

Development of Inflexal[®]V

From history to presence

10 Years Anniversary Inflexal[®] Symposium
Hotel Allegro Kursaal, Bern, Switzerland
April 25-27, 2007

Reinhard Glueck
Executive Vice President R&D,
Vaccine Discovery,
Crucell - Berna Biotech
President Etna Biotech
President Swiss Biotech Association



Introduction

- The idea to develop a new alternative influenza vaccine evolved from different fields of scientific operations:
 - investigations of the biological fusion process of influenza virus
 - studies to investigate the influence of the biological fusion process
 - immunological investigations of different forms of antigenic presentation of the HA (all virus, subunit)

J. Biological Chemistry, 1996

THE JOURNAL OF BIOLOGICAL CHEMISTRY
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Vol. 271, No. 23, Issue of June 7, pp. 14117-14121, 1996
Printed in U.S.A.

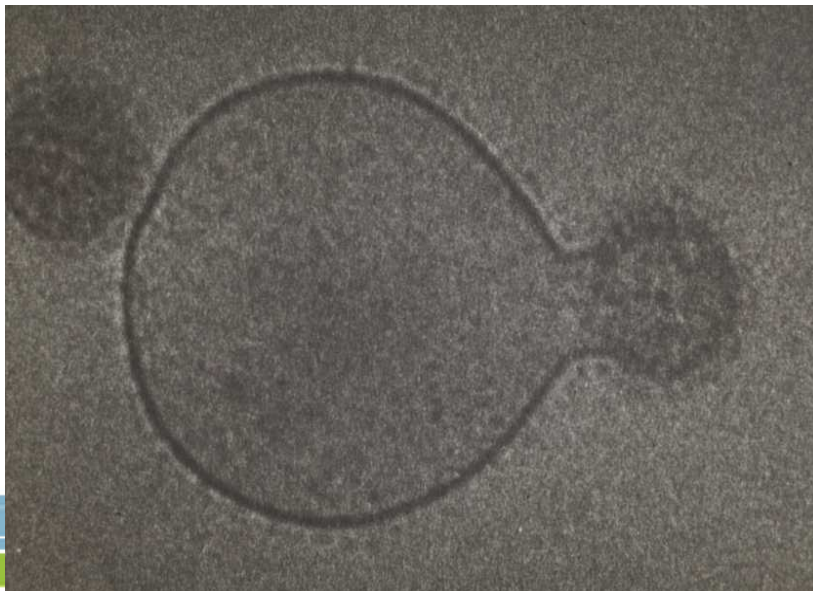
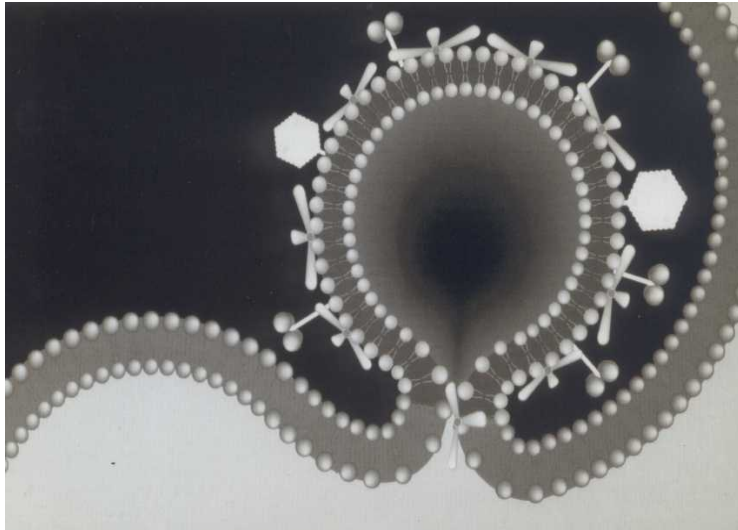
H⁺-induced Membrane Insertion of Influenza Virus Hemagglutinin Involves the HA2 Amino-terminal Fusion Peptide but Not the Coiled Coil Region*

(Received for publication, December 26, 1995, and in revised form, March 14, 1996)

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Biological fusion of influenza virosomes with target membranes



Fusion is catalysed by influenza envelope glycoprotein (hemagglutinin). The fusion protein of influenza virus is best characterized and has provided the paradigm for virus fusion proteins

P. Dürrer et al. The J. Biolol. Chemistry, 271, 23, 13417-13421, 1996

Importance of biological fusion capacity on the growth of influenza virus

Antiviral Research 14 (1990) 39–50
Elsevier

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AVR 00427

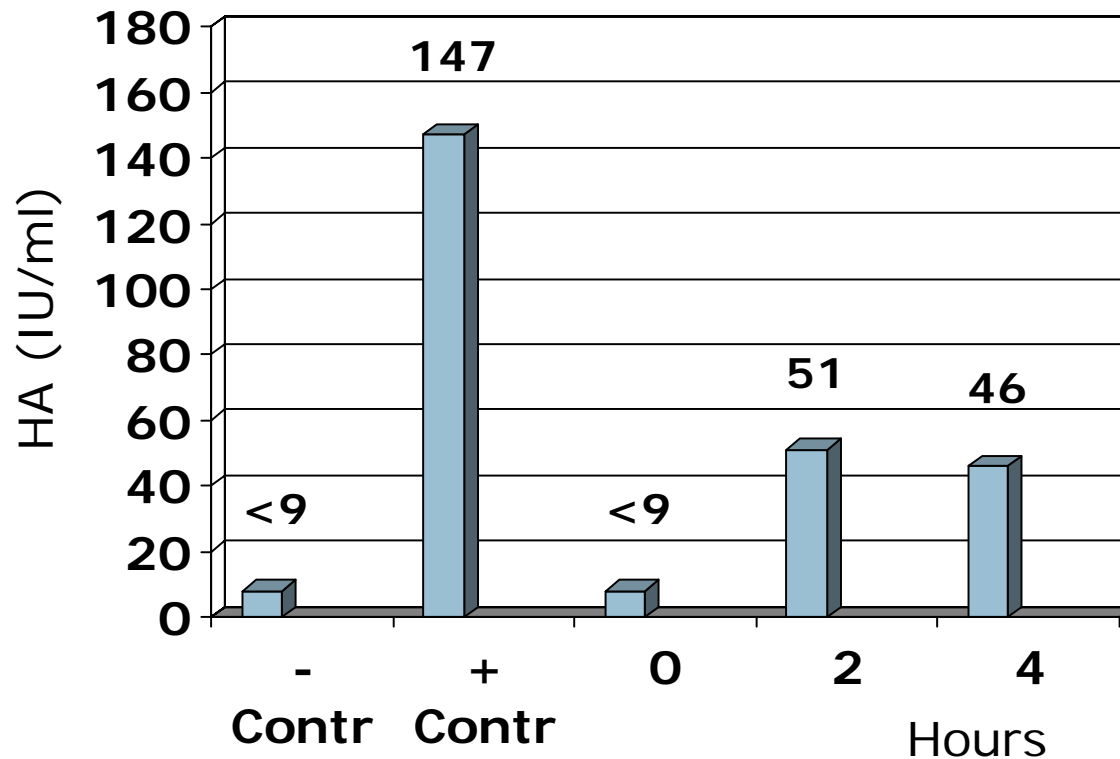
Dextran sulfate inhibits the fusion of influenza virus with model membranes, and suppresses influenza virus replication in vivo

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(Received 7 December 1989; accepted 29 March 1990)

Importance of biological fusion capacity on the growth of influenza virus



Effect of dextran sulfate on production of influenza A virus. Dextran sulfate was added at either 0, 2 or 4 h after infection.

Lüscher-Mattli M. et al, Antiviral Research 14, 39-50, 1990

Importance of biological fusion capacity on the growth of influenza virus

Arch Virol (1993) 130: 317–326

Archives
of
Virology
Springer-Verlag 1993
Printed in Austria

A comparative study of the effect of dextran sulfate on the fusion and the in vitro replication of influenza A and B, Semliki Forest, vesicular stomatitis, rabies, Sendai, and mumps virus

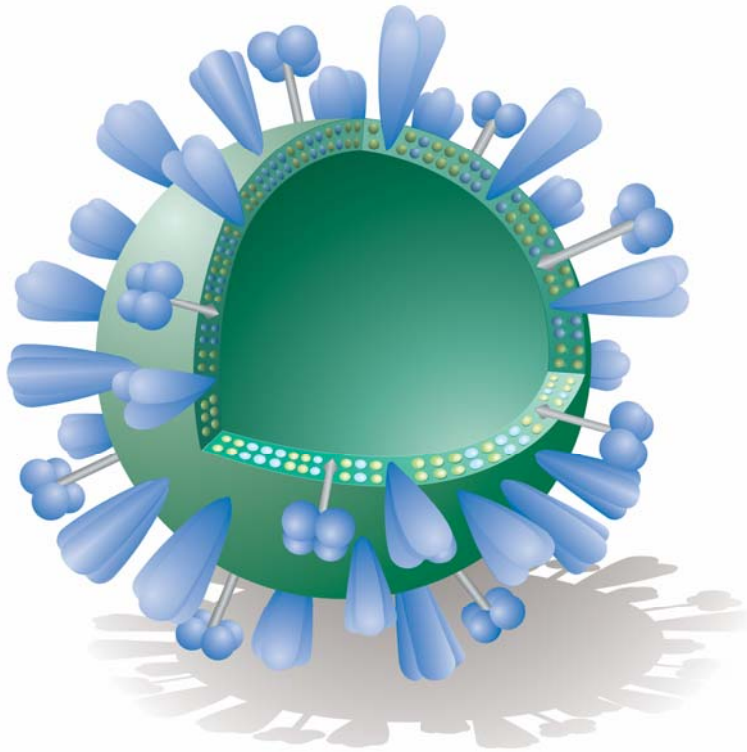
M. Lüscher-Mattli¹, R. Glück², C. Kempf¹, and M. Zanoni-Grassi²

¹ Institute of Biochemistry, University of Berne

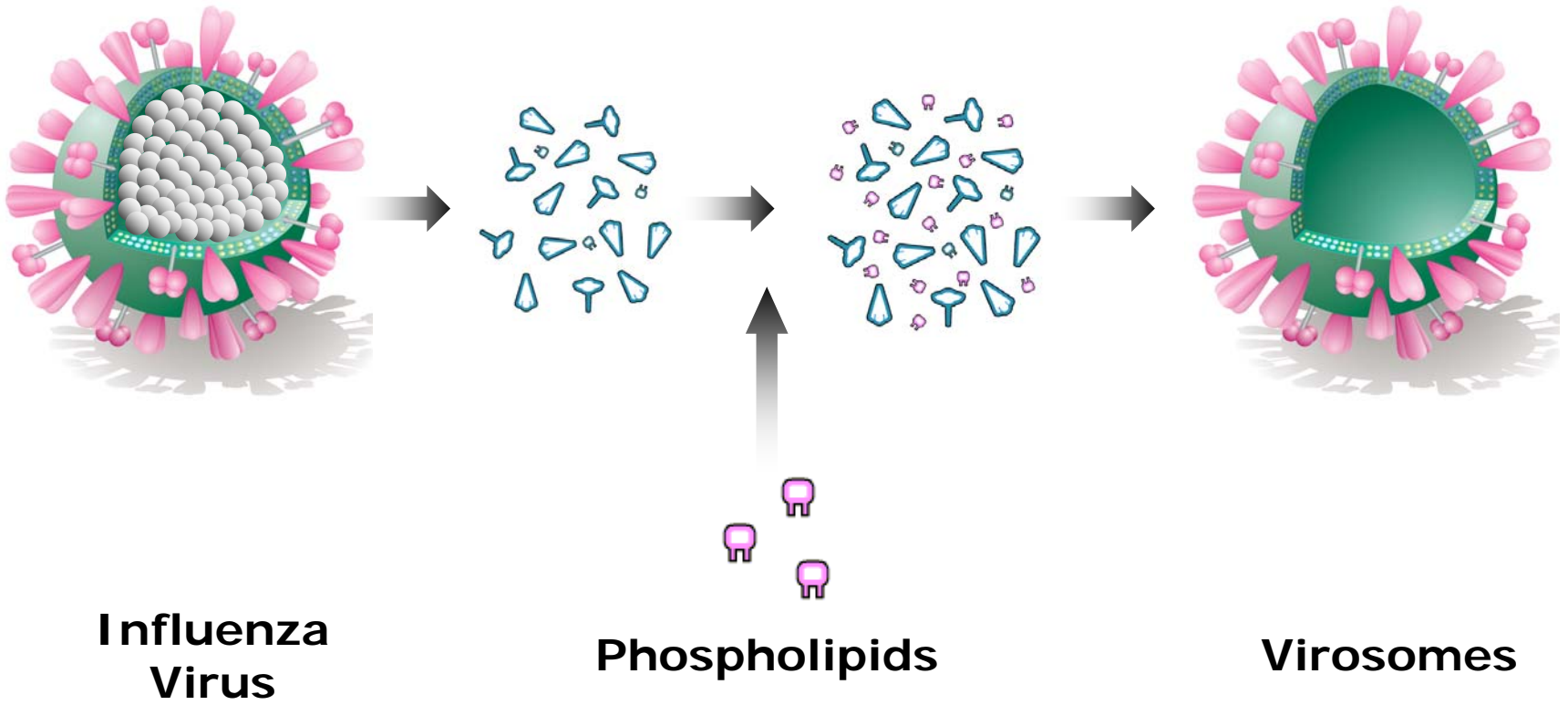
² Swiss Serum and Vaccine Institute, Berne, Switzerland

Accepted December 10, 1992

Influenza virosomes



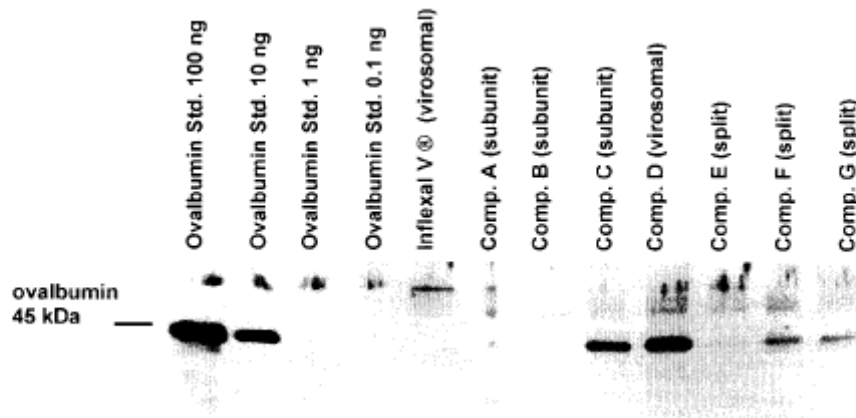
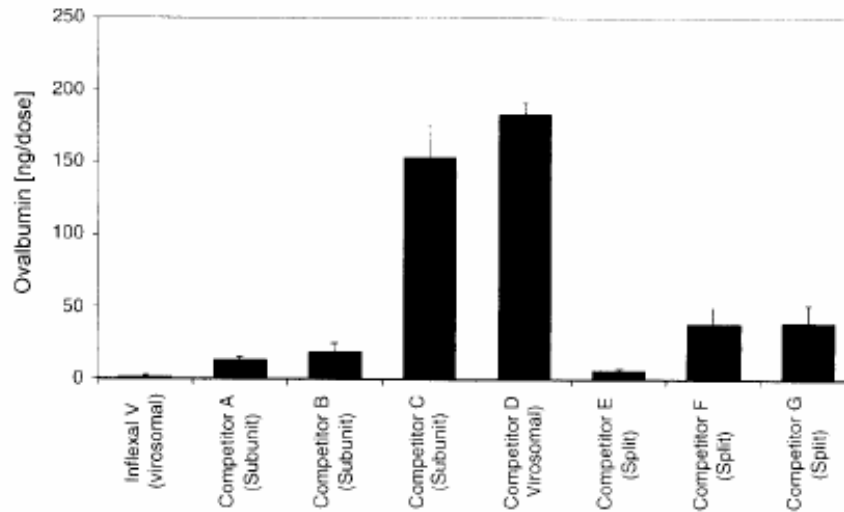
Inflexal V



Comparison of different flu vaccines season 2000/2001

Vaccine Type	Lot No.	HA A/NC µg/mL	HA A/Pa µg/mL	HA B/Ya µg/mL	Detergent	ppm OvA/ 1 µg HA	V-Size nm
Split	18514C9	32,8	35,1	30,2	Positive	100	122,1
Split	18531A9	31,8	33,1	30,3	Positive	63	126,7
Split	030021	10,1	14,5	10,0	Negative	404	252,8
Subunit adjuvanted	1402	34,2	31,9	32,7	Negative	1190	178,6
Subunit	R-0805	34,3	28,9	32,6	Negative	750	93,4
Inflexal V	00IVFB32	34,3	30,9	32,1	Negative	51	162,9

Inflexal V - the influenza vaccine with the lowest ovalbumin content



Kürsteiner O. et al, Vaccine 24, 6632-6635, 2006

Inflexal V

- First influenza vaccine worldwide based on the patented virosomal technology
- > 34 million doses distributed since 1997 worldwide
- October 2001: positive outcome of the European 'Mutual Recognition Procedure'
- Licensed in 43 countries worldwide

EMA assessment criteria for influenza vaccine immunogenicity

Parameters	18-60 years	> 60 years
Seroprotection (SP) [#] rate	> 70%	> 60%
Seroconversion (SC) [*] rate	> 40%	> 30%
GMT fold-increase	> 2.5	> 2.0

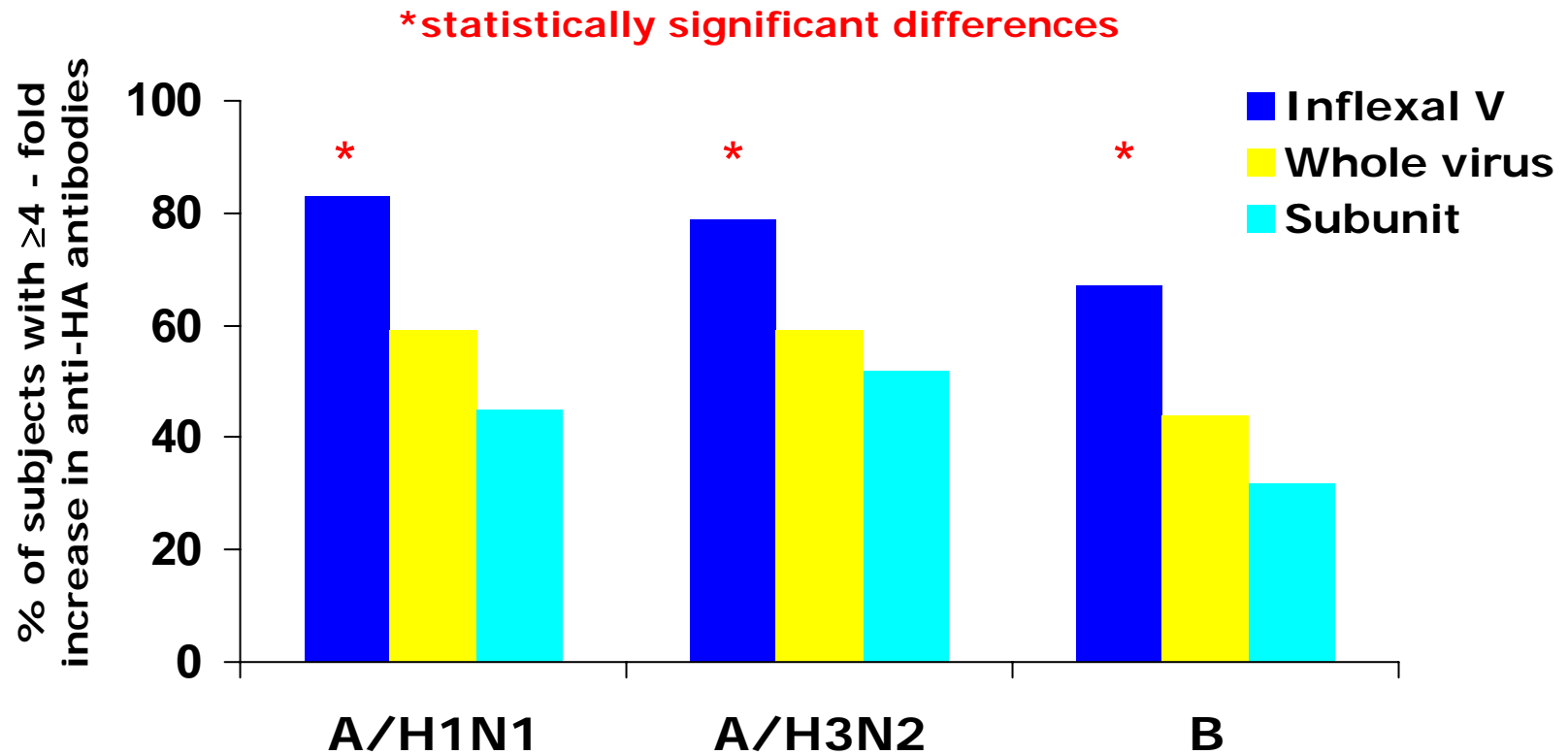
SP = HI antibody titer of $\geq 1:40$

* SC = ≥ 4 -fold increase and achievement of $\geq 1:40$ in HI antibody titer

NOTE: To confirm immunogenicity, at least one of the above described criteria has to be met for each influenza strain

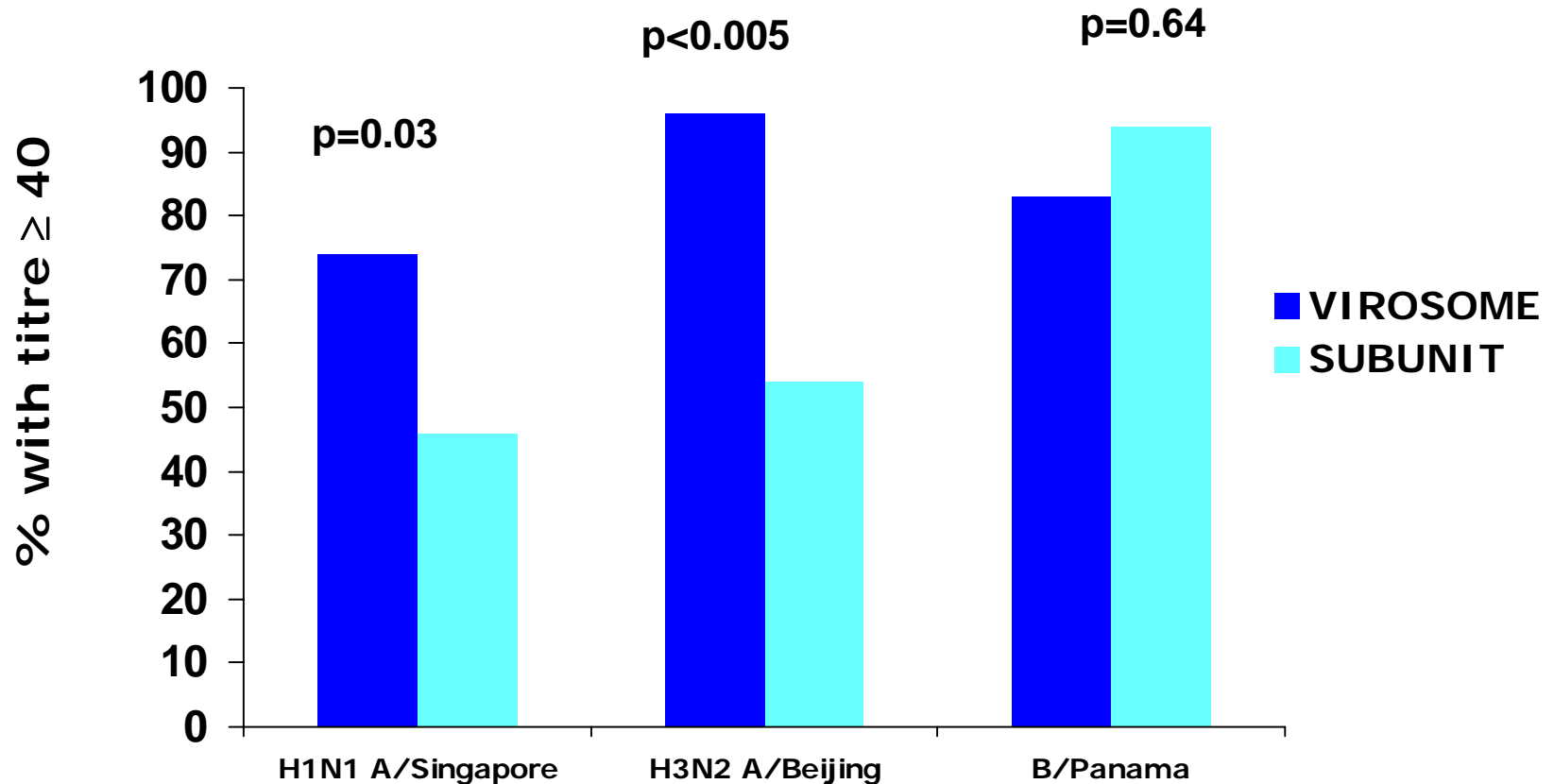
Inflexal V: immunogenicity

Superior immunogenicity compared to conventional vaccine types



Inflexal V: immunogenicity and tolerability

Superior immunogenicity and tolerability in elderly people compared to Influvac (subunit vaccine)



Solicited local tolerability: adults

Symptom	Inflexal V® (n=51)	Fluarix® (n=50)
Pain/tenderness	51.0%	60.0%
Induration	17.6%	38.0%
Redness	7.8%	20.0%
Bruising	2.0%	2.0%

Solicited local tolerability: elderly

Symptom	Inflexal V® (n=23)	Fluarix® (n=24)
Pain/tenderness	0.0%	16.7%
Induration	4.3%	16.7%
Redness	4.3%	16.7%
Bruising	4.3%	4.2%

Investigator driven studies

Pregliasco et al., Aging Clin Exp Res 2001

Objective: immunogenicity and safety of three commercial influenza vaccines in elderly

Design: prospective, observer-blinded, randomized, multicenter

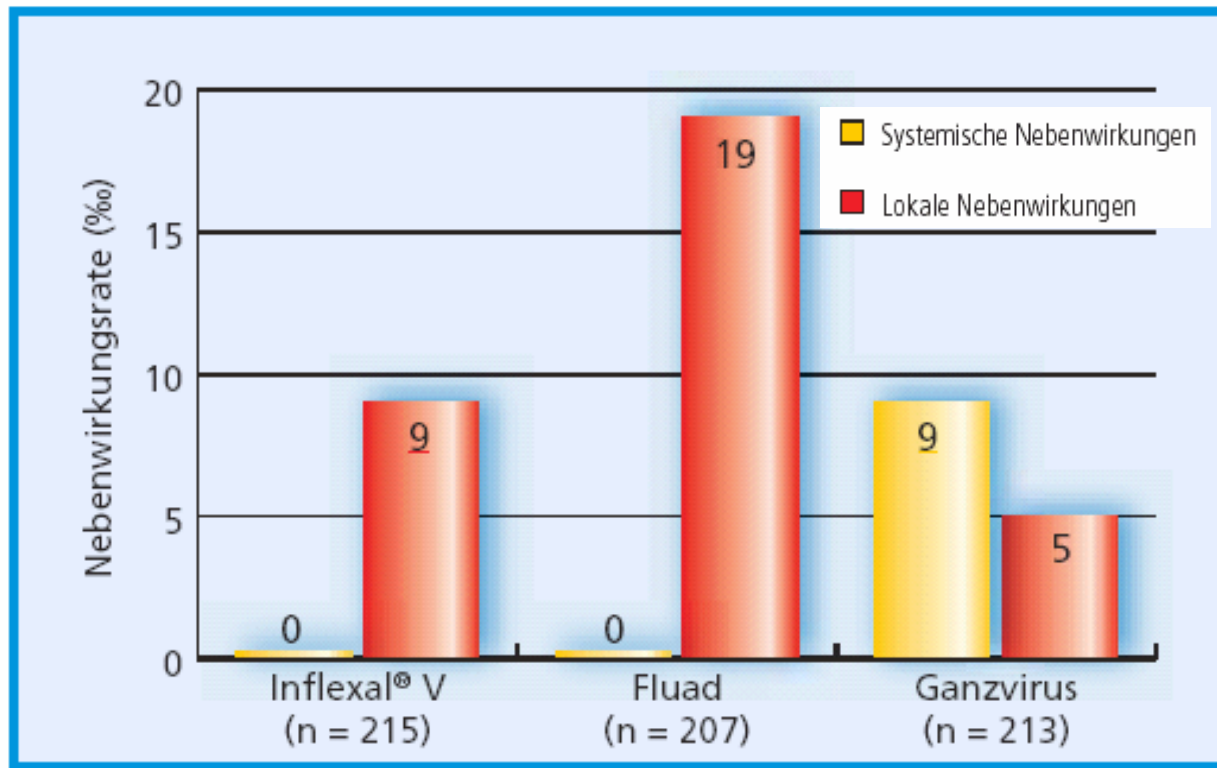
Study groups:

Inflexal Berna	213
Inflexal V	215
Fluad	207

Immunogenicity: virosomal subunit vaccine is better in terms of HI antibody titers

Safety: all vaccines considered to be safe

Immunogenicity and safety of three commercial influenza vaccines in institutionalised elderly



Investigator driven studies

Amendola et al., J Med Virol 2002

Objective: immunogenicity of Inflexal V in HIV pos. and HIV neg. former intravenous drug users

Study groups:

HIV neg	337
HIV pos	72

Immunogenicity: HI response HIV neg > HIV pos

Safety: well tolerated

HIV-infected children and Inflexal V

N = 23 (20x CDC class 1; 3x CDC class 2)

median age 7.2 yrs

one month follow-up for immunogenicity

three months follow-up for safety/flu-like illness

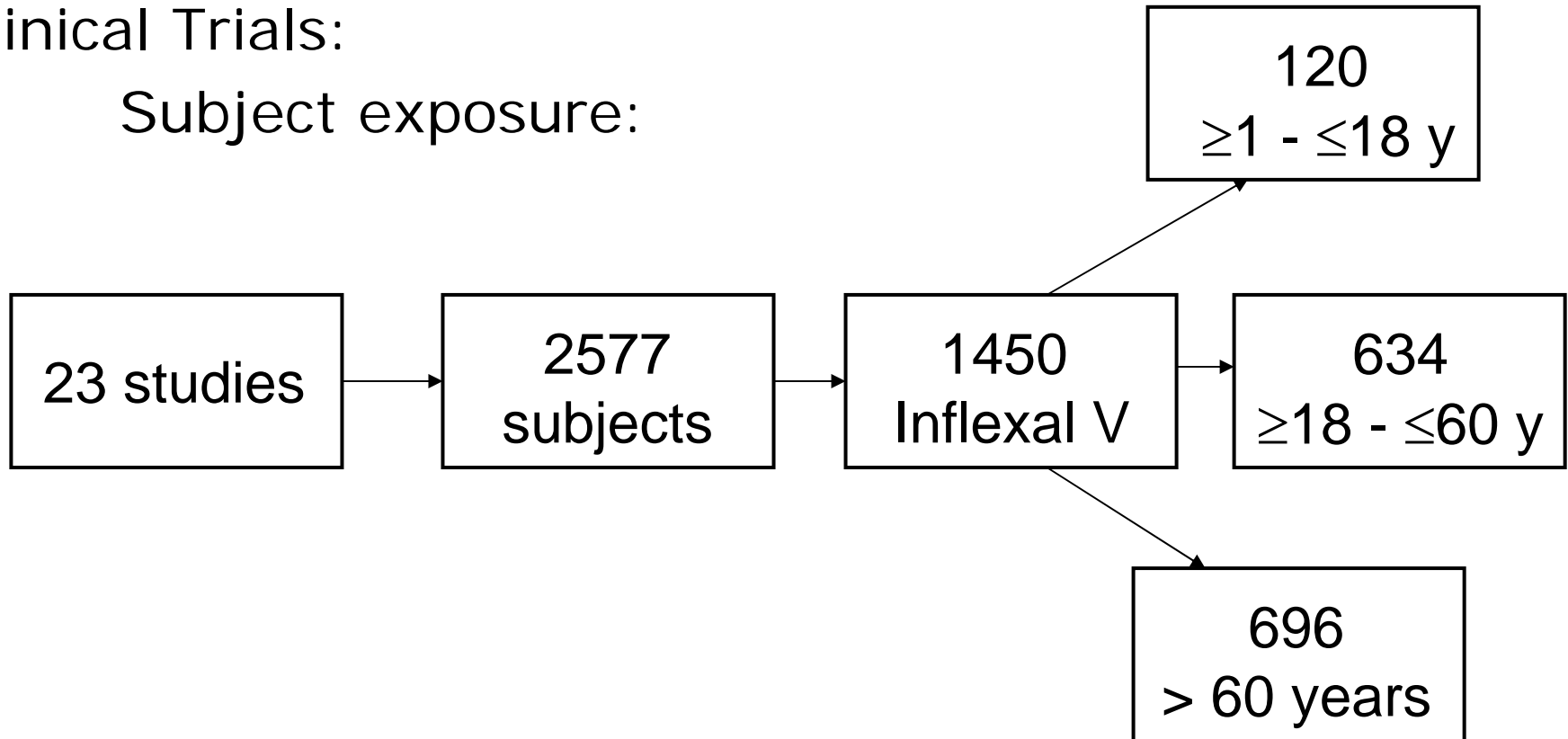
	H3N2		H1N1		B	
GMT	base	1 month	base	1 month	base	1 month
	13.5	70.9	5.8	24.7	9.1	34.4
Seroprotection	82.60%		56.60%		60.90%	
Seroconversion	73.90%		56.50%		52.20%	

Vaccination well tolerated, no influenza or ILI during 3 months follow-up. No significant changes were observed regarding the CD4+ count and viral load

Inflexal V

Clinical Trials:

Subject exposure:



Postmarketing surveillance (10/1997 - 4/2002)

Subject exposure:

approx. 34 million doses sold since 1997

Spontaneous ADR reporting rate:

50 cases (13 serious) involving /10 million sold
113 adverse symptoms (22 serious)
/10million sold

overall 1.02 cases / 100'000 doses sold
(0.69 - 1.65 cases / 100'000 doses sold)

Inflexal V

- Optimal antigen presentation
- Maximal purity
- Biologically degradable
- Without preservatives (thiomersal)
- Data from clinical trials and from postmarketing experience affirm:
 - Optimal immunogenicity & protective efficacy
 - Optimal tolerability