Risk Analysis for Gene Drives

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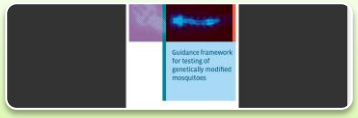
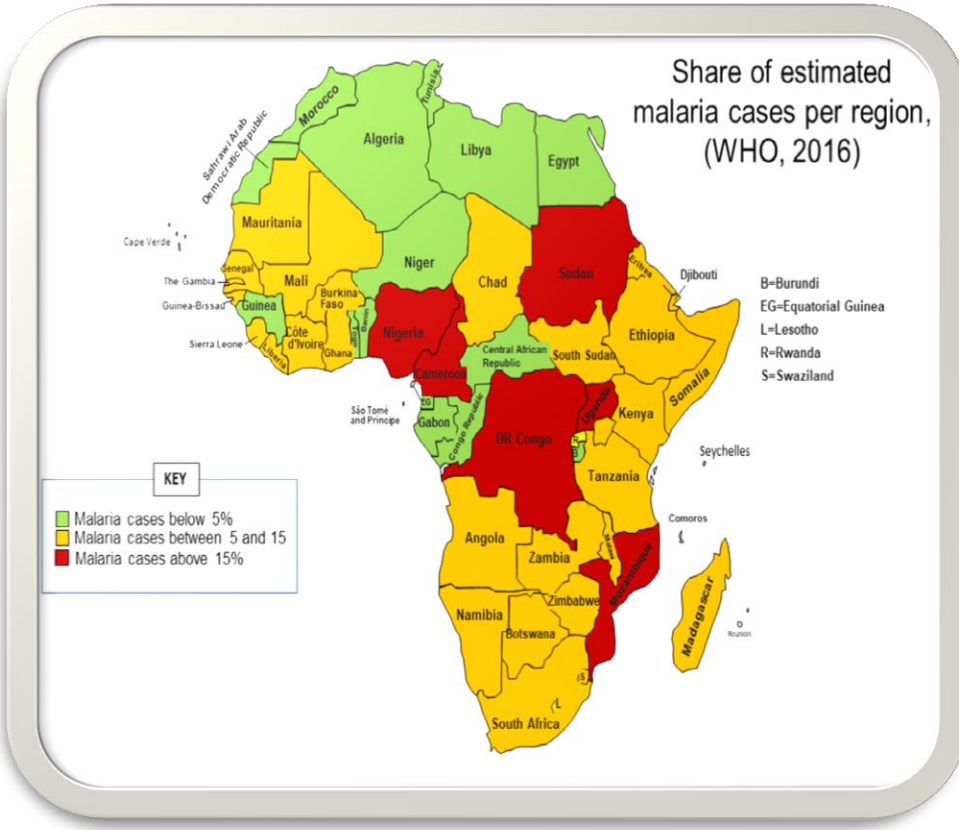
Presentation Outline

- Problem of Malaria in Africa
- Gene Drives- AMRH, ABNE, USNIH
- Risk Analysis- RA, RM, RC, WHO Guideline
- 

WHO Guidelines for Testing GMMs
- Reference International Treaties and Agreements-CBD, CPB, EFSA
- Regional Platform ECOWAS, COMESA
- Projection on Scenerio in Africa

The Malaria Burden in Africa

- **WHO Estimates, 216 million new malaria cases and 445,000 deaths worldwide in 2016**
- **Of which Africa accounting for 90% of the cases and 91% of the deaths(WHO, 2017).**
- **Children under five years of age are the most affected.**



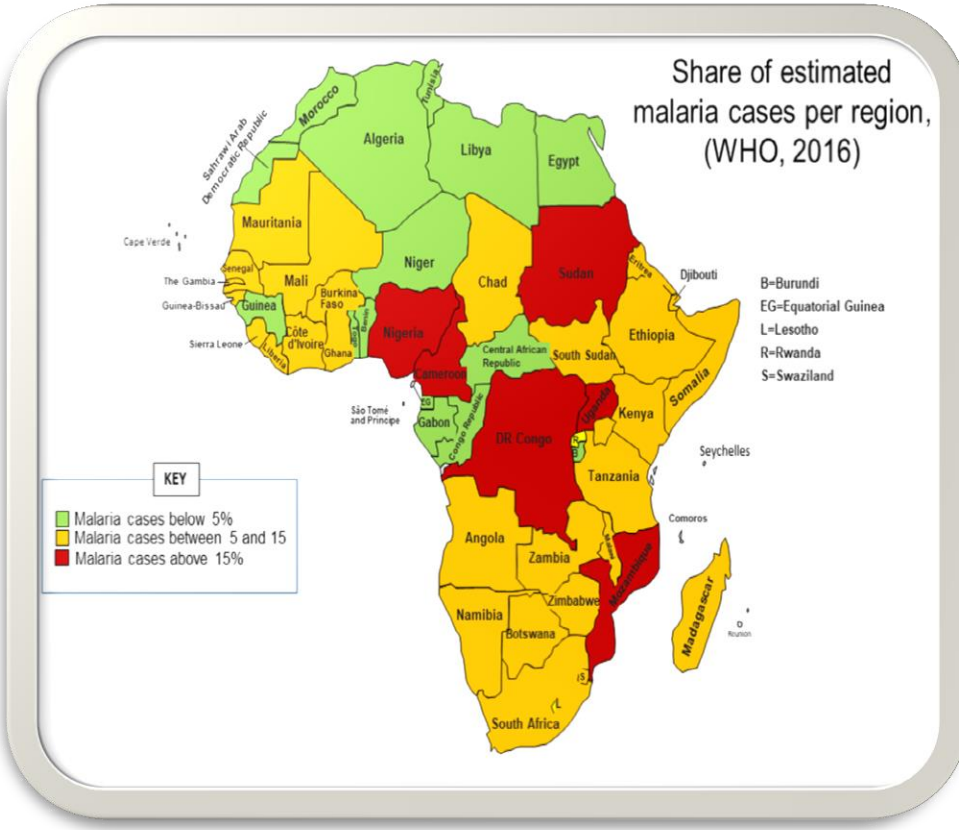
Malaria burden in African countries (Data Source: WHO 2016 World Malaria Report)

The Malaria Burden in Africa

In 2016, the global burden of malaria concentrated in 14 African countries, all accounted for 80% of global malaria cases and deaths.

Today, the Democratic Republic of Congo and Nigeria alone constitute 40% of the global malaria deaths(WHO, 2016)

WHO (data) DRC, Nigeria , Mozambique, Cameroon, Uganda, Tanzania, Kenya and Somalia have the highest prevalence rates, accounting for about half of the global malaria burden



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The Malaria Burden in Africa

- The Eastern Mediterranean Regional off ice of the World Health Organization, also known as EMRO
- In 2015, about 291 million people in 8 out of the 21 countries in the WHO EMRO Region were at some risk of malaria, with 111 million at high risk
- Three African countries: Djibouti, Somalia and Sudan are part of EMRO and have areas of high malaria transmission.

http://www.who.int/hac/network/who/ro_emro/en/

The Malaria Burden in Africa

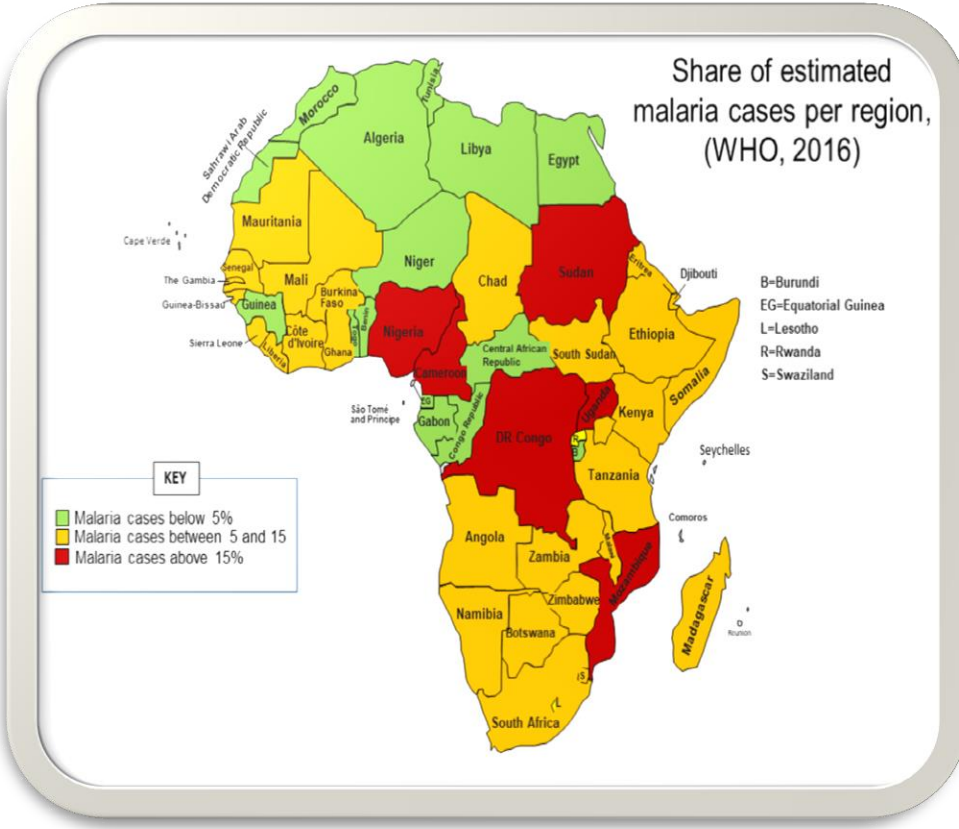
Malaria in Africa is widely recognized as both a cause and consequence of poverty, The malaria-related losses were estimated to cost up to 1.3 % of Africa's GDP, and about US$12 billion per year in direct costs, as of 2002(Gallup & Sachs, 2001; Sachs & Malaney, 2002).

Countries severely affected by malaria have up to five times lower Gross Domestic Product (GDP) than those without malaria(Jobin, 2014).

WHO/RBM Action and Investment plan to defeat malaria, estimates if malaria were eliminated, the return on investment for Africa would be as high as 60:1, effectively unlocking extensive human and economic development on the continent (WHO/RBM, 2015).

The Malaria Burden in Africa

- Suppressing or modifying vector populations to eliminate malaria, offer enormous health benefits to Africa, and public health delivery systems will be the major primary beneficiaries of the technologies
- The end goal for malaria- African Union, 2030 is target date for elimination(African Union, 2016)
- Decision makers need to objectively review new technologies with potentially high impact, such as gene drive, and determine a suitable pathway for future development and deployment.



Malaria burden in African countries (Data Source: WHO 2016 World Malaria Report)

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Gene Drive Technology options- Population Alteration

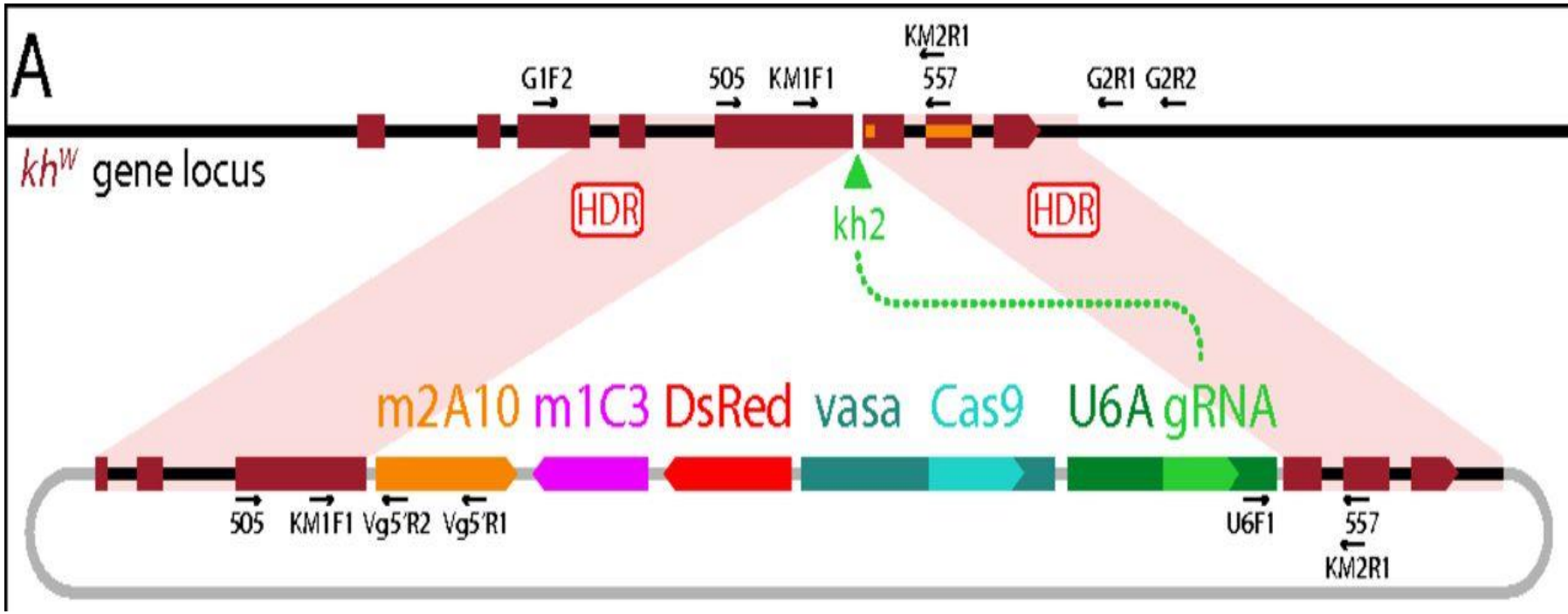
In population alteration, the gene constructs introduced are those that reduce organisms' ability to transmit specific pathogens. specific genetic segments that code for parasite binding proteins in the mosquito are altered so that malaria parasites can no longer bind to these receptors

Scientists in California have created a highly efficient CRISPR/Cas-9 mediated gene drive, achieved 98% modification of a laboratory population of *Anopheles stephensi*- could no longer transmit the malaria parasite, *Plasmodium falciparum*(Gantz et al., 2015).

Approach equally leads to use in large-scale malaria elimination efforts, with potentially high impact over short durations(Eckhoff et al., 2016).

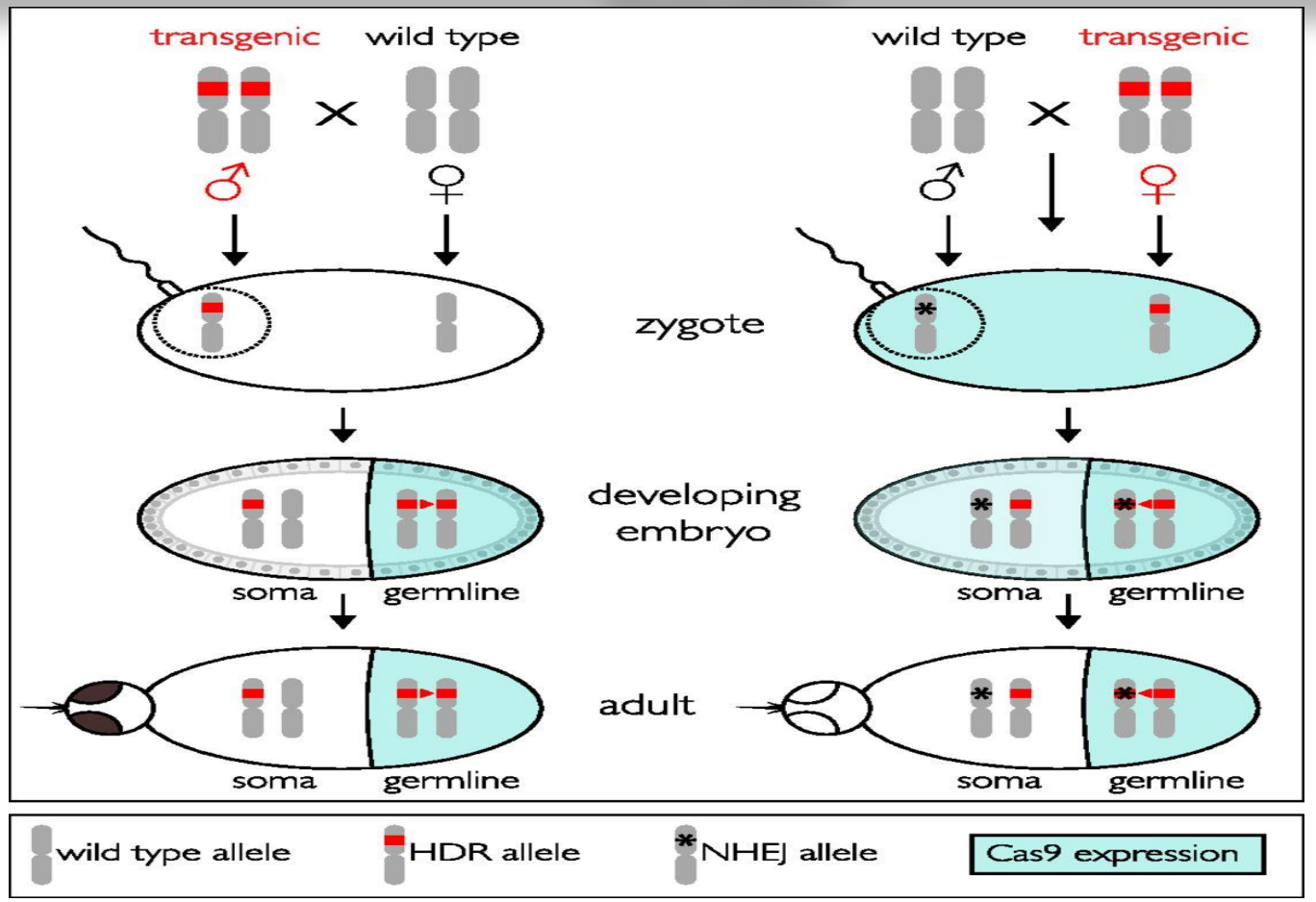
Unlike population suppression systems, the artificial gene constructs are intended to spread throughout the vector population and persist.

Site-specific integration into the An. stephensi kynurenine hydroxylasewhite locus



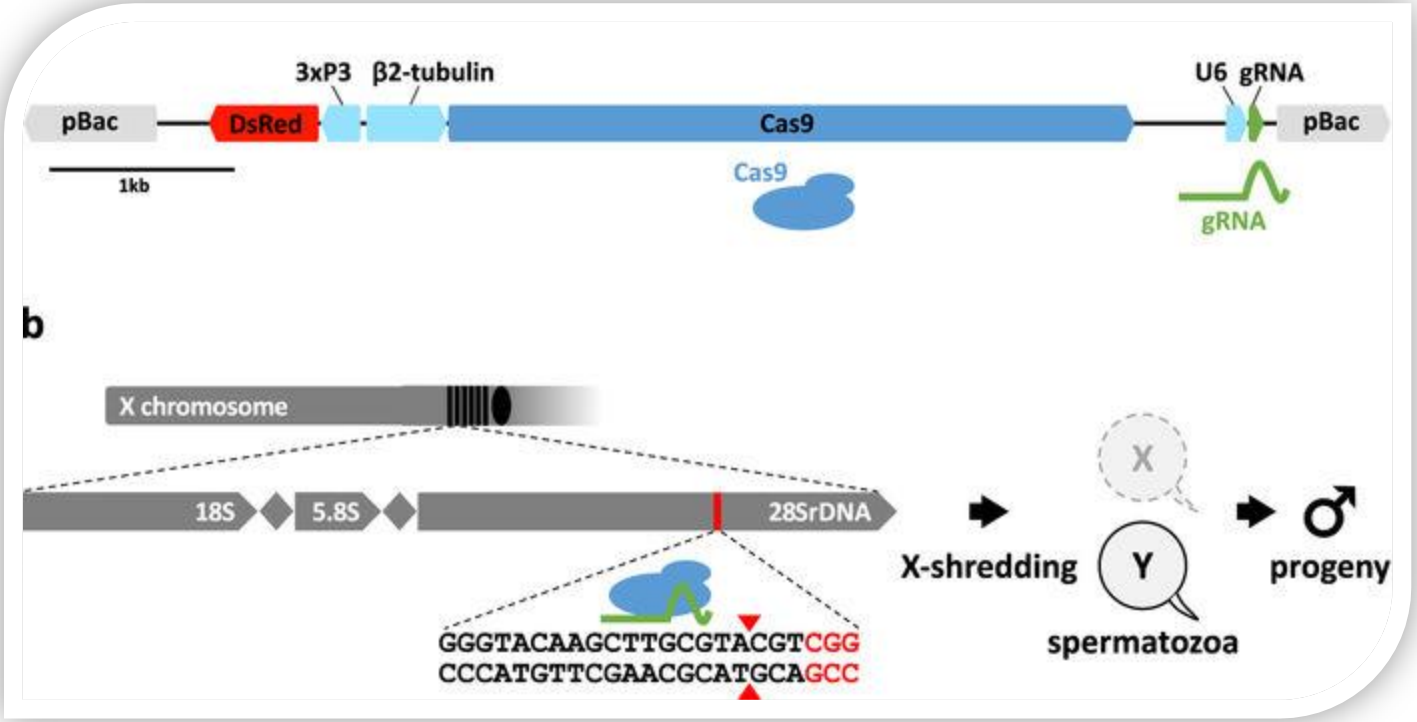
Gantz et al (2015)-http://www.pnas.org/content/pnas/112/49/E6736.full.pdf

Model of AsMCRkh2 transgene activity in adult males & females

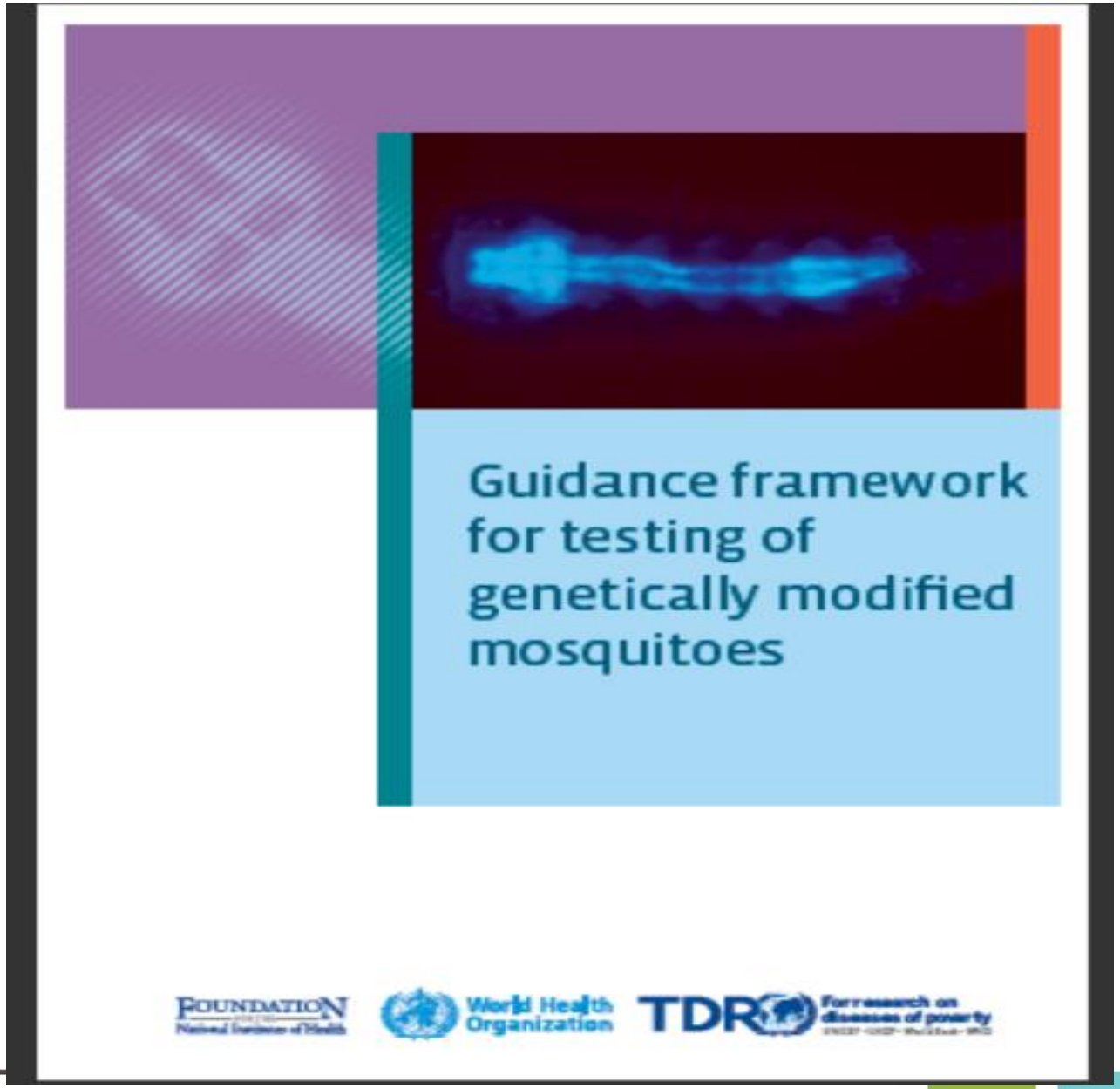


Gantz et al (2015)-http://www.pnas.org/content/pnas/112/49/E6736.full.pdf

Generation of a CRISPR-Cas9 sex-ratio distortion system

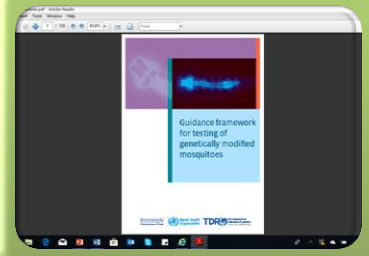


Galizi, et al (2016) *Scientific Reports* **6**, 31139


Guidance framework for testing of genetically modified mosquitoes
World Health Organization
TDR

Phased Testing Approaches of Gene drives

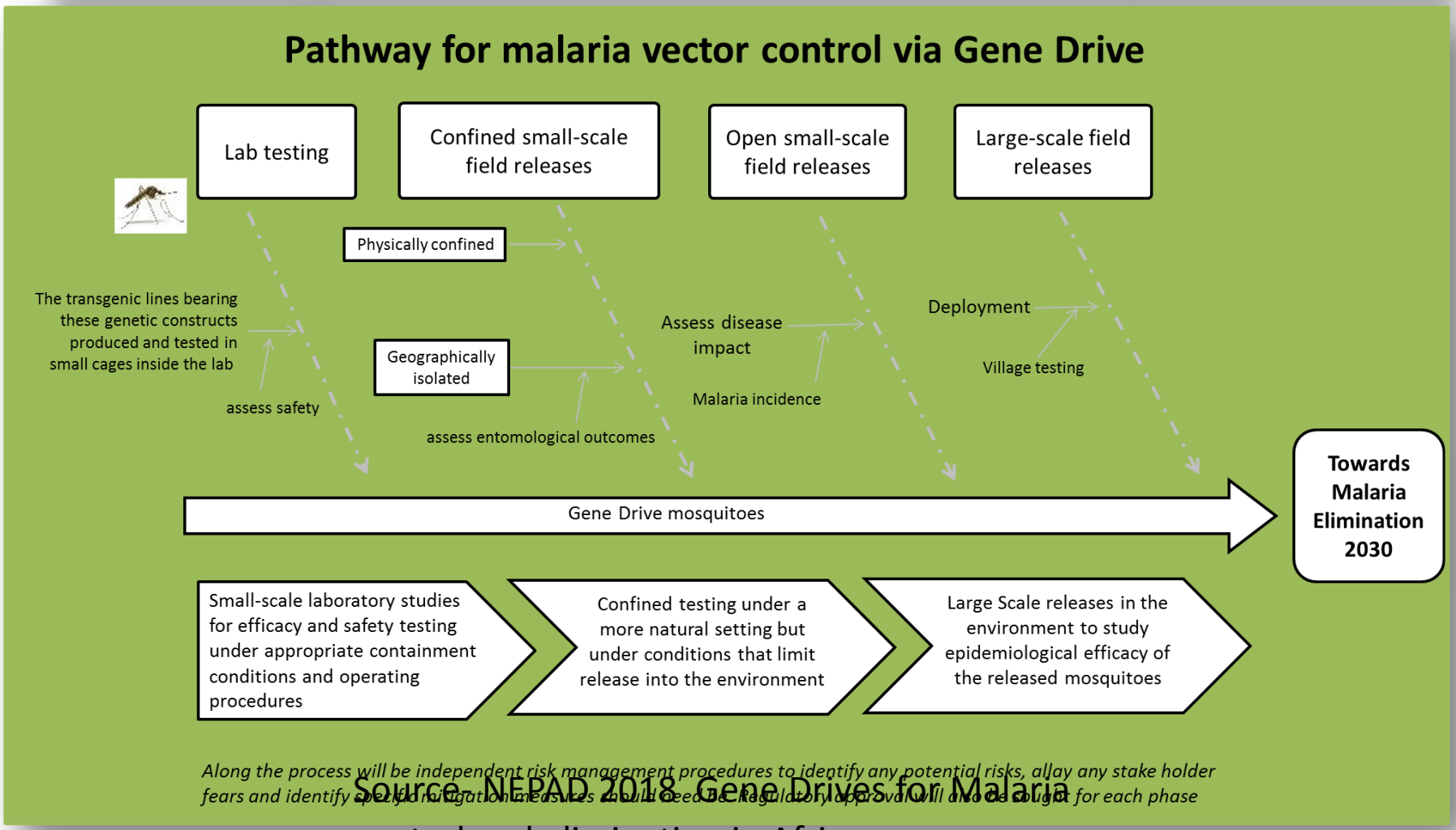
Stepwise approach to guide the preparation and conducting research from laboratory and continues through, if applicable, environmental monitoring



Recommended by WHO Guidelines for testing genetically modified mosquitoes (World Health Organization, 2014), and

US National Academies for Sciences, Engineering and Mathematics report (National Academies of Sciences & Medicine, 2016)

Pathway for Malaria Vector Control via Gene Drive



Source- NEPAD 2018. Gene Drives for Malaria control and elimination in Africa

Three stages envisioned for testing gene drives

- Laboratory development and assessments to determine safety and efficacy in small-scale laboratory cages;
- Small-scale studies, beginning with testing under physically contained field cages and followed by additional small-scale studies- gene drive mosquitoes are released, first in ecologically-confined areas such as islands
- Large-scale controlled field releases to assess the impact of the intervention in clinical parameters of the disease,

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Risk Analysis = RA + RM + RC

The Components of risk Analysis have described under several venues Australian Office of Gene Technology Regulator (OGTR), The Convention on Biological Diversity (CBD, 2012), Cartagena Protocol on Biosafety (CPB), the EFSA (2006, 2013), United Kingdom's Department of Environment, Food and Rural Affairs (DEFRA), the USA Environmental Protection Agency (EPA, 1998).Office of the Gene Technology Regulator. Risk Analysis Framework 2013.http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/raffinal5-toc.

Stepwise Approach to EIA (EFSA)

- Problem Formulation
- Hazard Characterization
- Exposure Characterization
- Risk Characterization
- Risk Management Strategies
- Risk Conclusion

Four Categories of End Point- (Roberts et al. 2017)

- Human Health
- Animal Health
- Biodiversity
- Other considerations

Problem Formulation for Gene Drives in Mosquitoes

Human Health- Because• Because *An. gambiae* is an important disease vector, consideration should be given to potential alterations in disease transmission

Proteins introduced into An gambiae, including components of the gene drive and markers should be considered with respect to allergenecity and toxicity

Biodiversity- Gene flow to other species within the *An. gambiae* s.l. complex through hybridization is likely, and does not create additional pathways to harm

Animal Health-Potential harm could occur from pathogen altered dynamics to transmission to livestock

Cross-Cutting Important Aspects

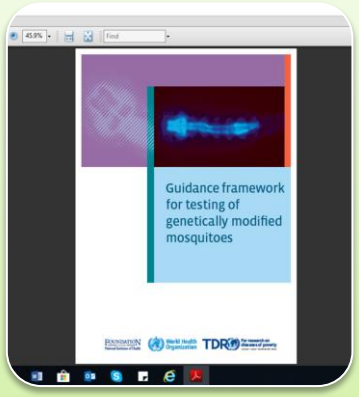
- Choice of site
- Appropriate Comparators
- Hazard Characterization
- GMM Characterization
- Utility of Mathematical Modeling in RA

IMPORTANT CROSS CUTTING ASPECTS RISK ANAYSIS					
	Site Selection	Appropriate Comparators	Hazard Characterization	GMM Characterization	Use of Mathematical Model
Phase 1- Laboratory					
Phase 2- Confinement					
Phase 3- Staged-Open					
Phase 4- Open Release					

Interphase- phases and RA and RM

Phased Approach	Risk Assessment	Risk Management	RA for Deployment
Phase 1- Laboratory			
Phase 2- Confinement			
Phase 3- Staged-Open			RA and Benefits
Phase 4- Post Release			

Biosafety in Development of GMMs



Focuses on reducing to acceptable levels any potential risks to human health and environment that might arise from the technology keeping in mind the adverse effects of vector borne disease (WHO, 2015)

Risk Analysis contributes to achievement of acceptable levels of safety .

The Biosafety Risk Analysis should determine

- The potential Hazard
- Impact of GMM on wild populations of target and non-target organisms
- The magnitude or likelihood of impact of any harm on the receiving environment
- The levels and consequences of uncertainty associated with these effects

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Studies in Phase 1 (WHO, (2014)

Studies in Phase 1 can provide data on risks that can be addressed by observing changes in behaviour and ecologically relevant characteristics of mosquito populations in small scale laboratory experiments.

With respect to biosafety testing, this Phase 1 primarily focuses on the relevant characteristics of GMOs themselves, and on laboratory experiments that can assess pathways that might lead to harm

PARAMETERS RELEVANT IN LABORATORY STUDIES (PHASES 1 AND 2) AS PART OF THE RA FOR GMMS (WHO, 2014)

Parameters	Example hazards	Assessment methods	Assessment endpoints
Female fecundity Oviposition rate	Increased vector abundance	Cohort experiment; Life Table analysis	Is it limited by population density and /or Individual physiology? Is there a significance difference?
Egg development rate Larval survival Pupal survival	Increased growth potential; Reduced predation	Cohort experiment; Life Table analysis	Is there a significance difference?
Egg survival Larval survival Pupal Survival	Increased Vector Abundance	Cohort Experiments Life table analysis Population level modeling	Is it density dependent What is the type of density dependent It it under or over compensatory Doest it differ signficantlty
Adult emergence	Increased vector abundance	Cohort experiment; life Table analysis	Does the timing of Adult emergence? differ significantly?
Adult Size	Increased vector fitness	Increased vector fitness	Is adult size significantly different?
Adult Survival	Increased vector activity; More effective mating potential; Increased biting efficiency for females	Cohort experiment; Life table analysis; Population level modelling	Is it density- dependent? Is it significantly enhanced/ diminished by the modification?

Interphase- phases and RA and RM

Phased Approach	Risk Assessment	Risk Management	RA for Deployment
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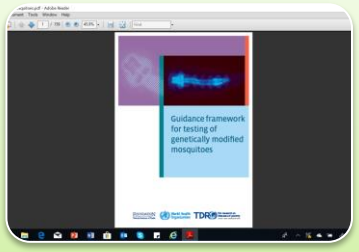
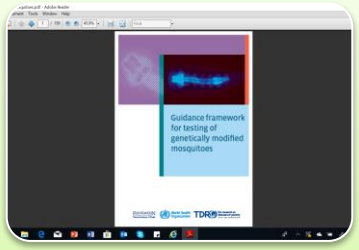
Phase 4- Post Release			

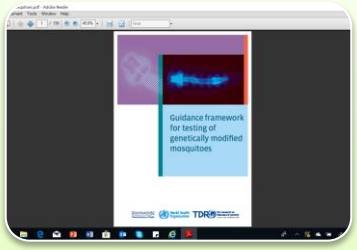
Studies in Phase 2



In Phase 2, RA data are obtained in trials conducted under physically or ecologically confined conditions.



This phase gathers RA data to reduce uncertainty regarding effects identified in Phase 1



Allows assessment of health and ecological effects under more realistic level of exposure

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Interphase- phases and RA and RM

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Phase 4- Post Release			

Studies in Phase 3- Staged- Open Release

Staged open field trials under Phase 3 can gather data under even more realistic conditions

Using less confined measures than in the previous phases

Parameters relevant in open--field studies for RA of GMMs (WHO 2014)

Parameters	Example hazards	Assessment methods	Assessment endpoints
Population size	Increased vector abundance; ecosystem disruption	Field population monitoring; Population level modelling	What is the Impact of the release? Relationship between release rate, timing, method and outcome?
Density dependence	Increased vector abundance; ecosystem disruption	Comparator studies at range of densities in laboratory; field Population monitoring; Population level modelling	Does the transgenic strain disease significantly in the role of this ecological process?
Spatial distribution	Increased vector abundance; Ecosystem disruption	Field population monitoring; population--- level modelling; life---table experiments	Limits the spread of transgenic organism? Rate of spread of transgenic insect, under a range of conditions
Vector Capacity	Increased transmission per bite; increased biting rate	Comparator studies; post--- release monitoring	Is the capacity to harbour and transmit pathogens increased?

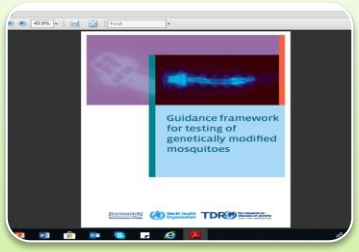
Parameters relevant in open-field studies for RA of GMMs (WHO 2014)

Parameters	Example hazards	Assessment methods	Assessment endpoints
Behavioural Resistance	Change in behaviour that avoids, or reduces efficacy of conventional management	Change in behaviour that avoids, or reduces efficacy of conventional management	Under field conditions, what limits the appearance and spread of resistance due to mosquito behaviours? Is there potential for assortative mating in the field?
Biochemical resistance	Change in physiology that avoids, or reduces efficacy of, conventional Management	Comparator studies; Cohort studies on Physiological changes In different life stages; post--release surveillance; population--level modelling	Is the likelihood or rate of resistance Development enhanced In transgenic mosquito strains?
Mass rearing quality indices	Quality of released Insects is different from planned, affecting negative outcomes	Cohort experiments; Comparator studies Before release; ooperational design And audit; pre---release monitoring; post---release monitoring	Do specific aspects of released Mosquito quality affect mosquito densities, pathogen transmission and transgene stability?

Interphase- phases and RA and RM

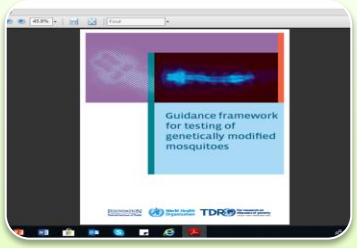
Phased Approach	Risk Assessment	Risk Management	RA for Deployment
Phase 1- Laboratory			
Phase 2- Confinement			
Phase 3- Staged-Open			RA and Benefits
Phase 4- Post Release			

Studies in Phase 4- Open Release



RA should include issues such as the potential for the movement of GMMs beyond the boundaries for release areas- National and Regional Approval

Deployment of GMMs as Public Health Tool



The evolution of resistance, and will determine the necessary scope of post-implementation Monitoring and management

APET REPORT ON GENE DRIVES- June 2018

1.REGULATORY AND SAFETY REQUIREMENTS- in this aspect there will be some important considerations to adopt from the current regulatory framework that will include- there will be need to reference regulation the GMMs to relate the regulation to **international conventions/treaties (CBD and CPB**); there is need to incorporate **regional regulatory approaches-** this is important because the mosquitoes will move across borders; there is need to **expand the role of health regulators** beyond their current mandate; there is need for regulatory information sharing process and capacity strengthening; there is need for robust **training especially on risk assessment**.

Interphase- phases and RA and RM

Phased Approach	Risk Assessment	Risk Management	RA for Deployment
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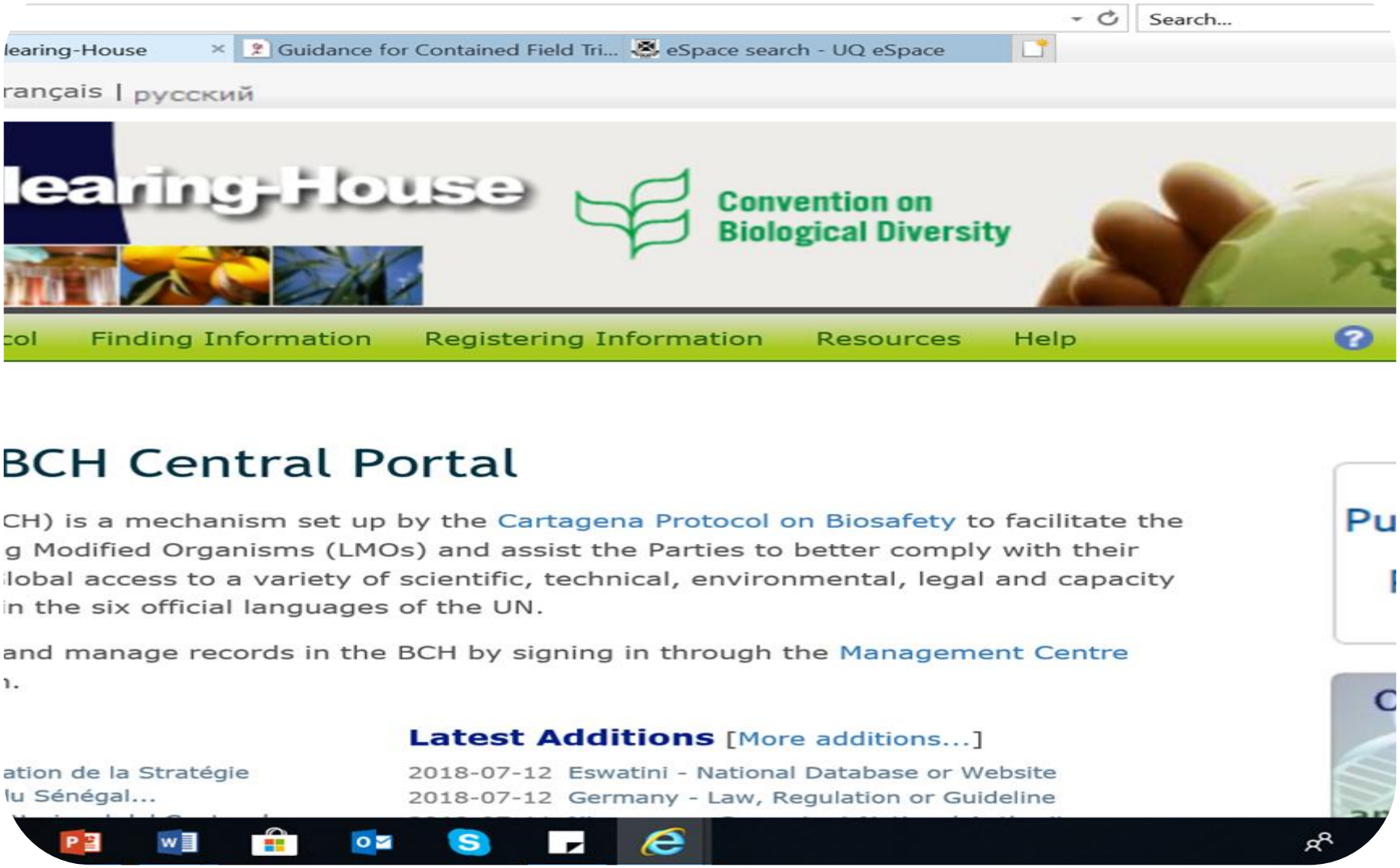
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Finding Information
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Resources
Help
BCH Central Portal
CH) is a mechanism set up by the Cartagena Protocol on Biosafety to facilitate the
g Modified Organisms (LMOs) and assist the Parties to better comply with their
lobal access to a variety of scientific, technical, environmental, legal and capacity
in the six official languages of the UN.
and manage records in the BCH by signing in through the Management Centre
Latest Additions [More additions...]
ation de la Stratégie
lu Sénégal...
2018-07-12 Eswatini - National Database or Website
2018-07-12 Germany - Law, Regulation or Guideline

ACKNOWLEGEMENTS

NEPAD Agency)- Aggrey Ambali, Hudu Mogtari, Justina Dugbazah, Barbara Glover, Moussa Savadogo, Olalekan Akinbo; Jeremy T. Ouédraogo, Sunday Igu Rocks, Wolde Sinebo, Modupe Bamidele Adeyemo , Silas Obukosia

National Biosafety Agency- Burkina Faso, Mali and Uganda, WAHO- West Africa Health Organization

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Danforth Plant Centre and US FNIH- Hector Quemada, Tonui Willy