PATOLOGIE EMERGENTI E RIEMERGENTI

Globalizzazione e Salute: l'importanza della vaccinazione

TAVOLA ROTONDA:
PIANO NAZIONALE VACCINI: ESPERIENZE A CONFRONTO

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PIANO NAZIONALE VACCINAZIONI 2010 - 2012

VACCINI anti -		GRUPPI VACCINALI	
		Età infantile	Età adulta
Infezioni virali	(*) Poliomielite	3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	suscettibili a rischio
	(*) Epatite B	(***) 3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	gruppi a rischio, operatori sanitari
	Morbillo	13°-15° mese; 5°-6° anno; 12°-14° anno	suscettibili a rischio
	Parotite	13°-15° mese; 5°-6° anno; 12°-14° anno	suscettibili a rischio
	Rosolia	13°-15° mese; 5°-6° anno; 12°-14° anno	donne età fertile suscettibili
	(**) Varicella	13°-15° mese; 5°-6° anno; 12°-14° anno (proposta)	conviventi di bambini a rischio
	Epatite A	dal 2° al 14° anno in soggetti a rischio	viaggiatori e gruppi a rischio
	Influenza	secondo prescrizioni annuali	➢ 65 anni e gruppi a rischio
	(**) HPV	12° anno	gruppi a rischio
Infezioni batteriche	(*) Tetano	3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	ogni 10 anni
	(*) Difterite	3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	ogni 10 anni
	Pertosse	3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	suscettibili a rischio
	Hemophilus influenza b	3° mese; 5°-6° mese; 11°-13° mese; 5°-6° anno	soggetti con deficit immunitario
	(**) Pneumococco (coniugato)	3° mese; 5°-6° mese; 11°-13° mese (proposta)	soggetti con deficit immunitario
	(**) Meningococco C "	13° mese; 12°-14° anno (proposta)	soggetti con deficit immunitario

(*) regime di obbligatorietà
(**) introdotti ex novo

(***) alla nascita per bambini nati da madre HBsAg positiva

VACCINI VIRALI E BATTERICI
RELATIVI AL PIANO NAZIONALE VACCINAZIONI 2010 - 2012

Vaccini		Tipo di vaccino	Metodo di produzione	Adiuvante
Vaccini virali	Poliomielite	inattivato, attenuato	coltura cellulare	-
	Epatite B	subunità (HBsAg)	ricombinazione genetica	sali Al
	Morbillo	vivo attenuato	coltura cellulare	-
	Parotite	“ “	“ “	-
	Rosolia	“ “	“ “	-
	Varicella	“ “	“ “	-
	Epatite A	inattivato	“ “	IRIV, Alum
	Influenza	Inattivato, split	uova embrionate	MF59, IRIV
	HPV	Subunità (L1)	ricombinazione genetica	ASO4, Alum, VLPs carrier
Vaccini batterici	Tetano	tossoide	purificazione ed inattivazione da colture batteriche	sali Al
	Difterite	“	“ “	sali Al
	Pertosse	tossoide, subunità	“ “	Alum, sali Al
	Hemophilus influenza b	coniugato	“ “	proteina carrier, sali Al
	Pneumococco	“	“ “	proteina carrier, sali Al
	Meningococco C	“	“ “	proteina carrier, Alum

Some characteristics of an ideal vaccine

- Shown an impeccable safety profile in all populations, including young infants, the elderly and immunocompromised subjects (such as HIV-positive subjects)
- Elicits a high level of long-lived efficacy, including in young infants and the elderly
- Requires only a single dose (or at most two doses spaced fairly close together) to confer protection
- Stimulates protection within 2 weeks of administration
- Administrable without a needle and syringe; that is, orally, nasally or transcutaneously or with a needle-free injection device
- Administrable in combination with (in the same formulation) or concomitantly (coadministered) with other vaccines
- Can be manufactured in large scale and with quality control by relatively uncomplicated and economical processes
- Amenable to production in formulations that are resistant to high and low temperatures and therefore free from strict storage requirements

M.M. Levine *et al*., Nature Immunology, 2004, 5: 460

Strategies of optimization of new generation vaccines

- epitope enhancement
- induction of higher CTL avidity
- use of cytochines, chemokines and co-stimulatory molecules
- enhancement of mucosal immunity
- implementation of DNA-based vaccines
- use of dendritic cells on vaccine vehicles

Adjuvant categories

- Mineral salts
- Tensoactive compounds* *
- Microorganism-derived* *
- Emulsions
- Particulate antigen delivery systems
  - Liposomes*
  - Polymeric microspheres*
  - Nano-beads*
  - ISCOMs* *
  - Virus-like particles*
- Cytokines* * *
- Polysaccharides* *
- Nucleic acid-based* *
- Adjuvant formulations
- TLRs ligands* *

* *Carrier*
* * *Immunostimulant*
* * * *Immunomodulant*

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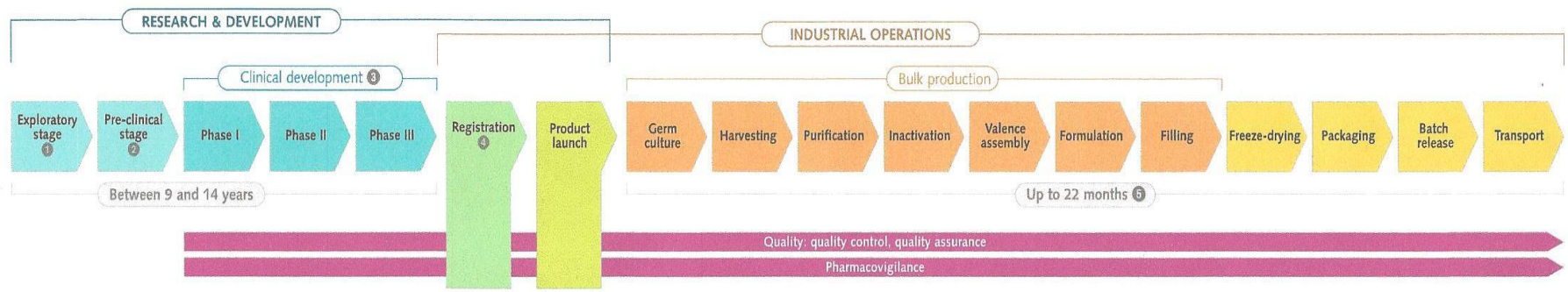
THE VACCINE DEVELOPMENT CYCLE



Average development time for a vaccine: **12 years**

70% of a vaccine's production time dedicated to quality control.

Comments

❶ **Exploratory stage: 2 to 4 years**
Identifying antigens to prevent or treat a disease. Selected candidate vaccines will continue the process.

❷ **Pre-clinical stage: 1 to 2 years**
Assessing antigens' safety in animals and selecting the best candidate vaccine to continue the process.

❸ **Clinical development: 6 to 8 years**
Testing the candidate vaccine in humans.
Phase I: test of **safety** on 10 to 100 subjects
Phase II: **Evaluation of the immune response** in 100 to 3,000 subjects
Phase III: Large-scale tests of the **vaccine's efficacy** and **tolerance** on 3,000 to 40,000 subjects.

❹ **Registration: synthesis stage from 12 to 18 months**
All of the data that have been collected during the preceding stages are gathered in a file and submitted to the health authorities in order to obtain a marketing authorization.

❺ The infectious germs are cultured, harvested and purified.
After formulation and freeze-drying (which stabilizes the more fragile vaccines), the vaccines are filled, primarily in vials and syringes and then packed.
When the manufacturing process is complete, the cold chain must be constantly maintained during all stages, from distribution to vaccine administration to patients.

ORGANISMI EUROPEI COINVOLTI NEI PROCESSI AUTORIZZATIVI, DI SORVEGLIANZA E CONTROLLO DEI VACCINI PER USO UMANO

European Commission

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Dep.t health and consumers
(SANCO)

↓

European Medicine Agency
(EMA)

↓

Committee for Medical products for human use
(CHMP)

↓

Vaccine working party
(V W P)

Council of Europe

↓

European Directorate for quality of medicine and health care
(EDQM)

↓

Official Medicine Control Laboratories
(OMCLs)

↓

Official Control Authorities Batch Release
(OCABR)

Vaccines Working Party (V W P)

Provides recommendations to the Committee for Medicinal Products for Humans (CHMP) on all matters relating directly or indirectly to vaccines.

The VWP's tasks include:

- preparation, reviewing and updating of guidelines;
- supporting dossier evaluation of new marketing-authorisation applications for vaccines;
- at the request of the CHMP, providing scientific advice on general and product-specific matters;
- European co-operation on vaccine-specific issues, in conjunction with EC, EDQM, OMCLs;
- providing advice, through the CHMP, to the EC, CMD(h) and WHO on vaccine-related issues;
- acting as a focus and catalyst for training on the quality, preclinical and clinical assessment of vaccines;
- on request of the CHMP, constituting a rapid-acting crisis group;
- supporting the conduct of vaccine-specific epidemiological studies;
- supporting the implementation of the Vaccine Identification Standards Initiative (VISI);
- monitoring the development of new vaccine technologies.

OFFICIAL MEDICINE CONTROL LABORATORIES
(OMCLs)

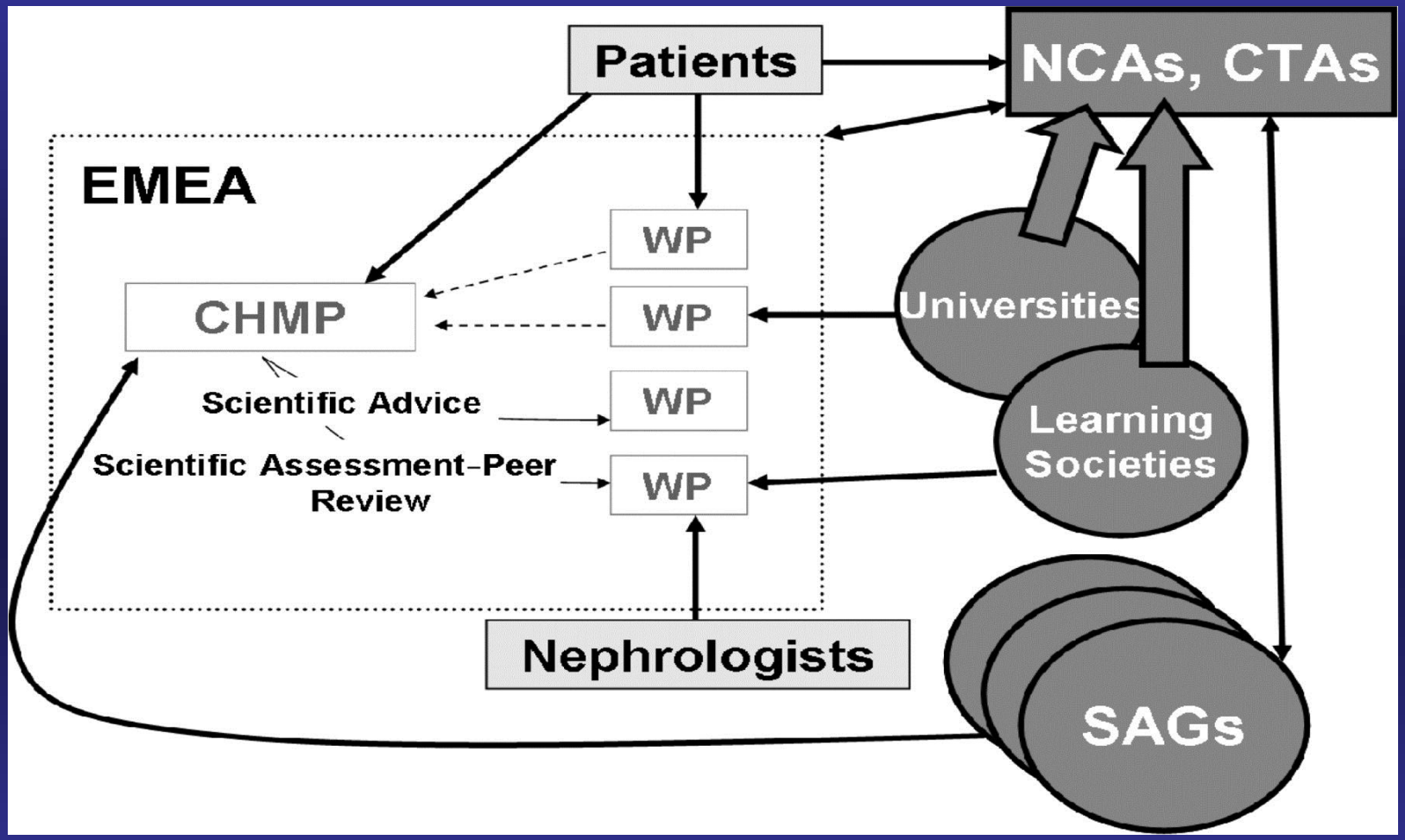
- Are organized in a General OMCLs network for harmonization of working methods and standards and elaboration of the European Pharmacopeia

- Support regulatory Authorities (EMA and National Authorities) in controlling quality of vaccines as Centrally Authorized Products (CAP) by Mutual Recognition Procedures (MRP) and Decentralized Procedures (DCP) and post marketing surveillance

- Perform independent testing of single lots of vaccines as Official Control Authority Batch Release (OCABR) according to Directives 2001/83/EC and 2004/27/EC art. 19 and art. 114

- During the annual meetings of all OMCLs, strategies and methods of testing, batches tested and results, as well as, lists of approved lots for each vaccine for EU distribution are reported and discussed

Diagram illustrating the interactions within the European Medicines Agency (EMEA) and between the EMEA and external groups.



Wiecek A , Mikhail A Nephrol. Dial. Transplant. 2006;21:v17-v20

TESTING REQUIREMENTS FOR RELEASE OF VARICELLA VIRUS VACCINE, LIVE*

Type of Test	*Test System*	*Stage of Preparation*
Identity of production cells Sterility	Karyology Thioglycollate/soybean-casein digest	Production control cells Working cell bank Control harvest fluids Virus harvest fluids Pre-clarified bulk Clarified bulk Final formulated bulk Filled container
Mycoplasma tests	Broth/agar – aerobic & anaerobic cell culture system	Working cell bank Control harvest fluids Pre-clarified bulk
Tissue culture safety	Simian kidney & MRC-5 cell cultures	Working cell bank Control harvest fluids Pre-clarified bulk
Animal safety	Adult & suckling mouse Chick embryo (yolk sac & allantoic)	Working cell bank Pre-clarified bulk Working cell bank
General safety	Guinea pig & rabbit Guinea pig & mouse	Working cell bank Filled container
Test for hemadsorbing viruses Mycobacteria, in vitro Bovine albumin Color, appearance, form Moisture Tissue culture identity Infectivity titration	Guinea pig red blood cells Broth and medium slants Immunoassay Visual examination Coulometric method Antibody neutralization Tissue culture plaque assay	Production control cells Pre-clarified bulk Clarified bulk Filled container Filled container Filled container Clarified bulk Filled container

* This is a subset of tests performed for this product

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TESTING REQUIREMENTS FOR RELEASE OF RECOMBINANT HEPATITIS B VACCINES

Type of Test	*Test System*	*Stage of Preparation*
Plasmid retention	Percentage of host cells with expression construct	Fermentation product
Purity and identity	SDS-PAGE DNA hybridization Antigenic activity (ELISA) Protein (SDS-PAGE)	Nonadsorbed bulk Nonadsorbed bulk Nonadsorbed bulk Nonadsorbed bulk and final container
Sterility	Thioglycollate medium	Final bulk Final container
General safety	Guinea pigs and mice	Final container
Pyrogen	LAL	Final container
Purity	Total protein nitrogen Aluminium Thimerosal	Final container Final container Final container
Identity and Potency	In vivo; in vitro	Final container

VACCINI PER USO UMANO MONOVALENTI

VIRALI			BATTERICI		
Vaccino anti -	*Nome commerciale*	*Produttore*	*Vaccino anti -*	*Nome commerciale*	*Produttore*
EPATITE A	AVAXIM EPAXAL EPAXAL HAVRIX Adulti HAVRIX Bambini	SANOFI PASTEUR BIOTECH CRUCELL GLAXO-SMITHKLINE GLAXO-SMITHKLINE	HAEMOPHILUS INFLUENZAE B	ACT-Hib HIBERIX VAXEM Hib	SANOFI PASTEUR GLAXO-SMITHKLINE NOVARTIS
EPATITE B	ENGERIX-B Adulti ENGERIX-B Bambini FENDRIX HBVAXPRO Adulti HBVAXPRO Bambini HBVAXPRO Pazienti in predialisi/dialisi	GLAXO-SMITHKLINE GLAXO-SMITHKLINE GLAXO-SMITHKLINE MERCK SHARP & DOHME MERCK SHARP & DOHME MERCK SHARP & DOHME	MENINGOCOCCO	NEISVAC MENVEO MENCEVAX ACWY MENINGITEC MENJUGATE Kit	BAXTER NOVARTIS GLAXO-SMITHKLINE BERNA BIOTECH NOVARTIS
INFLUENZA	AGRIPPAL S1 FLUAD FLUARIX INFLEXAL V VAXIGRIP Adulti VAXIGRIP Bambini INFLUVAC S INFLUVAC S SOLVAY INFLUPOZZI Adiuvato INFLUPOZZI Subunità ISIGRIP ZONALE SPLIT INTANSA ISIFLU FOCETRIA	NOVARTIS NOVARTIS GLAXO-SMITHKLINE CRUCELL SANOFI PASTEUR SANOFI PASTEUR ABBOTT NOVARTIS NOVARTIS NOVARTIS SANOFI PASTEUR SANOFI PASTEUR CRUCELL NOVARTIS	PNEUMOCOCCO	PNEUMOVAX PREVENAR PREVENAR 13	MERCK SHARP & DOHME WYETH-LEDERLE WYETH-LEDERLE
HPV	CERVARIX GARDASIL	GLAXO-SMITHKLINE MERCK SHARP & DOHME	TETANO	ANATETALL IMOVAX TETANO	NOVARTIS SANOFI PASTEUR
POLIOMIELITE	POLIORAL	NOVARTIS			
VARICELLA	VARILRIX VARIVAX	GLAXO-SMITHKLINE MERCK & Co.			

VACCINI PER USO UMANO COMBINATI

VACCINI COMBINATI		
Vaccino anti -	*Nome commerciale*	*Produttore*
DIFTERITE - TETANO	DIFTVAX Adulti DIFTVAX Bambini DITANRIX Pediatrico DITANRIX Adulti DIFTETALL	SANOFI PASTEUR SANOFI PASTEUR GLAXO-SMITHKLINE GLAXO-SMITHKLINE NOVARTIS
DIFTERITE – TETANO – PERTOSSE acellulare	BOOSTRIX INFANRIX	GLAXO-SMITHKLINE GLAXO-SMITHKLINE
DIFTERITE – TETANO – POLIOMIELITE inattivato	REVAXIS	SANOFI PASTEUR
DIFTERITE – TETANO – PERTOSSE acellulare – EPATITE B ricombinante	INFANRIX HepB	GLAXO-SMITHKLINE
DIFTERITE – TETANO – PERTOSSE acellulare – POLIOMIELITE inattivato	TETRAVAC BOOSTRIX POLIO	SANOFI PASTEUR GLAXO-SMITHKLINE
DIFTERITE – TETANO – PERTOSSE acellulare – POLIOMIELITE inattivato – HAEMOPHILUS INFLUENZAE B	PENTAVAC	SANOFI PASTEUR
DIFTERITE – TETANO – PERTOSSE acellulare – POLIOMIELITE inattivato – EPATITE B ricombinante - HAEMOPHILUS INFLUENZAE B	INFANRIX HEXA	GLAXO-SMITHKLINE
EPATITE A - EPATITE B ricombinante	TWINRIX Adulti TWINRIX Pediatrico	GLAXO-SMITHKLINE GLAXO-SMITHKLINE
MORBILLO - ROSOLIA	MORUVIRATEN	BERNA
MORBILLO – ROSOLIA - PAROTITE	PRIORIX MMR VAX PRO	GLAXO-SMITHKLINE MERCK & Co.
MORBILLO – ROSOLIA – PAROTITE - VARICELLA	PRIORIX TETRA	GLAXO-SMITHKLINE

CONCLUSIONI

- Un complesso e strettamente regolamentato sistema autorizzativo e di sorveglianza è attivo in Europa per i vaccini per uso umano e loro applicazioni nelle campagne vaccinali

- Gli Organismi Internazionali Europei e Nazionali coinvolti operano in stretto coordinamento con il contributo di gruppi tecnici di antica e di recente istituzione e sono costituiti da esperti di tutti i settori disciplinari coinvolti

- Tali strutture rappresentano un'importante strumento per il successo dei piani di vaccinazione