WRAIR
RTS,S AND MALARIA VACCINE RESEARCH

AN HISTORICAL AND BIBLIOMETRIC ANALYSIS

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AN HISTORICAL REVIEW

BACKGROUND
The Walter Reed Army Institute of Research (WRAIR) and its component overseas labs, particularly those in Kenya and Thailand, have contributed significantly to vaccine development against malaria and its plasmodium host.

WRAIR investigations through the years have provided essential foundational research leading researchers to the most recent experimental study showing that the RTS/S vaccine showed significant protection against the deadly disease. As reported in October 2011 by a frequent WRAIR collaborating organization, SmithKline, in Phase III trials, RTS/S reduced the risk of malaria infection by half in African children aged 5 to 17 months.

This analysis examines selected fundamental papers documenting WRAIR RTS/S research and its precursor research, providing evidence of its significant influence on this research overall.
• Literature reviews of the history of vaccine development were examined to identify key milestones in the development of the RTS/S vaccine and to identify groundbreaking WRAIR science on this subject.\(^{1-5}\)

• A subject search of Web of Science yielded 599 citations to WRAIR papers (articles, proceedings paper, meeting abstract and reviews) related to malaria vaccine development.


PRECURSORS
ROOTS OF THE RTS/S VACCINE
Experiments on sporozite attenuation on immunization against schistosomiasis, done by WRAIR with X-irradiated Cercariae (6, 7), inspired similar studies by NYU and other researchers focused on mosquitoes.


WRAIR studies the role of immunity in rodent malaria. (8-9)


Investigations suggest that protective antibody exerts its influence on the schizonts and/or the merozoites of malaria parasites. 

NEXT STEPS

DECODING OF THE GENES FOR CIRCUMSPOROZITE PROTEIN
In 1984, WRAIR entered into a Collaborative Research and Development Agreement with GlaxoSmithKline to provide a malaria vaccine using genetic engineering techniques.
• WRAIR adopted a new approach and began to focus on the development of a synthetic vaccine based on peptide constituents of Circumsporozite protein (CSP)
Early experiments involved use of monoclonal antibodies to isolate CSP and resulted in the cloning of the CSP genes of several species of the malaria parasite(11)

Research studies in animals showed that synthesized CS proteins induced antibodies with biologic activity correlated with protection(13).

Research continued on the safety and efficacy of a plasmodium falciparum sporozoite vaccine (14-15)


INITIAL STUDIES

RT,S/S DEVELOPMENT
In the early 1990’s, studies in Western Kenya involved 25 adult male volunteers with prior exposure to malaria who received recombinant sporozite vaccine or placebo(16)

- Results of this study showed that response to recombinant sporozite vaccine mirrored response to mature sporozite antigen

Paper published in the Journal of Infectious Diseases in 1995 described the production of RTS,S particles and the first phase 1 safety, immunogenicity and efficacy trial of P. falciparum sporozoite challenge of human volunteers using RTS,S/alum and RTS,S/alum/MPL(17).


Preliminary results of the field trial testing safety and efficacy of three formulations of recombinant circumsporozoite-protein vaccines (SBAS4, SBAS3, and SBA52) against *P. falciparum* (vaccinating a population without prior exposure to malaria) were published in 1997.\(^{(18)}\)
FURTHER STRIDES

RTS,S VACCINE AND STUDIES OF RTS,S(AS02)
Research on RTS,S was extremely productive in this decade (19-22) and involved numerous WRAIR researchers who presented at meetings and published papers on this topic.


A key paper published in December 2001 described a randomized clinical field trial of RTS,S/AS02, a pre-erythrocytic malaria vaccine based on the circumporozite surface protein of *P. falciparum* fused to HBsAg and incorporating the adjuvant AS02.

- Conducted by WRAIR in Africa, this 1998 study of semi-immune adult men in Gambia proved the RTS,S/AS02 vaccine safe and immunogenic and established the first pre-erythrocytic vaccine that provided significant protection against *P. falciparum* infection.

WRAIR research on RTS,S/AS02 (25-26) continues to be a vital part of malaria vaccine development efforts


WRAIR research on RTS,S explores the prime boost approach(27).

WRAIR research on RTS,S/AS01 and RTS,S/AS02 (28-29) involves field trials on adults in Africa.


Waitumbi JN, Anyona SB, Hunja CW, Kifude CM, Polhemus ME, Walsh DS, Ockenhouse CF, Heppner DG, Leach A, Lievens M, Ballou WR, Cohen JD, Sutherland CJ. Impact of RTS,S/AS02(A) and RTS,S/AS01(B) on Genotypes of *P. falciparum* in Adults Participating in a Malaria Vaccine Clinical Trial. *Plos One.* [Article]. 2009 Nov;4(11).

A 2011 WRAIR paper presented the examination of the immunological characteristics of RTS,S/AS, demonstrating that in addition to TNF-alpha, IL-2 is also a significant contributing factor to RTS,S/AS vaccine induced immunity and that both T(E/EM) and T(CM) cells are major producers of IL-2(30).
ROLE OF OVERSEAS LABS

MALARIA VACCINE
OVERSEAS FIELD TRIALS AND STUDIES

Results of AFRIMS field trials and research were published as early as 1980(31) and such studies continue today.(32)

Representing twelve percent (12%) of the WRAIR total, seventy-four (74) papers involving AFRIMS scientists were published on malaria vaccine research.


Similarly, work emanating from field trials in Africa and studies produced by USAMRU-Kenya were published as early as 1987 (15) and research on malaria vaccines continues to be a focal point in Africa.(33)

Representing ten percent (10%) of the WRAIR total, fifty-nine (59) papers involving USAMRU-Kenya researchers and resulting from work in Africa were published on this topic.


BEYOND

RTS,S VACCINE
CURRENT THRUSTS

WRAIR malaria vaccine research is evolutionary and current forward-thinking initiatives include a study indicating that AMA1 might be useful in a multicomponent malaria vaccine(34) and an examination of a new technique for optical mapping of multiple malaria genomes(35).


IMPACT OF WRAIR MALARIA (RTS,S) VACCINE RESEARCH

A BIBLIOOMETRIC ANALYSIS
BIBLIOMETRIC ANALYSIS
PERFORMED USING WEB OF KNOWLEDGE® TOOLS

- **Web of Science® (publication years 1898-2011*)**
  
  Database of citations to the scholarly literature in the sciences, social sciences, arts, and humanities including proceedings of international conferences, symposia, seminars, colloquia, workshops, and conventions (using citations as of October 24, 2011).

- **Essential Science Indicators ®**
  
  Compilation of essential science performance statistics and science trend data derived from Thomson Reuters data. The chief indicators of productivity (overall influence) are journal article publication counts. Total citation counts and cites per paper are indicators of influence and impact (weighted influence). Used specifically the “Highly Cited Papers” component of this tool. Updated as of September 1, 2011 to cover a 10-year + 6-month period, January 1, 2001-June 30, 2011.

- **Journal Citation Reports® 2010**
  
  A resource tool for journal evaluation, using citation data drawn from over 11,000 journals from over 3,300 publishers in over 80 nations. Updated annually.

*2011 represents a partial period
WRAIR researchers published a total of 599 papers related to immunology and malaria vaccine research (i.e., articles, meeting abstracts, proceedings papers, and review) covered in Web of Science in the period 1972-2011*.

Publishing on this subject increased to over 50 papers per year in the mid-1980’s and increased regularly through the early 2000’s. The number of publications published in 2005-09 more than doubled over the previous five-year period, illustrating the strength of malaria immunology and vaccine research focus at WRAIR.

*Represents a partial period
### Earliest Citation in Web of Science

- Presented at a meeting of the Helminthological Society of Washington, this paper is the earliest WRAIR citation identified in Web of Science on the immunology of rodent malaria, an early research focus.


### Most Current Citation in Web of Science

- The most current citation on malaria vaccine discusses a field trial in which 400 Malian children were immunized with either the malaria vaccine FMP2.1/AS02(A), a recombinant protein based on apical membrane antigen 1 (AMA1) or a control (rabies) vaccine and followed for 6 months. Results indicates that AMA1 might be useful in a multicomponent malaria vaccine.

Citations to WRAIR papers on malaria vaccine jumped dramatically higher in 2004 to over 1,000 citations per year and continue to rocket higher.

Overall, WRAIR publications in this area average 32.84 citations per paper.

WRAIR malaria vaccine publishing has a high overall h-index of 68, a level commonly associated with high honors (e.g., membership in the NAS).

*2011 represents a partial period
A majority (59%) of WRAIR papers on this topic appear most commonly in these top ten (10) journal sources.

• Representing a facet of 21st century science and the importance of vaccinology and genetics in modern research, three of these journals (identified in red) have been in existence only since the 1980’s and two others (noted in blue) only since the early-mid 2000’s.

<table>
<thead>
<tr>
<th>Source Titles</th>
<th># of Papers</th>
<th>%</th>
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<tbody>
<tr>
<td>AMERICAN JOURNAL OF TROPICAL MEDICINE AND HYGIENE</td>
<td>121</td>
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<tr>
<td>INFECTION AND IMMUNITY</td>
<td>56</td>
<td>9.349</td>
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<tr>
<td>VACCINE</td>
<td>44</td>
<td>7.346</td>
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<td>JOURNAL OF INFECTIOUS DISEASES</td>
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<tr>
<td>JOURNAL OF IMMUNOLOGY</td>
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<td>MALARIA JOURNAL</td>
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<td>PLOS ONE</td>
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<tr>
<td>FASEB JOURNAL</td>
<td>13</td>
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The vast majority (81%) of WRAIR publishing on malaria vaccine appears as original research articles, illustrating its contribution to groundbreaking science.
Analyzed using JCR, 7 of the top 10 journal sources have an impact factor > 3 and one title, FASEB Journal, has a high impact factor of 7.201.
HIGHLY CITED PAPERS USING ESSENTIAL SCIENCE INDICATORS

ISI Web of Knowledge™

Essential Science Indicators™

HIGHERLY CITED PAPERS FOR (MALARI* AND VACCIN*)

Sorted by: Citations

1 - 18 (of 18)

Total of unique papers in these searches combined = 20

HIGHERLY CITED PAPERS FOR (PLASMOD* AND VACCIN*)

Sorted by: Citations

1 - 8 (of 8)
WRAIR researchers contributed to the most highly cited paper in ESI on this topic. It has been cited 261 times in ESI* and 285 times in Web of Science*.

Using ESI baselines, a paper in the field of clinical medicine published in 2001 is expected to have 195 cites to be rated in the top 1% of papers. Cited 261 times in ESI, this paper is definitively a key paper in its field.

(Note: the blue hyperlinks for authors and institutions and fields indicate that these elements also are ranked in ESI).
GLOBAL INFLUENCE OF WRAIR MALARIA VACCINE RESEARCH
Understandably, scientists in the USA are the primary collaborators for WRAIR research and American scientists have worked with WRAIR on 579 of the 599 papers published.

In addition, WRAIR research on malaria vaccine and RTS,S is international in scope and has involved working with researchers in fifty-nine (59) countries. The chart shows fifteen (15) nations, other than the USA, that have worked with WRAIR more than ten (10) times, one indicator of the importance of this research to the global community.

*Chart shows only the first 15 countries*

This one WRAIR paper has been cited 464 times in Web of Science and 253 times by American researchers. Interestingly, researchers in eighteen (18) countries have cited this paper more than 10 times, indicating that the paper has had a global reach.
Research on malaria vaccine, and on RTS,S in particular, has long and deep roots at WRAIR

WRAIR researchers have contributed significantly since the 1960’s, sharing their research by publishing in journals and presenting at meetings

WRAIR research on RTS,S and malaria vaccine in general has had a critical impact on the progress of research to this point

Field trials in Africa and Thailand and the cooperation of WRAIR overseas labs, AFRIMS and USAMRU-Kenya, have been invaluable to progress in malaria vaccine research

Researchers worldwide rely on WRAIR research as a foundation to international endeavors on malaria vaccine