Vaccines: (inter)national regulation and quality in resource limited settings

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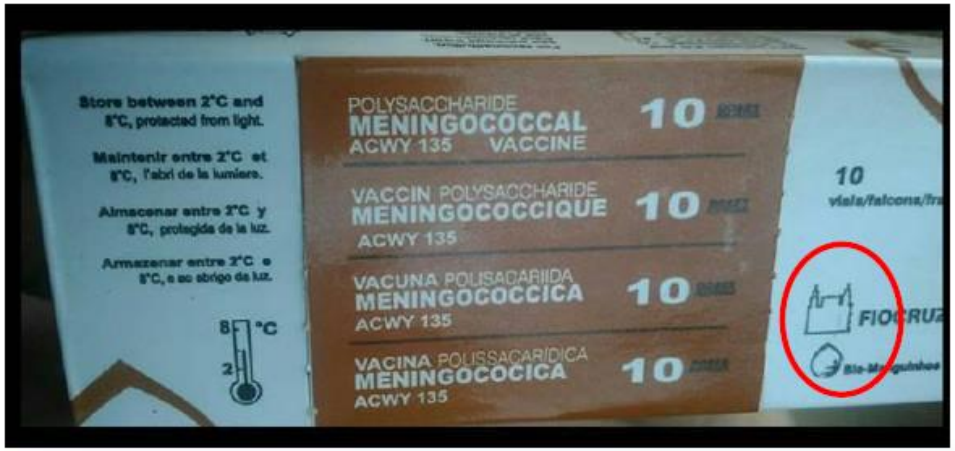
12th July 2017

Based on a presentation of Carmen Rodriguez Hernandez, WHO, EMP/RHT/PQT

Thanks to Joelle Daviaud for the critical inputs

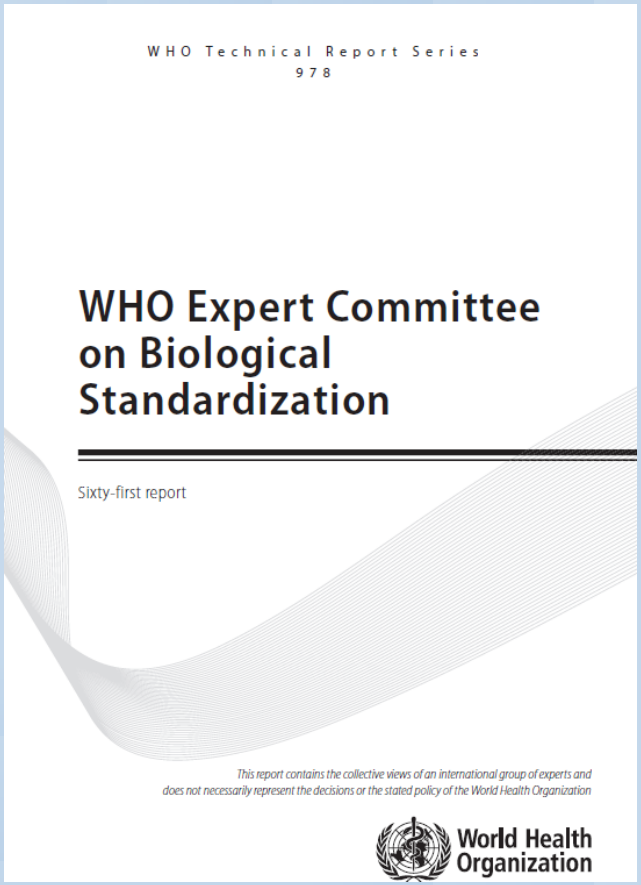
Quality of vaccines: challenges



Fake vaccines in West Africa (HHO/HIS/EMP June 2017)

Quality of vaccines: challenges

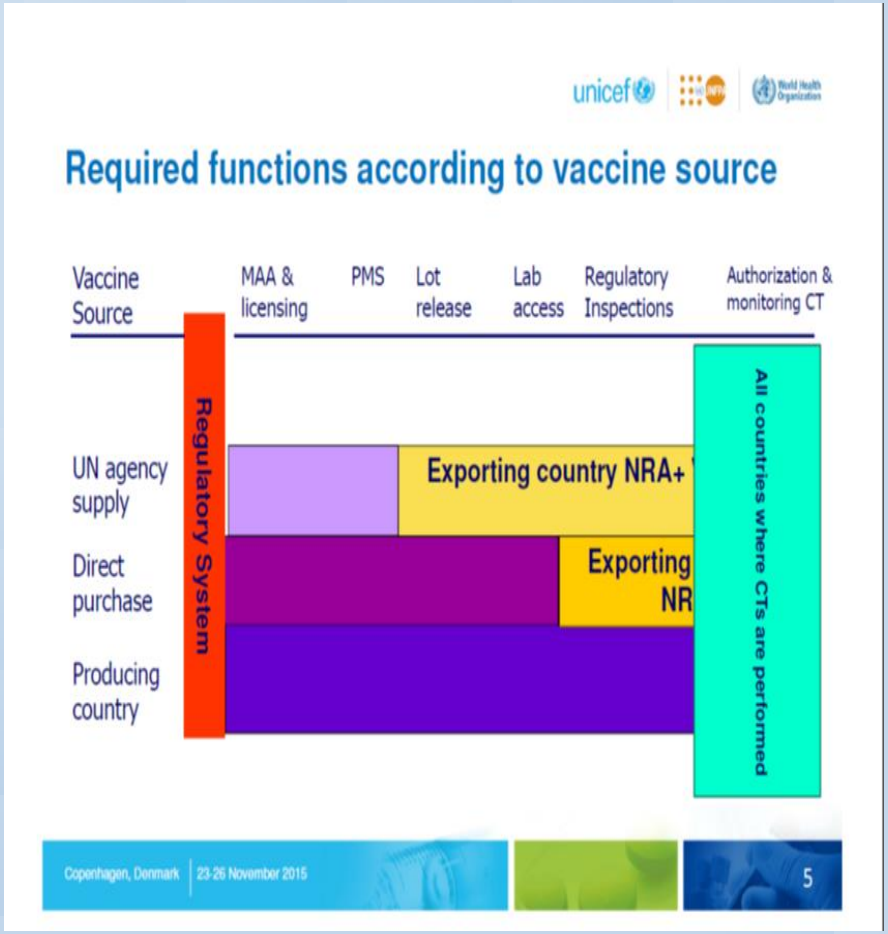
- Consistent safety and efficacy is critical for immunization programmes
- Complex biological products with *inherent variability between produced batches (different from medicines!)*
- The NRA *in the manufacturing country* must be functional for regulatory oversight, including:
  - access to a functional control laboratory
  - ability to perform lot release, including risk-based laboratory testing



WHO concept of vaccine regulation

National Regulatory System : governance + six essential functions

- 1. Marketing Authorization and Licensing Activities
- 2. Post-marketing activities, including surveillance of *Adverse Events Following Immunization* (AEFI)
- 3. NRA Lot Release
- 4. Laboratory access
- 5. Regulatory Inspections
- 6. Approval of Clinical Trials



The approach of the WHO PQ Vaccines Programme

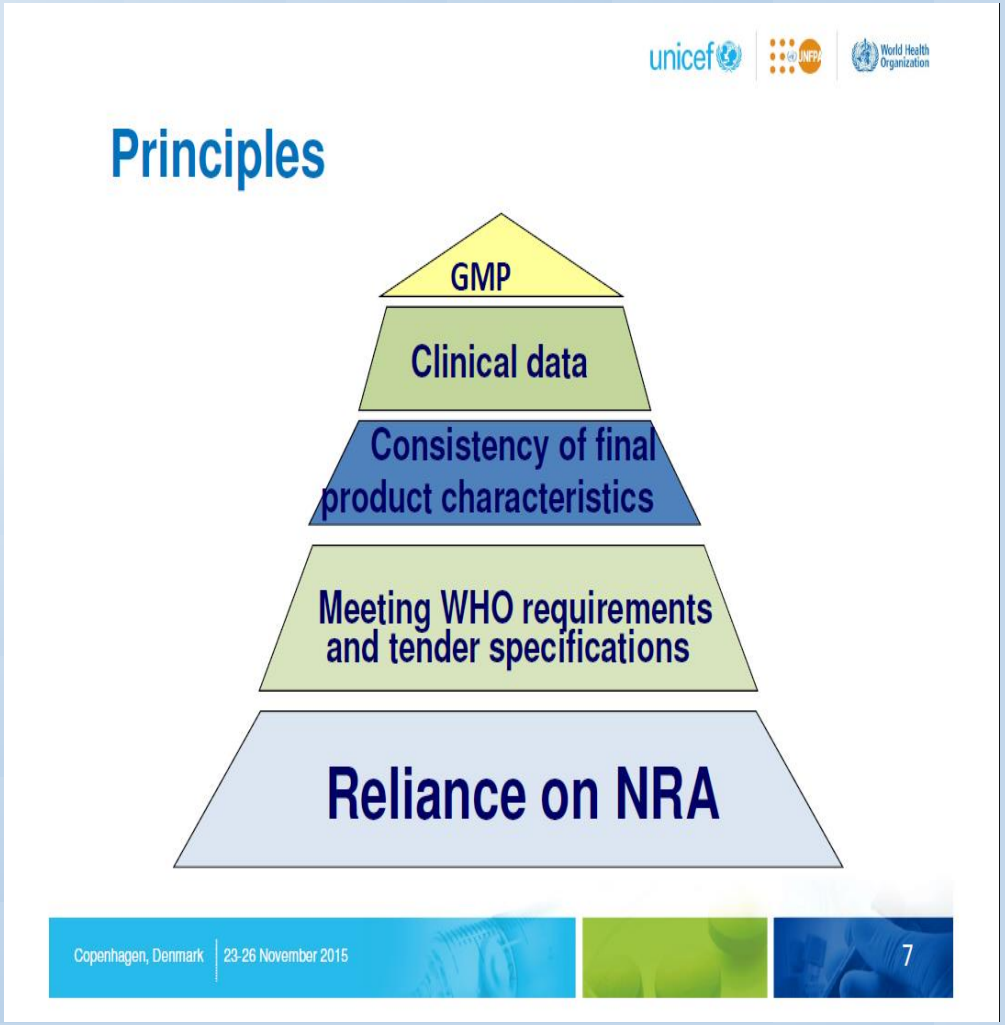
Vaccines quality

- **WHO goal:** “100%” of vaccines used in all national immunization programmes are of assured quality
- **Definition of “Vaccines of Assured Quality” (*)**
  - NRA in the manufacturing country is independent from vaccine manufacturer & procurement system
  - NRA is functional
  - Positive evaluation by the WHO PQ
  - No unresolved reported problems

(*) WHO guidance by Experts Committee on Standardization of Biologicals (ECBS) recommendations on safety, efficacy and quality issued in WHO Technical Report Series (TRS)

Purpose & principles of WHO vaccines PQ programme

- Service to UN purchasing agencies
- Independent opinion/advice on quality, safety, efficacy of vaccines for purchase
- Ensures that candidate vaccines are suitable for target population and meet programme's needs
- Ensures continuing compliance with standards and specifications



Pre-conditions for PQ evaluation

Reliance on the NRA of the exporting country

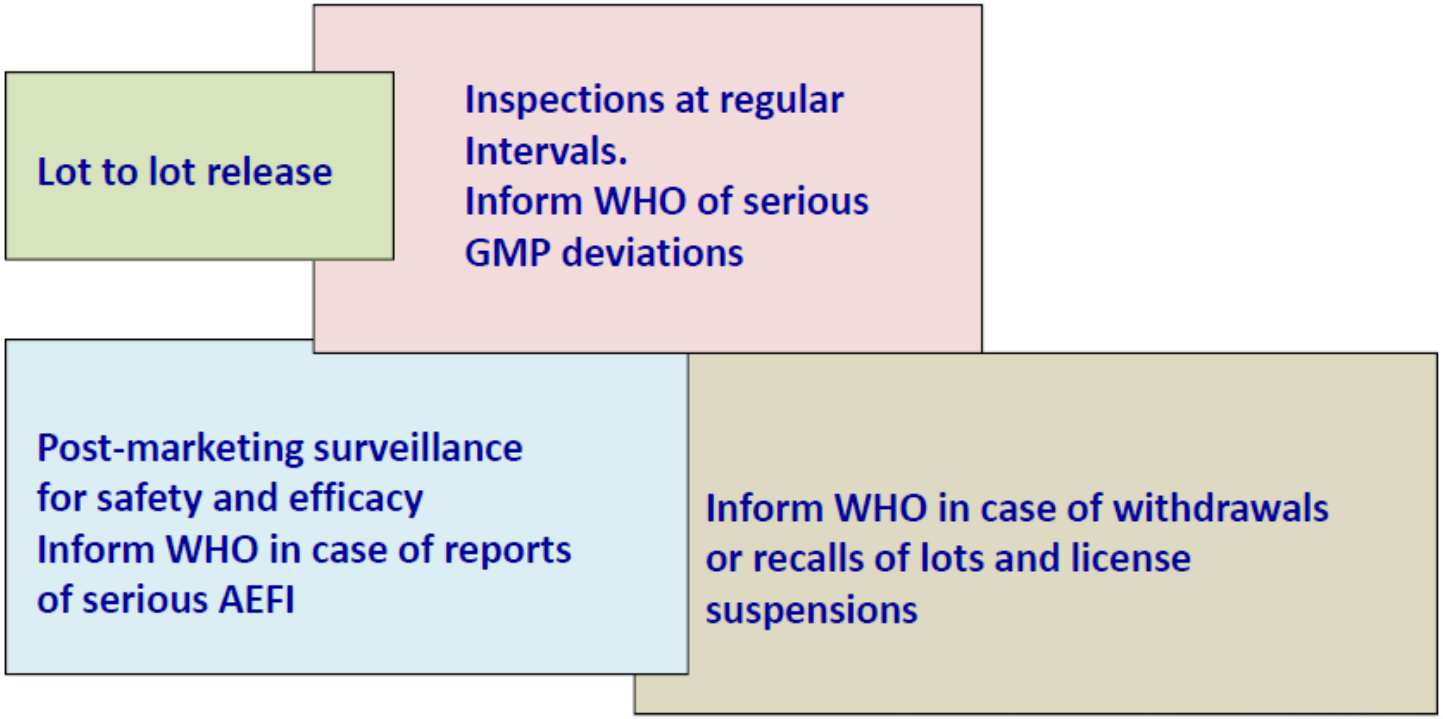
- Functional NRA ← WHO's NRA assessment tool
  - NRA's functional status sustained over time
  - Continued regulatory oversight by NRA
  - Continued communication with WHO about potential problems
  - Agreements with the NRAs for information exchange when a vaccine is about to be prequalified
- Vaccine licensed/registered by the responsible NRA (scientific opinion by EMA also accepted)
- WHO guidelines/recommendations available (TRS)
- Listed in the vaccine priority list

Prequalification process + monitoring performance

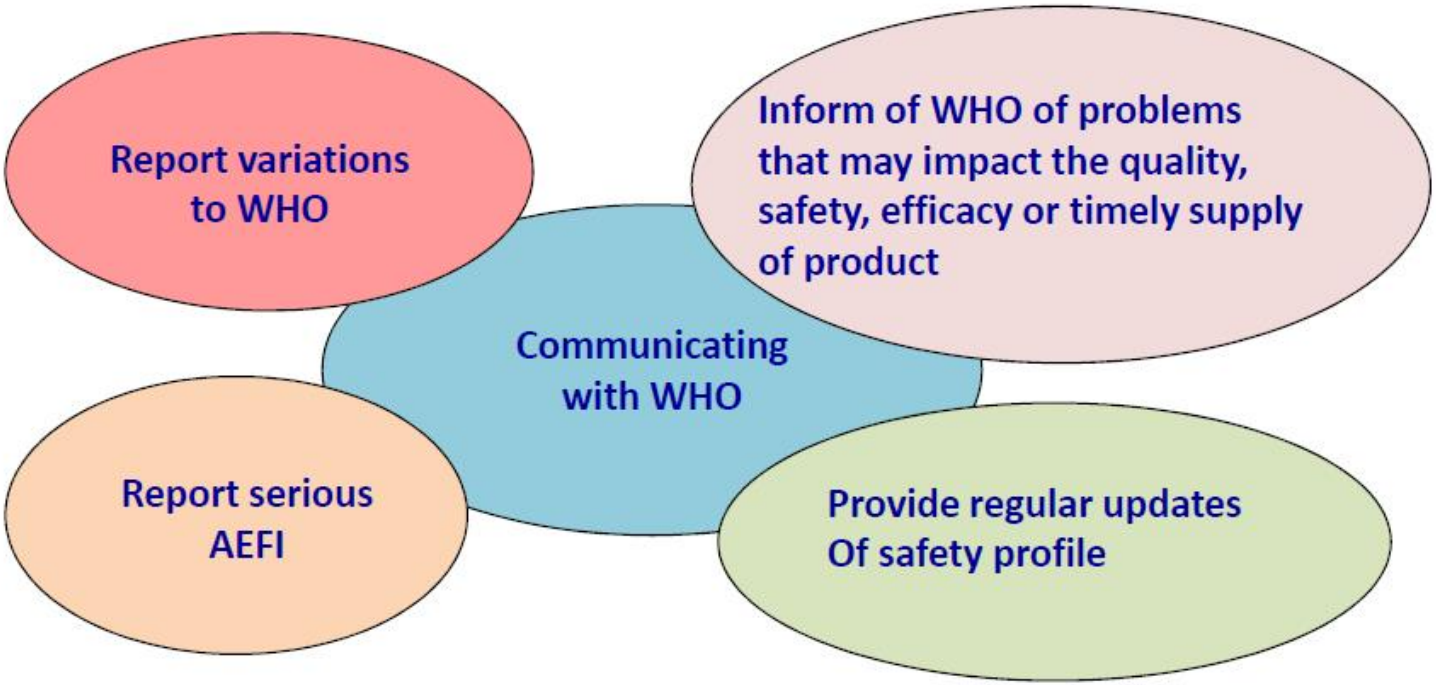
- Scientific review of quality dossier
- Scientific review of clinical data
- Testing of samples
- Consultation with responsible NRA
- Audit of manufacturing facilities

- Targeted yearly testing of samples of lots shipped to countries (WHO contracted labs)
- Monitoring and resolution of complaints and AEFIs
- Reassessments' frequency defined on risk analysis basis

Condition for WHO PQ evaluation: ongoing oversight and commitments by the NRA



Condition for WHO PQ evaluation: commitments by the manufacturer



Programmatic suitability and its assessment

- Vaccines produced in high-income countries may not take into account programmatic challenges in LMICs
- Examples:
  - *Security of injection*, e.g. auto-disable prefilled syringe presentations
  - Stability of components in the event of *cold chain* breakdown
  - *Vaccine vial monitor* (different depending on vaccines)
  - *Transportation procedures* for cold chain

Lot release testing

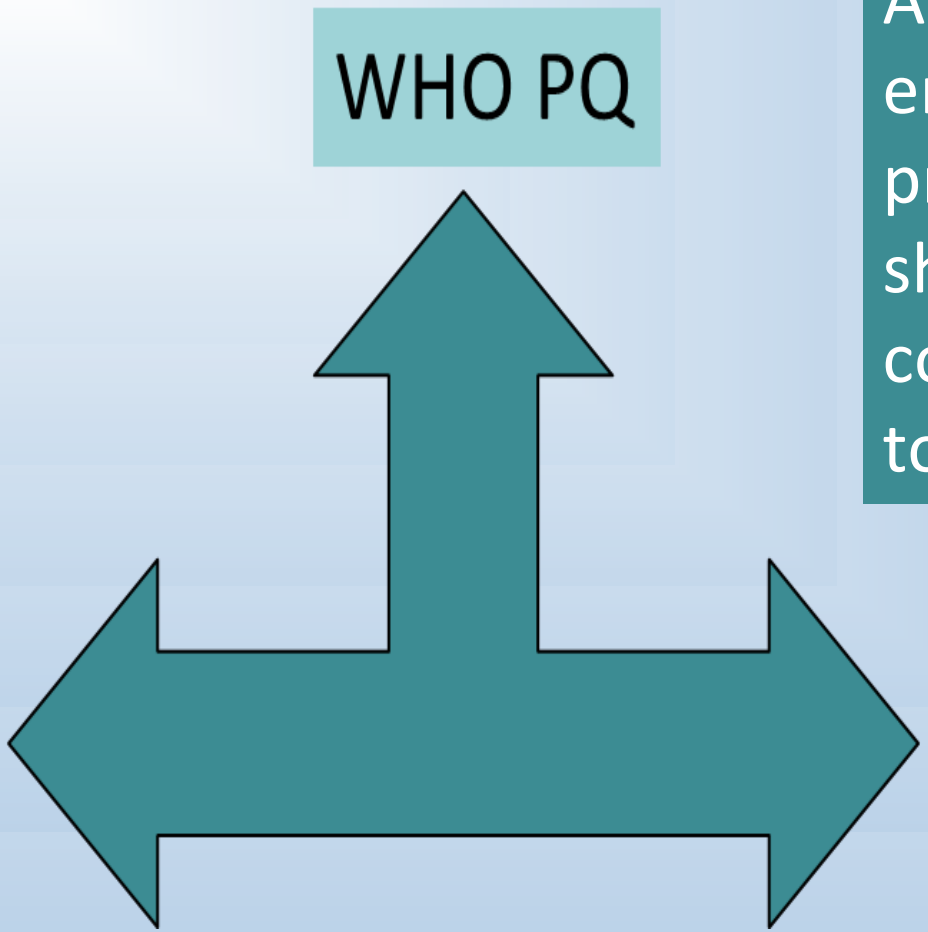
- Demanding, resource intensive → need for national control laboratories (NCLs) to collaborate
  - A new network of NCLs involved in testing of WHO-PQ vaccines
- New emerging concepts based on a risk assessment evaluation

Table 1: **Participating national vaccine control laboratories**

Region	Country	(a)	(b)	(c)	Region	Country	(a)	(b)	(c)
Europe	Belgium	Yes	Yes	Yes	Africa	Senegal	Yes		
	Bulgaria	Yes		Yes		South Africa	No	Yes	
	Denmark	Yes		Yes	Americas	Brazil	Yes		
	France	Yes	Yes	Yes		Canada	Yes	Yes	Partially
	Germany	Yes	Yes	Yes		Cuba	Yes		
	Hungary	No	Yes[d]	Yes		United States[f]	Yes		
	Italy	Yes	Yes	Yes	South East Asia	India	Yes		
	Netherlands	Yes	Yes	Yes		Indonesia	Yes		
	Serbia	No				Thailand	Yes	Yes	
	Switzerland	No	Yes	Partially	Western Pacific	China	Yes		
	United Kingdom	Yes	Yes[e]	Yes		Japan	Yes		
	Russian Federation [f]	Yes		Yes		Republic of Korea	Yes	Yes	
	Sweden[f]	Yes				Australia[f]	Yes		

WHO Drug Information Vol. 31, No. 1, 2017

Vaccines WHO PQ: an ongoing interaction



Any problems encountered with pre-qualified vaccines should be communicated timely to the WHO PQ

Be aware & Follow WHO Alerts!

World Health Organization

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

Ref. RHT/SAV/MD/2/2015 22ND May 2015

Medical Product Alert No. 2/2015

Falsified Meningitis Vaccines circulating in West Africa

This Medical Product Alert relates to the confirmed circulation of falsified versions of Meningitis Vaccines in Niger.

Following a report submitted to the WHO Surveillance and monitoring system for substandard and falsified medical products by the focal point within the Niger Regulatory Authority, increased vigilance is requested for the following lots/batches of vaccines and solvents.

Product:	**Mencevax ACW**
Batch Number:	**AMENA020AA**
Manufacturing date:	**12-2014**
Expiry Date:	**11-2017**

The batch number is genuine but the manufacturing and expiry dates are false. The genuine version of this batch expired in 2011. The product contains 50 doses per vial.

Photographs of falsified "Mencevax" products

Fig. 1.: Falsified Mencevax, batch number AMEHA020AA

Fig. 2. : Falsified Mencevax, batch number AMENA020AA

Fig. 3.: Falsified diluent for Mencevax, batch number A003B128AA

Role of the focal point within the Niger RA

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Ref. RHT/SAV/MD/3/2015 27th May 2015

Medical Product Alert No. 3/2015

Falsified Meningitis Vaccines circulating in West Africa
UPDATE

This Medical Product Alert relates to the confirmed circulation of falsified versions of Meningitis Vaccines in Niger and follows Medical Product Alert 2/2015 issued on the 22nd May 2015

Following a report submitted to the WHO Surveillance and monitoring system for substandard and falsified medical products by the focal point within the Niger Regulatory Authority, increased vigilance is requested for the following falsified lots/batches of vaccines and diluants.

Product:	**Menomune ACY-W135**
Batch Number:	**UH 301AA**
Expiry Date:	**29 APR 17**

The batch number is genuine but the expiry date is false. The genuine version of this batch of vaccine expired in 2014. This falsified product contains 10 doses per vial.

Fig. 1: Menomune ACYW-135;
Batch Number: UH301AA; Expiry Date: 28FEB16

Fig. 2: Menomune ACYW-135 ;
Batch Number: UH299AA ; Expiry Date: 28FEB16

Fig. 4: Diluent for MenomuneACYW-135;
Batch Number: UH262AA; Expiry Date: 25OCT16

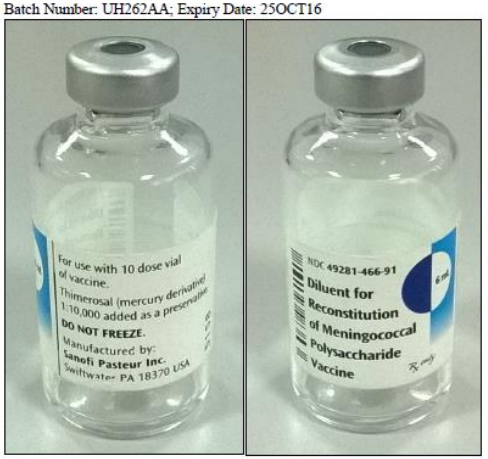

Fig. 5: Diluent for Menomune ACYW-135;
Batch Number: D0953-1; Expiry Date: 20-2017

Role of the focal point within the Niger RA

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Ref. RHT/SAV/Alert 2.2016 11 February 2016

Medical Product Alert N° 2/2016

Falsified AMARIL yellow fever vaccines circulating in South East Asia

This Medical Product Alert relates to the confirmed circulation of falsified versions of "AMARIL stabilised vaccine" in South East Asia.

This vaccine is used to immunise against yellow fever and is a WHO prequalified product. Yellow fever vaccine is on the WHO list of Essential Medicines.

On the 9th of February 2016, the Pasteur Institute in Dakar, Senegal, informed WHO that they had identified a falsified version of their "AMARIL stabilised vaccine" circulating in Bangladesh.

Genuine AMARIL vaccines and solvents are manufactured by the Pasteur Institute in Dakar, Senegal

The Pasteur Institute in Dakar has confirmed there are a number of falsified elements on the packaging, including a falsified expiry date, as well as other inconsistencies that were identified through visual inspection of photographs of the falsified products, as compared to the genuine products. Laboratory analysis is pending.

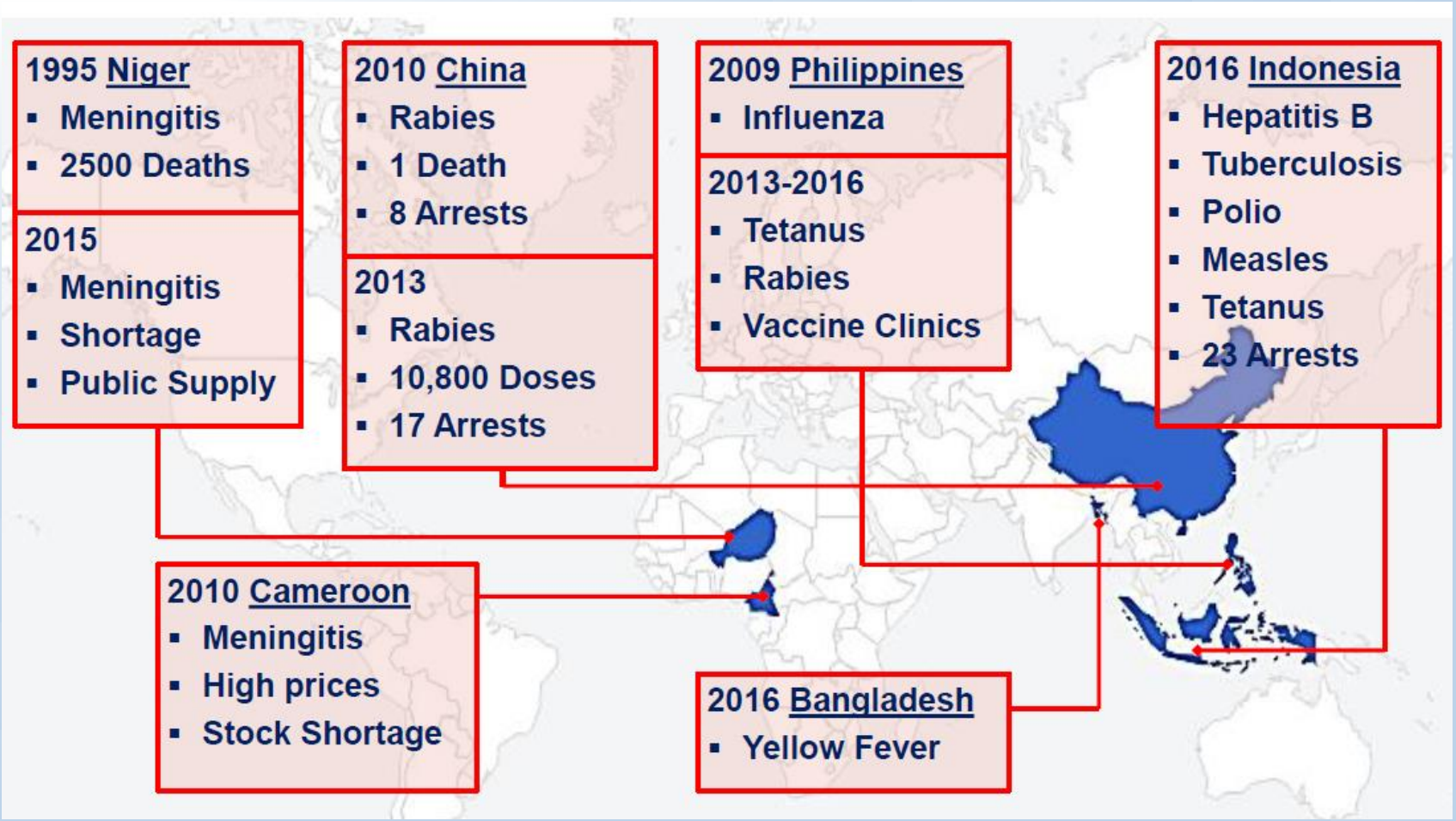
Product Name: AMARIL stabilised yellow fever vaccine
Batch Number: 2265
Expiry Date: June 2017
Manufacturer: Pasteur Institute in Dakar

Photographs of the falsified versions available in annex.

Falsified "AMARIL stabilised vaccine" discovered in 2016 in Bangladesh:

Role of the manufacturer (Institut Pasteur)

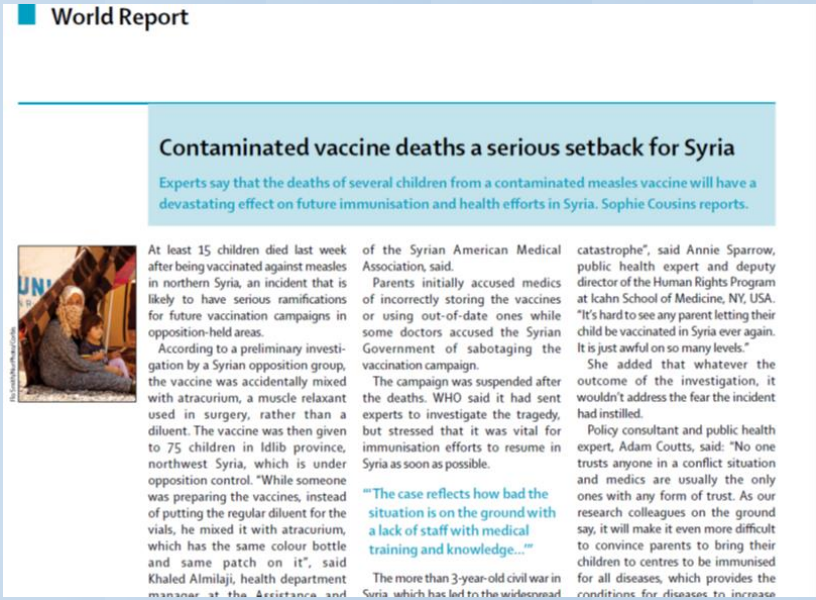
Other examples of fake vaccines
(WHO/HIS/EMP June 2017)



Administration mistakes with fatal outcomes

- 2014: At least 15 children died after being vaccinated against measles.
- According to a preliminary investigation the vaccine was accidentally mixed with atracurium, a muscle relaxant, rather than a diluent.
- The vaccine was given to 75 children in Idlib province, northwest Syria, under opposition control

www.thelancet.com Vol 384, 2014



World Report

Contaminated vaccine deaths a serious setback for Syria

Experts say that the deaths of several children from a contaminated measles vaccine will have a devastating effect on future immunisation and health efforts in Syria. Sophie Cousins reports.

At least 15 children died last week after being vaccinated against measles in northern Syria, an incident that is likely to have serious ramifications for future vaccination campaigns in opposition-held areas.

According to a preliminary investigation by a Syrian opposition group, the vaccine was accidentally mixed with atracurium, a muscle relaxant used in surgery, rather than a diluent. The vaccine was then given to 75 children in Idlib province, northwest Syria, which is under opposition control. "While someone was preparing the vaccines, instead of putting the regular diluent for the vials, he mixed it with atracurium, which has the same colour bottle and same patch on it", said Khaled Almilaji, health department manager at the Assistance and

of the Syrian American Medical Association, said.

Parents initially accused medics of incorrectly storing the vaccines or using out-of-date ones while some doctors accused the Syrian Government of sabotaging the vaccination campaign.

The campaign was suspended after the deaths. WHO said it had sent experts to investigate the tragedy, but stressed that it was vital for immunisation efforts to resume in Syria as soon as possible.

"'The case reflects how bad the situation is on the ground with a lack of staff with medical training and knowledge...'"

The more than 3-year-old civil war in Syria, which has led to the widespread

catastrophe", said Annie Sparrow, public health expert and deputy director of the Human Rights Program at Icahn School of Medicine, NY, USA. "It's hard to see any parent letting their child be vaccinated in Syria ever again. It is just awful on so many levels."

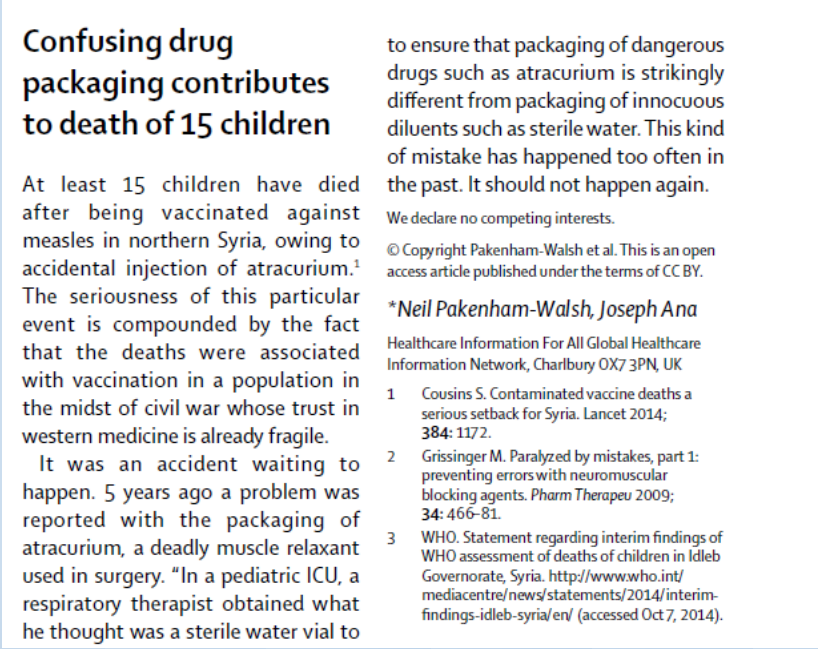
She added that whatever the outcome of the investigation, it wouldn't address the fear the incident had instilled.

Policy consultant and public health expert, Adam Coutts, said: "No one trusts anyone in a conflict situation and medics are usually the only ones with any form of trust. As our research colleagues on the ground say, it will make it even more difficult to convince parents to bring their children to centres to be immunised for all diseases, which provides the conditions for diseases to increase

Avoidable deaths & mistrust toward vaccination

Packaging – logistics – training

- WHO formal statement: *"The Atracurium ampoules were incorrectly added to vaccination packs prepared in one District Vaccine Distribution Centre …."*



Confusing drug packaging contributes to death of 15 children

At least 15 children have died after being vaccinated against measles in northern Syria, owing to accidental injection of atracurium.[1] The seriousness of this particular event is compounded by the fact that the deaths were associated with vaccination in a population in the midst of civil war whose trust in western medicine is already fragile.

It was an accident waiting to happen. 5 years ago a problem was reported with the packaging of atracurium, a deadly muscle relaxant used in surgery. "In a pediatric ICU, a respiratory therapist obtained what he thought was a sterile water vial to to ensure that packaging of dangerous drugs such as atracurium is strikingly different from packaging of innocuous diluents such as sterile water. This kind of mistake has happened too often in the past. It should not happen again.

We declare no competing interests.

*Neil Pakenham-Walsh, Joseph Ana

Healthcare Information For All Global Healthcare Information Network, Charlbury OX7 3PN, UK

1 Cousins S. Contaminated vaccine deaths a serious setback for Syria. Lancet 2014; **384:** 1172.

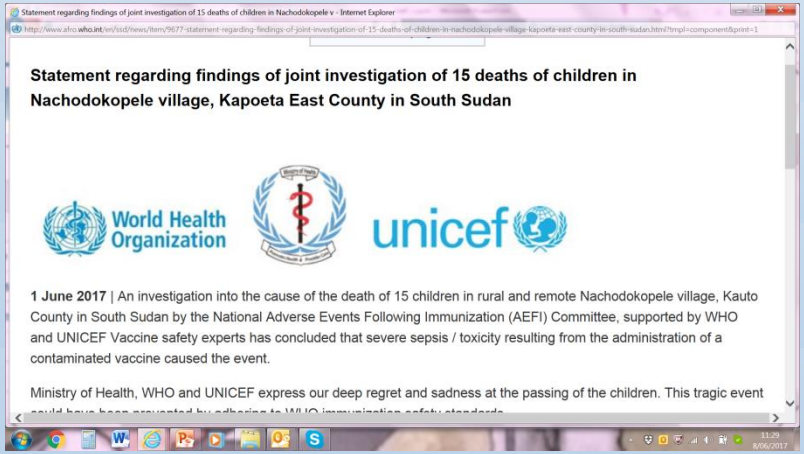
2 Grissinger M. Paralyzed by mistakes, part 1: preventing errors with neuromuscular blocking agents. *Pharm Therapeu* 2009; **34:** 466-81.

3 WHO. Statement regarding interim findings of WHO assessment of deaths of children in Idleb Governorate, Syria. http://www.who.int/mediacentre/news/statements/2014/interim-findings-idleb-syria/en/ (accessed Oct 7, 2014).

- "***Curiously, the statement does not acknowledge that atracurium and sterile water vials both have similar purple colour labels***" (*www.thelancet.com/lancetgh Vol 2 2014)*

Statement regarding findings of joint investigation of 15 deaths of children in Nachodokopele village, in South Sudan (1/6/2017)

An investigation by the National AEFI Committee has concluded that severe sepsis/toxicity resulting from the administration of a contaminated vaccine caused the event.



Statement regarding findings of joint investigation of 15 deaths of children in Nachodokopele village, Kapoeta East County in South Sudan

World Health Organization

unicef

1 June 2017 | An investigation into the cause of the death of 15 children in rural and remote Nachodokopele village, Kauto County in South Sudan by the National Adverse Events Following Immunization (AEFI) Committee, supported by WHO and UNICEF Vaccine safety experts has concluded that severe sepsis / toxicity resulting from the administration of a contaminated vaccine caused the event.

Ministry of Health, WHO and UNICEF express our deep regret and sadness at the passing of the children. This tragic event

…. the vaccination team did not adhere to the WHO-approved immunization safety standards.

A single reconstitution syringe was used for multiple vaccine vials for the entire four days of the campaign instead of being discarded after single use…..

The vaccines were stored in a building with no cold chain facilities for four days.

http://www.afro.who.int/en/ssd/news/item/9677-statement-regarding-findings-of-joint-investigation-of-15-deaths-of-children-in-nachodokopele-village-kapoeta-east-county-in-south-sudan.html

Quality of vaccines: essential for health and for public trust

Wakefield's article linking MMR vaccine and autism was fraudulent

Clear evidence of falsification of data should now close the door on this damaging vaccine scare

FEATURE, p 77

Fiona Godlee editor in chief, *BMJ*, London, UK
fgodlee@bmj.com
Jane Smith deputy editor, *BMJ*, London, UK
Harvey Marcovitch associate editor, *BMJ*, London, UK

Cite this as: *BMJ* 2011;342:c7452
doi: 10.1136/bmj.c7452

"Science is at once the most questioning and . . . sceptical of activities and also the most trusting," said Arnold Relman, former editor of the *New England Journal of Medicine*, in 1989. "It is intensely s the possibility of error, but totally trus possibility of fraud."[1] Never has this be the 1998 *Lancet* paper that implied a li measles, mumps, and rubella (MMR) vac syndrome" of autism and bowel disease.

Authored by Andrew Wakefield and paper's scientific limitations were clear w in 1998.[2 3] As the ensuing vaccine scare quickly pointed out that the paper was a s with no controls, linked three common

relied on parental recall and beliefs.[4] Over the following decade, epidemiological studies consistently found no evidence of a link between the MMR vaccine and autism.[5-8]

thebmj

BMJ 2016;355:i6545 doi: 10.1136/bmj.i6545 (Published 5 December 2016)

NEWS

CrossMark
click for updates

Andrew Wakefield calls Trump "on our side" over vaccines after meeting

Owen Dyer

Montreal

Anti-vaccine advocates across the US are optimistic about the prospect of one of their own occupying the Oval Office, after vaccine injury compensation program, which does not accept autism as a vaccine injury.

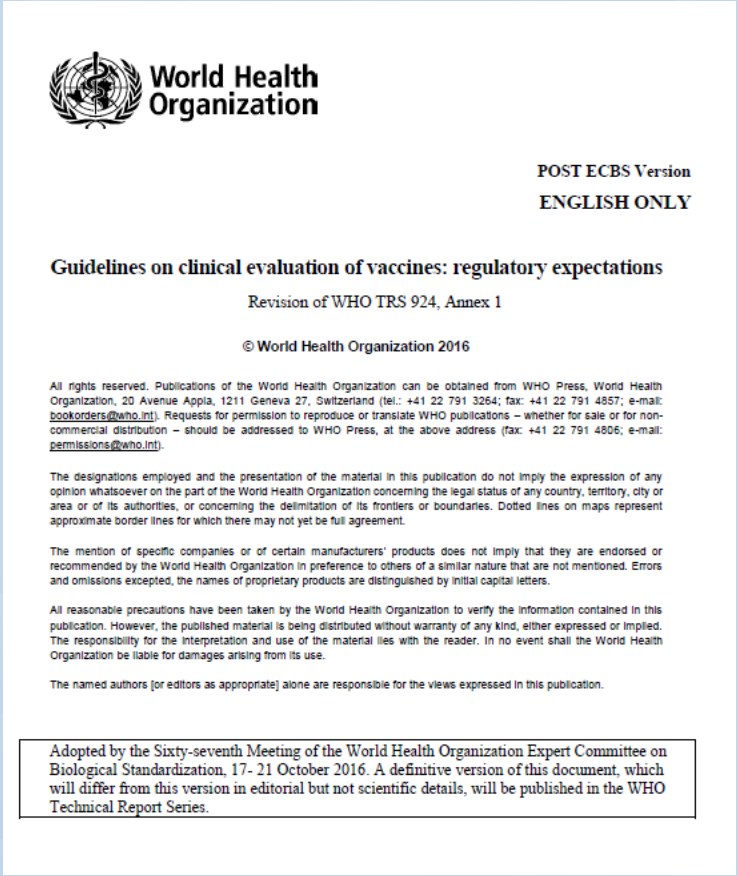
Extra slides

WHO PQ challenges

Quality	Clinical	Programmatic	GMP
Incomplete dossier Lack of data at commercial scale No history of characterization Master and Working cell banks Inappropriate devices: nasal administration	Lack of clinical consistency data, unclear ethical oversight Clinical trial comparator product not acceptable Lack of access to data and/or old data not meeting current GCP Lack of registration of CTs	Deviation Programmatic suitability criteria (PSPQ): eg, non autodisable prefilled syringes, stability profile and VVM	Quality systems Manufacturing process
Regulatory	National Vs WHO requirements: Test methodologies and GMP Schedules and target population Monodose Vs multidose presentation (preferred)		

(Other challenges: clinical development programmes)

- Phase I: safety of different amounts of the antigen(s), with or without an adjuvant…
- Phase II: further safety and immunogenicity trials
- Phase III (pivotal): provide robust clinical evidence in support of licensure
- Post-licensure clinical evaluations
- Immunogenicity
- Characterization of the immune response
- ……



World Health Organization

POST ECBS Version
ENGLISH ONLY

Guidelines on clinical evaluation of vaccines: regulatory expectations

Revision of WHO TRS 924, Annex 1

Adopted by the Sixty-seventh Meeting of the World Health Organization Expert Committee on Biological Standardization, 17- 21 October 2016. A definitive version of this document, which will differ from this version in editorial but not scientific details, will be published in the WHO Technical Report Series.

Guidelines on clinical evaluation of vaccines: regulatory expectations. Revision of WHO TRS 924, Annex 1. 2016