Bioavailability, bioefficacy and wash resistance
Bioavailability, bioefficacy and wash resistance

What about the surface chemistry should we be measuring along the life cycle of ITNs, and what methods do we need to measure it?

Dr Rosemary Lees and Assoc Prof Corine Ngufor
Setting the Scene

- Setting the scene
- Relevant issues arising from the PQT/VCP Product Review Report
- Introducing presenters for the session
- Key questions to address in this session
Relevance of Surface Chemistry to ITNs

- Quantification of AI or synergist on the surface of the fibres
  - Dynamic – AI released from the reservoir to the surface, regenerates after washing
- Presentation of AI or synergist
  - Physical state (amorphous or crystalline)
  - Crystalline particle size and shape
  - Distribution of AI or synergist on the surface of the polymer
  - Bio-available fraction of AI / synergist → Pick up by mosquito
PQT/VCP Product Review Report of pyr+ ITNs

PQT/VCP Public Report
Product Review Report
Insecticide Treated Nets Formulated with Pyrethroid+PBO
and Pyrethroid+2nd Active

Prequalification Unit – Vector Control Products Assessment (PQT/VCP)
Regulation and Prequalification Department (RPQ)
Access to Medicines and Health Products (MHP)
World Health Organization (WHO)
PQT/VCP Product Review Report of pyr+ ITNs

• Methodological issues highlighted:
  • “data... often generated in a manner which deviated from the intent of the product, possibly in order to align with the standards/methods... Product testing should be conducted to support the use of the product.”

We should be measuring criteria that relate to performance and criteria that reflect the specific nature of the net
  • “Data requirements and methodology for the Wash Resistance Index should be reviewed to consider the impact of selected wash intervals.”

Regeneration times should be reviewed and linked to product performance
  • “there needs to be a defined distinction between bioassays for the purpose of characterization of quality related information... and testing to investigate efficacy.”

Different methods may be needed and different endpoints measured for QC and for efficacy testing
PQT/VCP Product Review Report of pyr+ ITNs

• Formulation issues relevant to surface chemistry:
  • “... a product which delivers continuous and controlled release of the active substance(s)…”

Formulation is critical to bioefficacy as it relates to presentation and bioactivity of the AI
  • “...changes to source materials, formulations and manufacturing processes may limit the usefulness of historic data.”

Therefore, any changes need to be considered for their impact on performance
  • “approved storage conditions and maximum storage period” and “validation of accelerated storage methods”

Surface chemistry should be considered in validating storage conditions and times
Current Guidelines on Washing

- Wash Resistance Index and Regeneration Times

### Table 1. Main parameters assessed in phase I, II and III studies of long-lasting insecticidal mosquito nets

<table>
<thead>
<tr>
<th>Phase</th>
<th>Type of study</th>
<th>Parameters measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Laboratory</td>
<td>Regeneration of insecticidal activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy and wash-resistance</td>
</tr>
<tr>
<td>II</td>
<td>Small-scale field trial</td>
<td>Wash-resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy as measured by vector mortality and blood-feeding inhibition</td>
</tr>
<tr>
<td>III</td>
<td>Large-scale field trial</td>
<td>Long-lasting insecticidal efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rate of loss or attrition of nets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physical durability of netting material</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Community acceptance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Safety</td>
</tr>
</tbody>
</table>

\[ w = 100 \times \sqrt[4]{\frac{t_4}{t_0}} \]

where: \( w \) = wash resistance index, expressed as a percentage; \( t_4 \) = total active ingredient content (in g/kg) after 4 washing cycles; and \( t_0 \) = total active ingredient content (in g/kg) before washing (no washing).

### 2.3 Efficacy criteria for phase I studies

Nets washed at least 20 times that meet the criteria of WHO cone bioassays (\( \geq 80\% \) mortality or \( \geq 95\% \) knock-down) or of the tunnel test (\( \geq 80\% \) mortality or \( \geq 90\% \) blood-feeding inhibition) meet the criteria for undergoing phase II testing.

### 3.11 Efficacy criteria for phase II studies

A candidate LN is considered to meet the phase II efficacy criteria if, after 20 washes, it performs as well as or better than the reference LN when washed 20 times in terms of blood-feeding inhibition and mortality. Such candidate LNs are given an interim recommendation.
Introducing our Presenters

- **Svetlana Ryazanskaya**, IVCC - Relevance of Chemical Assessments for ITN
- **Bart Kahr**, NYU – polymorphism, blooming and inhibiting crystallization, with bioefficacy data from LSTM
- **Seth Irish**, Swiss TPH – Cone bioassays for estimating bioefficacy in quality assurance
- **Ole Skovmand** – Two proposed methods to measure bioavailable surface AI
- **Moussa Cisse**, LBMA-USTTB - C-vue HPLC method
Key Questions for this session

• **What surface chemistry characteristics would be informative?**
  - Critical to efficacy and durability, and product performance
  - What to measure when? Product development, demonstrating bioefficacy, predicting efficacy, defining specifications, quality assessment including durability monitoring...

• **What methods should be/are being developed?**
  - What questions do we need them to address?
  - Where should our focus be?
  - Identifying, developing and validating informative methods

• **What research questions should be addressed to support this work?**
  - Ongoing or gaps to be filled
Thank you
PQT/VCP Product Review Report of pyr+ ITNs

• Why are we discussing Surface Chemistry?
  • “The physical/chemical data requirements... should be reviewed with particular attention paid to meaningfulness/value of each current data requirement, gaps in information, availability of methodology, potential need for establishing attribute specific standards.”
  • “The focus of chemistry assessments should be shifted from total AI/synergist content to surface concentration and further that which is bioavailable.”
  • “Method development for direct measurement of surface concentration should be a longer-term goal with the use of modelling of expected surface concentrations until direct methods are available.”
  • ITN specifications “could include physical and chemical properties that are critical to efficacy and durability...”
  • “Consideration should be given to development of testing to assess surface concentrations, which parameters are critical to physical durability, and whether a single measure of wash resistance is appropriate for ITNs.” – also presentation of chemistry?
PQT/VCP Product Review Report of pyr+ ITNs

• Recommendations for improved guidance on:
  • Study designs for wash regeneration, wash resistance, and Experimental Hut Trials (EHTs), including statistical power calculations
  • Selection of mosquito strains to be used in bioassay and efficacy testing - resistance mechanisms, intensity, or other characteristics relevant to the intended action of the ITN
  • Selection of meaningful methods and endpoints which are appropriate and relevant to the investigation of the intended action of the ITN. This should include guidance on the weighting of different endpoints to improve the interpretation of the generated data.
  • Purpose of positive and negative controls in bioassays, as well as the interpretation of control data for informing the validity of the study and correction of test results (e.g., control corrected mortality)
  • Reporting of bioassay and efficacy data that captures the variability of test methods and products and standardises result reporting accordingly.
  • Where to use cone tests, tunnel tests, or both
Relevance of Chemical Assessments for ITN
Relevance of Chemical Assessments for ITN

Dr Svetlana Ryazanskaya Randle
May 2022
Introduction – ITN product lifecycle

- Stability and chemical durability
- Migration and regeneration
- Insecticidal presentation

KEY INDICATORS:
- Chemical interactions
- Insecticidal dosage/stability
- Migration/regeneration/chemical durability
- Insecticidal presentation

NET PERFORMANCE

- Manufacturing
- Storage
- Distribution
- R&D Formulation Development
- Use in people’s home
ITN chemical assessment – total vs surface

- **Total insecticidal content**
- **Surface available insecticide**
- **Distribution of surface available insecticide**
- **Presentation of surface available insecticide**
- **Pick up of bio-available insecticide**

- **Quantitative analyses of the total insecticide (starting with the target dose)**
- **Quantitative analyses of the surface available insecticide**
- **Qualitative analyses of insecticides on the surface of the polymer**
- **Qualitative analyses of physical presentation of insecticides on the surface of the polymer**
- **Quantitative analyses of mosquito extracts**
Product related questions

Understanding NET performance

Changes in physical state of a.i. (amorphous or crystalline) and how it is presented to the mosquito.

Evaluation of the physical state:
- SEM
- MALDI-ToF
- PXRD

Lower than expected surface availability of actives on the surface of the polymer/substrate.

Evaluation of bio-availability of a.i.:
- SEM
- MALDI-ToF
- GC/HPLC
- Mass Spectrometry

Irreversible molecular changes (degradation) during manufacturing/storage/usage.

Evaluate its molecular changes by:
- GC/HPLC
- MALDI-ToF
- Mass Spectrometry

Distribution of surface bio-available a.i. on the surface of the polymer/substrate.

Evaluation of the distribution of active(s):
- MALDI-ToF
- SEM

Changes in pick up of bio-available fraction from the surface of the polymer.

Evaluation of the pick up of active(s):
- Mass Spectrometry
- GC/HPLC

Complementary analytical techniques

Changes in pick up of bio-available fraction from the surface of the polymer.
ITN chemical assessment – total vs surface active content example data

Quantitative analyses:
- Total active content (target dosage)
- Surface available content
- Over time (washability, regeneration, storage, use)
- Different formulations
- Correlation with bio-efficacy and surface presentation, distribution and availability

HPLC analysis of total insecticide content vs surface available insecticide at different target dosages (dotted line).
ITN chemical assessment – active distribution on the surface of the polymer

Example data

ITN chemical assessment → Distribution of surface available insecticide → Qualitative analyses of insecticides on the surface of the polymer

Qualitative analyses:
- Distribution of active(s) on the surface
- Over time (washability, regeneration, storage, use)
- Using different formulations
- Correlation with bio-efficacy and surface presentation, distribution and availability

Imaging MALDI-ToF analysis of active on the surface of the polymer before the wash and 24 hours after wash. Optical images of the nets aligned with 2D images (distribution of active) and 3D images (mass spectral fingerprints, m/z intensity) of the active detected on the surface of the polymer.
ITN chemical assessment – active presentation on and in the polymer example data

Qualitative analyses:
- Presentation of active(s) on the surface
- Over time (washability, regeneration, storage, use)
- Using different formulations

[A] - SEM analysis of incorporated ITN, where the presentation of crystalline active is assessed before and after heat stress at 54 °C for 7 days.

[B] - SEM analysis of coated ITN with EDS fingerprint of active on the surface of the polymer.
ITN chemical assessment – active pick up by mosquito example data

Quantitative analyses:

• Mosquito cuticle
• Mosquito homogenates
• Over time (washability, regeneration, storage, use)
• Exposure time - 3, 30, 60 minutes, overnight
• Different formulations (Net A vs Net B)
• Correlation with bio-efficacy and surface presentation, distribution and availability
Food for thought

Laboratory tools

Field tools

Affordable
Non-destructive
While in use
Hand-held
Real-time measurement

While in use
Hand-held
Real-time measurement
Thank you
Mosquito Meets Crystal
Mosquito Meets Crystal

Bart Kahr, Michael Ward, Bryan Erriah, Leilani Smith, Alexander Shtukenberg

New York University

Liverpool School of Tropical Medicine

19 May 2022
1946 Sherwin-Williams promotional film

What is happening here?

Insect foot pad
Crystallization
Painted surface
Polymorphism: Different arrangements of molecules in crystals

- Ubiquitous
- Hard to predict
- Hard to control
- Consequential
Mosquito meets polymorphous crystals
Polymorphism dependent lethality: Crystal form matters a lot

Imidacloprid

Deltamethrin
Heating DeltaDust increases knockdown speed of susceptible *Anopheles* >10-fold

Rosemary & Jessie showed that it works for pyrethroid resistant *Anopheles*

Transformations among solid forms is consequential.

Heating ITNs shown to restore fxn.
We must know which crystals grow where under what circumstances.

Chlorfenapyr in blown PE. 

\( P_{\text{na}2_1}, a=11.497(2) \text{ Å}, b=13.712(2) \text{ Å}, \text{ and } c=12.972(2) \text{ Å}. \)

\( \alpha\)-cypermethrin on Interceptor G1

\( P_{2_1}/n, a=11.497(2) \text{ Å}, b=13.712(2) \text{ Å}, \text{ and } c=12.972(2) \text{ Å}, \beta=98.349(2)^\circ \)
Which crystal almost as important as which mosquito.
Lian Yu, 2012 (6 polymorphs). 2022 (13 polymorphs)
Quantification…

...by absorbance spectroscopy…

...or secondary ion mass spectrometry.
1% deltamethrin bloomed in 4 hrs from PE fiber
Tailor-made crystal growth inhibitors
The focus of chemistry assessments should be shifted from total Al/synergist content to surface concentration and further that which is bioavailable.

Need to amplify the signal by a factor of $10^3$ or $10^6$ or $10^9$. 

Fibre Surface

OP, $\nu$CN = 2226 cm$^{-1}$

R, $\nu$CN = 2211 cm$^{-1}$

Y, $\nu$CN = 2231 cm$^{-1}$

ON, $\nu$CN = 2223 cm$^{-1}$
Raman enhancement techniques: Stimulated Raman scattering or surface enhanced Raman scattering or SERS (10^6 enhancements)

Professor Wei Min
Columbia U.

Need to build a special microscope
or
Prepare fibers with embedded metal nanoparticles
How fast insecticide from a dissolving crystal can get to the nervous system by diffusion through a leg?

- Diffusion transport between a contact with a crystal \((x = 0)\) and the beginning of femur \((x = L)\); \(L = 4 \text{ mm}\).
- Concentration of insecticide at \(x = 0\) is equal to the highest spontaneously attainable concentration of insecticide in hemolymph i.e. to its solubility \(c_s\). This concentration is established immediately upon contact with the crystal and does not change over time \(c(x=0, t) = c_s\).
- We assume \(c_s = 100 \text{ mg/mL}\), solubility of insecticide in organic solvents. Likely much smaller.
- Initial concentration in tibia is zero, \(c(x, t=0) = 0\).
- Diffusion coefficient is assumed to be close to that for water, \(D = 10^{-5} \text{ cm}^2/\text{s}\). Likely much smaller.
Mosquito legs are long. Not much gets very far very fast.

\[ c(x) = c_s \left[ 1 - \text{erf} \left( \frac{x}{\sqrt{Dt}} \right) \right] \]

**LD\textsubscript{50}** permethrin 2 ng/mg.
mosquito = 2 mg
4 ng/mosquito
mosquito = 2 \( \mu \)L
4 \times 10^{-9} \text{g}/2 \times 10^{-6} \text{L} = 2 \times 10^{-3} \text{g/L}
2 \times 10^{-6} \text{g/mL} = 2 \text{\mu g/mL}
\( c_s = 100 \text{ mg/mL} \)
Mass spectrometry imaging for measuring diffusion through leg

1 exposure
2 sectioning
3 mass spectrometry
4 concentration maps
Bryan Erriah

- Prof. Michael D. Ward
- Prof. Alexander Shutkenberg
- Leilani Smith

- Dr. Jingxiang Yang (now Prof. in Nankai)
- Dr. Xiaolong Zhu (now at Merck)

- Dr. Ye He (City University of New York)
- Dr. Tai-de Li (City University of New York)
Cone bioassays for estimating bioefficacy in quality assurance
Cone bioassays for estimating bioefficacy in quality assurance

Seth Irish
(on behalf of Stephen Mbwambo and colleagues)
What I will talk about today

The results from cone tests with susceptible mosquitoes are broadly reproducible between sites, particularly when mortality is the endpoint and at high and low mortalities.

Bioassays have intrinsic variability - this needs to be considered, and this variability in bioassays may be considered rather than just putting in a hard threshold.

Cone tests can identify nets that are performing poorly.

Mortality appears to be a more stringent endpoint and better correlated between labs.

According to the literature, the large majority of nets tested prior to distribution met and exceeded the 80% mortality threshold.
Background

- Millions of ITNs being distributed each year
- A subsample of nets from each shipment are submitted for pre-distribution quality control
- While chemical content is assessed, there is no assessment of bioefficacy of the insecticide on the surface of the net
- As a result, occasionally nets have arrived in country that do not fulfil the recommended level of bioefficacy (≥ 80% mortality after 24 h or ≥ 95% knock-down 60 min after exposure)
- While cone tests are routinely used for assessment of ITNs in the field, there is some reluctance to use them for quality control, due to variation in the assay
- However, until there is a standardized way of assessing bioefficacy by other means, the cone test may be the best option.

Aim of this work:

- Determine whether cone bioassays can provide reproducible results when the same nets are tested in two laboratories
- Review relevant literature
For each net, 5 samples were cut

For each net piece, 4 cones were used (5 mosquitoes per cone)

<table>
<thead>
<tr>
<th>5 net brands/years</th>
<th>4 nets of each brand</th>
<th>5 samples taken from each net</th>
<th>4 cones used per net sample</th>
<th>5 mosquitoes tested per net sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 net brands</td>
<td>20 nets</td>
<td>100 net samples</td>
<td>400 cone tests</td>
<td>2000 mosquitoes</td>
</tr>
</tbody>
</table>
# Methods

<table>
<thead>
<tr>
<th></th>
<th>Bioassay test in IHI</th>
<th>Cone bioassay test in PNGIMR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of ITNs tested</strong></td>
<td>20 nets (100 net pieces)</td>
<td>20 nets (100 net pieces)</td>
</tr>
<tr>
<td><strong>Mosquitoes exposed</strong></td>
<td>20 per net piece (cone bioassay)</td>
<td>20 per net piece (cone bioassay)</td>
</tr>
<tr>
<td></td>
<td>100 per net piece (tunnel tests)</td>
<td></td>
</tr>
<tr>
<td><strong>Experiment conditions</strong></td>
<td><em>27±1°C (cone bioassay)</em></td>
<td><em>28 ±4°C (cone bioassay)</em></td>
</tr>
<tr>
<td></td>
<td><em>55% - 82% RH (cone bioassay)</em></td>
<td><em>53% - 71% RH (cone bioassay)</em></td>
</tr>
<tr>
<td></td>
<td><em>27ºC ± 2 ºC (tunnel tests)</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>60% - 100% RH (tunnel tests)</em></td>
<td></td>
</tr>
<tr>
<td><strong>Mosquito species</strong></td>
<td>Pyrethroid susceptible <em>An. gambiae s.s</em></td>
<td>Pyrethroid susceptible <em>An. farauti s.s</em></td>
</tr>
<tr>
<td><strong>Mosquito age</strong></td>
<td>3-5 days (cone bioassay)</td>
<td>2-5 days (cone bioassay)</td>
</tr>
<tr>
<td></td>
<td>5-8 days (tunnel tests)</td>
<td></td>
</tr>
<tr>
<td><strong>WHO efficacy criteria</strong></td>
<td>≥ 95%KD60 or ≥80% M24 (cone bioassay)</td>
<td>≥ 95% KD60 or ≥80% M24 (cone bioassay)</td>
</tr>
<tr>
<td></td>
<td>≥ 90% BFI and/or ≥80% M24 (tunnel tests)</td>
<td></td>
</tr>
</tbody>
</table>
Methods

- Literature review
  - conducted to look at all cone bioassays on pyrethroid-treated nets in countries pre-distribution

- Statistical analysis
  - Evaluation of knockdown and mortality using standard WHO thresholds
  - Spearman rank correlation coefficient to look at correlation
  - Bland-Altman methods to assess agreement between the measurements of the two sites
  - Cohen’s kappa to evaluate pass/fail results
Results

- At PNGIMR, **8/20** nets met initial cone test criteria (≥95% knockdown or ≥80% mortality)
- At IHI, **13/20** nets met initial cone test criteria, but all nets not passing the cone test did meet the tunnel test criteria (≥90% blood feeding inhibition or ≥80% mortality)
Results

• The relationship between knockdown and mortality was examined:
  • IHI: $R=0.36$, showing low correlation of KD and mortality
  • PNGIMR: $R=0.78$, showing higher correlation of KD and mortality
Results

• Correlation between IHI and PNGIMR results
  • Knockdown (R=0.6, p=0.002)
  • Mortality (R=0.9, p<0.001)

Figure 3 Correlation of cone bioassay tests results between IHI and PNGIMR testing facilities. Dash line is the WHO threshold 95% KD60 (A) and 80% M24 (B). Large dots represent averages per sampled nets (4 per net type) and small dots represent all subsamples (5 per net).
Results

• Bias (difference between 0 and the mean of the differences- IHI vs PNGIMR) was 15.5 and -17%

• The confidence intervals were -25 to 57% for knockdown and -61 to 27% for mortality. No acceptable range was predefined.

• Less than 5% of the measurements were outside the 95% CI indicating agreement, but is this agreement acceptable?
Results

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• Less than 5% of the measurements were outside the 95% CI indicating agreement, but is this agreement acceptable?
Results

- When confidence intervals were set to the WHO thresholds, the IHI and PNGIMR results resulted in the same “pass” or “fail” determination for 90% of the nets.
- Agreement in determination was good $K=0.79$ (0.53-1.0)
Results

Literature review

• Majority of pre-distribution pyrethroid-treated nets had high knockdown and mortality (mean KD: 96%, mean mortality 92%)

• Out of 83 unwashed ITN results reported, only 12 reported knockdown of less than 95%, and only 8 reported mortality less than 80%
Discussion

• There are important considerations when thinking about pre-distribution quality control
  • Chemical content vs bioefficacy
  • Storage conditions
  • Variability inherent in cone bioassay (due to mosquito rearing, test procedures, etc).
  • Laboratory differences

• The finding of nets that succeeded in the pre-shipment assays but failed in bioassays indicate that some pre-distribution testing may be necessary

• While not perfect, cone bioassays appear to be a viable method for assessment of ITNs.
MERCI. ASANTE SANA. THANK YOU

- VCPTU team at IHI
- PNG National Malaria Control Programme
- Leo Makita
- Rotarians against malaria PNG

Research Article
Cone Bioassays Provide Reproducible Bioefficacy Estimates with Different Anopheline Mosquitoes and Can Be Used for Quality Assurance of Pyrethroid Insecticide Treated Nets

Stephen Gabriel Mvambo¹ Email
Nakei Bubun²
Emmanuel Mmba¹
Jason Moore¹
Kaiseri Mbina¹
Dismas Kamando¹
Moses Leman²
Emmanuel Mpolya²
Olukayode Odufuwa¹
Tim Freeman²
Stephan Karl²
Sarah J Moore¹ ORCID
On the surface: Two simple chemical methods to determine the bioavailable surface concentration of insecticide for insecticide treated net (ITN) evaluation.
On the surface: Two simple chemical methods to determine the bioavailable surface concentration of insecticide for insecticide treated net (ITN) evaluation.

Ole Skovmand,
D M Dang, T Q Tran, R Bossellman, SJ Moore
What I will talk about today

• Quantification of Al or synergist on the surface of the fibres using two chemical methods
  1. SWAM – Surface Wash Analytical Method
  2. BAM – Before and After Method

• Relationship between chemical methods and bioefficacy measured by MKDT median knock down time
Applications for methods to determine surface concentration

- Product development – fast way to measure wash interval once minimum surface concentration is established with test systems
- Predicting efficacy without the constraints of mosquito strain differences
- Quality assessment of surface concentration post shipment
- Durability monitoring – check that surface concentrations still biologically relevant after 1, 2, 3 years
Two main ITN production methods

**Incorporation:**
insecticide mixed with a polymer to extrude mono filament yarn

- **Advantages:** strength, durability
- **Producer controls yarn quality, knitting and incorporation**
- **Limitations:** not all insecticides can be incorporated

**Surface treatment:**
insecticide (mixed in a resin or a polymer) bound to netting fibres by dipping (or spraying) techniques

- **Advantages:** ease of application, lower capacity costs
- **Nets mostly not in control of final producer,**
- **Limitations:** not all insecticides can be coated, difficult to add 2 AIs, multifilament yarns more fragile
Evidently only insecticide at the ITN surface is relevant.

Polyester mulifilament yarn

Surface exposed insecticide

Polyethylene Monofiber yarn
We need accurate means to measure surface concentration

• To correctly estimate regeneration time
  • “Data requirements and methodology for the Wash Resistance Index should be reviewed to consider the impact of selected wash intervals.”

Skovmand et al. From the factory to the field: Malar J 20, 363 (2021).
Two methods for determining surface concentration

**BAM:**
Before and After Method
Measure total concentration before and after wash, the difference is what was washed off

**SWAM:**
Surface Wash Analytical Method
Analyse the surface wash off
PE nets can be washed with cold acetone or soap water, coated nets may lose coating and surface insecticide.

Nets with Deltamethrin or Alphacypermethrin form crystals at the surface.

**Acetone** will remove all at the surface but not from inside the yarn.

**Soap** wash will not remove all crystals, but removes all molecular (bioactive) insecticide.
Store at 30±2ºC

Initial soap wash

Initial acetone wash

Dry 2 hours at 30º

Initial Wash

3x soap

1x acetone

Regeneration

Day
1
2
3
4
5
6
7
10
15
20

Surface wash

MKDT Bioassay

"Wash"

Acetone extract

1x acetone wash

Surface wash off

Surface Wash Analytical Method
Total surface content is determined from acetone extracts

<table>
<thead>
<tr>
<th>Days</th>
<th>After soap Wash</th>
<th>After Acetone dipping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (mg/kg)</td>
<td>DM (mg/kg)</td>
</tr>
<tr>
<td>2/24</td>
<td>25,4</td>
<td>49,1</td>
</tr>
<tr>
<td>1</td>
<td>70,1</td>
<td>65,9</td>
</tr>
<tr>
<td>2</td>
<td>92,1</td>
<td>59,8</td>
</tr>
<tr>
<td>3</td>
<td>119,5</td>
<td>81,9</td>
</tr>
<tr>
<td>5</td>
<td>134,0</td>
<td>83,5</td>
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<tr>
<td>7</td>
<td>119,5</td>
<td>91,8</td>
</tr>
<tr>
<td>10</td>
<td>136,6</td>
<td>105,5</td>
</tr>
<tr>
<td>15</td>
<td>175,1</td>
<td>102,5</td>
</tr>
<tr>
<td>20</td>
<td>185,4</td>
<td>102,0</td>
</tr>
</tbody>
</table>
Correlation between Median Knock Down Time and deltamethrin measured by SWAM was better with the initial soap wash.
• When species with different sensitivity to PYR are used to test regeneration time the MKDT values are different but the number of days to a stable level is the same.

• In a classic WHO regeneration time, we would have 1 day for *An dirus* and 5 to 15 days for *Culex*. 
There was very high correlation between Median Knock Down Time (MKDT) for the susceptible and resistant strain.
• The regeneration time measured by MKDT and regeneration of PBO and DM to the surface measured by acetone extraction
• Within 20% of the 20-day value by day 5 and fully regenerated by day 10
Before and after method

Classic WHO chemical analysis are BAM data and can be used to calculate surface concentrations.
Evaluation of BAM

• Two commercial nets tested
• Wash off was conducted with either a CIPAC soap wash or dipping in acetone using SWAM
• Results were informed by bioefficacy testing with Median Knock Down Time (MKDT)
Surface concentration measured by before and after method (BAM). Wash off from soap or acetone wash measured in commercial ITNs. Data are grams per kilogram. Labels show surface concentration "out of the bag" as a percentage of total active ingredient.

**PermaNet 3.0 PBO**
- Start: 20.5
- After Soap Wash: 16.2
- After Acetone Wash: 9.5

**PermaNet 3.0 DM**
- Start: 23.7
- After Soap Wash: 9.5
- After Acetone Wash: 23.7

**Tsara Boost PBO**
- Start: 4.0
- After Soap Wash: 5.0
- After Acetone Wash: 5.0

**Tsara Boost DM**
- Start: 6.2
- After Soap Wash: 5.0
- After Acetone Wash: 6.2

MKDT PermaNet® 3.0 402 seconds
MKDT Tsara® Boost 443 seconds

$z = 1.492, p = 0.171$
Comparison SWAM and BAM on 4 net samples, 2-4 determinations per sample

<table>
<thead>
<tr>
<th>Sample</th>
<th>Pbo</th>
<th>Deltamethrin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aver</td>
<td>std dev</td>
</tr>
<tr>
<td>1st wash water</td>
<td>459.38</td>
<td>71.17</td>
</tr>
<tr>
<td>2nd wash water</td>
<td>30.82</td>
<td>1.93</td>
</tr>
<tr>
<td>3rd wash water</td>
<td>17.54</td>
<td>2.54</td>
</tr>
<tr>
<td>re-extract 1.st water</td>
<td>12.49</td>
<td>1.53</td>
</tr>
<tr>
<td>Nets before wash</td>
<td>13334.50</td>
<td>367.14</td>
</tr>
<tr>
<td>Nets after wash</td>
<td>12603.25</td>
<td>404.76</td>
</tr>
<tr>
<td>SWAM (sum of wash waters)</td>
<td>520.23</td>
<td>95.01</td>
</tr>
<tr>
<td>BAM (Total Before-After)</td>
<td>731.25</td>
<td>665.46</td>
</tr>
</tbody>
</table>

One BAM DM was negative
Two methods for determining surface concentration by washing

**BAM**
- depends on net homogeneity
- sample destructive
- can be used X time after a washing provided no evaporation

**SWAM**
- does not depend on net homogeneity
- not sample destructive
- access to soap water solution needed
Conclusions

BAM and SWAM can measure bio-relevant surface concentration of AI in ITNs

MKDT is a better method than cone test for determining regeneration time (RT)

Surface concentrations and MTKD correlates and provide the same RT, independent of resistance level of the mosquito strain used

Wash intervals were longer than measured by standard WHO method

Combining MTKD and SWAM or BAM could improve predictions of ITN performance and further validations are warranted
Use of a portable field-adapted liquid chromatographic system (c-vue machine) to determine deltamethrin surface level on insecticide-treated nets as part of a three-year durability monitoring in Mali.
USE OF A PORTABLE FIELD-ADAPTED LIQUID CHROMATOGRAPHIC SYSTEM (C-VUE MACHINE) TO DETERMINE DELTAMETHRIN SURFACE LEVEL ON INSECTICIDE-TREATED NETS AS PART OF A THREE-YEAR DURABILITY MONITORING IN MALI

Prof Moussa BM CISSE
March, 19th 2022
The US President Malaria Initiative supported ITN durability monitoring in Mali from 2018 to 2020.

The ability to monitor insecticide levels on ITNs is hampered in certain situations by the cost and availability of the equipment and resources required for analysis.

LBMA in collaboration with CDC used a portable field-adapted liquid chromatographic system (C-Vue machine) to determine the surface level of deltamethrin on ITNs. Moreover WHO cone bioassays were used to determine ITNs bio efficacy.
OBJECTIVES

PRIMARY OBJECTIVE

• Assess the insecticidal effectiveness of ITNs (Yorkool and PermaNet 2.0) in two villages at 12, 24 and 36-months after a mass net distribution

SECONDARY OBJECTIVES

1. Determine the nets handling, using and washing practices of the communities,
2. Assess the nets bio efficacy at 12, 24 and 36-months after distribution using WHO-Cone bioassays,
3. Estimate insecticide content at 12, 24 and 36-months after distribution using C-Vue HPLC method
METHODS 1/5

**Figure 1. Nets Collection Sites and Period**

<table>
<thead>
<tr>
<th>Site</th>
<th>Net brand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenieba</td>
<td>Yorkool</td>
</tr>
<tr>
<td>Kita</td>
<td>PermaNet 2.0</td>
</tr>
</tbody>
</table>

**Legend:**
- **Borders of the country**
- **Borders of health districts**
- **Site of study**

**Timeline:**
- **Baseline:** March-May 2018
- **Distribution:**
  - 0 ITNs
  - 6 ITNs
  - 12 ITNs
  - 24 ITNs
  - 36 ITNs
- **Sampling:** Subsample (30/site) for bioassay and HPLC

**Periods:**
- Dec 2018
- Nov-Dec 2019
- Nov-Dec 2020
DETERMINATION OF NETS HANDLING, USING AND WASHING PRACTICES

The information about nets handling, using and washing practices was collected by using questionaries.
METHODS 3/5

ASSESSMENT WITH WHO-CONE BIOASSAY

Laboratory-reared susceptible colony of Anopheles coluzzii (Ngousso)

Optimal effectiveness: Knock Down 60 min ≥ 95% or mortality ≥ 80%

Minimal effectiveness: Knock Down 60 min ≥ 75% or mortality ≥ 50%

WHOPES criteria: at least 80% of recommended ITN brand should achieve optimal effectiveness 36 months post distribution
ASSESSMENT WITH C-VUE HPLC

SURFACE INSECTICIDE COLLECTION ITEMS

1. Spring-type wooden clothespins.
2. Sampling Caps (20-ml vial caps, 23 mm diameter, notched to accommodate clothespin).
3. Lens paper (100 x 50 mm for sampling and 25 x 20 mm squares for internal standard and calibration samples).
4. Bottle Cap (26 mm inner diameter, e.g. Coca-cola bottle cap).
5. Rubbing platform – 125 x 30 mm polypropylene plastic cut from the tops of 200-ul pipet tip container.
6. Binder clips – spring type, medium size with gripping lips made from plastic tubing.
METHODS 4/5

ASSESSMENT WITH C-VUE HPLC

NET SAMPLING DEVICE USED TO COLLECT SURFACE LEVELS OF DELTAMETHRIN

C-VUE HPLC COMPONENTS USED TO MEASURE DELTAMETHRIN SURFACE LEVEL
ASSESSMENT WITH C-VUE HPLC

- The equation derived from the plot, \( \log Y = 0.0232x - 1.37 \), was used to estimate total deltamethrin levels and failure rate.
- The deltamethrin surface level associated with a new net containing the total level of 55 mg/m\(^2\) is 0.81 mg/m\(^2\) (95%CI: 0.63, 1.02).
- A comparison for validation was made with the “Gold Standard” WHO-recommended HPLC technique for deltamethrin analysis (CIPAC).
RESULTS AND DISCUSSION 1/5

NET WASHING PRACTICES

<table>
<thead>
<tr>
<th>Variable</th>
<th>12 months</th>
<th>24 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>KENIEBA/ YORKOOL</td>
<td>N=30</td>
<td>N=30</td>
<td>N=29</td>
</tr>
<tr>
<td>Washes last 6 months (all)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.2</td>
<td>2.8</td>
<td>2.0</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Soap used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>country soap bar</td>
<td>38.1%</td>
<td>32.1%</td>
<td>21.7%</td>
</tr>
<tr>
<td>detergent or bleach</td>
<td>52.3%</td>
<td>57.1%</td>
<td>43.4%</td>
</tr>
<tr>
<td>mix</td>
<td>9.5%</td>
<td>10.7%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Kita/ PermaNet 2.0</td>
<td>N=30</td>
<td>N=30</td>
<td>N=30</td>
</tr>
<tr>
<td>Washes last 6 months (all)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.4</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Soap used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>country soap bar</td>
<td>36.0%</td>
<td>37.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>detergent or bleach</td>
<td>64.0%</td>
<td>27.5%</td>
<td>50.0%</td>
</tr>
<tr>
<td>mix</td>
<td>0.0%</td>
<td>34.4%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

- Nets had been washed an average of three times over the previous 6 months
- The main product used to wash them was detergent, bleach or regular bar soap in both sites
RESULTS AND DISCUSSION 2/5

INSECTICIDAL EFFECTIVENESS USING WHO-CONE TEST

**Figure. Box Plot of Cone Bioassay using a Susceptible Colony of An. coluzzii Ngoussu on Yorkool and PermaNet 2.0 ITNs**

- **Optimal effectiveness** (KD60 $\geq$ 95% or mortality $\geq$ 80%): < 80% at 12–24 and 36-month for both brands. Based on WHO criteria there is a potential problem with low bio efficacy of both ITN brands.

- **Minimal effectiveness** (KD60 $\geq$ 75% or mortality $\geq$ 50%): >80% at 12 and 24-month for both brands.
Deltamethrin surface level concentration decreased significantly \((p<0.05)\) over the study period in both net brands. It has decreased from:

- 0.69 mg/m\(^2\) at 6-month to 0.08 mg/m\(^2\) at 36-month with Yorkool.
RESULTS AND DISCUSSION 4/5

INSECTICIDAL EFFECTIVENESS USING C-VUE HPLC

Figure. Box plot of ITNs chemical surface level concentration results using a portable HPLC C-VUE

Kita/PermaNet 2.0

Deltamethrin surface level concentration decreased significantly ($p<0.05$) over the study period in both net brands. It has decreased from:

- 0.46 mg/m\(^2\) at 6-month to 0.06 mg/m\(^2\) at 36-month with PermaNet 2.0.
RESULTS AND DISCUSSION 5/5

INSECTICIDAL EFFECTIVENESS USING C-VUE HPLC AND CIPAC (GOLD STANDARD) METHOD

Figure. Passing and Bablok regression analysis for two instruments: instrument #1 is the Agilent 1200 Series, and instrument #2 is the C-Vue® Portable Liquid Chromatograph Model CH2B.

Figure. Residual plot of the distribution of differences around the fitted regression line.
CONCLUSION

• The use of detergent, bleach or regular bar soap in order to wash the nets were associated to the reduction of nets’ bio efficacy.

• The WHO standardized cone bioassay and C-Vue evaluation respectively demonstrated that the effectiveness and insecticide content of both net types were consistently lower than expected at 3 years.

• The C-Vue was used successfully for the first time in Mali to measure the insecticide surface levels of ITNs. Results that were consistent with cone bioassays and gold standard HPLC methodology.

• This affordable new technology is less cumbersome than the standard HPLC typically used to perform ITNs chemical analysis for durability monitoring in malaria endemic countries.
• Propose the C-vue method for ITN durability monitoring in malaria endemic countries
• Validate the use of C-vue method determine the surface level of PBO or chlorfenapyr, pyriproxyfen on ITNs
THANK YOU
Overview of charrette group inputs
## Challenges & Solutions -- Arrival of ITNs in country

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
<th>Implementation Ideas</th>
</tr>
</thead>
</table>
| Pre-shipment inspection | • Trust deficit in the pre-shipment testing process | • Rotation of inspectors to be built into the system  
• Transparent and open data sharing of pre-shipment assessments | • Procurers to stipulate rotation/ best practice in contracts with 3rd party inspectors  
• Look at ways to share data more widely, such as procurers sharing data between themselves and with programs |
| Post shipment inspection | • Non-standardized post-shipment testing may cause rejection of good products or acceptance of poor products | • Develop harmonized guidance on pre- and post delivery inspection criteria and SOPs | • LQAG (procurers QA group), WHO PQ and NMCP partners working group  
• Need to understand what inspection is done post shipment |
| QMS | • Balance and optimise roles of QMS and inspections to drive ITN quality improvements | • Build trust and understanding  
• Define intended purpose and rationale of QMS and inspections from multiple stakeholder perspectives  
• Full implementation of ISO 9001 | • Produce advocacy brief on QMS and inspection  
• Clear definitions between testing, inspections and QMS to be developed and used by all partners |
## Challenges & Solutions -- Arrival of ITNs in country

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION IDEAS</th>
</tr>
</thead>
</table>
| **Port delays and storage** | • Delays and storage at port including customs clearance and distribution related delays  
• Storage conditions may need to be tailored to individual products  
• Landlock-country challenges are magnified (e.g. tracking and container availability) | • Understand magnitude and impact of this challenge  
• Advocacy to facilitate rapid customs clearance  
• Definition of and guidance on optimal storage conditions (net specific where necessary)  
• Audit, upgrade and improve storage capacity  
• Improved demand forecasting to facilitate greater adherence to delivery date forecasts and storage planning | • AMP may have information/data on impact Scale of problem  
• Research collaboration between academia and GF/procurers/shipping companies  
• Potential use of contract to define conditions during shipping  
• NMCP/MoH to contact customs agencies  
• Manufacturers to provide information as part of PQ dossier  
• Donors and funders may need to support storage upgrades |
| **In-country testing capacity** | • Insufficient in-country capacity: funding, staff infrastructure and other resources for conducting ITN testing. | • Facilitate countries with an interest in conducting optional in-country quality tests  
• Ensuring countries have most up to date SOPs and other resources to support methods | • Secure funding for countries to develop the capacity to conduct independent tests to define the need for tests and responsible parties within this |
### Challenges & Solutions -- Distribution of ITNs

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION IDEAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usage/Care</strong></td>
<td>• Lack of proper care and use instructions</td>
<td>• Community engagement based on feedback/listen to communities</td>
</tr>
<tr>
<td></td>
<td>• Lack of BCC/budget constraints for BCC</td>
<td>• Provide funding for BCC</td>
</tr>
<tr>
<td></td>
<td>• Inappropriate storage/transport conditions at different levels</td>
<td>• More data on ITN usage using new tools and approaches to collect (e.g., accelerometer approach)</td>
</tr>
<tr>
<td></td>
<td>(national and subnational)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No guidelines for warehousing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Budget constraints, including lack of domestic &amp; private sector</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resources, impede proper storage/transport</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Invest in warehouse infrastructure</td>
<td></td>
</tr>
<tr>
<td><strong>Storage &amp; Transport</strong></td>
<td>• Research on impact of storage conditions on performance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Agree and enforce guidelines and SOPs surrounding storage and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>transport at national and subnational level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Enforce quality assurance at different steps in the supply chain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Phased delivery to reduce storage time</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Train NMCPS on net storage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Suppliers to lead post-market surveillance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Develop guidelines for inspection of storage facilities and for response to non-conformity in transport/storage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Data generation to inform engineering of nets with better resistance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>to temperature and humidity</td>
<td></td>
</tr>
</tbody>
</table>
## Challenges & Solutions -- Distribution of ITNs

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
<th>Implementation Ideas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of clear distribution strategy/microplans and delays in distribution at different levels perhaps leading inappropriate storage</td>
<td>Develop clear/proactive distribution strategy/ microplanning</td>
<td>Engagement with AMP efforts around coordination of stakeholders for guidance and distribution planning/learning around best practice.</td>
</tr>
<tr>
<td>Oversupply of nets and associated use of old nets</td>
<td>Digital real-time data collection systems/proper data capture and use/Digital tracing of nets</td>
<td></td>
</tr>
<tr>
<td>Over-simplification of 3-year campaign cycle and sufficient data to inform adjustments</td>
<td>Quality management of distribution channels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flexibility of funding for countries to adjust campaign cycle based on durability data</td>
<td></td>
</tr>
</tbody>
</table>
### Challenges & Solutions -- ITN usage and data generation

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
<th>Implementation Ideas</th>
</tr>
</thead>
</table>
| Available data | • Lack of data on performance/ bioefficacy  
• Insufficient data on durability monitoring/risk factors in country that influence life of a net  
• Lack of information on how performance of nets evolve over time and how this is linked to specifications | • Post market surveillance on retention, bioefficacy, AI concentration, physical integrity and use  
• Publication of data to make appropriate data available to all | • Funding for data collection  
• Need to define as a community what data is needed and what data is already available for post market surveillance |
| Data use | • Feedback loop not sufficient for informing decisions based on data  
• Data biased (perception or real)  
• Capacity to assess bioefficacy of new ITNs in country is limited (if post distribution surveillance should be implemented) | • Feedback system in place for durability monitoring -> PQT -> ITN manufacturing -> product improvement  
• Funding for entomology labs | • Data flow used to inform user-centered design updates to products [as a community to work with manufacturers to define data needs and use cases for product updates (fixing problems, innovation and incentives for innovation)]  
• Funding for analysis of existing data |
## Challenges & Solutions -- ITN usage and data generation

<table>
<thead>
<tr>
<th>CHALLENGES</th>
<th>SOLUTIONS</th>
<th>IMPLEMENTATION IDEAS</th>
</tr>
</thead>
</table>
| **Lack of common vocab** | • Lack of clarity of what post market surveillance is for  
• Misinterpretation of specifications, what they represent and when they should be applied  
• Unclear distinction between quality and performance | • Develop glossary of terms  
• Communication of and commitment to glossary by stakeholders | |
| **Usage by end user** | • Less than optimal handling of nets (drying practices, frequency of washing, methods of washing, environmental stressors)  
• Risks to net during storage  
• Inadequate repair of nets | • Effective communication through the right channels on appropriate use and care  
• New ways of collecting relevant data to inform user-centered design for products  
• Funding for SBC | • Clarify value of increased lifetimes [work ongoing] and translate that to flexible processes that can be informed by data [donors, procurers, countries] |
| **Data quality** | • Concerns around quality control of data collection & design of surveys | • Collaboration around design protocols for surveys | |
# Challenges & Solutions -- ITN usage and data generation

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Solutions</th>
<th>Implementation Ideas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guidance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lack of sufficient guidance on handling nets</td>
<td>• SOPs/guidelines for use of bed nets</td>
<td>• Technical solution: indicator for monitoring number of washes</td>
</tr>
<tr>
<td>• Guidance is available but not used (e.g., packaging lost/not aligned)</td>
<td>• Specify what performance standards are needed and/or reasonable and how they would be used</td>
<td>• Better instructions and labelling on packaging</td>
</tr>
<tr>
<td>• Lack of guidance on performance standards for nets &amp; associated lack of incentive to improve performance due to lack of standards</td>
<td></td>
<td>• Consensus building on reasonable expectations for performance standards</td>
</tr>
</tbody>
</table>

| Context | | |
| • Food insecurity leading to mis-use of new nets | • Promote/incentivize durable net design | |
| • Insecurity, flooding & natural disasters leading to loss/destruction of nets | • Review how we can be flexible for procurement and distribution given established variability of net duration in the field | |
| • Housing construction | | |
| • Rodents | | |
| • Access to nets affecting retention time | | |
**Theory of Change**

- Generally resonated with people
- Suggested updates to focus and clarity in some areas
- Roles, responsibilities and timelines needed

<table>
<thead>
<tr>
<th>User centered approach to surveillance</th>
<th>QMS implementation support</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can inform ITN design, specifications and SBC activities</td>
<td>• Governance of ISO 9000 module implementation</td>
</tr>
<tr>
<td>• What data do we need to get and what tools do we have to collect it?</td>
<td>• Raw material specifications and inspections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Build out cross cutting activities</th>
<th>Need to emphasize price</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Foundation on which the ToC rests and driver of trust</td>
<td>• Understand incentives to drive innovation</td>
</tr>
<tr>
<td>• Identify how key data can be shared and interpreted, particularly change management</td>
<td>• What data/characteristics can drive value-based procurement?</td>
</tr>
</tbody>
</table>
Discussion: does this summary reflect your discussions? Is there anything missing?
Consolidated focus areas and next steps
Key focus areas for post-shipment ITN quality issues

Post-market surveillance

1. Definition of terms for post-shipment surveillance, what this includes, what data is available and what is needed

2. Building trust in pre-shipment inspection: Standardization of tests, Stipulation of best practices for third party inspectors, Data sharing for pre-shipment assessments, Advocacy brief on QMS and auditing implementation of ISO-9001

User-centered design

3. Data on user preferences and usages to inform product updates, including to fix identified problems and to support innovation.

4. Clarify value of increased lifetimes [work ongoing] and translate that to flexible processes that can be informed by data [donors, procurers, countries]

5. Review design factors, labelling and packaging to support appropriate handling for users

Cross-cutting issues

6. Broader glossary of terms covering pre and post shipment quality processes

7. Performance standards: what can reasonably be expected from performance standards and how can user data be incorporated?

8. Guidelines for in-country storage and transportation of nets, including for inspections of storage facilities and response for non-conformity
Discussion: any key focus areas/activities you think are missing here?
What priority would you assign to the following items?

1st: Broad glossary of terms
2nd: Performance Standards
3rd: Building trust in pre-shipment inspection
4th: Data on user preferences and usages to inform product updates
5th: Definition of terms for post-shipment surveillance
6th: Clarify value of increased lifetimes and translate that to flexible processes
7th: Guidelines for in-country storage and transportation
8th: Review design factors, labelling and packaging
## Next steps for post-shipment quality concerns

<table>
<thead>
<tr>
<th>Themes</th>
<th>Activities</th>
<th>Next steps</th>
<th>Lead/Key stakeholders</th>
<th>Timelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-cutting</td>
<td>Develop a clear glossary of terms</td>
<td>PQ working on these</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global policy guidelines -</td>
<td>Develop specifications that link net quality to performance</td>
<td>PQ working on these</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimum standards</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procurement - tendering</td>
<td>Document and measure characteristics that lead to better performance and</td>
<td>Eddie to update</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>have this reflected in procurement decisions.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convening 2</td>
<td>Glossary of terms</td>
<td>PQ working on this Communication plan and review process</td>
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<tr>
<td>Convening 2</td>
<td>Performance Standards</td>
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<tr>
<td>Convening 2</td>
<td>Building trust in PDI</td>
<td>Sharing data more broadly, need better understanding of where trust issue</td>
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<td></td>
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<td>comes from and clarifying process</td>
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