



Report to SAGE : other Advisory Committees in Immunization

**WHO Expert Committee on
Biological Standardization
Geneva**

October 15 – 19, 2012

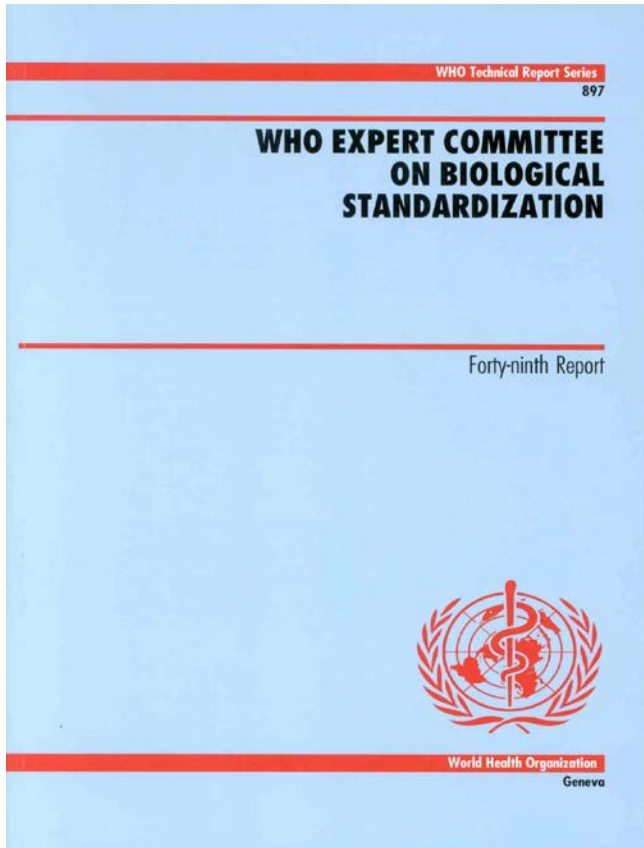


Vaccines

- Availability of vaccines of consistent safety and efficacy , and of assured quality, is key to the success of any immunization programme
- **ECBS develops global norms and standards which underpin this need**
- Setting global norms and standards and promoting their implementation is a core activity of WHO for the period 2008 - 2013

Biological standards – WHO products

Global written standards



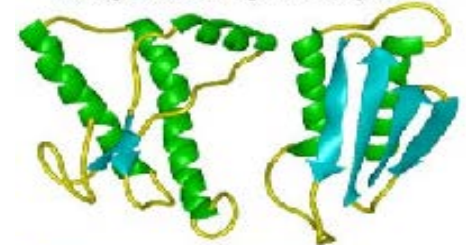
Global measurement standards



Standards evidence base



Pathogenesis: Change in Prion protein





Global Written Standards

- **Recommendations-** may be adopted as definitive national requirements
- **Guidelines** - greater flexibility than Recommendations with respect to expected future developments in the field.
- Both now contain non-clinical and clinical sections in addition to quality
- Both underpin the WHO Pre-qualification process
- Developed by considerable global public consultation (2-3 years)



ECBS 2012: Key outcomes

Written Standards adopted

- Revised Recommendations for oral polio vaccines (live attenuated)
- Revised Recommendations for Diphtheria, Tetanus and DT-combined vaccines
- Revised Recommendations for live attenuated Japanese Encephalitis vaccine
- New Guidelines on recombinant Malaria vaccine

Physical Standards established



Recommendations for oral polio vaccines (live attenuated) - Revised

- Significant scientific advances since document last fully updated in 1989; now incorporates addenda issued since 1989
- New sections on non-clinical and clinical evaluation and details of the origin of different strains used to produce OPV
- Three SOPs are also updated. MAPREC Test, neurovirulence test in monkeys and neurovirulence test in transgenic mice.
- Provides rationale for choosing the monkey or transgenic mouse neurovirulence test



Recommendations for Diphtheria and Tetanus Toxoids and for DT-combined vaccines - Revised

- The revision recognizes the major developments that have occurred since last full updating in 1990 in Tetanus, Diphtheria and DT combination vaccines
- D and T form the basis of numerous combination vaccines – acellular/whole cell Pertussis, IPV, Hibconj, HepB surface
- The 3 documents include new sections on non-clinical and clinical evaluation and give scenarios for evaluation of new combinations



Recommendations for Diphtheria and Tetanus Toxoids and for DT-combined vaccines - Revised

- For Tetanus potency, now a provision to use mouse IU in mouse assays in addition guinea pig IU with consistency specifications
- Minimum potencies retained for D and T but product specific specifications with consistency limits also acceptable based on results of clinical studies



Recommendations for live attenuated JE Vaccine- Revised

- **Guidelines** (2002) adopted with recognition that further improvements on production and evaluation would follow
- Guidelines now **Recommendations**
- Based on improvements in quality control of two different vaccines and licensing in several countries (attenuated SA14-14-2 strain {primary hamster kidney cells}, chimeric vaccine based on Yellow Fever vaccine strain 17D {produced in Vero cells})
- Updated sections on quality of both vaccine types



Recommendations for live attenuated JE Vaccine - Revised

- Additional specifications for monitoring the **upper limit** of the potency in addition to existing minimum potency of the immunizing dose
- Incorporate new parts – non- clinical and clinical evaluation sections
- Include new environmental risk assessment section for assessing live JE vaccine seed



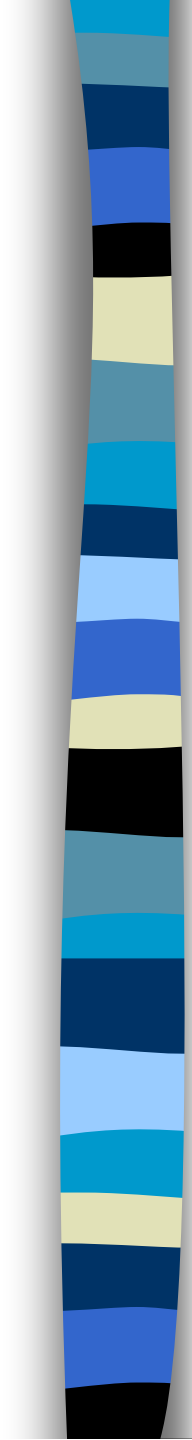
Guidelines on recombinant malaria vaccines - new

- Covers vaccines specifically targeting the pre-erythrocytic and blood stages of *Plasmodium falciparum* infection
- No licensed malaria vaccine.
- Principles may also apply to the evaluation of significantly different products
- Contain sections on quality, non-clinical and clinical expectations



Guidelines on recombinant malaria vaccines - new

- These sections differ somewhat in scope reflecting the different stages of malaria vaccine development and the diversity of production platforms and vaccine targets.
- Some detailed methodological considerations in the quality section are included as examples based on protocols used by the manufacturer of the most advanced candidate vaccine.
- Not an endorsement of any one candidate



International (physical) Standards 2012 relevant to immunization

- Anti HPV -18 serum - **1st International Standard**
- Diphtheria antitoxin, Human- **1st International Standard**
- Antibody to influenza H1N1 pdm virus – **2nd International Standard**
- BCG Moreau – **Reference Reagent**
- Endotoxin- **3rd International Standard** (same material as EP and USP , a collaborative project)



New reference preparation projects

- ◆ ECBS agreed the following new projects:
- ◆ Proposal for 1st WHO International Standard of EV71 neutralizing antibody assay
- ◆ Proposal for 1st WHO International Standard of EV71 inactivated vaccine antigen content assay



SAGE Request for Guidance on off-label use of vaccines

- ECBS agreed to develop a guidance paper on regulatory pathways and studies needed to support changes in labels
- ECBS thinks this should clarify differences between regulatory and public health recommendations and touch on legal and programmatic implications
- The ECBS emphasized that product-specific data were of paramount importance in this respect due to the nature of biologicals



IPAC Request for harmonized labelling for vaccines

- Reported that IPAC and Vaccine Presentation and Packaging Advisory Group (VPPAG) have reached a consensus on presentation and packaging issues
- ECBS sets vaccine nomenclature – International names / abbreviations (eg DT - Combined Vaccines 2012)
- ECBS agreed that it will consider proposals to revise existing labelling requirements in TRS 822(GMP for Biological Products)



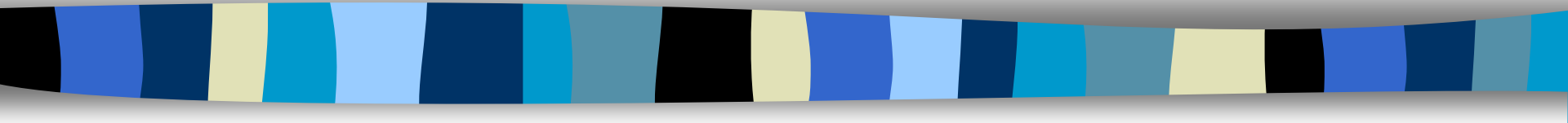
Other ECBS Business

- Report on establishment of **Network** of WHO Collaborating Centres for the Standardization and Regulatory Evaluation of Vaccines
- Currently 6 designated CCs with a wide range of expertise and capacities in vaccines area - NIBSC (UK), NIID Department of Bacterial Pathogenesis (Japan), CBER/FDA (USA), TGA Immunobiology and Biochemistry Group (Australia), KFDA (Korea), BGTD/Health Canada (Canada)
- Developing terms of reference / defining interactions with ECBS and other groups



Thank you for your attention

Spare slides

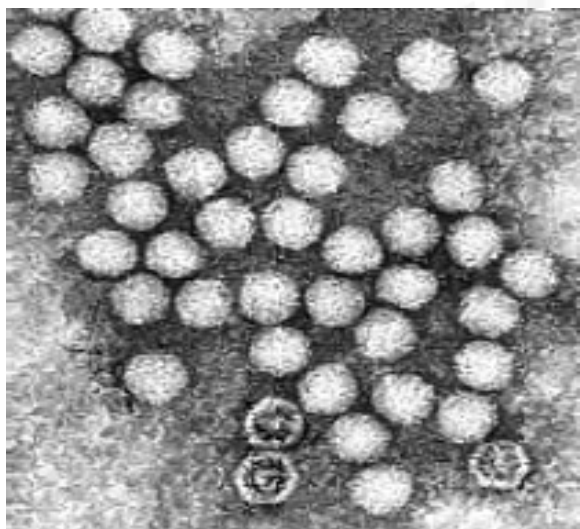


Background

What's Enterovirus 71 (EV71)?

EV71 was first isolated in the US state of California In 1969. It is a highly infectious agent that causes hand-foot-mouth disease (HFMD) in humans.

(Schmidt NJ, et al. *J Infect Dis*, 1974.)



- ◆ A single positive-stranded RNA virus
- ◆ 20-surface symmetry spheroidal particle
- ◆ ~7410 nucleotides

1 serotype; 3 genotypes; 11 subgenotypes

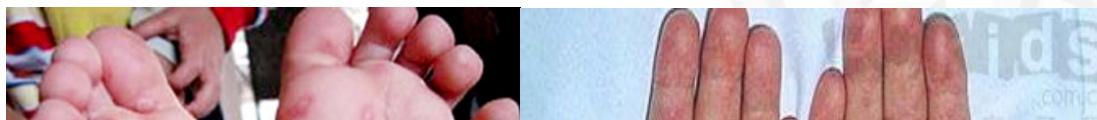
Subtype of C2,C4,C5,B4,B5 were circulated in Asia-Pacific region since 2005 ; C4 in China Mainland since 1998.

(Wong, *Epidemiol Infect*, 2010.)

(A Guide to clinical management and public health response for HFMD, WHO, 2011)

Background

Clinical symptoms caused by EV71



- <5-year old pediatric patients

In fact, EV71 is considered the most severe neurotoxic enterovirus in the “post-polio” era.

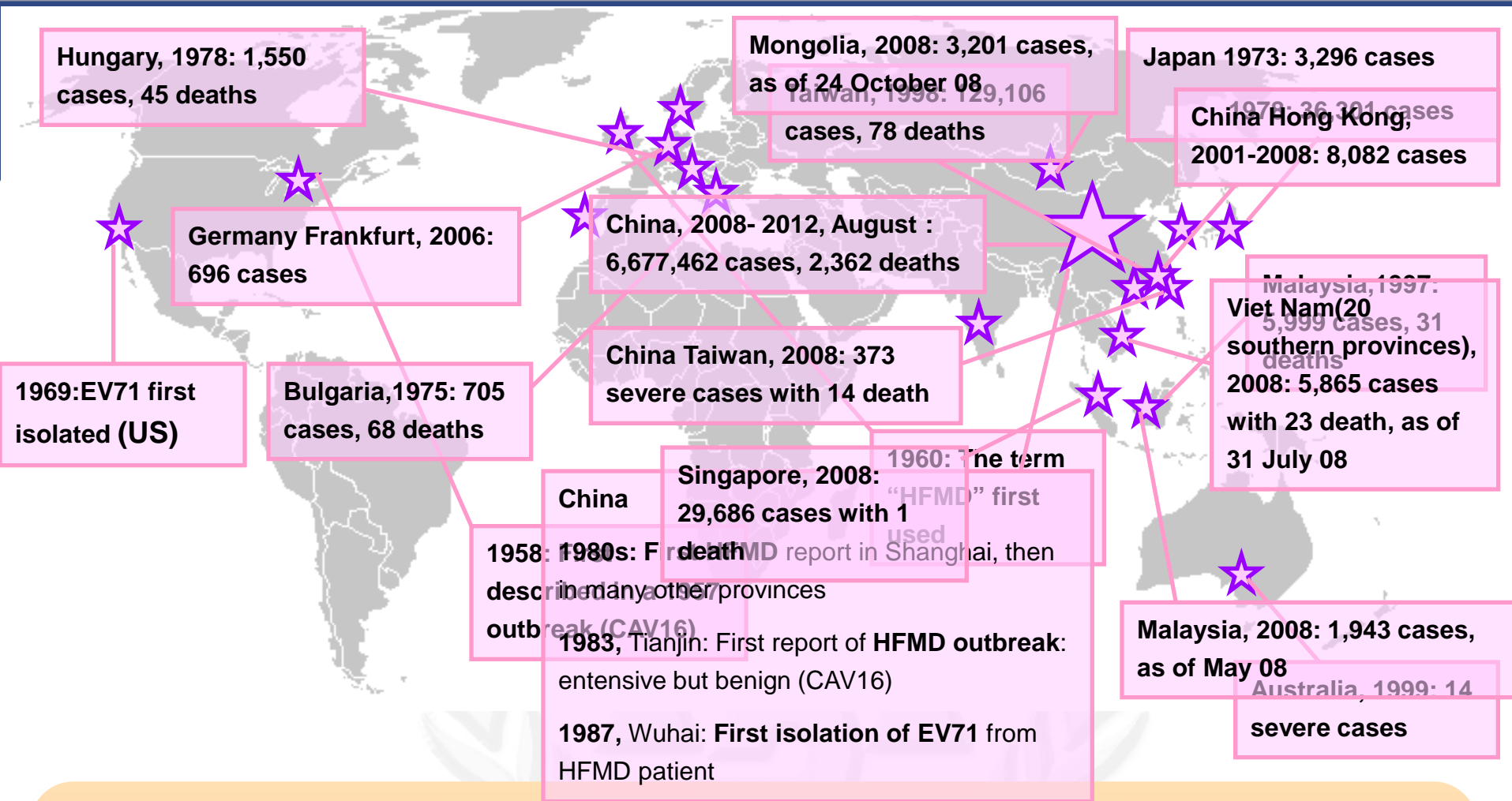
(Xu J. Vaccine 2010.)

- *Covered clinical symptoms:*

(Bible JM. Rev Med Virol 2007.)

neurogenic pulmonary edema , cardiac failure, neurological sequelae, even death.





■ Due to the lack of effective medicine, vaccine is the only effective method to control cases

■ At present, several units have initiated EV71 vaccine R&D in Chinese mainland, Chinese Taiwan and Singapore.

Background

Progress of EV71 vaccines

No.	Country	Manufactures	Vaccine	Research state	Clinical trials.gov No.	Cell substrates
1	Chinese Mainland	National Vaccine & Serum Institute	inactivated	Phase III	NCT01508247	Bioreactor (Vero cell)
2	Chinese Mainland	Sinovac Biotech	inactivated	Phase III	NCT01507857	Cell factory(Vero cell)
3	Chinese Mainland	Kunming Institute	inactivated	Phase III	NCT01569581	Bioreactor (KMB17)
4	Chinese Taiwan	National Health Research Institute	inactivated	Phase I	NCT01268787	Bioreactor (Vero cell)
5	Singapore	Invitrogen Pte. Ltd.	inactivated	Phase I	NCT01376479	/ (Vero cell)
6	Chinese					
7						
8						
9						
10						
11	Chinese Mainland	Taizhou	inactivated	Pre-clinical	/	Roller battle(Vero cell)
12	Chinese Taiwan	AdImmune	inactivated	Pre-clinical	/	Bioreactor (Vero cell) Roller battle and

International Standards of EV71 neutralizing antibody assay & EV71 inactivated vaccine antigen content assay are needed