ITN Bioefficacy Landscaping

1 DECEMBER 2021

Executive Summary

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.
- Significant efforts are ongoing to ensure test criteria for insecticidal efficacy of ITNs are clear, reproducible, and relevant.

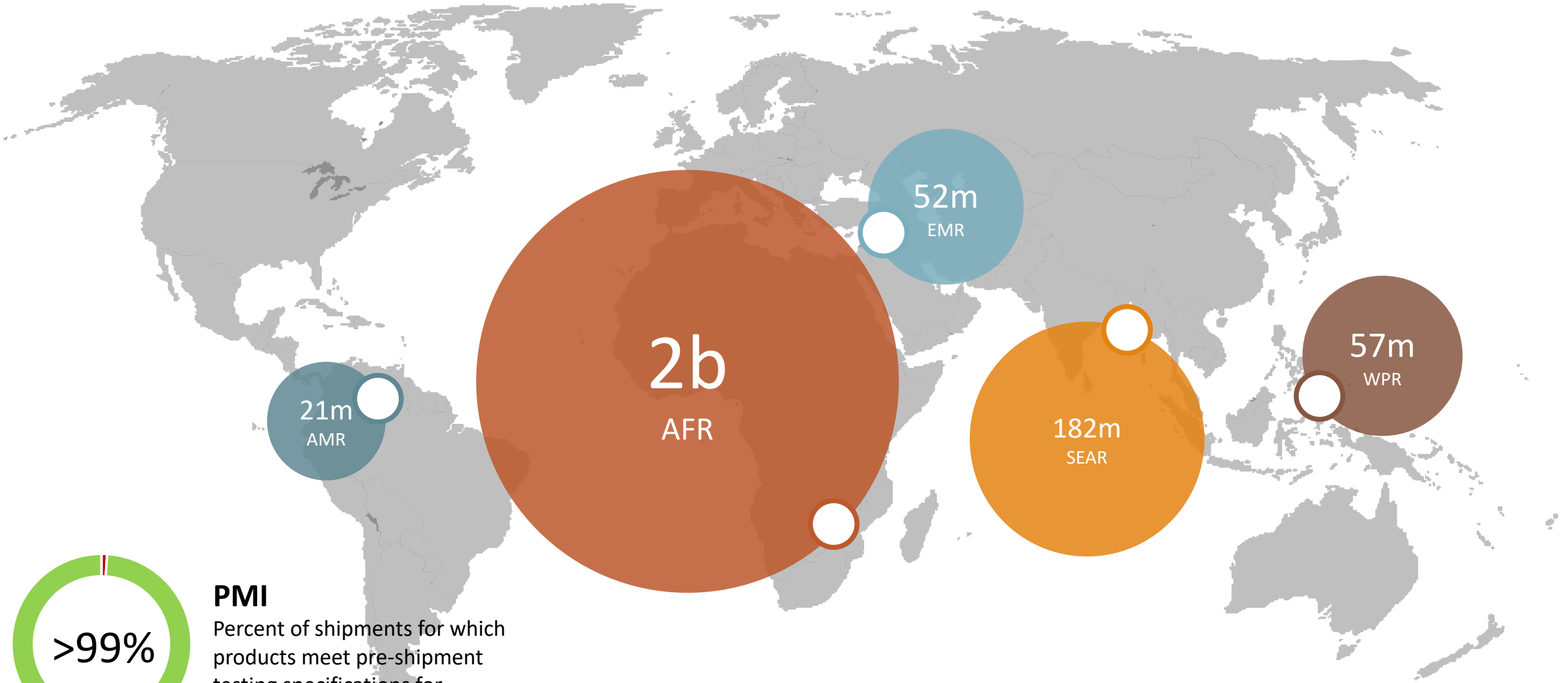
Areas of potential risk

- 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.

Over 2 billion ITNs have been delivered to malaria-endemic countries since 2004



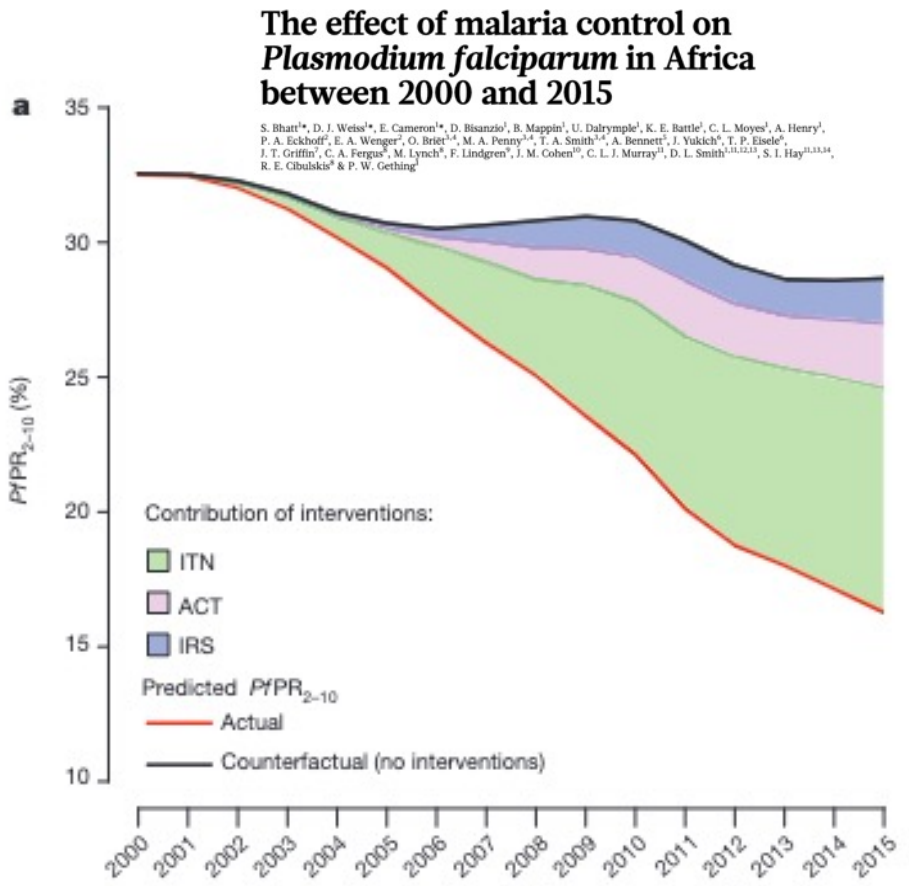
PMI

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

AFR total since 2004; other regions' totals since 2009. AMP Net Mapping Project

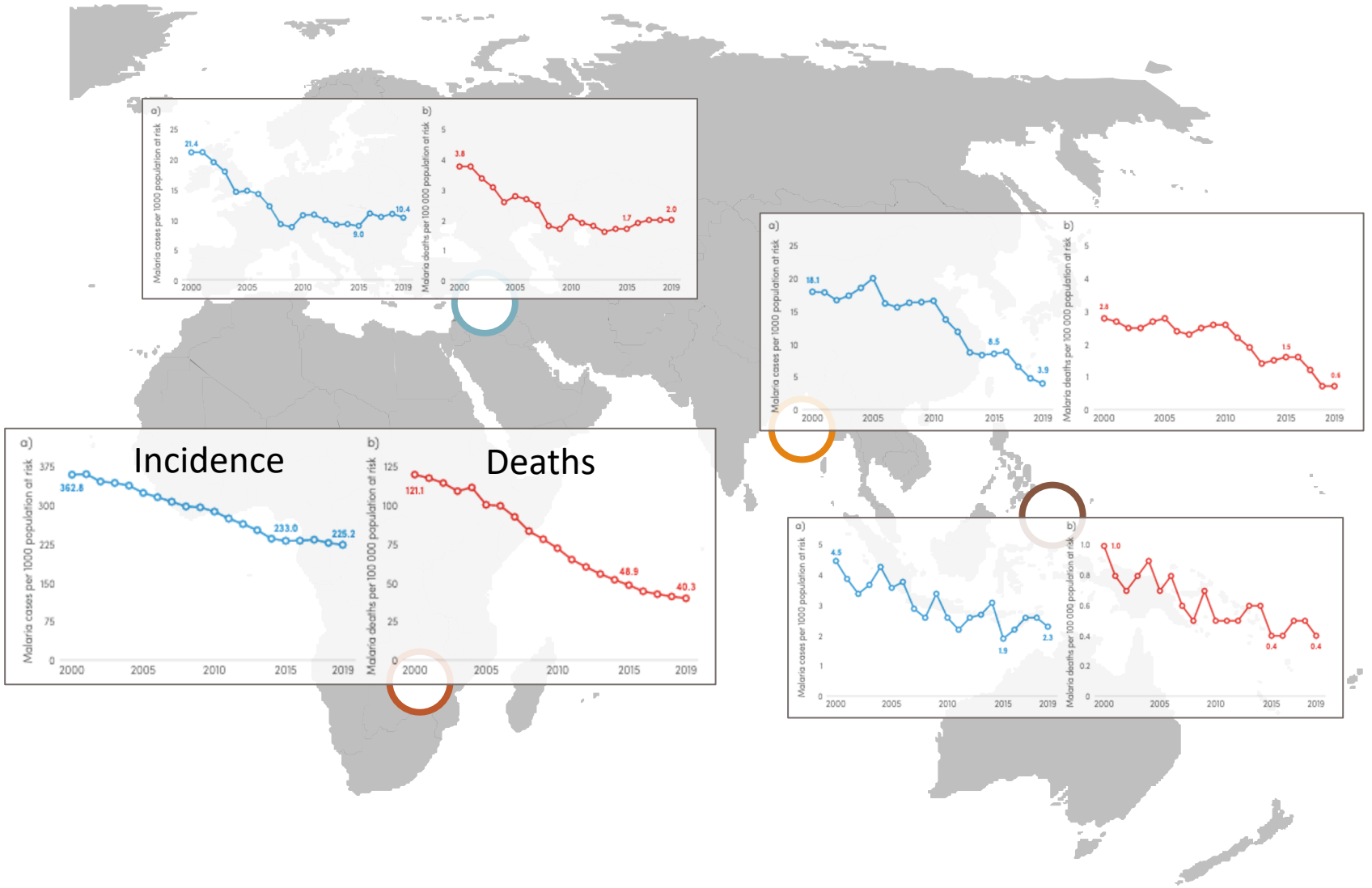
ITNs have significantly reduced malaria burden over the past two decades

- ITNs are the cornerstone of malaria control efforts worldwide
- They are responsible for two-thirds of the reduction in burden from 2000-2015[1]
- They are the most widely deployed vector control intervention and are highly cost-effective[1]
- Over 87% of people with access to an ITN in 2020 used one the previous night[2]

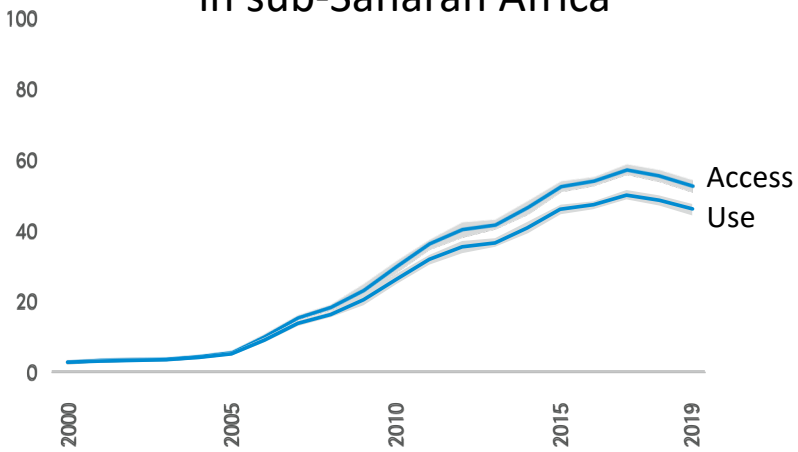


1. Bhatt et al, 2015, *Nature*
2. Bertozzi-Villa et al, 2021, *Nature Communications*

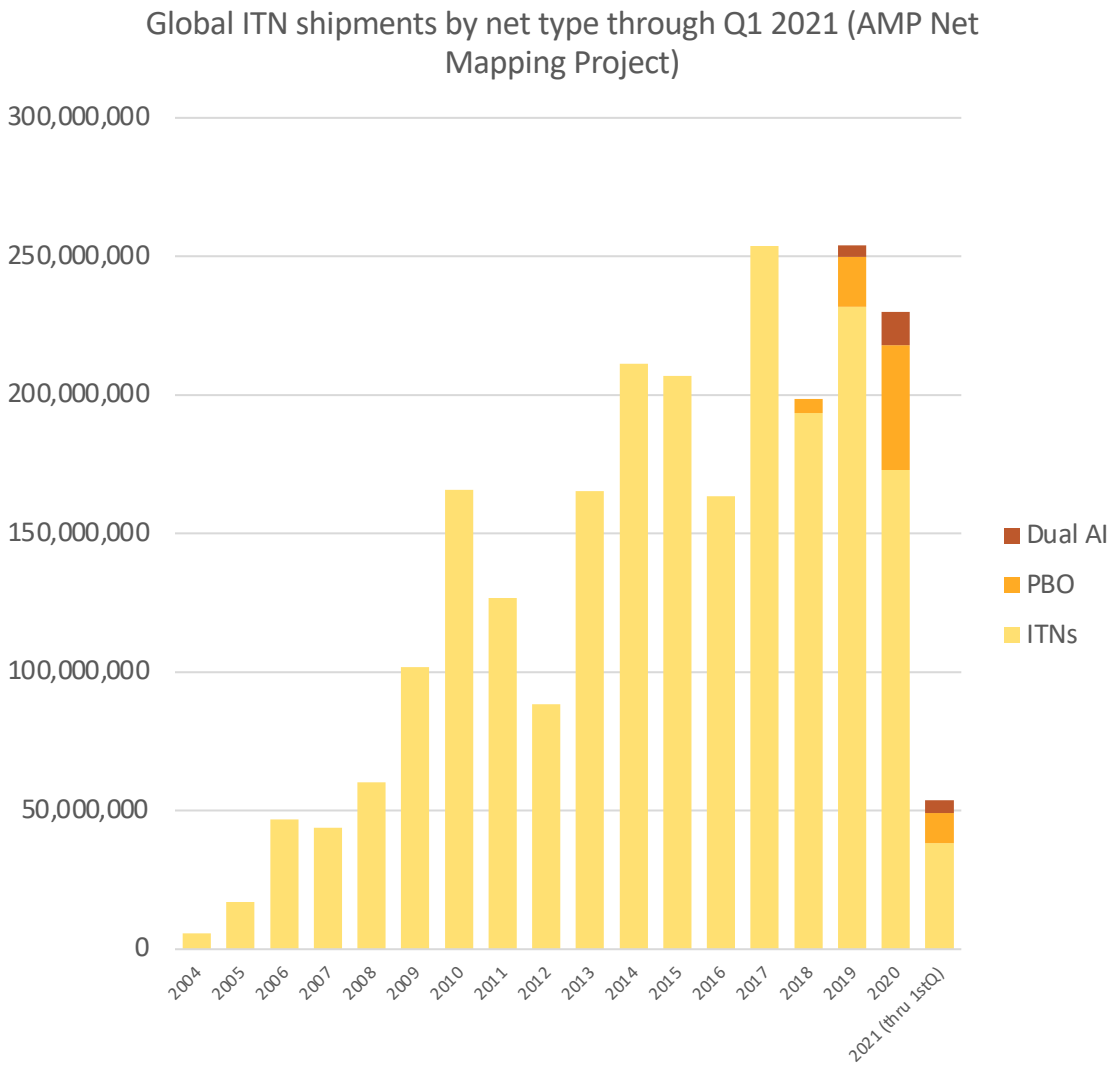
Reductions in malaria case incidence per 1000 population and malaria deaths per 100,000



Population access to and use of ITNs in sub-Saharan Africa



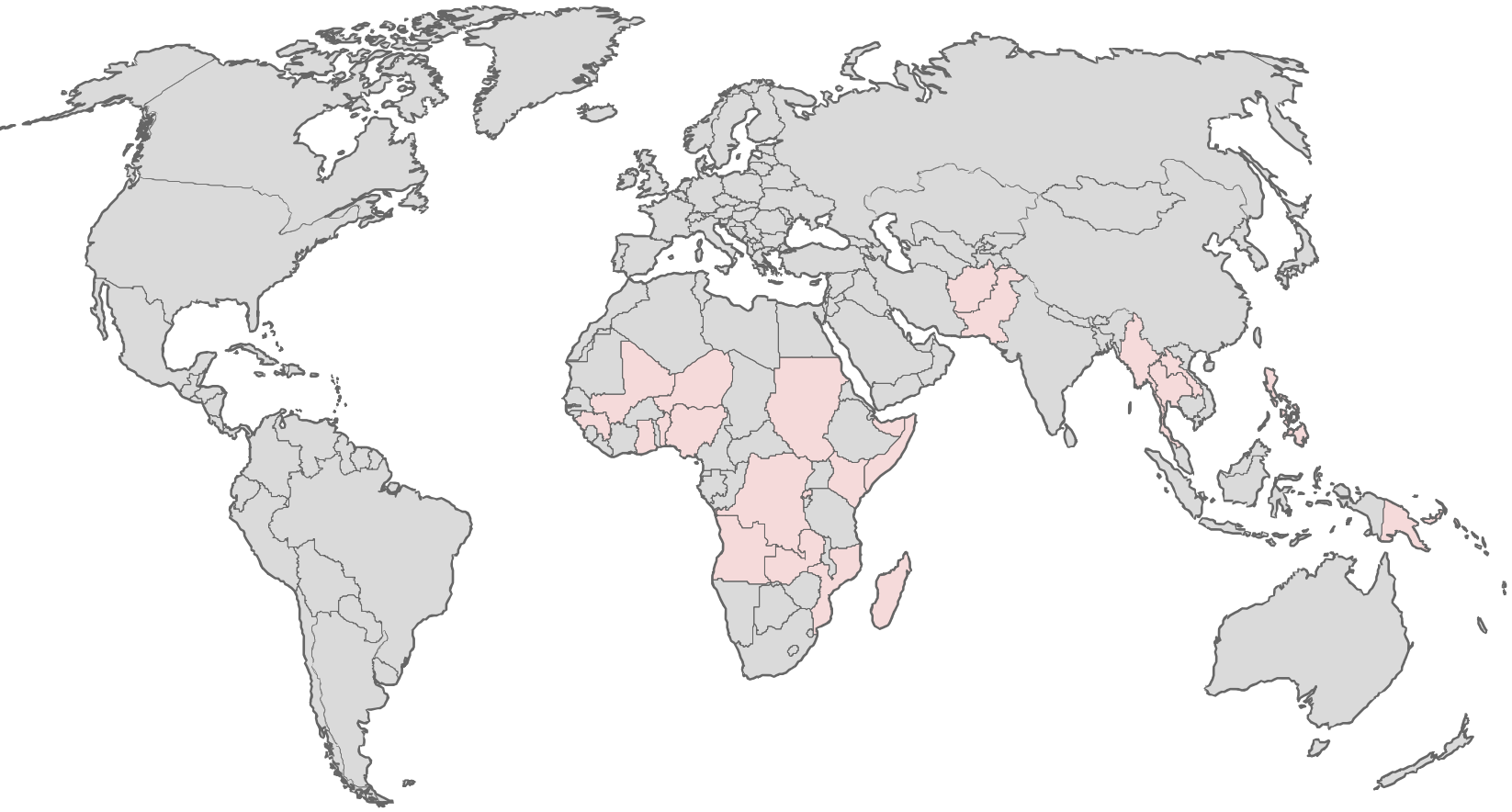
Figures from 2020 World Malaria Report



New nets

- ITNs with synergist (PBO) that restore mosquitoes' susceptibility to pyrethroids
- ITNs with pyrethroids plus additional active ingredients (AI) that use different modes of action to kill (chlorfenapyr) or reduce fecundity of (pyriproxyfen) mosquitoes
- These and other ITNs in development are promising tools for mitigating the impact of pyrethroid resistance, and accelerating the fight against malaria

Recent quality concerns have raised questions about bioefficacy



- Global Fund OIG report estimating 52 million DawaPlus ITNs distributed in 21 countries with insufficient insecticide
- Out-of-specifications for chemical content and other investigations raising questions about consistency of production and mechanisms to identify ITNs with insufficient or insufficiently available AI before shipment
- Review opportunities for improving upon existing approaches and procedures to ensure ITNs are as effective as possible

Maximising Impact: Effectiveness of ITNs

Product backed by **WHO policy / recommendation** confirming public health value

Product **pre-qualified by WHO** confirming safety, efficacy, and quality

Product specification published by WHO/FAO and sufficiently defines product characteristics essential to impact

Product is **produced to consistent standard** in line with specification

Quality assurance sampling and testing is sufficient to confirm products are in specification

Supply chain from manufacturer to point of distribution: under conditions specified by the manufacturer according to product characteristics

Context of use: ento and epi setting, including IR profile regularity of use, durability, attrition

Impact on malaria

Procurement policies and procedures: Governments, TGF, PMI, others

Figure: End-to-end analysis of factors influencing potential for impact from an ITN

Objectives of landscaping

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.

Not in scope:

1. Quality issues other than bioefficacy (i.e. physical parameters)
2. Bioefficacy post-distribution (i.e. data from durability monitoring and field performance; influence of user behaviors)

NOTE: recommendations arising from this review will potentially support quality improvements beyond the current focus of bio-efficacy prior to distribution; these are indicated in the recommendations.

Methods

01

Document review

Review of publicly available reports, documentation, and published literature.

02

Stakeholder mapping

Collaborative snowball sampling of 66 potential key informants across seven stakeholder groups.

03

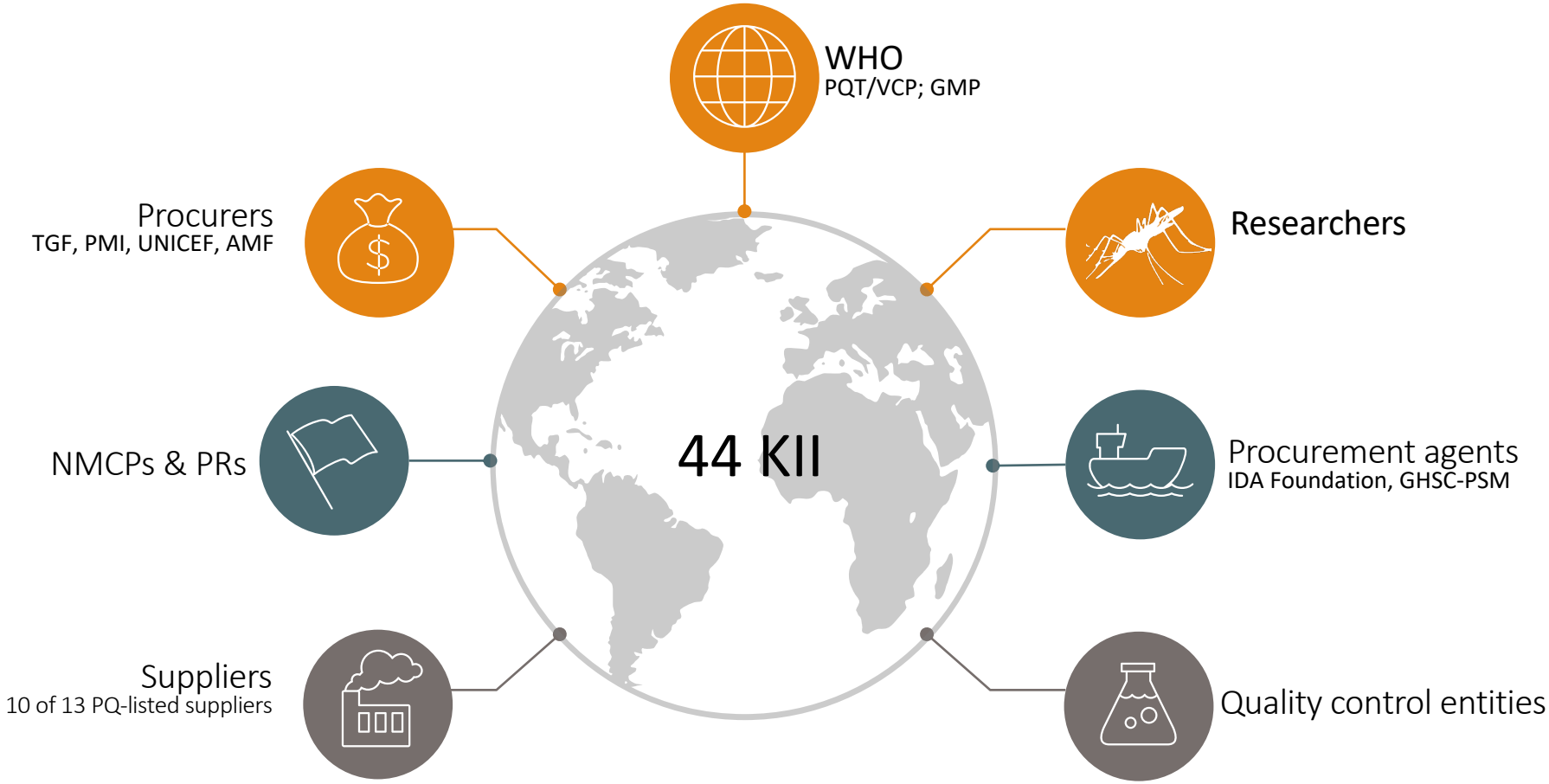
Key informant interviews

Forty-four interviews conducted via Zoom during April and May 2021.

04

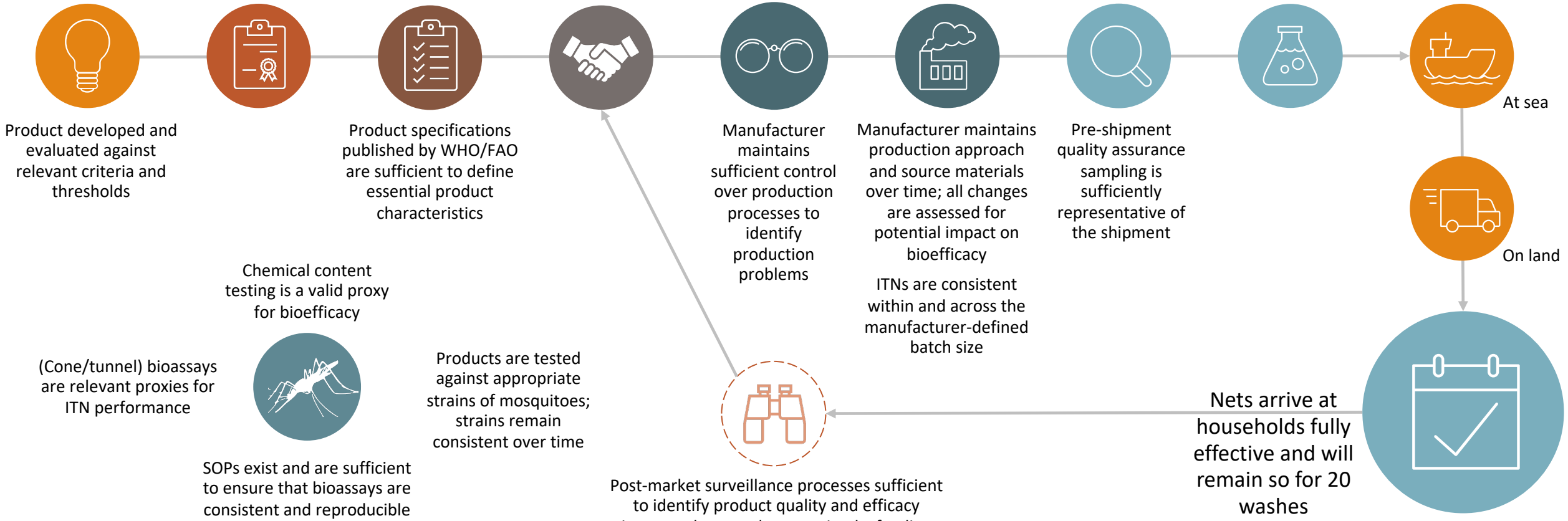
Synthesis and write-up

Review of transcripts, synthesis, and report writing.



Assumptions along the product lifecycle

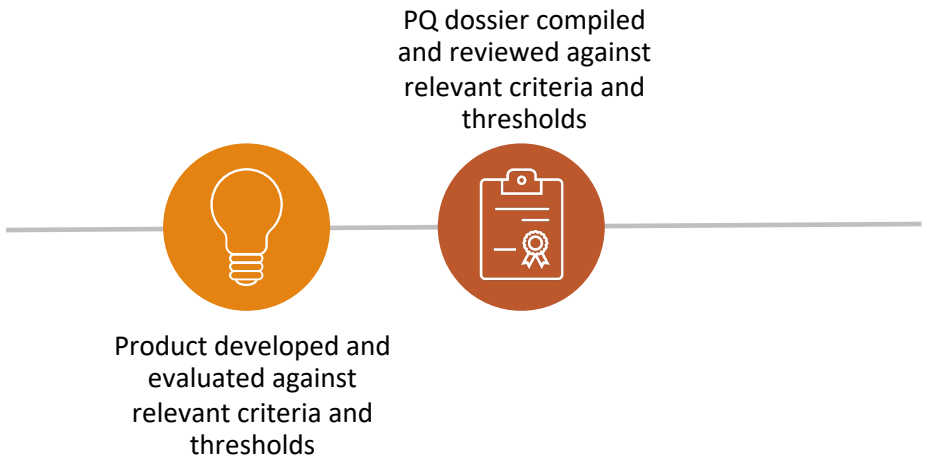
Assumptions along the product lifecycle



Assumptions along the product lifecycle

Product development

Dossier submission



Strengths

A. Strong appreciation for clarity and professionalism of PQ process. Dossier requirements and communication are clear.

B. Manufacturing site inspections at ISO-9001 standard are seen as a crucial tool and perceived to have led directly to quality improvements.

C. Ongoing work towards consensus methods for assessing bioefficacy; public health value of new products.

D. PQT/VCP ITN Project is reviewing data requirements, specifications, testing standards, and more.

Weaknesses

A. Concerns about limited resources within PQ, contributing to heavy workload for a small staff.

B. ISO-9001:2015 standard was felt to be necessary but not sufficient to assess quality measures specific to ITNs.

C. 2013 Guidelines for lab and field testing of ITNs yet to be updated; provides latitude for nets with new modes of action but lacks critical detail. Evaluation design is left up to GLP-accredited sites in consultation with suppliers and experts.

Challenges

A. Budgetary support limitations for PQ

B. Next-level ISO (18435 for medical devices) not appropriate for ITNs.

C. Efficacy thresholds for new ITN products with novel modes of action take time to be validated and agreed

Opportunities

A. Identifying additional support for PQ

B. Developing ITN-specific QMS standards in collaboration with suppliers, manufacturers, regulators, and researchers.

C. Update of 2013 Guidelines for lab and field testing of ITNs is urgently needed; in process

Assumptions along the product lifecycle

Product specifications

Product specifications published by WHO/FAO are sufficient to define essential product characteristics

Strengths

A. Specifications related to chemical content are relevant and measurable

Weaknesses

A. Total chemical content not always correlated with bioefficacy

B. Inconsistencies in specifications across products; 9 of 22 products include fabric weight; storage stability criteria differ for some products; WRI ranges across products

C. No specification related to surface concentration of AI

Challenges

A. Limited feasibility of including bioefficacy in product specifications

B. Time and resources needed to develop surface AI method that will work across different textiles and AIs.

Opportunities

A. Review the need for harmonization of inconsistent product specifications

B. Invest in development of viable, accurate, validated surface AI methods for all listed products

Assumptions along the product lifecycle

Tendering

Tendering criteria and allocation algorithms incentivize quality and reduce risk of procuring substandard products

Strengths

A. Increased attention to technical factors including quality during tendering and contracting.

B. Supplier performance directly linked to future allocations.

C. Current efforts to harmonize quality-related requirements across procurers.

Challenges

A. Harmonization of tendering criteria across procurers, esp. quality requirements, hampered by institutional policies.

B. Overall perception that price competition and excess capacity has led or will lead to cost-cutting measures that can impact bioefficacy.

C. Supplier concerns about cost implications of additional quality requirements (upgrades to QMS; reporting), particularly for smaller suppliers.

Weaknesses

A. Tendering is widely perceived to be focused on price. Most stakeholders were not aware of other factors considered during tendering, or felt these were so secondary as to be almost irrelevant.

Opportunities

A. Continue to incentivize and reward quality in the tendering and contracting process. Risk ratings and/or quality over time metrics have been useful in other settings.

B. Continued review and harmonization of procurement and quality criteria across procurers, including bioefficacy.

C. Improve communication of the relative weights of cost and technical factors during tendering and allocation.

D. Use of third-party contractors to review manufacturing process data, via automated process monitoring with digital upload of data to provide more transparency and accountability

Assumptions along the product lifecycle

Manufacturing

ISO 9001:2015 is sufficient to ensure quality production systems

Efforts to reduce costs to remain competitive in the market do not impact bioefficacy

Manufacturer maintains sufficient control over production processes to identify production problems

Manufacturer maintains production approach and source materials over time; all changes are assessed for potential impact on bioefficacy

ITNs are consistent within the manufacturer-defined batch size

Strengths

A. PQ requirement to notify of any changes to products, and consequences for not doing so.

B. Manufacturing site inspections at ISO-9001 standard are seen as a crucial tool and perceived to have led directly to quality improvements.

Challenges

A. Lack of industry-specific QMS standards.

B. Excess capacity and price competition have the potential to incentivize cost-cutting measures that could influence bioefficacy.

C. Possibility that product changes would neither be reported nor caught by pre-shipment chemical content testing yet could affect bioefficacy

Weaknesses

A. Unclear whether product changes occurred prior to PQ transition, and how these might be handled.

B. Supplier oversight of manufacturing sites may be variable.

C. Several manufacturing parameters may influence bioefficacy. These vary by method (coating vs incorporation) and AI.

D. ISO-9001 requires a QMS but does not evaluate the appropriateness of a given QMS.

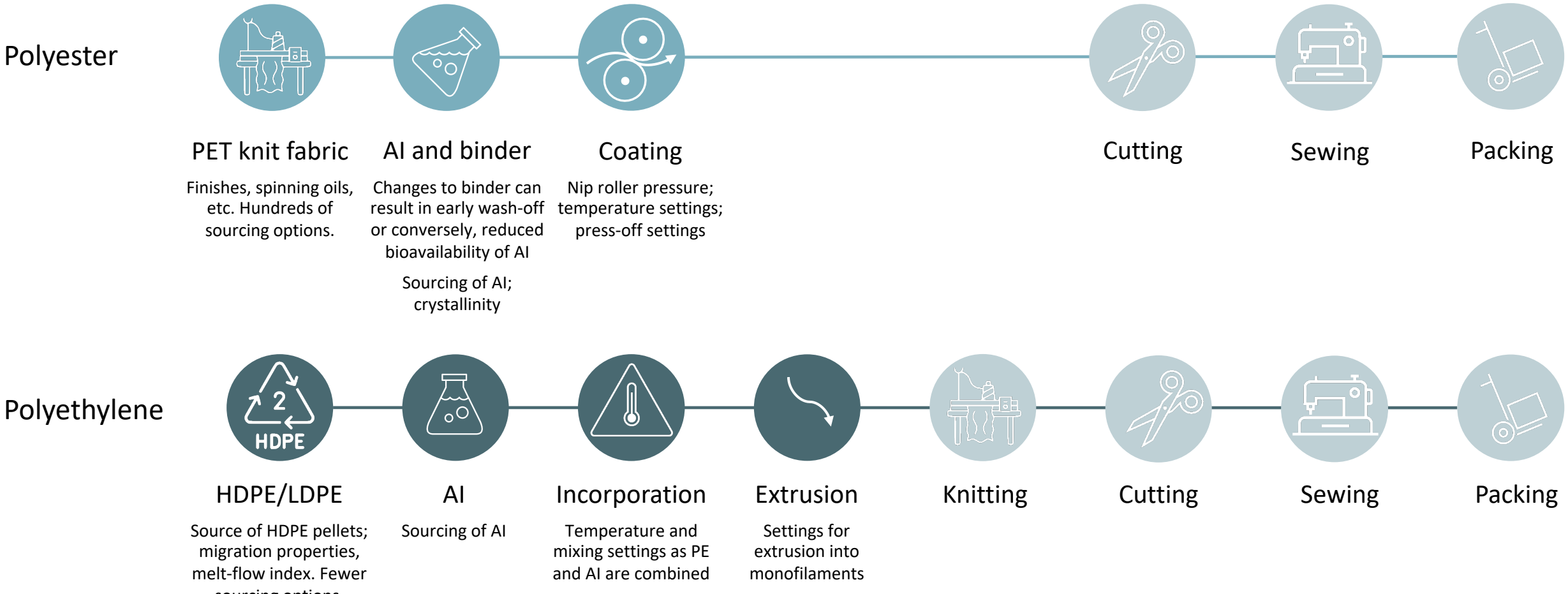
Opportunities

A. Developing ITN-specific QMS standards in collaboration with suppliers, manufacturers, regulators, and researchers.

B. Devising effective, feasible incentives for QMS improvement

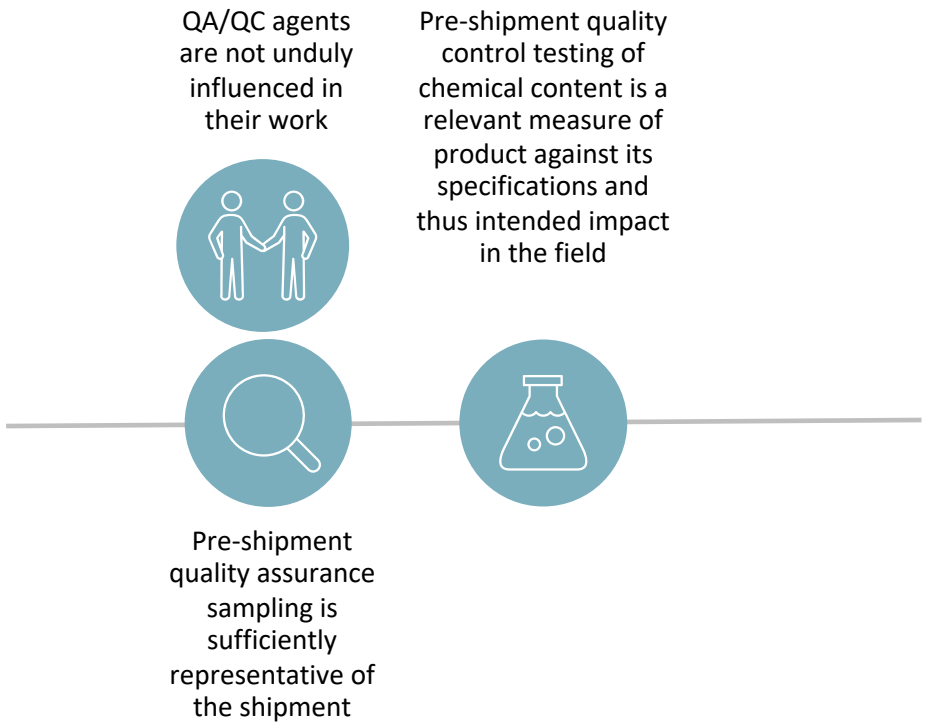
C. Better identify which material parameters best predict or influence bioefficacy

Production parameters impacting bioefficacy



Assumptions along the product lifecycle

Quality assurance/control



Strengths

- A Independent testing labs with GLP certification following CIPAC protocols provide confidence in validity of test results.
- B Required reporting of OOS or COC to procurement agencies prior to shipment is largely effective in ensuring ITNs with potential bioefficacy issues are identified before distribution.
- C Sharing of information about OOS investigations among procurers and PQ; retention of samples by suppliers to facilitate investigations.

Weaknesses

- A Small number of sampling agencies and in-country inspectors perceived to be a risk for collusion between inspectors and manufacturing site representatives.
- B Concerns that ITN products received a COC and were later found to be out of compliance with specifications, raising questions regarding validity of COC.
- C Batch definitions and sizes vary by supplier (50,000 to 3,000,000)

Challenges

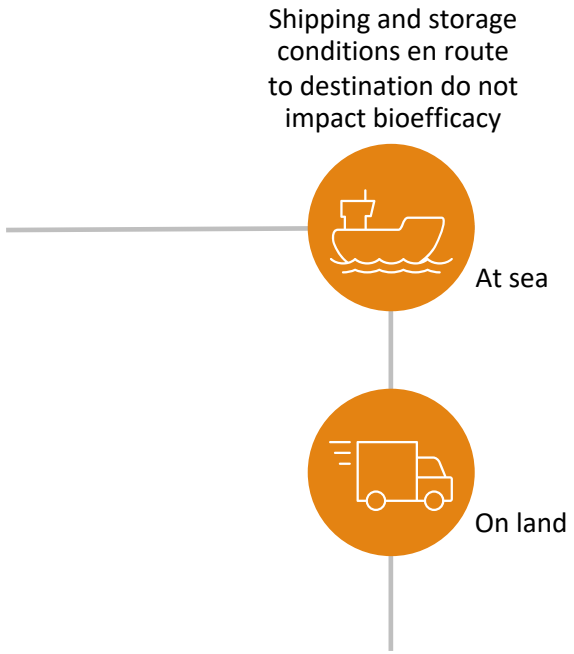
- A Due to high costs of testing, limited samples (2-8) are taken for chemical content tests per lot.
- B Sampling approaches may vary by procurement or sampling agency.

Opportunities

- A Standardization of sampling procedures and batch/lot sizes.
- B Determining whether further oversight needed of sampling agencies, and if so, how and by whom

Assumptions along the product lifecycle

Transport



Strengths

A. Most countries have appropriate storage facilities for ITNs at central level; storage at lower levels generally limited to several weeks.

B. Temperature and humidity aboard cargo ships is relatively well-characterized from other sectors; at-sea max temperatures are relatively stable around 30-36 C and are unlikely to pose significant threats for ITN bioefficacy.

Weaknesses

A. On land, daily max temperatures inside a container can reach 60°C when ambient temperatures are 40°C and container is not shaded; this may occur during customs clearance and land transport depending on conditions. Max temperatures may only be reached for 1-2 hours each day, but the cumulative impact on bioefficacy over periods of weeks or months is not well understood.

B. Deltamethrin may convert to R-isomer particularly above 50°C. This conversion reduces the bioavailability of deltamethrin to mosquitoes.

Challenges

A. 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.

Opportunities

A. Conduct research to characterize temperatures encountered and duration during clearance, land transport.

B. Conduct research assessing impact of above temperature fluctuations and duration on bioefficacy across ITN products.

Assumptions along the product lifecycle

Post-market surveillance

Post-market surveillance processes sufficient to identify product quality and efficacy issues and respond appropriately, feeding into future tendering and production

Strengths

A. PQT-VC includes post-market requirements in their guidance, including change notification, 3 yearly manufacturing site inspections, product review, and complaints.

B. PQT-VC may issue notifications of concern regarding products, suspend them pending investigation, or delist.

Challenges

A. Unlike medicines or vaccines, there are no robust systems in place for reporting issues. ITNs are not used in a clinical setting and do not have the same types of adverse events.

B. Due to testing variations (next slide) confirmatory testing required when results are inconclusive. Triangulation of results across different settings (as in durability monitoring) is challenging given many confounding factors.

C. Post-shipment inspection approaches are not harmonized across countries and rarely include bioefficacy testing.

D. Funding is currently a barrier for post-shipment bioefficacy testing at country level. Decision to reject a shipment at 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.

E. Process for submitting complaints to PQT is not clear. Some stakeholders were concerned that complaints could be made by competitors.

F. Limited complaint investigation resources within PQT.

Weaknesses

A. Post-market surveillance guidance for countries and NRAs yet to be developed

B. Surveillance 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.

C. No formalized mechanism or clear mandate for pulling together bioefficacy data across post-market surveillance activities

Opportunities

A. Develop consensus approach for post-shipment testing at country level.

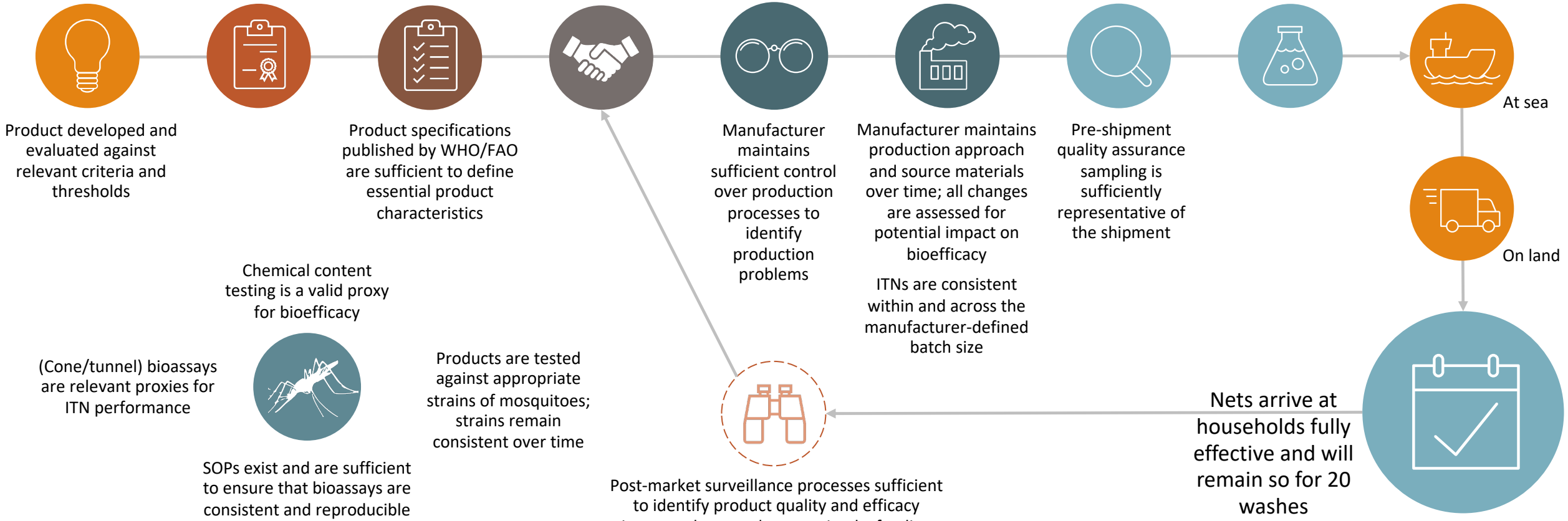
B. Build in relevant post-market surveillance activities (post-shipment testing; durability monitoring) into the cost of ITN delivery systems

C. Strengthen role of NRAs and local research institutions to conduct post-market surveillance

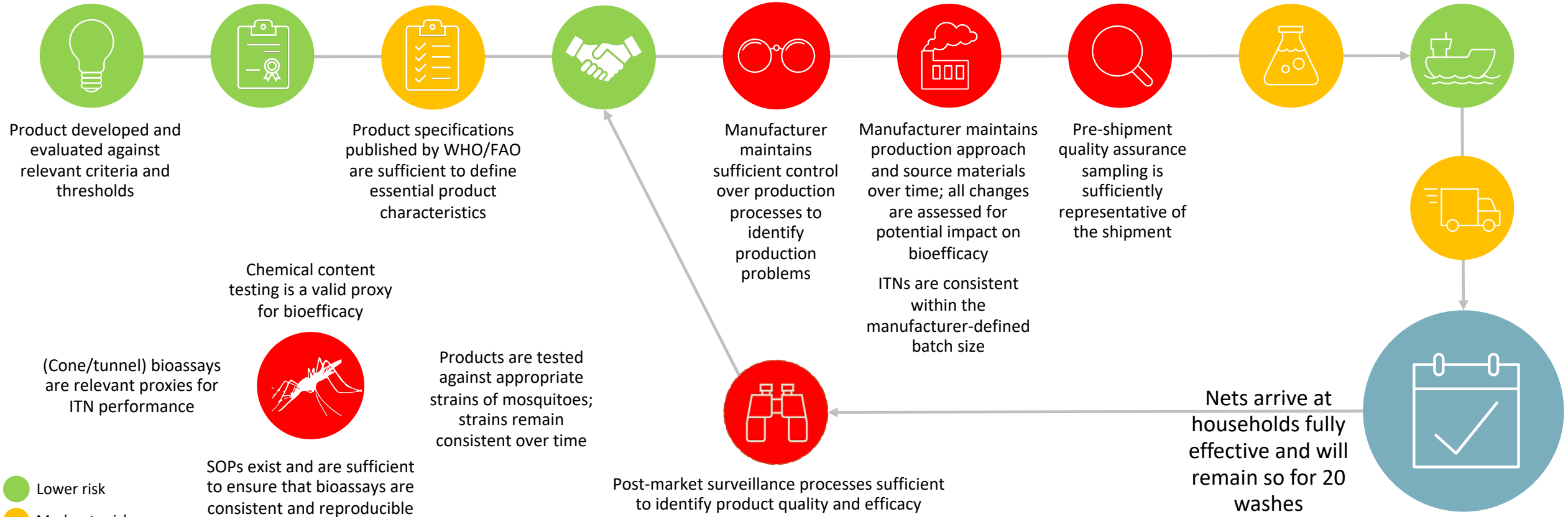
D. Clarify complaints submission and investigation process for broader stakeholders, particularly its link with OOS results and procurer investigations

Ranking risk along the product lifecycle

Assumptions along the product lifecycle



Risk ratings along the product lifecycle

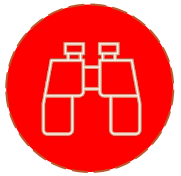


Priority risk areas

- Variability inherent in biological assays across labs contributes to confusion
- 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

- ISO-9001 standard necessary but not sufficient to identify key ITN production challenges essential for ensuring bioefficacy
- Potential for cost-cutting measures to impact bioefficacy

- Variability in batch/lot size and implications for representativeness of samples taken
- Concerns of collusion between in-country inspectors/sampling agents and staff at contracted manufacturing sites



- Insufficient financial resources to conduct desired levels of bioefficacy testing during ITN lifecycle
- Uncertainty whether product drift, if it has occurred, has impacted malaria control efforts
- Periodic re-evaluation of product bioefficacy has not occurred

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

- 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

Recommendations: Partnership

- **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 to ensuring ITN quality and bioefficacy. The process should be as inclusive as possible to ensure commitment to the final purpose.
- **Proposed lead**: WHO PQT/VCP
- **Proposed stakeholders**: 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

Recommendations: Procurement

- **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 **scoring of manufacturer 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

Recommendations: 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 ; WHO-GMP
- **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

Recommendations: QA/QC (1)

- **Introduce more granularity in evaluating ITN quality –**
  - Jointly develop QMS standards specific to ITN production - to be included in tenders and assessed in 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 provision of QMS data by suppliers to procurement agencies 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

Recommendations: QA/QC (2)

- **Carefully consider cost and time implications of additional bioefficacy testing when deciding whether to increase testing requirements.**
- **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

Recommendations: QA/QC (3)

- **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

Recommendations: Transport

- **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.
- **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

Recommendations: Post-shipment testing

- **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. 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 ERG
- **Proposed stakeholders**: WHO PQT/VCP, WHO-GMP, Suppliers, funders, procurement agencies, research institutions, NCM/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.

Recommendations: PQ

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

THANK YOU