H5N1 vaccine in Hungary
Development, evaluation, production

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Background

INTERPANDEMIC

INFLUENZA

VACCINE

PRODUCTION

„ A purified precipitated virus obtained by a new, simple method.”

Gy. Takátsy, Acta Microbiol. Hung. 1953.

Dr Gyula Takátsy
1914-1980

Registration of FLUVAL^{AB} influenza vaccine,
Onminvest Ltd; 1995
Registration number:
National Institute of Pharmacy,
Hungary: OGYI-T-8998/01.

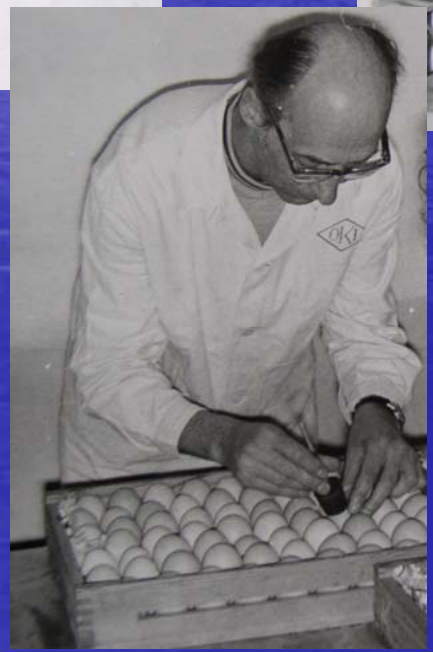
FLUVAL AB

Active ingredient:
Influenza A/New Caledonia/20/99(H1N1) min. 15 µg HA,
Influenza A/NYHC(H3N2) min. 15 µg HA
Influenza B/Shanghai/361/02 min. 15 µg HA.

Adjuvant:

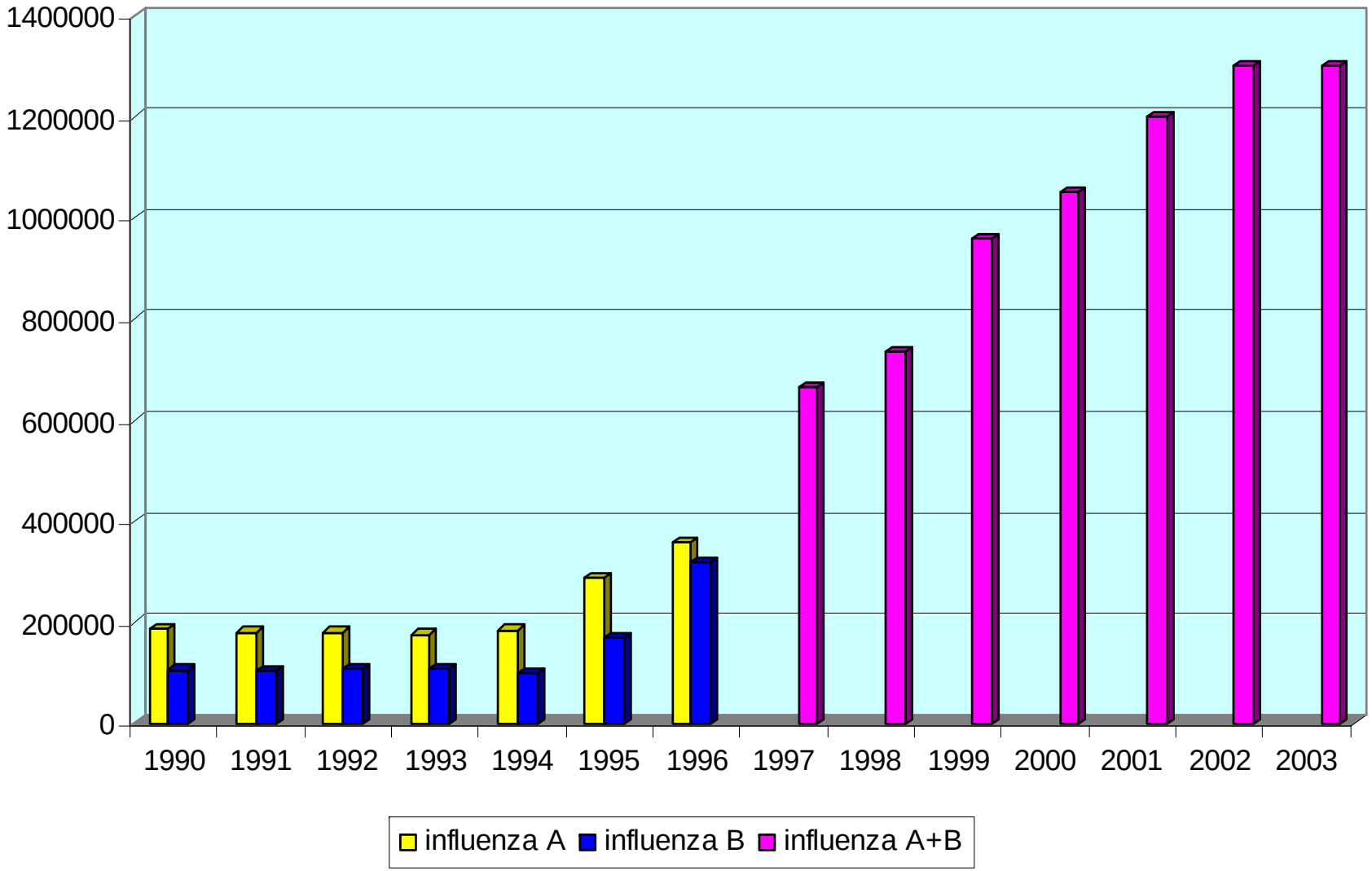
Al*** (in AlPO4 form)	Ph.Hg.VII.	0,25 mg
NaCl	Ph.Hg.VII.	1,66 mg
KCl	Ph.Hg.VII.	0,04 mg
KH2PO4	Ph.Hg.VII.	0,31 mg
Na2HPO4 x 2H2O	Ph.Hg.VII	0,19 mg
Merthiolát	Ph.Hg.VII.	0,05 mg
Aqua destillata pro inj.	Ph.Hg.VII	ad 0,5 ml

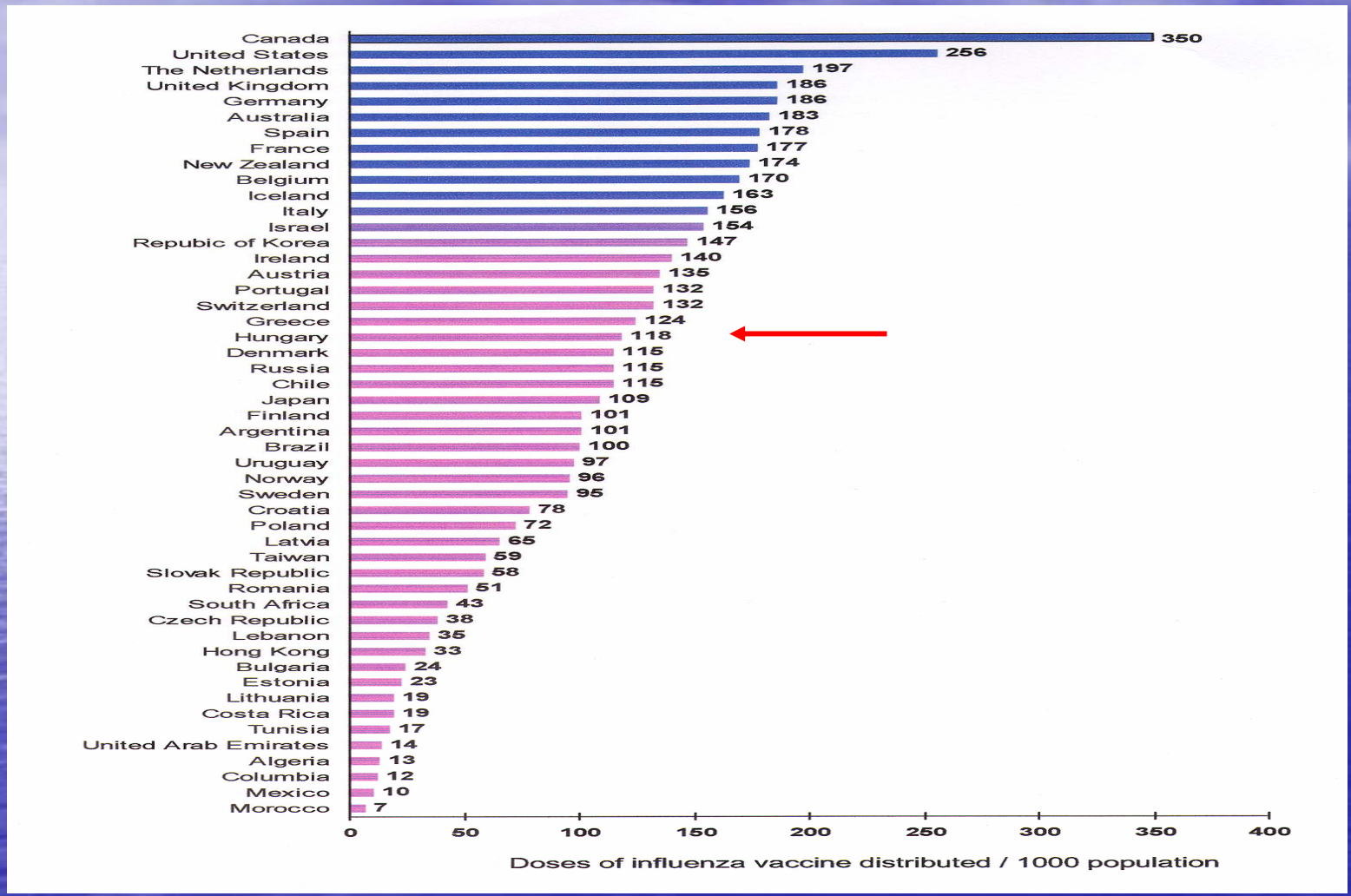
INFLUENZA VACCINE PRODUCTION
1972, HUNGARY

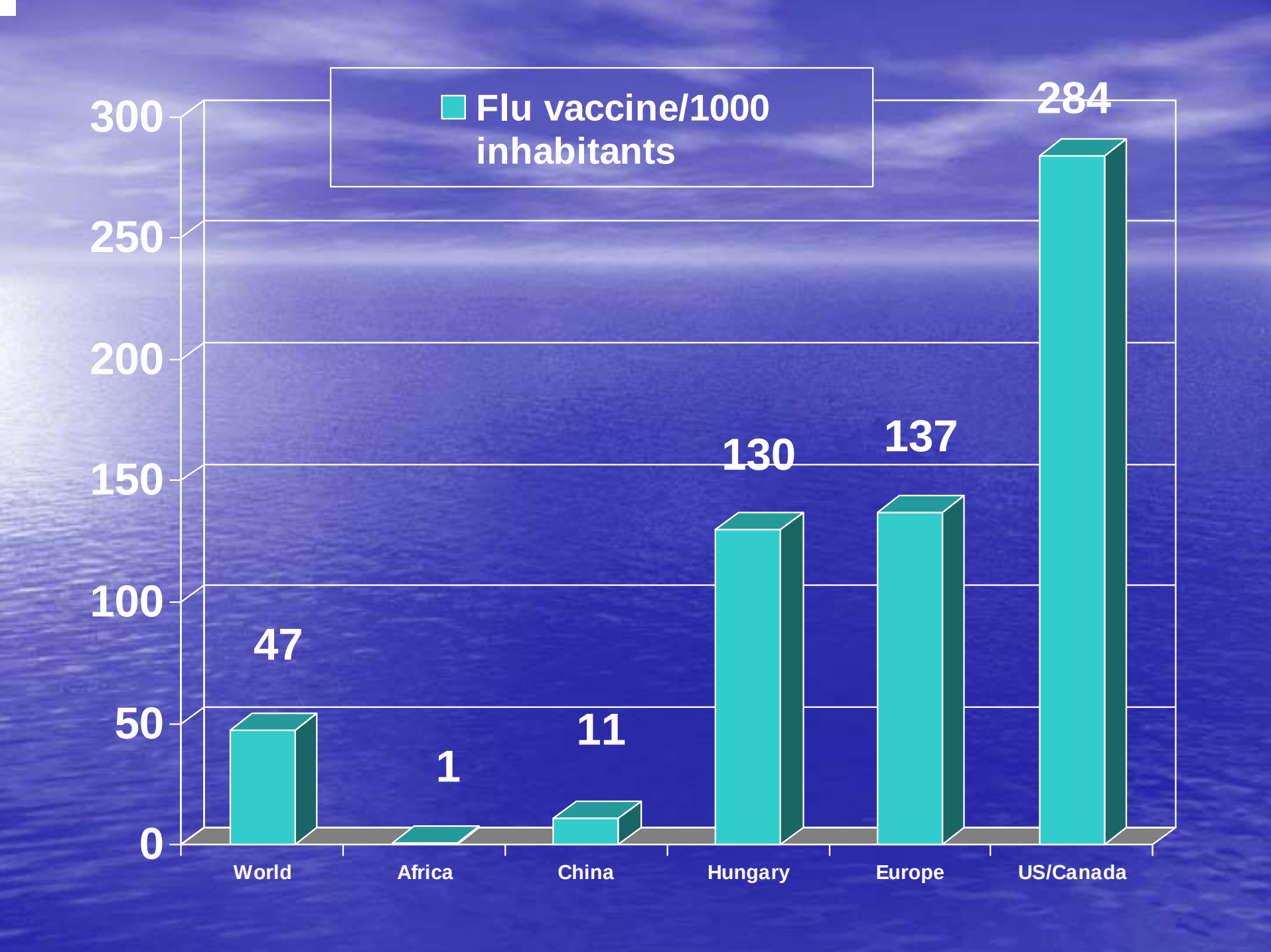


INFLUENZA VACCINE PRODUCTION
1995, HUNGARY

Coverage of Vaccination 1990-2003, Hungary




Canada 350
United States 256
The Netherlands 197
United Kingdom 186
Germany 186
Australia 183
Spain 178
France 177
New Zealand 174
Belgium 170
Iceland 163
Italy 156
Israel 154
Republic of Korea 147
Ireland 140
Austria 135
Portugal 132
Switzerland 132
Greece 124
Hungary 118
Denmark 115
Russia 115
Chile 115
Japan 109
Finland 101
Argentina 101
Brazil 100
Uruguay 97
Norway 96
Sweden 95
Croatia 78
Poland 72
Latvia 65
Taiwan 59
Slovak Republic 58
Romania 51
South Africa 43
Czech Republic 38
Lebanon 35
Hong Kong 33
Bulgaria 24
Estonia 23
Lithuania 19
Costa Rica 19
Tunisia 17
United Arab Emirates 14
Algeria 13
Columbia 12
Mexico 10
Morocco 7
0 50 100 150 200 250 300 350 400
Doses of influenza vaccine distributed / 1000 population


Flu vaccine/1000 inhabitants
300
250
200
150
100
50
0
47
1
11
130
137
284
World
Africa
China
Hungary
Europe
US/Canada

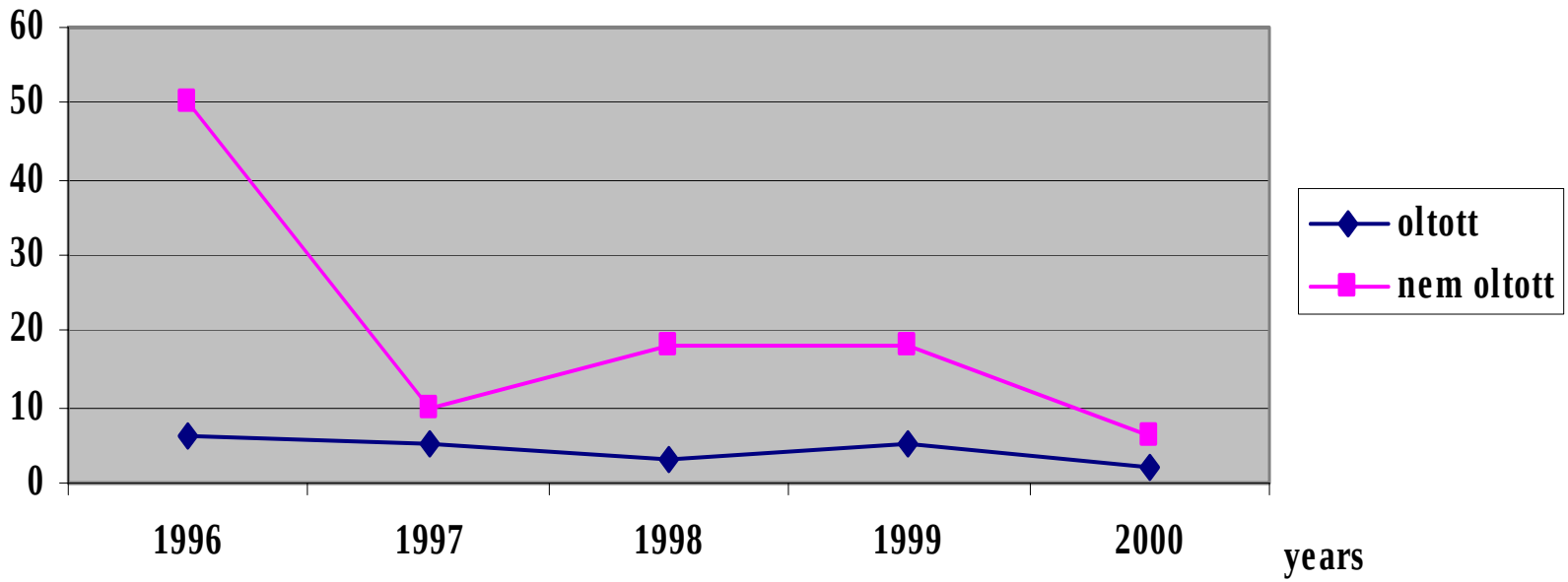
ANNUAL UPDATE STUDIES AND CHMP CRITERIA FOR IMMUNOGENECITY OF FLUVALAB IN HEALTHY ADULTS

YEAR	strain (sub-) type	Seroprotection Rate	Seroconversion /4-fold /Increase rate	Mean fold Increase	CHMP Requirement met
		CHMP criteria			
		> 70 %	> 40 %	>2,5	
1997	A/H1N1	84 % +	41 % +	3,0 +	YES
	A/H3N2	85 % +	46 % +	3,4 +	
	B	75 % +	43 % +	3,3 +	
1998	A/H1N1	86 % +	56 % +	4,7 +	YES
	A/H3N2	82 % +	50 % +	3,6 +	
	B	86 % +	68 % +	4,2 +	
2000	A/H1N1	84 % +	72 % +	3,5 +	YES
	A/H3N2	70 % -	56 % +	3,3 +	
	B	72 % +	62 % +	3,0 +	
2001	A/H1N1	84 % +	47 % +	3,4 +	YES
	A/H3N2	84 % +	46 % +	3,1 +	
	B	79 % +	49 % +	3,4 +	
2002	A/H1N1	88 % +	62 % +	3,3 +	YES
	A/H3N2	90 % +	66 % +	3,9 +	
	B	80 % +	54 % +	3,9 +	
2005	A/H1N1	72 % +	46 % +	3,38 +	YES
	A/H3N2	76 % +	54 % +	2,56 +	
	B	86 % +	48 % +	3,68 +	

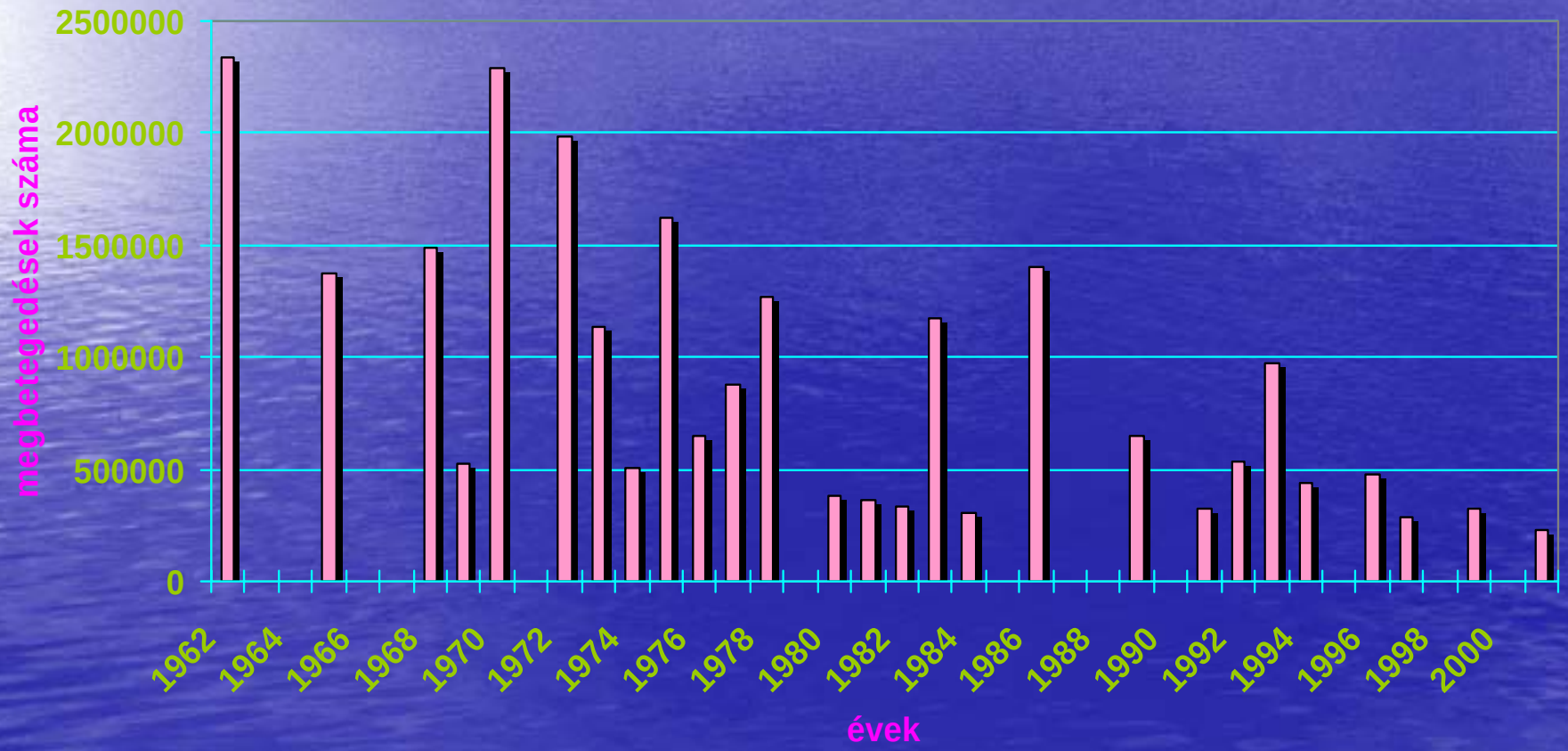
ANNUAL UPDATE STUDIES AND CHMP CRITERIA FOR IMMUNOGENECITY OF FLUVALAB IN ELDERLY

YEAR	strain (sub-) type	Seroprotection Rate	Seroconversion /4-fold /Increase rate	Mean fold Increase	CHMP Requirement met
		CHMP criteria			
		> 60 %	> 30 %	>2,0	
1997	A/H1N1	52 % -	32 % +	2,9 +	YES
	A/H3N2	68 % +	38 % +	2,8 +	
	B	58 % -	31 % +	3,1 +	
1998	A/H1N1	62 % +	36 % +	2,9 +	YES
	A/H3N2	70 % +	44 % +	2,7 +	
	B	78 % +	58 % +	4,0 +	
2000	A/H1N1	68 % +	44 % +	2,6 +	YES
	A/H3N2	70 % +	52 % +	2,8 +	
	B	74 % +	56 % +	2,8 +	
2001	A/H1N1	67 % +	40 % +	2,9 +	YES
	A/H3N2	69 % +	38 % +	2,8 +	
	B	70 % +	41 % +	2,7 +	
2002	A/H1N1	72 % +	38 % +	3,1 +	YES
	A/H3N2	82 % +	36 % +	3,2 +	
	B	88 % +	44 % +	3,9 +	
2005	A/H1N1	72 % +	36 % +	3,29 +	YES
	A/H3N2	70 % +	32 % +	3,07 +	
	B	84 % +	38 % +	3,16 +	

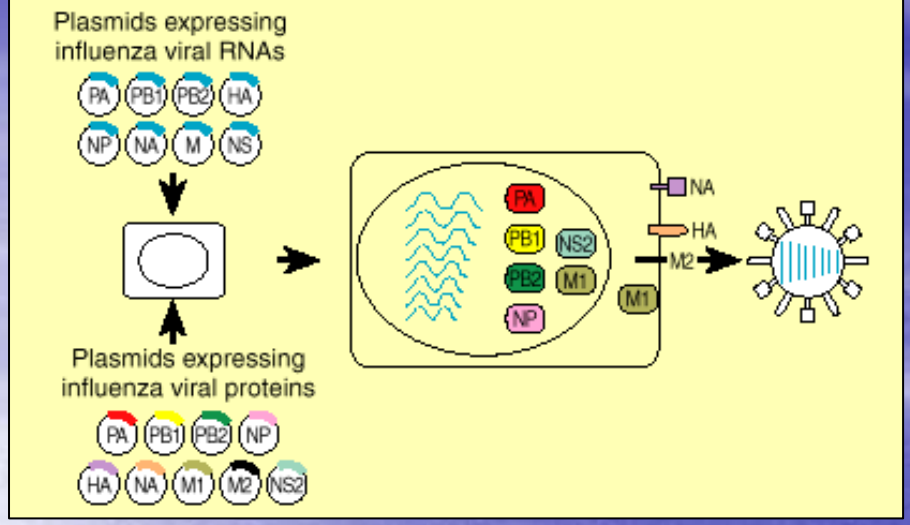
Influenza megbetegedések kumulatív incidencia hánya da az oltottak és oltatlanok csoportjában



Flu epidemics in Hungary
1962-2001



H5N1 vaccine in Hungary



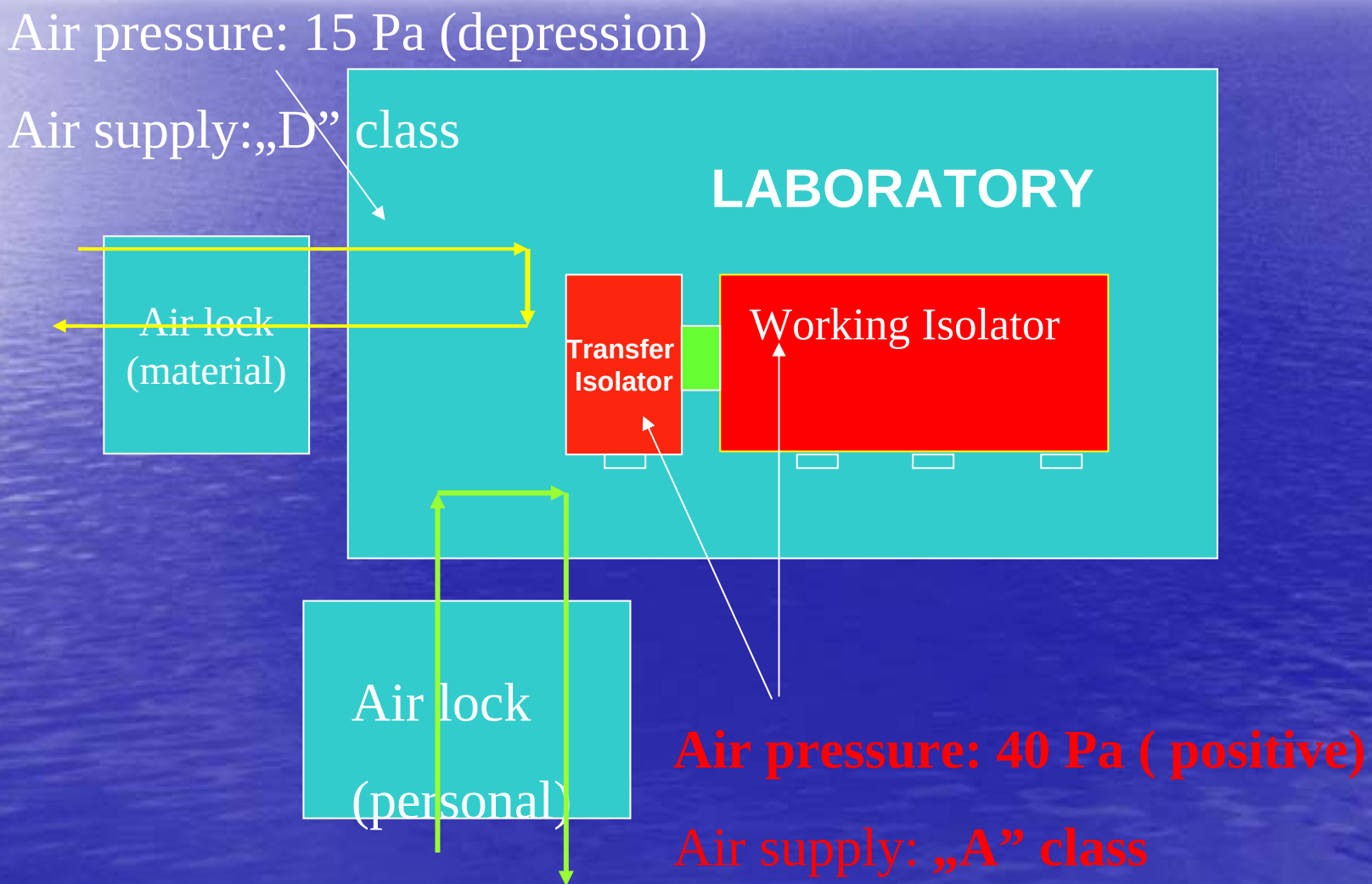
- **Virus:** (NIBRG-14) .

Virus description: a reverse genetics derived 2:6 reassortant between A/Viet Nam/1194/2004 (H5N1) and PR8.

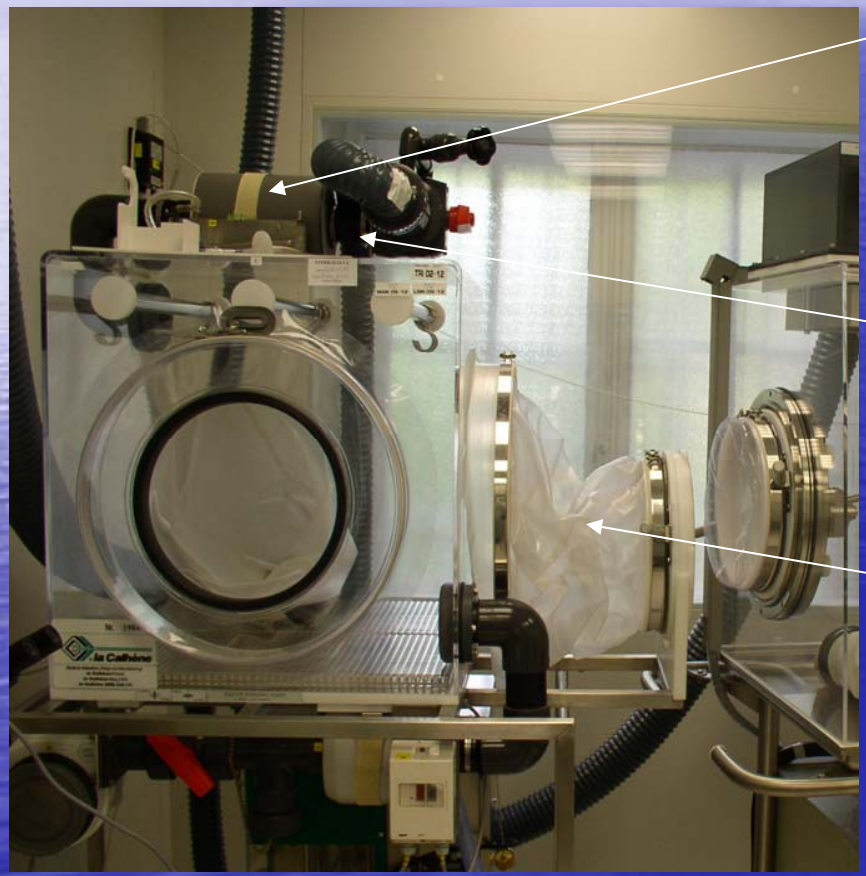
Passage history:Vero1, Egg2

- Virus was obtained from NIBSC, London, kindly supplied by Prof. Dr. J. Wood.
- May, 2005

BSL2+ laboratory



TRANSFER IZOLATOR



- Pressure detector
- HEPA filters
- Material air-lockó

WORKING IZOLATOR

- Pressure detector
- HEPA filters
- Gloves
- Particule detector
- Air-lock joint

Protection of laboratory workers

Immunogenecity of whole virus vaccine in mouse

Immunization	Animal	HI titer			
H5N1 antigen A NIBRG-14 - 92 µg total virus protein/dose (approx. 30 µg HA) 0,31 mg Al (in $AlPO_4$ form)		H1	H3	B	H5
	1	5	5	5	160
	2	5	5	5	160
	3	5	5	5	160
	4	5	5	5	80
	5	5	5	5	160
	GMT	5	5	5	139
Control vaccine FLUVAL AB	1	160	320	320	5
Control vaccine FLUVAL AB	2	320	320	320	5

Immunogenecity of whole virus vaccine in guinea pigs

Immunization	Animal	HI titer			
H5N1 antigen A NIBRG-14 - 92 µg total virus protein/dose (approx. 30 µg HA) 0,31 mg Al (in $AlPO_4$ form)		H1	H3	B	H5
	1	5	5	5	80
	2	5	5	5	160
	3	5	5	5	160
	4	5	5	5	80
	5	5	5	5	80
	GMT	5	5	5	105
Control vaccine FLUVAL AB	1	160	320	320	5
Control vaccine FLUVAL AB	2	320	320	320	5

- **CLINICAL TRIAL PHASE IV. PROTOCOL**

- **NIBRG-14 H5N1 01-2005 avian influenza virus mock-up vaccine provided by WHO based on recommendation for pandemic preparedness**

- **PERMISSION NUMBER: 19147/05 AD 19071/40/2005**

  NATIONAL INSTITUTE OF PHARMACY, HUNGARY

AIM OF THE TRIAL

- to carry out serological tests for mock up vaccine based on WHO recommendation to obtain data for the new active ingredient of the vaccine in consideration of lack of available data

- ***Eligibility criteria:***
  - voluntary enrollment,
  - age over 18,
  - signed written consent of voluntary statement

- ***Exclusion criteria:***
  - diseased condition with fever,
  - pregnancy,
  - allergy to egg proteins or to one of the component of the vaccine

- ***Study procedure***:
  - planned sample size 50-150.
  - The enrolled eligible healthy voluntareer undergoes data recording, medical examination and blood sampling for immunological tests on the day 0.
  - Rapid test is carried out for exclusion of gravidity among women younger than 60, since gravidity is an exlusion criteria. On the day 21 medical examination and blood sampling is performed for immunological tests.
  - On the day 90 and 180 medical examination and blood sampling carried out to check possible side effects and for immunological tests.

- Serological data

The following serological assessments will be performed and one of the assessments should meet the indicated requirements:

Number of seroconversions or significant increase in antihaemagglutinin antibody titre >40%

Mean geometric increase >2.5

The proportion of subjects achieving an HI titre $\geq$ 40 should be > 70%

Immunization	Personal Code	HI titer	
		Pre-vaccinated	Post-vaccinated
H5N1 antigen A/NIBRG-14 92 µg total virus protein/dose (approx. 30 µg HA) 0,31 mg Al (in $AlPO_4$ form)	001	5	80
	002	5	160
	003	5	80
	004	5	40
	005	5	40
	006	5	80
	007	5	5
	008	5	5
	009	5	40
	010	5	40
	011	5	40
	012	5	80
	013	5	40
	014	5	40
	015	5	40
	016	5	40
	017	5	80
	018	5	80
	019	5	40
	020	5	40
	GMT	5	42,87

Preliminary evaluation

Number of seroconversions or significant increase in antihaemagglutinin antibody titre >40%

90%

Mean geometric increase >2.5

8,57

The proportion of subjects achieving an HI titre ≥ 40 should be > 70%

90%

Final evaluation

- November – December 2005:
  - Process validation
- February 2006
  - Data evaluation after endpoint (days 180) of clinical trial

Acknowledgements

WHO

NIBSC