 600 scientists, clinicians, public health experts working on the MMV pipeline and access & delivery projects
- Activities in 33 countries (Bilingual English/French)
- 7 Pharma partners/Biotec
- 28 Universities/Public Research Institutes
- 25 CROs
- 24 clinical Trial Sites
- All operating under 160 active contracts
- About 20 high-value new classes of drugs in discovery



MMV works with partners in 33 countries



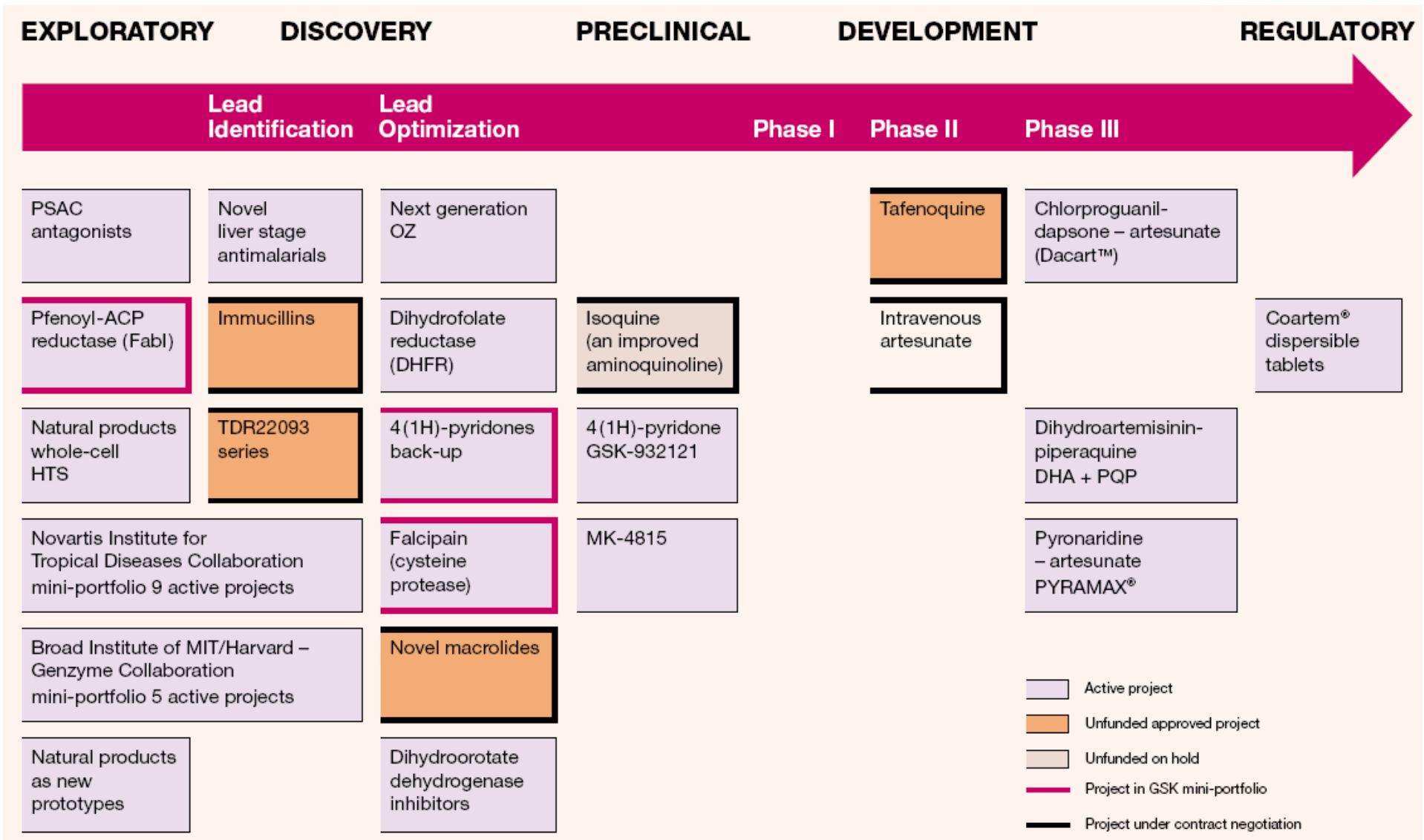
- Over 80 academic, industry and endemic country partners
- More than 600 scientists, clinicians, public health experts



MMV has a strong antimalarial portfolio



MMV's Project Portfolio 2007



Coartem® Dispersible



	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Pedatric Coartem	Filing		Registration				Launch					

- Partenaire: Novartis (artéméther 20/luméfántrine 120)
- Principal avantage: nouvelle formulation pédiatrique, comprimés se dissolvant facilement avec goût masqué (cerise)
- Etude de phase III de non-infériorité vs comprimés classiques écrasés (890 enfants) terminée en février 2007
- Enregistrement auprès de SwissMedic: Dossier soumis au 4ème trimestre 2007. Enregistrement et lancement attendu au cours du 2ème semestre 2008



Dihydroartemisinin–Piperaquine



	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
DHA Piperaquine	III				Filing	Reg.			Launch			

- Partenaires: Sigma-Tau, Holley, Université d'Oxford
- Avantages principaux: prix peu élevé, très bonne tolérance
- Efficacité de Pipéraquline bien évaluée, Les comprimés chinois et vietnamiens ont été très utilisés en Asie du Sud-Est
- Bases de données pour les études de phase III gelées:
 - Enfants africains vs artéméther/luméfantrine
 - Adults et adolescents asiatiques vs artésunate/méfloquine
- Soumission du dossier prévue pour le 1er trimestre 2008, Enregistrements auprès de EMEA et FDA en tant que produit “orphelin”



Chloproguanil–Dapsone-Artesunate



	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
CDA	III				Filing		Reg.					

- Partenaires: GSK, WHO/TDR, Université de Liverpool
- Histoire: chlorproguanil-dapsone enregistré avec MHRA et dans 14 pays d'Afrique
- Avantage principal: CDA a une $\frac{1}{2}$ vie très courte (moins de résistance); moins cher que Coartem
- Etudes de phase III terminées vs artéméter-luméfantrine (1395) août 2007 et vs chlorproguanil-dapsone (900) mai 2007
- Soumission du dossier d'enregistrement à EMEA (article 058) et en Afrique au 1^{er} semestre 2008 avec enregistrement et lancement attendus en fin de 1^{er} semestre 2009



Pyronaridine–Artesunate

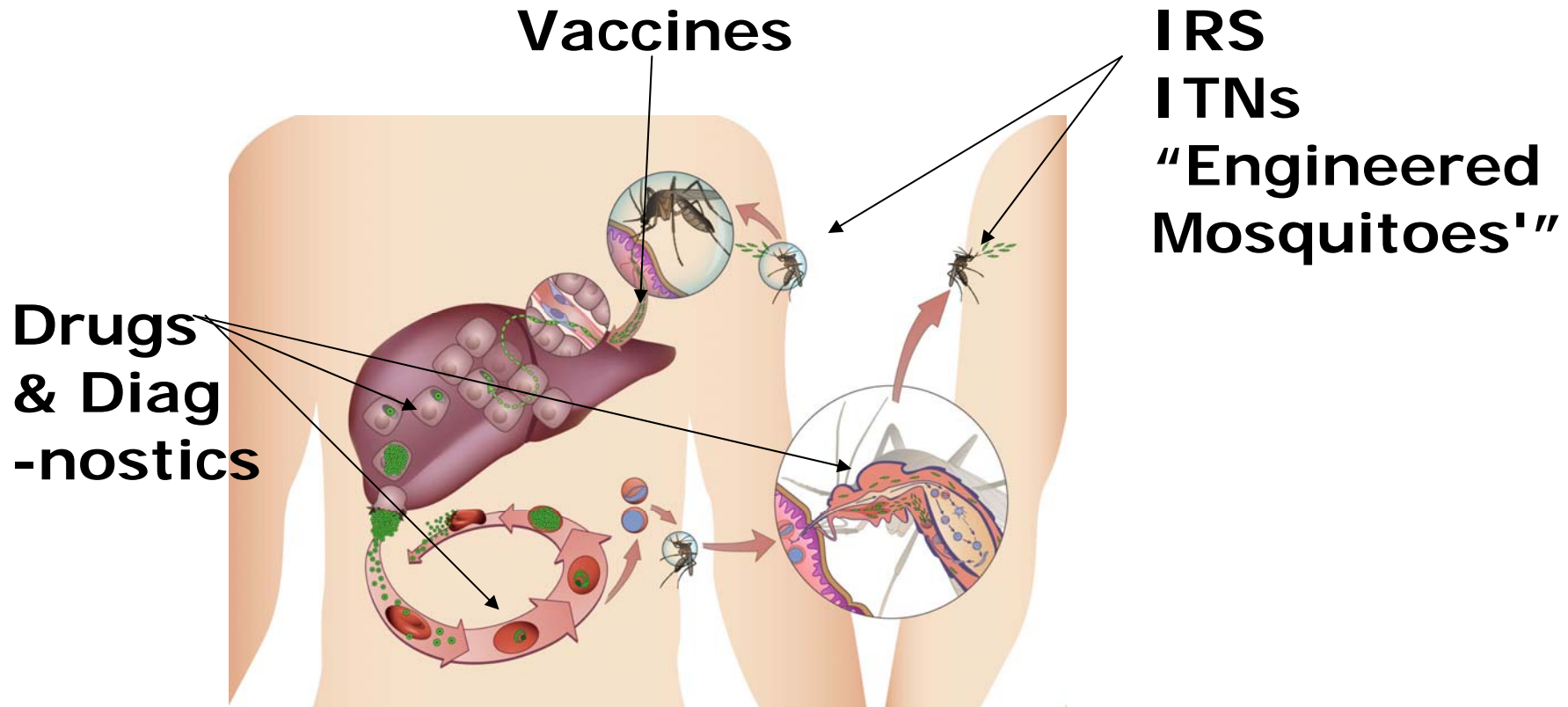


	2007				2008				2009			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Pyramax	III				Filing				Registration			

- Partenaires: Shin Poong, Université d'Iowa
- Avantage principal: pyronardine est un produit bien évalué en Chine dans les années 70 avec quelques études réalisés en Afrique.
- 4 études de Phase III devant se terminer en fin 2007
 - artésunate-méfloquine (*P. falciparum* - 1269),
 - artéméther-luméfántrine (*P. falciparum* - 1269)
 - chloroquine (*P. vivax* - 456)
 - pédiatrique (534)
- Enregistrement avec EMEA (article 058), la FDA de Corée du Sud et en Afrique au 4ème trimestre 2008



Integration of all innovative control strategies will be needed to achieve eradication



" $R_0 < 1$ then the disease goes extinct, whereas if $R_0 > 1$ then the disease remains endemic."

In Conclusion:



Mission of the Product R&D Constituency

- To ensure **accelerated access** to and **responsible use** of innovative products to achieve short-term health impact.
- The R&D pipeline has never looked better – but needs to refocus efforts for long term eradication

