TROPICAL HEALTH

Landscaping of ITN Bioefficacy Report for The Global Fund

1 December 2021

Executive summary

Key points

- This report is a landscaping of processes and factors along the ITN value chain that are meant to ensure that ITNs are fully effective against mosquitoes when they are distributed to households. This includes systems within which ITNs are produced, approved, regulated, procured, quality assured, and managed.
- Areas of current strengths
  - Available evidence indicates that the vast majority of ITNs are likely to contain sufficient insecticide when they are delivered to households.
  - Documentation requirements and quality systems put in place by WHO Prequalification Unit, procurers, and suppliers have improved in recent years, and significant efforts are ongoing to ensure test criteria for insecticidal efficacy of ITNs are clear, reproducible, and relevant.
- Areas of potential risk
  - While competition drives innovation and efficiency, pressures to reduce costs could impact sourcing of raw materials and oversight by suppliers and contracted manufacturers, with potential negative impacts on bioefficacy. It is not clear that current quality control tests and systems are robust enough to identify all problems.
  - Limited data sharing when potential issues arise, along with variability in test methods and results across labs, contribute to doubts of the overall efficacy of ITNs as our primary vector control tool.
- Key recommendations
  - Improve coordination, data transparency, and communication around ITN bioefficacy quality issues, ideally through clarifying post-market surveillance roles and responsibilities.
  - Review and realign testing methods to ensure they are relevant for the products, particularly for new types of ITNs
  - Continue and expand use of quality performance data to inform tendering and allocation decisions, and reward high quality products.

Background

The scope of this review is to provide a detailed overview of issues potentially affecting the biological efficacy of ITNs against mosquitoes, up to the point at which ITNs are distributed to households. This includes systems within which ITNs are produced, approved, regulated, procured, quality assured, and managed. The scope does not include physical durability of ITNs nor durability of bioefficacy post-distribution, both critically important areas that are better addressed separately. It is also true, however, that many of the issues identified and recommendations made through the current work will have wider impact, including on the area of ITN durability.

Findings

Across stakeholders at all levels, there was commitment to ensuring ITN bioefficacy throughout the value chain. The vast majority of ITNs pass preshipment testing (over 99% of shipments according to PMI), but there are doubts about the relevance and consistency of the proxy tests used to measure bioefficacy, and the representativeness of the samples taken, and thus the robustness of current systems to be able to identify poor quality ITNs before they leave the factory. WHO PQ has implemented a number of important changes to ensure quality, from manufacturing site inspections to periodic

product reviews, and PMI and Global Fund have instituted or are in the process of instituting additional quality assurance requirements. Both agencies use quality performance metrics to inform decisions about allocations.

Resource constraints were cited across the value chain: WHO PQ has a large portfolio with very limited staff; the costs of preshipment testing limit the number of samples that are taken; innovative, rapid tests to assess the insecticide on the surface of the net where mosquitoes encounter it lack funding for development and deployment; national programmes lack funding to conduct confirmatory testing when nets arrive in-country. Products containing more than a single pyrethroid must be tested against resistant mosquitoes, increasing the time and resources required. Suppliers reported feeling significant pressure to lower costs in order to remain in the market; potentially leading them to source cheaper raw materials or reduce oversight. ITNs are chemically complex and small changes in manufacturing can have a large impact on bioefficacy. WHO PQ requires all product changes to be reported and evaluated, but it remains unclear to what extent if any products were changed before 2017, and if changes have had a real impact on bioefficacy. There is as yet no coordinated post-market surveillance system for ITNs.

An overall lack of data, communication, and coordination around these issues contributes to perceptions that ITNs may not be working as they were intended, and fosters distrust within the ITN stakeholder community.

Recommendations

As a first step, a number of **existing data gaps should be filled**. Critical to this is WHO PQ's ITN Project, which will provide a review of ITN performance, including data requirements, product specifications, standards for testing, methodology, recommended use, and labelling. In addition, gaps in our understanding of ITN transport conditions and in determinants of bioefficacy post-distribution should be addressed. Reviewing and realigning quality control testing methods should ensure they are relevant for the products, particularly for new types of ITNs.

Second, there is a need for ongoing **coordination, data transparency, and communication** around ITN bioefficacy quality issues, ideally through clarifying post-market surveillance roles and responsibilities. A system for post-market surveillance where data can be triangulated, acted upon, and communicated outward is urgently needed. Additional transparency around bioefficacy quality issues, their investigation, and resolution would be helpful to combat mistrust.

A **low-cost, rapid testing method** would be a powerful tool to expand bioefficacy quality monitoring both pre- and post-shipment. This method would ideally assess the availability of active ingredients at the surface of the net where mosquitoes encounter it. Several promising candidates are in development but further investments would be needed to bring these to market.

Finally, procurers should continue and expand their **use of quality performance data** to inform tendering and allocation decisions, and reward high quality products.

A **shared purpose and commitment** has not yet been articulated collectively by partners, but it will be important for stakeholders to share their individual visions, objectives, and perspectives on needs in this area. Agreeing a shared way forward related to ensuring ITN quality and bioefficacy must be done inclusively.

Partner support will be key to ensure these projects are **fully resourced**.

Acknowledgments

This report was made possible by support from the Global Fund, who commissioned the work after consultation with other key stakeholders including WHO, PMI and UNICEF. The authors would like to recognize the invaluable input received from all stakeholders interviewed and thank them for their time and preparation.

Abbreviations

AI – active ingredient

AMP – The Alliance for Malaria Prevention

CAPA – corrective and preventive action

ERG – Expert Review Group

GLP – Good Laboratory Practice

GMP – World Health Organization Global Malaria Programme

I2I – Innovation to Impact

ITN – insecticide treated nets

IVCC – Innovative Vector Control Consortium

JMPS – Joint Meeting on Pesticide Specifications

KII – key informant interviews

LLIN – Long-lasting insecticide treated nets

MPAC – Malaria Policy Advisory Group

NTD – World Health Organization Neglected Tropical Diseases

OIG – Office of the Inspector General

OOS – out of specification

PBO – piperonyl butoxide

PMI – President's Malaria Initiative

PQ – prequalification

TGF – The Global Fund to Fight AIDS, Tuberculosis and Malaria

QA – quality assurance

QC – quality control

QMS – quality management system

RBM Partnership to End Malaria – Roll Back Malaria Partnership to End Malaria

SOP – standard operating procedure

STAG – Strategic and Technical Advisory Group for neglected tropical diseases

UN – United Nations

UNICEF – United Nations Children's Emergency Fund

USAID – United States Agency for International Development

VCAG – Vector Control Advisory Group

WHO – World Health Organization

WHOPES – World Health Organization Pesticide Evaluation Scheme

WHOPIR – World Health Organization Public Inspection Report

WHO PQT/VCP – World Health Organization Prequalification Unit Vector Control Product Assessment Team

Definitions

Bioefficacy – insecticidal activity as measured by mortality or feeding inhibition of susceptible mosquitos exposed to a vector control product

Bioavailability – in the context of ITNs, the amount of insecticide that may enter into mosquitoes that contact the net

Cone test – bioassay to determine bioefficacy of ITNs where ~200 susceptible mosquitos (in 40 batches of 5) are exposed for three minutes using a standard cone, to pieces of netting from a given net. Mosquitoes are then observed to measure knock-down after 60 minutes and mortality after 24 hours.

Durability – in the context of durability monitoring of ITNs, refers to the persistence of physical integrity and bioefficacy of the ITN over time.

Manufacturer – company manufacturing nets and/or source materials

Pre-shipment testing – quality control testing conducted prior to shipment

Post-shipment testing – quality control testing conducted after arrival in-country, prior to distribution

Procurer – organization procuring ITNs

Procurement Agency – company providing procurement services to procurers

Quality – consistent safety and efficaciousness

Quality Assurance – design and implementation of processes that ensure/provide confidence that a given product is/will be produced to agreed standards. QA is generally proactive, aiming to prevent defects before they occur through process design, SOPs, etc.

Quality Control – testing of products against standard reference products to ensure that regularly produced products fulfill quality requirements for safety and efficacy. QC is generally reactive, to identify defects after they have occurred but before products are released.

Quality management system – a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives

Supplier – company supplying ITNs from their own or contracted manufacturing sites; also referred to as legal manufacturers and entirely responsible for the manufacturing of the ITN

Tunnel test - bioassay to determine bioefficacy of ITNs and other vector control products where ~100 susceptible mosquitos are introduced a test tunnel containing a bait animal behind a piece of treated

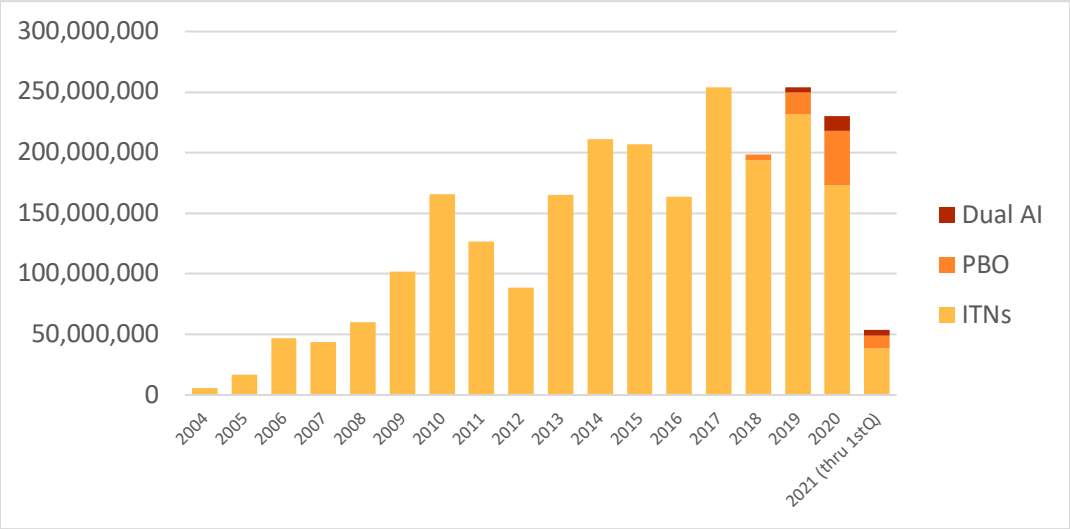
netting and ~100 in a control tunnel with a bait animal behind an untreated piece of netting for 12-15 hours, after which blood feeding and mortality are assessed.

Contents

Background

Insecticide-treated nets (ITNs) are the cornerstone of malaria prevention and are responsible for two-thirds of the reductions in malaria burden over the past decade [1]. Since 2004, over two billion ITNs have been delivered to populations at risk of malaria across the globe, primarily through periodic mass distribution campaigns and at health facilities to vulnerable groups including pregnant women and caretakers of infants. Over time, these distributions have increased the proportion of the population with access to an ITN to an estimated 52% in 2019 [2]. The achievement of target levels of access of 80% is hampered by wear and tear of ITNs, leading to discarding, and by financial and operational challenges in reaching at-risk populations with new ITNs when they are needed. Despite these challenges, over 80% of people with access to an ITN sleep under it [3], making ITNs one of the most cost-effective and large-scale malaria prevention tools in the current arsenal.

Figure 1: Global ITN shipments by net type through Q1 2021 (AMP Net Mapping Project)



ITNs provide protection by acting as both a physical barrier between the mosquito vector and humans, and by insecticidal action which kills or critically weakens the mosquito upon exposure. As of June 2021, ITNs are produced by 13 suppliers and 23 products are prequalified by the World Health Organization (WHO) [4]. These include 15 products containing a single pyrethroid (deltamethrin, alpha-cypermethrin, or permethrin), six products that contain both a pyrethroid and a synergist (piperonyl butoxide), one product that contains a pyrethroid with chlorfenapyr, and one product containing a pyrethroid with pyriproxyfen (Appendix B).

These active ingredients are either incorporated *into* polyethylene fibers or coated *onto* to polyester fibres with a binder. They are required to retain bioefficacy for at least 20 WHO standard washes under laboratory conditions and three years of use under field conditions in order to meet the efficacy criteria for WHO prequalification. Many procurers opt to only procure WHO prequalified products, in order to benefit from this initial assurance of product efficacy, safety and quality. Quality assurance processes within manufacturing sites and quality control testing of ITN shipments during procurement processes, serve to ensure products meet physical and chemical content specifications prior to delivery to malaria-endemic countries for

PMI

Percent of shipments for which products meet pre-shipment testing specifications for chemical content (2016-present)

distribution. The overwhelming majority of shipments pass pre-shipment quality control testing for chemical content and physical specifications.

In the past several years, however, there have been instances of concern related specifically to reduced ITN bioefficacy. These instances have been identified from several different points in the QA/QC process and ITN lifecycle, including pre-market factory inspections, supplier reports, pre- and post-shipment inspections, and phase III field trials following interim product listing; these reports have varied in scale and severity. In 2013-14, NetProtect LN was found, as part of its Phase III three-year field trials, to have increasing proportions of inactive deltamethrin; the product's interim recommendation was withdrawn. More recently, TANA Netting FZ-LLC (TANA) was found by the Global Fund OIG to have manufactured ITNs using an unapproved chemical formula in 2017 and 2018, affecting an estimated 52 million nets [5]. Peer-reviewed articles have also reported reduced bioefficacy (as tested in cone bioassays only) of unused PermaNet 2.0 ITNs manufactured after 2013 and stored in Papua New Guinea, while identical unused nets from pre 2013 met WHO cone bioassay criteria. A subsequent investigation found that the nets (in the unwashed state) were compliant with WHO criteria in tunnel tests (20x washed samples have not yet been tested in tunnel tests). Questions have been raised about the consistency of product manufacturing over time and whether this may impact malaria transmission [6–8].

Prior to 2017, ITN products were reviewed and recommended by the WHO Pesticide Evaluation Scheme (WHOPES). Under WHOPES, products underwent Phase I (laboratory testing, including bioassays and chemical content) and Phase II testing (small-scale field trials) and could then receive an interim recommendation, allowing them to be procured. Phase III testing, involving two large-scale field trials over three years, was required for a full recommendation, and these studies were organized by WHOPES. The evaluation of vector control products transitioned to the WHO Prequalification Unit Vector Control Product Assessment Team (WHO PQT/VCP) in January 2017. This transition has resulted in the establishment of pre-market factory inspections. Since 2015, 35 non-compliance and out-of-specification events have been reported, across 17 manufacturing sites. Reports noted that the main deficiencies are data integrity/data manipulation, poor documentation practices, poor manufacturing practices, non-authorized variation in design / manufacturing process / testing specifications, lack of efficacy, inadequate labelling and packaging, poor management of critical subcontractors, poor practices in managing complaints. Corrective actions were taken for each case. While not all of these events may directly affect bioefficacy, the cumulative effects of these influence the design and quality of the final product.

Objectives

In this context, TGF has commissioned this landscaping and analysis of ITN efficacy in order to:

1. Identify all the product manufacturing, approval, regulation, procurement, quality assurance, supply chain and deployment issues potentially affecting efficacy of ITNs, and prioritize these issues according to their relative impact on countries' abilities to obtain effective ITNs for use in the country.

2. Identify mitigating measures and recommendations for each of the identified issues, and describe the roles, responsibilities, and timelines associated with implementing the proposed solutions.

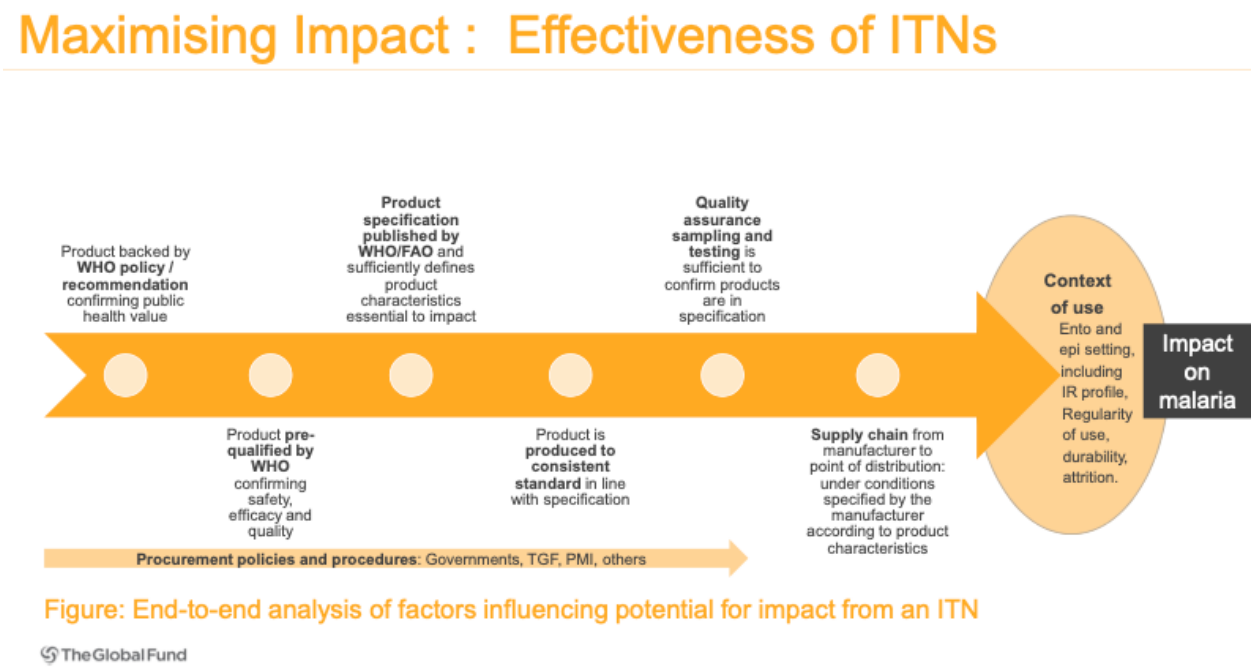
3. Explicitly look at ways in which quality assurance processes can be improved and empowered to proactively identify and prevent quality issues, i.e. at earlier stages of the production process.

Scope

The scope of this review is to provide a detailed overview of issues potentially affecting ITN efficacy, up to the point at which ITNs are distributed to households. This includes systems within which ITNs are produced, approved, regulated, procured, quality assured, and managed.

Many of these issues were discussed at the September 2019 Suppliers Meeting in Singapore and summarized by The Global Fund in the diagram below.

Figure 2: Summary of processes involved in ensuring ITN quality



This landscaping report addresses the elements along the arrow above but **does not include** the context of ITN use nor durability of physical integrity and insecticidal activity in the final oval. It is clear from published research that the ways in which households use, store, wash, and dry their ITNs can significantly impact on how well ITNs retain physical integrity and bioefficacy [9]. The entomological and epidemiological context, including the development of insecticide resistance in mosquito populations, can also impact ITN bioefficacy following deployment. These post-distribution aspects, including results from bioassays conducted as part of durability monitoring activities, are beyond the scope of this landscaping review, though their importance is referenced when relevant. Where issues raised or recommendations made under this current work are likely to have impact on ITN quality and durability beyond bioefficacy at the time of distribution, this is noted.

Methods

This landscaping review was conducted in two phases. The first consisted of a desk review of background documents available publicly or provided by various stakeholders, as well as any available relevant data on ITN bioefficacy at the time of distribution. The second phase involved key informant interviews (KIIs) with stakeholders across the entire ITN lifecycle to gather perspectives on issues affecting ITN bioefficacy and current or planned measures to monitor or address these issues.

In the first phase, quantitative data were requested from key stakeholders and compiled into tables and maps. A literature review was conducted to identify published articles with information on ITN

bioefficacy, publicly available reports, and resources from WHOPES, WHO GMP, WHO PQT/VCP, TGF, PMI, and I2I.

A total of 66 stakeholders were identified as key informants and invited to participate in interviews in the second phase (see Appendix A for list of key informants invited for interview). Stakeholders represented WHO, procurers, procurement agencies, suppliers, national malaria control or elimination programs, quality control laboratories, quality control sampling entities, researchers, and non-governmental partners supporting ITN distribution and research.

Forty-four interviews were conducted over a period of six weeks in April and May 2021. A structured interview guide was used to facilitate discussion on stakeholder areas of expertise. Transcripts were generated along with detailed interview notes. All informants consented to recording; recordings and transcripts remain confidential.

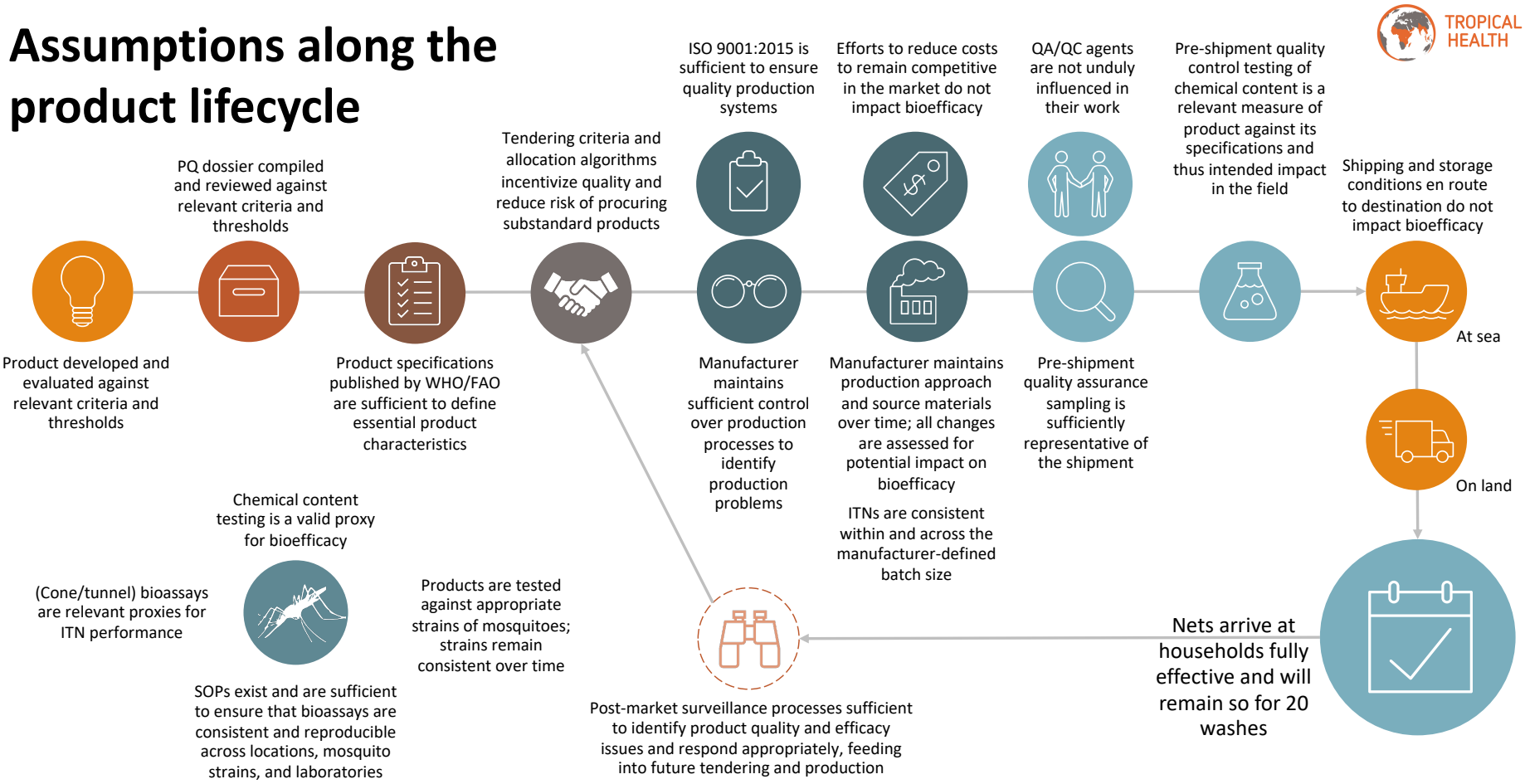
Information was synthesized across the recommendations from interviews as well as compilation of quantitative data and document review to identify current strengths, weaknesses, challenges, and opportunities related to current production, procurement, quality assurance, and supply chain and deployment of ITNs.

Findings and Discussion

Assumptions in the ITN value chain

Stakeholders mentioned a variety of assumptions as they described the processes by which ITNs are produced and delivered to households. These represent elements that the malaria community expects to happen along the product lifecycle and is not exhaustive. Key elements related to bioefficacy are summarized in Figure 3 below. For each element, the current landscape, roles and responsibilities, strengths, weaknesses, challenges, and opportunities are then synthesized in the remainder of this section.

Figure 3: Assumptions involved in ensuring ITN quality



Product development and pre-qualification

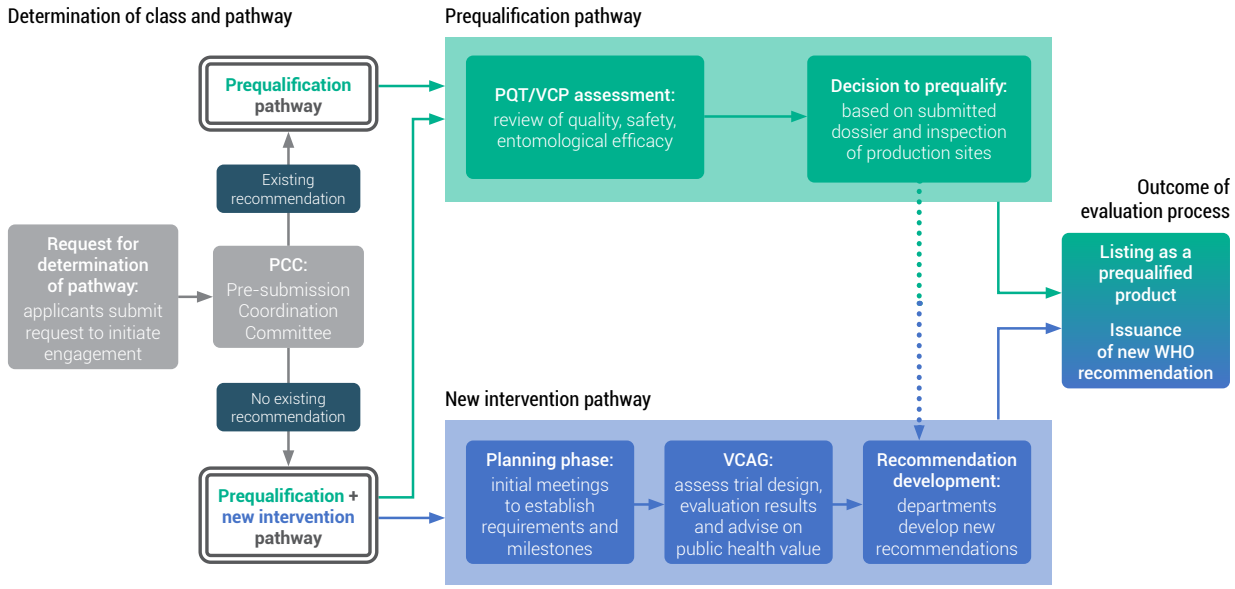
Current landscape

ITN products are developed by suppliers in collaboration with manufacturers and in-house or independent testing facilities. Internal testing is conducted throughout the development process. For products that fall into an existing WHO recommended ITN class (i.e. meet the criteria to be covered by a WHO recommendation for a class of products evaluated to have public health value), suppliers submit the products to WHO PQT/VCP for consideration.

ITNs are submitted to WHO PQT/VCP by completing a product dossier containing information on safety, entomological efficacy, and quality. Entomological efficacy data include lab and field-testing following the 2013 WHO Guidelines for Laboratory and Field Testing of LLINs, which include latitude for bioassays and evaluations of fecundity for ITNs with new modes of action. WHO PQT/VCP screens the dossier for completeness and conducts assessment of the dossier's modules, in parallel with a desk audit of manufacturing site documentation. This desk audit is followed by an onsite inspection. Site inspections assess compliance with ISO-9001:2015 using teams composed of WHO staff and external experts. Nonconformities are assessed and must be addressed through a corrective action plan. These are summarized in publicly available WHO Public Inspection Reports (WHOPIRs). Currently five ITN production sites have yet to undergo site inspections. Inspections are repeated every three to five years or as deemed necessary by WHO.

For prequalification dossier submission of ITNs that do not fall under an existing policy recommendation, assessment of public health value by the Vector Control Advisory Group (VCAG) and policy recommendation development are required in addition to the requirements for products with existing policy recommendations. Products can be reviewed for quality, safety, and entomological efficacy by WHO PQT/VCP in parallel with randomized control trials of their effectiveness for epidemiological outcomes as part of the new intervention pathway.

Figure 4: WHO PQT/VCP Pathway to prequalification. Source: WHO Prequalification of Vector Control Products Overview of the WHO Prequalification Assessment of Vector Control Products, June 2021.



Stakeholder roles and responsibilities

Suppliers

- Develop products which fall into an existing WHO product class and/or innovate new products, demonstrating public health value
- Generate and share data required for WHO PQT/VCP dossier (and/or VCAG evaluation pathway)

Manufacturers

- Produce ITN samples for testing and generation of WHO PQT/VCP dossier data
- Establish and document standard production and QA/QC processes for product

Testing laboratories, both internal and independent

- Adhere to Good Laboratory Practices (GLP), any other required standards
- Follow current JMPS/WHO/CIPAC SOPs to generate dossier data

WHO PQT/VCP

- Assess product safety, quality and efficacy

- Inspect manufacturing facilities to ensure quality; ISO-9001:2015 compliance

Advisory groups including VCAG, GMP, NTD, MPAC/STAG

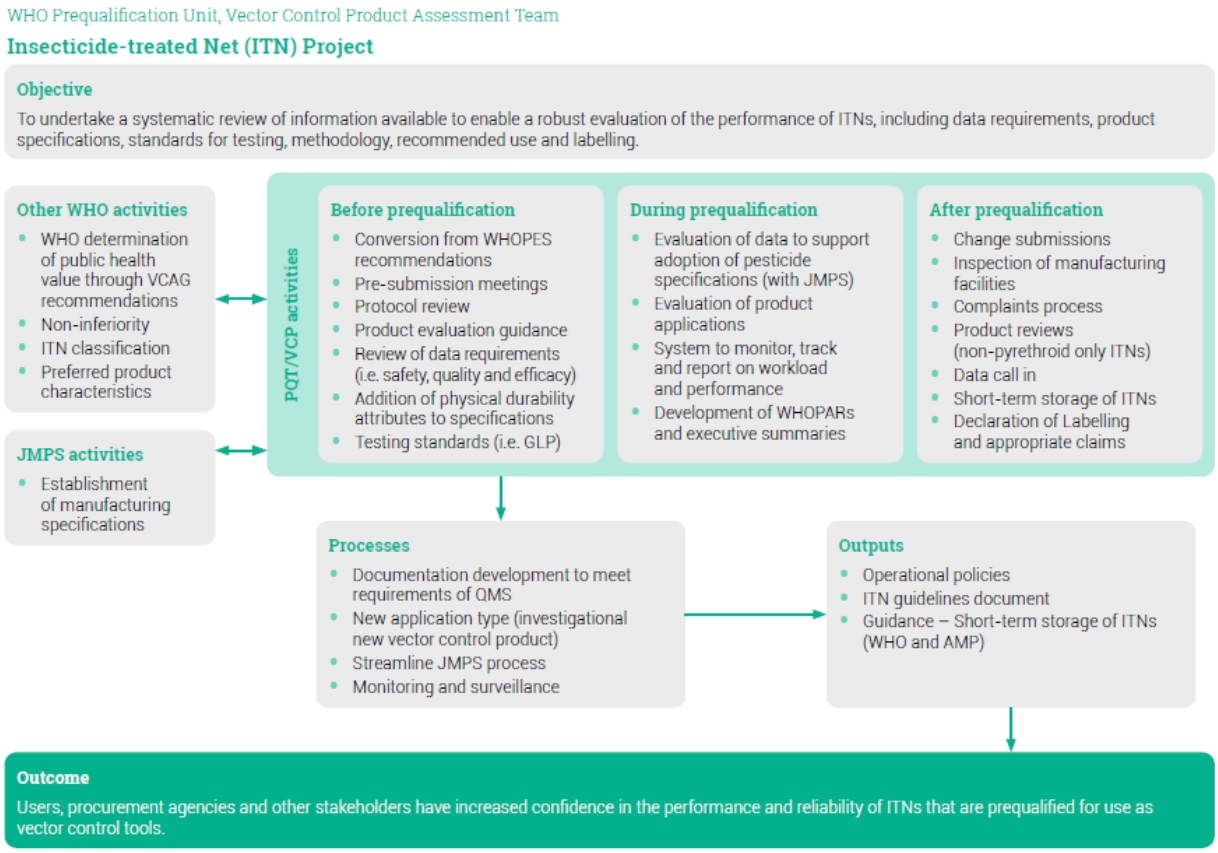
- Assess public health value when WHO recommendation does not exist
- Develop relevant WHO recommendations when appropriate

Strengths, weaknesses, challenges, and opportunities

Several strengths were identified in how ITN bioefficacy is currently ensured during product development and evaluation for prequalification.

- Feedback was overwhelmingly positive regarding the rigor and updates introduced by the WHO PQT/VCP. The team is seen to have a crucial role in several key activities contributing to ITN bioefficacy, including prequalification, pre-market manufacturing site inspections, and response to complaints and potential issues identified through inspections, pre-shipment QC, post-shipment testing, and durability monitoring.
- Requirements for generating ITN prequalification dossier data are clearly described for single pyrethroid ITNs, with WHO guidelines for entomological efficacy and safety data, JMPS guidance on AI quality assessment, CIPAC protocols for chemical testing, and GLP criteria for laboratory procedures.
- WHO PQT/VCP offers pre-submission meetings with suppliers to ensure clarity and understanding of the prequalification process and data requirements and offers to review testing protocols to provide advice.
- Manufacturing facility inspections for ISO-9001:2015 compliance have been introduced by WHO PQT/VCP as part of prequalification.
- WHO thresholds for cone bioassays (80% mortality or 95% knockdown) and tunnel tests (80% mortality or 90% blood feeding inhibition) were perceived to be relevant, with wide acknowledgement that additional detail is required for nets with novel modes of action.
- Consensus methods for assessing bioefficacy for dual-AI products are in development; evaluations of public health value of new products are underway.
- The WHO PQT/VCP ITN Project will provide a review of ITN performance, including data requirements, product specifications, standards for testing, methodology, recommended use, and labelling (Figure 5)

Figure 5: Overview of WHO PQT/VCP ITN Project. Source: Presentation for Industry Stakeholder Meeting 7 June 2021



Strengths according to stakeholders

- Outstanding professionalism and rigor of WHO PQT/VCP in updating, communicating, and implementing the prequalification process
- Addition of manufacturing site inspections to the WHO PQT/VCP dossier evaluation for ITNs is an important improvement which will positively impact ITN quality

Several weaknesses and challenges were also identified in ensuring bioefficacy of ITNs during the development and evaluation stages.

- No industry-specific QMS standards have been developed as in other industries.
- ISO-9001:2015 compliance does not guarantee that QMS are equivalent or equally effective across manufacturing sites.
- The 2013 Guidelines for laboratory and field testing of ITNs are yet to be updated and thus do not account for or provide sufficient detail on, testing approaches for new modes of action and/or products designed to work against pyrethroid resistant strains of mosquitoes. Evaluation design is left up to GLP-accredited sites in consultation with suppliers and experts. Validation of

bioassay standard operating procedures and agreement on efficacy thresholds requires consultation and time.

Weaknesses/challenges according to stakeholders

- Perceived need for additional resources for WHO PQT/VCP to carry out prequalification evaluations, including manufacturing site inspections, in timely manner
- Employing manufacturing site inspectors with necessary familiarity and experience with ITN production processes

These strengths, weaknesses, and challenges highlight several opportunities to improve how ITN bioefficacy is ensured during product development and evaluation for prequalification; several of these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution.

- Identifying gaps in the data supporting methods and thresholds used to determine adequate entomologic efficacy of ITNs during prequalification assessment and generating data which are currently lacking to reach consensus on methods and foster sense of fairness.
- An update to the 2013 Guidelines for laboratory and field testing of ITNs is urgently needed.
- Developing ITN-specific QMS standards for suppliers and manufacturers. There are many examples from other industries to draw from, and such additional requirements specific to ITN production would address current concerns regarding the stringency of ISO-9001:2015 standards. Building on existing forums bringing suppliers and manufacturers together to discuss these issues would also help build trusting relationships.
- Evaluating how WHO PQT/VCP could benefit from additional resources and identifying sources of additional support.
- Developing a detailed Terms of Reference for manufacturing site inspectors which captures all necessary training and/or experience.

Product specifications

Current landscape

ITN product specifications follow the LN Specification Template last updated by WHO and FAO in June 2019 and include a number of criteria related to physical and chemical characteristics. These include the textile, the AI and its concentration, denier, bursting strength, wash resistance index, dimensional stability, mesh size, flammability, and storage stability. Fabric weight is included in some product specifications but not all. Of these, AI concentration (loading dose) and wash resistance index are the most closely related to bioefficacy. Storage stability and fabric weight are likewise relevant. These specifications are used to evaluate ITNs post-production, for instance in identifying and investigating OOS, and for QA by manufacturers during production.

Stakeholder roles and responsibilities

WHO PQT/VCP

- Regularly review, update product specifications to ensure adequacy, using data produced and shared by researchers, suppliers, and advisory groups

Researchers

- Produce and publish data on relationships between ITN characteristics (materials and material properties including polymers, AI, binders etc) and bioefficacy

Suppliers

- Organize and support the production of data on relationships between ITN characteristics and bioefficacy, share data with advisory groups

Strengths, weaknesses, challenges, and opportunities

Current strengths of product specifications in terms of ensuring ITN bioefficacy are their largely standardized content and standardized methods for assessing each specification, which facilitates pre-shipment QC testing and determine liability along the custody chain. Respondents deemed the product specifications to be relevant and measurable with several notable gaps.

Weaknesses and challenges also exist in the role of product specifications in ensuring bioefficacy. These are summarized here and further detail is provided in the Bioefficacy Testing section of the report.

- Certain specifications are inconsistent across products:
    - Fabric weight: Only nine of the twenty-two prequalified products include fabric weight.
    - Storage stability: Three products have a 40°C x 8-week storage stability standard; all others meeting the 54°C x 2-week standard.
    - Wash resistance: ranges for acceptable wash resistance vary across and within ITN product groups. Polyester products coated with deltamethrin vary from 80-98% for PermaNet 2.0 and Yorkool, to 85-99% for Yahe, to 90-100% for Tsara Soft. The first three products have identical loading AI concentrations of 55 mg/m2 while the latter has a loading dose of 80mg/m2; all four are produced in the same denier. For polyester products with alpha-cypermethrin or polyethylene products, wash resistance index is generally 90-100% or 95-100%.
- Certain specifications were felt to be insufficient proxies for real-world conditions.
    - The wash-resistance index (WRI) serves as a proxy for the long-lastingness of the AI, but there was substantial disagreement about the appropriateness and consistency of current assay parameters such as time allowed for recovery, number of days between washes, temperature, soaps/detergents or methods used for washing, and choice of four sample points to extrapolate a trend line.

    - Storage stability is included in product specifications, but it is not clear that current testing and reporting conventions reflect real-world transit and storage conditions. [10]
- Chemical content specifications are inconsistently correlated with bioefficacy
    - It is possible for ITNs to have sufficient chemical content but for the AI to remain unavailable to mosquitoes. Chemical content is an important specification but was not considered sufficient to predict bioefficacy.
- Bioefficacy is not part of product specifications
    - Bioefficacy is evaluated as part of WHO prequalification and published specifications are intended to be sufficient to reflect bioefficacy of a given product. While it is unlikely to be feasible to include bioefficacy within product specifications and subsequently the related testing within pre-shipment QC, this gap should not go unstated.
- No method to evaluate surface concentration of the active ingredients
    - Currently, surface AI concentration is not included in product specifications, nor are there widely used test methods to evaluate it. Stakeholders agreed, however, that a validated, low-cost, easy-to-implement lab-based method of assessing surface AI content is urgently needed to provide a relevant quality metric that assesses the bioavailability of active ingredients to mosquitoes. While a number of methods have been developed or are in exploration, none are currently available for widespread use.

Weaknesses/challenges according to stakeholders

- Identifying and validating low-cost, easy-to-implement, lab-based method of assessing surface AI content to allow inclusion of surface content in specifications

These challenges to ensuring bioefficacy through product specifications present several opportunities; these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution.

- Review the need for harmonization of inconsistent product specifications, following detailed review of data and potential impact on suppliers and supply chain
- Identification of viable, accurate surface AI content measure and subsequent creation of standard data sets demonstrating relationship between surface content and bioefficacy for all prequalified products

Tendering and contracting

Current landscape

Four major agencies procure over 85% of all ITNs annually – The Global Fund, the U.S. President's Malaria Initiative, UNICEF, and the Against Malaria Foundation (AMF) [9]. With internal departments (UNICEF and AMF) or working with their contracted procurement agents (Global Fund and PMI), tenders are issued every 1-2 years and evaluated on published criteria. Suppliers selected under the tender then establish a framework or long-term agreement for a specified volume. These allocations are based on an algorithm which considers the scores from the tender and an assessment of implementation risks, including quality, price, product and registration constraints, lead-times, and available capacity. This volume generally represents a ceiling and suppliers may be granted a framework or long-term

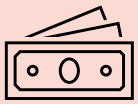
agreement with no allocation, or have allocations adjusted based on performance. Tender criteria for agencies focus on both price and technical aspects:

- For the Global Fund, 55% of the score is based on commercial factors (base price and total landed cost), while the remaining 45% of the score is comprised of several technical factors, including product coverage (number of products offered), innovation (next-generation bed net availability), country registration coverage (the number of countries in which the product has a national regulatory body registration), on-time-in-full (OTIF) delivery performance, and production footprint in sub-Saharan Africa. These evaluation criteria are reapplied at annual performance reviews for the next allocation period.
- For PMI, supplier eligibility is determined based on prequalification as well additional criteria related to label claims, past performance, financial viability, and programmatic consistency. Additional criteria, including demonstrated field effectiveness per label claims and evidence from non-inferiority trials, are applied to products deemed as "equivalent" through the PQ conversion process. Eligible suppliers are issued tenders which are scored on price (total landed cost), performance (OTIF delivery), quality control (nets in line with specifications), registration coverage, and product coverage.
- For UNICEF, long-term agreements are established following the tender process. Criteria include landed cost and prequalification, among others. Supplier performance on timeliness and quality is monitored.
- For AMF, emphasis is placed on procuring ITNs that will be most effective given the insecticide-resistance profile of the country. AMF's supplier pool has been limited in the past but has expanded in recent years.

Framework agreements, long-term agreements, and contracts across the major procurers increasingly include requirements related to ITN quality. These include:

- Record and product retention – product samples as well as in-process quality monitoring data
- Batch definitions
- Desk audits and in some cases site inspections of QMS, in-place SOPs, ISO-9001 and certification documentation
- Environmental health and safety and OCH certification
- Compliance with GMP / QMS standards
- Notification of changes that may impact quality (via WHO PQT/VCP)
- Designation of a QA Responsible Person at the supplier level
- Notifications of out-of-specifications (OOS); subsequent investigations/root cause analysis and CAPA
- Traceability of batches via GS1 bar coding standards
- Demonstrated oversight of subcontractors

Stakeholder roles and responsibilities



Procurers

- Issue tenders and evaluate against specified criteria to ensure consistent supply, quality, and cost-effectiveness
- Revise allocations in response to quality concerns

Procurement agents

- Advise on volume allocations according to specified algorithms

Suppliers

- Respond to tenders with required documentation
- Adhere to contractual requirements

Strengths, weaknesses, challenges, and opportunities

Several strengths were identified within the tendering and contracting processes.

- An increased attention to technical factors within the tendering and contracting processes that are intended to ensure ITN quality
- The annual reevaluation of supplier volume allocations based on performance criteria including quality.
- Efforts to harmonize quality-related criteria across major procurers are a strength.
- Several respondents noted that PMI's TraceNet project will help link net testing results back to specific batches and production data, facilitating investigations, root cause analysis, and their resolution.
- Price reductions for ITNs over time mean that more nets can be procured, leading to greater protection for populations at risk of malaria

Weaknesses and challenges were also identified in the tendering and contracting processes.

- The harmonization of tendering criteria across major procurers is hampered by institutional requirements and policies, as well as in some cases resource constraints to be able to review and evaluate additional data and documentation submitted.
- An overall perception that price competition and excess capacity has led or will lead to cost-cutting measures that can impact bioefficacy.
- Suppliers and other stakeholders perceived an overall focus on lowest price. Most stakeholders were not aware of other factors considered during tendering, or felt these were so secondary as to be almost irrelevant. Suppliers reported that QMS requirements were necessary and welcome, but that competition on price remained their most pressing business concern.

Together these strengths and challenges present some opportunities; these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution:

- Incentivizing suppliers and manufacturers to improve their QMS in order to ensure adequate control of ITN production processes and, in turn, product bioefficacy
- The use of third party contractors to review manufacturing process data, material COAs, etc. Procurers and suppliers could invest in automated process monitoring with digital upload of data to provide more transparency and accountability.
- Continued review and harmonization of procurement criteria across major procurers, with specific focus on criteria related to ITN bioefficacy.
- Improve communication of the emphasis and weight given to technical factors during the tendering and allocation process.

Production

Current landscape

Suppliers contract manufacturing sites to produce ITN products; suppliers may have several manufacturing sites, and a single manufacturing site may produce ITNs for more than one supplier. Variability in production arrangements has led to concerns regarding supply continuity, transparency, consistent quality management, anti-competitive practices, and business commitment.

A product's ability to maintain bioefficacy over time is related to the choice of polymer, polymer characteristics, the AI loading, the mass of the ITN, the AI migration properties of the ITN, the method of AI application (incorporation or coating), the choice of binder (for coated products), and temperatures and processes by which binders and AI are applied. Table 1 summarizes these parameters for polyester and for polyethylene ITNs.

Table 1: Overview of key production parameters that can influence bioavailability of AI

Production Step	Polyester	Polyethylene
Textile or polyethylene polymer is procured; textile generally represents the majority of the cost of an ITN	Source of polyester yarn, fabric and any finishes, spinning oils, etc used in production. There may be hundreds of sourcing options for polyester fabric.	Choice of polymer and its migration rate. There are fewer sources for HDPE and LDPE than for polyester yarns and fabrics.
Insecticide is applied to textile or incorporated into fibers	Choice and sourcing of binder – binder differences can result in early wash-off of AI or entrapment of AI within the binder such that it is less bioavailable to mosquitoes Choice and sourcing of AI; its crystallinity, loading of AI	Choice and sourcing of AI and process of producing masterbatch
	Application of binder and AI to polyester fabric; nip roller pressure	Loading of AI, temperature at which PE pellets are melted and mixed with masterbatch, uniformity of AI within extruded yarn
	Heating/setting of binder and AI	Extrusion into monofilaments

After the processes above, polyethylene monofilaments are knitted into fabric; both products then go through processes of cutting, sewing, and finishing prior to packaging, baling, and ultimately shipment. Batch definitions vary by supplier but are meant to represent a consistent production of ITNs, from e.g. a single masterbatch. Suppliers however acknowledged frequent variation of AI content within a given net due to the factors noted above, and that QMS systems are designed to identify variations outside

tolerance limits. However, there is disagreement that current specifications and tolerance limits ensure bioefficacy, as earlier stated.

Suppliers and manufacturers often optimize their production processes over time to remain competitive for procurement tenders. The WHO PQT/VCP requires that suppliers submit a change request for both major and minor changes in the production process for a given ITN.

Stakeholder roles and responsibilities

Suppliers

- Maintain sufficient control over production processes to ID problems
- Submit change requests to WHO PQT/VCP when production approach/source materials are modified
- Ensure cost reduction measures do not impact product quality
-

Manufacturers

- Ensure ITNs are consistent within batches
- Notify supplier of any changes to production approach/source materials

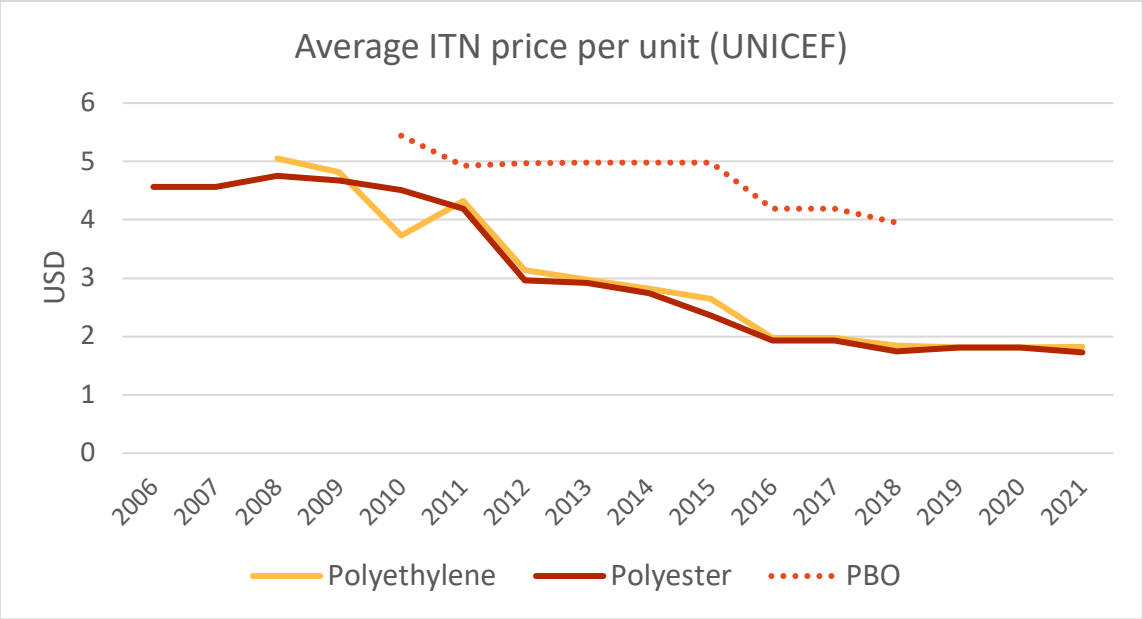
Strengths, weaknesses, challenges, and opportunities

The requirement for suppliers to submit change requests for any minor or major modifications to production processes or source materials is a strength in terms of ensuring bioefficacy of ITNs at the production stage. Suppliers reported that manufacturing site inspections conducted by PQ have been helpful overall for improving production processes.

Difficulty enforcing the requirement to submit changes for PQ review is one weakness that might impact ITN bioefficacy over time. It is not clear whether changes to product occurred prior to the PQ transition, or how such changes would be identified and handled. Suppliers also face challenges in ensuring they have sufficient control over manufacturer's procedures. Finally, product drift is a potential weakness during ITN production, where cost cutting measures might impact the bioefficacy of a product over time. As noted in Table 1, there are a number of manufacturing processes that could affect bioefficacy; many but not all of these would result in changes identifiable using chemical content testing.

Stakeholders felt that focus on price in market shaping strategies and tendering decisions was a major factor in driving down ITN prices over time, and caution was needed to avoid implications for product quality.

Figure 6: ITN Prices over time. Source: UNICEF



In this context, there are several opportunities to improve how bioefficacy is ensured during ITN production; several of these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution.

- Developing strategies to ensure change reports are submitted by suppliers for all product or source material changes.
- Determining whether additional measures are needed to assess product drift over time.
- Address the scientific gap in correlating ITN bioefficacy and material properties, to identify which material parameters best predict or influence bioefficacy. A better understanding of these correlations could inform improved standards and improved performance, along with the ability to monitor upstream quality metrics.
- Rewarding measures taken by suppliers and manufacturers to ensure quality, including bioefficacy, during production.

Supplier & Manufacturer Quality Assurance and Quality Control

Current landscape

Suppliers reported various quality assurance and quality control approaches; it was beyond the scope of this landscaping to obtain or report on these in detail. However, suppliers uniformly reported monitoring quality at each stage of production and conducting quality control testing of samples at pertinent stages, against product specifications. One supplier reported conducting bioassays on a limited number of samples annually. For specific shipments, suppliers conduct QC testing of samples against physical and chemical specifications and provide results to the procurement agent with a Certificate of Analysis (COA).

Stakeholder roles and responsibilities

Suppliers

- Design and oversee QMS for ITN production; review in-process QC reports and data provided by manufacturers
- Provide Certificate of Analysis to procurement agent
- Share in-process QC data with procurers, procurement agents, and PCT-VCP as requested

Manufacturers

- Implement QMS for ITN production
- Test product samples at various stages against product specifications and report results to suppliers

Strengths, weaknesses, challenges, and opportunities

The comprehensive quality control activities reported by suppliers indicate a strength in ensuring bioefficacy at this point of the life cycle. As noted in earlier sections, PQ site inspections at the ISO-9001:2015 standard, along with enhanced QMS requirements in tendering and contracting have contributed to overall improvements in QMS across suppliers. PMI is also reportedly considering implementing a QMS review for ITN manufacturers which could inform improvements for the sector.

However, several weaknesses and challenges were identified in current internal QA and QC processes.

- Lack of ITN industry-specific QMS standards
- Costs of QMS improvement requirements, which may impact ITN pricing and/or incentivize other cost-cutting measures

There are clear opportunities to better ensure ITN bioefficacy during internal QA and QC (and with implications beyond bioefficacy), including:

- Developing ITN industry-specific QMS standards
- Devising effective, feasible incentives for QMS improvement
- Several suppliers noted willingness to share relevant internal QA/QC data with other key stakeholders to enrich information on ITN quality, including bioefficacy, and to work collaboratively to identify best practices and potential issues, including product drift.
- Investment in automated process monitoring and digital upload of data, using third parties to review the information and submit reports.

Pre-shipment Quality Control

Current landscape

Quality control testing of ITNs before shipment (pre-shipment QC) is conducted in two steps. First, samples for testing are obtained from the manufacturing site by a small number of agencies contracted by the procurement agents, following SOPs (which may vary by procurement agent or as required by the procurer). Sampling agencies may have a limited number of inspectors in a given country. Sampling procedures for physical inspection are different from those for chemical content testing, and may likewise vary between procurers. Given the high cost of chemical content testing, frequently only 2-8 samples are taken per lot. Lot size may vary from 50,000 nets to over 3,000,000 nets, depending on how the supplier defines its batch size.

In the second step, samples are sent to one of 3-4 laboratories contracted by procurement agents such as IDA (for Global Fund) and GHSC-PSM (for PMI). Chemical content testing is conducted and the results, along with physical inspection, are provided to the procurement agent as a Certificate of Conformity (COC) or an Out of Specification (OOS). The overall percentage of shipments that are found to have an OOS for chemical content in recent years was reported to be less than 1% for PMI and around 3% for Global Fund. OOS for chemical content have been for loading doses both below and above the +/- 25% tolerance limits.

If an OOS for chemical content is found, confirmatory testing of samples at a second contract laboratory is conducted. If the second lab also finds an OOS, the shipment is rejected and root cause investigation is conducted by the procurement agent with the supplier, frequently involving a CAPA. When confirmatory testing contradicts the first result, additional testing is conducted.

From 2015-2019, 35 non-conformities and OOS were identified, across 17 manufacturing sites, involving more than 50 consignments. Deficiencies included data integrity/manipulation, poor documentation practices, poor manufacturing practices, unauthorized variation in design/manufacturing processes and testing specifications, inadequate labelling and packaging, poor management of critical subcontractors, poor practices in managing complaints, and lack of efficacy. These deficiencies were investigated and improvements recommended in QMS, complain and vigilance, design verification/validation, registration, and storage and transport practices.

Stakeholder roles and responsibilities

Manufacturer

- Provide access to manufacturing sites to sampling agents

Sampling agency

- Sample products following standardized sampling methodologies
- Arrange shipment of samples from manufacturing sites to testing laboratories

Testing laboratories

- Test samples against product specifications using CIPAC or other agreed upon SOPs
- Report OOS or COC to procurement agency

Strengths, weaknesses, challenges, and opportunities

Several strengths were identified in the pre-shipment QC period which help ensure ITN bioefficacy.

- Use of independent testing labs with GLP certification following CIPAC protocols provide confidence in the validity of test results from the samples provided.
- Tests results for chemical content are generally available rapidly.
- Required reporting of OOS or COC to procurement agency prior to product release is effective in ensuring ITNs with potential quality or bioefficacy issues are identified prior to shipment.
- PMI, UNICEF, and The Global Fund reported sharing information about OOS investigations with each other and with PCT-VCP on an ongoing basis. PMI maintains electronic files of QC test reports which can be requested by PMI country teams; requests for specific test results by third parties are considered on a case-by-base basis. Similar files are maintained by both UNICEF and The Global Fund.

Strengths according to stakeholders

- Separation and independence of sampling agencies and testing laboratories from one another and from suppliers is essential to prevent biased sampling or test results

There are also several key weaknesses and challenges in the pre-shipment QC process which could affect ITN bioefficacy.

- Lack of standardized sampling methods may impact representativeness of pre-shipment QC samples, impairing the ability to detect potential issues with bioefficacy
- Lack of industry-wide SOPs for sampling agencies leads to variability in methods used which can impact the representativeness of samples used for pre-shipment QC testing
- The costs of chemical content testing are a significant barrier to increasing the number of samples tested per lot or shipment

- No system in place to regularly compare ITN QC testing results between all WHO recommended laboratories, leaving open possibility of variation in results

Weaknesses/challenges according to stakeholders

- Small number of sampling agencies and close relationships between manufacturers and sampling agencies were perceived to pose a high risk of undue influence in pre-shipment QC sampling process
- Stakeholders expressed concerns that ITN products that were later found to be non-compliant with specifications had received an earlier Certificate of Conformity.
- Batch definitions vary by supplier and by product, contributing to confusion about interpretation of results from sampling

These strengths, weaknesses, and challenges present several opportunities to better ensure ITN bioefficacy in the pre-shipment QC phase; these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution.

- Standardizing sampling procedures, including sampling methods, across procurers, procurement agents, and sampling agencies
- Developing standardized framework to regularly compare results of QC testing between all WHO recommended laboratories using a standardized sample of ITNs
- Determining whether further oversight needed of sampling agencies, and if so, how and by whom
- Investing in automated data collection technology at manufacturing sites

Shipping and Storage

Current Landscape

When the shipment has a COA and a COC it is released by the supplier to the procurement agency, who becomes responsible and liable for transport. In most cases the supplier is responsible for loading the containers, while the procurement agency organizes the containers and ships involved in transport and is responsible for their condition.

Containers holding ITNs are transported from the manufacturing site and loaded onto cargo ships (or transported by road when feasible). The position of the container within the cargo shipment is seldom under the control of the procurement agent. Containers may be placed under other containers, providing some protection from direct sunlight. Cargo ships may take 1-2 months at sea before being unloaded at the destination port.

ITNs arrive at port (or at their overland destination) and go through customs clearance and unloading, where custody is transferred to the NMCP or its distribution partner. Bales are counted and total quantities confirmed. In some countries, additional post-shipment inspections are conducted; most of these focus on physical inspection for holes and seams (workmanship). A small number of countries conduct testing of nets against physical specifications (mesh size; bursting strength). Very infrequently, chemical or bioassay testing is conducted prior to onward transport of ITNs to distribution points. Beginning in 2021, PMI-funded durability monitoring activities began pulling samples of ITNs from

shipments prior to distribution; bioassay testing is conducted concurrently with or after distribution, however, to avoid delays.

Following clearance, ITNs are transported onward to central or subnational warehouses, following the country's logistics plan. ITNs are for the most part distributed within a period of weeks to months after arrival. In some settings, however, they may be stored for up to a year or more prior to distribution, particularly in areas of challenging geographic access that delay campaign implementation. While there is guidance on appropriate storage conditions, nets may be subject to a variety of ambient temperatures. In extreme cases, nets stored in metal containers without ventilation or shade can reach temperatures of more than 60 degrees Celsius.

At outside temperatures of 40°C, the inside of an uninsulated container in direct sunlight can reach temperatures of 60°C [10]. Temperature studies of containers observe maximum temperatures of 30-36°C while at sea, where temperature fluctuations are relatively minimal, particularly for containers out of direct sunlight [10,11]. At port and during land transport, however, internal container temperatures up to 40°C are frequently observed and can briefly reach 57°C on days when ambient maximum temperatures reach 35°C[12]. Anecdotally, ITNs stored at the top of containers subject to full tropical sun were said to be at higher risk of damage; ITNs in the middle area of containers or in containers not in the top layer on cargo ships were deemed to be reasonably well-protected; this is consistent with the 2006 Xerox study [12]. Efforts by PMI to use data-loggers within ITN containers to monitor temperatures during shipping were confounded by loss of the loggers and difficulties accessing them because of Port Authority security restrictions. More complete data may be needed to fully characterize the extent of temperature changes during transit and storage of nets.

All but three prequalified ITN products have a storage stability specification of 54°C x 2-week standard test. The other three products, all polyester LN coated with deltamethrin, specify the 40°C x 8-week test. Deltamethrin LNs have long-term stability at temperatures up to and about 40°C, but may convert to the R-isomer particularly above 50°C, impacting bioefficacy; above 80°C deltamethrin is lost completely due to volatilization [13].

Stakeholder roles and responsibilities

Manufacturers

- Loading of containers

Procurement agencies

- Procure containers and arrange transport to destination
- Assure ITN transport under proper conditions

Distribution partners including NMCPs

- Assure ITN transport and storage under proper conditions
- Design and implement post-shipment testing

Advisory groups including VCAG, GMP, NTD, MPAC/STAG

- Develop evidence-based recommendations for post-shipment testing
- Update transport and storage guidance based on available data

Strengths, weaknesses, challenges, and opportunities

There are several strengths in how bioefficacy is ensured in the transport and storage of ITNs prior to household distribution.

- Countries usually store nets centrally in large, climate-controlled warehouses for longer periods, with storage in peripheral facilities with more variable temperatures limited to several weeks.
- AMP has published guidelines on container storage of ITNs, noting that containers should not be used for storage for more than 2 weeks due to exposure to high temperatures and humidity.
- Efforts have been made to collect data on transport and storage conditions, including temperature.
- The conditions ITNs may be subject to while aboard cargo ships are relatively well-characterized given research from other commercial sectors; average temperatures of 30-36°C pose little risk to products.

Weaknesses and challenges were also identified related to ensuring bioefficacy in transit and storage of ITNs.

- It remains unclear whether ITNs may be at risk of AI degradation under the specific temperature fluctuations encountered during transport and storage, and whether risk may be higher for polyester ITNs coated with deltamethrin that have a storage stability criteria of 40°C x 8 weeks.
- The correlation between storage stability tests, intended to approximate extended shelf life under normal conditions, and ITN bioefficacy after repeated exposure to high temperatures, is not clear.
- Lack of coordination and standardization of post-shipment QC testing can lead to inefficient use of resources and ITN distribution delays.
- The inclusion of bioassays in post-shipment testing would provide important data on bioefficacy, but current timelines and costs for bioassays are likely to be prohibitive at this point in the ITN life cycle

In this context, there are several opportunities to improve how bioefficacy is ensured during transit and storage of ITNs, with some implications for physical quality in addition to bioefficacy.

- Conduct research to characterize temperatures encountered and duration during clearance and land transport.
- Conduct research assessing impact of above temperature fluctuations and duration on bioefficacy across ITN products.
- Reaching consensus on best strategy for post-shipment QC, developing and implementing guidelines based on consensus

Post-market surveillance

Post market surveillance for medicines and vaccines relies on stringent regulatory authorities and reporting systems in clinical settings. Similar post-market surveillance systems are not in place for vector control products given their regulatory context. PMI and some Global Fund grantees fund durability monitoring of ITNs which collects data on attrition, physical integrity, and bioefficacy of nets after use, but variation by setting appears to be more important than product differences [14], and bioefficacy data from these studies has yet to be compiled and reviewed. Post-shipment inspections conducted by countries vary substantially in scope, with most countries conducting a simple count to confirm quantities delivered, some countries conducting additional physical inspection. Only rarely are cone bioassays conducted.

Current landscape

WHO PQT/VCP describes several post-prequalification activities in their Overview of of the WHO PQ Assessment Process for Vector Control Products, including:

- Fulfillment of prequalification commitments – completion of pending field trials, compliance with manufacturing site inspection improvements, etc.
- Change notification – suppliers are required to notify PQ of changes to their products prior to implementation, and PQ conducts an assessment to determine that the product meets all prequalification requirements.
- Routine re-inspections of manufacturing sites – every 3-5 years, or earlier if deemed necessary.
- Post-market surveillance is currently limited to the review of complaints submitted to WHO PQ. Contact information for complaint submission for vector control is not yet finalized on the PQ website.
- Compliance with established WHO specifications – verified during inspection, re-inspection, post-market testing, or quality assurance testing.
- Product review – of a subset of products sharing certain attributes, to identify new information or data gaps, review existing information, and potentially reevaluate products with new information.

Roles and responsibilities

WHO-PQT

- Review and investigate, if necessary, submitted complaints
- Assess changes to products when notified
- Track and provide updates on other post-prequalification activities
- Take appropriate action (notifications of concern, suspension, delisting) in response to investigations

Suppliers

- Notify WHO-PQT of changes to products
- Comply with post-prequalification requirements

Funders/Researchers

- Share data/findings relevant to ITN bioefficacy and quality with WHO-PQT and suppliers, to facilitate investigations, product reviews, etc.

Strengths, weaknesses, challenges, and opportunities

Several strengths were identified regarding ITN post-market surveillance. PQT-VC includes post-market requirements in their guidance, including change notification, three-yearly manufacturing site inspections, product review, and complaints. They have several options when problems are identified, including issuing notifications of concern regarding products, suspension pending investigation, or delisting.

A number of weaknesses and challenges were also identified.

- Post-market surveillance guidance for countries and NRAs is yet to be developed or agreed.
- Surveillance is currently limited to durability monitoring and post-shipment inspection. Post-shipment inspection procedures do not typically include bioefficacy testing due to cost and time constraints.
- There is no formalized mechanism or clear mandate for pulling together bioefficacy data across post-market surveillance activities.
- Due to testing variations across laboratories and mosquito strains, confirmatory testing is required when results are inconclusive. Triangulation of results across different settings (as in durability monitoring) is challenging given many confounding factors.
- Post-shipment inspection approaches are not harmonized across countries and rarely include bioefficacy testing.
- Funding is currently a barrier for post-shipment bioefficacy testing at country level. The decision to reject a shipment at the post-shipment stage was felt to be 'too late' by Northern stakeholders; in-country stakeholders felt it was important to maintain this accountability step despite cost and time implications.
- The process for submitting complaints to PQT was not clear to stakeholders. Some stakeholders were concerned that complaints could be made by competitors.
- Limited complaint investigation resources within PQT.

These strengths and weakness also bring several opportunities; several of these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution:

- Development of a consensus approach for post-shipment testing at country level.
- Building in relevant post-market surveillance activities (post-shipment testing; durability monitoring) into the cost of ITN delivery systems
- Strengthening the role of NRAs and local research institutions to conduct post-market surveillance
- Clarifying the complaints submission and investigation process for broader stakeholders, particularly its link with OOS results and procurer investigations.

Bioefficacy testing methods

The methods and thresholds used to evaluate ITN bioefficacy are fundamental for setting standards and testing product performance. This theme cuts across all phases of the ITN life cycle, from product development and evaluation to QA and QC measures and evaluation of the impact of temperature during transit and storage. The following section outlines the current landscape of ITN bioefficacy testing strategies, indicates roles and responsibilities, and highlights strengths, weaknesses, challenges, and opportunities.

Current landscape

WHO guidelines for laboratory and field testing of ITN include detailed procedures and thresholds to be used in Phase I, II, and III testing of ITNs. In Phase I (laboratory testing), entomological efficacy and wash-resistance are assessed. The time required for insecticidal regeneration after washing is determined by washing samples and subsequently conducting bioassays and chemical content assays. Data from the chemical assays is used to determine the wash-resistance index, and between- and within-net variability is assessed. Regeneration time is calculated by washing and drying net samples three times and then conducting cone bioassays on successive days to generate efficacy curves for mosquito mortality and knock-down. Tunnel tests are conducted for nets washed at least 20 times that do not meet criteria in a cone bioassay (80% mortality or 95% knock-down). Nets that meet WHO effectiveness criteria after 20 washes can undergo Phase II testing, which involves small-scale field trials where free-flying mosquitoes are introduced into experimental huts and their blood-feeding rate and mortality are assessed against nets washed 20 times. Phase III testing involves large-scale field trials to assess physical durability, attrition, and bioefficacy after normal use over three years in households.

Bioefficacy testing is seldom conducted outside initial product testing and evaluation. Exceptions are during ITN durability monitoring and in rare cases as part of supplier QC processes (with a limited number of tests run per year), post-shipment inspections (notably Papua New Guinea), and as a result of OOS investigations.

Cone bioassays are the norm and were universally described as faster, cheaper, and easier than tunnel tests. In cone tests, five mosquitoes are placed in a cone and exposed for 3 minutes to a piece of treated netting, then monitored for knockdown (60 minutes) and mortality (24 hours) in holding cages. Multiple cones are run on each net piece. Tunnel tests, by contrast, require 100 mosquitoes to be released into a 60cm glass tunnel, separated from a small mammal by a piece of 20cm x 20cm netting with 9 1-cm holes to allow mosquitoes access to the animal, and left overnight for 12-15 hours. Mortality and blood feeding inhibition is then measured [24]. While tunnel tests were felt to be in principle similar to the mechanism mosquitoes use to reach humans, rabbits and guinea pigs are not the preferred host for most malaria vectors, potentially overestimating blood-feeding inhibition. The time, expense, and challenges (ethical and veterinary) of maintaining rabbits and guinea pigs in lab settings were noted as significant barriers to conducting regular tunnel tests.

Current WHO guidelines for phase I efficacy testing note that “the efficacy of treated nets may be underestimated if judged based on the outcome of standard cone bioassays. This is true particularly for insecticides that have a high excito-repellent effect, such as permethrin and etofenprox. In such cases, the efficacy of LNs washed 20 times or more that no longer meet the criteria in standard cone bioassays should be studied in a tunnel in the laboratory.”[1] Efficacy criteria state that for Phase I studies, nets

[1] Guidelines for laboratory and field-testing of LLINs, pp 10

washed 20 times must meet ≥80% mortality or ≥95% knock-down in cone tests, or ≥80% mortality or ≥90% blood-feeding inhibition in tunnel tests to advance to Phase II testing in experimental huts.

During Phase III long-term field testing, which follows nets that have been used by households over time, guidelines state that bioefficacy "should be determined in WHO cone tests and, when necessary, in tunnel tests". A given LN that does not meet optimal criteria in the cone test "should be subjected to a tunnel test". Efficacy criteria for Phase III studies are that 80% of sampled nets should meet optimal effectiveness criteria in either cone or tunnel tests.

Total AI content is a key product specification which acts as a proxy for bioefficacy in pre-shipment QC and some during post-market ITN assessments. During pre-shipment QC total chemical content must be within 25% +/- of the specified 'loading dose' and this loading dose is expected to be sufficient to achieve 100% mosquito mortality in bioassays. Many respondents cited an assumption that prequalification provides assurance of ITN bioefficacy as long as product specifications continue to be met. However, if products are manufactured closer to the -25% threshold level of chemical content and are also at the lower end of wash-resistance index tolerances (80-90% vs 90-100%), they may contain less than minimal concentrations of AI before reaching 10 washes.

New ingredients such as the synergist piperonyl butoxide, the pro-insecticide chlorfenapyr, and the insect growth regulator pyriproxyfen require differentiated approaches to bioassay testing. Nets with more than one AI must undergo bioassays to assess both the pyrethroid component in the net and, separately, the synergist or second AI. This increases time and costs to conduct these assays and requires large numbers of resistant mosquitoes whose resistance mechanisms have been fully characterized. Current SOPs for bioassays for PBO nets involve cone bioassays on both susceptible and resistant mosquitoes, but face challenges in providing sufficient detail (e.g. on strains) to ensure standardization of testing. SOPs for nets with chlorfenapyr, which is metabolized only as mosquitoes fly around, involve cone bioassays for susceptible mosquitoes and tunnel tests with resistant mosquitoes. Mortality is assessed after 72 hours to allow time for metabolic processes to take place. Nets with pyriproxyfen require cone bioassays with both susceptible and resistant strains of mosquitoes; the latter are then assessed for reduced fecundity. Lab capacity to conduct these types of bioassays is limited due to resource constraints, training gaps, and the significant challenges of maintaining characterized resistant mosquito colonies over time.

Research is ongoing to identify reliable and feasible methods to assess other viable proxies for ITN bioefficacy, such as surface AI content. Stakeholders agreed that a validated, low-cost, easy-to-implement lab-based method of assessing surface AI content is urgently needed to provide a relevant quality metric that assesses the bioavailability of active ingredients to mosquitoes. While a number of methods have been developed or are in exploration (summarized in Table 2), none are currently available for widespread use.

Table 2: Summary of approaches to measuring surface AI concentration on ITNs

Method	Description
Wash-off [15]	Acetone wash used to wash off surface AI (permethrin) from the net; wash liquid's AI content then measured using gas chromatography. Results showed no correlation with bioassay data.
Controlled rub-off [16]	Lens paper used to collect insecticide from permethrin-incorporated nets; acetone used to extract AI from paper, then analyzed with gas

	chromatography. Designed as a pass/fail test, this method has not been validated for quantitative assessment of surface concentration.
Time of Flight Secondary Ion Mass Spectrometer (TOF-SIMS) [17]	Ion beam blows off AI (permethrin) from surface of the fiber; mass spectrometer measures the fragments. The charge-mass ratio of the ions is calculated by the time of flight. Mass spectrometers are expensive equipment and method has not been correlated against bioefficacy.
Energy dispersive X-ray spectroscopy	SEM/EDS used to measure the crystal size and formation on the surface of fabric. Equipment is expensive. Not a rapid method.
Cyanopyrethroid Field Test [7,18,19]	Surface levels of deltamethrin measured by wiping with filter paper at a consistent pressure using magnetized disks. Filter paper then soaked in reagent and activated with sodium hydroxide for a total of 10 minutes before recording the intensity of purple color with digital camera. Limited to nets with deltamethrin coated on polyester; cannot be used for permethrin or for incorporated nets.
Dieval 'improved method' [20]	Martindale machine used to rub small discs of non-abrading cotton fabric in a Lissajous figure on Olyset net fabric. Permethrin was removed from the cotton fabric using methanol and sonication, and the solution was analyzed by HPLC. Insecticidal activity was evaluated in a limited number of samples.
Electromagnetic sensor for alpha-cypermethrin [21]	Rapid method being developed for IRS; in principle applicable to ITNs. Uses a horn antenna at a frequency range between 1 GHz to 6 GHz to assess dosage of alpha-cypermethrin. Additional work is ongoing to expand to other IRS classes.
Tracer III-SD handheld X-ray fluorescence (XRF) [22]	Non-surface method correlated with bioefficacy in limited studies. Handheld analyzer developed by Bruker Nano Analytics, Inc; measures intensity of 11.549-12.248 keV X-rays emitted by bromine atoms of deltamethrin. Folding the net into 24 layers allows for a non-destructive and relatively rapid measurement of average deltamethrin content across the net. Limited to nets with deltamethrin coated on polyester.

Roles and responsibilities

Researchers

- Generate data on:
  - Cone and tunnel test comparability in different contexts
  - WRI methods and thresholds
  - Correlations between chemical content and bioefficacy
  - Material properties that impact AI migration and bioefficacy
- Continue to develop/validate surface AI content and other methodologies

Advisory groups, WHO GMP, WHO PQT/VCP

- Develop new and update existing bioefficacy testing guidelines as new data become available

- Develop guidance on post-shipment testing, or identify who should coordinate this work

Strengths, weaknesses, challenges, and opportunities

Several strengths were identified regarding ITN bioefficacy testing methods.

- Collaboration among academic research teams, African research institutions, product developers and regulatory representatives is ongoing, coordinated under I2I, to develop and publish consensus SOPs for bioassay testing for ITNs with synergists and dual AIs, addressing known gaps
- Research groups are also preparing publications with needed data on wash resistance index methods and thresholds
- IVCC is exploring the possibility of a project to develop a method for assessing surface AI concentration

There are also several weaknesses and challenges related to bioefficacy testing strategies at different points across the ITN life cycle.

- While there is agreement that total AI content is a necessary quality metric, and its measurement is standardized through CIPAC protocols, there were mixed opinions on whether total AI content is sufficient by itself as a quality indicator.
- Insufficient financial resources exist to conduct suggested levels of bioefficacy testing at relevant points in the ITN life cycle (during production; pre-shipment testing; post-shipment testing), coupled with high costs and long timelines of current testing methods.
- WRI serves as a proxy for the long-lastingness of the AI, but there was substantial disagreement about the appropriateness and consistency of current assay parameters such as time allowed for recovery, number of days between washes, temperature, soaps/detergents or methods used for washing, and choice of four sample points to extrapolate a trend line.
- Surface concentration of insecticide: A validated method to measure surface concentration would fill an important gap, particularly if it were feasible to use during pre-shipment QC.
- Cone bioassays used to assess bioefficacy are subject to influence of temperature fluctuations, angle of the cone, health of the colony, level of resistance (susceptible strains can evolve over time to become more resistant; resistant strains may gradually become less resistant), and lab technician experience. While some stakeholders felt it should be reasonable with current SOPs to conduct comparable cone bioassays across many labs, others noted experiences where contradictory results were obtained when samples were retested.
- Mixed opinions on relevance of tunnel tests, particularly for nets without a highly repellent AI or chlorfenapyr; they are time and mosquito-intensive, with added challenges of raising strains specifically to feed on small mammals. Respondents noted the process by which the tunnel test was added to WHO Guidelines – first for nets with high excito-repellency and then broadened to serve as a secondary testing method for all nets that did not pass cone bioassays.
- Tunnel tests are seldom conducted during OOS investigation and durability monitoring after failed cone tests, contrary to WHO guidelines.
- While resistance is outside the scope of this landscaping review, relevant concerns were raised regarding the consistency of mosquito strains over time, particularly resistant strains, and the challenges of scaling up lab capacity to implement SOPs for nets with more than a single pyrethroid.

Weaknesses/challenges according to stakeholders

- Validated, low-cost, easy-to-implement lab-based method for assessing surface AI content is urgently needed; while a number of methods have been developed or are in exploration, none are currently available for widespread use
- Correlation between tunnel and cone tests not clear, nor is relevance of using tunnel tests on nets that do not contain a highly repellent AI or chlorfenapyr.
- Conducting bioassays at additional time points in the ITN life cycle using currently validated methods would be very resource and time intensive, current lab capacity is not sufficient

In this context, there are several clear opportunities to improve and build upon existing ITN bioefficacy testing strategies; these also have wider implications for ITN quality beyond bioefficacy up to the point of distribution.

- Generate data to:
  - support WRI methods and thresholds used for all prequalified products
  - support bioassay methods (cone and/or tunnel) and thresholds for all prequalified products
  - determine the consistency of mosquito strains over time
  - Review cone and tunnel bioassay and chemical content correlations
- Update existing and develop new SOPs for bioassays to address most recent evidence and ensure consistent, reproducible results across locations, mosquito strains, and laboratories.
- Development of a surface AI concentration method.
- Investment in lab capacity to conduct bioassays.
- Clarify performance thresholds to stakeholders for standard, PBO, and dual-AI ITNs, including the role of chemical content, cone, and tunnel assays in determining legal liability of suppliers, and in expected product efficacy.

Quality assurance from in vitro diagnostics

ITN manufacturing and quality assurance and quality control, as well as regulatory processes, are generally agreed to be a less mature stage than other product areas such as pharmaceuticals, medical devices, and in vitro diagnostics which have had a much longer history. The following table compares the processes and resources in the in vitro diagnostics value chain that are intended to assure quality, against those currently used for ITNs.

Table 3: Quality aspects for in vitro diagnostics as compared to those for ITNs

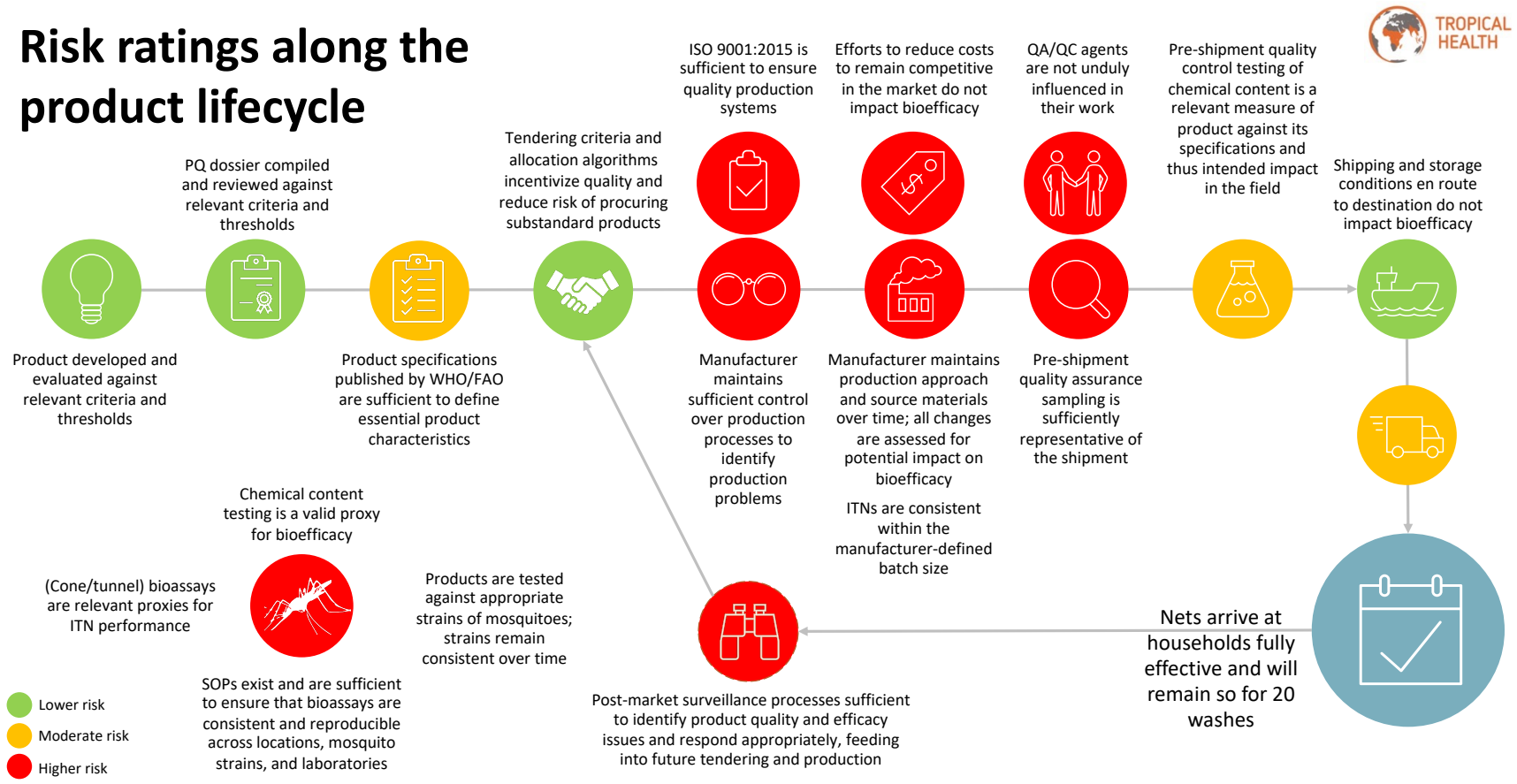
Quality aspects of IVD product development	**Comparison to ITN quality aspects**
Quality system run under **ISO-9001 certification combined with ISO-13485**, which is more detailed and specific for the manufacture of medical devices.	Quality system run under ISO-9001 certification. Companies may develop their own quality systems.

Companies may develop their own quality system within frameworks used by certified bodies to audit IVD quality systems. These requirements are tied to respective regulatory directives applicable for product launch (e.g. IVD Directive for EU, FDA requirements for the US, etc).	ISO-9001 does not assess the quality or appropriateness of QMS content.
Regular internal and external audits conducted. The frequency of internal QC audits are determined by a company's Quality head. External audits by a contracted certified body are mandatory and usually done every 1-2 years.	Internal audit schedule varies by supplier External audits by PQ every 3-5 years or as deemed necessary; additional audits by some procurers
Project run under **audited project management system**. Documentation follows requirements mandated by regulatory agencies, and may vary between companies as long as the company continues to pass ISO audits successfully. Smaller companies may not have comparable QS to large multinational corporations.	Documentation at similar levels of stringency does not appear to exist. Additional critical QC factors beyond specifications should be identified and reviewed for inclusion in site inspections and QS audits.
Products are required to have a '**design master file'**, where product design, changes to it, complaints, and corrective action taken are recorded in detail and are most frequently audited by the certified body.	PQ requires a 'site master file' and additional documentation. Dating from the PQ transition, changes to products, complaints, and corrective action are recorded. However, from information gathered during the landscaping, it seemed unlikely that any changes to product design prior to PQ transition would have been recorded or been audited.
Post-market requirements are clearly defined.	Post-market requirements are not yet clearly defined.

Priority Areas of Risk

Overall, this landscaping considers that the evidence from pre-shipment testing indicates that the vast majority of ITNs are likely to contain compliant concentrations of insecticide at the time they are delivered to households. Considerable efforts have been made on the part of WHO PQT/VCP, procurers, and suppliers to enhance quality systems through the prequalification process, tendering and contract requirements, and manufacturing site improvements. There are nonetheless several areas of risk that should be addressed to further reduce opportunities for substandard ITNs to reach households. From the results of the landscaping and stakeholder interviews, the following are priority areas of risk posed to ITN bioefficacy quality.

Figure 7: Risk ratings along the ITN product lifecycle



Bioassay Testing Methods

- The variability inherent in biological assays can lead to confusion and distrust when comparing results from different labs.
- Tunnel test seldom conducted on deltamethrin/alphacypermethrin products when they fail cone bioassay, in contrast to Guidelines – as tunnel tests are seen as less relevant for these products which lack a strong repellent effect
- Clear need for updated Guidelines for laboratory and field testing of ITNs, reflecting diversity of ITN modes of action

Production

- ISO-9001:2015 standard is necessary but not sufficient to identify key ITN-specific production challenges essential for ensuring bioefficacy.
- Excess capacity and price competition have the potential to incentivize cost-cutting measures that could influence bioefficacy.
- Variability in batch definition and batch size across products pose challenges in harmonizing QC approaches, including sampling methodologies.

QA/QC

- Concerns of collusion between in-country inspectors/sampling agents and staff at contracted manufacturing sites.
- Insufficient financial resources to conduct desired levels of quality testing at relevant points in the ITN life cycle (during production; pre-shipment testing; post-shipment testing), coupled with high costs of current testing methods.

Post-market surveillance

- Periodic re-evaluation of product bioefficacy has not occurred.
- There is uncertainty whether such product drift, if it has occurred, has impacted malaria control efforts.

Specifications

- Concerns that product specifications, particularly chemical content, are not sufficient to ensure and confirm bioefficacy

Land Transport

- Limited understanding of frequency, duration, and impact on bioefficacy of extreme temperature fluctuations encountered in some environments – primarily on land – during ITN transport and storage

Recommendations

Considering the priority risk areas identified and taking into account suggestions provided by key stakeholders, the following recommendations are proposed to ensure ITN bioefficacy throughout the product life cycle:

- **Collectively articulate shared purpose and commitment; identify issues and agree on a roadmap**
    - **Why?** There are a wide range of stakeholders with perspectives and needs around ITN bioefficacy (and quality and durability more widely). A forum for stakeholders to share their individual visions, objectives, and perspectives on needs in this area could be the basis for agreeing a shared way forward related to ensuring ITN quality and bioefficacy. The process should be as inclusive as possible to ensure commitment to the final purpose.

    - **Proposed stakeholders:** WHO PQT/VCP, WHO-GMP, Suppliers, funders, procurement agencies, research institutions, NMC/EP, national procurement agencies, national standards bodies
    - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential to positively impact other issues including ITN durability, safety and ecological impact

Prequalification

- **Clarify whether additional resources are needed for WHO PQT/VCP activities**; if so, determine the amount needed and how these resources can be provided.
- **Address concerns about potential product drift –** consider implementing a product review to assess product drift and/or recertify ITNs on bioefficacy criteria on a regular basis
- **Revise and publish** updated laboratory and field testing guidelines for ITNs as quickly as possible
- **Conduct the ITN Project** to review ITN performance, data requirements, product specifications, standards for testing, methodology, recommended use, and labelling
    - **Why?:** Clarification is needed on performance thresholds to stakeholders for standard, PBO, and dual-AI ITNs, including the role of chemical content, cone, and tunnel assays in determining legal liability of suppliers, and in expected product efficacy

    - **Proposed lead:** WHO PQT/VCP
    - **Proposed stakeholders:** Suppliers, research institutions
    - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential to address additional WHO PQT/VCP resource needs for vector control products beyond ITNs and potential for positive impact on other aspects potentially impacted by product drift, including durability, safety, and ecological impact

Specifications

- Conduct a review of **chemical content and bioefficacy correlations**
- Conduct a review of the **wash resistance index specification**
    - **Why?:** A review of product specifications will ensure they are relevant and specific enough to ensure quality and bioefficacy.

    - **Proposed lead:** WHO PQT/VCP

- **Proposed stakeholders:** Suppliers, research institutions
- **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential for positive impact on other ITN characteristics, including durability, safety, and ecological impact

Tendering

- Continue to include the **cost and value of improved quality** for ITNs in procurement criteria, in addition to price and lead times
  - **Why?**: Procurement procedures for other health commodities frequently include risk assessments of products, based on **quality performance metrics and ratings of QMS**. Manufacturers have the option of meeting baseline levels of QMS or demonstrating they conduct additional QMS, thus improving their quality score and lowering risk for the buyer and the PR. Similar scoring could be considered for ITNs.

  - **Proposed lead**: QA Task Force (PMI, TGF, Unicef, WHO PQT/VCP)
  - **Proposed stakeholders**: Suppliers, procurement agencies, research institutions, NMC/EP, national procurement agencies
  - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential for positive impact on other ITN characteristics, including durability, safety, and ecological impact

Production, Quality Assurance and Quality Control

QMS

- **Introduce more granularity in evaluating ITN quality**:
  - **Jointly develop QMS standards specific to ITN production** - to be included in tenders and to be considered as part of PQ site inspections. PMI's proposed review of QMS is very welcome in this regard.
  - **Increase resources for manufacturing site inspections –** most stakeholders felt that more frequent site inspections would be beneficial to monitor manufacturing compliance, while recognizing the time and resource challenges this would entail.
  - **Consider additional transparency for internal QMS data.** The feasibility of regular or automated provision of QMS data by suppliers to procurement agencies, including review by contracted third parties, should be evaluated.

    - **Why?:** ITNs are complex products and current QC approaches must mature to reflect them.
    - **Proposed lead**: QA Task Force (PMI, TGF, Unicef, WHO PQT/VCP)
    - **Proposed stakeholders**: Suppliers, funders, procurement agencies, NMC/Eps, national standards bodies, WHO-GMP
    - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution)::** potential to impact all ITN characteristics related to quality, including durability, safety, and ecological impact

Quality Control

- Carefully consider **cost and time implications** of additional bioefficacy testing when deciding whether to increase testing requirements – a strong case would need to be made to increase

requirements for bioefficacy testing given current laboratory capacity, comparability between labs, and the resources and time needed to conduct these assays.

- **Align QC sampling SOPs across procurers** – this should include review and harmonization of lot testing sizes, along with sampling approaches. The joint work by PMI, Global Fund, UNICEF, and WHO PQT/VCP is an important recent effort.
- **Conduct a review and trend analysis of OOS** and a mechanism for updating this on an ongoing basis.

    - **Why?:** Gaps were identified throughout the QA/QC processes; QC approaches must mature to reflect ITNs
    - **Proposed lead**: QA Task Force (PMI, TGF, Unicef, WHO PQT/VCP)
    - **Proposed stakeholders**: Suppliers, funders, procurement agencies, research institutions, NMC/EP, national procurement agencies, national standards bodies, WHO-GMP
    - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential to impact all ITN characteristics related to quality, including durability, safety, and ecological impact; potential to facilitate streamlining and optimization of manufacturing procedures

QC Testing

- **Fund development and validation of a QC surface AI concentration method**
    - **Why?**: A rapid, low-cost, non-destructive, lab-based method is urgently needed for all currently-used AI.

    - **Proposed lead**: IVCC
    - **Proposed stakeholders**: Suppliers, research institutions, WHO PQT/VCP
    - **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential to impact production and testing of other textiles treated with relevant AI, such as insect repellent clothing

Transport and Storage

- **Fund and publish operational research** subjecting ITNs to extreme transport and storage conditions encountered
    - **Why?:** To better understand the impact (if any) of such conditions on bioefficacy. Such work may help to improve transport and storage guidance and/or to rule out this element as an area of significant risk.

    - **Proposed lead:** Key funder(s) with mechanisms for this type of research
    - **Proposed stakeholders:** WHO PQT/VCP**,** suppliers, procurement agencies, research institutions, NMC/EPs, national standards bodies, WHO-GMP
    - **Impact beyond ITN bioefficacy:** potential to impact all ITN characteristics related to quality, including durability, safety, and ecological impact

Post-shipment

- **Develop guidelines on effective use of resources for post-shipment testing**
    - **Why?:** Approaches to post-shipment testing vary considerably across countries and cost and time pressure are a significant barrier to conducting. Recommendations on effective approaches for post-shipment testing as well as the expected use of all data are needed. Work could also be done to identify the most critical points for evaluating bioefficacy

across the ITN lifecycle, leading to recommendations around its use in post-shipment testing.

- **Proposed lead**: WHO Expert Review Group (ERG)
- **Proposed stakeholders**: WHO PQT/VCP, WHO-GMP, suppliers, funders, procurement agencies, research institutions, NMC/EPs, national standards bodies
- **Wider impact (i.e. beyond ITN bioefficacy prior to distribution):** potential to impact all ITN characteristics related to quality, including durability, safety, and ecological impact; potential to stimulate development of post-shipment testing guidelines for other vector control products
    - While outside the scope of the present landscaping, further work is needed to review and assess the **factors that influence product bioefficacy post-distribution**, as products are used by households, and the duration of bioefficacy under field conditions. This should include a review to date of bioassay results from durability monitoring studies.

References

1. Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature [Internet]. 2015;526:207–11. Available from: http://www.nature.com.ezp.welch.jhmi.edu/nature/journal/v526/n7572/pdf/nature15535.pdf

2. WHO. World Malaria Report 2020 [Internet]. 2011 p. 299. Available from: https://www.who.int/publications/i/item/9789240015791

3. Bertozzi-Villa A, Bever CA, Koenker H, Weiss DJ, Vargas-Ruiz C, Nandi AK, et al. Maps and metrics of insecticide-treated net access, use, and nets-per-capita in Africa from 2000-2020. Nat Commun. 2021;12:3589.

4. PQT W. Prequalified Vector Control Products [Internet]. [cited 2021 May 31]. Available from: https://extranet.who.int/pqweb/vector-control-products/prequalified-product-list?field_product_type_tid=100&field_pqt_vc_ref_number_value=&title=&field_applicant_tid=&field_active_ingredient_synergis_tid=

5. Global Fund OIG Investigation Report: Tana Netting [Internet]. [cited 2021 Jun 22]. Available from: https://www.theglobalfund.org/media/10650/oig_gf-oig-21-001_report_en.pdf

6. Vinit R, Timinao L, Bubun N, Katusele M, Robinson LJ, Kaman P, et al. Decreased bioefficacy of long-lasting insecticidal nets and the resurgence of malaria in Papua New Guinea. Nature Communications. 2020;1–7.

7. Villalta EL, Bravo AMS, Vizcaino L, Dzuris N, Delgado M, Green M, et al. Evaluation of the durability and use of long-lasting insecticidal nets in Nicaragua. Malaria J. 2021;20:106.

8. Roey KV, Sovannaroth S, Sochantha T, Touch M, Pigeon O, Sluydts V, et al. A phase III trial to evaluate the efficacy, fabric integrity and community acceptance of Netprotect® using a recommended long-lasting insecticidal net as positive control. Malar J [Internet]. 2014;13:256–12. Available from: http://download.springer.com/static/pdf/538/art%253A10.1186%252F1475-2875-13-256.pdf?originUrl=http%3A%2F%2Fmalariajournal.biomedcentral.com%2Farticle%2F10.1186%2F1475-2875-13-256&token2=exp=1464978931~acl=%2Fstatic%2Fpdf%2F538%2Fart%25253A10.1186%25252F1475-2875-13-256.pdf*~hmac=351225c61d7d29ea9ea2093d421cb9870b54578fd0fec3a44f16648be388ebac

9. Milliner J. Net Mapping Project [Internet]. 2021. Available from: https://allianceformalariaprevention.com/working-groups/net-mapping/

10. Marquez, L., Dunstall, S., Bartholdi, J., et al. “Cool or hot”: a study of container temperatures in Australian wine shipments [Internet]. Australasian Journal of Regional Studies. 2012 [cited 2021 May 31]. Available from: https://publications.csiro.au/publications/publication/PIprocite:57560db9-bb2f-4d3f-bc84-d467a37aa173

11. Weiskircher R. Summary of Prior Experiments Regarding Temperature in Sea Containers. 8AD; Available from: https://moam.info/queue/summary-of-prior-experiments-regarding-temperature-in-sea-_59ee1c851723dd8332340554.html

12. Leinberger D. Temperature & Humidity in Ocean Containers [Internet]. 2027 [cited 2006 Feb 27]. Available from: https://www.yumpu.com/en/document/read/10676010/temperature-humidity-in-ocean-containers

13. pesticides W specifications and evaluations for public health. Deltamethrin Long-lasting (coated onto filaments) insecticidal net. 2017 Jul.

14. Kilian A, Obi E, Mansiangi P, Abílio AP, Haji KA, Blaufuss S, et al. Variation of physical durability between LLIN products and net use environments: summary of findings from four African countries. Malar J. 2020;1–11.

15. Tami A, Mubyazi G, Talbert A, Mshinda H, Duchon S, Lengeler C. Evaluation of Olyset insecticide-treated nets distributed seven years previously in Tanzania. Malar J [Internet]. 2004;3:19. Available from: http://malariajournal.biomedcentral.com/articles/10.1186/1475-2875-3-19

16. Azondekon R, Gnanguenon V, Oke-Agbo F, Houevoessa S, Green M, Akogbeto M. A tracking tool for long-lasting insecticidal (mosquito) net intervention following a 2011 national distribution in Benin. Parasit Vectors. 2014;7:6.

17. Smith SC, Zhou C, Stevie FA, Garcia R. Imaging and quantitative analysis of insecticide in mosquito net fibers using Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS). Xu B, editor. PloS one [Internet]. 2018;13:e0209119-19. Available from: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0209119&type=printable

18. Green MD, Atieli F, Akogbeto M. Rapid colorimetric field test to determine levels of deltamethrin on PermaNet® surfaces: association with mosquito bioactivity. Trop Med Int Health. 2009;14:381–8.

19. Green MD, Mayxay M, Beach R, Pongvongsa T, Phompida S, Hongvanthong B, et al. Evaluation of a rapid colorimetric field test to assess the effective life of long-lasting insecticide-treated mosquito nets in the Lao PDR. Malar J. 2013;12:57.

20. Dieval F, Bouyer J, Fafet J-F. An improved extraction method for surface dosage of insecticides on treated textile fabrics. Malaria J. 2017;16:14.

21. Kot P, Muradov M, Ryecroft S, Pedrola MO, Shaw A, Hemingway J, et al. Identification of Optimal Frequencies to Determine Alpha-Cypermethrin Using Machine Learning Feature Selection Techniques. 2018 Ieee Congr Evol Comput Cec. 2018;00:1–7.

22. Castellanos ME, Rodas S, Juárez JG, Lol JC, Chanquin S, Morales Z, et al. Evaluation of the durability of long-lasting insecticidal nets in Guatemala. Malaria J. 2021;20:219.

Appendix A – Key Informants Contacted and Interviewed

Organizations Contacted	Interviewed
A-Z Textile Mills	X
Against Malaria Foundation	X
Avient (Formerly Clariant Masterbatches)	
BASF	X
Bayer CropScience	X
Centers for Disease Control and Prevention	X
Centre de Recherches Entomologiques de Cotonou	X
Chemonics	X
Citeve	
Crown Agents	
Disease Control Technologies	X
Fujian Yamei	
Global Health Supply Chain-Procurement and Supply Management	X
IDA Foundation	X
Ifakara Health Institute/Swiss Tropical and Public Health Institute	X
Innovation to Impact	X
Innovative Vector Control Consortium	X
ITN production and research consultants (independent)	X
LIFE IDEAS Biological Technology	
Liverpool School of Tropical Medicine	X
London School of Hygeine and Tropical Medicine	X
Mainpol	X
Ministry of Health South Sudan	X
NMCP Burundi	X
NMCP Ghana	X
NMCP Madagascar	X
NMCP Nigeria	

NMCP Papua New Guinea	
NMCP Rwanda	
NMCP Tanzania	X
NMCP Uganda	
NRS Moon Netting	X
Pan African Mosquito Control Association	X
Papua New Guinea Institute of Medical Research	X
Population Services International	
Real Relief	X
Rotarians Against Malaria Papua New Guinea	X
SGS	X
Shobikaa Impex	
Sumitomo	
The Bill & Melinda Gates Foundation	X
The Global Fund to Fight AIDS, Tuberculosis and Malaria	X
Tianjin Yorkool International Trading	X
Tüv PSB Singapore	X
U.S. President's Malaria Initiative	X
UNICEF	X
Vestergaard	X
VKA Polymers	X
Walloon Agricultural Research Centre	X
WHO Global Malaria Programme Vector Control and Entomology	X
WHO Neglected Tropical Diseases	
WHO Prequalification Unit Vector Control Product Assessment Team	X

Appendix B – Pre-qualified ITNs as of October 27, 2021

Table available at https://extranet.who.int/pqweb/vector-control-products/prequalified-product-list?field_product_type_tid=100&field_pqt_vc_ref_number_value=&title=&field_applicant_tid=&field_active_ingredient_synergis_tid=

PQT/VC Ref Number	Product Name	Applicant	Active Ingredient/Synergist	Date of Prequalification
006-001	DuraNet LN	Shobikaa Impex Private Limited	Alpha-cypermethrin	07 Dec 2017
006-003	DuraNet Plus	Shobikaa Impex Private Limited	Alpha-cypermethrin, Piperonyl Butoxide (PBO)	13 Aug 2020
002-001	Interceptor	BASF AGRO B.V. Arnhem (NL) Freienbach Branch	Alpha-cypermethrin	08 Dec 2017
002-002	Interceptor G2	BASF AGRO B.V. Arnhem (NL) Freienbach Branch	Alpha-cypermethrin, Chlorfenapyr	29 Jan 2018
014-001	MAGNet	V.K.A. Polymers Pvt. Ltd	Alpha-cypermethrin	19 Feb 2018
009-001	MiraNet	A to Z Textile Mills Limited	Alpha-cypermethrin	21 Feb 2018
001-004	OLYSET Net	Sumitomo Chemical Co., Ltd	Permethrin	07 Dec 2017
001-005	OLYSET PLUS	Sumitomo Chemical Co., Ltd	Permethrin, Piperonyl Butoxide (PBO)	29 Jan 2018
026-001	Panda Net 2.0	Life Ideas Biotechnology Co. Ltd	Deltamethrin	03 May 2018
005-001	PermaNet 2.0	Vestergaard Sarl	Deltamethrin	08 Dec 2017
005-002	PermaNet 3.0	Vestergaard Sarl	Deltamethrin, Piperonyl Butoxide (PBO)	29 Jan 2018
036-002	Reliefnet Reverte	Real Relief Health ApS	Deltamethrin	25 Jan 2021
003-003	Royal Guard	Disease Control Technology LLC	Alpha-cypermethrin, Pyriproxyfen	29 Mar 2019
003-001	Royal Sentry	Disease Control Technology LLC	Alpha-cypermethrin	07 Dec 2017
003-002	Royal Sentry 2.0	Disease Control Technology LLC	Alpha-cypermethrin	06 Feb 2019
018-001	SafeNet	Mainpol GmbH	Alpha-cypermethrin	19 Feb 2018
028-002	Tsara	Moon Netting FZCO	Deltamethrin	14 Aug 2020
028-001	Tsara Boost	Moon Netting FZCO	Deltamethrin, Piperonyl Butoxide (PBO)	29 Jan 2018
028-004	Tsara Plus	Moon Netting FZCO	Deltamethrin, Piperonyl Butoxide (PBO)	29 Jan 2018
028-003	Tsara Soft	Moon Netting FZCO	Deltamethrin	09 Oct 2020
014-002	VEERALIN	V.K.A. Polymers Pvt. Ltd	Alpha-cypermethrin, Piperonyl Butoxide (PBO)	29 Jan 2018
015-001	Yahe LN	Fujian Yamei Industry & Trade Co. Ltd	Deltamethrin	19 Feb 2018
021-001	Yorkool LN	Tianjin Yorkool International Trading Co., Ltd	Deltamethrin	19 Feb 2018