Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG)

Vraag en antwoord Griepvaccinatie

Pieter Neels, MD
CHMP Member
Vice-Chair Vaccine Working Party

18/02/2011

Vraag 1

Bestaat er onafhankelijk, dubbelblind, gerandomiseerd en placebo geïmpliceerd onderzoek dat aantoont dat een vaccinatie zin heeft, dwz dat de persoon zelf beschermd is en ook dat hij zijn omgeving niet meer kan besmetten?

Deze vraag werd gesteld met kritiek op de griepvaccins, het antwoord zal dan ook hoofdzakelijk over griepvaccinatie gaan.

Vraag 1

De vraag in vier stukken:

1. **Wat is onafhankelijk onderzoek?**
2. **Is prospectief placebo gecontroleerd dubbel blind onderzoek alleen zaligmakend?**
3. **Welke evidentie is er?**
4. **Kan iemand zijn omgeving besmetten?**

Vraag 1

4. **Kan iemand zijn omgeving besmetten?**
   - **In België: alle griepvaccins op de markt zijn split vaccins**
   - **In EU tijdens pandemie, 1 whole cell inactivated, Celvapan**

⇒ **Dode materie: kan niemand anders infecteren**

   - **In EU 1 levend geattenueerd griepvaccin geregistreerd, maar (nog) niet op de markt, Fluenz**

Vraag 1

1. **Wat is onafhankelijk onderzoek?**
   - **Geen sponsoring**
   - **Geen geld voor voordrachten**
   - **Geen aandelen in firma's**
   - **Partner/kinderen niet in industrie, noch aandelen (wat met maîtresse?)**

Iemand zonder financieel "Conflict of Interest" kan wel een "Intellectueel Conflict of Interest" hebben: de drang om te scoren is soms groter dan de drang om eerlijk te zijn…

Vraag 1

1. **Wat is onafhankelijk onderzoek?**
   - **Wetenschappelijk onderzoek, placebo gecontroleerd, dubbel blind**

= **Duur, zeer duur**

Wie kan miljoenen euro's op tafel leggen?

Dit soort onderzoek is zeer duur: om een verschil te kunnen aantonen dient men duizenden patiënten te includeren, dus het gaat over miljoenen €'s!

Via PPP's: Public Private Partnership

Vraag 1

2. Is prospectief placebo gecontroleerd dubbel blind onderzoek alleen zaligmakend?

- Ideale wereld
- Maar ethisch?
  - Bij ouderen placebo gecontroleerd onderzoek met griepvaccin: ONMOGELIJK
- Retrospectief, epidemiologisch onderzoek: ook best interessant

3. Welke evidentie is er? Vraag 1

Eerst: het wordt steeds moeilijker om goede trials te doen:

Lessons from 40 years' surveillance of influenza in England and Wales

D. M. FLEMING* and A. J. ELLIOT

Epidemiol Infect. 2008 July; 136(7): 866-875

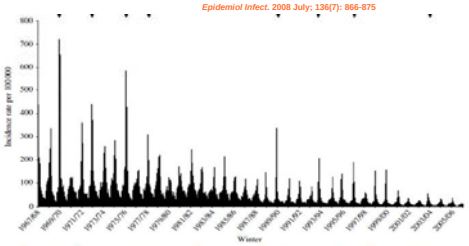

Fig. 1. Influenza-like illness (ILI) 1967/68 to 2006/07: mean weekly incidence rate per 100 000 population in 4-weekly periods. The influenza viruses (type, subtype and strain) are highlighted for winters of significant activity.

3. Welke evidentie is er? Vraag 1

Research articles

"I-MOVE" TOWARDS MONITORING SEASONAL AND PANDEMIC INFLUENZA VACCINE EFFECTIVENESS: LESSONS LEARNT FROM A PILOT MULTI-CENTRIC CASE-CONTROL STUDY IN EUROPE, 2008-9

Acknowledgements
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3. Welke evidentie is er? Vraag 1

I move:

- 5 landen (Dk, Hu, Po, Ro, Sp) CC 2008-9
- 160 GP's, ILI ≥65j swabbed
- Griep + werden vergeleken met griep -
- 138 + vgl met 189 -

TABLE 3

Vaccination coverage for the seasonal 2008-9 influenza vaccine by control group and country study, Denmark, Hungary, Portugal, Romania, and Spain, 2008-9

Study	Vaccine coverage (%) in ILI positive cases	Vaccine coverage (%) in test-negative controls	Vaccine coverage (%) in non-ILI GP patients	Vaccine coverage in community controls	Vaccine coverage in participating GPs catchment area
Denmark	55	71.4	N/A	53.6**	N/A
Hungary***	41.9	48.7	42.7	N/A	38.5
Portugal	42.9	53.3	70	54.4*	N/A
Romania	48.7	67.6	N/A	N/A	86.9
Spain	61.4	89.2	80.7	N/A	65.3

N/A : not applicable
*Community controls sample selected for national telephone survey (Lisboa: Instituto Nacional de Saúde Dr. Ricardo Jorge. Observatório Nacional de Saúde)
** Community controls randomly selected from the Danish population register
*** Results apply to ages 65 years and above, apart from Hungary where the study was carried out for 60 year-olds and older

3. Welke evidentie is er? Vraag 1

I move:

TABLE 4

Country specific and pooled crude and adjusted vaccine effectiveness (VE), Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

		Crude analysis			Adjusted analysis			Variables used for adjustment
		N	VE	95% CI	N	VE	95% CI	
Country specific estimates	Spain	81	80.8	36.0 - 94.2	76	82.9	30.6 - 95.8	age, sex, chronic disease, smoking, functional status
	Portugal	29	34.4	-184.3 - 84.9	28	82.3	-70.5 - 98.2	age, sex, chronic disease, smoking
	Denmark	41	51.1	-78.2 - 86.6	34	90.9	-43 - 99.4	age, sex, chronic disease, smoking, previous influenza vaccination
	Romania	98	58.2	-0.4 - 82.6	92	86.8	38.0 - 97.2	age, sex, chronic disease, smoking, previous influenza vaccination
	Hungary	78	28.6	-78.5 - 71.5	72	43.6	-119.4 - 85.6	age, sex, chronic disease, smoking, previous influenza vaccination
Pooled estimates	65+	327	55.1	27.8 - 72.1	292	59.1	15.3 - 80.3	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	65-74 years				196	65.4	15.6 - 85.8	study, sex, chronic disease, smoking, previous influenza flu vaccination, functional status, previous hospitalisation
	75+ years				96	59.6	-72.6 - 90.6	study, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	A(H1) strain				259	56.4	-6.2 - 81.0	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous

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Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

A Randomized Controlled Trial

Carolyn Buxton Bridges, MD
William W. Thompson, PhD
Martin I. Meltzer, PhD
Gordon R. Reeve, PhD
Walter J. Talamonti, MD, MPH
Nancy J. Cox, PhD
Heather A. Lilac, RN
Henrietta Hall, BS
Alexander Klimov, PhD
Keiji Fukuda, MD, MPH

THE COST-EFFECTIVENESS OF INactivated influenza vaccination in reducing influenza illness, hospitalization, and death

Context Although the cost-effectiveness and cost-benefit of influenza vaccination are well established for persons aged 65 years or older, the benefits for healthy adults younger than 65 years are less clear.

Objective To evaluate the effectiveness and cost-benefit of influenza vaccine in preventing influenzalike illness (ILI) and reducing societal costs of ILI among healthy working adults.

Design Double-blind, randomized, placebo-controlled trial conducted during 2 influenza seasons.

Setting and Participants Healthy adults aged 18 to 64 years and employed full time by a US manufacturing company (for 1997-1998 season, n=1184; for 1998-1999 season, n=1191).

Interventions For each season, participants were randomly assigned to receive either trivalent inactivated influenza vaccine (n=595 in 1997-1998 and n=587 in 1998-1999) or sterile saline injection (placebo; n=589 in 1997-1998 and n=604 in 1998-1999). Participants in 1997-1998 were rerandomized if they participated in 1998-1999.

Main Outcome Measures Influenzalike illnesses and associated physician visits and work absenteeism reported in biweekly questionnaires by all participants, and serologic

3.Welke evidentie is er? Vraag 1

Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

Author Affiliations: Influenza Branch, Division of Viral and Rickettsial Diseases (Drs Bridges, Thompson, Cox, Klimov, and Fukuda and Ms Hall) and Office of the Director(Dr Meltzer), National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Ga; Ford Motor Co, Dearborn, Mich (Drs Reeve and Talamonti); and the Oak Ridge Institute for Science and Education, Oak Ridge, Tenn (Ms Lilac).

Funding/Support: This study was funded by the National Center for Infectious Diseases, Centers for Disease Control and Prevention.

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3.Welke evidentie is er? Vraag 1

Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

- **Gezonde adults tsn 18 - 64 years and employed full-time by a US manufacturing**
- **1997-1998 season, n=1184; for 1998¬1999 season, n=1191**
- **Gerandomiseerd voor ofwel**
  - **TIV (n=595 in 1997-1998 and n=587 in 1998¬1999) ofwel**
  - **Placebo (n=589 in 1997-1998 and n=604 in 1998-1999).**

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3.Welke evidentie is er? Vraag 1

Effectiveness and Cost-Benefit of Influenza Vaccination of Healthy Working Adults

Resultaten:

- **In 1997-8 verschilde het circulerende virus van het vaccin, en was VE laag: 50% en vaccinatie reduceerde niet het aantal GP consultaties**
- **1998-9 echter: veel beter virus/ vaccin match met VE 86% met reductie van consultatie, werk verlet…**

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3.Welke evidentie is er? Vraag 1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines

Arnold S. Monto, M.D., Suzanne E. Ohmit, Dr.P.H., Joshua G. Petrie, M.P.H., Emileigh Johnson, B.S., Rachel Truscon, M.P.H., Esther Teich, M.A., Judy Rotthoff, R.N., Matthew Boulton, M.D., M.P.H., and John C. Victor, Ph.D., M.P.H.

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The NEW ENGLAND JOURNAL of MEDICINE

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We thank the study staff at Central Michigan University, Eastern Michigan University, and Western Michigan University for their significant contributions to the success of the study; Dr. Janet Gilsdorf, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, for serving as the independent safety monitor; and the staff of the Influenza Division, Centers for Disease Control and Prevention, for identifying the strains of viruses isolated and for sharing their realtime PCR protocol.

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3.Welke evidentie is er? Vraag 1

Vergelijking TIV met LAIV

- **Gerandomiseerd, dubbelblind, placebo gecontroleerd, gezonde vrijwilligers, 2007-8**
- **1952 individuen gerandomiseerd**
- **90% van de griep activiteit was H3N2**

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3. Welke evidentie is er? Vraag 1

Vergelijking TIV met LAIV

Table 1. Baseline Characteristics of the 1952 Subjects, According to Study Group, during the 2007–2008 Influenza Season in Michigan.*

Characteristic	TIV Group (N=814)	LAIV Group (N=813)	Placebo Group (N=325)†	Total (N=1952)
Total participants — %	41.7	41.6	16.7	100.0
Age — yr	23.2±7.4	23.5±7.7	22.9±6.7	23.3±7.4
Age category — no. (%)				
18–19 yr	289 (35.5)	283 (34.8)	114 (35.1)	686 (35.1)
20–24 yr	355 (43.6)	340 (41.8)	140 (43.1)	835 (42.8)
25–34 yr	90 (11.1)	99 (12.2)	44 (13.5)	233 (11.9)
35–49 yr	80 (9.8)	91 (11.2)	27 (8.3)	198 (10.1)
Sex — no. (%)				
Female	494 (60.7)	519 (63.8)	201 (61.8)	1214 (62.2)
Male	320 (39.3)	294 (36.2)	124 (38.2)	738 (37.8)
Race or ethnic group — no. (%)‡				
White	697 (85.6)	682 (83.9)	264 (81.2)	1643 (84.2)
Nonwhite	117 (14.4)	131 (16.1)	61 (18.8)	309 (15.8)
Previous receipt of influenza vaccine — no. (%)	307 (37.7)	288 (35.4)	136 (41.8)	731 (37.4)

* Plus–minus values are means ±SD. LAIV denotes trivalent live attenuated influenza vaccine, and TIV trivalent inactivated influenza vaccine.
† Placebo was physiologic saline administered as an intramuscular injection (in 163 participants) or as an intranasal spray (in 162 participants). For the purposes of efficacy analyses, the two placebo groups were considered equivalent and were combined.
‡ Race or ethnic group was self-reported. "Nonwhite" included black, Asian, Hispanic, and other or mixed.

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3. Welke evidentie is er? Vraag 1

Vergelijking TIV met LAIV

Table 2. Estimated Absolute and Relative Efficacies of the Trivalent Inactivated and Live Attenuated Influenza Vaccines.*

Confirmation of Symptomatic Influenza†	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Relative Reduction (95% CI)‡		
	TIV (N=813)	LAIV (N=814)	Placebo (N=325)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV	Absolute Efficacy, TIV vs. Placebo	Absolute Efficacy, LAIV vs. Placebo	Relative Efficacy, TIV vs. LAIV
	no. of participants (%)								
Positive culture	21 (2.6)	38 (4.7)	31 (9.5)	0.27 (0.15–0.49)	0.49 (0.30–0.81)	0.55 (0.31–0.97)	73 (51–85)	51 (19–70)	45 (3–69)
Positive PCR	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)
Positive culture, positive PCR, or both	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)

The study population included all 1952 enrolled participants who were randomly assigned to a vaccine or a placebo group and who actually received vaccine or placebo. The trivalent inactivated influenza vaccine (TIV) used was Fluzone (Sanofi Pasteur), and the trivalent live attenuated influenza vaccine (LAIV) used was FluMist (MedImmune). The placebo was physiologic saline administered as an intramuscular injection or as an intranasal spray. Exact 95% confidence intervals (CI) were calculated.
Case-eligible episodes of symptomatic influenza-like illness were confirmed by culture, real-time polymerase-chain-reaction (PCR) assay, or both. Confirmation by culture was defined as isolation of virus by cell culture and subsequent identification by fluorescence antibody assay.
The percent relative reduction in vaccine efficacy was defined as (1−relative risk)×100.

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3. Welke evidentie is er? Vraag 1

Is vaccinatie van gezondheidswerkers zinvol?

Acknowledgments

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THE LANCET

FAGG/PN 18/02/2011

Carman et al., *Lancet* 2000; 355: 93–97

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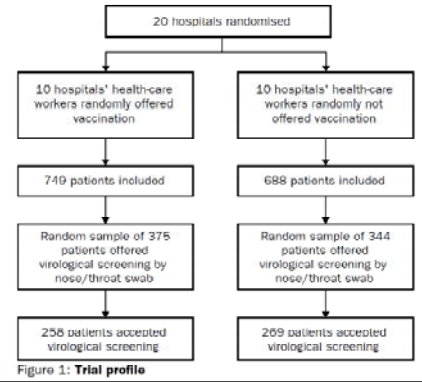

Figure 1: **Trial profile**

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3. Welke evidentie is er? Vraag 1

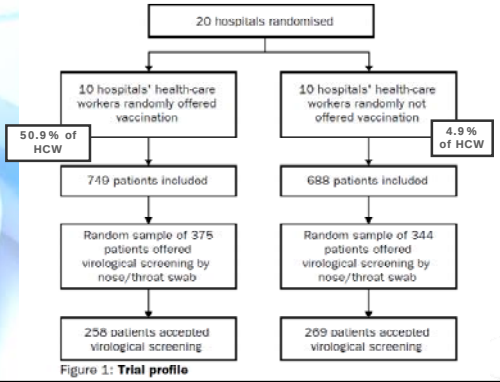

Figure 1: **Trial profile**

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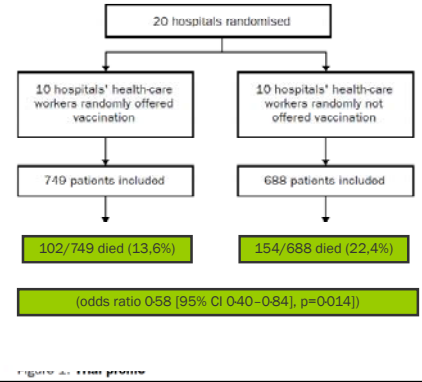
3. Welke evidentie is er? Vraag 1



3. Welke evidentie is er? Vraag 1

Is vaccinatie van gezondheidswerkers zinvol?

Effectiveness … to prevent d… cluster rand…

Andrew C Hayward, … John M Watson

We thank the lead nurses in the care homes who helped to implement the intervention and collect the data.

Contributors: All authors were substantially involved in the conception and design of the study, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. ACH was the principal investigator and is guarantor.

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staff … nts: … ial, …

BMJ

Hayward et al., *BMJ* 2007; 1-6

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3. Welke evidentie is er? Vraag 1

Is vaccinatie van gezondheidswerkers zinvol?

Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial

Andrew C Hayward, Richard Harling, Sally Wetten, Anne M Johnson, Susan Munro, Julia Smedley, Shahed Murad, John M Watson

23 intervention homes	23 control homes
1249 residents	1323 residents
1610 staff	1766 staff

BMJ

FAGG/PN 18/02/2011

Hayward et al., *BMJ* 2007; 1-6

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23 intervention homes	23 control homes
1249 residents	1323 residents
1610 staff	1766 staff
Vaccination coverage HCW: 35%	**Vaccination coverage HCW: 5%**
Death: 11.2%	Death: 15.3%
ILI: 11.4%	ILI: 22.7%
GP use for ILI: 10.0%	GP use for ILI: 18.7%
Hospitalisation: 8.4%	Hospitalisation: 10.9%
ILI Hospitalisation: 0.3%	ILI Hospitalisation: 1.7%

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Hayward et al., *BMJ* 2007; 1-6

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Death:	11.2%	Death:	15.3%
ILI:	11.4%	ILI:	22.7%
GP use for ILI:	10.0%	GP use for ILI:	18.7%
Hospitalisation:	8.4%	Hospitalisation:	10.9%
ILI Hospitalisation:	0.3%	ILI Hospitalisation:	1.7%

Of anders uitgedrukt, bij een verschil in vaccinatiegraad van 30% van de gezondheidswerkers werden per 100 residenten 5 overlijdens voorkomen…

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Hayward et al., *BMJ* 2007; 1-6

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Conclusie Vraag 1

Is er evidentie: ja

Maar hebben we betere griepvaccins nodig?
Ja inderdaad

Echter, zal de ontwikkeling eenvoudig zijn?
Neen

De belangrijkste les die ik geleerd heb uit het pandemie verhaal is: griep is en blijft een uiterst moeilijk verhaal

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