Author notes
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- Do the figures convey the intended message?
- Are all the labels accurate and in the right place?
- Are all the arrows in the right place?
- Are any chemical structures correct?
- Have shapes and colours been used consistently and accurately throughout the figures?
- Have any of the figures been previously published, or have they been supplied by a colleague(s) who is not a named author on the article?

To mark up any corrections, please use the commenting tools in the PDF, or print and draw by hand, rather than directly editing the PDFs.
Malaria endemicity
- Countries endemic for malaria, 2015
- Countries endemic in 2000, no longer endemic in 2015
- Countries not endemic for malaria, 2000
- Not applicable
- *P. falciparum* prevalent
- *P. vivax* prevalent

**Fig 3**

- **Merozoite**
  - Coat
  - Dense granule
  - Rhoopry
  - Microneme

- **CyPPA**
  - *PfRipr*
  - *PfPh5*
  - Basigin

- **Red blood cell**
  - *Hb*
  - *CyPPA*
  - *CHQ*
  - *PfCRT*
  - *PfDHFR*
  - *PfDHODH*
  - *PfPI(4)K*
  - *P218*
  - *Cycloguanil*
  - *ATO*
  - *DMS265*
  - *CHQ*
  - *PyR*
  - *DMS265*
  - *PyR P218 Cycloquaniil*

- **Food vacuole**
  - *ATO*
  - *PyR P218 Cycloquaniil*
  - *DMS265*
  - *PyR P218 Cycloquaniil*

- **Plasmodium mitochondria**
  - *PfATP4*
  - *PfDHFR*
  - *Hb*

- **Current drugs**
- **Drug candidates**
- **Enzymatic drug target**
- **Resistance marker**
Malaria endemicity
- Countries endemic for malaria, 2015
- Countries endemic in 2000, no longer endemic in 2015
- Countries not endemic for malaria, 2000
- Not applicable
- P. falciparum prevalent
- P. vivax prevalent

Merozoite
- Coat
- Dense granule
- Rhozyty
- Microneme

Red blood cell
- Hb
- Heme (toxic)
- Haemoglobin (non toxic)
- Haemozoin

Current drugs
- ATO
- Cipargamin
- DMS265
- MMV048

Drug candidates
- P1ATP4
- PyR
- P218

Enzymatic drug target
- PfATP4
- PfDHFR
- PfCRT
- PfDHODH

Resistance marker
- PfPh5
- PfRipr
- Basigin
- CHQ
- Pfcytb
**Fig 4**

*Plasmodium falciparum*

![Image of Plasmodium falciparum stages with labels](image)

**Fig 5**

**Product development (WHO Pesticide Evaluation Scheme)**

<table>
<thead>
<tr>
<th>Research categories</th>
<th>Phase I (Lab trials)</th>
<th>Phase II (Small-scale (hut) trials)</th>
<th>Phase III (Large-scale (field) trials)</th>
<th>Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-purposed crop protection development compounds, including fungicides (2019–2020)</td>
<td>LLIRS/re-purposed active ingredients from crop protection (Bayer, BASF, Sumitomo; 2020–2022)</td>
<td>LLIN Combination (BASF, Sumitomo)</td>
<td>LLIN Interceptor G2 Chlorfenapyr/α-cypermethrin (BASF/IVCC)</td>
<td>K-Othrine Polyzone (Bayer/IVCC, since 2013)</td>
</tr>
<tr>
<td>Resistance-breaking net formulations</td>
<td>Resistance-breaking net formulations</td>
<td>VECTA001 Novel Al (Syngenta/IVCC)</td>
<td>Chorfenapyr IRS (BASF/IVCC, since 2013)</td>
<td>Actellic CS LLIRS (Syngenta/IVCC, since 2012)</td>
</tr>
<tr>
<td>Bivalent carbamates (U. of Florida, USA); Indoxacarb + α-cypermethrin for LLINs (LSHTM, PAMVERC)</td>
<td>Chlorfenapyr IRS (BASF/IVCC, since 2013)</td>
<td>*Project Venus’ (Akzo Nobel)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Re-purposed compound
- Novel compound
- Bed net formulation
- Bivalent carbamates
Fig 4

Plasmodium falciparum

Development (hours)

0 12 24 36 48

Nature Reviews | Disease Primers

Fig 5

Research categories

Re-purposed crop protection development compounds, including fungicides (2019–2020)

Novel target-based discovery (Foundation for the NIH)

Resistance-breaking net formulations

Bivalent carbamates (U. of Florida, USA; Indoxacarb + α-cypermethrin for LLINs (LSHTM, PAMVERC)

Product development (WHO Pesticide Evaluation Scheme)

Research categories

Phase I (Lab trials)

Phase II (Small-scale (hut) trials)

Phase III (Large-scale (field) trials)

Registration

Access

Re-purposed compound

Novel compound

Bed net formulation

Bivalent carbamates

Re-purposed crop protection development compounds, including fungicides (2019–2020)

LLIRS/re-purposed active ingredients from crop protection (Bayer, BASF, Sumitomo; 2020–2022)

Non-pyrethroid insecticide-treated durable wall lining

VECTA001 Novel Al (Syngenta/IVCC)

"Project Venus’ (Akzo Nobel)

K-Othrine Polyzone (Bayer/IVCC, since 2013)

LLIN Interceptor G2 Chlorfenapyr/α-cypermethrin (BASF/IVCC)

LLIN Olyset Duo: Pyriproxyfen/permethrin (Sumitomo/IVCC, 2017–2018)

Momfluorothrin (Sumitomo, since 2014)

Chlorfenapyr IRS (BASF/IVCC, since 2013)

Actellic CS LLIRS (Syngenta/IVCC, since 2012)

Bivalent carbamates
**Fig 6**

**Preclinical development**
- **P. falciparum**
  - Full-length MSP1 (U. of Oxford, D)
  - Novel B cell targets (Seattle Biomed, JHU, NIAID, WRAIR, NMRRC, Attreca)
  - Novel T cell targets (NIAID)
  - PICelTOS FMP012 (WRAIR)
  - ChAd63/MVA ME-TRAP+Matrix (U. of Oxford, UK)
  - Pf55-IMX313 (U. of Oxford, UK)
  - Pf55/45 and CSP mAb (PATH)
  - Pfs25-IMV VLP (FhCMB)
  - PfCelTOS FMP012 (WRAIR)
  - VMP002/PvCSP (WRAIR)

**Clinical development**
- **P. falciparum**
  - RH5.1/AS01 (U. of Oxford, UK)
  - NMRC-M3V-Ad-Pf5 (NMRC)
  - PAMCPH/PlacMalVac (U. of Copenhagen, DK)
  - PRIMVAC (PRIMALVAC) (INSERM)
  - ChAd63/MVA ME-TRAP (U. of Oxford, EVI, MRCG, CNRFP, KMRI, UCAP)
  - P27A/PPF0165c (CHUV)

**D. vivax**
- Pfs25-IMX313 (U. of Oxford, UK)
- Pf55/45 (Radboud U., NL; KCMC)
- Pfs25-EPA + Pfs230-EPA (NIAID)
- ChAd63/MVA PvDBP (U. of Oxford, UK)

**Fig 7**

**a**
- NPC11618 (Mississippi)
- GSK030 (CSK)
- GSK567 (CSK)
- PA92 (Drexel/UW/GNF)
- AN13762 (Anacor)
- DDD498 (Merck/Dundee)
- UCT043 (UCT)
- JPC3210 (Jacobus)

**b**
- Cipargamin (KAE609) (Novartis/MMV)
- Methylene Blue/AQ (Heidelberg)
- ACT-451840 (Actelion)

**Chemoprevention**
- Dihydroartemisinin piperine (Paediatric)
- Tafenoquine (1st, 2nd generation, MMV/MMV, MMV/US Army)
- Ferroquine/Artemenol (OZ439b, Sanofi/MMV)
- N-tert butyl isoquinone (LSTM/Liverpool/GSK)
- Artemisinin naphthoquinone (Kunming Pharma Co.)
- Fosmidomycin Piperazine (Jomaa Pharma/GmbH)
- Artemether sub-lingual spray (MRC/Suda)
- Co-trimoxazole (ITM/Anwerp)
- SJ557733® (St Jude/Eisai/MMV)
- Artremione (UHKST)
- CDRI 9778 (CDRI)
- SAR97276 (Sanofi)
- AQ13 (Immtech)

**Relapse prevention**
- MMV/390048® (MMV/UCT)
- DSM265® (Takeda/MMV, UTSW/UW/ Monash)

**Asexual blood stages**
- Asexual blood stages Transmission reduction
- Asexual blood stages Relapse prevention

**Chemoprevention**
- Asexual blood stages Transmission reduction
- Asexual blood stages Chemoprevention

**Relapse prevention**
- Asexual blood stages Chemoprevention

Nature Reviews | Disease Primers
**Fig 6**

### Preclinical development

<table>
<thead>
<tr>
<th>Parasite</th>
<th>Malaria Vaccine</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PfSPZ-GA1 (Sanaria, Inc.)</td>
<td>(Sanaria, Inc., U. Leuden)</td>
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<tr>
<td></td>
<td>Pfs25-IMX313 (U. of Oxford, UK)</td>
<td>(EBA175)/Rh5 (NIAID)</td>
</tr>
<tr>
<td></td>
<td>PfSPZ-CVac (Sanaria, Inc.)</td>
<td>(Sanaria, Inc., U. Leuden)</td>
</tr>
<tr>
<td></td>
<td>Pf 48/45 and CSP mAb (PATH)</td>
<td>(Sanaria, Inc.)</td>
</tr>
<tr>
<td></td>
<td>Pf25-AIMV VLP (FhCMBl)</td>
<td>(Sanaria, Inc.)</td>
</tr>
<tr>
<td></td>
<td>PAMCPH/PlacMalVac (U. of Copenhagen, DK)</td>
<td>(Sanaria, Inc.)</td>
</tr>
<tr>
<td></td>
<td>PVBP3-5 (WEHI)</td>
<td>(Sanaria, Inc.)</td>
</tr>
<tr>
<td></td>
<td>VMP002/PvCSP (WRAIR)</td>
<td>(Sanaria, Inc.)</td>
</tr>
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</table>

### Clinical development

<table>
<thead>
<tr>
<th>Malaria Vaccine</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMP112</td>
<td>(Evip, UK, SSI, ASH, AMANET, NHRC, CNRF, LSHTM, MUK, MRCG)</td>
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<tr>
<td>MSP3 [181-276]</td>
<td>(AMANET, EvI, CHUV, Bamako U., IP, CNRF)</td>
</tr>
<tr>
<td>PIPEBS (Vac44II, IP, Sentinex, Therapeutics, EvI, CHUV, NIMR)</td>
<td>(EvI, CHUV, NIMR)</td>
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</table>

**Fig 7**

### Relapse prevention

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td>Cipargamin</td>
<td>(Novartis/Phys.)</td>
</tr>
<tr>
<td>Methylene Blue</td>
<td>(Heidelberg)</td>
</tr>
<tr>
<td>ACT-451840</td>
<td>(Actelion)</td>
</tr>
<tr>
<td>Tafenoquine</td>
<td>(GSK/MMV, GSK/US Army)</td>
</tr>
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</table>

### Asexual blood stages

<table>
<thead>
<tr>
<th>Drug</th>
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<tbody>
<tr>
<td>Dihydroartemisinin piperazine</td>
<td>(Sigma-Tau/Pierre Fabre)</td>
</tr>
<tr>
<td>Ferroquine/Artelenone</td>
<td>(OZ439b)</td>
</tr>
<tr>
<td>N-tert butyl Isoquine</td>
<td>(LSTM/Liverpool/GSK)</td>
</tr>
<tr>
<td>Artemisinin naphthoquinone</td>
<td>(Kuming Pharma Co.)</td>
</tr>
<tr>
<td>Fosmidomycin Piperazine</td>
<td>(Jomaa Pharma/GmbH)</td>
</tr>
<tr>
<td>Artemether sub-lingual spray</td>
<td>(MRC/Suda)</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>(ITM Antwerp)</td>
</tr>
<tr>
<td>SJ(557)733B</td>
<td>(St Jude/Eisai/MMV)</td>
</tr>
<tr>
<td>LSA03</td>
<td>(Leiden University)</td>
</tr>
</tbody>
</table>
|//\[

### Chemoprevention

<table>
<thead>
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<th>Drug</th>
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<td>LSA03</td>
<td>(Leiden University)</td>
</tr>
</tbody>
</table>
Fig 8

Trimethoprim: part of Co-trimoxazole (ITM Antwerp)

AQ13 (Immtech)

Ferroquine (Sanofi/MMV)

Cipargamin (KAE609) (Novartis/MMV)

Fosmidomycin (Jomaa Pharma/GmbH)

MMV(390)048 (MMV/UCT)

Tafenoquine (St Jude/Eisai/MMV)

DSM265 (Takeda/MMV, UTSW/UW/Monash)

ACT-451840 (Actelion)

KAF156 (Novartis/MMV)

Naphthoquine (Kunming Pharma Co)

Artefenomel (OZ439) (Sanofi/MMV)

Methylene Blue (Heidelberg)

CDRI 9778 (CDRI)

P218 (Biotec Thailand)

SAR97276 (Sanofi)

Box 4