PDMC guidelines development

Overview of ‘evidence’ shared with WHO & new PDMC WHO guidelines

Dr Titus K Kwambai

US Centers for Disease Control and Prevention, Kisumu, Kenya

PDMC consortium
Funded by Research Council of Norway

Overview

- Background: burden of post-discharge morbidity
- Package presented to WHO's Guidelines Development Group (GDG)
  - Meta-analysis safety and efficacy
  - Implementation and qualitative research
  - Cost-effectiveness

- WHO update malaria chemoprevention guidelines

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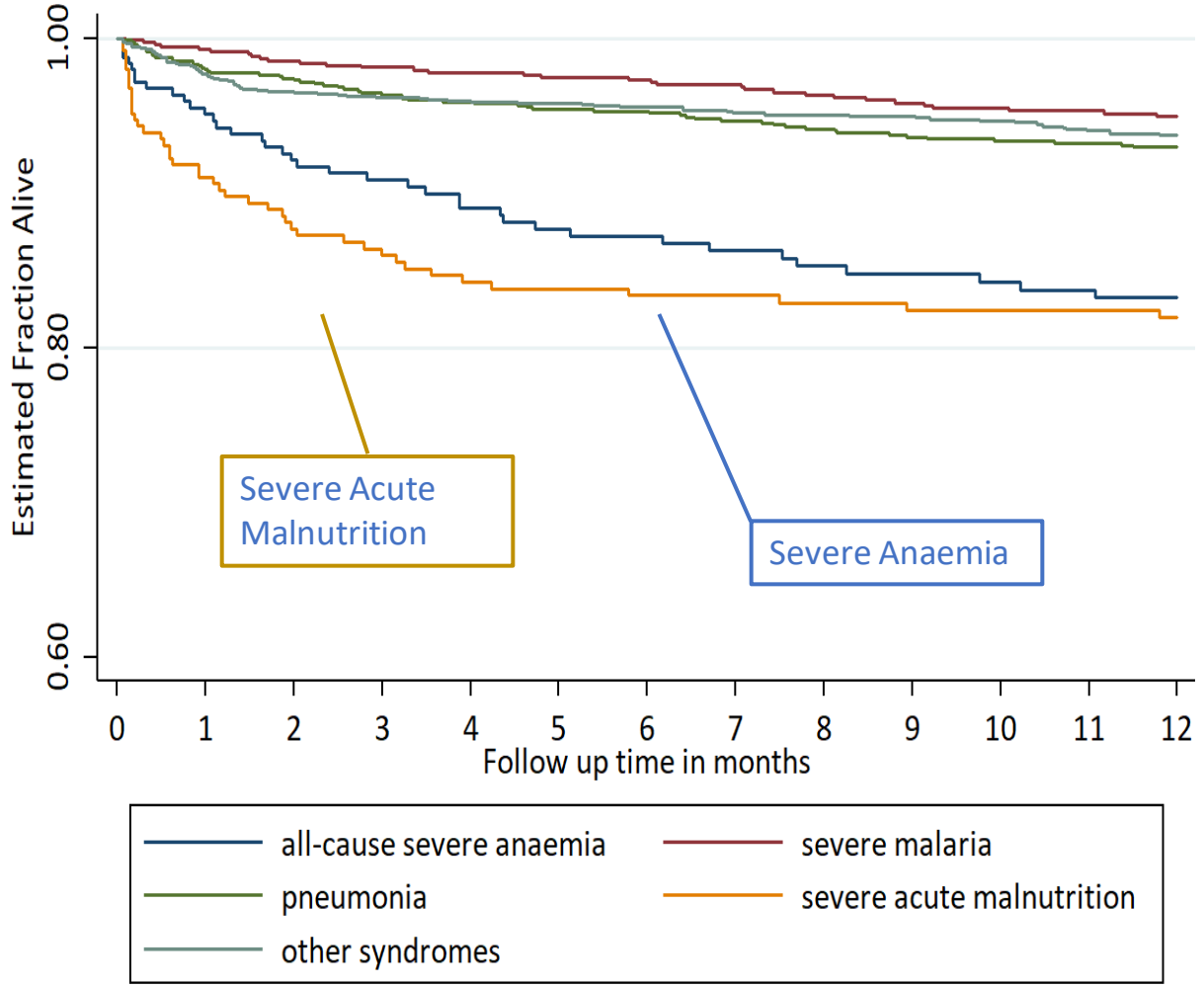
Burden post discharge morbidity

- 15 to 33% of children recently discharged from hospital after recovery from severe anaemia die or are readmitted during the first six months after discharge
- In malaria endemic areas, post-discharge mortality is 2.69 higher in children with severe anaemia than in children with other health conditions (except severe acute malnutrition)
- The odds of dying within 6 months after discharge are 1.72 higher than during the initial hospital admission
- Malaria, important contributing factor to post-discharge events



Kwambai et al, 2022,Lancet CAH and AJHTM, 2023

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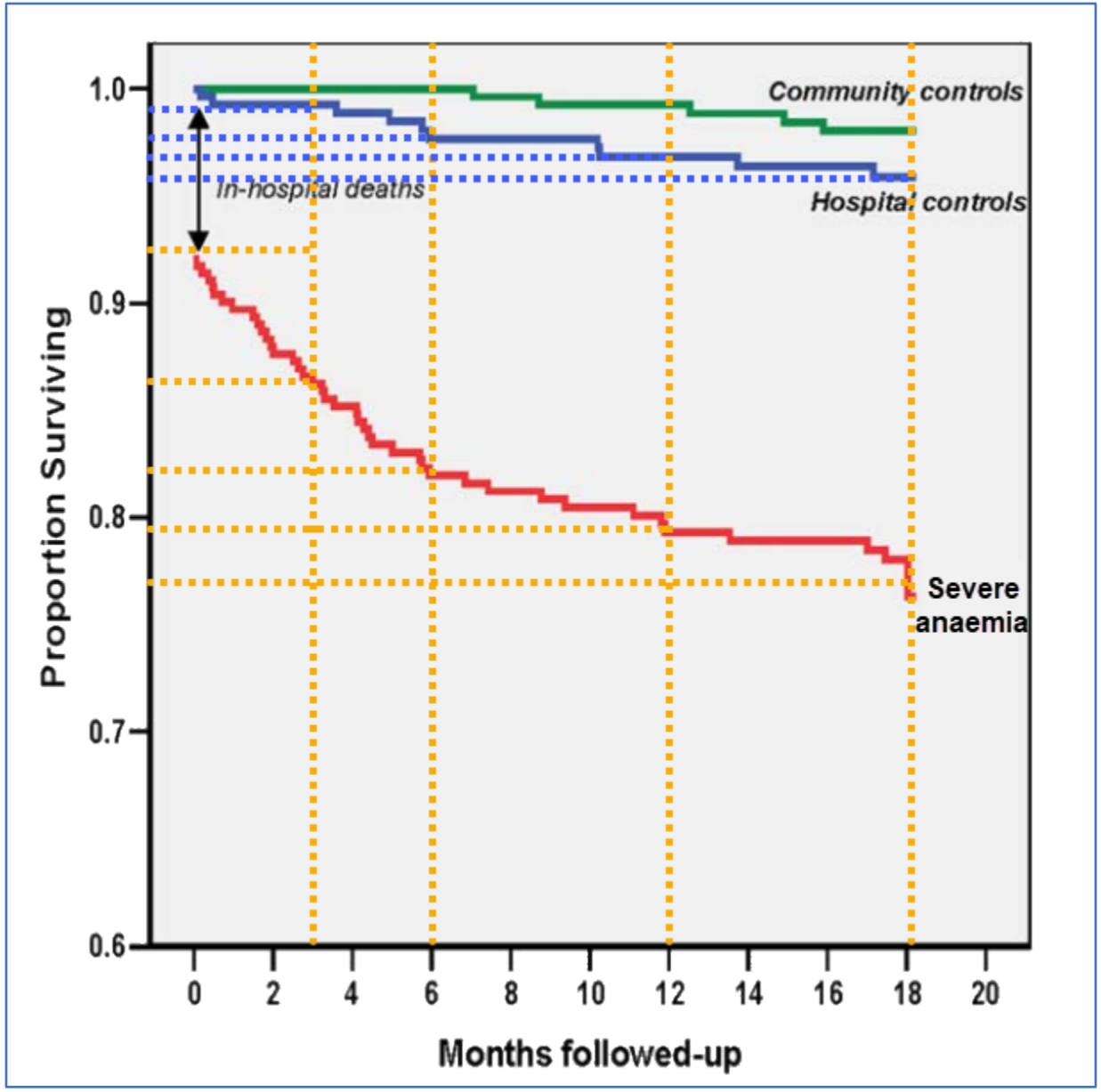
How long does the increased risk of death post-discharge last?

OPEN ACCESS Freely available online August 2008 | Volume 3 | Issue 8 | e2903 PLoS one

Long Term Outcome of Severe Anaemia in Malawian Children

Kamija S. Phiri[1]*, Job C. J. Calis[1,2], Brian Faragher[3], Ernest Nkhoma[1], Kondwani Ng'oma[1], Bridget Mangochi[1], Malcolm E. Molyneux[1,3], Michaël Boele van Hensbroek[1,2,3]

- At least 18 months
- Greatest risk in first 6 months
- But still excess mortality between 6-11m and 12-18m compared to hospital and community controls



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Meta-analysis efficacy trials

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Bojang et al, PlosOne, 2010

- The Gambia, 2003-04
- Monthly SP during transmission season
- Average 3.1 courses
- Hb < 7 g/dL

OPEN ACCESS Freely available online

PLoS one

Prevention of the Recurrence of Anaemia in Gambian Children Following Discharge from Hospital

Kalifa A. Bojang[1]*, Paul J. M. Milligan[2], David J. Conway[1], Fatou Sisay-Joof[1], Muminatou Jallow[1], Davis C. Nwakanma[1], Ismaela Abubakr[1], Fanta Njie[1], Brian Greenwood[2]

Phiri et al, Lancet ID, 2012

- Malawi, 2006-09
- Monthly AL at 4 and 8 weeks
- Hb < 5 g/dL + malaria

Articles

www.thelancet.com/infection Published online December 14, 2011

Intermittent preventive therapy for malaria with monthly artemether–lumefantrine for the post-discharge management of severe anaemia in children aged 4–59 months in southern Malawi: a multicentre, randomised, placebo-controlled trial

Kamija Phiri, Michael Esan, Michael Boele van Hensbroek, Carole Khairallah, Brian Faragher, Feiko O ter Kuile

Kwambai et al, NEJM, 2020

- Kenya and Uganda, 2016-18
- Monthly DHA-PiP at 2, 6, 10 weeks
- Hb < 5 g/dL

The NEW ENGLAND JOURNAL of MEDICINE DECEMBER 3, 2020

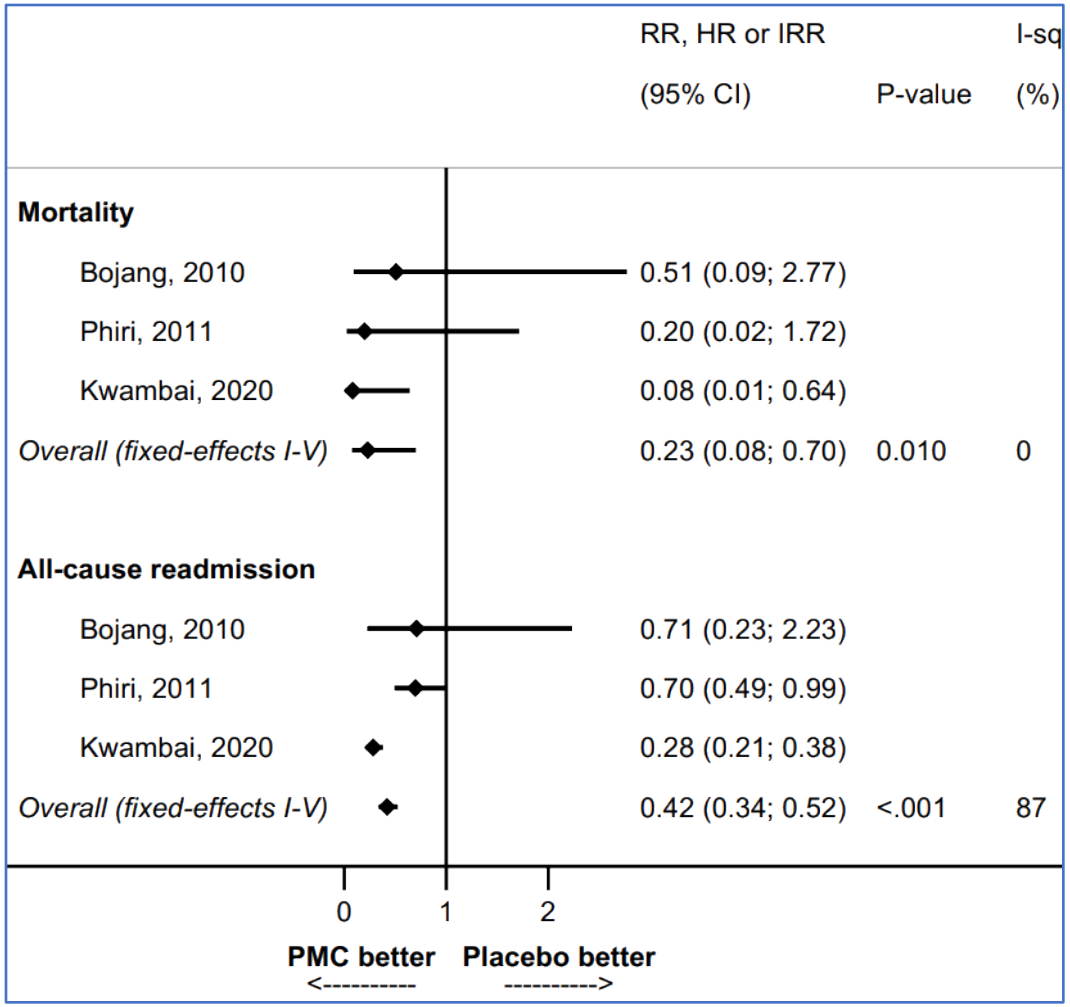
ORIGINAL ARTICLE

Malaria Chemoprevention in the Postdischarge Management of Severe Anemia

T.K. Kwambai, A. Dhabangi, R. Idro, R. Opoka, V. Watson, S. Kariuki, N.A. Kuya, E.D. Onyango, K. Otieno, A.M. Samuels, M.R. Desai, M. Boele van Hensbroek, D. Wang, C.C. John, B. Robberstad, K.S. Phiri, and F.O. ter Kuile

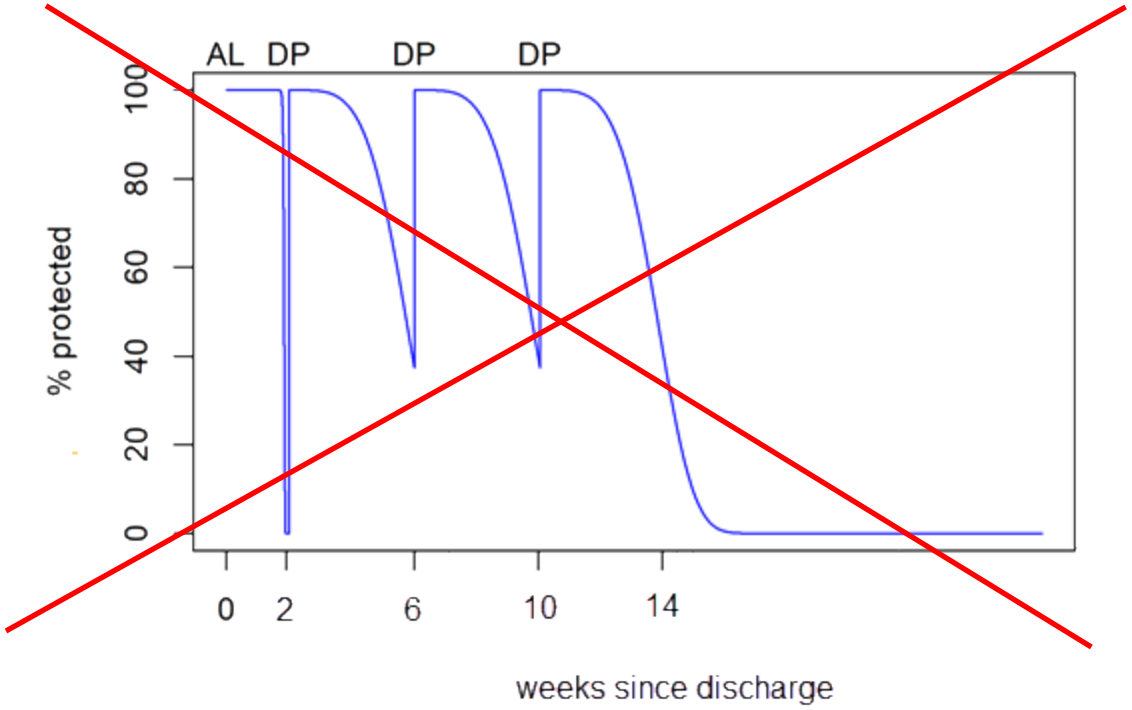
Summary meta-analysis safety & efficacy

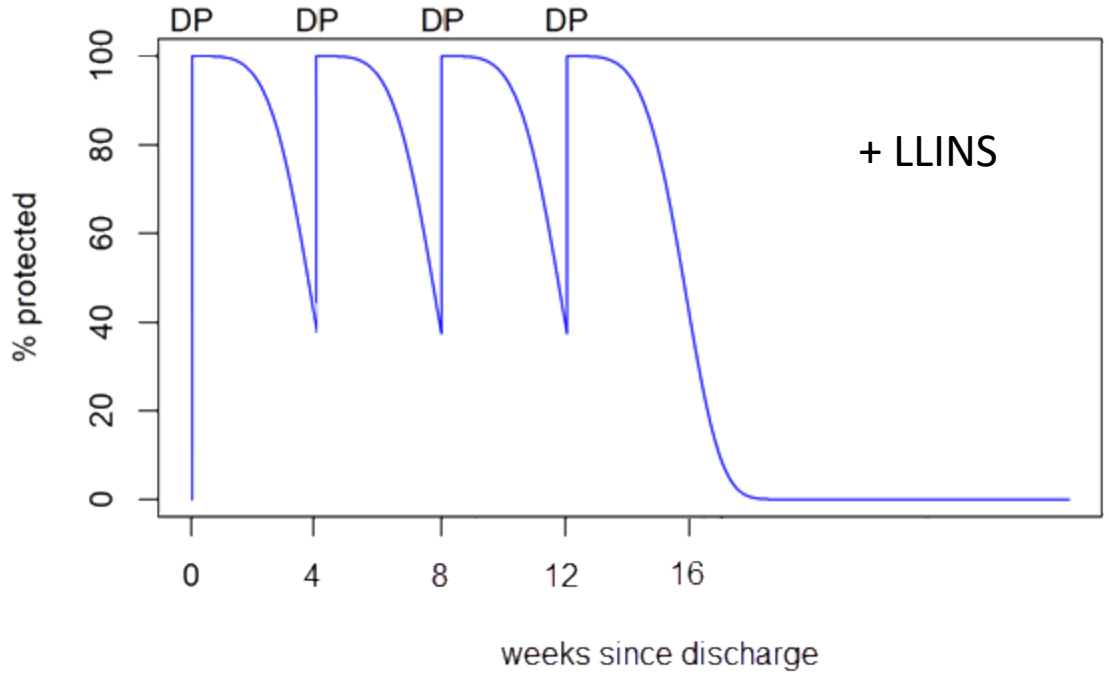
- PDMC is associated with a
  - 77% reduction in all-cause mortality (NNT = 83)
  - 58% reduction in all-cause readmissions (NNT = 11)
- The protective effect is restricted to the intervention period
- Effect of DHA-PiP and AL is highly malaria specific
  - No effect on non-malarial outcomes (DHA-PiP)
  - Most effect in those with malaria on admission (severe malarial anaemia)
- Monthly SP may also provide benefits on non-malaria morbidity & growth
- All regimens were well tolerated
- Piperaquine associated QT prolongation not a limiting factor (no events >480ms)



Regimen recommendation

- Minimum 3 months = 4 courses = 4 months of chemoprevention
  - First course at discharge, regardless of malaria on admission
  - 2nd, 3rd, and 4th at 1, 2, 3 months post-discharge
- E.g. 4 courses of DP (East & southern Africa), AQAS *or* SP (West-Africa)
- Plus long-lasting insecticide treated nets (LLINs)





Implementation and qualitative research

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PDMC Delivery mechanism trial: Malawi

Study design

Setting: Zomba Central hospital, Malawi

Design: Cluster randomized trial

Population: Children < 5y with severe anemia, transfused and stable (N=371)

Results: Community-based vs Facility-based delivery

- Full adherence: 70.6% vs 52.0%
- IRR=1.24 (95% CI 1.06–1.44), p = 0.006

Conclusion: Providing all three post-discharge courses to the caregiver at discharge to administer at home results in 24% better adherence than asking caregivers to return to the facility to collect each course of PDMC

Nkosi-Gondwe et al, PLoS ONE, 2021

PLOS ONE September 10, 2021

RESEARCH ARTICLE

Adherence to community versus facility-based delivery of monthly malaria chemoprevention with dihydroartemisinin-piperaquine for the post-discharge management of severe anemia in Malawian children: A cluster randomized trial

Thandile Nkosi-Gondwe[1,2*], Bjarne Robberstad[2], Mavuto Mukaka[3,4], Richard Idro[5], Robert O. Opoka[5], Saidon Banda[1], Melf-Jakob Kühl[2], Feiko O. Ter Kuile[6,7], Bjorn Blomberg[2,8,9], Kamija S. Phiri[1]

Qualitative sub-studies Malawi

- PDMC is **highly accepted by caregivers and health care staff including CHW**
- **Intrinsic motivation is high**
- Caregivers preference
  - Prefer to be given all medication – **community-based strategy**
  - No need for SMS reminders; **health passport is sufficient**
  - **No need for CHWs** (high workload, lack of incentive low pay, poor training supervision)
- Caregivers challenges
  - Forgetfulness
  - Poor storage

Svege S et al, BMC Health Serv Res, 2018 Nkosi-Gondwe et al, BMC Health Serv Res, 2018

Cost-effectiveness

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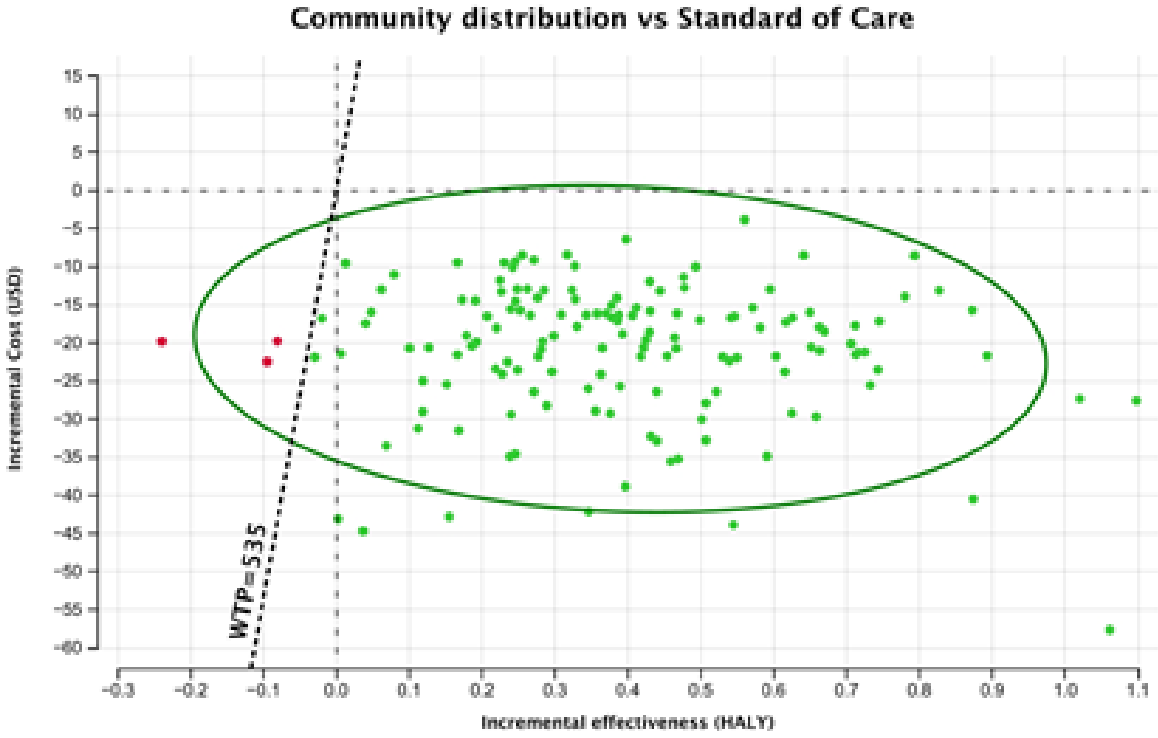
Cost-effectiveness

- PDMC is cheap with high potential to reduce costly hospital readmissions and death
- PDMC has 94% probability of being cost-saving. It is less costly and more effective at increasing health-adjusted life expectancy than the current standard of care
- Provision of PDMC at discharge is less costly for providers and households and more effective than facility-based delivery
- Results are consistent in all three countries, confirmed in sensitivity analyses

incremental cost-effectiveness ratios



Kuhl et al 2022, Cost-effectiveness of PDMC

Conclusions PDMC research studies

- PDMC can be a valuable strategy for the post-discharge management of recently discharged children who have recovered from severe anaemia in malaria-endemic Africa
- PDMC is cost-saving: Less costly and more effective in increasing health-adjusted life expectancy than the current standard of care
- Could avert 36,000 readmissions per year
- Highly acceptable by community health workers, facility staff and caregivers

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New WHO guidelines

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New WHO guidelines for malaria chemoprevention 03 June 2022

https://app.magicapp.org/#/guideline/6287

WHO Guidelines for malaria - 3 June 2022

v4.0 published on 6/3/22

Post-discharge malaria chemoprevention (2022)

Children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission should be given a full therapeutic course of an antimalarial medicine at predetermined times following discharge from hospital to reduce re-admission and death.

- Post-discharge malaria chemoprevention (PDMC) should be given to children following admission with severe anaemia [129] that is not due to blood loss following trauma, surgery, malignancy or a bleeding disorder.
- PDMC implementation should be tailored to admissions of children with severe anaemia and consider the duration of protection of the selected antimalarial, and the feasibility and affordability of delivering each additional PDMC course (see "Practical info").
- Moderate to high perennial malaria transmission settings are defined as areas with a *P. falciparum* parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000 [29]. These thresholds are indicative and should not be regarded as absolute for determining applicability of the PDMC recommendation.

Research evidence (1) | Evidence to Decision | Justification | Practical info | More Info | Feedback

New WHO guidelines for malaria chemoprevention 03 June 2022: https://app.magicapp.org/#/guideline/6287

Target group

- All-cause severe anaemia
  - (not just severe malarial anaemia)
  - exceptions
    - blood loss following trauma, surgery
    - malignancy
    - bleeding disorders
- Age
  - <5 years,
  - or <5 years

Regimen

- **Drugs**: AL, DHA-PiP, SP
- **Dose:** standard treatment course: weight-based
- **Frequency:** based on the duration of post-treatment prophylaxis
  - DHA-PIP: monthly
  - AL: every 2 or 3 weeks
    - Not in countries where AL is 1st line Rx
  - SP: monthly, but only in low resistance areas
    - SP is not recommended in East and Southern Africa because of high-grade SP resistance)
- **Number of courses:**
  - 4 courses
    - 1x discharge plus
    - 3x post-discharge
  - Examples
    - AL at discharge, DHA-PIP at 2, 6, 10 weeks post-discharge
    - DHA-PiP at discharge and 4, 8 and 12 weeks post-discharge

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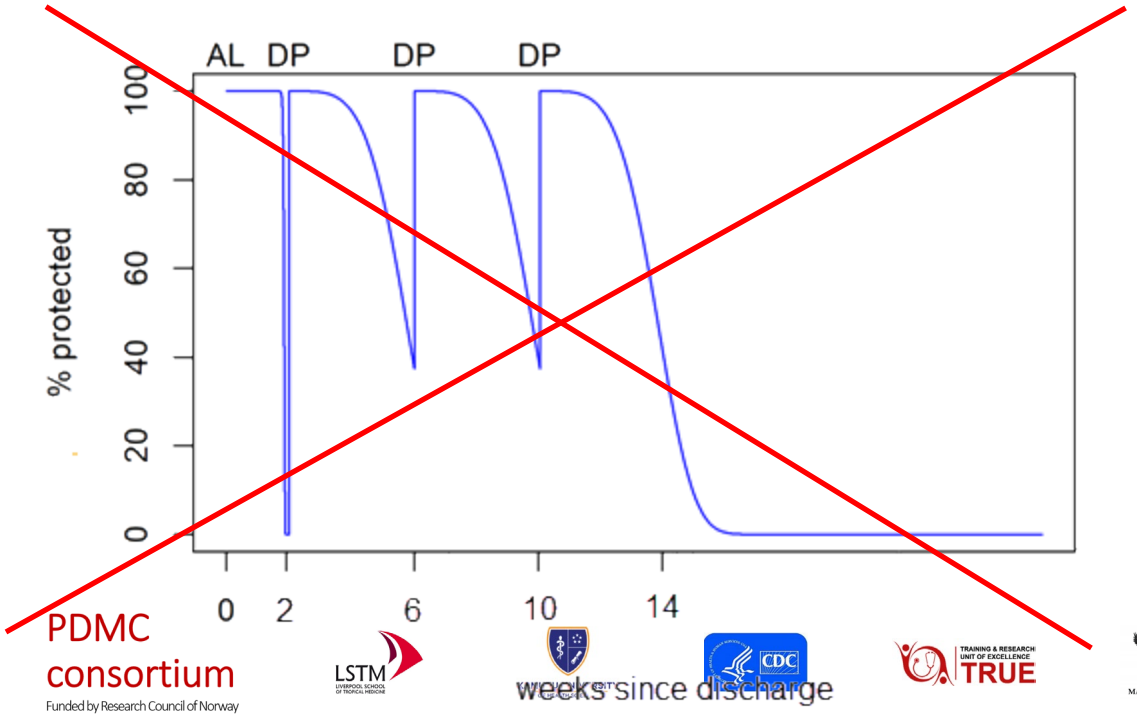
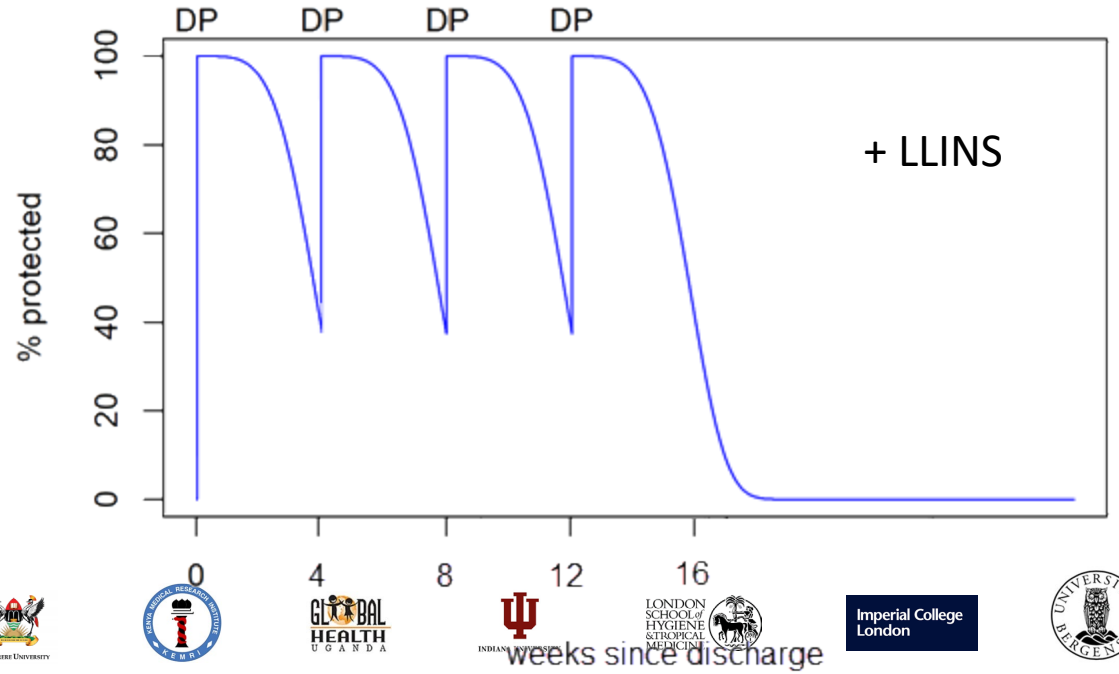
Regimen recommendation

- Minimum 3 months = 4 courses = 4 months of chemoprevention
  - First course at discharge, regardless of malaria on admission
  - 2nd, 3rd, and 4th at 1, 2, 3 months post-discharge
- E.g. 4 courses of DP (East & southern Africa), AQAS-SP (West-Africa)
- Plus long-lasting insecticide treated nets (LLINs)





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New WHO guidelines for malaria chemoprevention 03 June 2022: https://app.magicapp.org/#/guideline/6287

Contra-indications

- Other forms of malaria chemoprevention
  - SMC, PMC (IPTi) or MDA.
  - If other malaria chemoprevention programmes are unable to effectively screen and exclude individuals receiving PDMC
- Sickle cell disease
  - should be included in PDMC,
  - unless they are already receiving regular chemoprevention due to sickle cell disease
- Children who develop severe acute illness following discharge
  - those who are unable to take oral medication
- Received the same drug in the last 30 days
- Allergic to any of the drugs being used
- PDMC-SP [or SP-AQ] should not be given to individuals on co-trimoxazole for HIV

Delivery

- Community-based delivery is preferred by caregivers and associated with increased adherence compared to facility-based strategies
  - Community-based delivery, caregivers received all courses of PDMC on discharge,
  - Facility-based delivery, the caregiver had to collect the PDMC drugs from a health facility each month.
- Instructions on PDMC administration can be written on the child's health card

Implementation

"A guide to support implementation of PDMC will be developed [by WHO] in due course"

New WHO guidelines for malaria chemoprevention 03 June 2022: https://app.magicapp.org/#/guideline/6287

Evaluation

- PDMC programmes should be routinely monitored for safety, efficacy, drug resistance and effectiveness. The impact of introducing PDMC may be evaluated using routine hospital, clinic and/or CHW data.
- The potential effect of PDMC on the spread of drug resistance is likely to be modest, given the small proportion of the population receiving the intervention.
    - Resistance may be monitored by the analysis of molecular markers associated with treatment outcomes, although the correlation between molecular markers and the efficacy of antimalarials for chemoprevention is unclear and should be interpreted with caution.

WHO's Research recommendations PDMC

- The optimal duration for PDMC in different geographical and transmission settings, and understanding of the short-, medium- and long-term benefits of PDMC of different durations; these evaluations should recognize the underlying pattern of post-discharge death and/or re-admission, and the higher risk of some groups dying soon after discharge; to minimize bias, the overall impact during the whole intervention and follow-up period should be considered;
- a better understanding of risk factors (including age) for adverse outcomes following discharge with severe anaemia, and potential differential effects of PDMC in different risk groups;
- patient adherence to PDMC when deployed at scale;
- costs of and coverage achieved by alternative approaches to delivering PDMC;
- feasibility of different coordination mechanisms between hospital and outpatient/community settings for PDMC;
- feasibility of implementing PDMC in parallel with other malaria chemoprevention interventions (e.g. SMC and PMC);
- the long-term (e.g. 12 months and longer) impact of PDMC on child survival;
- the effectiveness of PDMC on severe anaemia of different etiologies;
- the effectiveness of PDMC for children diagnosed with severe anaemia and malaria in low transmission settings;
- the feasibility, costs and effects of combining PDMC with additional interventions (e.g. ITNs) to reduce the household's risk of further infection and adverse health outcomes.

Acknowledgments

Investigators

Kamija S. Phiri
Titus Kwambai
Aggrey Dhabangi
Robert Opoka
Richard Idro
Amani Thomas Mori
Lucy Okell
Kalifa Bojang
Carole Khairallah
Kasia Stepniewska
Matt Cairns
Siri Lange
Melf Kuhl
Bjarne Robberstad
Brian Greenwood
Feiko ter Kuile

Funding

The Research Council of Norway

WWARN

BILL & MELINDA GATES foundation

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Thank you

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Some points for discussion?

- Target group: ‘all-cause’ or severe malaria anaemia?
- Age range: <5y or <9y?
- Regimen? 3 or 4 courses?
  - 3 courses (AL, followed by week 2, 6, 10) or
  - 4 courses (week 0, 4, 8, 12)
- Drugs
  - Long acting (DHA-PiP, AQ-SP)
- Overlap with other chemoprevention strategies
  - Exclude/include in SMC areas?
  - Perennial malaria chemoprevention / IPTi
  - Sickle cell disease

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