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New vaccines – EMA perspective

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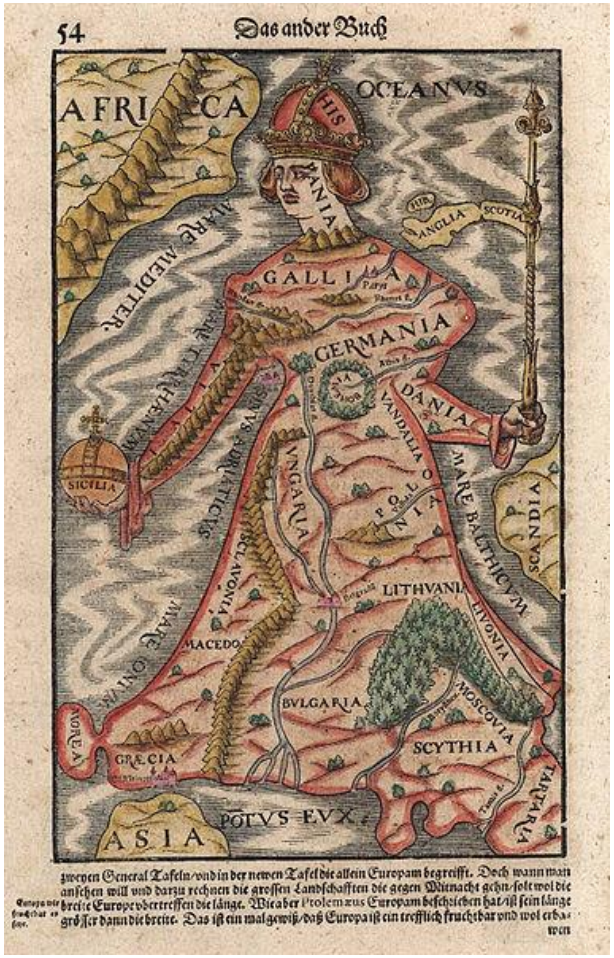
Overview



- Vaccine specifics
- Regulatory landscape in Europe
- Scientific advice
- Marketing authorisation

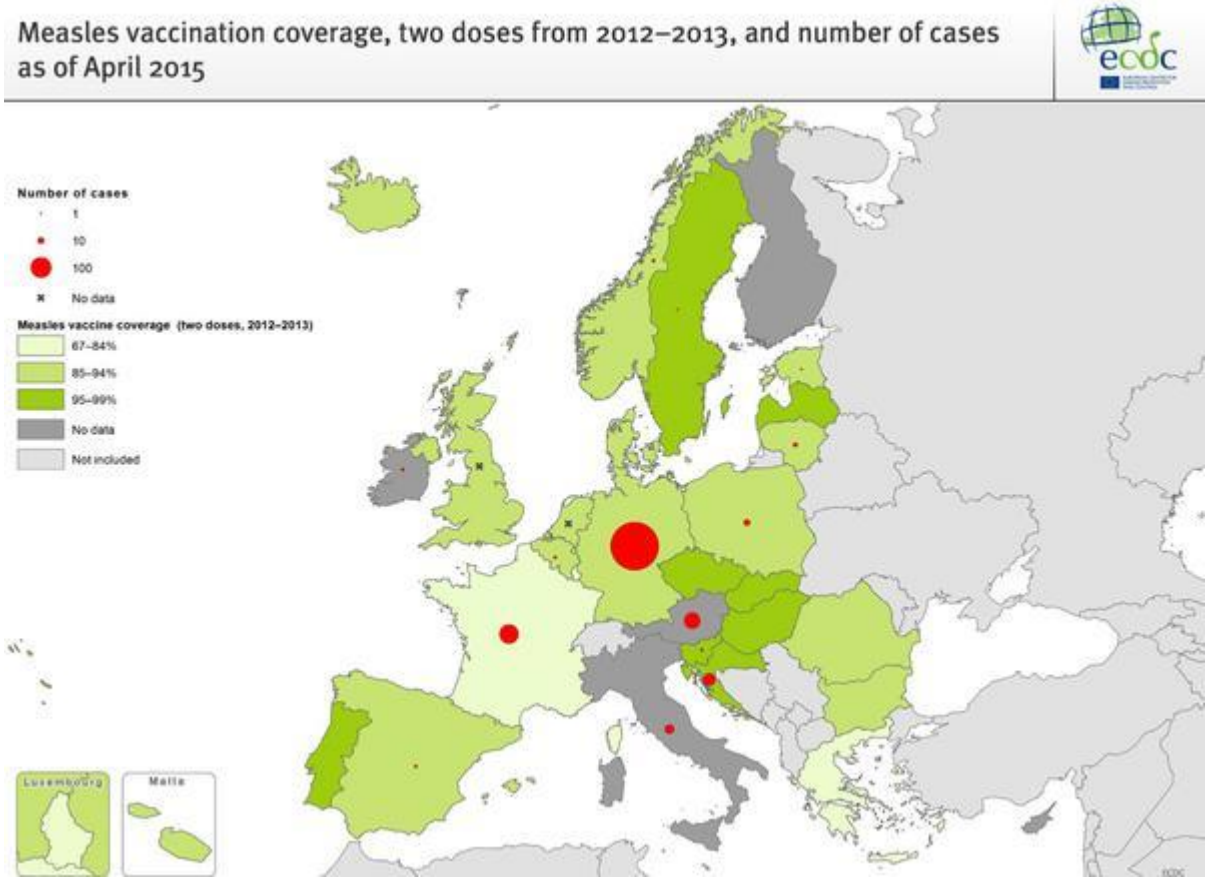
Sebastian Munster, 1570 CE

The particulars of vaccines: science and medicine

- Complex group of medicinal products (biologics)
- Complex mechanism of action
- Administered to large populations of healthy individuals
- Also indicated for specific vulnerable populations
  - Infants, pre-term infants
  - Pregnant women
  - Elderly
  - Frail individuals
  - Individuals with (multiple) acute and/or chronic underlying disease(s)
- Compatibility with a variety of vaccination schedules and recommendations expected

The particulars of vaccines: society

- High expectations of the healthy target population
  - Benefit of vaccine and health threats through infectious diseases not always and immediately recognizable for the population (and doctors!)
    - Increasing problem in countries that previously had a high vaccination rate
    - Vaccine prevented disease not encountered anymore
  - Risk perception skewed with vaccination
    - „Vaccines are not allowed to have side effects“
- Change of attitude towards expert judgement and advice
- False, misleading or confusing information spread by individuals opposed to vaccination with disproportionate media attention


Measles vaccination coverage, two doses from 2012–2013, and number of cases as of April 2015
ecdc
Number of cases
1
10
100
No data
Measles vaccine coverage (two doses, 2012–2013)
67–84%
85–94%
95–99%
No data
Not included
Luxembourg
Malta

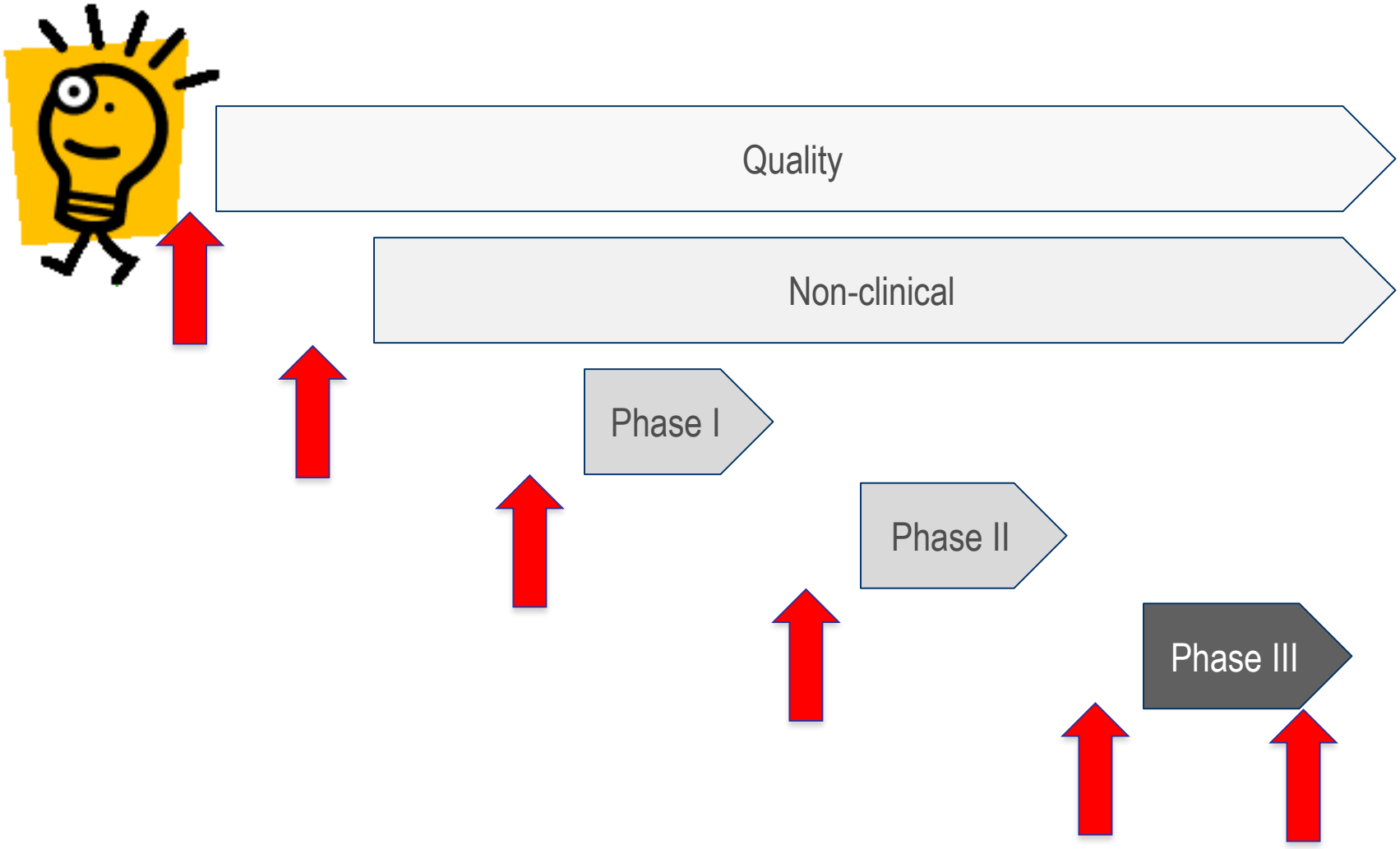
The particulars of vaccines: development, production

- Development
  - Typically long duration
  - Costly
  - Mostly international/global

- Chances for success similar to other drugs
  - One of 10 vaccines that enter clinical development finally obtains marketing authorisation

- Ressource allocation
  - Invest in R/D of new product
  - Development of existing product
  - Scale up of manufacturing capacity (is there stable demand?)

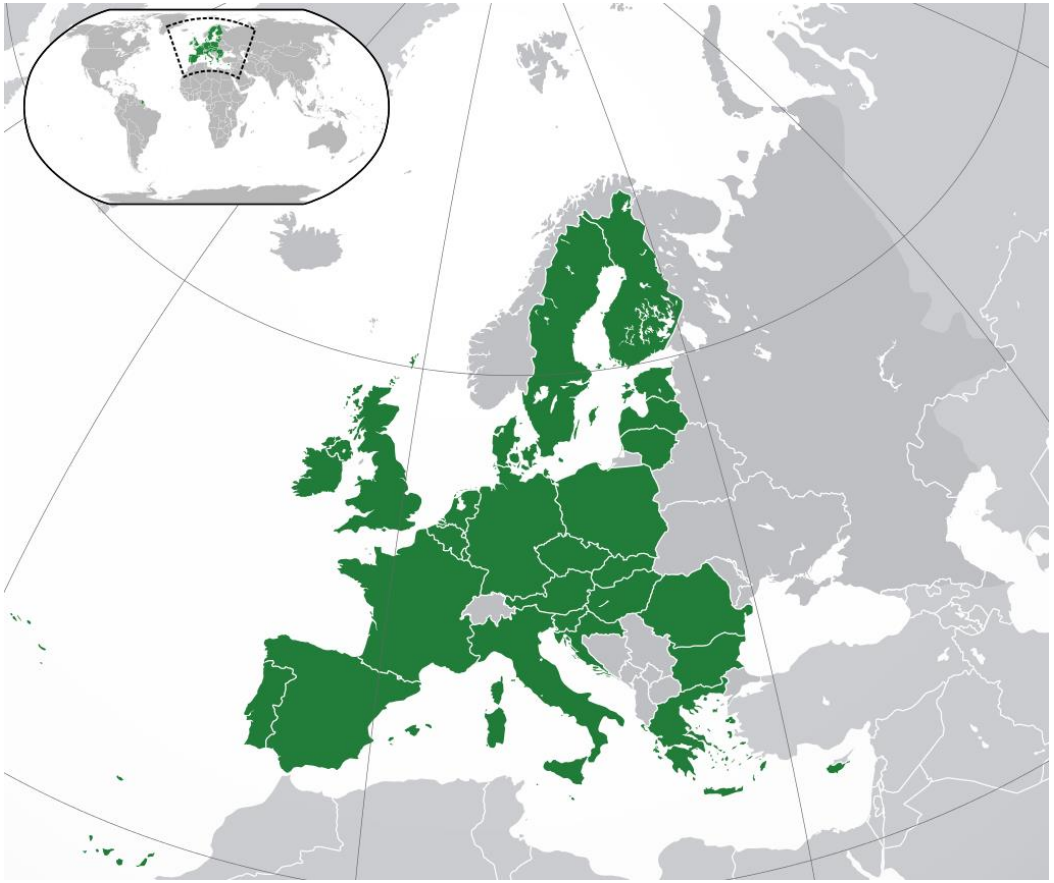
Interaction of developers and regulators



European procedures

- Innovation task force
- Scientific Advice
- Centralised procedure
- Art. 58 procedure
- Referrals

- National procedure
- Decentralised procedure
- Mutual recognition



Innovation task force EMA

- Discussion platform for early dialogue with developers, in particular micro, small and medium-sized enterprises
- Voluntary, informal, no fee

- Meetings 2010-6/2015: 161

- Vaccines 9
  - Specific pathogens 4
  - Platform technologies, novel manufacturing 2
  - „Adjuvants“ 3
- Diagnostic 1

Scientific advice CHMP

- Voluntary, fee applies
- Advices 2010-6/2015 app. 2500
- Vaccines 84
  - Specific pathogens
    - Established 23
    - Innovative 55
  - Platform technologies/ novel manufacturing 5
  - „Adjuvants“ 1
- Diagnostic 2

Centralised procedure: Marketing Authorisation

- Mandatory for new vaccine, optional in specific situations
- Overall 2010-6/2015 app. 400
- Vaccines 8
  - Men $ACW_{135}Y$ 2
  - Men B 1
  - DTP-IPV-HBV-HiB 1
  - Influenza (live attenuated) 2
  - Human papilloma virus 1
  - Smallpox (MVA) 1

Art. 58 of Regulation 726/2004

Article 58

1. The Agency may give a scientific opinion, in the context of cooperation with the World Health Organisation, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. ….

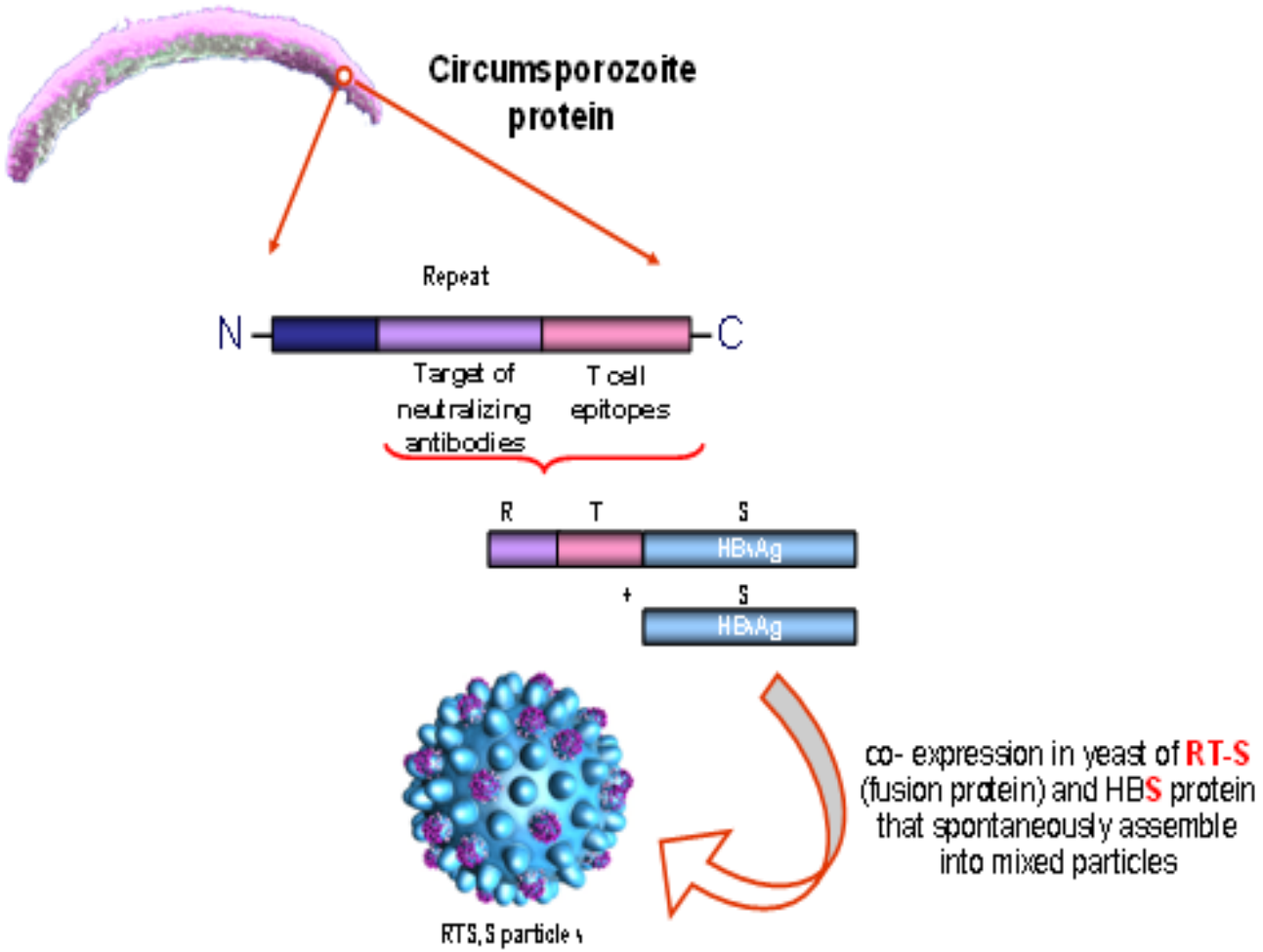
- DTP-IPV-HBV-HiB 2013
- RTS,S-AS01 2015

Evaluation of efficacy

RTS,S-AS01	vaccine efficacy
Influenza (live attenuated)	vaccine efficacy
Human papilloma virus	vaccine efficacy, immunogenicty
Men $ACW_{135}Y$	immunogenicity, NI*
DTP-IPV-HBV-HiB	immunogenicity, NI
DTP-IPV-HBV-HiB	immunogenicity, NI
Men B	immunogenicity
Smallpox (MVA)	immunogenicity, animal

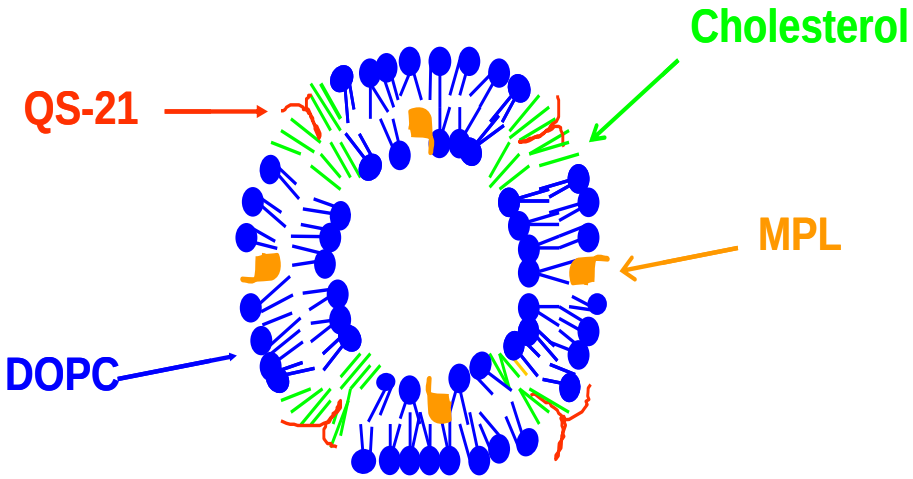
* NI: non-inferiority

RTS, S

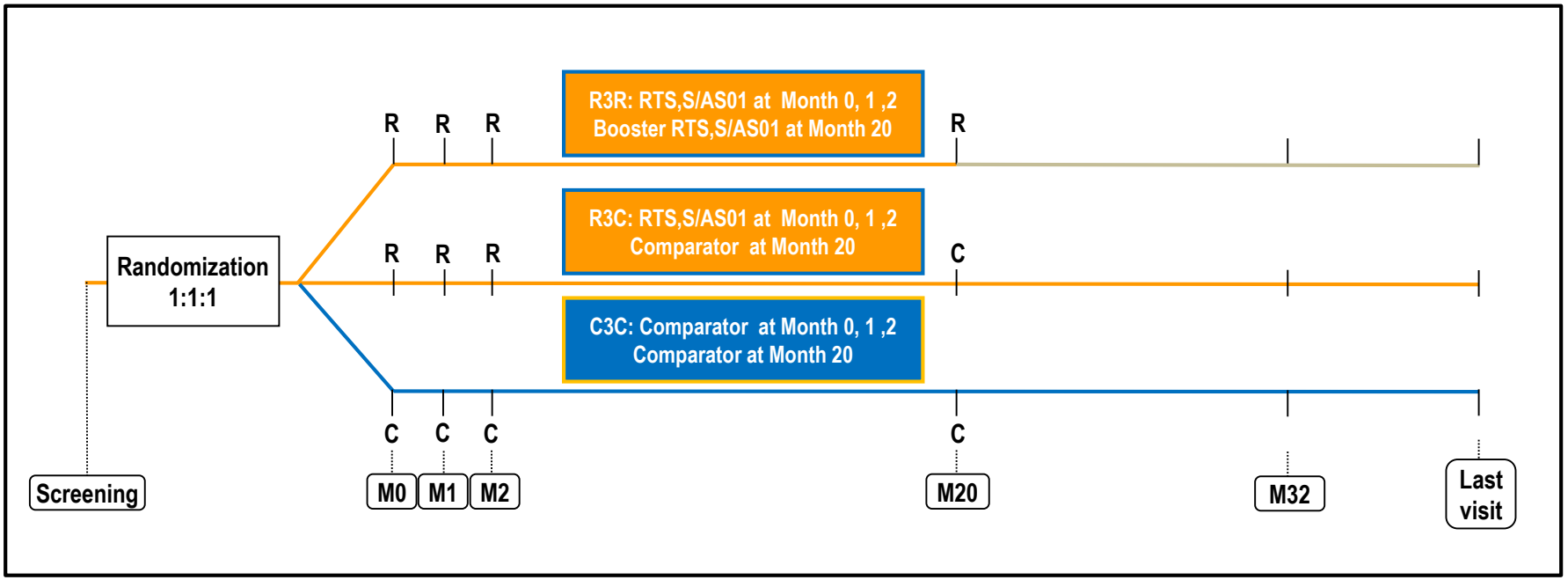

Circumsporozoite protein
Repeat
N
C
Target of neutralizing antibodies
T cell epitopes
R
T
S
HBsAg
+
S
HBsAg
RTS,S particles
co- expression in yeast of RT-S (fusion protein) and HBS protein that spontaneously assemble into mixed particles

AS01

- Adjuvant system
  - MPL: prepared from LPS of Salmonella minessota
  - QS21: saponin purified from bark of molina tree
  - Combined in a liposome



Malaria 055



- Comparator vaccines:
  - Children 5 -17 months: rabies vaccine
  - Infants 6 -12 weeks: meningococcal serogroup C conjugate vaccine

Data on „boosting“: 6-12 weeks at primary vaccination R3R or R3C compared to C3C

Primary case definition	Vaccine efficacy (unadjusted for covariates)		
R3R	(%)	95% CI	
M2.5-M20 (primary phase) *	26.55	20.25	32.36
M21-M32	30.33	22.98	36.97
M33-M48 (extension)	12.38	1.91	21.73
R3C			
M2.5-M20 (primary phase) *	26.55	20.25	32.36
M21-M32	8.09	-0.43	15.89
M33-M48 (extension)	3.87	-7.55	14.08

Data on „boosting“: 5-17 months at primary vaccination R3R or R3C compared to C3C

Primary case defintion	Vaccine efficacy (unadjusted for covariates)		
R3R	(%)	95% CI	
M2.5-M20 (primary phase) *	45.72	41.71	49.46
M21-M32	38.45	32.24	44.09
M33-M48 (extension)	14.62	5.79	22.62
R3C			
M2.5-M20 (primary phase) *	45.72	41.71	49.46
M21-M32	13.52	5.41	20.93
M33-M48 (extension)	0.09	-9.85	9.14

Human papilloma virus, 9-valent

- Vaccine for HPV types 6, 11, 16, 18, authorisation in 2006
- Additional 5 types (31, 33, 45, 52, 58) causing ca. 20% of cervical cancers
- No accepted correlate of protection
- Efficacy study: 4-valent vs. 9-valent
  - Demonstration of vaccine efficacy for additional 5 types
  - Non-inferior immunogenicity for shared types

Results of main studies

Primary endpoint		9vHPV and qHPV
HPV 31/33/45/52/58-related CIN 2/3, AIS, cervical cancer, VIN 2/3, VaIN 2/3, vulvar cancer, and vaginal cancer	Vaccine efficacy	96.7%
	95% CI	80.9%; 99.8%
	P-value	<0.0001

- Non-inferior serological responses to HPV 6, 11, 16 and 18 compared to 4-valent
- Similar protection against HPV 6/11/16/18-Related Cervical, Vulvar, and Vaginal Disease compared to qHPV

Men B vaccine (3 recomb. antigens + outer membrane vesicles)

- Efficacy trial not feasible because of low incidence
- Serum bactericidal antibody (SBA): antibody capable of recognising bacterial surface antigens and initiating complement-mediated lysis
- External evidence from naturally acquired infection and vaccine trial using outer membrane vesicle indicated that titer ≥ 1:4 correlated with efficacy
- Three phase III studies
  - Infants 2 months of age
  - Toddlers booster/catch-up
  - Adolescents 11-17 years of age

Infants, hSBA ≥ 1:5, 1 month after third dose

Strain		rMenB All	Routine
44/76-SL		**N=1156**	**N=119**
	Baseline	35 (3%) (2-4)	4 (3%) (1-8)
	1 Month After 3rd Vaccination	1146 (100%) (99-100) N=1149	3 (3%) (1-7) N=117
5/99		**N=1154**	**N=120**
	Baseline	45 (4%) (3-5)	8 (7%) (3-13)
	1 Month After 3rd Vaccination	1149 (100%) (99-100) N=1152	2 (2%) (0-6) N=116
NZ98/254		**N=1160**	**N=121**
	Baseline	14 (1%) (1-2)	1 (1%) (0.021-5) N=120
	1 Month After 3rd Vaccination	965 (84%) (82-86) N=1152	2 (2%) (0-6)

Role of the regulator

- Establish „efficacy“ in the vaccinated population
  - Efficacy trials
    - Influenza: prevention of influenza
    - HPV: prevention of HPV related disease (composite)
    - RTS,S-AS01: prevention of clinical malaria episodes
  - Comparison to established vaccines
    - Non-inferior immunogenicity, accepted correlates of protection
  - Inference from animal models and human immunogenicity
    - When no other options and high medical need

- Make a judgement of the **benefit-risk balance** for the vaccinated population, i.e. the individual being vaccinated

Not for consideration by the regulator (?)

- Population effects
  - Effects of incomplete vaccination coverage on epidemiology of wild type infection, e.g. age shifts
  - Impact of herd immunity

- Role of the vaccine use in national healthy systems
  - National decisions on vaccination strategies, (compatibility with particular vaccination schedules)
  - National economic considerations

  - “Product X is given according to official recommendations.”

Referrals

- Majority of vaccines authorised in Europe by national competent authorities
- Historically independant, different approaches
- Harmonisation necessary when products are authorised by „mutual recognition“
- Harmonisation of information in Summary of Product Characteristics (SmPC) desirable

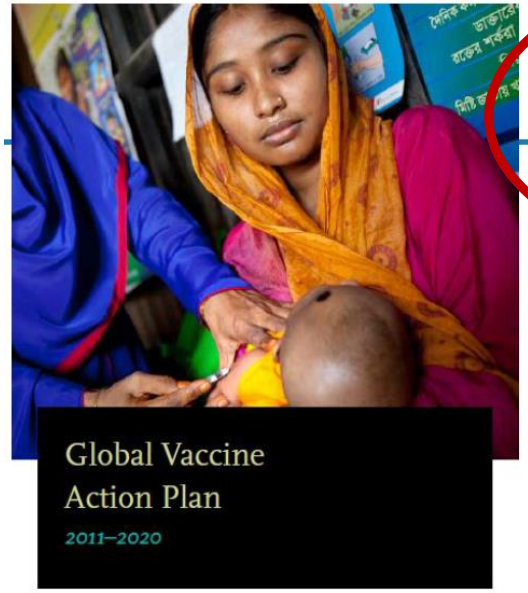
- Scientific evaluation by CHMP if no agreement between member states
  - E.g. approach to vaccination of pregnant women

Benefit and risks beyond clinical B/R discussion

- Assessment of changes to manufacturing (variation)
- Assessment of unexpected quality findings, e.g. PCV in rotavirus vaccines
- Inspections (GMP, PhV)
- Batch testing and release (Official Medicines Control Laboratory, OMCL)
- Pharmacovigilance
  - Post authorisation safety studies (PASS)
  - Post authorisation efficacy studies (PAES)

Decade of Vaccines – Global Vaccine Action Plan

- Initiative of WHO, UNICEF, B&MGF, GAVI, NIAID
- Global Vaccine Action Plan adopted by 194 member states of the World Health Assembly in 2012



"We envision a world in which all individuals and communities enjoy lives free from vaccine-preventable diseases".

"The mission of the Decade of Vaccines is to extend, by 2020 and beyond, the full benefits of immunization to all people, regardless of where they are born, who they are, or where they live."

http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/

Overview vaccine developments

- In 2012 there were about 577 vaccine development programs for 110 pathogens (Jordan 2012) www.niaid.nih.gov/topics/vaccines/pages/Jordan2012.aspx

- In 2014 WHO selected 20 pathogens für evaluation (PDVAC)
  - ‘Unmet public health need’
  - General activity in the specific field with a high probability for achieving technical feasibility and obtaining marketing authorisation
  - Will engagement of WHO have an added value (e.g. importance for developing countries)

Pipeline analyses/ diseases - WHO

- HIV, tuberculosis, malaria
- Universal influenza, RSV
- Group A streptococci, S. pneumoniae
- Rotavirus, E. coli, Shigella, S. paratyphi, non-typhoid salmonella, campylobacter, norovirus
- HSV, trypanosoma (Chagas), leishmania, schistosoma, human hook worm

Priority topic: vaccination of pregnant women

- Protection of the woman
  - Influenza
- Protection of the newborn by transplancental passage of maternal antibodies
  - Influenza
  - Tetanus
  - Pertussis (UK, USA)
  - In development: RSV, Group B streptococci B, CMV

Novel vaccines – new concepts

Novel adjuvant systems

- Highly purified recombinant antigens induce insufficient immune response
- Targeted stimulation of components of the immune systems by adjuvants or adjuvant systems (combination of different components)
  - Aluminum salts
  - Monophosphoryl lipid A (MPL)
  - Liposomes
  - Emulsions
  - Saponin (QS21)
- Risk of unexpected rare adverse events

Vaccines:

recombinant protein zoster vaccine, RTS,S malaria vaccine

Novel vaccines

Vector based vaccine

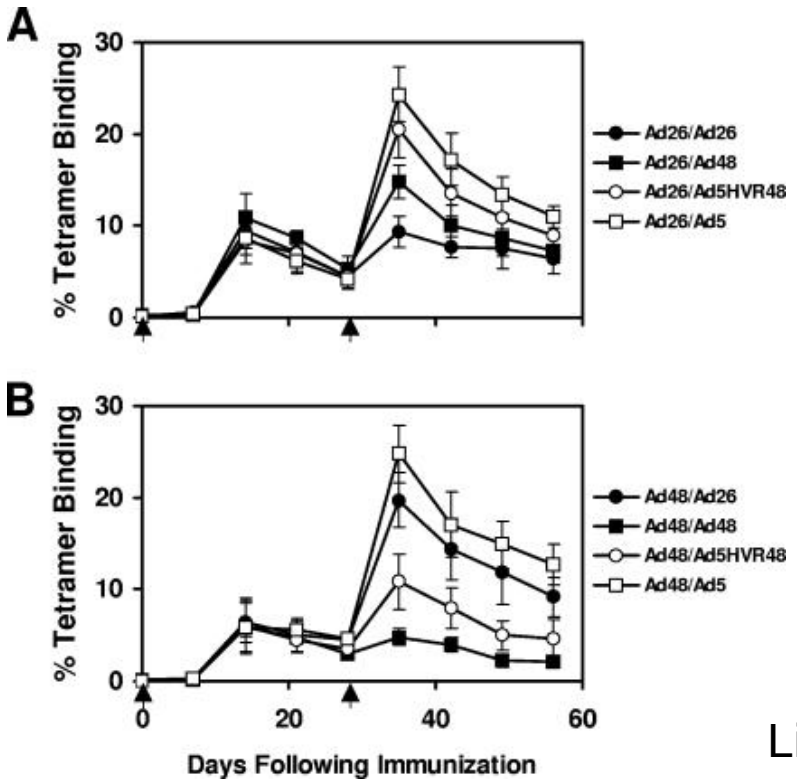
- Replication competent vectors:
  - Yellow fever vaccine virus or attenuated Dengue virus 2 as vector for chimeric live vectored vaccines (Japanese encephalitis vaccine, Dengue vaccine)
  - VSV vectors (Ebola)

- Replikation incompetent vectors
  - MVA vectors (Ebola, tuberculosis, MERS corona)
  - Adenovirus vectors ChAd5, Ad26, Ad35 (Ebola, Marburg, malaria)

Novel concepts

Prime-boost with heterologous vaccine vectors
(z.B. Ad26/Ad35, Ad26/MVA)

- Improved immunogenicity



Liu et al. J Virol 2008

Vector based vaccine

Uncertainties

- Pre-existing natural immunity against the vector may cause reduced immune reaction
- Risk of unexpected AE because of changed cellular tropism (biodistribution)
- Transmission to non-immune population including vulnerable subjects (replication competent)
- Release of genetically modified organisms
  - Environmental risk assessment

Vaccine development of global manufacturers

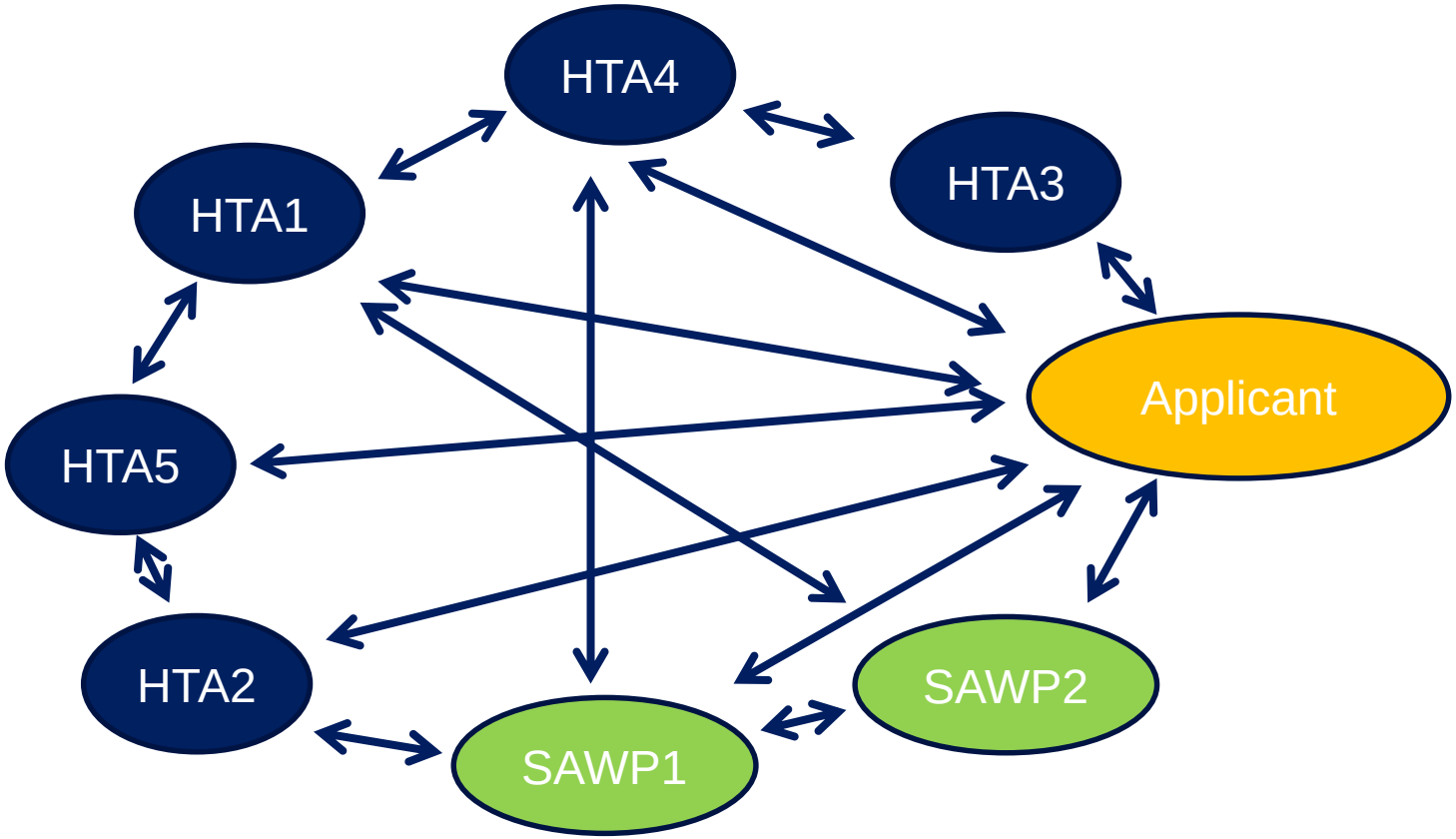
Early phase Phase I /II	Late phase Phase II/III
DTP-IPV-HBV-Hib-MenC	DTP-IPV-HBV-Hib
Pneumococci, conjugated	Varicella Zoster Virus (recombinant or inactivated)
Meningococci A, B, C, Y, W135 conjugated	Clostridium difficile
Meningococci A, C, Y, W135 conjugated	Rotavirus
Pseudomonas aeruginosa	RSV
Group B Streptococci	Tetravalent influenza vaccine
M. tuberculosis	Tetravalent Dengue-vaccine
Rabies virus	Ebolavirus
Norovirus	
Ebolavirus	
RSV	
HepC virus	

Source: GSK, Merck, Pfizer, Sanofi Pasteur, Novartis, clinicaltrials.gov

Regulator	HTA	Payer
Can it work?	Does it work?	Is it worth it?
Does the product do more good than harm for patients with defined indications in this jurisdiction?	HTA seeks to support decisions on whether an intervention offers useful, appropriate, and affordable benefits for patients in a particular healthcare system	Will the product offer useful, appropriate (and affordable) benefits for some or all eligible patients in this healthcare system?

Modified from: Int J Technol Assess Health Care 2011;27:253–260

Parallel HTA-EMA advice



Summary

- Recognition of the importance of interaction with developers and vaccine manufacturers
- European regulatory system supports development of vaccines on many levels
- European regulatory system evaluates dossiers for vaccines at request of WHO for vaccines not marketed in Europe
- Groundwork for interaction of HTA, payers and regulators is being laid in non-vaccine field
  - May require involvement of totally different set of stakeholders!

Acknowledgments

- Organising Committee and Fundisa for the invitation
- Heidi Meyer and Michael Pfleiderer for slides

Thank you