Ending malaria, *rewriting the future*

MMV Medicines for Malaria Venture

25 YEARS

Considerations for LAI Microsuspension Development

CMC aspects

Laxman Cherkupally

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Malaria and Child Mortality

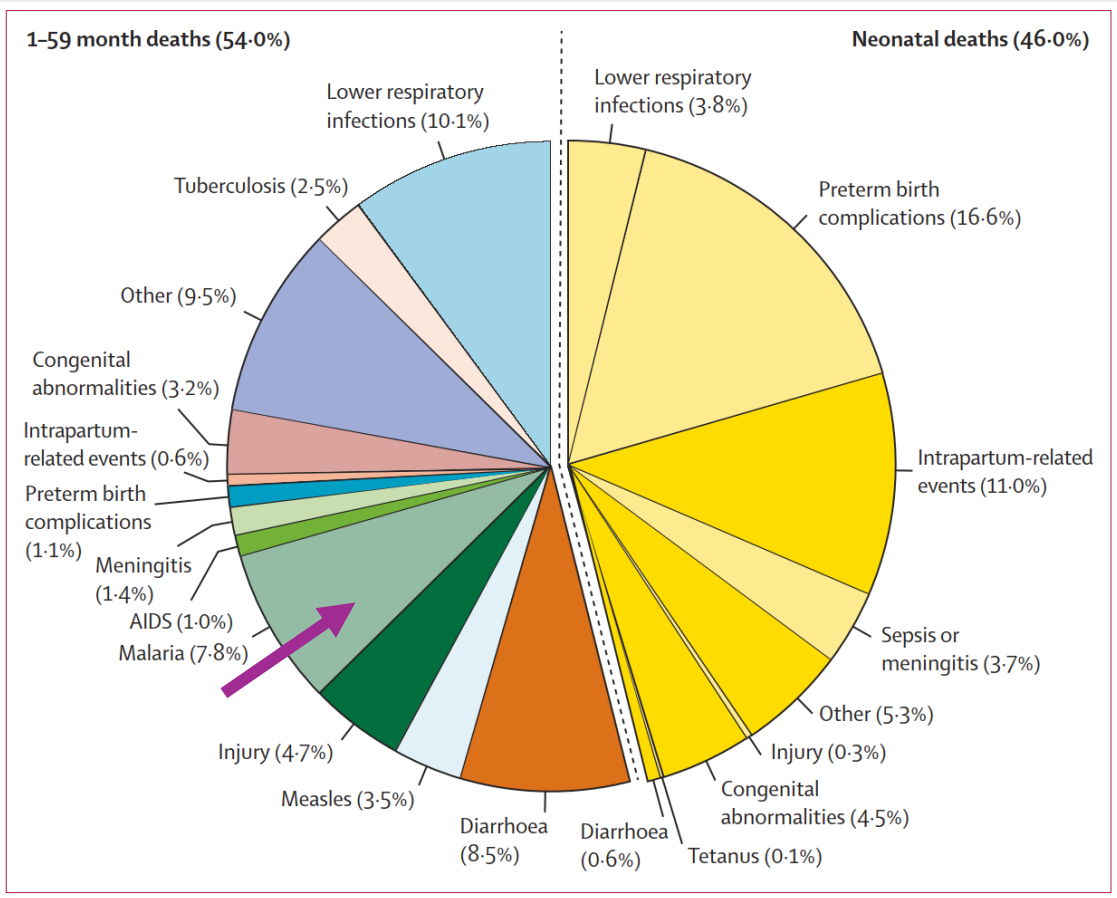


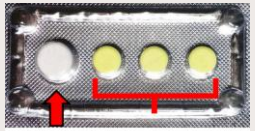
Figure 1: **Global causes of under-5 deaths in 2019**
Deaths of neonates (aged 0–27 days) are on the right-hand side and deaths of children aged 1–59 months are on the left-hand side.

- Malaria is a public health imperative ; 95% of cases and 96% of deaths occur in sub-Saharan Africa
- If not treated within 24 hours, malaria can progress to severe illness and can result in death.
- Children are more vulnerable to malaria than adults. 79% of deaths in sub saharan africa occur in children under five.
- Each malaria episode keeps a child away from school for ≥ 3 days.
- Prevention is better than cure. Seasonal Malaria Chemoprevention (SMC with SPAQ) is the WHO recommended chemoprevention intervention during high transmission period in endemic countries

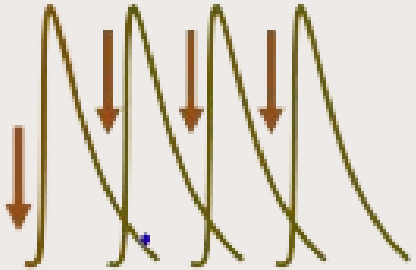
Source: *Global, regional and national causes of under 5 mortality in 2000-19 : an updated systematic analysis with implications for the sustainable development goals, Jamie Perin et al., Lancet child Adolesc Health, 2022;6, 106-15. ; WHO World malaria report 2023*

Why LAIs for Malaria ?

PRESENT



Day 1	Day 2	Day 3
SP + AQ	AQ	AQ



- 3-day dosing regimen per cycle
- Monthly interval/cycle
- Protection : 28 days
- Cost per full cycles : 1.2 USD*

Limitations :

- Require regular administration
- Adherence challenges
- Mainly for < 5 years ; older children unprotected

FUTURE

- Single dose per season
- Every 3-4 months
- Protection : ≥ 3 months
- Expected cost per dose : 1-2 USD**

Benefits :

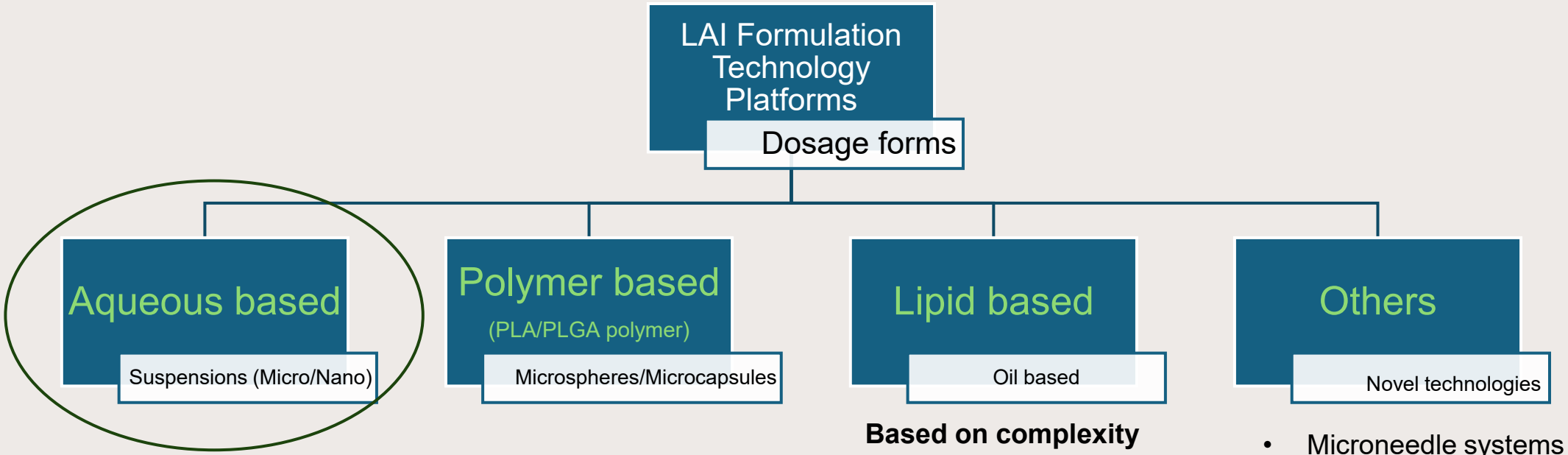
- Adherence with one visit
- No cold chain ; stability in tropical conditions
- Regimen simplification

SMC: Seasonal Malaria Chemoprevention ; SP : Sulfadoxine-Pyrimethamine ; AQ: Amodiaquine LAI : Long acting Injectable

* Includes access cost ** It doesn't include implementation/access cost

25 YEARS

Formulation Technologies- Aqueous suspensions



Based on PSD
- Micro suspensions
- Nano suspensions

Based on preparation/use
- Ready to use
- Reconstituted/Lyophilized

- Microparticulates
  - Microspheres
  - Microcapsules
- Implants
- *In situ* implants/gels

Based on complexity
- Simple
  - Solutions
  - Suspensions
- Complex
  - Liposomes
  - Oleogels/emulsions
  - Liquid crystals

- Microneedle systems
- Implantable systems
  - Osmotic pumps
  - Chips
  - Nanochannels

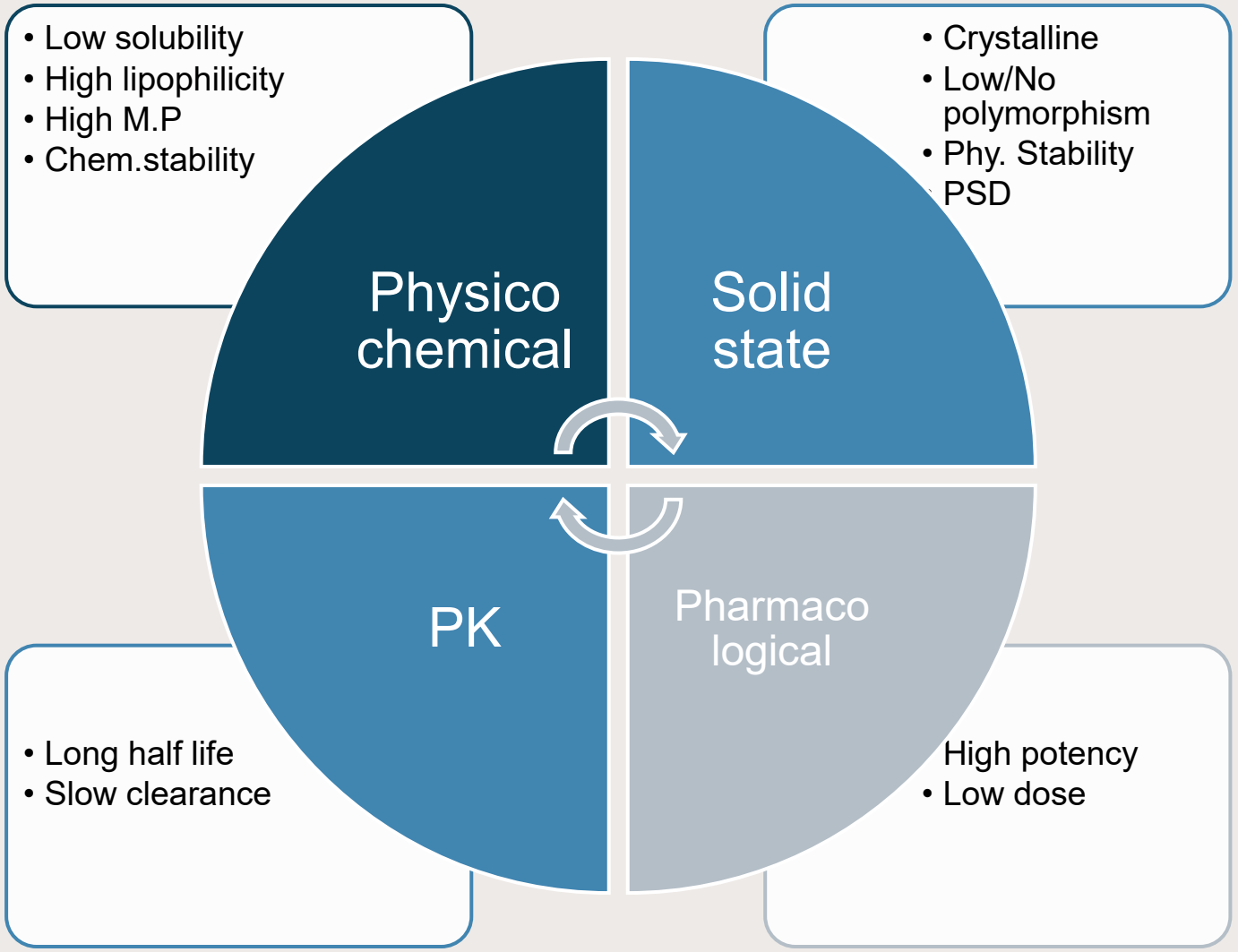
Solubility / Dissolution

Erosion → Diffusion

Diffusion → Digestion

PLA : Poly (D,L-lactic acid) and PLGA : Poly(D,L-lactic-co-glycolic acid)

Ideal drug profile for microsuspension



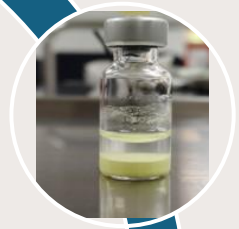
MMV LAI Strategy for Malaria

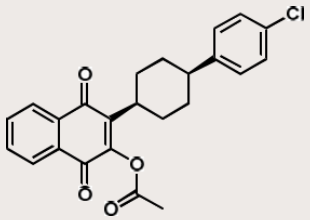
- Atovaquone acetate : a prodrug of atovaquone
- Aqueous crystalline micro suspension : 223mg/mL
- Aqueous solubility : 4 µg/mL (practically insoluble)

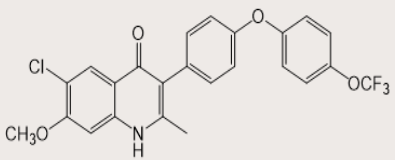
MMV371

LAI

(Microsuspension)







MMV055

- A NCE small molecule (ELQ300)
- Aqueous crystalline micro suspension : 200mg/mL
- Aqueous solubility : 1 µg/mL (practically insoluble)

FDC

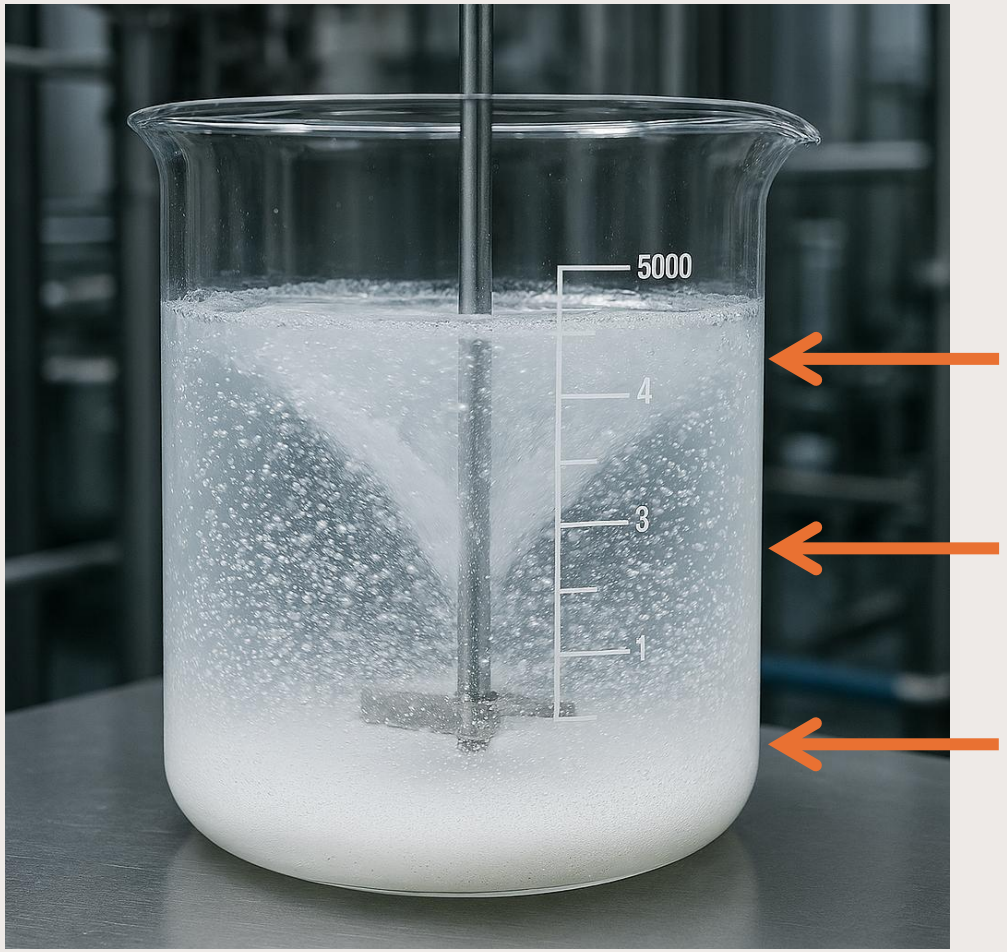
- Fixed ratio of two drugs
- Similar composition
- Avoids risk of resistance with monotherapy
- No cross resistance

25 YEARS

Microsuspension – Key CMC Considerations

- IPC
  - Bulk uniformity and content uniformity
- Final product
  - Fill volume :
    - Extractable volume – Residual volume – Excess volume
  - Resuspendability :
    - Shaking time – Holding time – Residence Time
  - Syringeability – Injectability :
    - Tissue back pressure – Needle size
  - Stability – Zone IV a & b conditions

Uniformity of bulk and dosage units



Bulk uniformity (Top, Middle and Bottom)

Fill uniformity (Start, Middle and End)

Fill volume

Definitions :

- **Fill volume** : Actual volume filled into vial/container
- **Extractable volume** : Volume that can be withdrawn from a vial using syringe
- **Residual volume** : Volume of liquid remaining in vial (Loss -dead volume)
- **Labelled volume** : Declared volume on product : minimum volume available
- **Excess volume** : Additional volume (over fill) filled into vial beyond labelled volume

Relationships :

- Fill volume = Labelled volume + Excess volume
- Excess volume = Residual volume + Safety margin*
- Extractable volume ≥ Labelled volume

*account for variability during filling, dead space in device/vials, container geometry etc.

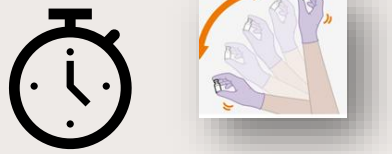
Example :

Fill volume = 1mL (labelled) + 0.2mL (residual) and +0.1mL (safety margin)

Total fill volume = 1.3mL

Resupendability

- Hand Shaking Time : Shaking time required for making a uniform suspension



Ideal : ≤ 10 seconds

- Holding Time : Time between first shaking and withdrawal into syringe

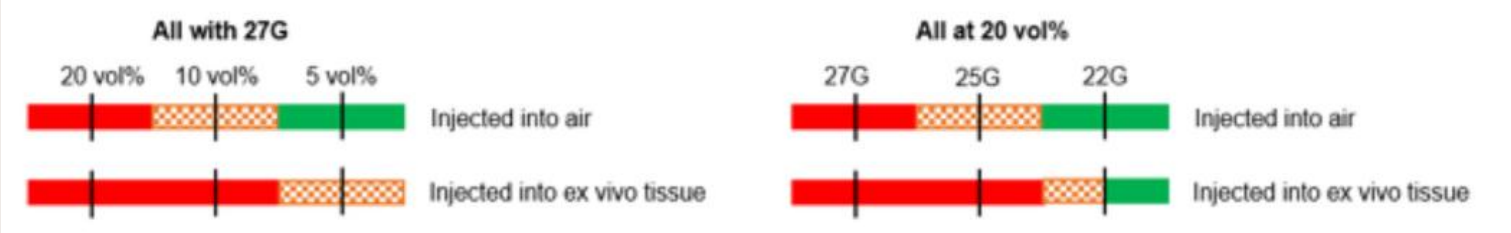
Ideal : varies / case by case

- Residence Time: Time between withdrawal into syringe and injection to site

Ideal : : varies / case by case

Syringeability and Injectability

- Definitions :
  - Syringeability : The ease with which a formulation can be drawn into syringe from a vial
  - Injectability : The ease with which a formulation can be expelled from syringe and administered into a muscle/tissue.
  - They are interdependent but distinct.
- Influencing Factors :
  - Needle Gauge, tissue resistance/back pressure, drug load/viscosity, dose volume



K. Kowsari et al. / Journal of Pharmaceutical Sciences 113 (2024) 3525−3537

- In vitro / ex vivo assessment tools for evaluation of injectability of drug product
  - To assess the various factors and suggest the needle choices

Summary

- LAI is a potential chemoprevention intervention to defeat malaria.
- It will be first FDC (fixed dose combination) in LAI platform.
- Aqueous suspension preferred as it is cost-effective and simple technology.
- MMV371 Phase I study completed and MMVV055 Phase I study is ongoing.
- CMC aspects are key for rational development and success of project
- Lessons learned from CMC are helping us shape next generation LAIs development.

Acknowledgments

MMV Medicines for Malaria Venture

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Thank you