Recent research advances in malaria prevention and control

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Introduction

• Cover the recent research advances in malaria prevention and control with a focus on product development and combined interventions
Vaccines
Candidates

• Blood stage vaccine
  – MSP1, AMA1, MSP3, GLURP etc..
  – Pf RH5

• RTS,S/AS01

• Whole organism vaccine

• Transmission blocking vaccines
Why so many failures of malaria vaccine candidates?
Prevalence of MSP-1\textsubscript{19} haplotypes over three years in Bandiagara, Mali

Strain-specific efficacy of an AMA1 based vaccine

A full-length recombinant Plasmodium falciparum PfRH5 protein induces inhibitory antibodies that are effective across common PfRH5 genetic variants.

Bustamante LY, Bartholdson SJ, Crosnier C, Campos MG, Wanaguru M, Nguon C, Kwiatkowski DP, Wright GJ, Rayner JC.

Malaria Programme, Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, United Kingdom.

Abstract
RTS,S/AS01 malaria vaccine

• Administered with EPI, 50% protection in children aged 5-17 months, and ~30% protection in children aged 6-12 weeks

• “It is too early to draw conclusions about the public health role of RTS,S/AS01. This vaccine will be evaluated as a potential addition to, not a replacement for, integrated approaches of existing preventive, diagnostic and treatment measures tailored to a given endemic setting”. (Malaria Policy Advisory Committee and Secretariat Malaria Journal 2013, 12:213)
Protection Against Malaria by Intravenous Immunization with a Nonreplicating Sporozoite Vaccine.


Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20852, USA.

Abstract

Consistent high-level, vaccine-induced protection against human malaria has only been achieved by inoculation of Plasmodium falciparum (Pf) sporozoites (SPZ) by mosquito bites. We report that the PfSPZ vaccine, composed of attenuated, aseptic, purified, cryopreserved PfSPZ, was safe and well-tolerated when administered 4 to 6 times intravenously (IV) to 40 adults. 0/6 subjects receiving 5 doses, 3/9 subjects receiving 4 doses of 1.35 x 10^5 PfSPZ vaccine, and 5/6 nonvaccinated controls developed malaria following controlled human malaria infection (P = 0.015 in the 5-dose group and P = 0.028 for overall, both versus controls). PfSPZ-specific antibody and T cell responses were dose-dependent. These data indicate that there is a dose-dependent immunological threshold for establishing high-level protection against malaria that can be achieved by IV administration of a vaccine that is safe and meets regulatory standards.
Barriers to malaria vaccine development

- Paucity of well-characterized target immunogens
- Absence of clear correlates of protection
- Limited number of safe and effective delivery systems for long-lived protective immunity
- Lack of a clear clinical and regulatory pathway to licensure for vaccines targeting sexual stage and/or mosquito antigens. *(Birkett AJ et al, Vaccine 2013 Apr 18;31)*

“Continued creative application and integration of tools from multiple disciplines, including epidemiology, immunology, molecular biology, and evolutionary genetics and genomics, will likely be required to develop broadly protective vaccines against Plasmodium” *(Plowe CV, 2009)*
A few reasons for hope

• Human challenge for controlled human malaria infection to speed up product development
  – Use to be performed in Western countries
  – African countries increasingly involved (Kenya, Tanzania, Mali)
• Vaccines that interrupt malaria transmission (VIMT) may be key for elimination
  – Pfs25 Phase 1 in Mali
  – Pfs40, Pfs28, Pvs48/45, Pvs47 etc
  – Need for harmonization of protocols, SMFA, Direct skin feed
• Vaccine against malaria in pregnancy
• Increase cellular response by virus-like particules and prime-boost strategies
• Challenges in delivering whole-organism vaccines in the field
• Increased research in malaria biology and genetics
Drugs
ACTs – Artemisinin resistance

Dondorp AM, White NJ et al, 2009
Plasmodium population structure and artemisinin resistance in Asia

Genetic markers of artemisinin resistance

Takala-Harrison, Plowe CV et al, PNAS 2013
Current issues with antimalarial drugs

• Need molecular tools to monitor the spread of artemisinin resistance in the World
• Need to develop novel drugs and combination therapy regimens without artemisinins
• Need to quickly deploy the existing ACTs and other tools to speed-up malaria elimination
Seasonal Malaria Chemoprevention
SMC formerly IPTc

• Uses amodiaquine + sulphadoxine-pyrimethamine (AQ-SP) 3-4 times during peak season of transmission

• Strong evidence for high efficacy (approximately 80% reduction in malaria cases) and cost-effectiveness in areas with marked seasonality in malaria transmission (defined as 60% of cases occurring within four months)

• Actively being implemented in West Africa
% of total annual rainfall in 3 months

Yellow-red = IPTc areas
Green = borderline
Blue = insufficient seasonality

Map the areas suitable for IPTc (I)
Distribution of dhps position 540 mutation in Africa

SP + AQ suitable

Alternative regimen needed

Source: Naidoo and Roper, Parasitology, 2011
SMC research issues

• Need to develop alternative regimens for Southern Africa where SP resistance is high
• Long term efficacy
• Development of resistance and impact on efficacy
• Impact on transmission
• Which ages are ideal
Drugs for elimination/eradication

• Transmission interrupting drugs
  – Gametocytocidal drugs
  – Drugs targeting parasite stages in the mosquito
  – Drugs targeting the vector

• Combination therapies with matching PK

• Drugs safe enough for MDA campaigns

• Develop drugs with Single Encounter Radical Cure and Prophylaxis (SERCaP) profile (malERA Consultative Group on Drugs, PloS Med, 2011)
Vector control
Challenges in vector control

• Efficient delivery of tools (bednets and IRS)
• Mosquito behaviour changes
• Climate changes
Insecticide resistance

• Increasing prevalence of insecticide resistance
• Need for better tools for monitoring insecticide resistance and its spread
• Develop novel insecticides
• Develop and deploy combinations of insecticides
• Develop novel strategies for outdoor biting mosquitoes
Diagnostics for elimination/eradication

• Microscopy
  – Need constant training of microscopists
  – Critical mass training, refresher training, certification

• RDTs
  – Improve sensitivity/specificity
  – Improve stability in tropical conditions
  – Cover all malaria species

• More sensitive diagnostics
  – Serology tools
  – Molecular methods including field adapted ones

• Multi-task diagnostic tools: parasite + stages + specy + drug resistance profile etc.
Capacity development
Building strong research and development Capacity
WANECAM GUINEA Lab (Before)
Microscopy lab
Maferenya - Guinea
Wanecam Clinical lab
Patient recruitment
Maferenya Guinea
Internet connectivity
Maferenyanya Guinea
Health systems strengthening

The mAICERA Consultative Group on Health Systems and Operational Research
Summary & Conclusion

• Large regional partnerships offer opportunity for collaboration for maximum scientific output and impact on public health problems.

• As we move to EDCTP2, we need
  – to build on the successes of EDCTP1
  – Expand to include all phases of clinical development
  – Include health systems research and strengthening
  – Better engage African governments
  – Look beyond malaria
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